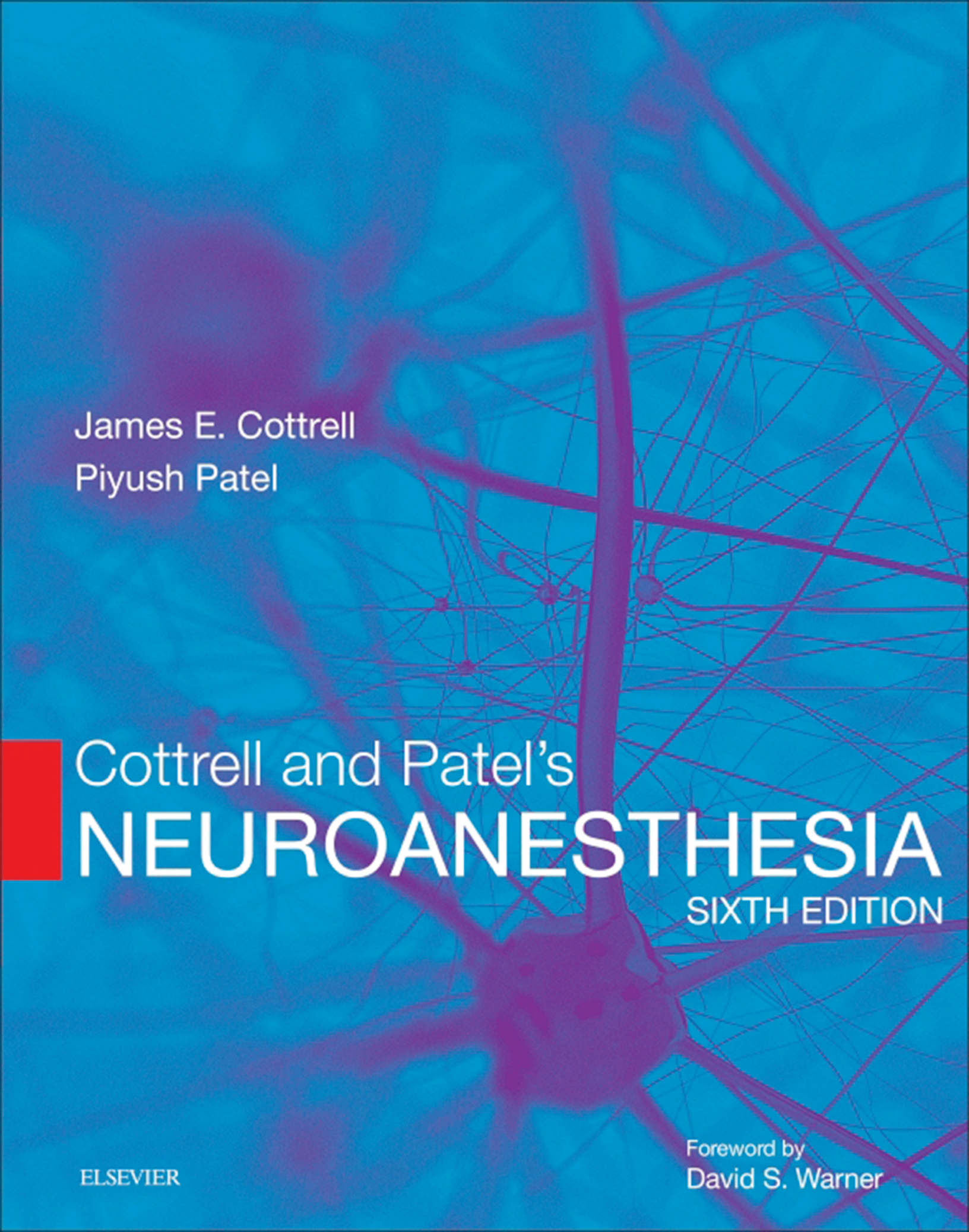

James E. Cottrell
Piyush Patel
Cottrell and Patel's
NEUROANESTHESIA
SIXTH EDITION
ELSEVIER
Foreword by
David S. Warner

Expert CONSULT Built with inkling | E books

Any screen. Any time. Anywhere.

Activate the eBook version of this title at no additional charge.

Expert Consult eBooks give you the power to browse and find content, view enhanced images, share notes and highlights—both online and offline.

Unlock your eBook today.

1. Visit **expertconsult.inkling.com/redeem**
2. Scratch off your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign up
6. Go to "My Library"

It's that easy!

Scan this QR code to redeem your eBook through your mobile device:

Place Peel Off Sticker Here

For technical assistance:
email expertconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8200 (outside the US)

ELSEVIER

Cottrell and Patel's

NEUROANESTHESIA

This page intentionally left blank

Cottrell and Patel's NEUROANESTHESIA

SIXTH EDITION

Edited by

James E. Cottrell MD FRCA
Dean for Clinical Practice
Distinguished Service Professor
Chair, Department of Anesthesiology
SUNY Downstate Medical Center
Brooklyn, New York

Piyush Patel MD
Professor of Anesthesiology
University of California San Diego;
Staff Anesthesiologist
VA Medical Center
San Diego, California

Foreword by

David S. Warner MD
Distinguished Professor
Department of Anesthesiology
Duke Univeristy School of Medicine
Durham, North Carolina

ELSEVIER
Edinburgh London New York Oxford Philadelphia St Louis Sydney Toronto 2017

ELSEVIER

First edition 1980
Second edition 1986
Third edition 1994
Fourth edition 2001
Fifth edition 2010
Sixth edition 2017

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-323-35944-3

Printed in United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Executive Content Strategist: William R. Schmitt/Dolores Meloni
Content Development Specialist: Helen Leng
Content Coordinator: Latha Vadivelu
Senior Project Manager: Beula Christopher King
Designer: Miles Hitchen
Illustration Manager: Lesley Frazier
Marketing Manager: Melissa Fogarty

Dedication to William L. Young, MD (1954 – 2013)

William (Bill) Young served as co-editor of the previous edition. Working with Bill was like having problems solved before I noticed them.

Bill was a remarkable clinician scientist who made a number of seminal contributions. Chief amongst these was the fundamental change in our understanding of the pathogenesis and treatment of arteriovenous malformations. Bill proposed a radical hypothesis wherein he posited that AVMs are an acquired postnatal phenomenon in patients who have an underlying genetic susceptibility and that vascular growth factors are key to the unregulated vessel growth. With the support of preclinical data, generated primarily by Bill, he initiated Phase I trials of bevacizumab for high-risk patients with AVMs for whom conventional therapy was not feasible. This was the first new *medical* treatment of AVMs for two decades. A logical extension of the premise that AVMs are acquired in genetically susceptible individuals is genetic screening to identify at-risk patients and the development of biomarkers for purposes of risk stratification. Bill organized an international collaboration to evaluate gene loci associated with AVM development and identification of risk factors for AVM rupture. This is a remarkable record of achievement. Bill was one of the few clinician scientists able to bring basic discoveries in the laboratory to the clinic for the difficult management of patients with AVMs.

I first met Bill at NYU when he started as a resident, all hungry for knowledge and with a relentless energy. Bill's many contributions were outlined in a tribute by David S. Warner and William Lanier in the *Journal of Neurosurgical Anesthesiology* Vol. 26, #1, January 2014. Perhaps his greatest contribution was bringing like-minded people together, whether it was in music, science, travel or simply friendship.

Thank you, Bill.

Acknowledgment

We thank our respective departments of anesthesiology, each of which has provided, despite recent economic adversity, the practical and intellectual background that makes it possible for colleagues like ourselves to write, assemble, and edit such books as *Cottrell and Patel's Neuroanesthesia*. Special thanks are also due to David S. Warner for the new Foreword; Theon Doobay for editorial assistance; Tania Baron for coordinating the project; the publishing staff at Elsevier, Helen Leng and William R. Schmitt; and especially the contributing authors whose expertise has been particularly important in making this edition possible. We also thank our families for helping us find time to complete such an undertaking.

James E Cottrell, MD, FRCA
Piyush Patel, MD

Contents

Foreword

I have generally believed that textbooks present a suboptimal medium for communicating the science and practice of medicine. They are not peer-reviewed, the writing is often relegated to authors just entering the field, and publication delays may allow an out-of-date perspective while the ink is still drying. Hence, the authoritative nature of textbook content can be easily questioned. *Cottrell and Patel's Neuroanesthesia* refutes this view in that it offers an example of how a textbook can serve as a valid foundation for learning and practice at all levels of experience.

The subspecialty of neuroanesthesiology has always prided itself on pursuing and inculcating scientific evidence into our practice and educational endeavors. Science is different from art in that art is intended to present a personal perception and interpretation of a real or imagined existence. It is for the viewer to determine validity and that determination cannot be tested. In contrast, science is an assemblage of physical properties that should hold true through time, space, and for all individuals, regardless of persuasion. But science and art share a precious element. Beauty. Beauty can be immediately apparent or may require knowledge of the structure and history behind a project to understand its significance. After reviewing the galley proofs for *Cottrell and Patel's Neuroanesthesia*, I must call it a beautiful work.

As an erudite neuroanesthesiologist, I approached the galley proofs for *Cottrell and Patel's Neuroanesthesia* with skepticism. It became clear within moments that this work is exceptional. The reader is instantly drawn to the high-quality images and the progression of concepts from the most elementary principles to complex and state-of-the-art science and implications. The book is comprehensive, detailed, and wholly relevant to the practice of neuroanesthesiology. There simply is no other source for this level of organization of our knowledge. It will enable the initiate to quickly grasp key concepts, while experienced clinicians and scientists can not only refresh but also extend their understanding of how and why we do what we do for our patients. It is a must read for all.

There are bastions that define our specialty including the Society for Neurosciences in Anesthesiology and Critical Care and the Journal of Neurosurgical Anesthesiology, both of which James Cottrell served to found. These entities represent the best and brightest of our scientists and clinicians. The authorship of *Cottrell and Patel's Neuroanesthesia* reflects the same population and is edited by two of the most longstanding and innovative authorities in our field. The 5th edition of *Neuroanesthesia* was substantially advanced by the inclusion of William L. Young, M.D. as co-editor. Dr. Young was a paramount scientist and set the tone for evidence-based medicine the reader will encounter in the current edition of *Cottrell and Patel's Neuroanesthesia*. Dr. Young's untimely passing left a space almost impossible to fill. Having known Bill closely, I am certain that he would be thrilled that Piyush Patel accepted the challenge of maintaining a quality of scientific excellence worthy of our specialty in this authoritative text. Dr. Patel has succeeded. Congratulations to all of the authors for providing this superb compendium of knowledge that can only serve to advance patient care.

David S. Warner, MD
Distinguished Professor
Department of Anesthesiology
Duke Univeristy School of Medicine
Durham, North Carolina

Preface

With a new co-editor, Piyush Patel, twenty-three new authors, five new chapters, eight chapters with all new authors, fifteen new chapters with one or more new authors and the incorporation of suggestions made in reviews of the fifth edition, this edition of *Cottrell and Patel's Neuroanesthesia* is both track-tested and up to date.

We have added a new chapter on neurocritical care issues, added a section on diagnosis and management of brain death and end-of-life care, added a section on neuroanatomy, and added more on multimodality monitoring, brain tissue oxygenation, oximetry, microdialysis and depth of anesthesia monitors. Sections were also added on stereotactic surgery, deep brain stimulation, brain biopsy, and gene therapies. There was, of course, no option. Ours is a fast moving field.

As the Red Queen said to Alice in Wonderland, "Now, *here* you see, it takes all the running you can do, to keep in the same place." In this case, "*here*" is neurosurgical anesthesiology, and "*the same place*" is state-of-the-art knowledge.

Medicine advances through a sort of trickle-down process. Information flows from basic scientists to laboratory animal researchers to clinical investigators to scientific journals to clinical textbooks, and finally, to clinicians. The closer the connections between the first four way stations and the textbook, the better clinicians are served. We have kept those connections tight by gathering authors who are, in various combinations, basic scientists, laboratory researchers, clinical investigators, journal authors, journal editors, and of course, clinicians.

The emphasis of this book has always been clinical application of tested basic science principals and that focus has only been sharpened in this sixth edition. We want this book to serve its readers by helping them serve their patients.

James E. Cottrell, MD, FRCA
Piyush Patel, MD

List of Contributors

The editors would like to acknowledge and offer grateful thanks for the input of all previous editions' contributors, without whom this new edition would not have been possible.

A.E. Abramowicz, MD

Associate Professor of Clinical Anesthesiology
Anesthesiology Department
New York Medical College
Valhalla, New York

A.A. Artru, MD

Professor of Anesthesiology and Pain Medicine
University of Washington School of Medicine;
Chief of Anesthesia, Associate Medical Director, and Chief of Staff
University of Washington Medical Center
Seattle, Washington

F. Asgarzadie, MD, FAANS

Acting Chair of Neurosurgery
Chief of Spine Surgery
Associate Professor of Neurosurgery
Loma Linda University Medical Center
Loma Linda, California

A.A. Bendo, MD

Distinguished Service Professor and Executive Vice Chair
Department of Anesthesiology
SUNY Downstate Medical Center
Brooklyn, New York

N.J. Bruder, MD

Professeur
Service d'Anesthésie-Réanimation
CHU Timone – Aix Marseille Université
Marseille, France

J. Chui, MBChB, FANZCA, FHKCA, PgDip (Biostat and Epi)

Consultant Anesthesiologist
Department of Anesthesia and Perioperative Medicine
London Health Sciences Centre
Western University
London, Ontario, Canada

D.J. Cole, MD

Professor of Clinical Anesthesiology
Ronald Reagan UCLA Medical Center
Los Angeles, California

J.E. Cottrell, MD, FRCA

Dean for Clinical Practice
Distinguished Service Professor
Chair, Department of Anesthesiology
SUNY Downstate Medical Center
Brooklyn, New York

G. Crosby, MD

Associate Professor of Anesthesia
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

D.J. Culley, MD

Associate Professor of Anesthesia
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

M. Czosnyka, PhD

Professor of Brain Physics
Division of Neurosurgery
University of Cambridge Department of Clinical Neurosciences
Addenbrooke's Hospital
Cambridge, United Kingdom

S.C. Daly, MD

Assistant Professor of Anesthesiology
University of California San Diego
San Diego, California

T.R. Deer, MD

President and CEO
The Center for Pain Relief
Clinical Professor of Anesthesiology
West Virginia University
Charleston, West Virginia

S.T. DeKosky, MD, FACP, FANA, FAAN

Aerts-Cosper Professor of Alzheimer's Research
Deputy Director, McKnight Brain Institute
Associate Director, 1Florida ADRC
Professor of Neurology and Aging and Geriatrics Research
University of Florida College of Medicine
Gainesville, Florida

K.B. Domino, MD, MPH

Professor of Anesthesiology and Pain Medicine
University of Washington School of Medicine
Seattle, Washington

C.F. Dowd, MD

Professor
Clinical Radiology and Biomedical Imaging
Neurosurgery, Neurology, and Anesthesia and Perioperative Care
University of California San Francisco School of Medicine
San Francisco, California

J.C. Drummond, MD, FRCPC

Professor of Anesthesiology
University of California San Diego,
Staff Anesthesiologist
VA Medical Center
San Diego, California

J.M. Ehrenfeld, MD, MPH

Associate Professor of Anesthesiology, Surgery, Biomedical Informatics and Health Policy
Associate Director
Vanderbilt Anesthesiology and Perioperative Informatics Research Division
Vanderbilt University School of Medicine
Nashville, Tennessee

J.A. Ellis, MD

Chief Resident
Department of Neurological Surgery
Columbia University Medical Center
New York, New York

L. Emory, MD

Director of Neuroanesthesiology
Ochsner Health System
New Orleans, Louisiana

M.B. Friese, MD, PhD

Instructor of Anesthesia
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

D.R. Gambling, MB, BS, FRCPC

Clinical Professor of Anesthesiology (Voluntary)
University of California San Diego;
Head, Department of Anesthesiology
Sharp Mary Birch Hospital for Women and Newborns
San Diego, California

A.W. Gelb, MD

Distinguished Professor
Department of Anesthesia and Perioperative Care
University of California San Francisco
San Francisco, California

T.L. Griffiths, MD, BM

Staff Anesthesiologist
Department of Cardiothoracic and General Anesthesiology
Southern California Permanente Medical Group
Pasadena, California

J. Hensley, MD

Assistant Professor
Department of Anesthesiology
West Virginia University
Morgantown, West Virginia

I.A. Herrick, MD, MPA, FRCPC

Associate Professor
Anesthesia and Clinical Pharmacology
Department of Anesthesia and Perioperative Medicine
Western University/London Hospitals
London, Ontario, Canada

R.T. Higashida, MD

Chief, Neuro Interventional Radiology
Clinical Professor of Radiology, Neurological Surgery, Neurology, and Anesthesiology
University of California, San Francisco Medical Center
San Francisco, California

J.Y. Hou, MD

TBI/Polytrauma Fellow
Physical Medicine and Rehabilitation Service
Richmond, Virginia;
Research Assistant Professor
Department of Anesthesiology
SUNY Downstate Medical Center
Brooklyn, New York

P.J. St. Jacques, MD

Associate Professor
Quality and Patient Safety Director
Department of Anesthesiology
Vanderbilt University Medical Center
Nashville, Tennessee

L.C. Jameson, MD

Associate Professor, Vice Chair, Anesthesiology
University of Colorado, School of Medicine
Aurora, Colorado

D.J. Janik, MD

Associate Professor, Anesthesiology
University of Colorado School of Medicine;
Co-Director Intraoperative Neuromonitoring
University of Colorado Hospital
Aurora, Colorado

S. Joshi, MD

Assistant Professor of Anesthesiology
Columbia University Medical Center
New York, New York

I.S. Kass, PhD

Professor
Anesthesiology and Physiology and Pharmacology Departments
SUNY Downstate Medical Center
Brooklyn, New York

M.A. Kirkman, MBBS, PGCert, MRCS, MEd, DIC, AFHEA, MSc

Honorary Fellow in Neurocritical Care
National Hospital for Neurology and Neurosurgery
University College London Hospitals
London, United Kingdom

W.A. Kofke, MD, MBA, FCCM, FNCS

Professor, Director Neuroscience in Anesthesiology and Critical Care Program
Co-Director Neurocritical Care, Department of Neurosurgery
Co-Director Perioperative Medicine and Pain Clinical Research Unit
University of Pennsylvania
Philadelphia, Pennsylvania

A. Koht, MD

Professor of Anesthesiology, Neurological Surgery and Neurology
Chief, Neurosurgical Anesthesia
Director, Fellowship Program, Neurosurgical Anesthesia
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

R. Kutteruf, MD

Associate
Physicians Anesthesia Service
Seattle, Washington

A.M. Lam, MD, FRCPC, FNCS

Medical Director of Neuroanesthesia and Neurocritical Care
Swedish Neuroscience Institute, Swedish Medical Center;
Clinical Professor
Department of Anesthesiology and Pain Medicine
University of Washington
Seattle, Washington

M.T. Lawton, MD

Professor in Residence of Neurological Surgery
Tong Po Kan Endowed Chair
Chief, Cerebrovascular Surgery
Director, Cerebrovascular Disorders Program
Co-Director, Skull Base and Cerebrovascular Laboratory
Chief, Vascular Neurosurgery
University of California
San Francisco, California

C.Z. Lee, MD, PhD

Professor
Associate Director, Division of Neuroanesthesia
Department of Anesthesia and Perioperative Care
University of California
San Francisco, California

B. Lei, MD, PhD

Clinical Assistant Professor
Department of Anesthesiology
SUNY Downstate Medical Center
Brooklyn, New York

P.H. Manninen, MD, FRCPC

Associate Professor
University of Toronto
Department of Anesthesia and Pain Medicine
Toronto Western Hospital
Toronto, Canada

M. Matsumoto, MD, PhD

Professor and Chair
Department of Anesthesiology
Yamaguchi University Graduate School of Medicine
Ube, Yamaguchi, Japan

B. Matta, MB, BA, FRCA, FFICM

Consultant in Anesthesia and Neuro-Critical Care
Divisional Director, Cambridge University Hospitals
Divisional Director, MSK, Digestive Diseases, Major Trauma and Perioperative Care
Cambridge, United Kingdom

M.L. McManus, MD, MPH

Associate Professor, Anaesthesia (Pediatrics)
Harvard Medical School;
Senior Associate, Anesthesiology and Critical Care Medicine
Boston Children's Hospital
Boston, Massachusetts

A. Minokadeh, MD

Clinical Professor
Division Chief and Vice Chair, Anesthesiology Critical Care Medicine
UCSD School of Medicine
San Diego, California

J.D. Moreno, PhD

David and Lyn Silfen University Professor
Medical Ethics and Health Policy
History and Sociology of Science and Philosophy (by courtesy)
University of Pennsylvania
Philadelphia, Pennsylvania;
Senior Fellow
Center for American Progress
Washington, District of Columbia

E. Ornstein, MD, PhD

Associate Professor
Department of Anesthesiology
Columbia University Medical Center
New York, New York

P. Patel, MD

Professor of Anesthesiology
University of California San Diego;
Staff Anesthesiologist
VA Medical Center
San Diego, California

R.D. Phan, MD

Anesthesiology Physician
U.S. Anesthesia Partners
Dallas, Texas

R.P. Pong, MD

Anesthesiology Faculty
Virginia Mason Medical Center
Seattle, Washington

J.E. Pope, MD, DABPM, FIPP

President, Summit Pain Alliance
Board of Directors, Membership Committee Chair, Advocacy Fellowship Program Co-Chair
Scientific Program Chair, North American Neuromodulation Society
Neuromodulation Special Interest Group Co-Chair, American Society of Regional Anesthesia
Secretary, California Society of Interventional Pain Physicians
Santa Rosa, California

P. Ravussin, MD

Professor, Anesthesiology
Hôpital de Sion
Sion, Switzerland

T. Rizvi, MBBS, MD, DM

Clinical Instructor
Diagnostic Neuroradiology Division
University of Virginia Health System
Charlottesville, Virginia

I. Rozet, MD, DEAA

Associate Professor
Anesthesiology and Pain Medicine
University of Washington
VA Puget Sound Health Care System
Seattle, Washington

R. Rusa, MD

Anesthesiology
KPNW – Kaiser Sunnyside Medical Center
Clackamas, Portland, Oregon

T. Sakabe, MD, PhD

Director General
Yamaguchi Industrial Injury Hospital
Japan Organization of Occupational Health and Safety
Sanyo-Onoda, Yamaguchi, Japan;
Professor Emeritus
Yamaguchi University Graduate School of Medicine
Ube, Yamaguchi, Japan

R.A. Schlichter, MD

Associate Professor
Clinical Anesthesiology and Critical Care
Chief of Neuroanesthesia
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

P. Schoettker, MD, PD, MER

Chief of Neuro, ENT and Trauma Anesthesia
Service d'Anesthésiologie
Lausanne, Switzerland

A. Schubert, MD, MBA

Chair
Department of Anesthesiology
Ochsner Health System
New Orleans, Louisiana;
Professor of Anesthesiology
Ochsner Clinical School
University of Queensland
Queensland, Australia;
Vice President of Medical Affairs
Ochsner Medical Center
New Orleans, Louisiana

T.B. Sloan, MD, MBA, PhD

Professor Emeritus
Department of Anesthesiology
University of Colorado School of Medicine
Aurora, Colorado

M. Smith, MBBS, FRCA, FFICM

Consultant and Honorary Professor, Neurocritical Care
University College London Hospitals
UCLH/UCL National Institute for Health Research Biomedical Research Centre
London, United Kingdom

D.S. Smith, MD, PhD

Associate Professor
Anesthesiology and Critical Care
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

S.G. Soriano III, MD

Professor, Anaesthesia
Harvard Medical School;
Endowed Chair in Pediatric Neuroanesthesia
Anesthesiology, Perioperative and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

G.R. Stier, MD, FACP, MBA

Associate Professor
Anesthesiology, Internal Medicine, Critical Care
Medical Director, Neuro-Critical Care Unit
Loma Linda University Medical Center
Loma Linda, California

P.O. Talke, MD

Professor
Department of Anesthesia and Perioperative Care
University of California
San Francisco, California

H.S. U, MD

Professor
Division of Neurosurgery
UCSD School of Medicine
La Jolla, California

K. Vagnerova, MD

Assistant Professor of Anesthesiology and Perioperative Medicine
Oregon Health and Science University
Portland, Oregon

L. Venkatraghavan, MBBS, MD, DNB, FRCA, FRCPC

Assistant Professor
University of Toronto;
Director of Neuroanesthesia
Department of Anesthesia and Pain Medicine
Toronto Western Hospital
Toronto, Ontario

M. Wintermark, MD, MAS, MBA

Professor and Chief of Neuroradiology
Department of Radiology
Stanford University
Stanford, California

D.J. Wlody, MD

Professor of Clinical Anesthesiology
Vice Chair for Education
SUNY Downstate Medical Center
Brooklyn, New York

S.H. Worah, MD

Program Director, Anesthesiology Critical Care Medicine
Clinical Assistant Professor
SUNY Downstate Medical Center
Brooklyn, New York

G.T. Yocum, MD

Assistant Professor
Department of Anesthesiology
Columbia University Medical Center
New York, New York

This page intentionally left blank

Brain Metabolism, the Pathophysiology of Brain Injury, and Potential Beneficial Agents and Techniques

1

I.S. Kass • J.E. Cottrell • A.E. Abramowicz • J.Y. Hou • B. Lei

Brain metabolism involves both the production and the utilization of energy; catabolism is the breakdown and anabolism is the synthesis of components and molecules in the cells. For energy formation the main catabolic process is the breakdown of glucose with the ultimate formation of high-energy phosphate in the form of adenosine triphosphate (ATP). Other catabolic processes break down structural and enzymatic proteins, lipids, and carbohydrates; these processes are necessary to replace damaged and nonfunctional molecules. These molecules are resynthesized by anabolic processes that renew the cells and maintain optimal function. Cellular function also requires the maintenance of ionic homeostasis, which for neurons requires a large amount of energy. The pathophysiologic mechanisms of brain injury are incompletely understood but ultimately represent a failure of anabolic processes to maintain normal cell function. In this chapter we explore the putative mechanisms of brain injury. The causes of neuronal damage are multifaceted, and one pathway alone cannot explain how the injury occurs. Some pathophysiologic mechanisms are common to damage caused by ischemic, epileptogenic, and traumatic injury, whereas others are discrete for each of these processes. This review focuses on some common triggers of neuronal damage, such as altered ionic gradients, and explores how they in turn lead to long-term damage. We also discuss pharmacologic agents and clinical procedures that may lead to a reduction in long-term brain damage.

BRAIN METABOLISM

The main substance used for energy production in the brain is glucose. Because glucose is not freely permeable across the blood–brain barrier, it requires a transporter to enter the brain. This transporter does not require energy and can move glucose only down its concentration gradient, from a higher to a lower concentration. Normally the blood levels of glucose are well regulated so glucose concentrations in the brain are adequate; however, if blood levels of glucose fall the supply of glucose cannot meet the energy requirements of the brain. Thus adequate blood glucose levels are critical for normal brain activity. During insulin shock or other conditions that cause a reduction in blood glucose, unconsciousness can result from insufficient energy due to low brain glucose levels. When glucose and oxygen levels are sufficient, glucose is metabolized to pyruvate in the glycolytic pathway (Fig. 1.1). This biochemical process generates ATP from adenosine diphosphate (ADP) and inorganic phosphate and produces nicotinamide adenine dinucleotide reduced (NADH) from nicotinamide adenine dinucleotide (NAD^+). Pyruvate from this reaction then enters the citric acid cycle which, with regard to energy production, primarily generates NADH from NAD^+. The mitochondria use oxygen to couple the conversion of NADH back to NAD^+ with the production of ATP from ADP and inorganic phosphate. This process, called *oxidative phosphorylation*, forms three ATP molecules for each NADH converted and yields a maximum of 38 ATP molecules for each glucose molecule metabolized.[1] Because numerous parts of this pathway supply other metabolic requirements, such as amino acid synthesis and the formation of reducing equivalents for other synthetic pathways, the normal yield of this energy pathway is approximately 30 to 35 ATP molecules for each glucose molecule.

This pathway requires oxygen; if oxygen is not present the mitochondria can neither make ATP nor regenerate NAD^+ from NADH. The metabolism of glucose requires NAD^+ as a cofactor and is blocked in its absence. Thus, in the absence of oxygen, glycolysis proceeds by a modified pathway termed "anaerobic glycolysis"; this modification involves the conversion of pyruvate to lactate, regenerating NAD^+. This process produces hydrogen ion, which may accentuate neuronal damage if the intracellular pH falls. A major problem with anaerobic glycolysis, in addition to lowering pH, is that only two molecules of ATP are formed for each molecule of glucose metabolized. This level of ATP production is insufficient to meet the brain's energy needs. In addition, ischemia curtails the supply of glucose so even anaerobic glycolysis is blocked.

When the oxygen supply to a neuron is reduced, mechanisms that reduce and/or slow the fall in ATP levels include the following: (1) the utilization of phosphocreatine stores (a high-energy phosphate that can donate its energy to maintain ATP levels), (2) the production of ATP at low levels by anaerobic glycolysis, and (3) a rapid cessation of spontaneous electrophysiologic activity.

CELLULAR PROCESSES THAT REQUIRE ENERGY

Pumping ions across the cell membrane is the largest energy requirement in the brain. The sodium, potassium, and calcium concentrations in a neuron are maintained against large electrochemical gradients with respect to the outside of the cell. When sodium (Na), calcium (Ca) and potassium (K) are mentioned throughout the chapter we are referring to their ionic form (Na^+, Ca^{++} and K^+); this is the only form of these compounds that is present in living cells. When a neuron is not excited, there are slow leaks of potassium out of the cells and of sodium into the cells. The resting potential of a neuron depends mainly on the electrochemical equilibrium potential for potassium, which in most neurons is approximately −94 mV. There is some permeability to sodium and calcium so the resting potential for a neuron is usually −60 to −70 mV. Because the cell's membrane potential is not equal to the equilibrium potential for an ion, there is leakage of ions down their electrochemical gradients. If this leakage were not corrected by energy-dependent ion pumps, the membrane potential would fall to 0 mV and the cell would depolarize and die. The ion pumps fall into two major categories: (1) those that use ATP directly to pump ions and (2) those that use the energy of the Na gradient to cotransport another ion or molecule. The ultimate energy for the latter pumps comes from ATP via the Na/K

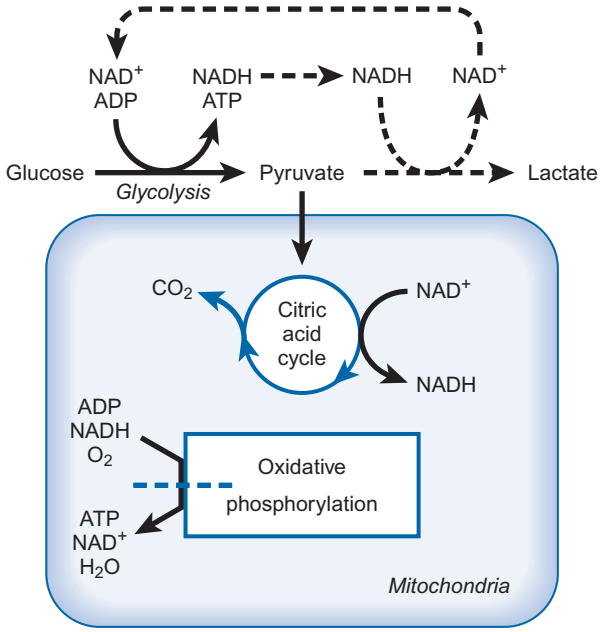


Fig. 1.1 Energy metabolism in the brain. Lines indicate metabolic pathways, dashed lines indicate anaerobic glycolysis. The *dashed line* across the oxidative phosphorylation reaction indicates this reaction is blocked during ischemia. ADP, adenosine diphosphate; ATP, adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide reduced.

ATPase, which transports Na ions and maintains the energy gradient of Na; examples of these exchange pumps include the Na/Ca, the Na/H and the Na/glutamate transporters. Examples of the former category of pump are the Na/K ATPase, the major user of energy in neurons, and the Ca ATPase. The primary ion pumps that directly use ATP are important because they establish the electrochemical gradients necessary for the secondary pumps, the ion exchange pumps, to work in the desired direction. Indeed, during ischemia these pumps do not have enough energy to operate, and this condition is a primary cause of neuronal depolarization and cell death. Neuronal activity markedly increases the flow of sodium, potassium, and calcium by opening Na, K, and Ca ion channels; this opening raises the rate of ion pumping required to maintain normal cellular ion concentrations. Because ion pumping uses ATP as an energy source, the ATP requirement of active neurons is greater than that of unexcited neurons. Approximately 60% of the energy the brain uses is required for functional activity, and the remainder is used to maintain cellular integrity. Anesthetics reduce neuronal activity and thereby ATP utilization by functional activity, but they do not reduce the energy required for the integrity of the brain. If energy production does not meet the demand of energy use in the brain, the neurons become first unexcitable and then irreversibly damaged.

Neurons require energy to maintain their structure and internal function. Each cell's membranes, internal organelles, and cytoplasm are made of carbohydrates, lipids, and proteins that require energy for their synthesis. Ion channels, enzymes, and cell structural components are important protein molecules that are continuously formed, modified, and broken down in the cell. If ATP is not available, protein synthesis cannot continue, and the neuron will die. Carbohydrates and lipids are also continuously synthesized and degraded in normally functioning neurons; their metabolism also requires energy. Most cellular synthesis takes place in the cell body, and energy is required for transport of components down the axon to the nerve terminals. Thus, energy is required to maintain the integrity of neurons even in the absence of electrophysiologic activity.

NEUROANATOMY

The brain is regionally differentiated structurally and functionally; this section will provide an overview of the functionality of the different brain regions. This is important with regard to stroke, since when an artery is blocked the function of the neurons in the region perfused by that artery is compromised. The details of the neuroanatomy and neurophysiology of the brain would require a book of its own; two that are recommended for detail are *Clinical Neuroanatomy*, by RS Snell and *Neurophysiology and Principles of Neural Science* by Kandel et al.[2,3]

The cerebral cortex has four main lobes on each side: the frontal, parietal, occipital, and temporal lobes (Fig. 1.2). Sensory pathways from one side of the body cross the midline and provide input to the opposite somatosensory cortex. Motor pathways that originate from the motor cortex on one side decussate in the medulla, travel down the spinal cord in the lateral corticospinal tracts, synapse on ventral motor neurons in the gray matter of the cord and deliver motor output to the opposite side of the body. The anterior part of the frontal lobe (prefrontal area) influences personality, orientation, concentration, and judgment; it is important for directing intellectual activity towards a goal. The precentral gyrus of the frontal lobe is the primary motor cortex, has output to the motor neurons in the spinal cord, and controls fine movement. Premotor association areas are located rostral to it and receive input from other motor areas of the brain, such as the basal ganglia, cerebellum, and red nucleus. Thus the premotor and motor cortex are responsible for integrating input from motor areas throughout the brain leading to purposeful movement. Adjacent to the precentral gyrus, across the central sulcus is the postcentral gyrus of the parietal lobe; this is the primary somatosensory cortex and receives information about fine touch. Posterior to the postcentral gyrus are the somatosensory association areas which help interpret and analyze touch sensations. All primary sensory areas of the brain have sensory association areas which further analyze and interpret these signals. The temporal lobe is located below the frontal and parietal lobe and contains the primary auditory and auditory association areas. One hemisphere in the brain is considered dominant and one particular area in it is important for the interpretation of language and the production of speech; this area has been labelled Wernicke's area. Wernicke's area is of critical importance and lesions in it lead to profound aphasia; it is generally considered to include the posterior part of superior temporal gyrus and the angular gyrus in the dominant cerebral hemisphere. The angular gyrus is an important multimodal association area in the parietal lobe adjacent to the temporal lobe. Multimodal association areas analyze input from single sensory association areas and provide complex analysis of the inputs and determine the response to complex stimuli. Wernicke's area of the brain is most carefully mapped out during neurosurgery and damage to it is assiduously avoided if possible. It is supplied by the middle cerebral artery and there are profound deficits following occlusion of this artery due to ischemic stroke. Lesions in this area are isolating to the person and he/she cannot communicate or understand verbal or written communication. This area directly activates Broca's area in the frontal lobe, a premotor speech area. Lesions to the parietal lobe of the nondominant hemisphere lead to visuospatial deficits and hemi-neglect (ignoring half of external space).

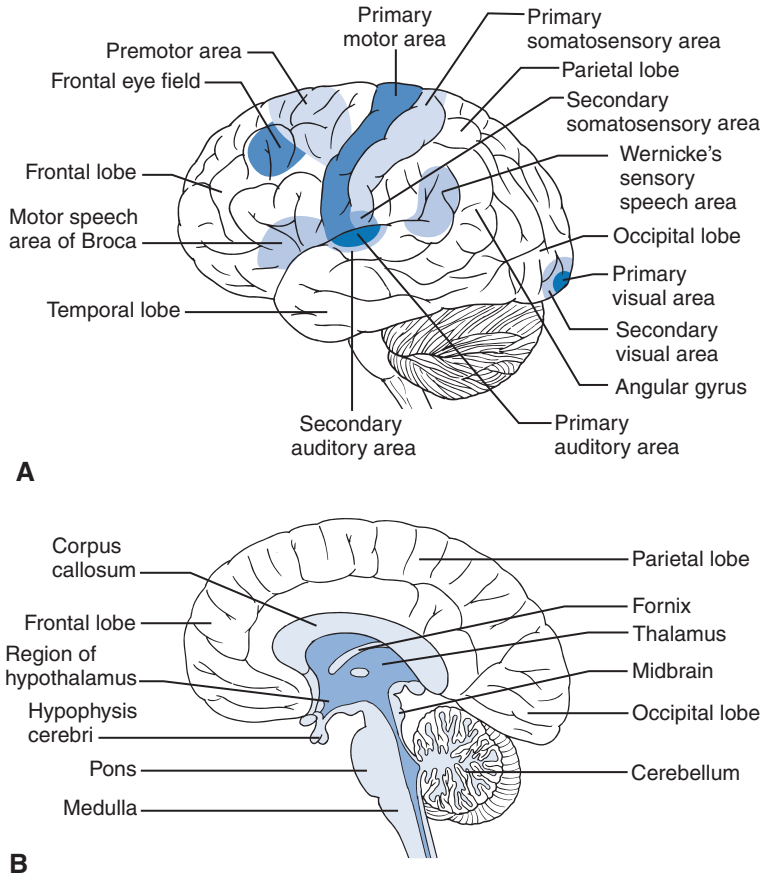


Fig. 1.2 Neuroanatomy of the brain. **A,** A lateral view of the left cerebral cortex. **B,** A medial view of the right cortex. *(Modified from Snell RS. Clinical Neuroanatomy. 9th ed. Philadelphia: F.A. Davis; 2009.)*

The thalamus is located medially and is an important relay center for information to and from the cerebral cortex. The hypothalamus, located below the thalamus, is important for a number of regulatory functions of the body such as hunger, thirst, and temperature regulation and the hypothalamus integrates behavioral and motivational activity from the limbic system with autonomic responses. The limbic system includes limbic cortex, hippocampus, and amygdala and is associated with feelings of reward and punishment, emotional behavior, learning, and memory. The hippocampus and the medial temporal lobe are important for long-term memory formation; the amygdala conveys the emotional content of memory. The basal ganglia are also located medial to the cortex and are important for motor function and the initiation of movements. Parkinson's disease is due to lesions in the substantia nigra, a dopaminergic area, leading to resting tremor and bradykinesia. Dementia is a nonmotor correlate of basal ganglia diseases and indicates these areas, primarily thought to be motor, can also profoundly influence behavior.

The cerebellum is located above the brainstem and plays an important role in rapid learned motor activity as well as postural control; it receives input from the motor cortex and proprioceptive feedback from the body to compare the intended movement with the actual movement caused by the muscles. It is important to know that the lateral cerebellum is not crossed and controls the same side of the body; e.g., the right cerebellum controls muscles on the right side of the body, which is also controlled by the left motor cortex. Thus information from the cerebellar cortex crosses the midline on its way to the cerebral cortex.

The brainstem consists of the midbrain, pons, and medulla and is structurally continuous with the spinal cord. The cranial nerves III to XII originate from the brainstem and/or brainstem nuclei. Ascending and descending neuronal pathways traverse this part of the brain and synapse with neurons in it; this area contains the reticular formation and the reticular activating system, an area responsible for maintaining alertness and consciousness. This area is important for the control of blood pressure, heart rate, breathing, swallowing, and other bodily functions. Lesions in this area can lead to coma or rapid death.

The spinal cord allows the brain and the body to communicate and contains ascending sensory pathways and descending motor pathways. The anterolateral spinothalamic tracts convey crude touch, temperature, and pain; they enter the gray matter of the cord, synapse in the dorsal horn; the axons of the postsynaptic neurons cross the midline and ascend the spinal cord to the brainstem and thalamus in the anterolateral tracts. The dorsal columns convey fine touch and proprioception and ascend the cord on the same side of the body and cross the midline after first synapsing in nuclei in the medulla. The final destination of these axons is the thalamus and information is relayed from there to the somatosensory cortex on the postcentral gyrus. The dorsal column axons also send branches into the spinal cord at or near to the level of the spinal cord they enter. The spinal cord has neuronal circuitry that modifies input to the brain and also mediates local reflexes such as withdrawal from pain and the control of muscle tension and tone.

PATHOPHYSIOLOGY

Ischemia

When the blood supply to the brain is limited, ischemic damage to neurons can occur; the brain is the organ most sensitive to ischemic damage. The area of the brain corresponding to

the territory of the cerebral artery blocked determines what functions are altered or lost subsequent to focal ischemia; this corresponds to the functional anatomy described in the previous section. The neurons in the ischemic areas are damaged by the loss of energy; the rest of this section describes the cellular events subsequent to ischemia that lead to this damage.

The central event precipitating damage by hypoxia or ischemia is reduced energy production due to blockage of oxidative phosphorylation. This causes ATP production per molecule of glucose to be reduced by 95%. At this rate of production, ATP levels fall, leading to the loss of energy-dependent homeostatic mechanisms. Additionally, during ischemia the supply of glucose is interrupted, as is the washout of metabolites. The activity of ATP-dependent ion pumps is reduced and the intracellular levels of sodium and calcium increase, whereas intracellular potassium levels decrease (Fig. 1.3).[4] These ion changes cause the neurons to depolarize and release excitatory amino acids such as glutamate.[5] In addition, glutamate is released from neurons owing to the reversal of the glutamate transporter, which pumps glutamate into the extracellular compartment when the cellular sodium and potassium ion gradients are disrupted.[6] High levels of glutamate further depolarize the neurons by activating AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and NMDA (*N*-methyl-D-aspartate) receptors, increasing sodium and potassium ion conductance.[7] The NMDA receptor also allows calcium to enter, triggering additional damaging pathways. Glutamate activates metabotropic receptors, which via second-messenger systems can increase the release of calcium from intracellular stores and activate other biochemical processes.[8] The damage due to excess glutamate has been termed *excitotoxicity* and is caused by activation of glutamate receptors and the accompanying ionic and biochemical changes.[5]

In addition to increased influx through membrane channels, cytosolic calcium is increased through reduced calcium pumping from the cell and the enhanced release of calcium from intracellular organelles such as the endoplasmic reticulum (Fig. 1.4).[9] The high cytoplasmic calcium level is thought to trigger a number of events that lead to the ischemic damage. These include increasing the activity of proteases and phospholipases. Phospholipases raise the levels of free fatty acids, such as arachidonic acid, and free radicals. Free radicals are also generated by incomplete mitochondrial oxidation.[9] One of the most damaging free radicals is peroxynitrite, which is formed by the combination of nitric oxide and another free radical.[9] Free radicals are known to damage proteins and lipids, whereas free fatty acids interfere with membrane function.

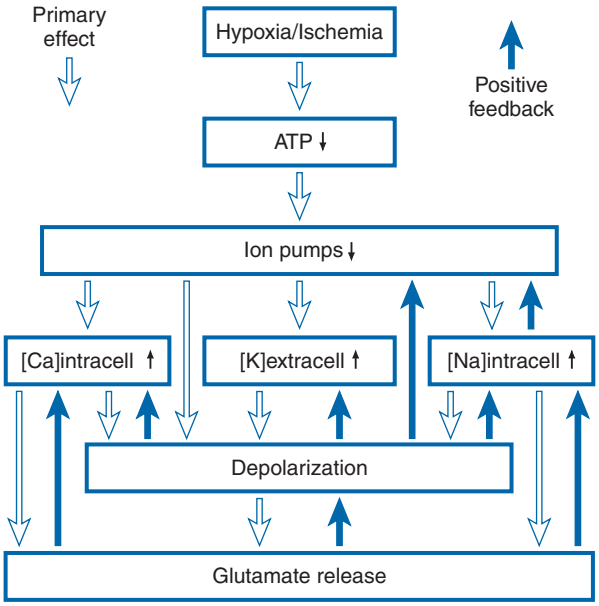


Fig. 1.3 Line diagram of cellular ionic events occurring during anoxia or ischemia. The events indicated are the primary triggers of events leading to neuronal cell death. Positive feedback loops are unstable and rapidly worsen events. ATP, adenosine triphosphate; extracell, extracellular; intracell, intracellular; ↑, increase; ↓, decrease.

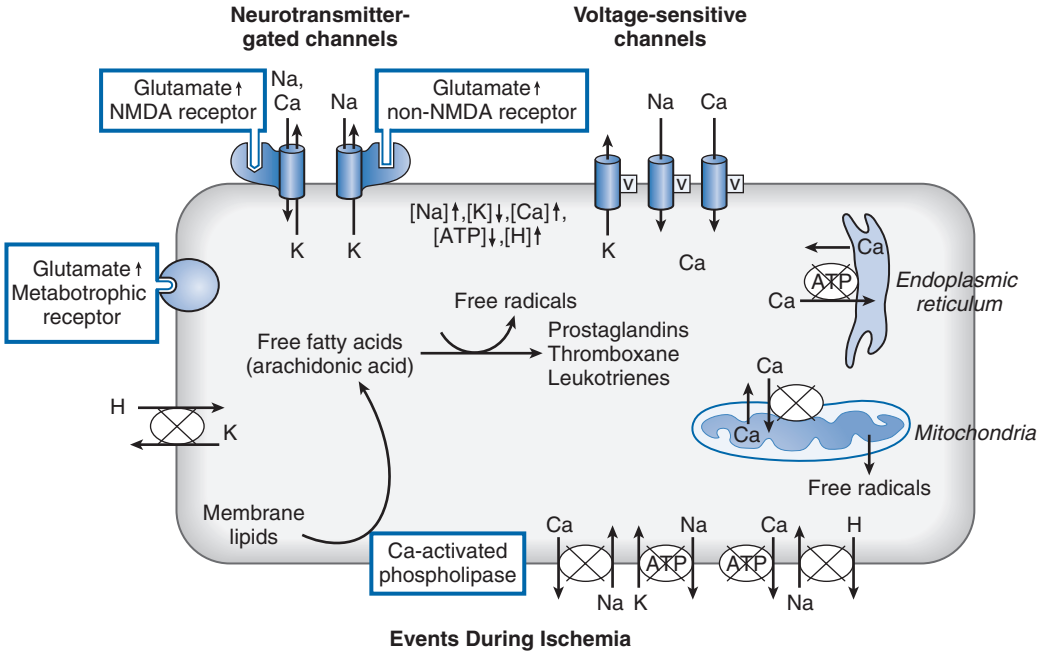


Fig. 1.4 The effect of ischemia on ion and metabolite levels in neurons. For clarity, ion channels are shown on the *top* membrane and ion pumps on the *bottom* membrane; their actual location can be on any membrane surface. *Circles* indicate energy-driven pumps; an *x* through a *circle* indicates that the pump is blocked or has reduced activity during ischemia. *V* indicates a voltage-dependent channel. ATP, adenosine triphosphate; NMDA, *N*-methyl-D-aspartate.

BOX 1.1 Brain Metabolism and Cell Death: Triggers, Effectors, and Functional Changes

- Triggers
  - Adenosine triphosphate ↓
  - Extracellular potassium ↑
  - Intracellular sodium ↑
  - Intracellular calcium ↑
  - Free radical levels ↑
  - Depolarization ↑
  - Glutamate level ↑
- Effectors
  - Protease activity ↑
  - Free radical action ↑
  - DNA damage ↑
  - Phospholipase activity ↑
  - Mitochondrial factors ↑ (cytochrome *c* → caspase activation)
- Critical Functional Changes
  - Mitochondrial damage ↑
  - Apoptotic cascade activation ↑
  - Antiapoptotic factors ↓
  - Protein damage ↑
  - Protein synthesis ↓
  - Cytoskeletal damage ↑
- End Stage
  - Apoptosis ↑ (programmed cell death)
  - Necrosis ↑ (cell disintegration)

↑, increases; ↓, decreases; →, leads to
Adapted from Lipton P. Ischemic cell death in brain neutrons. Physiol Rev 1999; 79:1431–1568.

BOX 1.2 Consequences of Ischemia

- Vascular Changes
  - Vasospasm
  - Red cell sludging
  - Hypoperfusion
  - Platelet aggregation
  - Endothelial injury
  - Leukocyte-endothelial adhesion
  - Blood–brain barrier disruption
- Neuronal Changes
  - Adenosine triphosphate reduction
  - Sodium influx
  - Potassium efflux
  - Intracellular acidosis
  - High cellular calcium concentrations
  - Calcium-activated proteases
  - Caspase activation
  - Phospholipase activation
  - Arachidonic acid formation and breakdown
  - Free radical production
  - Excitatory amino acid release
  - Disruption of ion and amino acid transporters
  - Autophagy
  - Apoptosis
  - Necrosis

There is a buildup of lactate and hydrogen ions during ischemia, which lowers the intracellular pH and this can lead to further formation of free radicals.[10] All of these processes, coupled with the reduced ability to synthesize proteins and lipids, contribute to the irreversible damage that occurs with ischemia (Box 1.1).

Additionally, phospholipase activation leads to the production of excess arachidonic acid, which upon reoxygenation can form eicosanoids, including thromboxane, prostaglandins, and leukotrienes. These substances can cause strong vasoconstriction, reduce blood flow in the postischemic period, alter the blood–brain barrier, and enhance free radical formation after reperfusion.[11,12]

Procedures that protect against ischemic damage should interfere with the cellular changes brought on by ischemia (Box 1.2). In addition to these direct triggering events, there is long-term damage that becomes apparent hours and days after the ischemic insult. Some of this delayed damage is necrotic and the lysis of the cells causes microglial activation.[13] Lymphocytes, polymorphonuclear cells, and macrophages can invade the central nervous system, leading to additional damage.[14,15] Although histamine receptor activation is generally associated with immune system activation, the histamine receptor involved with this is the H_1 receptor. In the central nervous system, the H_2 receptor is the one primarily activated, and it reduces immunologic processes and improves recovery from ischemia.[16,17] Blocking immune system activation can reduce damage.[16] It is clear there is also programmed cell death as a result of the insult.[18] This apoptotic programmed cell death, which is similar to the cell death that occurs during neuronal development, can continue days after the initial insult.

Necrosis versus Apoptosis

There are two major processes leading to neuronal death. The first, necrosis, is due to a more severe insult in which mitochondrial function is lost; it is characterized by a disintegration of the cell and an activation of microglia and the immune response.[13] The immune response and inflammation activate and recruit neutrophils and macrophages, which produce free radicals and damage adjacent neurons. This process expands the lesion in volume and time, allowing for continued and expanded neuronal damage.[13] In the second, apoptosis, the cell dies without breaking apart and there is no microglial or immune system involvement with the potential for excess damage to adjacent neurons. This process is frequently delayed and can lead to the activation of immediate early genes (IEGs) such as c-Jun and c-Fos; these genes are thought to affect gene expression and lead to the production of apoptotic or antiapoptotic proteins, which determine whether the neurons will survive or die.[18,19] One set of proteins that lead to neuronal death are the cysteine proteinases, referred to as *caspases*. These enzymes are expressed as proenzymes, which undergo proteolytic processing to yield active enzymes that degrade important proteins in the cell (Fig. 1.5).[20,21] There are both intrinsic and extrinsic pathways to activate caspases and apoptosis, Fig. 1.5 shows the intrinsic pathway activated by mitochondrial cytochrome c release. In addition cell death receptors on the neuron membrane may be activated by death factors such as Fas ligand or tumor necrosis factor, which directly activate caspases. The final apoptotic pathway to cell death converges and is the same for both the intrinsic or extrinsically activated pathways.[22] Blockade of caspases has been shown to block apoptosis.[23] Because these enzymes are now known to be present as proenzymes before ischemia, new protein synthesis is not needed to induce apoptosis.[22] However, proapoptotic proteins are synthesized under certain conditions, and their synthesis may lead to delayed neuronal cell death. Another set of proteins can be induced that block apoptosis and promote neuronal survival after ischemia; examples of these proteins are neuronal apoptosis inhibitory protein, heat shock proteins, and certain antiapoptotic Bcl-2 family proteins.[22,24] Thus the fate of ischemic neurons rests on the balance between apoptotic inhibitory and activating processes (Fig. 1.6).[24,25] The synthesis of certain trophic factors can improve neuronal survival by inhibiting apoptosis (see Fig. 1.5). The activation and

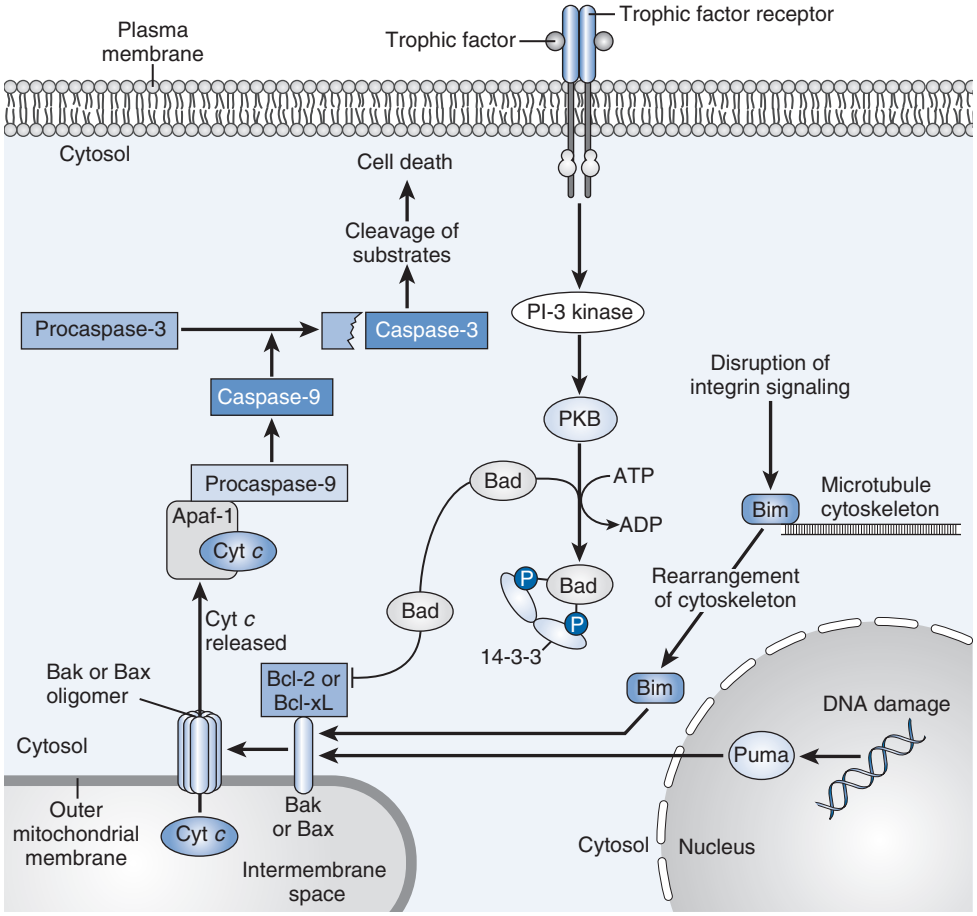


Fig. 1.5 Trophic factors and apoptosis. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt c, cytochrome c; PI, phosphoinositide; PKB, protein kinase B (also called Akt); other abbreviations (Akt, Apaf, Bad, Bax, Bcl, 14-3-3) are names of proteins. When the intrinsic apoptotic pathway is activated: (1) Bad protein inhibits Bcl-2, Bcl-xl proteins; (2) these proteins can no longer inhibit Bax or Bak and, therefore, Bax and Bak form a channel that allows (3) cytochrome c release from the mitochondria to the cytosol and the activation of Apaf 1 which, finally, (4) activates caspase 9 and apoptosis. When apoptosis is inhibited (1) trophic factor binds to a receptor and activates protein kinases; (2) this leads to the phophorylation of Bad and its inactivation; (3) Bad can no longer inhibit Bcl-2 and Bcl-xl and these 2 proteins can now inhibit Bax and Bak, blocking channel formation, cytochrome c release and apoptosis. *(From Lodish H, Berk A, Kaiser, et al [Eds]: Molecular Cell Biology, 7th ed. New York, WH Freeman and Co, 2012: page1012, information from D. Ren et al 2010, Science 330:1390.)*

release of certain cytokines, such as tumor necrosis factor and interleukin-1β, are thought to be damaging.[26,27]

Thus necrosis and apoptosis can be contrasted, with the former being a result of more severe ischemia and leading to the damage of adjacent tissue (Fig. 1.7). Apoptosis is subject to modulation, so once started down the apoptotic pathway, cells have a chance of being rescued by trophic substances (see Fig. 1.6).

Global versus Focal Ischemia

Ischemia can be either global or focal in nature; an example of the former would be cardiac arrest, and of the latter, localized stroke. Although the mechanisms leading to neuronal damage are probably similar for the two types of ischemia, there are important distinctions between them. In focal ischemia there are three regions. The first region, called the ischemic core, receives no blood flow and responds in the same way as globally ischemic tissue; the second region, called the *penumbra*, receives collateral flow and is partially ischemic; the third region is normally perfused. If the insult is maintained for a prolonged period, the neurons in the penumbra die and the infarct (ischemic core) increases in size. More neurons in the penumbra region survive if collateral blood flow is increased or if reperfusion is established in a timely manner by opening the blocked vessel. With total global ischemia, the time until the circulation is re-established is critical, and only very short ischemic times (on the order of minutes) are survivable. The selective neurologic damage after survival subsequent to global ischemia is mainly due to the differential sensitivity of certain neurons and brain regions. The hippocampus, especially the cornu ammonis 1 (CA1) pyramidal cell region, is extremely vulnerable to ischemic damage; loss of learning and memory is common after global ischemia and hypoxia.[28,29] Other areas of enhanced sensitivity to global ischemia and hypoxia are the caudate, and putamen, as well as certain areas of the cerebellum and cerebral cortex.[30,31]

Genetic Influences on Neuronal Damage

Genetic factors play an important role in an individual's susceptibility to ischemic stroke. Both environmental (such as diet and stress) and genetic factors combine to determine the risk of stroke. A study of the Icelandic population found that polymorphisms (genetic changes) in genetic locus ALOX5AP, which encodes 5-lipoxygenase–activating protein, and PDE4D, which encodes phosphodiesterase 4D, increase the susceptibility to stroke.[32,33] In addition, polymorphisms of both apolipoprotein B and apolipoprotein E have been found to enhance the susceptibility to stroke.[34,35] The genetic factors could target neuronal risk but more likely raise the vascular risk, which is associated with an increase in both stroke and cardiac disease. If a patient's genetic susceptibility to injury were known, it would be possible to choose

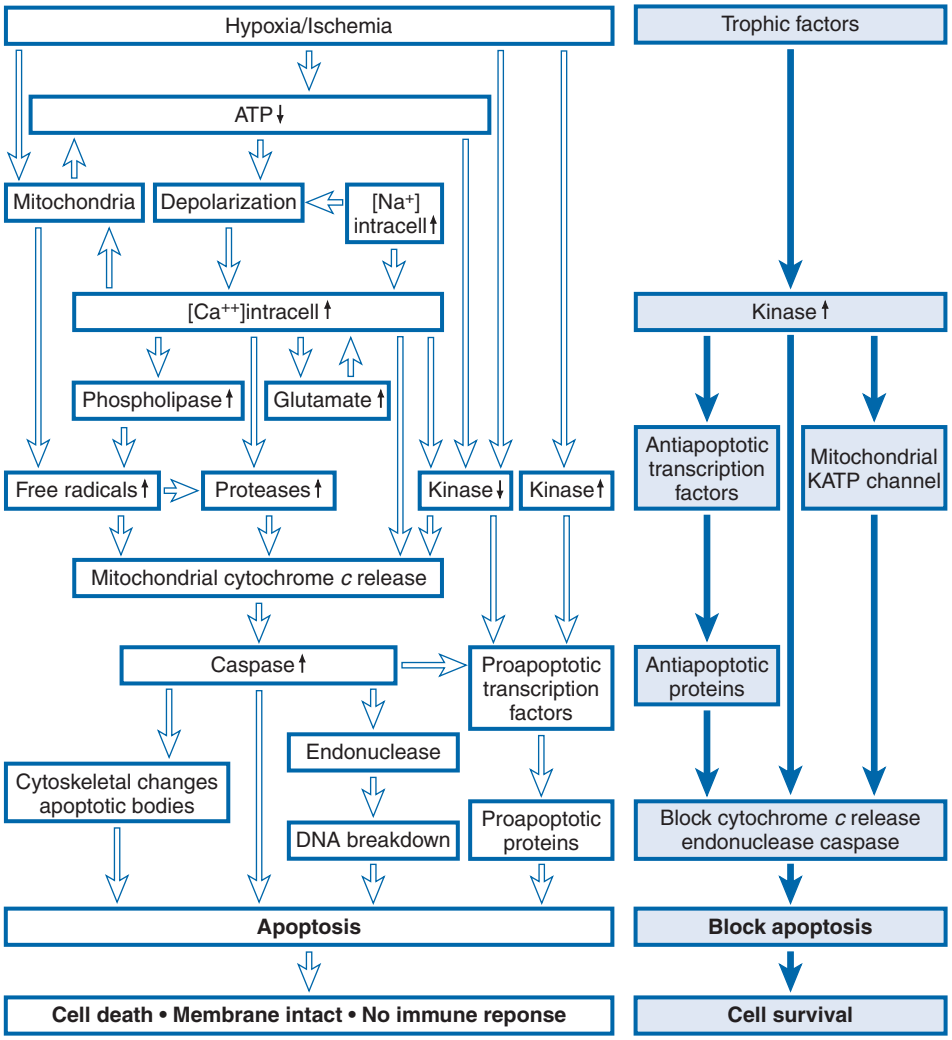


Fig. 1.6 Apoptosis subsequent to hypoxia or ischemia. The apoptotic cascade of biochemical changes evoked by hypoxia or ischemia. Similar events may also be occurring during epileptic and trauma-induced damage; they lead to depolarization, reduced adenosine triphosphate (ATP), sodium influx, and high cytosolic calcium levels. There is no cellular membrane disruption during apoptosis, and inflammation is not triggered. The apoptotic biochemical cascade can be modulated and opposed by trophic factors. intracell, intracellular; KATP channel, ATP-sensitive potassium channel; ↑, increase; ↓, decrease; the large open arrows indicate damaging pathways, the large closed arrows indicate protective pathways.

therapeutic strategies individually for the patient to improve outcome.

Genetic factors have been shown to influence cardiovascular risk, particularly with respect to hyperlipidemia; controlling these factors with statins not only reduces cardiac disease but also reduces cerebral vascular disease and stroke rates.[36]

POTENTIAL TREATMENTS FOR CEREBRAL ISCHEMIA

Reperfusion Strategies

The goal for treatment of ischemic stroke is to achieve prompt restoration of perfusion and to preserve brain tissue in the ischemic penumbra. Reperfusion therapies include intravenous thrombolysis, intra-arterial thrombolysis, and endovascular mechanical thrombectomy. Comprehensive guidelines for early management of acute ischemic stroke were updated in 2013; this chapter can only very briefly summarize some of these important guidelines.[36] Throughout this section recommendations that are not directly referenced are from this paper, any deviation from these guidelines will be explicitly stated. The most successful technique for improving recovery from embolic stroke is prompt restoration of spontaneous perfusion as soon as possible after the onset of a stroke. To date, despite recent evidence that for large vessel occlusion, intracranial mechanical thrombectomy is superior to pharmacological intervention alone,[37–41] the only U.S. Food and Drug Administration (FDA)-approved method is the use of the thrombolytic agent, recombinant tissue plasminogen activator (rtPA); as one would predict, the effects of rtPA would markedly worsen hemorrhagic stroke.[36,42,43] Thus detecting, classifying, and treating stroke rapidly after its onset is critical to a successful outcome.[44] Thrombolytics cannot be used in patients with a high risk of bleeding; such as those with head trauma, recent surgery or with reduced clotting ability due to drugs such as warfarin, direct thrombin inhibitors and direct factor Xa inhibitors. Warfarin treated patients with an INR below 1.4 can be given rtPA treatment; however, the newer agents create a problem since the ability to assess coagulation function in patients taking these drugs is difficult and recommendations are under review.[36]

The major side effect of rtPA is intracerebral hemorrhage, which can be devastating. It is essential that a noncontrast computed tomography scan be performed and analyzed shortly after patient presentation to the hospital in order to rule out a hemorrhagic stroke, because rtPA must be administered

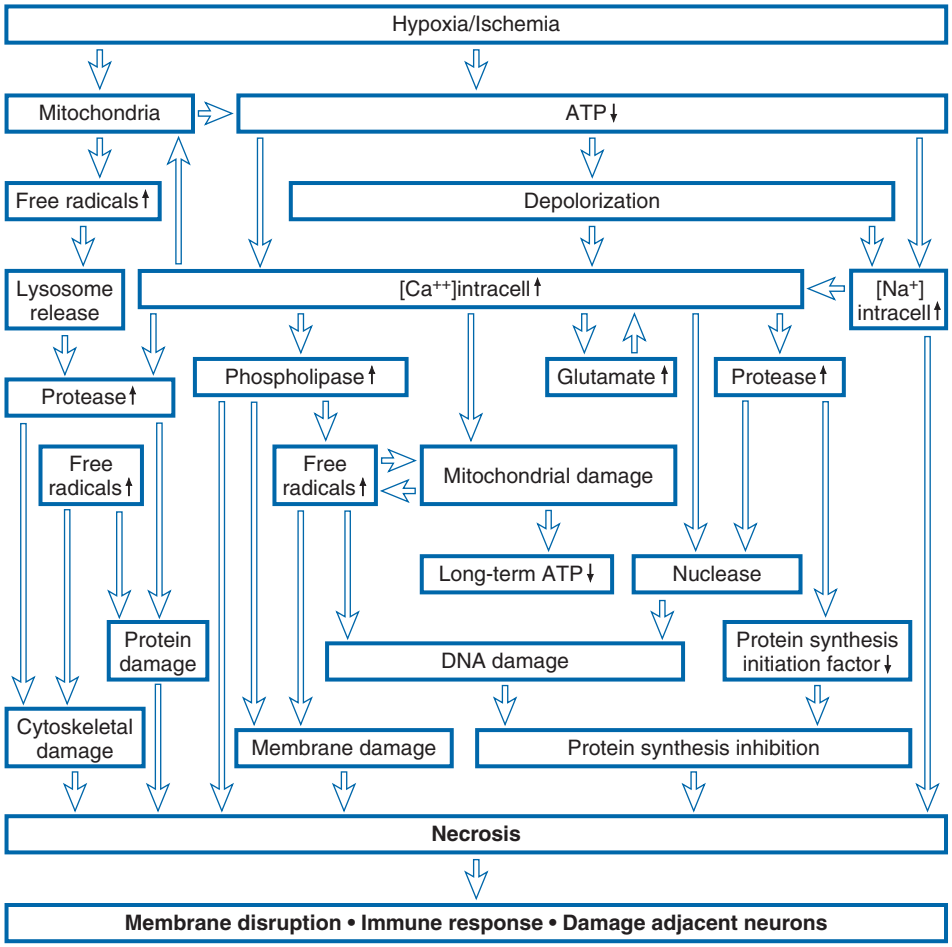


Fig. 1.7 Necrosis subsequent to hypoxia and ischemia. The necrotic cascade of biochemical changes evoked by hypoxia or ischemia. Similar events may also be occurring during epileptic and trauma-induced damage; they lead to depolarization, reduced adenosine triphosphate (ATP), sodium influx, and high cytosolic calcium levels. These changes are more severe than those with apoptosis and lead to the disruption of the cells and activation of inflammation. The damage cannot be reversed, and surrounding intact neurons can be damaged by secondary processes. intracell, intracellular; ↑, increase; ↓, decrease; large arrows indicate damaging pathways.

within 3 hours of an occlusive stroke onset to be effective. The guidelines from the AHA/ASA indicate that rtPA can be given to patients between 3 and 4.5 hours of stroke onset if patients are less than 80 years of age, not taking oral anticoagulants, and without a history of stroke and diabetes; this recommendation is not an FDA indication for rtPA.[36] It is clear that the sooner rtPA is given the better the outcome is likely to be.

It is of key importance when exploring additional therapies to identify patients in whom an area of reduced perfusion has not progressed to irreversible neuronal damage. These studies use advanced imaging to identify at-risk tissue (penumbra) that can still be salvaged if reperfusion can be established. Diffusion-weighted magnetic resonance imaging (DWI) identifies core ischemic areas where water has shifted into the intracellular compartment and has reduced diffusibility. Areas that have not yet converted to core ischemia can potentially be rescued from irreversible damage. Perfusion-weighted magnetic resonance imaging indicates regions with reduced perfusion that will ultimately proceed to irreversible damage if not reperfused. The ratio of penumbral ischemic tissue volume to infarcted core volume is named penumbral mismatch. However, due to the importance of rapid reperfusion and the delay in carrying out MRI imaging, current practice uses multiphase CT angiography to determine if a large vessel is occluded, the location of the occlusion, and an assessment of either core-infarct volume or penumbral mismatch. Since rtPA is less effective and intra-arterial mechanical clot removal techniques are more effective for large occlusions, mechanical thrombectomy should be considered rapidly; with all reperfusion techniques an increase of the time to reperfusion equals increased brain tissue loss. A region with reduced perfusion that has not yet progressed to irreversible damage will benefit from endovascular reperfusion therapy.[45]

The Merci Retriever (Concentric Medical, Inc., Mountain View, CA), the Penumbra System (Penumbra, Inc., Alameda, CA), the Solitaire Device (Covidien, Irvine, CA) and the Trevo Retriever (Stryker Neurovascular, Freemont, CA) are approved by the U.S. Food and Drug Administration for mechanical removal of clots. The Merci Retriever, a corkscrew shaped device, has been shown to provide a higher rate of good clinical outcome compared to historical controls, although the intracerebral hemorrhage rate was 7.8%, which is not different from IV rt-PA.[46] Recent studies have demonstrated that the Solitaire FR and Trevo stent retrievers are superior to the Merci device.[47,48] In all cases patients eligible for intravenous rtPA should be given that treatment as rapidly as possible even if intra-arterial mechanical clot removal is being considered.[36] Recent studies have found a clear outcome benefit of mechanical intra-arterial treatment for stroke;[37–41,49,49a] experience, rapidity of treatment and new devices have improved this technique to the point where its on-demand availability is rapidly becoming the standard of care for stroke centers. The 2015 AHA/ASA focused guideline update concludes that "Certain endovascular procedures have been demonstrated to

provide clinical benefit in selected patients with acute ischemic stroke. Systems of care should be organized to facilitate the delivery of this care."[50] Patients for mechanical thrombectomy should have confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions.[40] As yet, however, there is no consensus as to the type of neuroimaging and the exact imaging criteria for patient eligibility, the rapidity of the assessment is critical, since delays lead to more infarcted brain. The accepted time window for treatment with mechanical thrombectomy is 6 hours from the onset of symptoms. For now, the most widely used effective treatment for ischemic stroke remains the administration of intravenous rtPA within 3 hours of stroke onset, or for up to 4.5 hours for certain patients.[36,51] This treatment is underutilized because of the short time window for safe administration of rtPA, the many contraindications to its use, and the frequent delay in presentation of patients to the hospital after the onset of symptoms. This problem can and is being addressed by community education about the signs of stroke through the FAST campaign (FACE, ARMS, SPEECH, TIME to call 911) and the need for emergency transport to an appropriate hospital with a stroke center. The guidelines for early management and treatment of stroke are frequently updated and should be consulted and examined for the latest recommendations.[36]

Hypothermia

Deep hypothermia has long been used in neonatal heart surgery to provide protection against irreversible brain injury during circulatory arrest. It has also been used during the repair of giant aneurysms. However, there are numerous complications of profound hypothermia (27 °C or lower) that limit its usefulness (Box 1.3). Profound hypothermia reduces cerebral metabolism to such an extent that the brain can survive relatively long periods without perfusion (Box 1.4). Experimental studies indicate that moderate hypothermia has a protective effect without many of the complications of profound hypothermia, although myocardial depression has been documented.[52–54] There are many in vitro and in vivo animal studies to support the use of moderate hypothermia to protect against ischemic damage. Indeed, moderate hypothermia has come into common use even though it has not been unequivocally shown to improve recovery in a major clinical trial.[55] A European study published in 2002 indicates that mild hypothermia, target temperature 32° to 34 °C, after cardiac arrest improves neurologic outcome and survival 6 months after the arrest.[56] However, recent larger studies have found no benefit to mild hypothermia compared to maintaining the temperature below 36 °C; avoiding hyperthermia appears to be important and may explain the benefit found in earlier studies.[57,58] The recommendation for hypothermia following cardiac arrest may soon be replaced by the avoidance of hyperthermia. However, with respect to hypothermia after stroke there is no Class I evidence of benefit; cooling to levels between 34° and 35 °C leads to fewer complications and slow rewarming is important to reduce deleterious effects.[36] Mild hypothermia did not improve outcome from surgery for intracranial aneurysm surgery and a Cochrane systematic review did not find benefit or harm from hypothermia during acute stroke.[55,59] If hypothermia does demonstrate some benefit for certain types of stroke patients, its degree and duration as well as the rate of rewarming will need to be better determined.

It is clear that even minor amounts of hyperthermia worsen clinical outcome of ischemia and increase neuronal damage, and this must be carefully guarded against.[57,58]

BOX 1.3 Complications of Deep Hypothermia

- Cardiovascular Complications
  - Myocardial depression
  - Dysrhythmia including ventricular fibrillation
  - Hypotension
  - Inadequate tissue perfusion
  - Ischemia
- Coagulation
  - Thrombocytopenia
  - Fibrinolysis
  - Platelet dysfunction
  - Increased bleeding
- Metabolism
  - Slowed metabolism of anesthetic agents
  - Prolonged neuromuscular blockade
  - Increased protein catabolism
- Shivering
  - Increased oxygen consumption
  - Increased carbon dioxide production
  - Increased cardiac output
  - Arterial oxygen desaturation
  - Hemodynamic instability

BOX 1.4 Proposed Mechanisms of Protection by Hypothermia

- Decrease in cerebral metabolism
- Delayed anoxic/ischemic depolarization
- Preservation of ion homeostasis
- Decrease excitatory neurotransmission
- Prevention or reduction of damaging secondary biochemical changes

Glucose

Glucose is the main source of energy for neurons in the brain, and some in vitro studies reported improved recovery with hyperglycemia. However, in vivo and clinical studies found a clear worsening of damage with hyperglycemia, which is thought to be due to enhanced cellular acidosis.[10,61] The precise mechanism by which hyperglycemia exacerbates damage is not known. Clinical recommendations are to maintain normal serum glucose levels and to treat hyperglycemia greater than 180 mg/dL in order to reduce the glucose value closer to normal.[62] It is important for the patient not to be hypoglycemic, as hypoglycemia would also worsen outcome. Intensive tight glucose control did not improve outcome after stroke and a more recent study demonstrated a higher mortality in patients managed with levels from 81 to 108 mg per deciliter compared to patients managed to a target of 140–180 mg per deciliter.[63,64] Episodes of hypoglycemia due to excessive insulin used to control glucose levels likely explains the worsened outcome with intensive glucose control. Control to maintain glucose below 180 is recommended but tight control is clearly detrimental; stronger evidence indicates treatment of hypoglycemia if glucose falls below 60 mg/dL.[36]

Pharmacologic Agents

Animal studies have demonstrated that a number of agents can improve outcome from experimental stroke; there is controversy why none of these agents have led to clinical improvement. Many drugs have been proposed as potential agents to reduce permanent neuronal damage subsequent to ischemia, but none has proved useful in clinical trials.[36,65] The theoretical basis for choosing drugs that block specific damaging pathways is sound. Blocking one pathway to damage may not be

efficacious, however, owing to the many parallel paths that lead to permanent damage (see Fig. 1.7). For example, one can block voltage-sensitive calcium channels but cytoplasmic calcium can increase through influx via the NMDA receptor ion channel or release from intracellular organelles. Thus effective therapy might require multiple agents to block the parallel pathways simultaneously.

It must be recognized that no pharmacologic agent or combination of agents that shows clear protection in animals has been shown to improve neurologic recovery clinically after a stroke.[36,65] However, some agents do appear promising in animal studies and may yet prove to be efficacious clinically.[36,65,66] One major problem with stroke treatments and a reason for the discrepancy between animal and human results is that most animal studies apply the protective agents either before or during the insult, whereas clinical stroke treatment is always delayed. In the perioperative environment, drugs and treatments can be applied before an insult, at the beginning of a high-risk surgery; thus, agents that fail to protect against stroke when used after the insult may be efficacious if given before surgery. Because only very few patients undergoing high-risk surgery will suffer an ischemic insult, the agents used must have a high safety factor and/or must be required for surgery (e.g., anesthetics). The deleterious effects of any agent used will be shared among all patients, but its protective effects will benefit only ischemic patients. In the following sections classes of potentially protective strategies are discussed.

Sodium Blockade

Blocking sodium influx during anoxia and ischemia has been shown to improve recovery. [67,68] The neuronal depolarization during anoxia and ischemia leads to massive flux of sodium and calcium into the neurons and of potassium out of the neurons.[69,70] Blocking sodium influx delays and attenuates the depolarization and delays the drop in ATP during anoxia and ischemia.[71] Lidocaine has improved recovery by delaying and attenuating the anoxic/ischemic depolarization and reducing anoxic sodium influx when given at concentrations that do not block sodium channels under normal conditions.[71,72] Lidocaine reduced the infarct size and improved neurologic outcome following focal cerebral ischemia. It appears to work, at least in part, by blocking apoptotic pathways in the penumbra.[73] When lidocaine application was delayed until 45 minutes after the onset of focal cerebral ischemia, there was improved neuronal survival in the core and penumbra, but the size of the infarct was not significantly reduced.[74] This illustrates the importance of the rapid administration of agents for them to have any benefit. The administration of an antiarrhythmic dose of lidocaine improved the survival of rat CA1 pyramidal neurons after temporary global cerebral ischemia, as well as performance on a hippocampal dependent cognitive task.[75] Two small clinical studies of lidocaine have indicated better cognitive outcome following cardiac surgery. A more recent clinical study did not find improvement with lidocaine given during cardiac surgery; however, one subgroup, nondiabetic patients, did show improvement.[76–78] A study examining lidocaine in nondiabetic heart surgery patients is ongoing. A recent study with lidocaine administered after supratentorial surgery did not find improvement, though the damage in the untreated group was very low after 6 months.[79] The recovery was, however, similar to that of demographically similar non-neurosurgical patients.[80] Future studies of lidocaine should examine older and/or sicker patients with a higher likelihood of cognitive dysfunction in the untreated group.

Calcium Blockade

Nimodipine, a blocker of the voltage sensitive calcium channel, has been shown to improve recovery from subarachnoid hemorrhage, while the closely related nicardipine has not; nimodipine is, therefore, indicated only in this setting to prevent or treat vasospasm.[36,81] A large clinical study of the effectiveness of nimodipine after stroke was discontinued due to higher mortality in the nimodipine group.[82] Clearly nimodipine cannot be recommended subsequent to cerebral ischemia. Indeed, during ischemia and anoxia calcium channels are already inhibited and direct protection of neurons with nimodipine was not observed in in vitro preparations.[83,84] Magnesium, an agent that blocks many voltage-sensitive and transmitter-activated channels (including the NMDA activated channels that induce excitotoxicity), would reduce the influx of calcium and other ions. Magnesium has recently been shown to be of benefit during focal cerebral ischemia; however, a clinical trial did not show benefit from the administration of intravenous magnesium after stroke.[85] There was a subgroup of lacunar stroke that did show benefit with magnesium, but this would require a large new trial to confirm.[86] A study of the use of magnesium in preterm birth to protect infant brains from damage did not yield significant improvement with magnesium treatment.[87] Clearly, further studies are needed before it can be recommended. A major problem is the limited access of Mg to the central nervous system due to poor permeability across the blood–brain barrier.[88] One criticism of the magnesium clinical trials, and many of the other studies, was of the delay in administering the drugs; in most animal studies the drugs were administered before or very shortly after the onset of ischemia, which is not applicable clinically. At the time of writing a study administering magnesium in the ambulance has just been completed; while it demonstrated that rapid magnesium administration following stroke was possible, there was no benefit shown.[89] Blockade of secondary calcium activated pathways during and after ischemia appears promising in animal studies.[90]

Free Radical Scavenging

Free radicals have been implicated as causes of cellular damage and subsequently neuronal damage after ischemia. Both apoptotic and necrotic damage are thought to have a component of free radical damage. Use of free radical scavengers such as NXY-059, alpha-tocopherol, tirilizad and *N*-tert-alpha-phenyl-butylnitrone (PBN) has been shown to improve ischemia in animals; however, none of these agents has been shown to improve the outcome clinically.[36,91–93] Anti-inflammatory drugs such as methylprednisolone have also not been demonstrated to improve recovery after cortical trauma or ischemia.[36] Corticosteroids suppress the immune system, increase infection, and may actually enhance some free radical damage. Nitric oxide has been implicated as enhancing neuronal damage, and lubeluzole, an inhibitor of nitric oxide formation, has shown some promise in animal studies[94] but has not been found to benefit patients with ischemia.[36,95]

Agents that Reduce Excitotoxicity

Excitatory amino acids are implicated in the damaging cascade following ischemia, trauma, and epilepsy. Although blockers of NMDA and AMPA glutamate receptors have improved recovery in vitro and in vivo in a number of preparations, the results of clinical trials have been disappointing.[36,65,95] It appears that these agents are toxic and may actually cause neuronal damage. Indeed, clinical trials with some of these agents have been terminated early due to adverse outcomes.[36,96]

An alternative to blocking excitatory activity is enhancing inhibitory activity, which would also reduce excitotoxicity.

Clomethiazole and diazepam, 2 GABA enhancers, did not improve outcome following stroke.[97,98]

Antiapoptotic Agents

Work with apoptosis indicates that specific blockers of caspases and modulators of apoptosis might improve recovery after ischemia, trauma, or epilepsy.[20,66,99] Although in vivo animal experiments are encouraging, these agents have not been shown to improve outcome clinically. A more useful technique might be to encourage neurons to synthesize antiapoptotic proteins, such as Bcl-2 and Bcl-xl, by inducing preconditioning with certain volatile anesthetics.

Cytokines and Trophic Factors

Cytokines such as tumor necrosis factor-alpha and interleukin-1β can activate the immune system and enhance damage; indeed, antibodies to these compounds have been shown to reduce cerebral ischemic damage in some animals.[65] However, tumor necrosis factor-alpha can also be beneficial, assisting neuronal survival in some circumstances; so targeting it can have mixed results.

Neurons have receptors for trophic factors such as nerve growth factor, neurotrophins, and brain-derived growth factor, which are required for neuronal survival even in the absence of any injury. These factors activate receptors that phosphorylate amino acids on certain proteins, thereby inhibiting apoptosis.[22,25] If these growth factors are not present, the receptors are not activated and the proteins are not phosphorylated; the neurons then undergo apoptosis.[22,26] The loss of growth factors subsequent to neuronal degeneration after ischemia can exacerbate delayed neuronal loss.

Erythropoietin is a trophic factor for blood cells that is also present in the nervous system. Animal studies indicate that it may protect neurons from apoptosis after ischemia by activating the trophic factor antiapoptotic pathway.[100] Despite continuing investigation there is no convincing evidence of clinical benefit with erythropoietin.[36,101,102]

Anesthetic Agents

Anesthetic agents have been examined for their ability to improve recovery from ischemia. The intuitive theory is that they reduce neuronal activity and metabolic rate and, therefore, should lower energy demand, enhance energy supply, and attenuate ischemic damage (Table 1.1). However, the different anesthetics also have specific actions, including effects on intracellular signaling pathways, ion conductances, and neurotransmitters, as well as systemic and cerebral hemodynamic effects; these other actions may help explain their differential effects on neuronal damage (Table 1.2). Studies comparing general anesthesia with conscious sedation for endovascular treatment for acute stroke indicate that patients with general anesthesia have a worse outcome.[103–105] The mechanism is unclear, but this should lead to caution when concluding that anesthetics can improve outcome in patients as they do in animals. It is possible a reduction in blood pressure due to general anesthesia is driving the worsened outcome independent of direct anesthetic effects.[104] Since all the studies of anesthesia type in endovascular treatment of acute stroke

Table 1.1 Effects of Anesthetics on Cerebral Blood Flow (CBF) and the Cerebral Metabolic Rate for Oxygen ($CMRO_2$)

Anesthetic	CBF	$CMRO_2$	Direct Cerebral Vasodilation
Halothane	↑↑↑	↓	Yes
Enflurane	↑↑	↓	Yes
Isoflurane	↑	↓↓	Yes
Desflurane	↑	↓↓	Yes
Sevoflurane	↑	↓↓	Yes
N_2O	↑	↑	—
N_2O with volatile anesthetics	↑↑	↑	—
N_2O with intravenous anesthetics	0	0	—
Thiopental	↓↓↓	↓↓↓	No
Etomidate	↓↓	↓↓	No
Propofol	↓↓	↓↓	No
Midazolam	↓	↓	No
Dexmedetomidine	↓	0	No
Ketamine	↑↑	↑	No
Fentanyl	↓/0	↓/0	No

↑, increases ↓, decreases (number of arrows indicates relative strength of effect); 0, no effect; —, not determined

Table 1.2 Effect of Anesthetics on Recovery after and Biochemical Changes during Hypoxia

Agent	Protects Electrophysiologic Response	Delays Hypoxic Depolarization	Reduce Na^+ In	Improves Adenosine Triphosphate	Reduce Ca^{2+} In
Thiopental (600 μM)	Yes	Yes	Yes	Yes	Yes
Midazolam (100 μM)	Yes	—	—	Yes	Yes
Propofol (20 μg/mL)	No	No	Yes	Yes	Yes
Etomidate (3 μg/mL)	No	—	No	No	—
Lidocaine (10 μM)	Yes	Yes	Yes	Yes	No
Lidocaine (100 μM)	Yes	Yes	Yes	Yes	Yes
Nitrous oxide (50%)	No	—	No	No	No
Isoflurane (2%)	No	No	Yes	Yes	No
Sevoflurane (4%)	Yes	Yes	Yes	Yes	Yes
Desflurane (6%)	Yes	Yes	Yes	Yes	Yes

—, not determined, experiment not done; Na^+ in, cytosolic sodium; Ca^{2+} in, cytosolic calcium

are retrospective, the caveat was that patients requiring general anesthesia are likely to have had a more severe stroke and poorer preoperative neurological condition. The recent study of 369 stroke patients from a Dutch registry who either had general anesthesia or not (strictly per local hospital protocol) showed that there were better outcomes without general anesthesia, but no imbalance in stroke severity between groups. The cause of the difference is speculative, but treatment was initiated sooner in the nonanesthetized patients.[49,49a] Even if anesthetics reduce damage when given before ischemia, in the setting of stroke it is unlikely they will reach the site of benefit because of reduced blood flow and agent delivery to the tissue most in need of protection.

Barbiturates

Barbiturates are the only anesthetics that have been shown to have protective efficacy clinically, but only in a highly specific context.[106,107] The mechanism of their protection has not been established and, indeed, may be multifaceted. Among its many actions, thiopental blocks Na, K, and calcium fluxes, scavenges free radicals, blocks seizures, improves regional blood flow, and decreases intracranial pressure (ICP).[106,107] Perhaps it is the multiple actions blocking parallel damaging pathways that allow this agent to protect against ischemic damage. It is important to note that very high barbiturate coma doses were needed to demonstrate clinical improvement after cardiac surgery.[107] In vitro studies also showed improved efficacy with very high doses.[108]

Etomidate

Etomidate, like thiopental, reduces the cerebral metabolic rate if given to burst suppression doses; however, it does not share many of thiopental's other actions. Etomidate has not been demonstrated to improve recovery from ischemic and anoxic damage under normal conditions.[55,106,109] It cannot be assumed that an anesthetic that reduces the cerebral metabolic rate to the same extent as thiopental will provide the same cerebral protection. Animal studies found that etomidate inhibits NO synthase, which might reduce brain tissue perfusion, and etomidate worsened outcome from focal cerebral ischemia compared to halothane.[110] These studies suggest that etomidate is not a drug of choice if cerebral ischemia is anticipated.

Propofol

Propofol is a widely used intravenous anesthetic. Animal studies indicate that propofol may reduce ischemic damage, but it may not be as potent as thiopental.[111–114] Propofol demonstrated similar protection to pentobarbital and was beneficial when compared to awake animals.[115,116] As with all other anesthetic agents, clinical protective efficacy has not been demonstrated.

Dexmedetomidine

Dexmedetomidine is an alpha 2a adrenergic agonist that has sedative, analgesic, and anxiolytic effects. It reduces sympathetic activity by inhibiting norepinephrine (noradrenaline) release from presynaptic nerve terminals. Dexmedetomidine can lead to hypotension, which could be detrimental in patients with cerebral ischemia. However, animal studies examining ischemic injury to the brain and spinal cord demonstrated reduced injury with dexmedetomidine indicating a direct protective effect of the drug.[117,118] No studies have demonstrated clinical protective efficacy.

Xenon

Xenon is an inert gas that exhibits anesthetic effects at very high doses, it is not used clinically as an anesthetic but has shown protective efficacy in adult animals.[119] Sub anesthetic doses of xenon have been shown to reduce brain injury after neonatal asphyxia and may attenuate anesthetic-induced memory decline in neonatal mice.[120] Xenon is not used clinically.

Nitrous Oxide

In animal studies nitrous oxide has been demonstrated to reduce recovery from ischemia and anoxia in comparison with other anesthetics, therefore caution is required when using it in patients with the potential for compromised cerebral perfusion.[121,122]

Benzodiazepines

The most commonly used benzodiazepine in anesthesia practice is midazolam, and its effect on cerebral metabolism and ischemic damage has been examined. Benzodiazepines enhance neuronal inhibition in the nervous system and reduce brain metabolism by potentiating the effect of the neuronal transmitter gamma-aminobutyric acid (GABA) on the GABA receptor. High doses of midazolam have been shown to reduce cerebral metabolism and cerebral blood flow, an effect that is reversed by the benzodiazepine antagonist flumazenil.[123,124] Midazolam improved neuronal recovery after anoxia and ischemia in animals, but there are no studies showing a better clinical outcome.[124–127] Flumazenil should be used cautiously, if at all, to reverse benzodiazepine effects in situations in which an increase in cerebral metabolic rate is undesirable, because this agent has been shown to increase cerebral metabolic rate, cerebral blood flow, and ICP.[123]

Volatile Anesthetic Agents

Isoflurane is a volatile anesthetic whose protective efficacy is controversial. It does not cause greater damage and appears to have a better outcome than fentanyl–nitrous oxide anesthesia.[55,106,128,129] Sevoflurane and desflurane have metabolic and blood flow effects similar to those of isoflurane, and they have been reported to have neuroprotective effects (see Box 1.1).[130] There is an indication that isoflurane, but not sevoflurane, increases cytosolic Ca levels and can be cytotoxic to neurons in cell culture.[131] Sevoflurane was found to improve recovery in brain slices; it delayed and attenuated the hypoxic/ischemic depolarization and reduced the Ca and Na rises inside neurons. At equivalent minimal alveolar concentrations, sevoflurane was more effective than isoflurane and sevoflurane demonstrated sustained improvement after cerebral ischemia in comparison with nitrous oxide–fentanyl anesthesia.[132,133] Desflurane was also protective in brain slices and after cerebral ischemia in vivo.[134–138]

Preconditioning

In both heart and brain tissue, ischemic preconditioning—a short period of ischemia that allows recovery—can make tissue more resistant to a longer, normally damaging, period of ischemia. However, ischemic preconditioning can lead to subtle damage.[139] Anesthetics, when given before ischemia, have been shown to induce preconditioning; these agents are most likely less damaging than ischemic preconditioning. There is much evidence indicating that isoflurane improves recovery from cerebral ischemia by preconditioning the neurons, but most of the studies have been done on male animals. A later study indicates that male, but not female mice have better recovery from isoflurane-induced preconditioning administered 1 day before ischemia.[140] Thus, it is important to remember there may be gender-specific aspects to protection from ischemic brain damage. This is a topic requiring further investigation.

Both anesthetic preconditioning and ischemic preconditioning have two time courses: delayed preconditioning

is demonstrated beginning a day after the preconditioning stimulus and lasts for several days; immediate preconditioning requires treatment only minutes to an hour before the ischemia.[141] Sevoflurane has been shown to induce preconditioning in vitro and in vivo if present only shortly before the ischemia.[29] The mechanism and extent of protection with sevoflurane in vitro was similar to that when sevoflurane was present before and during hypoxia; this finding suggests that a major portion of sevoflurane-induced protection is due to an alteration of biochemical pathways before the insult.[29] Sevoflurane preconditioning for 60 minutes, starting 90 minutes before the ischemia, with either 4% or 2% sevoflurane, increased the number of surviving CA1 pyramidal cells 6 weeks after temporary global cerebral ischemia in rats (Fig. 1.8).[29]

Anesthetic preconditioning must be demonstrated clinically before it can be applied widely; however, if one is choosing an anesthetic in a patient at risk for ischemia, it might be prudent to use an agent that has been shown to be beneficial in animals.

Anesthetic Agents in Young Children

Animal studies have demonstrated that anesthetic agents, when given to neonatal animals, can lead to cognitive and behavioral deficits.[142–144] Social interaction in mice treated with sevoflurane in the neonatal period is reduced, confirming that behavioral function is altered by anesthetic exposure.[143,144] These observations indicate that clinical studies examining behavioral deficits in children subsequent to anesthetic exposure

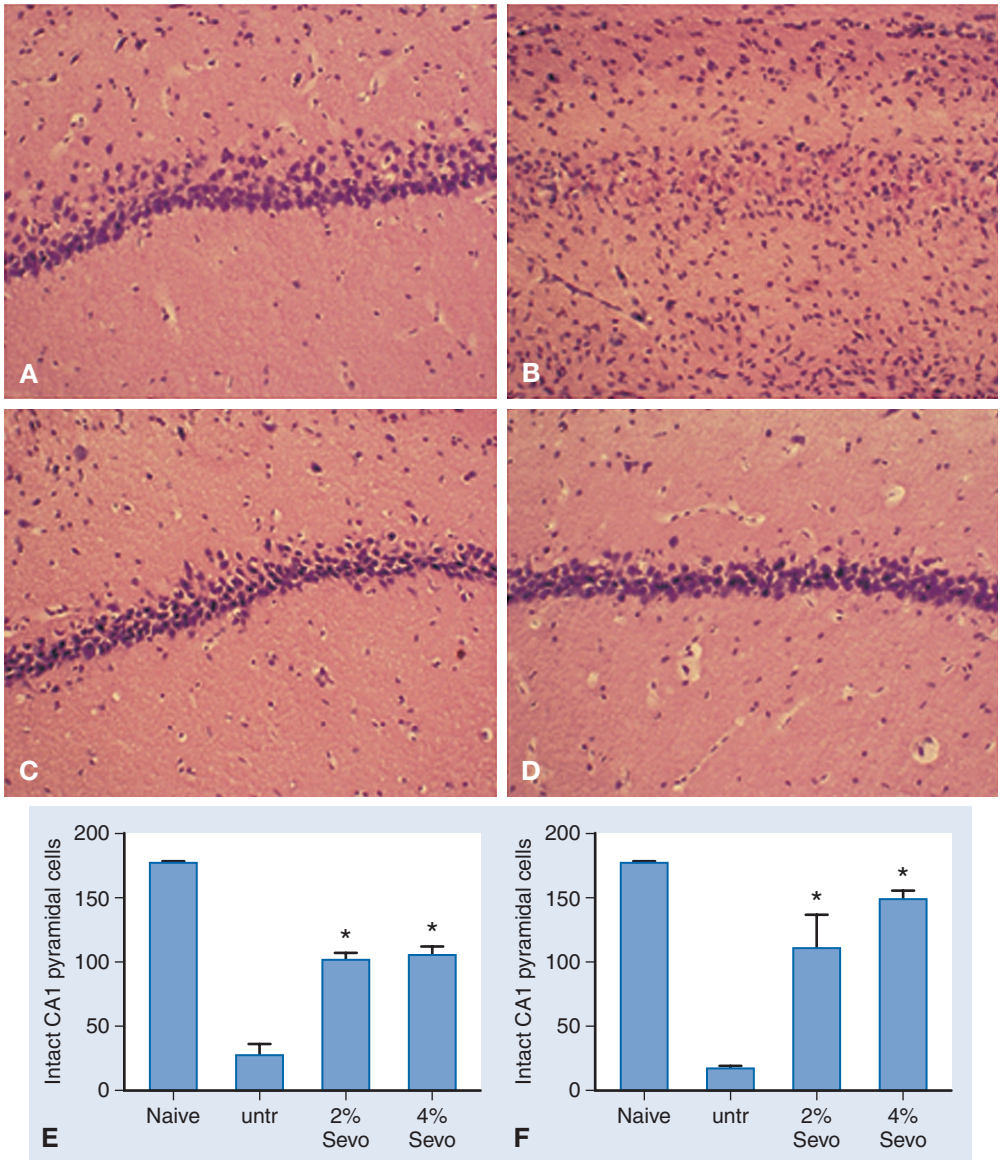


Fig. 1.8 CA1 pyramidal neurons after global cerebral ischemia. **A** to **D,** Representative hematoxylin and eosin–stained cryostat sections (16 μm) from the CA1 pyramidal cell layer of the experimental groups 6 weeks after the global cerebral ischemia are shown at approximately ×250 magnification. **A,** Tissue from naïve rats not subjected to ischemia. **B,** Tissue from rats subjected to 10 minutes of global ischemia without preconditioning. **C,** Tissue from rats preconditioned with 2% sevoflurane for 1 hour before ischemia. **D,** Tissue from rats preconditioned with 4% sevoflurane for 1 hour before ischemia. **E** and **F,** The data were quantitated through counting the number of intact CA1 neurons per 475-μm length of stratum pyramidale in each hemisphere at the same level of coronal section under light microscopy (250× magnification); the observer was blind to the experimental treatment. The numbers were averaged across both hemispheres to yield a single value for each rat and expressed as number/mm (mean ± standard deviation). There were significantly more intact CA1 pyramidal cells in the rats with sevoflurane treatment (Sevo) than in the untreated ischemic group (untr) ($P < .01$) at both 1 week **(E)** and 6 weeks **(F)** after ischemia. *From Wang J, Lei B, Popp S, Cottrell JE, Kass IS. Sevoflurane immediate preconditioning alters hypoxic membrane potential changes in rat hippocampal slices and improves recovery of CA1 pyramidal cells after hypoxia and global cerebral ischemia. Neuroscience 2007; 145:1097–1107.*

may be warranted. There is some indication that there may be deleterious effects on young children given anesthesia, though it is difficult to separate the direct effects of the anesthetic from the surgical and medical conditions that prompted the surgery and, therefore, the anesthetic.[145] It is an open question whether anesthetics, and which anesthetics at what dose, lead to cognitive deficits in children. The theoretic advantages of postponement of elective surgery must be weighed against harm that may be attendant with a delay in surgery.[145]

Treatment

In summary, anesthetics have differential effects on neuronal metabolism, ionic fluxes, and membrane potentials. Anesthetics have multiple mechanisms of action; this feature complicates scientific studies but may enhance clinical protection. Hypothermia, lidocaine, thiopental, and sevoflurane have been shown to be protective against ischemia in animal studies.

Clinically, hypothermia and lidocaine show the most promise, but there is no conclusive evidence that they improve recovery from ischemia in patients. Thiopental requires very high concentrations to exert its protection, whereas sevoflurane needs further study to ascertain whether it will protect patients when given in clinically usable concentrations. Because anesthesia is required during surgery, it may prove prudent to choose an anesthetic that appears protective in animals even if it has not been demonstrated to be protective clinically; sevoflurane might be a good choice because it appears to be protective in the clinical dose range. Thiopental requires too high a dose to be used as an anesthetic in these cases, because awakening would be delayed; however, its use in the critical care setting, in which awakening is not an issue, might be beneficial. Limiting the ischemia by improving perfusion is the most effective mechanism for preventing neuronal damage from stroke. Thrombolysis and the prevention of clot formation and embolization are effective strategies.[36,44]

SEIZURE INDUCED DAMAGE

Epileptic activity (status epilepticus) consists of sudden, excessive, and synchronous discharges of large numbers of neurons.[146] Aside from those patients with established epilepsy, this massive increase in activity can be seen in patients with ionic and electrolyte imbalances, disorders of brain metabolism, infection, brain tumor, brain trauma, and elevated body temperature. The electroencephalographic record shows spikes, which are rapid changes in voltage corresponding to excess activity in many neurons. During the epileptiform activity, sodium and calcium ions enter the cells, and potassium leaves. Thus the cells use more energy (ATP) for ion pumping. The resultant high extracellular potassium may be responsible for the large and progressive depolarization of the neurons that is commonly found. The mechanisms that lead to permanent neuronal damage with epilepsy may be similar to those that damage cells during ischemia. The epileptic activity leads to glutamate release, NMDA receptor activation and excitotoxicity; this can lead to neuronal damage.[146] Activation of metabotropic glutamate receptors can contribute to the excess excitability and prolong seizures.[147] Intracellular calcium levels rise, possibly precipitating the damage. There is evidence that at least some of the permanent neuronal damage is apoptotic-like. It is clear that during epileptiform activity the energy demand and, therefore, the cerebral metabolic rate and blood flow increase greatly. Thus, in conditions in which blood flow to the brain may be compromised, it is imperative to avoid excess brain activity. Anticonvulsant medications increase neuronal inhibition or reduce excitatory processes in the brain.[148] Epileptic activity may be accompanied by systemic lactic acidosis, reduced arterial oxygenation, and increased carbon dioxide; therefore, it is important to maintain ventilation, oxygenation, and blood pressure in a patient with such activity.[149] Prolonged or recurring epileptic activity can lead to profound brain damage.

Epileptic Treatment

For patients in status epilepticus, immediate treatment to stop the seizure is necessary. Benzodiazepines such as midazolam and lorazepam are used to rapidly stop the seizure. Loading with i.v. maintenance anticonvulsants, such as phenytoin, should begin immediately after the benzodiazepines. If these agents do not break the epileptiform activity, barbiturates (e.g., phenobarbital) are indicated.[149] The change, immediate loading with i.v. maintenance agents, was suggested by a neurologist who specializes in epilepsy. It represents current practice. If the seizure is new onset it is essential to identify and treat correctable precipitating causes such as hyperthermia, electrolyte imbalance, infection or tumor. In combination with ischemia, seizures can cause rapid and devastating neuronal damage and should be treated aggressively.

TRAUMATIC BRAIN INJURY

Trauma is the leading cause of death in individuals ages 1 to 44—more than one-half of these deaths are due to brain trauma. Approximately 1.7 million traumatic brain injuries (TBI) occur in the United States each year—they lead to 52,000 deaths and 1.4 million emergency room visits.[150]

TBI is commonly classified using the Glasgow Coma Scale (GCS) scores; GCS scores of 13 to 15 are considered mild injury, 9 to 12 moderate injury, and 8 or less severe traumatic brain injury.[151] The pathophysiology of trauma-related brain injury is divided into two categories: primary brain injury and secondary brain injury. Current approaches to the management of TBI focus on the two phases of brain injury.[151,152] Primary brain injury is the direct disruption of the brain parenchyma and its blood supply by the trauma and occurs at the time of trauma. This primary damage can be caused by direct neuronal injury from contusions and diffuse axonal injury (DAI), brain herniation, or the severing of blood vessels in the brain that results in hematoma or direct ischemia. Reversal of the primary damage is not possible, and, therefore, is not amenable to medical intervention; however, much of the brain injury in trauma patients is secondary to this primary brain injury, occurring as a cascade of biochemical, cellular, and molecular events that are initiated at the time of initial trauma and continue for hours or days.[152] Mechanisms of secondary injury include excitotoxicity, inflammatory responses, secondary ischemia from vasospasm, focal microvascular occlusion and vascular injury, and energy failure and resultant apoptosis.[152] These events lead to neuronal cell death as well as secondary cerebral edema and increased intracranial pressure that can further exacerbate the brain injury. This injury shares many features of the ischemic cascade during and after acute stroke. Calcium influx resulting from the trauma has been implicated as a trigger for the damage.[152] Secondary damage may be reduced with proper monitoring and treatment. The identification, prevention, and treatment of secondary brain injury are the principal focus of neurointensive care management for patients with severe TBI. Treatment may involve lowering ICP (below 20 is a reasonable target),

maintaining cerebral perfusion pressure (CPP) (the difference between mean arterial pressure and ICP), aggressively treating hyperthermia, evacuation of hematomas, surgical decompression and, perhaps, using pharmacologic agents that interfere with the cascade of events leading to neuron damage.[152,153,154] Cerebral ischemia was a common finding in histologic studies of terminal trauma cases.[153,154] It is of great importance to prevent the secondary ischemia that frequently follows brain trauma and is possibly due to the release of vasoconstrictive substances during reperfusion. Cytotoxic and vasogenic cerebral edema commonly follows head trauma and can lead to a marked increase in ICP. This can result in hypoperfusion of the brain, even if blood pressure is maintained. Intracranial hemorrhage may increase intracranial blood volume and ICP, thereby reducing cerebral perfusion pressure. The intracranial blood can cause damage by directly promoting free radical formation catalyzed by the iron in hemoglobin.[151,152] Hypotension has been associated with markedly worse outcome, therefore an important intervention for improving outcome in trauma patients is to maintain near normal blood pressure to prevent secondary cerebral ischemia.[155] Maintaining adequate CPP rather than only controlling ICP is of great importance; CPP should target 60 mmHg to ensure optimal cerebral blood flow. High-dose corticosteroids are not effective and have been shown to increase mortality of traumatic brain injury; they are contraindicated according to the Brain Trauma Foundation guidelines.[154] Short-term (1 week) prophylactic use of antiepileptic drugs (phenytoin) may be recommended for the prevention of early seizures; they do not affect long-term development of seizures and have not been shown to improve outcome.[153,154]

SUMMARY

For several pathophysiologic events in the brain, ionic imbalance (particularly, high intracellular calcium levels) and energy depletion have been implicated as possible triggers of brain damage. In neurons, subsequent to a pathophysiologic insult, molecular biological and biochemical changes are triggered, which can lead to either apoptotic or necrotic cell death. Thus common mechanisms of neuronal cell death for various pathophysiologic events may exist.

Thrombolysis is recommended for ischemic stroke if it can be instituted within 4.5 hours of onset; this treatment worsens hemorrhagic stroke, so careful diagnosis is required. If there is an occlusion of a large cerebral artery, intra-arterial mechanical reperfusion has recently been shown to be of benefit compared to intravenous rtPA alone. Very high-dose barbiturates have also been shown to improve ischemic outcome; other encouraging agents from animal studies such as sodium channel blockers, free radical scavengers, and antiapoptotic agents have not been shown to have clinical benefits. Clinical trials with NMDA and calcium channel blockers have been disappointing. Prevention of hypoperfusion and ischemia after trauma is important to reduce secondary injury. Anticonvulsant medications should be used to immediately arrest status epilepticus. Thus a number of treatments can be employed with some hope of reducing permanent brain damage.

REFERENCES

1. Lodish H, Berk A, Kaiser CA, et al. Cellular energetics. In: *Molecular Cell Biology*. 6th ed. New York: W. H. Freeman and Co; 2008:479–527.
2. Snell RS. *Clinical Neuroanatomy*. 9th ed. Philadelphia: F. A. Davis; 2009.
3. Kandel ER, Hudspeth AJ. The brain and behavior. In: Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ, eds. *Principles of Neural Science*. 5th ed. New York: McGraw Hill Medical; 2013:5–20.
4. Hansen AJ. Effect of anoxia on ion distribution in the brain. *Physiol Rev*. 1985;65:101–148.
5. Choi DW. Excitotoxic cell death. *J Neurobiol*. 1992;23:1261–1276.
6. Lipton P. Ischemic cell death in brain neurons. *Physiolo Rev*. 1999;79:1431–1568.
7. MacDermott AB, Dale N. Receptors, ion channels and synaptic potentials underlying the integrative actions of excitatory amino acids. *Trends Neurosci*. 1987;10:280–284.
8. Maiese K, Swiriduk M, TenBroeke M. Cellular mechanisms of protection by metabotropic glutamate receptors during anoxia and nitric acid toxicity. *J Neurochem*. 1996;66:2419–2428.
9. Kristian T, Siesjo BK. Calcium in ischemic cell death. *Stroke*. 1998;29:705–718.
10. Siesjo BK, Katsura K, Kristian T. Acidosis-related damage. *Adv Neurol*. 1996;71:209–236.
11. Betz AL. Alterations in cerebral endothelial cell function in ischemia. *Adv Neurol*. 1996;71:301–314.
12. Chopp M, Zhang R-L, Jiang N. The role of adhesion molecules in reducing cerebral ischemic cell damage. *Adv Neurol*. 1996;71:315–328.
13. Minghetti L, Levi G. Microglia as effector cells in brain damage and repair: Focus on prostanoids and nitric oxide. *Prog Neurobiol*. 1998;54:99–125.
14. Koroshetz WJ, Moskowitz MA. Emerging treatments for stroke in humans. *Trends Pharmacol Sci*. 1996;17:227–233.
15. Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. *J Neuroimmunol*. 2007;184:53–68.
16. Adachi N. Cerebral ischemia and brain histamine. *Brain Res Brain Res Rev*. 2005;50:275–286.
17. Hiraga N, Adachi N, Liu K, et al. Suppression of inflammatory cell recruitment by histamine receptor stimulation in ischemic rat brains. *Eur J Pharmacol*. 2007;557:236–244.
18. MacManus JP, Linnik MD. Gene expression induced by cerebral ischemia: An apoptotic perspective. *J Cereb Blood Flow Metab*. 1997;17:815–832.
19. Herdegen T, Claret FX, Kallunki T, et al. Lasting *N*-terminal phosphorylation of c-Jun and activation of c-Jun *N*-terminal kinases after neuronal injury. *J Neurosci*. 1998;18:5124–5135.
20. Namura S, Zhu J, Fink K, et al. Activation and cleavage of caspase-3 in apoptosis induced by experimental cerebral ischemia. *J Neurosci*. 1998;18:3659–3668.
21. Chen J, Nagayama T, Jin K, et al. Induction of caspase 3 like protease may mediate delayed neuronal death in the hippocampus after transient cerebral ischemia. *J Neurosci*. 1998;18:4914–4928.
22. Lodish H, Berk A, Kaiser CA, et al. Stem cells, cell asymmetry and cell death. In: *Molecular Cell Biology*. 7th ed.New York: W. H. Freeman and Co; 2012:977–1018.
23. Cheng Y, Deshmukh M, D'Costa A, et al. Caspase inhibitor affords neuroprotection with delayed administration in a rat model of neonatal hypoxic-ischemic brain injury. *J Clin Invest*. 1998;101:1992–1999.
24. Abe H, Nowak Jr TS. The stress response and its role in cellular defense mechanisms after ischemia. *Adv Neurol*. 1996;71:451–468.
25. Wieloch T, Hu B-R, Boris-Moller A, et al. Intracellular signal transduction in the postischemic brain: Implications for neurotransmission and neuronal survival. *Adv Neurol*. 1996;71:371–388.
26. Nikolics K, Hefti F, Thomas R, Gluckman PD. Trophic factors and their role in the post ischemic brain. *Adv Neurol*. 1996;71:389–404.
27. Lavine SD, Hofman FM, Zlokovic BV. Circulating antibody against tumor necrosis factor-alpha protects rat brain from reperfusion injury. *J Cereb Blood Flow Metab*. 1998;18:52–58.
28. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci*. 1986;6:2950–2967.
29. Wang J, Lei B, Popp S, et al. Sevoflurane immediate preconditioning alters hypoxic membrane potential changes in rat hippocampal slices and improves recovery of CA1 pyramidal cells after hypoxia and global cerebral ischemia. *Neuroscience*. 2007;145:1097–1107.
30. Konaka K, Miyashita K, Naritomi H. Changes in diffusion-weighted magnetic resonance imaging findings in the acute and subacute phases of anoxic encephalopathy. *J Stroke Cerebrovasc Dis*. 2007;16:82–83.
31. Payabvash S, Souza LCS, Wang Y, et al. The need for location specific computed tomography perfusion thresholds in acute stroke patients. *Stroke*. 2011;42:1255–1260.
32. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, et al. The gene encoding phosphodiesterase 4D confers risk of ischemic stroke. *Nat Genet*. 2003;35:131–138.

33. Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat Genet*. 2004;36:233–239.
34. Mustafna OE, Novikova LB, Nasibullin TR, et al. An analysis of association between the apolipoprotein B gene EcoR1 polymorphism and ischemic stroke [Russian]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2006;(suppl 17):66–70.
35. Saidi S, Slamia LB, Ammou SB, et al. Association of apolipoprotein E gene polymorphism with ischemic stroke involving large-vessel disease and its relation to serum lipid levels. *J Stroke Cerebrovasc Dis*. 2007;16:160–166.
36. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke*. 2013;44:870–947.
37. Berkhemer OA, Fransen PSS, Beumer LA, et al, for the MR CLEAN Investigators. A randomized trial of intra-arterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.
38. Goyal M, Demchuk AM, Menon M, et al, for the ESCAPE Trial Investigators. Randomized assessment of rapid stroke endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030.
39. Saver JL, Goyal M, Bonafe A, et al, for SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295.
40. Jovin TG, Chamorrow A, Cobo E, et al, for the REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306.
41. Campbell BCV, et al, for the EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018.
42. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
43. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous T-PA therapy for stroke. *Stroke*. 1997;28:2109–2118.
44. Charchaflieh J. Management of acute ischemic stroke. *Prog Anesthesiol*. 1998;12:195–212.
45. Suwanwela N, Koroshetz WJ. Acute ischemic stroke: overview of recent therapeutic developments. *Annu Rev Med*. 2007;58:89–106.
46. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. *Stroke*. 2005;36:1432–1438.
47. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): A randomized, parallel group, non-inferiority trial. *Lancet*. 2012;380:1241–1249.
48. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2): A randomized trial. *Lancet*. 2012;380:1231–1240.
49. Penumbra pivotal stroke trial investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke*. 2009;40:2761–2768.
49a. Van Den Berg LA, Koelman DL, Berkhemer OA, et al, for the MR CLEAN pretrial study group. Type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic Stroke. *Stroke*. 2015;46:1257–1262.
50. Powers WJ, Derdeyn CP, Biller J, et al, on behalf of the American Heart Association Stroke Council. 2015 AHA/ASA focused updated of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. *Stroke*. 2015;46:3020–3035.
51. Hacke W, Kaste M, Bluhmki E. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
52. Busto R, Dietrich WD, Globus MY-T, et al. Small differences in intraischemic brain temperature critically determine the extent of is chemic neuronal injury. *J Cereb Blood Flow Metab*. 1987;7:729–738.
53. Ridenour TR, Warner DS, Todd MM, McAllister AC. Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. *Stroke*. 1992;23:733–738.
54. Frank SM, Beattie C, Christopherson R, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia: The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology*. 1993;78:468–476.
55. Todd MM. *Anesthesia for Intracranial Vascular Surgery. 1997 ASA Annual Refresher Course Lectures*. Park Ridge, IL: American Society of Anesthesiologists; 1997:151-1–151-7.
56. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
57. Mark DG, Vinson DR, Hung Y-Y, et al. Lack of improved outcomes with increased use of targeted temperature management following out of hospital cardiac arrest: A multicentre retrospective cohort study. *Resuscitation*. 2014;85:1549–1556.
58. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. *N Engl J Med*. 2013;369:2197–2206.
59. Den Hertog HM, van der Worp HB, Tseng MC, et al. Cooling therapy for acute stroke. *Cochrane Database Syst Rev*. 2009;1. CD001247.
60. Kammersgaard LP, Jorgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke: The Copenhagen Stroke Study. *Stroke*. 2002;33:1759–1762.
61. Myers RE, Yamaguchi M. Effects of serum glucose concentration on brain response to circulatory arrest. *J Neuropathol Exp Neurol*. 1976;35:301.
62. Gentile NT, Seftchick MW, Huynh T, et al. Decreased mortality by normalizing blood glucose after acute ischemic stroke. *Acad Emerg Med*. 2006;13:174–180.
63. Gray CS, Hildreth AJ, Sandercock PA, et al, for the GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglcaemia: The UK glucose insulin stroke trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406.
64. NICE-SUGAR study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
65. Green AR. Pharmacological approaches to acute ischaemic stroke: Reperfusion certainly, neuroprotection possibly. *Br J Pharmacol*. 2008;153(suppl 1):S325–S338.
66. Mehta SL, Manhas N, Raghubir R. Molecular targets in cerebral ischemia for developing novel therapeutics. *Brain Res Rev*. 2007;54:34–66.
67. Boening JA, Kass IS, Cottrell JE, Chambers G. The effect of blocking sodium influx on anoxia damage in the rat hippocampal slice. *Neuroscience*. 1989;33:263–268.
68. Cao H, Kass IS, Cottrell JE, Bergold PJ. Pre- or postinsult administration of lidocaine or thiopental attenuates cell death in rat hippocampal slice cultures caused by oxygen-glucose deprivation. *Anesth Analg*. 2005;101:1163–1169.
69. Kass IS, Lipton P. Mechanisms involved in irreversible anoxic damage to the in vitro rat hippocampal slice. *J Physiol*. 1982;332:459–472.
70. Tanaka E, Yamamoto S, Kudo Y, et al. Mechanisms underlying the rapid depolarization produced by deprivation of oxygen and glucose in rat hippocampal CA1 neurons in vitro. *J Neurophysiol*. 1997;78:891–902.
71. Raley-Susman KM, Kass IS, Cottrell JE, et al. Sodium influx blockade and hypoxic damage to CA1 pyramidal neurons in rat hippocampal slices. *J Neurophysiol*. 2001;86:2715–2726.
72. Fried E, Amorim P, Chambers G, et al. The importance of sodium for anoxic transmission damage in rat hippocampal slices: Mechanisms of protection by lidocaine. *J Physiol*. 1995;489:557–565.
73. Lei B, Popp S, Capuano-Waters C, et al. Lidocaine attenuates apoptosis in the ischemic penumbra and reduces infarct size after transient focal cerebral ischemia in rats. *Neuroscience*. 2004;125:691–701.
74. Lei B, Popp S, Capuano-Waters C, et al. Effects of delayed administration of low-dose lidocaine on transient focal cerebral ischemia in rats. *Anesthesiology*. 2002;97:1534–1540.
75 Popp SS, Kelemen E, Fenton A, et al. Effects of low-dose lidocaine administration on transient global cerebral ischemia in rats. Presented at *American Society of Anesthesiologists Annual Meeting, San Francisco*, Oct 13–17, 2007.
76. Mitchell SJ, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg*. 1999;67:1117–1124.
77. Wang D, Wu X, Li J, et al. The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. *Anesth Analg*. 2002;95:1134–1141.
78. Mathew JP, Mackensen GB, Phillips-Bute B, et al. Randomized double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke*. 2009;40:880–887.
79. Peng Y, Zhang W, Zhou X, et al. Lidocaine did not reduce neuropsychological-cognitive decline in patients 6 months after supratentorial tumor surgery: A randomized, controlled trial. *J Neurosurg Anesthesiol*. 2016;28: 6–13.
80. Chan MT, Cheng BC, Lee TM, et al. BIS guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25:33–42.
81. Mayberg MR, Batjer HH, Dacey R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Circulation*. 1994;90:2592–2605.
82. Legault SW, Furberg CD, Wagenknecht LE, et al. Nimodipine neuro-protection in cardiac valve replacement: Report of an early terminated trial. *Stroke*. 1996;27:593–598.
83. Kass IS, Abramowicz AE, Cottrell JE, et al. Anoxia reduces depolarization induced calcium uptake in the rat hippocampal slice. *Brain Res*. 1994;633:262–266.

84. Kass IS, Cottrell JE, Chambers G. Magnesium and cobalt, not nimodipine protect neurons against anoxic damage in the rat hippocampal slice. *Anesthesiology*. 1988;69:710–715.
85. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): Randomised controlled trial. *Lancet*. 2004;363:439–445.
86. Aslanyan S, Weir CJ, Muir KW, Lees KR. Magnesium for treatment of acute lacunar stroke syndromes: Further analysis of the IMAGES trial. *Stroke*. 2007;38:1269–1273.
87. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: The randomised controlled PREMAG trial*. *BJOG*. 2007;114:310–318.
88. Mercieri M, De Blasi RA, Palmisani S, et al. Changes in cerebrospinal fluid magnesium levels in patients undergoing spinal anaesthesia for hip arthroplasty: Does intravenous infusion of magnesium sulphate make any difference? A prospective randomized, controlled study. *Br J Anaesth*. 2012;109:208–215.
89. Saver JL, Starkman S, Eckstein M, et al. Prehospital use of magnesium sulphate as neuroprotection in acute stroke. *N Engl J Med*. 2015;372:528–536.
90. Saatman KE, Murai H, Bartus RT, et al. Calpain inhibitor AK295 attenuates motor and cognitive deficits following experimental brain injury in the rat. *Proc Natl Acad Sci U S A*. 1996;93:3428–3433.
91. van der Worp HB, Bar PR, Kappelle LL, Wildt DJ. Dietary vitamin E levels affect outcome of permanent focal cerebral ischemia in rats. *Stroke*. 1998;29:1002–1005.
92. Cao X, Phillis JW. alpha-Phenyl-tert-butyl-nitrone reduces cortical infarct and edema in rats subjected to focal ischemia. *Brain Res*. 1994;644:267–272.
93. Kuroda S, Tsuchidate R, Smith ML, et al. Neuroprotective effects of a novel nitrone, NXY-059, after transient focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab*. 1999;19:778–787.
94. De Ryck M. Protection of neurological function in stroke models and neuroprotective properties of lubeluzole. *Cerebrovasc Dis*. 1997;7(suppl 2):18–30.
95. Lyden P, Wahlgren NG. Mechanisms of action of neuroprotectants in stroke. *J Stroke Cerebrovasc Dis*. 2000;9:9–14.
96. Onal MZ, Fisher M. Acute ischemic stroke therapy: A clinical overview. *Eur Neurol*. 1997;38:141–154.
97. Lyden P, Shuaib A, Ng K, et al. Clomethiazole acute stroke study in ischemic stroke (CLASS-I): Final results. *Stroke*. 2002;33:122–128.
98. Lodder J, van Raak L, Hilton A, et al. Diazepam to improve acute stroke outcome: Results of the early GABA-ergic activation study in stroke trial, a randomized double blinded placebo controlled trial. *Cerebrovasc Dis*. 2006;21:120–127.
99. Barinaga M. Stroke-damaged neurons may commit cellular suicide. *Science*. 1998;218:1302–1303.
100. Wang Y, Zhang ZG, Rhodes K, et al. Post-ischemic treatment with erythropoietin or carbamylated erythropoietin reduces infarction and improves neurological outcome in a rat model of focal cerebral ischemia. *Br J Pharmacol*. 2007;151:1377–1384.
101. Ehrenreich H, Hasselblatt M, Dembowski C, et al. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med*. 2002;8:495–505.
102. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. *Stroke*. 2009;40:e647–e656.
103. Abou-Chebl A, Lin R, Hussain MS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke. *Stroke*. 2010;41:1175–1179.
104. Davis MJ, Menon BK, Baghirzada LB, et al. Anesthetic management and outcome in patients during endovascular therapy for acute stroke. *Anesthesiology*. 2012;116:396–405.
105. Li F, Deshaies EM, Singla A, et al. Impact of anesthesia on mortality during endovascular clot removal for acute ischemic stroke. *J Neurosurg Anesthesiol*. 2014;26:286–290.
106. Patel PM, Drummond JC, Lemkuil BP. Cerebral physiology and the effects of anesthetic drugs. In: Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier Saunders; 2015:387–422.
107. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. *Anesthesiology*. 1986;64:165–170.
108. Kass IS, Abramowicz AE, Cottrell JE, Chambers G. The barbiturate thiopental reduces ATP levels during anoxia but improves electrophysiological recovery and ionic homeostasis in the rat hippocampal slice. *Neuroscience*. 1992;49:537–543.
109. Amadeu ME, Abramowicz AE, et al. Etomidate does not alter recovery after anoxia of evoked population spikes recorded from the CA1 region of rat hippocampal slices. *Anesthesiology*. 1998;88:1274–1280.
110. Drummond JC, McKay LD, Cole DJ, et al. The role of nitric oxide synthase inhibition in the adverse effects of etomidate in the setting of focal cerebral ischemia in rats. *Anesth Analg*. 2005;100:841–846.
111. Amorim P, Chambers G, Cottrell JE, Kass IS. Propofol reduces neuronal transmission damage and attenuates the changes in Ca, K and Na during hyperthermic anoxia in the rat hippocampal slice. *Anesthesiology*. 1995;83:1254–1265.
112. Zhu H, Cottrell JE, Kass IS. The effect of thiopental and propofol on NMDA- and AMPA-mediated glutamate excitotoxicity. *Anesthesiology*. 1997;87:944–951.
113. Engelhard K, Werner C, Eberspacher E, et al. Influence of propofol on neuronal damage and apoptotic factors after incomplete cerebral ischemia and reperfusion in rats: A long-term observation. *Anesthesiology*. 2004;101:912–917.
114. Kobayashi M, Takeda Y, Taninishi H, et al. Quantitative evaluation of the neuroprotective effects of thiopental sodium, propofol, and halothane on brain ischemia in the gerbil: Effects of the anesthetics on ischemic depolarization and extracellular glutamate concentration. *J Neurosurg Anesthesiol*. 2007;19:171–178.
115. Gelb AW, Bayona NA, Wilson JX, et al. Propofol anesthesia compared to awake reduces infarct size in rats. *Anesthesiology*. 2002;96:1183–1190.
116. Pittman JE, Sheng H, Pearlstein R, et al. Comparison of the effects of propofol and pentobarbital on neurologic outcome and cerebral infarct size after temporary focal ischemia in the rat. *Anesthesiology*. 1997;87:1139–1144.
117. Jeon Y-T, Hwang J-W, Lim Y-J, et al. Postischemic sevoflurane offers no additional neuroprotective benefit to preischemic dexmedetomidine. *J Neurosurg Anesthesiol*. 2013;25:184–190.
118. Bell MT, Puskas F, Bennett DT, et al. Dexmedetomidine an α-2a adrenergic agonist, promotes ischemic tolerance in a murine model of spinal cord ischemia-reperfusion. *J Thorac Cardiovasc Surg*. 2014;147:500–506.
119. Ma D, Yang H, Lynch J, et al. Xenon attenuates cardiopulmonary bypass induced neurologic and neurocognitive dysfunction in the rat. *Anesthesiology*. 2003;98:690–698.
120. Luo Y, Ma D, Leong E, et al. Xenon and sevoflurane protect against brain injury in a neonatal asphyxia model. *Anesthesiology*. 2008;109:782–789.
121. Amorim P, Chambers G, Cottrell J, Kass IS. Nitrous oxide impairs electrophysiologic recovery after severe hypoxia in rat hippocampal slices. *Anesthesiology*. 1997;87:642–651.
122. Sugaya T, Kitani Y. Nitrous oxide attenuates the protective effect of isoflurane on microtubule-associated protein2 degradation during forebrain ischemia in the rat. *Brain Res Bull*. 1997;44:307–309.
123. Fleischer JE, Milde JH, Moyer TP, Michenfelder JD. Cerebral effects of high-dose midazolam and subsequent reversal with Ro 15-1788 in dogs. *Anesthesiology*. 1988;68:234–242.
124. Baughman VL, Hoffman WE, Miletich DJ, Albrecht RF. Cerebral metabolic depression and brain protection produced by midazolam and etomidate in the rat. *J Neurosurg Anesthesiol*. 1989;1:22–28.
125. Abramowicz AE, Kass IS, Chambers G, Cottrell JE. Midazolam improves electrophysiologic recovery after anoxia and reduces the changes in ATP levels and calcium influx during anoxia in the rat hippocampal slice. *Anesthesiology*. 1991;74:1121–1128.
126. Ito H, Watanabe Y, Isshiki A, Uchino H. Neuroprotective properties of propofol and midazolam, but not pentobarbital, on neuronal damage induced by forebrain ischemia, based on the GABAA receptors. *Acta Anaesth Scand*. 1999;43:153–162.
127. Lei B, Popp S, Cottrell JE, Kass IS. Effects of midazolam on brain injury after transient focal cerebral ischemia in rats. *J Neurosurg Anesthesiol*. 2009;21:131–139.
128. Kass IS, Amorim P, Chambers G, et al. The effect of isoflurane on biochemical changes during and electrophysiological recovery after anoxia in rat hippocampal slices. *J Neurosurg Anesthesiol*. 1997;9:280–286.
129. Patel PM, Drummond JC, Cole DJ, et al. Isoflurane and pentobarbital reduce the frequency of transient ischemic depolarizations during focal ischemia in rats. *Anesth Analg*. 1998;86:773–780.
130. Pasternak JJ, Lanier WL. Neuroanesthesiology review—2006. *J Neurosurg Anesthesiol*. 2007;19:70–92.
131. Wang QJ, Li KZ, Yao SL, et al. Different effects of isoflurane and sevoflurane on cytotoxicity. *Chin Med J (Engl)*. 2008;121:341–346.
132. Wang J, Meng F, Cottrell J, Kass I. The differential effects of volatile anesthetics on electrophysiological and biochemical changes during and recovery after hypoxia in rat hippocampal slice CA1 pyramidal cells. *Neuroscience*. 2006;140:957–967.
133. Pape M, Engelhard K, Eberspacher E, et al. The long-term effect of sevoflurane on neuronal cell damage and expression of apoptotic factors after cerebral ischemia and reperfusion in rats. *Anesth Analg*. 2006;103:173–179.
134. Dimaculangan D, Bendo AA, Sims R, et al. Desflurane improves the recovery of evoked postsynaptic population spike from CA1 pyramidal cells after hypoxia in rat hippocampal slices. *J Neurosurg Anesthesiol*. 2006;18:78–82.
135. Haelewyn B, Yvon A, Hanouz JL, et al. Desflurane affords greater protection than halothane against focal cerebral ischemia in the rat. *Br J Anaesth*. 2003;91:390–396.

136. Tsai SK, Lin SM, Hung WC, et al. The effect of desflurane on ameliorating cerebral infarction in rats subjected to focal cerebral ischemia-reperfusion injury. *Life Sci*. 2004;74:2541–2549.
137. Wise-Faberowski L, Raizada MK, Sumners C. Desflurane and sevoflurane attenuate oxygen and glucose deprivation-induced neuronal cell death. *J Neurosurg Anesthesiol*. 2003;15:193–199.
138. Wang J, Cottrell JE, Kass IS. Effects of desflurane and propofol on electrophysiological parameters during and recovery after hypoxia in rat hippocampal slice CA1 pyramidal cells. *Neuroscience*. 2009;160:140–148.
139. Sommer C. Ischemic preconditioning: postischemic structural changes in the brain. *J Neuropathol Exp Neurol*. 2008;67:85–92.
140. Kitano H, Young JM, Cheng J, et al. Gender-specific response to isoflurane preconditioning in focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2007;27:1377–1386.
141. Clarkson AN. Anesthetic-mediated protection/preconditioning during cerebral ischemia. *Life Sci*. 2007;80:1157–1175.
142. Jevtovic-Todorovic V, Absalom AR, Blomgren K, et al. Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth*. 2013;111:143–151.
143. Satomoto M, Satoh Y, Terui K, et al. Neonatal sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. *Anesthesiology*. 2009;110:628–637.
144. Lin D, Liu J, Cottrell JE, Kass IS. Toward a mechanism underlying the effects of neonatal sevoflurane on neuropsychiatric like behavioral changes. *J Neurosurg Anesthesiol*. 2014;26:489.
145. Olsen EA, Brambrink AM. Anesthesia for the young child undergoing ambulatory procedures: Current concerns regarding harm to the developing brain. *Curr Opin Anaesthesiol*. 2013;26:677–684.
146. Meldrum B. Epileptic seizures. In: Siegel GJ, Agranoff BW, Albers RW, Molinoff PB, eds. *Basic Neurochemistry*. New York: Raven Press; 1994:885–898.
147. Bianchi R, Wong RKS, Merlin LR. Glutamate receptors in epilepsy, group I mGluR mediated epileptogenesis. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds. *Jasper's Basic Mechanisms of the Epilepsies*. 4th ed. New York: Oxford University Press; 2012.
148. Brophy GM, Bell R, Claassen J, et al. Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17:3–23.
149. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998;338:970–976.
150. Coronado VG, Xu L, Basavaraju SV, et al, Center for Disease Control and Prevention. Surveillance for traumatic brain injury related deaths-United States 1997–2007. *MMWR Surveill Summ*. 2011;60:1–32.
151. Kolias AG, Guilfoyle MR, Helmy A, et al. Traumatic brain injury in adults. *Pract Neurol*. 2013;13:228–235.
152. Rosenfeld JV, Maas AI, Bragge P, et al. Early management of severe traumatic brain injury. *Lancet*. 2012;380:1088–1098.
153. Helmy A, Vizcaychipi M, Gupta AK. Traumatic brain injury: Intensive care management. *Br J Anaesth*. 2007;99:32–42.
154. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, et al. Guidelines for the management of severe traumatic brain injury. www.braintrauma.org. *J Neurotrauma*. 2007;24(suppl 1):S1–S106.
155. Pietropaoli JA, Rogers FB, Shackford SR, et al. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. *J Trauma*. 1992;33:403–407.

Cerebral and Spinal Cord Blood Flow

2

J.A. Ellis • G.T. Yocum • E. Ornstein • S. Joshi

Studies of cerebral circulation have improved the understanding of the function and pathophysiology of the central nervous system (CNS).[1] The purpose of this chapter is to review the basic mechanisms of CNS circulatory behavior and the tools used to understand them. The chapter begins with a discussion on regulation of cerebral blood flow in health and the failure of regulation in disease states, and proceeds to discuss the methodology for measuring cerebral blood flow (CBF). A discussion of spinal cord blood flow follows; the chapter ends with a discussion of the applied aspects of manipulating cerebral blood flow and monitoring CBF in the clinical setting.

PHYSIOLOGY OF THE CEREBRAL CIRCULATION

Regional Cerebral Blood Flow Requirements

The lack of a substrate reserve in the CNS and its inability to sustain anaerobic metabolism for more than a few minutes requires a constant blood flow that is finely tuned to the metabolic needs of the tissue. The CNS is a complex and structurally diverse organ that comprises multiple functional subdivisions. Neurons account for approximately half of the brain volume; the remainder consists of glial and vascular elements. In addition to mechanical support of neurons, the glia have important regulatory functions (eg, neurotransmitter handling and maintenance of the metabolic milieu of the neuropile) that, at present, are imperfectly understood.

Metabolic rates differ considerably within the brain tissue; for instance, there is an approximately fourfold difference in cerebral metabolic rate for oxygen ($CMRO_2$) and CBF between cortical gray matter and white matter. Flow and metabolism are coupled, and under physiologic conditions, including sedation and general anesthesia, this coupling is generally preserved (Figs. 2.1 and 2.2).[2–4] Intravenous anesthetic agents such as propofol seem to preserve flow-metabolism coupling better than volatile agents.[5] In humans, this coupling is evident during anesthetic-induced electroencephalogram (EEG) burst suppression, as demonstrated by transcranial Doppler ultrasonography (TCD) studies during normothermia[6,7] and during mild-to-moderate hypothermic cardiopulmonary bypass.[8]

Regulation of Cerebral Blood Flow

A precise regulatory system has evolved in the CNS whereby instantaneous increases in metabolic demand can be met by a local increase in CBF and substrate delivery. As has been known for a long time and demonstrated with multiple imaging modalities, the time course of this regulatory process is rapid.[9,10] Contralateral cortical areas manifest increased flow with hand movement, and a variety of motor and cognitive tasks can be mapped with CBF techniques.[11–13] Visual stimulation results in almost immediate increases in flow velocity through the posterior cerebral arteries. Positron emission tomography (PET), magnetic resonance imaging (MRI) and time-resolved near-infrared spectroscopy (NIRS) are beginning to unravel the interrelated functions and their temporal relationships in various cortical areas activated by complex phenomena such as language and visual processing.[14–16] As in

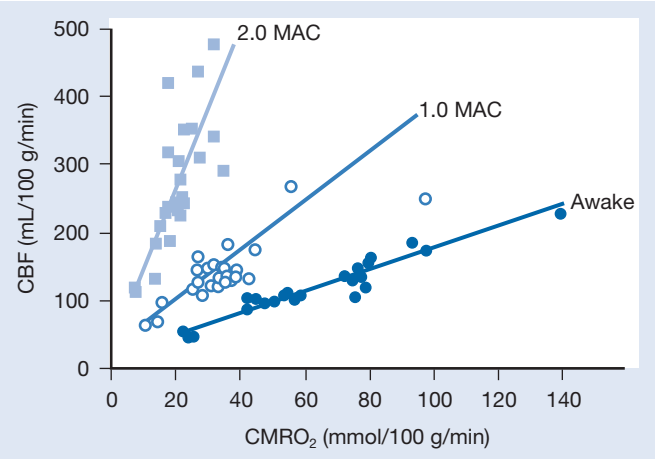


Fig. 2.1 Cerebral blood flow (CBF) as a function of the cerebral metabolic rate for oxygen ($CMRO_2$) in different brain regions of the rat, as determined by autoradiography during isoflurane anesthesia. Three groups are shown: awake, 1.0 MAC, and 2.0 MAC. Note that the volatile anesthetic does not uncouple flow and metabolism; rather, flow-metabolism coupling is "reset" along a different line. *(Modified from Maekawa T, Tommasino C, Shapiro HM, et al: Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. Anesthesiology 1986;65:144–151. Figure courtesy Dr. David S. Warner, University of Iowa.)*

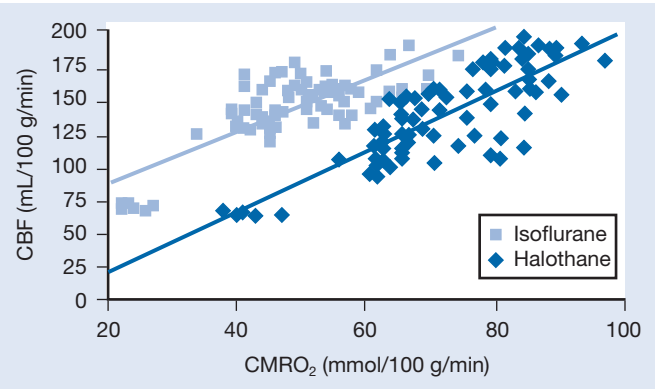


Fig. 2.2 Cerebral blood flow (CBF) as a function of the cerebral metabolic rate for oxygen ($CMRO_2$) in different brain regions of the rat, as determined by autoradiography during halothane and isoflurane anesthesia. As in Fig. 2.1, flow and metabolism remained coupled for both anesthetics. Note that for a given $CMRO_2$ value, flow is actually higher for isoflurane than for halothane. *(From Hansen TD, Warner DS, Todd MM, et al: The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: Evidence for persistent flow-metabolism coupling. J Cereb Blood Flow Metab 1989;9:323–328.)*

most specialized vascular beds, this flow-metabolism coupling is critical during times of stress or extreme physiologic conditions, such as hypotension hypoxia and hypothermia.[8] These pathologic processes engage regulatory mechanisms to keep flow at physiologic levels.

The term autoregulation is used by some to describe the hemodynamic response of flow to changes in perfusion pressure independent of flow-metabolism coupling. The problem with this approach is that the precise mechanisms responsible for maintenance of CBF are poorly understood.[17] One could argue that *autoregulation* principally implies a matching of flow to metabolism, irrespective of the underlying mechanism. For example, the ability of the cerebral vasculature to dilate in response to tissue hypoxia certainly qualifies as an autoregulatory phenomenon, and it may be an oxygen-sensitive mechanism that regulates vascular resistance.[18] Perhaps when the mediators of these "autoregulatory" events are more precisely known, better terminology can be devised. *Autoregulatory* responses are those that maintain the internal milieu of the CNS. Those that endanger CNS well-being are *dysregulatory*. Semantics aside, a clinical distinction can be made between two distinct processes that may or may not be mechanistically related—flow-metabolism coupling and active vasomotion in response to circulatory perturbation. There seems to be an elegant dichotomy of control in the cerebral vascular bed. The "distal vascular" bed can respond rapidly to the sudden changes in the metabolic needs of the tissue, whereas the "proximal vasculature" ensures adequate delivery of blood across a range of perfusion pressures. The two systems probably communicate with each other, in part through nonadrenergic, noncholinergic neurons that innervate the distal penetrating arterioles.[19,20]

Since Roy and Sherrington[21] put forth their hypothesis more than 100 years ago, the prevailing paradigm has been that local metabolic factors are involved in flow-metabolism coupling. However, pure changes in perfusion pressure undoubtedly involve a myogenic response in vascular smooth muscle as well (Bayliss effect).[22] This myogenic response may actually consist of two separate mechanisms, one responding to mean blood pressure changes and the other sensitive to pulsatile pressure.[23] Evidence shows that flow, independent of pressure, may affect vascular resistance.[24] An overwhelming number of metabolic mediators for CBF regulation have been proposed, including hydrogen ion, potassium, adenosine, glycolytic intermediates, and phospholipid metabolites.[17,22] Both neurons and astrocytes seem to participate in flow-metabolism coupling.[25,26] Endothelium-derived factors[27] such as nitric oxide (NO) enable the endothelium to function as a transducer that controls the tone of the vascular smooth muscles.[28] The interactions between the endothelium and the smooth muscle cells are complex and have built in redundancy. Cellular mechanisms within the endothelium and the vascular smooth muscles often converge on intracellular Ca^{2+} as their final common pathway. However, no single mechanism seems to play a preeminent role in regulating blood flow to the brain.[20,29]

Independent assessment of CBF and oxygen utilization by means of PET reveals that the increase in brain activity in response to sensory stimulation results in a minimal increase in O_2 consumption ($CMRO_2$, ~5%) but a considerably greater increase (~30% to 50%) in blood flow. Such an increase in CBF is coupled to the increase in the cerebral metabolic rate for glucose. The disproportionate increases in CBF and cerebral metabolic rate for glucose in comparison with $CMRO_2$ raise the possibility of anaerobic metabolism in the brain.[30]

The issue of anaerobic metabolism in the brain has been debated ever since these observations were first made and conflicting evidence has been presented in this area. In support of anaerobic metabolism, evidence shows transient lactate production during photoptic stimulation.[31] On the other hand, evidence of an early rapid increase in tissue deoxyhemoglobin concentrations during cortical activity suggests a rise in oxygen use.[32] The temporal relationship between neuronal activation, glucose utilization, and blood flow coupling is still being debated. It is now believed that neuronal activation prompts immediate anaerobic glucose metabolism to meet the energy demands for glutamate release. However, clearance of glutamate requires oxidation of glucose in amounts that are in excess of oxygen utilization, resulting in a net efflux of lactate.[33] Under physiologic conditions, lactate is subsequently oxidized to generate additional energy.

Perivascular innervation in the brain has been recognized since Willis first described the cerebral circulation in 1664. Nevertheless, the precise function of this innervation remains obscure. The current paradigm suggests that autonomic nerves are not necessary for regulatory responses but may modify them in several important ways.[34] A major deficiency in the "local metabolic," or "negative-feedback" theory is that the necessary temporal relationship between accumulation of vasoactive metabolites and flow increases has not been adequately demonstrated. In addition, in many situations, CBF and $CMRO_2$ change in the same direction but CBF increases out of proportion to metabolic rate, such as during seizure activity. There is mounting evidence that local neuronal and glial influences play a greater role in regulation of CBF than previously appreciated. Though the understanding of these mechanisms is still evolving, they may better explain the discrepancy seen between the magnitudes of increases in CBF and $CMRO_2$.[26]

Cellular Mechanisms of Cerebral Vasomotion

The remarkable ability of the cerebral vessels to respond to changes in cerebral metabolism, perfusion pressure, and milieu interior, such as $PaCO_2$, is mediated by a number of cellular mechanisms. These mechanisms involve nitric oxide, prostaglandins (PGE_2, PGI_2, and $PGF_{2\alpha}$), vasoactive peptides, potassium channels, and endothelin.[20,29,35]

Nitric Oxide

Although it is unlikely to be directly involved in pressure autoregulation itself,[36] NO is the subject of intense scrutiny as a mediator of vascular tone[37] and as a neurotransmitter.[38,39] The interest in NO results from the identification of the multiple biologic roles it plays as a messenger molecule.[38] Although until recently no evidence had shown it to have any biologic function at all in vertebrates, NO now appears to have at least the following major roles: (1) bactericidal and tumoricidal effects in white blood cells, (2) a neurotransmitter, and (3) a moderator/mediator of vascular tone, functioning as an "endothelium-derived relaxing factor."[20]

NO is synthesized from L-arginine by nitric oxide synthase (NOS). There are at least three isoforms of NOS: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS).[40] Of these, eNOS and nNOS exist in the normal brain, whereas iNOS synthesis can be induced by endotoxins and cytokines. Endogenous inhibitors of NOS, such as asymmetric dimethyl-L-arginine (ADMA), are produced during protein catabolism and may reach concentrations sufficient to inhibit NOS activity in the brain.[35] NO action has been studied

through the use of arginine analogues such as NG-nitro-L-arginine methyl ester (L-NAME), 7-nitroindazole, and aminoguanidine, which can nonselectively or selectively block NO synthesis. NO appears to influence basal tone,[41] as well as the endothelium-dependent response to acetylcholine in cerebral arteries[42] and vasogenic dilation from stimulation of nonadrenergic, noncholinergic nerves.[43] In general, topical, systemic, and intra-arterial application of NO donors increases CBF in several animal species.[44,45] Intra-arterial injection of the NO donor nitroprusside into angiographically normal territories in patients with cerebral arteriovenous malformations failed to augment CBF.[46–48] A similar failure of intra-arterial nitroprusside was seen in healthy primates.[49,50] In contrast, a study in human volunteers found that systemic and intra-arterial administration of NG-monomethyl-L-arginine (L-NMMA), a nonspecific inhibitor of eNOS, decreases CBF.[47,51] The latter findings suggest that NO may be involved in regulation of basal cerebrovascular tone. After synthesis, NO diffuses into the vascular myocyte and activates guanylate cyclase, forming cyclic guanosine monophosphate (cGMP). A protein kinase is stimulated by cGMP, resulting in phosphorylation of the light chain of myosin and thus vascular relaxation.[38] NO may also act partly through calcitonin gene-related peptide (CGRP) and ATP-sensitive potassium (KATP) channels.[52] NO partly acts also by suppressing endothelial generation of vasoconstrictors such as thromboxane A_2. In pathologic settings, such as vasospasm and hypoxia, Rho kinase, a serine threonine kinase, is emerging as a potent mediator of sustained vasoconstriction that in part acts through the NO pathway.[53] Inhibition of Rho kinase increases cerebral blood flow.[54] In middle cerebral artery occlusion models, Rho kinase inhibition improves neurologic outcome.[55,56] Rho kinase inhibition increases eNOS synthesis, and Rho kinase seems to negatively regulate eNOS activity.[57] Calcium is intimately involved in vascular relaxation by NO. NO appears to be formed on demand and is not stored in vesicles—the traditional fate of neurotransmitters.

The role of NO in the vasodilitatory response due to changes in perfusion pressure or carbon dioxide (CO_2) remains to be coherently defined. For example, nonspecific inhibition of NOS in primates does not affect pressure autoregulation but impairs response to CO_2.[36] However, in humans, nonspecific inhibition of NOS results in a decrease in CBF but does not affect response to hypercapnia.[51] In rodents, nonspecific inhibition of NOS impairs autoregulatory response to hypotension in basilar artery irrigation.[58] While selective nNOS inhibition by 7-nitroindazole has no effect on baseline blood flow, 7-nitroindazole can prevent the increase in blood flow due to neural activation.[59] In canines, 7-nitroindazole decreases collateral blood flow during middle cerebral artery occlusion.[60]

Some investigators have reported that NO appears to play a role in dilation in response to CO_2.[61–63] In other experiments, however, its participation in hypocapnia-induced vasoconstriction could not be demonstrated.[64] Iadecola and Zhang[65] proposed that NO plays either an "obligatory" or a "permissive" role in CO_2-induced vasodilation. *Obligatory* implies that NO directly mediates vasodilation through that mechanism. For example, topical application of glutamate agonists results in vasodilation that can be markedly attenuated by inhibition of NOS. Therefore, NO seems to play an obligatory role in glutamate-mediated vasodilation. *Permissive* implies that NO facilitates relaxation but near-complete inhibition of NOS only partly attenuates the vasodilator response. Because hypercapnic response is only partly attenuated by NOS inhibition, NO's role is described as permissive, with other mechanisms also contributing to hypercapnic dilation. NO appears to play a much greater role in hypercapnic vasodilation in adults than in neonates.[52] The site of action for CO_2-induced NO production may not be in the endothelium but, rather, in the perivascular structures, such as astrocytes.[61]

The participation of NO in hypoxia-induced vasodilation does not appear to be physiologically important.[62,66,67] In regard to anesthetic effects on CBF, NO appears to interact with the cerebral vasodilatory effects of both halothane[68] and isoflurane.[69] The role of NO as a neurotransmitter undoubtedly will prove to be significant for care of the patient with neurologic disease through its interactions with anesthetic depth[70] and cerebral ischemic states,[67,71] in particular the pathogenesis of vasospasm after subarachnoid hemorrhage (SAH).[29] Inhibition of NO synthesis leads to vasoconstriction due to unopposed effects of endothelial prostanoids, such as thromboxane A_2 and prostaglandin $F_{2\alpha}$.[72] Vascular abnormalities in disease states that significantly predispose the brain to damage, such as diabetes mellitus, may also be related to an NO-mediated mechanism.[62]

Vasoactive Peptides

In the cerebral circulation, perivascular nerves contain several vasodilator peptides, including CGRP, substance P, and neurokinin A.[73–76] Vasodilation with CGRP, unlike with substance P and neurokinin A, is independent of endothelin. CGRP acts by increasing intracellular cyclic adenosine monophosphate (cAMP) concentrations and partly mediates cerebral vasodilation in response to hypotension, cortical spreading depression, and cerebral ischemia. Vasodilation by NO is in part mediated by CGRP.[75,76] CGRP probably does not play a role in vasodilator response to hypoxia or hypercapnia.[77] The physiologic roles of substance P and neurokinin A are not yet understood. Substance P may mediate vasodilation during pathologic derangements such as cerebral and meningeal inflammation and edema.[35]

Potassium Channels

Of the several potassium channels in the cerebral vessels,[78] two are of particular importance in the regulation of vascular tone: KATP channel and calcium-activated potassium (KCa) channel. A third potassium channel, pH-sensitive delayed rectifier potassium channel, may play a role in hypercapnia. Opening of potassium channels triggers potassium efflux from the vascular smooth muscle cell, hyperpolarizes the cell membrane, closes the voltage-dependent calcium channels, decreases calcium entry into the cells, and ultimately relaxes the muscles.[79] KATP channels are opened by a decrease in intracellular pH and are inhibited by an increase in intracellular ATP concentrations and by sulfonylureas.[80] Activation of KATP channels may partly mediate vasodilation by acetylcholine, CGRP, or norepinephrine (noradrenaline).[79] KATP channels may play some role in vasodilation during hypotension, hypercapnia, acidosis, and hypoxia.[81–83] KCa channel-mediated vasodilation is due partly to astrocyte-derived carbon monoxide, which diffuses into the smooth muscle cells. Large-conductance KCa (BKCa) channels are the most important of the several KCa channels found in the cerebral circulation.[81] These channels can be selectively blocked by tetraethylammonium, charybdotoxin, and iberiotoxin.[84] Inhibition of BKCa channels results in cerebral vasoconstriction in the large arteries, suggesting that BKCa channels may be involved in the regulation of basal cerebrovascular tone in these vessels.[85] BKCa channels are activated by cGMP, cyclic adenosine monophosphate, and NO and are partly responsible for hypoxia-induced vasodilation of cerebral arteries.[78,83,86,87]

Prostaglandins

Prostaglandins such as PGE_2 and PGI_2 are vasodilators but thromboxane A_2 and $PGF_{2\alpha}$ are vasoconstrictors in the cerebral circulation. Synthesis of prostaglandin H_2 from membrane phospholipids involves two critical enzymes, phospholipase and cyclooxygenase. Prostaglandin H_2 is converted into other prostaglandins by subsequent enzymatic steps. Although cyclooxygenase can be inhibited by aspirin, naproxen, and indomethacin,[88–90] only indomethacin impairs hypercapnic vasodilation in humans.[90,91]

Prostaglandins probably play a more significant role in the regulation of CBF in neonates than in adults.[92] Inhibition of phospholipase by quinacrine hydrochloride abolishes the cerebrovascular response to hypercapnia, and hypoxia in newborn animals.[93] Endothelial damage and indomethacin also abolish hypercapnia-induced vasodilation and the increase in cerebrospinal fluid (CSF) PGI_2 concentrations.[94–96] However, indomethacin-impaired CO_2 reactivity can be restored by very low concentrations of PGE_2.[97] This suggests that prostaglandins may not be direct mediators of hypercapnic vasodilation but that small amounts of prostaglandins are necessary for the CO_2 response to hypercapnia to occur and that prostaglandins thus play a so-called permissive role.[94]

Endothelin

Endothelin is a vasoactive peptide that is synthesized by the brain and the vascular endothelium. There are three isoforms of endothelin. The brain synthesizes endothelin-1 (ET-1) and endothelin-3 (ET-3) but not endothelin-2 (ET-2). The vascular endothelium synthesizes ET-1. The two receptors for endothelin are endothelin A (ETA) and endothelin B (ETB).[98] Activation of ETA receptors causes vasoconstriction, and activation of ETB receptors may cause either vascular relaxation or constriction. Vascular relaxation is thought to be mediated by endothelin receptors on the endothelium, whereas constriction is probably mediated by endothelin receptors located on the smooth muscle cells.[35] ETA receptors are probably more sensitive to ET-1 and ET-2 than to ET-3. The ETB receptor is equally sensitive to all isoforms of endothelin.[98,99] Endothelin most likely acts through influx of extracellular calcium, which is probably mediated by protein kinases.[100] The vascular smooth muscle contraction caused by endothelin is sustained, suggesting that endothelin is not involved in rapid adjustment of cerebrovascular resistance (CVR).[101] Topical applications of endothelin receptor antagonists do not alter resting CVR.[102] Endothelin has been implicated in vascular spasm after SAH.[103,104] In experimental models of SAH, ETA and ETB receptor antagonists prevent evolution vasospam.[105] Endothelin-induced vasospasm can also be reversed nonspecifically by calcium channel blockade and seems to be more responsive to intra-arterial nicardipine than to verapamil.[106,107] Early results of clinical trials showed that intravenous infusion of an ETA receptor antagonist, clazosentan, resulted in a decrease in the incidence of vasospasm after SAH. Intravenous clazosentan infusion reduces the severity of the established cerebral vasospasm.[107] However, despite improvements in angiographic vasospasm with ETA receptor antagonists, more recent clinical analyses have shown no improvement in vasospasm-related cerebral infarction, new cerebral infarction, or case-fatality. Furthermore, treatment with ETA receptor antagonists was associated with higher incidence of pulmonary complications, hypotension, and anemia. Thus, enthusiasm for using these agents has waned.[108]

Anatomic Considerations

The primary arterial supply to the brain consists of the anterior circulation, which comprises the two carotid arteries and their derivations, and the posterior circulation, consisting of the two vertebral arteries, which join to form the basilar artery. Collateral arterial inflow channels are a cornerstone of CBF compensation during ischemia. The principal pathways are embodied in the circle of Willis. This hexagonal ring of vessels lies in the subarachnoid space and encircles the pituitary gland (Fig. 2.3). In many patients the circle of Willis is incomplete. The primary routes of collateral circulation are the Willisian channels (anterior communicating artery [ACA] and posterior communicating artery [PCA]) and the ophthalmic artery via the external carotid artery. In a normal individual, there is probably no net flow through these communicating vessels but rather a to-and-fro movement of blood that maintains patency by preventing thrombosis and atresia. These vessels allow flow when a pressure differential develops. The second main recourse for collateral flow in the hemispheres is the surface connections between pial arteries that bridge major arterial territories (ACA-PCA, ACA–middle cerebral artery [MCA], MCA-PCA). These connections are called by various names. "Pial-to-pial anastomoses" or "collaterals" seem to be the most logical terms, but they are also called "leptomeningeal pathways."[109] These pathways may protect the so-called border zones or watershed areas between vascular territories. A considerable amount of confusion in terminology is found in this domain.[110] Physiologically, a more precise term might be "equal pressure boundary,"[111] that is, where, under normal circumstances, pial flow does not cross collateral pathways into an adjacent territory because the pressures on either side of this distal territorial boundary are equal. Considerable variation exists in the anatomic location of these boundaries, and they may change during the course of treatment, if the vascular architecture is altered, such as after multiple arteriovenous malformation (AVM) embolizations.

Collateral pathways are most efficacious during chronic ischemia, when they may gradually enlarge over time. In the acute stage, it is frequently necessary to augment blood pressure to effectively drive flow across them. Absence of adequate

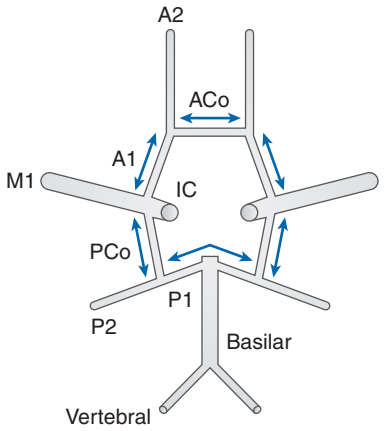


Fig. 2.3 Circle of Willis with collateral pathways. Principal pathways for collateral flow are marked by *arrows*. Not shown are potential pathways from the extracranial circulation (eg, retrograde flow through the ophthalmic artery). A1, proximal anterior cerebral arteries; A2, distal anterior cerebral arteries; ACo, anterior communicating artery; IC, internal carotid artery; Ma, middle cerebral artery; P1, proximal posterior cerebral arteries; P2, distal posterior cerebral arteries; PCo, posterior communicating artery. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

collateral pathways, especially in the circle of Willis, is a normal anatomic variant, so deliberate hypertension is not guaranteed to succeed. A complete circle of Willis with well-developed symmetrical components is present in only 18% to 20% of the population. Hypoplasia of the PCA, the proximal segment of the anterior cerebral artery, or the ACA is often encountered.[112] The size of the collateral vessels may influence the clinical course following acute vascular occlusion. Computer modeling suggests that any change in the ACA diameter, even within the normal range (0.6 to 1.4 mm), has a profound effect on collateral blood flow when an internal carotid artery is occluded.[113] Clinical observations suggest that a PCA diameter of less than 1 mm, measured by MR angiography, may be associated with an increased risk of watershed stroke.[114] The external and internal carotid arteries have the potential for communication, which most commonly manifests as flow from the external carotid artery, via facial pathways, to the ophthalmic artery. Thus retrograde flow is provided to the circle of Willis. Several other pathways may develop between the carotid and vertebrobasilar systems.[109] In rare situations, meningeal collaterals may develop into the intracranial circulation (eg, AVMs and moyamoya disease).

In summary, an elegant microcirculatory arrangement is provided for recruiting accessory inflow channels to the endarterial perfusion territories of the brain. In normal circumstances these channels either lie dormant or are underused, becoming functional (critical) only when a pathologic stress is imposed on the circulation. In general, the circle of Willis and the leptomeningeal communications compensate for an acute interruption of the circulation; other pathways described previously are more likely to compensate for chronic cerebral insufficiency.

Regulation of CVR takes place primarily in the smaller arteries and arterioles (muscular or resistance vessels) and not the larger arteries that are visible on an angiogram (elastic or conductance vessels). However, the contribution of both venules and capillaries[115] and larger conductance arteries to regulatory activity is a subject of controversy.[116,117] There is probably a continuum of varying participation in autoregulatory function as one proceeds distally along the arterial tree.[117,118] In humans, the venous drainage of the brain is complex and considerably more variable than the anatomy of the arterial tree. The typically thin walled and valveless intracerebral conduits terminate into thicker-walled venous sinuses, which are rigid by virtue of bony attachments. Because of the confluence of the larger venous sinuses, a considerable admixture of venous blood draining the cerebral hemispheres takes place, and it is not uncommon to note, in the later venous phase of an angiogram, that one side of the venous drainage appears to be dominant. This finding may be of interest in the choice of internal jugular vein for cannulation.

Hemodynamic Factors

Pressure Regulation

Conceptually, a convenient way to model the cerebral circulation is to envision a parallel system of rigid pipes in which Ohm's law would apply:

$$F = \frac{P_i - P_o}{R} \qquad (2.1)$$

where F is flow, P_i is input pressure, P_o is outflow pressure, and R is resistance.

The term $P_i - P_o$ is usually referred to as *cerebral perfusion pressure* (CPP) and is calculated as MAP minus the outflow pressure. The cerebral venous system is compressible and may act as a "Starling resistor." True CPP often is overestimated because a small gradient exists between systemic and cerebral vessels,[119] which may be particularly important in patients with cerebral AVMs.[120] It is useful to conceptualize pressure and resistance as independent variables in the preceding equation and flow as the dependent variable (ie, the pressure or resistance is affected by disease or treatment, and flow follows suit). For example, drugs exert effects on CBF by changing CPP and CVR (directly for vasodilators and indirectly by metabolic depressants).

Circulatory resistance can be modeled in terms of the Hagen–Poiseuille relationship (Eq. 2.2), as follows:

$$R = \frac{8l\mu}{r^4} = \frac{P_i - P_o}{F} \qquad (2.2)$$

where l is length of conduit; μ is blood viscosity; and r is radius of vessel. Other symbol definitions were given previously. As is the case for Ohm's law, when this equation is applied to an intact vascular system, a number of critical assumptions are clearly not met. The equation applies to newtonian fluids during nonturbulent flow through rigid tubes. Circulation, in contrast, is pulsatile with capacitance and the potential for turbulence. Also, a decrease in CPP can be a result of a decrease in systemic blood pressure or an increase in ICP or jugular venous pressure. Some groups have reported that the cerebral vascular bed responds in a similar way to changes in CPP, whether as a result of a decrease in the MAP or an increase in intracranial or jugular venous pressure.[121] However, other investigators have reported that for a given change in CPP, the effect on vessel inner diameter due to an increase in ICP is different from that due to a decrease in MAP.[122]

From a purely practical standpoint, examination of the previous relationship leaves little question as to why vessel diameter evolved into the preeminent mode of vascular regulation. Although viscosity and vessel length influence resistance in a linear manner, the fact that flow is proportional to the fourth power of the conduit's radius makes this the most efficient means of controlling resistance.

In the normal individuals, CBF remains constant with CPP in the range of approximately 50 to 150 mmHg (Fig. 2.4). As the ability of the cerebral vasculature to respond to changes in pressure is exhausted, CBF passively follows changes in CPP. At the extremes, resistance probably does not stay fixed. Vessel collapse and passive vascular dilation may actually potentiate the predicted decline or increase caused by CPP changes. Thus, resistance does not remain linearly related to pressure. Although the general concept put forth in Fig. 2.4 is important, it is only a statistical description of how the general population responds, and a value of 50 mmHg, even in a normotensive individual, does not guarantee that a particular patient's cerebral circulation remains within the "autoregulatory plateau." Individual responses vary widely.[123] Ideally, at the lower limit of cerebral autoregulation, a near maximal vasodilation is thought to take place. However, evidence shows that even below the lower limit of autoregulation, pharmacologic vasodilation may be possible.[124,125] The relevance of the idealized cerebral autoregulation curve, in particular the lower limit of autoregulation, has been questioned by some writers.[126]

In its simplest form, a cerebral autoregulation curve expressing CBF as a function of CPP is often represented by three straight lines. Two sloping lines intersect a horizontal line at points that represent the lower and upper limits of cerebral autoregulation. The horizontal segment represents the

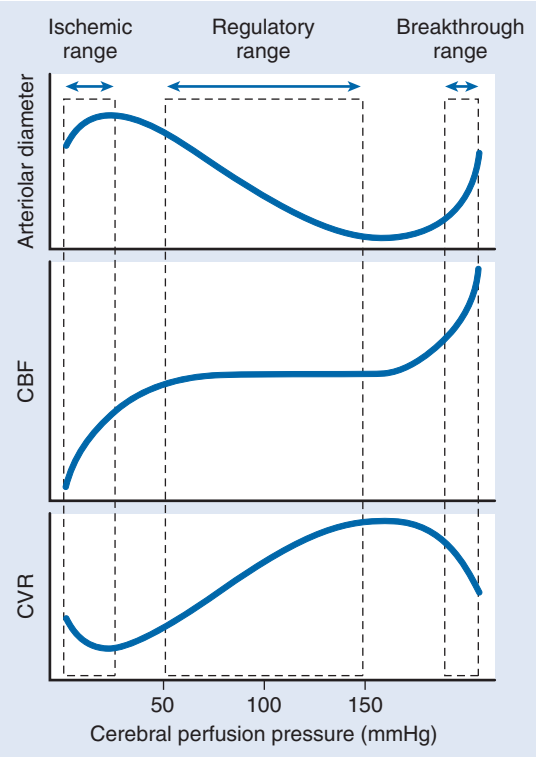


Fig. 2.4 Idealized depiction of pressure autoregulation in terms of cerebral blood flow (CBF), cerebrovascular resistance (CVR), and arteriolar diameter. See text for further explanation. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

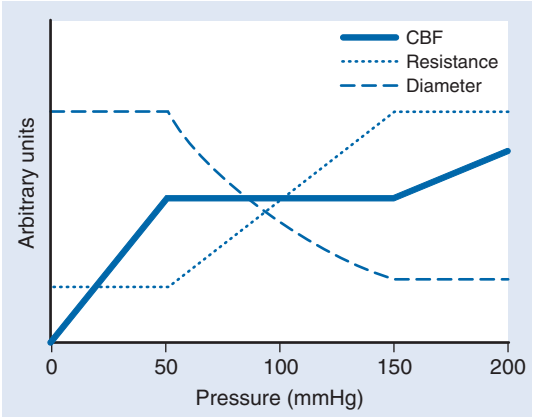


Fig. 2.5 Fixed maximal vasoreactivity type of autoregulation. Cerebral blood flow (CBF), cerebrovascular resistance, and arteriolar diameter are shown for the fixed maximal vasoreactivity type of autoregulation. Between the lower limit of autoregulation (LLA) and the upper lower limit of autoregulation (ULA), the CBF is autoregulated through a change of the vessel diameter. The vessel dilates as pressure decreases, and reaches its maximal size when pressure falls to less than LLA. Similarly, the vessel constricts as pressure increases, and maintains its minimal size when pressure exceeds ULA. Note that the two *sloped lines* are not parallel with each other (compare with variable maximal vasoreactivity type shown in Fig. 2.6). *(From Gao E, Young WL, Pile-Spellman J, et al: Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. Am J Physiol 1998;274:H-1023-H1031.)*

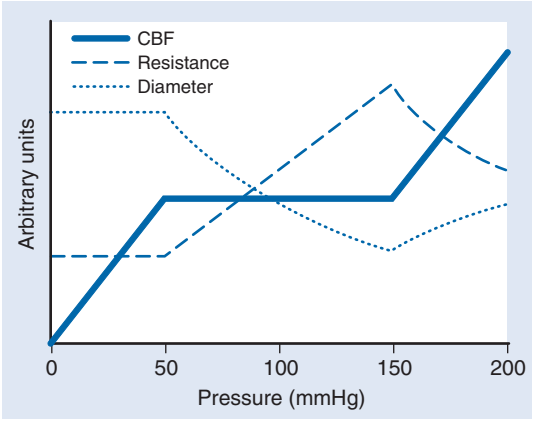


Fig. 2.6 Variable maximal vasoreactivity type of autoregulation. Cerebral blood flow (CBF), cerebrovascular resistance, and arteriolar diameter are shown for the variable maximal vasoreactivity type of autoregulation. At the pressure below the upper lower limit of autoregulation (ULA), this type is the same as the fixed maximal vasoreactivity type. However, when pressure exceeds ULA, CBF increases at the same rate as it does when pressure is below LLA. This pattern implies that the arteriole dilates when pressure exceeds ULA. Note that the two *sloped lines* are parallel with each other (compare with Fig. 2.5). *(From Gao E, Young WL, Pile-Spellman J, et al: Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. Am J Physiol 1998;274:H1023-H1031.)*

pressure-independent flow within the autoregulatory range, whereas the sloping lines represent pressure-dependent flow outside the range of autoregulation. In mathematical terms, an autoregulatory curve can be characterized by four principal autoregulatory parameters: lower limit of pressure autoregulation, upper limit of pressure autoregulation, slope below the lower limit of autoregulation, and slope above the lower limit of autoregulation. Using mathematical modeling, Gao and colleagues[127] observed that the three previously described autoregulatory curves did not accurately predict the experimentally observed principal autoregulatory parameters (Figs. 2.5 to 2.8). Computer modeling was most successful in predicting experimental results when the arterial resistive bed was compartmentalized into a series of four compartments on the basis of arterial/arteriolar diameter. These study findings suggest that there are multiple sites of autoregulation in the cerebral arterial resistive bed.[127–129]

A time constant is associated with autoregulatory changes. Fig. 2.9A depicts the response of a simple tube (or a dysregulating vascular bed) to a step change in pressure. Because resistance does not change (assuming nonturbulent flow), flow passively follows the change in pressure. Fig. 2.9B depicts the response that is typical of a normal circulatory bed. With the step change in pressure comes an instantaneous drop in flow, but as the bed actively autoregulates and resistance decreases, flow gradually increases and returns to baseline. When the pressure is returned to normal, there is a transient period of hyperemia while the resistance is reset.[130]

Venous Physiology

The influence of the cerebral venous system on overall autoregulation is unclear, primarily because of the difficulty of direct observation. The smooth muscle content and the innervation of the venous system are less extensive than those of the arterial system, and many believe that the venous system is a passive recipient of the "regulated" arterial inflow. Asymptomatic occlusion of cortical veins in animals can impair the local autoregulatory response to systemic hypotension.[131] In addition, the venous system contains most of the cerebral blood volume (CBV); therefore slight changes in vessel diameter may have a profound effect on intracranial blood volume. Available evidence suggests that the venous system may be regulated more by neurogenic than by myogenic or metabolic factors.[128]

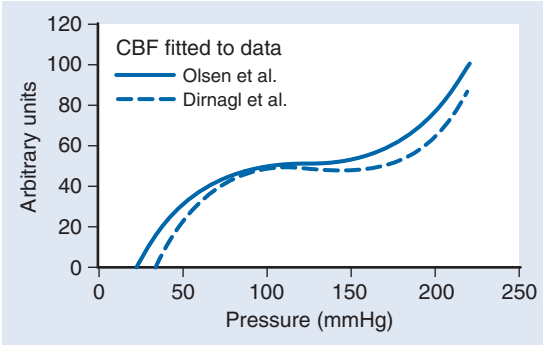


Fig. 2.7 Cerebral blood flow (CBF) of autoregulation curves of type 3. CBF curve was obtained by curve-fitting to the third-order polynomial of data reported by Dirnagl and Pulsinelli (J Cereb Blood Flow Metab, 1990) (*dashed line*) and Olsen et al. (Br J Anaesth, 1995) (*solid line*). The prediction that blood flow ceases if pressure is below 30 or 20 mmHg conflicts with experimental observations. *(From Gao E, Young WL, Pile-Spellman J, et al: Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. Am J Physiol 1998;274:H1023-H1031.)*

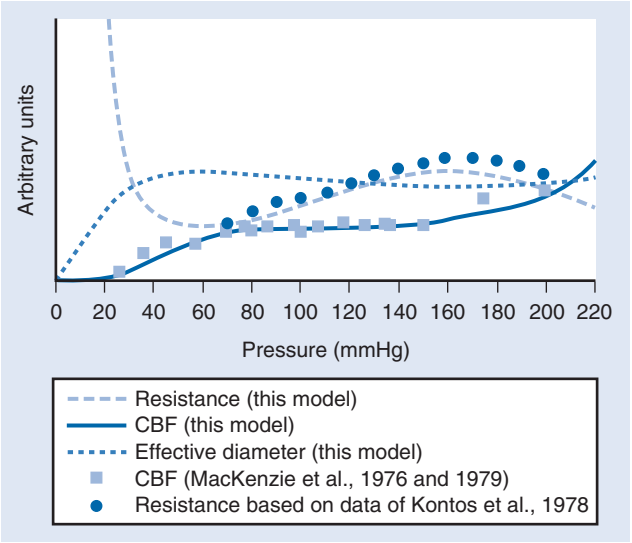


Fig. 2.8 Regression results of cerebrovascular resistance, blood flow, and effective diameter of an autoregulation device (ARD) in the compartmental model. When the pressure decreases below the lower limit of autoregulation (LLA), the vessel continues to dilate until it finally reaches the maximum at a lower pressure of 40 mmHg for three small vessels (diameter = 50, 150, and 200 μm) or 70 mmHg for the large vessel (diameter = 300 μm). Some experimental data are also plotted in the figure. Resistance (*closed circles*) is calculated directly from experimental data of Kontos et al. (Am J Physiol, 1978). The experimental data for CBF are readings of two head-fitted curves of the data reported by MacKenzie et al. (Circ Res, 1976) *(From Gao E, Young WL, Pile-Spellman J, et al: Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. Am J Physiol 1998;274:H1023-H1031.)*

Pulsatile Perfusion

Both a fast component and a slow component to the myogenic response to changes in perfusion pressure have been proposed. This consideration is of particular interest in the patient undergoing cardiac surgery.[132] During cardiopulmonary bypass, the pulsatile variations in blood pressure transmitted to the cerebral vasculature appear to influence CBF, perhaps by interaction with endothelium-derived mediators of vascular tone.[133] Although the importance of these effects has not been completely determined, the loss of pulsatility may worsen the outcome of a cerebral ischemic event.[119] Sudden restoration of pulsatile perfusion to a previously dampened circulatory bed may be a mechanism to explain certain instances of cerebral hyperemia.[134]

Cardiac Output

A proposed theory is that an increase in cardiac output may be responsible for improved CBF and outcome after SAH. However, there is little evidence for increased cardiac output as an operative mechanism of improving cerebral perfusion. Improvement in perfusion by volume loading is indirectly accomplished by improving blood rheology and directly accomplished by increasing systemic blood pressure and preventing occult decreases in systemic pressure.[135] Studies examining the possible relationship between a change in cardiac output and a change in CBF have, for the most part, assessed the effect of drugs that increase cardiac output during

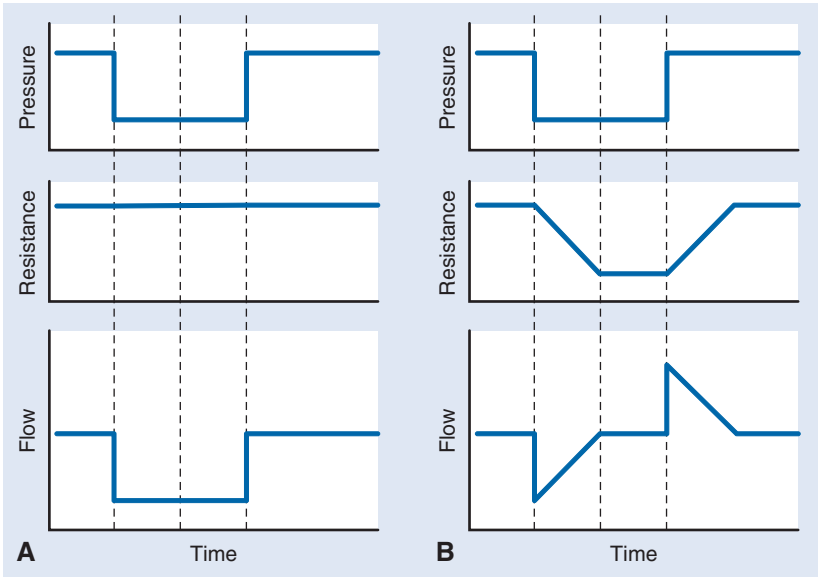


Fig. 2.9 Flow, resistance, and pressure as a function of time. *Dotted vertical lines* represent a time scale of "minutes." **A,** In a rigid pipe (or a totally vasoparalyzed circulation), a step decrease in pressure leads to an instantaneous drop in flow, because resistance stays fixed. **B,** In a conduit with autoregulation, a step decrease in pressure is first met with an instantaneous drop in flow. As resistance falls, however, flow increases toward baseline. With the step restoration of pressure to control level, there is an instantaneous hyperemic response, and subsequently, flow decreases as resistance decreases toward control levels. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

either normotension or induced hypertension. Some investigators suggest, however, that during deliberate drug-induced hypotension, a decrease in cardiac output might be reflected by a decrease in CBF, even when blood pressure is kept above the lower autoregulatory threshold.[136] The effects of altering cardiac output on CBF are more likely to be indirect effects on central venous pressure and large cerebral vessel tone (ie, sympathetic tone).

Rheologic Factors

Clinically, hematocrit is the main influence on blood viscosity,[137] and, as shown in Eq. 2.2, blood viscosity is a major determinant of vascular resistance. Muizelaar and associates[138] have proposed that viscosity directly participates in hemodynamic autoregulation. As discussed later, viscosity may be the only determinant of CVR subject to manipulation in certain settings. An inverse relationship exists between hematocrit (Hct) and CBF. A continuing controversy concerns whether this relationship is, in fact, purely rheologic or a function of changes in oxygen delivery to the tissue.[139]

Todd and coworkers[140] demonstrated a significant CBF increase, from 30 ± 14 mL/100 g/min (baseline Hct = 42 ± 2%, mean ± SD) to 100 ± 20 mL/100 g/min at Hct = 12 ± 1% in normal cerebral hemispheres of rabbits. The increase in regional CBF was markedly smaller after focal cryogenic cerebral injury, suggesting that a CBF increase produced by hemodilution is an active vasodilatory process rather than a passive response to changing blood viscosity. In another animal experiment, when blood was replaced by ultrapurified polymerized bovine hemoglobin, the viscosity of which does not depend on shear rate, a fourfold increase in viscosity did not significantly affect CBF. This finding suggests that blood viscosity alone may not significantly affect CBF.[141]

The Hagen–Poiseuille model does not accurately describe the behavior of flow at the microcirculatory level.[142,143] When red blood cells (RBCs) flow near vessel walls, they create shear forces, which add resistance. (The *shear rate* is the change in velocity moving from the wall toward the center of the vessel.) Therefore in all vessels the RBC velocity is faster in the center of the vessel and slower at the periphery. In small vessels, cells move faster than the plasma (the Fahraeus effect), thereby reducing microvascular hematocrit. This reduction in hematocrit causes a reduction in viscosity (the Fahraeus–Lindqvist effect).[144] Another contribution of the smaller microvascular hematocrit is that as the vessels become progressively smaller, the relative size of the annular periphery (with reduced flow velocity) becomes larger.

Cerebral hematocrit in humans is approximately 75% of systemic values, but it is affected by $PaCO_2$[145] and presumably by other vasoactive influences. Relative hypercapnia reduces cerebral hematocrit, and it is presumed that the other vasodilators do as well.

Metabolic and Chemical Influences

Carbon Dioxide

CO_2 is a powerful modulator of CVR. At one time, CO_2 was thought to be the "coupler" between flow and metabolism, because an increase in metabolism generates CO_2 and therefore releases a cerebral vasodilator into the local environment. Rapid diffusion across the blood–brain barrier (BBB) allows CO_2 to modulate extracellular fluid pH and affect arteriolar resistance.[146] Metabolically induced changes in pH in the systemic circulation do not have the same effect in the presence of an intact BBB, but metabolic production of H^+ released into the CSF or extracellular space from ischemic lactic acidosis does. The mechanism of vasodilation by CO_2 may be different in adults and neonates (Fig. 2.10). Evidence shows that NO and cyclic guanosine monophosphate pathways are probably more important in adults, whereas prostaglandins and cyclic adenosine monophosphate are more important in neonates.[52] By active, though somewhat sluggish, exchange of HCO_3^- the CSF eventually buffers itself against alterations in pH by CO_2 diffusion. Although CO_2-induced cerebral vasoconstriction wanes over a period of 6 to 10 hours,[147] this period can be variable in an individual patient. Also important in this regard are chronic states of either hypocapnia or hypercapnia, because sudden normalization of $PaCO_2$ can result in relative hypoperfusion or hyperperfusion.

At normotension, there is a nearly linear response of CBF at a $PaCO_2$ between 20 and 80 mmHg (CBF changes approximately 2% to 4% for each mmHg change in $PaCO_2$). The linearity of

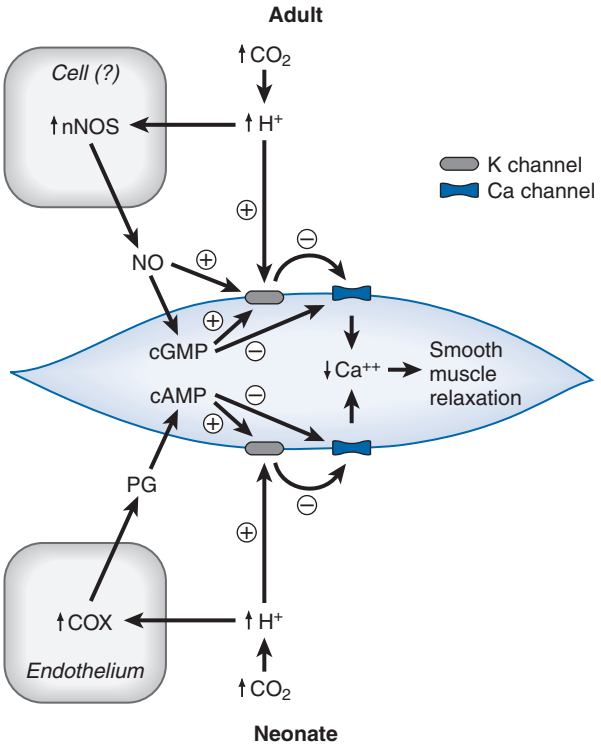


Fig. 2.10 The exact mechanism of hypercapnic vasodilation remains to be fully defined and may differ in adults and neonates. This figure illustrates one proposed sequence of events that results in hypercapnic vasodilation. In adults, hypercapnia decreases extracellular pH, activates the neuronal isoform of nitric oxide synthase (nNOS), and increases production of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP). Subsequent activation of potassium channels by NO or cGMP results in hyperpolarization of the vascular smooth muscle (VSM) cell membrane. Extracellular acidosis may activate potassium channels directly. Hyperpolarization of VSM cell membrane inhibits voltage-gated calcium channels and decreases intracellular calcium concentrations. cGMP can also directly inhibit calcium channels, reducing intracellular calcium concentrations. A decrease in intracellular calcium results in vasorelaxation. In neonates, hypercapnia-induced extracellular acidosis increases prostaglandin (PG) synthesis by activating endothelial cyclooxygenase (COX). Prostaglandins play a "permissive role" in hypercapnic vasodilation (see text). Increased prostaglandin concentration activates adenylate cyclase and results in an increased intracellular cyclic adenosine monophosphate (cAMP) concentration in VSM. Increased cAMP concentrations in VSM activate potassium (K) channels and inhibit calcium (Ca) channels, resulting in a decrease in intracellular calcium (Ca^{++}) concentration and vascular relaxation. As in adults, extracellular acidosis may also directly activate potassium channels and hyperpolarize the VSM cell membrane. CO_2, carbon dioxide; H^+, hydrogen ion. *(Modified from Brian JE Jr: Carbon dioxide and the cerebral circulation. Anesthesiology 1998;88:1365–1386.)*

the response breaks down as $PaCO_2$ approaches the extremes. The values quoted for either percentage change or absolute levels in CBF change per unit CO_2 are highly variable, depending on the methods employed and whether hemispheric or cortical flow is measured.[148–150]

In general, doubling $PaCO_2$ from 40 to 80 mmHg doubles CBF, and halving $PaCO_2$ from 40 to 20 mmHg halves CBF. This highly reproducible cerebrovascular CO_2 response is often used as a way of validating and comparing different CBF methods.[148]

In a fashion analogous to blood pressure autoregulation, the CO_2 response is limited by either maximal vasodilation at extreme hypercapnia or maximal vasoconstriction at extreme hypocapnia. Hypocapnia, however, may adversely affect cellular metabolism and shift the oxyhemoglobin dissociation curve to the left.[150] Severe hypocapnia (approximately 10 mmHg) can result in anaerobic glucose metabolism and lactate production.[151,152] Although clinical experience clearly demonstrates impaired mentation with less severe degrees of hyperventilation, it is not clear whether this impairment represents impairment of tissue oxygenation or some effect of tissue alkalosis and transcellular ionic shifts. Clinically, inducing such extreme levels of hypocapnia is almost never necessary, and $PaCO_2$ levels below 25 mmHg are best avoided except in extraordinary circumstances. The routine use of profound hypocapnia in all neurosurgical settings should undergo reevaluation.[153,154]

Arteriolar tone, set by the systemic arterial blood pressure, modulates the effect of $PaCO_2$ on CBF. Moderate hypotension blunts the ability of the cerebral circulation to respond to changes in $PaCO_2$, and severe hypotension abolishes it altogether (Fig. 2.11).[155] Conversely, $PaCO_2$ modifies pressure autoregulation, and from hypercapnia to hypocapnia there is a widening of the "autoregulatory plateau" (Fig. 2.12).[156]

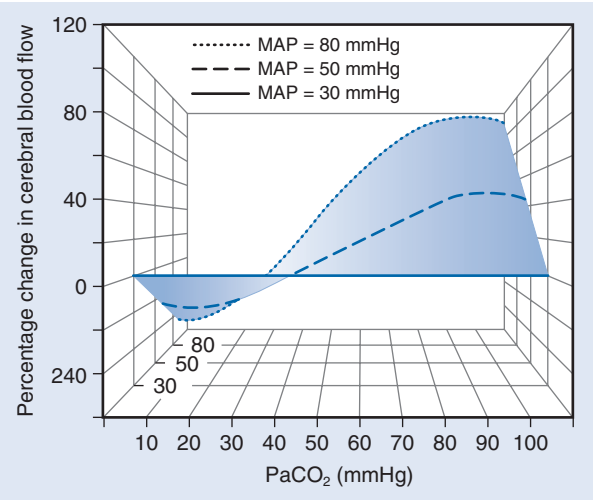


Fig. 2.11 Influence of blood pressure on CBF response to $PaCO_2$. Effects of alteration in $PaCO_2$ on cortical blood flow in dogs with normotension (mean arterial pressure [MAP]: 80 mmHg, *upper trace*), moderate hypotension (50 mmHg, *middle trace*), and severe hypotension (30 mmHg, *lower trace*). *(From Harper AM: The interrelationship between a Pco-$_2$ and blood pressure in the regulation of blood flow through the cerebral cortex. Acta Neurol Scand Suppl 1965;41:94–103. Modified from McCulloch J. In Knezevic S, Maximilian VA, Mubrin Z, et al (eds): Handbook of Regional Cerebral Blood Flow. Hillsdale, Lawrence Erlbaum Associates,1988, page 1, using data from Harper AM: Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiatry 1966;29:398–403.)*

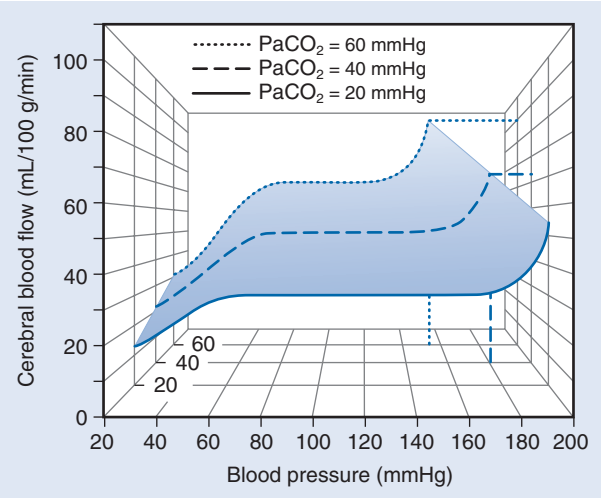


Fig. 2.12 Influence of $PaCO_2$ on pressure autoregulation of cerebral blood flow. *(Modified from Paulson OB, Strandgaard S, Edvinsson L: Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990;2:161–192.)*

There might be gender-based differences in CO_2 reactivity due to the underlying levels of prostaglandins. For example, suppression of prostaglandin synthesis by indomethacin treatment causes a greater attenuation of CO_2 reactivity in premenopausal women than in men.[157] $PaCO_2$ responsiveness also varies by region.[158] This difference may be due to the relative metabolic requirements present in each area, but this mechanism is not understood. Healthy female subjects demonstrated a greater increase in MCA flow velocity after 5% CO_2 inhalation than male subjects. This finding confirms a gender-dependent response to CO_2 in healthy subjects.[159] Decreased CO_2 reactivity can be a function of local decreases in CPP distal to a spastic or stenotic vessel. In addition, it may reflect deranged metabolism or structural damage in a number of disease states, including head injury,[160] SAH,[161–163] and ischemic cerebrovascular disease.[163] In comatose patients, impaired CO_2 reactivity suggests a poor prognostic outcome.[164]

Oxygen

Within physiologic ranges, PaO_2 does not affect CBF. Hypoxemia, however, is a potent stimulus for arteriolar dilation,[165] as a result of tissue hypoxia and concomitant lactic acidosis, although the precise mechanism is unclear. Vasodilation in response to hypoxia probably involves adenosine and KATP channels.[166] CBF begins to increase at a PaO_2 of about 50 mmHg and roughly doubles at a PaO_2 of 30 mmHg. States that impair CO_2 reactivity are likely to interfere with O_2 reactivity as well. The response of CBF to changes in both PaO_2 and the oxygen content of blood is shown in Fig. 2.13. Hyperoxia decreases CBF, producing a modest 10% to 15% decrease at 1 atmosphere. Hyperbaric oxygenation in humans decreases CBF, but high atmospheric pressure alone probably does not affect CBF.[167]

Temperature

As is true for other organ systems, cerebral metabolism decreases with diminishing temperature. For each 1 °C decrease in body temperature, $CMRO_2$ drops by approximately 7%. Alternatively, this relationship may be characterized by the metabolic temperature coefficient, *Q10*, which is defined as the ratio of $CMRO_2$ at temperature T, divided by the $CMRO_2$ at a temperature that is 10 °C lower (T – 10). The value for cerebral Q10 in the physiologic range of 27° to 37 °C is between

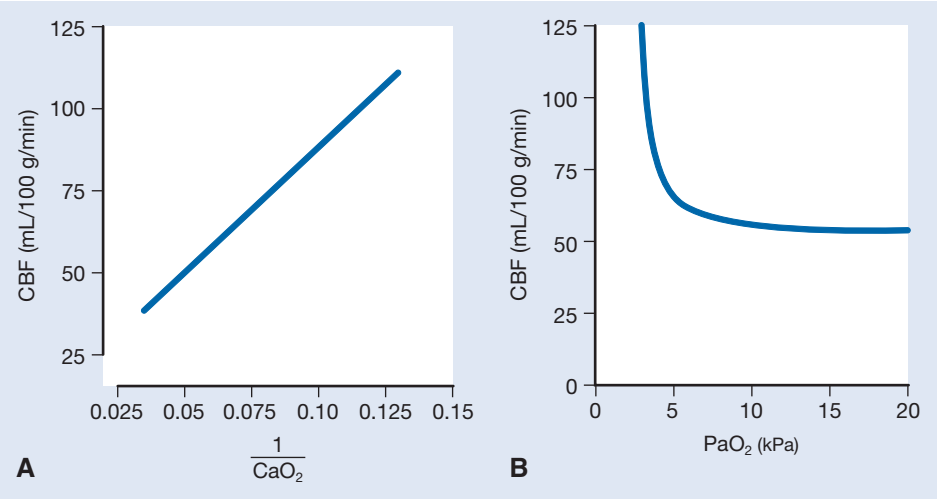


Fig. 2.13 Influence of oxygen content (CaO_2) and PaO_2 on cerebral flood flow (CBF). **A,** CBF is inversely proportional to CaO_2. **B,** Replotting the straight line in **A** by applying a sigmoid O_2 dissociation curve and taking the reciprocal produces the more familiar asymptotic curve of PaO_2 versus CBF, which disguises the dependence of CBF on CaO_2. 5 kPa is approximately 40 mmHg. *(Redrawn by Lesser PJA, Jones JG. In Scurr C, Feldman S, Soni N [eds]: Scientific Foundations of Anaesthesia: The Basis of Intensive Care, 2nd ed. St. Louis, Mosby, 1990, page 205; from original data reported by Brown MM, Wade JPH, Marshall J: Fundamental importance of arterial oxygen content in the regulation of cerebral blood flow in man. Brain 1985;108:81–93.)*

2.0 and 3.0.[168] Below 27 °C, however, Q10 increases to near 4.5. This finding has been explained on the basis of the neuroelectrical effects, wherein the major suppression of neuronal function occurs between 17 ° and 27 °C. Thus the lower Q10 between 27 ° and 37 °C simply reflects the decrease in the rates of biochemical reaction (basal $CMRO_2$), and the higher Q10 between 17 ° and 27 °C is due to the additive effect of the decrease in neuronal function.[151,168] Because moderate hypothermia, without major suppression of neuronal functions, provides better neuroprotection than isoelectric doses of barbiturates, identifying the biochemical mechanisms that contribute to basal $CMRO_2$ is important.[169]

The regulation of CBF is known to be closely coupled to cerebral metabolism and it is not surprising that this hypothermia-induced reduction in $CMRO_2$ is reflected by a parallel decrease in CBF. Some heterogeneity is found in this response, however; so CBF changes are most apparent in the cerebral and cerebellar cortex, less apparent in the thalamus, and not significant in the hypothalamus and brainstem.[170]

Intraoperative hypothermia is most often encountered during cardiopulmonary bypass. CBF in this setting has been shown to correlate with nasopharyngeal temperature, with a maximum 55% reduction in CBF occurring, in one study, at the lowest measured temperature, 26 °C. This finding corresponds to a 56% calculated reduction in $CMRO_2$.[171] $CMRO_2$ continues to decrease with further lowering of temperature up to the point of EEG silence. In dogs, this level is reached at 18 °C. CBF during cardiopulmonary bypass with profound hypothermia (18° to 20 °C) is disproportionately maintained[172] and is determined by arterial blood pressure and not pump flow rate.[173,174] However, during rewarming, CBF velocity remains lower than the prebypass value, probably because of hypothermia-induced changes in the cerebral vasculature. A period of cold full-flow reperfusion may improve cerebral perfusion during rewarming.[175]

The effects of hypothermia and anesthetic drugs may be additive to the point at which EEG activity ceases. Thiopental administered during hypothermia in doses that enhance the hypothermia-induced suppression of EEG activity produces a further reduction in $CMRO_2$, which is paralleled by an additional decrease in CBF. Although similar effects on $CMRO_2$ can be brought about by isoflurane, no additional drop in CBF appears to take place.[176]

Autoregulation, as well as CO_2 reactivity, is well preserved during cardiopulmonary bypass at moderate hypothermia.[171] Some investigators suggest, however, that autoregulation may become impaired if the CO_2 content of blood is allowed to rise. This effect can occur when exogenous CO_2 is administered to provide a "normal" $PaCO_2$ corrected to the patient's actual temperature during "pH-stat" acid–base management.[177] Recalculating the $PaCO_2$ at 37 ° C for "alpha-stat" acid–base management reveals patients so treated to be markedly hypercapnic, which explains the grossly elevated values of CBF reported in some cardiopulmonary bypass studies.[178,179]

Pharmacology

Dose-related anesthetic or drug effects (eg, isoflurane, desflurane, and sevoflurane) can alter vasoactive responses just as blood pressure and CO_2 do (Fig. 2.14).[180,181] The significant vasodilatory effects of volatile anesthetic agents are apparent

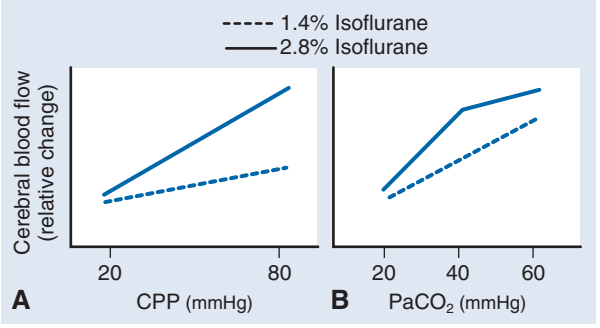


Fig. 2.14 Influence of vasodilators on blood pressure autoregulation and CO_2 reactivity in the isoflurane-anesthetized dog. Comparing 1 and 2 MAC isoflurane: **A,** With changing cerebral perfusion pressure (CPP), autoregulation for blood pressure is not as efficient, and cerebral blood flow (CBF) flow appears to increase more between 20 and 40 mmHg than between 40 and 60 mmHg. **B,** However, CBF increases at each of the three levels of $PaCO_2$ (at 1 MAC isoflurane). With 2 MAC isoflurane, CBF increases only between 20 and 40 mmHg. Presumably the circulation is maximally vasodilated at 2 MAC isoflurane and a $PaCO_2$ of 40 mmHg, so that raising $PaCO_2$ to 60 mmHg has less of an effect on total cardiovascular resistance. *(Redrawn from data in McPherson RW, Brian JE, Traystman RJ: Cerebrovascular responsiveness to carbon dioxide in dogs with 1.4% and 2.8% isoflurane. Anesthesiology 1989;70:843–850.)*

at minimum alveolar concentrations (MACs) exceeding 1.5. At higher MACs, volatile anesthetic agents can blunt the CO_2 response or render CBF pressure passive. Absolute CO_2 reactivity is preserved during intraoperative use of a narcotic, such as fentanyl or remifentanil.[182] CO_2 reactivity is also preserved with intravenous propofol anesthesia. Total intravenous anesthesia with propofol and remifentanil generally preserves response to CO_2 and protects pressure autoregulation better than that with volatile anesthetic agents. Because of preserved flow-metabolism coupling, progressively increasing depth of propofol anesthesia results in a decrease in CBF. In contrast, volatile anesthetic agents in concentrations exceeding 1.5 MAC are associated with a disproportionate increase in CBF. Although intravenous anesthetic agents such as propofol seem to preserve flow-metabolism coupling better than volatile agents,[183] the addition of nitrous oxide further impairs flow-metabolism coupling.[184] In clinical practice, prophylactic mild hyperventilation is used to offset the vasodilatory effects of volatile anesthetics. Interestingly, intracarotid injections of intravenous anesthetic drugs in doses sufficient to cause burst suppression do not decrease blood flow, suggesting an uncoupling of blood flow and metabolism with intra-arterial injections.[185] The apparent loss of flow-metabolism coupling with intra-arterial injections of anesthetic drugs may be due either to the biomechanical effects of the injection or to direct vascular effects.

The effect of ketamine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist used with increasing frequency as an adjuvant intravenous anesthetic, on CBF is complex. In awake volunteers, sub-sedative doses of ketamine increased CBF and $CMRO_2$ in some brain regions. In anesthetized patients, however, these effects can be reduced by coadministration of benzodiazepines and controlled ventilation.[186] Ketamine did not abolish auto-regulation in normocapnic pigs.[187] Dexmedetomidine, an intravenous α2 receptor agonist, reduces CBF[188,189] but animal studies have demonstrated it does not decrease $CMRO_2$.[190] Dog studies suggest this may at least in part be a result of direct action on vasculature, not a result of systemic hypotension or decreased $CMRO_2$.[190]

Vasoactive drugs may affect different aspects of autoregulatory behavior, as illustrated by evidence that nitroprusside impairs the ability of the circulation to maintain CBF when CPP is lowered but not when CPP is increased.[191] Independent of autoregulatory impairment,[192] anesthesia with volatile drugs appears to result in a trend for CBF to decrease over time in animal models.[193–195] This does not, however, involve an effect on CSF pH. Not only do absolute flow levels decrease, but CO_2 responsiveness changes as well.[195,196] This time-dependent CBF decrease has been proposed to be operative during cardiopulmonary bypass in humans.[195]

The cause of these flow decreases (or, possibly, return to "normal") has not been adequately explained. Evidence that flow does not decrease in other carefully controlled studies raises the question that this time effect may be a methodologic artifact.[197,198] In conditions of temperature flux, declines in CBF during the initial period of cardiopulmonary bypass with the skull closed probably reflect temperature equilibration in the brain. Interestingly, however, with the skull open and direct monitoring of cortical temperature, there does not appear to be a lag during cooling and rewarming during cardiopulmonary bypass.[199]

Neurogenic Influences

Autonomic Nervous System

One of the most striking differences between the systemic and cerebral circulations is the relative lack of humoral and autonomic influences on normal cerebrovascular tone. The systemic circulation is regulated to a large extent by sympathetic nervous activity, but autonomic factors do not appear to control the cerebral circulation. Thus autonomic nerves are not necessary for regulatory responses, but they may modify these responses in several important ways.

The innervation of the cerebral vasculature is extensive,[200,201] involving serotonergic, adrenergic, and cholinergic systems of both intracranial and extracranial origin. The physiologic significance of this intricate and extensive system of innervation is not fully understood. One confounding factor in the interpretation of experimental studies is a marked interspecies difference in the CBF response to sympathetic stimulation.[202] Thus in monkeys, acute sympathetic denervation has no effect on CBF, but acute sympathetic stimulation reduces CBF during normotension and during hypertension. In cats and dogs, by contrast, sympathetic stimulation has no effect during normotension. However, when acute hypertension is induced in cats by aortic ligation, electrical stimulation of the cervical sympathetic chain attenuates the increase in CBF and decreases disruption of the BBB.[201]

Under normal circumstances, the presence of baseline sympathetic tone exerted on the cerebral vasculature in humans is controversial. The lack of baseline tone is supported by studies demonstrating that phentolamine-induced α-adrenergic receptor blockade does not affect CBF.[203] In contrast, Hernandez and colleagues[204] have demonstrated in monkeys that unilateral superior cervical ganglion excision leads to a 34% increase in CBF on the affected side, with no effect on autoregulation.

The effect of increased sympathetic tone on CBF in altered physiologic states, on the other hand, is well recognized. For example, using intense stimulation of the stellate ganglion in dogs, D'Alecy[205] could produce a decrease in CBF greater than 60%. Thus acute sympathetic stimulation can shift the autoregulatory curve to the right. Reflex increases in sympathetic tone have been shown to attenuate the transient increases in CBF that are observed during severe hypertensive episodes.[206] Sympathetic stimulation is also associated with a small decrease in the hyperemia seen during hypercapnia in normotensive rabbits.[207] The cerebrovascular effects are more pronounced during bilateral sympathetic nerve stimulation.[208] These effects are seen despite acidosis, which inhibits the release of norepinephrine.[209,210]

Sympathetic stimulation probably constricts the larger conductance and pial vessels, thereby interposing an additional "resistor" proximal to the arterioles. In those situations in which an increase in CBF occurs as a result of a rise in cerebral metabolic rate (ie, seizures), even bilateral activation of sympathetic nerves has no effect on CBF. In such situations, metabolic factors are the overwhelming determinants of CBF, with only a minimal contribution from the sympathetic nervous system.[211]

At the lower limits of autoregulation, sympathetic activity modifies the autoregulatory response of CBF to a decrease in arterial blood pressure (Fig. 2.15). At equivalent blood pressures, CBF is lower during hemorrhagic hypotension than during pharmacologically induced hypotension.[212] Thus when reflex sympathetic constriction of larger cerebral arteries in response to hypotension is prevented by acute surgical sympathectomy or α-adrenergic receptor blockade, CBF is better maintained because autoregulation is preserved to a MAP that is 35% of control, in contrast to 65% of control pressure in untreated baboons. This observation explains why drug-induced hypotension during anesthesia is better tolerated than hypotension resulting from hemorrhagic shock. Although never studied, the sympathetic stimulation that occurs with severe pain may also shift the autoregulatory curve to the right.

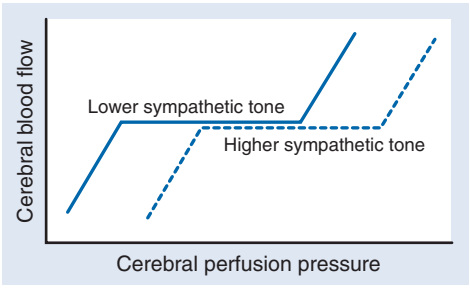


Fig. 2.15 Autonomic effects on autoregulation. Higher sympathetic tone, through the addition of a "proximal resistor" to the arteriolar bed, shifts the upper and lower ends of autoregulation to the right.

Parasympathetic fibers surround the vessels of the circle of Willis and the cortical pial vessels. These fibers contain a wide variety of vasodilatory mediators, which include substance P, neurokinin A, and CGRP, whose mechanism of action was discussed earlier. Stimulation of parasympathetic fibers promotes a vasodilatory reaction to ischemia. Thus in rats rendered ischemic by branch occlusion of the MCA, sectioning of these nerves has been shown to lead to a greater cerebral infarction volume.[213] Any protective effect, however, may be overshadowed by an increase in postischemic hyperemia mediated by stimulation of these same fibers.[214] Parasympathetic fibers may also attenuate cerebral hyperemia after release of carotid arterial occlusion. Parasympathetic vasoconstrictor response is probably mediated by neuropeptide Y.[215–217] Because of species differences, these results cannot reasonably be extrapolated to humans. In summary, despite extensive innervation of the intracerebral vessels, the purpose of these pathways currently remains unclear.

Local Neural-glial Regulation of Cerebral Blood Flow

There is an evolving paradigm shift in our understanding of local cerebral blood flow regulation. This new line of thought holds that input from neurons and glial cells, particularly astrocytes, regulates local blood flow directly by a "feed forward mechanism." This new paradigm downplays the traditional "local metabolite" theory of a "negative feedback" loop consisting of increased metabolic products leading to local vasodilation.[26] Evidence suggests that activation of neuronal NMDA receptors during glutamatergic excitatory neurotransmission leads to activation of nNOS and neuronal NO release. At least in the cerebellum, this NO appears to dilate cerebral vasculature directly.[218] In the cortex, neuronally-generated NO vasodilates nearby vessels by inhibiting production of 20-hydroxy-eicosatetraenoic acid (20-HETE), a vasoconstrictor, in neighboring astrocytes.[219]

Astrocytes reside between neurons and vascular smooth muscle cells with their endfoot processes wrapped around cerebral vessels, positioning them to serve as mediators of neurovascular communication. Several mechanisms have been suggested to describe how astrocytes may do this.[26] Perhaps most notably, it has been proposed that glutamate released from nearby neurons during excitatory neurotransmission activates astrocyte metabotrophic glutaminate receptors (mGlutRs), leading to an increase in intracellular calcium concentration and activation of phospholipase A2. This leads to an increase in arachidonic acid production from membrane phospholipids and an increase in prorelaxant prostaglandins (likely PGE_2) and epoxyeicosatrienoic acids (EETs), all of which are arachidonic acid metabolites.[220] Others have proposed that elevations in astrocyte calcium concentration activates large-conductance Ca^{2+}-activated K^+ (BK) channels in astrocyte endfeet, leading to release of K^+ on neighboring vessels. This local, modest increase in extracellular K^+ is purported to hyperpolarize vascular smooth muscle cells and limit Ca^{2+} entry via voltage-gated Ca^{2+} channels.[26,221]

In a seeming contradiction, elevations in astrocyte calcium concentration and the resultant generation of arachidonic acid can also cause vasoconstriction. This likely results from the conversion of arachidonic acid to proncontractile 20-HETE in vascular smooth muscle itself.[220] Whether astrocytes ultimately mediate prorelaxant or procontractile effects may depend on the existing vascular tone[222] and local O_2 concentration.[26]

AUTOREGULATORY FAILURE

Cerebral autoregulation is disturbed in a number of disease states. Most diseases that affect the CNS will, in one way or another, affect the ability of the circulation to regulate itself. Examples are acute ischemia, mass lesions, trauma, inflammation, prematurity, neonatal asphyxia, and diabetes mellitus. Despite a wide range of causes, the final common pathway of dysfunction, in its most extreme state, may be termed *vasomotor paralysis*.

What causes autoregulation to fail? The simplistic approach is to invoke tissue acidosis or local accumulation of "noxious metabolites," but it does not account for all cases. Localized damage that results in loss of autoregulation at sites distant from the injury is more difficult to explain.[223,224] Furthermore, Paulson and associates[22] coined the term "dissociated vasoparalysis" to describe retained CO_2 responsiveness with loss of autoregulatory capacity to changes in blood pressure.[156] This response can be observed in regions contralateral to tumor or infarction or during hyperperfusion after AVM resection.[225] Such a dissociation between two preeminent vasomotive stimuli emphasizes that pressure regulation is much more vulnerable than loss of CO_2 reactivity or, possibly, other metabolic influences on regulatory mechanisms. Total loss of CO_2 responsiveness is probably a preterminal event. A related phenomenon is *diaschisis,* the occurrence of hypoperfusion and hypometabolism remote from a damaged area.[226,227]

"False autoregulation" is an additional phenomenon that has been described in the setting of head injury.[223] In a paralyzed circulatory bed, pressure-passive increases in CBF may result in local pressure gradients in the most damaged areas. Local swelling may then keep CBF constant despite rising systemic pressures.

Autoregulatory failure (Fig. 2.16) can be divided into "right-sided" (hyperperfusion) and "left-sided" (hypoperfusion) autoregulatory failure. Although the following sections discuss the parenchymal consequences of dysregulation in a homogeneous light, there are differing regional susceptibilities to ischemia and circulatory "breakthrough." Portions of the hippocampus, for example, are exquisitely sensitive to ischemia. Previously this feature was thought to be simply a function of the basal metabolic state of the tissue—that is, the higher the metabolic rate, the more susceptible the tissue is to ischemia. However, this sensitivity undoubtedly involves other mechanisms.[228]

Hypoperfusion and Ischemia

Hypoperfusion leads to cerebral ischemia. However, there is no reason to believe that the fundamental metabolic consequences of reduced CBF to the neurons are any different for any of the various modes of flow reduction. The distinction of complete versus incomplete ischemia, however, may have

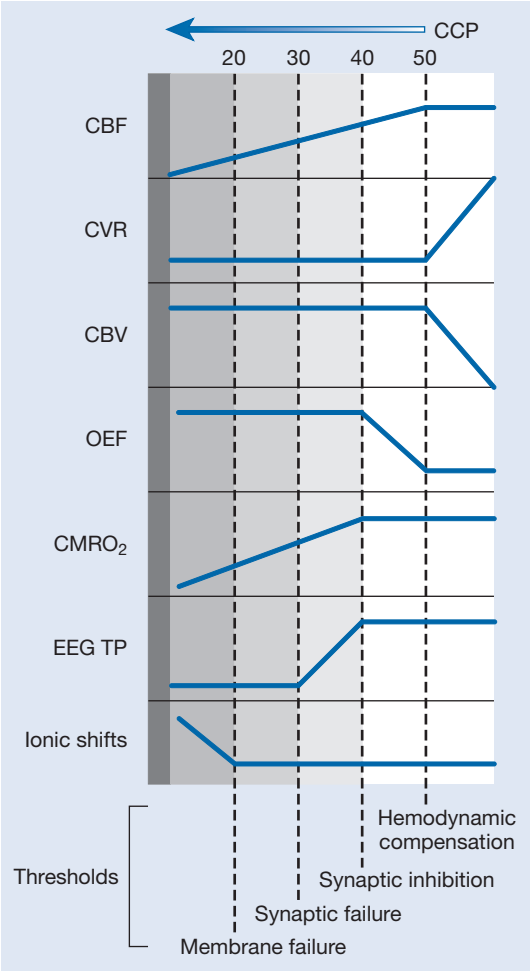


Fig. 2.16 Autoregulatory failure. The left side of Fig. 2.4 is expanded here to show idealized changes in various physiologic functions (some of the pathophysiologic events indicated overlap). The values for cerebral perfusion pressure (CPP) are only approximate, and many of the changes in the various covariates may overlap. They are stylized here for the sake of clarity. Cerebral blood flow (CBF), cerebrovascular resistance (CVR), cerebral blood volume (CBV), oxygen extraction fraction (OEF), cerebral metabolic rate for oxygen ($CMRO_2$), total power of the cortical EEG signal (EEG TP), and ionic shifts (eg, water and Na^+ into the cells and K^+ out of the cells) are shown along the *left* of the figure. The various CBF thresholds are indicated by the *broken lines* and labeled at the bottom of the figure. The functional state between thresholds is shown along the *bottom*. In this figure the loss of EEG power is still above the line for membrane failure. Clinically, any event that results in EEG signs of ischemia should be assumed to represent the potential for irreversible damage and should be treated accordingly. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

metabolic consequences, and, most importantly, regional or focal ischemia carries with it the possibility of collateral supply of CBF.

Fig. 2.16 is an idealized expansion of the left side of the autoregulatory curve shown in Fig. 2.4. As CPP decreases toward the lower limit of autoregulation (approximately 50 mmHg), arteriolar resistance vessels dilate and CBV increases. At the lower limit of autoregulation, however, the capacity for vasodilation is exhausted, the circulation cannot decrease resistance further to maintain flow, and CBF begins to decline passively as CPP decreases further. At first, an increase in oxygen extraction compensates for the passive decline in CBF. When oxygen extraction is maximum, $CMRO_2$ begins to diminish. Accordingly, synaptic transmission becomes impaired and eventually fails completely, as manifested by an isoelectric EEG. At this point, sufficient energy is available to keep the neurons alive, but neuronal "work" is abolished. Proceeding to even lower flow levels results in "membrane failure" (Na^+, Ca^{2+}, and water enter, and K^+ exits the cell; i.e., cytotoxic edema). Such reductions in CBF are in the lethal range and result in infarction if not corrected.

The development of cerebral infarction depends both on the degree to which flow is reduced to ischemic levels and on its duration (Fig. 2.17). Neuronal tissue can receive flow at a level that prevents normal function but does not result in permanent damage. If flow is returned to adequate levels, function returns. As shown in Fig. 2.17, two such states may exist, the penlucida, from which tissue recovers function irrespective of the ischemic time, and the penumbra, from which tissue is salvageable only if flow is restored within a certain time. The term penumbra, which means "almost shadow," was introduced by Branston and associates.[229] They originally used the term to denote all such tissue that was nonfunctional but that had the capacity to regain function. To make the distinction between tissue that survives without intervention and tissue that succumbs if left untended, Drummond and colleagues[230] designated the former as ischemic penlucida ("almost light").

Although any clinical event that results in EEG changes suggesting ischemia should be assumed to represent a threat for irreversible damage and should be treated accordingly, many such events probably reflect flow reduction to the penumbral range (see Fig. 2.16). An example of this phenomenon is the patient undergoing carotid endarterectomy in whom EEG changes suggesting ischemia develop after carotid clamping. With shunt placement, the EEG normalizes, and the patient awakens without sequelae.

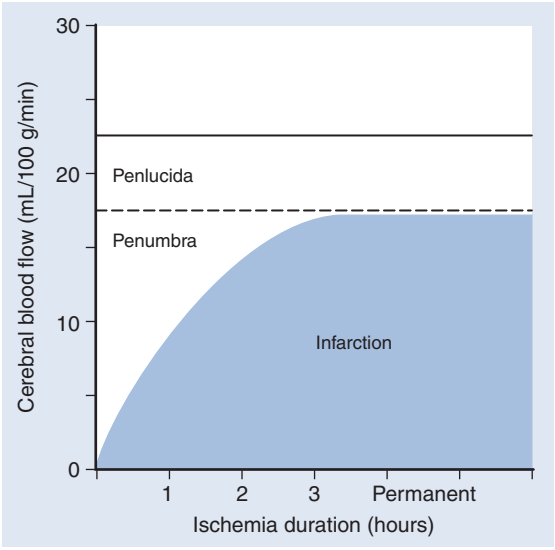


Fig. 2.17 Interaction of extent and duration of flow reductions on neurologic function. Tissue receiving flow between approximately 18 and 23 mL/100 g/min is functionally inactive, but function can be restored at any time with re-institution of increased perfusion (*penlucida*). For tissue perfused at lower blood flows, the development of infarction is a function of time. If tissue is restored to adequate perfusion before the time limit for infarction, it will recover function (*penumbra*). *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999; modified from data in Jones TH, Morawetz RB, Crowell RM, et al: Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981;54:773–782.)*

Hyperperfusion and Circulatory Breakthrough

If CPP exceeds the upper limit of autoregulation, flow initially increases with a fixed maximal arteriolar resistance. At some point, the arteriolar bed dilates under the increasing pressure, and the resistance falls as well. Clinically, one may observe brain swelling from this intravascular engorgement, vasogenic edema from opening of the BBB, and intracerebral hemorrhage from vessel rupture.[22,225,231] The different types of brain swelling and their primary fluid compartment alterations are shown in Table 2.1.

To explain the occurrence of postoperative brain swelling and intracerebral hemorrhage after AVM resection, the concept "normal pressure perfusion breakthrough" (NPPB)[232] or "circulatory breakthrough"[233] has been proposed. This theory holds that the low-resistance AVM shunt system results in arterial hypotension and venous hypertension in the relatively normal circulatory beds irrigated by vessels in continuity with feeding arteries and draining veins adjacent to the lesion. Regional CBF in these neighboring areas is kept in a normal range by appropriate autoregulatory vasodilation. This long-standing state of maximal dilation may result in vasomotor paralysis; the resistance vessels may no longer be capable of autoregulation should perfusion pressure increase. When the AVM fistula is interrupted, the pressure "normalizes" in the neighboring circulation. However, the presence of a vasomotor paralysis in newly normotensive circulatory beds prevents the appropriate increase in CVR necessary to maintain flow at a constant level, and cerebral hyperemia occurs. This hyperperfusion and abrupt increase in perfusion pressure may result in swelling and hemorrhage, although the precise mechanism is speculative. Postoperative swelling and hemorrhage after carotid endarterectomy[231] and after obliteration of a jugular-carotid fistula[234] are probably mechanistically related to normal pressure perfusion breakthrough.

Many of the aspects of "perfusion breakthrough" are controversial and supported by anecdotal evidence only. As observed in rats, 12 weeks after creation of carotid-jugular fistulas that result in chronic cerebral hypoperfusion, perfusion breakthrough occurs at a much lower systemic pressure than in normal animals (130 vs. 180 mmHg). This finding suggests that chronic cerebral hypoperfusion decreases the upper limit of autoregulation and could account for the pressure breakthrough phenomena when CPP is restored in hypoperfused vascular beds.[235] The syndromes of pressure breakthrough that result in postoperative catastrophes are clearly a clinical problem, but the precise mechanisms and relative importance of the contributing circulatory physiology remain to be elucidated.[236] Young and colleagues[237] reported that after AVM resection, cerebral hyperemia—not feeding artery pressure—was the predictor of "breakthrough" complications.[237] This finding argues against a simple hydraulic explanation of the breakthrough complications and points toward other possible causes.[238] There is growing interest in the notion that neuroeffector mechanisms[19,64] may participate in the pathogenesis of pressure breakthrough phenomena.

Table 2.1 Types of Brain Swelling

Type of Swelling	Primary Fluid Compartment Alteration
Cytotoxic	Shift of fluid from extracellular to intracellular space
Vasogenic	Shift of fluid from intravascular to extracellular space
Interstitial	Shift of cerebrospinal fluid into extracellular space
Hyperemic	Increase in intravascular volume

Reperfusion Injury

Many of the pathophysiologic events leading to irreversible neuronal damage are probably due to injury sustained during reperfusion of the ischemic tissue, perhaps as a result of reoxygenation.[239] Specifically in regard to CBF, the syndrome of delayed hypoperfusion is evident.[240]

The significance of the hypoperfusion in relation to neuronal damage is not clear. Most likely, CBF is grossly and appropriately coupled to a decreased metabolic rate after ischemia[241]; however, certain areas of the brain may be left with a mismatched CBF-metabolism ratio.[240] Adhesion of neutrophils to the vascular endothelium may also prevent restoration of tissue perfusion after cerebral ischemia. Mice deficient in intercellular adhesion molecules are relatively resistant to stroke following transient cerebral ischemia.[242] Reperfusion injury can also be mitigated by aminoguanidine, a selective inhibitor of inducible NOS, and ifenprodil, a polyamine site *N*-methyl-D-aspartate (NMDA) receptor antagonist.[243,244]

Hemodynamic Considerations during Autoregulatory Failure

Cerebrovascular Reserve

If cerebral vessels are stenotic, specific areas may have reduced inflow pressure. These regions often follow the distribution of a main arterial supply, such as the anterior, middle, or posterior cerebral arteries, or may be limited to a smaller distribution. Distal to an area of stenosis, a drop in perfusion pressure occurs, and, thus, even at normal systemic blood pressure, the arterial bed distal to the stenosis is relatively hypotensive and may operate near or on the pressure-passive area of the autoregulatory curve (see Figs. 2.4 and 2.16). The resting flow to a tissue bed may be normal, but there is no further potential for vasodilation if a drop in perfusion pressure occurs. Therefore these areas have an exhausted "cerebrovascular reserve,"[245] that is, the capacity for further vasodilation and maintenance of flow at appropriate levels. A way to assess cerebrovascular reserve is by challenging the circulation with a vasodilator. Clinically, both acetazolamide and CO_2 are used.[246]

In structurally normal regions (by MRI or CT scans) that have decreased vasodilatory response to such challenges, one may infer that the perfusion pressure is decreased. Application of this sort of testing has been proposed, for example, to determine which patients might benefit from extracranial-to-intracranial revascularization procedures or to assess the effects of an acute arterial occlusion. Use of such methods, however, is still in its infancy in clinical practice. PET[247] and single-photon emission computed tomography (SPECT)[248] may ultimately provide more sensitive measures by simultaneously determining the ratio of CBF to CBV as an index of cerebrovascular reserve.

CBF is often lower in patients with cerebrovascular disease than control levels. Clinically asymptomatic patients with risk factors for cerebrovascular disease can have reduced CBF and CO_2 reactivity.[249] These reductions do not necessarily depend on the presence of angiographically demonstrable vessel occlusions. The mechanism of these flow reductions and impaired vasomotion remains to be elucidated.

Newer theories on the pathogenesis of stroke in sickle cell disease combine elements of the concepts discussed in this

and previous sections concerning hemodynamic regulation. Pavlakis et al.[248] and Prohovnik et al.[250] have proposed that the pathogenesis of infarcts in patients with sickle cell disease is due to large proximal vessel occlusion with a resultant drop in distal perfusion pressure; the distal irrigation of major vascular territories (eg, MCA) is rendered hypotensive. These patients, however, have already exhausted their arteriolar vasodilatory capacity to compensate for decreased oxygen delivery resulting from the anemia. Watershed infarcts are the clinical result.

Cerebral Steal

A concept related to reserve is cerebral "steal." Steal is a colorful but physiologically misleading term.[251] It refers to the decreased flow to ischemic areas caused by blood vessel dilation in nonischemic areas, such as can be induced by hypercapnia.[252] Blood is "stolen" from one area and given to another only if a pressure gradient exists between the two circulatory beds. Cerebral steal is also said to occur in patients with cerebral AVMs in whom significant blood flow occurs through the lesion and results in progressive focal neurologic symptoms. However, in a large sample of patients with AVM, no pressure gradient between feeding and nonfeeding vessels to the lesion could be demonstrated, raising debate about whether steal is responsible for neurologic symptoms in such patients.[253]

If an ischemic area is maximally vasodilated, the addition of CO_2 causes vasodilation of normal adjacent brain regions and may result in a net decrease in flow, presumably by lowering local input pressure, to the ischemic focus. Conversely, vasoconstriction in the normal brain may result in redistribution of blood to ischemic regions, a condition referred to as *inverse steal* or the Robin Hood effect. This mechanism may also be operative for other cerebral vasodilators, such as volatile anesthetics, and systemic vasodilators, such as nitroprusside, hydralazine, and nitroglycerin, although data are lacking on the clinical importance of all such interactions.

Vessel Length and Viscosity

After exhaustion of vasodilatory capacity, flow is both pressure passive and highly dependent on vessel length and blood viscosity (primarily determined by hematocrit).[137] Thus with maximal distal vasodilation, the areas with the lowest pressure resulting in hypoperfusion are those farthest from the arterial input. This concept is important clinically because brain regions that are farthest from their arterial input, watershed areas (such as the border between the arterial distributions of the MCA and ACA), are the regions most likely to become ischemic during systemic hypotension.

Viscosity reduction is also pertinent to the prevention or treatment of cerebral vasospasm in patients with aneurysmal SAH.[254] Although the conductance vessels (as visualized angiographically) are seen to be in spasm (with a large pressure drop across constricted segments), the distal resistive bed may be maximally vasodilated.[255] In Eq. 2.2, therefore, the resistance term can no longer be influenced by changing vessel caliber. Because the vessel length term stays fixed, only blood viscosity can potentially affect CVR, provided that oxygen-carrying capacity is not adversely affected.[137] In the clinical setting, however, the relative influence of hemodilution on the improved outcome with volume loading remains to be determined.

Excessive hemoglobin concentration may produce a hyperviscous state. Although polycythemia decreases CBF and is a risk factor for thromboembolic stroke, uniform guidelines for phlebotomy are lacking in clinical practice. Certainly patients with hematocrit values in excess of 60% should be anesthetized only in urgent circumstances.

Collateral Failure

After carotid occlusion in a patient with a normal cerebral circulation, the vessels in the ipsilateral hemisphere experience a fall in input pressure; accordingly, the resistance network of arteriolar vessels undergoes vasodilation. This response allows collateral blood flow from a patent circle of Willis or other channels to compensate and restore perfusion. However, if these channels do not exist or the affected resistance vessels are already maximally vasodilated, no compensation occurs, and a condition of cerebral ischemia ensues.

THERAPY FOR ENHANCING PERFUSION

Induced Hypertension

Rationale

Maintenance of a high perfusion pressure, in concert with optimal viscosity and oxygen delivery, may reduce cell death in a threatened vascular territory. As reviewed by Young and Cole,[134] ample experimental evidence is given for this strategy in the form of improvements in cerebral perfusion, electrophysiologic evoked responses, and histopathologic and neurologic outcomes. By augmenting systemic perfusion pressure, one can mitigate the pressure drop across a stenotic vessel or collateral pathway to an ischemic area (Fig. 2.18).[256] Even small increases in CBF may shift a region from the penumbra (destined for infarction) to the penlucida and perhaps to a level of perfusion enabling normal function. However, the hazards of induced hypertension include worsening ischemic (vasogenic) edema and transformation of a pale infarct into a hemorrhagic one. If blood pressure is used to increase CPP during brief periods of carotid or intracranial artery occlusion,[252,257] these concerns are less important. However, pharmacologically induced hypertension with any attendant tachycardia would raise the risk of cardiac ischemia; hence, α-adrenergic agonists may be preferable in these settings.[258]

Applications

Application of induced hypertension during acute thromboembolic stroke is controversial[134] but has relevance to anesthetic practice. Elevation of blood pressure during carotid endarterectomy has been discussed for some time; many writers have recommended keeping blood pressure elevated during the period of temporary occlusion of the carotid artery.[252,259,260] Both anastomotic CPP,[259,260] as measured in the distal stump of the carotid artery after clamping, and CBF[252] are increased by elevation of systemic pressure. Fortunately, phenylephrine only minimally increases venous sinus pressure; therefore, during induced hypertension, the drug is unlikely to adversely affect CPP.[260] Despite claims that distal stump pressures do not correlate with CBF changes during carotid endarterectomy,[261] the technique is a simple, low-risk, and cost-effective method to assess the adequacy of CPP.[262] False-negative results may occur (ie, normal stump pressure with inadequate CBF); however, if the angiogram demonstrates normal intracranial vessels, a severe stump pressure reduction (ie, 20 mmHg) is potentially useful information.

An evolving practice during neurovascular surgery is the use of temporary vascular occlusion to secure cerebral aneurysms.[263] Temporary occlusion techniques require some modification of the traditional anesthetic management of cerebral aneurysm clipping.[257,264] During temporary vascular occlusion of a major intracranial artery, not only must systemic hypotension be avoided but blood pressure augmentation may also be necessary.[134,256,265]

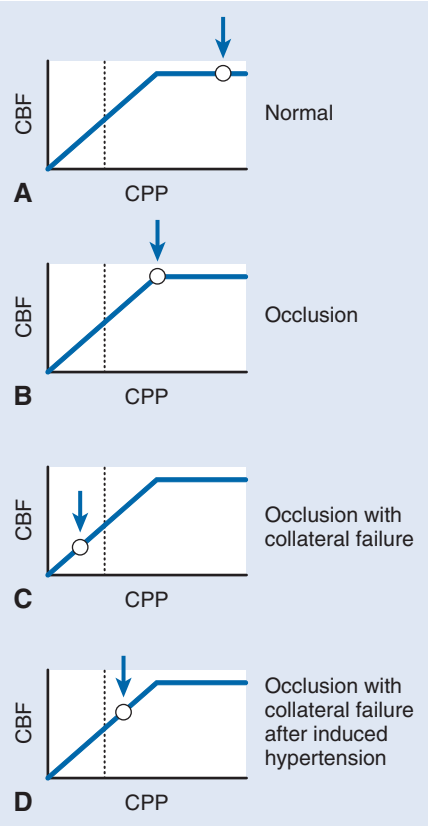


Fig. 2.18 Induced hypertension model. **A,** Normal. *Arrow* indicates operating point on the autoregulatory curve; in this case, the circulatory bed is in mid-position in the full range of autoregulation. Lower limit of autoregulation is the knee of the curve. *Dotted vertical line* represents the ischemic flow threshold. **B,** Inflow occlusion. If a major inflow channel to this vascular territory is interrupted, input pressure drops in the resistive bed. Autoregulatory function now adjusts for this decrease in input pressure by vasodilation of the bed. How much the input pressure falls after the major inflow occlusion is determined by the number and caliber of available collateral vascular pathways. In the example shown, there is sufficient collateral perfusion pressure (CPP) to keep the operating point above the threshold for ischemia, although the operating point has entered the pressure-passive range (ie, this bed is maximally vasodilated). **C,** Inflow occlusion with collateral failure. If one assumes atresia or stenosis of collateral pathways (high collateral resistance), then, with occlusion of the major inflow channel, input pressure drops to a much lower level distal to the occlusion. Cerebral blood flow (CBF) is lower because the drop in pressure has exhausted the ability of the resistive bed to compensate by further vasodilation. Now the operating point is below the ischemic threshold. This situation demands treatment. **D,** Augmentation of CPP. At this point, systemic mean arterial pressure is increased. Pressure transmitted across the collateral pathways, although not sufficient to restore normal pressure in the ischemic bed, is sufficient to raise input pressure, allowing CBF to rise to just above the ischemic threshold (albeit still on the pressure-passive point on the curve). This small shift above the ischemic threshold may be crucial in determining the final extent of the infarct and the ultimate functional outcome after an ischemic event. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

Induced hypertension has been used in the management of aneurysmal SAH.[266–268] In this setting, hypertension is employed in conjunction with hypervolemic hemodilution; thus the relative contribution made by raising perfusion pressure is not well defined.[269]

Inverse Steal

Undoubtedly, inverse steal can redistribute CBF to ischemic areas, as demonstrated unequivocally in animal studies.[270] Ideally, in clinical settings the treatment should be tailored to individual patients' responses, which are likely to be more variable. A practical problem is the lack of bedside methods to assess regional cerebral perfusion.

Hypocapnia

The concept that hypocapnia can favorably influence CBF during ischemia is not new,[271–273] but not all investigators have been able to demonstrate favorable flow redistribution. Many of the early studies did not support a beneficial effect of hypocapnia.[274] Some of the early animal models used prolonged ischemia that could have masked benefits of hypocapnia.[275] Furthermore, human studies showing trends of improved outcome with hypocapnia lacked sufficient statistical power.[276,277] As in the case of induced hypertension in the setting of carotid endarterectomy, some early reports suggested that collateral perfusion pressure appears to improve in the presence of hypocapnia.[260,278,279] Since then, in the absence of demonstrable benefits of hyperventilation and hypocapnia, the emerging trend has been to maintain normocapnia with mild hypertension to improve collateral perfusion.

Pharmacologic Manipulation

Vasoactive drugs that cause constriction of the normal vasculature may produce a favorable intracerebral redistribution of CBF to an ischemic focus. In contrast, vasodilators would be expected to work in a fashion analogous to hypercapnia. However, no good evidence supports improvement in outcome from such an effect.

One of the mechanisms proposed for the salutary effects of barbiturates on focal ischemia has been the redistribution of CBF from normal to ischemic areas.[229,280] Despite this idea, the clinical role of barbiturates remains a controversial topic. Except in cardiopulmonary bypass, outcome studies are lacking, if not impractical.[141] Nevertheless, most authorities would agree that in the intraoperative setting, barbiturates are to be recommended in the setting of acute temporary focal ischemia. Whether steal or inverse steal has any bearing on clinical anesthetic management is open to debate.[281]

Augmenting CBF is often necessary in the settings of cerebral vasospasm. Both proximal and distal vasospasms are initially treated with hypertensive, hypervolemic hemodilution therapy. Endovascular interventions are usually reserved for drug-resistant vasospasm. There is emerging evidence that vasospasm in the proximal and distal cerebral arteries may require different interventions.[282] Proximal vasospasm is often better treated with mechanical stenting that has a sustained benefit, whereas distal vasospasm is best treated with intra-arterial vasodilator therapy. Intra-arterial papaverine has been the mainstay of such treatment.[283,284] Owing to transient neurologic complications, calcium channel blocking drugs, such as verapamil and nicardipine, are emerging as alternatives to papaverine.[284–287] Because of the risk of increased ICP with intra-arterial vasodilator therapy, optimum treatment of cerebrovascular insufficiency during vasospasm requires monitoring of ICP.[288]

Intra-Arterial Drug Delivery

Advances in endovascular surgery now permit highly targeted intra-arterial delivery of drugs for the treatment of a variety of brain diseases.[284,285,289,290] However, the keys to effective drug delivery to the brain are the careful adjustment of bolus characteristics (volume and concentration) and, if possible, the careful transient reduction of CBF.[291–294] Although computer simulations and experimental evidence suggest that the increase in regional blood flow will raise the local concentrations of intra-arterial drug, there is no clinical consensus yet

as to the role of blood flow manipulations in augmenting drug deposition in brain tissue.[293,295–299] In the treatment of brain tumors, doses of intra-arterial drugs are often increased with greater regional blood flows so as to increase the maximum dose that can be safely delivered.[298] In other centers, cardiac output, and thereby CBF, is increased during intra-arterial chemotherapy to enhance local delivery.[300] One of the fundamental challenges in the understanding of drug kinetics is the inability to determine tissue drug concentrations within the short time it takes for the drug to transit the cerebral circulation.[301] Modern optical technology promises to overcome this limitation with tissue-noninvasive, high-speed drug concentration measurements.[302–304] Another, major hurdle to intra-arterial delivery of drugs is the precise control of BBB disruption.[305] Intra-arterial mannitol is often used to disrupt the BBB.[306] Reducing CBF seems to augment dose response to intra-arterial mannitol.[307] Monitoring CBF, therefore, is likely to play a critical role in the understanding of the kinetics of intra-arterial drugs and improvement of drug delivery. Intra-arterial drug delivery is likely to be used for delivery of "smart" neuropharmaceuticals and stem cells.

MEASUREMENT OF CEREBRAL BLOOD FLOW

The choice of CBF measurement method depends on many considerations: local availability of equipment and expertise, cost, subject (human vs. animal), desired anatomic resolution, and so on (Table 2.2). The method used is important because it determines the range of normal and pathologic values, the anatomic specificity or resolution, and the set of assumptions necessary for interpreting the data. A particularly important consideration is the ability to perform repeated measures in a given patient or subject. Historically important methods including the Kety-Schmidt technique, arteriovenous difference in oxygen content, hydrogen clearance, autoradiography, radioactive xenon, radioactive microphsheres, and xenon computed tomography are briefly reviewed in Table 2.2 and in Figs. 2.19 to 2.23. For a general review of CBF methods, including historical aspects, see Bell.[1]

Positron Emission Tomography

Current PET technology allows precise imaging of glucose and oxygen metabolism, CBV, CBF, pH, numerous presynaptic and postsynaptic receptor and transmitter events, and protein synthesis.[247,308] For example, critical reduction in CBF after SAH can be assessed by studies using ^{15}O-labeled water ($H_2{}^{15}O$).[309,310] ^{11}C-labeled flumazenil may be able to demonstrate irreversible cell damage after ischemic brain injury.[311] However, disadvantages of this technique include its cost and complexity.[312–315]

Certain unstable radioisotopes decay by producing positrons, which are equal in mass to an electron but have the opposite charge. After a few millimeters' travel through the tissue, the positron encounters an electron, and mutual annihilation takes place. This collision results in the formation of two γ energy photons, which are emitted in exactly opposite directions. By recording the simultaneous arrival of these photons on each side of the head with electronically linked coincidence detectors, one can reconstruct tomographic, three-dimensional images of tracer activity. An advantage of this method is that it controls for tissue scattering because random deflections result in the loss of coincidence.

The resolution of PET is excellent (≤1 cm), but limitations of current instruments include the fact that point sources of tracer activity cannot be perfectly separated. Reconstruction of the image results in partial volume averaging; that is, the radioactivity is smeared somewhat, and any activity in a region of interest is partially contaminated by adjacent regions. The ability to discern point sources in brain imaging is referred to as full-width, half-maximum (FWHM), which denotes the separation between two point sources required for the instrument to discern them.

Isotopes currently used are those that can be incorporated into naturally occurring organic molecules (eg, ^{11}C, ^{13}N, and ^{15}O) or isotopes that can be used to label biologically occurring molecules, such as ^{18}F. The positron-emitters are all short lived and, except for ^{18}F, require on-site production with a cyclotron. The short half-life allows repeated studies and enables large doses to be used without excessive radiation exposure for the patient.

Measurement of CBF with the use of several tracers and techniques has been described. The earliest method developed used inhaled ^{15}O-labeled CO_2. The ^{15}O (half-life 123 seconds) is rapidly transferred to $H_2{}^{15}O$ by carbonic anhydrase in the RBCs. After 10 minutes, tracer entry into brain is in equilibrium, with venous outflow and radioactivity decay. The arterial input function is assessed from peripheral blood. With use of the model described previously for tissue autoradiography, CBF can be calculated. A variation of this approach is to use an intravenous infusion, thus avoiding air passage artifact. Several variations using bolus injections have also been proposed. Alternative tracers include ^{18}F-fluromethane and ^{15}O-butanol.[30] Albumin microspheres have also been used.[316] The many methodologic issues are beyond the scope of this chapter, but partition coefficient and the flow limitations of $H_2{}^{15}O$ as a tracer are some of the drawbacks of current PET CBF studies.

Single-Photon Emission Computed Tomography

SPECT is the image produced by gamma scintillation counting (like two-dimensional ^{133}Xe methods) that is reconstructed in three dimensions by some form of rotating or moving camera (Fig. 2.24).[317] It is a general term, and any camera that views an organ from more than one angle and uses a computer to achieve tomographic reconstruction may be considered a SPECT instrument. Most nuclear medicine departments have rotating gamma cameras that fulfill this definition. However, dedicated brain scanners that are specifically optimized for the intracranial cavity have become increasingly available. SPECT technology offers slightly less resolution than PET, yet has formidable anatomic specificity. Although it requires expensive hardware and software, it is significantly cheaper than PET. The full-width, half-maximum value with newer generation devices (7 to 9 mm) approaches that of PET scanners. Scattered radiation problems and partial volume effects produce inherent problems with data analysis.

For perfusion imaging, the only tracers that currently can be reliably quantitated are Xe isotopes. Although ^{133}Xe can be used, it provides poor resolution, and ^{127}Xe is preferable because of its higher energy. Unfortunately, however, ^{127}Xe has a significantly longer half-life. Administration and CBF calculations are roughly similar to those for the two-dimensional ^{133}Xe methods.

One may also use lipophilic tracers that are taken up by the tissue in proportion to flow and then trapped or bound. These include, at present, SPECTamine (*N*-isopropyl-$^{123}{}_{\text{I-p}}$-iodoamphetamine) and Ceretec (^{99m}Tc-HMPAO, a propylene-amine oxime).[318] SPECT tracers are generally heavier metallic elements with longer half-lives (hours) that decay by single-photon γ emission, as opposed to PET tracers, which are low-atomic number organic elements with

Table 2.2 **A Comparison of Cerebral Blood Flow Measurement Methodologies**

Methodology	Human (H) or Animal (A)	Relative Cost[†]	Resolution	Time Scale	Repeated Measurement Possible?	Invasiveness	Tracer(s)	Radiation?	Relative Flow Values[‡] (mL/100 g/min unless noted)
Hemispheric									
Kety-Schmidt	H	+	Hemispheric	15 min	Yes	Jugular puncture	N_2 ^{133}Xe ^{83}Kr	No Yes Yes	50
$AVDO_2$	H	+	Hemispheric	<1 min	Yes	Jugular puncture	NA	No	Relative change
Two-Dimensional Clearance									
Intracarotid ^{133}Xe	H	+	3–4 cm cortical[§]	<1 min for gray matter 3–11 min for white matter	Yes	Carotid puncture or transfemoral catheter	^{133}Xe	Yes	80 gray matter 20 white matter 50 initial slope index (mean hemispheric flow)
Intravenous ^{133}Xe	H	+	3–4 cm cortical	3–11 min	Yes	IV	^{133}Xe	Yes	As intracarotid ^{133}Xe
Inhaled ^{133}Xe	H	+	3–4 cortical	3–11 min	Yes	No	^{133}Xe	Yes	As intracarotid ^{133}Xe
Thermal clearance	H	+	<1–2 cm cortical	<1 min	Yes	Exposed cortex	Heat	No	Relative change
Hydrogen clearance	A	+	<5 mm cortical	<1 min	Yes	Exposed cortex, electrode placement	H_2	No	150–220
Cold xenon	H	+++	<1 cm, three-dimensional	Several minutes	Limited	No	sXe	Yes[¶¶]	
Perfusion-computed tomography	H	++	2–3 cm sections	Several minutes	Limited	IV	Iodinated contrast	Yes[¶¶]	
Positron emission tomography	H	++++++	<1 cm, three-dimensional	Several minutes per section level	Limited	IV	Short $t_{1/2}$, lighter-weight positron emitters; see text	Yes	50-70 gray matter 20 white matter
Single-photon emission computed tomography	H	+++	<1 cm, three-dimensional	Several minutes per section level	Limited	IV	(1) Longer $t_{1/2}$, heaver-weight γ emitters or (2) ^{127}Xe or ^{133}Xe; see text	Yes	Relative change for γ emitters; quantitive change for Xe

Perfusion-weighted magnetic resonance imaging, with contrast Gd-DTPA	H[¶]	+++	<1 cm, three-dimensional	Several minutes	Limited	IV	Gadopentate dimeglumine (Gd-DTPA)	Magnetic[¶¶]	
Perfusion-weighted magnetic resonance imaging Spin-labeling	H	++++	<1 cm, three-dimensional	Several minutes	Limited	None	None	Magnetic[¶¶]	
Autoradiography	A	++	<5 mm, three-dimensional	<1 min	No	Sacrifice	^{3}H, ^{14}C, ^{18}F	Yes	90–150gray matter 20–30 white matter
Other Methodology									
Microspheres	A	+++	<1 cm	<1 min	Yes	Sacrifice	^{153}Gd, ^{57}Co, ^{141}Ce, ^{51}Cr, ^{113}Sn, ^{103}Rd, ^{46}Sc, ^{85}Sr, ^{95}Nb	Yes	50–70 gray matter 20 white matter
Doppler Methods									
Laser Doppler flowmetry	H	+	<5 mm	<1 min	Yes	Exposed cortex	NA	Light	Relative changes
Transcranial Doppler ultrasonography	H	+	Hemispheric	<1 min	Yes	No	NA	Ultrasound	40–80 cm/s
Mixed Methodologies									
Sagittal sinus outflow	A	+	Hemispheric	<1 min	Yes	Sagittal sinus cannulation	NA	No	50

[†]Does not separate equipment investment from individual study cost.
[‡]Values are approximate normal values for rough comparison between methods; for precise details, refer to reference citations in text.
[§]Depends on detector size and collimator angle.
[¶¶]No radiation from the tracer, only from the scan itself.
[¶]No clinically approved tracers for tissue perfusion; current paramagnetic tracers are for transit time with rapid-sampling magnetic resonance imaging.
NA Not applicable

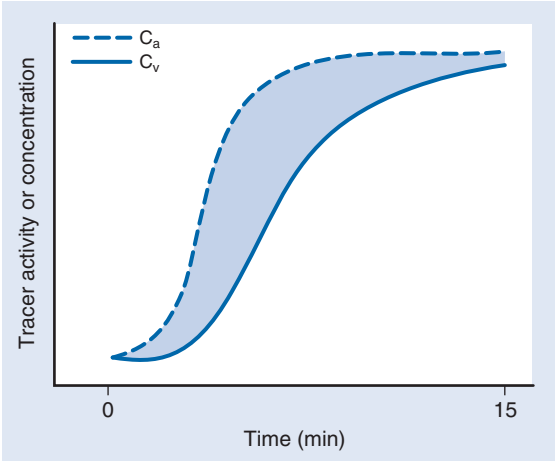


Fig. 2.19 Graphic depiction of the Kety-Schmidt cerebral blood flow (CBF) technique. A freely diffusible tracer is given until (theoretically) equilibrium exists between the arterial (C_a) and venous (C_v) concentrations. The area between the two curves is proportional to CBF.

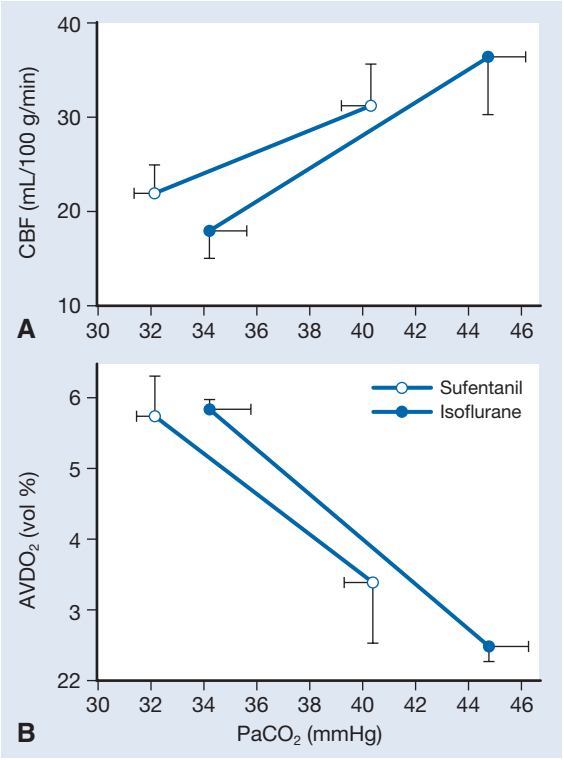


Fig. 2.20 **A** and **B,** Simultaneous cerebral blood flow (CBF) and arteriovenous difference in oxygen content ($AVDO_2$) measurements. Comparison of CBF and $AVDO_2$ values for sufentanil (*open circles*) and isoflurane (*closed circles*) anesthesia. The abscissa is $PaCO_2$ for both **A** and **B.** There was a significant effect of $PaCO_2$ concentration on the increase in CBF ($P < .0001$) and the decrease in $AVDO_2$ ($P < .001$); the product of CBF and $AVDO_2$, which reflects cerebral metabolic oxygen consumption, remained constant ($P = .364$). There was no significant difference in effect between anesthetics. *(From Young WL, Prohovnik I, Correll JW, et al: A comparison of the cerebral hemodynamic effects of sufentanil and isoflurane in humans undergoing carotid endarterectomy. Anesthesiology 1989;71:863–869.)*

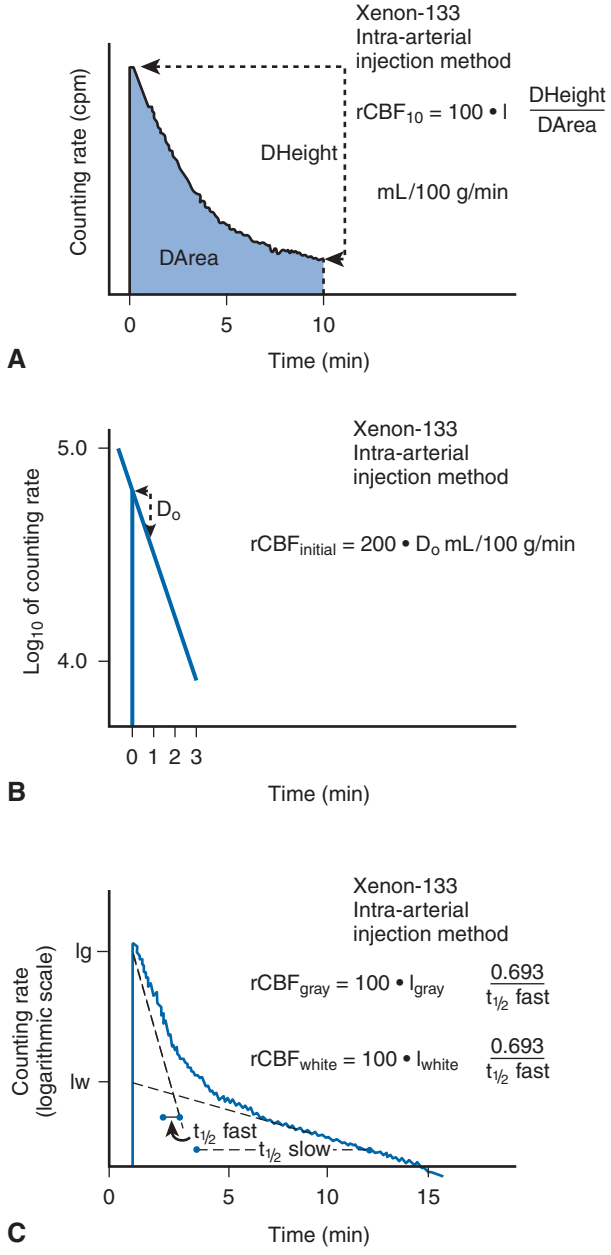


Fig. 2.21 Depiction of cerebral blood flow (CBF) calculations for the intracarotid radioactive (^{133}Xe) method. CBF indices used by the intracarotid method. **A,** Height-over-area determination of mean flow, based on integration of the area under the curve to 10 minutes. **B,** Initial slope estimate of gray matter flow obtained from the first minute of clearance on a semilog plot. The constant, 200, represents 100 times the product of λ (assumed to be 0.87) and the factor for converting base 10 to natural logarithms. **C,** Compartmental analysis, in which the curve is resolved into fast-clearing (gray matter) and slow-clearing (white matter) components, calculated from the half-times ($t_{1/2}$) on a semilog plot. cpm, counts per minute; D_0, determinants; rCBF, regional CBF. *(From Obrist WD, Wilkinson WE: Regional cerebral blood flow measurement in humans by xenon-133 clearance. Cerebrovasc Brain Metab Rev 1990;2:283–327.)*

short half-lives (minutes) decaying by positron emission. A problem with repeat SPECT studies in patients with subacute ischemic strokes is hyperfixation of ^{99m}Tc-HMPAO, which may lead to spuriously high subsequent estimates of CBF.[319] Technetium-99 m-L,L-ethyl cysteinate dimer (ECD) has been proposed as a chemical microsphere for SPECT studies. It has been shown that the ECD count density correlates with the regional CBF measurements with 133Xe SPECT.[320]

SPECT is increasingly being used for the diagnosis and management of cerebrovascular diseases, provides an early assessment of the hemodynamic effects of cerebral thromboembolism, and can be used with CO_2 or acetazolamide to assess cerebrovascular reserve.[321,322] It is being used with increasing frequency to assess the adequacy of collateral circulation before surgical procedures in which the internal carotid artery must be sacrificed, such as skull base tumor resection.

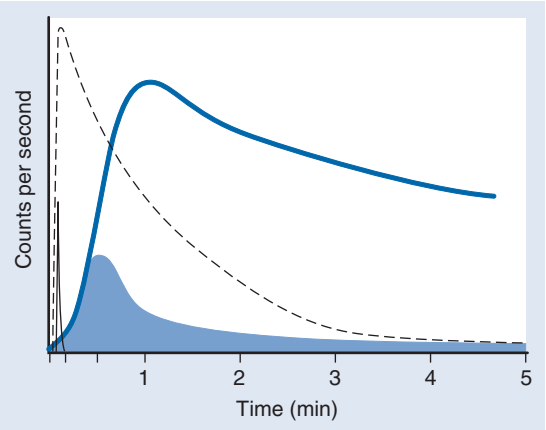


Fig. 2.22 Idealized input functions and washout curves recorded at the scalp after intracarotid and intravenous injections of radioactive xenon (^{133}Xe). Intracarotid head curve (*dotted line*) is shown with its input function (*shaded spike*), which is considered to be instantaneous and purely cerebral. Intravenous head curve (*solid line*) is accompanied by its input function (as recorded from continuous end-tidal sampling of expired ^{133}Xe), which is shared by extracerebral compartments. Note that the input function (*shaded curve* underneath) is delayed (and smeared). This results in a slower rise and decay of head curve activity after intravenous injection. Solutions for calculating cerebral blood flow rely on deconvolution of the head curve by the delayed input function. *(From Young WL, Prohovnik I, Schroeder TT, et al: Intraoperative ^{133}Xe cerebral blood flow measurements by intravenous versus intracarotid methods. Anesthesiology 1990;73:637–643.)*

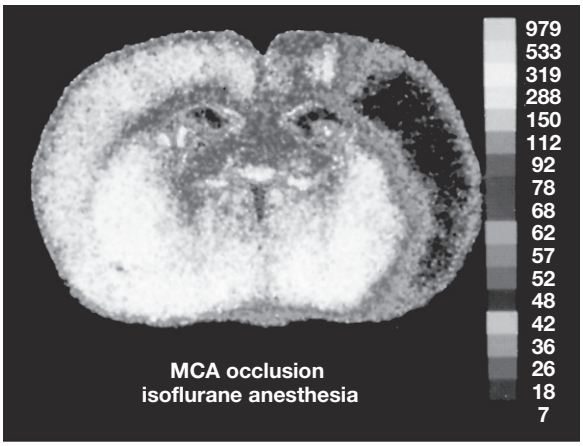


Fig. 2.23 Example of cerebral autoradiography. This coronal section of brain is from a rat that was subjected to middle cerebral artery (MCA) occlusion during isoflurane anesthesia. The lookup table, shown on the *right* side of the illustration, corresponds to flow units of mL/100 g/min. Note that the low-flow cortical infarct area is sharply delineated from the remainder of the section. *(Courtesy of Dr. David S. Warner, University of Iowa.)*

In addition to CBF, CBV can be assessed with plasma or RBC labeling.[145] Some units can image ^{18}F, offering the possibility of studying receptor systems and cerebral metabolism of glucose. Several single-photon-emitting receptor ligands are now becoming available for SPECT (for instance, dopaminergic [d_2], cholinergic, muscarinic, and some types of benzodiazepine and opiate receptors). ^{18}F has a longer half-life than most positron emitters, making it an appealing choice for use in centers with no on-site cyclotron.

Magnetic Resonance Imaging

MRI is becoming increasingly important to the study of vascular anatomy as MR angiography begins to supplant standard contrast X-ray techniques. Two approaches have evolved in determining blood flow with MRI. The first technique uses

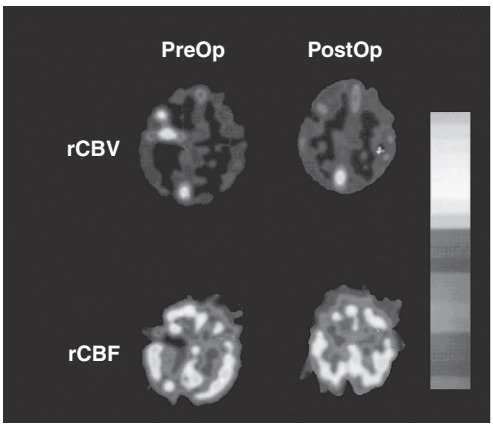


Fig. 2.24 Example of single-photon emission computed tomography (SPECT). Double-label methodology is used to simultaneously image both regional cerebral blood flow (rCBF) (SPECTamine; ^{131}I-iodoamphetamine) and cerebral blood volume (rCBV) (technetium Tc99m-labeled red blood cells [RBCs]). The lookup table is relative, and the *lighter shades* reflect increasing flow or volume. Flow and volume imaging currently cannot be quantitated (as opposed to positron emission tomography techniques). This patient had a temporal cerebral arteriovenous malformation (AVM), and these scans were obtained before (PreOp) and after (PostOp) surgery. The CBF was normal except for a flow defect that corresponded to the AVM location demonstrated on magnetic resonance imaging. The CBF tracer does not image the fistula because there are no capillaries. In the rCBV image, a hot spot can be seen on the posterior midline that represents the sagittal sinus. The larger temporal enhancement is the AVM nidus; the smaller one is a large draining vein. *(Courtesy Isak Prohovnik, PhD, and W.L. Young, MD, Columbia University.)*

paramagnetic tracers that can be excited in a magnetic field, so that one may directly examine cerebral perfusion.[323] Capillary transit time can be assessed with currently available intravascular tracers, such as gadolinium-labeled agents, thus providing an indirect index of CBF and CBV.[227,324] CBF values are similar when CBF is determined by contrast MRI and $H_2{}^{15}O$ PET imaging. However, it is possible that MRI values are more weighted toward the more numerous smaller (30- to 4-μm) blood vessels and hence are more suitable for investigating flow changes in small blood vessels, such as those in tumors.[325] More importantly, with development of freely diffusible paramagnetic drugs, wash-in and wash-out can be determined in ways similar to those with current radioisotope methods.[326]

The second technique, known as *spin labeling*, uses radiofrequency to magnetically label arterial water content. The basic concept is that water, being freely diffusible, transfers its magnetic properties to the brain tissue. By comparing perfusion images with and without spin contrast, one can determine the blood flow. Other things being equal, the rate of transfer of magnetic properties is a function of blood flow. The spin labeling could be continuous or pulsed. In continuous spin labeling, radiofrequency pulses are continuously applied to the feeding artery and magnetic transfer is assessed downstream at the imaging plane. Continuous spin labeling therefore has to correct for the decay of the spin from the magnetization plane to the imaging plane and magnetization transfer characteristic of the tissue.[327] The alternative approach, known as *pulsed spin labeling*, is to apply a short pulse of radiofrequency close to the imaging plane so that there is a minimal delay in contrast transfer. Several techniques use pulsed spin labeling to measure blood flow, as discussed in the reviews by Calamente and associates.[328–330]

MRI resolution and the ability to correlate CBF information with structural information could make this the "gold standard."[326] MRI also can image other cerebral physiologic

functions, such as hemoglobin saturation, intracellular energy stores, sodium, and pH.[326,330–332] The noninvasive nature of MRI permits longitudinal follow-up of physiologic and anatomical parameters, thus providing valuable insights into brain diseases.[333]

Thermal Clearance

Although thermal clearance is a well-known technique for quantitating cardiac output, bolus thermal techniques applied to the brain can introduce artifacts because of the effects of temperature on physiologic functions (such as CO_2 reactivity).[334] Thermal conductivity of cortical tissue varies proportionally with CBF, and measurement of thermal gradients (diffusion) at the cortical surface can be used for quantitative CBF determination.[334] The probe is placed directly on the cortical surface but away from large surface vessels or areas of direct brain retraction. There are several measurement variations. In one system, a large gold disk at the tip of the probe is equipped with an active temperature sensor and a heater, and a smaller disk with a neutral thermistor temperature sensor. When power is applied to the heater, the temperature of the gold disk increases while the temperature of the smaller disk remains at brain temperature. The difference in temperature between the two disks is inversely proportional to the thermal conductivity of the brain tissue.

The resulting thermal gradient would be maximal when there is no flow through the opposing cerebral cortex. As CBF increases, the temperature difference (transduced in millivolts) decreases in proportion to CBF, so that the following equation would apply:

$$1\,\mathrm{CoCBF} = \phi\left(\frac{1}{\Delta V} - \frac{1}{\Delta V_0}\right) \tag{2.3}$$

where *1CoCBF* is local cortical CBF; ø is a constant value used as a scale factor; ΔV_0 is maximum temperature difference at zero blood flow; and ΔV is the actual temperature difference.

The thermal diffusion CBF technique has been used to describe autoregulatory dysfunction in a number of surgical settings, including cerebral aneurysm and AVM surgery. The greatest strength of thermal diffusion is the ability to obtain continuous quantitative assessment of cortical perfusion.[335,336] The time resolution is 1 to 2 seconds.[337] If CBF changes take place in an entire vascular supply territory (eg, MCA), the focal flow changes in the probe's area should reflect the regional changes.

Extraneous thermal influences, such as operating room lights, electrocautery interference, and irrigation of the surgical field, may result in erroneous CBF measurements. Another problem is frequent separation of the probe from the cortical surface. Therefore, any detected CBF change must be carefully related to activity in the operative field. The use of the probe is sometimes also limited in febrile patients so as to avoid local thermal injury.[338]

Several assumptions are made in the derivation of the CBF values. First, the thermal conductivity of tissue from patient to patient is assumed to be constant. Thermal conductivity depends on the chemical composition of normal cortical tissue and appears to be constant within many different species, including humans. Proper calibration depends on knowledge of the ΔV_0 term in Eq. 2.3, which represents no flow. Although this term has been experimentally determined in animals, it cannot be done in the clinical setting. Therefore, the nature of the CBF information is probably better viewed as a reflection of relative changes in perfusion, rather than as the frequently reported absolute values. Because the method does not require sophisticated equipment, does not use ionizing radiation, and is theoretically easy to use, it deserves further development for use during neurosurgery.[336]

Doppler Techniques

Transcranial Doppler Ultrasonography

TCD was introduced by Aaslid and colleagues[339,340] in 1982. Doppler-based devices are in wide use for clinical imaging, and the general method is similar for all applications. TCD uses a 2-MHz probe and is range gated; therefore, the ultrasonic beam can be focused on a target volume at a specific depth. No actual image of the vessel is obtained, as with "duplex" devices. The probe is placed over low-density bone regions of the skull, and the beam is focused on the desired vessel. The Doppler shift of the ultrasonic beam after its reflection on the moving blood column within the vessel is proportional to blood flow velocity.

This technique can provide continuous assessment of the systolic, diastolic, and mean flow velocities in the target vessel. Evidence has shown that the downstream vascular resistance is proportional to the difference between systolic and diastolic velocities. Several resistance indices have been proposed; a popular one is the "pulsatility index" (*PI*), defined as follows:[341]

$$\mathrm{PI} = \frac{\text{Systolic velocity} - \text{Diastolic velocity}}{\text{Mean velocity}} \tag{2.4}$$

Although a correlation may be found between PI and CVR, it was not evident in an experimental study. During hypercapnia, PI correlated with the change in CVR, but there was no correlation with CVR during hemorrhagic hypotension, trimetaphan-induced systemic hypotension, or increased ICP.[342]

Flow velocity in large vessels in the circle of Willis and its major branches can be determined. The signals obtained document the direction and velocity of the vessel flow insonated by the beam. In addition, spectral analysis of the signal allows estimation of the severity of stenosis much as extracranial duplex Doppler ultrasonography does. To insonate the distal internal carotid, anterior cerebral, middle cerebral, and posterior cerebral arteries, the probe is positioned above the zygomatic arch from 1 to 5 cm in front of the ear, the so-called temporal bone window. The basilar artery is insonated by directing the probe through the foramen magnum suboccipitally over the first cervical vertebra. For intraoperative application, a probe can be affixed to the temporal bone window with a strap. During craniotomy, adhesive can be used to directly mount a small probe against the skin.

TCD does not measure CBF; rather, it determines velocity and direction of the moving column of blood in a major artery (Fig. 2.25). The bulk flow (*F* [mL/min], not *f* [mL/100 g/min]), is the product of the diameter of the vessel (*d*) and the velocity (*v*), as follows:

$$F = dv \tag{2.5}$$

Ample criticisms of the technique have been made.[343] TCD indirectly estimates flow from the peak flow velocity in a given blood vessel. Hence, to equate TCD measurements over a given vessel with "CBF velocity" is inappropriate, because doing so implies measurement of hemispheric CBF. If flow in the MCA is being described, "MCA velocity" is preferable.

Although tissue perfusion is relatively constant among similar patient populations, there is a much greater between-subject variation with TCD velocities because of varying proportions of hemispheric flow carried by the different vessels and the natural variability in arterial diameters. When TCD is

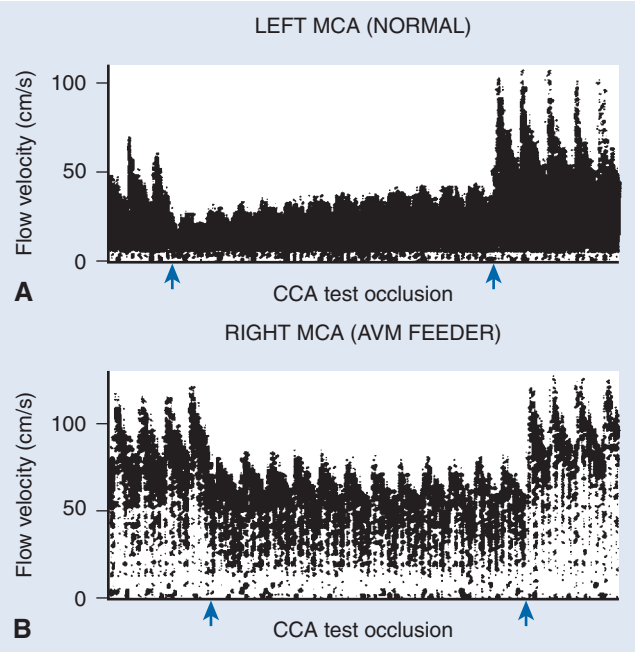


Fig. 2.25 Transcranial Doppler ultrasonography studies in a patient with an arteriovenous malformation (AVM). **A,** Carotid compression of the ipsilateral normal carotid artery yields a drop in the left middle cerebral artery (MCA) velocity. Gradually, over the course of the compression, flow is recruited from collateral pathways. With release of compression, there is a brief period of hyperemia. **B,** The right MCA also feeds a large AVM. The low-resistance fistula of the AVM results in much higher flow velocities through the MCA stem. Ratio of systolic to diastolic velocities is different, with the diastolic velocity being much higher in relation to systolic velocity, indicating decreased pulsatility. There is no apparent autoregulatory recruitment of collateral flow and no reperfusion increase in flow velocity, in comparison with the ipsilateral, normal side. *(From Aaslid R: Transcranial Doppler Sonography. New York, Springer-Verlag, 1986.)*

used to monitor clinical changes with repeated measurement, the key assumption is that the diameter of the insonated vessel remains the same. This is probably true in the majority of cases.[344,345] Yet, evidence has shown that vasoactive drugs such as L-NMMA may lead to constriction of the MCA such that a decrease in CBF with this agent may not be evident by flow velocity measurements over the artery.[346] Dynamic change in vessel diameter may also be observed during cerebral vasospasm, which limits the applicability of flow measurements by TCD in such settings.[347] Furthermore, the traditional Doppler measurements are based on laminar flows through rigid tubes in which the maximal Doppler shift is proportional to the axial flow velocity. In clinical settings, these assumptions may not be valid. One approach to overcome the problem of nonlaminar flow is to measure the so-called intensity-weighted mean velocity. This approach differs from the traditional Doppler measurements, because it takes into consideration the entire spectrum and not merely the maximal frequency of Doppler shift. The intensity-weighted velocity indices yield blood flow velocities with nonlaminar flows and can also be used to estimate the diameter of the blood vessels.[345,348,349]

Other problems with TCD are related to the inherent error in the natural variability of the exact angle of insonation. The error is proportional to the cosine of the angle of insonation, and with less than 20° angles, this error is negligible in normal patients. Nonetheless, in certain neurosurgical patients with distorted intracranial anatomy, this error can become significant.[350] Another problem is difficulty in finding the vessel. With experience, this difficulty should occur less than 5% to 10% of the time, but its incidence depends on the patient population.[351]

TCD's greatest advantages are that it is relatively inexpensive, noninvasive, and nonradioactive and that it furnishes beat-to-beat (ie, continuous) information about the cerebral circulation. It has proved valuable to the neurologist in the diagnosis of intracranial stenoses and abnormal collateral blood flow patterns.[278,352] It might have potential as a powerful monitoring method during anesthesia and critical care. Also, it can be used to study functional[353] and pressure[354] autoregulatory phenomena noninvasively on a beat-to-beat basis. Spontaneous fluctuations in MCA flow velocity (MCAFV) can be detected and quantified by frequency domain analysis and can provide a useful tool to investigate the nature and dynamic regulation of cerebral circulation. For example, MCAFV, much like the arterial blood pressure (ABP), can be diffracted into three specific frequency ranges: high, low, and very low. High-frequency and low-frequency components of MCAFV are coherent with ABP, indicating a similarity of MCAFV and ABP in these frequency ranges.[355] TCD may also provide information about the venous circulation.[13]

Some writers have proposed absolute values for TCD that correspond to EEG ischemic thresholds during carotid endarterectomy.[356] In a comparison of TCD, NIRS, stump pressure, and somatosensory evoked responses during carotid artery surgery, the percentage changes in TCD velocity and in NIRS and stump pressure values had similar accuracy in detecting ischemia. However, TCD measurements were not possible in 21% of the patients.[357] Thus, technical difficulties in insonating cerebral arteries often limit applications of TCD. As with many other methods, however, TCD information is best considered in relative terms. Flow information is most reproducible when coupled with a physiologic challenge, such as CO_2.[358] Relative CO_2 reactivity of TCD velocities is roughly similar to those reported for CBF.[359,360] Possible routes of development for TCD, in addition to monitoring of hemispheric perfusion, include noninvasive ICP monitoring,[361] determining the adequacy of pulsatile perfusion during cardiopulmonary bypass,[362] and detection of intracranial arterial air emboli.[363] In general, volatile anesthetic agents such as sevoflurane, desflurane, isoflurane, and nitrous oxide increase blood flow velocity through a decrease in cerebral vascular resistance. Intravenous anesthetic agents such as propofol and sodium thiopental, but not ketamine, decrease the velocity of blood flow. Narcotics, on the other hand, have variable effect; remifentanil does not alter blood flow velocity, fentanyl increases it, and sufentanil decreases it.[364]

Other Ultrasound Methods

With a 20-MHz probe, direct interrogation of surface vessels exposed during neurosurgical procedures is possible.[364,365] This method has potential application during neurovascular surgery, including revascularization, aneurysm clipping, and AVM resection.

Intravascular Doppler ultrasonography is used primarily for cardiac purposes and has been adapted to neuroradiologic purposes with the introduction of a 0.018-inch flexible, steerable guidewire that has an integrated 12-MHz piezoelectric transducer. This system allows continuous determination of blood flow velocity in intracranial vessels.[366–368]

Experiments suggest that the injection of albumin "microspheres" during Doppler interrogation give the technique greater sensitivity than existing techniques and offer the possibility of quantitatively measuring intravascular transit time. Furthermore, it may be possible to simulate "autoradiography" of the exposed brain by interrogating a field of view during passage of the tracer.[369]

Optical Assessment of Cerebral Blood Flow

Perhaps the most significant development in the last decade has been the rapid advances in optical technologies that promise to generate novel insights into the regulation of CBF.[370–375] In preclinical research, for example, three-dimensional optical imaging methods can image cerebral vasculature at near micrometer resolution.[376–379] These methods can map directional flow velocities in individual vessels, with temporal sampling rates approaching millisecond resolution. Furthermore, availability of laser diodes, compact tunable lasers and high-intensity diffuse light-emitting diodes makes it possible to detect several tissue fluorescence and absorption parameters. The major drivers of this optical revolution in neuroscience are the developments of several technologies that were recently listed by Dover et al.[378] These technologies can enable:

1. spatial imaging of cortical metabolism and vascular reactivity at a cellular level
2. tracking of metabolic changes and flow response after stimulation in a milisecond time frame
3. tracking of endogenous optical signals by light absorption (such as hemoglobin and deoxyhemoglobin) or by fluorescence (such as NADH)
4. imaging cellular processes by using novel optical sensors (such a voltage or calcium sensitive dyes, quantum dots)
5. optical manipulation of neuronal activity, blood flow or metabolism
6. undertaking of depth interrogation of the cortex in the zone of penetrating arterioles to understand the mechanisms of neurovascular coupling without compromising cortical structural integrity.

Imaging CBF changes concurrent with tissue metabolic changes by optical means could considerably advance the understanding of CBF regulation in the next decade.[380,381] We can broadly divide optical CBF measurement methods into two groups: (i) optical methods in preclinical research and (ii) those approved for or being developed for clinical application.

Optical Methods for Preclinical Research

Intra-Vital Microscopy

Intravital microscopy can be used to image a wide range of tissue parameters both anatomical and physiological.[382] High-speed intra-vital microscopy (IVM) with strobe illumination can determine vascular geometry, shear stress and axial red cell flow velocity.[383] By injecting optically tagged red cells, microspheres or quantum dots, the IVM method can be further improved and blood flow changes can be monitored over days.[384] However, the method requires exposure of the cortex and usually implantation of a cranial window. Of concern is the observation that velocity of blood flow varies in the cerebral micro-circulation often as a function of vessel size.[383] As with the RBCs, in vivo assessment of vascular diameter and microsphere velocity can be used to determine the net regional flow. In addition, regional blood flow over time can be mapped by imaging the distribution of different colored microspheres in the postmortem tissue sample if color bearing microspheres are injected at different time points.

Laser Doppler Blood Flow

Laser Doppler measurements can assess CBF from an exposed cortex or though a thinned skull. The method detects the Doppler shift of laser light after its reflection from the moving RBCs.[385] The contact device usually samples a small volume of cortical tissue. The cortical area interrogated by the probe is probably only about a mm^3 in volume. The depth of CBF measurements is approximately 100 to 400 µm.[386] The technique is inexpensive and nonradioactive, and it furnishes continuous information. In addition, one can adjust the time resolution to examine events with a very short time constant, such as the effects of pulsatile pressure on local flow.[387] It is noninvasive in the sense that it may be used during an open skull operation with no additional preparation. It is well suited to animal studies,[388–390] and improved probe design, such as small-diameter implantable fiberoptic probes, may widen applications in human subjects.[391–393] Although current instruments claim to be calibrated in terms of absolute flow (mL/100 g/min), the results are most meaningful when expressed as relative change from baseline.

Laser Doppler Perfusion Imaging

The lack of spatial resolution of laser Doppler devices has been overcome by scanning a larger region of interest.[385] This is usually achieved by manipulating the laser beam with a mirror. The back scattered light is analyzed after capture by a camera. Typically these devices lack temporal resolution. The delay is both due to image acquisition and analysis. The temporal resolution of modern devices has been increased by undertaking analysis in parallel with image acquisition. Intraoperative laser Doppler scans have been used to map out ischemic injury and CO_2 reactivity.[393] However, the brain surface shows heterogeneous response to physiologic and pathologic challenges that limits applications of such scans.[394] Development of better algorithms that correct for the spatial variability in laser Doppler imaging, such as those using cluster analysis, could improve the accuracy of the technique.[395]

Speckled Laser Doppler Flow Mapping

In speckled imaging, coherent light is diffused over a large area and is imaged by a charge-coupled device.[396,397] For speckled measurement, either the cortex has to be exposed or the skull has to be sufficiently thinned to reveal cortical vessels. Speckling is due to the random interference of coherent light. Movement of particles in the field results in variation in the intensity of reflected light signal. Temporal and spatial analysis of the reflected light can be used to describe particle velocity. There are various ways to analyze this information often by integrating the raw speckled data (over 1–10 s) and using either spatial, temporal or spatio-temporal analysis. Speckled flow measurements have been used for functional brain imaging, for mapping flow changes after cortical spreading depression and for assessing CBF in experimental stroke.[398]

Infrared Thermal Imaging

Imaging regional variations in brain temperature is significant in two ways. First, brain temperature is a marker of cerebral metabolism.[399] The temperature increases rapidly with cortical excitation and decrease with the interruption of blood flow. For example, sensory stimulation increases not only the CBF but also the cortical temperature, by as much as 0.03–0.04 °C. This increase in cortical temperature persists despite calcium channel blockade that prevents the increase in blood flow. Simultaneous measurements of cortical blood flow and brain temperature reveal a direct correlation between brain temperature changes and laser Doppler blood flow during ischemia and brain perfusion. Therefore, thermal imaging can provide a surrogate measure of cortical perfusion.[400]

Photo-Acoustic Tomography and Functional Brain Imaging

Photo-acoustic tomography (PAT) uses a pulsed laser of specified wavelengths, which vibrates the target tissue due to the

thermo-elastic effect. A highly sensitive ultrasonic detector or a detector array reconstructs anatomical images from these vibrations.[401] Depending of the wavelength of the exciting laser, images to a depth of 5 cm can be obtained. No skull or scalp resection is necessary in small animals. For functional brain imaging and to determine tissue characteristics, tunable lasers can be used.[402] Typically, for vascular imaging, a 570 nm laser is used which is isosbestic with deoxyhemoglobin and oxyhemoglobin.[403] A second laser with a wavelength of 560 or 580 nm determines the oxyhemoglobin content at that wavelength. Together, an anatomical and functional map of the tissue can be generated and blood flow changes in response to sensory stimulation can be observed.[404] In addition, optical tracers such as indocyanine green (ICG) can be used to generate detailed angiograms.[405,406] The skull scatters both light and ultrasound signals that limit the application of PAT in larger animals. However, PAT has been successfully used in nonhuman primates.[407] In smaller animals, such as the mouse, capillary level image resolution has been achieved with photo-acoustic microscopy. The main advantage of PAT is the ability to follow structural changes over time, as images can be acquired through an intact skull. However, temporal resolution of the device is limited and data acquisition can take several seconds. A second limitation of PAT is that the head of the animal has to be enclosed in a water bath for ultrasonic imaging, which limits access during the procedure. Better image integration models are likely to extend the use of the technology to larger animals, possibly even humans.[408,409]

Two-Photon Microscopy

Two-photon microscopy can yield three-dimensional imaging of fluorescent tissue structures. However, due to the low temporal resolution of two-photon microscopy, its application in CBF measurements has hitherto been somewhat limited. To address this problem, investigators have used fluorescein isothiocyanate-labeled dextran. It is thus possible to image capillaries in different layers of the cortex and measure the transit time of unlabeled RBCs every 15–20 ms, to assess vascular dilation and flow velocity. By characterizing blood flow in this manner, considerable variability was found in flow velocities across cortical capillaries but a time locked increase in speed and flux of RBCs was observed during stimulation, consistent with stimulation-triggered decrease in capillary resistance. The arterioles responded to transient stimulation while venular dilation was only seen with sustained stimulation.[410,411]

Optical Coherence Tomography

Optical coherence tomography (OCT) images tissue structures and blood flow by analyzing the interference pattern generated by tissue back scattered light.[412] The method was initially developed for imaging the retina but has been widely adapted for imaging cerebral vasculature and, more recently, for measuring blood flow.[375,413] The light source is usually a high power LED or pulsed laser, usually in the NIRS range, but beyond the visual spectrum. A beam splitter transfers a part of that light to a reference mirror and the remainder of the light is projected onto the tissue. The wavelength of the light affects the depth and resolution of the image. Longer wavelengths offer greater penetration but less resolution. With longer wavelengths, commercially available OCT devices can achieve a depth resolution of up to 12 mm.[414,415]

There are many commercially available systems that use frequency domain or time domain methods for OCT imaging. However, many investigators develop their own systems. Srinivasan et al. recently described spectral OCT to determine absolute flow in the cerebral vascular bed.[416] While OCT imaging can give 3–4 µm resolution, it requires exposure of the cortex and often implantation of a cranial window.[414,417] Recent developments in OCT systems with two-photon microscopy have greatly improved the resolution of the cerebral angiograms. Capillary level images of tissue oxygen delivery are now feasible using these methods.

Optical Methods for Clinical Assessment of Cerebral Blood Flow

Jugular Venous Oximetery

In human subjects, CBF can be assessed using jugular venous sampling by measuring clearance of nitrous oxide using the classical Kety-Schmidt method, thermal diffusion, ultrasound or optical means.[418–420] The most frequent method to assess CBF by optical means is cerebral venous oximetery. The method has been used during neurovascular surgery, management of head trauma, and in the ICU.[421–424] Jugular venous oximetery uses two or three wavelengths of light that are transmitted through a fiberoptic cable to the sampling site in the jugular bulb. For dual wavelength sensors, such as Edslab Sat II, hemoglobin correction is necessary to determine venous blood saturation. For three wavelength sensors, such as Opticath Oximeterix, hemoglobin input is not necessary.[425] An alternate approach to assess CBF with jugular venous oximetery is to measure the transit of a thermal or dye indicator or both.[420]

There are many concerns about the application of jugular venous return-based measurements that have probably limited their clinical applications. In most subjects, two-thirds of the jugular venous return is ipsilateral while one-third is contralateral. Thus, unilateral measurements may not provide correct information regarding blood flow changes in the ipsilateral cerebral hemisphere. Second, there may be streaming of blood in the jugular venous bulb and the blood returning from the two hemispheres might not be mixed completely. Thus one could obtain different values depending on the location of the sampling catheter or the oximeter. Third, the rate of blood aspiration could also affect the extent of mixing of intracranial and extracranial blood. Fourth, jugular venous drainage may be asymmetrical. The dominant jugular outflow may be on the left or the right side in any given patient. This dominance in an ICU setting can be determined by observing the ICP monitored in response to jugular venous bulb compression. The side that causes a greater rise in ICP on bulb compression is the dominant side. Finally, jugular venous oximetery requires accurate positioning of the catheter or oximeter in the jugular bulb. The bulb is located at the base of the skull corresponding to the lower border of C-1 on lateral cervical spine X-ray. The facial veins drain into the jugular vein just caudal to the bulb. Thus a misplaced catheter may sample blood from both the external and the internal carotid irrigations, leading to measurement errors. Thus anatomical variations could limit the value jugular venous oximetery.[425]

Near-Infrared Spectroscopy

Physical Basis

NIRS provides an indirect assessment of CBF by quantifying concentrations of oxy- and deoxyhemoglobin. The major impediment to the interrogation of tissues with light has been an ubiquitous presence of high concentrations of hemoglobin. Jobsis emphasized that the absorption of visible and infrared light by hemoglobin between 700 and 1300 nm is minimal, such that considerable tissue penetration can be achieved by light in this spectral range.[426] The ideal window for NIRS measurements is between 650 and 950 nm. Below 650 nm, the

absorption by hemoglobin is fairly strong, and beyond 950 nm, the absorption by water progressively becomes a significant issue. Even in this narrower spectral range, some degree of light is absorbed by melanin, cytochrome, collagen, bilirubin, and lipid.[427] Of these chromophores, changes in cytochrome redox state that can be rapid, have the potential to confound hemoglobin oxygen saturation measurements by NIRS.

The underlying concepts of light absorption by tissues, which is at the heart of NIRS technology, goes back to 1729 when Pierre Bouguer observed that as light passes through sheets of glass, its intensity decreases by a constant fraction.[428] The attenuation of light in media is a function of the path-length, the absorption coefficient and the scattering coefficient. Therefore for concentration measurements it is necessary to determine these parameters independently. It is now realized that the quantification of chromophore concentrations is difficult using Beer-Lambert's Law, which states that light transmission through a medium is a function of concentration, path-length, and the coefficient of absorption. The latter is a function of both light scattering and absorption. Due to the structural and optical complexity of tissue, and in order to overcome the difficulty in applying the modified Beer's Law, more sophisticated methods to describe photon migration using light diffusion equations, radiative transfer equations, and Monte Carlo simulations have emerged.[429–433] These light transfer models can be tested in digital, and physical models.[434,435] Such mathematical and physical models sometimes use human MRI or CT data to better understand the underlying optical physics. Such sophisticated approaches are highly relevant to the newer NIRS instruments that use complex light delivery methods.

Methods Used for Near-Infrared Spectroscopy

Continuous Wave Spectroscopy. In a typical continuous wave (CW) cerebral oximeter, dual wavelengths are employed. At one wavelength around 850 nm, light is equally absorbed by both hemoglobin and deoxyhemoglobin and at the second wavelength, usually 690–760 nm, the absorption spectra are widely separated. Furthermore, two sets of detectors monitor the light transmission. The near detector, usually 1–3 cm from the source, monitors light backscattered from the scalp and skull, whereas the second detector at 4 cm monitors light backscattered from the brain surface. The difference between the two light signals gives a measure of oxygen saturation in the outer layers of the cortex. This signal is generated by blood in the arteries (25%), capillaries (5%), and veins (70%); therefore, it is heavily biased by the venous blood oxygen saturation. This basic approach of tracking two chromophors (oxy- and reduced hemoglobin) with two wavelengths of light has been expanded to include other light sources that can monitor other parameters, such as water, cytochrome oxidase, and lipids. Some NIRS devices may include as many as five light sources. In addition to endogenous chromophores, extraneous chromophores such as ICG can also be tracked with the NIRS devices and ICG clearance has been used to assess cerebral blood flow. Photodetectors for CW spectroscopy could range from photovoltaic optodes to photomultiplier tubes, avalanche photo-detectors, and charged coupled devices. Most CW devices are simple in design, compact, lightweight, and portable. They usually consist of paired detectors for application to the bi-frontal cortex. Wearable multichannel CW systems are available for ambulatory patients that wirelessly communicate data to the analytic computer. Due to the simplicity and low cost of the source/detectors combinations, several detectors are combined and as many as 2049 detectors have been used to map brain functions.[427]

Time Domain Imaging. By using a short pulse laser light it is possible to obtain time of flight measurements of individual photons by using time-resolved detection. By using such a method, for example, the path-length of the photons in the rat brain was determined to be 5.3 ± 0.3 times the head diameter. Differential path-length is the term used to describe the mean distance travelled by the photon between the source and the detector. By accurately determining the differential path-length, time domain imaging makes it possible to determine more accurately the hemoglobin concentrations in brain tissue. The method also permits deeper interrogation of the cortex.[436] Time domain methods are being applied in the clinical arena for functional brain mapping, assessment of CBF and cerebral tissue oxygenation, and autoregulation.[437–440]

Frequency Domain Spectroscopy. Unlike the continuous wave where there is a stable flux of photons, frequency domain spectroscopy uses sinusoidal modulation of light intensity to create an afferent photon wave. The backscattered photons are analyzed for changes in their frequency and amplitude. With such light modulation, not only the absorption coefficient, but also the light scattering and path length can be determined. This makes it possible to determine absolute concentrations of hemoglobin and deoxyhemoglobin. Multiple source detector combinations have been developed to map out changes in cerebral oxygen saturation with cortical activation at several Hz.[427,428,441–443]

The ability of time and frequency modulated NIRS methods to provide accurate measurements of oxygenated and reduced hemoglobin concentrations has permitted the determination of the tissue oxygenation index (TOI) which is expressed as the fraction of oxygenated to total hemoglobin.

Advantages and Disadvantages of Near-Infrared Spectroscopy Monitoring

The main advantages of NIRS are the safety, the ability to repeat measurements of tissue oxygen saturation in a sub-second time domain, and convenience of use. Although about 50% of the cerebral cortex can be monitored by the NIRS method, areas of the temporal cortex, deeper regions of the brain and the posterior fossa remain inaccessible to NIRS measurements.

For observational research—when there is time to optimize device functions, when multiple channels can be monitored, and when trend analysis, not absolute values, is sufficient—there has been a dramatic increase in the use of CW-NIRS.[374,444] In contrast, during the clinical application of NIRS—when limited monitoring is possible, device testing and optimization protocols have to be simplified, and absolute values are needed to guide therapeutic interventions—somewhat more controversy exits.[445] In addition to regional hypoperfusion, several other clinical parameters also affect regional O_2 saturation. These include mean arterial pressure, cardiac output, arterial pH, hyper- or hypocapnia, position, thickness of the skull, inspired O_2 and hemoglobin concentrations, and the presence of other chromophores, such as conjugated bilirubin. Baseline NIRS tissue oxygen saturation values differ and there is usually no consensus on the normal value for regional brain tissue oxygen saturation. Regional oxygen saturation values greater than 80% or less than 50% or a $\geq$10% difference between the two sides is often considered to be abnormal. The clinical significance of tissue oxygen saturation measured by the NIRS method is limited unless there is a temporal context. Even with absolute measurements, most assessments of the treatment response will require observation of the trend in the values of tissue oxygen saturation. Even so, single values

obtained by the NIRS method, such as those with subdural hematoma, can lead to immediate therapeutic intervention.

Perioperative Applications of Near-Infrared Spectroscopy

In many institutions NIRS is routinely used for certain clinical procedures, such as cardiopulmonary bypass or carotid endarterectomy. In others, the method is treated with a great degree of skepticism.[446] Each side in this debate can present anecdotal evidence where the NIRS had worked or failed.[446–449] The widely used dual channel NIRS monitoring method samples only a small region of the cerebral cortex. With limited sampling, traditional bi-frontal NIRS measurements are bound to miss some focal neurological injuries. To address this problem, multichannel monitoring is being introduced to the operating rooms, although the technique is complicated. Furthermore, as a global monitor of tissue oxygenation, it must be realized that tissue saturation determined by NIRS is dominated by the venous blood saturation value. Thus, factors that affect venous oxygen saturation, e.g., hemoglobin concentrations, or venous blood volume changes due to positioning, will affect the measurements.

Proponents of the use of NIRS technology point to the failures of other neurological injury monitors, the simplicity of the use of the instrument, and the fact that the instrument provides some assessment of brain metabolism that conventional flow measurement methods, such as transcranial Doppler, do not. NIRS provides early warning in 21% of adverse events during cardiac surgery and studies also show that the neurological complication rate and duration of ICU stay are reduced with NIRS monitoring in the same population. The opponents of the method point to a lack of hard evidence supporting a clinical impact of the instrument, the lack of defined thresholds for interventions, and the cost of monitoring. There is agreement that the NIRS method is useful when dramatic changes in CBF are anticipated. If we accept the NIRS to be only a trend monitor, its utility is somewhat enhanced, especially when used in conjunction with another monitor which could supplement the NIRS data. For example, when there are subtle changes in rSO2, the second method could verify NIRS results to guide therapeutic interventions. With significant changes in rSO2 values, this cross confirmation might not be necessary. As a descriptive research tool, documenting relative changes, NIRS technology is far more acceptable where it plays a much more significant role in understanding the flow dynamics in a wide range of neurological, psychological, and psychiatric brain diseases. In these situations NIRS technology is very attractive, as there is ample time to optimize the device functions, response time is exceedingly fast, and the devices are easy to use—even with full head multichannel monitoring. Additionally, NIRS measurements are very safe when compared to fMRI or PET.

Carotid Endartertomy. There are several reasons to use NIRS during CAE: (1) to monitor the reduction in blood flow at clamping; (2) to optimize hemodynamics and to assess the need for shunt placement if a reduction is seen with clamping; and (3) to monitor hyperperfusion responses with the release of the arterial clamp.

There are a large number of studies that have investigated the usefulness of NIRS in monitoring carotid surgery. Perhaps the best sub-set of studies to review are those with multimodal monitoring, particularly during awake CAE. In a study with 99 patients who underwent awake CAE, a 20% reduction in cerebral oxygen saturation had 80% sensitivity and 82% specificity in the detection of clinical symptoms of ischemia.[450] In a later study on 50 patients who underwent CAE under sedation and regional block, 10% of patients demonstrated deterioration on clinical and EEG parameters, and when compared to those who did not show any deterioration, they had a 17% vs. 8% decrease in regional oxygen saturation during clamping, respectively. These studies support much larger studies in anesthetized patients, indicating an appropriate threshold for detecting ischemia during CAE to be a reduction by 20%. Higher thresholds such as 30% reduction in rSO2 increase the specificity to 98% but markedly reduce the sensitivity of the test to 30%. During CAE a >12% reduction in rSO2 suggests a need for therapeutic intervention. However, as a cautionary note, with this threshold 24 of the 323 cases undergoing CAE showed a significant reduction in rSO2 without corresponding changes in EEG/SSEP. Therefore, no shunt placement was deemed necessary and no neurological complications were encountered. Thus, overall, NIRS measurements seem to have high specificity but low sensitivity, with higher negative than positive predictive values. If used alone during CAE, NIRS could lead to unnecessary shunt placement.

An important complication of CAE is the hyperperfusion syndrome that can occur after the removal of the atheromatous plaque. The syndrome clinically presents with headache and neurological deterioration, and could lead to catastrophic intracranial bleeding. When NIRS is used to monitor reperfusion, a regional oxygen saturation increase of 5% has a 50% positive and a 100% negative predictive value.

Cardiopulmonary Bypass. In many institution NIRS is routinely used in all cases of cardiopulmonary bypass (CPB) while in others its use is restricted to those where cerebral perfusion changes are likely to be profound and monitoring is not possible by other means. These include cases of deep hypothermic circulatory arrest, isolated brain perfusion, and pediatric cardiac surgery. Indications for NIRS during CPB include the possibility of cerebral hypoperfusion or ischemic events due to embolization and vascular injury. Proponents of routine NIRS monitoring point to studies that show that correction of cerebral hypoperfusion decreases the incidence of postoperative neurological complications. There is a 50% reduction in perioperative strokes if corrective measures are undertaken during bypass based on NIRS monitoring. However, those who argue against routine cerebral oximetery during cardiopulmonary bypass point to the lack of absolute values to guide interventions. There is agreement that in certain procedures such as those on the aortic arch that may require isolated cerebral perfusion, NIRS can be exceedingly useful. A reduction of 20% saturation over 10 minutes is often the threshold for interventions and indicates a need to increase tissue perfusion.

Critical Care Applications of Near-Infrared Spectroscopy

Neonatal Neurological Injury Monitoring. The size and reduced thickness of the neonatal skull, permit easy interrogation of the neonatal brain tissue by NIR light. Serious long-term consequences of brain hypoxia in the neonatal period have driven application of NIRS technology in the neonatal ICU. Several applications of NIRS have been developed. These include:

1. *Detection of cerebral hypoxia:* As in the adult a wide range of values for neonatal rSO2 exist. This problem is confounded by the fact that the rSO2 values increase in the first 3 days of life. Normal tissue oxygen index (TOI) of a neonatal brain is $62 \pm 10\%$. A decrease in TOI below 50% is considered significant and could be a result of systemic and local factors such as, systemic desaturation, hypotension, decreased cardiac output or anemia. Local factors that could decrease rSO2 include hyperventilation and hypocapnia.

2. *Measurement of cerebral blood flow:* There are two approaches to determine CBF by using the NIRS method; both employ the Fick's principle. The first method is to increase the FiO2, while the second uses clearance of ICG.[451–455] In the oxygen challenge method arterial oxygen saturation is abruptly increased by increasing the FiO2. The consequent increase in rSO2 is used to deduce the CBF. There are several problems with this approach as it is not always possible to increase arterial oxygen saturation by increasing FiO2, for example, in patients with lung disease. There could also be a confounding effect of increased FiO2 on CBF. Furthermore, ethics of increasing FiO2 are questionable when there is potential for oxygen-induced retinopathy. The oxygen challenge method has been validated against ^{133}Xe CBF measurements in critically ill neonates.[456] The alternative method is to use ICG whose concentrations can be measured by the NIRS method. Both the oxygen challenge and the ICG clearance methods have been validated as methods to determine cerebral blood flow.[453]

Synthesis and Comment

An often confusing aspect of the medical literature in general and CBF techniques in particular is that different methods often appear to be in competition. However, the various methods examine different aspects of the same or related biologic phenomena, and different techniques may be required to completely elucidate a process. Examples of complementary methods are shown in Figs. 2.24 to 2.26.

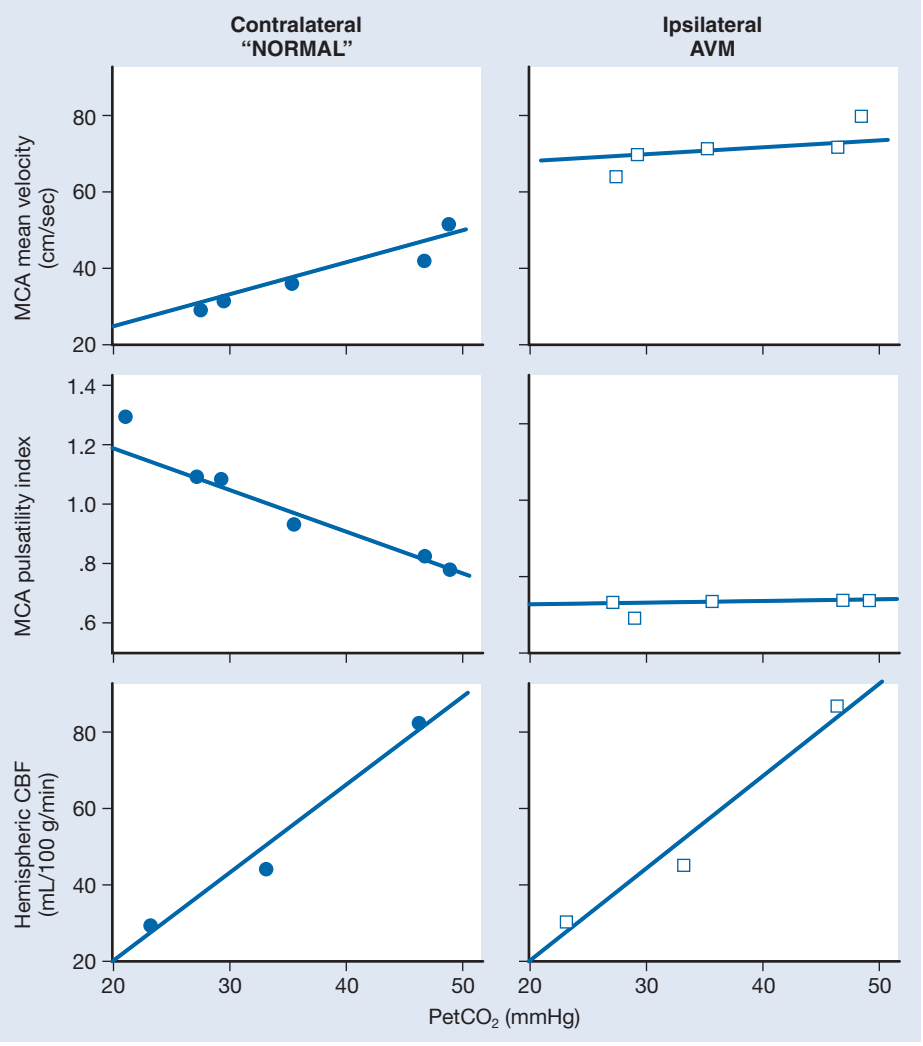


Fig. 2.26 Intraoperative xenon 133 (^{133}Xe) cerebral blood flow (CBF) and transcranial Doppler ultrasonography (TCD) studies in a patient with an arteriovenous malformation (AVM) fed by the middle cerebral artery (MCA). CBF was measured 5 to 6 cm away from the AVM nidus and in an equivalent homologous site over the contralateral hemisphere. TCD mean velocity was recorded from the proximal MCA via the temporal bone window. These data illustrate the different natures of the information obtained from these two complementary imaging techniques. As shown by the ^{133}Xe CBF study, $PaCO_2$ reactivity was preserved in both hemispheres. Values for ^{133}Xe washout, which measures tissue perfusion in the cortex underlying the detectors, were similar in the two hemispheres. The TCD responses to increased $PaCO_2$ are similar on the contralateral hemisphere, in that mean velocity increases and the pulsatility index decreases, reflecting vasodilation of the resistance vessels with increasing end-tidal CO_2 pressure ($PetCO_2$). TCD examination of the ipsilateral hemisphere reveals a different response. Because there is a large shunt in parallel with the normal resistance bed, its effect overshadows that of the normal adjacent circulation. The law of parallel resistances states that normal resistance (R_{normal}) decreases with increasing $PaCO_2$, as follows:

$$\frac{1}{R_{total}} = \frac{1}{R_{AVM}} + \frac{1}{R_{normal}}$$

where R_{total} is total resistance and R_{AVM} is resistance of the AVM shunt. The extremely low resistance of the AVM shunt (R_{AVM}), however, completely masks resistance changes in the adjacent circulation. Although a high baseline mean velocity and a low pulsatility are present, these parameters remain relatively constant with increased $PaCO_2$ because R_{total} changes so little. *(From Young W: Clinical Neuroscience Lectures. Munster, Cathenart, 1999.)*

SPINAL CORD BLOOD FLOW

Compared with the voluminous literature about regulation of CBF, there has been limited experience in delineating the determinants of spinal cord blood flow (SCBF). Technology readily applicable to measurement of CBF has not yet had a major effect on the study of SCBF. Some of the difficulties encountered are (1) the lack of a suitable site for venous sampling, in light of the complexity and small size of the spinal cord venous drainage system, (2) the difficulty in cannulation and the tendency for vasospasm with radicular artery injection, and (3) the difficulty in isolating spinal cord tissue and the resultant low count rates with external scintillation detectors.[457] An often-asked question is whether the spinal cord is a vascular microcosm of the brain.[458]

Spinal Cord Blood Flow Anatomy

Like the cerebral circulation there is extensive collateral blood flow around the spinal cord. The spinal cord is perfused by the anterior spinal artery (ASA), a pair of posterior spinal arteries (PSA) and the circumferential arterial plexus. The ASA supplies the anterior two-thirds of the spinal cord. It arises from the vertebral artery in the cervical region and descends in the anterior spinal groove. It receives supplementary branches from the segmental arteries. It tapers down in the cervical region. The ASA receives redicular arteries at each spinal segment. At the level of T-10, a major arterial collateral supplies the ASA, the artery of Adamkiewicz, which is critical for cord perfusion. In the lower lumbar and sacral regions, the ASA is supplemented by several other arteries. The PSAs can originate from the vertebral artery, posterior inferior cerebellar or the posterior redicular artery at C-2. The arteries descend medial to the posterior nerve roots. The pial arterial plexus arises from the ASA and the PSAs and it encircles the cord. It gives rise to penetrating arteries that supply the outer portions of the spinal cord. There are a pair of redicular arteries at each segmental level; 31 pairs in all. They usually do not penetrate the spinal cord. They supply blood to the dura, nerve root, and spinal ganglia. The artery of Adamiewiczi is the major supply to the distal cord.

Clinical Significance

The presence of extensive collateral circulation on the one hand protects against ischemia and on the other hand can lead to a decrease in spinal cord perfusion due to the shunting of blood away from the spine during surgery due to systemic vasodilation. Occlusion of the ASA below the artery of Adamiewiczi leads to paraplegia but occlusion of the ASA above it is better tolerated. Occlusion of the artery of Adamiewiczi is a major risk to the spinal cord that has a greater effect on the thoracic spine. High spinal cord injury, above T6, also affects CBF in part by altering cerebral autoregulatory responses as well as neurovascular coupling.[459]

Measurement Techniques

The first measurements of SCBF historically were obtained with autoradiography. Because this method requires the sacrifice of the animal for the generation of flow values, repeated measurements in the same subject over a prolonged period are not possible. Thus this technique offers little in the ability to detect changes caused by drug administration or other provocative challenges. SCBF values obtained with this technique have varied from 10 to 20 mL/100 g/min for white matter and from 41 to 63 mL/100 g/min for gray matter.[460]

A variation of the 133Xe clearance technique was used by Smith and colleagues[457] to study SCBF in goats. The isotope was injected directly into the spinal cord, and tissue washout was measured with external scintillation detectors. With this technique, the response to manipulation of $PaCO_2$ could be demonstrated as an increase in SCBF with hypercapnia and as a decrease with hypocapnia. The same technique was used to systematically study the effect of changes in $PaCO_2$, $PaCO_2$, and blood pressure on SCBF in dogs.[461–463] White matter flow values during anesthesia were relatively independent of the spinal cord segment at which the isotope was injected and varied from 10 to 30 mL/100 g/min. Under halothane anesthesia, an increase in $PaCO_2$ from 43 to 80 mmHg led to a 57% rise in SCBF. In a fashion analogous to CBF, SCBF does not change with decreased O_2 tension unless PaO_2 drops below 60 mmHg, at which point there is a rise in SCBF. The response of SCBF during hemorrhagic hypotension was also investigated. In normocapnic, normoxic dogs, SCBF was well maintained to an MAP of 60 mmHg. Below this level, blood flow decreased with further reduction of pressure. With concurrent hypoxia, autoregulation was usually, but not invariably, impaired. The lower limit of autoregulation shifted to 110 mmHg in some cases. With hypercapnia to a $PaCO_2$ of 80 mmHg, autoregulation was either markedly impaired or absent, with SCBF becoming blood pressure passive. This series of studies, however, did not examine the response to increases in blood pressure, so the upper limit of SCBF autoregulation could not be determined.

Intraspinal injection of xenon has been criticized, for several reasons. It is often difficult to determine the anatomic location of the injection or to characterize the variable contributions of gray matter and white matter. Spinal cord damage may result from intramedullary injection and may affect the flow measurements. In addition, this method is limited to flow measurement in one small cord area at a time.

The application of the noninvasive radioisotope technology (intravenous or inhalational) for the measurement of SCBF is limited primarily by the necessity of a reasonable count rate, which can be ensured only by the use of large doses of isotope. Were large doses practical, separation of the region of interest from the surrounding tissue and background would still be difficult. Attempts made to circumvent these problems in the early 1970s involved the placement of detectors close to the spinal cord. These include small vacuum mass spectrometer probes for the aspiration of cold argon tracer and miniature platinum electrodes for the detection of clearance of the hydrogen gas that had been added to the inspired gas mixture. Neither of these techniques has had widespread acceptance.[460] To improve the technique, attempts have been made to measure improved hydrogen delivery by intra-arterial injections and by measuring clearance with catheters placed in the epidural space.[464]

There seems to be no consensus as yet regarding the best techniques to measure SCBF noninvasively, and different techniques seem to yield different perfusion parameters. Clearance of the contrast agent iohexol during CT yields the following values: SCBF 8.9 mL/100 g/min, blood volume approximately 1.2 mL/100 g, and contrast transit time 1.9 seconds. These measurements differ from data obtained by MRI; CT measurements, however, are consistent among observers and with different methods of data analysis.[465] In rodents, SCBF has been measured with arterial spin labeling technique during MRI. The spinal gray matter blood flow value (330 ± 90 mL/100/min) is similar to the brain gray matter value (295 ± 22 mL/min).[466] Pre- and post-contrast administration image analysis during MRI yields a spinal blood volume in humans of approximately 4.3 ± 0.7 mL per 100 mL of tissue volume.[467] During surgery the exposure of the spinal cord offers the possibility of measuring blood flow directly. Doppler ultrasound

techniques have been used to measure distal arterial blood flow during aortic clamping.[468] SCBF changes can be investigated with laser Doppler flow measurements in experimental animals and in clinical settings.[469–471] Although the method is invasive, it can provide continuous data. Laser Doppler blood flow measurements during scoliosis surgery suggest that unilateral occlusion of the segmental spinal artery is usually well tolerated but bilateral occlusion critically decreases the blood flow.

Comparison of Cerebral Blood Flow and Spinal Cord Blood Flow

Sato and colleagues[158] obtained simultaneous recordings of blood flow from different parts of the cat central nervous system by using hydrogen clearance during ketamine–nitrous oxide anesthesia. The SCBF of 46 mL/100 g/min during normocapnia and normotension was significantly lower than the 86 mL/100 g/min recorded in the cerebrum. In the spinal cord, gray matter blood flow is approximately five times greater than white matter blood flow. Regional differences in blood flow exist for the spinal cord in much the same way as they do in the brain. Thus mean blood flow is approximately 40% higher in the cervical and lumbar segments than in the thoracic segments. This difference is most likely related to the relative paucity of gray matter in the thoracic cord. SCBF is metabolically linked to the local level of electrical activity. Thus, unilateral stimulation of the sciatic and femoral nerves is reflected by a 50% increase in flow in the ipsilateral lumbosacral gray matter.[472]

Blood Pressure

Autoregulation of SCBF has been demonstrated in many species. In rats, SCBF seems to be autoregulated in the range of 50 to 140 mmHg and is not affected by propofol anesthesia.[473] Using hydrogen clearance in the monkey, Kobrine and associates[474] determined that, as a result of compensatory vasoconstriction, there was no change in SCBF with MAP values between 50 and 135 mmHg. At MAP below 50 mmHg, the vasculature became maximally dilated, leading to a passive drop in SCBF with decreasing blood pressure. After the upper autoregulatory limit of 135 mmHg was exceeded, vascular resistance actually decreased, presumably because of physical dilation resulting from high intraluminal pressure. This finding was accompanied by a marked increase in SCBF. Hickey and coworkers[458] demonstrated that during thiopental anesthesia, autoregulation in several regions of the rat spinal cord roughly mirrors regional autoregulation in the brain. Comparing autoregulation in the spinal cord with that in the cerebrum, Sato and colleagues[158] found that the upper and lower limits of the autoregulatory plateau were strikingly similar for the two regions in cats. Despite this finding, evoked potential data obtained during reduction of blood pressure below the autoregulatory minimum suggest that the spinal cord is less susceptible than the brain to ischemic damage due to reductions in regional blood flow.

Carbon Dioxide and Oxygen Tension

As mentioned previously, SCBF increases with hypercapnia and decreases with hypocapnia.[461] Inasmuch as baseline blood flow levels are lower in the spinal cord than in the cerebrum, the absolute change in CBF per unit change in CO_2 tension (between 20 and 80 mmHg) is greater than the corresponding change in SCBF. Blood flow changes expressed as a percentage change are, however, the same for the two regions.[158] Nitric oxide plays a major role in CO_2 responsiveness in the spinal cord. Inhibition of NOS by NG-nitro-l-arginine normally decreases SCBF; however, after spinal cord injury it may cause a regional increase in blood flow.[469] The manipulation of SCBF by regulation of arterial CO_2 tension seems to have no beneficial effect on the outcome of spinal cord injury. Therefore, it is likely that the steal and inverse steal known to occur in the cerebral circulation probably occur in the spinal circulation as well.[475]

Temperature

Studies have confirmed that SCBF decreases with hypothermia.[476] Local spinal cord hypothermia within 4 hours of injury has been advocated for limiting the progression of spinal cord injury.[477] However, in both experimental and clinical settings, the effects of spinal hypothermia remain unproven, in part because of a concomitant reduction in blood flow.[478–482]

Neurogenic Control

Data are limited regarding the autonomic control of SCBF. Neither chemoreceptor nor baroreceptor stimulation seems to affect SCBF in dogs, despite the fact that spinal cord blood vessels are richly innervated.[483]

Anesthetics

SCBF is affected by anesthetics in much the same way as CBF. Thus thiopental administered to dogs, in a dose sufficient to induce EEG burst suppression, reduced SCBF by 50% prompting the investigators to suggest that barbiturate coma may provide spinal cord protection.[482] Pentobarbital–nitrous oxide anesthesia in sheep resulted in a decrease in SCBF, which became more apparent with longer exposure times (up to 3 hours). SCBF was better preserved with isoflurane anesthesia than with ketamine anesthesia during experimental intraoperative cardiac tamponade. In assessment of the effects of anesthetic drugs on SCBF, due attention must be paid to their hemodynamic effects.[484] Low doses of midazolam preserved SCBF, but higher doses result in a decrease owing to the reduction in perfusion pressure.[485]

Effect of Cord Compression on Spinal Cord Blood Flow

With the increasing number of instrumentation procedures on the spinal cord, the effects of direct pressure on cord perfusion has been investigated both in experimental animals and in biomechanical simulations. By using a pressure probe with a built-in laser Doppler flow meter, Hamamoto et al. applied direct pressure to an exposed spinal cord. The blood flow decreased with 5 gm weight compression to 40% of the baseline value, while 10 gm weight decreased blood flow to 13% of baseline value. They found that ischemia of 20 minutes' duration was reversible and the animals exhibited no loss of function, but ischemia of 40 minutes' duration was associated with injury and loss of function.[486] From a clinical standpoint it has to be realized that while monitoring cord function during spinal instrumentation surgery, ischemic changes might not manifest immediately, but could be reversible if the pressure was immediately removed.

SUMMARY

CBF monitoring has elucidated mechanisms in a number of specific disease states and has offered a means to both instigate treatment and monitor its effects for SAH, AVM, head injury, and thromboembolic stroke. CBF monitoring has also been used as an adjunct in the determination of brain death. Nevertheless, the method must realistically be viewed as

remaining in its infancy in regard to the clinical care of patients.[487] In the care of the anesthetized or critically ill patient, the clinician must either make an educated guess about what is happening to the cerebral circulation or resort to logistically improbable imaging modalities (transport to the radiology department for angiography or SPECT). However, with the development of bedside methods, discussed previously, physicians will be able to more rationally care for the patient with actual or impending brain injury.

One particular bias in the anesthesia community that has held back the development of such methods is the somewhat unreasonable expectation that CNS monitoring must have absolute prognostic meaning rather than simple descriptive use. With the development of reasonably priced methods to assess cerebral perfusion at the bedside, physicians will no longer be faced with a plethora of questions regarding patient management, particularly those about blood pressure and ventilation.

ACKNOWLEDGMENTS

The authors would like to express their gratitude and great respect for the late William L. Young, MD, James P. Livingston Professor and Vice Chair, Department of Anesthesiology, University of California, San Francisco. Bill was an author of this chapter in the last three editions of this book. Bill's unsurpassed clarity of thought laid the foundations for this chapter in its current form. Bill's sage advice will always be missed but his vision and contributions to cerebral blood flow physiology will inspire future generations of clinicians and researchers.

The author would also like to thank Mei Wang, MPH, Research Associate Scientist, in the Department of Anesthesiology, College of Physicians & Surgeons of Columbia University, New York, who as with the previous edition, helped in preparation of the manuscript.

REFERENCES

1. Bell BA. A history of the study of the cerebral circulation and the measurement of cerebral blood flow (Review article). *Neurosurgery*. 1984;14(2):238–246.
2. Veselis R, Reinsel R, Feshchenko V, et al. Midazolam Sedation Decreases rCBF in Brain Regions Important in Memory; a PET Study (abstract). In: 43rd Annual Meeting, Boston, MA, May 16–19; Association of University Anesthesiologists; 1996:P33.
3. Alkire MT. Quantitative EEG, correlations with brain glucose metabolic rate during anesthesia in volunteers. *Anesthesiology*. 1998;89(2):323–333.
4. Sturzenegger M, Newell DW, Aaslid R. Visually evoked blood flow response assessed by simultaneous two-channel transcranial Doppler using flow velocity averaging. *Stroke*. 1996;27(12):2256–2261.
5. Oshima T, Karasawa F, Satoh T. Effects of propofol on cerebral blood flow and the metabolic rate of oxygen in humans. *Acta Anaesthesiol Scand*. 2002;46(7):831–835.
6. Lam AM, Matta BF, Mayberg TS, Strebel S. Change in cerebral blood flow velocity with onset of EEG silence during inhalation anesthesia in humans: Evidence of flow-metabolism coupling? *J Cereb Blood Flow Metab*. 1995;15(4):714–717.
7. Doyle PW, Matta BF. Burst suppression or isoelectric encephalogram for cerebral protection: Evidence from metabolic suppression studies. *Br J Anaesth*. 1999;83(4):580–584.
8. Arrica M, Bissonnette B. Therapeutic hypothermia. *Semin Cardiothorac Vasc Anesth*. 2007;11(1):6–15.
9. Feng CM, Liu HL, Fox PT, Gao JH. Dynamic changes in the cerebral metabolic rate of O2 and oxygen extraction ratio in event-related functional MRI. *Neuroimage*. 2003;18(2):257–262.
10. Mackert BM, Leistner S, Sander T, et al. Dynamics of cortical neurovascular coupling analyzed by simultaneous DC-magnetoencephalography and time-resolved near-infrared spectroscopy. *Neuroimage*. 2008;39(3):979–986.
11. Olesen J. Contralateral focal increase of cerebral blood flow in man during arm work. *Brain*. 1971;94:635–646.
12. Lassen NA, Ingvar DH, Skinhoj E. Brain function and blood flow: Changes in the amount of blood flowing in areas of the human cerebral cortex, reflecting changes in the activity of those areas, are graphically revealed with the aid of a radioactive isotope. *Sci Am*. 1978;239:62–71.
13. Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard K-F. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke*. 1991;22(9):1148–1154.
14. Hammeke TA, Yetkin FZ, Mueller WM, et al. Functional magnetic resonance imaging of somatosensory stimulation. *Neurosurgery*. 1994;35(4):677–681.
15. Petersen SE, Fox PT, Snyder AZ, Raichle ME. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science*. 1990;249(Aug 31):1041–1044.
16. Martin C, Martindale J, Berwick J, Mayhew J. Investigating neural-hemodynamic coupling and the hemodynamic response function in the awake rat. *Neuroimage*. 2006;32(1):33–48.
17. Lou HC, Edvinsson L, MacKenzie ET. The concept of coupling blood flow to brain function: Revision required? *Ann Neurol*. 1987;22(3):289–297.
18. Wei EP, Kontos HA. Increased venous pressure causes myogenic constriction of cerebral arterioles during local hyperoxia. *Circ Res*. 1984;55(2):249–252.
19. Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure (Review). *Circ Res*. 1990;66(1):8–17.
20. Iadecola C. The role of nitric oxide in cerebrovascular regulation and stroke. In: Mathie RT, Griffith TM, eds. *The Haemodynamic Effects of Nitric Oxide*. London: Imperial College Press; 1999:207–253.
21. Roy CS, Sherrington CS. On the regulation of the blood-supply of the brain. *J Physiol*. 1890;11:85–108.
22. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2(2):161–192.
23. Symon L. Physiological studies of blood flow in the middle cerebral arterial territory. *Stroke*. 1974;IX:5–8.
24. Garcia-Roldan J-L, Bevan JA. Flow-induced constrictions and dilation of cerebral resistance arteries. *Circ Res*. 1990;66(5):1445–1448.
25. Koehler RC, Gebremedhin D, Harder DR. Role of astrocytes in cerebrovascular regulation. *J Appl Physiol*. 2006;100(1):307–317.
26. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. 2010;468(7321):232–243.
27. Harder DR, Kauser K, Lombard JH, Roman RJ, Rubanyi GM. Pressure-induced activation of renal and cerebral arteries depends upon an intact endothelium. In: Rubanyi GM, Vanhoutte PM, eds. *Endothelium-Derived Contracting Factors* (1st International Symposium on Endothelium-derived vasoactive factors, Philadelphia, PA, May 1-3, 1989. Sponsors: Physiol Soc Philadelphia / Schering / Berlex Lab / Cedar Knolls). Basel: S Karger AG; 1990:8–13.
28. Faraci FM. Endothelium-derived vasoactive factors and regulation of the cerebral circulation. *Neurosurgery*. 1993;33(4):648–659.
29. Dietrich HH, Dacey Jr. RG. Molecular keys to the problems of cerebral vasospasm. *Neurosurgery*. 2000;46(3):517–530.
30. Fox PT, Raichle ME, Mintun MA, Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. *Science*. 1988;241(July):462–464.
31. Prichard J, Rothman D, Novotny E, et al. Lactate rise detected by ^{1}H NMR in human visual cortex during physiologic stimulation. *Proc Natl Acad Sci U S A*. 1991;88(13):5829–5831.
32. Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: Implications for functional brain mapping. *Science*. 1996;272(5261):551–554.
33. Shulman RG, Hyder F, Rothman DL. Lactate efflux and the neuroenergetic basis of brain function. *NMR Biomed*. 2001;14(7-8):389–396.
34. Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *J Appl Physiol*. 2006;100(3):1059–1064.
35. Brian Jr JE, Faraci FM, Heistad DD. Recent insights into the regulation of cerebral circulation. *Clin Exp Pharmacol Physiol*. 1996;23(6-7):449–457.
36. Thompson BG, Pluta RM, Girton ME, Oldfield EH. Nitric oxide mediation of chemoregulation but not autoregulation of cerebral blood flow in primates. *J Neurosurg*. 1996;84(1):71–78.
37. Long CJ, Berkowitz BA. What is the relationship between the endothelium derived relaxant factor and nitric oxide? *Life Sci*. 1989;45:1–14.
38. Bredt DS, Snyder SH. Nitric oxide, a novel neuronal messenger (Review). *Neuron*. 1992;8(Jan):3–11.
39. Johns RA. EDRF/Nitric oxide: The endogenous nitrovasodilator and a new cellular messenger (Editorial). *Anesthesiology*. 1991;75(6):927–931.
40. Pelligrino DA. Saying NO, to cerebral ischemia (Editorial). *J Neurosurg Anesthesiol*. 1993;5(4):221–231.

41. Tanaka K, Gotoh F, Gomi S, et al. Inhibition of nitric oxide synthesis induces a significant reduction in local cerebral blood flow in the rat. *Neurosci Lett*. 1991;127:129–132.
42. Faraci FM, Heistad DD. Regulation of cerebral blood vessels by humoral and endothelium-dependent mechanisms. Update on humoral regulation of vascular tone. *Hypertension*. 1991;17(6 Pt 2):917–922.
43. Gonzalez C, Estrada C. Nitric oxide mediates the neurogenic vasodilation of bovine cerebral arteries. *J Cereb Blood Flow Metab*. 1991;11(3):366–370.
44. Fernandez N, Garcia JL, Garcia-Villalon AL, Monge L, Gomez B, Dieguez G. Cerebral blood flow and cerebrovascular reactivity after inhibition of nitric oxide synthesis in conscious goats. *Br J Pharmacol*. 1993;110(1):428–434.
45. Auer L. The action of sodium nitroprusside on the pial vessels. *Acta Neurochir (Wien)*. 1978;43(3–4):297–306.
46. Joshi S, Young WL, Pile-Spellman J, et al. Intra-arterial nitrovasodilators do not increase cerebral blood flow in angiographically normal territories of arteriovenous malformation patients. *Stroke*. 1997;28(6):1115–1122.
47. Joshi S, Young WL, Duong DH, et al. Intracarotid infusion of the nitric oxide synthase inhibitor, L-NMMA, modestly decreases cerebral blood flow in human subjects. *Anesthesiology*. 2000;93(3):699–707.
48. Joshi S, Young WL, Duong H, et al. Intracarotid nitroprusside does not augment cerebral blood flow in human subjects. *Anesthesiology*. 2002;96(1):60–66.
49. Joshi S, Duong H, Mangla S, et al. In nonhuman primates intracarotid adenosine, but not sodium nitroprusside, increases cerebral blood flow. *Anesth Analg*. 2002;94(2):393–399.
50. Joshi S, Hartl R, Sun LS, et al. Despite in vitro increase in cyclic guanosine monophosphate concentrations, intracarotid nitroprusside fails to augment cerebral blood flow of healthy baboons. *Anesthesiology*. 2003;98(2):412–419.
51. White RP, Deane C, Vallance P, Markus HS. Nitric oxide synthase inhibition in humans reduces cerebral blood flow but not the hyperemic response to hypercapnia. *Stroke*. 1998;29(2):467–472.
52. Brian Jr. JE. Carbon dioxide and the cerebral circulation (Review). *Anesthesiology*. 1998;88(5):1365–1386.
53. Janjua N, Mayer SA. Cerebral vasospasm after subarachnoid hemorrhage. *Curr Opin Crit Care*. 2003;9(2):113–119.
54. Shin HK, Salomone S, Potts EM, et al. Rho-kinase inhibition acutely augments blood flow in focal cerebral ischemia via endothelial mechanisms. *J Cereb Blood Flow Metab*. 2007;27(5):998–1009.
55. Riley RH, Lincoln CA. Intra-arterial injection of propofol. *Anaesth Intensive Care*. 1990;18(2):269–270.
56. Yamashita K, Kotani Y, Nakajima Y, et al. Fasudil, a Rho kinase (ROCK) inhibitor, protects against ischemic neuronal damage in vitro and in vivo by acting directly on neurons. *Brain Res*. 2007;1154:215–224.
57. Jin HG, Yamashita H, Nagano Y, et al. Hypoxia-induced upregulation of endothelial small G protein RhoA and Rho-kinase/ROCK2 inhibits eNOS expression. *Neurosci Lett*. 2006;408(1):62–67.
58. Toyoda K, Fujii K, Ibayashi S, Nagao T, Kitazono T, Fujishima M. Role of nitric oxide in regulation of brain stem circulation during hypotension. *J Cereb Blood Flow Metab*. 1997;17(10):1089–1096.
59. Stefanovic B, Schwindt W, Hoehn M, Silva AC. Functional uncoupling of hemodynamic from neuronal response by inhibition of neuronal nitric oxide synthase. *J Cereb Blood Flow Metab*. 2007;27(4):741–754.
60. Robertson SC, Loftus CM. Effect of N-methyl-D-aspartate and inhibition of neuronal nitric oxide on collateral cerebral blood flow after middle cerebral artery occlusion. *Neurosurgery*. 1998;42(1):117–123. discussion 123–124.
61. Iadecola C. Does nitric oxide mediate the increases in cerebral blood flow elicited by hypercapnia? *Proc Natl Acad Sci U S A*. 1992;89(May):3913–3916.
62. Pelligrino DA, Miletich DJ, Albrecht RF. Diminished muscarinic receptor-mediated cerebral blood flow response in streptozotocin-treated rats. *Am J Physiol*. 1992;262:E447–E454.
63. Iadecola C, Yang G, Xu S. 7-Nitroindazole attenuates vasodilation from cerebellar parallel fiber stimulation but not acetylcholine. *Am J Physiol*. 1996;270(4 Pt 2):R914–R919[4 Pt 2].
64. Faraci FM. Role of endothelium-derived relaxing factor in cerebral circulation: Large arteries vs. microcirculation. *Am J Physiol*. 1991;261:H1038–H1042.
65. Iadecola C, Zhang F. Permissive and obligatory roles of NO in cerebrovascular responses to hypercapnia and acetylcholine. *Am J Physiol*. 1996;271(4 Pt 2):R990–R1001.
66. Kozniewska E, Oseka M, Stys T. Effects of endothelium-derived nitric oxide on cerebral circulation during normoxia and hypoxia in the rat. *J Cereb Blood Flow Metab*. 1992;12(2):311–317.
67. Iadecola C. Bright and dark sides of nitric oxide in ischemic brain injury. *Trends Neurosci*. 1997;20(3):132–139.
68. Koenig HM, Pelligrino DA, Albrecht RF. Halothane vasodilation and nitric oxide in rat pial vessels (abstract). *J Neurosurg Anesthesiol*. 1992;4(4):301.
69. Moore L, Kirsch J, Helfaer M, McPherson R, Traystman R. Isoflurane induced cerebral hyperemia: Role of prostanoids and nitric oxide in pigs (abstract). *J Neurosurg Anesthesiol*. 1992;4(4):304.
70. Johns RA, Moscicki JC, DiFazio CA. Nitric oxide synthase inhibitor dose-dependently and reversibly reduces the threshold for halothane anesthesia. *Anesthesiology*. 1992;77(4):779–784.
71. Siesjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology (Review). *J Neurosurg*. 1992;77(2):169–184.
72. Roman RJ, Renic M, Dunn KM, Takeuchi K, Hacein-Bey L. Evidence that 20-HETE contributes to the development of acute and delayed cerebral vasospasm. *Neurol Res*. 2006;28(7):738–749.
73. McCulloch J, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: Functional role in cerebrovascular regulation. *Proc Natl Acad Sci U S A*. 1986;83(Aug):5731–5735.
74. Edvinsson L, Hamel E. Perivascular nerves in brain vessels, chapter 3. In: Edvinsson L, Krause DN, eds. *Cerebral Blood Flow and Metabolism*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2002:43–67.
75. Hong KW, Pyo KM, Lee WS, Yu SS, Rhim HY. Pharmacological evidence that calcitonin gene-related peptide is implicated in cerebral autoregulation. *Am J Physiol*. 1994;266:H11–H16.
76. Wei EP, Moskowitz MA, Boccalini P, Kontos HA. Calcitonin gene-related peptide mediates nitroglycerin and sodium nitroprusside-induced vasodilation in feline cerebral arterioles. *Circ Res*. 1992;70(6):1313–1319.
77. Moskowitz MA. Trigeminovascular system (editorial; comment). *Cephalalgia*. 1992;12(3):127.
78. Nishimura M, Takahashi H, Nanbu A, Sakamoto M, Nakanishi T, Yoshimura M. Cerebral ATP-sensitive potassium channels during acute reduction of carotid blood flow. *Hypertension*. 1995;25(5):1069–1074.
79. Kitazono T, Faraci FM, Taguchi H, Heistad DD. Role of potassium channels in cerebral blood vessels. *Stroke*. 1995;26(9):1713–1723.
80. Faraci FM, Brian Jr. JE. Nitric oxide and the cerebral circulation. *Stroke*. 1994;25(3):692–703.
81. Nelson MT, Quayle JM. Physiological roles and properties of potassium channels in arterial smooth muscle (Review). *Am J Physiol*. 1995;268(4 Pt 1):C799–C822.
82. Faraci FM, Sobey CG. Role of potassium channels in regulation of cerebral vascular tone. *J Cereb Blood Flow Metab*. 1998;18(10):1047–1063.
83. Taguchi H, Heistad DD, Kitazono T, Faraci FM. ATP-sensitive K+ channels mediate dilatation of cerebral arterioles during hypoxia. *Circ Res*. 1994;74(5):1005–1008.
84. Nelson M, Bonsor G, Lamb JT. Cost implications of different policies for the treatment of arteriovenous malformations of the brain. *Neuroradiology*. 1991;33(suppl):203–205.
85. Brayden JE, Nelson MT. Regulation of arterial tone by activation of calcium-dependent potassium channels. *Science*. 1992;256(5056):532–535.
86. Robertson BE, Schubert R, Hescheler J, Nelson MT. cGMP-dependent protein kinase activates Ca-activated K channels in cerebral artery smooth muscle cells. *Am J Physiol*. 1993;265(1 Pt 1):C299–C303.
87. Paterno R, Faraci FM, Heistad DD. Role of Ca^{2+}-dependent K^+ channels in cerebral vasodilatation induced by increases in cyclic GMP and cyclic AMP in the rat (with Editorial Comment by Joseph E Brayden). *Stroke*. 1996;27(9):1603–1608.
88. Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol Scand*. 1983;117(2):203–211.
89. Onoue H, Katusic ZS. Role of potassium channels in relaxations of canine middle cerebral arteries induced by nitric oxide donors. *Stroke*. 1997;28(6):1264–1270; discussion 1270–1271.
90. Wang Q, Paulson OB, Lassen NA. Indomethacin abolishes cerebral blood flow increase in response to acetazolamide-induced extracellular acidosis: A mechanism for its effect on hypercapnia? *J Cereb Blood Flow Metab*. 1993;13(4):724–727.
91. Markus HS, Vallance P, Brown MM. Differential effect of three cyclooxygenase inhibitors on human cerebral blood flow velocity and carbon dioxide reactivity. *Stroke*. 1994;25(9):1760–1764.
92. Brian Jr JE, Heistad DD, Faraci FM. Effect of carbon monoxide on rabbit cerebral arteries. *Stroke*. 1994;25(3):639–643; discussion 643–644.
93. Wagerle LC, Mishra OP. Mechanism of CO2 response in cerebral arteries of the newborn pig: Role of phospholipase, cyclooxygenase, and lipoxygenase pathways. *Circ Res*. 1988;62(5):1019–1026.
94. Leffler CW, Mirro R, Pharris LJ, Shibata M. Permissive role of prostacyclin in cerebral vasodilation to hypercapnia in newborn pigs. *Am J Physiol*. 1994;267(1 Pt 2):H285–H291.
95. Leffler CW, Busija DW. Prostanoids in cortical subarachnoid cerebrospinal fluid and pial arterial diameter in newborn pigs. *Circ Res*. 1985;57(5):689–694.

96. Leffler CW, Mirro R, Shanklin DR, Armstead WM, Shibata M. Light/dye microvascular injury selectively eliminates hypercapnia-induced pial arteriolar dilation in newborn pigs. *Am J Physiol*. 1994;266(2 Pt 2):H623–H630.
97. Wagerle LC, DeGiulio PA. Indomethacin-sensitive CO_2 reactivity of cerebral arterioles is restored by vasodilator prostaglandin. *Am J Physiol*. 1994;266(4 Pt 2):H1332–H1338.
98. Sakurai T, Yanagisawa M, Takuwa Y, et al. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor [see comments]. *Nature*. 1990;348(6303):732–735.
99. Arai H, Hori S, Aramori I, Ohkubo H, Nakanishi S. Cloning and expression of a cDNA encoding an endothelin receptor. *Nature*. 1990;348(6303):730–732.
100. Murray MA, Faraci FM, Heistad DD. Effect of protein kinase C inhibitors on endothelin- and vasopressin- induced constriction of the rat basilar artery. *Am J Physiol*. 1992;263(6 Pt 2):H1643–H1649.
101. Durieu-Trautmann O, Federici C, Creminon C, et al. Nitric oxide and endothelin secretion by brain microvessel endothelial cells: Regulation by cyclic nucleotides. *J Cell Physiol*. 1993;155(1):104–111.
102. Kitazono T, Heistad DD, Faraci FM. Enhanced responses of the basilar artery to activation of endothelin-B receptors in stroke-prone spontaneously hypertensive rats. *Hypertension*. 1995;25(4 Pt 1):490–494.
103. Foley PL, Caner HH, Kassell NF, Lee KS. Reversal of subarachnoid hemorrhage-induced vasoconstriction with an endothelin receptor antagonist. *Neurosurgery*. 1994;34(1):108–112. discussion 112–113.
104. Zuccarello M. Endothelin: the "prime suspect" in cerebral vasospasm. *Acta Neurochir - Suppl*. 2001;77:61–65.
105. Zuccarello M, Boccaletti R, Romano A, Rapoport RM. Endothelin B receptor antagonists attenuate subarachnoid hemorrhage-induced cerebral vasospasm. *Stroke*. 1998;29(9):1924–1929.
106. Lavine SD, Wang M, Etu JJ, Meyers PM, Joshi S. Augmentation of cerebral blood flow and reversal of endothelin-1-induced vasospasm: A comparison of intracarotid nicardipine and verapamil. *Neurosurgery*. 2007;60(4):742–748; discussion 748–749.
107. Vajkoczy P, Meyer B, Weidauer S, et al. Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: Results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study. *J Neurosurg*. 2005;103(1):9–17.
108. Vergouwen MD, Algra A, Rinkel GJ. Endothelin receptor antagonists for aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis update. *Stroke; a journal of cerebral circulation*. 2012;43(10):2671–2676.
109. Day AL. Arterial distributions and variants. In: Wood JH, ed. *Cerebral Blood Flow: Physiologic and Clinical Aspects*. New York: McGraw-Hill Book Company; 1987:19–36.
110. Bladin CF, Alexandrov AV, Norris JW. Carotid endarterectomy and the measurement of stenosis (Letter to the editor). *Stroke*. 1994;25(3):709–712.
111. Van der Zwan A, Hillen B, Tulleken CAF, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. *J Neurosurg*. 1992;77(6):927–940.
112. Riggs HE, Rupp C. Variations in form of circle of Willis. *Arch Neurol*. 1963;8(January):24–30.
113. Cassot F, Vergeur V, Bossuet P, Hillen B, Zagzoule M, Marc-Vergnes JP. Effects of anterior communicating artery diameter on cerebral hemodynamics in internal carotid artery disease: A model study. *Circulation*. 1995;92(10):3122–3131.
114. Schomer DF, Marks MP, Steinberg GK, et al. The anatomy of the posterior communicating artery as a risk factor for ischemic cerebral infarction. *New Engl J Med*. 1994;330(22):1565–1570.
115. Nakai K, Imai H, Kamei I, et al. Microangioarchitecture of rat parietal cortex with special reference to vascular "sphincters": Scanning electron microscopic and dark field microscopic study. *Stroke*. 1981;12(5):653–659.
116. Heistad DD, Marcus ML, Abboud FM. Role of large arteries in regulation of cerebral blood flow in dogs. *J Clin Invest*. 1978;62(4):761–768.
117. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson Jr JL. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol*. 1978;234(4):H371–H383.
118. Shapiro HM, Stromberg DD, Lee DR, Wiederhielm CA. Dynamic pressures in the pial arterial microcirculation. *Am J Physiol*. 1971;221(1):279–283.
119. Fein JM, Lipow K, Marmarou A. Cortical artery pressure in normotensive and hypertensive aneurysm patients. *J Neurosurg*. 1983;59:51–56.
120. Kader A, Young WL. The effects of intracranial arteriovenous malformations on cerebral hemodynamics. *Neurosurg Clin N Am*. 1996;7(4):767–781.
121. Wagner EM, Traystman RJ. Hydrostatic determinants fo cerebral perfusion. *Crit Care Med*. 1986;14(5):484–490.
122. Auer LM, Ishiyama N, Pucher R. Cerebrovascular response to intracranial hypertension. *Acta Neurochir (Wien)*. 1987;84:124–128.
123. Strandgaard S. The lower and upper limit for autoregulation of cerebral blood flow (abstract). *Stroke*. 1973;4(May-June):323.
124. Joshi S, Young WL, Pile-Spellman J, et al. Manipulation of cerebrovascular resistance during internal carotid artery occlusion by intraarterial verapamil. *Anesth Analg*. 1997;85(4):753–759.
125. Joshi S, Hashimoto T, Ostapkovich N, et al. Effect of intracarotid papaverine on human cerebral blood flow and vascular resistance during acute hemispheric arterial hypotension. *J Neurosurg Anesthesiol*. 2001;13(2):146–151.
126. Drummond JC. The lower limit of autoregulation: Time to revise our thinking? (letter). *Anesthesiology*. 1997;86(6):1431–1433.
127. Gao E, Young WL, Pile-Spellman J, Ornstein E, Ma Q. Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. *Am J Physiol*. 1998;274(3 Pt 2):H1023–H1031 [March].
128. Capra NF, Kapp JP. Anatomic and physiologic aspects of venous system. In: Wood JH, ed. *Cerebral Blood Flow: Physiologic and Clinical Aspects*. New York: McGraw-Hill Book Company; 1987:37–58.
129. Gao E, Young WL, Hademenos GJ, et al. Theoretical modeling of arteriovenous malformation rupture risk: A feasibility and validation study. *Med Eng Phys*. 1998;20(7):489–501.
130. Florence G, Seylaz J. Rapid autoregulation of cerebral blood flow: A laser-Doppler flowmetry study. *J Cereb Blood Flow Metab*. 1992;12(4):674–680.
131. Nakase H, Nagata K, Otsuka H, Sakaki T, Kempski O. Local cerebral blood flow autoregulation following "asymptomatic" cerebral venous occlusion in the rat. *J Neurosurg*. 1998;89(1):118–124.
132. Hickey PR, Buckley MJ, Philbin DM. Pulsatile and nonpulsatile cardiopulmonary bypass: Review of a counterproductive controversy. *Ann Thorac Surg*. 1983;36(6):720–737.
133. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. I. Mortality and cardiovascular morbidity. *J Thorac Cardiovasc Surg*. 1995;110(2):340–348.
134. Young WL, Cole DJ. Deliberate hypertension: Rationale and application for augmenting cerebral blood flow. *Probl Anesth*. 1993;7(1):140–153.
135. Solomon RA, Post KD, McMurtry III JG. Depression of circulating blood volume in patients after subarachnoid hemorrhage: Implications for the management of symptomatic vasospasm. *Neurosurgery*. 1984;15(3):354–361.
136. Ornstein E, Young WL, Prohovnik I, Ostapkovich N, Stein BM. Effect of cardiac output on CBF during deliberate hypotension (abstract). *Anesthesiology*. 1990;73:A169.
137. Gaehtgens P, Marx P. Hemorheological aspects of the pathophysiology of cerebral ischemia (Review). *J Cereb Blood Flow Metab*. 1987;7(3):259–265.
138. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Cerebral blood flow is regulated by changes in blood pressure and in blood viscosity alike. *Stroke*. 1986;17(1):44–48.
139. Todd MM, Weeks JB, Warner DS. Cerebral blood flow, blood volume, and brain tissue hematocrit during isovolemic hemodilution with hetastarch in rats. *Am J Physiol*. 1992;263(1 (Pt 2)):H75–H82.
140. Todd MM, Wu B, Warner DS. The hemispheric cerebrovascular response to hemodilution is attenuated by a focal cryogenic brain injury. *J Neurotrauma*. 1994;11(2):149–160.
141. Todd MM, Hindman BJ, Warner DS. Barbiturate protection and cardiac surgery: A different result (Editorial). *Anesthesiology*. 1991;74(3):402–405.
142. Chien S, Usami S, Skalak R. Blood flow in small tubes. In: Renkin EM, Michel CC, Geiger SR, eds. *Handbook of Physiology: A Critical Comprehensive Presentation, Section 2: The Cardiovascular System (Volume 4: Microcirculation, Part 1)*. Bethesda, MD: American Physiological Society; 1984:217–249.
143. Zweifach BW, Lipowsky HH. Pressure-flow relations in blood and lymph microcirculation. In: Renkin EM, Michel CC, Geiger SR, eds. *Handbook of Physiology: A Critical Comprehensive Presentation, Section 2: The Cardiovascular System (Volume 4: Microcirculation, Part 1)*. Bethesda, MD: American Physiological Society; 1984:251–307.
144. Hudetz AG. Blood flow in the cerebral capillary network: A review emphasizing observations with intravital microscopy. *Microcirculation*. 1997;4(2):233–252.
145. Sakai F, Nakazawa K, Tazaki Y, et al. Regional cerebral blood volume and hematocrit measured in normal human volunteers by single-photon emission computed tomography. *J Cereb Blood Flow Metab*. 1985;5(2):207–213.

146. Koehler RC, Traystman RJ. Bicarbonate ion modulation of cerebral blood flow during hypoxia and hypercapnia. *Am J Physiol*. 1982;243: H33–H40.
147. Raichle ME, Posner JB, Plum F. Cerebral blood flow during and after hyperventilation. *Arch Neurol*. 1970;23(Nov):394–403.
148. Anderson RE, Sundt Jr. TM, Yaksh TL. Regional cerebral blood flow and focal cortical perfusion: A comparative study of ^{133}Xe, ^{85}Kr, and umbelliferone as diffusible indicators. *J Cereb Blood Flow Metab*. 1987;7:207–213.
149. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J Clin Invest*. 1948;27:484–492.
150. Siesjo BK. *Brain Energy Metabolism*. New York: John Wiley & Sons; 1978: 607.
151. Alexander SC, Smith TC, Strobel G, Stephen GW, Wollman H. Cerebral carbohydrate metabolism of a man during respiratory and metabolic alkalosis. *J Appl Physiol*. 1968;24:66–72.
152. Wollman H, Smith TC, Stephen GW, Colton III ET, Gleaton HE, Alexander SC. Effects of extremes of respiratory and metabolic alkalosis on cerebral blood flow in man. *J Appl Physiol*. 1968;24(1):60–65.
153. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg*. 1991;75(5):731–739.
154. Young WL, Ravussin PA. Y a-t-il encore une place pour l'hypocapnie profonde de routine en chirurgie intracrânienne? [Is there still a place for routine deep hypocapnia for intracranial surgery?]. *Ann Fr Anesth Reanim*. 1995;14:70–76.
155. Harper AM. Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral coretex. *J Neurol Neurosurg Psychiat*. 1966;29:398–403.
156. Paulson OB, Olesen J, Christensen MS. Restoration of autoregulation of cerebral blood flow by hypocapnia. *Neurology*. 1972;22(March):286–293.
157. Kastrup A, Happe V, Hartmann C, Schabet M. Gender-related effects of indomethacin on cerebrovascular CO2 reactivity. *J Neurol Sci*. 1999;162(2):127–132.
158. Sato M, Pawlik G, Heiss W-D. Comparative studies of regional CNS blood flow autoregulation and responses to CO_2 in the cat: Effects of altering arterial blood pressure and $PaCO_2$ on rCBF of cerebrum, cerebellum, and spinal cord. *Stroke*. 1984;15(1):91–97.
159. Kastrup A, Thomas C, Hartmann C, Schabet M. Sex dependency of cerebrovascular CO2 reactivity in normal subjects. *Stroke*. 1997;28(12):2353–2356.
160. Enevoldsen EM, Jensen FT. Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. *J Neurosurg*. 1978;48(May):689–703.
161. Ishii R. Regional cerebral blood flow in patients with ruptured intracranial aneurysms. *J Neurosurg*. 1979;50:587–594.
162. Shinoda J, Kimura T, Funakoshi T, Araki Y, Imao Y. Acetazolamide reactivity on cerebral blood flow in patients with subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1991;109:102–108.
163. Bullock R, Mendelow AD, Bone I, Patterson J, Macleod WN, Allardice G. Cerebral blood flow and CO_2 responsiveness as an indicator of collateral reserve capacity in patients with carotid arterial disease. *Br J Surg*. 1985;72(May):348–351.
164. Berre J, Moraine J-J, Melot C. Cerebral CO2 vasoreactivity evaluation with and without changes in intrathoracic pressure in comatose patients. *J Neurosurg Anesthesiol*. 1998;10(2):70–79.
165. Brown MM, Wade JPH, Marshall J. Fundamental importance of arterial oxygen content in the regulation of cerebral blood flow in man. *Brain*. 1985;108(Pt 1):81–93.
166. Wilderman MJ, Armstead WM. Role of neuronal NO synthase in relationship between NO and opioids in hypoxia-induced pial artery dilation. *Am J Physiol*. 1997;273(4 Pt 2):H1807–H1815.
167. Omae T, Ibayashi S, Kusuda K, Nakamura H, Yagi H, Fujishima M. Effects of high atmospheric pressure and oxygen on middle cerebral blood flow velocity in humans measured by transcranial Doppler. *Stroke*. 1998;29(1):94–97.
168. Steen PA, Newberg L, Milde JH, Michenfelder JD. Hypothermia and barbiturates: Individual and combined effects on canine cerebral oxygen consumption. *Anesthesiology*. 1983;58(June):527–532.
169. Klementavicius R, Nemoto EM, Yonas H. The Q_{10} ratio for basal cerebral metabolic rate for oxygen in rats. *J Neurosurg*. 1996;85(3):482–487.
170. Hoffman WE, Albrecht RF, Miletich DJ. Regional cerebral blood flow changes during hypothermia. *Cryobiology*. 1982;19:640–645.
171. Govier AV, Reves JG, McKay RD, et al. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg*. 1984;38(6):592–600.
172. Schwartz AE, Michler RE, Young WL. Cerebral blood flow during low-flow hypothermic cardiopulmonary bypass in baboons (abstract). *Anesth Analg*. 1992;74(2S):S267.
173. Schwartz AE, Kaplon RJ, Young WL, Sistino JJ, Kwiatkowski P, Michler RE. Cerebral blood flow during low-flow hypothermic cardiopulmonary bypass in baboons. *Anesthesiology*. 1994;81(4):959–964.
174. Schwartz AE, Minanov O, Stone JG, et al. Phenylephrine increases cerebral blood flow during low-flow hypothermic cardiopulmonary bypass in baboons. *Anesthesiology*. 1996;85(2):380–384.
175. Jonassen AE, Quaegebeur JM, Young WL. Cerebral blood flow velocity in pediatric patients is reduced after cardiopulmonary bypass with profound hypothermia. *J Thorac Cardiovasc Surg*. 1995;110(4 Part I): 934–943.
176. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenzie FN. Pharmacologic EEG suppression during cardiopulmonary bypass: Cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. *Anesthesiology*. 1987;67:218–224.
177. Hindman BJ, Funatsu N, Harrington J, et al. Differences in cerebral blood flow between alpha-stat and pH-stat management are eliminated during period of decreased systemic flow and pressure: A study during cardiopulmonary bypass in rabbits. *Anesthesiology*. 1991;74(6):1096–1102.
178. Henriksen L, Hjelms E, Lindeburgh T. Brain hyperperfusion during cardiac operations. Cerebral blood flow measured in man by intra-arterial injection of xenon 133: Evidence suggestive of intraoperative microembolism. *J Thorac Cardiovasc Surg*. 1983;86(2):202–208.
179. Stephan H, Sonntag H, Lange H, Rieke H. Cerebral effects of anaesthesia and hypothermia. *Anaesthesia*. 1989;44:310–316.
180. Hoffman WE, Edelman G, Kochs E, Werner C, Segil L, Albrech RF. Cerebral autoregulation in awake versus isoflurane-anesthetized rats. *Anesth Analg*. 1991;73(6):753–757.
181. McPherson RW, Brian JE, Traystman RJ. Cerebrovascular responsiveness to carbon dioxide in dogs with 1.4% and 2.8% isoflurane. *Anesthesiology*. 1989;70:843–850.
182. Ostapkovich ND, Baker KZ, Fogarty-Mack P, Sisti MB, Young WL. Cerebral blood flow and CO_2 reactivity is similar during remifentanil/N_2O and fentanyl N_2O anesthesia. *Anesthesiology*. 1998;89(2):358–363.
183. Koenig HM, Pelligrino DA, Albrecht RF. Halothane vasodilation and nitric oxide in rat pial vessels. *J Neurosurg Anesth*. 1993;5(4):264–271.
184. Kaisti KK, Langsjo JW, Aalto S, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology*. 2003;99(3):603–613.
185. Wang M, Joshi S, Emerson RG. Comparison of intracarotid and intravenous propofol for electrocerebral silence in rabbits. *Anesthesiology*. 2003;99(4):904–910.
186. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg*. 2005;10(2):524–534. table of contents.
187. Schmidt A, Ryding E, Akeson J. Racemic ketamine does not abolish cerebrovascular autoregulation in the pig. *Acta Anaesthesiol Scand*. 2003;47(5):569–575.
188. Prielipp RC, Wall MH, Tobin JR, et al. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. *Anesth Analg*. 2002;95(4):1052–1059. table of contents.
189. Zornow MH, Maze M, Dyck JB, Shafer SL. Dexmedetomidine decreases cerebral blood flow velocity in humans. *J Cereb Blood Flow Metab*. 1993;13(2):350–353.
190. Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesth Analg*. 1990;70(6):624–630.
191. Stange K, Lagerkranser M, Sollevi A. Nitroprusside-induced hypotension and cerebrovascular autoregulation in the anesthetized pig. *Anesth Analg*. 1991;73(6):745–752.
192. Albrecht RF, Miletich DJ, Madala LR. Normalization of cerebral blood flow during prolonged halothane anesthesia. *Anesthesiology*. 1983;58:26–31.
193. Brian Jr JE, Traystman RJ, McPherson RW. Changes in cerebral blood flow over time during isoflurane anesthesia in dogs. *J Neurosurg Anesthesiol*. 1990;2(2):122–130.
194. Turner DM, Kassell NF, Sasaki T, Comair YG, Boarini DJ, Beck DO. Time-dependent changes in cerebral and cardiovascular parameters in isoflurane-nitrous oxide-anesthetized dogs. *Neurosurgery*. 1984;14(2):135–141.
195. Rogers AT, Stump DA, Gravlee GP, et al. Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass: Influence of $PaCO_2$ management. *Anesthesiology*. 1988;69(4):547–551.
196. McPherson RW, Traystman RJ. Effect of time on cerebrovascular responsivity to $PaCO_2$ during isoflurane anesthesia. *Anesthesiology*. 1989;71(3A):A105.
197. Bissonnette B, Leon JE. Cerebrovascular stability during isoflurane anaesthesia in children. *Can J Anaesthesia*. 1992;39(2):128–134.

198. Roald OK, Forsman M, Steen PA. The effects of prolonged isoflurane anaesthesia on cerebral blood flow and metabolism in the dog. *Acta Anaesthesiol Scand*. 1989;33:210–213.
199. Stone JG, Young WL, Smith CR, Solomon RA, Ostapkovich N, Wang A. Do temperatures recorded at standard monitoring sites reflect actual brain temperature during deep hypothermia? (abstract). *Anesthesiology*. 1991;75(3A):A483.
200. Edvinsson L, Owman C, Siesjo B. Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. *Brain Res*. 1976;117:519–523.
201. Beausang-Linder M, Bill A. Cerebral circulation in acute arterial hypertension—Protective effects of sympathetic nervous activity. *Acta Physiol Scand*. 1981;111:193–199.
202. Heistad DD, Marcus ML, Abboud FM. Role of large arteries in regulation of cerebral blood flow in dogs. *J Clin Invest*. 1978;62(Oct):761–768.
203. Skinhoj E. The sympathetic nervous system and the regulation of cerebral blood flow. *Euro Neurol*. 1971/72;6:190–192.
204. Hernandez MJ, Raichle ME, Stone HL. The role of the sympathetic nervous system in cerebral blood flow autoregulation. *Europ Neurol*. 1971/72;6:175–179.
205. D'Alecy LG. Relation between sympathetic cerebral vasoconstriction and CSF pressure. *Europ Neurol*. 1971/72;6:180–184.
206. Heistad DD. Summary of symposium on cerebral blood flow: Effect of nerves and neurotransmitters—Cardiovascular Center, University of Iowa, Iowa City, Iowa, June 16-18, 1981. *J Cereb Blood Flow Metab*. 1981;1:447–450.
207. Beausang-Linder M. Effects of sympathetic stimulation on cerebral and ocular blood flow. *Acta Physiol Scand*. 1982;114:217–224.
208. Busija DW, Heistad DD. Effects of activation of sympathetic nerves on cerebral blood flow during hypercapnea in cats and rabbits. *J Physiol*. 1974;347:195.
209. Puig M, Kirpekar SM. Inhibitory effect of low pH on norepinephrine release. *J Pharmacol Exp Ther*. 1967;176:134–138.
210. Verhaeghe RH, Lorenz RR, McGrath MA, Shepherd JT, Vanhoutte PM. Metabolic modulation of neurotransmitter release – adenosine, adenine nucleotides, potassium, hyperosmolarity, and hydrogen ion. *Fed Proc*. 1978;37:208–211.
211. Faraci FM, Mayhan WG, Werber AH, Heistad DD. Cerebral circulation: Effects of sympathetic nerves and protective mechanisms during hypertension. *Circ Res*. 1987;61(suppl II):II-102–II-106.
212. Fitch W, Ferguson GG, Sengupta D, Garibi J, Harper AM. Autoregulation of cerebral blood flow during controlled hypotension in baboons. *J Neurol Neurosurg Psychiatry*. 1976;39:1014–1022.
213. Kano M, Moskowitz MA, Yokota M. Parasympathetic denervation of rat pial vessels significantly increases infarction volume following middle cerebral artery occlusion. *J Cereb Blood Flow Metab*. 1991;11(4):628–637.
214. Moskowitz MA, Sakas DE, Wei EP, et al. Postocclusive cerebral hyperemia is markedly attenuated by chronic trigeminal ganglionectomy. *Am J Physiol*. 1989;257:H1736–H1739.
215. Branston NM, Umemura A, Koshy A. Contribution of cerebrovascular parasympathetic and sensory innervation to the short-term control of blood flow in rat cerebral cortex. *J Cereb Blood Flow Metab*. 1995;15(3):525–531.
216. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39(April):183–238.
217. Olesen J. Quantitative evaluation of normal and pathologic cerebral blood flow regulation to perfusion pressure. *Arch Neurol*. 1973;28 (March):143–149.
218. Yang G, Zhang Y, Ross ME, Iadecola C. Attenuation of activity-induced increases in cerebellar blood flow in mice lacking neuronal nitric oxide synthase. *Am J Physiol Heart Circ Physiol*. 2003;285(1):H298–H304.
219. Lindauer U, Megow D, Matsuda H, Dirnagl U. Nitric oxide: A modulator, but not a mediator, of neurovascular coupling in rat somatosensory cortex. *Am J Physiol*. 1999;277(2 Pt 2):H799–H811.
220. Metea MR, Newman EA. Glial cells dilate and constrict blood vessels: A mechanism of neurovascular coupling. *J Neurosci*. 2006;26(11):2862–2870.
221. Ou JW, Kumar Y, Alioua A, Sailer C, Stefani E, Toro L. Ca2+- and thromboxane-dependent distribution of MaxiK channels in cultured astrocytes: From microtubules to the plasma membrane. *Glia*. 2009;57(12):1280–1295.
222. Blanco VM, Stern JE, Filosa JA. Tone-dependent vascular responses to astrocyte-derived signals. *Am J Physiol Heart Circ Physiol*. 2008;294(6):H2855–H2863.
223. Cold G, Christensen M, Schmidt K. Effect of two levels of induced hypocapnia on cerebral autoregulation in the acute phase of head injury coma. *Acta Anaesthesiol Scand*. 1981;25:397–401.
224. Shiokawa O, Sadoshima S, Kusuda K, Nishimura Y, Ibayashi S, Fujishima M. Cerebral and cerebellar blood flow autoregulations in acutely induced cerebral ischemia in spontaneously hypertensive rats—Transtentorial remote effect. *Stroke*. 1986;17(6):1309–1313.
225. Young WL, Prohovnik I, Ornstein E, et al. The effect of arteriovenous malformation resection on cerebrovascular reactivity to carbon dioxide. *Neurosurgery*. 1990;27(2):257–267.
226. Andrews RJ. Transhemispheric diaschisis: A review and comment. *Stroke*. 1991;22(7):943–949.
227. Edelman RR, Mattle HP, Atkinson DJ, et al. Cerebral blood flow: Assessment with dynamic contrast-enhanced T2*-weighted MR imaging at 1.5-T[1]. *Radiology*. 1990;176(1):211–220.
228. Choi DW. Cerebral hypoxia: Some new approaches and unanswered questions. *J Neurosci*. 1990;10(8):2493–2501.
229. Branston NM, Hope DT, Symon L. Barbiturates in focal ischemia of primate cortex: Effects on blood flow distribution, evoked potential and extracellular potassium. *Stroke*. 1979;10(6):647–653.
230. Drummond JC, Oh Y-S, Cole DJ, Shapiro HM. Phenylephrine-induced hypertension reduces ischemia following middle cerebral artery occlusion in rats. *Stroke*. 1989;20(11):1538–1544.
231. Schroeder T, Sillesen H, Engell HC. Hemodynamic effect of carotid endarterectomy. *Stroke*. 1987;18:204–209.
232. Spetzler RF, Wilson CB, Weinstein P, Mehdorn M, Townsend J, Telles D. Normal perfusion pressure breakthrough theory. *Clin Neurosurg*. 1978;25:651–672.
233. Nornes H, Knutzen HB, Wikeby P. Cerebral arterial blood flow and aneurysm surgery: Part 2. Induced hypotension and autoregulation capacity. *J Neurosurg*. 1977;47:819–827.
234. Halbach V, Higashida RT, Hieshima G, Norman D. Normal perfusion pressure breakthrough occurring during treatment of carotid and vertebral fistulas. *Am J Neuroradiol*. 1987;8:751–756.
235. Irikura K, Morii S, Miyasaka Y, Yamada M, Tokiwa K, Yada K. Impaired autoregulation in an experimental model of chronic cerebral hypoperfusion in rats. *Stroke*. 1996;27(8):1399–1404.
236. Young WL, Kader A, Prohovnik I, et al. Pressure autoregulation is intact after arteriovenous malformation resection. *Neurosurgery*. 1993;32(4):491–497.
237. Young WL, Kader A, Ornstein E, et al. Cerebral hyperemia after arteriovenous malformation resection is related to "breakthrough" complications but not to feeding artery pressure. *Neurosurgery*. 1996;38(6):1085–1093. discussion 1093–1095.
238. Joshi S, Young WL. Arteriovenous malformation. In: Atlee JL, ed. *Complications in Anesthesia*. Philadelphia: WB Saunders Co; 1999:744–747.
239. Halsey Jr JH, Conger KA, Garcia JH, Sarvary E. The contribution of reoxygenation to ischemic brain damage. *J Cereb Blood Flow Metab*. 1991;11(6):994–1000.
240. Pulsinelli WA, Levy DE, Duffy TE. Regional cerebral blood flow and glucose metabolism following transient forebrain ischemia. *Ann Neurol*. 1982;11(5):499–509.
241. Michenfelder JD, Milde JH, Katusic ZS. Postischemic canine cerebral blood flow is coupled to cerebral metabolic rate. *J Cereb Blood Flow Metab*. 1991;11(4):611–616.
242. Connolly Jr E, Winfree CJ, Springer TA, et al. Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion. Role of neutrophil adhesion in the pathogenesis of stroke. *J Clin Investig*. 1996;97(1):209–216.
243. Cockroft KM, Meistrell 3rd. M, Zimmerman GA, et al. Cerebroprotective effects of aminoguanidine in a rodent model of stroke. *Stroke*. 1996;27(8):1393–1398.
244. Dogan A, Rao AM, Baskaya MK, et al. Effects of ifenprodil, a polyamine site NMDA receptor antagonist, on reperfusion injury after transient focal cerebral ischemia. *J Neurosurg*. 1997;87(6):921–926.
245. Prohovnik I, Knudsen E, Risberg J. Accuracy of models and algorithms for determination of fast-compartment flow by noninvasive 133Xe clearance. In: Magistretti PL, ed. *Functional Radionuclide Imaging of the Brain*. New York: Raven Press; 1983:87–115.
246. Kazumata K, Tanaka N, Ishikawa T, Kuroda S, Houkin K, Mitsumori K. Dissociation of vasoreactivity to acetazolamiode and hypercapnia. Comparative study in patients with chronic occlusive major cerebral artery disease. *Stroke*. 1996;27(11):2052–2058.
247. Powers WJ, Raichle ME. Positron emission tomography and its application to the study of cerebrovascular disease in man (Progress Review). *Stroke*. 1985;16(3):361–376.
248. Pavlakis S, Bello J, Prohovnik I, et al. Brain infarction in sickle cell anemia: Magnetic resonance imaging correlates. *Ann Neurol*. 1988;23:125–130.
249. Yamamoto M, Meyer JS, Sakai F, Yamaguchi F. Aging and cerebral vasodilator responses to hypercarbia: Responses in normal aging and in persons with risk factors for stroke. *Arch Neurol*. 1980;37(Aug):489–496.

250. Prohovnik I, Knudsen E, Risberg J. Theoretical evaluation and simulation test of the Initial Slope Index for noninvasive rCBF. In: Hartmann A, Hoyer S, eds. *Cerebral Blood Flow and Metabolism Measurement*. Berlin: Springer Verlag; 1985:56–60.
251. Wade JPH, Hachinski VC. Cerebral steal: Robbery or maldistribution?. In: Wood JH, ed. *Cerebral Blood Flow: Physiologic and Clinical Aspects*. New York: McGraw-Hill Book Company; 1987:467–480.
252. Boysen G, Engell HC, Henriksen H. The effect of induced hypertension on internal carotid artery pressure and regional cerebral blood flow during temporary carotid clamping for endarterectomy. *Neurology*. 1972;22(11):1133–1144.
253. Mast H, Mohr JP, Osipov A, et al. "Steal" is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. *Stroke*. 1995;26(7):1215–1220.
254. Solomon RA, Fink ME, Lennihan L. Prophylactic volume expansion therapy for the prevention of delayed cerebral ischemia after early aneurysm surgery. *Arch Neurol*. 1988;45(March):325–332.
255. Grubb RL, Raichle ME, Eichling JO, Gado MH. Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans. *J Neurosurg*. 1977;46(April):446–453.
256. Duong H, Hacein-Bey L, Vang MC, Pile-Spellman J, Joshi S, Young WL. Management of cerebral arterial occlusion during endovascular treatment of cerebrovascular disease. *Probl Anesth: Controversies in Neuroanesthesia*. 1997;9(1):99–111.
257. Young WL, Solomon RA, Pedley TA, et al. Direct cortical EEG monitoring during temporary vascular occlusion for cerebral aneurysm surgery. *Anesthesiology*. 1989;71:794–799.
258. Miller JA, Dacey Jr RG, Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke*. 1995;26(12):2260–2266.
259. Ehrenfeld WK, Hamilton FN, Larson Jr CP, Hickey RF, Severinghaus JW. Effect of CO_2 and systemic hypertension on downstream cerebral arterial pressure during carotid endarterectomy. *Surgery*. 1970;67(1):87–96.
260. Fourcade HE, Larson Jr CP, Ehrenfield WK, Hickey RF, Newton TH. The effects of CO_2 and systemic hypertension on cerebral perfusion pressure during carotid endarterectomy. *Anesthesiology*. 1970;33(4):383–390.
261. McKay RD, Sundt TM, Michenfelder JD, et al. Internal carotid artery stump pressure and cerebral blood flow during carotid endarterectomy: Modification by halothane, enflurane, and innovar. *Anesthesiology*. 1976;45(4):390–399.
262. Archie Jr JP. Technique and clinical results of carotid stump backpressure to determine selective shunting during carotid endarterectomy. *J Vasc Surg*. 1991;13(2):319–327.
263. Batjer HH, Frankfurt AI, Purdy PD, Smith SS, Samson DS. Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. *J Neurosurg*. 1988;68(Feb):234–240.
264. Buckland MR, Batjer HH, Giesecke AH. Anesthesia for cerebral aneurysm surgery: Use of induced hypertension in patients with symptomatic vasospasm. *Anesthesiology*. 1988;69:116–119.
265. Drummond JC. Deliberate hypotension for intracranial aneurysm surgery: Changing practices (Letter to the editor). *Can J Anaesth*. 1991;38(7):935–936.
266. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery*. 1982;11(3):337–343.
267. Awad IA, Carter LP, Spetzler RF, Medina M, Williams Fred WJ. Clinical vasospasm after subarachnoid hemorrhage: Response to hypervolemic hemodilution and arterial hypertension. *Stroke*. 1987;18(2):365–372.
268. Muizelaar JP, Becker D. Induced hypertension for the treatment of cerebral ischemia after subarachnoid hemorrhage. *Surg Neurol*. 1986;25:317–325.
269. Joshi S, Ornstein E, Young WL. Points of View: Augmenting cerebral perfusion pressure: When is enough too much? (editorial). *J Neurosurg Anesthesiol*. 1996;8(3):249–253.
270. Warner DS, Hansen TD, Vust L, Todd MM. Distribution of cerebral blood flow during deep isoflurane vs. pentobarbital anesthesia in rats with middle cerebral artery occlusion. *J Neurosurg Anesthesiol*. 1989;1(3):219–226.
271. Soloway M, Moriarty G, Fraser JG, White RJ. Effect of delayed hyperventilation on experimental cerebral infarction. *Neurology*. 1971;21:479–485.
272. Soloway M, Nadel W, Albin MS, White RJ. The effect of hyperventilation on subsequent cerebral infarction. *Anesthesiology*. 1968;29:975–980.
273. Drummond JC, Ruta TS, Cole DJ, Zornow MH, Shapiro HM. The effect of hypocapnia on cerebral blood flow distribution during middle cerebral artery occlusion in the rat. *J Neurosurg Anesthesiol*. 1989;1(2):163–164.
274. Artru AA, Merriman HG. Hypocapnia added to hypertension to reverse EEG changes during carotid endarterectomy (Case report). *Anesthesiology*. 1989;70:1016–1018.
275. Michenfelder JD, Sundt Jr TM. The effect of $PaCO_2$ on the metabolism of ischemic brain in squirrel monkeys. *Anesthesiology*. 1973;38(5):445–453.
276. Baker WH, Rodman JA, Barnes RW, Hoyt JL. An evaluation of hypocarbia and hypercarbia during carotid endarterectomy. *Stroke*. 1976;7(5):451–454.
277. Christensen MS, Brodersen P, Olesen J, Paulson OB. Cerebral apoplexy (stroke) treated with or without prolonged artificial hyperventilation: 2. Cerebrospinal fluid acid-base balance and intracranial pressure. *Stroke*. 1973;4:620–631.
278. Mohr JP, Petty GW, Sacco RL. Recent advances in cerebrovascular disease. *Curr Neurol*. 1989;9:77–108.
279. Pistolese GR, Faraglia V, Agnoli A, et al. Cerebral hemispheric "counter-steal" phenomenon during hyperventilation in cerebrovascular diseases. *Stroke*. 1972;3(July-Aug):456–461.
280. Ochiai C, Asano T, Takakura K, Fukuda T, Horizoe H, Morimoto Y. Mechanisms of cerebral protection by pentobarbital and Nizofenone correlated with the course of local cerebral blood flow changes. *Stroke*. 1982;13(6):788–795.
281. Young WL, Prohovnik I, Correll JW, Ornstein E, Matteo RS, Ostapkovich N. Cerebral blood flow and metabolism in patients undergoing anesthesia for carotid endarterectomy: A comparison of isoflurane, halothane, and fentanyl. *Anesth Analg*. 1989;68:712–717.
282. Oskouian Jr RJ, Martin NA, Lee JH, et al. Multimodal quantitation of the effects of endovascular therapy for vasospasm on cerebral blood flow, transcranial doppler ultrasonographic velocities, and cerebral artery diameters. *Neurosurgery*. 2002;51(1):30–41; discussion 41–43.
283. Kassell NF, Helm G, Simmons N, Phillips CD, Cail WS. Treatment of cerebral vasospasm with intra-arterial papaverine. *J Neurosurg*. 1992;77(6):848–852.
284. Joshi S, Emala CW, Pile-Spellman J. Intra-arterial drug delivery: A concise review. *J Neurosurg Anesthesiol*. 2007;19(2):111–119.
285. Joshi S, Meyers PM, Ornstein E. Intracarotid delivery of drugs: The potential and the pitfalls. *Anesthesiology*. 2008;109(3):543–564.
286. Feng L, Fitzsimmons BF, Young WL, et al. Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: Safety and 2-year experience. *AJNR: Am J Neuroradiol*. 2002;23(8):1284–1290.
287. Badjatia N, Topcuoglu MA, Pryor JC, et al. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *AJNR: Am J Neuroradiol*. 2004;25(5):819–826.
288. Cross III DT, Moran CJ, Angtuaco EE, Milburn JM, Diringer MN, Dacey Jr RG. Intracranial pressure monitoring during intraarterial papaverine infusion for cerebral vasospasm. *Am J Neuroradiol*. 1998;19(7):1319–1323.
289. Joshi S, Ornstein E, Bruce JN. Targeting the brain: Rationalizing the novel methods of drug delivery to the central nervous system. *Neurocrit Care*. 2007;6(3):200–212.
290. Joshi SEJ, Emala CW. Revisiting intra-arterial drug delivery for treating brain diseases or is it "déjà- vu, all over again"? *J Neuroanaesthesiol Crit Care*. 2014;1(2):108–115.
291. Joshi S, Wang M, Etu JJ, Nishanian EV, Pile-Spellman J. Cerebral blood flow affects dose requirements of intracarotid propofol for electrocerebral silence. *Anesthesiology*. 2006;104(2):290–298.
292. Joshi S, Wang M, Etu JJ, Pile-Spellman J. Bolus configuration affects dose requirements of intracarotid propofol for electroencephalographic silence. *Anesth Analg*. 2006;102(6):1816–1822.
293. Joshi S, Wang M, Etu JJ, et al. Transient cerebral hypoperfusion enhances intraarterial carmustine deposition into brain tissue. *J Neurooncol*. 2008;86(2):123–132.
294. Joshi S, Wang M, Etu JJ, Pile-Spellman J. Reducing cerebral blood flow increases the duration of electroencephalographic silence by intracarotid thiopental. *Anesthesia & Analgesia*. 2005;101(3):851–858.
295. Dedrick RL. Arterial drug infusion: pharmacokinetic problems and pitfalls. *J Natl Cancer Inst*. 1988;80(2):84–89.
296. Dedrick RL. Interspecies scaling of regional drug delivery. *J Pharm Sci*. 1986;75(11):1047–1052.
297. Cloughesy TF, Gobin YP, Black KL, et al. Intra-arterial carboplatin chemotherapy for brain tumors: A dose escalation study based on cerebral blood flow. *J Neurooncol*. 1997;35(2):121–131.
298. Gobin YP, Cloughesy TF, Chow KL, et al. Intraarterial chemotherapy for brain tumors by using a spatial dose fractionation algorithm and pulsatile delivery. *Radiology*. 2001;218(3):724–732.
299. Joshi SS-MR, Wang M, Chaudhuri D, Straubinger N, Straubinger R, Bigio IJ. The effectiveness of transient cerebral hypoperfusion assisted intra-arterial delivery of cationic liposomes. *J Neurosurg Anesthesiol*. 2013;25(4):488–489.

300. Elkassabany NM, Bhatia J, Deogaonkar A, et al. Perioperative complications of blood brain barrier disruption under general anesthesia: A retrospective review. *J Neurosurg Anesthesiol*. 2008;20(1):45–48.
301. Jones DR, Hall SD, Jackson EK, Branch RA, Wilkinson GR. Brain uptake of benzodiazepines: Effects of lipophilicity and plasma protein binding. *J Pharmacol Exp Ther*. 1988;245(3):816–822.
302. Mourant JR, Johnson TM, Los G, Bigio IJ. Non-invasive measurement of chemotherapy drug concentrations in tissue: Preliminary demonstrations of in vivo measurements. *Phys Med Biol*. 1999;44(5):1397–1417.
303. Kanick SC, Eiseman JL, Joseph E, Guo J, Parker RS. Noninvasive and nondestructive optical spectroscopic measurement of motexafin gadolinium in mouse tissues: Comparison to high-performance liquid chromatography. *J Photochem Photobiol B*. 2007;88(2-3):90–104.
304. Reif R, Wang M, Joshi S, A'Amar O, Bigio IJ. Optical method for real-time monitoring of drug concentrations facilitates the development of novel methods for drug delivery to brain tissue. *J Biomed Opt*. 2007;12(3):034036.
305. Neuwelt E, Abbott NJ, Abrey L, et al. Strategies to advance translational research into brain barriers. *Lancet Neurol*. 2008;7(1):84–96.
306. Bellavance MA, Blanchette M, Fortin D. Recent advances in blood-brain barrier disruption as a CNS delivery strategy. *AAPS J*. 2008;10(1):166–177.
307. Wang M, Etu J, Joshi S. Enhanced disruption of the blood brain barrier by intracarotid mannitol injection during transient cerebral hypoperfusion in rabbits. *J Neurosurg Anesthesiol*. 2007;19(4):249–256.
308. Frost JJ, Wagner Jr HN. *Quantitative Imaging: Neuroreceptors, Neurotransmitters, and Enzymes*. New York: Raven Press; 1990.
309. Enblad P, Valtysson J, Andersson J, et al. Simultaneous intracerebral microdialysis and positron emission tomography in the detection of ischemia in patients with subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 1996;16(4):637–644.
310. Ingvar M, Eriksson L, Greitz T, et al. Methodological aspects of brain activation studies: Cerebral blood flow determined with [^{15}O] butanol and positron emission tomography. *J Cereb Blood Flow Metab*. 1994;14(4):628–638.
311. Heiss W-D, Graf R, Fujita T, et al. Early detection of irreversibly damaged ischemic tissue by flumazenil positron emission tomography in cats. *Stroke*. 1997;28(10):2045–2052.
312. Alkire MT, Haier RJ, Shah NK, Anderson CT. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. *Anesthesiology*. 1997;86(3):549–557.
313. Archer DP, Labrecque P, Tyler JL, et al. Measurement of cerebral blood flow and volume with positron emission tomography during isoflurane administration in the hypocapnic baboon. *Anesthesiology*. 1990;72:1031–1037.
314. Firestone LL, Gyulai F, Mintun M, Adler LJ, Urso K, Winter PM. Human brain activity response to fentanyl imaged by positron emission tomography. *Anesth Analg*. 1996;82(6):1247–1251.
315. Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao J. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography [see comment in Anesthesiology 1995 Oct;83(4):888-889]. *Anesthesiology*. 1995;82(2):393–403; discussion 27A.
316. Brooks DJ, Frackowiak RSJ, Lammertsma AA. A comparison between regional cerebral blood flow measurements obtained in human subjects using ^{11}C-methylalbumin microspheres, the C$^{15}O_2$ steady-state method, and positron emission tomography. *Acta Neurol Scand*. 1986;73:415–422.
317. Van Heertum RL, Tikofsky RS. *Advances in Cerebral SPECT Imaging: An Atlas and Guideline for Practitioners*. Philadelphia: Lea & Febiger; 1989. p. 62.
318. Lassen NA, Blasberg RG. Technetium-99 m—d, l-HM-PAO. The development of a new class of 99mTc-labeled tracers: An overview. *J Cereb Blood Flow Metab*. 1988;8:S1–S3.
319. Sperling B, Lassen NA. Hyperfixation of HMPAO in subacute ischemic stroke leading to spuriously high estimates of cerebral blood flow by SPECT. *Stroke*. 1993;24(2):193–194.
320. Devous Sr. MD, Payne JK, Lowe JL, Leroy RF. Comparison of technetium-99 m-ECD to xenon-133 SPECT in normal controls and in patients with mild to moderate regional cerebral blood flow abnormalities. *J Nucl Med*. 1993;34(5):754–761.
321. Yudd AP, Van Heertum RL, Masdeu JC. Interventions and functional brain imaging. *Semin Nucl Med*. 1991;21(2):153–158.
322. Hirano T, Minematsu K, Hasegawa Y, Tanaka Y, Hayashida K, Yamaguchi T. Acetazolamide reactivity on ^{123}I-IMP single photon emission computed tomography in patients with major cerebral artery occlusive disease: Correlation with positron emission tomography parameters. *J Cereb Blood Flow Metab*. 1994;14(5):763–770.
323. Roussel SA, van Bruggen N, King MD, Gadian DG. Identification of collaterally perfused areas following focal cerebral ischemia in the rat by comparison of gradient echo and diffusion-weighted MRI. *J Cereb Blood Flow Metab*. 1995;15(4):578–586.
324. Belliveau JW, Cohen MS, Weisskoff RM, Buchbinder BR, Rosen BR. Functional studies of the human brain using high-speed magnetic resonance imaging. *J Neuroimaging*. 1991;1(1):36–41.
325. Branch CA, Helpern JA, Ewing JR, Welch KMA. ^{19}F NMR imaging of cerebral blood flow. *Magn Reson Med*. 1991;20(1):151–157.
326. Larson KB, Perman WH, Perlmutter JS, Gado MH, Ollinger JM, Zierler K. Tracer-kinetic analysis for measuring regional cerebral blood flow by dynamic nuclear magnetic resonance imaging. *J Theor Biol*. 1994;170(1):1–14.
327. Calamante F, Gadian DG, Connelly A. Quantification of perfusion using bolus tracking magnetic resonance imaging in stroke: Assumptions, limitations, and potential implications for clinical use. *Stroke*. 2002;33(4):1146–1151.
328. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques [In Process Citation]. *J Cereb Blood Flow Metab*. 1999;19(7):701–735.
329. Thomas DL, Lythgoe MF, Calamante F, Gadian DG, Ordidge RJ. Simultaneous noninvasive measurement of CBF and CBV using double-echo FAIR (DEFAIR). *Magn Reson Med*. 2001;45(5):853–863.
330. Posse S, Olthoff U, Weckesser M, Jancke L, Muller-Gartner H-W, Dager SR. Regional dynamic signal changes during controlled hyperventilation assessed with blood oxygen level-dependent functional MR imging. *Am J Neuroradiol*. 1997;18(October):1763–1770.
331. Litt L, Gonzalez-Mendez R, Severinghaus JW, et al. Cerebral intracellular changes during supercarbia: An in vivo ^{31}P nuclear magnetic resonance study in rats. *J Cereb Blood Flow Metab*. 1985;5(4):537–544.
332. Ra JB, Hilal SK, Oh CH, Mun IK. In vivo magnetic resonance imaging of sodium in the human body. *Magn Reson Med*. 1988;7(1):11–22.
333. Calamante F, Vonken EJ, van Osch MJ. Contrast agent concentration measurements affecting quantification of bolus-tracking perfusion MRI. *Magn Reson Med*. 2007;58(3):544–553.
334. Hoehner PJ, Dean JM, Rogers MC, Traystman RJ. Comparison of thermal clearance measurement of regional cerebral blood flow with radiolabelled microspheres. *Stroke*. 1987;18:606–611.
335. Mazzeo AT, Bullock R. Effect of bacterial meningitis complicating severe head trauma upon brain microdialysis and cerebral perfusion. *Neurocrit Care*. 2005;2(3):282–287.
336. Vajkoczy P, Roth H, Horn P, et al. Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a novel thermal diffusion microprobe. *J Neurosurg*. 2000;93(2):265–274.
337. Joshi S, Hartl R, Wang M, et al. The acute cerebrovascular effects of intracarotid adenosine in nonhuman primates. *Anesthesia & Analgesia*. 2003;97(1):231–237.
338. Jaeger M, Soehle M, Schuhmann MU, Winkler D, Meixensberger J. Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. *Acta Neurochir (Wien)*. 2005;147(1):51–56; discussion 56.
339 Aaslid R, Markwalder T-M, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57(Dec):769–774.
340. Aaslid R. *Transcranial Doppler Sonography*. New York: Springer-Verlag; 1986:177.
341. Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. *Proc Roy Soc Med*. 1974;67:447–449.
342. Czosnyka M, Richards HK, Whitehouse HE, Pickard JD. Relationship between transcranial Doppler-determined pulsatility index and cerebrovascular resistance: An experimental study. *J Neurosurg*. 1996;84(1):79–84.
343. Kontos HA. Validity of cerebral arterial blood flow calculations from velocity measurements (Editorial). *Stroke*. 1989;20(1):1–3.
344. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries: Angiographic determination in man. *Invest Radiol*. 1967;2(Jan-Feb):17–32.
345. Poulin MJ, Robbins PA. Indexes of flow and cross-sectional area of the middle cerebral artery using Doppler ultrasound during hypoxia and hypercapnia in humans. *Stroke*. 1996;27(12):2244–2250.
346. White RP, Deane C, Vallance P, Markus HS. Nitric oxide synthase inhibition in humans reduces cerebral blood flow but not the hyperemic response to hypercapnia. *Stroke*. 1998;29(2):467–472.
347. Laumer R, Steinmeier R, Gonner F, Vogtmann T, Priem R, Fahlbusch R. Cerebral hemodynamics in subarachnoid hemorrhage evaluated by transcranial Doppler sonography: Part 1. Reliability of flow velocities in clinical management. *Neurosurgery*. 1993;33(1):1–9.
348. Romner B, Bellner J, Kongstad P, Sjoholm H. Elevated transcranial Doppler flow velocities after severe head injury: Cerebral vasospasm or hyperemia? *J Neurosurg*. 1996;85(1):90–97.
349. Giller CA, Hatab MR, Giller AM. Estimation of vessel flow and diameter during cerebral vasospasm using transcranial Doppler indices [with

Comments by Newell DW, Aaslid R; and Macdonald RL, Smith RR, Awad IA]. *Neurosurgery*. 1998;42(5):1076–1082.
350. Finn JP, Quinn MW, Hall-Craggs MA, Kendall BE. Impact of vessel distortion on transcranial Doppler velocity measurements: Correlation with magnetic resonance imaging. *J Neurosurg*. 1990;73(Oct):572–575.
351. Halsey JH. Effect of emitted power on waveform intensity in transcranial Doppler. *Stroke*. 1990;21(11 (Nov)):1573–1578.
352. Lindegaard K-F, Grolimund P, Aaslid R, Nornes H. Evaluation of cerebral AVM's using transcranial Doppler ultrasound. *J Neurosurg*. 1986;65(Sept):335–344.
353. Aaslid R. Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke*. 1987;18(4):771–775.
354. Aaslid R, Lindegaard K-F, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989;20(1):45–52.
355. Kuo TB-J, Chern C-M, Sheng W-Y, Wong W-J, Hu H-H. Frequency domain analysis of cerebral blood flow velocity and its correlation with arterial blood pressure. *J Cereb Blood Flow Metab*. 1998;18(3):311–318.
356. Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. *Stroke*. 1989;20:53–58.
357. Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: A comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology*. 2007;107(4):563–569.
358. Bishop CCR, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: A validation study. *Stroke*. 1986;17(5):913–915.
359. Markwalder T-M, Grolimund P, Seiler RW, Roth F, Aaslid R. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure—A transcranial ultrasound Doppler study. *J Cereb Blood Flow Metab*. 1984;4:368–372.
360. Pilato MA, Bissonnette B, Lerman J. Transcranial Doppler: Response of cerebral blood-flow velocity to carbon dioxide in anaesthetized children. *Can J Anaesth*. 1991;38(1):37–42.
361. Lam AM, Manninen PH, Ferguson GG, Nantau W. Monitoring electrophysiologic function during carotid endarterectomy: A comparison of somatosensory evoked potentials and conventional electroencephalogram. *Anesthesiology*. 1991;75(1):15–21.
362. Murkin JM, Lee DH. Transcranial Doppler verification of pulsatile cerebral blood flow during cardiopulmonary bypass (abstract). *Anesth Analg*. 1991;72:S194.
363. Bunegin L, Wahl D, Albin MS. Detection and volume estimation of embolic air in the middle cerebral artery using transcranial Doppler sonography. *Stroke*. 1994;25(3):593–600.
364. Gilsbach J, Hassler W. Intraoperative Doppler and real time sonography in neurosurgery. *Neurosurg Rev*. 1984;7:199–208.
365. Hassler W. Hemodynamic aspects of cerebral angiomas. *Acta Neurochir (Wien)*. 1986;(Suppl 37):136. Vienna: Springer-Verlag.
366. Chaloupka JC, Vinuela F, Malanum RP, et al. Technical feasibility and performance studies of a Doppler guide wire for potential neuroendovascular applications. *Am J Neuroradiol*. 1994;15(3 (March)):503–507.
367. Chaloupka JC, Vinuela F, Kimme-Smith C, Robert J, Duckwiler GR. Use of a Doppler guide wire for intravascular blood flow measurements: A validation study for potential neurologic endovascular applications. *AJNR Am J Neuroradiol*. 1994;15(3):509–517.
368. Henkes H, Nahser HC, Klotzsch C, Diener HC, Kuhne D. Endovascular Doppler sonography of intracranial blood vessels. Technical indications and potential applications. [German]. *Radiologe*. 1993;33(11):645–649.
369. Rampil IJ. Cerebral perfusion mapping with ultrasound contrast. *Anesthesiology*. 1991;75(3A):A1006.
370. Roche-Labarbe N, Fenoglio A, Radhakrishnan H, et al. Somatosensory evoked changes in cerebral oxygen consumption measured non-invasively in premature neonates. *Neuroimage*. 2014;85(Pt 1):279–286.
371. Sakadzic S, Mandeville ET, Gagnon L, et al. Large arteriolar component of oxygen delivery implies a safe margin of oxygen supply to cerebral tissue. *Nat Commun*. 2014;5:5734.
372. Selb J, Boas DA, Chan ST, Evans KC, Buckley EM, Carp SA. Sensitivity of near-infrared spectroscopy and diffuse correlation spectroscopy to brain hemodynamics: Simulations and experimental findings during hypercapnia. *Neurophotonics*. 2014;1(1).
373. Yao J, Wang LV. Breakthrough in photonics 2013: Photoacoustic tomography in biomedicine. *IEEE Photonics J*. 2014;6(2).
374. Ehlis AC, Schneider S, Dresler T, Fallgatter AJ. Application of functional near-infrared spectroscopy in psychiatry. *Neuroimage*. 2014;85(Pt 1): 478–488.
375. Srinivasan VJ, Atochin DN, Radhakrishnan H, et al. Optical coherence tomography for the quantitative study of cerebrovascular physiology. *J Cereb Blood Flow Metab*. 2011;31(6):1339–1345.
376. Srinivasan VJ, Radhakrishnan H, Lo EH, et al. OCT methods for capillary velocimetry. *Biomed Optic Express*. 2012;3(3):612–629.
377. Srinivasan VJ, Sakadzic S, Gorczynska I, et al. Depth-resolved microscopy of cortical hemodynamics with optical coherence tomography. *Opt Lett*. 2009;34(20):3086–3088.
378. Devor A, Sakadzic S, Srinivasan VJ, et al. Frontiers in optical imaging of cerebral blood flow and metabolism. *J Cereb Blood Flow Metab*. 2012;32(7):1259–1276.
379. Blinder P, Tsai PS, Kaufhold JP, Knutsen PM, Suhl H, Kleinfeld D. The cortical angiome: an interconnected vascular network with noncolumnar patterns of blood flow. *Nat Neurosci*. 2013;16(7):889–897.
380. Yaseen MA, Srinivasan VJ, Sakadzic S, et al. Microvascular oxygen tension and flow measurements in rodent cerebral cortex during baseline conditions and functional activation. *J Cereb Blood Flow Metab*. 2011;31(4):1051–1063.
381. Yuzawa I, Sakadzic S, Srinivasan VJ, et al. Cortical spreading depression impairs oxygen delivery and metabolism in mice. *J Cereb Blood Flow Metab*. 2012;32(2):376–386.
382. Jain RK, Munn LL, Fukumura D. Dissecting tumour pathophysiology using intravital microscopy. *Nat Rev Cancer*. 2002;2(4):266–276.
383. Rovainen CM, Woolsey TA, Blocher NC, Wang DB, Robinson OF. Blood flow in single surface arterioles and venules on the mouse somatosensory cortex measured with videomicroscopy, fluorescent dextrans, nonoccluding fluorescent beads, and computer-assisted image analysis. *J Cereb Blood Flow Metab*. 1993;13(3):359–371.
384. Cabrales P, Carvalho LJ. Intravital microscopy of the mouse brain microcirculation using a closed cranial window. *J Vis Exp*. 2010;45.
385. Humeau A, Steenbergen W, Nilsson H, Stromberg T. Laser Doppler perfusion monitoring and imaging: Novel approaches. *Med Biol Eng Comput*. 2007;45(5):421–435.
386. Fukuda O, Endo S, Kuwayama N, Harada J, Takaku A. The characteristics of laser-Doppler flowmetry for the measurement of regional cerebral blood flow. *Neurosurgery*. 1995;36(2):358–364.
387. Meyerson BA, Gunasekera L, Linderoth B, Gazelius B. Bedside monitoring of regional cortical blood flow in comatose patients using laser Doppler flowmetry. *Neurosurgery*. 1991;29(5):750–755.
388. Dirnagl U, Pulsinelli W. Autoregulation of cerebral blood flow in experimental focal brain ischemia. *J Cereb Blood Flow Metab*. 1990;10:327–336.
389. Kramer MS, Vinall PE, Katolik LI, Simeone FA. Comparison of cerebral blood flow measured by laser-Doppler flowmetry and hydrogen clearance in cats after cerebral insult and hypervolemic hemodilution. *Neurosurgery*. 1996;38(2):355–361.
390. Fabricius Mt, Lauritzen M. Laser-Doppler evaluation of rat brain microcirculation: Comparison with the [^{14}C]-iodoantipyrine method suggests discordance during cerebral blood flow increases. *J Cereb Blood Flow Metab*. 1996;16(1):156–161.
391. Steinmeier R, Fahlbusch R, Powers AD, Dotterl A, Buchfelder M. Pituitary microcirculation: Physiological aspects and clinical implications. A laser-Doppler flow study during transsphenoidal adenomectomy. *Neurosurgery*. 1991;29(1):47–54.
392. Johnson WD, Bolognese P, Miller JI, Heger IM, Liker MA, Milhorat TH. Continuous postoperative ICBF monitoring in aneurysmal SAH patients using a combined ICP-laser Doppler fiberoptic probe. *J Neurosurg Anesthesiol*. 1996;8(3):199–207.
393. Nakase H, Kaido T, Okuno S, Hoshida T, Sakaki T. Novel intraoperative cerebral blood flow monitoring by laser-Doppler scanner. *Neurol Med Chir (Tokyo)*. 2002;42(1):1–4.
394. Steinmeier R, Bondar I, Bauhuf C, Fahlbusch R. Laser Doppler flowmetry mapping of cerebrocortical microflow: Characteristics and limitations. *Neuroimage*. 2002;15(1):107–119.
395. Friedrich DH, Baethmann A, Plesnila N. Cluster analysis: A useful tool for the analysis of cerebral laser-Doppler scanning data. *J Neurosci Methods*. 2005;146(1):91–97.
396. Kazmi SM, Balial S, Dunn AK. Optimization of camera exposure durations for multi-exposure speckle imaging of the microcirculation. *Biomed Opt Express*. 2014;5(7):2157–2171.
397. Richards LM, Kazmi SM, Davis JL, Olin KE, Dunn AK. Low-cost laser speckle contrast imaging of blood flow using a webcam. *Biomed Opt Express*. 2013;4(10):2269–2283.
398. Boas DA, Dunn AK. Laser speckle contrast imaging in biomedical optics. *J Biomed Opt*. 2010;15(1):011109.
399. Kastek M, Piatkowski T, Polakowski H, et al. Thermal camera used for the assessment of metabolism and functions of the rat brain. In: Colbert F, Hsieh S-J, eds. *Proc. of SPIE*. 2013; 910507 1-9.
400. Suzuki T, Ooi Y, Seki J. Infrared thermal imaging of rat somatosensory cortex with whisker stimulation. *J Appl Physiol*. 2012;112(7):1215–1222.
401. Zhang Y, Hong H, Cai W. Photoacoustic imaging. *Cold Spring Harb Protoc*. 2011;2011(9).

402. Burton NC, Patel M, Morscher S, et al. Multispectral opto-acoustic tomography (MSOT) of the brain and glioblastoma characterization. *Neuroimage*. 2013;65:522–528.
403. Hu S, Maslov K, Tsytsarev V, Wang LV. Functional transcranial brain imaging by optical-resolution photoacoustic microscopy. *J Biomed Opt*. 2009;14(4):040503.
404. Liao LD, Li ML, Lai HY, et al. Imaging brain hemodynamic changes during rat forepaw electrical stimulation using functional photoacoustic microscopy. *Neuroimage*. 2010;52(2):562–570.
405. Shan L. Indocyanine green-enhanced, cyclic Arg-Gly-Asp-conjugated, PEGylated single-walled carbon nanotubes. *Molecular Imaging and Contrast Agent Database (MICAD)*; 2004. Bethesda (MD).
406. Wang L, Xie X, Oh JT, et al. Combined photoacoustic and molecular fluorescence imaging in vivo. *Conf Proc IEEE Eng Med Biol Soc*. 2005;1:190–192.
407. Jo J, Zhang H, Cheney PD, Yang X. Photoacoustic detection of functional responses in the motor cortex of awake behaving monkey during forelimb movement. *J Biomed Opt*. 2012;17(11):110503.
408. Zhang Y, Wang Y, Zhang C. Efficient discrete cosine transform model-based algorithm for photoacoustic image reconstruction. *J Biomed Opt*. 2013;18(6):066008.
409. Nie L, Cai X, Maslov K, Garcia-Uribe A, Anastasio MA, Wang LV. Photoacoustic tomography through a whole adult human skull with a photon recycler. *J Biomed Opt*. 2012;17(11):110506.
410. Driscoll JD, Shih AY, Drew PJ, Cauwenberghs G, Kleinfeld D. Two-photon imaging of blood flow in the rat cortex. *Cold Spring Harb Protoc*. 2013;2013(8):759–767.
411. Drew PJ, Shih AY, Kleinfeld D. Fluctuating and sensory-induced vasodynamics in rodent cortex extend arteriole capacity. *Proc Natl Acad Sci U S A*. 2011;108(20):8473–8478.
412. Osiac E, Balseanu TA, Catalin B, et al. Optical coherence tomography as a promising imaging tool for brain investigations. *Rom J Morphol Embryol*. 2014;55(2 Suppl):507–512.
413. Zysk AM, Nguyen FT, Oldenburg AL, Marks DL, Boppart SA. Optical coherence tomography: A review of clinical development from bench to bedside. *J Biomed Opt*. 2007;12(5):051403.
414. Wang RK, An L. Doppler optical micro-angiography for volumetric imaging of vascular perfusion in vivo. *Opt Express*. 2009;17(11):8926–8940.
415. Wang RK, Jacques SL, Ma Z, Hurst S, Hanson SR, Gruber A. Three dimensional optical angiography. *Opt Express*. 2007;15(7):4083–4097.
416. Srinivasan VJ, Sakadzic S, Gorczynska I, et al. Quantitative cerebral blood flow with optical coherence tomography. *Opt Express*. 2010;18(3):2477–2494.
417. Yu L, Nguyen E, Liu G, Choi B, Chen Z. Spectral Doppler optical coherence tomography imaging of localized ischemic stroke in a mouse model. *J Biomed Opt*. 2010;15(6):066006.
418. Meyer JS, Ishikawa S, Lee TK, Thal A. Quantitative measurement of cerebral blood flow with electromagnetic flowmeters. Recording internal jugular venous flow of monkey and man. *Trans Am Neurol Assoc*. 1963;88:78–83.
419. Stuart AG, Sharples PM, Eyre JA, Aynsley-Green A, Heaviside DW. The Kety Schmidt technique revisited: Bedside measurement of cerebral blood flow and metabolism in children during and after cardiopulmonary bypass surgery. *J Cardiothorac Anesth*. 1989;3(5 Suppl 1):69.
420. Wietasch GJ, Mielck F, Scholz M, von Spiegel T, Stephan H, Hoeft A. Bedside assessment of cerebral blood flow by double-indicator dilution technique. *Anesthesiology*. 2000;92(2):367–375.
421. Kadoya T, Kurosaka S, Shiraishi M, Uehara H, Yamamoto T. Monitoring of jugular venous oxygen saturation during superficial temporal artery-middle cerebral artery anastomosis under intraaortic balloon pumping: A case report. *Masui*. 2014;63(8):890–893.
422. Gupta AK, Hutchinson PJ, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. *Anesth Analg*. 1999;88(3):549–553.
423. Gopinath SP, Valadka AB, Uzura M, Robertson CS. Comparison of jugular venous oxygen saturation and brain tissue Po2 as monitors of cerebral ischemia after head injury [see comments]. *Crit Care Med*. 1999;27(11):2337–2345.
424. Hindman BJ. Jugular venous hemoglobin desaturation during rewarming on cardiopulmonary bypass: What does it mean, what does is matter? (editorial; comment). *Anesthesiology*. 1998;89(1):3–5.
425. Schell RM, Cole DJ. Cerebral monitoring: Jugular venous oximetry. *Anesth Analg*. 2000;90(3):559–566.
426. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*. 1977;198(4323):1264–1267.
427. Scholkmann F, Kleiser S, Metz AJ, et al. A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. *Neuroimage*. 2014;85(Pt 1):6–27.
428. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *Neuroimage*. 2012;63(2):921–935.
429. Gantri M. Solution of radiative transfer equation with a continuous and stochastic varying refractive index by legendre transform method. *Comput Math Methods Med*. 2014;2014:814929.
430. Sassaroli A, Martelli F. Equivalence of four Monte Carlo methods for photon migration in turbid media. *J Opt Soc Am A Opt Image Sci Vis*. 2012;29(10):2110–2117.
431. Arridge SR, Cope M, Delpy DT. The theoretical basis for the determination of optical pathlengths in tissue: Temporal and frequency analysis. *Phys Med Biol*. 1992;37(7):1531–1560.
432. Arridge SR, Hebden JC. Optical imaging in medicine: II. Modelling and reconstruction. *Phys Med Biol*. 1997;42(5):841–853.
433. Arridge SR, Schweiger M, Hiraoka M, Delpy DT. A finite element approach for modeling photon transport in tissue. *Med Phys*. 1993;20(2 Pt 1):299–309.
434. Selb J, Ogden TM, Dubb J, Fang Q, Boas DA. Comparison of a layered slab and an atlas head model for Monte Carlo fitting of time-domain near-infrared spectroscopy data of the adult head. *J Biomed Opt*. 2014;19(1):16010.
435. Hallacoglu B, Sassaroli A, Fantini S. Optical characterization of two-layered turbid media for non-invasive, absolute oximetry in cerebral and extracerebral tissue. *PLoS One*. 2013;8(5).e64095.
436. Jelzow A, Wabnitz H, Tachtsidis I, Kirilina E, Bruhl R, Macdonald R. Separation of superficial and cerebral hemodynamics using a single distance time-domain NIRS measurement. *Biomed Opt Express*. 2014;5(5):1465–1482.
437. Zweifel C, Dias C, Smielewski P, Czosnyka M. Continuous time-domain monitoring of cerebral autoregulation in neurocritical care. *Med Eng Phys*. 2014;36(5):638–645.
438. Torricelli A, Contini D, Pifferi A, et al. Time domain functional NIRS imaging for human brain mapping. *Neuroimage*. 2014;85(Pt 1):28–50.
439. Wabnitz H, Moeller M, Liebert A, Obrig H, Steinbrink J, Macdonald R. Time-resolved near-infrared spectroscopy and imaging of the adult human brain. *Adv Exp Med Biol*. 2010;662:143–148.
440. Re R, Muthalib M, Contini D, et al. Cerebral cortex activation mapping upon electrical muscle stimulation by 32-channel time-domain functional near-infrared spectroscopy. *Adv Exp Med Biol*. 2013;789:441–447.
441. Schweiger M, Arridge SR. The finite-element method for the propagation of light in scattering media: Frequency domain case. *Med Phys*. 1997;24(6):895–902.
442. Hillman EM. Optical brain imaging in vivo: techniques and applications from animal to man. *J Biomed Opt*. 2007;12(5):051402.
443. Calderon-Arnulphi M, Alaraj A, Amin-Hanjani S, et al. Detection of cerebral ischemia in neurovascular surgery using quantitative frequency-domain near-infrared spectroscopy. *J Neurosurg*. 2007;106(2):283–290.
444. Obrig H. NIRS in clinical neurology – a 'promising' tool? *Neuroimage*. 2014;85(Pt 1):535–546.
445. Nielsen HB. Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. *Front Physiol*. 2014;5:93.
446. Zacharias DG, Lilly K, Shaw CL, et al. Survey of the clinical assessment and utility of near-infrared cerebral oximetry in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2014;28(2):308–316.
447. Ono M, Brady K, Easley RB, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg*. 2014;147(1):483–489.
448. Morel J, Bouchet JB, Vola M, et al. Tissue near infra red spectroscopy change is not correlated with patients' outcome in elective cardiac surgery. *Acta Anaesthesiol Scand*. 2014;58(7):835–842.
449. Menke J, Moller G. Cerebral near-infrared spectroscopy correlates to vital parameters during cardiopulmonary bypass surgery in children. *Pediatr Cardiol*. 2014;35(1):155–163.
450. Samra SK, Dy EA, Welch K, Dorje P, Zelenock GB, Stanley JC. Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. *Anesthesiology*. 2000;93(4):964–970.
451. Schytz HW, Wienecke T, Jensen LT, Selb J, Boas DA, Ashina M. Changes in cerebral blood flow after acetazolamide: An experimental study comparing near-infrared spectroscopy and SPECT. *Eur J Neurol*. 2009;16(4):461–467.
452. Keller E, Nadler A, Alkadhi H, Kollias SS, Yonekawa Y, Niederer P. Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution. *Neuroimage*. 2003;20(2):828–839.
453. Patel J, Marks K, Roberts I, Azzopardi D, Edwards AD. Measurement of cerebral blood flow in newborn infants using near infrared spectroscopy with indocyanine green. *Pediatr Res*. 1998;43(1):34–39.

454. Liebert A, Wabnitz H, Steinbrink J, et al. Bed-side assessment of cerebral perfusion in stroke patients based on optical monitoring of a dye bolus by time-resolved diffuse reflectance. *Neuroimage*. 2005;24(2):426–435.
455. Skov L, Pryds O, Greisen G. Estimating cerebral blood flow in newborn infants: Comparison of near infrared spectroscopy and 133Xe clearance. *Pediatr Res*. 1991;30(6):570–573.
456. Bucher HU, Edwards AD, Lipp AE, Duc G. Comparison between near infrared spectroscopy and 133Xenon clearance for estimation of cerebral blood flow in critically ill preterm infants. *Pediatr Res*. 1993;33(1):56–60.
457. Smith A, Pernder J, Alexander S. Effects of PCO2 in spinal cord blood flow. *Am J Physiol*. 1969;216:1158–1163.
458. Hickey R, Albin MS, Bunegin L, Gelineau J. Autoregulation of spinal cord blood flow: Is the cord a microcosm of the brain? *Stroke*. 1986;17(6):1183–1189.
459. Phillips AA, Ainslie PN, Krassioukov AV, Warburton DE. Regulation of cerebral blood flow after spinal cord injury. *J Neurotrauma*. 2013;30(18):1551–1563.
460. Sandler AN, Tator CH. Review of the measurement of normal spinal cord blood flow. *Brain Res*. 1976;118(2):181–198.
461. Griffiths IR. Spinal cord blood flow in dogs: 2. The effects of the blood gases. *J Neurol Neurosurg Psychiat*. 1973;36:42–49.
462. Griffiths IR. Spinal cord blood flow in dogs: 1. The "normal" flow. *J Neurol Neurosurg Psychiat*. 1973;36:34–41.
463. Griffiths IR. Spinal cord blood flow in dogs: The effect of blood pressure. *J Neurol Neurosurg Psychiat*. 1973;36:914–920.
464. Harakawa I, Yano T, Sakurai T, Nishikimi N, Nimura Y. Measurement of spinal cord blood flow by an inhalation method and intraarterial injection of hydrogen gas. *J Vasc Surg*. 1997;26(4):623–628.
465. Bisdas S, Rumboldt Z, Surlan K, Koh TS, Deveikis J, Spampinato MV. *Perfusion CT measurements in healthy cervical spinal cord: feasibility and repeatability of the study as well as interchangeability of the perfusion estimates using two commercially available software packages*. *Eur Radiol*. 2008;18(10):2321–2328.
466. Duhamel G, Callot V, Cozzone PJ, Kober F. Spinal cord blood flow measurement by arterial spin labeling. *Magn Reson Med*. 2008;59(4):846–854.
467. Lu H, Law M, Ge Y, et al. Quantitative measurement of spinal cord blood volume in humans using vascular-space-occupancy MRI. *NMR Biomed*. 2008;21(3):226–232.
468. Shibata K, Takamoto S, Kotsuka Y, et al. Doppler ultrasonographic identification of the critical segmental artery for spinal cord protection. *Eur J Cardiothorac Surg*. 2001;20(3):527–532.
469. Hitchon PW, Mouw LJ, Rogge TN, Torner JC, Miller AK. Response of spinal cord blood flow to the nitric oxide inhibitor nitroarginine. *Neurosurgery*. 1996;39(4):795–803.
470. Milhorat TH, Kotzen RM, Capocelli Jr AL, Bolognese P, Bendo AA, Cottrell JE. Intraoperative improvement of somatosensory evoked potentials and local spinal cord blood flow in patients with syringomyelia. *J Neurosurg Anesthesiol*. 1996;8(3):208–215.
471. Schneider SJ, Rosenthal AD, Greenberg BM, Danto J. A preliminary report on the use of laser-Doppler flowmetry during tethered spinal cord release. *Neurosurgery*. 1993;32(2):214–218.
472. Marcoux FW, Goodrich JE, Dominick MA. Ketamine prevents ischemic neuronal injury. *Brain Res*. 1988;452:329–335.
473. Werner C, Hoffman WE, Kochs E, Schulte am Esch J, Albrecht RF. The effects of propofol on cerebral and spinal cord blood flow in rats. *Anesth Analag*. 1993;76(5):971–975.
474. Kobrine A, Doyle T, Rizzoli H. Spinal cord blood flow as affected by changes in systemic arterial blood pressure. *J Neurosurg*. 1976;44:12–15.
475. Ford RWJ, Malm DN. Therapeutic trial of hypercarbia and hypocarbia in acute experimental spinal cord injury. *J Neurosurg*. 1984;61:925–930.
476. Sakamoto T, Monafo WW. Regional blood flow in the brain and spinal cord of hypothermic rats. *Am J Physiol*. 1989;257:H785–H790.
477. Albin MS. Resuscitation of the spinal cord. *Crit Care Med*. 1978;6(4):270–276.
478. Westergren H, Farooque M, Olsson Y, Holtz A. Spinal cord blood flow changes following systemic hypothermia and spinal cord compression injury: An experimental study in the rat using Laser-Doppler flowmetry. *Spinal Cord*. 2001;39(2):74–84.
479. Halstead JC, Wurm M, Etz C, et al. Preservation of spinal cord function after extensive segmental artery sacrifice: Regional variations in perfusion. *Ann Thorac Surg*. 2007;84(3):789–794.
480. Bernhard M, Gries A, Kremer P, Bottiger BW. Spinal cord injury (SCI) – prehospital management. *Resuscitation*. 2005;66(2):127–139.
481. Hitchon P, Lobosky J, Yamada T, Torner J. Effect of laminectomy and anesthesia upon spinal cord blood flow. *J Neurosurg*. 1984;61:545–549.
482. Hitchon P, Kassell N, Hill T, Gerk M, Sokoll M. The response of spinal cord blood flow to high-dose barbiturates. *Spine (Phila Pa 1976)*. 1982;7:41–45.
483. Hempfing A, Dreimann M, Krebs S, Meier O, Notzli H, Metz-Stavenhagen P. Reduction of vertebral blood flow by segmental vessel occlusion: An intraoperative study using laser Doppler flowmetry. *Spine (Phila Pa 1976)*. 2005;30(23):2701–2705.
484. Crystal GJ, Metwally AA, Salem MR. Isoflurane preserves central nervous system blood flow during intraoperative cardiac tamponade in dogs. *Can J Anaesth*. 2004;51(10):1011–1017.
485. Nishiyama T. Spinal cord blood flow change by intravenous midazolam during isoflurane anesthesia. *Anesth Analg*. 2005;101(1):242–245. table of contents.
486. Hamamoto Y, Ogata T, Morino T, Hino M, Yamamoto H. Real-time direct measurement of spinal cord blood flow at the site of compression: Relationship between blood flow recovery and motor deficiency in spinal cord injury. *Spine (Phila Pa 1976)*. 2007;32(18):1955–1962.
487. Young WL. Neuroanesthesia: A look into the future. *Anesth Clinics North Am*. 1992;10(3):727–746.

3 Cerebrospinal Fluid

A.A. Artru

The first section of this chapter reviews cerebrospinal fluid (CSF) with respect to the anatomy of the CSF-containing spaces, physiology, and the effects of anesthetics and other influences. The second section reviews the relationship between CSF dynamics and intracranial pressure (ICP), anesthetics and drug-induced changes in CSF dynamics that increase or decrease ICP, and clinical situations wherein therapy to alter CSF dynamics may affect neurologic outcome.

ANATOMY OF CEREBROSPINAL FLUID SPACES AND PROPERTIES OF CEREBROSPINAL FLUID

The CSF is formed in the brain and circulates through macroscopic and extracellular fluid (ECF) spaces that are in continuity. The total volume of the macroscopic spaces ranges from 50 mL in infants to 140–150 mL in adults (Table 3.1). Ventricular volume accounts for about 16% to 17% of macroscopic CSF volume in adults. Studies to determine the volumes of portions of the macroscopic CSF space using noninvasive imaging technology are ongoing.[1] The ECF space surrounds the neuronal and glial elements of the central nervous system. Brain ECF volume is about 300 to 350 mL in adults exclusive of the macroscopic CSF space.

Macroscopic Spaces

The choroid plexuses (CPs) of the lateral ventricles extend from the inferior horn to the central part of the ventricle. The CPs in the body of the lateral and third ventricles receive their blood supply from the posterior and anterior choroidal arteries, respectively. The CPs in the temporal horns and the fourth ventricle are supplied by the superior and posterior inferior cerebellar arteries, respectively.[2] The nervous supply to the CPs includes branches of the vagus, glossopharyngeal, and sympathetic nerves.

Table 3.1 Cerebrospinal Fluid Pressure and Volume in Humans

	Range*
Cerebrospinal fluid (CSF) pressure (mmHg):	
Children	3.0–7.5
Adults	4.5–13.5
CSF volume (mL):	
Infants	40–60
Young children	60–100
Older children	80–120
Adults	100–160

*Values based on references 122–127.

Extracellular Fluid Spaces

The ECF spaces of the brain and spinal cord, unlike those of other organs in the body, are small in diameter (180 Å). Exchange between cerebral capillaries and the ECF is limited because the capillary membrane is highly impermeable. This blood–brain barrier (BBB) consists of two elements. First, the cells of the cerebral capillary endothelium are joined by tight junctions (zonula occludens) that restrict the intercellular movement of molecules having a diameter of 20 Å or more. Second, astrocyte foot processes surround the capillaries. Evidence shows that the ECF spaces communicate with lymphatic channels.

COMPOSITION OF CEREBROSPINAL FLUID

CSF is a clear aqueous solution that, compared with plasma, contains higher concentrations of sodium, chloride, and magnesium, and lower concentrations of glucose, proteins, amino acids, uric acid, potassium, bicarbonate, calcium, and phosphate (Table 3.2). Differences between the composition of CSF

Table 3.2 Composition of Cerebrospinal Fluid and Plasma in Humans

Feature or Component	Mean Cerebrospinal Fluid (CSF) Value or Concentration*	Mean Plasma Value or Concentration*
Specific gravity	1.007	1.025
Osmolality (mOsm/kg H_2O)	289	289
pH	7.31	7.41
PCO_2 (mmHg)	50.5	41.1
Sodium (mEq/L)	141	140
Potassium (mEq/L)	2.9	4.6
Calcium (mEq/L)	2.5	5.0
Magnesium (mEq/L)	2.4	1.7
Chloride (mEq/L)	124	101
Bicarbonate (mEq/L)	21	23
Glucose (mg/100 mL)	61	92
Protein (mg/100 mL):	28	7000
Albumin	23	4430
Globulin	5	2270
Fibrinogen	0	300

*Average values based on references 122–127.

and an ultrafiltrate of plasma indicate that active secretion occurs during CSF formation. The concentrations of these and other substances in the macroscopic spaces vary according to the sampling site because diffusion between CSF and ECF occurs as CSF passes through the ventricles and subarachnoid spaces. Concentrations of CSF constituents are significantly altered during neuroendoscopy.[3]

CEREBROSPINAL FLUID FORMATION

The rate of CSF formation ($\dot{V}_f$) is about 0.35 to 0.40 mL/min, or 500 to 600 mL/day in humans. Approximately 0.25% of total adult CSF volume is replaced by freshly formed CSF each minute. The turnover time for total CSF volume is 5 to 7 hours, yielding a turnover rate of about four times per day. The traditional view is that about 40% to 70% of CSF enters the macroscopic spaces via the CP, and 30% to 60% enters across the ependyma and pia. However, some recent studies suggest bidirectional fluid exchange at the BBB far exceeding choroidal CSF formation.[4]

Cerebrospinal Fluid Formation at the Choroid Plexus

Unlike the capillary endothelium of other cerebral vessels, the capillary endothelium of the CP does not possess tight junctions between its cells.[5] Instead, the capillary endothelium of the CP is fenestrated. Blood entering CP capillaries is filtered across this endothelium and forms a protein-rich fluid within the CP stroma that is similar in composition to interstitial fluid in other tissues of the body.[6] Selected constituents of the stromal fluid are transported across the relatively impermeable CP epithelium by the combined processes of ultrafiltration and secretion.[7] Stroma fluid enters clefts between the CP epithelial cells as a result of hydrostatic pressure and bulk flow (Fig. 3.1).

Extrachoroidal Cerebrospinal Fluid Formation

Sixty percent of extrachoroidal CSF formation results from oxidation of glucose (into water and carbon dioxide) by the brain, and 40% from ultrafiltration from cerebral capillaries.[8] In neurons and glial cells water resulting from oxidation of glucose passes into the brain ECF. In most of the cerebral vasculature, passage of large and polar molecules across the "blood–ECF" interface is restricted by capillary tight junctions and specialized heterolytic vesicles within endothelial cells. Water, electrolytes, glucose, amino acids, urea, lipid-soluble materials, and a number of small nonelectrolytes pass more freely across this interface.[9] Some of these substances may be actively transported by the astrocyte layer that envelops the capillary endothelium, whereas others may diffuse into the brain ECF. Osmotic forces appear to play a major role in water movement.[10] Pericapillary spaces provide less restricted passage of water and electrolytes than most of the cerebral vasculature.[11] This glucose-rich and protein-poor "lymph" diffuses through the ECF space toward the macroscopic CSF spaces (Fig. 3.2).

Movement of Glucose

The concentration of glucose in CSF at the CP or in mixed samples is approximately 60% of that in blood. This ratio remains constant unless blood glucose rises to more than 15 to 20 mM (270 to 360 mg/dL). Glucose in blood enters CSF by facilitated transport, so that glucose crosses the blood–CSF barrier more quickly than would be predicted on the basis of its lipid solubility.[12] Transport follows saturable kinetics, with the rate being directly related to serum glucose concentration and independent of the serum-to-CSF glucose concentration gradient.[13] Movement of glucose in the opposite direction, from the cerebral ventricles into the surrounding brain and blood, occurs via ouabain-sensitive sodium-potassium ATPase and ouabain-insensitive fluxes and diffusion.

Movement of Protein

Protein entry into CSF from blood at the CP and extrachoroidal sites is limited, so CSF protein concentrations are normally 0.5% or less of the respective plasma or serum concentrations. The permeability of the blood–CSF barrier to albumin increases with age and does not differ between genders.[14] If a

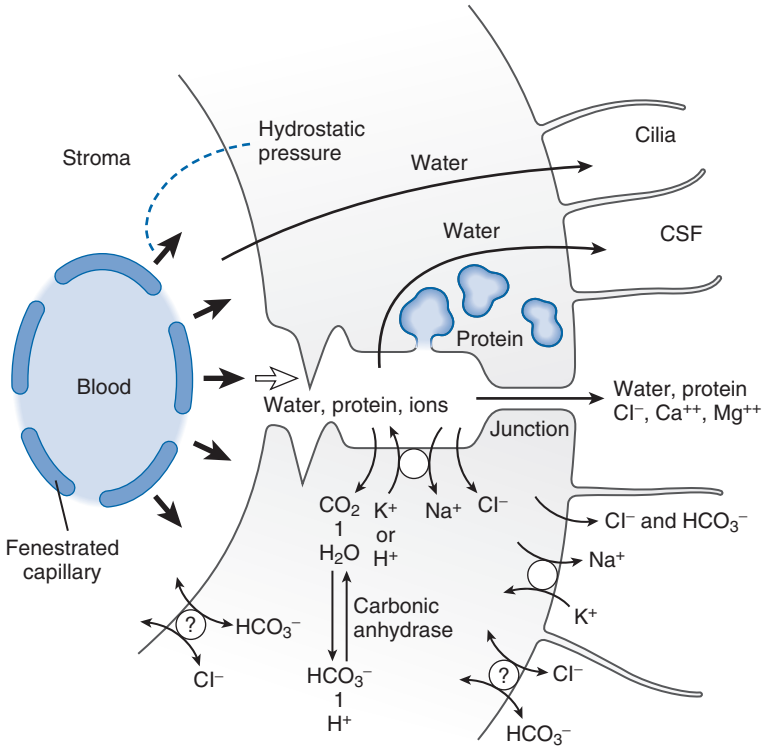


Fig. 3.1 Some of the processes involved in cerebrospinal fluid (CSF) formation at the choroid plexus are shown in schematic form. Adenosine triphosphate-dependent membrane "pumps" transport Na^+ across the abluminal surface to within the choroid plexus cell and across the secretory surface, into the macroscopic CSF space, in exchange for K^+ and H^+. Water moves from the stroma into CSF as it follows the concentration gradient produced by the ionic "pumps." *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

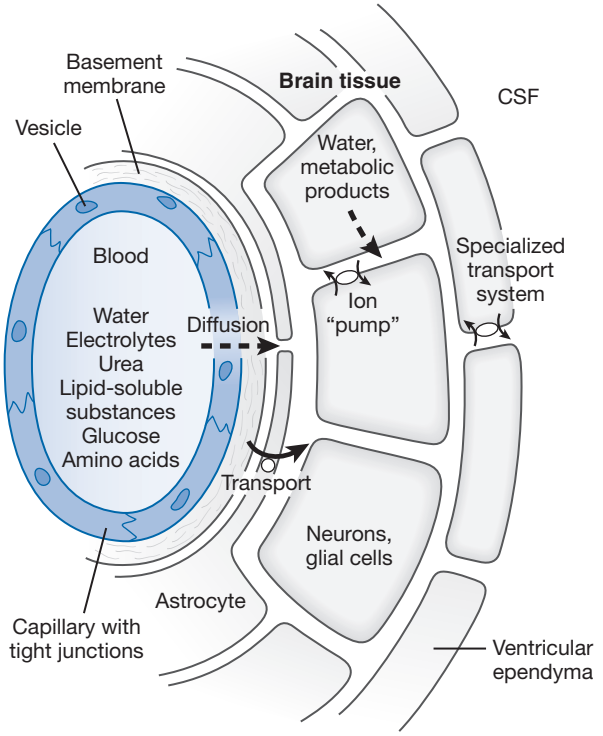


Fig. 3.2 Water and other constituents of plasma cross the blood–brain barrier (capillary endothelial cells, basement membrane, and astrocyte foot processes) into the brain extracellular fluid (ECF) space by diffusion or transport. This fluid diffuses toward the macroscopic cerebrospinal fluid (CSF) space and subarachnoid space. Water and other cellular metabolites are added to the ECF from neurons and glial cells.

structural barrier between the brain ECF and the macroscopic CSF space is absent, proteins entering the brain ECF drain into the macroscopic CSF space by bulk flow. Once in CSF, proteins are transported along with CSF through the macroscopic pathways and are cleared from the CSF space into dural venous sinuses. This "sink effect" of flowing CSF keeps the CSF and brain protein concentration low and far from equilibrium with blood.[8] In normal infants and adults, CSF protein concentrations are lowest in the ventricles (about 26 mg/100 mL), intermediate in the cisterna magna (about 32 mg/100 mL), and highest in the lumbar sac (42 mg/100 mL).[15] Under normal conditions, 60% of protein entry into CSF occurs at the CP, and 40% at extrachoroidal sites.

Effects of Increased Intracranial Pressure on Cerebrospinal Fluid Formation

The negative correlation between $\dot{V}_f$ and increased ICP is weak; the relationship between $\dot{V}_f$ and cerebral perfusion pressure (CPP) is somewhat stronger.[16] Increase of ICP to 20 mmHg produces no change in $\dot{V}_f$ as long as CPP remains above ~70 mmHg.[17] When CPP falls below ~70 mmHg, whether from arterial hypotension or because of the combination of arterial hypotension with increased ICP, $\dot{V}_f$ diminishes. These $\dot{V}_f$ results are consistent with reported effects of changes in CPP on cerebral blood flow (CBF), lateral ventricle CP blood flow (CPBF), and fourth ventricle CPBF.[16] A decrease of CPP to 70 mmHg by arterial hypotension, combined with increased ICP, reduces CBF and CPBF. A drop of CPP to 50 mmHg causes a further decline in CPBF when CPP is reduced by an even greater increase in ICP, but not when CPP is reduced solely by arterial hypotension.

CIRCULATION OF CEREBROSPINAL FLUID

The hydrostatic pressure of CSF formation, 15 cm H_2O, produces CSF flow where it is freshly formed. Cilia on ependymal cells generate currents that propel CSF toward the fourth ventricle and its foramina into the subarachnoid spaces. Respiratory variations and vascular pulsations of the cerebral arteries and CP cause ventricular excursions, supplying additional momentum for CSF movement. The pressure differences between mean CSF pressure, 15 cm H_2O, and superior sagittal sinus pressure, 9 cm H_2O, provides a 6 cm H_2O pressure gradient for passage of CSF across the arachnoid villi. The high velocity of blood flow through the fixed diameter of the sinuses and the low intraluminal pressure that develops at the circumference of the sinus wall where the arachnoid villi enter cause a "suction-pump" action that may explain how the circulation of the CSF continues through a wide range of postural pressures.

Radioisotope studies show that labeled CSF moves from the ventricles to the basal cisterns within a few minutes and collects along the superior sagittal sinus area at 12 to 24 hours. The labeled fluid enters the low cervical–high thoracic region at 10 to 20 minutes, the thoracolumbar area at 30 to 40 minutes, the lumbosacral cul de sac at 60 to 90 minutes, and the basal cisterns at 2 to 2.5 hours.[18] About 20% to 33% of the labeled CSF reaches the intracranial cavity within 12 hours. More recent studies emphasize the "mixing and swirling" and "to-and-fro" movement of CSF.[19,20] The central canal within the spinal cord alters these oscillatory flows.[21] CSF circulation concludes with reabsorption across arachnoid villi into the superior sagittal sinus and spinal dural sinusoids located on dorsal nerve roots (Fig. 3.3).

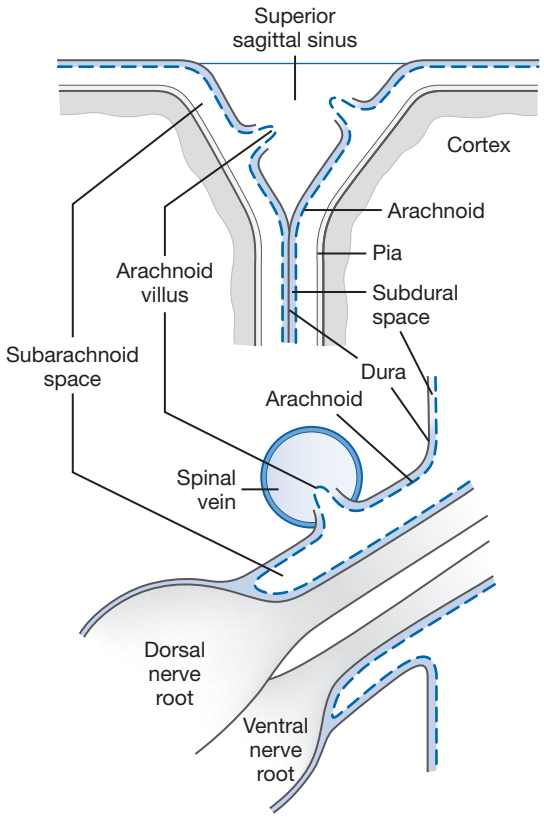


Fig. 3.3 Cerebrospinal fluid is reabsorbed via arachnoid villi at the sagittal sinus and at spinal veins on dorsal nerve roots. *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

REABSORPTION OF CEREBROSPINAL FLUID

CSF passes from the subarachnoid space into venous blood through microscopic arachnoid villi and macroscopic arachnoid granulations. Intracranial arachnoid villi are located within the dural wall bordering the superior sagittal sinus and venous lacunae, and spinal arachnoid villi are located within the dural wall bordering dural sinusoids on dorsal nerve roots. Traditional estimates were that under usual conditions, 85% to 90% of CSF is reabsorbed at intracranial sites, and 10% to 15% at spinal sites. Newer studies add the role of CSF drainage into lymphatic pathways and CSF reabsorption throughout the entire CSF-interstitial fluid interface.[9,22,23] The arachnoid villus or granulation is composed of arachnoid cells protruding from the subarachnoid space into and through the wall of an adjacent venous sinus[24] (Fig. 3.4). Under normal conditions, an endothelium composed of arachnoid cells joined by tight junctions covers the villus. In adults, this endothelial covering may be multilayered.

Normal Intracranial Pressure

The endothelium covering the villus acts as a CSF–blood barrier that limits the rate of passage of CSF and solute into venous blood. The rate at which CSF passes through the subarachnoid space and arachnoid villi and across the endothelium is determined by (1) the transvillous hydrostatic pressure gradient (CSF pressure–venous sinus pressure) and (2) a pressure-sensitive resistance to CSF outflow at the arachnoid villus. Because the endothelium is highly permeable, transvillous osmotic differences probably do not play a major role in determining CSF movement through arachnoid villi. CSF may exit the villus by passing between or through endothelial cells. CSF may pass through endothelial cells via pinocytotic vesicles and transcellular openings formed by chains of fused vesicles extending from one surface of the epithelium to the other.[25] These vesicles transport macromolecular tracers, as well as fluid, from CSF to blood. Although micropinocytotic vesicles appear to be the primary route of CSF transport at resting CSF pressure, both pathways contribute to the total resistance to CSF outflow.

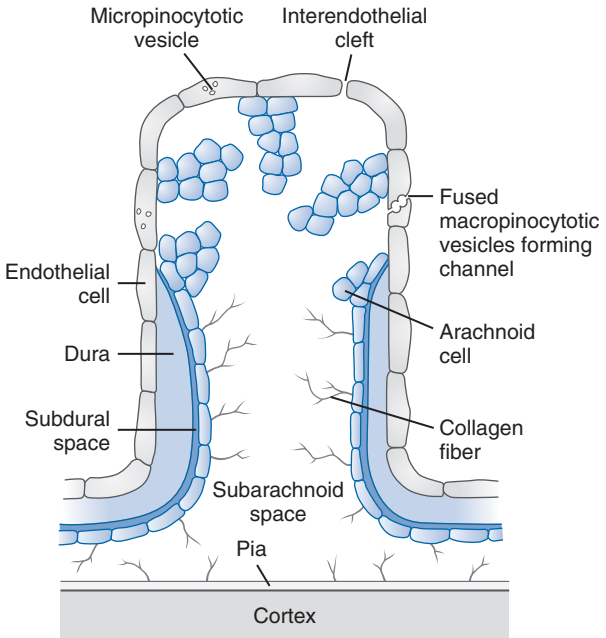


Fig. 3.4 Schematic drawing of the microscopic anatomy of an arachnoid villus. *(From Cucchiara RF, Michenfelder JD, editors: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

Increased Intracranial Pressure

The rate of reabsorption of CSF ($\dot{V}_a$) increases as the pressure gradient across the villus (CSF pressure – venous sinus pressure) increases. Resistance to reabsorption of CSF (R_a) remains close to "normal" as CSF pressure increases to more than 30 cm H_2O. Thereafter, with further increases in CSF pressure, R_a declines.[26–29] An increase in the size and number of endothelial vesicles was reported when CSF pressure was increased from 9 to 30 cm H_2O.[30] At CSF pressures greater than 30 cm H_2O, growing numbers of transcellular channels were present concurrent with progressive increases in steady-state pressures and decreases in R_a.

Clearance of Brain Interstitial Fluid

Normal Intracranial Pressure

Under normal conditions, there is relatively little bulk flow across cerebral capillaries and through the parenchyma of the brain.[31] Molecules in the brain ECF move through that space primarily by diffusion. The rate at which molecules exit the brain ECF relates to their molecular size, tissue concentration gradients, and the ability of the molecules to cross the BBB and reenter the vascular system.

Cerebral Edema

Vasogenic brain edema results from damage to cerebral vessels. Vasogenic edema resolves in part through passage of edema fluid into ventricular CSF. One factor favoring fluid movement out of brain ECF is the pressure gradient between edematous brain tissue and CSF. A second factor is the "sink" action of CSF.[32] Clearance of edema fluid was reported to increase when ICP was decreased, presumably because of a rise in the pressure gradient between edematous brain tissue and CSF.[33] Clearance of brain ECF proteins occurs by intraglial uptake, and this step is believed to play an important role in the resolution of vasogenic brain edema.[34]

FUNCTION OF CEREBROSPINAL FLUID

The varied and complex functions of CSF include protection, support, and chemical regulation of the brain. The low specific gravity of CSF (1.007) relative to that of the brain (1.040) reduces the effective mass of a 1400-g brain to only 47 g. In continuity with the brain ECF, CSF provides a stable supply of substrates, primarily glucose, even though concentrations of substrates in plasma are continuously changing. CSF maintains the chemically precise environment required for neurotransmission and removes the metabolic products, unwanted drugs, and harmful substances resulting from CNS injury.

Nutrition

Certain nutritive and other substrates for the brain are actively transported by systems in the capillary-glial complex. Simple sugars, certain vitamins, eicosanoids, monosaccharides, neutral and basic amino acids (brain tissue does not appear to contain an acidic amino acid transport system), and monocarboxylic acids are transported by specialized pump mechanisms (equilibrating carriers) between blood and brain ECF.[35–37] Also, CSF may mediate uptake of certain vitamins, such as ascorbic acid.

Control of the Chemical Environment

Exchange between CSF and neural tissue ECF occurs readily because the maximum distance for diffusion between CSF and any brain area in humans is 15 mm and the interstitial space of the brain and spinal cord is continuous with the macroscopic CSF spaces. The acid–base characteristics of CSF influence respiration, CBF, autoregulation of CBF, and cerebral metabolism.[38] CSF calcium, potassium, and magnesium levels influence heart rate, blood pressure, vasomotor and other autonomic reflexes, respiration, muscle tone, and emotional states. Calcium, potassium, magnesium, and bicarbonate ions are actively transported by "primary pumps," whereas hydrogen and chloride ions are passively transferred by "secondary pumps." Within limits, CSF composition of larger molecules is regulated by the BBB with the almost total exclusion of toxic or potentially toxic large, polar, and lipid-insoluble drugs, humoral agents, and metabolites.

Excretion

Accumulation of metabolites and substances in brain ECF is prevented by their passage into CSF, cerebral veins, or cervical lymphatics. Although passage into CSF may occur by two mechanisms, net diffusion and bulk flow of ECF, bulk flow accounts for most passages of many substrates of different molecular weights.[39]

Intracerebral Transport

Because CSF circulates to regions of the brain known to participate in neuroendocrine activity, it serves as a convenient vehicle for intracerebral transport of neurotransmitters. Neurohormone-releasing factors are synthesized in the hypothalamus and released into the brain ECF and CSF by means of axonal contact between neurons with specialized cells of the ependyma. These factors are carried by the CSF to the median eminence, where they stimulate the dendrites of receptor neurons. Opioid effects—such as analgesia and respiratory depression—may be mediated by third-ventricle cellular elements in contact with CSF, because electrical stimulation of the medial thalamus or periaqueductal gray matter increases the level of β-endorphins in ventricular CSF.[40–42]

EFFECTS OF ANESTHETICS AND OTHER INFLUENCES ON FORMATION AND REABSORPTION OF CEREBROSPINAL FLUID

Methods of Determining Cerebrospinal Fluid Formation Rate and Resistance to Cerebrospinal Fluid Reabsorption

Experimental Animals

Three currently used methods for determining $\dot{V}_f$, R_a, and other CSF dynamics in animals are ventriculocisternal perfusion, manometric infusion, and volume injection or withdrawal. Ventriculocisternal perfusion was first described by Heisey and colleagues[43] and Pappenheimer and associates[44] in the early 1960s. The method requires placement of cannulas in one or both lateral ventricles and in the cisterna magna. Labeled mock CSF is infused into the ventricles, and a mixed sample composed of labeled mock CSF and native CSF is collected from the cisterna magna. A portion of the continuous outflow of mock-native CSF from the cisternal cannula is collected, and the volume of the sample is determined. The concentration of the label in the outflow sample is measured, and the time over which the sample was obtained is noted. $\dot{V}_f$ is calculated according to the following formula:

$$\dot{V}_f = \dot{V}_i\left(\frac{C_i - C_o}{C_o}\right) \tag{3.1}$$

where $\dot{V}_i$ is the mock CSF inflow rate, C_i is the concentration of the label in mock CSF, and C_o is the concentration of the label in the mixed outflow solution.

$\dot{V}_a$ is calculated by either of two formulas; the first is as follows:

$$\dot{V}_a = \frac{\dot{V}_i C_i - \dot{V}_o C_o}{C_o} \tag{3.2}$$

where $\dot{V}_o$ is the outflow rate of CSF from the cisternal cannula. The second formula for calculation of $\dot{V}_a$ is as follows:

$$\dot{V}_a = \dot{V}_i + \dot{V}_f - \dot{V}_o \tag{3.3}$$

R_a is a reciprocal measure of the slope relating $\dot{V}_a$ to CSF pressure. For calculation of R_a, $\dot{V}_a$ must be determined at several CSF pressures. If the slope relating $\dot{V}_a$ to CSF pressure is linear, a single R_a value adequately describes the data. If the $\dot{V}_a$/CSF pressure slope is not linear, multiple R_a values must be calculated. For any CSF pressure, the corresponding R_a value is the inverse of tangent to the $\dot{V}_a$ /CSF pressure slope.

Manometric infusion, as it is currently used, was described by Maffeo and colleagues[45] and Mann and associates[28] in the late 1970s. For this technique, a manometric infusion device is inserted into the spinal or supracortical subarachnoid space. Mock CSF is infused into the subarachnoid space, and CSF pressure is measured at the same site as the infusion. Each steady-state CSF pressure (P_S) is paired with its associated $\dot{V}_i$. Next, each pair of $\dot{V}_i$:P_S values is plotted on a semilog plot of $\dot{V}_i$ versus P_S. A linear slope is then fit through the three to six data points. For determination of $\dot{V}_f$, the linear slope is extrapolated toward the origin (to the left). The $\dot{V}_i$ value at resting CSF pressure (P_o)—that is, the $\dot{V}_i$ value corresponding to the intersection of a perpendicular from P_o and the extrapolated semilog plot—is considered to be $\dot{V}_f$. R_a is determined with the use of observed values and two calculated, species-dependent parameters: M (transport capacity) and P_R (pressure at maximum resistance). These species-dependent parameters are calculated on the basis of the following formula:

$$\dot{V}_i = \frac{1}{M} e P_s / P_R \tag{3.4}$$

Simultaneously solving this equation for the three to six pairs of $\dot{V}_i$:P_S values used to calculate $\dot{V}_f$ yields one unique pair of M and P_R values. R_a is then calculated according to the following formula:

$$R_a = M P_e - P_S / P_R \tag{3.5}$$

In addition, the compliance *(C)* of the CSF compartment can be calculated according to the following formula:

$$C = \frac{\dot{V}_i}{\Delta P / \Delta t} \tag{3.6}$$

where *P* is CSF pressure, *t* is time, and $\Delta P/\Delta t$ is the slope of the linear rise in CSF pressure during infusion of mock CSF.

Volume injection or withdrawal was described by Marmarou and colleagues[46] and Miller[47] in the mid-1970s. A ventricular or spinal subarachnoid catheter is inserted to permit injection or withdrawal of CSF and measurement of the CSF pressure change that accompanies injection or withdrawal. P_o is determined, and then a known volume of CSF (ΔV) is injected into (or withdrawn from) the catheter while a timed recording of CSF pressure is made. $\dot{V}_f$ and R_a are determined first through a calculation of the pressure volume index (PVI) as follows:

$$PVI = \Delta V / [\log P_P / P_o] \quad (3.7)$$

where P_P is peak CSF pressure (increase after volume injection and decrease after volume withdrawal).

R_a is then calculated on the basis of the following formula:

$$R_a = \frac{t \cdot P_o}{PVI \cdot \log_{10}\left(\frac{P_2(P_P - P_o)}{P_P(P_2 - P_o)}\right)} \quad (3.8)$$

where P_2 is CSF pressure measured some time between P_P and the return of CSF pressure to P_o and t is time from volume injection or withdrawal to P_2.

$\dot{V}_f$ is calculated on the basis of the following formula:

$$P_o = P_v \left(R_a \bullet \dot{V}_f\right) \quad (3.9)$$

which can be rewritten as follows:

$$\dot{V}_f = \frac{P_v - P_o}{R_a} \quad (3.10)$$

where P_v is the venous blood pressure of the sagittal sinus.

C is calculated on the basis of the following formula:

$$C = \frac{0.4343 \bullet PVI}{P_o} \quad (3.11)$$

Humans

Ventriculocisternal perfusion, manometric infusion, and volume injection or withdrawal have also been used to calculate $\dot{V}_f$, R_a, and C in patients.[28] For ventriculocisternal perfusion, the outflow catheter is placed in the lumbar subarachnoid space, and ventricular and spinal CSF pressures are closely monitored to ensure that CSF pressure does not increase to potentially hazardous levels as a result of obstructed perfusion. For manometric infusion, the number of infusions is reduced, and infusion rates are limited to 1.5 to 15 times the $\dot{V}_f$ —that is, 0.01 to 0.1 mL/sec. Infusions are restricted to 20 to 60 seconds, being discontinued at CSF pressures of 60 to 70 cm H_2O or if a rapid rise in CSF pressure with no apparent tendency toward stabilization is observed. The procedures and formulas for calculation of $\dot{V}_f$, R_a, and C in humans are the same as those in experimental animals.

Because of the hazards associated with prolonged infusion of mock CSF, ventriculocisternal perfusion and manometric infusion are less commonly used in patients than volume injection or withdrawal. An obvious advantage of this last method is that when ICP is of concern, CSF withdrawal is therapeutic—as well as useful for calculating $\dot{V}_f$, R_a, and C. The risk of infection is minimized because the system can remain completely closed. For repeated testing, CSF can be alternately withdrawn and then injected, with the net change of CSF volume being made according to the patient's ICP responses. Calculation of CSF dynamics requires only a single change of CSF volume and pressure lasting for several minutes. In contrast, with ventriculocisternal perfusion, more than 1 hour of infusion of mock CSF may be needed for tracer equilibration, and the manometric technique requires multiple infusions. Recently, some investigators have expressed the view that the reward:risk ratio is sufficient for some conditions to justify diagnostic or therapeutic infusion/perfusion.[48,49]

Anesthetic and Drug Induced Changes in CSF Dynamics and Transport

Anesthetics

Anesthetics influence many aspects of CSF dynamics (Table 3.3). Early studies with enflurane reported that 1 minimum alveolar concentration (MAC) increased $\dot{V}_f$ by 50% to 80% on initial exposure in rats and dogs.[50,51] $\dot{V}_f$ gradually returned to normal over several hours. Enflurane also increased R_a, but R_a did not return to normal when administration of enflurane was continued for several hours.[51,52] Enflurane produced these alterations of CSF dynamics when administered with either nitrogen (60% to 70%) or nitrous oxide (60% to 70%) in oxygen. Later studies with enflurane reported that its effects on $\dot{V}_f$ and R_a are dose related. High concentrations of enflurane (2.6% and 3.5% end-expired) increased $\dot{V}_f$ (by about 40% when corrected for the effects of time), whereas low concentrations (0.9% and 1.8%) did not.[53] Conversely, low concentrations increased R_a, but high concentrations did not. Halothane (1 MAC) generally is reported to decrease $\dot{V}_f$ [54] and increase R_a.[55] In addition, halothane enhances transport of glucose into brain[56] as well as movement of albumin and immunoglobulin (Ig) G[57,58] and of sodium, chloride, and water[59,60] into CSF. Nitrous oxide (66%) is reported to produce no change in R_a or $\dot{V}_f$ [50,54] and to decrease brain glucose influx and efflux.[61]

Early studies with isoflurane reported that 1 MAC of that anesthetic decreased R_a and caused no change in $\dot{V}_f$.[52,62] Later studies with isoflurane reported that its effects on R_a are dose related. R_a was normal at 0.6% (end-expired)

Table 3.3 Effects of Inhaled Anesthetics on Cerebrospinal Fluid Dynamics

Inhaled Anesthetic	$\dot{V}_f$	R_a	Predicted Effect on Intracranial Pressure
Desflurane	0,+,a	0	0,+,a
Enflurane:			
Low concentration	0	+	+
High concentration	+	0	+
Halothane	–	+	+
Isoflurane:			
Low concentration	0	0,+,b	0,+,b
High concentration	0	–	–
Nitrous oxide	0	0	0
Sevoflurane	–	+	?

R_a, Resistance to reabsorption of CSF; $\dot{V}_f$, rate of CSF formation; +, increase; 0, no change; –, decrease; a, effect occurs only during hypocapnia combined with increased CSF pressure, and under such conditions treatment with furosemide (but not mannitol, dexamethasone, or fentanyl) decreases $\dot{V}_f$; b, effect depends on dose; ?, uncertain.

isoflurane, increased at 1.1%, and decreased at 1.7% and 2.2%.[53] At 2% (inspired) isoflurane, the BBB transfer coefficient for small hydrophilic molecules was decreased.[63] The concentration of glutamate in CSF was higher during isoflurane anesthesia than during propofol anesthesia.[64] Sevoflurane (1 MAC) is reported to decrease $\dot{V}_f$ by about 40% and to increase R_a in comparison with 50% nitrous oxide in oxygen.[65] Studies with desflurane reported that its effects on $\dot{V}_f$ are related to CSF pressure and $PaCO_2$. At normocapnia and normal CSF pressure, normocapnia and increased CSF pressure, and hypocapnia and normal CSF pressure, both 0.5 and 1 MAC desflurane caused no change in $\dot{V}_f$ or R_a.[66] However, at hypocapnia and increased CSF pressure, both concentrations of desflurane increased R_a. During the combination of desflurane, hypocapnia, and increased CSF pressure, furosemide (2 mg/kg)—but not dexamethasone (0.2 mg/kg), mannitol (2 g/kg), or fentanyl (48 µg/kg followed by 0.6 µg/kg/min)—decreased $\dot{V}_f$, whereas none of the treatments significantly altered R_a.[67]

Ketamine (40 mg/kg/h) increases R_a but does not alter $\dot{V}_f$ (Table 3.4).[51] In addition, ketamine (150 mg/kg) decreases the transport of small hydrophilic molecules across the BBB.[68] Low doses of etomidate (0.86 mg/kg, followed by 0.86 or 1.72 mg/kg/h) do not alter R_a or $\dot{V}_f$, whereas high doses (2.58 or 3.44 mg/kg/h) decrease both R_a and $\dot{V}_f$.[69] Low doses of thiopental (6 mg/kg, followed by 6 or 12 mg/kg/h) increase or do not alter R_a and do not alter $\dot{V}_f$, whereas high doses (18 or 24 mg/kg/h) decrease both R_a and $\dot{V}_f$.[69] Thiopental (100 µg/mL but not 25 or 50 µg/mL) but not methohexital (10 to 50 µg/mL) increases the permeability of brain microvascular endothelial cells to α-aminoisobutyric acid but not to sucrose or to Evans blue albumin.[70] Propofol (6 mg/kg, followed by 12, 24, and 48 mg/kg/h) and pentobarbital (40 mg/kg) produce no change in R_a or $\dot{V}_f$.[51,71] In addition, pentobarbital decreases transport of glucose,[72] amino acids,[73] and small hydrophilic molecules[68] into the brain.

Among the sedative-hypnotic drugs, the effects of midazolam appear to be the most variable. Low doses of midazolam (1.6 mg/kg, followed by 0.5 mg/kg/h) increase R_a and do not alter $\dot{V}_f$, intermediate doses (1 to 1.5 mg/kg/h) cause no change, and high doses (2 mg/kg/h) increase R_a and decrease $\dot{V}_f$.[69] The benzodiazepine antagonist, flumazenil, caused no change in $\dot{V}_f$ when given either to dogs receiving midazolam (1.6 mg/kg, followed by 1.25 mg/kg/h) or to dogs not receiving midazolam.[74] Low-dose flumazenil (0.0025 mg/kg) caused no change in R_a, and high-dose flumazenil (0.16 mg/kg) decreased R_a. In dogs receiving midazolam, low-dose flumazenil increased R_a (perhaps because of partial reversal of midazolam so that CSF dynamics approximated those of low-dose midazolam), whereas after high-dose flumazenil, R_a returned to normal (that is, to values characteristic of dogs not receiving midazolam).

Early studies with fentanyl reported that 60 µg/kg, followed by 0.2 µg/kg/min decreased R_a[55] and did not alter $\dot{V}_f$.[54] More recent studies reported that its effects on $\dot{V}_f$ and R_a are dose related (Table 3.5). High doses of fentanyl decreased $\dot{V}_f$, whereas low doses did not.[75] R_a was decreased at the two low doses, normal at one high dose, and increased at the highest dose. Fentanyl (25 to 100 µg/mL) causes no change in the permeability of brain microvascular endothelial cells to α-aminoisobutyric acid, sucrose, or Evans blue albumin.[70] All doses of sufentanil studied caused no change in $\dot{V}_f$.[75] R_a was decreased at the two low doses, increased at one high dose, and normal at the highest dose. In addition, sufentanil (0.5 µg/kg, followed by 0.1 µg/kg/h) combined with thiopental

Table 3.4 Effects of Sedative-Hypnotics and Antagonist Drugs on Cerebrospinal Fluid Dynamics

Sedative–Hypnotic	$\dot{V}_f$	R_a	Predicted Effect on Intracranial Pressure
Etomidate:			
Low dose	0	0	0
High dose	–	0, –,a	–
Midazolam*:			
Low dose	0	+, 0, a	+, 0, a
High dose	–	0, +, a	–, ?, a
Pentobarbital	0	0	0
Propofol	0	0	0
Thiopental:			
Low dose	0	+, 0, a	+, 0, a
High dose	–	0, –, a	–
Antagonists			
Flumazenil:			
Low dose	0	0	0
High dose	0	–	–

R_a, Resistance to reabsorption of cerebrospinal fluid (CSF); $\dot{V}_f$, rate of CSF formation; +, increase; 0, no change; –, decrease; a, effect depends on dose; ?, uncertain.
* Partial reversal with flumazenil causes CSF dynamics similar to that with lowest dose of midazolam, and complete reversal with flumazenil causes CSF dynamics similar to that with pre-midazolam (control) values.

Table 3.5 Effects of Opioids and Other Anesthetics on Cerebrospinal Fluid Dynamics

	$\dot{V}_f$	R_a	Predicted Effect on Intracranial Pressure
Opioids			
Alfentanil:			
Low dose	0	–	–
High dose	0	0	0
Fentanyl:			
Low dose	0	–	–
High dose	–	0, +	–, ?
Sufentanil:			
Low dose	0	–	–
High dose	0	+, 0	+, 0
Other Anesthetics			
Cocaine	0	0	0
Ketamine	0	+	+
Lidocaine	0, –, a	0	0, –, a

R_a, Resistance to reabsorption of cerebrospinal fluid (CSF); $\dot{V}_f$, rate of CSF formation; +, increase; 0, no change; –, decrease; a, effect depends on dose; ?, uncertain.

(2 to 5 mg/kg, followed by 1 to 4 mg/kg/h) caused no greater movement of albumin or IgG into CSF.[58] None of the doses of alfentanil studied caused a change in $\dot{V}_f$.[75] R_a was decreased at the two low doses and normal at the two high doses. Lidocaine (0.5 mg/kg followed by 1 µg/kg/min, 1.5 mg/kg followed by 3 µg/kg/min, and 4.5 mg/kg followed by 9 µg/kg/min) produced a dose/time-related decrease of $\dot{V}_f$ with no change in R_a.[76] Cocaine, in the same doses as lidocaine, caused no significant change of $\dot{V}_f$ or R_a.[76]

The mechanism(s) by which inhalational and intravenous anesthetics alter CSF dynamics is uncertain. The increase in $\dot{V}_f$ with enflurane may result from an enflurane-induced increase in CP metabolism.[77] The decrease of $\dot{V}_f$ with halothane may result from halothane-induced stimulation of vasopressin receptors.[78]

Anesthetics and analgesics move from blood into CSF at varying rates. The free concentration of propofol in CSF was about 30% of the total concentration in CSF and about 60% of the free plasma concentration when propofol was infused intravenously as a component of total intravenous anesthesia.[79–82] Entry of intravenous ketoprofen, indomethacin, and ketorolac into CSF is limited.[83–85] Intravenous acetaminophen and ibuprofen permeate readily into CSF.[86,87] CSF concentrations frequently exceed free plasma concentrations. Acetaminophen reaches peak concentrations in CSF at about 1 hour, and concentrations are sufficient to enable rapid central analgesic and antipyretic effects. Ibuprofen peak CSF concentrations occur at about 30 to 40 minutes.

Diuretics

Although diuretics differ in their mechanisms of action, most are reported to decrease $\dot{V}_f$. Acetazolamide reduces $\dot{V}_f$ by up to 50%. Acetazolamide inhibits carbonic anhydrase, the enzyme that catalyzes the hydration of intracellular carbon dioxide, which decreases the amount of hydrogen ions available for exchange with sodium on the abluminal border of the epithelial cell. Acetazolamide may also decrease $\dot{V}_f$ through an indirect action on ion transport mediated by an effect on bicarbonate. Another view is that acetazolamide constricts CP arterioles, reducing CPBF. Methazolamide, another carbonic anhydrase inhibitor, also is reported to reduce $\dot{V}_f$ by up to 50%. The effects of carbonic anhydrase inhibitors are additive with those produced by drugs that work by other mechanisms. For example, the combination of acetazolamide and ouabain decreases $\dot{V}_f$ by 95%.

Ethacrynic acid decreases $\dot{V}_f$, presumably by inhibiting the exchange of sodium ions for potassium or hydrogen at the abluminal border of the cell. Spironolactone and amiloride decrease $\dot{V}_f$, probably by minimizing the entry of sodium into cells at the abluminal transport site. Furosemide decreases $\dot{V}_f$ by reducing either sodium or chloride transport, which is linked to sodium transport on the abluminal surface but follows an electrochemical gradient on the luminal surface. Mannitol decreases $\dot{V}_f$ because of reductions in both CP output and ECF flow from cerebral tissue to the macroscopic CSF compartment.[88–90]

Steroids

Numerous steroids are reported to alter R_a and $\dot{V}_f$. With increased R_a secondary to pneumococcal meningitis, methylprednisolone reduced R_a to a value that was intermediate between control and untreated animals.[91] It was speculated that methylprednisolone improved CSF flow in the supracortical subarachnoid space or arachnoid villi. When R_a was increased as a result of pseudotumor cerebri, prednisone decreased R_a to a value that was intermediate between pretreatment and normal values for patients.[92] CSF reabsorption may have risen because impaired transport across arachnoid epithelial cells was improved or because metabolically induced changes in the structure of the villi were reversed. Cortisone was reported to decrease $\dot{V}_f$. Rapid uptake of radioactively labeled hydrocortisone into the CP suggests that cortisone exerts its action at the CP rather than at extrachoroidal sites. Dexamethasone decreases $\dot{V}_f$ by up to 50%, probably because it inhibits sodium-potassium adenosine triphosphatase, thereby reducing the activity of the sodium-potassium pump at the CP epithelial membrane.

Other Drugs

Many other drugs are reported to alter $\dot{V}_f$ and R_a. Theophylline increases $\dot{V}_f$, presumably because inhibition of phosphodiesterase elevates CP cyclic adenosine monophosphate levels, stimulating the CP epithelial sodium-potassium pump.[93] Cholera toxin is also reported to increase $\dot{V}_f$.[94] Vasopressin decreases $\dot{V}_f$, perhaps by constricting CP blood vessels. Others contend that physiologic doses of vasopressin provide insufficient CP vascular effect to explain the observed decrease of $\dot{V}_f$.[93,94] Vasopressin also decreases R_a.[94] Hypertonic saline (3%) decreases $\dot{V}_f$, presumably by reducing the osmolality gradient for movement of fluid out of plasma and into the CP stroma or across brain tissue and into CSF.[95] Hypertonic saline increases R_a at some doses but not others. Dinitrophenol decreases $\dot{V}_f$, probably as a result of its ability to uncouple oxidative phosphorylation, thereby reducing the energy available for active secretory and transport processes, such as the membrane pumps. Atrial natriuretic peptides decrease $\dot{V}_f$ by stimulating production of cyclic guanine monophosphate.[94] Digoxin and ouabain decrease $\dot{V}_f$ by inhibition of the sodium-potassium adenosine triphosphatase of the CP epithelial sodium-potassium pump.

In contrast to the aforementioned drugs, both succinylcholine (continuous infusion) and vecuronium (continuous infusion) produce no change in $\dot{V}_f$ or R_a.[96] Prostaglandin E_1, when used to induce deliberate, controlled hypotension, caused no change in $\dot{V}_f$.[97]

Neurogenic Regulation of Cerbrospinal Fluid Formation and Resistance to its Reabsorption

Structural Aspects

Adrenergic nerves form networks around the small arteries and veins of the CP, and their nerve terminals are located between the CP endothelium and the underlying fenestrated capillaries.[98] For the most part, these adrenergic nerves originate in the superior cervical ganglia, although some fibers in the CP of the fourth ventricle derive from lower ganglia.[99] Innervation of the lateral ventricles is unilateral, whereas innervation of the midline ventricles is bilateral.

Cholinergic nerves also form networks around the small arteries and veins of the CP, with terminals located between the endothelium and adjacent capillaries.[100] The CP of the third ventricle is richly supplied by cholinergic nerves, but the fourth ventricle is almost devoid of cholinergic innervation. Adrenergic and cholinergic terminals have been identified at the bases of choroid epithelial cells, in the clefts between cells, and near the smooth muscle cells of the choroid arterioles.

Peptidergic nerves are also found in the CP, but their density is less than that of adrenergic and cholinergic nerves.[101] As in the adrenergic and cholinergic networks, peptidergic nerves are located between the small blood vessels of the CP

and the overlying CP epithelium.[102] Peptidergic nerves contain vasoactive intestinal peptide or substance P, both of which are potent dilators of cerebral vessels.

Functional Aspects

Studies of the effects of adrenergic stimulation on isolated anterior CP arteries suggest that the adrenergic system plays a role in regulating CPBF.[103] Constriction occurs via α-adrenergic receptors, and relaxation occurs via β-adrenergic receptors. The adrenergic system also appears to exert a functional influence on CP epithelial cells. Carbonic anhydrase activity increased by 125% to 150% in CP homogenate after sympathectomy achieved by surgical removal of the superior cervical ganglion or injection of reserpine. In another study, sympathetic denervation was found to alter epithelial cell transport of organic acids and bases in isolated CP.[104]

In addition, the adrenergic system is reported to alter $\dot{V}_f$. Cervical sympathetic stimulation decreased $\dot{V}_f$ by 32%,[99,105,106] and bilateral excision of the superior cervical ganglia increased $\dot{V}_f$ by 33%. Low norepinephrine concentrations decreased $\dot{V}_f$ by a β-adrenoreceptor–mediated effect on the secretory epithelium, whereas the reduction at high concentrations represents α-adrenoreceptor-mediated CP vasoconstriction. The β-adrenoceptor-induced decrease in $\dot{V}_f$ appears to derive from a direct, inhibitory action on the CP epithelium via β_1-adrenoreceptors.

The cholinergic system is also reported to alter $\dot{V}_f$. Intraventricular perfusion with carbocholine or with acetylcholine in the presence of the cholinesterase inhibitor neostigmine reduced $\dot{V}_f$ by 25% to 55%.[107] Cholinergic receptors presumably are muscarinic because the effect of carbachol is blocked by atropine but is not altered by hexamethonium. The site of action of cholinergic agonists or antagonists is uncertain. They are believed to act on the CP epithelium, rather than on the CP vasculature, because carbocholine has no vasomotor effect on isolated anterior choroidal arteries.

Metabolic Regulation of Cerebrospinal Fluid Formation and Resistance to its Reabsorption

Alterations in metabolism or physiologic status affect $\dot{V}_f$ and $\dot{V}_a$. Hypothermia decreases $\dot{V}_f$, probably by reducing the activity of active secretory and transport processes and by decreasing CBF.[2] Each 1 °C reduction in temperature between 41° and 31 °C decreases $\dot{V}_f$ by 11%. In one study, hypercapnia raised $\dot{V}_f$ to normal values if $\dot{V}_f$ was decreased at normocapnia but did not change $\dot{V}_f$ if it was normal at normocapnia.[108] Normalization of $\dot{V}_f$ by hypercapnia may have occurred because CPBF improved. In contrast, hypocapnia acutely decreases $\dot{V}_f$, because of reductions of either CPBF or the availability of hydrogen ion for exchange with sodium at the abluminal surface of the CP epithelial cells. After several hours of hypocapnia, $\dot{V}_f$ returns to normal values.[109,110] Prolonged hypercapnia or hypocapnia does not significantly change $\dot{V}_f$.[108,109] Metabolic acidosis does not change $\dot{V}_f$, but metabolic alkalosis decreases $\dot{V}_f$, presumably as a result of a pH effect unrelated to ion or substrate availability.

Wald and associates[111] found that reduced osmolarity of ventricular CSF or increased osmolarity of serum decreased $\dot{V}_f$; similarly, increased osmolarity of ventricular CSF or reduced osmolarity of serum increased $\dot{V}_f$. The increase or decrease of $\dot{V}_f$ caused by the change in serum osmolarity was four times greater than that caused by a comparable change in ventricular fluid osmolarity. Presumably the changes in $\dot{V}_f$ resulting from altered ventricular fluid osmolarity occurred at the CP, whereas the changes resulting from altered serum osmolarity occurred at extrachoroidal sites.

CEREBROSPINAL FLUID DYNAMICS AND INTRACRANIAL PRESSURE

Equilibrium Between Cerebrospinal Fluid Formation and Reabsorption

Within limits, $\dot{V}_f$ is not affected by an increase or decrease of ICP. Thus, $\dot{V}_f$ remains "normal" whether ICP is 2 cm H_2O or 22 cm H_2O (Fig. 3.5). Only when ICP rises sufficiently to reduce CPP below ~70 mmHg will $\dot{V}_f$ decrease. In contrast, $\dot{V}_a$ is quite sensitive to change of ICP. At ICPs below ~7 cm H_2O, minimal reabsorption occurs.[112] At ICPs greater than 7 cm H_2O, $\dot{V}_a$ increases directly as ICP increases. The relationship between $\dot{V}_a$ and ICP is linear for ICPs up to ~30 cm H_2O. The equilibrium pressure occurs at the intersection of the plots of $\dot{V}_f$/ICP and $\dot{V}_a$/ICP. At that ICP, $\dot{V}_f$ equals $\dot{V}_a$, and no net change in CSF volume occurs.

Anesthetic- and Drug-Induced Changes in Intracranial Pressure

Treatments that alter $\dot{V}_f$ or $\dot{V}_a$ alter ICP. For example, theophylline is reported to increase $\dot{V}_f$.[93] Assuming no change in $\dot{V}_a$, the plots of $\dot{V}_f$/ICP and $\dot{V}_a$/ICP after administration of theophylline intersect at an ICP value that is higher than "normal" (Fig. 3.6A). Stated another way, theophylline increases $\dot{V}_f$ so that the volume of CSF formed each minute exceeds the volume reabsorbed each minute. As a result, CSF volume expands, causing ICP to increase. ICP continues to rise as CSF volume expands, and as ICP rises it provides an increasingly greater "driving force" for reabsorption of CSF. $\dot{V}_a$ increases as ICP increases until $\dot{V}_a$ equals $\dot{V}_f$. A new equilibrium state is achieved when formation and reabsorption are equal and no net change in CSF volume or further change in ICP occurs. The net effect of these changes is that by increasing $\dot{V}_f$,

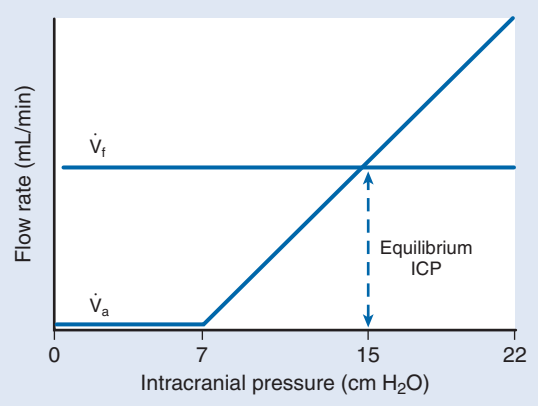


Fig. 3.5 Rates of cerebrospinal fluid (CSF) formation ($\dot{V}_f$) and reabsorption ($\dot{V}_a$) are plotted as functions of intracranial pressure (ICP). As long as choroid plexus pressure (CPP) remains above ≈ 70 mmHg, $\dot{V}_f$ is unaffected by ICP. At ICP < 7 cm H_2O, $\dot{V}_a$ is minimal. At ICP values between 7 and 25 to 30 cm H_2O, the resistance to CSF reabsorption (R_a) is relatively constant, and $\dot{V}_a$ is linearly related to ICP. ICP stabilizes at a value where $\dot{V}_f$ equals $\dot{V}_a$. *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

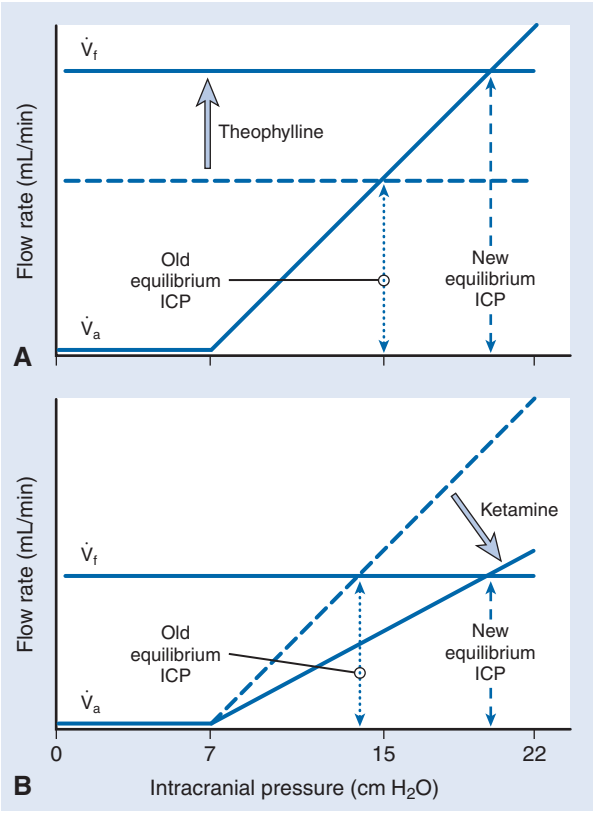


Fig. 3.6 **A,** Theophylline increases the rate of cerebrospinal fluid (CSF) formation ($\dot{V}_f$) ("elevating" the slope of $\dot{V}_f$ plotted against intracranial pressure [ICP]). **B,** Ketamine increases the resistance to CSF resorption (R_a) ("flattening" the $\dot{V}_f$ /ICP slope). With both treatments, $\dot{V}_f$ equals rate of CSF absorption ($\dot{V}_a$) at increased ICP. *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

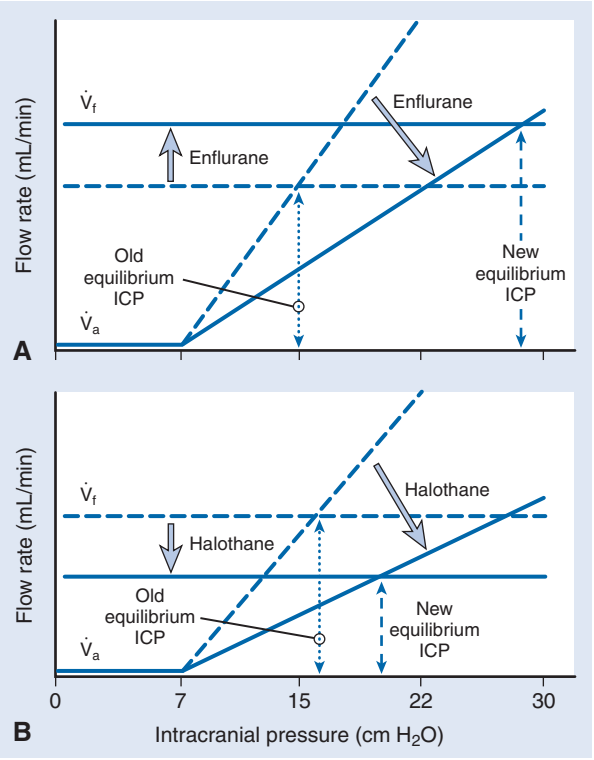


Fig. 3.7 **A,** Enflurane at intermediate concentrations increases both the rate of cerebrospinal fluid (CSF) formation ($\dot{V}_f$) ("elevating" the slope of $\dot{V}_f$ plotted against intracranial pressure [ICP]) and resistance to CSF reabsorption (R_a) ("flattening" the $\dot{V}_a$ /ICP slope). **B,** Halothane decreases $\dot{V}_f$ ("lowering" the $\dot{V}_f$ /ICP slope) and increases R_a. With both anesthetics, $\dot{V}_f$ equals $\dot{V}_a$ at increased ICP. *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

theophylline should cause a rise in ICP, provided that other CSF dynamics are not altered.

Ketamine is reported to increase R_a.[51] By definition, R_a is the inverse of the slope of the relationship between $\dot{V}_a$ and ICP. Increased R_a produces a "flattening" of the $\dot{V}_a$/ICP regression line. Assuming no change in $\dot{V}_f$, the plots of $\dot{V}_f$/ICP and $\dot{V}_a$/ICP after administration of ketamine intersect at an ICP that is higher than normal (Fig. 3.6B). Stated another way, ketamine reduces $\dot{V}_a$ because "normal" ICP does not provide sufficient driving force to cause the usual amounts of CSF to be reabsorbed now that R_a has increased. As a result, the volume of CSF formed each minute exceeds the volume reabsorbed each minute. CSF volume expands, causing ICP to increase. ICP continues to increase as CSF volume expands, and as ICP increases it provides a progressively greater driving force for reabsorption of CSF. $\dot{V}_a$ increases as ICP increases until $\dot{V}_a$ equals $\dot{V}_f$. A new equilibrium is achieved, at which formation and reabsorption are equal and no net change in CSF volume or further change of ICP occurs. The net effect of these changes is that by increasing R_a, ketamine should cause a rise in ICP, provided that other CSF dynamics are not altered.

Enflurane alters ICP because it increases both $\dot{V}_f$ and R_a (Fig. 3.7A).[50,52,53] Halothane also has combined effects on $\dot{V}_f$ and R_a.[54,55] However, unlike those of enflurane, its effects are opposing rather than additive (Fig. 3.7B).[113] Fentanyl is an example of a drug that decreases ICP. Fentanyl decreases R_a, so the $\dot{V}_a$/ICP regression line becomes "steeper" (Fig. 3.8).[75] Consequently, "normal" ICP, the driving force for reabsorption of CSF, is in excess of what is needed for "normal" $\dot{V}_a$. $\dot{V}_a$ is greater than $\dot{V}_f$, causing a contraction of CSF volume and a reduction of ICP.

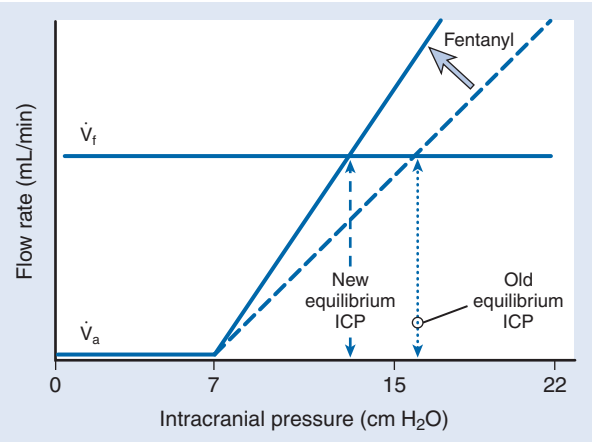


Fig. 3.8 Fentanyl in low doses decreases resistance to cerebrospinal fluid (CSF) reabsorption (R_a) ("steepening" the slope of the plot of CSF absorption [$\dot{V}_a$] against intracranial pressure [ICP]). As a result, the rate of CSF formation ($\dot{V}_f$) equals $\dot{V}_a$ at decreased ICP.

ICP gradually diminishes, resulting in a lesser driving force for reabsorption of CSF. $\dot{V}_a$, initially greater than $\dot{V}_f$, gradually decreases until, at some reduced ICP, $\dot{V}_a$ is lowered to a value that matches $\dot{V}_f$. A new equilibrium between formation and reabsorption is achieved, and ICP drops no farther.

Furosemide is another example of a drug that decreases ICP. Furosemide decreases $\dot{V}_f$, "lowering" the $\dot{V}_f$/ICP regression line (Fig. 3.9A). As a result, at "normal" ICP, $\dot{V}_a$ exceeds $\dot{V}_f$, causing a contraction of CSF volume and a reduction in ICP. ICP continues to decrease, providing a lesser driving force for

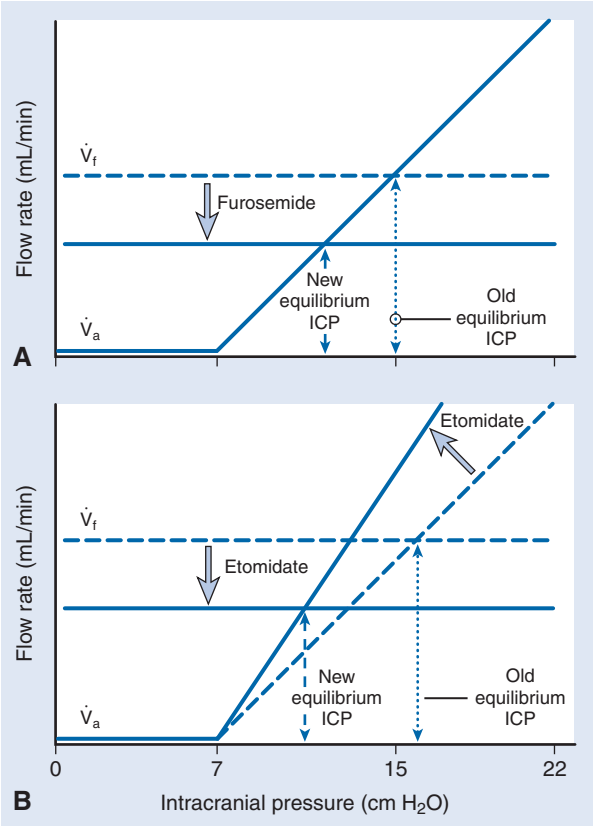


Fig. 3.9 **A,** Furosemide decreases the rate of cerebrospinal fluid (CSF) formation ($\dot{V}_f$) ("lowering" the slope of $\dot{V}_f$ plotted against intracranial pressure [ICP]). **B,** Etomidate in high doses decreases $\dot{V}_f$ and the resistance to CSF reabsorption (R_a) ("steepening" the slope of CSF fluid reabsorption [$\dot{V}_a$] plotted against ICP). With both treatments, $\dot{V}_f$ equals $\dot{V}_a$ at decreased ICP. *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

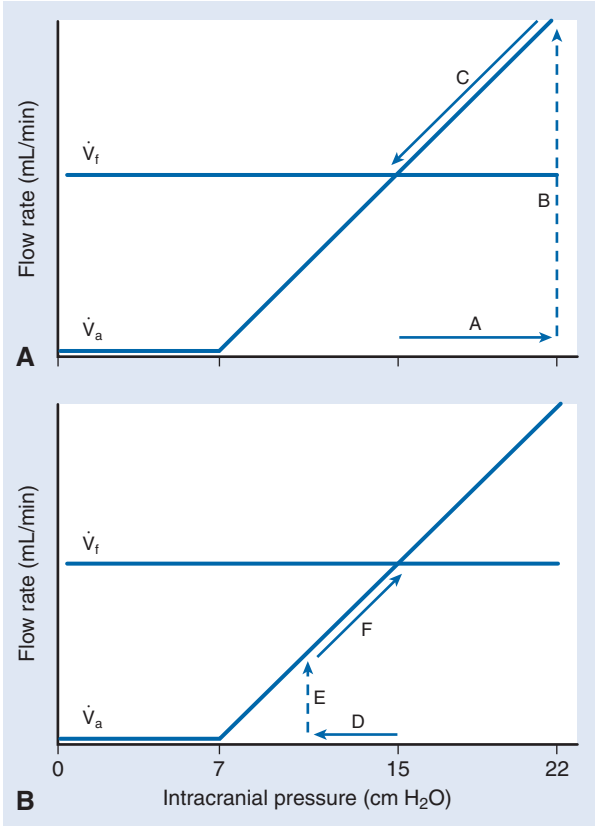


Fig. 3.10 Plots of cerebrospinal fluid (CSF) formation ($\dot{V}_f$) versus intracranial pressure (ICP) and rate of CSF reabsorption ($\dot{V}_a$) versus ICP show how CSF volume alters to offset alterations in intracranial volume, thereby minimizing ICP changes. **A,** Increase in intracranial volume raises ICP. **(A)** At higher ICP, $\dot{V}_a$ exceeds $\dot{V}_f$, **(B)** so CSF volume decreases. As CSF volume decreases, ICP decreases **(C)** until $\dot{V}_f$ equals $\dot{V}_a$. If $\dot{V}_f$ and the resistance to CSF reabsorption (Ra) are not altered, ICP returns to "normal." **B**, Decrease in intracranial volume decreases ICP **(D)**. At decreased ICP, $\dot{V}_a$ **(E)** is less than $\dot{V}_f$, so CSF volume increases. As CSF volume increases, ICP increases **(F)** until $\dot{V}_f$ equals $\dot{V}_a$. If $\dot{V}_f$ and R_a are not altered, ICP returns to "normal." *(From Cucchiara RF, Michenfelder JD [eds]: Clinical Neuroanesthesia. New York, Churchill Livingstone, 1990.)*

reabsorption of CSF. At some reduced ICP, $\dot{V}_a$ is decreased enough to match the reduced $\dot{V}_f$. Formation and reabsorption are in equilibrium at that reduced ICP, and no further decrease of ICP occurs. High doses of etomidate reduce ICP through combined effects on $\dot{V}_f$ and R_a (Fig. 3.9B).[69]

Cerbrospinal Fluid Volume Change to Compensate for Intracranial Volume Change

When the volume of intracranial blood, brain tissue, gas, or other material increases, CSF volume contracts through translocation of intracranial CSF to the spinal subarachnoid space and through reabsorption of CSF. Conversely, when the volume of intracranial blood, brain tissue, gas, or other material decreases, CSF volume expands by means of cephalad translocation and a temporary decrease in $\dot{V}_a$. CSF volume and ICP responses to increases or decreases in intracranial volume are easily illustrated by use of the $\dot{V}_f$ /ICP and $\dot{V}_a$ /ICP relationships discussed previously. For example, subdural hematoma adds volume to the intracranial contents, thereby raising ICP, as shown in Fig. 3.10A: increased ICP *(A)* provides a driving force for reabsorption of CSF, so $\dot{V}_a$ increases *(B)* to a value greater than $\dot{V}_f$ (which does not change). Consequently, the volume of CSF reabsorbed each minute exceeds the volume of CSF formed each minute. Gradually, CSF volume contracts, and as it does, total intracranial volume decreases, causing ICP to fall *(C)* from its increased level. As ICP approaches "normal," $\dot{V}_a$ falls toward "normal," and the mismatch between $\dot{V}_a$ and $\dot{V}_f$ becomes progressively reduced. When ICP returns to pre-hematoma values, $\dot{V}_f$ and $\dot{V}_a$ once again are in equilibrium, and no further change of CSF volume or ICP occurs. At the new equilibrium state, ICP and total intracranial volume are much the same as before the subdural hematoma, but cerebral blood volume (CBV) (part of it in the form of the hematoma) is increased, and CSF volume is decreased.

Conversely, surgical removal of brain tissue reduces intracranial volume, thereby decreasing ICP, as shown in Fig. 3.10B: reduced ICP *(D)* provides only a weak driving force for reabsorption of CSF, so $\dot{V}_a$ *(E)* is less than $\dot{V}_f$ (which does not change). Thus over the ensuing minutes, the volume of CSF reabsorbed is less than the volume formed. Gradually, CSF volume expands, and as it does, total intracranial volume increases, causing ICP to rise *(F)* from its reduced level. Rising ICP stimulates $\dot{V}_a$. When ICP reaches presurgical values, $\dot{V}_f$ and $\dot{V}_a$ once again are in equilibrium, and no further change of CSF volume or ICP occurs. At the new equilibrium state, ICP and total intracranial volume are much the same as before surgical removal of brain tissue, but brain tissue volume is decreased and CSF volume is increased.

CONDITIONS IN WHICH ALTERED CEREBROSPINAL FLUID DYNAMICS CHANGE INTRACRANIAL PRESSURE

Responses to Increased Intracranial Pressure

Work in animal models and in clinical studies has demonstrated how $\dot{V}_f$ and R_a affect CSF volume and contribute to ICP change in clinically relevant ways.

Intracranial Mass

Rapid expansion of an intracranial mass causes an increase in ICP followed by compensatory decreases in CBV, CSF volume, and brain tissue volume. For delineation of these changes and the contribution of $\dot{V}_f$ and R_a, three groups of dogs were studied.[114] As reported, hypocapnia initially reduced CBV, and during 4 hours of hypocapnia, CBV reexpanded and CSF volume changed reciprocally (group 1). In group 2, an increase in ICP with an intracranial balloon caused a decrease in CBV and an increase in R_a that were stable for 4 hours. In group 3, balloon inflation reduced CBV, hypocapnia caused a further decrease of CBV, and, during 4 hours of hypocapnia, CBV reexpanded and CSF volume changed reciprocally. Brain tissue composition was not different among the groups.

Effects of Anesthetics

Anesthetics may affect the initial increase in ICP and subsequent compensatory decreases in CBV, CSF volume, and brain tissue volume caused by rapid expansion of an intracranial mass. For examination of these changes and the contribution of $\dot{V}_f$ and R_a, five groups of dogs were anesthetized with inhalational or intravenous agents while an intracranial mass was present, and hypocapnia was used to reduce ICP.[59] With enflurane- and halothane-induced anesthesia, $\dot{V}_f$, R_a, or both were high, and ICP progressively rose because CSF volume did not contract to the same extent that CBV reexpanded. With isoflurane-, fentanyl-, or thiopental-induced anesthesia, $\dot{V}_f$ and R_a were normal, and ICP did not progressively increase because reexpansion of CBV was minimal (fentanyl) or because CSF volume contracted to the same extent that CBV reexpanded (isoflurane and thiopental).

Causes of Increased Intracranial Pressure

Many clinical conditions are accompanied by an increase in ICP. Laboratory and clinical studies have demonstrated the role of altered $\dot{V}_f$ or R_a in clinical conditions in which ICP is increased.

Acute Subarachnoid Hemorrhage

Acute subarachnoid hemorrhage often results in increased ICP. In studies examining the effect of blood components on $\dot{V}_f$ and $\dot{V}_a$, and determining the effects of $\dot{V}_f$ and $\dot{V}_a$ on ICP, animals were intrathecally given (1) heparinized whole blood, (2) plasma, (3) dialysate of plasma, (4) serum (fibrinogen free), and (5) saline.[27,28,115,116] $\dot{V}_a$ values were determined by manometric infusion. Whole blood and plasma raised ICP and produced a threefold to tenfold rise in R_a, respectively. Electron microscopic examination of the arachnoid villi revealed decreased numbers of transendothelial channels and fibrin deposits within the villi.

Chronic Changes after Subarachnoid Hemorrhage

Hydrocephalus often follows subarachnoid hemorrhage. In both animals and patients examined at various intervals after subarachnoid hemorrhage, scanning electron microscopic studies of the CSF pathways and arachnoid villi revealed extensive fibrosis resulting from blood within these spaces.[117] The researchers concluded that after subarachnoid hemorrhage, as well as after other clinical conditions in which leptomeningeal scarring exists, chronic obstruction to CSF outflow results from functional narrowing or blockage of CSF outflow pathways. By this mechanism, R_a is increased within both the subarachnoid space and the arachnoid villi.

Bacterial Meningitis

Bacterial meningitis is often accompanied by increased ICP. In a study examining the effect of meningitis on $\dot{V}_f$ and $\dot{V}_a$, and determining the effects of $\dot{V}_f$ and $\dot{V}_a$ on ICP, animals were intrathecally given (1) *Streptococcus pneumoniae* or (2) *Escherichia coli*.[91] $\dot{V}_f$ and $\dot{V}_a$ were determined before inoculation, 16 to 24 hours after inoculation, and after therapy. ICP rose in both groups. R_a was increased 25-fold with *S. pneumoniae* and 36-fold with *E. coli*, and, although antibiotic therapy sterilized the CSF and prevented mortality, R_a remained elevated at 2 weeks after treatment. Methylprednisolone reduced R_a to a value that was intermediate between those in control and infected animals.

Pseudotumor Cerebri

The increased ICP seen in pseudotumor cerebri is thought to result from (1) increased R_a, (2) increased $\dot{V}_f$, (3) greater water movement into brain across cerebral capillaries, (4) increased CBF and CBV, or (5) glial or neuronal cellular edema.[92] Currently, most evidence favors altered CSF dynamics as the principal cause of increased ICP.[118] In a study to determine the role of CSF dynamics, $\dot{V}_f$ and R_a were measured in both control patients and patients with pseudotumor cerebri.[119] Resting ICP was 33 cm H_2O in patients with pseudotumor cerebri and 14 cm H_2O in controls. Maximal R_a was 10 times greater, and R_a at resting ICP was six times greater in the pseudotumor patients than in controls. $\dot{V}_f$ was decreased 39% in the pseudotumor patients, as compared with controls. These results are comparable with results previously reported by others and support the view that in pseudotumor patients, impaired CSF reabsorption is a principal mechanism leading to increased ICP.[120] Prednisone decreased R_a to a value that was intermediate between controls and untreated pseudotumor patients.

Head Injury

Head injury often results in increased ICP. In one study, the PVI was used to determine $\dot{V}_f$, R_a, and the contribution of altered $\dot{V}_f$ and R_a to increased ICP in head-injured patients.[121] Results showed that R_a was increased but $\dot{V}_f$ was within normal limits for 75% of the patients studied. As calculated, about 20% of the ICP rise in this population derived from $\dot{V}_f$ and R_a.

SUMMARY

CSF plays a key role in brain well-being. It cushions the brain, provides pathways for nutrients and other substrates, regulates the concentrations of ions and other chemicals, provides routes of clearance for unwanted substances, and transports neurohormones and neurotransmitters. Alteration of $\dot{V}_f$ causes a change in ICP, with an increase (or decrease) in $\dot{V}_f$ causing an increase (or decrease) in CSF volume. Alteration of R_a not only causes a change in ICP, but also determines the pressure-buffering capacity of the CSF "compartment," with an increase in R_a reducing the ability of CSF volume to

contract in response to greater intracranial volume, and vice versa. Studies in animal models of increased ICP report that anesthetic-induced changes in $\dot{V}_f$ and R_a significantly alter the effectiveness of treatments employed to lower ICP. Studies in patients with increased ICP report that $\dot{V}_f$ and R_a may be significant (though not the major) factors altering the effectiveness of treatments to lower ICP.

REFERENCES

1. Sullivan J.T., Grouper S., Walker M.T., et al. Lumbosacral cerebrospinal fluid volume in humans using three-dimensional magnetic resonance imaging. *Anesth Analg*. 2006;103:1306–1310.
2. Milhorat T.H.. *Pediatric Neurosurgery*. Philadelphia: FA Davis; 1978:91–135. Plum F, McDowell FH, eds. Contemporary Neurology series; vol 16.
3. Salvador L., Valero R., Carrero E., et al. Cerebrospinal fluid composition modifications after neuroendoscopic procedures. *Minim Invasive Neurosurg*. 2007;50:51–55.
4. Brinker T., Stopa E., Morrison J., et al. A new look at cerebrospinal fluid circulation. *Fluids Barriers CNS*. 2014;11:10–15.
5. Mortazavi M.M., Griessenauer C.J., Adeeb N., et al. The choroid plexus: A comprehensive review of its history, anatomy, function, histology, embryology, and surgical considerations. *Childs Nerv Syst*. 2014;30:205–2014.
6. Damkier H.H., Brown P.D., Praetorius J.. Cerebrospinal fluid secretion by the choroid plexus. *Physiol Rev*. 2013;93:1847–1892.
7. Christensen H.L., Nguyen A.T., Pedersen F.D., et al. Na(+) dependent acid-base transporters in the choroid plexus; insights from slc4 and slc9 gene deletion studies. *Front Physiol*. 2013;4:304.313.
8. Rapoport S.I.. *The Blood-Brain Barrier in Physiology and Medicine*. New York: Raven Press; 1976:43–86.
9. Chikly B., Quaghebeur J.. Reassessing cerebrospinal fluid (CSF) hydrodynamics: A literature review presenting a novel hypothesis for CSF physiology. *J Bodyw Mov Ther*. 2013;17:344–354.
10. Buishas J., Gould I.G., Linninger A.A.. A computational model of cerebrospinal fluid production and reabsorption driven by Starling forces. *Croat Med J*. 2014;55:481–497.
11. Igarashi H., Tsuujita M., Kwee I.L., et al. Water influx into cerebrospinal fluid is primarily controlled by aquaporin-4, not by aquaporin-1: 170 JJVCPE MRI study in knockout mice. *Neuroreport*. 2014;25:39–43.
12. Hochwald G.M., Gandhi M., Goldman S.. Transport of glucose from blood to cerebrospinal fluid in the cat. *Neuroscience*. 1983;10:1035–1040.
13. Hochwald G.M., Magee J., Ferguson V.. Cerebrospinal fluid glucose: Turnover and metabolism. *J Neurochem*. 1985;44:1832–1837.
14. Pakulski C., Drobnik L., Millo B.. Age and sex as factors modifying the function of the blood-cerebrospinal fluid barrier. *Med Sci Monit*. 2000;6:314–318.
15. Weisner B., Bernhardt W.. Protein fractions of lumbar, cisternal and ventricular cerebrospinal fluid. *J Neurol Sci*. 1978;37:205–214.
16. Pollay M., Stevens F.A., Roberts P.A.. Alteration in choroid-plexus blood flow and cerebrospinal fluid formation by increased ventricular pressure. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:687–695.
17. Weiss M.H., Wertman N.. Modulation of CSF production by alterations in cerebral perfusion pressure. *Arch Neurol*. 1978;35:527–529.
18. DiChiro G., Hammock M.K., Bleyer W.A.. Spinal descent of cerebrospinal fluid in man. *Neurology*. 1976;26:1–8.
19. Matsumae M., Hirayama A., Atsumi H., et al. Velocity and pressure gradients of cerebrospinal fluid assessed with magnetic resonance imaging. *J Neurosurg*. 2014;120:218–227.
20. Oreskovic D., Klarica M.. A new look at cerebrospinal fluid movement. *Fluids Barriers CNS*. 2014;11:16–24.
21. Drosdal I.N., Mardal K.A., Stovenrud K., et al. Effect of the central canal in the spinal cord on fluid movement within the cord. *J Neuroradiol*. 2013;26:585–590.
22. Laman J.D., Weller R.O.. Drainage of cells and soluble atigen from the CNS to regional lymph nodes. *J Neuroimmune Pharmacol*. 2013;8:840–856.
23. Chen L., Elias G., Yostos M.P., et al. Pathways of cerebrospinal fluid outflow: A deeper understanding of resorption. *Neuroradiology*. 2015;57:139–147.
24. Upton M.L., Weller R.O.. The morphology of cerebrospinal fluid drainage pathways in human arachnoid granulations. *J Neurosurg*. 1985;63:867–875.
25. Simionescu N., Simionescu M., Palade G.E.. Structural basis of permeability in sequential segments of the microvasculature of the diaphragm. II: Pathways followed by microperoxidase across the endothelium. *Micro-vasc Res*. 1978;15:17–36.
26. Johnson R.N., Maffeo C.J., Butler A.B., et al. Intracranial hypertension in experimental animals and man: Quantitative approach to system dynamics of circulatory cerebrospinal fluid. In: New York: Plenum Press; 1983:687–695. Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2 New York: Plenum Press; 1983:697–706.
27. Johnson R.N., Maffeo C.J., Mann J.D., et al. Intracranial pressure regulation: A comparative model of cerebrospinal fluid systems. *TIT J Life Sci*. 1978;8:79–92.
28. Mann J.D., Butler A.B., Rosenthal J.E., et al. Regulation of intracranial pressure in rat, dog, and man. *Ann Neurol*. 1978;3:156–165.
29. Mann J.D., Butler A.B., Johnson R.N., et al. Clearance of macromolecular and particulate substances from the cerebrospinal fluid system of the rat. *J Neurosurg*. 1979;50:343–348.
30. Butler A.B., Mann J.D., Maffeo C.J., et al. Mechanisms of cerebrospinal fluid absorption in normal and pathologically altered arachnoid villi. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:707–726.
31. Fenstermacher J.D., Patlak C.S.. The movement of water and solutes in the brain of mammals. In: Pappius H.M., Feindel W., eds. *Dynamics of Brain Edema*. New York: Springer-Verlag; 1976:87.
32. Reulen H.J., Graham R., Spatz M., et al. Role of pressure gradients and bulk flow in dynamics of vasogenic brain edema. *J Neurosurg*. 1977;46:24–35.
33. Reulen H.J., Prioleau G.R., Tsuyumu M., et al. Clearance of edema fluid into cerebrospinal fluid: Mechanisms for resolution of vasogenic brain edema. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:777–787.
34. Klatzo I., Chui E., Fujiwara K., et al. Resolution of vasogenic brain edema (VBE). *Adv Neurol*. 1980;28:359–373.
35. Bito L.Z.. Absorptive transport of prostaglandins and other eicosanoids across the blood-brain barrier system and its physiological significance. In: Suckling A.J., Rumsby M.G., Bradbury M.W.B., eds. *The Blood-Brain Barrier in Health and Disease*. Chichester, UK: Ellis Horwood Ltd; 1986:109–121.
36. Pratt O.E., Greenwood J.. Movement of vitamins across the blood-brain barrier. In: Suckling A.J., Rumsby M.G., Bradbury M.W.B., eds. *The Blood-Brain Barrier in Health and Disease*. Chichester, UK: Ellis Harwood Ltd; 1986:87–97.
37. Rosenberg G.A.. Glucose, amino acids, and lipids. In: Rosenberg G.A., ed. *Brain Fluids and Metabolism*. New York: Oxford University Press; 1990:119–144.
38. Leusen I.R., Weyne J.J., Demeester G.M.. Regulation of acid-base equilibrium of cerebrospinal fluid. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:25–42.
39. Cserr H.F., Cooper D.M., Milhort T.J.. Flow of cerebral interstitial fluid as indicated by the removal of extracellular markers from rat caudate nucleus. *Exp Eye Res*. 1977;25(Suppl):461–473.
40. Akil H., Richardson D.E., Borchas J.D., et al. Appearance of betaendorphin-like immunoreactivity in human ventricular cerebrospinal fluid upon analgesic electrical stimulation. *Proc Natl Acad Sci U S A*. 1978;75:5170–5172.
41. Hosobuchi Y., Rossier J., Bloom F.E., et al. Stimulation of human periaqueductal gray for pain relief increases immunoreactive beta-endorphin in ventricular fluid. *Science*. 1979;203:279–281.
42. Jeffcoate W.J., Rees L.H., McLoughlin L., et al. β-Endorphin in human cerebrospinal fluid. *Lancet*. 1978;2(8081):119–121.
43. Heisey S.R., Held D., Pappenheimer J.R.. Bulk flow and diffusion in the cerebrospinal fluid system of the goat. *Am J Physiol*. 1962;203:775–781.
44. Pappenheimer J.R., Heisey S.R., Jordan E.F., et al. Perfusion of the cerebral ventricular system in unanesthetized goats. *Am J Physiol*. 1962;203:763–774.
45. Maffeo C.J., Mann J.D., Butler A.B., et al. Constant flow perfusion of the cerebrospinal fluid system of rat, dog, and man: a mathematical model. In: Saha S., ed. *Proceedings of the Fourth New England Bioengineering Conference*. New York: Pergamon Press; 1976:447.
46. Marmarou A., Shapiro K., Shulman K.. Isolating factors leading to sustained elevations of the ICP. In: Beks J.W.F., Bosch D.A., Brock M., eds. *Intracranial Pressure III*. New York: Springer-Verlag; 1976:33–35.
47. Miller J.D.. Intracranial pressure-volume relationships in pathological conditions. *J Neurosurg Sci*. 1976;20:203–209.
48. Swallow D.M., Fellner N., Varsos G.V., et al. Repeatability of cerebrospinal fluid constant rate infusion study. *Acta Neurol Scand*. 2014;130:131–138.
49. Gwak H.S., Joo J., Shin S.H., et al. Ventriculolumbar perfusion chemotherapy with methotrexate for treating leptomeningeal carcinomatosis: A Phase II Study. *Oncologist*. 2014;19:1044–1045.
50. Artru A.A., Nugent M., Michenfielder J.D.. Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. *Anesthesiology*. 1982;57:255–260.
51. Mann J.D., Mann E.S., Cookson S.L.. Differential effect of pentobarbital, ketamine hydrochloride, and enflurane anesthesia on CSF formation rate and outflow resistance in the rat. In: Miller J.D., Becker D.P., Hochwald G., et al., eds. *Intracranial Pressure IV*. New York: Springer-Verlag; 1980:466–471.

52. Artru A.A.. Effects of enflurane and isoflurane on resistance to reabsorption of cerebrospinal fluid in dogs. *Anesthesiology*. 1984;61:529–533.
53. Artru A.A.. Concentration-related changes in the rate of CSF formation and resistance to reabsorption of CSF during enflurane and isoflurane anesthesia in dogs receiving nitrous oxide. *J Neurosurg Anesthesiol*. 1989;1:256–262.
54. Artru A.A.. Effects of halothane and fentanyl on the rate of CSF production in dogs. *Anesth Analg*. 1983;62:581–585.
55. Artru A.A.. Effects of halothane and fentanyl anesthesia on resistance to reabsorption of CSF. *J Neurosurg*. 1984;60:252–256.
56. Nemoto E.M., Stezoski S.W., MacMurdo D.. Glucose transport across the rat blood-brain barrier during anesthesia. *Anesthesiology*. 1978;49:170–176.
57. Hannan Jr C.J., Kettler T.M., Artru A.A., et al. Blood-brain barrier permeability during hypocapnia in halothane-anesthetized monkeys. *Ann N Y Acad Sci*. 1988;528:172–174.
58. Pashayan A.G., Mickle J.P., Vetter T.R., et al. Blood-CSF barrier function during general anesthesia in children undergoing ventriculoperitoneal shunt placement (abstract). *Anesthesiol Rev*. 1988;15:30–31.
59. Artru A.A.. Reduction of cerebrospinal fluid pressure by hypocapnia: Changes in cerebral blood volume, cerebrospinal fluid volume and brain tissue water and electrolytes. II: Effects of anesthetics. *J Cereb Blood Flow Metab*. 1988;8:750–756.
60. Schettini A., Furniss W.W.. Brain water and electrolyte distribution during the inhalation of halothane. *Br J Anaesth*. 1979;51:1117–1124.
61. Alexander S.C., Helmer P.H., Ramirez O., et al. Effects of general anesthesia on canine blood-brain barrier glucose transport. In: Harper M., Jennett B., Miller O., et al., eds. *Blood Flow and Metabolism in the Brain*. Edinburgh: Churchill Livingstone; 1975:9-37–9-41.
62. Artru A.A.. Isoflurane does not increase the rate of CSF production in the dog. *Anesthesiology*. 1984;60:193–197.
63. Chi O.Z., Anwar M., Sinha A.K., et al. Effects of isoflurane anesthesia on the blood-brain barrier transport. *Anesthesiology*. 1990;73:A682.
64. Stover J.F., Kempski O.S.. Anesthesia increases circulating glutamate in neurosurgical patients. *Acta Neurochir (Wien)*. 2005;147:847–853.
65. Sugioka S.. Effects of sevoflurane on intracranial pressure and formation and absorption of cerebrospinal fluid in cats. *Masui (Jap J Anesth)*. 1992;41:1434–1442.
66. Artru A.A.. Rate of cerebrospinal fluid formation, resistance to reabsorption of cerebrospinal fluid, brain tissue water content, and electroencephalogram during desflurane anesthesia in dogs. *J Neurosurg Anesthesiol*. 1993;5:178–186.
67. Artru A.A., Powers K.M.. Furosemide decreases cerebrospinal fluid formation during desflurane anesthesia in rabbits. *J Neurosurg Anesthesiol*. 1997;9:166–174.
68. Saija A., Princi P., Pasquale R., et al. Modifications of the permeability of the blood-brain barrier and local cerebral metabolism in pentobarbital- and ketamine-anaesthetized rats. *Neuropharmacology*. 1989;28:997–1002.
69. Artru A.A.. Dose-related changes in rate of cerebrospinal fluid formation and resistance to reabsorption of cerebrospinal fluid following administration of thiopental, midazolam, and etomidate in dogs. *Anesthesiology*. 1988;69:541–546.
70. Fischer S., Renz D., Schaper W., et al. In vivo effects of fentanyl, methohexital, and thiopental on brain endothelial permeability. *Anesthesiology*. 1995;82:451–458.
71. Artru A.A.. Propofol combined with halothane or with fentanyl/halothane does not alter the rate of CSF formation or resistance to reabsorption of CSF in rabbits. *J Neurosurg Anesthesiol*. 1993;5:250–257.
72. Gjedde A., Rasmussen M.. Pentobarbital anesthesia reduces blood-brain glucose transfer in the rat. *J Neurochem*. 1980;35:1382–1387.
73. Sage J.I., Duffy T.E.. Pentobarbital anesthesia: Influence on amino acid transport across the blood-brain barrier. *J Neurochem*. 1979;33:963–965.
74. Artru A.A.. The rate of CSF formation, resistance to reabsorption of CSF, and aperiodic analysis of the EEG following administration of fumazenil to dogs. *Anesthesiology*. 1990;72:111–117.
75. Artru A.A.. Dose-related changes in the rate of CSF formation and resistance to reabsorption of CSF during administration of fentanyl, sufentanil, or alfentanil in dogs. *J Neurosurg Anesthesiol*. 1991;3:283–290.
76. Artru A.A., Bernards C.M., Mautz D.S., et al. Intravenous lidocaine decreases but cocaine does not alter the rate of cerebrospinal fluid formation in anesthetized rabbits. *J Neurosurg Anesthesiol*. 1997;9:31–43.
77. Meyer R.R., Shapiro H.M.. Paradoxical effect of enflurane on choroid plexus metabolism: Clinical implications. *Abstracts of the Am Soc Anesthsiol*. 1978;489–490. The 1978 ASA Annual Meeting was held in Chicago, Oct. 21—25 at the Conrad Hilton & Chicago Marriott.
78. Maktabi M.A., El Bokl F.F., Todd M.M.. Effect of halothane anesthesia on production of cerebrospinal fluid: Possible role of vasopressin V1 receptors (abstract). *J Cereb Blood Flow Metab*. 1991;11:S268.
79. Dawidowicz A.L., Kalitynski R., Fijalkowska A.. Free and bound propofol concentrations in human cerebrospinal fluid. *Br J Clin Pharmacol*. 2003;56:545–550.
80. Dawidowicz A.L., Kalitynski R., Fijalkowska A.. Relationships between total and unbound propofol in plasma and CSF during continuous drug infusion. *Clin Neuropharmacol*. 2004;27:129–132.
81. Luo W., Li Y.H., Yang J.J., et al. Cerebrospinal fluid and plasma propofol concentration during total intravenous anaesthesia of patients undergoing elective intracranial tumor removal. *J Zhejiang Univ Sci B*. 2005;6:865–868.
82. Dawidowicz A.L., Kalitynski R., Mardarowicz M.. The changes of propofol concentration in human cerebrospinal fluid after drug infusion. *Clin Neuropharmacol*. 2006;29:3–5.
83. Mannila A., Hokki H., Heikkinen M., et al. Cerebrospinal fluid distribution of ketoprofen after intravenous administration in young children. *Clin Pharmacokinet*. 2006;45:737–743.
84. Mannila A., Kumpulainen E., Lehtonen M., et al. Plasma and cerebrospi-nal fluid concentrations of indomethacin in children after intravenous administration. *J Clin Pharmacol*. 2007;47:94–100.
85. Kumpulainen E., Kokki H., Laisalmi M., et al. How readily does ketorolac penetrate cerebrospinal fluid in children? *J Clin Pharmacol*. 2008;48:495–501.
86. Kumpulainen E., Kokki H., Halonen T., et al. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics*. 2007;119:766–771.
87. Kokki H., Kumpulainen E., Lehtonen M., et al. Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. *Pediatrics*. 2007;120:e1002–e1008.
88. Rosenberg G.A., Kyner W.T.. Effect of mannitol-induced hyperosmolarity on transport between brain interstitial fluid and cerebrospinal fluid. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:765–775.
89. Rosenberg G.A., Kyner W.T., Estrada E.. Bulk flow of brain interstitial fluid under normal and hyperosmolar conditions. *Am J Physiol*. 1980;238:F42–F49.
90. Sahar A., Tsipstein E.. Effects of mannitol and furosemide on the rate of formation of cerebrospinal fluid. *Exp Neurol*. 1978;60:584–591.
91. Dacey R.G.J., Scheld W.M., Winn H.R.. Bacterial meningitis: Selected aspects of cerebrospinal fluid pathophysiology. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:727–738.
92. Mann J.D., Johnson R.N., Butler A.B., et al. Cerebrospinal fluid circulatory dynamics in pseudotumor cerebri and response to steroid therapy. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 2. New York: Plenum Press; 1983:739–751.
93. Wright E.M.. Transport processes in the formation of cerebrospinal fluid. *Rev Physiol Biochem Pharmacol*. 1978;83:1–34.
94. Rosenberg G.A.. Physiology of cerebrospinal and interstitial fluids. In: Rosenberg G.A., ed. *Brain Fluids and Metabolism*. New York: Oxford University Press; 1990:36–57.
95. Foxworthy J.C.I., Artru A.A.. Cerebrospinal fluid dynamics and brain tissue composition following intravenous infusion of hypertonic saline in anesthetized rabbits. *J Neurosurg Anesthesiol*. 1990;2:256–265.
96. Artru A.A.. Muscle relaxation with succinylcholine or vecuronium does not alter the rate of CSF production or resistance to reabsorption of CSF in dogs. *Anesthesiology*. 1988;68:392–396.
97. Fujita N.. Prostaglandin E1-induced hypotension: Its effect on rate of cerebrospinal fluid formation in anesthetized cats. *J Osaka Dent Univ*. 1993;27:67–76.
98. Lindvall M.. Fluorescence histochemical study on regional differences in the sympathetic nerve supply of the choroid plexus from various laboratory animals. *Cell Tissue Res*. 1979;198:261–267.
99. Lindvall M., Edvinsson L., Owman C.. Sympathetic nervous control of cerebrospinal fluid production from the choroid plexus. *Science*. 1978;201:176–207.
100. Lindvall M., Edvinsson L., Owman C.. Histochemical study on regional differences in the cholinergic nerve supply of the choroid plexus from various laboratory animals. *Exp Neurol*. 1977;55:152–159.
101. Larsson L.I., Edvinsson L., Fohrenkrug J., et al. Immunohistochemical localization of a vasodilatory peptide (VIP) in cerebrovascular nerves. *Brain Res*. 1976;113:400–404.
102. Lindvall M., Alumets J., Edvinsson L., et al. Peptidergic (VIP) nerves in the mammalian choroid plexus. *Neurosci Lett*. 1978;9:77–82.
103. Edvinsson L., Lindvall M.. Autonomic vascular innervation and vasomo-tor reactivity in the choroid plexus. *Exp Neurol*. 1978;62:394–404.
104. Winbladh B., Edvinsson L., Lindvall M.. Effect of sympathectomy on active transport mechanisms in choroid plexus in vitro. *Acta Physiol Scand*. 1978;102:85A.
105. Haywood J.R., Vogh B.P.. Some measurements of autonomic nervous system influence on production of cerebrospinal fluid in the cat. *J Pharmacol Exp Ther*. 1979;208:341–346.

106. Lindvall M., Edvinsson L., Owman C.. Effect of sympathomimetic drugs and corresponding receptor antagonists on the rate of cerebrospinal fluid production. *Exp Neurol*. 1979;64:132–148.
107. Lindvall M., Edvinsson L., Owman C.. Reduced cerebrospinal fluid formation through cholinergic mechanisms. *Neurosci Lett*. 1978;10:311–316.
108. Heisey S.R., Adams T., Fisher M.J., et al. Effect of hypercapnia and cerebral perfusion pressure on cerebrospinal fluid production in the cat. *Am J Physiol*. 1983;244:R224–R227.
109. Artru A.A., Hornbein T.F.. Prolonged hypocapnia does not alter the rate of CSF production in dogs during halothane anesthesia or sedation with nitrous oxide. *Anesthesiology*. 1987;67:66–71.
110. Martins A.N., Doyle T.F., Newby N.. PCO2 and rate of formation of cerebrospinal fluid in the monkey. *Am J Physiol*. 1976;231:127–131.
111. Wald A., Hochwald G.M., Gandhi M.. Evidence for the movement of fluid, macromolecules and ions from the brain extracellular space to the CSF. *Brain Res*. 1978;151:283–290.
112. Brumback R.A.. Anatomic and physiologic aspects of the cerebrospinal fluid space. In: Herndon R.M., Brumback R.A., eds. *The Cerebrospinal Fluid*. Boston: Kluwer Academic; 1989:15–43.
113. Artru A.A.. Relationship between cerebral blood volume and CSF pressure during anesthesia with halothane or enflurane in dogs. *Anesthesiology*. 1983;58:533–539.
114. Artru A.A.. Reduction of cerebrospinal fluid pressure by hypocapnia: Changes in cerebral blood volume, cerebrospinal fluid volume, brain tissue water and electrolytes. *J Cereb Blood Flow Metab*. 1987;7:471–479.
115. Butler A.B., Maffeo C.J., Johnson R.N., et al. Impaired absorption of CSF during experimental subarachnoid hemorrhage: effects of blood components on vesicular transport in arachnoid villi. In: Shulman K., Marmarou A., Miller J.D., et al., eds. *Intracranial Pressure IV*. New York: Springer-Verlag; 1980:245–248.
116. Johnson R.N., Maffeo C.J., Dacey R.G., et al. Mechanism for intracranial hypertension during experimental subarachnoid hemorrhage: Acute malfunction of arachnoid villi by components of plasma. *Trans Am Neurol Assoc*. 1978;103:138–142.
117. Suzuki S., Ishii M., Iwabuchi T.. Posthaemorrhagic subarachnoid fibrosis in dogs: Scanning electron microscopic observation and dye perfusion study. *Acta Neurochir*. 1979;46:105–117.
118. Johnston I.. The definition of a reduced CSF absorption syndrome: A reappraisal of benign intracranial hypertension and related syndromes. *Med Hypotheses*. 1975;1:10–14.
119. Mann J.D., Johnson R.N., Butler A.B., et al. Impairment of cerebrospinal fluid circulatory dynamics in pseudotumor cerebri and response to steroid treatment (abstract). *Neurology*. 1979;29:550.
120. Johnston I., Paterson A.. Benign intracranial hypertension. II: CSF pressure and circulation. *Brain*. 1974;97:301–312.
121. Becker D.P.. *Isolation of factors leading to raised ICP in head-injured patients*, Atlanta. In: *53rd Annual Meeting of the American Association of Neurological Surgeons*; 1985. A preliminary report (abstract).
122. Diem K., Lentner C., eds. Cerebrospinal fluid. In: *Scientific Tables*. 7. Basel: JR Geigy; 1970:635–640.
123. Hochwald G.M.. Cerebrospinal fluid mechanisms. In: Cottrell J.R.E., Turndorf H., eds. *Anesthesia and Neurosurgery*. St Louis: Mosby; 1986:33–53.
124.. Wood J.H.. Physiology, pharmacology, and dynamics of cerebrospinal fluid. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid*; vol 1. New York: Plenum Press; 1980:1–16.
125. Majumdar A., Jana A., Jana A., et al. Importance of normal values of CSF parameters in term versus preterm neonates. *J Clin Neunatol*. 2013;2:166–168.
126. Hegen H., Auer M., Deisenhammer F.. Serum glucose adjusted cut-off values for normal cerebrospinal fluid/serum glucose ratio: Implications for clinical practice. *Clin Chem Lab Med*. 2014;52:1335–1340.
127. Avery R.A.. Reference range of cerebrospinal fluid opening pressure in children: Historical overview and current data. *Neuropediatrics*. 2014;45:206–211.

Effects of Anesthetic Agents and Other Drugs on Cerebral Blood Flow, Metabolism, and Intracranial Pressure

4

M. Matsumoto • T. Sakabe

INTRODUCTION

The major goals in neurosurgical anesthesia are to provide adequate tissue perfusion to the brain (and spinal cord) so that the regional metabolic demand is met and to provide adequate surgical conditions (a "relaxed brain"). If anesthetic drugs or anesthetic techniques are improperly used, they can worsen the existing intracranial pathologic condition and may produce new damage. Some anesthetics or anesthetic techniques may help protect the brain subjected to metabolic stress or even ameliorate damage from such an insult. Thus, knowledge of the effects of anesthetics and anesthetic techniques on cerebral circulation, metabolism, and intracranial pressure (ICP) both in normal and pathologic conditions is important. In addition, special attention must be paid in the case of functional neurosurgery or minimally invasive surgery, such as awake surgery, stereotaxic surgery, identification of epileptic foci, and neuroradiological interventional procedures, in which anesthesiologists should consider using anesthetics and adjuvant drugs that allow control of asleep-awake-asleep status or sedation with analgesia and no or minimal interference with brain electrophysiologic monitoring or neurologic findings. While providing such a state, the anesthesiologist should ensure patency of the airway with well-maintained ventilation and circulatory stability.

In this chapter, physiologic and pharmacologic considerations in relation to neurosurgical anesthesia are summarized, followed by a review of the effects of anesthetics and other drugs on cerebral blood flow (CBF), cerebral metabolism, and ICP, focusing on human data. Data from animal studies are cited only when there are not sufficient human data. The clinical relevance of these issues to the practice of neurosurgical anesthesia is discussed.

PHYSIOLOGIC AND PHARMACOLOGIC CONSIDERATIONS IN RELATION TO NEUROSURGICAL ANESTHESIA

Blood Flow and Metabolism Changes in Relation to Functional Changes

Under physiologic conditions, the brain vessel diameter changes within seconds in response to the changes in neuronal activity that immediately influence metabolic demand. Although the cellular mechanisms underlying the coupling of neuronal activation to cerebral blood vessel responses are not fully determined, it has been proposed that the energy (metabolic) demand caused by neuronal activity increases blood flow. The underlying metabolic signals could be a lack of O_2 or glucose, or the production of CO_2.[1] However, studies have demonstrated that blocking the enzymes that generate nitric oxide (NO) and arachidonic acid derivatives downstream of glutamate receptors greatly reduces functional hyperemia with little effect on the energy use associated with neuronal activity.[2,3] From these data, a "feed-forward mechanism" has been proposed in which glutamate released from presynaptic nerve terminals activates both neurons and astrocytes, leading to the release of vasoactive substances from both cell types.[1] As this feed-forward mechanism is not driven by energy demand, the fractional increase in blood flow induced by sustained neuronal activity is greater than the increase in neuronal adenosine triphosphate (ATP) consumption.[4] The vasoactive substances include NO, prostaglandin E_2 (PGE_2), potassium ions (K^+), epoxyeicosatrienoic acid (EET), and arachidonic acid. NO, PGE_2, K^+, and EET dilate vessels. In contrast, arachidonic acid released from astrocytes is converted to 20-hydroxyeicosatetraenoic acid (20-HETE) in vascular smooth muscle cells, which constricts vessels. Whether astrocytic activation leads to vasodilation or vasoconstriction may depend on preexisting vessel tone.

Traditionally, blood flow is controlled solely by arteriole smooth muscle. However, recent evidence suggests that vasodilatory substances, such as PGE_2 or related substances, can actively relax the pericytes that regulate the diameter of capillaries.[5] In an animal study, it was demonstrated that capillaries dilate before arterioles in response to neuronal activity and that most of the increase in blood flow can be attributed to capillary dilation.[5] The role of pericytes in controlling cerebral blood flow remains to be determined.

As neurons have a limited energy reserve, sufficient ATP should be generated to match energy demand, which changes dramatically with neuronal activity. To explain how ATP is generated on demand, the "astrocyte-neuron lactate shuttle hypothesis" was proposed, in which astrocytic activation by glutamate released from neurons stimulates glucose uptake into astrocytes; glucose is processed glycolytically, resulting in a release of lactate as an energy substrate for neurons.[6] This hypothesis is based on the finding that cerebral activation resulted in a much greater increase in glucose consumption than in oxygen consumption.[7] However, a smaller discrepancy between the increase of glucose and oxygen use was also reported.[8] Recent quantitative work has shown that most of the ATP produced in response to increased neuronal activity is generated by oxidative phosphorylation.[9] It appears that the extent to which astrocytes feed neurons still remains controversial.[10]

Anesthetics cause functional alterations in the central nervous system and produce metabolic changes. In general, intravenous anesthetics decrease cerebral metabolic rate (CMR) and CBF in parallel fashion, whereas most inhalational anesthetics decrease CMR with an increase in CBF. At first sight, the coupling of CMR and CBF is maintained with intravenous anesthetics, whereas it is lost with inhalational anesthetics. However, a strong correlation exists between CMR and CBF within individual brain structures during anesthesia. Indeed, during burst and suppression phases of electroencephalogram

(EEG) with isoflurane anesthesia, cerebral blood flow velocity of middle cerebral artery (Vmca) appears to increase and decrease, respectively.[11,12] In addition, seizure activity or noxious stimuli during anesthesia produce parallel increases in CBF and CMR. Because the net effect of anesthetics on CBF is a balance between their direct effects on cerebral vessels and indirect effects caused by CMR changes, it is probable that the coupling of CMR and CBF is maintained with anesthetics but is modified by direct effects of anesthetics on vascular tone.

Blood Flow Changes in Relation to Cerebral Perfusion Pressure and CO_2

Cerebral perfusion pressure (CPP) and carbon dioxide tension in the arterial blood ($PaCO_2$) are the important variables that influence CBF. Autoregulation is the physiologic maintenance of constant CBF over a wide range of CPP values. Traditionally, CPP is determined as the difference between mean arterial blood pressure (MABP) and the greater of ICP or CVP. In the patient with intracranial hypertension, effective downstream pressure is determined by ICP. Advances in flow measurement techniques have demonstrated beat-to-beat flow changes and the concept of apparent zero flow pressure, at which flow ceases. Apparent zero flow pressure has been proposed as an estimate of critical closing pressure that may better estimate CPP.[13] Zero-flow pressure is extrapolated by linear regression analysis of the arterial blood-pressure–Vmca relationship. The arterial blood pressure-axis intercept of the regression line determines zero-flow pressure. In conditions of increased cerebrovascular tone, such as hypocapnia or pharmacologically induced vasoconstriction, ICP does not uniquely determine effective downstream pressure.

CO_2 can produce marked changes in cerebrovascular resistance (CVR) and CBF. Over a range of $PaCO_2$ values of 20 to 80 mmHg, for each 1 mmHg increase or decrease in $PaCO_2$ there is a 2% to 4% increase or decrease in CBF. Changes in the extracellular hydrogen ion (H^+) concentration, NO, prostanoids, cyclic nucleotides, intracellular calcium, and potassium channel activity have been regarded as regulatory factors for cerebrovascular reactivity to CO_2.[14] Compared with adults, children have less cerebral reactivity to CO_2 changes. Whether this difference is related to possible domination of prostaglandin and cyclic guanosine monophosphate in regulating vascular tone in children remains to be determined.

As CO_2 affects CVR and CBF, the autoregulation curve changes according to CO_2 levels. During hypercapnia, the plateau ascends and shortens, the lower limit shifts rightward, and the upper limit shifts leftward. In contrast, during hypocapnia, the plateau descends and the lower limit remains unchanged. How the upper limit moves during hypocapnia is not clear.[15]

Changes in Cerebral Blood Flow and Intracranial Pressure Regulation in Pathologic Conditions

Patients who undergo neurosurgery may have various types of intracranial pathologic conditions as well as systemic diseases, and their responses to anesthetics may be different from those of normal subjects. Brain tissue hypoxia, acidosis, and edema are the main pathologic consequences of most brain disorders. Cerebral vasoparalysis occurs, and coupling between blood flow and metabolism is impaired. Under these circumstances, autoregulation and CO_2 reactivity are also disturbed. Strict blood pressure control and respiratory management are required.

In the event of focal cerebral ischemia, hypercapnia can dilate the vessels in the normal area but not in the damaged area, and, consequently, blood flow may be shunted from the ischemic to the normal area (intracerebral steal or the "reversed Robin Hood effect"). As intracerebral steal has been documented in acute ischemic stroke patients, hypercapnia should be avoided in these patients.[16] Conversely, hypocapnia can divert blood from the normal area to the ischemic area (inverse intracerebral steal, or the "Robin Hood effect"). However, no beneficial effect was found in an animal experiment when hyperventilation was initiated at 1 hour after focal cerebral ischemia.[17] Because of a lack of evidence indicating the possible beneficial effect on outcome, hyperventilation cannot be recommended in patients who have experienced stroke.[18]

Although the effect is not confirmed for every anesthetic, experimental data in animals suggest that intracerebral steal or inverse intracerebral steal may also be induced pharmacologically. However, the effect of anesthetics on cerebral blood flow redistribution is unpredictable because anesthetics modulate cerebral vessel diameter by both their direct vasoactive property and indirect effects caused by CMR changes.

Anesthesia alters ICP through changes in cerebral blood volume (CBV). Although correlation between CBV and CBF does not always exist, the changes in CBV, in general, appear to be proportional to the changes in CBF. Therefore, an increase in CBF causes an increase in CBV and, thus ICP. Increases in blood pressure, especially when autoregulation is impaired, also produce an increase in CBV. Mechanical effects, such as the patient's position and respiratory pattern (by influencing intrathoracic pressure) also may affect ICP.[19,20] Muscle activity during the patient's movement may raise central venous pressure (CVP) and ICP. Anesthetic agents also affect ICP by changing the rate of production and reabsorption of cerebrospinal fluid (CSF) (see Chapter 3). Intracranial physiology and pathophysiology in relation to the use of anesthetics and adjuvant drugs are summarized in Fig. 4.1.

EFFECTS OF SPECIFIC ANESTHETIC DRUGS AND OTHER DRUGS

Inhalational Anesthetics

In general, all inhalational anesthetics are cerebral vasodilators and possess the capability of increasing ICP. Inhalational anesthetics, with the possible exception of nitrous oxide (N_2O), usually depress metabolism. Although the coupling of neuronal activation to cerebral blood vessel responses seems to work even with high concentrations of inhalational anesthetics, direct vasodilation surpasses indirect vasoconstriction by the reduction of $CMRO_2$, resulting in a higher $CBF/CMRO_2$ ratio. Table 4.1 summarizes the effects of inhalational anesthetics on CBF, CMR, and ICP.

Nitrous Oxide

It is generally agreed that N_2O increases CBF, CMR, and ICP; however, in humans, some studies did not observe an increase in CMR. The magnitude of changes varies substantially.[21] The cause of this variation may be the concentrations examined and its use in combination with other drugs that may modify its original effect. The most dramatic increases in CBF and ICP occurred when N_2O was administered alone or with minimal background anesthetics. The increases in CBF and $CMRO_2$ with N_2O do not appear to be related solely to the sympathetic hyperactivity. N_2O appears to have no direct vasodilating effect.[22]

Marked heterogeneity in regional cerebral blood flow (rCBF), regional CBV (rCBV), and regional CMR (rCMR)

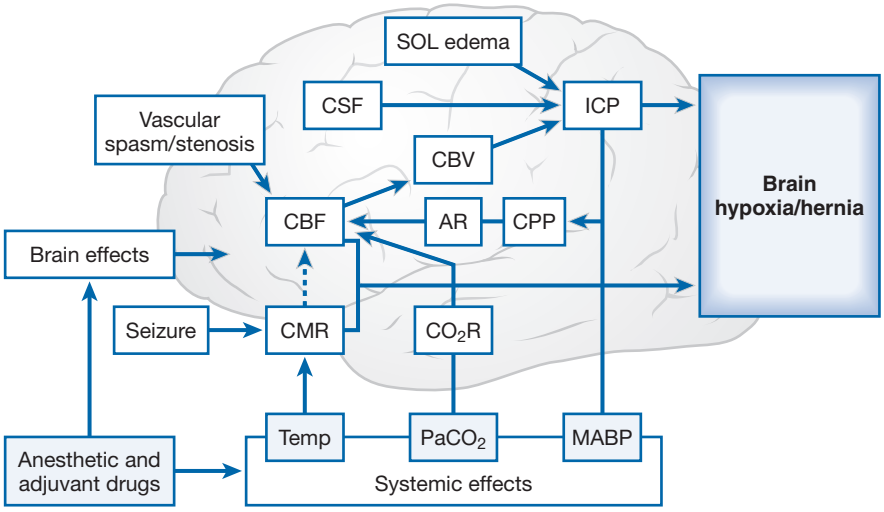


Fig. 4.1 Intracranial physiology and pathophysiology in relation to use of anesthetics and adjuvant drugs. The interaction of brain effects with the systemic effects of anesthetics and adjuvant drugs must be considered. Improvement of oxygen (substrate) supply/demand balance and prevention of intracranial hypertension are key points to prevent brain tissue hypoxia or ischemia and brain herniation and to obtain a better outcome. AR, autoregulation; CBF, cerebral blood flow; CBV, cerebral blood volume; CMR, cerebral metabolic rate; CO_2R, cerebrovascular reactivity to CO_2; ICP, intracranial pressure; MABP, mean arterial blood pressure; SOL, space-occupying lesion; Temp, temperature.

Table 4.1 Summary of the Effects of Inhalational Anesthetics on Cerebral Blood Flow, Cerebral Metabolic Rate, and Intracranial Pressure

	Cerebral Blood Flow	Cerebral Metabolic Rate	Intracranial Pressure
N_2O	↑↑	↑ or →	↑↑
Xenon	↓ (Gray) ↑ (White)	↓	↑ or →
Isoflurane	↑ or →	↓↓	→ or ↗ or ↑
Sevoflurane	↓ or → or ↗	↓ or ↓↓	→ or ↗ or ↑
Desflurane	↓ or ↑	↓↓	↑ or →

during administration of N_2O alone has been revealed with positron emission tomography (PET) and magnetic resonance imaging (MRI). Subanesthetic concentrations of N_2O (20%) increase rCBF and rCMR in the anterior cingulate cortex, with opposite effects occurring in the posterior cingulate, hippocampus, parahippocampal gyrus, and visual cortices.[23] N_2O 30% increased CBF in the global gray matter by 22%, with no change detected in global $CMRO_2$.[24] At N_2O 50%, rCBF and rCBV increased in all gray-matter regions, although the increase in rCBF was less pronounced in basal ganglia.[25] Global cerebral metabolic rates for glucose (CMRg) was unchanged with N_2O 50%, but regional metabolism was changed; regional CMRg increased in the basal ganglia and thalamus and this effect was present 1 hour after discontinuation of N_2O.[26]

N_2O, when added to volatile anesthetics, raises CBF,[27–29] but CMR is either increased[29] or unchanged.[27] Indirect evidence—measurements of Vmca—has shown that N_2O raises CBF.[30,31] In patients with brain tumors, N_2O increased Vmca, but the increase was completely reversed by hyperventilation.[32,33]

The addition of N_2O 70% to anesthesia with propofol (EEG isoelectric) in non-neurosurgical patients produced a 20% increase in Vmca with greater oxygen and glucose use in association with EEG activation.[34] A PET study in humans showed that N_2O 70% counteracted almost all rCBF reductions and some of $rCMRO_2$ reductions produced by propofol at a dose of clinical anesthesia (EEG activity remained).[29] In contrast, in animal studies, a high dose of thiamylal or pentobarbital has been shown to abolish the N_2O-induced increases in CBF or $CMRO_2$. Regional metabolic studies in rats demonstrated that N_2O 67% did not change local cerebral metabolic rates for glucose ($lCMR_g$), with a nearly isoelectric EEG by pentobarbital.[35] Whether the differences in modification of N_2O-induced increases in CBF or CMR by other anesthetics are due to the differences in species, methods, or the dose ranges of the anesthetics examined is not clear.

An increase in ICP caused by N_2O has been repeatedly demonstrated. The rise in ICP can be attenuated by prior administration of thiopental, diazepam, or morphine, or by induction of hypocapnia. It is advisable to use hypocapnia, cerebral vasoconstricting drugs, or both, when N_2O is administered, especially in patients with reduced intracranial compliance.

Some authorities have proposed that N_2O has neurotoxic properties based on data from experimental animals. It has been reported that *N*-methyl-D-aspartate (NMDA) receptor blockade during synaptogenesis in the immature brain can induce neuronal degeneration. This effect occurs not only with anesthetics with an NMDA receptor blocking property (N_2O, xenon, and ketamine) but also with those acting as gamma-aminobutyric acid (GABA) receptor modulators (propofol, midazolam, barbiturates, and isoflurane).[36] However, it has been demonstrated that NMDA receptor antagonists protect against ischemic brain injuries. N_2O may have both neuroprotective[37] and neurotoxic[38] properties. In humans, post-hoc analysis of data acquired as part of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) showed no detrimental effect on the long-term gross neurological or neuropsychological outcome with the use of N_2O during cerebral aneurysm clipping.[39,40]

N_2O enlarges the volume of potential air space, and thus its use is restricted in patients with intracranial or intravascular air compartment. Further, the incidence of nausea and vomiting appears to increase in patients exposed to N_2O for more than 1 hour,[41] which may also restrict its use in neurosurgical patients.[42] Since drugs that provide easily controllable analgesia are available, such as remifentanil, the use of N_2O in neurosurgical anesthesia has decreased.

Xenon

PET showed that xenon 1 MAC decreases absolute rCBF by 11% in the gray matter and increases it by 22% in the white matter,[43] with greater reductions in the cerebellum (by 35%), thalamus (by 23%), and cortical areas (by 9%). The decreased rCBF in the gray matter may be a result of reduced metabolism, as evidenced by the comparable reductions in CMRg in the corresponding brain areas.[44] A later study that determined concomitant changes in rCBF and rCMRg in the same individuals during 1 MAC xenon anesthesia supported the results of these studies.[45] Xenon anesthesia induces a uniform reduction in rCMRg, whereas rCBF decreased in 7 of 13 brain regions. The mean decreases in gray matter were 32% and 15% for rCMRg and rCBF, respectively, resulting in signs of moderate luxury perfusion in some brain areas including the pre- and postcentral gyri, insula, and anterior and posterior cingulate.[45] Though the reduction in CMR is less pronounced than those reported with volatile anesthetics, the metabolic pattern produced with xenon resembles those produced with volatile anesthetics rather than with N_2O.[26,46,47]

During steady state xenon 70% inhalation in rats, having achieved stable cardiovascular conditions, mean values of CBF and CMRg did not change from conscious control values, but during short inhalation of xenon 70%, CBF increased by 40–50%.[48] In pigs, xenon 79% increased rCBF approximately 40% more than total intravenous anesthesia control.[49] However, xenon (30–70%) was reported to have no effect on rCBF and autoregulation in pigs sedated with propofol.[50] It should be noted that MAC of xenon varies among species (71% in humans, 98% in monkeys, 119% in pigs, 85% in rabbits, 161% in rats), and this variation may explain the different results among the species.

The effects of xenon on ICP in patients with head injury are variable; ICP has been found to either increase by 7 mmHg[51] or not to change[52] with xenon 0.45 MAC. In animals either with normal ICP[53] or with elevated ICP,[54,55] xenon (0.34–0.7 MAC) did not change ICP. At present, in humans, xenon appears to be a mild cerebral metabolic depressant and its effect on CBF and ICP is mild. In a newborn global hypoxic-ischemic pig model under propofol and remifentanil anesthesia, post-insult administration of xenon reportedly preserves autoregulation.[56]

Because xenon is an antagonist of the NMDA receptor, it may have neuroprotective effects. Indeed, neuroprotection by inhalation of xenon before injury was demonstrated in both in-vitro[57] and in-vivo cerebral ischemia[58,59] and traumatic brain injury[60] models, the effect being observed even with post-treatment after hypoxic-ischemic insult in neonatal rats[61] and after traumatic brain injury in adult mice.[60] In combination with either hypothermia (35 °C)[62] or the α_2-adrenergic agonist dexmedetomidine,[63] xenon exhibited neuroprotection in the same model. Also, it was reported that preconditioning by xenon (70%) reduced brain damage from hypoxia-ischemia in neonatal rats.[64] A later study has demonstrated that xenon (50%) provides long-term neuroprotection in a neonatal hypoxia-ischemia model and that this protection is augmented by concomitant application of moderate hypothermia (32 °C).[65] In a rat transient middle cerebral artery occlusion model, the combination of 30% xenon and subtherapeutic hypothermia (36 °C) after reperfusion has also been demonstrated to provide long-term neuroprotection.[66] However, xenon was also reported to cause neuronal cell death in an in-vitro model of the developing rodent brain at 1 MAC, as does isoflurane and sevoflurane at similarly potent concentrations.[67]

With its low blood/gas partition coefficient of 0.115, xenon may offer advantage for neuroanesthesia use, because early neurologic examination after the emergence period is possible and may be desirable. However, this agent's effects when combined with other anesthetics should be further determined.

Halothane

Most studies demonstrated that halothane induces cerebral vasodilation and increases CBF, provided that the systemic blood pressure is maintained. The increase in cortical CBF appears greater with halothane than with isoflurane at equi-MAC concentrations. It is probably true that the potency of overall vasodilating property of halothane appears to be most prominent among available volatile anesthetics.

A dose-related cerebral metabolic depressive effect of halothane has been demonstrated repeatedly. At clinical levels of anesthesia, the decrease in global $CMRO_2$ ranges from 10% to 30%. A study using PET demonstrated that halothane anesthesia titrated to a point just beyond the loss of consciousness is associated with a 40% reduction of whole-brain glucose metabolism,[46] the magnitude of reduction being similar to that with isoflurane.

Halothane raises ICP in a dose-related fashion, and the rise in ICP is parallel to that in CBF. The elevation of ICP with halothane appears to be most prominent among the commonly used volatile anesthetics. However, at 0.5 MAC or less, the effect on ICP is minimal. The increased ICP that, with halothane, often occurs in association with systemic hypotension results in reduced CPP. This response may augment the risk of cerebral ischemia. The increase in ICP may be attenuated either by hyperventilation or by barbiturates. However, the beneficial effects of hypocapnia may not be obtained when the initial ICP is very high or reactivity to CO_2 is lost globally.

In summary, although halothane in low concentrations (less than 1%) can be safely used in clinical neuroanesthesia practice when $PaCO_2$ is reduced and barbiturates (and probably propofol) also are given, the margin of safety is probably wider with isoflurane, desflurane, or sevoflurane than with halothane.

Isoflurane

In general, the increase in global CBF is smaller with isoflurane than with halothane. However, at a given level of metabolic rate, isoflurane possesses greater cerebral vasodilating capabilities than halothane. It has been demonstrated that halothane, isoflurane, and desflurane at 0.5 MAC produces a similar increase in Vmca in humans during propofol-induced isoelectric EEG, whereas at 1.5 MAC, isoflurane and desflurane have greater vasodilating effects than halothane.[68] The net effect of inhalational anesthetics on CBF is a balance between a reduction in CBF caused by CMR suppression and augmentation of CBF due to direct cerebral vasodilation; the reported smaller increases in CBF with isoflurane than with halothane may occur from a more potent cerebral metabolic depressive effect of isoflurane. The hypothetical illustrations of changes in CBF with rising concentrations of halothane and isoflurane are shown in Fig. 4.2.

In PET studies in humans, isoflurane (0.2–1.0 MAC) was reported to produce no change in global CBF but to cause regional increase (anterior cingulate and insula regions) and decrease (cerebellum, thalamus, and lingual gyrus) in relative CBF.[69] Additionally, isoflurane (0.5%) was reported to reduce whole brain metabolism by almost 50%, and this reduction was fairly uniform throughout the brain.[47]

It is unlikely that any single mechanism is entirely responsible for the vasodilative property of isoflurane. Some investigators

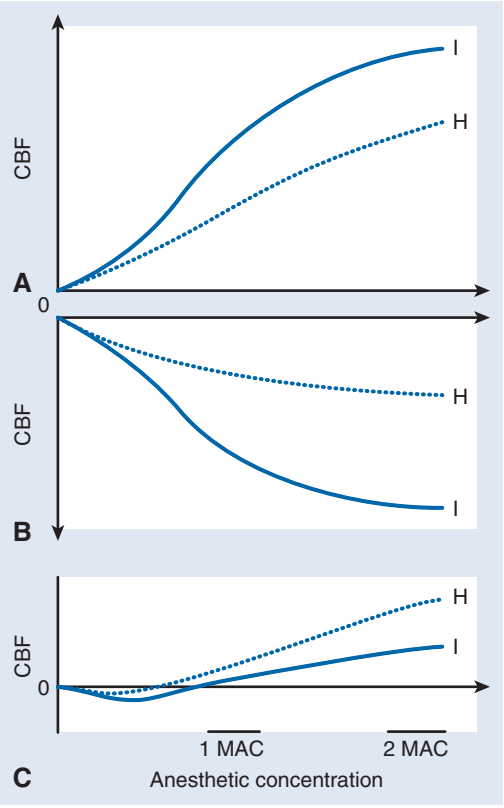


Fig. 4.2 Changes in cerebral blood flow (CBF) with rising anesthetic concentrations. The graph is drawn on basis of hypothesis that CBF changes exhibit a net result of the direct effect and metabolism-coupled effect of anesthetics. Also, the graph is based on the assumption that isoflurane (I) possesses greater direct vasodilating effect and metabolic-depressing effect than halothane (H). **A,** CBF changes caused by the direct vasodilating effect of anesthetics. **B,** CBF changes caused by the metabolic depressive effects of anesthetics (metabolism-coupled changes). **C,** Net CBF changes caused by both direct and metabolism-coupled effects. In normal subjects, halothane produces greater increase in CBF than isoflurane **(C)**. In contrast, in patients whose baseline metabolism is maximally depressed either with other drugs or from an intracranial pathologic condition, metabolism-coupled flow changes may not occur, and CBF changes are simply determined by direct vasodilating effects of anesthetics, provided that the mechanisms for direct vasodilating effect are intact. If this is the case, isoflurane produces a greater increase in CBF than halothane, with rising anesthetic concentration **(A)**. MAC, minimum alveolar concentration.

speculate that the vasodilative property of isoflurane may be related to NO. It was also reported that approximately one-third of the cortical hyperemic response to isoflurane measured by laser Doppler flowmetry is mediated by NO, prostaglandins, and epoxyeicosatrienoic acid, and that the remaining part of the response appears to be mediated by a direct action on smooth muscle.[70] A study using a closed cranial window model demonstrated that an adenosine triphosphate (ATP)-sensitive K^+ channel blocker, glibenclamide, attenuates isoflurane (and sevoflurane)-induced cerebral vasodilation, suggesting that vasodilation with these anesthetics is mediated, at least in part, via activation of ATP-sensitive K^+ channels.[71]

Gray matter rCBV is increased with isoflurane when the systemic blood pressure is maintained (0.45%),[72] and thus ICP can increase. Data on ICP appear to be inconsistent, and lumbar cerebrospinal fluid pressure (CSFP) increased in one study,[73] while ICP did not change in another.[74] Because ICP was reported to be lower in the patients anesthetized with propofol-fentanyl than those anesthetized with isoflurane-fentanyl, propofol-fentanyl may be preferable in the setting of unstable ICP.[75] In the intensive care unit (ICU) setting, two studies have showed that isoflurane (0.5–0.8 MAC) does not cause a clinically relevant increase in ICP in patients with subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke if baseline ICP values are low or only moderately elevated.[76,77]

Because of the potent cerebral metabolic depressive effect, isoflurane was predicted to have cerebral protective effects, which may be produced by a variety of the mechanisms, including inhibition of excitatory neurotransmission, potentiation of $GABA_A$ receptor, regulation of intracellular calcium responses, and activation of TWIK (tandem of P domains in a weak inwardly rectifying K^+ channel)-related K^+ (TREK)-1 two-pore-domain K^+ channels.[78] Indeed, many animal studies demonstrated the neuroprotective properties of isoflurane within clinically relevant concentrations. However, the protection with isoflurane is only applicable to mild insults, being inferior to and less durable than mild hypothermia in its neuroprotective effect.[79] Also, it is important to note that isoflurane has preconditioning[80,81] and postconditioning[82] effects. In the developing brain, the neurotoxicity of isoflurane has been reported.[83]

In the clinical setting, there is no good evidence that isoflurane uniquely protects against ischemic central nervous system injury. Suggestive observations include those in a large retrospective review of changing anesthetic management practices during carotid endarterectomy in humans.[84] The critical CBF below which ischemic EEG changes occur was greater in patients anesthetized with halothane than in patients anesthetized with isoflurane. At a comparable level of rCBF, the incidence of EEG ischemic changes with isoflurane has been reported to be significantly lower than that seen with halothane.

In summary, isoflurane appears to produce a mild increase in CBF and a pronounced decrease in cerebral metabolism. The accumulated evidence in basic research strongly suggests that isoflurane has a cerebral protective effect, although it is not proven clinically. However, isoflurane may be a desirable anesthetic for many neurosurgical procedures, including carotid endarterectomy. The increase in ICP caused by isoflurane, if it occurs, may be mild and can be prevented by hypocapnia. However, when ICP elevation should definitely be avoided, propofol in combination with synthetic opioid may be preferable.

Sevoflurane

Studies using PET demonstrated that either a decrease[85] or no change[86] in global CBF occurred with the use of sevoflurane. MAP decreased significantly with sevoflurane in the former study, whereas MAP was unchanged in the latter study. Therefore, it seems likely that global CBF is unchanged with sevoflurane when MAP is maintained. Although global CBF did not change, heterogeneity of the rCBF response was observed; an increase of relative rCBF in the anterior cingulate and a decrease in the cerebellum.[86] Regional heterogeneity of the cerebrovascular response to hyperventilation was also observed with the use of sevoflurane 1 MAC, with the greatest values being observed in the thalamus.[87]

The results obtained with the use of the transcranial Doppler technique revealed that sevoflurane at both 0.5 and 1.5 MAC produced smaller increases in Vmca than isoflurane during propofol-induced isoelectric EEG, suggesting that sevoflurane has less vasodilating effects than isoflurane.[88] Vmca varies according to age. In adults, Vmca was reported to decrease with the use of sevoflurane (0.5–1.5 MAC) despite no change

of MAP.[31,74] A study of the use of sevoflurane 3% in infants younger than 2 years showed that Vmca was unchanged until MAP dropped below 60% of baseline in infants older than 6 months.[89] However, in infants younger than 6 months, Vmca started to decrease when MAP dropped below 80% of baseline.

Sevoflurane 1 MAC was reported to decrease rCMRg in all regions of the human brain, with the most marked suppression in the lingual gyrus (by 71%), occipital lobe in general (by 68%), and thalamus (by 68%).[90] CBF equivalent (an index of flow–metabolism relationship) was shown slightly higher than normal but was comparable to or slightly lower than the values of equi-MAC isoflurane.[91] Taken together, studies show that sevoflurane decreases CMR but its effect on CBF seems weaker than that of isoflurane.

Sevoflurane, either with or without N_2O, produced no or small increases in ICP in animals and humans. These effects seem to be consistent with the fact that sevoflurane does not affect CBV even though it reduces CBF.[29] The increase in ICP, if any, can be blocked by hyperventilation.[92] When sevoflurane is compared with isoflurane and desflurane, the extent of the increase in ICP is in the following order in animals: desflurane > isoflurane > sevoflurane.[93] In patients undergoing transsphenoidal pituitary surgery (no mass effect),[94] lumbar CSFP was increased with sevoflurane, but mean increase was small (by 2 mmHg) and comparable to those reported with isoflurane and desflurane.[73] In patients with cerebral tumors (midline shift less than 10 mm) anesthetized with propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl, the values of ICP were in the order of propofol-fentanyl < isoflurane-fentanyl = sevoflurane-fentanyl anesthesia. The effects of propofol-fentanyl were less than those of isoflurane-fentanyl and sevoflurane-fentanyl anesthesia.[75] The ICP raising properties of a clinical dose of sevoflurane appear to be mild, but propofol would be preferable in a patient for whom ICP must be rigidly controlled.

The neuroprotective effect of sevoflurane reported earlier in middle cerebral artery occlusion (MCAO) model in rats may be assumed to be due to temperature reduction with anesthetics.[95] However, several other studies demonstrated neuroprotective effects,[96] and the agent's favorable effect appears to be similar to that of isoflurane.[97] In addition, sevoflurane-induced early or late ischemic tolerance has been shown in rats.[98] However, neurotoxic effects of sevoflurane, as in isoflurane, in the developing brain have been reported.[99]

In the clinical setting, there is no unequivocal evidence of neuroprotective effect of sevoflurane. Indirect evidence includes the observation that critical rCBF, below which ischemic EEG changes occur during carotid cross-clamp, was found to be similar to that previously determined in patients anesthetized with isoflurane.[100] At present, the neuroprotective effects of sevoflurane, though inconclusive, appear to be similar, if they occur, to those of isoflurane.

Desflurane

When using a modified Kety-Schmidt technique with argon, desflurane 1 MAC decreases CBF by 22% in association with decreases by half in $CMRO_2$ and CMRg by 35% with cerebrovascular CO_2 reactivity being preserved.[101] During propofol-induced isoelectric EEG, desflurane at 0.5 MAC produced increases in Vmca that were similar to those seen with isoflurane. At 1.5 MAC, the increase produced by desflurane was also similar to that with isoflurane.[68] This finding may suggest that desflurane, used when cerebral metabolism is maximally suppressed, increases CBF in a dose-dependent manner. During hypocapnia ($PaCO_2$ 25 mmHg) in patients receiving desflurane, the CBF at 1 MAC was lower than, and the CBF at 1.5 MAC was similar to, those measured during an equi-MAC isoflurane anesthesia.[102] After the induction of anesthesia with propofol, patients receiving desflurane 1.5 MAC had significantly greater Vmca, heart rate, and MAP than those receiving equi-MAC sevoflurane. As desflurane 1.5 MAC was reported to impair autoregulation, it seems likely that the increase in Vmca was caused by the increase in MAP with desflurane.[103]

In patients with supratentorial mass lesions with a midline shift, desflurane 1 MAC (7%) was reported to produce an increase in CSFP despite prior establishment of hypocapnia,[104] but not to raise ICP in patients without a midline shift,[105] whereas isoflurane 1 MAC was reported not to change CSFP or ICP in either case.[104,105] In animals subjected to intracranial hypertension, desflurane increased ICP more than sevoflurane but less than isoflurane, whereas during hypocapnia, no significant differences in ICP were observed among three agents.[93]

Many studies have demonstrated neuroprotective effects of desflurane in in-vivo[106–108] and in-vitro[109] models in experimental animals. The degree of protection afforded by desflurane appears to be comparable to that of isoflurane.[106,107] However, the neurotoxic effects of desflurane were also reported in the developing brain of animals.[110] In the clinical setting, brain tissue oxygen pressure measured in patients undergoing craniotomy was elevated when desflurane concentration was increased from 3% to 9%, and the blood pressure was maintained with intravenous phenylephrine.[111]

In summary, because of a low blood/gas partition coefficient (0.42) relative to other clinically used volatile inhalational anesthetics, desflurane can provide rapid onset and offset of anesthesia, which facilitate early neurologic evaluation. In general, desflurane decreases CMR, but CBF may either be increased or decreased, depending on the doses used. Desflurane's neuroprotective effects appear to be comparable to those of isoflurane. However, because desflurane may have slightly greater ICP-elevating effects than isoflurane or sevoflurane, desflurane should be used cautiously in patients with unstable ICP.

Intravenous Anesthetics

In general, intravenous anesthetics cause a decrease in CBF and $CMRO_2$. However, these anesthetics might not be vasoconstrictors in a strict sense, because in-vitro barbiturates, for example, dilate isolated cerebral vessels. The decrease in CBF induced by most intravenous anesthetics appears to be the result of reduced cerebral metabolism secondary to cerebral functional depression. Among the intravenous anesthetics, ketamine may be unique because it produces an increase in both CBF and $CMRO_2$. Table 4.2 summarizes the effects of intravenous anesthetics on CBF, CMR, and ICP.

Barbiturates

Thiopental produces a dose-dependent reduction in CBF and $CMRO_2$. Other barbiturates, such as phenobarbital and pentobarbital, essentially have similar effects. A dose-dependent reduction in CBF and $CMRO_2$ occurs until the EEG becomes flat. At the point of EEG isoelectricity, no further $CMRO_2$ reduction occurs despite a further increase in barbiturate dose. A burst suppression dose of thiopental decreases both CBF and $CMRO_2$ to about 40% (near maximal reduction) of the awake value in humans. Thus, with barbiturates, functional depression appears to be coupled with the reduction in CBF and $CMRO_2$. If CMR is maximally depressed as a result of an intracranial pathologic condition, thiopental can increase CBF, possibly because of its direct effect, provided that blood pressure is maintained.

Table 4.2 Summary of the Effects of Intravenous Anesthetics on Cerebral Blood Flow, Cerebral Metabolic Rate, and Intracranial Pressure

	Cerebral Blood Flow	Cerebral Metabolic Rate	Intracranial Pressure
Barbiturates	↓↓	↓↓	↓↓
Etomidate	↓↓	↓↓	↓↓
Propofol	↓↓	↓↓	↓↓
Ketamine	↑↑	↑ or →	↑ or ↑↑
Benzodiazepines	↓	↓	↓ or →
Synthetic opioids	→ or ↗ ↘	→ or ↓	→ or ↗
Dexmedetomidine	↓	→ or ↓	→

ICP is reduced by barbiturates, possibly through the reduction in CBF and CBV. Barbiturates have been shown to result in lower CBV values than those resulting from use of volatile anesthetics. This effect might be exploited during the treatment of raised ICP in head-injured patients when blood pressure is maintained as well as in the induction of anesthesia in patients with decreased intracranial compliance. Barbiturates attenuate the cerebral vasodilation produced by N_2O and ketamine.

The neuroprotective effect of barbiturates has been repeatedly demonstrated in focal ischemia models. In a rat model of focal cerebral ischemia (90 minutes), significant reductions in infarct volume have been demonstrated with moderate doses of pentobarbital.[112] Increasing doses sufficient to produce burst suppression on EEG did not further decrease infarct volume. Moreover, in a rat model of focal cerebral ischemia (180 minutes), the burst suppression dose of thiopental, but not methohexital or pentobarbital, reduced infarct volume.[113] It has been suggested that burst suppression of EEG is not necessary to provide neuroprotection and that mechanisms other than metabolic depression may be involved for protection.[112] In humans, post hoc analysis of data acquired as part of the IHAST was not able to show the protective effects of thiopental in patients undergoing temporary clipping during cerebral aneurysm surgery.[114] In the developing brain, the neurotoxicity of pentobarbital was also reported.[115]

ICP-reducing effects and possible neuroprotective effects make the barbiturates favorable drugs for neurosurgical anesthesia, provided that cardiovascular stability is maintained. It should be noted, however, that prolonged use of barbiturate results in tissue accumulation because of its slow metabolism; this effect can lead to delayed emergence from barbiturate anesthesia. Because of similar cerebral hemodynamic effects and a shorter context-sensitive half-life, other intravenous agents, especially propofol, may be more appropriate for this application.

Etomidate

Etomidate does not have cardiovascular side effects. Almost parallel reductions in CBF and $CMRO_2$ are induced with etomidate. With clinical doses, CBF and $CMRO_2$ are decreased by approximately 30% to 50%. Reactivity to CO_2 is preserved during etomidate anesthesia. In animals, etomidate, like barbiturates, decreases $CMRO_2$ progressively until an isoelectric EEG appears. CBF decreases rapidly with the start of etomidate infusion. A maximal decrease in CBF was achieved before the maximal decrease in $CMRO_2$.[116] This finding may suggest that etomidate causes vasoconstriction through a different mechanism (possibly by direct action) from that of the barbiturates. Parallel decreases in ICP and CBF were observed.

Etomidate effectively decreases ICP without diminishing CPP. In severely head-injured patients, etomidate decreased ICP while electrocortical activity was present but was not effective when cortical electrical activity was already maximally suppressed.[117] This finding indicates that the decrease in ICP may be caused by the reduction of CBF (and CBV) that is induced by the functional (metabolic) depressant effects of etomidate.

Although etomidate was reported to have a small neuroprotective effect in a forebrain ischemia model (bilateral carotid artery occlusion with hypotension) in rats,[118] most studies failed to show significant protective effects. In fact, poor outcome or larger infarct volume was reported after incomplete cerebral ischemia and middle cerebral artery occlusion, respectively.[119–121] The injury-enhancing effect of etomidate in middle cerebral artery occlusion has been attributed to its ability to reduce NO levels in the ischemic brain tissue.[122] In addition, in some patients who underwent cerebral aneurysm surgery, etomidate led to cerebral deoxygenation, which was exaggerated with temporal cerebral artery occlusion.[123]

Adverse effects of this drug include adrenocortical suppression and frequent occurrence of involuntary muscle activity and seizure activity. Etomidate should be used with caution in patients who have a history of seizures.

Propofol

Propofol produces dose-related decreases in global CBF by 50–60%.[85,124] In PET studies, variation of rCBF reduction has been demonstrated; large decreases occurred preferentially in the medial thalamus, cuneus and precuneus, and posterior cingulate, orbitofrontal, and right angular gyri, which are implicated in the regulation of arousal, performance of associative functions, and autonomic control.[125] A subsequent study revealed that restoration of consciousness by physostigmine was associated with rCBF increases in the thalamus and precuneus of patients anesthetized with propofol.[126] As with barbiturates, the CBF decrease with propofol is attributable to its metabolic depressant effect. As the CBF decrease with propofol is greater than that with sevoflurane,[29] one may consider that propofol is not suitable for ischemic cerebral disease. However, ipsilateral internal carotid artery pressure during carotid endarterectomy[127] and rCBF in the frontal lobe during revascularization surgery for moyamoya disease[128] were reported to be better maintained with propofol than with sevoflurane, probably because cerebral steal phenomenon can be avoided with propofol.

As with the regional variation in CBF decrease, propofol was reported not only to depress CMR but to do so differently according to region.[129] Overall metabolism in the cortex was depressed (by 58%) more than overall metabolism in the subcortical brain areas (by 48%); in the cortical regions, rCMR was significantly lower in the frontal, parietal, and occipital lobes.[129] Several studies demonstrated that the incidence of a decrease in jugular bulb venous hemoglobin saturation of less than 50% was higher with propofol than with isoflurane-nitrous oxide or sevoflurane, suggesting that cerebral oxygen balance during propofol-based anesthesia can be impaired.[130] However, a study measuring rCBF and rCMRg in the same volunteers demonstrated that the magnitude of the decrease in rCMRg generally exceeded the reduction in rCBF, resulting in signs of moderate luxury perfusion in some brain regions.[124]

In patients with cerebral tumors with midline shift less than 10 mm, ICP was reported to be lower and CPP higher in patients anesthetized with propofol than in those anesthetized

with isoflurane or sevoflurane.[75] Nevertheless, in most circumstances, MABP is decreased with propofol. Therefore, if propofol is given to treat intracranial hypertension, like any other drug, attention should be paid to maintaining MABP (CPP). CO_2 reactivity is preserved with propofol. Thus, hyperventilation can decrease ICP during propofol anesthesia.

Regarding the neuroprotective effects of propofol, many studies in animals,[131,132] but not all,[133,134] proved favorable effects with burst suppression doses of propofol. The possible neuroprotective mechanisms include reduction of the CMR, antioxidant activity, activation of GABA receptors, attenuation of glutamate-mediated excitotoxicity, prevention of mitochondrial swelling, interaction of the endocannabinoid system, attenuation of autophagy activation, downregulation of aquaporin 4 expression, and inhibition of nicotinamide adenine dinucleotide phosphate oxidase.[135–137] Interestingly, protection was observed even in a light depth of propofol anesthesia (not a burst suppression dose) and even when propofol was administered after ischemic insults.[138] In the developing brain and in traumatic brain injury, the neurotoxicity of propofol was reported.[139,140] There is as yet no definitive clinical evidence showing an improvement or impairment of neurological outcome following acute cerebral injury in patients. As propofol has a rapid onset and offset of action with minimal interference with electrophysiological monitoring including motor evoked potentials, propofol seems to be a favorable anesthetic for various types of neurosurgery.

A number of case reports suggest that prolonged use of propofol caused systemic acidosis and progressive cardiac failure and even death in children.[141,142] Special attention should be paid when prolonged infusion of propofol is necessary, even in adult patients.

In summary, propofol seems to have cerebral hemodynamic and metabolic effects similar to those of barbiturates. This drug may be useful in the treatment of patients with intracranial pathologic conditions, provided that hypotension is prevented.

Ketamine

Intravenous ketamine (3 mg/kg) increases global CBF by approximately 60%, but global $CMRO_2$ does not change significantly.[143] PET studies showed that subanesthetic doses of ketamine increased rCBF and rCMRg without a global change in $rCMRO_2$;[144,145] the greatest rCBF increases were seen in the anterior cingulate, thalamus, putamen, and frontal cortex, and the greatest rCMRg increases were detected in the thalamus and the frontal and parietal cortices.[144] These data have been obtained with the use of commercially available formulations of ketamine containing both S(+)- and R(-)-ketamine enantiomers. S(+)-ketamine is more effective as an analgesic and anesthetic than a racemic mixture of two enantiomers (racemic ketamine) or R(-)-ketamine. The changes in CBF and CMR with S(+)-ketamine appear essentially similar with minor quantitative difference; subanesthetic doses increased global CBF by 14% without a change in global $CMRO_2$, with greatest increase in CBF detected in the anterior cingulate. The anesthetic dose of S(+)-ketamine increased global CBF by 36% without changes in global $CMRO_2$ or CMRg,[146] with the greatest increase in CBF detected in the insula, whereas $CMRO_2$ rose only in the frontal cortex, and CMRg increased only in the thalamus. Vasodilation by ketamine has been attributed, in part, to its metabolic stimulating effect, a direct dilating effect, and a cholinergic mechanism. In animals, pretreatment with thiopental completely blocks these CBF and $CMRO_2$ effects of ketamine, and diazepam pretreatment attenuates the increase in lCMRg in the hippocampus.

Ketamine markedly raises ICP. An increase in ICP can be blocked or attenuated by induced hypocapnia or by administration of thiopental or benzodiazepine. During propofol sedation in patients with traumatic brain injury, ketamine decreases ICP.[147] In patients with supratentorial tumor who are anesthetized with isoflurane (0.3% to 0.4%)/N_2O 50%, ketamine 1 mg/kg did not significantly raise ICP.[148] However, it was reported that midazolam (0.15 mg/kg) or diazepam (0.2 mg/kg) administered 1 minute before the administration of ketamine (1 mg/kg) was unable to block ketamine-induced ICP elevation at the induction of general anesthesia.[149] Thus ketamine may not be a first choice at the induction of general anesthesia, especially in patients with elevated ICP or decreased intracranial compliance.

Some animal experiments,[150] but not all,[151] demonstrated some neuroprotective effects of ketamine in various intracranial pathologic conditions, including ischemia and head injury, which could be related to NMDA receptor antagonism. Ketamine has also been shown to have potent anti-inflammatory effects.[152] However, improved outcomes in animal experiments were reported only in studies with brief recovery observation intervals.[153] In the developing rodent brain, ketamine was reported to induce neurotoxicity.[154] Clinical studies comparing ketamine sedation with fentanyl or sufentanil after traumatic brain injury failed to find any favorable effects on functional outcome after 6 months.[155,156] A definite neuroprotective effect of ketamine remains to be demonstrated in the clinical setting. There is a growing body of evidence that a low dose of ketamine (0.5 mg/kg) rapidly (within hours) improves the core symptoms of depression and the effect is sustained for 7 to 10 days.[157] This effect seems to be associated with increases in the number and function of synaptic connections.[158]

Benzodiazepines

Diazepam in combination with fentanyl and N_2O produces parallel decreases in CBF and $CMRO_2$. In the head-injured patient, diazepam produces proportional 25% decreases in CBF and $CMRO_2$. Contrary to the assumption that ICP would be decreased because of a lower CBF, diazepam (0.25 mg/kg) does not change ICP.[159]

Midazolam, like diazepam, produces parallel reductions in CBF and $CMRO_2$. With rising doses, the effects appear to reach a plateau, possibly reflecting saturation of the benzodiazepine receptors. The effect of midazolam is completely blocked by the specific benzodiazepine antagonist flumazenil. The PET study demonstrated that midazolam decreased global CBF by 12% and that the decrease in rCBF occurred in the areas associated with the functioning of arousal, attention, and memory, such as the insula, the cingulated gyrus, the prefrontal cortex, the thalamus, and parietal and temporal association areas.[160] Midazolam, even at a very low dose (0.03 mg/kg), appears to decrease rCBF in the left dorsolateral prefrontal cortex, left cingulate gyrus, and left posterior cingulate gyrus/precuneus.[161] Midazolam was reported to preserve CO_2 responsiveness[162] and improve dynamic cerebral autoregulation.[163]

Midazolam produces either a decrease or no change in ICP. Negative results may be due to normal ICP before the administration of the drugs. In patients with severe head injury, there was no significant difference in ICP values between midazolam and propofol.[164] Midazolam has been shown to maintain hemodynamic stability better than thiopental. However, caution must be used because of the possibility of CPP reduction in patients with critical conditions.

Midazolam may have protective effects against hypoxia or cerebral ischemia; the effects appear to be comparable with or

slightly less than those of barbiturates in animals. Lorazepam, triazolam, and flurazepam seem to have effects similar to those of diazepam and midazolam. In the developing brain, anesthesia with midazolam, isoflurane, and N_2O was reported to cause widespread apoptosis.[165]

Because a specific receptor antagonist is now available, benzodiazepine derivatives are useful as induction or supplemental drugs during neuroanesthesia. However, flumazenil, a competitive benzodiazepine receptor antagonist, also antagonizes the effects of midazolam on CBF, $CMRO_2$, and ICP. Thus one must use this drug cautiously when reversing benzodiazepine-induced sedation in patients with impaired intracranial compliance. Flumazenil-induced seizure probably produced by unmasking the anticonvulsant effect of benzodiazepine might also be considered.[166]

Synthetic Opioids

The reported effects of synthetic opioids on CBF, $CMRO_2$, and ICP are variable. The variability appears to be due to the background anesthetic and opioid dose. When vasodilating drugs are used as the background anesthetic, the effect of the opioid is consistently that of a cerebral vasoconstrictor. Conversely, when a vasoconstrictor is used as the background anesthetic or when no anesthetic is given, opioids either have no effect or even increase CBF. Large doses of opioids decrease CBF in the absence of background anesthetics.[167,168] When N_2O is also used, most opioids decrease $CMRO_2$. Variable ICP effects also depend on the background anesthetic and on the systemic blood pressure autoregulation status. Cerebrovascular autoregulation and CO_2 reactivity is preserved with opioids.

Fentanyl and Sufentanil

The combined use of fentanyl (5 μg/kg) and droperidol (0.25 mg/kg) has no significant effect on CBF and $CMRO_2$. A large dose of sufentanil (10 μg/kg + 0.15 μg/kg/min) was reported to decrease CBF and $CMRO_2$ by 29% and 22% in cardiac patients, respectively.[169] Increases in Vmca by approximately 25% were observed when fentanyl (16 μg/kg) or sufentanil (1.7 μg/kg) was used in unpremedicated humans.[170] In premedicated patients, Vmca was not changed with fentanyl (25 μg/kg) or sufentanil (3 μg/kg), but was decreased with sufentanil (6 μg/kg) by 27–30%.[167] This difference suggests that the CBF response depends on background state and the dose of agents. Sufentanil (1.5 μg/kg) decreased Vmca in patients with elevated ICP, and the decrease can be explained by low CPP.[171] A PET study in awake humans showed that fentanyl (1.5 μg/kg) showed heterogeneous changes in rCBF; rCBF increased in the anterior cingulate and contralateral motor cortex and decreased bilaterally in the thalamus and posterior cingulate.[172]

In rats, high doses (200–400 μg/kg) of fentanyl induce seizures, increase CBF in most structures throughout the brain, and activate subcortical brain metabolism. Whether the cerebral metabolism is compromised during seizures to the extent that ischemic brain damage occurs is not yet determined. In humans, the clinical significance of seizure activity observed with fentanyl in rats is not clear.

Earlier studies show that ICP is either not elevated or may be slightly decreased with fentanyl used alone or in combination with droperidol. Reported ICP increases in patients with space-occupying lesions have been attributed to hypercapnia. Herrick and colleagues[173] reported that fentanyl, sufentanil, and alfentanil did not affect brain retractor pressure in hyperventilated neurosurgical patients anesthetized with isoflurane, suggesting that these opioids appear safe for intraoperative administration after the cranium is open. Better cerebral relaxation has been noted when fentanyl or sufentanil was used in patients anesthetized with N_2O and isoflurane during craniotomy, suggesting that both fentanyl and sufentanil probably have cerebrovasoconstrictive activity.[174]

However, some reports showed that fentanyl and sufentanil increased ICP (or CSFP) in patients with severe head trauma.[175–177] Werner and colleagues[178] reported that when MABP was controlled and remained unchanged, sufentanil (3 μg/kg) had no significant effects on ICP in patients with brain injury, whereas the same dose of sufentanil caused a transient increase in ICP and a decrease in MABP. From these results, an increase in ICP appears to be attributable to the autoregulatory response, the decrease in cerebrovascular resistance secondary to CPP reduction.[178] However, in one study, there were no differences in the ICP-elevating effect of fentanyl (1.5 μg/kg) between patients with head trauma who had preserved autoregulation and those who had impaired autoregulation.[179] Thus, the cerebrovascular autoregulation may not be the only probable mechanism responsible for fentanyl-induced increases in ICP in patients with head trauma. Although an ICP rise may be only transient after bolus administration of fentanyl and sufentanil, attention should be paid to this effect in patients with unstable ICP.

Alfentanil and Remifentanil

Vmca and ICP did not change with low (25 μg/kg) and high (50 μg/kg) doses of alfentanil in patients anesthetized with isoflurane and N_2O, provided that MAP was maintained.[180] A low dose of remifentanil (0.1 μg/kg/min) increased rCBF in the white and gray matter in awake humans.[181] In contrast, large doses of remifentanil (2 and 4 μg/kg/min) decreased rCBF in humans who received 0.5–1 mg/kg propofol to facilitate laryngeal mask insertion.[168] In cardiac patients without background anesthetics, moderate doses of remifentanil (2 μg/kg IV + 1 μg/kg/min) did not change Vmca, whereas large doses (5 μg/kg IV + 3 μg/kg/min) decreased Vmca by 31%, despite no change of MAP.[182]

Both alfentanil and remifentanil essentially have a minimal effect on ICP.[183] As mentioned earlier, alfentanil did not affect brain retractor pressure in hyperventilated neurosurgical patients anesthetized with isoflurane.[173] No ICP elevation with alfentanil was observed in pediatric patients with hydrocephalus who were anesthetized with isoflurane and N_2O.[184] However, in an experimental brain injury model, Souter and colleagues[185] reported that rapid infusion of alfentanil increased ICP concomitant with reduction in MABP but with no CBF changes.

In a PET study in human volunteers, either increases or decreases in relative rCBF were observed with an infusion of low doses of remifentanil (0.05 μg/kg/min), depending on the structures, the increase being observed within structures involved in pain processing.[186] With moderate doses (0.15 μg/kg/min), changes in relative rCBF were observed in structures involved in modulating vigilance and alertness.[186] The increases in relative rCBF with painful heat stimulation detected in various structures, including the thalamus, were suppressed with rising remifentanil dosage (0.05 to 0.15 μg/kg/min), whereas relative rCBF rose in the cingulofrontal cortex and periaqueductal gray, where descending antinociceptive pathways exist.[187]

In summary, clinically used doses of most opioids have minimal to modest depressive effects on CBF and $CMRO_2$. During opioid-induced seizures in animals, there are a substantial increase in CBF and activation of subcortical brain metabolism, although they were not seen in humans. If adequate alveolar ventilation is instituted to maintain $PaCO_2$

(and PaO_2) within the normal range and rigidity is prevented, clinical doses of opioids have minimal or negligible effects on ICP. However, the possibility of an increase in ICP with synthetic opioids cannot be completely excluded. Whenever these opioids are used, slow administration and care to maintain MABP are recommended.[188] It seems probable that remifentanil with either propofol or dexmedetomidine may be a useful regimens for various neurosurgical procedures, including minimally invasive surgery.

Muscle Relaxants

Succinylcholine

Many studies have demonstrated that succinylcholine elevates ICP in animals and humans irrespective of the presence or absence of space-occupying intracranial lesions. The rise in ICP with succinylcholine was accompanied by muscle fasciculation, an increase in muscle spindle afferent activity, EEG arousal, and an elevation of CBF.[189] Fasciculation in the muscles of the neck, causing stasis in the jugular veins, might also be a factor contributing to increased ICP with succinylcholine. The rise in ICP was prevented or diminished by pretreatment with a nondepolarizing muscle relaxant,[190] the results contrasting with the animal study in which pretreatment with pancuronium did not attenuate the succinylcholine-induced increase in afferent muscle activity and CBF.[191]

Succinylcholine-induced increases in serum K^+ in a patient with subarachnoid hemorrhage is another concern. It seems independent of the presence of motor dysfunction and may not be significant at a relatively early stage (within 10 days). Nevertheless, the use of succinylcholine has been diminishing in clinical neuroanesthesia practice, with the exception of emergency situations, such as the patient with a full stomach in whom a rapid-sequence induction is recommended. In this situation, prior administration of small doses of nondepolarizing muscle relaxant or lidocaine is recommended.

Nondepolarizing Muscle Relaxants

Some nondepolarizing muscle relaxants or their metabolites may affect the cerebral circulation through a histamine-releasing property that has pharmacologic activity. Clinical dose of atracurium appears to have no significant effect on CBF, $CMRO_2$, or ICP. However, high doses of atracurium have the potential to release histamine, though the potential is considerably less than that of d-tubocurarine. Histamine can reduce CPP because of the increase in ICP caused by cerebral vasodilation and the decrease in MAP. The metabolite of atracurium, laudanosine, has been reported to cross the blood–brain barrier readily and cause seizures. However, the blood level of laudanosine after clinical doses of atracurium should not have undesirable consequences. No significant differences in seizure threshold for lidocaine have been reported in cats paralyzed with atracurium, pancuronium, and vecuronium.

Cisatracurium, an intermediate-acting muscle relaxant, produces and releases less laudanosine and histamine than atracurium. The cerebral effects of cisatracurium are essentially similar to or weaker than those of atracurium.[192]

Pancuronium, vecuronium, rocuronium, and pipecuronium have little or minimal effect on CBF, $CMRO_2$, or ICP. Pancuronium raises blood pressure and heart rate, which could be disadvantageous for certain patients, such as those with hypertension, especially if they have disturbed autoregulation. In these patients, a substantial elevation of ICP could occur. Vecuronium neither induces histamine release nor does it change blood pressure or heart rate, and thus it may be preferable. Rocuronium, because of its rapid onset of action in comparison with other nondeporalizing muscle relaxants and its lack of adverse activity, such as histamine release, may be preferable to succinylcholine during rapid induction of anesthesia.

In summary, if succinylcholine is used, prior administration of small doses of a nondepolarizing muscle relaxant or lidocaine is recommended, as well as maintenance of adequate depth of anesthesia. With respect to the use of nondepolarizing muscle relaxants, in most clinical situations the changes in CBF and ICP are minimal if respiration is well controlled and an increase in $PaCO_2$ is avoided. One should be aware of residual neuromuscular blockade after emergence from anesthesia, especially when renal function is compromised, as it could lead to hypercapnia and a concomitant increase in ICP.

Other Drugs

Lidocaine

Lidocaine has unique central nervous system effects that depend on the blood concentration; at low concentration, sedation occurs, but at higher concentration, seizures may occur. Non-seizure-inducing doses of lidocaine produce a dose-related reduction of $CMRO_2$ and CBF. Large doses of lidocaine reduce $CMRO_2$ by a maximum of 30% in dogs. If seizures are induced by lidocaine, $CMRO_2$ increases, as does CBF. Brain oxygenation seems to be adequate. However, regional flow-metabolism imbalance may not be excluded entirely.

Intravenous lidocaine 1.5 mg/kg has been reported to be effective in preventing circulatory changes and an elevation of ICP during tracheal intubation, endotracheal suctioning, or after application of a pin-type skull clamp or skin incision in patients undergoing craniotomy.[193]

Several sodium channel blockers have been investigated and suggested as possible neuroprotectants.[194] Although the protective effect of lidocaine was not demonstrated in severe forebrain ischemia,[195] it was demonstrated in transient focal cerebral ischemia.[196] The dosage regimen was clinically relevant. The mechanism for protection appears to be related to preservation of mitochondrial function,[197] inhibition of glutamate release,[198] and inhibition of apoptosis.[199] A small clinical trial demonstrated a benefit of a clinically relevant dose of lidocaine infusion during cardiac surgery in long-term (6 months) neuropsychological conditions.[200] However, subsequent large-scale, randomized, double-blind studies failed to demonstrate neurocognitive improvement through use of lidocaine.[201,202]

Alpha$_2$-Adrenergic Agonists

Dexmedetomidine (0.2–0.6 μg/kg/h) was reported to decrease global CBF by one-third, with rCBF in most of the cortical and subcortical brain regions being decreased.[203] Dexmedetomidine also decreased Vmca in a dose-dependent manner, with the maximum reduction being approximately 25% at the hypnotic doses.[204] Although animal studies demonstrated that dexmedetomidine reduced CBF without a concomitant reduction in CMR,[205] a reduction of the CBF/CMR ratio was not observed in humans. Indeed, dexmedetomidine reduced CMR equivalent (CMRe; this value is calculated by multiplying Vmca by the difference between arterial and cerebral jugular venous oxygen contents) in healthy volunteers in a dose-dependent manner.[206] The decreases in the CBF/CMR ratio that were anticipated from animal studies were not observed. In addition, no clinically significant reduction of brain tissue oxygenation occurred with dexmedetomidine (1 μg/kg + 0.5–0.7 μg/kg/h) in neurovascular surgery patients.[207]

A PET study in humans demonstrated a significant negative linear correlation between clonidine concentration and rCBF

in the thalamus, prefrontal, orbital and parietal association cortex, posterior cingulated cortex, and precuneus, suggesting that the pattern of regional deactivation during the sedation induced by clonidine is very close to the pattern of physiologic early stage of non-rapid eye movement (REM) sleep.[208] It was reported in humans that dexmedetomidine was seen to weaken dynamic cerebrovascular autoregulation.[209] In healthy human volunteers, oral administration of clonidine 5 μg/kg decreased Vmca by approximately 20% with slight attenuation of CO_2 reactivity.[210] CO_2 reactivity with dexmedetomidine in humans is preserved or may be impaired.[206,211]

As to the mechanisms of the cerebrovascular effects of α_2-antagonists, there are several animal studies. Clonidine, topically applied through a cranial window, constricted pial arteries and veins, and this effect was blocked by pretreatment of yohimbine, an α_2-antagonist.[212] The pretreatment with glibenclamide, a blocker of ATP-sensitive potassium channel, potentiated the vasoconstriction of pial arteries, indicating that α_2-agonist induced activation of ATP-sensitive potassium channels as a counterbalancing vasodilatory effect.[212] Neither inhibition of NO synthase nor blockade of β-adrenoreceptors affects the cerebral vasoconstriction induced by dexmedetomidine.[213]

In patients with normal ICP after transsphenoidal pituitary tumor surgery, dexmedetomidine (total dose approximately 1 μg/kg) had no effect on lumbar CSF pressure, but decreased MABP and CPP.[214] Also, in severely head-injured patients, a single dose of clonidine (2.5 μg/kg IV) did not significantly affect ICP but significantly reduced MABP and CPP.[215] Some patients displayed a transient increase (>10 mmHg) in ICP concomitant with a decrease in MABP, which may have resulted from cerebral autoregulatory vasodilation mechanism.[215]

A variety of in-vivo and in-vitro models demonstrated the neuroprotective effects of α_2 agonists, especially dexmedetomidine.[216] Of note, dexmedetomidine was reported to attenuate isoflurane- or ketamine-induced neurotoxicity in the rodent developing brain.[217,218] No clinical evidence of neuroprotective effects of dexmedetomidine is available as yet. Nevertheless, because of rapid onset and offset of effective sedation without respiratory depression, dexmedetomidine may be advantageous for awake craniotomy.

ANESTHETIC INTERACTIONS

Modification of autoregulation and CO_2 responses with anesthetics is important because these changes lead to unsatisfactory operative conditions and a potentially poor clinical outcome. Other important aspects are the interaction of anesthetics with surgical stimulation and with time (duration of anesthesia).

Autoregulation During Anesthesia

Autoregulation is characterized by both a rapid phase of cerebrovascular adaptation (dynamic autoregulation) and a steady-state phase (static autoregulation). In general, dynamic autoregulation is affected more easily by anesthetics than static autoregulation, and intravenous anesthetics preserve autoregulation, whereas volatile anesthetics impair it. Both dynamic and static autoregulation are preserved with propofol even at high doses. In contrast, both dynamic and static autoregulation are impaired with desflurane, even at a low concentration (0.5 MAC). With isoflurane, dynamic, but not static, autoregulation is impaired at 0.5 MAC and both dynamic and static autoregulation are abolished at 1.5 MAC.[219] Impaired autoregulation may last even after the depth of anesthesia was decreased. Such findings suggest that rapid normalization of blood pressure after induced hypotension might increase CBF profoundly and thus should be avoided. Sevoflurane 1.5 MAC preserves both dynamic and static autoregulation.[220,221] N_2O[222] and xenon[50,223] appear to preserve static autoregulation. However, a study in humans demonstrated that N_2O[224] and dexmedetomidine[209] have the potential to impair "dynamic" autoregulation.

Autoregulation is influenced not only by the anesthetic itself but also by the level of $PaCO_2$. In general, autoregulation is impaired more easily when vasodilatory anesthetics are used or patients are kept hypercapnic than when vasoconstricting agents, including intravenous anesthetics, are in use and during hypocapnia.

Autoregulation is usually impaired in patients with intracranial space-occupying lesions. When autoregulation is lost or disturbed, sudden blood pressure changes can produce ischemia or brain edema. Therefore, deep inhalational anesthesia and hypercapnia should definitely be avoided in such patients. During surgical incision and after extubation, suggestive increases in CBF in association with an increase in MABP were observed.[225] Thus careful management of blood pressure is critical in patients with intracranial pathologic conditions.

Cerebrovascular Reactivity to CO_2

As the decrease in CBF at clinically relevant levels of hypocapnia can impair cerebral metabolism,[226] it is important to know how anesthetics affect cerebrovascular reactivity to CO_2. At clinical levels of anesthesia, cerebrovascular responses to alterations in $PaCO_2$ are preserved when both inhalational and intravenous agents are used, although the magnitude of response may vary according to agent and anesthetic depth. CO_2 reactivity is maintained to barbiturate concentrations that produce burst suppression. In general, CO_2 reactivity appears to be greater when vasodilatory anesthetics (ie, volatile anesthetics) are used than when vasoconstrictor drugs (ie, intravenous anesthetics) are used. However, with high concentrations of volatile anesthetics, cerebrovascular reactivity appears to be attenuated. Indeed, isoflurane 2.3% decreased MAP to approximately 60 mmHg and attenuated CO_2 reactivity, though CO_2 reactivity was preserved better during isoflurane-induced hypotension than during sodium nitroprusside-induced hypotension.[227] With isoflurane 2 MAC in dogs, hypocapnia decreased CBF but hypercapnia failed to increase it when MAP was maintained.[228] The failure of increasing CBF by hypercapnia may be the result of the maximally dilated vasculature with high concentrations of isoflurane.

CO_2 reactivity has been reported to be present in anesthetized patients with intracranial space-occupying lesions. For this reason, hyperventilation is recommended in patients with increased ICP or decreased intracranial compliance. However, hyperventilation may cause ischemia, both in patients with head injury and in patients with ischemic cerebrovascular disease, and thus prolonged extreme hyperventilation should be avoided.[229] In moyamoya disease, both hypocapnia and hypercapnia appear to decrease CBF. CO_2 reactivity also varies by region. It also may be attenuated during anesthesia by associated diseases such as diabetes mellitus and peripheral vascular disease.[230]

Many neurosurgical procedures have been performed with the patient under mild-to-moderate hypothermia because decreases in temperature provide neuroprotective effects, although the multicenter trial IHAST did not demonstrate a significant protective effect for intraoperative mild hypothermia (33 °C) during surgery for intracranial aneurysm.[231] CO_2 reactivity at a corresponding level of moderate hypothermia appears to be maintained.

Surgical Stimulation

The changes in CBF, $CMRO_2$, and ICP that occur during surgical stimulation are important to note. Sciatic nerve stimulation has been shown to produce coupled increases in CBF and $CMRO_2$, accompanied by EEG desynchronization, during 0.5% and 1.0% halothane in dogs. During 1.4% halothane, stimulation produced an increase in CBF without a change in $CMRO_2$ or EEG or an increase in arterial blood pressure. During morphine anesthesia (0.5 mg/kg and 1.5 mg/kg with or without N_2O), nerve stimulation produced almost parallel increases in CBF and $CMRO_2$ and was accompanied by EEG desynchronization. During deep thiopental anesthesia, stimulation-induced changes in CBF, $CMRO_2$, or EEG were abolished, but were seen during light thiopental anesthesia. Therefore, irrespective of anesthetic depth, a tight relationship exists among changes in CBF, $CMRO_2$, and EEG with stimulation during thiopental anesthesia. These results suggest that anesthetics possessing cerebral vasodilator effects attenuate the coupling between flow and metabolism with stimulation and may disturb it at higher concentration, whereas cerebral vasoconstrictor drugs tend to maintain it.

Through autoradiographic techniques, cerebral vasodilation elicited by focal stimulation within the medullary reticular formation in rats anesthetized with alpha-chloralose has been reported.[232] Local glucose use in the brain (the hindlimb projection area) and in the dorsal horn of the lumbar spinal cord was increased by unilateral sciatic nerve stimulation in rats anesthetized with 0.5% and 2% enflurane. At 4% enflurane, stimulation induced an increase in glucose use only in spinal cord but not in the brain.[233] The results show that a threshold exists at which enflurane suppresses the metabolic responses to peripheral stimulation in the somatosensory cortex but not in the spinal cord. If electrical stimulation is regarded as analogous to surgical stimulation, a considerable increase in spinal cord metabolism may occur during surgery, even in a deeply anesthetized subject, even though the cerebral cortical responses are blocked with high anesthetic concentrations.

In humans anesthetized with 3.5% enflurane, no apparent increases in global CBF or $CMRO_2$ were observed with surgical stimulation, despite changes in EEG.[234] However, in that study, CBF and $CMRO_2$ were measured by the Kety-Schmidt method, and the regional changes in CBF and $CMRO_2$ with stimulation may not have been detected. Another study showed that cerebral Vmca increased with surgical stimulation at 1 and 2 MAC isoflurane anesthesia. The increase is not a function of changes in blood pressure. The data suggest that surgical stimulation raises CBF, possibly because of the changes in cerebral functional activity.[235] CBF changes evoked by surgical stimulation were reported to be dependent on the $PaCO_2$ level. In patients anesthetized with sevoflurane 1.7% and N_2O 60%, the increase in Vmca was attenuated by hypocapnia and augmented by hypercapnia, even within a clinically relevant ranges of $PaCO_2$.[236]

Comparing these reported data in animals and humans, one must consider the possibility that, during light anesthesia, surgical stimulation provokes a CBF increase in association with metabolic activation and may cause an increase in ICP. Blocking the noxious stimuli by other drugs would be recommended. This recommendation is supported by a study in which Vmca remained stable during surgery at 1 MAC isoflurane anesthesia with concomitant use of epidural local anesthetic.[237]

Interactions with Time

It is a matter of concern whether the increase of CBF induced by volatile anesthetics remains stable during prolonged anesthesia. Results from animal studies are inconsistent, some showed a gradual decrease, but others failed to show any gradual decrease over time. In contrast, human data are consistent and suggest that hyperemia induced by volatile anesthetics remains stable over time. In patients with intracranial mass lesions, no significant differences of CBF between two times of measurement during isoflurane or desflurane anesthesia appear.[102] Although the measurements were made only twice, at the beginning and at the end of the study, the results suggest that CBF does not change over time during anesthesia in humans. Kuroda and associates[91] found that the elevated CBF equivalent was preserved during prolonged anesthesia (1.5 MAC) over 3 hours with halothane, isoflurane, and sevoflurane. However, CBF equivalent provides only the global ratio of CBF to $CMRO_2$ for a certain period. There are two possible explanations for these results: CBF remains stable, or CBF changes in a parallel fashion to functional-metabolic changes during the observation period. As judged by relatively unchanged EEG patterns during 3 hours of anesthesia, it is unlikely the $CMRO_2$ exhibits consistent change over time. Thus the increase in CBF produced by volatile anesthetics is maintained during prolonged anesthesia without decay. The subsequent study using the transcranial Doppler ultrasonography technique showed no decay in Vmca over time during 3 hours of inhalation of volatile anesthetics at 1.5 MAC in humans.[12] No decay in Vmca over time is seen in children during isoflurane (1 MAC) exposure.[237] It seems likely that a time effect for gradual decrease in CBF does not take place in humans during prolonged volatile anesthetics.

SUMMARY

Anesthetic drugs and techniques influence cerebral circulation, metabolism, and ICP. Some anesthetic drugs may have potential neuroprotective effects, though some anesthetics might also have neurotoxic effects in limited circumstances. The issues discussed in this chapter are important for the anesthetic management of both patients undergoing neurosurgery and patients with brain disorders. The severely damaged brain cannot be restored. Anesthetic management thus should focus on preventing the extension of damage, preventing new damage, and providing appropriate surgical conditions. If a potent cerebral vasodilatory anesthetic is used in patients with intracranial space-occupying lesions or decreased intracranial compliance, a marked increase in ICP may occur. Induction of cerebral hyperemia in a patient with a space-occupying intracranial lesion, therefore, should be avoided. Induction of vasoconstriction, by either hyperventilation or concomitant use of vasoconstricting anesthetics, such as barbiturates and propofol, decreases and stabilizes the ICP. During carotid endarterectomy and bypass surgery, normocapnia may be recommended because the rCBF response of an ischemic area to altered $PaCO_2$ cannot be accurately predicted in individual patients. Autoregulation may be impaired by pathologic conditions as well as deep volatile inhalational anesthesia.

Furthermore, the CPP necessary to maintain adequate cerebral perfusion cannot be easily determined in an individual patient. Thus, during surgery for ischemic cerebrovascular diseases, arterial blood pressure should be kept at a value no lower than the lowest preoperative pressure. The metabolic depressive effect of barbiturates and propofol may also be

beneficial in such situations. Isoflurane and sevoflurane have been suggested as drugs of choice if an inhalational anesthetic is deemed desirable. However, other volatile anesthetics, when used at low concentrations, would not cause any harm. Noxious stimuli under inadequate anesthesia or seizure activity can produce undesirable events, such as increases in metabolism, CBV, and ICP. Synthetic opioids and supplemental local anesthetics are recommended. Special attention must be paid, in the case of functional neurosurgery, to obtain rapid control of asleep-awake-asleep state or sedation with analgesia through the use of anesthetics and adjuvant drugs with easy controllability.

REFERENCES

1. Attwell D, Buchan AM, Charpak S, et al. Glial and neuronal control of brain blood flow. *Nature*. 2010;468:232–243.
2. Offenhauser N, Thomsen K, Caesar K, et al. Activity-induced tissue oxygenation changes in rat cerebellar cortex: Interplay of postsynaptic activation and blood flow. *J Physiol*. 2005;565:279–294.
3. St Lawrence KS, Ye FQ, Lewis BK, et al. Measuring the effects of indomethacin on changes in cerebral oxidative metabolism and cerebral blood flow during sensorimotor activation. *Magn Reson Med*. 2003;50:99–106.
4. Lin AL, Fox PT, Hardies J, et al. Nonlinear coupling between cerebral blood flow, oxygen consumption, and ATP production in human visual cortex. *Proc Natl Acad Sci U S A*. 2010;107:8446–8451.
5. Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508:55–60.
6. Pellerin L, Bouzier-Sore AK, Aubert A, et al. Activity-dependent regulation of energy metabolism by astrocytes: An update. *Glia*. 2007;55:1251–1262.
7. Fox PT, Raichle ME, Mintun MA, et al. Nonoxidative glucose consumption during focal physiologic neural activity. *Science*. 1988;241:462–464.
8. Madsen PL, Cruz NF, Sokoloff L, et al. Cerebral oxygen/glucose ratio is low during sensory stimulation and rises above normal during recovery: Excess glucose consumption during stimulation is not accounted for by lactate efflux from or accumulation in brain tissue. *J Cereb Blood Flow Metab*. 1999;19:393–400.
9. Hall CN, Klein-Flugge MC, Howarth C, et al. Oxidative phosphorylation, not glycolysis, powers presynaptic and postsynaptic mechanisms underlying brain information processing. *J Neurosci*. 2012;32:8940–8951.
10. Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. *Neuron*. 2012;75:762–777.
11. Lam AM, Matta BF, Mayberg TS, et al. Change in cerebral blood flow velocity with onset of EEG silence during inhalation anesthesia in humans: Evidence of flow-metabolism coupling? *J Cereb Blood Flow Metab*. 1995;15:714–717.
12. Kuroda Y, Murakami M, Tsuruta J, et al. Blood flow velocity of middle cerebral artery during prolonged anesthesia with halothane, isoflurane, and sevoflurane in humans. *Anesthesiology*. 1997;87:527–532.
13. Weyland A, Buhre W, Grund S, et al. Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. *J Neurosurg Anesthesiol*. 2000;12:210–216.
14. Brian Jr JE. Carbon dioxide and the cerebral circulation. *Anesthesiology*. 1998;88:1365–1386.
15. Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. *Anesthesiology*. 2015;122:196–205.
16. Alexandrov AV, Sharma VK, Lao AY, et al. Reversed Robin Hood syndrome in acute ischemic stroke patients. *Stroke*. 2007;38:3045–3048.
17. Soloway M, Moriarty G, Fraser JG, et al. Effect of delayed hyperventilation on experimental cerebral infarction. *Neurology*. 1971;21:479–485.
18. Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. *Stroke*. 2007;38:3084–3094.
19. Lanier WL, Iaizzo PA, Milde JH, et al. The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. *Anesthesiology*. 1994;80:392–401.
20. Lanier WL, Albrecht 2nd. RF, Laizzo PA. Divergence of intracranial and central venous pressures in lightly anesthetized, tracheally intubated dogs that move in response to a noxious stimulus. *Anesthesiology*. 1996;84:605–613.
21. Pasternak JJ, Lanier WL. Is nitrous oxide use appropriate in neurosurgical and neurologically at-risk patients? *Curr Opin Anaesthesiol*. 2010;23:544–550.
22. Reinstrup P, Ryding E, Algotsson L, et al. Effects of nitrous oxide on human regional cerebral blood flow and isolated pial arteries. *Anesthesiology*. 1994;81:396–402.
23. Gyulai FE, Firestone LL, Mintun MA, et al. In vivo imaging of human limbic responses to nitrous oxide inhalation. *Anesth Analg*. 1996;83:291–298.
24. Dashdorj N, Corrie K, Napolitano A, et al. Effects of subanesthetic dose of nitrous oxide on cerebral blood flow and metabolism: A multimodal magnetic resonance imaging study in healthy volunteers. *Anesthesiology*. 2013;118:577–586.
25. Lorenz IH, Kolbitsch C, Hormann C, et al. The influence of nitrous oxide and remifentanil on cerebral hemodynamics in conscious human volunteers. *Neuroimage*. 2002;17:1056–1064.
26. Reinstrup P, Ryding E, Ohlsson T, et al. Regional cerebral metabolic rate (positron emission tomography) during inhalation of nitrous oxide 50% in humans. *Br J Anaesth*. 2008;100:66–71.
27. Algotsson L, Messeter K, Rosen I, et al. Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. *Acta Anaesthesiol Scand*. 1992;36:46–52.
28. Hoffman WE, Charbel FT, Edelman G, et al. Nitrous oxide added to isoflurane increases brain artery blood flow and low frequency brain electrical activity. *J Neurosurg Anesthesiol*. 1995;7:82–88.
29. Kaisti KK, Langsjo JW, Aalto S, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology*. 2003;99:603–613.
30. Strebel S, Kaufmann M, Anselmi L, et al. Nitrous oxide is a potent cerebrovasodilator in humans when added to isoflurane. A transcranial Doppler study. *Acta Anaesthesiol Scand*. 1995;39:653–658.
31. Cho S, Fujigaki T, Uchiyama Y, et al. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. Transcranial Doppler study. *Anesthesiology*. 1996;85:755–760.
32. Hormann C, Schmidauer C, Haring HP, et al. Hyperventilation reverses the nitrous oxide-induced increase in cerebral blood flow velocity in human volunteers. *Br J Anaesth*. 1995;74:616–618.
33. Hormann C, Schmidauer C, Kolbitsch C, et al. Effects of normo- and hypocapnic nitrous-oxide-inhalation on cerebral blood flow velocity in patients with brain tumors. *J Neurosurg Anesthesiol*. 1997;9:141–145.
34. Matta BF, Lam AM. Nitrous oxide increases cerebral blood flow velocity during pharmacologically induced EEG silence in humans. *J Neurosurg Anesthesiol*. 1995;7:89–93.
35. Sakabe T, Tsutsui T, Maekawa T, et al. Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. *Anesthesiology*. 1985;63:262–266.
36. Culley DJ, Xie Z, Crosby G. General anesthetic-induced neurotoxicity: An emerging problem for the young and old? *Curr Opin Anaesthesiol*. 2007;20:408–413.
37. David HN, Leveille F, Chazalviel L, et al. Reduction of ischemic brain damage by nitrous oxide and xenon. *J Cereb Blood Flow Metab*. 2003;23:1168–1173.
38. Jevtovic-Todorovic V, Beals J, Benshoff N, et al. Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain. *Neuroscience*. 2003;122:609–616.
39. McGregor DG, Lanier WL, Pasternak JJ, et al. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. *Anesthesiology*. 2008;108:568–579.
40. Pasternak JJ, McGregor DG, Lanier WL, et al. Effect of nitrous oxide use on long-term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. *Anesthesiology*. 2009;110:563–573.
41. Peyton PJ, Wu CY. Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. *Anesthesiology*. 2014;120:1137–1145.
42. Myles PS, Leslie K, Chan MT, et al. Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. *Anesthesiology*. 2007;107:221–231.
43. Laitio RM, Kaisti KK, Laangsjo JW, et al. Effects of xenon anesthesia on cerebral blood flow in humans: A positron emission tomography study. *Anesthesiology*. 2007;106:1128–1133.
44. Rex S, Schaefer W, Meyer PH, et al. Positron emission tomography study of regional cerebral metabolism during general anesthesia with xenon in humans. *Anesthesiology*. 2006;105:936–943.
45. Laitio RM, Langsjo JW, Aalto S, et al. The effects of xenon anesthesia on the relationship between cerebral glucose metabolism and blood flow in healthy subjects: A positron emission tomography study. *Anesth Analg*. 2009;108:593–600.
46. Alkire MT, Pomfrett CJ, Haier RJ, et al. Functional brain imaging during anesthesia in humans: Effects of halothane on global and regional cerebral glucose metabolism. *Anesthesiology*. 1999;90:701–709.

47. Alkire MT, Haier RJ, Shah NK, et al. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. *Anesthesiology*. 1997;86:549–557.
48. Frietsch T, Bogdanski R, Blobner M, et al. Effects of xenon on cerebral blood flow and cerebral glucose utilization in rats. *Anesthesiology*. 2001;94:290–297.
49. Schmidt M, Marx T, Kotzerke J, et al. Cerebral and regional organ perfusion in pigs during xenon anaesthesia. *Anaesthesia*. 2001;56:1154–1159.
50. Fink H, Blobner M, Bogdanski R, et al. Effects of xenon on cerebral blood flow and autoregulation: An experimental study in pigs. *Br J Anaesth*. 2000;84:221–225.
51. Plougmann J, Astrup J, Pedersen J, et al. Effect of stable xenon inhalation on intracranial pressure during measurement of cerebral blood flow in head injury. *J Neurosurg*. 1994;81:822–828.
52. Marion DW, Crosby K. The effect of stable xenon on ICP. *J Cereb Blood Flow Metab*. 1991;11:347–350.
53. Fukuda T, Nakayama H, Yanagi K, et al. The effects of 30% and 60% xenon inhalation on pial vessel diameter and intracranial pressure in rabbits. *Anesth Analg*. 2001;92:1245–1250.
54. Darby JM, Nemoto EM, Yonas H, et al. Stable xenon does not increase intracranial pressure in primates with freeze-injury-induced intracranial hypertension. *J Cereb Blood Flow Metab*. 1991;11:522–526.
55. Schmidt M, Marx T, Armbruster S, et al. Effect of xenon on elevated intracranial pressure as compared with nitrous oxide and total intravenous anesthesia in pigs. *Acta Anaesthesiol Scand*. 2005;49:494–501.
56. Chakkarapani E, Dingley J, Aquilina K, et al. Effects of xenon and hypothermia on cerebrovascular pressure reactivity in newborn global hypoxic-ischemic pig model. *J Cereb Blood Flow Metab*. 2013;33:1752–1760.
57. Wilhelm S, Ma D, Maze M, et al. Effects of xenon on in vitro and in vivo models of neuronal injury. *Anesthesiology*. 2002;96:1485–1491.
58. Homi HM, Yokoo N, Ma D, et al. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. *Anesthesiology*. 2003;99:876–881.
59. Schmidt M, Marx T, Gloggl E, et al. Xenon attenuates cerebral damage after ischemia in pigs. *Anesthesiology*. 2005;102:929–936.
60. Campos-Pires R, Armstrong SP, Sebastiani A, et al. Xenon improves neurologic outcome and reduces secondary injury following trauma in an in vivo model of traumatic brain injury. *Crit Care Med*. 2014.
61. Dingley J, Tooley J, Porter H, et al. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischemia. *Stroke*. 2006;37:501–506.
62. Ma D, Hossain M, Chow A, et al. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Ann Neurol*. 2005;58:182–193.
63. Rajakumaraswamy N, Ma D, Hossain M, et al. Neuroprotective interaction produced by xenon and dexmedetomidine on in vitro and in vivo neuronal injury models. *Neurosci Lett*. 2006;409:128–133.
64. Ma D, Hossain M, Pettet GK, et al. Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. *J Cereb Blood Flow Metab*. 2006;26:199–208.
65. Hobbs C, Thoresen M, Tucker A, et al. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. *Stroke*. 2008;39:1307–1313.
66. Sheng SP, Lei B, James ML, et al. Xenon neuroprotection in experimental stroke: Interactions with hypothermia and intracerebral hemorrhage. *Anesthesiology*. 2012;117:1262–1275.
67. Brosnan H, Bickler PE. Xenon neurotoxicity in rat hippocampal slice cultures is similar to isoflurane and sevoflurane. *Anesthesiology*. 2013;119:335–344.
68. Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane, and desflurane during propofol-induced isoelectric electroencephalogram in humans. *Anesthesiology*. 1995;83:980–985.
69. Schlunzen L, Cold GE, Rasmussen M, et al. Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission tomography. *Acta Anaesthesiol Scand*. 2006;50:306–312.
70. Kehl F, Shen H, Moreno C, et al. Isoflurane-induced cerebral hyperemia is partially mediated by nitric oxide and epoxyeicosatrienoic acids in mice in vivo. *Anesthesiology*. 2002;97:1528–1533.
71. Iida H, Ohata H, Iida M, et al. Isoflurane and sevoflurane induce vasodilation of cerebral vessels via atp-sensitive k+ channel activation. *Anesthesiology*. 1998;89:954–960.
72. Lorenz IH, Kolbitsch C, Hormann C, et al. Influence of equianaesthetic concentrations of nitrous oxide and isoflurane on regional cerebral blood flow, regional cerebral blood volume, and regional mean transit time in human volunteers. *Br J Anaesth*. 2001;87:691–698.
73. Talke P, Caldwell J, Dodsont B, et al. Desflurane and isoflurane increase lumbar cerebrospinal fluid pressure in normocapnic patients undergoing transsphenoidal hypophysectomy. *Anesthesiology*. 1996;85:999–1004.
74. Artru AA, Lam AM, Johnson JO, et al. Intracranial pressure, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane. *Anesth Analg*. 1997;85:587–592.
75. Petersen KD, Landsfeldt U, Cold GE, et al. Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: A randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. *Anesthesiology*. 2003;98:329–336.
76. Bosel J, Purrucker JC, Nowak F, et al. Volatile isoflurane sedation in cerebrovascular intensive care patients using anaconda((r)): Effects on cerebral oxygenation, circulation, and pressure. *Intensive Care Med*. 2012;38:1955–1964.
77. Villa F, Iacca C, Molinari AF, et al. Inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. *Crit Care Med*. 2012;40:2797–2804.
78. Fukuda S, Warner DS. Cerebral protection. *Br J Anaesth*. 2007;99:10–17.
79. Sano T, Drummond JC, Patel PM, et al. A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. *Anesthesiology*. 1992;76:221–228.
80. Kapinya KJ, Lowl D, Futterer C, et al. Tolerance against ischemic neuronal injury can be induced by volatile anesthetics and is inducible NO synthase dependent. *Stroke*. 2002;33:1889–1898.
81. Xiong L, Zheng Y, Wu M, et al. Preconditioning with isoflurane produces dose-dependent neuroprotection via activation of adenosine triphosphate-regulated potassium channels after focal cerebral ischemia in rats. *Anesth Analg*. 2003;96:233–237.
82. Lee JJ, Li L, Jung HH, et al. Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. *Anesthesiology*. 2008;108:1055–1062.
83. Liang G, Ward C, Peng J, et al. Isoflurane causes greater neurodegeneration than an equivalent exposure of sevoflurane in the developing brain of neonatal mice. *Anesthesiology*. 2010;112:1325–1334.
84. Messick Jr JM, Casement B, Sharbrough FW, et al. Correlation of regional cerebral blood flow (RCBF) with EEG changes during isoflurane anesthesia for carotid endarterectomy: Critical RCBF. *Anesthesiology*. 1987;66:344–349.
85. Kaisti KK, Metsahonkala L, Teras M, et al. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. *Anesthesiology*. 2002;96:1358–1370.
86. Schlunzen L, Vafaee MS, Cold GE, et al. Effects of subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study. *Acta Anaesthesiol Scand*. 2004;48:1268–1276.
87. Schlunzen L, Vafaee MS, Juul N, et al. Regional cerebral blood flow responses to hyperventilation during sevoflurane anaesthesia studied with pet. *Acta Anaesthesiol Scand*. 2010;54:610–615.
88. Matta BF, Heath KJ, Tipping K, et al. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. *Anesthesiology*. 1999;91:677–680.
89. Rhondali O, Mahr A, Simonin-Lansiaux S, et al. Impact of sevoflurane anesthesia on cerebral blood flow in children younger than 2 years. *Paediatr Anaesth*. 2013;23:946–951.
90. Schlunzen L, Juul N, Hansen KV, et al. Regional cerebral glucose metabolism during sevoflurane anaesthesia in healthy subjects studied with positron emission tomography. *Acta Anaesthesiol Scand*. 2010;54:603–609.
91. Kuroda Y, Murakami M, Tsuruta J, et al. Preservation of the ration of cerebral blood flow/metabolic rate for oxygen during prolonged anesthesia with isoflurane, sevoflurane, and halothane in humans. *Anesthesiology*. 1996;84:555–561.
92. Takahashi H, Murata K, Ikeda K. Sevoflurane does not increase intracranial pressure in hyperventilated dogs. *Br J Anaesth*. 1993;71:551–555.
93. Holmstrom A, Akeson J. Desflurane increases intracranial pressure more and sevoflurane less than isoflurane in pigs subjected to intracranial hypertension. *J Neurosurg Anesthesiol*. 2004;16:136–143.
94. Talke P, Caldwell JE, Richardson CA. Sevoflurane increases lumbar cerebrospinal fluid pressure in normocapnic patients undergoing transsphenoidal hypophysectomy. *Anesthesiology*. 1999;91:127–130.
95. Warner DS, McFarlane C, Todd MM, et al. Sevoflurane and halothane reduce focal ischemic brain damage in the rat. *Anesthesiology*. 1993;79:985–992.
96. Werner C, Mollenberg O, Kochs E, et al. Sevoflurane improves neurological outcome after incomplete cerebral ischaemia in rats. *Br J Anaesth*. 1995;75:756–760.
97. Nakajima Y, Moriwaki G, Ikeda K, et al. The effects of sevoflurane on recovery of brain energy metabolism after cerebral ischemia in the rat: A comparison with isoflurane and halothane. *Anesth Analg*. 1997;85:593–599.

98. Payne RS, Akca O, Roewer N, et al. Sevoflurane-induced preconditioning protects against cerebral ischemic neuronal damage in rats. *Brain Res*. 2005;1034:147–152.
99. Satomoto M, Satoh Y, Terui K, et al. Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. *Anesthesiology*. 2009;110:628–637.
100. Grady RE, Weglinski MR, Sharbrough FW, et al. Correlation of regional cerebral blood flow with ischemic electroencephalographic changes during sevoflurane-nitrous oxide anesthesia for carotid endarterectomy. *Anesthesiology*. 1998;88:892–897.
101. Mielck F, Stephan H, Buhre W, et al. Effects of 1 MAC desflurane on cerebral metabolism, blood flow and carbon dioxide reactivity in humans. *Br J Anaesth*. 1998;81:155–160.
102. Ornstein E, Young WL, Fleischer LH, et al. Desflurane and isoflurane have similar effects on cerebral blood flow in patients with intracranial mass lesions. *Anesthesiology*. 1993;79:498–502.
103. Bedforth NM, Hardman JG, Nathanson MH. Cerebral hemodynamic response to the introduction of desflurane: A comparison with sevoflurane. *Anesth Analg*. 2000;91:152–155.
104. Muzzi DA, Losasso TJ, Dietz NM, et al. The effect of desflurane and isoflurane on cerebrospinal fluid pressure in humans with supratentorial mass lesions. *Anesthesiology*. 1992;76:720–724.
105. Fraga M, Rama-Maceiras P, Rodino S, et al. The effects of isoflurane and desflurane on intracranial pressure, cerebral perfusion pressure, and cerebral arteriovenous oxygen content difference in normocapnic patients with supratentorial brain tumors. *Anesthesiology*. 2003;98:1085–1090.
106. Engelhard K, Werner C, Reeker W, et al. Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. *Br J Anaesth*. 1999;83:415–421.
107. Haelewyn B, Yvon A, Hanouz JL, et al. Desflurane affords greater protection than halothane against focal cerebral ischaemia in the rat. *Br J Anaesth*. 2003;91:390–396.
108. Tsai SK, Lin SM, Hung WC, et al. The effect of desflurane on ameliorating cerebral infarction in rats subjected to focal cerebral ischemia-reperfusion injury. *Life Sci*. 2004;74:2541–2549.
109. Dimaculangan D, Bendo AA, Sims R, et al. Desflurane improves the recovery of the evoked postsynaptic population spike from CA1 pyramidal cells after hypoxia in rat hippocampal slices. *J Neurosurg Anesthesiol*. 2006;18:78–82.
110. Istaphanous GK, Howard J, Nan X, et al. Comparison of the neuroapoptotic properties of equipotent anesthetic concentrations of desflurane, isoflurane, or sevoflurane in neonatal mice. *Anesthesiology*. 2011;114:578–587.
111. Hoffman WE, Charbel FT, Edelman G. Desflurane increases brain tissue oxygenation and pH. *Acta Anaesthesiol Scand*. 1997;41:1162–1166.
112. Warner DS, Takaoka S, Wu B, et al. Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a model of focal cerebral ischemia. *Anesthesiology*. 1996;84:1475–1484.
113. Cole DJ, Cross LM, Drummond JC, et al. Thiopentone and methohexital, but not pentobarbitone, reduce early focal cerebral ischemic injury in rats. *Can J Anaesth*. 2001;48:807–814.
114. Hindman BJ, Bayman EO, Pfisterer WK, et al. No association between intraoperative hypothermia or supplemental protective drug and neurologic outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery: Findings from the intraoperative hypothermia for aneurysm surgery trial. *Anesthesiology*. 2010;112:86–101.
115. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A*. 2002;99:15089–15094.
116. Milde LN, Milde JH, Michenfelder JD. Cerebral functional, metabolic, and hemodynamic effects of etomidate in dogs. *Anesthesiology*. 1985;63:371–377.
117. Bingham RM, Procaccio F, Prior PF, et al. Cerebral electrical activity influences the effects of etomidate on cerebral perfusion pressure in traumatic coma. *Br J Anaesth*. 1985;57:843–848.
118. Sano T, Patel PM, Drummond JC, et al. A comparison of the cerebral protective effects of etomidate, thiopental, and isoflurane in a model of forebrain ischemia in the rat. *Anesth Analg*. 1993;76:990–997.
119. Drummond JC, Cole DJ, Patel PM, et al. Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: A comparison of the extent of cerebral injury. *Neurosurgery*. 1995;37:742–748.
120. Hoffman WE, Charbel FT, Edelman G, et al. Comparison of the effect of etomidate and desflurane on brain tissue gases and ph during prolonged middle cerebral artery occlusion. *Anesthesiology*. 1998;88:1188–1194.
121. Guo J, White JA, Batjer HH. Limited protective effects of etomidate during brainstem ischemia in dogs. *J Neurosurg*. 1995;82:278–283.
122. Drummond JC, McKay LD, Cole DJ, et al. The role of nitric oxide synthase inhibition in the adverse effects of etomidate in the setting of focal cerebral ischemia in rats. *Anesth Analg*. 2005;100:841–846.
123. Edelman GJ, Hoffman WE, Charbel FT. Cerebral hypoxia after etomidate administration and temporary cerebral artery occlusion. *Anesth Analg*. 1997;85:821–825.
124. Schlunzen L, Juul N, Hansen KV, et al. Regional cerebral blood flow and glucose metabolism during propofol anaesthesia in healthy subjects studied with positron emission tomography. *Acta Anaesthesiol Scand*. 2012;56:248–255.
125. Fiset P, Paus T, Daloze T, et al. Brain mechanisms of propofol-induced loss of consciousness in humans: A positron emission tomographic study. *J Neurosci*. 1999;19:5506–5513.
126. Xie G, Deschamps A, Backman SB, et al. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: A positron emission tomography study. *Br J Anaesth*. 2011;106:548–557.
127. McCulloch TJ, Thompson CL, Turner MJ. A randomized crossover comparison of the effects of propofol and sevoflurane on cerebral hemodynamics during carotid endarterectomy. *Anesthesiology*. 2007;106:56–64.
128. Kikuta K, Takagi Y, Nozaki K, et al. Effects of intravenous anesthesia with propofol on regional cortical blood flow and intracranial pressure in surgery for moyamoya disease. *Surg Neurol*. 2007;68:421–424.
129. Alkire MT, Haier RJ, Barker SJ, et al. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. *Anesthesiology*. 1995;82:393–403.
130. Jansen GF, van Praagh BH, Kedaria MB, et al. Jugular bulb oxygen saturation during propofol and isoflurane/nitrous oxide anesthesia in patients undergoing brain tumor surgery. *Anesth Analg*. 1999;89:358–363.
131. Kochs E, Hoffman WE, Werner C, et al. The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage following incomplete ischemia in rats. *Anesthesiology*. 1992;76:245–252.
132. Cervantes M, Ruelas R, Chavez-Carrillo I, et al. Effects of propofol on alterations of multineuronal activity of limbic and mesencephalic structures and neurological deficit elicited by acute global cerebral ischemia. *Arch Med Res*. 1995;26:385–395.
133. Ridenour TR, Warner DS, Todd MM, et al. Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. *Anesthesiology*. 1992;76:807–812.
134. Pittman JE, Sheng H, Pearlstein R, et al. Comparison of the effects of propofol and pentobarbital on neurologic outcome and cerebral infarct size after temporary focal ischemia in the rat. *Anesthesiology*. 1997;87:1139–1144.
135. Adembri C, Venturi L, Pellegrini-Giampietro DE. Neuroprotective effects of propofol in acute cerebral injury. *CNS Drug Rev*. 2007;13:333–351.
136. Zhu SM, Xiong XX, Zheng YY, et al. Propofol inhibits aquaporin 4 expression through a protein kinase c-dependent pathway in an astrocyte model of cerebral ischemia/reoxygenation. *Anesth Analg*. 2009;109:1493–1499.
137. Cui D, Wang L, Qi A, et al. Propofol prevents autophagic cell death following oxygen and glucose deprivation in PC12 cells and cerebral ischemia-reperfusion injury in rats. *PLoS One*. 2012;7:e35324.
138. Bayona NA, Gelb AW, Jiang Z, et al. Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. *Anesthesiology*. 2004;100:1151–1159.
139. Cattano D, Young C, Straiko MM, et al. Subanesthetic doses of propofol induce neuroapoptosis in the infant mouse brain. *Anesth Analg*. 2008;106:1712–1714.
140. Thal SC, Timaru-Kast R, Wilde F, et al. Propofol impairs neurogenesis and neurologic recovery and increases mortality rate in adult rats after traumatic brain injury. *Crit Care Med*. 2014;42:129–141.
141. Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. *BMJ*. 1992;305:613–616.
142. Strickland RA, Murray MJ. Fatal metabolic acidosis in a pediatric patient receiving an infusion of propofol in the intensive care unit: Is there a relationship? *Crit Care Med*. 1995;23:405–409.
143. Takeshita H, Okuda Y, Sari A. The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology*. 1972;36:69–75.
144. Langsjo JW, Kaisti KK, Aalto S, et al. Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology*. 2003;99:614–623.
145. Langsjo JW, Salmi E, Kaisti KK, et al. Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. *Anesthesiology*. 2004;100:1065–1071.
146. Langsjo JW, Maksimow A, Salmi E, et al. S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology*. 2005;103:258–268.
147. Albanese J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology*. 1997;87:1328–1334.

148. Mayberg TS, Lam AM, Matta BF, et al. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. *Anesth Analg*. 1995;81:84–89.
149. Belopavlovic M, Buchthal A. Modification of ketamine-induced intracranial hypertension in neurosurgical patients by pretreatment with midazolam. *Acta Anaesthesiol Scand*. 1982;26:458–462.
150. Shapira Y, Lam AM, Eng CC, et al. Therapeutic time window and dose response of the beneficial effects of ketamine in experimental head injury. *Stroke*. 1994;25:1637–1643.
151. Ridenour TR, Warner DS, Todd MM, et al. Effects of ketamine on outcome from temporary middle cerebral artery occlusion in the spontaneously hypertensive rat. *Brain Res*. 1991;565:116–122.
152. Ward JL, Harting MT, Cox Jr CS, et al. Effects of ketamine on endotoxin and traumatic brain injury induced cytokine production in the rat. *J Trauma*. 2011;70:1471–1479.
153. Himmelseher S, Durieux ME. Revising a dogma: Ketamine for patients with neurological injury? *Anesth Analg*. 2005;101:524–534.
154. Soriano SG, Liu Q, Li J, et al. Ketamine activates cell cycle signaling and apoptosis in the neonatal rat brain. *Anesthesiology*. 2010;112:1155–1163.
155. Kolenda H, Gremmelt A, Rading S, et al. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. *Acta Neurochir (Wien)*. 1996;138:1193–1199.
156. Bourgoin A, Albanese J, Wereszczynski N, et al. Safety of sedation with ketamine in severe head injury patients: Comparison with sufentanil. *Crit Care Med*. 2003;31:711–717.
157. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47:351–354.
158. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: Potential therapeutic targets. *Science*. 2012;338:68–72.
159. Tateishi A, Maekawa T, Takeshita H, et al. Diazepam and intracranial pressure. *Anesthesiology*. 1981;54:335–337.
160. Veselis RA, Reinsel RA, Beattie BJ, et al. Midazolam changes cerebral blood flow in discrete brain regions: An H2(15)O positron emission tomography study. *Anesthesiology*. 1997;87:1106–1117.
161. Liang P, Manelis A, Liu X, et al. Using arterial spin labeling perfusion mri to explore how midazolam produces anterograde amnesia. *Neurosci Lett*. 2012;522:113–117.
162. Forster A, Juge O, Morel D. Effects of midazolam on cerebral hemodynamics and cerebral vasomotor responsiveness to carbon dioxide. *J Cereb Blood Flow Metab*. 1983;3:246–249.
163. Ogawa Y, Iwasaki K, Aoki K, et al. The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. *Anesth Analg*. 2010;111:1279–1284.
164. Sandiumenge Camps A, Sanchez-Izquierdo Riera JA, Toral Vazquez D, et al. Midazolam and 2% propofol in long-term sedation of traumatized critically ill patients: Efficacy and safety comparison. *Crit Care Med*. 2000;28:3612–3619.
165. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003;23:876–882.
166. Spivey WH. Flumazenil and seizures: Analysis of 43 cases. *Clin Ther*. 1992;14:292–305.
167. Hanel F, Werner C, von Knobelsdorff G, et al. The effects of fentanyl and sufentanil on cerebral hemodynamics. *J Neurosurg Anesthesiol*. 1997;9:223–227.
168. Klimscha W, Ullrich R, Nasel C, et al. High-dose remifentanil does not impair cerebrovascular carbon dioxide reactivity in healthy male volunteers. *Anesthesiology*. 2003;99:834–840.
169. Stephan H, Groger P, Weyland A, et al. The effect of sufentanil on cerebral blood flow, cerebral metabolism and the CO2 reactivity of the cerebral vessels in man. *Anaesthesist*. 1991;40:153–160.
170. Trindle MR, Dodson BA, Rampil IJ. Effects of fentanyl versus sufentanil in equianesthetic doses on middle cerebral artery blood flow velocity. *Anesthesiology*. 1993;78:454–460.
171. Weinstabl C, Mayer N, Spiss CK. Sufentanil decreases cerebral blood flow velocity in patients with elevated intracranial pressure. *Eur J Anaesthesiol*. 1992;9:481–484.
172. Firestone LL, Gyulai F, Mintun M, et al. Human brain activity response to fentanyl imaged by positron emission tomography. *Anesth Analg*. 1996;82:1247–1251.
173. Herrick IA, Gelb AW, Manninen PH, et al. Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. *Anesth Analg*. 1991;72:359–363.
174. Bristow A, Shalev D, Rice B, et al. Low-dose synthetic narcotic infusions for cerebral relaxation during craniotomies. *Anesth Analg*. 1987;66:413–416.
175. Sperry RJ, Bailey PL, Reichman MV, et al. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. *Anesthesiology*. 1992;77:416–420.
176. Albanese J, Durbec O, Viviand X, et al. Sufentanil increases intracranial pressure in patients with head trauma. *Anesthesiology*. 1993;79:493–497.
177. Hocker SE, Fogelson J, Rabinstein AA. Refractory intracranial hypertension due to fentanyl administration following closed head injury. *Front Neurol*. 2013;4:3.
178. Werner C, Kochs E, Bause H, et al. Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. *Anesthesiology*. 1995;83:721–726.
179. de Nadal M, Munar F, Poca MA, et al. Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: Absence of correlation to cerebral autoregulation. *Anesthesiology*. 2000;92:11–19.
180. Mayberg TS, Lam AM, Eng CC, et al. The effect of alfentanil on cerebral blood flow velocity and intracranial pressure during isoflurane-nitrous oxide anesthesia in humans. *Anesthesiology*. 1993;78:288–294.
181. Lorenz IH, Kolbitsch C, Schocke M, et al. Low-dose remifentanil increases regional cerebral blood flow and regional cerebral blood volume, but decreases regional mean transit time and regional cerebrovascular resistance in volunteers. *Br J Anaesth*. 2000;85:199–204.
182. Paris A, Scholz J, von Knobelsdorff G, et al. The effect of remifentanil on cerebral blood flow velocity. *Anesth Analg*. 1998;87:569–573.
183. Warner DS, Hindman BJ, Todd MM, et al. Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg*. 1996;83:348–353.
184. Markovitz BP, Duhaime AC, Sutton L, et al. Effects of alfentanil on intracranial pressure in children undergoing ventriculoperitoneal shunt revision. *Anesthesiology*. 1992;76:71–76.
185. Souter MJ, Andrews PJ, Piper IR, et al. Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury. *Br J Anaesth*. 1997;79:97–102.
186. Wagner KJ, Willoch F, Kochs EF, et al. Dose-dependent regional cerebral blood flow changes during remifentanil infusion in humans: A positron emission tomography study. *Anesthesiology*. 2001;94:732–739.
187. Wagner KJ, Sprenger T, Kochs EF, et al. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: A positron emission tomography activation study using remifentanil. *Anesthesiology*. 2007;106:548–556.
188. Lauer KK, Connolly LA, Schmeling WT. Opioid sedation does not alter intracranial pressure in head injured patients. *Can J Anaesth*. 1997;44:929–933.
189. Lanier WL, Iaizzo PA, Milde JH. Cerebral blood flow and afferent muscle activity following IV succinylcholine in dogs. *Anesthesiol Rev*. 1987;14:60–66.
190. Minton MD, Grosslight K, Stirt JA, et al. Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. *Anesthesiology*. 1986;65:165–169.
191. Lanier WL, Iaizzo PA, Milde JH. Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: The effects of pretreatment with a defasciculating dose of pancuronium. *Anesthesiology*. 1989;71:87–95.
192. Schramm WM, Papousek A, Michalek-Sauberer A, et al. The cerebral and cardiovascular effects of cisatracurium and atracurium in neurosurgical patients. *Anesth Analg*. 1998;86:123–127.
193. Bedford RF, Persing JA, Pobereskin L, et al. Lidocaine or thiopental for rapid control of intracranial hypertension? *Anesth Analg*. 1980;59:435–437.
194. Bacher A, Zornow MH. Lamotrigine inhibits extracellular glutamate accumulation during transient global cerebral ischemia in rabbits. *Anesthesiology*. 1997;86:459–463.
195. Warner DS, Godersky JC, Smith ML. Failure of pre-ischemic lidocaine administration to ameliorate global ischemic brain damage in the rat. *Anesthesiology*. 1988;68:73–78.
196. Lei B, Cottrell JE, Kass IS. Neuroprotective effect of low-dose lidocaine in a rat model of transient focal cerebral ischemia. *Anesthesiology*. 2001;95:445–451.
197. Niiyama S, Tanaka E, Tsuji S, et al. Neuroprotective mechanisms of lidocaine against in vitro ischemic insult of the rat hippocampal CA1 pyramidal neurons. *Neurosci Res*. 2005;53:271–278.
198. Lin TY, Chung CY, Lu CW, et al. Local anesthetics inhibit glutamate release from rat cerebral cortex synaptosomes. *Synapse*. 2013;67:568–579.
199. Lei B, Popp S, Capuano-Waters C, et al. Lidocaine attenuates apoptosis in the ischemic penumbra and reduces infarct size after transient focal cerebral ischemia in rats. *Neuroscience*. 2004;125:691–701.
200. Mitchell SJ, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg*. 1999;67:1117–1124.
201. Mitchell SJ, Merry AF, Frampton C, et al. Cerebral protection by lidocaine during cardiac operations: A follow-up study. *Ann Thorac Surg*. 2009;87:820–825.
202. Mathew JP, Mackensen GB, Phillips-Bute B, et al. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke*. 2009;40:880–887.

203. Prielipp RC, Wall MH, Tobin JR, et al. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. *Anesth Analg*. 2002;95:1052–1059.
204. Zornow MH, Maze M, Dyck JB, et al. Dexmedetomidine decreases cerebral blood flow velocity in humans. *J Cereb Blood Flow Metab*. 1993;13:350–353.
205. Zornow MH, Fleischer JE, Scheller MS, et al. Dexmedetomidine, an alpha-2 adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesth Analg*. 1990;70:624–630.
206. Drummond JC, Dao AV, Roth DM, et al. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. *Anesthesiology*. 2008;108:225–232.
207. Drummond JC, Sturaitis MK. Brain tissue oxygenation during dexmedetomidine administration in surgical patients with neurovascular injuries. *J Neurosurg Anesthesiol*. 2010;22:336–341.
208. Bonhomme V, Maquet P, Phillips C, et al. The effect of clonidine infusion on distribution of regional cerebral blood flow in volunteers. *Anesth Analg*. 2008;106:899–909.
209. Ogawa Y, Iwasaki K, Aoki K, et al. Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. *Anesthesiology*. 2008;109:642–650.
210. Lee HW, Caldwell JE, Dodson B, et al. The effect of clonidine on cerebral blood flow velocity, carbon dioxide cerebral vasoreactivity, and response to increased arterial pressure in human volunteers. *Anesthesiology*. 1997;87:553–558.
211. Kadoi Y, Saito S, Kawauchi C, et al. Comparative effects of propofol vs dexmedetomidine on cerebrovascular carbon dioxide reactivity in patients with septic shock. *Br J Anaesth*. 2008;100:224–229.
212. Ishiyama T, Dohi S, Iida H. The vascular effects of topical and intravenous alpha2-adrenoceptor agonist clonidine on canine pial microcirculation. *Anesth Analg*. 1998;86:766–772.
213. McPherson RW, Kirsch JR, Traystman RJ. Inhibition of nitric oxide synthase does not affect alpha 2-adrenergic-mediated cerebral vasoconstriction. *Anesth Analg*. 1994;78:67–72.
214. Talke P, Tong C, Lee HW, et al. Effect of dexmedetomidine on lumbar cerebrospinal fluid pressure in humans. *Anesth Analg*. 1997;85: 358–364.
215. ter Minassian A, Beydon L, Decq P, et al. Changes in cerebral hemodynamics after a single dose of clonidine in severely head-injured patients. *Anesth Analg*. 1997;84:127–132.
216. Ma D, Hossain M, Rajakumaraswamy N, et al. Dexmedetomidine produces its neuroprotective effect via the alpha 2a-adrenoceptor subtype. *Eur J Pharmacol*. 2004;502:87–97.
217. Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. *Anesthesiology*. 2009;110:1077–1085.
218. Duan X, Li Y, Zhou C, et al. Dexmedetomidine provides neuroprotection: Impact on ketamine-induced neuroapoptosis in the developing rat brain. *Acta Anaesthesiol Scand*. 2014;58:1121–1126.
219. Strebel S, Lam AM, Matta B, et al. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology*. 1995;83:66–76.
220. Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *Br J Anaesth*. 1997;79:469–472.
221. Summors AC, Gupta AK, Matta BF. Dynamic cerebral autoregulation during sevoflurane anesthesia: A comparison with isoflurane. *Anesth Analg*. 1999;88:341–345.
222. Jobes DR, Kennell E, Bitner R, et al. Effects of morphine-nitrous oxide anesthesia on cerebral autoregulation. *Anesthesiology*. 1975;42:30–34.
223. Schmidt M, Marx T, Papp-Jambor C, et al. Effect of xenon on cerebral autoregulation in pigs. *Anaesthesia*. 2002;57:960–966.
224. Girling KJ, Cavill G, Mahajan RP. The effects of nitrous oxide and oxygen on transient hyperemic response in human volunteers. *Anesth Analg*. 1999;89:175–180.
225. Engberg M, Oberg B, Christensen KS, et al. The cerebral arterio-venous oxygen content differences (AVDO2) during halothane and neurolept anaesthesia in patients subjected to craniotomy. *Acta Anaesthesiol Scand*. 1989;33:642–646.
226. Grune F, Kazmaier S, Sonntag H, et al. Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux. *Anesthesiology*. 2014;120:335–342.
227. Matta BF, Lam AM, Mayberg TS, et al. Cerebrovascular response to carbon dioxide during sodium nitroprusside- and isoflurane-induced hypotension. *Br J Anaesth*. 1995;74:296–300.
228. McPherson RW, Briar JE, Traystman RJ. Cerebrovascular responsiveness to carbon dioxide in dogs with 1.4% and 2.8% isoflurane. *Anesthesiology*. 1989;70:843–850.
229. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg*. 1991;75:731–739.
230. Kawata R, Nakakimura K, Matsumoto M, et al. Cerebrovascular CO2 reactivity during anesthesia in patients with diabetes mellitus and peripheral vascular disease. *Anesthesiology*. 1998;89:887–893.
231. Todd M, Hindman B, Clarke W, et al. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
232. Iadecola C, Nakai M, Arbit E, et al. Global cerebral vasodilatation elicited by focal electrical stimulation within the dorsal medullary reticular formation in anesthetized rat. *J Cereb Blood Flow Metab*. 1983;3:270–279.
233. Nakakimura K, Sakabe T, Takeshita H. Modulation of cerebrospinal metabolic responses to peripheral stimulation by enflurane anesthesia in rats. *J Neurosurg Anesthesiol*. 1989;1:333–338.
234. Sakabe T, Maekawa T, Fujii S, et al. Cerebral circulation and metabolism during enflurane anesthesia in humans. *Anesthesiology*. 1983;59:532–536.
235. von Knobelsdorff G, Kusagaya H, Werner C, et al. The effects of surgical stimulation on intracranial hemodynamics. *J Neurosurg Anesthesiol*. 1996;8:9–14.
236. Kawata R, Matsumoto M, Haranishi Y, et al. Changes in cerebral blood flow velocity elicited by surgical stimulation are dependent on the $PaCO_2$ level. *Can J Anaesth*. 2001;48:1029–1033.
237. Bisonnette B, Leon JE. Cerebrovascular stability during isoflurane anaesthesia in children. *Can J Anaesth*. 1992;39:128–134.

Modern Neuroradiology Relevant to Anesthetic and Perioperative Management

5

T. Rizvi • M. Wintermark

INTRODUCTION

Imaging, with its diverse array of modalities, forms an integral part of decision making in patients with neurological disorders. Diagnostic, prognostic, and pathophysiological information is provided in broadly two forms, anatomical (structural) and functional (physiologic). Anatomic or structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provides information about normal anatomic structures of skull, meninges, brain parenchyma, vascular supply, cerebrospinal (CSF) spaces, spine, spinal cord, and spinal nerves. Information about altered anatomy is obtained in the form of intracranial hemorrhage, infarcts, fractures, tumors, aneurysms, and vascular malformations. Functional or physiologic imaging techniques like perfusion-CT, diffusion-weighted MR imaging (DWI), diffusion tensor imaging (DTI), perfusion-weighted MR imaging (PWI), and MR spectroscopy (MRS) aid in better characterizing the lesion and its effects by providing molecular, physiological, and metabolic information. This chapter will provide an overview of the imaging modalities that are used in the evaluation of central nervous system (CNS) lesions. Then, we discuss representative neurological disorders and the role of recent technological advancements in their evaluation.

IMAGING MODALITIES

Structural Imaging Modalities

Plain Radiographs

Though plain radiographs were used for a lot of neurodiagnostic work, especially trauma patients, the advent of multiplanar imaging techniques, mainly CT and MRI, has relegated that role to the confines of history. Skull or spine radiographs can detect fractures; however, sensitivity is less than that of CT and intracranial and intraspinal injury cannot be as accurately evaluated by plain radiographs.[1–3] Besides trauma, one practical use for skull radiographs which is still used in present settings is to exclude metallic foreign body in orbits prior to MRI.[4]

Computed Tomography

It is not wrong to say that CT is the workhorse of a modern neurodiagnostic imaging facility, especially in emergent settings. Its widespread availability and short scan time make it the preferred imaging modality for initial evaluation of many intracranial lesions. The short scan time makes it especially useful in the settings of stroke and trauma in agitated, unstable patients who can benefit tremendously from the early detection of and neurosurgical intervention in incidences such as intracranial hemorrhage, hydrocephalus, and impending herniation. The early detection prompts early surgical intervention, which has been documented as improving patient outcomes.[5] This has resulted in the increased utilization of CT scans in emergency departments over the last decade.[6] Another advantage is volumetric data acquisition, which helps in better evaluation of intracranial and spinal structures in three dimensions. The principal disadvantage of CT is the ionizing radiation exposure, which has prompted, among other things, a campaign among clinicians and radiologists, the "Image Gently" campaign, to popularize a means of reducing the radiation dose in pediatric settings.[7] One of the other disadvantages of CT is its inability to assess lesions in areas such as the posterior fossa and the floor of the middle cranial fossa due to "beam hardening" artifacts resulting from the attenuation of the X-ray beam behind relatively dense structures such as the clivus and temporal bone. Contrast agents commonly used in CT are iodine-based, the majority now being nonionic, resulting in lesions being more conspicuous due to breakdown of the blood–brain barrier.

Magnetic Resonance Imaging

MRI is increasingly being used for the delineation of details of the anatomy and also of complex lesions of the central nervous system. It uses the signals emitted by the relaxation of ubiquitous hydrogen nuclei present in water after they have been excited by radiofrequency pulses in a strong magnetic field. By varying the different pulse sequences in obtaining images, the soft tissue contrast of visualized anatomical structures can be varied. On T1-weighted images, fat appears bright and water and cerebrospinal fluid (CSF) appear black. On T2-weighted images, fat has intermediate signal appearing gray, while water and CSF appear bright. Cortical bone, composed of relatively fixed protons, does not produce a signal. Flowing blood produces no signal resulting in a so-called "signal void." In general, pathologic processes usually contain excess amounts of free water and therefore are dark on T1-weighted images and bright on T2-weighted images. Hence, the rule of thumb is that anatomy is better seen on T1-weighted and pathology better on T2-weighted sequences. Contrast agents in the majority of cases are paramagnetic (eg, gadolinium-DTPA) and result in vessels and pathologic lesions being more conspicuous due to an increased T1 signal.[8] This is the reason that post-contrast sequences are T1-weighted.

Different pulse sequences can be used for different types of CNS lesions. One of the commonest sequences to be used in all brain MRIs is the DWI sequence, which is particularly helpful in detecting early ischemia. This we shall discuss further in the functional neuroimaging section. Fluid-attenuated inversion recovery (FLAIR) sequence increases the conspicuity of focal hyperintense T2 signal in pathologic lesions by eliminating (or "nulling") the hyperintense CSF signal. Thus, focal bright gray matter abnormalities in contusions or white matter abnormalities in diffuse axonal injuries (DAI)[9] or multiple sclerosis[10] are more easily appreciated against the adjacent "nulled" dark CSF spaces. FLAIR also has increased sensitivity for the presence of acute or subacute subarachnoid hemorrhage (SAH), which appears as a hyperintense signal

within the sulci and cisterns.[11] The gradient-echo (GRE) T2*-weighted MR sequence shows increased sensitivity for detection of intracranial blood.[12] However, susceptibility-weighted imaging (SWI) has now proven to be more sensitive and better in detecting hemorrhage and calcification.[13]

Magnetic resonance safety protocols and extensive pre-procedural screening are needed for the safety of the patients with the increasing use of biomedical implants and devices.[14] Cardiac pacemakers, intraocular metallic fragments, mechanical device implants such as cochlear implants, drug infusion pump, neurostimulators for deep brain stimulation, and ferromagnetic aneurysm clips are considered a contraindication to MR imaging.[15] Nonferromagnetic or weakly ferromagnetic aneurysm clips such as those of titanium alloy or pure titanium have been shown to be MR compatible and safe. Similar ferromagnetic objects may pose a risk of adverse effects including magnetically induced movements resulting in dislodgement and injury to organs, current, and heating.[15] Of secondary concern is the fact that the ferromagnetic materials can produce image artifacts, thereby degrading the image quality.

Conventional Cerebral Angiography

In conventional angiography, a flexible catheter is introduced through the right femoral artery to visualize the intracranial arteries. Other less commonly used sites for access include left femoral artery, axillary, and brachial artery. Mild intravenous sedation improves patient comfort and cooperation, and reduces anxiety. The clinical question and disease process generally determines which vessels need to be examined. Routinely a four-vessel angiogram is performed, in which bilateral internal carotid and vertebral arteries are investigated. In a six-vessel angiogram, both external carotid arteries are also studied. The cerebral vasculature is visualized by injecting an iodinated contrast agent into these arteries and subsequently performing digital subtraction angiography (DSA), in which bony details are subtracted from a "mask" image, thus leaving us with images of different vessels.[16] Serial fluoroscopic spot images are obtained throughout the procedure and standard angiographic views of the vessel of interest, including antero-posterior, lateral, and, if needed, oblique, are obtained. This principle can be extended for application in endovascular surgery, where cerebral angiographic techniques can not only be of diagnostic value, but also provide a route for endovascular therapy in entities such as cerebral aneurysms, arteriovenous malformation, and tumor embolization.[17]

Cerebral angiography is considered to be the gold standard for the evaluation of cerebrovascular diseases. But it is an invasive procedure with the associated procedural risk of neurological complications—0.3–1.3%, of which 0.07–0.5% are permanent complications.[18,19] The majority of these complications are minor and transient including groin hematomas, femoral artery injury, and minor allergic reactions. However, more severe complications occasionally occur, such as cerebral infarction, seizure, and death. Spinal angiography poses the same risks as cerebral angiography, with the added danger of cord infarction secondary to spinal artery embolus. For this reason, spinal angiography should only be performed when a vascular malformation is demonstrated by another imaging modality or when the patient has SAH with normal cerebral angiography and a spinal source is strongly suspected. With improvements in the detection rates of cerebrovascular disease with newer, relatively noninvasive modalities such as CT angiography (CTA) or MR angiography (MRA), conventional catheter-based DSA has been replaced by CTA or MRA in some centers as the screening and diagnostic tool for intracranial vascular disease.

Magnetic Resonance Angiography and Computed Tomography Angiography

MRA is noninvasive and offers the opportunity to accurately depict the intracranial vasculature from different angles using a variety of methods for obtaining angiographic data. Three different MRA techniques are routinely available: time-of-flight MRA (TOF MRA), phase-contrast MRA (PC MRA), and contrast-enhanced MRA (CE MRA). The simplest and most widely used approach, TOF MRA, relies on in-flow enhancement. Essentially, static tissue within a two- or three-dimensional slice gives a low signal due to the saturating effect of the long train of closely spaced excitation pulses used in forming the image. On flowing into the imaging volume, unsaturated blood appears hyperintense relative to the static surround.[20,21] Three-dimensional TOF MRA is recommended for arterial evaluation, and a two-dimensional TOF MRA technique for venous evaluation. The disadvantages of MRA include limited visualization of very small distal cortical or deep branches, and a dependence on flow or the patient's cooperation.[21] To better visualize the veins and small arterial branches, intravenous contrast enhanced MRA can be used, but with the disadvantages of increased cost, and superimposition of veins and of enhanced soft tissues.

Advances in multidetector row CT (MDCT) have facilitated the quick and accurate examination of the cerebral vasculature. CTA is widely available, with fast, thin-section, volumetric spiral CT images acquired during the injection of a time-optimized bolus of contrast material for vessel opacification.[22] With modern multisection CT scanners, the entire region from the aortic arch up to the circle of Willis can be covered in a single data acquisition, with excellent, three-dimensional spatial resolution. Multiplanar reformatted images, maximum intensity projection images (MIP), and three-dimensional reconstructions of axial CTA source images combine to provide images comparable, or even superior, to those obtained with conventional angiography (Fig. 5.1).

Myelography and Computed Tomography Myelography

Myelography involves the injection of iodinated, water-soluble contrast material into the spinal subarachnoid space via a lumbar or, very rarely, a lateral C1–C2 puncture. Plain radiographs are obtained in multiple projections while the contrast is moved cranially or caudally to evaluate multiple levels. Better contrast agents and smaller-gauge spinal needles now permit myelography to be performed on an outpatient basis. After the study, the contrast agent is left in the subarachnoid space, from which it is absorbed and excreted in the urine. Myelography is typically followed by immediate or delayed CT examination (CT myelography). Nonionic contrast agents have dramatically reduced the side effects and complications associated with myelography.[23] The most common post-procedural complication is mild-to-severe headache with nausea and/or vomiting. Because contrast material lowers the seizure threshold, patients with a history of seizures should be studied cautiously and patients on medications known to lower the seizure threshold (eg, tricyclic antidepressants) are commonly instructed to stop taking the drug 3 days before the myelography, to allow adequate drug clearance.

A CT myelogram has all the features of routine CT, including better spatial resolution with the added benefit of radio-opaque contrast material outlining the spinal cord and nerve roots. Pathologic lesions appear as abnormal filling defects within the contrast column, and any cord enlargement or deviation from anatomic position is easily appreciated (Fig. 5.2). Now, MRI has become the imaging spine modality

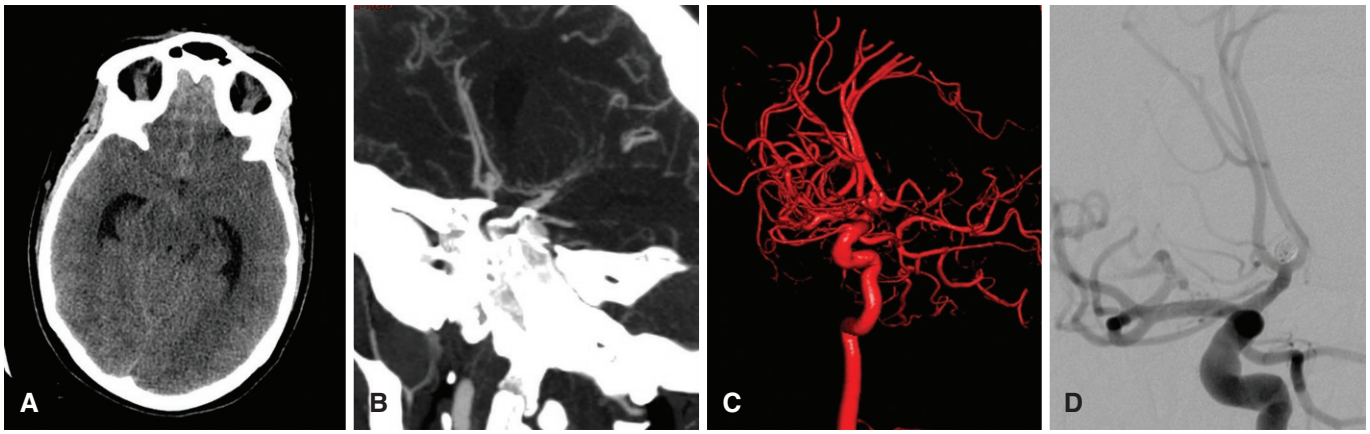


Fig. 5.1 A 26-year-old female who presented with sudden-onset severe headache. **A,** Noncontrast computed tomogtaphy (CT) of head shows diffuse subarachnoid hemorrhage, mainly in the anterior interhemispheric fissure with moderate hydrocephalus. **B,** Maximum intensity projection images reconstructed CT angiogram shows a lobulated anterior communicating artery aneurysm at right A1/A2 junction. **C,** Conventional catheter three-dimensional angiogram shows ruptured anterior communicating artery aneurysm, which was coiled successfully by two coils **(D)** in the same sitting.

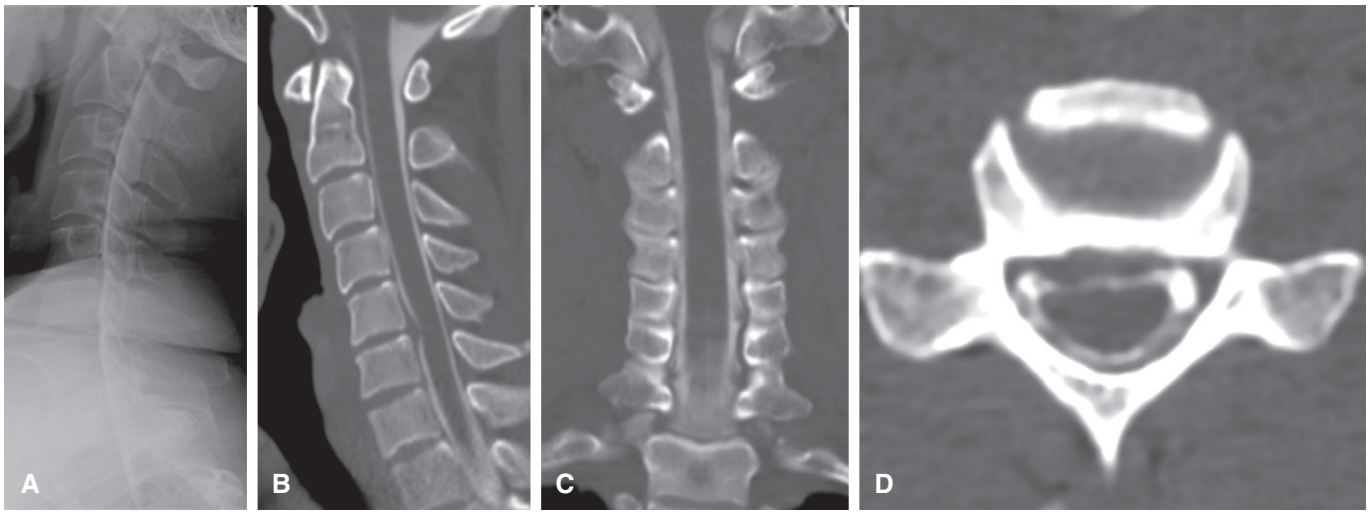


Fig. 5.2 A 38-year-old male shows a right paracentral broad-based disc at C5–6 level causing moderate canal and right neural foraminal stenosis on conventional cervical myelogram lateral view **(A)**, computed tomography myelogram, sagittal **(B)**, coronal **(C)** and axial **(D)** reconstructed images.

of choice, superseding both myelography and CT myelography, for the evaluation of spine pathology. The capability for multiplanar imaging, the use of nonionizing radiation, and the ability to obtain a myelographic-like image without an intrathecal contrast injection all provide distinct advantages. But still, myelography is preferred by some surgeons and is better in many circumstances, including postsurgical cases where MR quality is severely degraded due to artifacts from hardware.

Functional Imaging Modalities

Functional or physiologic imaging provides complementary information to structural imaging and thus facilitates a better characterization of CNS pathology. Imaging of cerebral function can potentially define the early pathophysiological processes responsible for neuronal injury, assess the efficacy of therapeutic interventions, and direct the design and implementation of future therapeutic interventions aimed at reversing or preventing neuronal injury.

Perfusion Computed Tomography

Based on the multicompartmental tracer kinetic model, dynamic perfusion CT imaging is performed by monitoring the first pass of an iodinated contrast agent bolus through the cerebral circulation (Fig. 5.3). As the change in CT enhancement (in Hounsfield units, HU) is proportional to the concentration of contrast, perfusion parameters are calculated by deconvolution from the changes in the density–time curve for each pixel using mathematical algorithms based around the central volume principle:[24,25]

1. Mean transit time (MTT) indicates the time difference between the arterial inflow and venous outflow.
2. Time to bolus peak (TTP) indicates the time from the beginning of contrast material injection to the maximum (peak) concentration of contrast material within a region of interest.
3. Cerebral blood volume (CBV) indicates the volume of blood per unit of brain mass (normal range in gray matter, 4–6 mL/100 g).
4. Cerebral blood flow (CBF) indicates the volume of blood flow per unit of brain mass per minute (normal range in gray matter, 50–60 mL/100 g/min). The relationship between CBF and CBV is expressed by the equation CBF = CBV/MTT.

The main advantage of perfusion-CT is its wide availability and quantitative accuracy.[26] Its main limitation is its inability

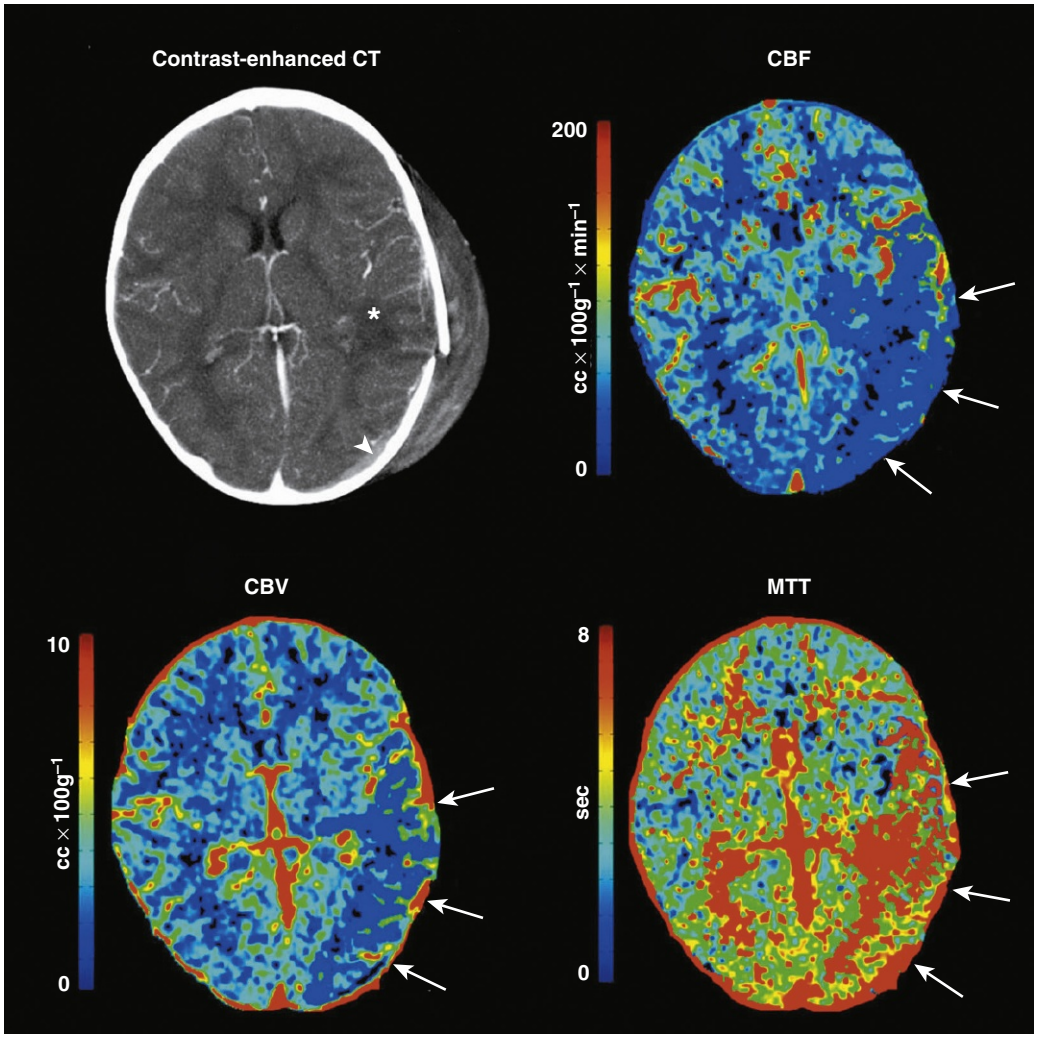


Fig. 5.3 A patient who has fallen from a 6-m height, admitted with a Glasgow Coma Scale score of 9. Neurological examination in the emergency room revealed an asymmetry of tone and deep tendon reflex involving both right upper and lower limbs. Admission contrast-enhanced cerebral computed tomography (CT) demonstrated a displaced left parietal skull fracture, associated with a large cephalhematoma. A small left parieto-occipital epidural hematoma (white arrowhead) and a small contusion area (white star) could also be identified on the conventional CT images. Perfusion-CT (PCT) demonstrated a much wider area of brain perfusion compromise (white arrows), with involvement of the whole left temporal and parietal lobes, the latter showing increased mean transit time (MTT) and decreased cerebral blood flow (CBF) and volume (CBV). Thus, PCT afforded a better understanding of the neurological examination findings on admission than conventional CT.

to image the whole brain, as it is limited to a 2–3 cm section of brain tissue per bolus. Now with the availability of 320-slice volumetric multimodal CT, it is possible to visualize dynamic changes in the blood flow of the entire brain.[27]

Diffusion-weighted Magnetic Resonance Imaging and Diffusion Tensor Imaging

DWI is based on the measurement of the random (Brownian) motion of water molecules and detects the degree of mobility (or diffusibility) of water molecules within tissues. By introducing spatial magnetic field gradients, it is possible to obtain MR sequences that are sensitive to the diffusivity of water along a chosen direction, obtaining so-called DWI. From the ratio of DWI images acquired at different levels of diffusion sensitization (known as b-value), it is possible to compute a quantitative measure of mean diffusivity, known as the apparent diffusion coefficient (ADC). The ADC measures water diffusion and, therefore, often mirrors changes in the DWI signal. In areas of increased diffusion like vasogenic edema, DWI signal intensity is low, and there is an increase in ADC. In regions of restricted diffusion like cytotoxic edema, DWI signal intensity is increased, and the ADC signal decreases.

This technique is widely used in acute ischemic stroke in which reduced diffusion resulting in increased DWI signal and reduced ADC is seen before the onset of visible abnormalities on conventional MR imaging.[28,29] In the affected region, there is a temporal evolution from restricted diffusion (ie, cytotoxic edema in the acute stroke setting) to unrestricted diffusion (ie, vasogenic edema and encephalomalacia in the chronic setting). DWI is also used to study other CNS processes such as cerebral and spinal abscesses, epidermoid cysts, traumatic brain injury (TBI),[30,31] and studying brain maturation and development, especially the myelination process.

Water diffusion properties also play a role in DTI—a related imaging technique. Whereas gray matter is microstructurally compact with no directional preference, white matter bundles are arranged in a highly directional manner. For this reason, while water usually diffuses in all directions (meaning diffusion is isotropic) in the brain, water diffuses preferentially along white matter tracts rather than across them (meaning diffusion in white matter is anisotropic). A mathematical algorithm known as diffusion tensor is commonly used to model anisotropic diffusion in white matter. Fractional anisotropy (FA) maps can be created—FA index varies between 0 (representing a symmetrical anisotropic medium where there is

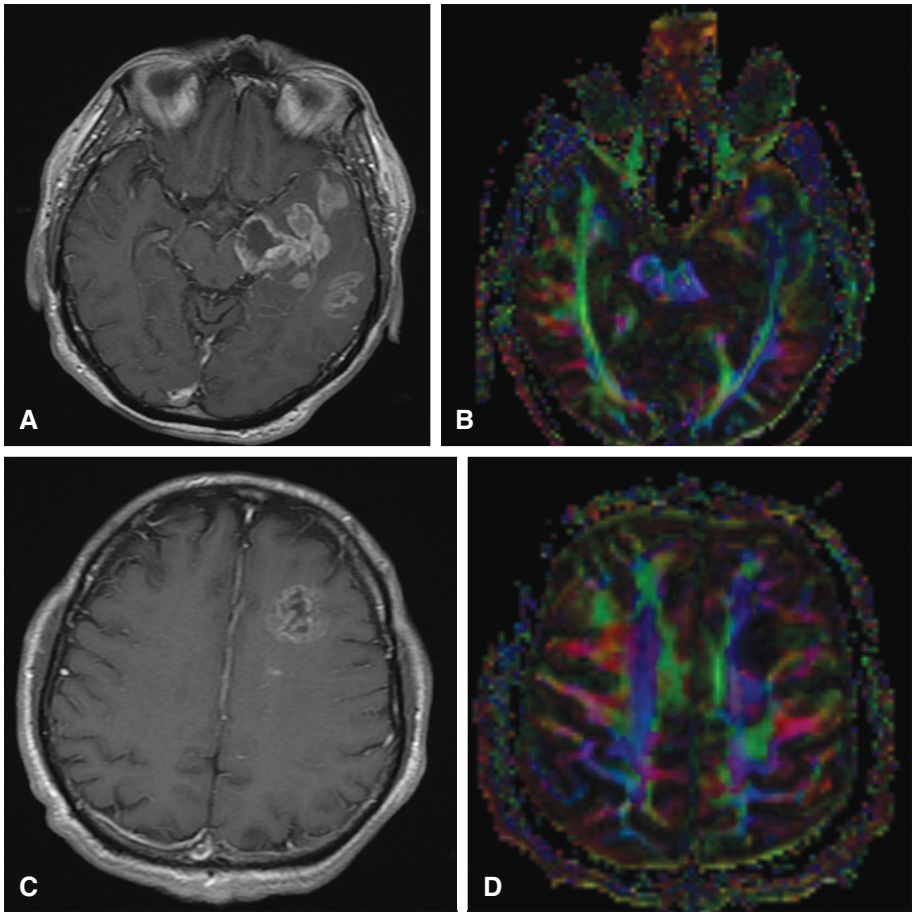


Fig. 5.4 A 66-year-old female with multiple peripherally enhancing centrally necrotic lesions involving left frontal lobe, basal ganglia, temporal lobe, and left cerebral peduncle, which was proven to be glioblastoma multiforme, WHO grade IV. On diffusion tensor imaging (DTI), there is noted displacement of left frontal corona radiata fibers and corticospinal tract in left cerebral peduncle. The colors have standard directional encoding: red is left-right, blue is superior-inferior and green is antero-posterior.

no directionality of the diffusion, for instance in water) and 1 (representing maximum anisotropy). Also, directionally encoded color maps and three-dimensional tractography can be performed to visually display white matter tracts (Fig. 5.4).

Perfusion-weighted Magnetic Resonance Imaging

While DWI is most useful for detecting irreversibly infarcted tissue, PWI may be used to identify areas of reversible ischemia as well. PWI techniques rely either on an exogenous method of achieving perfusion contrast (ie, the administration of an MR contrast agent typically gadopentate dimeglumine [Gd-DTPA, Magnevist®]) or on an endogenous method, which uses an endogenous diffusible tracer to measure CBF by applying magnetic resonance pulses to tag in-flowing water protons.[32,33] PWI is most commonly applied as bolus tracking following the intravenous administration of a bolus of gadolinium contrast. The passage of the contrast agent through the brain capillaries causes a transient loss of signal because of the susceptibility (T2*) effects of the contrast agent. A hemodynamic time-signal intensity curve is produced with subsequent calculation of MTT, TTP, CBF, and CBV perfusion maps using the same principles as those underlying perfusion CT imaging (Fig. 5.5).[24,34] PWI can also be performed using T1-weighted imaging, also following an injection of gadolinium contrast. This technique requires a longer acquisition, but can measure the permeability of the blood–brain barrier.

Brain perfusion can also be assessed using another MRI technique called arterial spin labeling (ASL) (Fig. 5.6). This method does not use an exogenous contrast agent, but rather uses an endogenous diffusible tracer to measure perfusion parameters by applying MR pulses to magnetically labeled in-flowing water protons. With increasing computer processing speeds and the speed of processing involved, this method is being increasingly used in clinical settings[35] moving slowly away from the domain of being a purely research tool. This method is especially useful in patients who cannot be administered with contrast due to renal failure.

Magnetic Resonance Spectroscopy

MRS allows noninvasive, in vivo assessment of brain metabolism. The physical basis of MRS is the chemical shift effect. It actually means that nuclei located in different molecular environments sense slightly different magnitudes of magnetic field, causing them to process at different rates. MRS provides plots or spectra of signal intensity, which is proportional to concentration, versus precession rate shift with respect to a reference, expressed in parts per million (ppm). Various biologically relevant metabolites can be identified based on subtly different resonant frequencies, which are a reflection of their specific chemical environment. These metabolites reflect aspects of neuronal integrity, energy metabolism, and cell membrane proliferation or degradation. In clinical practice, five major metabolites containing hydrogen nuclei (1H-MRS) are typically evaluated (Fig. 5.7):[36,37]

1. Creatine/phosphocreatine (Cr/PCr), 3.04 ppm: Creatine and phosphocreatine are involved in cellular energy metabolism and ATP production. As creatine and

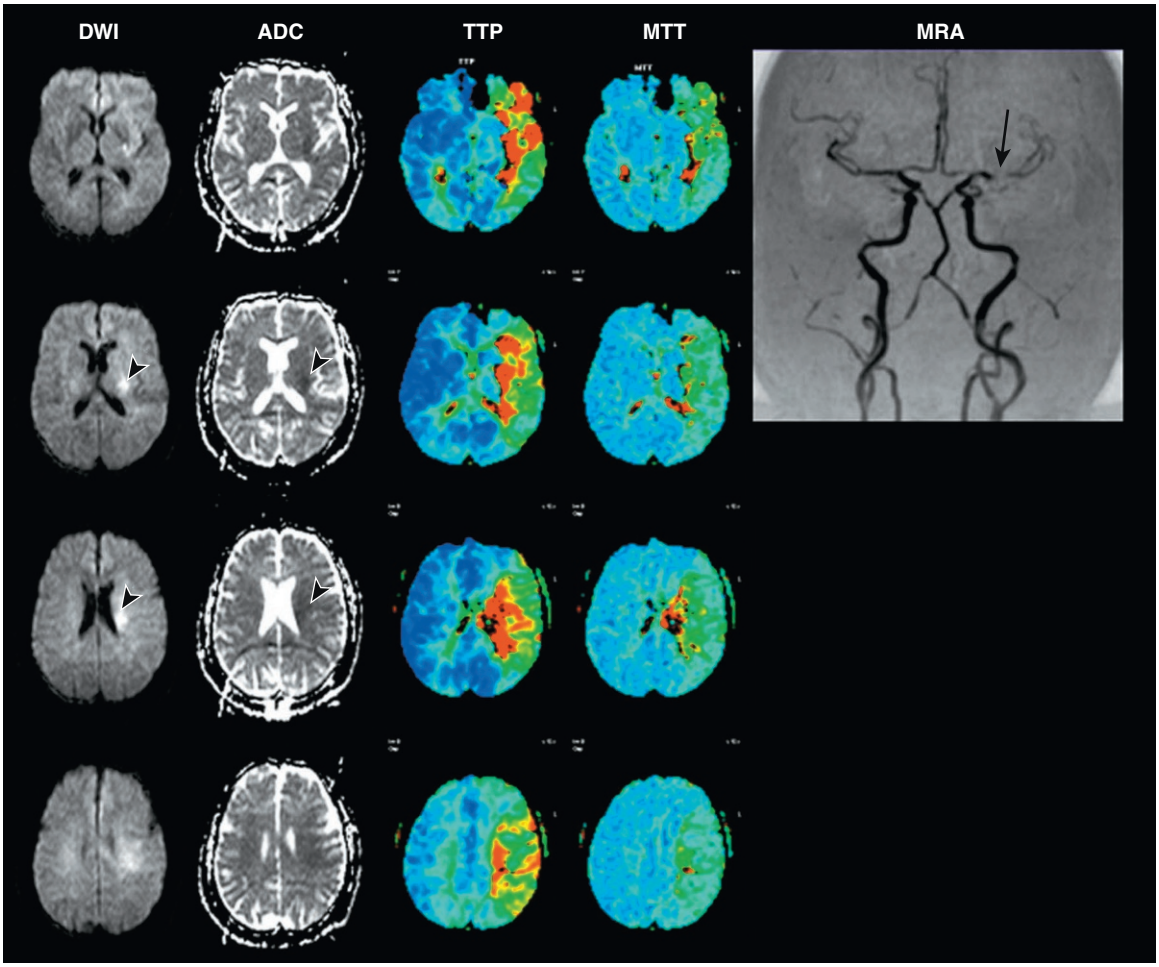


Fig. 5.5 A 64-year-old male patient admitted with aphasia and right-body motor deficit. Admission magnetic resonance angiography shows a proximal stenosis of the left middle cerebral artery (MCA) (arrow). Diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps feature a focus of restricted diffusion in the deep territory of MCA (arrowheads) consistent with acute stroke. Time-to-peak (TTP) and mean transit time (MTT) maps demonstrate an extensive alteration of brain hemodynamics. The DWI–PWI mismatch is classically considered as a hallmark of tissue at risk or penumbra. *(Courtesy Dr. Salvador Pedraza, Girona, Spain.)*

phosphocreatine levels tend to be relatively constant in the normal brain, they are used as a reference metabolite with the concentrations of other metabolites expressed as the ratio of the peak areas compared with the creatine peak.

2. N-acetyl aspartate (NAA), 2.02 ppm: NAA is a cellular amino acid and is a neuronal marker and a measure of neuronal density and integrity.[38] Reduced levels have been reported in a wide spectrum of conditions involving neuronal death or dysfunction, decreased neural metabolism, axonal/dendritic loss, reduced myelination.[38] As most brain tumors are of non-neuronal origin, NAA is absent or greatly reduced, as it is with other insults to the brain such as infarction or demyelination that produce neuronal dysfunction or loss. A decrease in NAA has also been observed after head injury.[39]
3. Choline (Cho), 3.24 ppm: Cho is a composite signal of choline compounds (glycerophosphocholine [GPC], phosphocholine [PC] and a small amount of free choline) and thus reflects total brain choline stores. Cho is a constituent of the phospholipid metabolism of cell membranes and reflects membrane turnover. A Cho increase is characteristic of brain tumors due to accelerated membrane turnover in rapidly dividing cancer cells.
4. Lactate (Lac), 1.33 ppm: Under normal conditions, lactate is barely detectable by MRS in the normal healthy brain. Increased lactate production occurs in disorders of energy metabolism and suggests altered energy metabolism and is consistent with cerebral ischemia.
5. Glutamate and glutamine (Glx), composite peak between 2.1 and 2.5 ppm: Glutamate is an excitatory neurotransmitter that plays a role in mitochondrial metabolism. Gamma-aminobutyric acid is an important product of glutamate. Glutamine plays a role in detoxification and regulation of neurotransmitter activities. Elevated glutamate levels lead to excitotoxic cell damage. Increased glutamine synthesis occurs as a result of increased blood ammonia levels.

Intraoperative Magnetic Resonance Imaging

The use of intraoperative MRI monitoring, a blend of MR imaging performed in an operative suite, is becoming increasingly common for precise navigation and resection of various intracranial and spinal lesions.[40] Hence, understanding the working of intraoperative MRI imaging suite is important for contemporary neuroanesthesiologists.

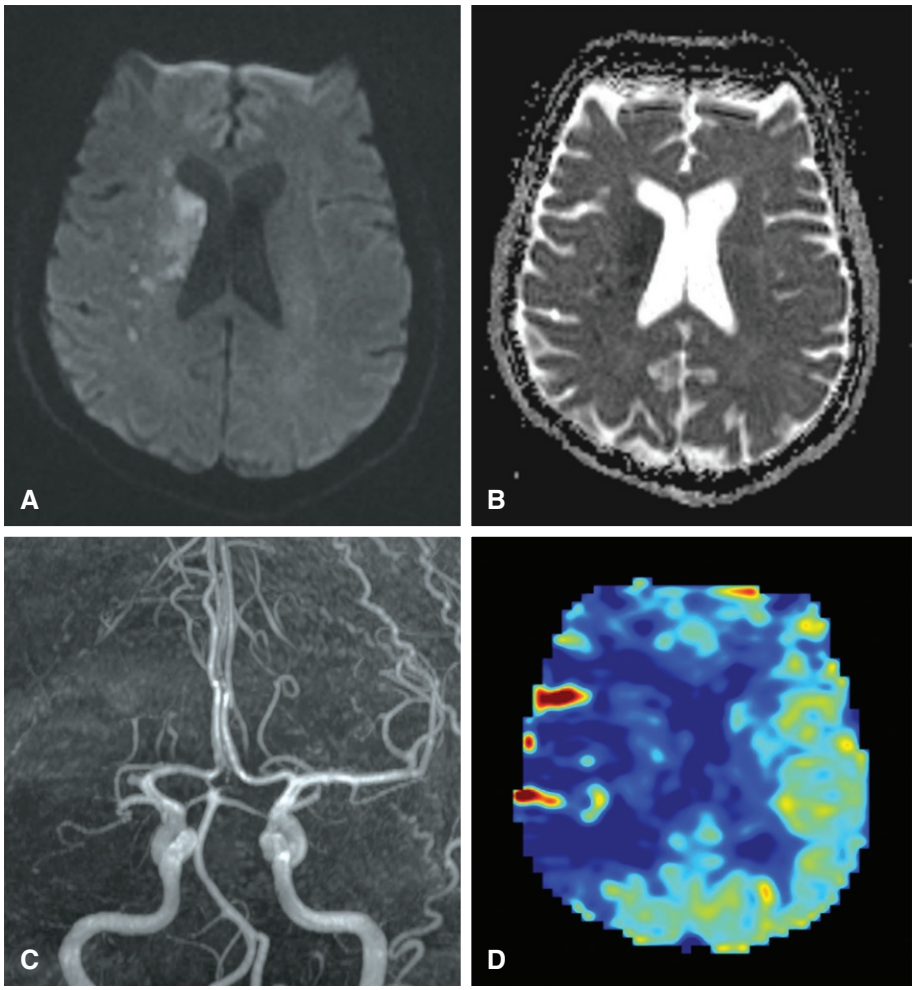


Fig. 5.6 A 57-year-old female who presented with left pronator drift and right gaze preference. She was found to have right middle cerebral artery territory infarct involving right basal ganglia and periventricular white matter on diffusion-weighted imaging (DWI) **(A)** and apparent diffusion coefficient (ADC) **(B)** maps. Time-of-flight magnetic imaging angiogram **(C)** showed abrupt cut-off of right middle cerebral artery in M1 segment. Arterial spin labelling (ASL) map **(D)** showed reduced perfusion in right MCA distribution.

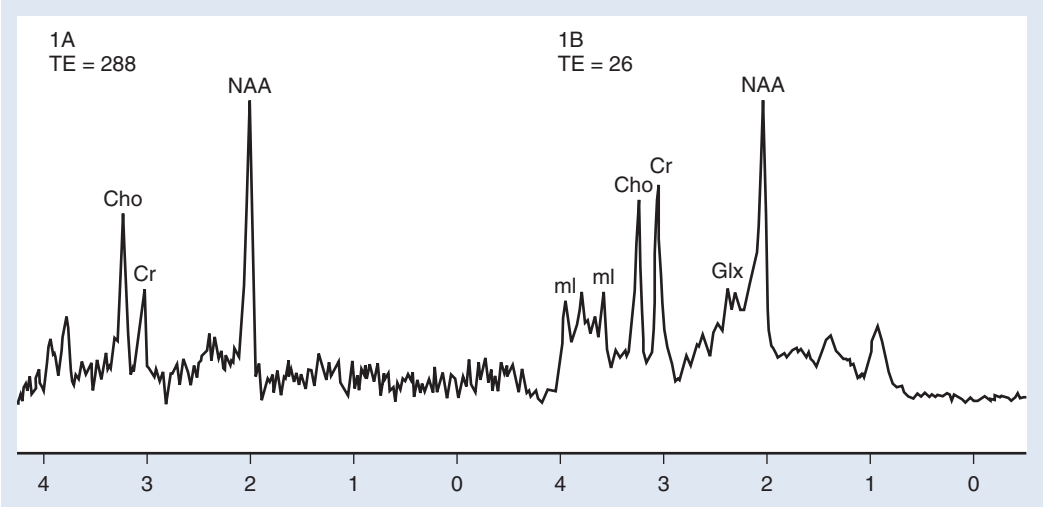


Fig. 5.7 **1A,** Normal long echo (TE = 288 msec) single voxel white matter spectrum demonstrating the N-acetyl aspartate (NAA), creatine (Cr) and choline resonances at 2.02, 3.02 and 3.22 parts per million (ppm), respectively. There is no evidence of lactate or lipid contributions at 0.9–1.3 ppm. **1B,** Normal short echo (TE = 26 msec) single voxel white matter spectrum demonstrating the N-acetyl aspartate (NAA), creatine (Cr) and choline resonances at 2.02, 3.02 and 3.22 parts per million (ppm), respectively. Contributions from glutamine and glutamate (Glx) are seen as a complex set of peaks at 2.2–2.5 ppm. Primary resonant peaks of myo-inositol are present at 3.56 and 4.06 ppm.

In 65–92% of cases in which neurosurgeons thought that they had achieved gross total resection, intraoperative MRI showed tumor that could still be resected.[41] Prior to the development of intraoperative MRI, various stereotactic navigational systems had been used for better localization and precision of resection. The first operating theater with an MRI was built at Brigham and Women's Hospital in 1994,[42] and since then this technology has proliferated and has been adopted by many centers worldwide. The "hostile" MRI environment poses many limitations on patient management. This includes MRI-compatible or MRI-safe equipment,[43] electromagnetic interference on monitoring equipment, and reduced access to the patient, all issues of importance for the anesthesiologist.

Three types of intraoperative MRI systems are in use. The original one consisted of an open system with a stationary magnet and stationary patient.[42] However, it had limitations in the ease of access for surgeons and anesthesiologists, and limits regarding the specific instruments that could be used for surgery and monitoring.[44] More commonly now, the other two systems consist of stationary magnet/movable patient and movable magnet/stationary patient. The most common type involves a movable magnet and a stationary patient[45] (Fig. 5.8). In this MRI setting, incompatible surgical instruments can be used. However, a drawback is that image acquisition can be done only after the patient has been placed in the magnet, which means increased time[46] and also the need to maintain a sterile field during imaging. The cost of developing such rooms also increases as there is need for specialized MRI shielding. The use of a stationary magnet and movable patient system has similar advantages and disadvantages to the movable magnet/stationary patient system. However, there is the additional advantage of including other imaging modalities such as positron imaging tomography and biplanar fluoroscopy.[47]

During preoperative assessment, history of acquired or implanted metallic devices, such as cerebrovascular clips, cochlear implants, cardiac pacemakers, intravascular wires, stents, bullets, extensive tattoos, and permanent eye make-up needs to be elicited.[48] Displacement or dislodgement may occur as these devices are ferromagnetic. Braces or dentures also generate significant artifacts and degrade obtained images. Heating of metallic implants can lead to severe burns. [45] Familiarity with the concept of safety zones, which are common to all MRI environments and were devised by the American College of Radiology (ACR),[49,50] is important in order to design processes at each stage of patient interaction in intraoperative MRI that facilitate optimal patient care. The ACR has divided the zones into four, with zone I being a general access area and zone IV within a high-strength magnetic field, with increasingly restricted access.

The use of intraoperative MRI also puts significant limitations on the equipment used, the patient, and the overall environment. An important concept in this regard is the 5 Gauss

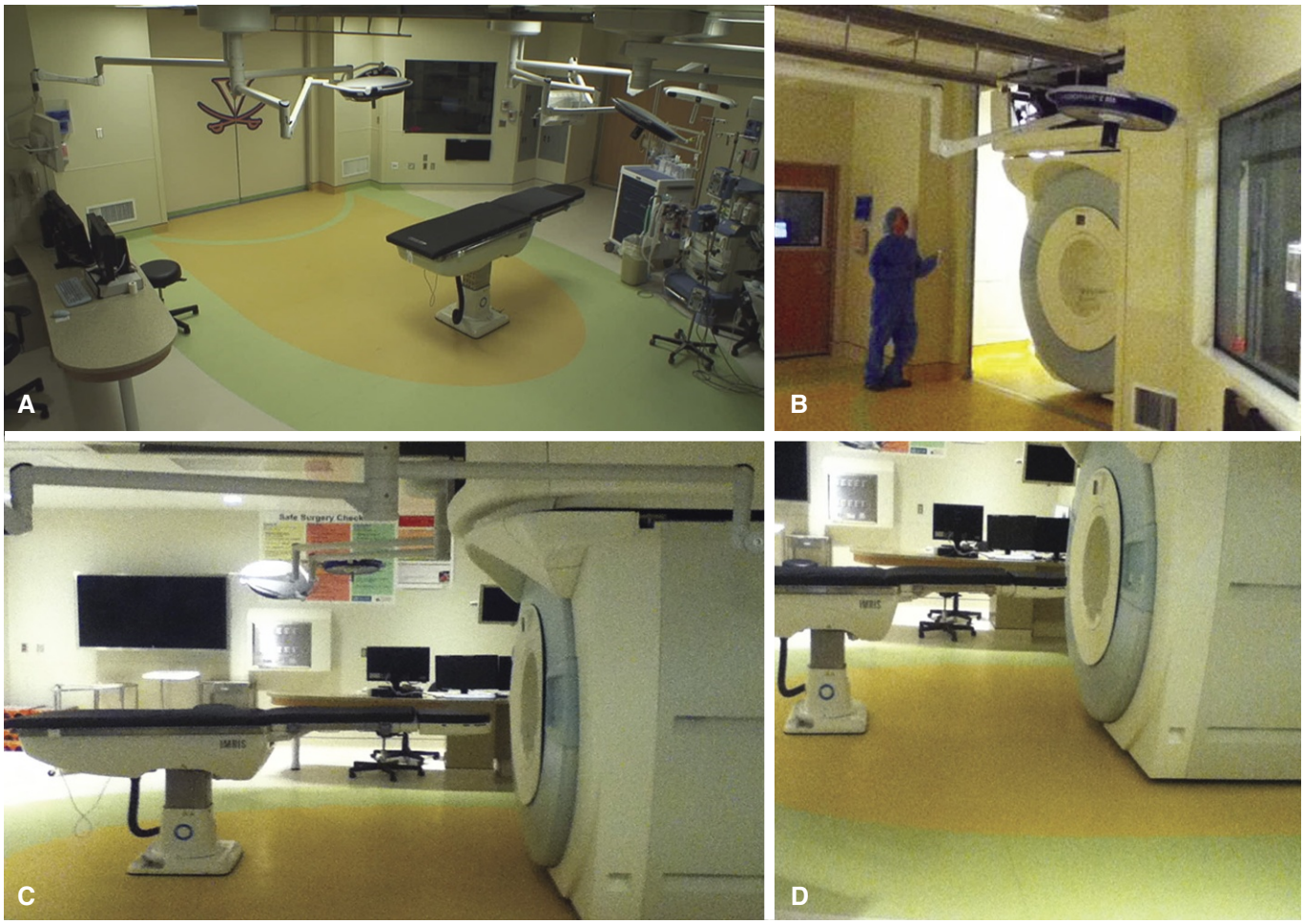


Fig. 5.8 Intraoperative magnetic resonance imaging (MRI) suite showing patient gantry in the operative suite **(A)**. The magnetic bore is brought in from its resting "bay" for scanning **(B)**. The movable magnet is ready to scan the stationary patient **(C,D)** during surgery and once that is done is sent back to its "bay". Note the yellow colored area refers to the 5-G line where only the MR safe devices can be used.

(5-G) line. The area within this line has a static magnetic field greater than 5G. Static magnetic field exposure of 5G or less is considered to be a minimal risk to bystanders.[45] In the intraoperative MRI suite, a clearly designated 5-G line and the use of MR safe devices is encouraged. In this regard, MRI safe means the item poses no risk in the MRI environment. MRI unsafe means that the item poses a hazard in all MRI environments and is contraindicated within zone IV. MRI conditional means that a given item has been shown to pose no known hazards in a specified MRI with particular conditions of use. An example is an MRI conditional anesthesia machine that is conditional to 100 Gauss in a 1.5 Tesla magnet, but unsafe in strengths higher than this, such as a 3 Tesla field strength.[51]

An MRI-compatible anesthesia machine, infusion pumps, pulse oximeter, end-tidal gas analyzer, electrocardiogram, blood pressure, and temperature monitoring devices are needed so that the patient does not suffer any injury such as a burn from MRI-unsafe leads. Inadvertent ferromagnetic substances become projectile in a high-strength field and monitoring equipment does not interfere with image quality. MR safe/conditional items such as defibrillators, fluid-warming devices, forced air-warming devices, Doppler ultrasound machines, peripheral nerve stimulators, and core temperature probes can be used in the nonimaging portion of the procedure when the patient is in zone III. Small children, especially neonates who have a limited ability to self-regulate temperature, need hot-air or fluid warmers, which are MR unsafe and need to be discontinued during imaging portions when the patient is placed in zone IV.[52] The patient must be covered in sterile drapes during this portion to maintain temperature.

A recent study found the average length of surgery was increased by 1 hour 47 minutes when comparing intraoperative MRI with conventional nonintraoperative MRI neurosurgical resection of intracranial lesions. In 42% of cases, imaging led to further tissue resection. There was an increase in early reoperation (within 2 weeks of surgery) in 7.7% in the nonintraoperative MRI group compared with 0% in the intraoperative MRI group. The authors felt that despite the cost and increased surgery time, the lower early reoperation rate and patient benefits justified intraoperative MRI usage and potentially lowered the costs in the long term.[53]

INTRACRANIAL DISORDERS

Imaging Patterns of Intracranial Disorders

Edema

By definition, cerebral edema or swelling results from an increase in one brain volume parenchymal compartment at the expense of another caused by a localized or diffuse abnormal fluid accumulation within the brain parenchyma. Typically, brain edema can be either cytotoxic, interstitial, or vasogenic:[54]

1. Vasogenic edema, which is predominantly associated with brain metastases, abscesses, trauma, and hemorrhage, develops due to a physical disruption of the vascular endothelium or functional alterations in endothelial tight junctions; subsequently the migration of fluid occurs via bulk flow mechanisms with transmural pressure gradients causing fluid extravasation from cerebral vessels to the extracellular fluid brain spaces. Vasogenic edema primarily involves the white matter (most commonly deep white matter of the cerebral hemispheres).
2. Cytotoxic (intracellular) edema is defined as fluid accumulating within cells as a result of injury, usually from toxicity, ischemia, or hypoxia. The mechanism of injury leads to energy failure due to failure of the sodium-potassium ATPase-dependent pumps. Cytotoxic edema involves both gray and white matter (in contrast to vasogenic edema). Hypo-osmolar states (eg, dilutional hyponatremia, acute sodium depletion, inappropriate antidiuretic hormone [ADH] syndrome) and osmotic disequilibrium syndromes (eg, hemodialysis, diabetic ketoacidosis) can also cause cytotoxic edema. In the early stages of cytotoxic edema fluid moves from the extracellular compartment to the intracellular compartment, with no net change in brain volume, but eventually the extracellular compartment will equilibrate with the intravascular compartment. Because it is associated with ischemia and infarction, cytotoxic edema has a more vascular distribution and produces less mass effect.
3. Interstitial edema results from CSF migration into the periventricular white matter, commonly due to conditions that impede CSF circulation and/or absorption.

Except for location and DWI (diffusion is reduced in cytotoxic edema, and increased in vasogenic edema), the imaging appearance of edema is essentially similar for all pathologic processes. On CT, any increase in water is visualized as a dark, hypodense area. On MRI, an increase in water is visualized as an area of hypointensity (black) on T1-weighted studies and as an area of hyperintensity (white) on T2-weighted images. Contrast enhancement may help define areas of edema and might suggest an etiology. As contrast accumulates in regions of blood–brain barrier breakdown, areas of vasogenic edema enhance, whereas cytotoxic edema areas usually do not (or only at later stages).

Recommendations have been recently formulated for the management of swelling associated with cerebral and cerebellar infarctions by the American Heart Association and the American Stroke Association.[55] Clinical signs that signify deterioration in swollen supratentorial hemispheric ischemic stroke include new or further impairment of consciousness, cerebral ptosis, and changes in pupillary size. In swollen cerebellar infarction, a decrease in the level of consciousness occurs as a result of brainstem compression and, therefore, may include early loss of corneal reflexes and the development of miosis. In swollen supratentorial hemispheric ischemic stroke, routine intracranial pressure monitoring or cerebrospinal fluid diversion is not indicated, but decompressive craniectomy with dural expansion should be considered in patients who continue to deteriorate neurologically. There is uncertainty about the efficacy of decompressive craniectomy in patients greater than 60 years of age. In swollen cerebellar stroke, suboccipital craniectomy with dural expansion should be performed in patients who deteriorate neurologically. Ventriculostomy to relieve obstructive hydrocephalus after a cerebellar infarct should be accompanied by decompressive suboccipital craniectomy to avoid deterioration from upward cerebellar displacement. In swollen hemispheric supratentorial infarcts, outcome can be satisfactory, but one should anticipate that one-third of patients will be severely disabled and fully dependent on care even after decompressive craniectomy. Surgery after a cerebellar infarct leads to acceptable functional outcome in most patients.

Hemorrhage

Intracranial hemorrhage may be traumatic or nontraumatic in origin. When blood is seen in the extra-axial space (epidural, subdural, subarachnoid), trauma is the most likely cause. Subarachnoid hemorrhage (SAH) may be traumatic

or associated with ruptured berry (saccular) or fusiform aneurysms. Arterial dissection, often though not always associated with trauma, may also present with SAH. Parenchymal hemorrhage is more likely to be nontraumatic in origin, and secondary to an underlying disease such as hypertension or neoplasm, or to a vascular anomaly such as an arteriovenous malformation. Regardless of location, acute hemorrhage is seen on a CT scan as a hyperdense area. Blood products evolve with time with a progressive decrease in density, subsequently becoming first isodense to brain parenchyma and then eventually becoming hypodense. A negative CT scan does not completely exclude hemorrhage as severely anemic patients may present with isodense extra-axial or intraparenchymal blood collections, where only the presence of mass effect suggests the presence of hemorrhage.

The appearance of hemorrhage on MR is complicated because of varying paramagnetic properties of blood breakdown products. One should consider the age of hemorrhage in relation to these breakdown products.[56–58] During the first hours after parenchymal hemorrhage, intact red blood cells containing oxyhemoglobin accumulate. Being diamagnetic, oxyhemoglobin is slightly hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images, mainly because of the concomitant presence of globin proteins. Over the next hours/days, hemoglobin becomes deoxygenated. Because deoxyhemoglobin is paramagnetic, the T2 intensity values fall (becoming hypointense), whereas the T1 values essentially remain the same. With respect to brain parenchyma, the acute hematoma appears dark on T2-weighted images and slightly dark to isointense on T1-weighted images. Between 3 and 7 days intracellular methemoglobin begins to accumulate, beginning peripherally and then advancing toward the center of the clot. During this stage, the T2 signal intensity remains stable, but T1 values begin to increase, with the periphery of the clot becoming hyperintense. The hematoma is dark on T2-weighted images and bright on T1-weighted images. Between 7 days and 2 to 3 months intracellular methemoglobin is released from erythrocytes (extracellular methemoglobin). During this stage, signal intensities on both T1 and T2 images increase (hyperintense on both T1- and T2-weighted images). During the final stage, which may begin within the first 2 weeks and last for years, phagocytic degradation of methemoglobin to hemosiderin occurs. This process, which also begins peripherally and extends toward the center effectively removes iron from the hematoma and deposits it at the periphery. Signal intensities again decrease, and hemosiderin appears black on T2-weighted images, beginning at the periphery as a ring, eventually replacing the entire hemorrhage. This progression represents a continuum of changing intensity values and is not an all-or-nothing phenomenon. In the acute/subacute phase, most hematomas produce a surrounding area of edema that should not be misinterpreted as an additional area of hemorrhage. Edema, dark on T1-weighted images and bright on T2-weighted images, gradually decreases over time.

Mass Effect, Shift and Herniation

An enlarging mass (eg, tumor or abscess), hemorrhage or edema can cause mass effect and lead to brain herniation, which can directly compress vascular structures, resulting in ischemia and infarct, and directly impinge upon cranial nerves and vital structures, ultimately causing death. Because hemorrhages frequently progress and large contusions often develop delayed hemorrhage or edema, repeat serial imaging is usually indicated, especially if changes in neurological status occur, as the degree of mass effect correlates with the level of consciousness.[59]

Imaging features of intracranial mass effect include sulcal effacement, midline shift, basal cistern effacement, obstructive hydrocephalus, and herniation.

Different types of brain herniation include subfalcine, transtentorial, and tonsillar herniation.

Subfalcine herniation occurs when a hemispheric mass pushes the cingulate or supracingulate gyri beneath the falx. It is easily recognized on CT or MR by deviation of the falx and extension of hemispheric structures across the midline.

Transtentorial herniation occurs when a mass on either side of the tentorium causes brain herniation through the tentorial incisura, either descending (downward) or ascending (upward). Descending herniation is usually more commonly caused by a supratentorial mass displacing the medial temporal lobe through the tentorial incisura. It may be anterior (involving the uncus), posterior (involving the parahippocampal or lingual gyri), or complete. On CT or MR, the herniated uncus or parahippocampal gyrus produces widening of the ipsilateral subarachnoid cistern and obliteration of the contralateral subarachnoid cistern as the brainstem is rotated and displaced to the opposite side.[60] Ascending transtentorial herniation is caused by an infratentorial mass that pushes the pons, vermis, and adjacent portions of the cerebellar hemispheres upward through the incisura. On CT or MR, the subarachnoid cisterns are effaced symmetrically as the cerebellar vermis bulges up through the incisura. The upper pons is pushed forward against the clivus, and often acute hydrocephalus is caused by compression of the sylvian aqueduct. Occipital lobe infarction (ipsilateral or contralateral) may also occur if the posterior cerebral artery is compressed between the temporal lobe and the crus cerebri.[61]

In tonsillar herniation, there is inferior displacement of the cerebral tonsils through the foramen magnum into the cervical spinal canal. It results in compression of the medulla producing dysfunction of the vital respiratory and cardiac rhythm centers. MRI, with its sagittal imaging abilities, is the primary imaging modality for demonstrating the presence of tonsillar herniation and its secondary effects on the brainstem. On CT, the cerebellar tonsils can be seen below the level of the foramen magnum.[60,62] If such a finding is seen, lumbar puncture should not be performed, as this can result in death of the patient, as explained in the beginning of this section.

Efforts have been made to correlate quantitative measures of herniation on imaging (ie, the degree of shift of structures) with clinical outcomes. For example, in subfalcine herniation (midline shift or cingulated herniation), the degree of displacement of the septum pellucidum from the midline is predictive of patient prognosis. In studies of descending transtentorial herniation, the degree of vertical descent did not always correlate well with neurological signs. Prior studies have shown a correlation between the degree of midline shift and the level of consciousness.[59]

Hydrocephalus

Hydrocephalus is classified as either obstructive or communicating.

Communicating hydrocephalus results from excessive CSF production by choroid plexus tumors or from an obstruction of arachnoid villi absorption of CSFcaused by a subarachnoid hemorrhage, meningitis, or leptomeningeal carcinomatosis.[63] CT and MR show symmetric enlargement of the lateral, third, and fourth ventricles with effacement of cerebral sulci. Under elevated pressure, CSF may leak from the ventricles into the brain (interstitial edema).

Obstructive hydrocephalus results secondary to obstruction along the CSF pathway between the lateral ventricles and

the fourth ventricular outlet. The CT and MR appearance is identical to that of communicating hydrocephalus with the exception that in obstructive hydrocephalus not all ventricles are enlarged. The ventricles dilate proximal but not distal to the obstruction. For example, in aqueduct obstruction, the fourth ventricle remains normal as the third and lateral ventricles enlarge. The cause of obstructive hydrocephalus can often be identified by CT or MR. MRI is the preferred modality for the evaluation of obstructive hydrocephalus for the following reasons:

1. MRI can provide multiplanar images, which are invaluable in demonstrating obstruction at the foramen of Monro, the aqueduct, or the level of the fourth ventricle.[64]
2. Tumors are readily seen, and webs or atresia of the aqueduct can occasionally be identified.
3. Techniques such as CSF flow phenomena, which can be evaluated by MRI, are helpful in classifying types of obstruction.[65]

Review of Main Surgical Intracranial Disorders

Traumatic Brain Injury

Traumatic brain injury (TBI) is a major cause of death and disability in the United States, contributing to about 30% of all deaths from injury.[66] In 2010, about 2.5 million emergency department (ED) visits, hospitalizations, or deaths were associated with TBI—either alone or in combination with other injuries—in the United States. TBI contributed to the deaths of more than 50,000 people. TBI was a diagnosis in more than 280,000 hospitalizations and 2.2 million ED visits. These consisted of TBI alone or TBI in combination with other injuries. Over the past decade (2001–2010), while rates of TBI-related ED visits increased by 70%, hospitalization rates only increased by 11% and death rates decreased by 7%.[64]

TBI classically can be subdivided into two categories: (1) primary injury (eg, cortical contusion, skull fracture, and white matter shearing injury), which is the result of the initial, mechanical insult, and (2) secondary (delayed) brain injury (eg, edema, hypoxia, intracranial hypertension, vasospasm), which is a sequela of the initial trauma. This classification is clinically important as early medical intervention might possibly ameliorate the deleterious effects associated with secondary injury that can ultimately lead to brain compromise and permanent brain injury.[67] In addition, TBI may also be classified according to lesion location (ie, intra- vs. extra-axial), clinical severity (minor, mild, moderate, severe), and mechanism of injury (penetrating vs. blunt/closed). The majority of TBI is mild, accounting for about 75% of traumatic brain injuries.[66]

Indications for Imaging in Traumatic Brain Injury Patients

As CT is readily available, cost-effective, fast, and accurately detects injuries (ie, hemorrhages and fractures) that might require surgical intervention, CT is the preferred imaging modality for the initial assessment of acute TBI.[68] CT shows an excellent ability for the detection of acute hemorrhage, the resulting mass effect, basal cistern effacement, and the presence of acute hydrocephalus. Excellent bone resolution facilitates assessment of the skull base, calvarium, and/or facial bone fractures. Indications for head CT in acute trauma include: GCS score <8 or a decrease of >3 in the GCS score, headache, vomiting, worsening level of consciousness, loss of consciousness >5 minutes, focal neurological findings, seizure, penetrating skull injuries, signs of a basal or depressed skull fracture, and physical evidence of trauma above the clavicle.[69,70]

Although CT is best for acute injuries such as hemorrhages, a number of intracranial lesions (eg, diffuse axonal injury, brainstem and deep gray matter injury) are difficult to appreciate using this method, and for this reason MRI shows greater sensitivity than CT for the detection of these subtle lesions and is also better suited for the evaluation of subacute and chronic TBI. In particular, MRI is ideal for the evaluation of a patient with neurological deficits that cannot be explained by the CT findings.[71] MRI is superior to CT in detecting axonal injury, small areas of contusion, and subtle lesions in the brainstem, basal ganglia, and thalami.[72] It is estimated that CT "misses" approximately 15–30% of abnormalities subsequently seen on MRI.[73] There has been a recent spurt in interest in the utilization of newer modalities such as DTI and MRS in the evaluation of TBI.[74]

Types of Traumatic Brain Injury

Primary TBIs are divided into extra-axial and intra-axial lesions.

Extra-axial lesions include skull fractures, and epidural, subdural, subarachnoid, and intraventricular hemorrhages. CT is the preferred modality to assess skull fractures, since it facilitates identification of associated brain injuries (eg, intra-axial/extra-axial hemorrhage, and/or CSF leak), which are not always obvious on plain radiographs.[75,76] Basal skull fractures may be associated with cranial nerve and/or vascular injury (vessels near skull base) (Fig. 5.9). For example, longitudinal and transverse temporal bone fractures are associated with facial paresis and sensorineural hearing loss, respectively.[77–79] Diagnosis of these fractures requires thin CT slice protocols and three-dimensional multiplanar CT reformats.[80–82] Skull fractures can lead to CSF leaks. Radionuclide cisternography, contrast-enhanced CT cisternography, and high-definition CT have been used for post-traumatic CSF leak detection.[83,84]

Damage to the meninges may lead to hemorrhage into the subdural, epidural, or CSF spaces (which result in subarachnoid hemorrhage and intraventricular hemorrhage).

Epidural hematomas (see Fig. 5.3) are relatively uncommon (1–4% of head trauma patients) and have an overall mortality of 5%. An epidural hematoma, an extra-axial blood collection that accumulates in the potential space between the dura mater and the inner table of the skull, occurs in 85–95% of cases secondary to a laceration of the middle meningeal artery (90%) or a dural venous sinus (10%) by an associated skull fracture.[85] The classic clinical presentation of an epidural hematoma is a so-called lucid, conscious interval that is soon followed by neurological deterioration; this "lucid interval" has been attributed to the absence of an underlying brain injury with subsequent epidural hematoma enlargement causing progressive neurological deterioration. However, this classic presentation occurs in only 20% of patients.[86] Epidural hematomas exhibit a lentiform or biconvex hyperdense appearance, the majority occurring in the temporoparietal area.[76] Less commonly, they may develop at the frontal pole, in the parieto-occipital region, between the occipital lobes, or in the posterior fossa. These are most often venous in origin and occur due to fractures overlying the major dural sinuses. In the parasagittal region, they occur as a result of a tear from the superior sagittal sinus, in the middle cranial fossa from injury to the sphenoparietal sinus or middle meningeal veins, and in posterior fossa/occipital region from rupture of the transverse or sigmoid sinus. Epidural hematomas usually do not cross the midline and suture lines (an exception being the sagittal suture). They can extend from the supratentorial to the infratentorial space, whereas

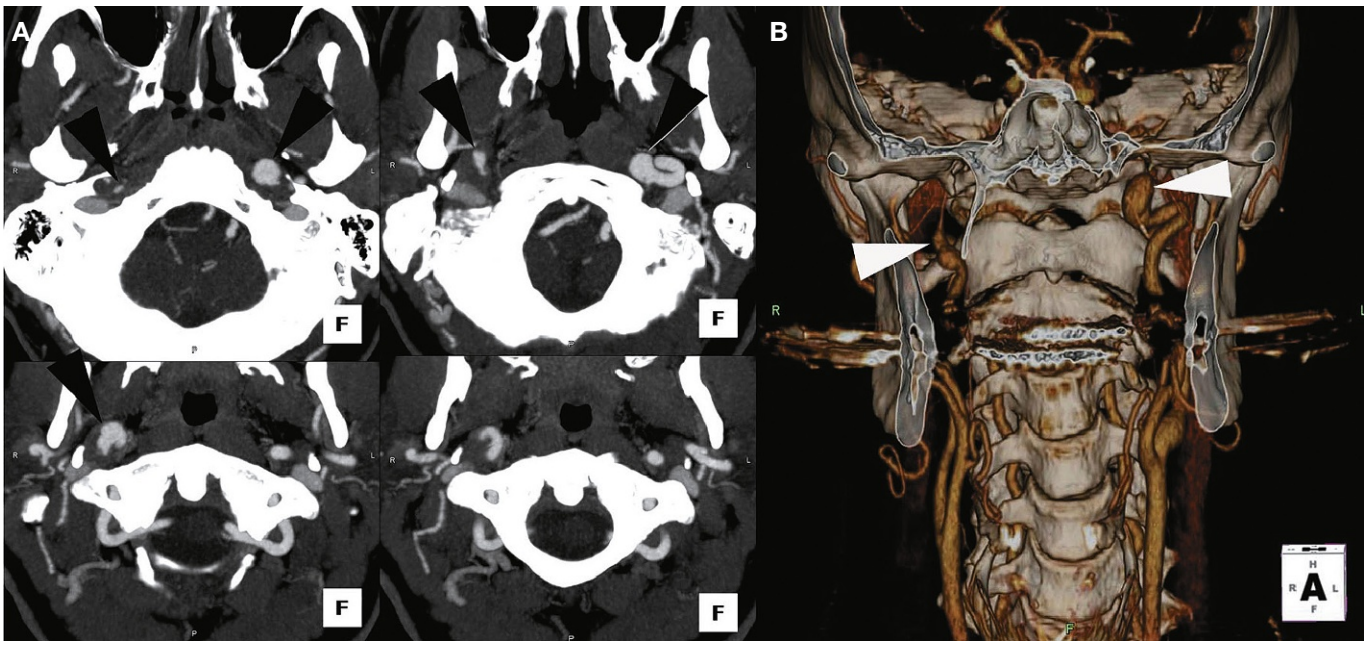


Fig. 5.9 A 50-year-old male patient who suffered several falls while snowboarding. Because of transient ischemic attack symptoms, the patient underwent a computed tomography angiogram (CTA). This CTA demonstrated bilateral internal carotid artery pseudoaneurysms (associated with a dissection on the right side) just below the skull base. This segment of the internal carotid arteries is particularly vulnerable to shear trauma forces, because it is a mobile segment adjacent to an immobile segment in the petrous portion of the carotid canal.

the subdural hematoma (SDH) is limited by the tentorium. The presence of hypodense regions within an otherwise hyperdense epidural hematoma ("the swirl sign") may represent areas of active hemorrhage.[87]

SDHs are common (10–20% of patients with head trauma) and have a high mortality rate (50–85%).[56] Typically, while epidural hematomas are located at the coup site, an acute SDH is a contre-coup lesion, which most commonly occurs due to a deceleration mechanism that causes traumatic bridging vein rupture. Subdural hematomas exhibit certain specific traits: SDHs are crescent-shaped, usually holohemispheric; they can cross suture lines, extend along the tentorium and the falx cerebri, and usually do not extend from the supratentorial space into the infratentorial space. Common locations for SDH include along the cerebral convexities, the falx cerebri, and the tentorium cerebelli. Although the common etiology for acute subdural hematomas is trauma, other etiologies include child abuse, rapid ventricular decompression, and spontaneous subdural hematomas. Usually these patients are on anticoagulation, elderly, or with an existing coagulopathy.[88,89]

A subarachnoid hemorrhage (SAH) is bleeding into the subarachnoid space surrounding the brain (ie, between the arachnoid and pia mater) and it may occur due to trauma or spontaneously, spontaneous or primary subarachnoid hemorrhage usually resulting from ruptured aneurysms.[90] The interpeduncular cistern and Sylvian fissures are two common locations for the accumulation of subarachnoid blood.[91] CT and MRI FLAIR are equally sensitive at detecting subarachnoid hemorrhage.[92] Subarachnoid blood acts as an irritant to the arteries coursing through the subarachnoid spaces, causing vasospasm. It can also interfere with normal CSF resorption at the level of the pacchionian (arachnoidal) granulations, thus leading to communicating hydrocephalus.

Traumatic intraventricular hemorrhage can occur by one of three methods: contiguous extension from a parenchymal hematoma, shearing of subependymal veins which line the ventricular cavities, or retrograde reflux of subarachnoid hemorrhage through the foramina of the fourth ventricle.[93] It may be isolated, but it is usually associated with superficial contusions and subarachnoid hemorrhage. Subtle intraventricular hemorrhage can be detected by the appearance of a fluid–fluid level layering dependently within the occipital horns of the lateral ventricles (so-called "hematocrit effect"), as fibrinolytic activators within the cerebrospinal fluid inhibit clotting. In some cases, the choroid plexus may act as a nidus for the blood to clot and form a ventricular cast or tumefactive blood clot. Large amounts of intraventricular blood may impede cerebrospinal fluid flow and result in noncommunicating hydrocephalus.

Intra-axial lesions include hemorrhagic and nonhemorrhagic contusions, parenchymal hematomas, and DAI.

Cortical brain contusions are relatively common, occurring in up to 40% of patients with blunt trauma.[93] They are peripheral lesions, involving the gyral crests, particularly those in contact with irregular skull bony prominences (eg, the orbital roof, sphenoid ridge, and petrous ridge). The terms "coup" and "contre-coup" are often used to describe the cortical contusion lesions, which are a result of the brain parenchyma striking the inner table at the site of impact ("coup") or at the opposite side of impact ("contre-coup"). On noncontrast CT, contusions appear as low attenuation foci if hemorrhage is absent and high attenuation foci if hemorrhage is present. Nonhemorrhagic contusions are initially often difficult to detect on CT, but become more conspicuous with time as they evolve and exhibit increased hypodensity due to edema within the contused tissue. Moreover, delayed hemorrhage can develop within previously nonhemorrhagic lesions. For these reasons, repeat or serial CT imaging is recommended. If CT is optimal for the acute evaluation of contusions, subacute and chronic cortical contusions are better evaluated using MRI.[56] On MRI, contusions that appear nonhemorrhagic on CT are often demonstrated to have hemorrhagic components, and consequently follow the time evolution of MRI signal of blood products. Contusions are particularly conspicuous on GRE images. With time, contusions shrink into gliotic scars. An old contusion is seen as a wedge-shaped area of peripheral

encephalomalacia with the apex of the wedge pointing centrally and the broad base facing the irregular surface of the skull. In the chronic stage, this triangular shape can resemble a remote ischemic infarct. The products of hemorrhage can be detected by MRI for years (rather than a few weeks, as on CT).

DAI, or shear-injury, typically occurs secondary to sudden acceleration and deceleration forces that cause microscopic axonal brain injury preferentially to deep white matter or gray/white matter interface. Pathologically, it is characterized by microscopic axonal lesions that most frequently involve the subcortical white matter, the corpus callosum (particularly the splenium), and the dorsolateral brainstem.[94,95] Early and exact identification of the extent of axonal injury is a major diagnostic challenge, because these injuries are seldom visible on CT, or conventional MRI sequences. With the advent of advanced MRI modalities, such as GRE, DWI or DTI, the ability to detect these shear injuries has improved dramatically.[95] Hemorrhagic DAI can sometimes be diagnosed on CT or conventional T1 or T2 images, but usually require GRE sequences.[96] Nonhemorrhagic DAI can usually only be seen on DWI or DTI.[97,98]

Concussion is the most common form of TBI, but diagnosis remains controversial because the brain appears quite normal in conventional CT and MRI. These conventional tools are not sensitive enough to detect diffuse traumatic axonal injury, and cannot depict aberrations in mild TBIs. Advanced MRI modalities including DTI, and MRS, make it possible to detect brain injuries in TBI. With the growing realization that even mild head injury can lead to neurocognitive deficits, medical imaging has assumed preeminence for detecting abnormalities associated with TBI. Advanced MRI modalities such as DTI and MRS have an important role in the diagnosis of lesions for TBI patients.[99] This is especially important in contact sports like football, where there is no evident structural finding on routine MRI, but cumulative mild injuries over a period of time lead to neurocognitive deficits.

Brain Neoplasms

Neuroimaging plays a crucial role in diagnosing brain neoplasms, planning their treatment, and monitoring the effects of these therapies. The radiological appearance of brain tumors includes some features that are common to most tumors: mass lesion, causing mass effect and sometimes hydrocephalus, CT hypodensity or MRI increased T2 signal reflecting either edema or tumor infiltration, abnormal enhancement in most cases, and hemorrhagic complication and/or cystic necrosis in some instances. Differential diagnosis can usually be narrowed based on patient's age and determining whether the lesion is solitary or multiple, intra-axial or extra-axial. Primary brain gliomas are intra-axial. Extra-axial tumors include meningiomas and schwannomas. Metastases are typically multiple, and can be both intra-axial and extra-axial.

In terms of imaging of brain tumors, CT is usually used to assess for tumor complications such as hemorrhage or mass effect, including hydrocephalus, while MRI is used for tumor diagnosis and classification, treatment planning, and post-treatment follow-up. Modern MRI techniques, such as PWI, DWI DTI, MRS, and functional MRI, have allowed significant progress in accurately delineating tumor margins, determining tumor grade, distinguishing treatment effects vs. residual/recurrent tumor, and differentiating eloquent cortex or white matter tracts from tumor. DWI is also used to differentiate between necrotic tumors (increased ADC values) and abscesses (decreased ADC) (Fig. 5.10).

Image Detection of Tumor Margins

Gliomas have a propensity for infiltration of the adjacent brain parenchyma, and tend to migrate along white matter tracts. Gliomas have been found to extend beyond the gross tumor margins as depicted by conventional MRI.[100,101] MRS has the ability to detect increased choline and reduced NAA peaks beyond the tumor margins within the normal-appearing parenchyma infiltrated by the tumor.[102,103] Similarly, DTI detects tumoral infiltration as a decrease in fractional anisotropy.[101,104–106] However, although both DTI and MRS were shown to be better than conventional MRI at defining the tumor margins, further studies have shown mixed results when compared to noninvasive tumors (eg, meningiomas and metastases) for DTI and normal brain and mild tumor infiltration for MRS.[107]

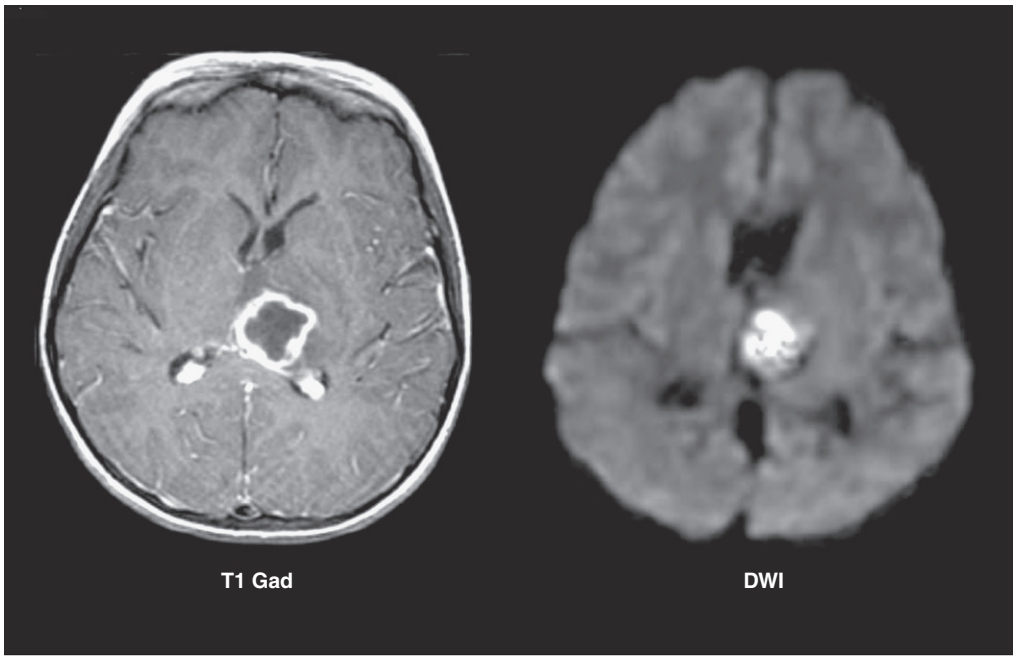


Fig. 5.10 A 47-year-old male patient with a rim-enhancing lesion in the left thalamus. The reduced diffusion within this rim-enhancing lesion makes it typical for an abscess, and allows it to be distinguished from a necrotic tumor.

Grading of Brain Tumors Based on Imaging

Although histology is the gold standard in determining tumor grade, MRI has a sensitivity and specificity of 65% and 95%, respectively, for the characterization of high-grade tumors.[108] The presence or absence of abnormal contrast enhancement does not correlate with tumor histology.[109] Newer MRI techniques are now used to noninvasively elucidate tumor biology: tumor cellularity (DWI), tumor metabolism (MRS), and tumor vascularity (PWI).

ADC and fractional anisotropy values inversely correlate with the degree of tumor cellularity and the proliferation index of the glioma.[105,110,111] ADC values have been found to be significantly lower in higher-grade gliomas compared to less cellular low-grade gliomas.[112] Similarly, the choline peak, lactate/lipid peak, and the Cho/NAA ratio have been correlated with cell density, proliferation markers, and tumor grade (Fig. 5.11).[113–117] Lastly, as increased angiogenesis and microvascular proliferation are markers of a more malignant process, certain perfusion parameters, such as CBV, have been used to provide a noninvasive method to grade gliomas.[118–120] However, this approach has pitfalls; for instance, oligodendrogliomas have higher CBV values than astrocytic tumors.[121] As a result, a low-grade oligodendroglioma might possibly be falsely graded as a higher-grade tumor (Fig. 5.12).

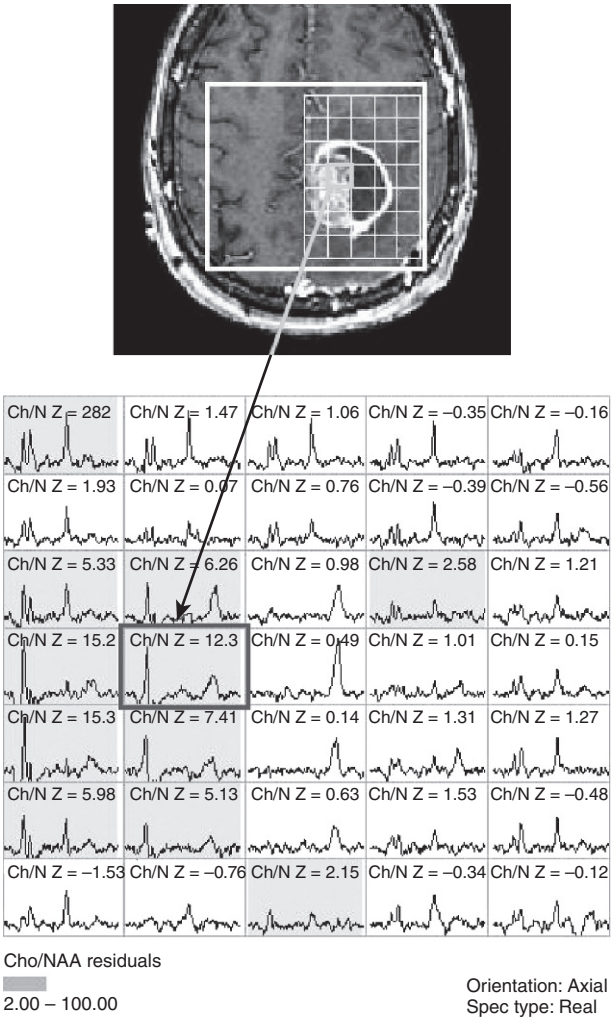


Fig. 5.11 Long echo (TE = 288 msec) three dimensional point resolved magnetic resonance spectroscopy in a patient with glioblastoma multiforme. The inset Green voxel corresponds to an area of abnormal enhancement on the diagnostic image at the margin of a cavitary lesion. An abnormal elevation of choline (Cho) (the dominant peak in the spectrum) with a notable absence of N-acetyl aspartate (NAA) is seen. Additionally, the second largest peak in the spectrum (at the far right of the voxel) represents lipid contributions from tumor necrosis. The three-dimensional acquisition facilitates comparison of normal and abnormal tissues in a single acquisition. Z-values represent abnormal primary peak ratios (NAA, Cr, Cho) which are more than two standard deviations greater than the expected ratios. Voxels with abnormal z-values are shaded gray for identification.

Imaging of Brain Tumor Treatment Effects

Conventional MR is limited in differentiating the post-treatment effects from tumor residual/recurrence. Also, current MRI methods, all based on structural imaging, rely on changes in tumor size to determine treatment response; however, evaluation of tumor physiology could provide an earlier assessment of treatment response and could potentially serve as a surrogate marker of treatment success.

ADC changes have been shown to correspond to changes in tumor volume and cellularity.[112] ADC changes are usually noticeable prior to their appearance on conventional MRI.

PWI allows differentiation between glial tumor, which has preserved the blood–brain barrier, and metastases, which have an abnormally permeable blood–brain barrier. It can also help differentiate between tumor recurrence, which shows increased CBV and treatment necrosis, which shows decreased CBV (Fig. 5.13).[122] PWI has been utilized to study the response for antiangiogenic or antivascular drugs, and to radiotherapy.[123]

MRS has also been used to distinguish between tumor recurrence where we find increased choline and decreased NAA, and treatment necrosis where there is decreased choline and decreased NAA.[124] MRS has also been reported to predict the response to therapy. In a cohort of patients with high-grade gliomas receiving radical radiotherapy (ie, 60 Gy in 30 fractions), the lactate/NAA ratio was the strongest predictor of response to radiotherapy and overall survival.[125]

Eloquent Cortex

DTI and functional MRI have the ability to "map" functional areas whereby disruption would lead to focal neurological deficits and to identify both areas of cortical activation and white matter tracts. This information may be important for the neurosurgeon to decide which surgical approach is best to minimize patients' deficit from tumor[126] or AVM resection (Fig. 5.14).

Intracranial Aneurysms and Other Intracranial Vascular Malformations

Approximately 10% of patients presenting with intracranial hemorrhage have a vascular malformation. SAH is the most highly morbid type of intracranial hemorrhage; vascular malformations are the most common cause of nontraumatic SAH in patients under the age of 40. There are five types of vascular malformations of the brain: intracranial aneurysms, arteriovenous malformations (AVMs) and fistulas, capillary telangiectasias, developmental venous abnormalities, and cavernomas (cavernous malformations). About 10% of cavernomas are associated with a heritable mutation and associated with multiple lesions; single lesions tend to be sporadic and tend to have a higher rate of association with a developmental venous anomaly (DVA).

Intracranial Aneurysms

There are four types of intracranial aneurysms: berry/saccular, fusiform/atherosclerotic, septic/mycotic, and pedicular aneurysms on the feeding arteries of AVMs. Berry (saccular) aneurysms are the most common, comprising up to 90% of

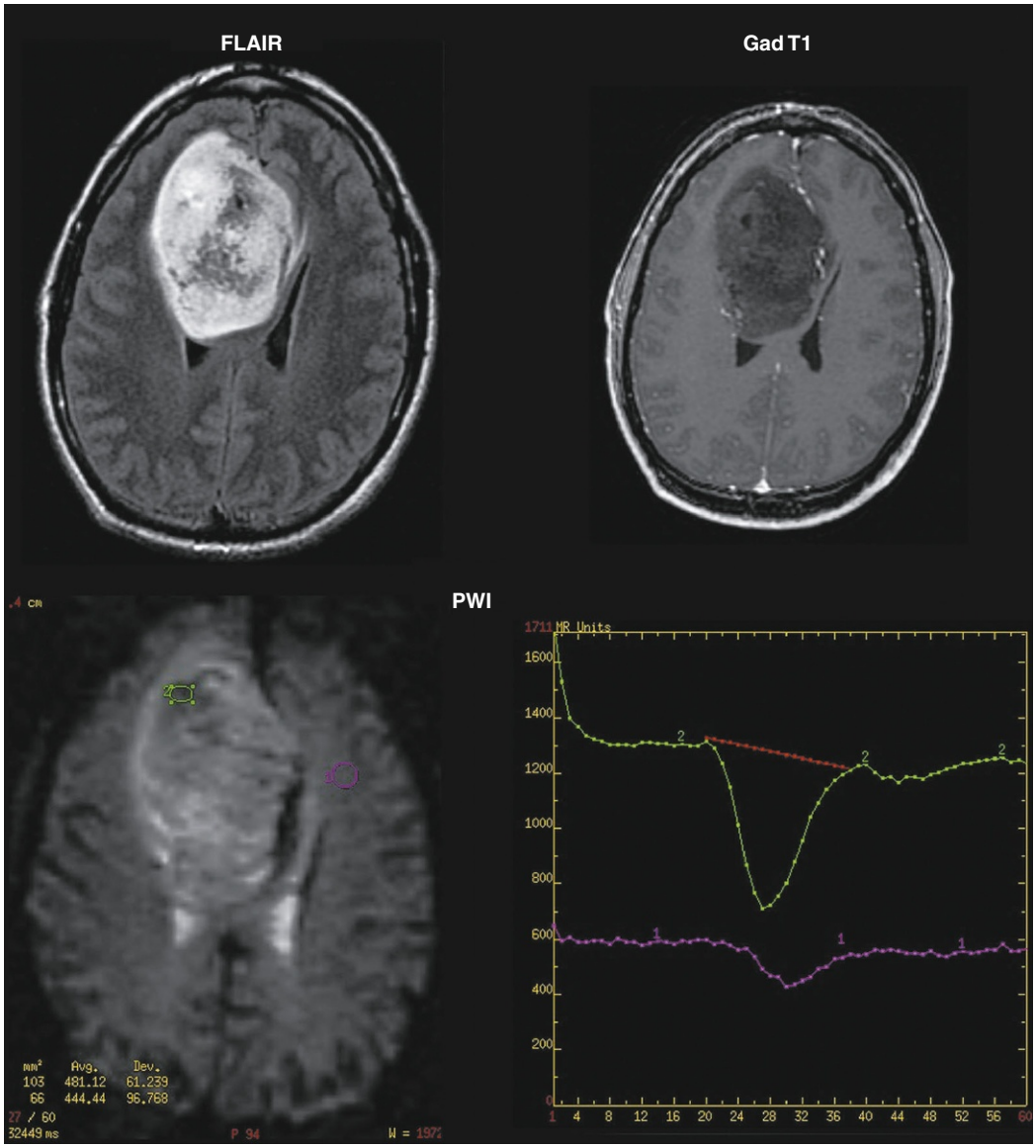


Fig. 5.12 A 28-year-old male patient with prior history of seizures. Conventional FLAIR and post-gadolinium T1-weighted images demonstrated a right mesiofrontal, heterogenous, but well-delineated, mass. Perfusion-weighted dynamic susceptibility imaging demonstrated increased area over the curve in a (green) region of interest placed within the mass compared to a region of interest (purple) placed within the normal contralateral frontal white matter. This increased area over the curve, corresponding to increased cerebral blood volume, combined with the low-grade appearance of the lesion on conventional imaging sequences, raised the suspicion of an oligodendroglioma, which is a low-grade tumor with a very rich blood supply. This diagnosis was confirmed histologically.

all aneurysms, and represent the leading cause of spontaneous SAH. The extent to which berry aneurysms are congenital is speculative; they can form during adult life, especially in patients with multiple aneurysms. Pathologically there is a thinning or absence of the arterial media with dilatation of the lumen, usually at a bifurcation and almost always in the proximal circle of Willis. Frequent locations are the origin of the posterior communicating artery from the internal carotid artery, the anterior communicating artery, and the middle cerebral artery bifurcation. The probability of rupture strongly correlates with the size of the aneurysm, and becomes significant when aneurysm diameter is more than 7 mm.

Noncontrast CT is usually used as a primary screening tool in patients suspected of SAH. Moreover, the pattern of SAH can offer clues to the possible location of the underlying cerebral aneurysm. The sensitivity of CT for SAH is more than 95% in the first 12 hours.

DSA is considered to be the gold standard for the detection of intracranial aneurysms and of aneurysm complications, and also represents a treatment modality as it permits coiling of ruptured and unruptured aneurysms and endovascular treatment of vasospasm by angioplasty and/or intra-arterial verapamil.

Now, CTA and MRA are considered as feasible alternatives for conventional angiography. CTA has been shown to exhibit 83–96% sensitivity and 97–100% specificity[127–130] for aneurysm detection (see Fig. 5.1), although the sensitivity decreases for smaller aneurysms, with a 40–91% sensitivity for aneurysms <3 mm.[128,129,131] Similarly, MRA has been shown to be highly sensitive and specific for the detection of intracranial aneurysms, but similar to CTA its sensitivity decreases with smaller aneurysm (ie, <3 mm in diameter).[130,131] PCT and CTA have also been reported as accurate noninvasive imaging techniques to assess for vasospasm (Fig. 5.15).[132,133]

Arteriovenous Malformations

AVMs are a vascular anomaly characterized by a network of abnormal vessels with an abnormal connection, or shunt, between a feeding artery and a draining vein bypassing an intervening

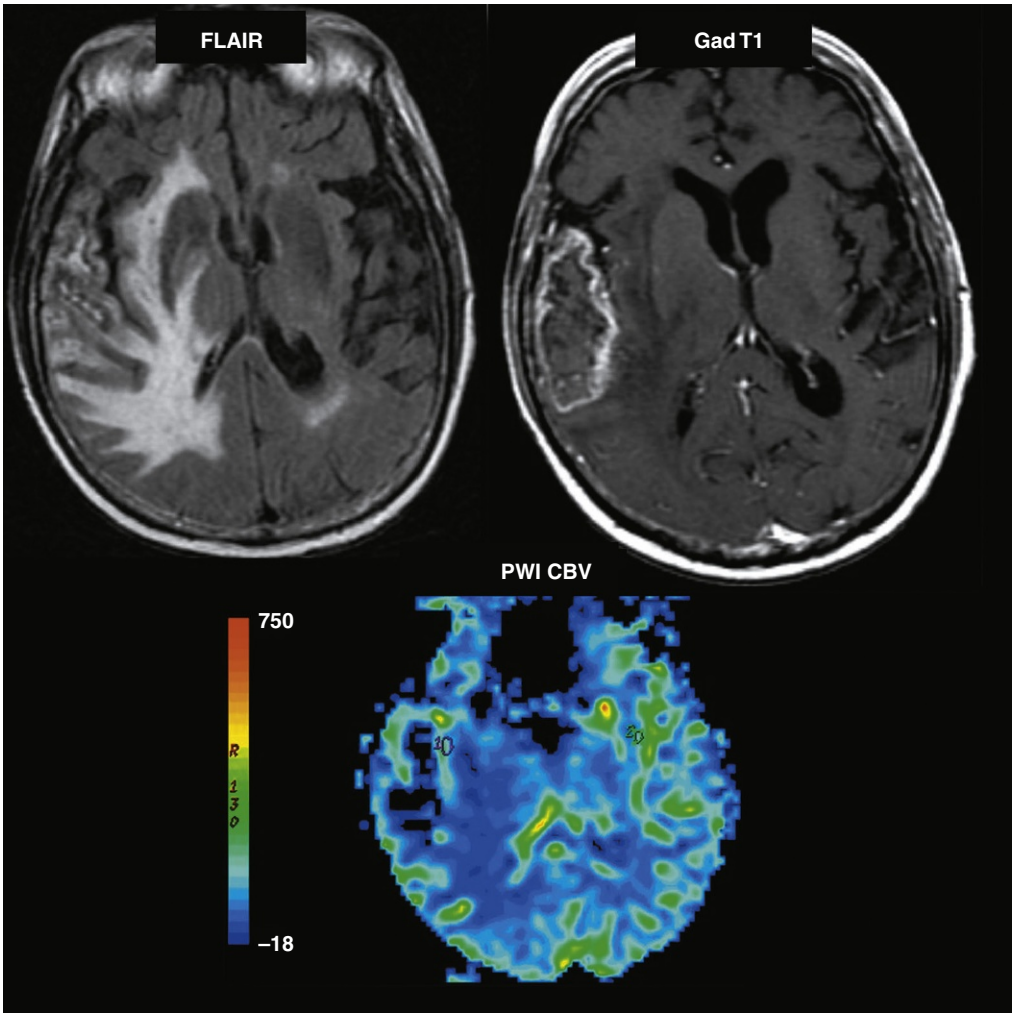


Fig. 5.13 An 82-year-old male patient radiated for external ear cancer underwent a magnetic resonance imaging study that showed an abnormally enhancing lesion in the right temporal lobe, without significant mass effect. Perfusion-weighted dynamic susceptibility imaging demonstrated no increased cerebral blood volume (no red) within this lesion, confirming the suspicion of radiation necrosis based on the clinical history.

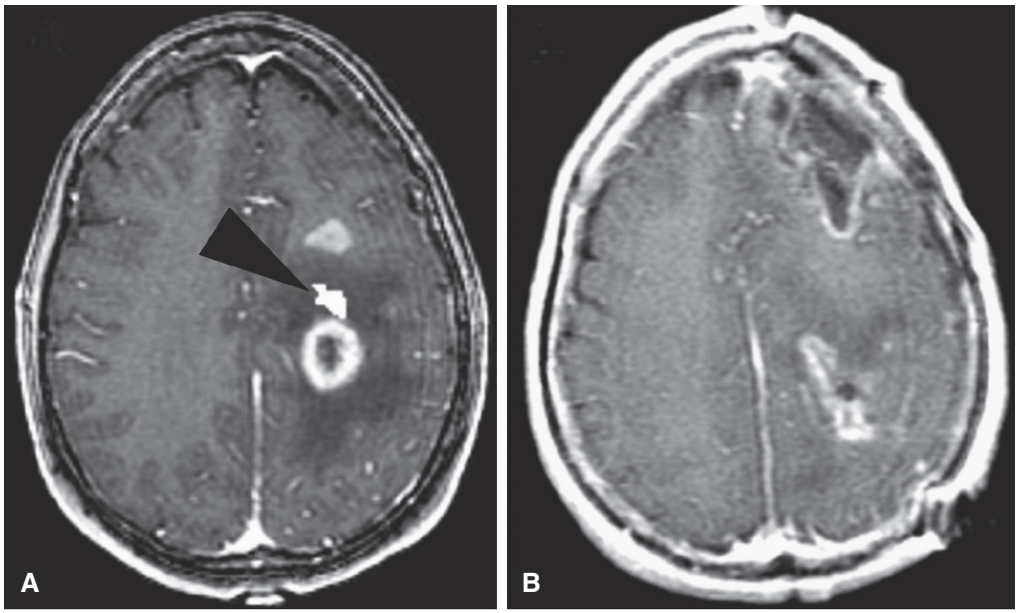


Fig. 5.14 A 66-year-old female patient with a left fronto-parietal glioblastoma multiforme. Diffusion tensor imaging (DTI) was obtained that demonstrated the corticospinal tract (arrowhead) to be located between two nodules of abnormal enhancement. The neurosurgeon took this information into consideration while planning his surgery. He used two approaches and performed two resection cavities, one anterior and one posterior, in order to spare the corticospinal tract.

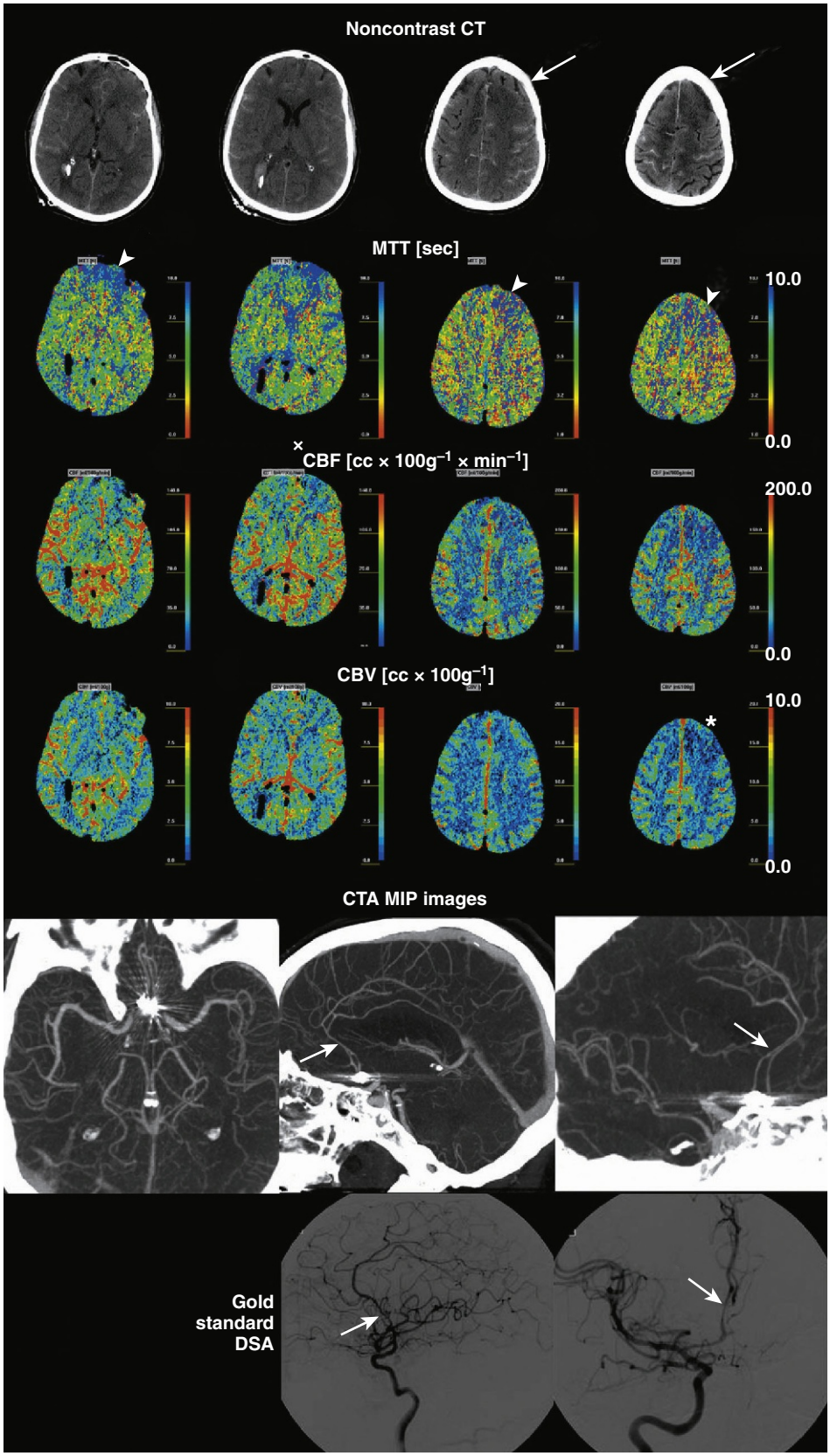


Fig. 5.15 Patient transferred at day 8 to neurovascular intensive care unit (ICU) from an outside institution after coiling of a ruptured anterior communicating artery aneurysm. Unenhanced brain computed tomography (CT) obtained at the admission of the patient in our neurovascular ICU demonstrated extensive residual subarachnoid hemorrhage and suspicious loss of gray–white matter contrast in the left superior frontal gyrus (white arrows). The tip of a right ventricular drain catheter is also visible.

On perfusion-CT, significantly abnormal brain perfusion in the distribution of the anterior and inferior branches of the left (and also, to a lesser extent, right) anterior cerebral arteries (ACA) (arrowheads) and of the right posterior middle cerebral artery (MCA) branches is seen primarily on mean transit time maps. The cerebral blood flow was also slightly decreased in the same territories, whereas cerebral blood volume was mainly preserved (it is lowered only in the left superior frontal gyrus (star)). CT angiogram confirmed the suspicion of moderate vasospasm of both A2 and A3 segments of the ACA (arrows), ultimately verified by gold standard digital subtraction angiography (DSA). No abnormality of the right posterior MCA branches was identified. Of note, the artifacts created by the coils on the CTA images, obscuring the A1 segments bilaterally and interfering with their evaluation.

Endovascular therapy (IA verapamil) was performed in the ACA territories during the DSA.

capillary bed.[134] Cortical arteriovenous fistulas, which are composed of one or a few arteriovenous shunts, are probably extreme cases of the more common angioarchitecture of an AVM that is made up of a number of shunts within the AVM nidus.

As a result, there is arteriovenous shunting with rapid flow and most probably accounting for the enlarged, flow-remodeled afferent and efferent vessels. Often presumed to be congenital lesions as a result of embryonic maldevelopment during the 4th to 8th week, there is remarkably little evidence for this assertion. Further, there have been multiple reports of AVMs that grow or regress. In addition, there are reported cases of de novo AVM formation.[135] There are substantial hemodynamic effects of AVMs.

DSA is the gold standard imaging technique for the evaluation of cerebral AVMs. Using DSA, one can obtain information regarding the angio-architecture of brain AVMs including vascular composition of the nidus, types of feeding arteries, and types and patterns of venous drainage. Ancillary findings include flow-related aneurysms, extranidal and intranidal aneurysms, venous strictures, and venous varices. The timing of imaging after hemorrhage is critical as nidus compression by the hematoma may lead to falsely negative DSA if it is done soon after the initial hemorrhage.[136] CT and MRI play a minor role in the diagnosis and management of cerebral AVMs. CT is the first-line imaging technique for patients presenting with a suspicion of acute ICH. The unruptured AVM may not be seen on noncontrast CT or may appear as a subtle, hyperdense region. After contrast administration, large, tortuous, high-density structures representing the serpentine vessels can be easily identified. MRI is used for AVM follow-up during and after treatment. On MRI, AVM features include enlarged cerebral arteries feeding the AVM, a cluster of signal voids representing the nidus, and enlarged draining veins. Secondary findings include gliosis or encephalomalacia from prior hemorrhage and/or areas of hypointensity caused by hemosiderin from prior hemorrhage.

Ischemic Strokes

Acute ischemic stroke is defined as abrupt onset of a focal neurological deficit due to a disturbance in the blood supply to a vascular territory in the brain. Rapid and accurate assessment is crucial for treatment, as acute intracerebral hemorrhage needs to be ruled out prior to the administration of known effective therapies such as intravenous thrombolytic drug therapy.[137] Guidelines are in place for early management (within 48 hours of stroke onset) of patients with acute ischemic stroke.[138] Nonenhanced CT scan should be obtained within 25 minutes of a patient's arrival in the ED. Brain imaging findings, including the size, location and vascular distribution of the infarction, presence of bleeding, severity of ischemic stroke, and/or presence of large vessel occlusion, affect immediate and long-term treatment decisions.[138] Imaging in acute stroke patients should be targeted toward the assessment of the four Ps: parenchyma, pipes, perfusion, and penumbra.[139] In other words, establish a diagnosis as early as possible, rule out ICH, and obtain accurate information about the intracranial vasculature (ie, identification of intravascular thrombi) and brain perfusion (differentiation of infarcted tissue from tissue at risk). Tissue at risk, or "penumbra," is defined as an area of markedly reduced perfusion, with compromised function yet still viable neurons, which might benefit from timely reperfusion thus preventing irreversible damage.[140,141]

Computed Tomography and Acute Stroke

Noncontrast CT of the brain has traditionally been the first-line imaging study in acute stroke as it can detect "early signs" of stroke and accurately rule out hemorrhage, a contraindication to thrombolytic stroke therapies.[142,143] Early CT findings of brain ischemia include (1) loss of contrast between white matter and grey matter (cortical ribbon and/or basal ganglia), (2) early mass effect, and (3) the presence of a hyperdense artery.[144–149] However, noncontrast CT has limited sensitivity (55–82%) for the hyperacute stage of ischemic stroke.[150,151] It may demonstrate subtle visible parenchymal damage within 3 hours.[152,153] Also, noncontrast CT cannot reliably differentiate between irreversibly damaged brain tissue and penumbra.

Emerging CT-based techniques have facilitated a more comprehensive multimodal evaluation of acute stroke. Noncontrast CT allows ruling out hemorrhage, CTA identifies intracranial thrombus, and PCT evaluates the functional state of ischemic brain tissue by differentiating between "at-risk" (the so-called "penumbra") and irreversibly damaged brain tissue (Fig. 5.16).[150]

CTA allows a quick and detailed evaluation of the intra- and extracranial vasculature with thin-section multiplanar views.[154,155] Its utility in acute stroke lies not only in its ability to detect large-vessel thrombi within intracranial vessels and to evaluate the carotid and vertebral arteries in the neck,[156–158] but also in its potential in guiding therapy. In particular, the exact location (ie, proximal vs. peripheral occlusions) and the extent of vascular occlusion have been shown to have prognostic value in the response to thrombolytics and determination of collateral circulation and possible risk of subsequent recanalization.[159] For example, "top of carotid" occlusions, proximal MCA branch occlusions, or significant thrombus burden might be poor candidates for intravenous thrombolytics, and possibly may be better candidates for intra-arterial or mechanical thrombolysis.[160] The sensitivity and specificity of CTA for detection of intracranial occlusions ranges between 92% and 100% and between 82% and 100% respectively, with a positive predictive value of 91–100%.[154,161]

PCT has now become the third component in the multimodal CT assessment of acute ischemic stroke.[162] Compared with MR imaging, xenon-enhanced CT, positron emission tomography, and single photon emission CT, PCT is more widely available and can be performed quickly on any standard helical CT scanner immediately after noncontrast CT.[163] PCT maps then can be generated in a short time at an appropriate workstation.[163] PCT has been shown to be more accurate than noncontrast CT for stroke detection[150] and for assessing the extent of the stroke.[164] MTT maps were more sensitive, while CBF and CBV maps were more specific for distinguishing ischemia from infarction.[164,165] PCT distinction of the infarct core from the penumbra is based on the concept of cerebral vascular autoregulation. In the penumbra, autoregulation is preserved, MTT is prolonged, but CBV is preserved because of vasodilatation and collateral recruitment as part of the autoregulation process. In the infarct core, autoregulation is lost, MTT is prolonged and CBV is down.[166] Thus, using appropriate MTT and CBV thresholds, infarct core and penumbra can be distinguished on PCT maps (see Fig. 5.16).[167]

Magnetic Resonance Imaging and Acute Stroke

Multimodal MRI including DWI, PWI and MRA affords similar results to the CT-based multimodal techniques described above. DWI shows the infarct core, the DWI-PWI mismatch represents the penumbra, and MRA allows the assessment of vascular patency across the whole brain with high-resolution structural imaging (see Fig. 5.6).[168,169]

Although acute infarcts may be seen early on conventional MRI, DWI is more sensitive for the detection of hyperacute ischemia. DWI hyperintensity and ADC hypointensity occur shortly after acute ischemia as a result of a failure of the ATPase

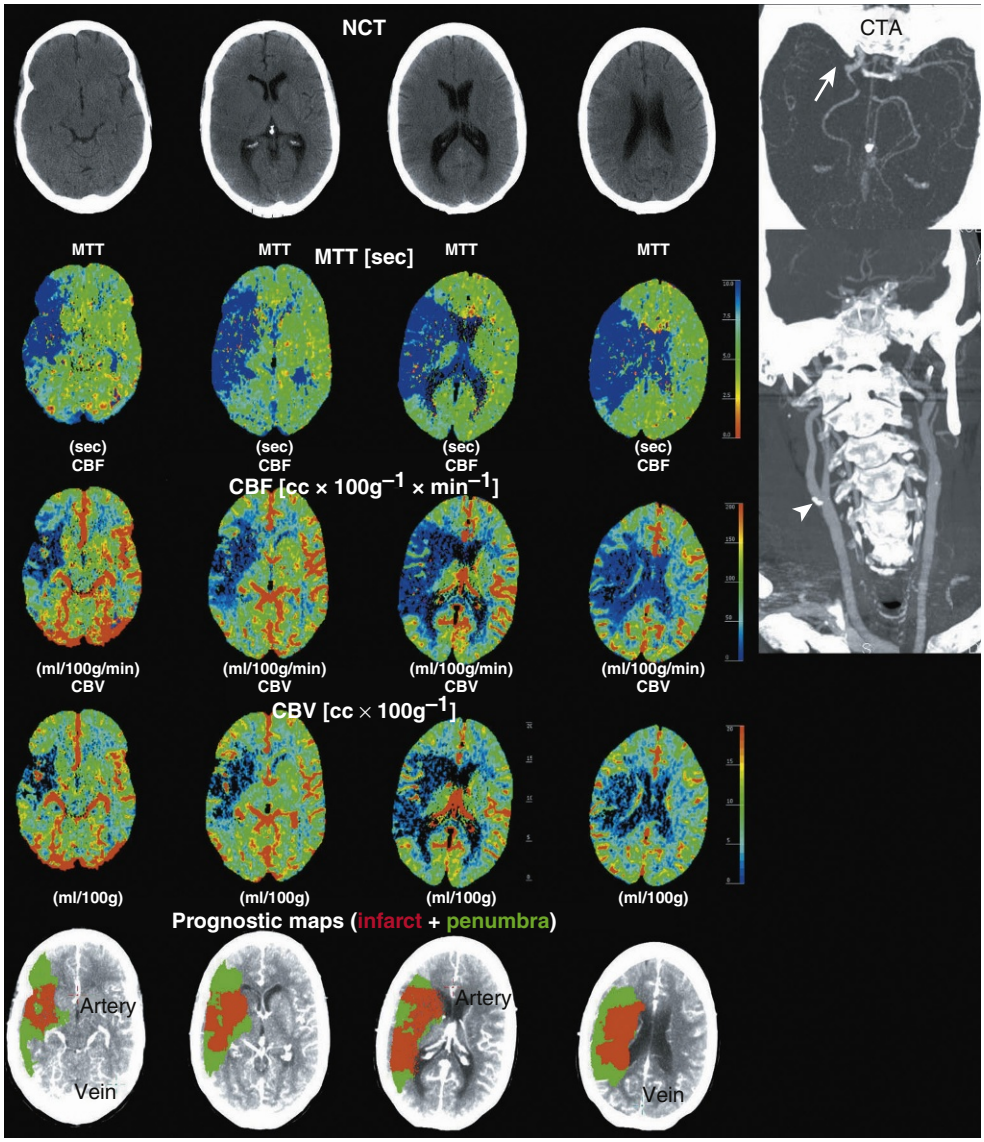


Fig. 5.16 Modern computed tomography (CT) survey in a 57-year-old male patient admitted in our emergency room with a left hemisyndrome, including an unenhanced CT (first row), a perfusionCT (PCT) (rows 2 through 5) and a CT-angiogram (CTA) (right column). The unenhanced CT ruled out a cerebral hemorrhage. From the PCT raw data, three parametric maps were extracted, relating to mean transit time (MTT, second row), cerebral blood flow (CBF, third row), and cerebral blood volume (CBV, fourth row), respectively. Application of the concept of cerebral vascular autoregulation led to a prognostic map (fifth row), describing the infarct in red and the penumbra in green; the latter being the target of acute reperfusion therapies. CTA identified an occlusion at the right M1-M2 junction (arrow) as the origin of the hemodynamic disturbance demonstrated by PCT. CTA also revealed a calcified atheromatous plaque at the right carotid bifurcation (arrowhead).

pump, subsequent loss of ion homeostasis, and the movement of water into the intracellular compartment where it is relatively restricted (cytotoxic edema).[24] These radiographic findings identify severely ischemic tissue within minutes of stroke onset, whereas conventional MRI and noncontrast CT images might be normal.

PWI changes precede the development of DWI lesions and, in the absence of reperfusion, the area of restricted diffusion spontaneously progresses within the region of perfusion abnormality. Conversely, spontaneous or therapeutic recanalization tends to prevent progression of this process. By combing the DWI and PWI image information, one can generate a composite so-called "diffusion-perfusion mismatch,"[170] that is theorized to represent the tissue at risk, or penumbra. Penumbra as defined by the DWI/PWI mismatch is very similar to the penumbra characterized by PCT.[171] In as many as 70% of acute strokes caused by MCA occlusion imaged within 6 hours of onset, a DWI–PWI mismatch is present, the PWI lesion (hypoperfusion) being larger than the DWI core.[170] Two other patterns can be observed: (1) DWI lesion = PWI lesion size (ie, tissue is irreversibly infarcted and no penumbra is present); and (2) DWI lesion > PWI lesion or DWI lesion with no perfusion defect (ie, usually indicates early reperfusion of ischemic tissue, and the DWI lesion size does not change over time).[172] However, there are some aspects of the mismatch concept that still need to be addressed. The initial DWI lesion abnormality can be reversible and thus includes areas of penumbral as well as infracted tissue.[173,174] In addition, the PWI parameter most representative of hypoperfusion has not been clearly defined (eg, prolonged MTT or TTP). Nevertheless, the importance of the DWI–PWI mismatch hypothesis is the ability to potentially appropriately select patients in whom there is evidence of potentially salvageable tissue for therapeutic intervention. Several recent trials have studied MRI perfusion/diffusion mismatch. EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) was designed to answer the question of whether intravenous rtPA given 3 to 6 hours after stroke onset promotes reperfusion

and attenuates infarct growth in patients who have a "mismatch" between perfusion-weighted and diffusion-weighted MRI. Intravenous rtPA was nonsignificantly associated with lower infarct growth but significantly associated with increased reperfusion in patients who had mismatch.[175] The Desmoteplase in Acute Ischemic Stroke (DIAS) 1 and 2 trials tested the concept of using advanced MR or CT for intravenous fibrinolysis triage in the 3- to 9-hour time window.[176,177] Unfortunately, there was no clinical benefit demonstrated, although favorable trends were seen in the MR-selected patients.[177] There are newer studies underway that incorporate the lessons learned from these experiences.

REFERENCES

1. Hofman PA, Nelemans P, Kemerink GJ, Wilmink JT. Value of radiological diagnosis of skull fracture in the management of mild head injury: Meta-analysis. *J Neurol Neurosurg Psychiatry*. 2000;68(4):416–422.
2. Lloyd DA, Carty H, Patterson M, Butcher CK, Roe D. Predictive value of skull radiography for intracranial injury in children with blunt head injury. *Lancet*. 1997;349(9055):821–824.
3. Masters SJ, McClean PM, Arcarese JS, et al. Skull X-ray examinations after head trauma. Recommendations by a multidisciplinary panel and validation study. *N Engl J Med*. 1987;316(2):84–91.
4. Murphy KJ, Brunberg JA. Orbital plain films as a prerequisite for MR imaging: Is a known history of injury a sufficient screening criterion? *AJR Am J Roentgenol*. 1996;167(4):1053–1055.
5. Seelig JM, Becker DP, Miller JD, Greenberg RP, Ward JD, Choi SC. Traumatic acute subdural hematoma: Major mortality reduction in comatose patients treated within four hours. *N Engl J Med*. 1981;304(25):1511–1518.
6. Lee J, Evans CS, Singh N, et al. Head computed tomography utilization and intracranial hemorrhage rates. *Emerg Radiol*. 2013;20(3):219–223.
7. Goske MJ, Applegate KE, Boylan J, et al. The Image Gently campaign: Working together to change practice. *AJR Am J Roentgenol*. 2008;190(2):273–274.
8. Bronen RA, Sze G. Magnetic resonance imaging contrast agents: Theory and application to the central nervous system. *J Neurosurg*. 1990;73(6):820–839.
9. Topal NB, Hakyemez B, Erdogan C, et al. MR imaging in the detection of diffuse axonal injury with mild traumatic brain injury. *Neurol Res*. 2008;30(9):974–978.
10. Yousry TA, Filippi M, Becker C, Horsfield MA, Voltz R. Comparison of MR pulse sequences in the detection of multiple sclerosis lesions. *AJNR Am J Neuroradiol*. 1997;18(5):959–963.
11. Verma RK, Kottke R, Andereggen L, et al. Detecting subarachnoid hemorrhage: Comparison of combined FLAIR/SWI versus CT. *Eur J Radiol*. 2013;82(9):1539–1545.
12. Yamada N, Imakita S, Nishimura T, Takamiya M, Naito H. Evaluation of the susceptibility effect on gradient echo phase images in vivo: A sequential study of intracerebral hematoma. *Magn Reson Imaging*. 1992;10(4):559–571.
13. Chen W, Zhu W, Kovanlikaya I, et al. Intracranial calcifications and hemorrhages: Characterization with quantitative susceptibility mapping. *Radiology*. 2014;270(2):496–505.
14. Sawyer-Glover AM, Shellock FG. Pre-MRI procedure screening: Recommendations and safety considerations for biomedical implants and devices. *J Magn Reson Imaging*. 2000;12(1):92–106.
15. Shellock FG, Crues JV. MR procedures: Biologic effects, safety, and patient care. *Radiology*. 2004;232(3):635–652.
16. Brant-Zawadzki M, Gould R, Norman D, Newton TH, Lane B. Digital subtraction cerebral angiography by intraarterial injection: Comparison with conventional angiography. *AJR Am J Roentgenol*. 1983;140(2):347–353.
17. Wang H, Fraser K, Wang D, Lanzino G. The evolution of endovascular therapy for neurosurgical disease. *Neurosurg Clin N Am*. 2005;16(2):223–229.
18. Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: A meta-analysis. *Stroke*. 1999;30(2):317–320.
19. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: Prospective analysis of 2,899 procedures and review of the literature. *Radiology*. 2003;227(2):522–528.
20. Ozsarlak O, Van Goethem JW, Maes M, Parizel PM. MR angiography of the intracranial vessels: Technical aspects and clinical applications. *Neuroradiology*. 2004;46(12):955–972.
21. Wilms G, Bosmans H, Demaerel P, Marchal G. Magnetic resonance angiography of the intracranial vessels. *Eur J Radiol*. 2001;38(1):10–18.
22. Vieco PT. CT angiography of the intracranial circulation. *Neuroimaging Clin N Am*. 1998;8(3):577–592.
23. Katayama H, Heneine N, van Gessel R, Taroni P, Spinazzi A. Clinical experience with iomeprol in myelography and myelo-CT: Clinical pharmacology and double-blind comparisons with iopamidol, iohexol, and iotrolan. *Invest Radiol*. 2001;36(1):22–32.
24. Latchaw RE, Yonas H, Hunter GJ, et al, Council on Cardiovascular Radiology of the American Heart Association. Guidelines and recommendations for perfusion imaging in cerebral ischemia: A scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke*. 2003;34(4):1084–1104.
25. Leiva-Salinas C, Provenzale JM, Kudo K, Sasaki M, Wintermark M. The alphabet soup of perfusion CT and MR imaging: Terminology revisited and clarified in five questions. *Neuroradiology*. 2012;54(9):907–918.
26. Wintermark M, Thiran JP, Maeder P, Schnyder P, Meuli R. Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: A validation study. *AJNR Am J Neuroradiol*. 2001;22(5):905–914.
27. Snyder KV, Mokin M, Bates VE. Neurologic applications of whole-brain volumetric multidetector computed tomography. *Neurol Clin*. 2014;32(1):237–251.
28. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. *Radiology*. 2000;217(2):331–345.
29. Schaefer PW, Copen WA, Lev MH, Gonzalez RG. Diffusion-weighted imaging in acute stroke. *Neuroimaging Clin N Am*. 2005;15(3):503–530, ix–x.
30. Moen KG, Skandsen T, Folvik M, et al. A longitudinal MRI study of traumatic axonal injury in patients with moderate and severe traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2012;83(12):1193–1200.
31. Huisman TA, Sorensen AG, Hergan K, Gonzalez RG, Schaefer PW. Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *J Comput Assist Tomogr*. 2003;27(1):5–11.
32. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. *J Cereb Blood Flow Metab*. 1999;19(7):701–735.
33. Petrella JR, Provenzale JM. MR perfusion imaging of the brain: Techniques and applications. *AJR Am J Roentgenol*. 2000;175(1):207–219.
34. Østergaard L. Principles of cerebral perfusion imaging by bolus tracking. *J Magn Reson Imaging*. 2005;22(6):710–717.
35. Deibler AR, Pollock JM, Kraft RA, Tan H, Burdette JH, Maldjian JA. Arterial spin-labeling in routine clinical practice, part 1: Technique and artifacts. *AJNR Am J Neuroradiol*. 2008;29(7):1228–1234.
36. Castillo M, Kwock L, Mukherji SK. Clinical applications of proton MR spectroscopy. *AJNR Am J Neuroradiol*. 1996;17(1):1–15.
37. Maheshwari SR, Fatterpekar GM, Castillo M, Mukherji SK. Proton MR spectroscopy of the brain. *Semin Ultrasound CT MR*. 2000;21(6):434–451.
38. Birken DL, Oldendorf WH. N-acetyl-L-aspartic acid: A literature review of a compound prominent in 1H-NMR spectroscopic studies of brain. *Neurosci Biobehav Rev*. 1989 Spring;13(1):23–31.
39. Garnett MR, Blamire AM, Corkill RG, Cadoux-Hudson TA, Rajagopalan B, Styles P. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain*. 2000;123(Pt 10):2046–2054.
40. Manninen PH, Kucharczyk W. A new frontier: Magnetic resonance imaging-operating room. *J Neurosurg Anesthesiol*. 2000;12(2):141–148. Review. PubMed PMID: 10774611.
41. Bradley WG. Achieving gross total resection of brain tumors: Intraoperative MR imaging can make a big difference. *AJNR Am J Neuroradiol*. 2002;23(3):348–349.
42. Black PM, Moriarty T, Alexander 3rd. E, et al. Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. *Neurosurgery*. 1997;41(4):831–842; discussion 842–845.
43. Jolesz FA, Morrison PR, Koran SJ, et al. Compatible instrumentation for intraoperative MRI: Expanding resources. *J Magn Reson Imaging*. 1998;8(1):8–11.
44. Society of Anesthesiologists Task Force on Anesthetic Care for Magnetic Resonance Imaging. Practice advisory on anesthetic care for magnetic resonance imaging: A report by the Society of Anesthesiologists Task Force on Anesthetic Care for Magnetic Resonance Imaging. *Anesthesiology*. 2009;110(3):459–479.
45. Bergese SD, Puente EG. Anesthesia in the intraoperative MRI environment. *Neurosurg Clin N Am*. 2009;20(2):155–162.
46. Archer DP, McTaggart Cowan RA, Falkenstein RJ, Sutherland GR. Intraoperative mobile magnetic resonance imaging for craniotomy lengthens the procedure but does not increase morbidity. *Can J Anaesth*. 2002;49(4):420–426.

47. König RW, Heinen CP, Antoniadis G, et al. Image guided aneurysm surgery in a Brainsuite® intraoperative MRI Miyabi 1.5 T environment. *Acta Neurochir Suppl*. 2011;109:107–110.
48. Gooden CK. Anesthesia for magnetic resonance imaging. *Curr Opin Anaesthesiol*. 2004;17(4):339–342.
49. Kanal E, Borgstede JP, Barkovich AJ, et al, American College of Radiology. American College of Radiology White Paper on MR Safety. *AJR Am J Roentgenol*. 2002;178(6):1335–1347.
50. Kanal E, Borgstede JP, Barkovich AJ, et al, American College of Radiology. American College of Radiology White Paper on MR Safety: 2004 update and revisions. *AJR Am J Roentgenol*. 2004;182(5):1111–1114.
51. Shellock FG, Woods TO, Crues 3rd. JV. MR labeling information for implants and devices: Explanation of terminology. *Radiology*. 2009;253(1):26–30.
52. McClain CD, Rockoff MA, Soriano SG. Anesthetic concerns for pediatric patients in an intraoperative MRI suite. *Curr Opin Anaesthesiol*. 2011;24(5):480–486.
53. Shah MN, Leonard JR, Inder G, et al. Intraoperative magnetic resonance imaging to reduce the rate of early reoperation for lesion resection in pediatric neurosurgery. *J Neurosurg Pediatr*. 2012;9(3):259–264.
54. Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. *Neurosurg Focus*. 2007;22(5):E1.
55. Wijdicks EF, Sheth KN, Carter BS, et al, American Heart Association Stroke Council. Recommendations for the management of cerebral and cerebellar infarction with swelling: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(4):1222–1238.
56. Bradley Jr. WG. MR appearance of hemorrhage in the brain. *Radiology*. 1993;189(1):15–26.
57. Gomori JM, Grossman RI. Mechanisms responsible for the MR appearance and evolution of intracranial hemorrhage. *Radiographics*. 1988;8(3):427–440.
58. Huisman TA. Intracranial hemorrhage: Ultrasound, CT and MRI findings. *Eur Radiol*. 2005;15(3):434–440.
59. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *N Engl J Med*. 1986;314(15):953–958.
60. Johnson PL, Eckard DA, Chason DP, Brecheisen MA, Batnitzky S. Imaging of acquired cerebral herniations. *Neuroimaging Clin N Am*. 2002;12(2):217–228.
61. Wernick S, Wells RG. Sequelae of temporal lobe herniation: MR imaging. *J Comput Assist Tomogr*. 1989;13(2):323–325.
62. Hahn FJ, Gurney J. CT signs of central descending transtentorial herniation. *AJNR Am J Neuroradiol*. 1985;6(5):844–845.
63. Sze G. Diseases of the intracranial meninges: MR imaging features. *AJR Am J Roentgenol*. 1993;160(4):727–733.
64. Sherman JL, Citrin CM, Bowen BJ, Gangarosa RE. MR demonstration of altered cerebrospinal fluid flow by obstructive lesions. *AJNR Am J Neuroradiol*. 1986;7(4):571–579.
65. Levy LM. MR imaging of cerebrospinal fluid flow and spinal cord motion in neurologic disorders of the spine. *Magn Reson Imaging Clin N Am*. 1999;7(3):573–587.
66. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
67. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth*. 2007;99(1):4–9.
68. Ahmadi J, Destian S. Head trauma. *Top Magn Reson Imaging*. 1989;2(1):17–24.
69. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PM. Indications for computed tomography in patients with minor head injury. *N Engl J Med*. 2000;343(2):100–105.
70. Moran SG, McCarthy MC, Uddin DE, Poelstra RJ. Predictors of positive CT scans in the trauma patient with minor head injury. *Am Surg*. 1994;60(7):533–535; discussion 535–536.
71. Sinson G, Bagley LJ, Cecil KM, et al. Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: Correlation with clinical outcome after traumatic brain injury. *AJNR Am J Neuroradiol*. 2001;22(1):143–151.
72. Ogawa T, Sekino H, Uzura M, et al. Comparative study of magnetic resonance and CT scan imaging in cases of severe head injury. *Acta Neurochir Suppl (Wien)*. 1992;55:8–10.
73. Mittl RL, Grossman RI, Hiehle JF, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol*. 1994;15(8):1583–1589.
74. Xiong KL, Zhu YS, Zhang WG. Diffusion tensor imaging and magnetic resonance spectroscopy in traumatic brain injury: A review of recent literature. *Brain Imaging Behav*. 2014;8(4):487–496.
75. Thornbury JR, Campbell JA, Masters SJ, Fryback DG. Skull fracture and the low risk of intracranial sequelae in minor head trauma. *AJR Am J Roentgenol*. 1984;143(3):661–664.
76. Zee CS, Hovanessian A, Go JL, Kim PE. Imaging of sequelae of head trauma. *Neuroimaging Clin N Am*. 2002;12(2):325–338, ix.
77. Alvi A, Bereliani 4th A. Trauma to the temporal bone: Diagnosis and management of complications. *J Craniomaxillofac Trauma*. 1996 Fall;2(3):36–48.
78. Kruse JJ, Awasthi D. Skull-base trauma: Neurosurgical perspective. *J Craniomaxillofac Trauma*. 1998 Summer;4(2):8–14; discussion 7.
79. Collins JM, Krishnamoorthy AK, Kubal WS, Johnson MH, Poon CS. Multidetector CT of temporal bone fractures. *Semin Ultrasound CT MR*. 2012;33(5):418–431.
80. Alder ME, Deahl ST, Matteson SR. Clinical usefulness of two-dimensional reformatted and three-dimensionally rendered computerized tomographic images: Literature review and a survey of surgeons' opinions. *J Oral Maxillofac Surg*. 1995;53(4):375–386.
81. Fatterpekar GM, Doshi AH, Dugar M, Delman BN, Naidich TP, Som PM. Role of 3D CT in the evaluation of the temporal bone. *Radiographics*. 2006;26(suppl 1):S117–S132.
82. Schuknecht B, Graetz K. Radiologic assessment of maxillofacial, mandibular, and skull base trauma. *Eur Radiol*. 2005;15(3):560–568.
83. Lloyd MN, Kimber PM, Burrows EH. Post-traumatic cerebrospinal fluid rhinorrhoea: Modern high-definition computed tomography is all that is required for the effective demonstration of the site of leakage. *Clin Radiol*. 1994;49(2):100–103.
84. Stone JA, Castillo M, Neelon B, Mukherji SK. Evaluation of CSF leaks: High-resolution CT compared with contrast-enhanced CT and radionuclide cisternography. *AJNR Am J Neuroradiol*. 1999;20(4):706–712.
85. Zimmerman RA, Bilaniuk LT. Computed tomographic staging of traumatic epidural bleeding. *Radiology*. 1982;144(4):809–812.
86. Bricolo AP, Pasut LM. Extradural hematoma: Toward zero mortality. A prospective study. *Neurosurgery*. 1984;14(1):8–12.
87. Al-Nakshabandi NA. The swirl sign. *Radiology*. 2001;218(2):433.
88. Lee KS, Bae WK, Bae HG, Doh JW, Yun IG. The computed tomographic attenuation and the age of subdural hematomas. *J Korean Med Sci*. 1997;12(4):353–359.
89. Smith Jr WP, Batnitzky S, Rengachary SS. Acute isodense subdural hematomas: A problem in anemic patients. *AJR Am J Roentgenol*. 1981;136(3):543–546.
90. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007;369(9558):306–318.
91. Yeakley JW, Patchall LL, Lee KF. Interpeduncular fossa sign: CT criterion of subarachnoid hemorrhage. *Radiology*. 1986;158(3):699–700.
92. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: Comparison with CT in hyperacute intracerebral hemorrhage. *Stroke*. 1999;30(4):765–768.
93. Young RJ, Destian S. Imaging of traumatic intracranial hemorrhage. *Neuroimaging Clin N Am*. 2002;12(2):189–204.
94. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: Definition, diagnosis and grading. *Histopathology*. 1989;15(1):49–59.
95. Hammoud DA, Wasserman BA. Diffuse axonal injuries: Pathophysiology and imaging. *Neuroimaging Clin N Am*. 2002;12(2):205–216.
96. Scheid R, Preul C, Gruber O, Wiggins C, von Cramon DY. Diffuse axonal injury associated with chronic traumatic brain injury: Evidence from T2*-weighted gradient-echo imaging at 3 T. *AJNR Am J Neuroradiol*. 2003;24(6):1049–1056.
97. Kinoshita T, Moritani T, Hiwatashi A, et al. Conspicuity of diffuse axonal injury lesions on diffusion-weighted MR imaging. *Eur J Radiol*. 2005;56(1):5–11.
98. Parizel PM, Ozsarlak, Van Goethem JW, et al. Imaging findings in diffuse axonal injury after closed head trauma. *Eur Radiol*. 1998;8(6):960–965.
99. Xiong KL, Zhu YS, Zhang WG. Diffusion tensor imaging and magnetic resonance spectroscopy in traumatic brain injury: A review of recent literature. *Brain Imaging Behav*. 2014 Jan 23.
100. Lunsford LD, Martinez AJ, Latchaw RE. Magnetic resonance imaging does not define tumor boundaries. *Acta Radiol Suppl*. 1986;369:154–156.
101. Price SJ, Jena R, Burnet NG, et al. Improved delineation of glioma margins and regions of infiltration with the use of diffusion tensor imaging: An image-guided biopsy study. *AJNR Am J Neuroradiol*. 2006;27(9):1969–1974.
102. Croteau D, Scarpace L, Hearshen D, et al. Correlation between magnetic resonance spectroscopy imaging and image-guided biopsies: Semiquantitative and qualitative histopathological analyses of patients with untreated glioma. *Neurosurgery*. 2001;49(4):823–829.
103. McKnight TR, von dem Bussche MH, Vigneron DB, et al. Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. *J Neurosurg*. 2002;97(4):794–802.

104. Price SJ, Jena R, Burnet NG, Carpenter TA, Pickard JD, Gillard JH. Predicting patterns of glioma recurrence using diffusion tensor imaging. *Eur Radiol*. 2007;17(7):1675–1684.
105. Provenzale JM, McGraw P, Mhatre P, Guo AC, Delong D. Peritumoral brain regions in gliomas and meningiomas: Investigation with isotropic diffusion-weighted MR imaging and diffusion-tensor MR imaging. *Radiology*. 2004;232(2):451–460.
106. Tropine A, Vucurevic G, Delani P, et al. Contribution of diffusion tensor imaging to delineation of gliomas and glioblastomas. *J Magn Reson Imaging*. 2004;20(6):905–912.
107. van Westen D, Lätt J, Englund E, Brockstedt S, Larsson EM. Tumor extension in high-grade gliomas assessed with diffusion magnetic resonance imaging: Values and lesion-to-brain ratios of apparent diffusion coefficient and fractional anisotropy. *Acta Radiol*. 2006;47(3):311–319.
108. Julià-Sapé M, Acosta D, Majós C, et al. Comparison between neuroimaging classifications and histopathological diagnoses using an international multicenter brain tumor magnetic resonance imaging database. *J Neurosurg*. 2006;105(1):6–14.
109. Ginsberg LE, Fuller GN, Hashmi M, Leeds NE, Schomer DF. The significance of lack of MR contrast enhancement of supratentorial brain tumors in adults: Histopathological evaluation of a series. *Surg Neurol*. 1998;49(4):436–440.
110. Beppu T, Inoue T, Shibata Y, et al. Fractional anisotropy value by diffusion tensor magnetic resonance imaging as a predictor of cell density and proliferation activity of glioblastomas. *Surg Neurol*. 2005;63(1):56–61. discussion 61.
111. Stadlbauer A, Ganslandt O, Buslei R, et al. Gliomas: Histopathologic evaluation of changes in directionality and magnitude of water diffusion at diffusion-tensor MR imaging. *Radiology*. 2006;240(3):803–810.
112. Sugahara T, Korogi Y, Kochi M, et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging*. 1999;9(1):53–60.
113. Fountas KN, Kapsalaki EZ, Gotsis SD, et al. In vivo proton magnetic resonance spectroscopy of brain tumors. *Stereotact Funct Neurosurg*. 2000;74(2):83–94.
114. Law M. MR spectroscopy of brain tumors. *Top Magn Reson Imaging*. 2004;15(5):291–313.
115. Law M, Yang S, Wang H, et al. Glioma grading: Sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. *AJNR Am J Neuroradiol*. 2003;24(10):1989–1998.
116. McKnight TR, Lamborn KR, Love TD, et al. Correlation of magnetic resonance spectroscopic and growth characteristics within Grades II and III gliomas. *J Neurosurg*. 2007;106(4):660–666.
117. Nafe R, Herminghaus S, Raab P, et al. Preoperative proton-MR spectroscopy of gliomas--correlation with quantitative nuclear morphology in surgical specimen. *J Neurooncol*. 2003;63(3):233–245.
118. Hakyemez B, Erdogan C, Ercan I, Ergin N, Uysal S, Atahan S. High-grade and low-grade gliomas: Differentiation by using perfusion MR imaging. *Clin Radiol*. 2005;60(4):493–502.
119. Shin JH, Lee HK, Kwun BD, et al. Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: Preliminary results. *AJR Am J Roentgenol*. 2002;179(3):783–789.
120. Sugahara T, Korogi Y, Kochi M, et al. Correlation of MR imaging-determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. *AJR Am J Roentgenol*. 1998;171(6):1479–1486.
121. Lev MH, Ozsunar Y, Henson JW, et al. Glial tumor grading and outcome prediction using dynamic spin-echo MR susceptibility mapping compared with conventional contrast-enhanced MR: Confounding effect of elevated rCBV of oligodendrogliomas [corrected]. *AJNR Am J Neuroradiol*. 2004;25(2):214–221. Erratum in: *AJNR Am J Neuroradiol*. 2004;25(3):B1.
122. Sugahara T, Korogi Y, Tomiguchi S, et al. Posttherapeutic intraaxial brain tumor: The value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. *AJNR Am J Neuroradiol*. 2000;21(5):901–909.
123. Barrett T, Brechbiel M, Bernardo M, Choyke PL. MRI of tumor angiogenesis. *J Magn Reson Imaging*. 2007;26(2):235–249.
124. Chernov MF, Hayashi M, Izawa M, et al. Multivoxel proton MRS for differentiation of radiation-induced necrosis and tumor recurrence after gamma knife radiosurgery for brain metastases. *Brain Tumor Pathol*. 2006;23(1):19–27.
125. Tomoi M, Kimura H, Yoshida M, et al. Alterations of lactate (+lipid) concentration in brain tumors with in vivo hydrogen magnetic resonance spectroscopy during radiotherapy. *Invest Radiol*. 1997;32(5):288–296.
126. Wilden JA, Voorhies J, Mosier KM, O'Neill DP, Cohen-Gadol AA. Strategies to maximize resection of complex, or high surgical risk, low-grade gliomas. *Neurosurg Focus*. 2013;34(2):E5.
127. Chappell ET, Moure FC, Good MC. Comparison of computed tomographic angiography with digital subtraction angiography in the diagnosis of cerebral aneurysms: A meta-analysis. *Neurosurgery*. 2003;52(3):624–631; discussion 630–631.
128. Dammert S, Krings T, Moller-Hartmann W, et al. Detection of intracranial aneurysms with multislice CT: Comparison with conventional angiography. *Neuroradiology*. 2004;46(6):427–434.
129. Tipper G, U-King-Im JM, Price SJ, et al. Detection and evaluation of intracranial aneurysms with 16-row multislice CT angiography. *Clin Radiol*. 2005;60(5):565–572.
130. White PM, Teasdale EM, Wardlaw JM, Easton V. Intracranial aneurysms: CT angiography and MR angiography for detection prospective blinded comparison in a large patient cohort. *Radiology*. 2001;219(3):739–749.
131. White PM, Wardlaw JM, Easton V. Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. *Radiology*. 2000;217(2):361–370.
132. Chaudhary SR, Ko N, Dillon WP, et al. Prospective evaluation of multidetector-row CT angiography for the diagnosis of vasospasm following subarachnoid hemorrhage: A comparison with digital subtraction angiography. *Cerebrovasc Dis*. 2008;25(1–2):144–150.
133. Wintermark M, Ko NU, Smith WS, Liu S, Higashida RT, Dillon WP. Vasospasm after subarachnoid hemorrhage: Utility of perfusion CT and CT angiography on diagnosis and management. *AJNR Am J Neuroradiol*. 2006;27(1):26–34.
134. Hofmeister C, Stapf C, Hartmann A, et al. Demographic, morphological, and clinical characteristics of 1289 patients with brain arteriovenous malformation. *Stroke*. 2000;31(6):1307–1310.
135. Du R, Hashimoto T, Tihan T, Young WL, Perry V, Lawton MT. Growth and regression of arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia. Case report. *J Neurosurg*. 2007;106(3):470–477.
136. Hino A, Fujimoto M, Yamaki T, Iwamoto Y, Katsumori T. Value of repeat angiography in patients with spontaneous subcortical hemorrhage. *Stroke*. 1998;29(12):2517–2521.
137. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581–1587.
138. Jauch EC, Saver JL, Adams Jr HP, et al, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947.
139. Rowley HA. The four Ps of acute stroke imaging: Parenchyma, pipes, perfusion, and penumbra. *AJNR Am J Neuroradiol*. 2001;22(4):599–601.
140. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke*. 1981;12(6):723–725.
141. Heiss WD. Ischemic penumbra: Evidence from functional imaging in man. *J Cereb Blood Flow Metab*. 2000;20(9):1276–1293.
142. Moulin T, Cattin F, Crépin-Leblond T, et al. Early CT signs in acute middle cerebral artery infarction: Predictive value for subsequent infarct locations and outcome. *Neurology*. 1996;47(2):366–375.
143. von Kummer R, Bourquain H, Bastianello S, et al. Early prediction of irreversible brain damage after ischemic stroke at CT. *Radiology*. 2001;219(1):95–100.
144. Barber PA, Demchuk AM, Hudon ME, Pexman JH, Hill MD, Buchan AM. Hyperdense sylvian fissure MCA "dot" sign: A CT marker of acute ischemia. *Stroke*. 2001;32(1):84–88.
145. Leys D, Pruvo JP, Godefroy O, Rondepierre P, Leclerc X. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. *Stroke*. 1992;23(3):317–324.
146. Tomsick T, Brott T, Barsan W, et al. Prognostic value of the hyperdense middle cerebral artery sign and stroke scale score before ultraearly thrombolytic therapy. *AJNR Am J Neuroradiol*. 1996;17(1):79–85.
147. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction: Obscuration of the lentiform nucleus. *Radiology*. 1988;168(2):463–467.
148. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri N, Norman D. Loss of the insular ribbon: Another early CT sign of acute middle cerebral artery infarction. *Radiology*. 1990;176(3):801–806.
149. von Kummer R, Meyding-Lamadé U, Forsting M, et al. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. *AJNR Am J Neuroradiol*. 1994;15(1):9–15; discussion 16–18.
150. Kloska SP, Nabavi DG, Gaus C, et al. Acute stroke assessment with CT: Do we need multimodal evaluation? *Radiology*. 2004;233(1):79–86.
151. von Kummer R, Nolte PN, Schnittger H, Thron A, Ringelstein EB. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 h of stroke. *Neuroradiology*. 1996;38(1):31–33.
152. Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SRNINDS rtPA Stroke Study Group, NIH. Importance of early ischemic computed

tomography changes using ASPECTS in NINDS rtPA Stroke Study. *Stroke*. 2005;36(10):2110–2115.
153. Dzialowski I, Hill MD, Coutts SB, et al. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: Prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. *Stroke*. 2006;37(4):973–978.
154. Lev MH, Farkas J, Rodriguez VR, et al. CT angiography in the rapid triage of patients with hyperacute stroke to intraarterial thrombolysis: Accuracy in the detection of large vessel thrombus. *J Comput Assist Tomogr*. 2001;25(4):520–528.
155. Prokop M. Multislice CT, angiography. *Eur J Radiol*. 2000;36(2):86–96.
156. Cumming MJ, Morrow IM. Carotid artery stenosis: A prospective comparison of CT angiography and conventional angiography. *AJR Am J Roentgenol*. 1994;163(3):517–523.
157. Katz DA, Marks MP, Napel SA, Bracci PM, Roberts SL. Circle of Willis: Evaluation with spiral CT angiography, MR angiography, and conventional angiography. *Radiology*. 1995;195(2):445–449.
158. Shrier DA, Tanaka H, Numaguchi Y, Konno S, Patel U, Shibata D. CT angiography in the evaluation of acute stroke. *AJNR Am J Neuroradiol*. 1997;18(6):1011–1020.
159. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol*. 2007;61(6):533–543.
160. Zaidat OO, Suarez JI, Santillan C, et al. Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. *Stroke*. 2002;33(7):1821–1826.
161. Skutta B, Fürst G, Eilers J, Ferbert A, Kuhn FP. Intracranial stenoocclusive disease: Double-detector helical CT angiography versus digital subtraction angiography. *AJNR Am J Neuroradiol*. 1999;20(5):791–799.
162. Miles KA. Brain perfusion: Computed tomography applications. *Neuroradiology*. 2004;46(suppl 2):s194–s200.
163. Wintermark M, Sesay M, Barbier E, et al. Comparative overview of brain perfusion imaging techniques. *J Neuroradiol*. 2005;32(5):294–314.
164. Wintermark M, Fischbein NJ, Smith WS, Ko NU, Quist M, Dillon WP. Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. *AJNR Am J Neuroradiol*. 2005;26(1):104–112.
165. Sparacia G, Iaia A, Assadi B, Lagalla R. Perfusion CT in acute stroke: Predictive value of perfusion parameters in assessing tissue viability versus infarction. *Radiol Med*. 2007;112(1):113–122.
166. Wintermark M, Reichhart M, Thiran JP, et al. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. *Ann Neurol*. 2002;51(4):417–432.
167. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke*. 2006;37(4):979–985.
168. Beauchamp Jr. NJ, Ulug AM, Passe TJ, van Zijl PC. MR diffusion imaging in stroke: Review and controversies. *Radiographics*. 1998;18(5):1269–1283. discussion 1283–1285.
169. Grandin CB, Duprez TP, Smith AM, et al. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Comparative study between relative and quantitative measurements. *Radiology*. 2002;223(2):361–370.
170. Schlaug G, Benfield A, Baird AE, et al. The ischemic penumbra: Operationally defined by diffusion and perfusion MRI. *Neurology*. 1999;53(7):1528–1537.
171. Wintermark M, Reichhart M, Cuisenaire O, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. *Stroke*. 2002;33(8):2025–2031.
172. Srinivasan A, Goyal M, Al Azri F, Lum C. State-of-the-art imaging of acute stroke. *Radiographics*. 2006;26(suppl 1):S75–S95.
173. Fiehler J, Foth M, Kucinski T, et al. Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke*. 2002;33(1):79–86.
174. Kidwell CS, Saver JL, Mattiello J, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol*. 2000;47(4):462–469.
175. Davis SM, Donnan GA, Parsons MW, et al, EPITHET investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): A placebo-controlled randomised trial. *Lancet Neurol*. 2008;7(4):299–309.
176. Hacke W, Albers G, Al-Rawi Y, et alDIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36(1):66–73.
177. Hacke W, Furlan AJ, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): A prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8(2):141–150.

6 Evoked Potentials

T.B. Sloan • L.C. Jameson • D.J. Janik • A. Koht

The use of evoked electrophysiological responses during surgery on the nervous system has become a common tool in the operating room. It is used to map the location of structures and to monitor the functional status of neural pathways to enhance intraoperative decision making and improve outcome. These techniques can be used during altered states of consciousness such as during anesthesia or coma. A wide variety of techniques are available and many have been in use since the 1970s.

BASICS OF EVOKED POTENTIALS

Different than the electroencephalogram (EEG), which records the spontaneous electrical activity of the brain's cerebral cortex, evoked potentials record the electrical potentials produced after stimulation of specific sensory or motor tracts. The evoked response is recorded as a plot of voltage versus time (Fig. 6.1). It usually has an initial artifact from stimulation of the nerve pathway followed by a series of peaks and valleys. The peaks arise from specific neural generators, often more than one neural structure. The amplitude (peak to adjacent trough) and the latency (time from the stimulation to the peak) are recorded. Peaks are usually named by convention (I through V, P_a, P_b, or by polarity and latency: P (positive) or N (negative) followed by the latency in milliseconds (msec) (eg, N_{20})).

When the response is large in comparison with background noise, one single evoked response may be sufficient (eg, muscle responses). However, for most sensory responses, the evoked response is very small (1–2 microvolts) compared to other electrical signals (eg, EEG, 10–1000 microvolts). As such signal averaging of many responses is used because the evoked response always occurs at a set time after stimulation, while the background activity acts as a random signal and averages out to zero. Some small responses may need several hundred to thousand signal averages requiring time for the recording.

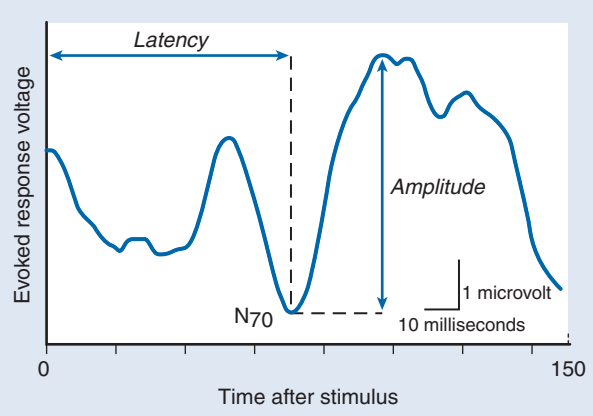


Fig. 6.1 Visual evoked response tracing of amplitude versus time after stimulus. The measurement of latency and amplitude for the negative peak at 70 msec (N_{70}) is shown.

Evoked responses are used for mapping and monitoring. Mapping involves stimulation and recording to identify the specific location of tracts or stimulation of an unknown structure to determine its function. Monitoring involves repeated stimulation of a neural tract at risk during a procedure to identify impending neural compromise by changes in amplitude or latency. Changes may be due to technical recording problems, alterations in anesthesia management, unfavorable physiological or positioning conditions as well as problems caused by the surgery or procedure.

As a general principle, an amplitude reduction of 50% or latency increase of 10% of a sensory evoked potential is considered significant and raises concern, although smaller changes may indicate impending compromise. For example, ischemia generally produces a loss of response, particularly if synaptic components are involved. Since the tolerance to ischemia (eg, time to irreversible injury) is related directly to the blood flow and metabolic demand, the monitoring may prompt actions to improve blood flow or to improve the tolerance to ischemia in order to reduce the chance of an injury. Fortunately the evoked response is altered at a level of blood flow well above the level that produces irreversible injury.

SOMATOSENSORY EVOKED POTENTIALS

The most commonly monitored sensory evoked potential is the somatosensory evoked potential (SSEP).[1,2] The SSEP is produced by stimulation of a peripheral sensory nerve with the response measured along the sensory pathway. The large, mixed motor and sensory nerves (and their component spinal roots) that are usually used are median (C6–T1), ulnar (C8–T1), and posterior tibial (L4–S2). Stimulation activates predominantly the large-diameter, fast-conducting Ia muscle afferent and group II cutaneous nerve fibers, which produce the recorded sensory response. Activation of motor fibers in the nerve results in a motor response seen as muscle contraction.

It is currently thought that the neural activity follows the pathway of proprioception and vibration that ascends the spinal cord in the ipsilateral dorsal column. It makes its first synapse near the nucleus cuneatus and nucleus gracilis and then decussates near the cervico-medullary junction, ascending via the contralateral medial lemniscus. A second synapse occurs in the ventro-postero-lateral nucleus of the thalamus, from which it projects to the sensory cortex contralateral to the side of stimulation. For the upper extremity, the evoked responses can be measured from electrodes placed over the antecubital fossa, supraclavicular fossa (brachial plexus), cervical spine, and cortex (Fig. 6.2); for the lower extremity, they can be recorded over the popliteal fossa, along the spinal cord (eg, epidural electrodes), and at cervical and cortical locations. Recordings are usually conducted at multiple recording sites

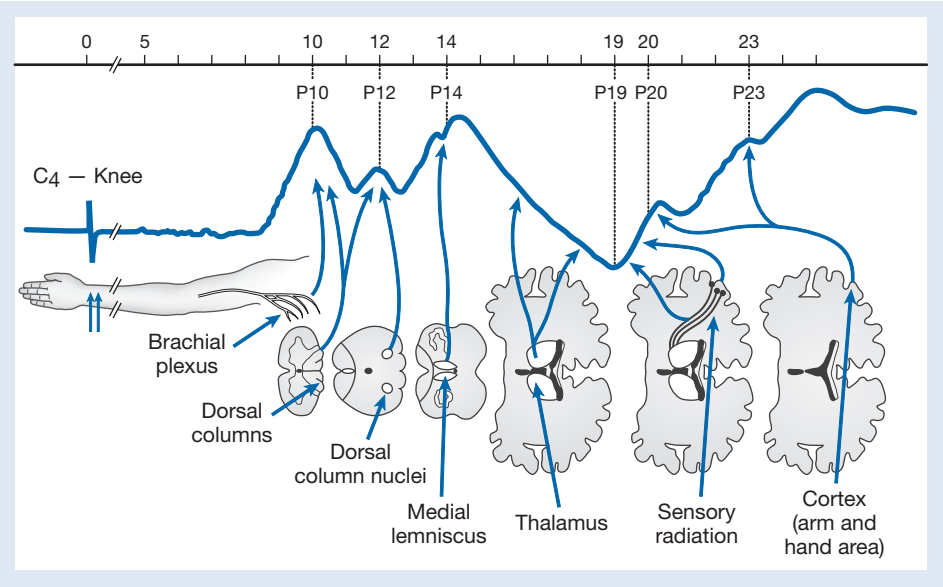


Fig. 6.2 Example of the somatosensory evoked potential peaks and the corresponding anatomy as recorded from the sensory cortex (C_4 in the international 10–20 system referenced to the knee). Positive peaks are labelled as "P" followed by the approximate time in milliseconds from median nerve stimulation. *(From Wiederholt WC, Meyer-Hardting E, Budnick B, et al: Stimulating and recording methods used in obtaining short-latency somatosensory evoked potentials[SEPs] in patients with central and peripheral neurologic disorders. Ann N Y Acad Sci 1982;388:349.)*

to verify that the nervous system is stimulated and to identify the anatomic location of neural compromise if the response is lost.

The cortical response is most frequently recorded over the primary somatosensory cortex of the sensory area of the nerve stimulated. The major cortical peaks are probably the result of the thalamocortical projections to the primary sensory cortex.[1] Responses recorded posteriorly over the cervical spine (subcortical response) probably represent responses of the tracts in the spinal cord or brainstem.[1]

Mapping Using Somatosensory Evoked Potentials

The SSEP can be used for mapping in the spinal cord and the somatosensory cortex. For example, if the surgeon wishes to make a midline posterior myelotomy for entry into the spinal cord to operate on a spinal cord tumor, the midline can be identified by placing a series of electrodes across the posterior spinal cord. The midline lies between the maximal response recorded from individual stimulation of the left and the right peripheral nerves.

The SSEP can also be used to identify the location of the sensory strip on the cerebral cortex.[3] Localization is accomplished by recording of the cortical component (N_{20}) of the median nerve SSEP with use of bipolar recording strips placed on the cortex. The central gyrus separating the motor and sensory strips is identified from a phase reversal (initial wave changes from positive to negative) of the response.[3]

Cortical Monitoring Using Somatosensory Evoked Potentials

The cortical SSEP has been used to detect ischemia in cortical tissue by amplitude reduction. Although the clinical examination becomes abnormal at a cortical blood flow of about 25 mL/min/100 g, the SSEP becomes abnormal at about 20 mL/min/100 g and is lost at 15 and 18 mL/min/100 g. Subcortical regions, brainstem, spinal cord, and nerve appear to be less sensitive to hypoperfusion. Hence, the SSEP is used to monitor procedures such as carotid endarterectomy (CEA) where changes have been used as an indication for shunt placement and to predict postoperative morbidity. In some respects, use of the EEG and SSEP in CEA are complimentary because the SSEP is able to detect ischemia in deep cortical structures, and the EEG assesses a wider area of surface cortex.

Similarly, the SSEP is employed during intracranial vascular procedures to determine the adequacy of collateral blood flow, tolerance to temporary vessel occlusion, or the adequacy of systolic blood pressure. Because the SSEP from the upper extremity is generated in the cerebral cortex supplied by the middle cerebral artery, it can be utilized during surgery for aneurysms of the internal carotid and middle cerebral arteries. Similarly, the SSEP from the lower extremity can be used to evaluate ischemia during vascular procedures on the anterior cerebral artery. Monitoring of ischemia in these arteries may require both upper and lower SSEPs, depending on the vascular perforators (eg, lenticulate striate perforators supplying the internal capsule) and their impact on the subcortical pathways (eg, the descending motor tracts requiring motor evoked potentials as below).

Monitoring during temporary clipping in aneurysm surgery has shown that a very prompt loss of cortical SSEP response (less than 1 minute after clipping) is associated with a permanent neurologic deficit. However, a delayed loss with prompt recovery after release of the clip is associated with collateral circulation and a markedly reduced incidence of neural morbidity. Symon and colleagues[4] have suggested that when the N_{20} of the median nerve SSEP disappears slowly (over 4 minutes), 10 additional minutes of occlusion can be tolerated safely. A correlation between outcome and monitoring during anterior circulation aneurysms has been observed.[5]

In addition, monitoring can be used to identify ischemia from vasospasm or when a combination of factors produces unexpected ischemia (eg, retractor pressure, hypotension, temporary clipping, and hyperventilation). SSEP monitoring during neuroradiological procedures like occlusion of vessels or during streptokinase dissolution of blood clots is equally effective.

Somatosensory Evoked Potential Monitoring in Spinal Surgery

The SSEP can be used during brainstem or spinal procedures. Perhaps the most common application has been to reduce the risks of spinal cord or axial surgery where it can identify mechanical or ischemic insults (Fig. 6.3). Monitoring is estimated to reduce the morbidity in spinal surgery by 50– 80%.[6]

The basis of monitoring spinal surgery in humans is founded in studies in animals where compromise of the spinal cord results in SSEP latency and amplitude changes simultaneous to loss of clinical motor function. Because current spinal instrumentation techniques present multiple potential insults, a nearly continuous monitoring technique (eg, SSEP) is an important advantage for identifying a specific insult. In addition, the SSEP may identify physiologic insults (eg, hypotension) or positioning problems. The once frequently used wake-up test is utilized less since the introduction of SSEP monitoring and is now often reserved for assessment of motor function when motor evoked potentials (MEPs) are not recordable or to confirm motor function when evoked responses deteriorate.

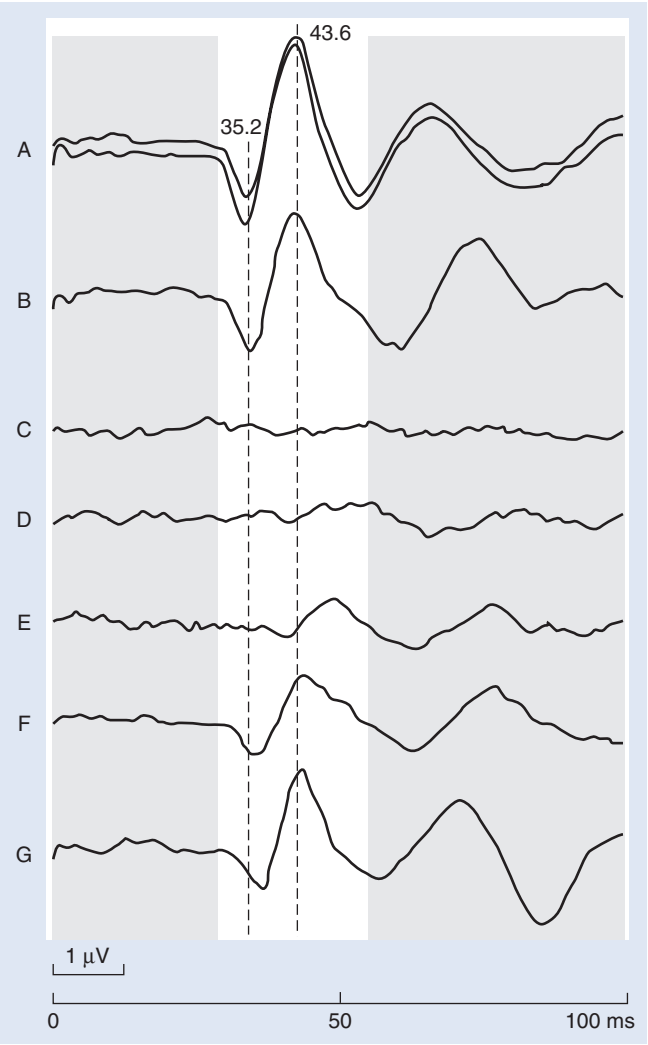


Fig. 6.3 Example of somatosensory evoked potential monitoring for a patient undergoing surgery. Baseline recordings the afternoon prior to operation were normal **(A)**. **B** shows recordings after the induction of anesthesia. Responses were abolished after passing sublaminar wires around the laminae **(C)**. The wake-up test showed inability to move the legs **(D)**. After 15 minutes, the poorly defined potentials reappeared **(E)**. After closure of the wound, evoked potentials showed a little increased latency **(F)**, with normal overall waveform **(G)**. *(From Mostegl A, Bauer R, Eichenauer M: Intraoperative somatosensory potential monitoring: A clinical analysis of 127 surgical procedures. Spine 1988;13:396.)*

Studies in humans also indicate that the SSEP is predictive of neural outcome.[7,8] The utility of the SSEP in spinal surgery was shown by the Scoliosis Research Society and European Spinal Deformities Society in 1995. In 51,263 spinal deformity operations (scoliosis, kyphosis, fractures, and spondylolisthesis) the overall injury incidence was 0.55%; well below the 0.7–4% historical average without monitoring.[9] This and other studies led the Scoliosis Research Society to develop a position statement that made monitoring a virtual standard of care.[10]

Based on these results, Nuwer estimated the economic impact of SSEP monitoring. Approximately 200 cases at a cost of $120,000 (1995 dollars) were required to prevent one major, persistent neurologic deficit, which is small compared with the cost of lifelong medical care.[9]

However, the correlation of SSEP and neural injury is not exact; the incidence of a major motor injury without SSEP warning was 0.063% (about 1 in 1500 procedures). This highlights the anatomic difference of the SSEP and motor pathways in the spinal cord. Therefore, the ability of the SSEP to predict most motor deficits probably results from insults that affect the entire cross-section of the spinal cord. More recent evidence-based reviews reinforce the use of monitoring in spine surgery.[7,8]

Recording Somatosensory Evoked Potentials from the Spinal Column

The spine has also been monitored using stimulation and recording from epidural or electrodes in the bony spine in an attempt to monitor motor tracts. Problems with these techniques include lack of laterality and that the actual neural tracts monitored are not known. The MEP (see below) has generally replaced spinal stimulation techniques since they may be primarily assessing sensory tracts.[11]

AUDITORY BRAINSTEM RESPONSES

The auditory brainstem response (ABR) is a sensory evoked potential which is produced when sound activates the auditory pathway. The term auditory brainstem response refers to the responses from the brainstem in the first 10 msec after stimulation (Fig. 6.4). They are also referred to as the brainstem auditory evoked response (BAER) and brainstem auditory evoked potential (BAEP). The sound activates the cochlea and the resulting nerve impulse travels via the eighth cranial nerve, the brainstem acoustic nuclei, and lemniscal pathways, eventually to activate the auditory cortex. Five ABR peaks are seen (numbered I–V) with monitoring of I, III, and V.[12] It is postulated that wave I is produced by the extracranial portion of cranial nerve (CN) VIII, wave III by the cochlear nucleus, and wave V by the lateral lemniscus and inferior colliculus in the contralateral pons.[13]

The ABR is used extensively for monitoring during posterior fossa surgery, because of its importance for hearing and the frequent involvement of the cochlear nerve by tumors in this region.[12,14] Quite resistant to the effects of anesthesia, a variety of factors alter the ABR. They include sound conduction problems in the external or middle ear, ischemia of the cochlea, traction on cranial nerve VIII, and ischemia or neural damage to the auditory pathways in the brainstem.

Common changes seen intraoperatively with ABR recordings are increases in the latency of wave V and increases in the interpeak latency of I–V with retractor placement in the

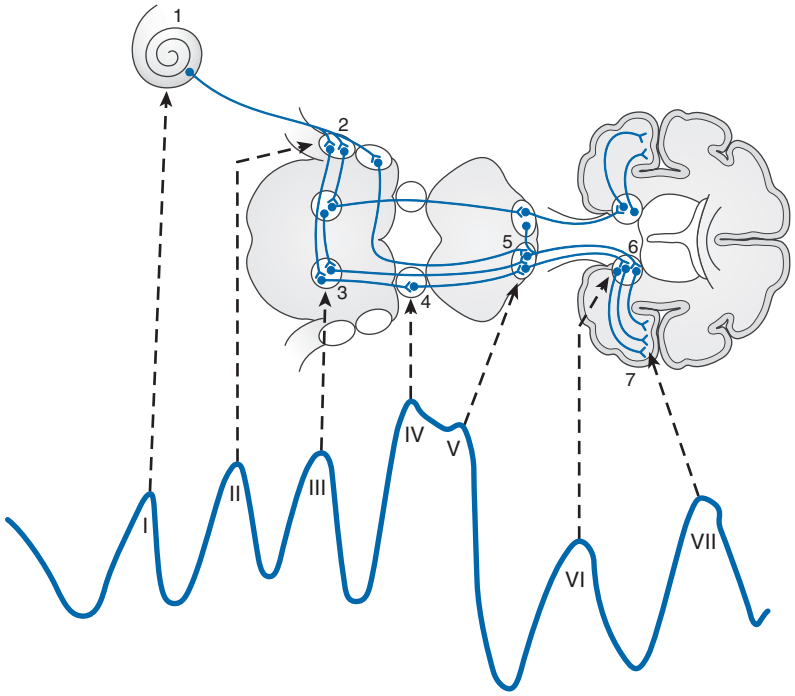


Fig. 6.4 Normal auditory brainstem response tracing and corresponding region of brainstem generating the response peaks (labeled by Roman numerals by convention). **I.** organ of Corti and extracranial cranial nerve VII; **II.** cochlear nucleus; **III.** superior olivary complex; **IV.** lateral lemniscus; **V.** inferior colliculus; **VI.** medial geniculate body; **VII.** auditory radiation. *(From Aravabhumi S, Izzo KL, Bakst BL, et al: Brainstem auditory evoked potentials: Intraoperative monitoring technique in surgery of posterior fossa tumors. Arch Phys Med Rehabil 1987;68:142.)*

posterior fossa. These changes, if mild, are reversible and considered part of a routine procedure. Complete loss of wave I can be due to the loss of the cochlear blood supply as a result of vascular obstruction or vasospasm[15] or transection of the nerve by the surgeon. In general, if waves I and V are preserved, hearing is preserved, but if they are both lost, there is little chance of preservation of hearing postoperatively.

ABRs are also used to evaluate general brainstem viability such as decompression of space-occupying defects in the cerebellum, removal of cerebellar vascular malformations, and microvascular decompression for relief of hemifacial spasm or trigeminal neuralgia. The SSEP and motor evoked potentials are typically combined with ABRs to more comprehensively monitor brainstem integrity.

VISUAL EVOKED POTENTIALS

Visual evoked potentials (VEPs) are produced in response to light stimulation of the eyes (see Fig. 6.1). The most commonly recorded responses appear to be generated bilaterally in the visual (occipital) cortex. Under anesthesia, flash stimulation through closed eyelids or stimulators mounted on scleral caps are used. The response of the retina (electroretinogram [ERG]) can also be measured. They are considered less useful in surgical monitoring because flash stimulation does not appear to measure the pathways of useful clinical vision, the typical large, bulky "goggles" pose technical problems, anesthetic sensitivity, and that the bilateral response from either eye obscures some focal changes.

BASIC ELECTROMYOGRAPHIC MONITORING

Recording muscle electrical activity using needle electrode pairs is called electromyography (EMG). Two types of intraoperative EMG monitoring are common: recording spontaneous activity and recording triggered responses subsequent to stimulation of motor nerves or motor pathways. The responses are sufficiently large (0–1.5 millivolts) so averaging is not necessary allowing immediate feedback. Spontaneous activity is observed continuously with stimulation used for specific activities. Direct feedback to the surgeon can be achieved by the playing of these responses through a loudspeaker. EMG monitoring has found wide application in surgery of the posterior fossa, skull base, spine, cauda equina, head and neck, and peripheral nerves.

The EMG response that results from irritation of a nerve is a recording of the generated motor unit potentials of individual axon-muscle fiber groups. Neurotonic discharges, caused by mechanical or metabolic stimuli, are high-frequency intermittent or continuous bursts of motor unit potentials and are a sensitive indicator of nerve irritation (Fig. 6.5). Activity can be bursts lasting less than 200 msec with single or multiple motor unit potentials firing at 30 to 200 Hz, or they can be long trains of activity lasting 1 to 30 seconds or more.[16] Short bursts represent nerve irritation exemplified by relatively synchronous motor unit discharges from a response of multiple axons from nerve irritation. When these are of sufficient amplitude or duration they raise concern. Causes of irritation include nearby mechanical stimulation (eg, dissection, ultrasonic aspiration or drilling), nerve retraction, thermal irritation (eg, heating from irrigation, lasers, drilling, or electrocautery), and chemical or metabolic insults. Prolonged irritation may lead to long trains of continuous, synchronous motor unit discharges and are associated with impending nerve injury (nerve compression, traction, or ischemia of the nerve). Sharp transection of nerves may fail to provoke any discharge.[17]

Direct stimulation of neural tissue can be used for mapping to locate a nerve of interest or to assess its function. The electrical responses recorded from intentional nerve stimulation (to determine whether the neural tract is intact) or MEPs (see later) are called compound muscle action potentials (CMAPs). The nerve is stimulated by bipolar or monopolar electrodes with fine tips. The EMG response that results from single or

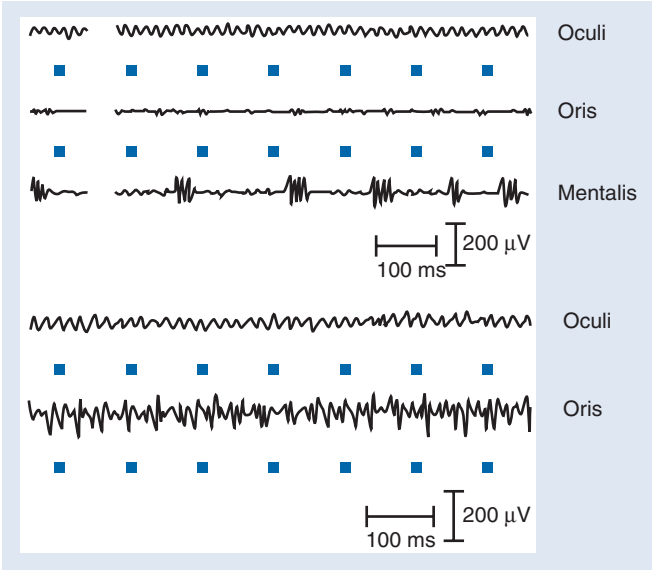


Fig. 6.5 Examples of continuously recorded muscle potentials during posterior fossa surgery. Responses are recorded from the orbicularis oculi, orbicularis oris, and mentalis muscles. *Top*, Multiple short responses (neurotonic bursts) in the mentalis muscle from dissection near the fifth cranial nerve. *Bottom,* Prolonged neurotonic discharges in the other muscles after irrigation with cool fluids. *(From Cheek JC: Posterior fossa intraoperative monitoring. J Clin Neurophysiol 1993;10:412.)*

multiple stimuli of low-intensity current (0.5–5 milliAmperes [mA]) and short duration (0.5–1 msec) will identify cranial nerves or assess damaged peripheral nerves.

Mapping techniques include stimulation to identify motor cranial nerves (CN) near or intertwined in brainstem tumors or identify the location of cranial nerve nuclei on the posterior surface of the brainstem. Locating CN nuclei allows "safe entry" zones to be located for surgery to resect deeper pathology. It has also been used to identify nerve rootlets for resection to minimize childhood spasticity.[18] Finally, mapping is extensively used in surgery on the cauda equina to determine if tissue tethering the spinal cord is functional (particularly to preserve key roots for anal and urethral sphincter control).

The EMG is resistant to the effects of most physiologic variables (temperature, blood pressure) and anesthetics, except for neuromuscular blockade (NMB). Electrically stimulated responses can usually be monitored with NMB with 75% or less suppression of baseline CMAPs. Small-amplitude responses from irritation, especially in damaged or poorly functioning nerves, may be difficult to detect during controlled muscle relaxation such that partial NMB should be used only when necessary.[19]

Cranial Nerve Monitoring

EMG is used to monitor cranial nerves because they are susceptible to intraoperative damage owing to their small size, limited epineurium, and complicated course. The damage occurs from either surgical trauma or ischemia and leads to paresis or paralysis with subsequent disability or deformity and, possibly, chronic pain. Cranial nerves are at risk during excision of tumors of the skull base, brainstem, and cerebellopontine angle. All cranial nerves with a motor component can be monitored using their respectively innervated muscles (Table 6.1).

Facial Nerve

The most commonly monitored cranial nerve is the facial nerve (CN VII). The muscles used for monitoring are the orbicularis oculi and orbicularis oris ipsilateral to the surgical site. The facial nerve may be intertwined within brainstem tumors so monitoring, stimulated and continuous, allows identification of the nerve in the operative site and warning of unrecognized proximity of the nerve to surgical activity. Identification is particularly helpful during surgery for vestibular schwanoma (acoustic neuroma), and monitoring increases the likelihood that the anatomic integrity of the nerve will be maintained. If intact at the end of surgery, more than 60% of patients will regain at least partial function by several months postoperatively.[15] A reduction in the size of stimulated CMAPs of the facial nerve (CN VII) and the presence and duration of the neurotonic discharges during surgery correlate with immediate and long-term changes in neurologic function.[20,21]

Because of the improvement in outcome in vestibular schwanoma surgery, a National Institutes of Health consensus panel concluded that facial nerve monitoring should be made a standard of care.[22] Because of its course and location, it is also commonly monitored in other procedures in the cerebellopontine angle. Facial nerve EMG monitoring is also utilized in surgery of the head and neck, particularly with parotid tumors, which may encase extracranial branches of the nerve.

Other Cranial Nerves

Monitoring of other cranial nerves has been used in surgery on the base of the skull, cavernous sinus, and posterior fossa.[12,15,17] Vagus nerve (CN X) monitoring is common in skull base and anterior neck procedures. Monitoring of the recurrent laryngeal and superior laryngeal branches via the vocalis muscles is used in procedures such as neck dissections, thyroid and parathyroid removal, and anterior cervical spine fusions.[12] Monitoring is frequently requested with thyroid surgery when the risk is increased as with malignancy, re-exploration for hemorrhage, during a second operation, and when anatomic distortion is present.[23]

In posterior fossa surgery, monitoring of EMG events correlates with postoperative neurologic status. In a study monitoring three cranial nerves (CN IX, X, XII) in pediatric

Table 6.1 Monitoring of Cranial Nerves

Cranial Nerve		Monitoring Site or Method*
I	Olfactory	No monitoring technique
II	Optic	Visual evoked potentials
III	Oculomotor	Inferior rectus muscle
IV	Trochlear	Superior oblique muscle
V	Trigeminal	Masseter muscle and/or temporalis muscle (sensory responses can also be monitored)
VI	Abducens	Lateral rectus muscle
VII	Facial	Orbicularis oculi and/or orbicularis oris muscles
VIII	Auditory	Auditory brainstem responses
IX	Glossopharyngeal	Stylopharyngeus muscle (posterior soft palate)
X	Vagus	Vocal folds, cricothyroid muscle
XI	Spinal accessory	Sternocleidomastoid and/or trapezius muscles
XII	Hypoglossal	Genioglossus muscle (tongue)

*Unless otherwise specified, monitoring is performed via electromyographic activity of the muscle(s) listed.

patients undergoing removal of tumors in the brainstem, a positive EMG event resulted in a postoperative deficit in 73% of patients. Recurrent spontaneous neurotonic EMG activity from all three nerves was always associated with a deficit. Postoperative aspiration pneumonia or a need for tracheotomy was always associated with abnormal intraoperative EMG activity in at least one of these nerves.[24]

Monitoring of the Peripheral Nervous System

EMG can be used for identifying peripheral nerves, localizing pre-existing disease along the course of a nerve, determining the functional continuity across lesions and the likelihood of nerve root avulsion, identifying targets for nerve biopsy and injured segments within the brachial plexus, and monitoring intact nerves to prevent inadvertent surgical injury. With nerve trauma, neuropraxic or axonotmetic injury is associated with continuity such that the nerve can be expected to recover over time through remyelination or axon growth. Absence of continuity across an injury site, signified by loss of distal CMAP, indicates complete disruption of the axon, sheath, and connective tissue (neurotmesis) and requires grafting for satisfactory outcome. In some cases the EMG response can be combined with a sensory response to define an area of lesion.[25]

EMG monitoring is employed when injury to a nerve root may occur during procedures on the spinal column with or without instrumentation, and for the removal of tumors and tethering the cauda equina. For monitoring of the spinal nerve roots, muscles are chosen based on their myotomes of the nerve roots at risk (Table 6.2).

Electromyography during spinal column surgery is more sensitive than SSEP for detecting nerve root injury because multiple nerve roots and overlapping sensory dermatomes contribute to the cortical SSEP and alteration of individual root may not be detected. Sensory responses from dermatomal stimulation have been used (dermatomal evoked potentials); however, these are not commonly used, particularly due to anesthetic sensitivity and slow acquisition time.

Nerve roots are at risk during spine surgery due to instrumentation, such as pedicle screw placement, that may medially violate the bony pedicle wall and irritate adjacent nerve roots (15–25% of cases).[26] EMG can be used to test screw placement through stimulation of the screw or screw-hole. Because the bone cortex has a higher resistance to current flow, a high threshold (eg, over 10 mA) indicates the screw is seated well in the bone. A lower threshold (eg, 6–10 mA) indicates a breach in the bony cortex prompting reassessment of the screw placement. A very low threshold (eg, less than 6 mA) suggests the screw may be near or touching the nerve (prompting consideration for removal and repositioning).[27] Abnormal nerve function resulting from conditions such as diabetes or chronic compression through mechanisms of axonotmesis, has a much higher threshold. Poor bone density may lower thresholds.[25,28] Numerous studies support the sensitivity of EMG monitoring in preventing nerve root injury.[29,30]

Electromyography has proven useful in monitoring procedures on the cauda equina. Release of tethered cord and tumor excision carry the risk of damage to nerve roots innervating the muscles of the leg, anal and urethral sphincters, and the parasympathetic innervation of the bladder detrusor muscle. Spontaneous and evoked EMG recordings of the cauda equina and tumor aid in differentiating nerves from non-neural tissue. The stimulation threshold for filum terminale fibers may be 100 times that for motor nerve fibers.[31] Monitoring can be predictive of postoperative deficits. If the caudal end of the spinal cord is stimulated to evoke a motor response after untethering, those patients in whom the voltage needed for muscle activation increased had worsening of motor function postoperatively.[32]

As with other spinal surgery, a multimodality approach is used for cauda equina procedures (EMG from anal and urethral sphincters, bladder pressure, tibial nerve SSEP, and motor pathway monitoring). Urethral sphincter EMG may be recorded using a bladder catheter with electrodes attached 2 cm from the inflating balloon.[33] Anal sphincter EMG probably provides the same information as bladder sphincter EMG since the innervation of both are from S2–S4 segments. Ensuring the integrity of the parasympathetic innervation to the detrusor muscle involves a technique of measuring bladder pressure in response to continuous stimulation of the filum.[34]

Table 6.2 Nerve Roots and Muscles Most Commonly Monitored

Spinal Cord	Nerve(s)	Muscle(s)
Cervical	C2–C4	Trapezoids, sternocleidomastoid
	C5, C6	Biceps, deltoid
	C6, C7	Flexor carpi radialis
Thoracic	C8–T1	Adductor pollicis brevis, abductor digiti minimi
	T5–T6	Upper rectus abdominis
	T7–T8	Middle rectus abdominis
	T9–T11	Lower rectus abdominis
	T12	Inferior rectus abdominis
Lumbar	L2	Adductor longus
	L2–L4	Vastus medialis
Lumbosacral	L4–S1	Tibialis anterior
	L5–S1	Peroneus longus
Sacral	S1–S2	Gastrocnemius
	S2–S4	Anal sphincter

Monitoring of Reflex Responses

Another method of monitoring the cauda equina, nerve roots, and spinal cord is to monitor the reflex responses that can be recorded in the peripheral nerve and muscle after stimulation of a peripheral nerve.[26] The recorded muscle response usually consists of three responses. The first is a CMAP from motor fiber stimulation (M response), second is the Hoffmann's (H) reflex resulting from a sensory to motor reflex in the spinal cord, and last is the F wave produced as the traveling wave in the motor nerve is reflected at the spinal cord. The H reflex is occasionally used to monitor the sensory and motor efferents in the nerve as well as the reflex pathway in the spinal cord.

These reflexes also monitor the integrity of the spinal cord more cephalad because several descending pathways contribute to the excitability of the anterior horn cell. Changes in these pathways can alter the reflex response such that injury to the spinal cord affects the more caudal H reflexes due to spinal shock. The extent of H reflex suppression correlates with the degree of spinal injury, a 90% depression correlates with a postoperative neurologic deficit.[35,36] The H reflex has been shown to be more sensitive than SSEPs to spinal cord injury. The most often recorded H reflex is the gastrocnemius response after stimulation of the posterior tibial nerve (S1 spinal segmental function).

MOTOR EVOKED POTENTIALS

The Motor evoked potential (MEP) is the most recent addition to the SSEP and EMG in routine intraoperative neurophysiologic monitoring (IOM) in surgeries where the motor tracts are at risk. The MEP is produced by transcranial multipulse electrical stimulation of the motor cortex using scalp electrodes.[37–40] Manipulation of the number of stimuli, time between stimuli, stimulus duration and stimulation voltage or current optimize the amplitude and complexity of the muscle response,[41–43] which results in a D wave (direct) and several subsequent I (indirect) waves which descend in the cortical spinal tract (CST). It crosses the midline in the brainstem and descends in the ipsilateral anterior funiculi of the spinal cord to the anterior horn and neuromuscular junction after which a compound muscle action potential (CMAP) of about 4–5% of the muscle fibers results[43] (Fig. 6.6). Routine stimulation uses three to seven high-frequency pulses at 100–600 V; stimulation above 600 volts can activate the CST in deeper regions of the cortex. Direct cortical simulation is sometimes utilized during craniotomy.

The CMAP which results from standard motor cortex stimulation is sufficiently large that a single response can be acquired in less than 10 seconds. This short testing time allows testing between critical surgical maneuvers so that muscle movement does not interfere with critical surgical events. The motor response involves all muscles such that the most common injury is a tongue laceration, which is avoided by placing a soft bite block in the mouth (often bilateral soft rolls between the molars).

Monitoring usually uses CMAP from muscles innervated by the regions of the central nervous system at risk. Muscle responses differentiate laterality and identify change in CST, gray matter, peripheral nerve, and muscle. Frequently the MEP is recorded from the upper extremity (abductor or flexor pollicis brevis) and lower extremity (primarily, abductor hallucis brevis and tibialis anterior) and other muscles as appropriate for the specific procedure. A typical CMAP is polyphasic with consistent onset latency and amplitude between 100 and 2000 μV[43] (see Fig. 6.6). In some cases spinal cord D wave responses are monitored using an epidural electrode. D waves do not differentiate laterality; the amplitude correlates with the number of functioning fibers of the corticospinal tract and mitigates the difficulty obtaining a CMAP due to neurologic conditions.

As opposed to the SSEP where a 50% amplitude reduction or 10% latency increase is cause for concern, identifying a significant change in a MEP CMAP response is less clear. Suggested criteria for concern have included loss of signal, significant decreases in amplitude (usually >70%), increases in latency, changes in the complexity of the response, and the failure of the signal amplitude to return to baseline. Another cause for concern is the need to increase the stimulation strength, such as increases in stimulus strength (>50 V) or increases in the number of stimuli required. Return of MEP after an intervention is associated with good outcomes; failure to recover is associated with postoperative neurologic change.[44–47]

MEP can be difficult to obtain due to pre-existing medical conditions or anesthetic conditions. In adults, vascular disease, poor perfusion and myelopathy are common predictors for failure to obtain MEP.[48–52] Other conditions associated with poor quality or absent responses are extremes of age, spinal cord injury, diabetic peripheral neuropathy, and genetic muscular dystrophies.[53] Anesthesia combined with pre-existing medical conditions can make a response difficult to obtain. Children under 6 years have an immature central nervous system that requires specialized MEP stimulation.[54,55] In these patients the anesthetic choice is critical (see below).

MEP monitoring has become favored in many procedures because changes correlate with postoperative motor outcome. This is due to the monitoring of the CST and because the motor pathways are more sensitive to ischemic insults caused by stretch, compression, vascular disruption or direct trauma. The increased MEP sensitivity, when compared to SSEP, is due to synaptic transmission through the spinal cord and decreased redundancy in perfusion. The MEP response recovers

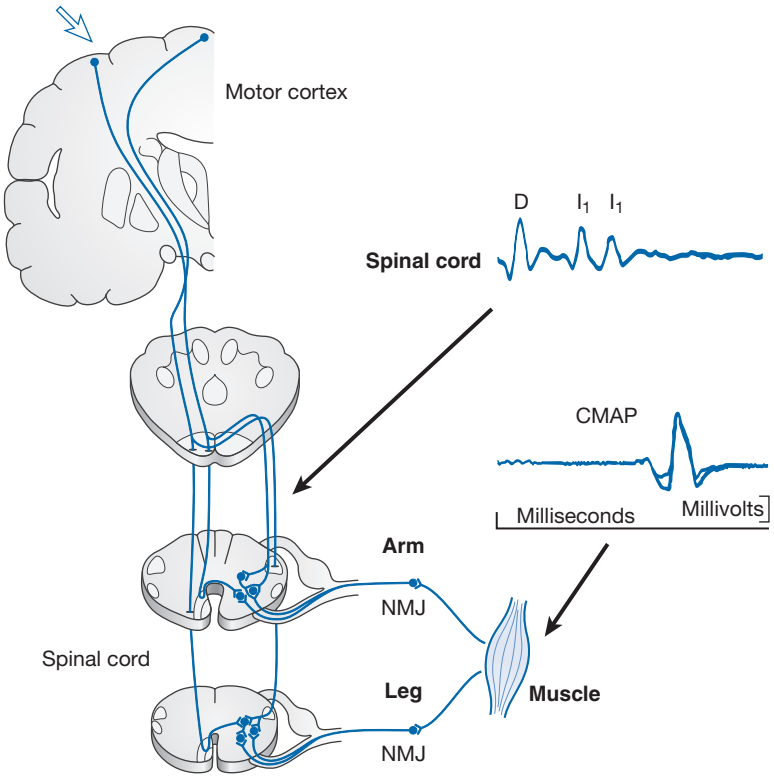


Fig. 6.6 Motor evoked potentials are produced by stimulation of the motor cortex (arrow). The response can be recorded epidurally over the spinal column as a D wave followed by a series of I waves. The pathway synapses in the anterior horn of the spinal cord and the response travels to the muscle through the neuromuscular junction (NMJ). The response is typically recorded in the muscle as a compound muscle action potential (CMAP). *(From Jameson LC, Sloan TB: Monitoring of the brain and spinal cord. Anesthesiol Clin 2006; 24:777.)*

quickly from transient but not prolonged ischemia, which correlates with long-term outcome.[44–47]

Direct MEP cortical stimulation or motor mapping is used to identify the motor cortex during intracranial procedures and to delineate the demarcation between functional tissue and tumors or a seizure focus. It is the only tool available to identify the motor cortex, brainstem motor nuclei, and spinal cord motor pathway in anesthetized patients.[56,57] During tumor excision, motor mapping guides surgical interventions, allowing a more complete resection while reducing the risk of potential surgical injury exceeding the gain in long-term well-being.

Changed outcome by determining the "edge" of the functional tissue thus modifying tumor excision is difficult to systematically evaluate. A review of the intracranial motor mapping with MEP when combined with fluorescein dye techniques provided the best long-term and immediate neurologic results in glioma resection.[57] The long-term outcome is significantly improved by more extensive tumor resection in both children and adults for all supratentorial tumors.[58] The only available large single center study (n = 883) found that the addition of MEP to awake craniotomy near the motor cortex reduced the persistent motor deficit to 5.9%, much lower than procedures without MEP.[59] A reduction in postsurgical motor loss has likewise been reported in brainstem surgery.

Similar to the SSEP, the MEP can be used to monitor during procedures to identify ischemia in the motor cortex. It is critical to adjust the stimulation parameters to ensure that the stimulated motor pathway includes only the motor cortex. The intensity of MEP stimulation should be at the lowest possible to prevent deeper stimulation of the internal capsule or the brainstem which bypasses the cortex at risk. Proper stimulation and the correct anesthesia regimen will also prevent unacceptable movements during testing.[60] The infusion of high doses of short-acting narcotics and propofol in addition to less than half MAC inhalation agents has been used to minimize movements during testing.[60]

A good example of use during intracranial surgery is during procedures on aneurysms and arteriovenous malformations (AVM) where areas of hypoperfusion can occur during the endovascular embolization, resection, or temporary and permanent clipping. MEP change followed by therapeutic intervention appears to substantially reduce permanent injury. Two large studies found between 13% and 33% of patients had reversible MEP changes; these patients had no persistent neurologic changes. Patients with permanent MEP change (about 20%), all had permanent neurologic deficits.[61–64]

MEP tends to be more sensitive to ischemia, detecting changes earlier than SSEP by about 15 minutes and detecting lesser degrees of ischemia. The use of SSEP and MEP can complement each other during the clipping of an aneurysm. SSEP is particularly effective when movement from MEP will be disruptive. Changing patient management in response to MEP changes has been reported to substantially reduce permanent injury. Reversible MEP changes occur in 13–33% of patients undergoing ablation of an aneurysm or AVM. These patients had no persistent neurologic changes while patients with permanent MEP change did have a postoperative deficit. About 20% of all patients had permanent neurologic deficits.[61–64] Because of the ability of the MEP to be completed in very short time compared with the SSEP, it can be used to give feedback more readily after clipping or testing periods. If burst suppression is induced with a high dose of propofol, a change or loss of MEP amplitude in the lower extremities may occur. This may require adjustment of the stimulating parameters to avoid false-positive changes.

The choice of muscles for monitoring cortical ischemia depends on the vascular structures at risk. Ischemia in the distribution of the middle cerebral artery (MCA) involves the motor and sensory cortex of the contralateral hand while ischemia in the anterior cerebral artery (ACA) involves the contralateral lower extremity. Trapping of an anterior communicating artery (ACOM) aneurysm requires the temporary clipping of both ACA arteries, which may lead to ischemia in the distribution of both anterior arteries and can result in changes of SSEP and MEP in either or both of the lower extremities. Trapping of a basilar artery aneurysm can result in changes in any of the upper or lower extremities (in addition to the ABR).

During certain deep and large aneurysms located at the carotid terminus or paraophthalmic artery, the neurosurgeon may elect to place an intracarotid balloon that can be inflated to supplement temporary clips on both MCA and ACA. This occlusion can lead to hemispheric ischemia with SSEP and MEP changes in both contralateral upper and lower extremities. In addition to cortex ischemia, clipping of aneurysms can be associated with inadvertent clipping of small perforating arteries which supply the subcortical CST.

During these procedures MEP changes after permanent clipping suggests clip repositioning may be needed. Early changes after temporary clips are associated with worse outcome and should be quickly addressed by unclamping the artery to restore circulation and waiting for signals to return. Changes can also be utilized during reconstruction of giant and large aneurysms. This requires both proximal and distal temporary clips so as to enable the opening of the aneurysm, removal of the clot, and reconstruction of the base of the aneurysm as a wall for the artery. During reconstruction, the surgeon is unable to release the temporary clips and restore blood flow. If SSEP or MEP changes occur, the surgeon needs to finish quickly to facilitate a response recovery after restoring blood flow. Reconstruction may be associated with narrowing of the blood vessel or vascular spasm, both of which may be associated with late MEP or SSEP changes. Anesthetic management can assist in moderating the ischemia (eg, anesthetic drug choice, blood pressure).

MEP has also been used during procedures in the brainstem as a general monitor of brainstem and CST viability. Occlusion of small perforating arteries during aneurysm clipping or embolization leads to CST hypoperfusion causing motor and sensory changes in upper and lower extremities. MEP of muscles innervated by the facial nerve, vagus-recurrent laryngeal nerve or other motor CN have also been used for continuous monitoring of procedures where these nerves are at risk (referred to as corticobulbar responses).[65]

In spine surgery, MEP is routinely combined with SSEP and continuous EMG. Since MEP and SSEP pathways are located in different topographic and vascular regions of the spinal cord, their combination improves the probability for the detection of pending injury and thus better postoperative motor outcome over SSEP alone. This multimodality monitoring can identify changes due to positioning, surgical events, perfusion, and other issues.[66] Failure to recover signals after interventions for monitoring changes was associated with permanent postoperative neurologic injury.[45,67] As such MEP monitoring has been advocated for all axial skeletal deformities. [7,8,38,44,46]

A 12,373 patient study over 25 years found in spine surgery, MEP changes occurred with primary surgery in 3.1% of patients and with revision surgery in 6.1% of patients. Intervention reversed these changes in 87% but patients

without signal recovery had permanent neurologic change.[44] A systematic review of MEP response found false-negatives (failure to detect an event that resulted in neurologic injury) occurred in 0–0.79% of patients with both MEP and SSEP monitoring. SSEP alone had a false-negative rate of 0.63–2.7%, more than three times greater.[46] Multimodal monitoring is effective in identifying possible spinal cord compromise that can be corrected by routine intervention. A recent evidence-based review by the American Academy of Neurology and American Clinical Neurophysiology Society confirmed the efficacy of MEP in spine surgery.[7,8]

Intramedullary spinal tumor surgery places specific risk to the motor tracts. MEP change identifies surgical encroachment on the CST.[68,69] Monitoring teams often determine the degree of amplitude change where surgical excision will be halted. D wave monitoring is often performed and surgery stopped when the D wave amplitude decreases to 50% of the original amplitude.

Similarly, due to its sensitivity to hypoperfusion of the spinal cord, MEP monitoring provides a unique contribution during surgery on the thoracic aorta.[70] The SSEP is less specific for ischemia in the motor tracts because the pathway is perfused by the posterior spinal artery (PSA). The MEP monitors the motor tracts which are primarily supplied by the anterior spinal artery (ASA) in a vascular network supplying the anterior two-thirds to four-fifths of the spinal cord. This includes the gray matter and anterior horn cells, which are more sensitive to ischemia than white matter. The ASA receives blood flow from radicular arteries from the aorta which may be at risk with the surgery. Disruption of blood flow through these vessels due to mechanical or pressure changes rapidly leads to deterioration in MEP and is used to prompt change in management (eg, reimplantation of radicular arteries, improvement in systemic perfusion, and cerebrospinal fluid drainage) (Fig. 6.7).

ANESTHETIC CONSIDERATIONS DURING MONITORING

During monitoring, several factors besides surgery can alter the responses. Positioning, physiologic management, and anesthetic choices all affect neural functioning and monitoring responses. Physiological alterations include conditions leading to inadequate oxygen delivery (eg, relative hypotension, raised intracranial pressure, regional ischemia, anemia, tissue or systemic hypoxia), hypothermia, electrolyte abnormalities, and hypoglycemia.[71] Although hypothermia may not be deleterious to the neural system, it can result in increased latency and decreased amplitude raising concern.

Hypotension is of particular interest, because some anesthetic plans include deliberate hypotension. There is a growing appreciation that the presumed lower limit of autoregulation is not always adequate in tissues undergoing surgical stress.[72] In addition, compression and stretch of arteries, venous congestion, intentional arterial occlusion, or other factors (such as, eg, pathology, excessive hyperventilation) may necessitate a higher mean blood pressure for adequate perfusion. Increasing the systemic blood pressure is one of the most commonly requested maneuvers when an IOM deterioration occurs. Hence monitoring may allow a more optimal assessment of adequate blood pressure and tissue perfusion.

Anesthesia management is critical for adequate monitoring. It involves the choice of a favorable drug combination and maintenance of a steady state (eg, avoiding changes in concentration or bolus drug delivery during critical monitoring periods).[73,74]

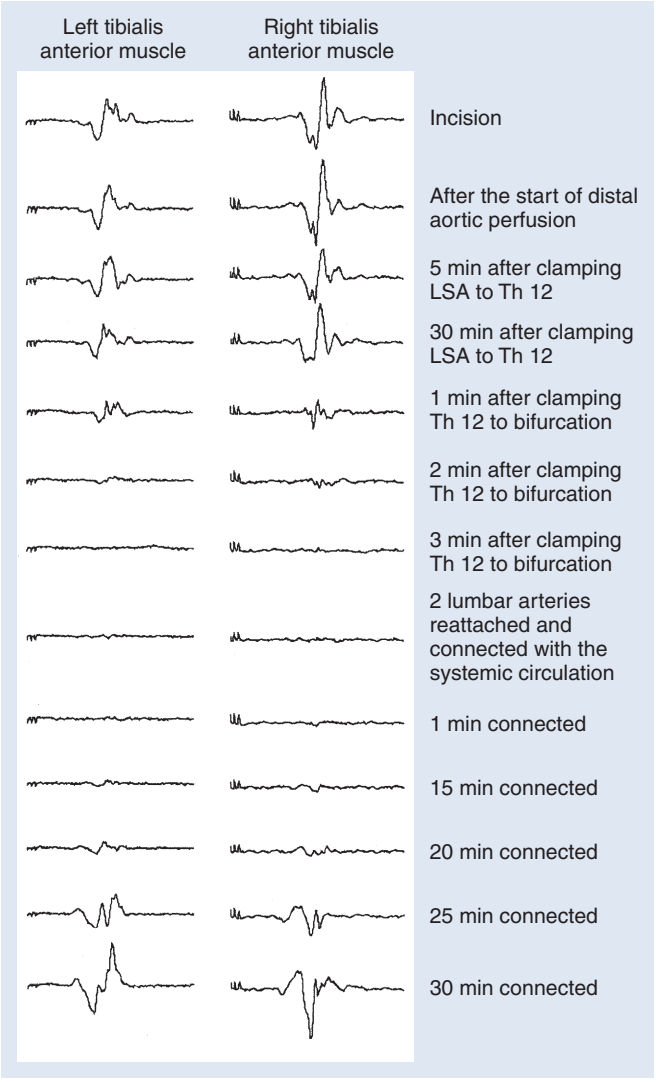


Fig. 6.7 Effect of ischemia on muscle evoked potential (MEP) response and recovery after reperfusion during a type II thoracoabdominal aneurysm. During the thoracic part of the operation, no MEP changes were observed, and eight intercostal arteries were ligated. During the abdominal part of the operation, MEP changes were observed within 2 minutes after placement of the clamps between T12 and the bifurcation. Two large lumbar spinal arteries (LSA) were identified and reattached to the graft. MEPs returned 15 minutes after the blood flow in the reattached lumbar spinal arteries was restored. *(From de Haan P, Kalkman CJ: Spinal cord monitoring: Somatosensory- and motor-evoked potentials. Anesthesiol Clin N Am 2001;19:923.)*

For the SSEP and MEP, anesthetic agents appear to have two major mechanisms of action. First, anesthetic agents act to reduce synaptic transmission resulting in marked changes in the cortical responses, but less at the brainstem and spinal cord. Second, anesthetic agents appear to produce gating of sensory information at the level of the thalamus through mechanisms activated in the brainstem.[75] In each pathway the depression of the evoked potential response increases with the number of synapses involved. This may explain why inhalational agents produce a dramatic nonlinear, dose-dependent reduction in cortical responses increases with the number of synapses involved. Brainstem ABR responses are minimally affected.[71]

The effects on MEP can similarly be explained by anesthetic action. MEP is more depressed by anesthetic agents acting in the spinal cord. Because no synapses are involved in the production of the D wave, recordings of the D wave in the epidural space are minimally altered by anesthetics. I waves are

sensitive to depression by anesthetic agents because they are produced through synaptic cortical pathways. Since the combination of D and I waves is necessary to bring the anterior horn cell to threshold to produce a CMAP response, the loss of I waves essentially blocks the response from single-pulse stimulation.[76] With MEP the current high-frequency, multipulse stimulation technique overcomes some of the anesthetic effects likely due to the multiple D waves produced.[77]

In general, the inhalational anesthetic agents have the most profound effect on monitoring. Not surprisingly, because of the effect on synapses, the effects and potency of specific agents parallel their effects on the EEG.[71] Among the inhalational agents, isoflurane is more potent than halothane or enflurane. Sevoflurane and desflurane appear similar to isoflurane at steady state, but owing to their relative insolubility, they may appear to be more potent during periods when concentrations are increasing.[78]

In the sensory responses, anesthetic effects of the inhalational anesthetics are prominent on the cortical responses, with marked depression of amplitude with concentrations above 0.5–1 minimal alveolar concentration (MAC).[71,78] Smaller effects are seen on the ABR and in SSEP responses recorded over the cervical spine, in the epidural space, or near peripheral nerves.

The inhalational agents produce minimal changes in the epidurally recorded D wave of the MEP with dramatic depression of the muscle response (CMAP). The CMAP response of the MEP appears most easily abolished by low concentrations of halogenated inhalational agents (eg, 0.2–0.5% isoflurane). In some patients 0.5 MAC desflurane or sevoflurane may prevent detection of the CMAP response, especially in the presence of neurologic disease. However, MEP monitoring of neurologically normal individuals undergoing spine surgery can frequently be accomplished with the use of 0.5 MAC of desflurane or sevoflurane.

Nitrous oxide (N_2O) also produces amplitude reduction and latency increases in cortical sensory responses or MEP CMAP responses when used alone or when combined with halogenated inhalational agents or opioid agents. As with halogenated agents, the effects on subcortical, epidural, and peripheral nerve responses are minimal.

In general, intravenous anesthetics suppress MEP responses much less than inhalational agents, so total intravenous anesthesia is preferred when MEPs are monitored in patients with neurologic disease. Opioids cause only mild depression of all responses. As such, opioid analgesia is commonly used during recording of cortical sensory responses and MEPs.

Propofol is currently the most commonly used sedative component of total intravenous anesthesia when SSEPs and MEPs are monitored. Induction produces amplitude depression in cortical SSEPs, with recovery after termination of infusion.[71] Recordings in the epidural space are unaffected, consistent with the site of anesthetic action of propofol in the cerebral cortex. The rapid metabolism of propofol makes it an excellent drug for infusion, because its sedative effect and its related effects on evoked responses can be adjusted quickly. An infusion of propofol with opioids can often be chosen that allows cortical SSEP and CMAP MEP monitoring, although depression of SSEP and MEP can occur at higher propofol doses.

The effects of ketamine on subcortical and peripheral responses are also minimal; it increases the amplitude of the cortical SSEP and MEP CMAP.[79] This feature has made ketamine a desirable agent for monitoring in children and patients with poor responses. Use of ketamine with propofol reduces the depressant effect of propofol while providing an enhancement effect on responses. Hence propofol with or without ketamine is frequently combined with opioids.[78,80] With use of total intravenous anesthesia, MEPs are successfully obtained in more than 90% of patients, failures being associated with preexisting neurologic disorders or equipment failure.[81]

Dexmedetomidine appears to have minimal effects on SSEP responses when combined with opioids. Dexmedetomidine has been successfully used with MEP, but case reports have appeared suggesting that it may prevent MEP monitoring, especially at higher doses or when combined with other agents.[82] The only prospective trial in scoliosis surgery found a synergistic depressant effect with administration of propofol and dexmedetomidine that required discontinuation of the study.[83] Midazolam produces mild depression of cortical sensory responses but long-lasting depression of MEPs at higher doses. It can be used in small doses to augment amnesia or reduce ketamine related psychological reactions. Etomidate produces an amplitude increase of cortical sensory components following injection with no changes in subcortical and peripheral sensory responses.[84,85] This amplitude increase appears coincident with the myoclonus seen with the drug, suggesting a heightened cortical excitability. The ABR and SSEP is virtually unaffected by doses of phenobarbital that produce coma, such that they have been used successfully to monitor neurologic function during barbiturate-induced coma.

Depression of the neuromuscular junction by neuromuscular blocking agents impairs or prevents MEP and EMG monitoring. Muscle relaxants are generally thought to have no effect on the SSEP and ABR. Stimulated EMG responses have been monitored successfully during partial neuromuscular blockade (NMB) (one of four twitches in train-of-four twitch monitors); however, fluctuations in partial NMB could result in changes similar to those caused by adverse surgical manipulation or physiologic change.[16] Further, because muscles vary in sensitivity to NMB, the extent of blockade must be assessed in the muscles monitored. Finally, partial NMB reduces the amplitude of motor unit potentials and could change the ability to detect impending axonal injury from nerve irritation. Hence it is considered preferable to avoid NMB when possible during EMG and MEP monitoring. When MEP baselines need to be acquired shortly after induction, NMB agents should be used with caution lest they obscure recording. In patients where partial NMB is desired, the technique called post-tetanic MEPs enhances conventional MEPs by delivering a tetanic stimulus to a peripheral nerve before the MEP (eg, 5-second 50-Hz tetanic stimulus to the posterior tibial nerve 6 seconds prior to transcranial MEP recorded in the abductor hallucis muscle) may be considered.[86]

CONCLUSION

Neurophysiologic mapping and monitoring with EMG and evoked sensory and motor responses have become important tools in the surgical management of some central and peripheral nervous system disorders. In general, multiple monitoring modalities are used with each operation to provide the greatest vigilance of the nervous system (Table 6.3). In some procedures, these methods have been demonstrated to reduce morbidity and have become a standard of care. They have been shown to be cost effective and have become part of routine management. For many surgeons these methods have become an indispensable intraoperative tool to improve outcome. The anesthesiologist, as a member of the surgical team, can make an important contribution to the success of the monitoring and can use the responses to guide physiologic management.

Table 6.3 Recommended Monitoring Modalities and Anesthetic Regimens for Surgical Procedures

	Monitoring Modalities					Anesthetic Recommendation	
			Electromyography				
Type of Procedure	*Somatosensory Evoked Potentials*	*Transcranial Motor Evoked Potentials*	*Free Run*	*Stimulated*	*Auditory Brainstem Responses*	*Volatile (Inhalational Anesthetics)*	*Total Intravenous Anesthesia*
Spine Skeletal							
Cervical	•	•	•	•			
Thoracic	•	•	•	•	•		
Lumbar instrumentation	•	•	•	•			
Lumbar disc	•	•	•				
Head and Neck							
Parotid	•	•	•				
Radical neck	•	•	•				
Thyroid	•	•	•				
Cochlear implant	•	•	•				
Mastoid	•	•	•				
Neurosurgery							
Spine							
Vascular	•	•	•				
Tumor	•	•	•				
Posterior Fossa							
Acoustic neuroma	•	•	•	•			
Cerebellopontine	•	±	•	•	±	•	
Vascular	•	•	•	±	•		
Supratentorial							
Middle cerebral artery aneurysm	•	•					
Tumor in motor cortex	•	•	•				

• Recommended for most surgeries, ± recommended for some procedures (depending on specific location of pathology)
Adapted from Jameson LC, Sloan TB, Jameson LC, et al: Monitoring of the brain and spinal cord. Anesthesiol Clin 2006; 24:777.

REFERENCES

1. Becker A, Rusy DA. Somatosensory evoked potentials. In: Koht A, Sloan TB, Toleikis JR, eds. *Monitoring the Nervous System for Anesthesiologists and Other Health Care Professionals*. New York, NY: Springer; 2012:3.
2. Toleikis JR. Intraoperative monitoring using somatosensory evoked potentials. A position statement by the American Society of Neurophysiological Monitoring. *Journal of Clinical Monitoring and Computing*. 2005;19:241.
3. Jameson LC, Sloan TB. Neurophysiologic monitoring in neurosurgery. *Anesthesiol Clin*. 2012;30:311.
4. Symon L, Momma F, Murota T. Assessment of reversible cerebral ischaemia in man: Intraoperative monitoring of the somatosensory evoked response. *Acta Neurochir Suppl (Wien)*. 1988;42:3.
5. Schramm J, Zentner J, Pechstein U. Intraoperative SEP monitoring in aneurysm surgery. *Neurol Res*. 1994;16:20.
6. Costa P, Bruno A, Bonzanino M, et al. Somatosensory- and motor-evoked potential monitoring during spine and spinal cord surgery. *Spinal Cord*. 2007;45:86.
7. Ney JP, van der Goes DN, Nuwer M, et al. Evidence-based guideline update: Intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Clinical Neurophysiology Society. *Neurology*. 2012;79:292.
8. Nuwer MR, Emerson RG, Galloway G, et al. Evidence-based guideline update: Intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials. *J Clin Neurophysiol*. 2012;29:101.
9. Nuwer MR, Dawson EG, Carlson LG, et al. Somatosensory evoked potential spinal cord monitoring reduces neurologic deficits after scoliosis surgery: Results of a large multicenter survey. *Electroencephalography & Clinical Neurophysiology*. 1995;96:6.
10. Scoliosis Research Society. *Position statement on somatosensory evoked potential monitoring of neurologic spinal cord function during surgery*. Illinois: Park Ridge; 1992.
11. Pereon Y, Bernard JM, Fayet G, et al. Usefulness of neurogenic motor evoked potentials for spinal cord monitoring: Findings in 112 consecutive patients undergoing surgery for spinal deformity. *Electroencephalography & Clinical Neurophysiology*. 1998;108:17.
12. Moller AR. Intraoperative Neurophysiologic Monitoring. 2nd ed. Totowa, NJ: Humana Press, Inc; 2006.
13. Möller AR. Neural generators for auditory brainstem evoked potentials. In: Burkard RF, Eggemont JJ, Manuel D, eds. *Auditory Evoked Potentials: Basic Principles and Clinical Applications*. Baltimore: Lippincott Williams & Wilkins; 2007:336.
14. Aravabhumi S, Izzo KL, Bakst BL, et al. Brainstem auditory evoked potentials: Intraoperative monitoring technique in surgery of posterior fossa tumors. *Archives of Physical Medicine & Rehabilitation*. 1987;68:142.

15. Yingling CD. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackman DE, eds. *Neurotology*. Mosby: St. Louis, MO; 1994:967.
16. Harper CM, Harper CM. Intraoperative cranial nerve monitoring. *Muscle Nerve*. 2004;29:339.
17. Harper CM, Daube JR, Harper CM, et al. Facial nerve electromyography and other cranial nerve monitoring. [see comment]. *Journal of Clinical Neurophysiology*. 1998;15(206).
18. Abbott R. Sensory rhizotomy for the treatment of childhood spasticity. In: Deletis V, Shils JL, eds. *Neurophysiology in neurosurgery*. Boston, MA: Academic Press; 2002:219.
19. Symon L, Jellinek D. Monitoring of auditory function in acoustic neuroma surgery. In: Schramm J, Moller AR, eds. *Intraoperative Neurophysiological Monitoring*. Berlin: Springer-Verlag; 1991:173.
20. Prell J, Rampp S, Romstock J, et al. Train time as a quantitative electromyographic parameter for facial nerve function in patients undergoing surgery for vestibular schwannoma. *J Neurosurg*. 2007;106:826.
21. Romstock J, Strauss C, Fahlbusch R. Continuous electromyography monitoring of motor cranial nerves during cerebellopontine angle surgery. *J Neurosurg*. 2000;93:586.
22. Anonymous: National Institutes of Health (NIH). Consensus development conference (held December 11-13, 1991). Consensus Statement: 9, 1991.
23. Petro ML, Schweinfurth JM, Petro AB, et al. Transcricothyroid, intraoperative monitoring of the vagus nerve. *Arch Otolaryngol Head Neck Surg*. 2006;132:624.
24. Glasker S, Pechstein U, Vougioukas VI, et al. Monitoring motor function during resection of tumours in the lower brain stem and fourth ventricle. *Childs Nervous System*. 2006;22:1288.
25. Holland NR, Holland NR. Intraoperative electromyography. *J Clin Neurophysiol*. 2002;19:444.
26. Leppanen RE. Intraoperative monitoring of segmental spinal nerve root function with free-run and electrically-triggered electromyography and spinal cord function with reflexes and F-responses. A position statement by the American Society of Neurophysiological Monitoring. *J Clin Monit Comput*. 2005;19(437).
27. Toleikis JR. Neurophysiological monitoring during pedicle screw placement. In: Deletis V, Shils JL, eds. *Neurophysiology in Neurosurgery*. New York: Academic Press; 2002:231.
28. Holland NR, Holland NR. Intraoperative electromyography during thoracolumbar spinal surgery. *Spine*. 1998;23:1915.
29. Balzer JR, Rose RD, Welch WC, et al. Simultaneous somatosensory evoked potential and electromyographic recordings during lumbosacral decompression and instrumentation. *Neurosurgery*. 1998;42:1318.
30. Djurasovic M, Dimar 2nd. JR, Glassman SD, et al. A prospective analysis of intraoperative electromyographic monitoring of posterior cervical screw fixation. *J Spinal Disord Tech*. 2005;18(515) [see comment].
31. Quinones-Hinojosa A, Gadkary CA, Gulati M, et al. Neurophysiological monitoring for safe surgical tethered cord syndrome release in adults. *Surg Neurol*. 2004;62:127.
32. Husain AM, Shah D. Prognostic value of neurophysiologic intraoperative monitoring in tethered cord syndrome surgery. *J Clin Neurophysiol*. 2009;26:244.
33. Paradiso G, Lee GY, Sarjeant R, et al. Multi-modality neurophysiological monitoring during surgery for adult tethered cord syndrome. *J Clin Neurosci*. 2005;12:934.
34. Kothbauer KF, Novak K, Kothbauer KF, et al. Intraoperative monitoring for tethered cord surgery: An update. *Neurosurg*. 2004;16.
35. Leis AA, Zhou HH, Mehta M, et al. Behavior of the H-reflex in humans following mechanical perturbation or injury to rostral spinal cord. *Muscle Nerve*. 1996;19:1373.
36. Leppanen RE. Intraoperative applications of the H-reflex and F-response: A tutorial. *J Clin Monit Comput*. 2006;20:267.
37. Deletis V. Basic methodological principles of multimodal intraoperative monitoring during spine surgeries. *Eur Spine J*. 2007;16(S147):S147–S152.
38. Hsu B, Cree AK, Lagopoulos J, et al. Transcranial motor-evoked potentials combined with response recording through compound muscle action potential as the sole modality of spinal cord monitoring in spinal deformity surgery. *Spine (Phila Pa 1976)*. 2008;33(1100).
39. Macdonald DB, Skinner S, Shils J, et al. Intraoperative motor evoked potential monitoring - a position statement by the American Society of Neurophysiological Monitoring. *Clinical Neurophysiology*. 2013;124:2291.
40. Jameson L. Transcranial motor evoked potentials. In: Koht A, Sloan T, Toleikis JR, eds. *Monitoring the Nervous System for Anesthesiologists and other Health Professionals*. New York: Springer; 2012:27.
41. Deletis V, Isgum V, Amassian VE. Neurophysiological mechanisms underlying motor evoked potentials in anesthetized humans. Part 1. Recovery time of corticospinal tract direct waves elicited by pairs of transcranial electrical stimuli. *Clinical Neurophysiology*. 2001;112(438).
42. Deletis V, Rodi Z, Amassian VE. Neurophysiological mechanisms underlying motor evoked potentials in anesthetized humans. Part 2. Relationship between epidurally and muscle recorded MEPs in man. *Clinical Neurophysiology*. 2001;112(445).
43. Muramoto A, Imagama S, Ito Z, et al. The cutoff amplitude of transcranial motor-evoked potentials for predicting postoperative motor deficits in thoracic spine surgery. *Spine*. 2013;38(E21).
44. Karadeniz U, Erdemli O, Yamak B, et al. On-pump beating heart versus hypothermic arrested heart valve replacement surgery. *J Card Surg*. 2008;23:107.
45. Pastorelli F, Di Silvestre M, Plasmati R, et al. The prevention of neural complications in the surgical treatment of scoliosis: The role of the neurophysiological intraoperative monitoring. 20 Suppl. *Eur Spine J*. 2011;1(S105).
46. Malhotra NR, Shaffrey CI. Intraoperative electrophysiological monitoring in spine surgery. *Spine*. 2010;35:2167.
47. Kobayashi S, Matsuyama Y, Shinomiya K, et al. A new alarm point of transcranial electrical stimulation motor evoked potentials for intraoperative spinal cord monitoring: A prospective multicenter study from the Spinal Cord Monitoring Working Group of the Japanese Society for Spine Surgery and Related Research. *J Neurosurg Spine*. 2014;20:102.
48. Deiner S. Highlights of anesthetic considerations for intraoperative neuromonitoring. *Semin Cardiothorac Vasc Anes*. 2010;14:51.
49. Deiner SG, Kwatra SG, Lin HM, et al. Patient characteristics and anesthetic technique are additive but not synergistic predictors of successful motor evoked potential monitoring. *Anesth Analg*. 2010;111:421.
50. Szelenyi A, Langer D, Beck J, et al. Transcranial and direct cortical stimulation for motor evoked potential monitoring in intracerebral aneurysm surgery. *Neurophysiol Clini*. 2007;37:391.
51. Neuloh G, Schramm J, Neuloh G, et al. Monitoring of motor evoked potentials compared with somatosensory evoked potentials and microvascular Doppler ultrasonography in cerebral aneurysm surgery. *J Neurosurg*. 2004;100:389.
52. Szelenyi A, Langer D, Kothbauer K, et al. Monitoring of muscle motor evoked potentials during cerebral aneurysm surgery: Intraoperative changes and postoperative outcome. *J Neurosurg*. 2006;105:675.
53. Allen MD, Major B, Kimpinski K, et al. Skeletal muscle morphology and contractile function in relation to muscle denervation in diabetic neuropathy. *J Appl Physiol (1985)*. 2014;116(5):545–552.
54. Sala F, Manganotti P, Grossauer S, et al. Intraoperative neurophysiology of the motor system in children: A tailored approach. *Childs Nervous System*. 2010;26:473.
55. Drake J, Zeller R, Kulkarni AV, et al. Intraoperative neurophysiological monitoring during complex spinal deformity cases in pediatric patients: Methodology, utility, prognostication, and outcome. *Childs Nervous System*. 2010;26:523.
56. Singh R, Husain AM. Neurophysiologic intraoperative monitoring of the glossopharyngeal and vagus nerves. *J Clini Neurophysiol*. 2011;28:582.
57. Sanai N. Emerging operative strategies in neurosurgical oncology. *Curr Opin Neurol*. 2012;25:756.
58. Sanai N, BM. Glioma extent of resection and its impact on patient outcome. *Neurosurgery*. 2008;62(4):753–764.
59. Chacko AG, Thomas SG, Babu KS, et al. Awake craniotomy and electrophysiological mapping for eloquent area tumours. *Clin Neurol Neurosurg*. 2013;115:329.
60. Hemmer LB, Zeeni C, Bebawy JF, et al. The incidence of unacceptable movement with motor evoked potentials during craniotomy for aneurysm clipping. *World Neurosurg*. 2014;81:99.
61. Matthies C, Rasian F, Schweitzwer T, et al. Facial motor evoked potentials in cerebellopontine angle surgery: Technique, pitfalls and predictive value. *Clinical Neuroloty & Neurosurgery*. 2011;113(872).
62. Kazmierski J, Kowman M, Banach M, et al. Incidence and predictors of delirium after cardiac surgery: Results from the IPDACS Study. *J Psychosom Res*. 2010;69:179.
63. Irie T, Yoshitani K, Ohnishi Y, et al. The efficacy of motor-evoked potentials on cerebral aneurysm surgery and new-onset postoperative motor deficits. *J Neurosurg Anesthesiol*. 2010;22:247.
64. Legatt AD. BAEPs in surgery. In: Nuwer MR, ed. *Intraoperative Monitoring of Neural Function*. Handbook of Clinical Neurophysiology. Amsterdam: Netherlands; 2008:334.
65. Dong CC, Macdonald DB, Akagami R, et al. Intraoperative facial motor evoked potential monitoring with transcranial electrical stimulation during skull base surgery. *Clin Neurophysiol*. 2005;116:588.
66. Raynor BL, Bright JD, Lenke LG, et al. Significant change or loss of intraoperative monitoring data: A 25-year experience in 12,375 spinal surgeries. *Spine (Phila Pa 1976)*. 2013;38:E101.

67. Thuet ED, Winscher JC, Padberg AM, et al. Validity and reliability of intraoperative monitoring in pediatric spinal deformity surgery: A 23-year experience of 3436 surgical cases. *Spine (Phila Pa 1976)*. 2010;35:1880.
68. Sala F, Palandri G, Basso E, et al. Motor evoked potential monitoring improves outcome after surgery for intramedullary spinal cord tumors: A historical control study. *Neurosurgery*. 2006;58:1129.
69. Abadin SS, Kaplan EL, Angelos P. Malpractice litigation after thyroid surgery: The role of recurrent laryngeal nerve injuries, 1989-2009. *Surgery*. 2011;148:718.
70. Sloan TB, Jameson LC. Electrophysiologic monitoring during surgery to repair the thoraco-abdominal aorta. *J Clin Neurophysiol*. 2007;24:316.
71. Sloan TB. Evoked potentials. In: Albin MA, ed. *Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives*. New York: McGraw-Hill; 1997:221.
72. Edmonds Jr. HL. Multi-modality neurophysiologic monitoring for cardiac surgery. *Heart Surg Forum*. 2002;5:225.
73. Sloan T. General anesthesia for monitoring. In: Koht A, Sloan T, Toleikis JR, eds. *Monitoring for the Anesthesiologist and Other Health Professionals*. New York: Springer; 2012:319.
74. Sloan TB, Jäntti V. Anesthetic effects on evoked potentials. In: Nuwer MR, ed. *Intraoperative Monitoring of Neural Function*. Handbook of Clinical Neurophysiology. Amsterdam, The Netherlands: Elsevier; 2008:94.
75. John ER, Prichep LS, John ER, et al. The anesthetic cascade: A theory of how anesthesia suppresses consciousness. [see comment], *Anesthesiology*. 2005;102(447).
76. Hicks RG, Woodforth IJ, Crawford MR, et al. Some effects of isoflurane on I waves of the motor evoked potential. *British J Anaesth*. 1992;69:130.
77. Taniguchi M, Cedzich C, Schramm J. Modification of cortical stimulation for motor evoked potentials under general anesthesia: Technical description. *Neurosurgery*. 1993;32:219.
78. Sloan TB. Anesthetic effects on electrophysiologic recordings. *J Clin Neurophysiol*. 1998;15:217.
79. Schubert A, Licina MG, Lineberry PJ. The effect of ketamine on human somatosensory evoked potentials and its modification by nitrous oxide. [erratum appears in Anesthesiology 1990 Jun;72(6):1104], *Anesthesiology*. 1990;72(33).
80. Kawaguchi M, Sakamoto T, Inoue S, et al. Low dose propofol as a supplement to ketamine-based anesthesia during intraoperative monitoring of motor-evoked potentials. *Spine*. 2000;25:974.
81. Legatt A. Current practice of motor evoked potential monitoring: Results of a survey. *J Clin Neurophysiol*. 2002;19:454.
82. Mahmoud M, Sadhasivam S, Sestokas AK, et al. Loss of transcranial electric motor evoked potentials during pediatric spine surgery with dexmedetomidine. *Anesthesiology*. 2007;106:393.
83. Mahmoud M, Sadhasivam S, Salisbury S, et al. Susceptibility of transcranial electric motor-evoked potentials to varying targeted blood levels of dexmedetomidine during spine surgery. *Anesthesiology*. 2010;112:1364.
84. Kochs E, Treede RD, Schulte am Esch J. [Increase in somatosensory evoked potentials during anesthesia induction with etomidate]. *Anaesthesist*. 1986;35:359.
85. Koht A, Schutz W, Schmidt G, et al. Effects of etomidate, midazolam, and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide. *Anesth Analg*. 1988;67:435.
86. Yamamoto Y, Kawaguchi M, Hayashi H, et al. The effects of the neuromuscular blockade levels on amplitudes of posttetanic motor-evoked potentials and movement in response to transcranial stimulation in patients receiving propofol and fentanyl anesthesia. *Anesth Analg*. 2008;106:930.

Transcranial Doppler Ultrasonography in Anesthesia and Neurosurgery

7

B. Matta • M. Czosnyka

Introduced in 1982 by Aaslid and colleagues,[1] transcranial Doppler (TCD) ultrasonography, sometimes termed a "stethoscope for brain," has become one of the most useful methods of noninvasive examination of cerebral circulation. Provided that the limitations of this technology are recognized, information about cerebral hemodynamics can be obtained that can be used in the perioperative and intensive care of neurologically injured patients (those with head injury, subarachnoid hemorrhage, poor grade stroke, etc.) and in the prevention of neurologic insult in patients at risk for cerebral ischemia (those undergoing carotid endarterectomy, cardiopulmonary bypass, liver transplant, etc.). This chapter discusses the principles and limitations that govern the use of TCD and describes current and potential future applications of this reliable, noninvasive, continuous, although indirect measure of cerebral blood flow (CBF).

PRINCIPLES OF TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

TCD ultrasonography calculates the velocity of red blood cells (FV) flowing through the large vessels at the base of the brain by means of the Doppler principle. This principle, first described by Christian Doppler in 1843, relates to the shift in the frequency of any wave, including an ultrasound wave, when either the transmitter or the receiver is moving relative to the wave-propagating medium. The change in the frequency of emitted pulse of ultrasound reflected by red blood cells is proportional to FV. By convention, the shift in Doppler frequency is expressed in centimeters per second to allow comparison of readings from instruments that operate at different emission frequencies. The frequency best suited for TCD applications is on the order of 2 MHz.[2]

A constant vessel diameter and an unchanged angle of insonation are the two main assumptions that govern the use of TCD as an indirect measure of CBF. The velocity detected by the probe as a fraction of the real velocity depends on the cosine of the angle insonation compared to a vector of FV (measured velocity = real velocity × cosine of angle of incidence). Therefore at 0 angle, the detected and true red cell velocities are equal (cosine of 0 = 1), whereas at 90 degrees, no detection of velocity is possible. Fortunately, the anatomic limitations of transtemporal insonation of the middle cerebral artery (MCA) are such that signal capture is possible only at narrow angles (<30 degrees). Thus the detected velocity is a very close approximation of the true velocity (87–100%). Furthermore, as long as the angle of insonation is kept constant by fixing the probe in position (and vessel diameter remains constant during examination – see later comments), changes in the detected velocity closely reflect changes in the true velocity.

The other main factor that affects the interpretation of TCD measurements is the cross-sectional area of the insonated vessel. The volume passing through a particular segment of a vessel depends on the velocity of red cells and the diameter of the vessel. Therefore for velocity to be a true reflection of flow, the diameter of the vessel must not change significantly during the measurement period. Factors that may affect the diameter of vessels are arterial carbon dioxide tension ($PaCO_2$), blood pressure, anesthetic agents, and vasoactive drugs. The basal cerebral arteries, being conductance vessels, do not dilate or constrict as the vascular resistance changes (smaller resistive vessel). It has been shown angiographically and through direct observation during brain surgery that change in $PaCO_2$, one of the most important determinants of cerebrovascular resistance (CVR), has no or very limited effect on the diameter of the basal arteries.[3] Moreover, CO_2 reactivity studies using TCD have demonstrated values similar to those obtained with conventional CBF measurements.[4] Similarly, changes in blood pressure have negligible influence on the diameter of the proximal segments of the basal arteries.[5] The effect of vasoactive drugs on cerebral conductance vessels is variable. Although sodium nitroprusside and phenylephrine do not significantly affect the proximal segments of the MCA,[6] significant vasodilation occurs when nitroglycerine is administered to healthy volunteers.[7]

The effect of anesthetic agents on the diameter of the basal vessels remains controversial. The intravenous agents are devoid of direct cerebrovascular effects, and it is accepted that these agents do not affect the diameter of the conductance vessels.[8] The situation is less clear-cut with the inhalational agents, with most but not all the evidence suggesting that they have negligible effects on the diameter of the conductance vessels.[9] It is generally accepted that during steady-state anesthetic conditions, changes in FV can be interpreted to mean corresponding changes in cortical CBF.

A factor that may affect the reliability of TCD measurements as true representations of CBF variation is the presence of intracranial pathology. Intracranial lesions and cerebral vasospasm have all been identified as factors that affect the accuracy of FV measurements, as a representative variable for changes in CBF.[10]

MEASUREMENTS USING TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

The Examination

Three main pathways for accessing the intracranial arteries are (1) the transtemporal route through the thin bone above the zygomatic arch to the anterior, middle, and posterior cerebral arteries, (2) the transorbital approach to the carotid siphon, and (3) the suboccipital route to the basilar and vertebral arteries.

Although a complete diagnostic examination usually incorporates all three approaches, because the probe can be easily secured in position once a signal is obtained, intraoperative monitoring usually utilizes the transtemporal route. In expert

hands, it is possible to transtemporally insonate the proximal segment (M1) of the MCA in more than 90% of people.[2] The MCA carries about 60–70% of the ipsilateral carotid artery blood flow and can be regarded as representative of hemispheric CBF. However, because the successful transmission of ultrasound through the skull depends on the thickness of the skull, which varies with gender, race, and age, the failure rate can be as high as 10–30%. The theoretical risk of eye damage limits the use of the transorbital route, and the lack of suitable means to secure the probe in position makes the suboccipital route impractical.

Through the temporal window, the MCA, anterior cerebral artery (ACA), and posterior cerebral artery (PCA) can be readily examined. In each patient, the same insonation window should be used throughout the entire study period. This can be accomplished by putting a small marker at the patient's temporal region. The TCD examination begins with the identification of the bifurcation of the intracranial portion of the internal carotid artery (ICA) into the MCA and ACA according to the method described by Aaslid.[2] This bifurcation can usually be identified at a depth of 60–65 mm. The typical Doppler signal from the carotid bifurcation, which consists of images above and below the zero line of reference, represents the flow directions toward and away from the ultrasound probe of the MCA and ACA, respectively. The depth of insonation is then reduced to follow the upward deflection image of the MCA FV as the vessel runs toward the skull. The MCA can usually be traced up to a depth of 30 mm, which is beyond the bifurcation of the MCA into the peripheral branches. The proximal portion of the main trunk of the MCA (the M1 segment) can be located at a depth of around 45–55 mm. The depth that gives the highest velocity is usually chosen for measurement. In children, this depth is usually 10 mm less than that in adults, but the same principles apply. This method of obtaining the MCA signal eliminates the possibility of mistaking the PCA for the MCA, because for anatomic reasons, the PCA signal cannot be obtained at a depth less than 55 mm.

After the MCA signal is obtained, the depth of insonation is increased so that the image of the carotid bifurcation can be seen again. The depth is increased further with the probe directed slightly anteriorly so that the ACA image can be found. The first part of the ACA (the A1 segment) is recognized from a direction of flow away from the probe. With the identification of the ACA, the depth of insonation is decreased until the carotid bifurcation signal is obtained. The probe is then angled slightly posteriorly until the signal of the PCA is seen. The PCA can be distinguished from the MCA signal because it has a lower FV and because the PCA signal cannot be obtained when the depth of insonation is decreased to less than 55 mm. A more detailed description of the TCD examination can be found in a standard textbook.[2] Fig. 7.1 illustrates various signals obtained from the most commonly insonated vessels.

Velocity Measurements

Although the most physiologic correlate with actual CBF is the weighted mean velocity (FV_{mean}), which takes into consideration the different velocities of the formed elements in the blood vessel insonated, the maximal FV (FV_{max} as depicted by the spectral outline) is generally used because of the higher signal-to-noise ratio. A good correlation also exists between the FV_{max} and FV_{mean} in the basal cerebral arteries as flow is usually laminar. The mean FV with time-averaged FV usually

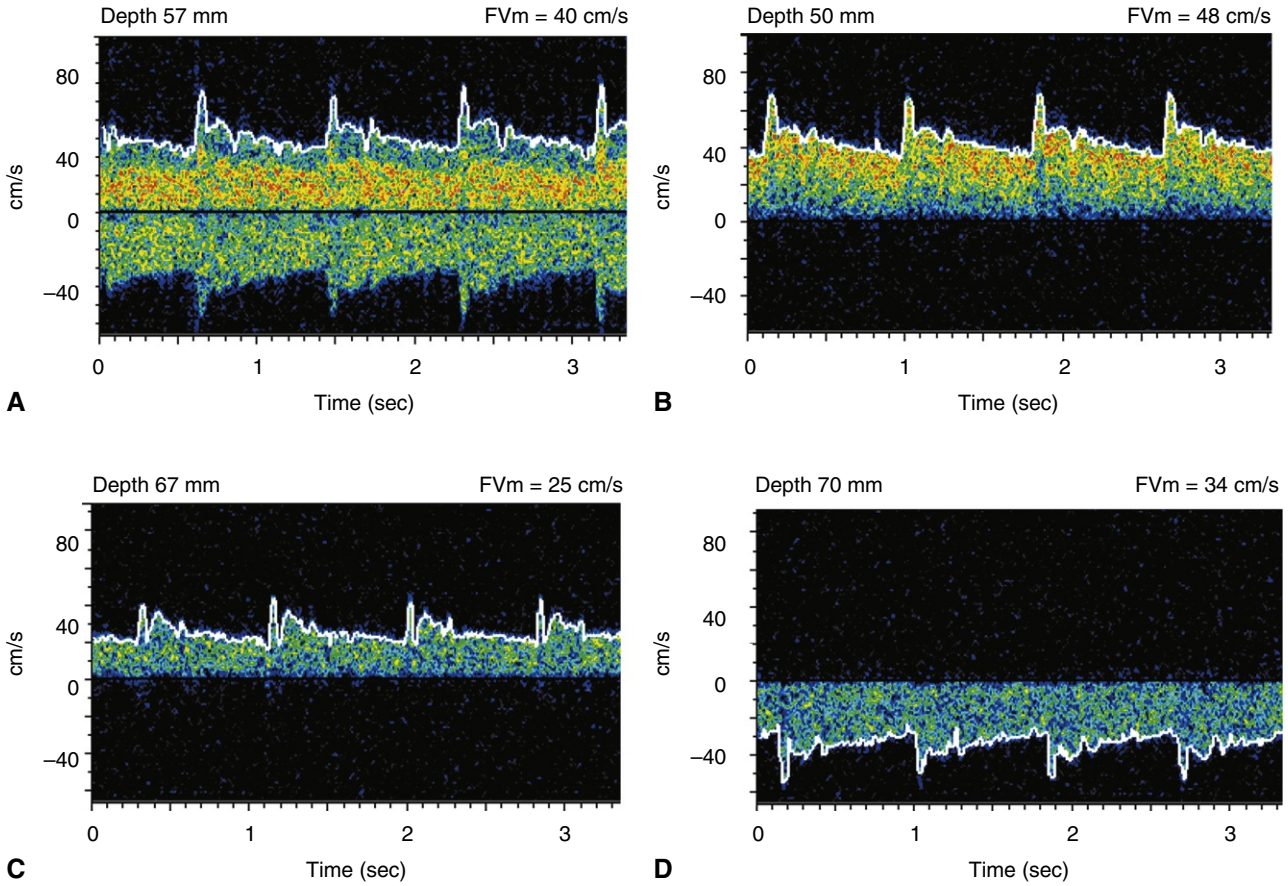


Fig. 7.1 Schematic representations of blood flow velocity (FV) traces obtained from the internal carotid artery bifurcation at 5.5 to 6.5 cm **(A),** the M1 segment of the middle cerebral artery (MCA) at 3 to 6 cm **(B),** the posterior cerebral artery (P1) at 6 to 8 cm **(C),** and the anterior cerebral artery (A1) at 6 to 8 cm **(D).** Flow above the horizontal is toward the probe, and flow below the horizontal is away from the probe.

refers to the mean velocity of FV_{max}. The time-averaged FV_{max} is determined from area under the spectral curve.

The volume of blood flowing through a vessel depends on the velocity of the moving cells and the diameter of vessel concerned. For a given blood flow the narrower the vessel, the higher the velocity. Although CBF in millilitres per minute per 100 g of brain tissue is relatively constant under conditions of constant brain metabolism and arterial content of carbon dioxide and oxygen, FV in the MCA ranges from 35 to 90 cm/sec in the awake resting state.[2] This range is due to inter-individual variations in vessel diameter and angles of insonation and probably accounts for the poor correlation between absolute FV and CBF in any given population. However, relative changes in FV accurately reflect variations in CBF.

Mean FV varies with age. MCA red cell velocity (FV_{MCA}) rises from 24 cm/sec at birth to a peak of 100 cm/sec at age 4 to 6 years. Thereafter the FV_{MCA} decreases steadily to about 40 cm/sec during the seventh decade of life.[1,11] Some of the reduction is the result of the genuine decrease in hemispheric CBF, which has been reported by several investigators.[12] Overall, the velocity trend seen in the MCA with age is similar to that in hemispheric CBF.

Mean FV is higher during hemodilution. A reduction in hematocrit has been shown to increase CBF in a linear fashion and probably accounts for the greater velocities reported in low hematocrit states.[13] However, low hematocrit may present diagnostic difficulties in patients with potential arterial stenotic lesions because the increase in velocity observed may be incorrectly interpreted as vessel stenosis. An example is subarachnoid-related vasospasm.

Women have higher hemispheric CBF than men, which is reflected in 3–5% higher mean FV_{MCA} values.[14] Although a convincing explanation for this difference in velocity has not yet been found, a lower hematocrit and slightly higher arterial CO_2 tension found in premenopausal women may partly explain this increase in velocity. [15]

Waveform Pulsatility

Pulsatility describes the shape of the maximal shift (the envelope) of the Doppler spectrum from peak systolic pressure to end-diastolic pressure with each cardiac cycle.[2] The FV waveform depends on the arterial blood pressure (ABP) waveform and the viscoelastic properties of the cerebrovascular bed, provided that blood rheology remains constant. The absence of vessel stenosis or vasospasm, with constant pulsatility of ABP, during constant cerebral perfusion pressure (CPP), and constant arterial blood CO_2 concentration, suggests that changes in pulsatility may reflect the changes in product of distal CVR, compliance of blood vessels and heart rate.[16] Two derived indices have been used to quantify pulsatility. The pulsatility index (PI), or Gosling index, is calculated as follows:

$$PI = \frac{\left(FV_{sys} - FV_{dias}\right)}{FV_{mean}} \qquad (7.1)$$

where FV_{dias} is diastolic FV and FV_{sys} is systemic FV. The resistance index (RI), or Pourcelot index, is calculated with the following equation:

$$RI = \frac{\left(FV_{sys} - FV_{dias}\right)}{FV_{sys}} \qquad (7.2)$$

In a highly pulsatile spectrum, FV_{sys} is peaked and much greater than end-FV_{dias}, whereas FV_{dias} greater than 50% of FV_{sys} gives a "damped" waveform. Normal PI ranges from 0.5 to 1 with no significant side-to-side or cerebral interarterial differences.[2]

In general, PI and RI correspond to each other, reflecting changes in central or cerebral hemodynamics. However, neither index provides meaningful information about the cause of the change; for example, an increase in PI can be caused by cerebral vasoconstriction (intrinsic, as in hyperventilation) or vasodilatation at low CPP, when vessels dilate because of the autoregulatory response.[17] Furthermore, PI is very sensitive to changes in heart rate and its values are best compared when measured during periods of similar heart rates. The advantage of PI is that it is dimensionless and, therefore, is not affected by the angle of insonation because the equation used to calculate PI has the cosine of the angle of incidence in both the numerator and the denominator. A PI value above 1.5 with normal or increased mean arterial pressure (MAP) in a normocapnic patient with normal pulsatility of blood pressure, may indicate elevated ICP. Also, asymmetry in PI values greater than 0.5 between the left and right hemispheres may give rise to concern about clinically relevant asymmetry of cerebral hemodynamics (unilateral carotid artery stenosis, acute subdural hematoma, brain contusion with a midline shift, etc.). PI is only superficially simple. It depends on numerous interrelated factors: ABP pulsatility, heart rate, $PaCO_2$, CPP, hematocrit, body temperature, CVR, compliance of the proximal cerebral vessels, ICP, and compliance of the cerebrospinal space.

DESCRIBING CEREBRAL HAEMODYNAMICS: TESTING AND MONITORING

All CBF-regulatory relationships—between CBF and CPP (autoregulation), CBF and $PaCO_2$ and PO_2 (chemoregulation), probably CBF and brain metabolism (flow-metabolism coupling) and autonomic activity (neuroregulation)—have non-linear characteristics. Most frequently tested is cerebral pressure autoregulation, with the static CBF–CPP relationship described as Lassen's curve.[18]

Almost all cerebrovascular reactivity testing methods rely on comparing changes in CBF velocity to changes (provoked or spontaneous) in controlling variables: CPP, $PaCO_2$, PaO_2 or other (breath holding, Valsalva maneuver, etc., make quantification more difficult).

However, cerebral vessels' reactivity responses have their own time inertia (from 6 to 12 seconds). Therefore, changes in CBF provoked by changes in CPP that are slower than 6 seconds will contain information about cerebral autoregulation, and changes provoked by CPP variations faster than that will describe the mechanoelastic properties of the cerebrovascular bed, like cerebrovascular resistance and compliance. Domain demarcation frequency is around 0.05 Hz, which means that slower waves of CPP and CBF carry information about cerebral autoregulation, while faster waves carry information about the mechanoelastic properties of the cerebrovascular system.[19]

Cerebrovascular Reactivity to CO_2

Cerebrovascular reactivity to CO_2 describes the relationship between arterial CO_2 tension and CBF. Within the limits of mild hypocapnia to mild hypercapnia, a slow change in $PaCO_2$ produces almost proportional change in CBF and FV. In deep hypocapnia and hypercapnia, this linear relationship saturates. The reactivity can be tested by observation of the change in CBF in response to a change in $PaCO_2$. If we accept that the

diameter of the basal arteries is unaffected or is affected to a negligible degree by changes in arterial CO_2 tension, then TCD is particularly suitable for such investigations because multiple paired measurements are taken and regression lines can be constructed more accurately than with a limited number of conventional blood flow measurements.[4] The percentage change in FV with a change in $PaCO_2$ shows a low dependence on the baseline value and is, therefore, a valid indicator of CO_2 reactivity and a more appropriate variable for use in comparing clinical conditions.

In normal individuals CBF (or FV) changes by approximately 2.5–3% for every mmHg change in $PaCO_2$. TCD can, therefore, be used in many clinical situations to assess cerebrovascular reserve, such as for patients with carotid artery stenosis and after head injury. The effect of anesthetics and vasoactive drugs on cerebral vasoreactivity to CO_2 can also be easily examined using TCD.[4,9] An induced change in $PaCO_2$ usually provokes a change in ABP. In such cases CO_2 reactivity values should be adjusted accordingly (Fig. 7.2).[20] Increasing and decreasing CO_2 tension test both the vasodilatory and vasoconstrictive capabilities of the cerebral circulation.

Cerebral Pressure Autoregulation

Cerebral autoregulation, a sensitive mechanism that can be impaired by pathologic processes and inhalational anesthesia, minimizes deviations in CBF when CPP changes between 50 and 170 mmHg.[21] Cerebral autoregulation has been traditionally assessed by repeated static measurements of CBF during a period of hypotension or hypertension. Before the TCD era, in addition to the bulky equipment or radioactive material necessary for these measurements, the process was labor intensive and assumed that cerebral autoregulation was a uniform and slow-acting process. Furthermore, the drugs used to induce hypertension or hypotension may have influenced cerebrovascular tone.

Cerebral autoregulation is a complex process composed of several physiologic mechanisms operating possibly at different rates. TCD studies have estimated the time constant of fast autoregulatory responses; FV_{MCA} as an index of CBF was fully restored to the baseline value as early as 6–12 seconds after a step decrease in blood pressure.[22] TCD allows noninvasive measurement of the autoregulatory response and can provide insight into both rapid and delayed components of cerebral autoregulatory mechanisms. Other continuous techniques, such as laser Doppler flowmetry and thermal methods, are invasive. Near-infrared spectroscopy seems to be the only competitor of TCD in this implementation,[23] but its clinical use needs more validation.

Although many methods for the assessment of cerebral autoregulation have been described, only the methods most commonly employed are discussed here. Examples of testing dynamic and static autoregulation are shown in Fig. 7.3.

Leg-Cuff Test

Dynamic autoregulation is tested by the measurement of the recovery in FV after a rapid transient decrease in mean blood pressure that has been induced by the deflation of large thigh cuffs. These large blood pressure cuffs that have been modified with larger tubes are placed around one or both thighs, and inflated to 50 mmHg above systolic pressure for 3 minutes. Deflation of cuffs usually produces an approximately 20-mmHg drop in ABP. Through the use of an algorithm previously validated,[22,24] the FV response to the drop in blood pressure is fitted to a series of curves to determine the rate

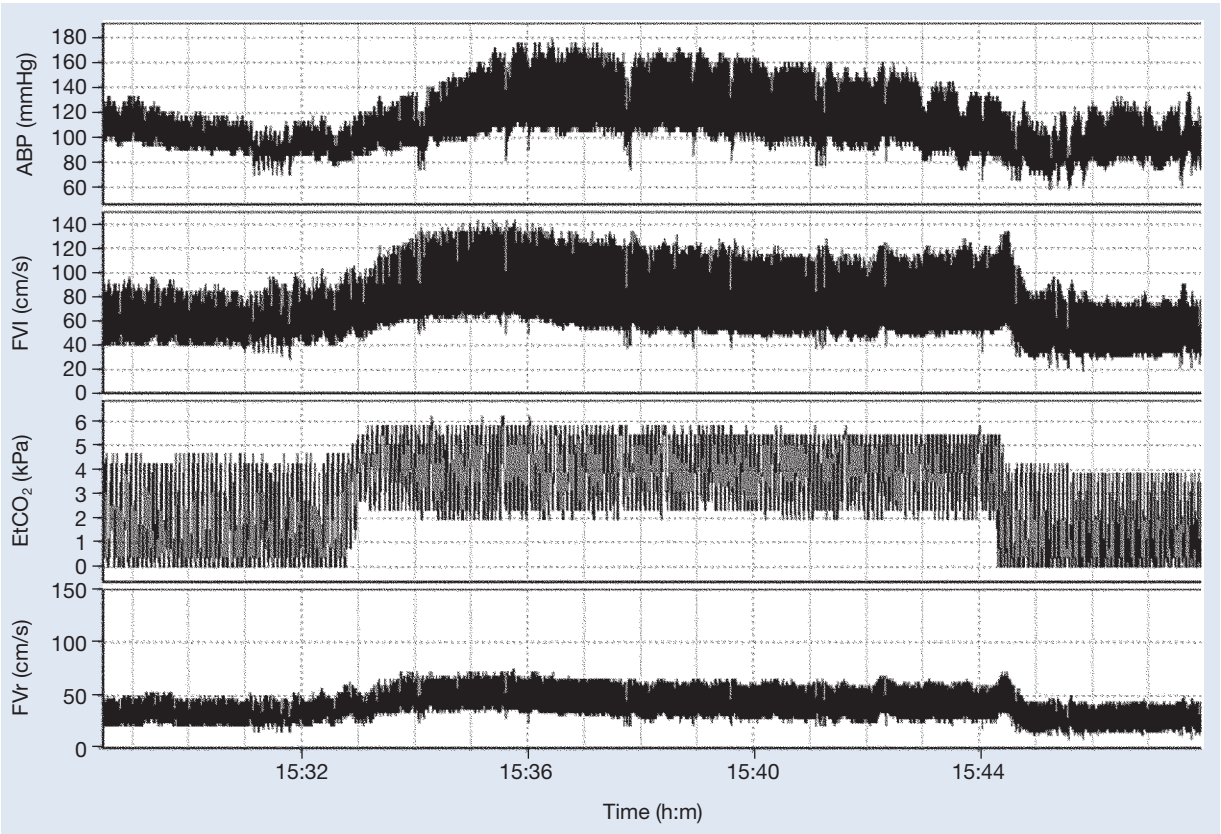


Fig. 7.2 CO_2 reactivity test performed in patient with right side common carotid artery stenosis (90%). Right side reactivity was 27%/kPa, and left side reactivity 14%/kPa. After corrections for change in arterial pressure, reactivity at left was 19%/kPa and right 9%/kPa, indicating that right side reactivity was severely depleted. ABP, arterial blood pressure, FVl, blood flow velocity in left middle cerebral artery (MCA); FVr, blood flow velocity in right MCA; $EtCO_2$, end-tidal CO_2 pressure.

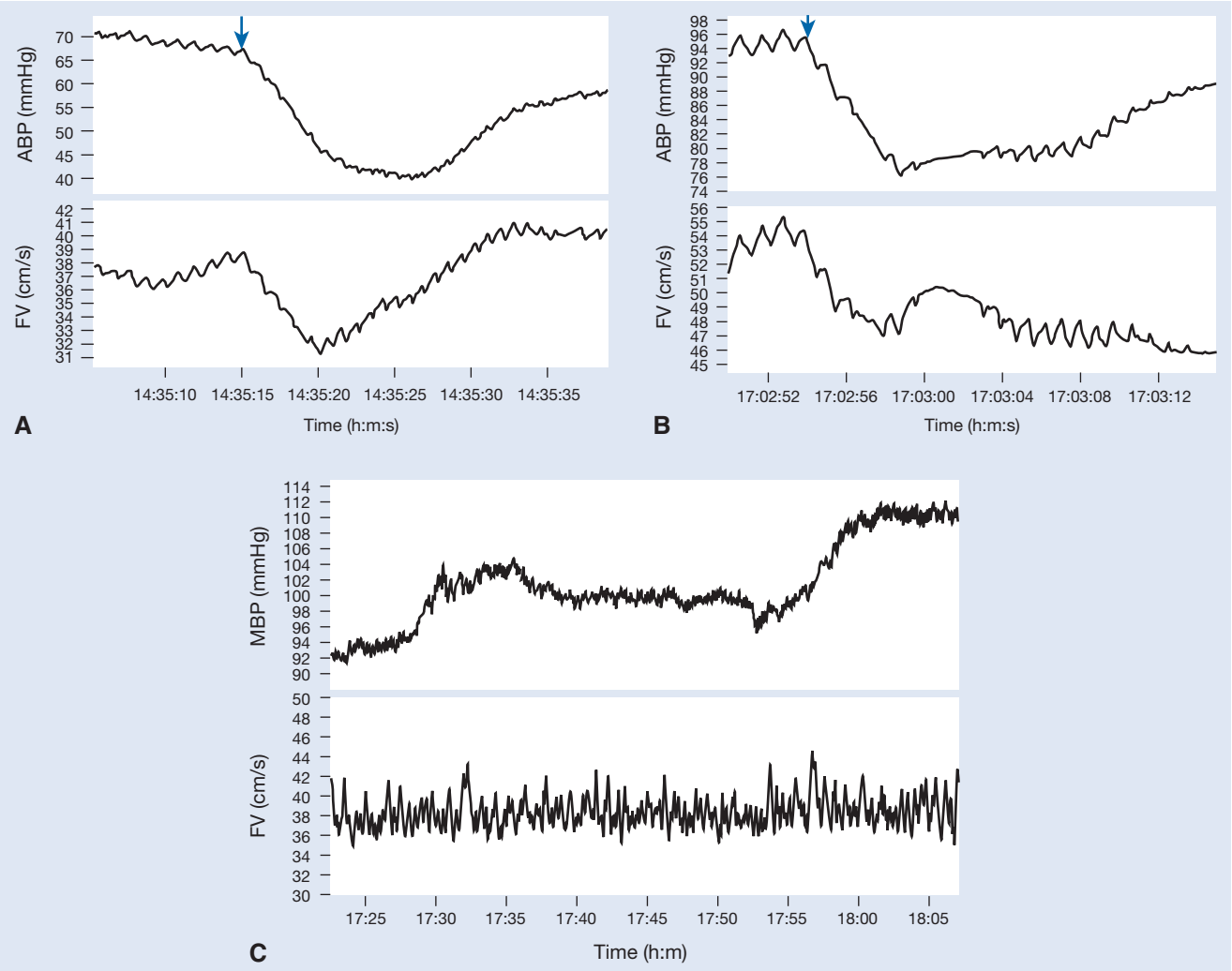


Fig. 7.3 **A,** The recovery in blood flow velocity (FV) after thigh cuff deflation (*arrows* point to start of decrease in arterial blood pressure [ABP] after deflation) is "steeper" in patients with intact dynamic autoregulation than the increase in ABP. **B,** In contrast, FV remains depressed after cuff deflation in patients with impaired autoregulation. **C,** Testing of static autoregulation during propofol anesthesia. *Top trace* represents mean blood pressure (MBP) in mmHg; *bottom trace* represents middle cerebral artery blood flow velocity. There is virtually no change in FV despite the increase in MBP as a result of dopamine infusion.

of dynamic cerebral autoregulation (dRoR) or autoregulation index (ARI). These curves are generated by a computer model of cerebral autoregulation that predicts the autoregulatory response on the basis of the continuous blood pressure record and compares its predictions with the measured response. The threshold for good and disturbed autoregulation is at an ARI value of around 5. The dRoR describes the rate of restoration of FV (percentage per second) with respect to the drop in MBP. The normal dRoR is 20%/sec (i.e., the process is complete within approximately 5 seconds).[24]

The time for autoregulation to normalize FV occurs well within the period of hypotension achieved with cuff deflation before the mean ABP returns to baseline (10–20 seconds).[24] Collection of autoregulation data in the first 10 seconds avoids the influence of the introduction of CO_2-rich blood from the legs after thigh cuff deflation. Figs. 7.3A and B show examples of leg cuff tests with intact (A) and defective (B) autoregulation.

Static Autoregulation

Static autoregulation can be tested by the induction of an approximately 20-mmHg increase in MBP through a 0.01% phenylephrine infusion with simultaneous recording of the FV. The FV and MBP recorded are then used for the subsequent calculation of the estimated CVR (CVRe; CVRe = ABP/FV). The static rate of autoregulation (SRoR) is the ratio of percentage change in estimated CVRe to percentage change in CPP, or if ICP is not measured, percentage change in MBP. Theoretically, no change in the FV would occur if the percentage change in CVRe was equal to the percentage change in MBP. Thus an SRoR of 100% implies perfect autoregulation, and an SRoR of 0% implies a complete disruption of autoregulation. Measurement of SRoR with MBP instead of CPP may cause an error called "false autoregulation." It happens in a nonautoregulating brain when a change in MBP produces a 1:1 increase in ICP, leaving CPP constant. This obviously does not produce any change in CBF, giving a false SRoR value equal to 1. Fig. 7.3C shows an example of static testing when autoregulation is fully functional.

Transient Hyperemic Response Test

The transient hyperemic response test is performed by compressing the common carotid artery for 5–8 seconds and observing the change in FV after the compression is ceased.[25] When the carotid artery is compressed, the distal cerebrovascular bed dilates in response to the drop in perfusion pressure. When the compression is ceased, an increase in FV_{MCA} is observed as a result of this dilation that persists until the distal cerebrovascular bed constricts to its former diameter. The compression results in this "transient hyperemia" only when

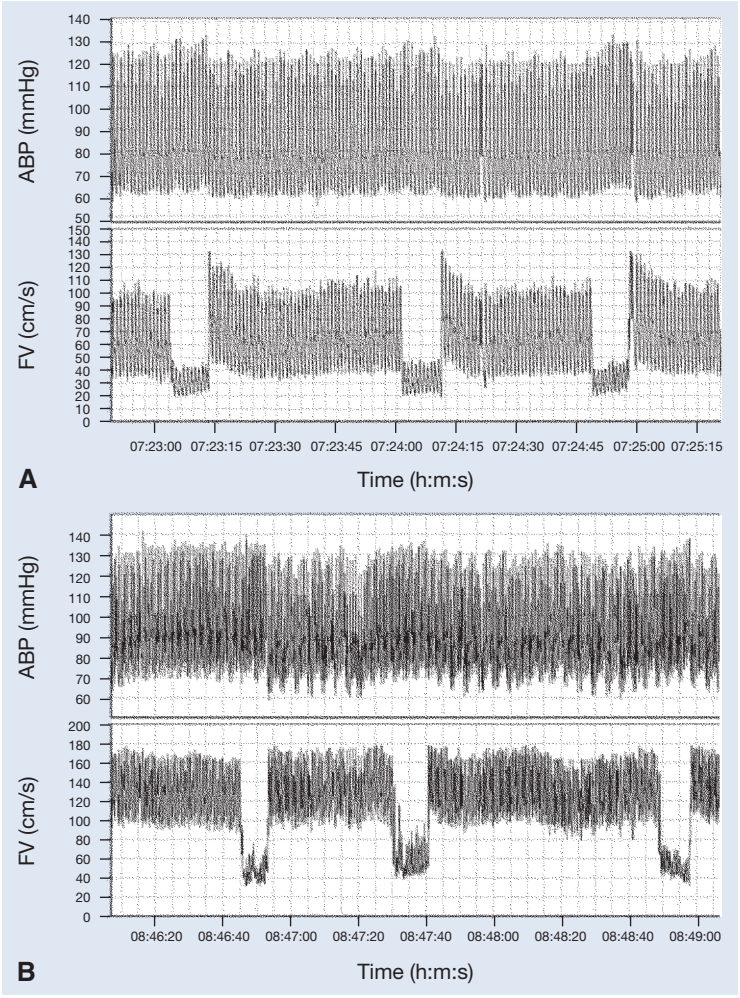


Fig. 7.4 Autoregulation testing using the transient hyperemic response test in two patients receiving intensive care. **A,** Transient hyperemia of blood flow velocity (FV) in the middle cerebral artery FV following short-term compression of the common carotid artery indicates intact autoregulation. **B,** The lack of response suggests impaired autoregulation. In clinical practice the test is repeated to improved accuracy, after scanning of the carotid artery to confirm that it is free of atherosclerotic plaque. ABP, arterial blood pressure.

autoregulation is intact. When autoregulation is impaired, no dilation of the distal cerebrovascular beds occurs in response to the compression, and hence no transient hyperemia is detected (Fig. 7.4).

Although the transient hyperemic response test is reproducible, easy-to-perform, and can be used to assess cerebral autoregulation in the neurologically injured patient, the results depend heavily on the compression technique.[26] Furthermore, it is contraindicated in patients with carotid disease, in whom there are theoretical risks associated with the maneuver, including the possibility of dislodging atheroma. Nevertheless, results indicate that the test may be useful in the assessment of outcome after head injury[26] or in the management of subarachnoid hemorrhage (SAH).[27]

Continuous Monitoring of Cerebral Autoregulation

Phase Shift between the Superimposed Respiratory and Arterial Blood Pressure Waves

An interesting noninvasive method of deriving autoregulatory status from natural fluctuations in MCA FV involves the assessment of the angle of the phase shift between the superimposed respiratory and ABP waves during slow and deep breathing. A 0-degree phase shift angle indicates absence of autoregulation, whereas a positive phase shift angle (>30 degrees) indicates intact autoregulation.[28]

Autoregulation Index-Transfer Function Analysis

For the assessment of dynamic cerebral autoregulation based on spontaneous fluctuations of ABP, more reliable values of the ARI are obtained by fitting the models proposed by Tiecks and colleagues[29] to the FV step response to a change in ABP. These researchers used transfer function analysis to quantify the dynamic relationship between mean ABP (input) and mean FV (output). This method has been further mastered and popularised by Panerai.[30] A fast Fourier transform (FFT) algorithm was applied to the time-series of beat-to-beat changes in mean ABP and mean FV, and the auto- and cross-spectra were calculated. The inverse Fourier transform was used to obtain the FV impulse response in the time domain, which was integrated to yield an estimate of the FV response to a hypothetical step change in ABP. Each of the 10 models proposed by Tiecks and colleagues,[29] corresponding to ARI values from 0 (absence of autoregulation) to 9 (best autoregulation), was fitted to the first 10 seconds of the FV step response, and the best fit, as selected by the minimum squared error, was selected as the representative value of ARI. Values of ARI are averaged for patients with more than one segment of data.

Time Correlation Method

Continuous monitoring over consecutive time-averaged samples of FV and CPP (thirty 10-second averages are usually taken) enables a correlation coefficient between

mean CPP and mean FV to be calculated. This coefficient has been termed the mean index (Mx index).[31] A positive coefficient signifies a positive association between FV and CPP, that is, disturbed autoregulation. A zero or negative correlation coefficient signifies an absent or negative association, implying intact autoregulation. The calculation may be repeated with a moving time window, so the Mx index may form new variables, indicating changes in cerebral autoregulation with time.

This index seems to be ideal for the monitoring of transient changes in autoregulation that occur in response to a cerebral intrinsic phenomenon. Group analysis has demonstrated that the autoregulation index averaged daily was related to clinical outcome after head injury; a positive Mx value (disturbed autoregulation) was associated with worse outcome.[32] The method has been positively cross-validated with the "gold standard," static rate of autoregulation, as well as with the leg-cuff test, ARI, phase shift analysis, and the transient hyperemic response test. Continuous monitoring of autoregulation is possible (however, probe positioning over a longer period is still a technical challenge). Following head injury, autoregulation fluctuates in time in response to changing clinical conditions. "Optimization" of CPP—that is, choosing a CPP value at which conditions for regulation of CBF are the best—is possible (Fig. 7.5). Similar techniques based on optimization of pressure reactivity (index based on changes in ICP and ABP) are already used in clinical practice.[33]

Noninvasive Assessment of Cerebral Perfusion Pressure and Intracranial Pressure

As ICP increases and CPP correspondingly decreases, a highly pulsatile FV pattern is seen. In deep intracranial hypertension, a progressive loss of diastolic flow to systolic spike and eventually to an oscillating flow pattern is observed. This oscillating flow pattern signifies the onset of intracranial circulatory arrest and, if not reversed, is terminal.[34]

The pulsatility index is inversely proportional to reductions in CPP.[16,35] This inverse relationship between CPP and PI has been proposed as a method of estimating CPP noninvasively. By relating the first harmonic component of the ABP pulse waveform to SPI, Aaslid and coworkers[36] demonstrated the ability to estimate CPP with a 95% confidence limit for prediction of around ±25 mmHg. An improved method of estimating CPP using MAP and diastolic and mean blood velocities has also been reported;[37] this method was able to estimate CPP noninvasively with errors less than 10 mmHg in more than 85% of the measurements. Furthermore, when it was used as a continuous monitor it was able to detect real-time changes in "true" CPP. Bilateral monitoring may also provide useful information about side-to-side variations in perfusion that, in turn, may allow clinical decisions to be made earlier.[38] An example of noninvasive estimation of CPP is illustrated in Fig. 7.6.

The ability to estimate CPP noninvasively has obvious advantages. This form of monitoring is particularly useful in

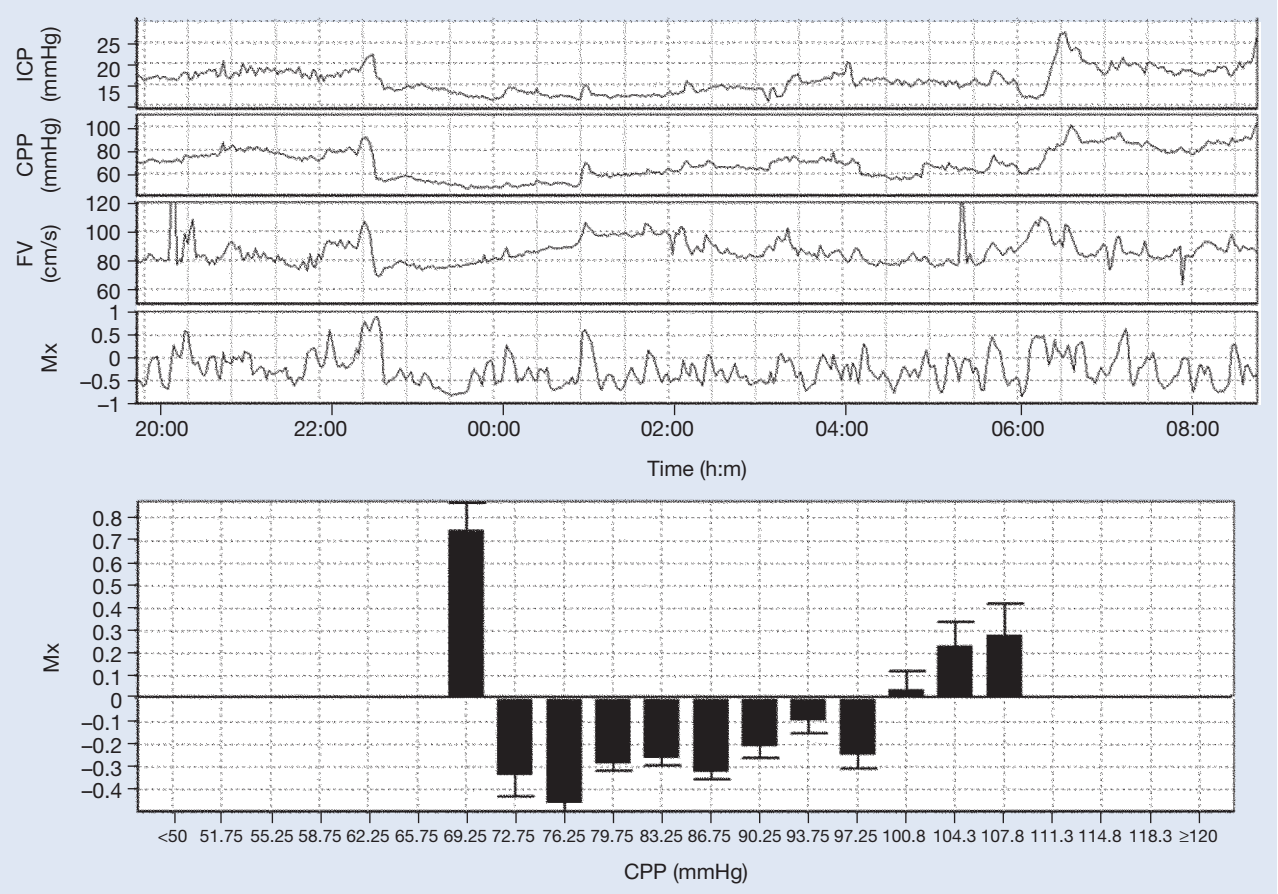


Fig. 7.5 Continuous monitoring of cerebral autoregulation using the mean index (Mx) after head injury. In this case, autoregulation was generally preserved (Mx value was negative) with the exception of short episodes around 22:30 and 1:00. Plotting of averaged Mx values against cerebral perfusion pressure (CPP) shows that the "optimal" CPP for this period (value of CPP for minimal Mx) was around 75 mmHg. FV, blood flow velocity; ICP, intracranial pressure.

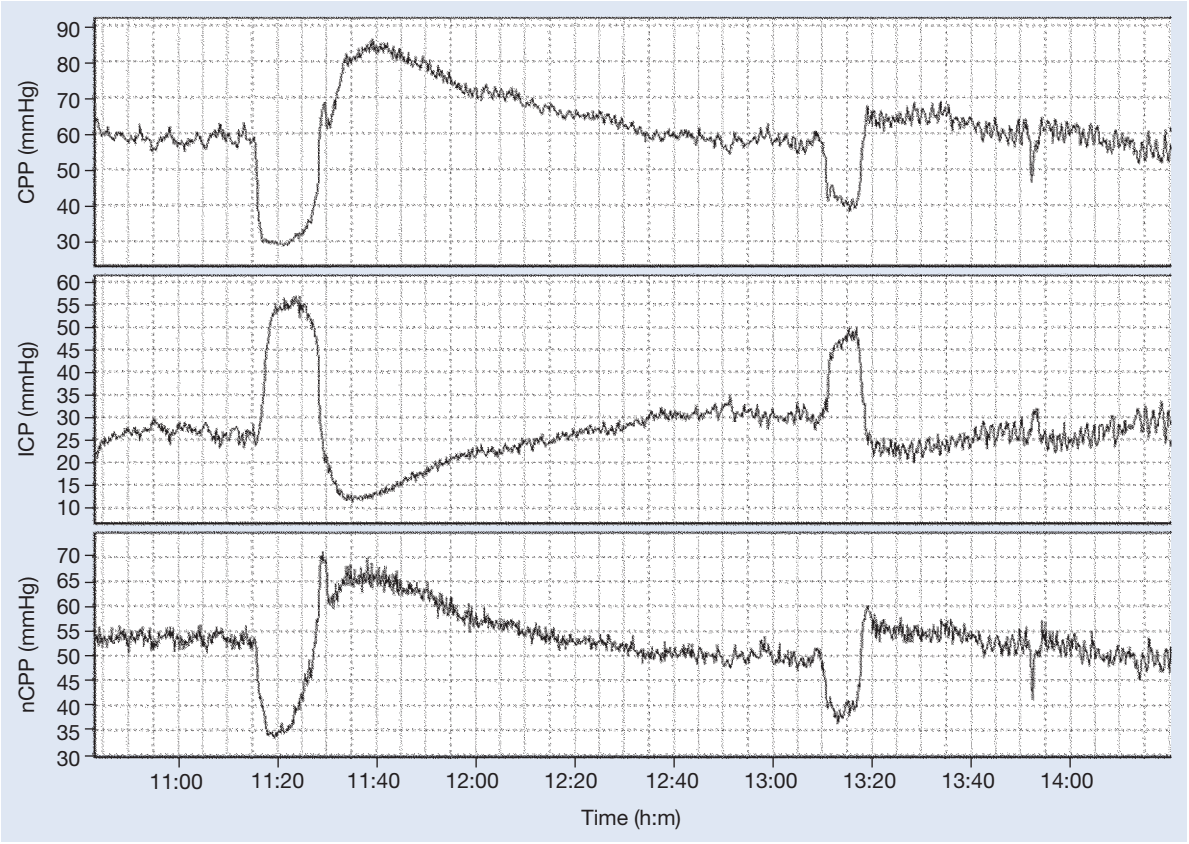


Fig. 7.6 Representative traces of cerebral perfusion pressure (CPP), intracranial pressure (ICP), and noninvasive CPP (nCPP) during an episode of intracranial hypertension (plateau waves) in a head-injured patient.

centers where ICP monitoring is not routinely used or in the patient for whom ICP monitoring is not indicated but who may have decreased intracranial compliance (e.g., after a concussion or mild closed-head injury). The role of TCD in noninvasive estimation of cerebral perfusion is promising.

A more complex method aimed at the noninvasive assessment of ICP has been introduced and tested by Schmidt and associates.[39] The method is based on the presumed transformation between ABP and ICP waveforms. Coefficients of these transformations are derived from the database of real ABP and ICP recordings. Similar linear transformation is built, using the same database between FV and ABP. Then, the model assumes a linear relationship between ABP and FV, and ABP to ICP transformations. Multiple regression coefficients are calculated. Finally, for each prospective study, ICP is calculated using ABP to ICP transformation, formed from ABP to FV transformation transposed using precalculated regression coefficients (see Fig. 7.6).

Critical Closing Pressure

Critical closing pressure (CrCP) was first described by means of a mathematical model showing that small vessels can collapse when the ABP approaches the given low value, defined as the *critical closing pressure*.[40] In cerebrovascular circulation this value was postulated to be the sum of ICP and a component proportional to the active tension of vascular smooth muscle.

For prediction of CrCP, arterial pressure should be first decreased below the lower limit of autoregulation with parallel measurements of CBF. A linear relationship between CBF and ABP can be then extrapolated to the value of pressure at which flow reaches zero. Aaslid and colleagues[41] and Panerai and associates[42] proposed methods for the calculation of CrCP using TCD. In this method the intercept point of a regression line between the single pulse pressure plotted along the x-axis and FV in the middle cerebral artery plotted along the y-axis can be used for the estimation of CCP. Alternative methods have been suggested that use ratios of first harmonics of FV pulse and ABP pulse. Arbitrary "geometrical" evaluation of the relationship between the pulses of FV and ABP sometimes produces negative values of CrCP, which cannot be interpreted physiologically. New methodology, based on model cerebrovascular impedance, has been recently proposed which does not produce negative values.[43] These methods are attractive from a clinical point of view because they make a continuous, noninvasive prediction of CrCP possible at the current "working point," without the need to decrease arterial pressure. CrCP is useful for the detection of changes in ICP (however, accuracy is worse than for noninvasive ICP; see the previous section) and cerebrovascular resistance. Interesting concept of "diastolic closing margin" associated with CrCP has been proposed. This is a difference between disatoloc ABP and CrCP. Theoretically, if this value reaches 0, diastolic FV disappears, as vessels in this phase collapse.[44]

Transcranial Doppler Ultrasonography in Multimodality Monitoring

TCD can be counted as an integral component of multimodality monitoring. However, the unsolved problems of long-term accurate fixation of the probes on MCA remain. Therefore, TCD has never been a good component of long-term multimodality monitoring. The longest recordings—8 to 12 hours—are still too short to explain the changes occurring over a few weeks. A possible strategy is daily monitoring over a 1–4-hour period and using intermittent information in order to understand the long-lasting pathophysiological processes.

Together with ICP measurement, jugular venous bulb oximetry (SjO_2), near-infrared spectroscopy, brain tissue oximetry, and brain microdialysis, TCD enables important minute-by-minute information to be obtained in the neurologically injured patient. Multimodal data are captured and examined at the bedside. The effect of interventions or pathologic processes on cerebral hemodynamics can be viewed from several angles. The main factor controlling the ability to process such information is data acquisition. Up to 30% of data collected are often discarded because of poor quality.

Nevertheless, dynamic and static relationships between signals like ICP, ABP, brain tissue oxygenation, TCD, and near-infrared spectroscopy [45] bring us one step closer to observing the "whole picture" of secondary ischemic brain insults.

"New Generation" of Model-Based Transcranial Doppler Parameters

Apart from cerebral autoregulation, which met with a great deal of interest with regard to its use in many clinical applications, "high frequency" components derived from TCD have only recently received attention. These are cerebrovascular impedance, compliance/resistance of cerebral arterial bed, and cerebrovascular time constant.

The concept of impedance is well characterized: dividing spectral components of ABP by FV for frequency greater than 0.05 Hz theoretically produces valid cerebrovascular impedance. A problem is that power in both signals is transmitted in selective frequencies: respiratory and pulse plus their higher harmonics. Calculating impedance modulus outside these frequencies is pointless: dividing zero by zero gives any number. Using respiratory and heart frequencies jointly is also questionable, as these two components have different input points into the cerebrovascular system: respiration affects venous outflow and heart rate is more reflective of arterial inflow. Impedance has two main physiologically interpretable components: cerebrovascular resistance and compliance. Both may be monitored with TCD. Obviously both are dependent on frequency; most reliable measurements are at a frequency equal to the heart rate (signal-to-noise ratio for both ABP and FV waveforms is highest). To calculate compliance, the FV waveform should be converted to cerebral arterial blood volume. The transformation used is time-integral of the current value of FV minus the mean value of FV averaged over one or a few heart cycles.[46] Since cerebral arterial blood volume has a pulsatile character, the amplitude of blood volume changes divided by the amplitude of arterial pulsation can estimate compliance of the cerebrovascular system (Ca).[47] Moreover, if ICP is monitored, the pulse amplitude of blood volume is divided by the pulse amplitude of ICP, and so compliance of the cerebrospinal space (Ci) can thus be calculated. Ca increases with the vasodilatation produced by hyperventilation in volunteers, with carotid artery stenosis, and during deep intracranial hypertension caused by plateau waves of ICP.[48]

The difficulty with interpretation of cerebrovascular compliance and resistance is that both variables depend on the unknown cross-sectional area of the insonated vessel; therefore, comparison between patients is impossible. The product of Ca and CVR is scaled in seconds; it is independent of the vessel's diameter, and represents the time-constant of the cerebrovascular bed. It theoretically describes how fast arterial blood arrives at a hypothetical demarcation zone between cerebral arterioles and capillaries. The time constant shortens with hypercarbia, in patients with carotid artery stenosis and during vasospasm after subarachnoid hemorrhage.[47,49]

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY IN CLINICAL PRACTICE

Carotid Artery Disease

Stroke is both the principal indication for and the major complication of carotid endarterectomy. The majority of perioperative strokes are embolic, but hypoperfusion, hyperperfusion, or both may be responsible for more than 40% of perioperative strokes.[50] Therefore, the maximum benefit of this procedure can be realized only if perioperative cerebral perfusion is optimized and embolic phenomena are minimized.[52] TCD is an attractive technique for the detection of cerebral ischemia during cross-clamping of the carotid artery, because it is continuous and noninvasive and the transducer probes can be used successfully without impinging on the surgical field. It is also an important tool in the preoperative assessment and postoperative care of patients with carotid disease.[50,51] In addition to providing the means for the preoperative assessment of cerebrovascular reserve and, possibly, for determining the need for shunting by examination of CO_2 reactivity, TCD is being increasingly used for the detection of preoperative and postoperative embolic phenomena and for testing the integrity of cerebral autoregulation.[53] Also, pressure autoregulation can be assessed; it is commonly impaired in any state in which collateral blood supply is poor[54] and improves gradually after surgery or stenting.[55]

Cerebral ischemia following clamping of the ICA is considered severe if FV_{MCA} is 15% or less of the preclamping value, mild if FV_{MCA} is 16–40% of the preclamping value, and absent if FV_{MCA} is greater than 40% of the preclamping value.[94] This criterion correlates well with subsequent ischemic electroencephalographic changes and hence can be used as an indication for shunt placement. An intravascular shunt used to bypass the clamped ICA is effective in restoring blood flow but has its own inherent problems, namely, potential dislodgment of embolus from the distal ICA, traumatic dissection of the vessel wall resulting in an occluding intimal flap, and a technically more difficult endarterectomy. Furthermore, in a nonrandomized multicenter study involving more than 1400 patients, Halsey[52] showed that the placement of shunts in patients with post-ICA clamping velocities greater than 40% of the preclamping value is associated with a higher risk of stroke (presumably embolic). Although there is no universal consensus on the magnitude of FV_{MCA} change that necessitates shunt placement, a reduction in FV_{MCA} to less than 40% of baseline before clamping is the most commonly accepted indication. Unnecessary shunting is best avoided. TCD can also instantly detect shunt malfunction caused by kinking or thrombosis.

Emboli are detected on TCD as short-duration, high-intensity "chirps," and waveform analysis can help differentiate air from particulate emboli.[56] Emboli can occur throughout the procedure but are more common during dissection of the carotid arteries, on release of ICA cross-clamping, and during wound closure.[57]

At operation, emboli are clearly audible,[56] and, interestingly, surgeons tend to adapt their operative technique to minimize embolus generation. After the introduction of intraoperative TCD monitoring, some centers have reported a reduction in operative stroke rates.[87,93] Although it is tempting to attribute this reduction to the introduction of TCD monitoring, many other factors have also changed during the same period.

After closure of the arteriotomy and release of carotid clamps, FV typically rises immediately to levels above the baseline (preclamping) value and gradually corrects back to

the preclamping value over a few minutes. This hyperemic response is to be expected as the dilated vascular bed vasoconstricts in an autoregulatory response to an increased perfusion pressure. However, approximately 10% of patients are at greater risk of cerebral edema or hemorrhage because of gross hyperemia, with FV at values 230% of baseline value lasting from several hours to days.[58] (Fig. 7.7) shows an example of monitoring of FV during carotid endarterectomy.

Intracranial Vascular Disease

Subarachnoid Hemorrhage

Cerebral vasospasm is the leading cause of morbidity and mortality in patients who survive a SAH. Although radiologic evidence of vasospasm has been reported in up to 70% of angiograms performed within the first week of aneurysmal rupture, the incidence of clinically significant vasospasm approximates 20%.[59] The cause still remains uncertain but appears to be related to the amount and distribution of blood in the subarachnoid space. In the patient with SAH, the appearance of new focal neurologic signs or a decrease in the level of consciousness may be an early sign of vasospasm. This finding is normally confirmed by computed tomography and angiography.

A constant vessel diameter is one of the main assumptions that govern the use of TCD as an indirect measure of CBF. Therefore, although TCD is unreliable as a measure of CBF in patients with SAH because of changes in vessel diameter, it has become valuable for diagnosing vasospasm noninvasively before the onset of clinical symptoms. As the vessel diameter is reduced for the same blood flow, the FV increases. Hence cerebral vasospasm is generally considered to present if the FV_{MCA} is greater than 120 cm/sec or the ratio between FV_{MCA} and FV in the ICA (FV_{ICA}) exceeds 3.[60] In the sedated patient, the diagnosis of cerebral vasospasm relies on gross neurologic signs as well as findings on computed tomography, cerebral angiography, and TCD. Cerebral angiography and computed tomography can be performed only intermittently, leaving TCD as the only way of diagnosing and judging the severity and efficacy of treatment of cerebral vasospasm. The ratio of FV_{MCA} to FV_{ICA} should decrease with effective treatment. Needless to say, to rule out cerebral vasospasm with TCD, one must perform a thorough examination of the basal arteries. Unfortunately, detection of small vessel spasm is not possible. Our policy is to perform daily TCD examinations in all patients with SAH. Initial impressions suggest that the incidence of TCD-diagnosed vasospasm is much higher than that of clinically significant vasospasm, and therefore therapy is not usually escalated on the basis of TCD findings alone. Cerebral autoregulation dysfunction that is overlapped by or precedes cerebral vasospasm correlates with neurologic deterioration.[61,62] Administration of statins in the acute phase after SAH improves autoregulation and decreases the incidence of vasospasm; however, it does not improve outcome after SAH.[63] The transient hyperemic response test is particularly useful for testing cerebral autoregulation in patients with SAH.[62]

In addition to the detection and treatment of vasospasm, TCD has been successfully used in the perioperative management of patients with cerebral aneurysms in a variety of other situations. Eng and coworkers[64] reported the advantages of TCD monitoring for the perioperative management of a patient in whom the aneurysm ruptured before dural incision.

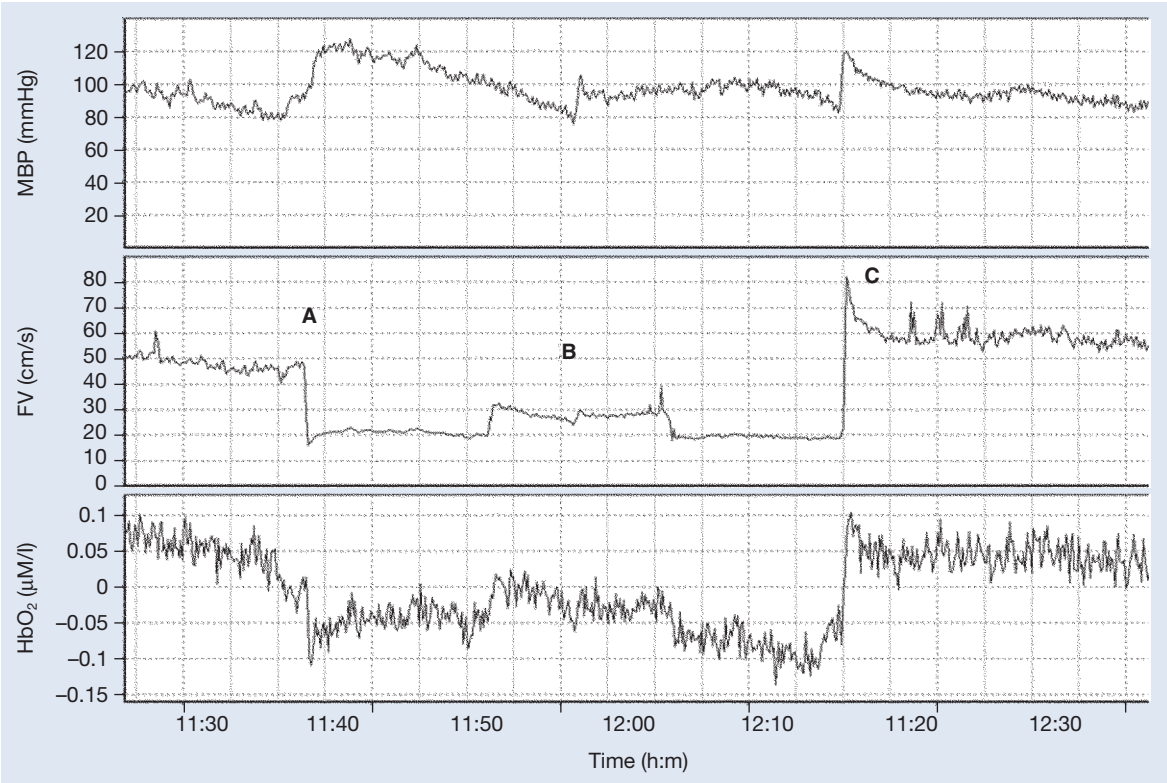


Fig. 7.7 Monitoring during carotid endarterectomy. At time of carotid cross-clamping **(A),** there was a rapid fall in blood velocity (FV), which was accompanied by a sustained fall in the cerebral oxygenation (HbO_2 monitoring using near-infrared spectroscopy). These changes were independent of any change in mean blood pressure (MBP). Signals recovered with the insertion of an intravascular shunt, with a second fall seen during shunt removal **(B).** Hyperemia occurred at the end of the procedure **(C).**

Arteriovenous Malformations

Arteries leading to an arteriovenous malformation (AVM), a developmental anomaly with abnormal embryonic vascular network, shunt blood to the venous side with flow rates out of proportion to the low metabolism within the AVM. These "feeder" vessels are characterized by high blood velocity, low pulsatility, low perfusion pressure, and decreased CO_2 reactivity.[65] Embolization or resection of AVMs results in normalization of FV, pulsatility, and CO_2 reactivity.[66] The potential use of intraoperative TCD with AVM resection lies with estimating the completeness of resection and the diagnosis and treatment of the hyperperfusion syndrome,[67] provided that the feeding vessel can be monitored. With simultaneous monitoring of both the feeding vessel and the contralateral nonfeeding vessel, theoretically, the preoperative difference in velocity and in pulsatility between the two sides should progressively disappear.

Closed-Head Injury

Although many factors affect outcome after head injury, episodes of hypoxemia, hypotension, and reduced cerebral perfusion caused by high ICP are predictive of poor outcome.[68] Because these episodes may only last a few minutes, their reliable detection and quantification requires real-time measurement. The greater availability of multimodal monitoring—simultaneous monitoring of ICP, CPP, jugular bulb oxygen saturation (SjO_2), and TCD—has made the detection of such pathophysiologic episodes possible. Furthermore, as more of the "picture" is seen with several monitors reflecting the changes at the same time, appropriate therapeutic interventions are made early. For example, Kirkpatrick and colleagues[69] demonstrated that it is possible to distinguish between rises in ICP due to low CPP and those due to hyperemia through the use of TCD as part of a multimodality setup. An example of multimodal monitoring in head injury is shown in Fig. 7.8.

TCD monitoring can be used to observe changes in FV, waveform pulsatility, critical closing pressure and diastolic closing margin (difference between diastolic blood pressure and critical closing pressure; when this margin becomes zero, diastolic blood flow as seen with TCD, ceases[44]), as well as for testing cerebrovascular reserve. Cerebral autoregulation is often impaired after head injury with an increased susceptibility to secondary ischemic insults and possible correlation with poor outcome.[70,71] The transient hyperemic response test,[65] cuff deflation–induced drops in MBP (both dynamic tests), and vasopressor-induced increases in MBP (static test) have all been used to test autoregulation after head injury. However, the most noninvasive and continuous assessment of autoregulation relies on correlation of the spontaneous fluctuations in FV_{MCA} waveform and CPP (Mx index).[72] When autoregulation is present, little change is observed in FV_{MCA} during changes in CPP. Conversely, in the patient with impaired autoregulation, a positive linear correlation between FV_{MCA} and CPP is observed. In addition, continuous recording of the FV_{MCA} enables easy detection of the autoregulatory "threshold" or "breakpoint," the CPP at which autoregulation fails, thus providing a target CPP value for treatment.

Cerebral vasospasm causing ischemia or noncontusion-related infarction remains an important cause of morbidity

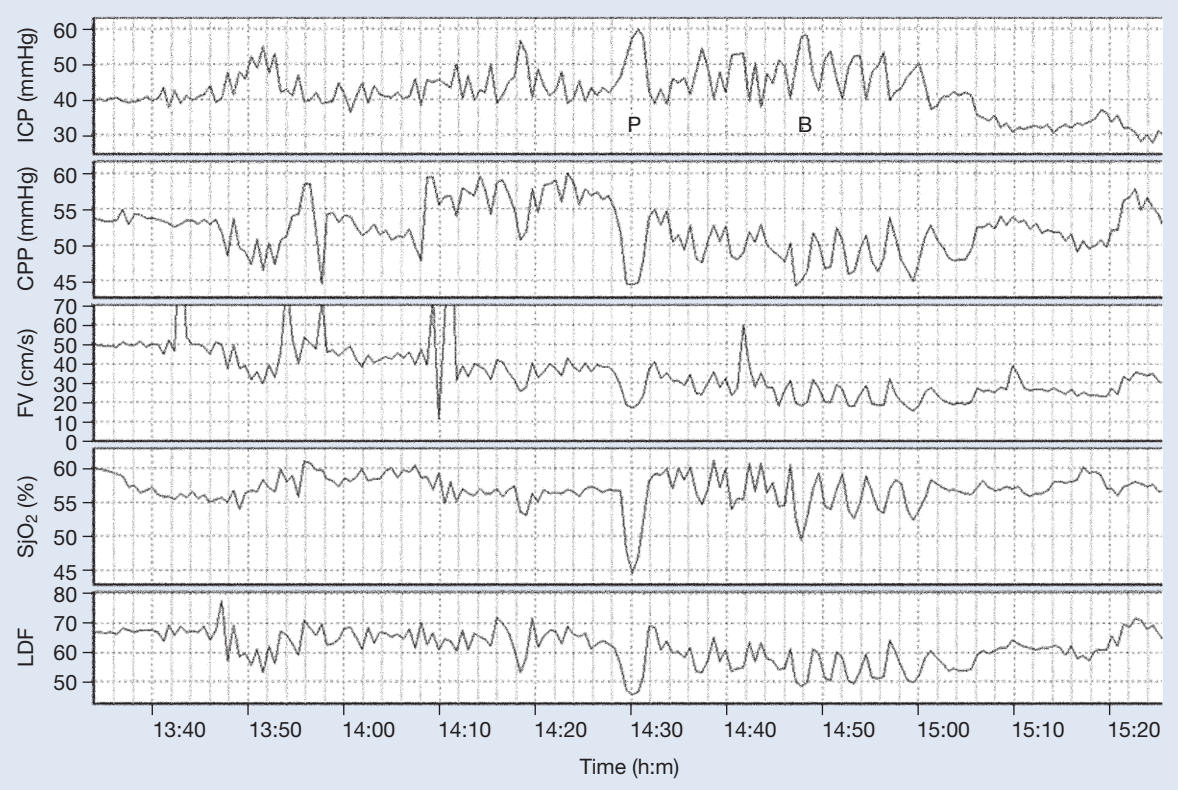


Fig. 7.8 Recording of events characterized by intracranial hypertension in a head-injured patient receiving intensive care. Using multimodality monitoring makes it possible to identify the cause of this increase. Increase in intracranial pressure (ICP) (plateau wave [P]) causes a fall in cerebral perfusion pressure (CPP), which in turn provokes the blood velocity (FV), the jugular bulb oxygen saturation values (SjO_2) and cortical blood flow (LDF, in arbitrary units) also falling, indicating hypoperfusion. Repetitive vasogenic waves of ICP (B waves [B]) are secondary to fluctuations of cerebral blood flow as SjO_2, and FV, and LDF increase and decrease in phase with ICP.

and mortality after head injury.[73,74] The appearance of new focal neurologic signs or a decrease in the level of consciousness after head injury may be an early sign of vasospasm. TCD can be used to diagnose and treat cerebral vasospasm with the use of the same criteria as for patients with SAH. Increased FV in combination with high SjO_2 and a ratio of FV_{MCA} to FV_{ICA} less than 2 indicates hyperemia, whereas high FV in the presence of low or normal SjO_2 values and a ratio of FV_{MCA} to FV_{ICA} greater than 3 suggests cerebral vasospasm.[75,76]

Although clinical decisions on outcome after head injury cannot be based solely on TCD findings, the information obtained may provide guidance for further therapy and likely outcome. Cerebral autoregulation and CO_2 vasoreactivity can be repeatedly tested in the intensive care unit. The loss of these hallmarks of a normal cerebral vasculature suggests poor prognosis.[72] Similarly, the oscillating FV pattern typically seen before complete circulatory arrest can be used to confirm the diagnosis of brain death.[77] A low value of diastolic flow velocity, suggesting a low diastolic closing margin, has been reported as an indicator of acute cerebral hemodynamic failure at admission to neuro-intensive care unit, mandating prompt use of aggressive monitoring and therapeutic protocol.[78,79] The use of TCD for noninvasive estimation of CPP, which is very useful in patients where invasive ICP monitoring cannot be used, has already been addressed.

Stroke

The development of fibrinolytic agents such as streptokinase and recombinant tissue-type plasminogen activator (rTPA) has raised the need for more precise knowledge of the pathophysiology of acute ischemic stroke. TCD can be used to identify cerebral arterial occlusion[80] and recanalization,[81] as well as to help determine the risk of hemorrhagic transformations of large-volume ischemic lesions.[82] Repeated TCD examinations within 6, 24, and 48 hours after admission with acute stroke can help identify both those patients at risk for further ischemic episodes and the sources of emboli.[83] Unilateral emboli most commonly originate from the carotid arteries, whereas bilateral emboli most commonly arise from cardiac sites. The effect of anticoagulation on reperfusion, recanalization, and outcome after acute stroke can also be evaluated with TCD.[84] In patients with stroke and poor status, in whom the possibility of brain edema and rise in ICP increases, noninvasive assessment of CPP and ICP using TCD seems to be useful. Also, assessment of cerebral autoregulation with TCD is promising,[85] although this area requires intensive clinical studies.

Miscellaneous Non-neurosurgical Applications

Because of its noninvasive nature, TCD has found many applications in fields other than neurosurgery and neurointensive care, mainly in patients at risk for neurologic injury secondary to primary pathologic conditions outside the central nervous system.

Cardiac Surgery

Detection of microemboli and the estimation of cerebral perfusion during cardiac surgery are probably the most important applications of TCD outside neurosurgery and neurointensive care. Although the incidence of stroke after cardiac surgery is estimated at 5%, subtler cognitive dysfunction has been reported in more than 60% of patients.[86]

Although changes in FV do not always accurately reflect changes in CBF during cardiopulmonary bypass,[87] there is little doubt about the benefits that TCD offers in detecting emboli both during and after cardiopulmonary bypass,[88] in testing cerebral autoregulation and CO_2 reactivity,[89] in comparing the effects of different techniques of blood gas management during cardiopulmonary bypass,[90] and in detecting hyperperfusion during cardiac surgery.[91] Furthermore, with the increase in minimally invasive cardiac surgery, TCD has been used to ensure correct positioning of endovascular aortic balloon clamps.[92] Recently "optimization" of arterial blood pressure according to state of cerebral autoregulation[93] has gained interest.

Orthoptic Liver Transplantation

Portal-systemic encephalopathy, a major complication of acute and chronic liver disease, has clinical and subclinical manifestations.[94] Alterations in CBF are implicated in the etiology of portosystemic encephalopathy, with possible cerebral vasodilation resulting in cerebral edema and reduced CPP.

TCD has been used successfully in patients with hepatic failure to assess CO_2 reactivity and cerebral autoregulation. Although cerebral autoregulation is often impaired in acute liver failure and may be restored by mechanical hyperventilation, CO_2 reactivity seems to be less affected.[95] TCD may also provide the means to noninvasively estimate CPP in patients with liver failure with the use of methods similar to those described for head-injured patients. The advantages of not inserting ICP measuring devices in patients with liver failure, who are often coagulopathic, are self-evident. An example of TCD monitoring during liver transplantation with continuous assessment CPP by means of noninvasive CPP monitoring and of autoregulation using the Mx index is presented in Fig. 7.9.

Pregnancy and Eclampsia

Abnormal pregnancies are usually associated with impairment of the maternal cerebral circulation. TCD has been used in two studies to measure FV in normal pregnancies and in mothers with preeclampsia. Up to 70% of abnormal pregnancies were found to be associated with higher FV than those in normal pregnancies.[96] Furthermore, the extent of toxemia was significantly correlated to the increase in FV, with progressive increases in FV often preceding neurologic symptoms. Although the significance of cerebral vasospasm in preeclampsia remains controversial, the cause of this increase in FV requires further investigation. Noninvasive assessments of ICP, CPP, and autoregulatory reserve remain to be rediscovered in this pathology.

SUMMARY

TCD is a useful noninvasive means of monitoring cerebral hemodynamics, for which benefits have been demonstrated in many specific instances. This "window" on the brain has been severely disadvantaged by the lack of means for fixing the probe in position.

Indirect measurement of CBF using TCD is extremely useful. It is not absolute values but the dynamic changes in blood flow velocity values that contain enormous amounts of information about cerebrovascular reactivity, autoregulation, abnormalities within the circle of Willis and also small vessel behavior, critical closing pressure, closing margin, and ICP.

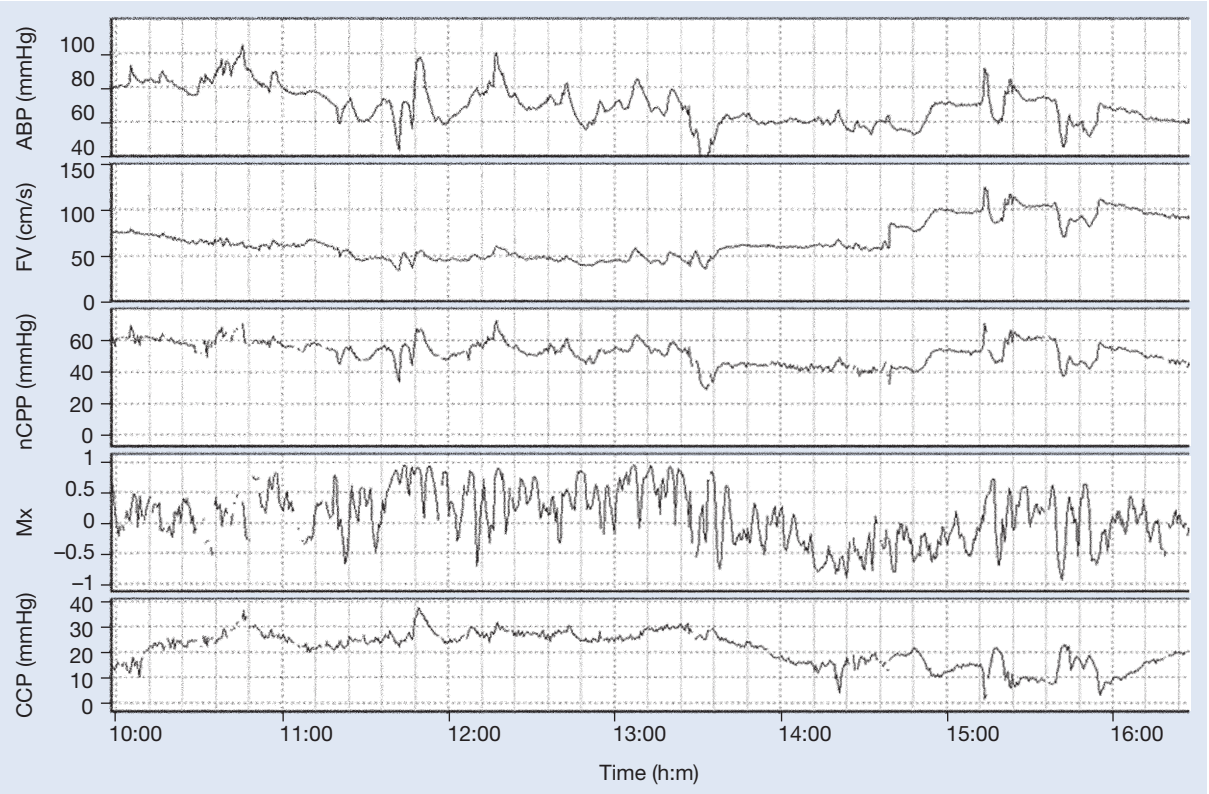


Fig. 7.9 Example of arterial blood pressure (ABP) and transcranial Doppler ultrasonography (TCD) monitoring during liver transplantation. Note worsening of autoregulation (positive mean index [Mx] value) during anhepatic phase, which improves during reperfusion (after 14:30). During reperfusion, noninvasive cerebral perfusion pressure (nCPP) and blood flow velocity (FV) values gradually improve, and critical closing pressure (CCP) decreases (which may indicate either a decrease in intracranial pressure or gradual vasodilation).

REFERENCES

1. Aaslid R, Markwalder TM, Nornes H. Non-invasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57:769.
2. Aaslid R. Transcranial Doppler examination techniques. In: Aaslid R, ed. *Transcranial Doppler Sonography*. New York: Springer-Verlag; 1986:39.
3. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries: Angiographic determination in man. *Invest Radiol*. 1967;2:17.
4. Markwalder TM, Grolimund P, Seiler RW, et al. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure: A transcranial ultrasound Doppler study. *J Cereb Blood Flow Metab*. 1984;4:368.
5. Newell WD, Aaslid R, Lam AM, et al. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke*. 1994;25:793.
6. Matta BF, Lam AM, Mayberg TS, et al. The cerebrovascular response to carbon dioxide during sodium nitroprusside- and isoflurane-induced hypotension. *Br J Anaesth*. 1995;74:296.
7. Dahl A, Russell D, Nyberg-Hansen R, et al. Effect of nitroglycerin on cerebral circulation measured by transcranial Doppler and SPECT. *Stroke*. 1989;20:1733.
8. Schregel W, Schafermeyer H, Muller C, et al. The effect of halothane, alfentanil and propofol on blood flow velocity, blood vessel cross section and blood volume flow in the middle cerebral artery. *Anaesthesist*. 1992;41:21.
9. Matta BF, Lam AM. Isoflurane and desflurane do not dilate the middle cerebral artery appreciably. *Br J Anaesth*. 1995;74:486P.
10. Kontos HA. Validity of cerebral arterial blood calculations from velocity measurements. *Stroke*. 1989;20:1.
11. Grolimund P, Seiler RW. Age dependence of the flow velocity in the basal cerebral arteries: A transcranial Doppler ultrasound study. *Ultrasound Med Biol*. 1988;14:191.
12. Leenders KL, Perani D, Lammertsma AA, et al. Cerebral blood flow, blood volume and oxygen utilisation: Normal values and effect of age. *Brain*. 1990;113:27.
13. Brass L, Pavlakis S, DeVivo D, et al. Transcranial Doppler measurements of the middle cerebral artery: Effect of hematocrit. *Stroke*. 1988;19:1466.
14. Thomas DJ, Marshall J, Ross Russell RW, et al. Effects of hematocrit on cerebral blood flow in man. *Lancet*. 1987;2(8564):941.
15. Brouwers P, Vriens EM, Musbach M, et al. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: Reference values at rest and during hyperventilation in healthy children and adolescents in relation to age and sex. *Ultrasound Med Biol*. 1990;16:1.
16. de Riva N, Budohoski KP, Smielewski P, et al. Transcranial Doppler pulsatility index: What it is and what it isn't. *Neurocrit Care*. 2012;17:58–66.
17. Czosnyka M, Smielewski P, Piechnik S, et al. Cerebral autoregulation following head injury. *J Neurosurg*. 2001;95:756.
18. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39:183.
19. Fraser 3rd. CD, Brady KM, Rhee CJ, et al. The frequency response of cerebral autoregulation. *J Appl Physiol*. 2013;115:52.
20. Dumville J, Panerai RB, Lennard NS, et al. Can cerebrovascular reactivity be assessed without measuring blood pressure in patients with carotid artery disease? *Stroke*. 1999;30:1293.
21. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161.
22. Aaslid R, Lindegaard KF, Sorteberg W, et al. Cerebral autoregulation in humans. *Stroke*. 1989;20:45.
23. Reinhard M, Wehrle-Wieland E, Grabiak D, et al. Oscillatory cerebral hemodynamics—the macro- vs. microvascular level. *J Neurol Sci*. 2006;250:103.
24. Aaslid R, Newell DW, Stooss R, et al. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke*. 1991;22:1148.
25. Giller CA. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. *Acta Neurochir*. 1991;108:7.
26. Smielewski P, Czosnycka M, Kirkpatrick PJ, et al. Validation of the computerised transient hyperemic response test as a method of testing autoregulation in severely head injured patients. *J Neurotrauma*. 1995;12:420.
27. Tseng MY, Czosnyka M, Richards H, et al. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: A phase II randomized placebo-controlled trial. *Stroke*. 2005;36:1627.
28. Diehl RR, Linden D, Lucke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure: A clinical test of autoregulation. *Stroke*. 1995;26:1801.
29. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*. 1995;26:1014.

30. Panerai RB, White RP, Markus HS, et al. Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. *Stroke*. 1998;29:2341.
31. Czosnyka M, Smielewski P, Kirkpatrick P, et al. Monitoring of cerebral autoregulation in head-injured patients. *Stroke*. 1996;27:1829.
32. Czosnyka M, Smielewski P, Piechnik S, et al. Cerebral autoregulation following head injury. *J Neurosurg*. 2001;95:756.
33. Czosnyka M, Miller C. Monitoring of cerebral autoregulation. *Neurocrit Care*. 2014; [Epub ahead of print].
34. Hassler W, Steinmetz H, Pirschel J. Transcranial Doppler study of intracranial circulatory arrest. *J Neurosurg*. 1989;71:195.
35. Chan KH, Miller DJ, Dearden M, et al. The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain trauma. *J Neurosurg*. 1992;77:55.
36. Aaslid R, Lundar T, Lindergaard KF, et al. Estimation of cerebral perfusion pressure from arterial blood pressure and transcranial Doppler recordings. In: Miller JD, Teasdale GM, Rowan JO, et al., eds. *Intracranial Pressure*; vol VI. Berlin: Springer-Verlag; 1986:226.
37. Czosnyka M, Matta BF, Smielewski P, et al. Cerebral perfusion pressure in head injured patients: A noninvasive assessment using transcranial Doppler ultrasonography. *J Neurosurg*. 1998;88:802.
38. Schmidt EA, Czosnyka M, Gooskens I, Piechnik, et al. Preliminary experience of the estimation of cerebral perfusion pressure using transcranial Doppler ultrasonography. *J Neurol Neurosurg Psychiatry*. 2001;70:198.
39. Schmidt B, Czosnyka M, Raabe A, et al. Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. *Stroke*. 2003;34:84.
40. Dewey RC, Pieper HP, Hunt WE. Experimental cerebral hemodynamics: Vasomotor tone, critical closing pressure, and vascular bed resistance. *Neurosurgery*. 1974;41:597.
41. Aaslid R, Lash SR, Bardy GH, et al. Dynamic pressure—flow velocity relationships in the human cerebral circulation. *Stroke*. 2003;34:1645.
42. Panerai RB. The critical closing pressure of the cerebral circulation. *Med Eng Phys*. 2003;25:621.
43. Varsos GV, Richards H, Kasprowicz M, et al. Critical closing pressure determined with a model of cerebrovascular impedance. *J Cereb Blood Flow Metab*. 2013;33:235.
44. Varsos GV, Richards HK, Kasprowicz M, et al. Cessation of diastolic cerebral blood flow velocity: The role of critical closing pressure. *Neurocrit Care*. 2014;20:40.
45. Budohoski KP, Zweifel C, Kasprowicz M, et al. What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury. *Br J Anaesth*. 2012;108:89.
46. Czosnyka M, Richards HK, Reinhard M, et al. Cerebrovascular time constant: Dependence on cerebral perfusion pressure and end-tidal carbon dioxide concentration. *Neurol Res*. 2012;34:17.
47. Varsos GV, Kasprowicz M, Smielewski P, et al. Model-based indices describing cerebrovascular dynamics. *Neurocrit Care*. 2014;20:142.
48. Kim DJ, Kasprowicz M, Carrera E, et al. The monitoring of relative changes in compartmental compliances of brain. *Physiol Meas*. 2009;30:647.
49. Kasprowicz M, Czosnyka M, Soehle M, et al. Vasospasm shortens cerebral arterial time constant. *Neurocrit Care*. 2012;16:213.
50. Spencer MP. Transcranial Doppler monitoring and causes of stroke from carotid endarterectomy. *Stroke*. 1997;28:685.
51. Jansen C, Vriens EM, Eikelboom BC, et al. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring: A prospective study in 130 operations. *Stroke*. 1993;24:665.
52. Halsey Jr JH. Risks and benefits of shunting in carotid endarterectomy: The International Transcranial Doppler Collaborators. *Stroke*. 1992;23:1583.
53. Jorgensen LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. *Eur J Vasc Surg*. 1993;7:370.
54. Gooskens I, Schmidt EA, Czosnyka M, et al. Pressure-autoregulation, CO2 reactivity and asymmetry of haemodynamic parameters in patients with carotid artery stenotic disease: A clinical appraisal. *Acta Neurochir (Wien)*. 2003;145:527.
55. Reinhard M, Roth M, Müller T, et al. Effect of carotid endarterectomy or stenting on impairment of dynamic cerebral autoregulation. *Stroke*. 2004;35:1381.
56. Marcus HS, Tegeler CH. Experimental aspects of high intensity transient signals in the detection of emboli. *J Clin Ultrasound*. 1995;23:81.
57. Gravilescu T, Babikian VL, Cantelmo NL, et al. Cerebral microembolism during carotid endarterectomy. *Am J Surg*. 1995;170:159.
58. Schroeder T, Sillesen H, Sorensen O, et al. Cerebral hyperperfusion syndrome following carotid endarterectomy. *J Neurosurg*. 1987;28:824.
59. Kassell NF, Torner JC, Jane JA, et al. The international co-operative study on the timing of aneurysm surgery. Part 1: Overall management results. *J Neurosurg*. 1990;73:18.
60. Lindegaard KF, Nornes H, Bakke SJ, et al. Cerebral vasospasm after sub-arachnoid hemorrhage investigated by means of transcranial Doppler ultrasound. *Acta Neurochirurg*. 1988;24:81.
61. Lam JM, Smielewski P, Czosnyka M, et al. Predicting delayed is chemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. *Neurosurgery*. 2000;47:819.
62. Budohoski KP, Czosnyka M, Smielewski P, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: A prospective observational study. *Stroke*. 2012;43:3230.
63. Kirkpatrick PJ, Turner CL, Smith C, et al. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): A multicentre randomised phase 3 trial. *Lancet Neurol*. 2014;13:666.
64. Eng CC, Lam AM, Byrd S, et al. The diagnosis and management of a perianesthetic cerebral aneurysmal rupture aided with transcranial Doppler ultrasonography. *Anesthesiology*. 1993;78:191.
65. Diehl RR, Henkes H, Nahser HC, et al. Blood flow velocity and vasomotor reactivity in patients with arteriovenous malformations: A transcranial Doppler study. *Stroke*. 1994;25:1574.
66. Petty GW, Massaro AR, Tatemichi TK, et al. Transcranial Doppler ultrasonographic changes after treatment for arteriovenous malformations. *Stroke*. 1990;21:260.
67. Matta BF, Lam AM, Winn HR. The intraoperative use of transcranial Doppler ultrasonography during resection of arteriovenous malformations. *Br J Anaesth*. 1995;75:242P.
68. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J Neurosurg*. 1991;75:S59.
69. Kirkpatrick PJ, Czosnyka M, Pickard JD. Multimodality monitoring in intensive care. *J Neurol Neurosurg Psychiatry*. 1996;60:131.
70. Panerai RB, Kerins V, Fan L, et al. Association between dynamic cerebral autoregulation and mortality in severe head injury. *Br J Neurosurg*. 2004;18:471.
71. Strebel S, Lam AM, Matta BF, et al. Impaired cerebral autoregulation after mild brain injury. *Surg Neurol*. 1997;47:128.
72. Liu X, Czosnyka M, Donnelly J, et al. Comparison of frequency and time domain methods of assessment of cerebral autoregulation in traumatic brain injury. *J Cereb Blood Flow Metab*. 2014; [Epub ahead of print].
73. Chan KH, Dearden NM, Miller JD. The significance of posttraumatic increase in cerebral blood flow velocity: A transcranial Doppler ultrasound study. *Neurosurgery*. 1992;30:697.
74. Martin NA, Patwardhan RV, Alexander MJ, et al. Characterisation of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. *J Neurosurg*. 1997;87:9.
75. Lee JH, Martin NA, Alsinda G, et al. Hemodynamically significant cerebral vasospasm and outcome after head injury. *J Neurosurg*. 1997;87:221.
76. Rommer B, Bellner J, Kongstad P, et al. Elevated transcranial Doppler flow velocities after severe head injury: Cerebral vasospasm or hyperemia? *J Neurosurg*. 1996;85:90.
77. Feri M, Ralli L, Felici M, et al. Transcranial Doppler and brain death diagnosis. *Crit Care Med*. 1994;22:1120.
78. Bouzat P, Francony G, Declety P, et al. Transcranial Doppler to screen on admission patients with mild to moderate traumatic brain injury. *Neurosurgery*. 2011;68:1603.
79. Bouzat P, Oddo M, Payen JF. Transcranial Doppler after traumatic brain injury: Is there a role? *Curr Opin Crit Care*. 2014;20:153.
80. Zanette EM, Fieschi C, Bozzao L, et al. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke*. 1989;20:899.
81. Toni D, Fiorelli M, Zanette EM, et al. Early spontaneous improvement and deterioration of ischemic stroke patients: A serial study with transcranial Doppler ultrasonography. *Stroke*. 1998;29:1144.
82. Alexandrov AV, Black SE, Ehrlich LE, et al. Prediction of hemorrhagic transformation occurring spontaneously and on anticoagulants in patients with acute ischemic stroke. *Stroke*. 1997;28:1198.
83. Sliwa U, Lingnau A, Stohlman WD, et al. Prevalence and time course of microembolic signals in patients with acute stroke: A prospective study. *Stroke*. 1997;28:358.
84. Yasaka M, O'Keefe GJ, Chambers BR, et al. Streptokinase in acute stroke: Effect on reperfusion and recanalization. Australian Streptokinase Trial Study Group. *Neurology*. 1998;50:626.
85. Reinhard M, Roth M, Guschlbauer B, et al. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke*. 2005;36(8):1684–9. Epub 2005 Jul 14.
86. Murkin JM. Anesthesia, the brain, and cardiopulmonary bypass. *Ann Thorac Surg*. 1993;56:1461.
87. Grocott HP, Amory DW, Lowry E, et al. Transcranial Doppler blood flow velocity versus 133Xe clearance cerebral blood flow during mild hypothermic cardiopulmonary bypass. *J Clin Monit Comput*. 1998;14:35.
88. Van der Linden J, Casmir-Ahn H. When do cerebral emboli appear during open heart operations? A transcranial Doppler study. *Ann Thorac Surg*. 1991;51:237.

89. Lundar T, Lindegaard KF, Froysaker T, et al. Dissociation between cerebral autoregulation and carbon dioxide reactivity during non pulsatile cardiopulmonary bypass. *Ann Thorac Surg*. 1985;40:582.
90. Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: Perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg*. 1995;59:1331.
91. Briliman J, Davis D, Clark RE, et al. Increased middle cerebral artery flow velocity during the initial phase of cardiopulmonary bypass may cause neurological dysfunction. *J Neuroimaging*. 1995;5:135.
92. Grocott HP, Smith MS, Glower DD, et al. Endovascular aortic balloon clamp malposition during minimally invasive cardiac surgery: Detection by transcranial Doppler monitoring. *Anesthesiology*. 1998;88:1396.
93. Joshi B, Brady K, Lee J, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg*. 2010;110:321.
94. Gitlin N, Lewis DC, Hinckley L. The diagnosis and prevalence of sub-clinical hepatic encephalopathy in apparently healthy, ambulant, nonshunted patients with cirrhosis. *J Hepatol*. 1986;3:75.
95. Strauss G, Hansen BA, Knudsen GM, et al. Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure. *J Hepatol*. 1998;28:199.
96. Demarin V, Rundek T, Hodek B. Maternal cerebral circulation in normal and abnormal pregnancies. *Acta Obstet Gynecol Scand*. 1997;76:619.

8 Multi-modality Neurologic Monitoring

M.A. Kirkman • M. Smith

INTRODUCTION

Monitoring systemic and central nervous system physiology is fundamental to the perioperative and critical care management of patients with neurologic disease. The clinical neurologic examination remains the cornerstone of neuromonitoring. In addition, several techniques are available for global or regional monitoring of cerebral hemodynamics, oxygenation, metabolism, and electrophysiology. The pathophysiology of acute brain injury (ABI) is complex, and involves changes in cerebral blood flow (CBF), oxygen and glucose delivery and utilization, and electrophysiological derangements (see Chapter 1). It is, therefore, not surprising that a single monitor is unable to detect all instances of cerebral compromise. Multi-modality monitoring, the measurement of multiple variables simultaneously, provides a more complete picture of the (patho) physiology of the injured brain and its response to treatment (Fig. 8.1). Multimodal monitoring has allowed a move away from rigid physiological target setting towards an individually tailored approach to the management of ABI. Some monitoring modalities are well established, whereas others are relatively new to the clinical arena and their indications still being evaluated; all have advantages and disadvantages (Table 8.1). The general indications for neuromonitoring are summarized in Box 8.1.

This chapter will review the brain monitoring techniques applicable to the perioperative and critical care management of patients with neurologic disease. The use of evoked potential monitoring during spine surgery is covered elsewhere in this book (Chapter 6) and will not be considered here.

CLINICAL ASSESSMENT

Fundamental to neuromonitoring is serial clinical assessment of neurologic status. The Glasgow Coma Scale (GCS) is an easy to use and standardized method for evaluating a patient's global neurologic status by recording best eye opening, and verbal and motor responses to physical and verbal stimuli. In combination with the identification and documentation of localizing signs such as pupil responses and limb weakness, the GCS has remained the mainstay of clinical assessment in the 40 years since its first description.[1] The main limitations of the GCS are that verbal responses are not assessable in intubated patients, and brainstem function is not directly considered. The Full Outline of UnResponsiveness (FOUR) score, which provides a more complete assessment of brainstem function, has been designed and validated to overcome these issues. The FOUR score measures ocular (as well as limb) responses to command and pain, along with pupillary responses and respiratory pattern, and can be used to differentiate further patients with a GCS of 3.[2] There is limited evidence that the FOUR score has greater prognostic value than the GCS alone.

Clinical assessment is limited in sedated patients or those with a decreased level of consciousness, and one or more neuromonitoring techniques can be used to identify or predict secondary brain insults and guide therapeutic interventions in such patients.

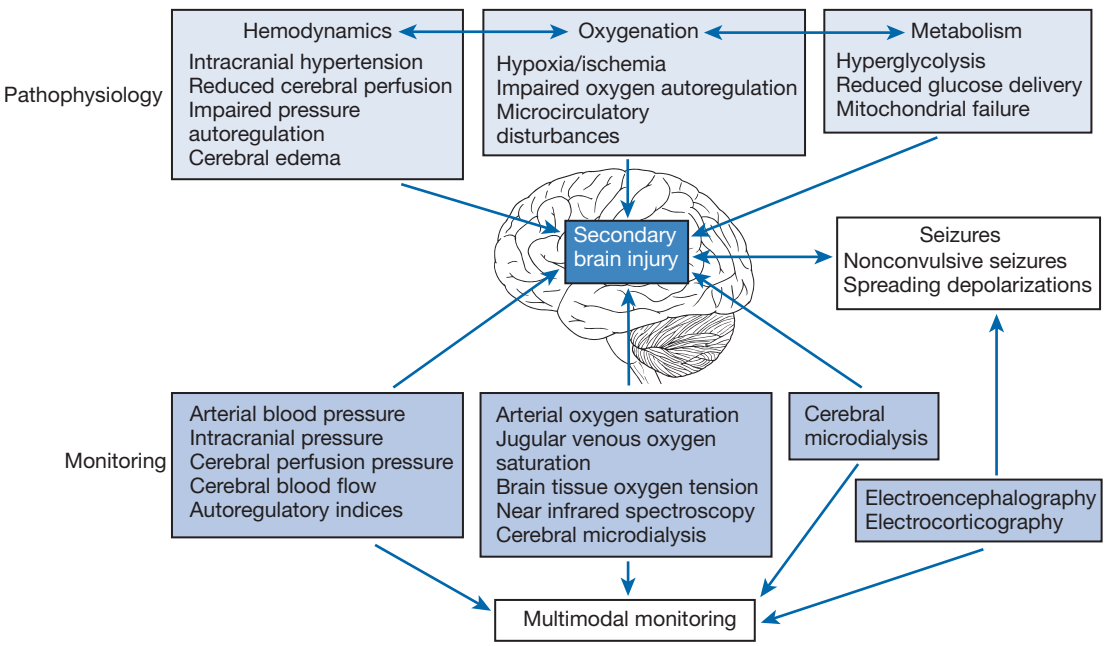


Fig. 8.1 Overview of the major pathophysiological processes underlying acute brain injury and the role of monitoring in the detection of secondary brain injury.

Table 8.1 **Advantages and Disadvantages of Bedside Neuromonitoring Techniques**

Technique	Monitored variable(s)	Advantages	Disadvantages
Intracranial Pressure			
Intraparenchymal microsensor	• ICP • CPP • Indices of autoregulation	• Easy to insert • Intraparenchymal/subdural placement • Low procedural complication rate • Low infection risk	• In vivo calibration not possible • Measures localized pressure • Small zero-drift with time
Ventricular catheter	• As above	• Measures global ICP • Therapeutic drainage of CSF • In vivo calibration	• Placement technically difficult • Risk of procedure-related hemorrhage • Risk of catheter-related ventriculitis
Cerebral Blood Flow			
Transcranial Doppler ultrasonography	• Blood flow velocity • Pulsatility index • Indices of autoregulation	• Noninvasive • Intermittent or continuous • Good temporal resolution	• Measures relative CBF • Operator dependent • Failure rate in 5–10% of patients (absent acoustic window)
Thermal diffusion flowmetry	• Regional CBF	• Measures absolute CBF in mL/100 g/min	• Limited clinical experience • Some concerns over accuracy and reliability • Minimally invasive
Cerebral Oxygenation			
Jugular venous oximetry	• Jugular venous oxygen saturation • Arteriovenous oxygen content difference	• Global assessment of balance between CBF and metabolism	• Non-quantitative assessment of cerebral perfusion • Insensitive to regional ischemia • Risk of extracranial contamination of samples
Brain tissue pO_2	• Brain tissue oxygen partial pressure • Oxygen reactivity	• Regional assessment of balance between CBF and metabolism • Continuous • Ischemic "thresholds" defined	• Minimally invasive • Measures oxygenation within a small region of interest • One hour "run-in" period limits intraoperative applications
Near infrared spectroscopy (cerebral oximetry)	• Regional cerebral oxygen saturation • Indices of autoregulation	• Noninvasive • Real time • Multisite measurement	• Lack of standardization between commercial oximeters • "Contamination" of signals by extracerebral tissue • $rScO_2$-derived "ischemic" threshold not defined
Cerebral Microdialysis	• Glucose • Lactate, pyruvate and LPR • Glycerol • Glutamate • Multiple biomarkers for research purposes	• Assessment of cerebral glucose metabolism • Detection of hypoxia/ischemia • Assessment of nonischemic causes of cellular bioenergetic dysfunction	• Focal measure • Thresholds for abnormality unclear • Not continuous • Labor-intensive
Electrophysiology			
Electroencephalography	• Seizures • Diagnosis-specific EEG patterns	• Noninvasive • Detection of nonconvulsive seizures • Correlates with cerebral ischemic and metabolic changes • Prognostication after ABI	• Skilled interpretation required • Affected by anesthetic/sedative agents
Electrocorticography	• Cortical EEG • Cortical SDs	• Seizure localization during surgery • Only method to identify SDs currently	• Highly invasive • No evidence that treatment of SDs improves outcome
Processed EEG	• Cortical EEG using limited electrode montage	• Depth of anesthesia monitoring • Automated seizure detection software • Prognostication after cardiac arrest	• No established indications for sedation titration on the ICU

ABI, acute brain injury; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; EEG, electroencephalography; ICP, intracranial pressure; ICU, intensive care unit; LPR, lactate to pyruvate ratio; $rScO_2$, regional cerebral oxygen saturation; SD, spreading depolarization.

INTRACRANIAL AND CEREBRAL PERFUSION PRESSURES

Intracranial pressure (ICP) is the pressure inside the skull and thus in the brain tissue; it is synonymous with the cerebrospinal fluid (CSF) pressure in the lateral ventricles. In addition to the measurement of absolute ICP, ICP monitoring allows calculation of cerebral perfusion pressure (CPP), identification and analysis of pathologic ICP waveforms, and derivation of indices of cerebrovascular pressure reactivity.

Intracranial Pressure

The first clinical measurements of ICP were made in 1951 using an electronic transducer to measure ventricular fluid

BOX 8.1 Indications for Neuromonitoring

- Monitoring the healthy but "at risk" brain:
  - carotid surgery
  - cardiac surgery
  - surgery in the beach chair position
- Early detection of secondary adverse events after acute brain injury:
  - intracranial hypertension
  - reduced cerebral perfusion
  - impaired cerebral glucose delivery/utilization
  - cerebral hypoxia/ischemia
  - cellular energy failure
  - nonconvulsive seizures
  - cortical spreading depolarizations
- Guiding individualized, patient-specific therapy after acute brain injury:
  - optimization of ICP and CPP
  - optimization of brain tissue PO_2
  - optimization of cerebral glucose delivery/utilization
  - monitoring cerebral vasospasm after subarachnoid hemorrhage
  - prognostication

pressure signals. Refinements in technique, a low adverse effect profile, and the introduction of microtransducer technology have combined to facilitate the widespread adoption of ICP monitoring into clinical practice.[3]

Technical Aspects

There are two main methods of monitoring ICP—an intraventricular catheter or parenchymal microtransducer device. Other techniques, such as subarachnoid or epidural devices, are less accurate and now rarely used.

Ventricular catheters measure global ICP (CSF pressure in the lateral ventricles) in one of two ways: using a standard catheter connected via a fluid-filled system to an external pressure transducer, or a catheter incorporating microstrain gauge or fiberoptic technology. In vivo calibration is possible with both methods. ICP monitoring via a ventricular catheter is the technique of choice in patients with established or incipient hydrocephalus as it allows therapeutic drainage of CSF.[4] Ventricular catheter insertion can be difficult, and there is a risk of placement-related hemorrhage and catheter-associated ventriculitis. The risk of ventriculitis increases with the length of time since catheter insertion, and can be reduced but not abolished by the use of antibiotic-impregnated or silver-coated catheters.

Parenchymal microtransducer ICP monitoring systems are of two types. Solid-state piezoelectric strain gauge devices incorporate pressure-sensitive resistors which translate pressure generated changes in resistance to an ICP value. Fiberoptic devices transmit light via a fiberoptic cable towards a displaceable mirror at the catheter tip. Changes in ICP distort the mirror and the difference in intensity of reflected light is converted into an ICP value. Both systems are easy to insert and are usually placed about 2 cm into brain parenchyma through a cranial access device or at craniotomy when they can also be sited in the subdural space. While intraventricular catheters have historically been considered the "gold standard" for ICP monitoring, intraparenchymal devices provide equivalent pressure measurement and are safer. In particular, the risk of hematoma and infection is low. Microtransducer systems are considered reliable, but zero drift can result in measurement error over several days and in vivo calibration is not possible.

Several noninvasive ICP monitoring techniques, which would be applicable in broader patient groups than invasive monitoring, have been described.[5] Transcranial Doppler (TCD) ultrasonography-derived pulsatility index is an imprecise assessment of ICP compared with invasively measured pressure, and there is large intra- and interoperator variability. Optic nerve sheath diameter (ONSD) can be measured using ultrasound or computed tomography (CT), and is able to predict intracranial hypertension. Although lacking the risks of invasive methods, noninvasive ICP monitoring techniques currently fail to measure ICP sufficiently accurately for routine clinical use.[6] They are also unable to monitor intracranial dynamics continuously.

Indications

Despite the absence of high-quality evidence demonstrating outcome benefits of ICP-guided management, ICP monitoring has become a standard of care after traumatic brain injury (TBI).[4] It can also provide valuable information in other brain injury types, as well as in patients with hydrocephalus (it can also be useful for chronic monitoring in normal pressure hydrocephalus), and those undergoing craniotomy for lesions producing mass effect.

The Brain Trauma Foundation (BTF) recommends ICP monitoring to guide ICP- and CPP-directed therapy after severe TBI in all salvageable patients with an abnormal cranial CT scan, as well as in those with a normal scan and two or more of: age >40 years, unilateral or bilateral motor posturing, and/or systolic blood pressure <90 mmHg.[7] A recent expert statement provides more detailed and updated guidance.[8] It recommends ICP monitoring in comatose TBI patients with cerebral contusions when interruption of sedation to check neurologic status is dangerous, or when the clinical examination is unreliable. ICP monitoring is also recommended following a secondary decompressive craniectomy and should be considered after evacuation of an acute supratentorial intracranial hematoma in salvageable patients at increased risk of intracranial hypertension, including those with a GCS motor score ≤5, pupillary abnormalities, prolonged/severe hypoxia and/or hypotension, cranial CT findings suggestive of raised ICP, or intraoperative brain swelling. The expert group recommended that ICP monitoring should also be considered in TBI patients with extracranial injuries requiring multiple surgical procedures and/or prolonged analgesia and sedation.

ICP monitoring is increasingly being incorporated into protocols for the critical care management of subarachnoid (SAH)[9] and intracerebral hemorrhage (ICH),[10] although these indications are not as well-defined or well-studied compared with TBI.

Thresholds for Treatment and Evidence

Normal ICP varies with age and body position; in healthy, resting supine adults, normal mean ICP is 5–10 mmHg. ICP greater than 20–25 mmHg is widely considered to require treatment after TBI,[7] although higher and lower thresholds are described.[4] The presence of intracranial hypertension is detrimental and the time spent above a defined ICP threshold, as well as absolute ICP, is an important determinant of poor outcome. Changes in the ICP waveform occur as ICP increases, and waveform analysis has been used to predict the development of intracranial hypertension.[11] While indication of critical reductions in intracranial compliance, before intracranial compensatory mechanisms have become exhausted, would allow more timely clinical intervention, clinical translation of this technique remains elusive.

A meta-analysis of 14 studies and 24,792 patients with severe TBI found that ICP monitoring-guided management of intracranial hypertension had no significant mortality benefit overall compared with treatment in the absence of ICP monitoring, although mortality was lower in patients who underwent ICP monitoring in studies published after 2012.[12] The only randomized controlled trial of ICP-guided management after TBI found no difference in 3- or 6-month outcomes in 324 patients in whom treatment was guided by ICP monitoring compared with imaging and clinical examination in the absence of ICP monitoring.[13] The non-ICP monitoring group in this study received protocol-specified but empirical treatment on a fixed schedule basis, and the wider applicability of such an approach is questionable given evidence that one of the interventions (mannitol) has a more beneficial effect when directed by monitored rises in ICP. In contrast to previous studies,[14] those undergoing ICP monitoring received significantly fewer days of ICP-directed treatment (hyperventilation, hypertonic saline/mannitol and barbiturates) than those in the ICP monitored group, although the length of intensive care unit (ICU) stay was similar. It remains to be seen whether the findings of this study, conducted in Bolivia and Ecuador, are applicable to populations with access to superior pre-hospital care and rehabilitation services. When interpreting this study it is also important to note that evaluation and diagnosis of intracranial hypertension, either by monitoring ICP or assessment of clinical and imaging variables, was fundamental to the management of all patients. It therefore reinforces the widely held view that assessment of ICP is an integral part of the monitoring and management of severe TBI.

Multimodal monitoring incorporating ICP, brain tissue partial pressure of oxygen ($PbtO_2$) and cerebral microdialysis (CMD) is significantly more accurate in predicting cerebral hypoperfusion than ICP monitoring alone,[15] and ICP monitoring is, therefore, best regarded as one part of a multimodal monitoring strategy rather than as a monitoring modality in isolation.[16]

Cerebral Perfusion Pressure

CPP and ICP monitoring are synonymous, as ICP must be measured to allow calculation of CPP.

Technical Aspects

CPP is calculated as the difference between mean arterial pressure (MAP) and ICP, and modifiable through this relationship. For the calculation of CPP to be accurate the arterial pressure transducer must be referenced at the level of the foramen of Monro (tragus of the ear), and the implications of failing to do this are profound. When the head of the bed is elevated, measuring arterial blood pressure (ABP) at the level of the heart results in a calculated CPP that is erroneously high; for example, a measured CPP reading of 60 mmHg may actually represent a "true" CPP of <45 mmHg.[16] Such measurement discrepancies are exacerbated in tall patients, with varying elevations of the head of the bed, and different sites of arterial cannulation.

Indications

The main indications for CPP monitoring are similar to those for ICP.[16] Although CPP-guided management is primarily applied in patients with TBI there is emerging evidence for a role in other brain injury types.[4] Postoperative ICP monitoring is indicated if there is a risk of intracranial hypertension, such as after surgery for large brain tumors with mass effect.

Thresholds for Treatment and Evidence

Recommendations for a CPP threshold have changed over time. Current BTF guidelines recommend that CPP be maintained between 50 and 70 mmHg after TBI, with evidence of adverse outcomes if CPP is lower or higher.[7] While lower CPP risks cerebral ischemia, higher CPP does not necessarily achieve a favorable outcome, and the administration of large fluid volumes and inotropes/vasopressors to maintain CPP carries a substantial risk of acute lung injury.[16] Rather than a single threshold for CPP, multimodal monitoring can be used to identify an "optimal" value for an individual, which aims to reduce the risks of an excessive CPP while minimizing the risks of cerebral hypoperfusion and worsening secondary brain injury.[4] Optimal CPP (CPPopt) can be determined using autoregulatory indices, which are discussed in the next section.

CEREBROVASCULAR REACTIVITY

Cerebrovascular reactivity is a key component of cerebral autoregulation (CA), and it is disturbed or abolished by intracranial pathology and some anesthetic and sedative agents. This may lead to derangements of the relationships between regional CBF and metabolic demand, and render the brain more susceptible to secondary ischemic insults. The ability to monitor cerebrovascular reactivity in the perioperative period or on the ICU is, therefore, an attractive proposition. Methods of testing static and dynamic CA are well established but most are interventional and intermittent, and may not be applicable in anesthetized or critically ill patients. Several continuous monitors of cerebrovascular reactivity have been described.

Technical Aspects

The ICP response to changes in ABP depends on the pressure reactivity of cerebral vessels, and disturbed reactivity implies disturbed pressure autoregulation. Continuous monitoring and analysis of slow waves in ABP allow derivation of a pressure reactivity index (PRx) as a surrogate and continuous marker of global CA. Under normal circumstances, an increase in ABP leads to cerebral vasoconstriction within 5–15 seconds and a secondary reduction in cerebral blood volume (CBV) and ICP. When cerebrovascular reactivity is impaired, CBV and ICP increase passively with ABP with opposite effects occurring during reduced ABP. PRx is calculated as the moving correlation coefficient of consecutive time averaged data points of ICP and ABP recorded over a 4-minute period.[17] A negative value for PRx, when ABP is inversely correlated with ICP, indicates a normal cerebrovascular reactivity, and a positive value a nonreactive cerebrovascular circulation. In the injured brain, cerebral vasoreactivity varies with CPP and optimizes within a narrow CPP range that is specific to an individual patient—referred to as CPP_{opt}. The continuous monitoring of PRx allows management of CPP levels according to an individual's pathophysiological requirements, rather than at a generic predetermined target.

An oxygen reactivity index (ORx) has similarly been described as the moving correlation between $PbtO_2$ and CPP. Cerebrovascular reactivity can also be assessed noninvasively using the correlation between ABP and TCD-derived mean and systolic blood flow velocity, and several near-infrared spectroscopy (NIRS)-derived variables.

Indications

Measurement of cerebrovascular reactivity using PRx and ORx has gained popularity in the management of TBI and,

more recently, after SAH and ICH. NIRS-derived measures of cerebrovascular reactivity have been used to guide brain protection protocols during cardiac surgery.

Thresholds for Treatment and Evidence

Abnormal autoregulatory responses, as indicated by positive PRx and ORx values, are associated with poor outcome, and PRx-guided optimization of CPP is associated with improved outcome after TBI.[18] Unlike PRx, which is a global measure of autoregulatory status, ORx represents regional autoregulation because of the focal nature of PbtO2. Thus, deranged ORx but normal PRx after ICH strongly suggests the presence of focal but not global autoregulatory failure.[19] The duration and magnitude of blood pressure below the lower limit of CA, as determined by NIRS-derived autoregulatory indices, have been shown to be independently associated with major morbidity and mortality after cardiac surgery.[20]

The incorporation of cerebrovascular reactivity into a multimodal monitoring strategy was the subject of a systematic review in 2014.[21] Monitoring cerebrovascular reactivity was found not only to be important for the optimization of CPP, but also to inform interpretation of, and interventions targeted to, other monitored variables, specifically the assessment of the relationships between CBF, oxygen delivery and demand, and cellular metabolism.

CEREBRAL BLOOD FLOW MONITORING

Under normal physiologic conditions cerebral pressure autoregulation maintains CBF constant over a wide range of CPP. However, as noted above, CA is often impaired in the acutely injured brain, and CBF becomes increasingly CPP-dependent as autoregulatory capacity is reduced. Kety and Schmidt described the first practical method for measuring CBF in 1945 using a technique incorporating the Fick principle. This method forms the basis of many CBF measurement techniques in use today and remains the gold standard against which new methods of measurement are validated.

Modern neuroimaging techniques such as positron emission tomography and magnetic resonance imaging provide detailed hemodynamic (including CBF) and metabolic information over multiple regions of interest. However, they only provide "snapshots" at a particular moment in time, and require transfer of (critically ill) patients to remote imaging facilities. Two bedside methods for assessing CBF continuously are available.

Transcranial Doppler Ultrasonography

Introduced in 1982, TCD is a noninvasive technique for assessing cerebral hemodynamics in real time. It measures relative changes rather than actual CBF. TCD is widely used in the diagnosis and management of cerebral vasospasm after SAH, and to monitor the adequacy of cerebral perfusion during carotid surgery. The TCD technique and its applications are described in detail in Chapter 7 and will not be considered further here.

Thermal Diffusion Flowmetry

Thermal diffusion flowmetry (TDF) is an invasive and continuous monitor of regional CBF. A commercially available TDF catheter consists of a thermistor heated to a few degrees above tissue temperature and a proximally located temperature probe. Temperature differences between the two reflect heat transfer and are translated into quantitative measurements of regional CBF in mL/100 g/min. TDF has been used to diagnose and monitor delayed cerebral ischemia after SAH, but clinical data in other disease states are limited and there have been concerns about accuracy and reliability.[6]

CEREBRAL OXYGENATION MONITORING

While ICP and CPP are crucially important and are routinely monitored variables, they do not provide an assessment of the *adequacy* of cerebral perfusion. Several studies confirm that brain hypoxia/ischemia can occur when ICP and CPP are within established thresholds for normality.[22] Cerebral oxygenation monitoring assesses the balance between cerebral oxygen delivery and utilization, and, therefore, the adequacy of both cerebral perfusion and oxygen delivery. Several methods are available to assess global and regional cerebral oxygenation.

Jugular Venous Oxygen Saturation

Jugular venous oxygen saturation ($SvjO_2$) monitoring was the first bedside method for the measurement of cerebral oxygenation, and formed the basis of our understanding of cerebral oxygenation changes after ABI.

Technical Aspects

$SvjO_2$ monitoring is performed through intermittent sampling of blood from a catheter in the jugular venous bulb, or continuously via a fiberoptic catheter. It provides a nonquantitative estimate of the adequacy of cerebral perfusion. The assessment of changes in $SvjO_2$ is based on the concept that the brain extracts more oxygen from hemoglobin when cerebral oxygen supply is insufficient to meet demand, resulting in a decreased oxygen saturation of blood draining from the brain.[23] Derived variables, such as the arterial to jugular venous oxygen concentration difference, have also been extensively studied in the assessment of CBF.

$SjvO_2$ is a flow-weighted measure that reflects global cerebral oxygenation only if sampling is from the dominant jugular bulb, although in practice the right side is often chosen. Contamination of samples from the extracranial circulation must be avoided and is minimal when the catheter tip lies above the lower border of the first cervical vertebra on a lateral cervical spine radiograph. Overly rapid aspiration of blood samples (>2 mL/min) can result in extracranial contamination from the facial vein even when the catheter is correctly positioned.

Indications

$SvjO_2$ monitoring has been used in a variety of intraoperative applications, most notably during cardiac surgery and craniotomy. Its primary role is in the ICU where it can be used to detect impaired cerebral perfusion, and guide optimization of CPP and other interventions after ABI.[23]

Thresholds for Treatment and Evidence

The range of normal $SvjO_2$ values is 55–75% and interpretation of changes is relatively straightforward. Jugular venous desaturation may indicate relative cerebral hypoperfusion secondary to decreased CPP or increased metabolic rate in the absence of a coupled increase in substrate supply, whereas $SjvO_2 > 85\%$ indicates relative hyperemia or arteriovenous shunting. Multiple or prolonged episodes of jugular venous desaturations <50%, and $SvjO_2$ values >85%, are associated

with poor outcome. Although cerebral ischemia is presumed when $SjvO_2$ is <50%, it cannot reliably be assumed to be absent at higher values since regional ischemia may be missed. The BTF cites level 3 evidence to support the maintenance of $SvjO_2$ > 50% after TBI,[7] but no interventional trials have confirmed a direct benefit of $SvjO_2$-directed therapy on outcome. $SjvO_2$ has been widely used for decades but is being superseded by newer oxygenation monitoring modalities.

Brain Tissue Oxygen Tension

$PbtO_2$ monitoring is increasingly being incorporated into neuromonitoring strategies wherever ICP monitoring is indicated.

Technical Aspects

Commercially available $PbtO_2$ monitoring probes incorporate a Clark-type cell with reversible electrochemical electrodes. Oxygen diffusing from brain tissue crosses a semipermeable membrane and is reduced by a gold polarographic cathode which produces a flow of electrical current that is directly proportional to the tissue oxygen tension.[24] To measure oxygenation in the most vulnerable areas of brain, $PbtO_2$ probes are often placed in tissue immediately surrounding a hematoma/contusion, or in appropriate vascular territories in cases of aneurysmal SAH. Such precise placement can be technically challenging and sometimes impossible. Another approach favors routine placement in normal-appearing frontal subcortical white matter on the nondominant side despite heterogeneity of brain oxygenation being well-recognized after ABI, even in "undamaged" brain regions. Correct probe placement should be confirmed with a cranial CT scan. A "run-in" period of around 1 hour is required because $PbtO_2$ readings are unreliable early after insertion, limiting elective intraoperative applications. An "oxygen challenge" (FiO_2 increased to 1.0 for approximately 20 minutes) should be performed post insertion and thereafter on a daily basis to confirm probe function and responsiveness.

$PbtO_2$ is a complex and dynamic variable resulting from the interaction of all factors affecting cerebral oxygen delivery and demand (oxygen metabolism), the relative proportion of arterial or venous vessels in the region of interest, and tissue oxygen diffusion gradients. $PbtO_2$ is, therefore, best considered a biomarker of cellular function rather than simply a monitor of hypoxia/ischemia.

Indications

$PbtO_2$ monitoring is recommended in the management of severe TBI[4,7] and, despite conflicting evidence, as a complement to TCD and radiological monitoring for the detection of vasospasm in comatose SAH patients.[25] It may also identify targets for optimal cerebral oxygenation in comatose patients with ICH,[10] and selection of patients with refractory intracranial hypertension who may benefit from surgical decompression. It is also used in some centers during surgery for intracranial aneurysms and arteriovenous malformations.

Thresholds for Treatment and Evidence

Normal brain $PbtO_2$ lies between 20 and 35 mmHg (2.66 to 4.66 kPa), and the ischemic threshold is usually defined as 10 to 15 mmHg (1.33 and 2.0 kPa).[24] The BTF recommends the institution of brain resuscitation measures when $PbtO_2$ is <15 mmHg (2 kPa),[7] but other authorities recommend intervention when $PbtO_2$ is <20 mmHg (2.66 kPa) since this value represents compromised brain oxygenation.[4,26] In addition to low $PbtO_2$ values, duration of hypoxia and chronological trends are important determinants of poor outcome after ABI. After TBI, outcome is influenced by brain tissue hypoxia independently of ICP and CPP.[22] Observational studies suggest a potential benefit when standard ICP/CPP-guided management is supplemented by $PbtO_2$-guided therapy after TBI.[26] There is limited evidence for any benefit being gained from $PbtO_2$-directed management in other brain injury types or during intracranial surgery, and there are conflicting data for an association between low $PbtO_2$ and outcome following SAH.

There is currently no consensus on how brain tissue hypoxia should be treated. Although strongly influenced by systemic blood pressure, $PbtO_2$ is also affected by several other factors including PaO_2, $PaCO_2$, and hemoglobin concentration.[27] Which intervention or combination of interventions to reverse brain hypoxia is most effective in improving outcome remains unclear. In fact it appears that the responsiveness of brain tissue hypoxia to a given intervention is the prognostic factor, with reversal of hypoxia being associated with reduced mortality.[26]

Near-Infrared Spectroscopy

NIRS-based cerebral oximetry monitors regional cerebral oxygen saturation ($rScO_2$) as a continuous assessment of the balance between cerebral oxygen delivery and utilization. It is noninvasive, has high temporal and spatial resolution, and offers simultaneous measurement over multiple regions of interest.[28,29] Although there has been interest in the use of NIRS to detect cerebral hypoxia/ischemia since its first description in 1977, the extensive use of the technology in the research setting has not been matched by widespread translation into the clinic.

Technical Aspects

NIRS is based on two key principles. Light in the near-infrared (NIR) spectrum (700–950 nm) can traverse biological tissue because of its relative transparency to light in this wavelength range, and several biological molecules, termed chromophores, have distinct absorption spectra in the NIR. NIRS systems are based on the transmission of NIR light and its differential absorption by different chromophores (most commonly oxyhemoglobin and deoxyhemoglobin) as it passes through brain tissue. NIR light cannot pass across the whole adult head so reflectance spectroscopy, in which the light source and detecting devices are placed a few centimeters apart on the same side of the head, is performed. This allows examination of the superficial cerebral cortex. NIRS interrogates arterial, venous, and capillary blood within the field of view so the derived saturation represents a weighted value from these three compartments. Commercial oximeters incorporate fixed arterial:venous (a:v) ratios into their algorithms, usually 30:70 or 40:60. In addition to cerebral a:v ratio, $rScO_2$ is also influenced by other physiological variables, including arterial oxygen saturation, $PaCO_2$, systemic blood pressure, hematocrit, and CBV.

Many commercial devices incorporate spatially resolved spectroscopy to derive a scaled absolute hemoglobin concentration (i.e., the relative proportions of oxy- and deoxyhemoglobin within the field of view), and display calculated $rScO_2$ as a simple percentage value. The algorithms incorporated into commercial devices vary (and are often unpublished), making comparisons between different manufacturers' devices difficult. Claims for $rScO_2$ thresholds for the identification of ischemia usually lack any form of validation so cerebral oximetry is currently best considered a trend monitor.[29]

The potential for "contamination" of the NIRS signals by extracranial tissue is a major concern for the clinical application of NIRS.[28] SRS has high sensitivity and specificity for

intracranial changes when appropriate $rScO_2$ thresholds are chosen, but is still prone to some degree of extracerebral contamination.[30] Advances in NIRS technology will increase the intracranial specificity of signals and also allow measurement of additional chromophores, such as cytochrome *c* oxidase (CCO).

CCO is the final electron acceptor in the mitochondrial electron transport chain and responsible for over 95% of oxygen metabolism. Its oxidation status reflects the balance between cerebral energy supply and demand, which, in association with measures of cerebral oxygenation, may assist in the determination of ischemic thresholds.[29] The NIRS-measured CCO signal is also highly specific for intracerebral changes, potentially making it a superior brain biomarker to hemoglobin-based NIRS variables. Technical advances, including the use of supercontinuum light sources and combined time-resolved and broadband spectroscopy, are likely to allow the introduction of a single NIRS-based device that will monitor absolute cerebral oxygenation, hemodynamics, and metabolic status, and provide optical "imaging" at the bedside.[31]

Indications

NIRS-based cerebral oximetry is used to monitor the brain and guide brain-protective strategies during cardiac surgery, particularly in pediatric cases.[32] During carotid surgery, NIRS has similar accuracy and reproducibility in the detection of cerebral ischemia compared with other monitoring modalities, and some advantages in terms of simplicity and temporal resolution.[33] The potential to monitor cerebral well-being continuously and noninvasively during routine surgical procedures under general anesthesia is an attractive proposition, but evidence that early detection of cerebral desaturation and targeted intervention might improve perioperative outcome has thus far proved elusive.[34] Hypotension-associated decreases in $rScO_2$ in anesthetized patients in the beach chair position are not associated with a higher incidence of postoperative cognitive dysfunction or serum biomarkers of brain injury,[35] so the clinical relevance of such "desaturations" is unclear.

The role of NIRS in the ICU management of ABI is undefined and there are no outcome studies of NIRS-guided treatment. The presence of intraparenchymal hematoma, cerebral edema, and SAH may invalidate some of the assumptions upon which NIRS algorithms are based, but technological advances are likely to overcome these difficulties.[28]

Thresholds for Treatment and Evidence

The "normal" range of $rScO_2$ is usually stated to lie between 60% and 75%, but there is substantial intra- and interindividual variability. Despite early retrospective studies suggesting an association between intraoperative cerebral desaturation and increased risk of perioperative cognitive decline after cardiac surgery, a 2013 systematic review concluded that only low-level evidence links low intraoperative $rScO_2$ to postoperative neurologic complications.[32] There was also insufficient evidence to conclude that interventions to prevent or treat reductions in $rScO_2$ are effective in preventing stroke or postoperative cognitive dysfunction. It is impossible to specify an $rScO_2$ threshold that can be widely applied to guide shunt placement and other neuroprotective interventions during carotid surgery; reductions in $rScO_2$ varying between 5% and 25% from baseline have been reported as potential ischemic thresholds.[29]

Worsening of NIRS-monitored cerebral oxygenation has been associated with increased mortality, intracranial hypertension and compromised CPP after TBI, and with vasospasm after SAH, including in patients where TCD was not diagnostic. While $rScO_2$ may be able to provide a noninvasive estimate of cerebral oxygenation after TBI,[36] there is currently no evidence that NIRS-guided treatment protocols are beneficial.

CEREBRAL MICRODIALYSIS

Well-established as a laboratory research tool, CMD was introduced into the clinic in 1995 for the bedside analysis of brain tissue biochemistry. CMD monitors both the supply of substrate and its cellular metabolism and is, therefore, a monitor not solely of cerebral ischemia but also of nonischemic causes of cellular energy dysfunction and the ensuing metabolic crisis.[37]

Technical Aspects

The microdialysis (MD) catheter is a small probe comprising two concentric tubes with a semipermeable MD membrane at the tip. A precision pump delivers perfusion fluid at a slow rate (usually 0.3 μL/min) via the outer tube to the dialysis membrane across which bidirectional diffusion of molecules between brain extracellular fluid (ECF) and perfusion fluid takes place. The concentration gradient driving this diffusion is maintained by the continuous flow of perfusion fluid (which lacks the substance of interest in the ECF) along the inner side of the dialysis membrane. The perfusion fluid, now termed the microdialysate because it contains substances that have diffused from the brain ECF, is returned via the inner tube of the MD catheter and collected in a small vial that is typically changed hourly.

Each sampled substance is a marker of a particular cellular process associated with glucose metabolism, hypoxia/ischemia, and cellular energy failure. In clinical practice, glucose, lactate, pyruvate, glycerol, and glutamate are the variables most commonly measured.[38] However, any molecule that can pass through the semipermeable dialysis membrane can in theory be sampled, allowing off-line analysis of the dialysate for multiple biomarkers, including macromolecules such as cytokines, for research purposes.

One of the main advantages of CMD is its ability to assess glucose metabolism.[39] Cerebral glucose utilization may increase dramatically after ABI (cerebral hyperglycolysis), leading to critical reductions in cerebral glucose levels even in the presence of adequate supply. Glucose is metabolized via glycolysis to pyruvate which, under normal oxidative conditions, enters the highly efficient energy-producing tricarboxylic acid (TCA) cycle. Under hypoxic conditions, or if mitochondrial function is compromised, pyruvate is metabolized to lactate outside the TCA cycle with consequent low energy yield. The ECF lactate to pyruvate ratio (LPR), in association with ECF glucose levels, provides useful clinical information after ABI. Two types of elevated LPR, related to the mechanism of the physiological perturbations, are described. Type 1 changes are associated with reduced ECF pyruvate and elevated lactate concentrations secondary to classic ischemia, whereas the type 2 pattern occurs when reduced pyruvate is the predominant metabolic perturbation, a situation that reflects impairment of the glycolytic pathway in the presence of adequate (or reduced) glucose supply.[40] CMD monitored glutamate is a marker of hypoxia/ischemia and excitotoxicity, and glycerol a marker of hypoxia/ischemia and cell membrane breakdown.[38]

CMD is a focal technique so the monitored variables must be interpreted with knowledge of catheter location. This can be confirmed by CT visualization of a gold marker at the MD catheter tip. It is generally recommended that the MD catheter be placed in "at risk" tissue to allow assessment of biochemical changes in the area of brain most susceptible to secondary injury.[41]

Indications

CMD monitoring can be considered in patients at risk of cerebral hypoxia/ischemia, cellular energy failure and glucose deprivation.[4] It is most commonly used in the critical care management of TBI and SAH, but may also have utility after ICH and acute ischemic stroke. Since CMD measures change at the cellular level, there is evidence that it may identify cerebral compromise before it is detectable clinically or by other monitored variables.[42] Early detection of impending hypoxia/ischemia would also be of significant benefit in the intraoperative setting, but a 2013 systematic review found limited and only low-quality evidence to support the use of CMD as a diagnostic tool during neurosurgery.[43] The current hourly sampling rate used in the critical care management of ABI is in any case unlikely to be sufficient for intraoperative monitoring. A continuous rapid-sampling cerebral MD technique has been described for research use, but such systems are not currently available for clinical applications.

Thresholds for Treatment and Evidence

Elevated LPR in combination with low brain glucose is a sign of severe hypoxia/ischemia and associated with poor outcome after TBI. Thresholds for abnormality often used clinically are LPR >40 and glucose <0.7–1 mmol/L.[44] However, there is no established value above which the LPR is definitively indicative of tissue hypoxia, and a lower threshold of abnormality (>25) is recommended by some investigators.[38] LPR has been used to guide optimization of CPP after TBI, but some studies have found that LPR may be abnormal despite CPP values that are customarily considered to be adequate.[45] This is perhaps unsurprising given the several nonhypoxic/ischemic causes of elevated LPR,[40] and highlights the importance of using physiological data from multiple sources to guide individualized patient management.

CMD has contributed to our understanding of the pathophysiology of brain injury but its clinical utility is still debated. The sensitivity and specificity of MD markers of ischemia and bioenergetic failure are not well characterized, and there are no data to confirm whether MD-guided therapy can influence outcome. Its use is, therefore, limited to a few research centers.

ELECTROENCEPHALOGRAPHY AND ELECTROCORTICOGRAPHY

The value of monitoring cerebral electrophysiological activity in patients with primary neurological disease is well established, and its role in critically ill patients generally is increasing with greater awareness that systemic illnesses, such as sepsis, have major impact on the brain.

Electroencephalography

Intermittent EEG monitoring is adequate for the diagnosis of seizures and some other neurological conditions, but continuous EEG (cEEG) monitoring is required for the reliable detection and management of nonconvulsive seizures (NCSz) and nonconvulsive status epilepticus (NCSE).[46]

Technical Aspects

A 21-electrode montage is the standard for EEG monitoring, but a simplified set-up using seven (or fewer) electrodes has high sensitivity for the detection of seizures and may facilitate wider application outside specialist centers. The usefulness of cEEG is limited by its attenuation by anesthetic and sedative agents. It is also a resource-intensive technique requiring interpretation by skilled personnel. Technological advances have led to the introduction of user-friendly processed EEG (pEEG) techniques, including automated seizure detection software. Telemedicine, which allows interpretation away from the bedside, may also increase the wider adoption of cEEG monitoring outside specialist centers.

The bispectral index (BIS) monitor is a pEEG device that was developed to monitor the depth of anesthesia. It uses a proprietary algorithm to process frontal EEG signals and derive a number between 0 and 98. Values above 90 reflect a preponderance of higher frequency beta waves suggesting wakefulness. With progressive EEG suppression, BIS value approaches 0.

Indications

Depth of anesthesia monitoring with BIS or other pEEG-based techniques may reduce the risk of awareness, facilitate earlier recovery and reduce the risk of postoperative delirium. A detailed discussion of the pros and cons of depth of anesthesia monitoring is beyond the scope of this chapter and the reader is referred elsewhere for further information.[47]

There is no evidence to support the use of BIS monitoring to guide sedation or other interventions on the ICU. Its raw EEG display in association with the BIS value has been used to titrate anesthetic agents during the management of status epilepticus (SE) prior to definitive EEG monitoring, but it should be emphasized that BIS does not replace formal EEG monitoring in these circumstances. There is some preliminary evidence that BIS values might have prognostic significance in determining which patients will not recover from cardiac arrest-associated brain anoxia.[48]

EEG monitoring is indicated to detect intraoperative cerebral ischemia in a variety of circumstances, most commonly to identify cerebral hypoperfusion necessitating shunt placement during carotid surgery. In the ICU, EEG monitoring provides dynamic information about brain function and allows early detection of changes in neurologic status, which is particularly useful when clinical examination is limited. cEEG is recommended over intermittent monitoring in refractory SE, and to rule out NCSz in brain-injured patients and comatose critically ill patients without primary brain injury with unexplained or persistent altered consciousness.[46] The EEG can also be used to detect and monitor cerebral ischemia in comatose SAH patients, and to improve prognostication of coma after cardiac arrest.

Thresholds for Treatment and Evidence

The value of EEG and cEEG monitoring in the diagnosis and management of seizures and SE is well established since prompt and aggressive seizure management improves outcome. The wider role of cEEG monitoring, though, is less clear. Integrating cEEG into multi-modal neuromonitoring strategies identifies associations between seizures, intracranial hypertension and metabolic derangements,[49] but the impact of cEEG-guided treatment of NCSz is not established.

Electrocorticography

Spreading cortical depolarizations (SDs) are pathological events characterized by near-complete, sustained depolarization of neurons and astrocytes that results in secondary injury related to mitochondrial damage, accumulation of intracellular calcium, and excitotoxicity. SDs can currently be detected only by electrocorticography (ECoG) which involves the placement of an electrode strip directly onto the cortical surface. Advances in scalp EEG and NIRS technology are likely to result in the development of noninvasive methods for the detection of SDs.

Indications

Episodes of SD are detected in the majority of patients with malignant stroke, in over 70% of those with SAH, 50–60% with TBI and 60% of those with ICH.[50] ECoG monitoring is, therefore, theoretically indicated in all brain injury types but, given its invasiveness, currently remains a research tool on the ICU. It is, however, used routinely during the resection of brain lesions that are associated with, or increase the risk of, seizures, and during epilepsy surgery (see Chapter 17).

Thresholds for Treatment and Evidence

SDs may represent potential targets for therapy, but a definite cause-and-effect relationship has not been proven. Only after TBI have SDs been shown to be independently associated with worse outcome, but treatment does not appear to modulate this. Until further evidence emerges, management should focus on controlling variables such as pyrexia, hypoxia, hypoglycemia and systemic hypotension, which are known to increase the incidence and duration of SDs.[50]

CHALLENGES OF MULTI-MODALITY NEUROMONITORING

Multi-modality neuromonitoring allows cross validation between monitored variables and gives greater confidence when making treatment decisions, but how clinicians should approach derangements in one physiological variable in the presence of normal values in another is not always obvious. Different neuromonitoring tools measure different physiological variables and their derangement, and the relative importance of each is dependent on the underlying pathophysiology and time since injury. It is for this reason that a "one size fits all" approach to monitoring and management after ABI is inappropriate.

Multimodal neuromonitoring produces large and complex datasets and, to maximize clinical relevance, systems have been developed to analyze and present these in a user-friendly and timely manner at the bedside.[4] Another approach to multimodal data interpretation is the use of computational models of cerebral oxygenation, hemodynamics and metabolism.[29] As well as interpreting complex datasets and providing timely summary outputs that can guide clinical decisions, computational models can also produce patient-specific simulations of clinically important but unmeasured physiological variables such as cerebral metabolism. Modelling approaches also have potential to provide clinicians with information about the underlying processes that are driving the (patho) physiological state of the brain, rather than simply the endpoints of the injurious processes.

SUMMARY

Given the physiological complexity of the human brain it is not surprising that a single variable or device is unable to adequately monitor all aspects of cerebral physiology and pathophysiology. Monitoring strategies on the ICU usually incorporate measurement of multiple variables simultaneously. The assessment of ICP, cerebral perfusion, oxygenation, metabolic status, and electrophysiology provides early detection of impending cerebral ischemia, hypoxia and metabolic crises, and identifies extended windows for monitoring-guided, individualized treatment strategies. Currently many neuromonitoring modalities are invasive but there is an expectation that reliable noninvasive monitors will emerge. This will broaden the application of neuromonitoring, including into the perioperative period. High-quality outcome studies are required to demonstrate the value of monitoring-guided therapy and which modalities, or combination of modalities, are most likely to lead to improved outcomes for patients.

REFERENCES

1. Teasdale G, Maas A, Lecky F, et al. The Glasgow Coma Scale at 40 years: Standing the test of time. *Lancet Neurol*. 2014;13:844–854.
2. Sharshar T, Citerio G, Andrews PJ, et al. Neurological examination of critically ill patients: A pragmatic approach. Report of an ESICM expert panel. *Intensive Care Med*. 2014;40:484–495.
3. Smith M. Monitoring intracranial pressure in traumatic brain injury. *Anesth Analg*. 2008;106:240–248.
4. Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40:1189–1209.
5. Kristiansson H, Nissborg E, Bartek Jr. J, et al. Measuring elevated intracranial pressure through noninvasive methods: A review of the literature. *J Neurosurg Anesthesiol*. 2013;25:372–385.
6. Oddo M, Villa F, Citerio G. Brain multimodality monitoring: An update. *Curr Opin Crit Care*. 2012;18:111–118.
7. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. *J Neurotrauma*. 2007;24:S1–S106.
8. Stocchetti N, Picetti E, Berardino M, et al. Clinical applications of intracranial pressure monitoring in traumatic brain injury: Report of the Milan consensus conference. *Acta Neurochir (Wien)*. 2014;156:1615–1622.
9. Sandsmark DK, Kumar MA, Park S, Levine JM. Multimodal monitoring in subarachnoid hemorrhage. *Stroke*. 2012;43:1440–1445.
10. Kirkman MA, Smith M. Supratentorial intracerebral hemorrhage: A review of the underlying pathophysiology and its relevance for multimodality neuromonitoring in neurointensive care. *J Neurosurg Anesthesiol*. 2013;25:228–239.
11. Asgari S, Bergsneider M, Hamilton R, et al. Consistent changes in intracranial pressure waveform morphology induced by acute hypercapnic cerebral vasodilatation. *Neurocrit Care*. 2011;15:55–62.
12. Yuan Q, Wu X, Sun Y, et al. Impact of intracranial pressure monitoring on mortality in patients with traumatic brain injury: A systematic review and meta-analysis. *J Neurosurg*. 2015;122:574–587.
13. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;367:2471–2481.
14. Cremer OL, van Dijk GW, Amelink GJ, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Crit Care Med*. 2005;33:2207–2213.
15. Bouzat P, Marques-Vidal P, Zerlauth JB, et al. Accuracy of brain multimodal monitoring to detect cerebral hypoperfusion after traumatic brain injury. *Crit Care Med*. 2015;43:445–452.
16. Kirkman MA, Smith M. Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/CPP-guided therapy: A standard of care or optional extra after brain injury? *Br J Anaesth*. 2014;112:35–46.
17. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry*. 2004;75:813–821.
18. Aries MJ, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med*. 2012;40:2456–2463.
19. Diedler J, Karpel-Massler G, Sykora M, et al. Autoregulation and brain metabolism in the perihematomal region of spontaneous intracerebral hemorrhage: An observational pilot study. *J Neurol Sci*. 2010;295:16–22.
20. Ono M, Brady K, Easley RB, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg*. 2014;147:483–489.
21. Lazaridis C, Andrews CM. Brain tissue oxygenation, lactate-pyruvate ratio, and cerebrovascular pressure reactivity monitoring in severe traumatic brain injury: Systematic review and viewpoint. *Neurocrit Care*. 2014;21:345–355.
22. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery*. 2011;69:1037–1045.
23. Schell RM, Cole DJ. Cerebral monitoring: Jugular venous oximetry. *Anesth Analg*. 2000;90:559–566.
24. De Georgia MA. Brain tissue oxygen monitoring in neurocritical care. *J Intensive Care Med*. 2015;30:473–483.
25. Diringer MN, Bleck TP, Claude HJ, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage:

Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care*. 2011;15:211–240.
26. Nangunoori R, Maloney-Wilensky E, Stiefel M, et al. Brain tissue oxygen-based therapy and outcome after severe traumatic brain injury: A systematic literature review. *Neurocrit Care*. 2012;17:131–138.
27. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. *Neurocrit Care*. 2011;14:361–369.
28. Ghosh A, Elwell C, Smith M. Review article: Cerebral near-infrared spectroscopy in adults: A work in progress. *Anesth Analg*. 2012;115:1373–1383.
29. Smith M. Shedding light on the adult brain: A review of the clinical applications of near-infrared spectroscopy. *Philos Transact A Math Phys Eng Sci*. 2011;369:4452–4469.
30. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. *Anesthesiology*. 2012;116:834–840.
31. Elwell CE, Cooper CE. Making light work: Illuminating the future of biomedical optics. *Philos Transact A Math Phys Eng Sci*. 2011;369:4358–4379.
32. Zheng F, Sheinberg R, Yee MS, et al. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: A systematic review. *Anesth Analg*. 2013;116:663–676.
33. Moritz S, Kasprzak P, Arlt M, et al. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: A comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology*. 2007;107:563–569.
34. Nielsen HB. Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. *Front Physiol*. 2014;5:93.
35. Laflam A, Joshi B, Brady K, et al. Shoulder surgery in the beach chair position is associated with diminished cerebral autoregulation but no differences in postoperative cognition or brain injury biomarker levels compared with supine positioning: The anesthesia patient safety foundation beach chair study. *Anesth Analg*. 2015;120:176–185.
36. Rosenthal G, Furmanov A, Itshayek E, et al. Assessment of a noninvasive cerebral oxygenation monitor in patients with severe traumatic brain injury. *J Neurosurg*. 2014;120:901–907.
37. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab*. 2005;25:763–774.
38. Tisdall MM, Smith M. Cerebral microdialysis: Research technique or clinical tool. *Br J Anaesth*. 2006;97:18–25.
39. Jalloh I, Carpenter KL, Helmy A, et al. Glucose metabolism following human traumatic brain injury: Methods of assessment and pathophysiological findings. *Metab Brain Dis*. 2015;30:615–632.
40. Larach DB, Kofke WA, Le Roux P. Potential non-hypoxic/ischemic causes of increased cerebral interstitial fluid lactate/pyruvate ratio: A review of available literature. *Neurocrit Care*. 2011;15:609–622.
41. Bellander BM, Cantais E, Enblad P, et al. Consensus meeting on microdialysis in neurointensive care. *Intensive Care Med*. 2004;30:2166–2169.
42. Belli A, Sen J, Petzold A, Russo S, et al. Metabolic failure precedes intracranial pressure rises in traumatic brain injury: A microdialysis study. *Acta Neurochir (Wien)*. 2008;150:461–469.
43. Bossers SM, de Boer RD, Boer C, Peerdeman SM. The diagnostic accuracy of brain microdialysis during surgery: A qualitative systematic review. *Acta Neurochir (Wien)*. 2013;155:345–353.
44. Timofeev I, Carpenter KL, Nortje J, et al. Cerebral extracellular chemistry and outcome following traumatic brain injury: A microdialysis study of 223 patients. *Brain*. 2011;134:484–494.
45. Vespa PM, O'Phelan K, McArthur D, et al. Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure. *Crit Care Med*. 2007;35:1153–1160.
46. Claassen J, Taccone FS, Horn P, et al. Recommendations on the use of EEG monitoring in critically ill patients: Consensus statement from the neurointensive care section of the ESICM. *Intensive Care Med*. 2013;39:1337–1351.
47. Escallier KE, Nadelson MR, Zhou D, Avidan MS. Monitoring the brain: Processed electroencephalogram and peri-operative outcomes. *Anaesthesia*. 2014;69:899–910.
48. Stammet P, Collignon O, Werer C, et al. Bispectral index to predict neurological outcome early after cardiac arrest. *Resuscitation*. 2014;85:1674–1680.
49. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. *Anesth Analg*. 2009;109:506–523.
50. Lauritzen M, Dreier JP, Fabricius M, et al. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab*. 2011;31:17–35.

9 Fluid Management During Craniotomy

K. Vagnerova • R. Rusa

The intraoperative fluid management of neurosurgical patients presents special challenges for the anesthesiologist. Neurosurgical patients often experience rapid changes in intravascular volume caused by hemorrhage, the administration of potent diuretics, or the onset of diabetes insipidus. The administration of volatile anesthetics and potent vasodilators during surgery may contribute to decreased cardiac filling pressures without causing actual changes in intravascular volume. In the midst of this dynamic situation, the anesthesiologist often faces the additional concern of minimizing increases in cerebral water content and, thus, intracranial pressure. Intracranial hypertension secondary to cerebral edema is now known to be one of the most common causes of morbidity and mortality in the intraoperative and postoperative periods.

In this chapter, we examine some of the physical determinants of water movement between the intravascular space and the central nervous system. Then we address specific clinical situations and make suggestions for the types and volumes of fluids to be administered.

OSMOLALITY, ONCOTIC PRESSURE, AND INTRAVASCULAR VOLUME

Osmolality

Osmolality is one of the four colligative properties of a solution. (The other three are vapor pressure, freezing point depression, and boiling point elevation.) The addition of 1 osmole of any solute to 1 kg of water causes the vapor pressure to fall by 0.3 mmHg, the freezing point to drop by 1.85° C, and the boiling point to rise by 0.52° C.[1] The colligative properties are determined solely by the *number* of particles in solution and are independent of the chemical structure of the solute. The solute may exist in either an ionized or a nonionized state, and the size (molecular weight) of the solute is of no importance. Although it may seem counterintuitive, equimolar concentrations of glucose, urea, and mannitol have the same effect on the colligative properties of a solution. Osmolality is strictly a function of the number of particles in solution.

For physiologic solutions, *osmolality* is commonly expressed as milliosmoles (mOsm) *per kilogram of solvent*, whereas the units of measure for *osmolarity* are milliosmoles *per liter of solution*. For dilute solutions (including most of those of physiologic importance), the two terms may be used interchangeably. Osmolarity can be calculated if the molecular weight of the solute and its tendency to disassociate in solution are known (Boxes 9.1 and 9.2). The osmolarities of some commonly used intravenous fluids are listed in Table 9.1.

Osmolarity is important in determining fluid movement between various physiologic compartments because of the osmotic pressure that is generated when solutions of unequal osmolarity are separated by a membrane permeable to water but not to solutes. According to the second law of thermodynamics, which states that all systems spontaneously change to maximize entropy, water has a tendency to move from the solution of lower osmolality, across the membrane, and into the solution of higher osmolality (Fig. 9.1).

This process continues until the solutions are of equal osmolality or the hydrostatic pressure is sufficient to preclude any further net flow of water across the membrane. The hydrostatic pressure that can be generated by osmolar differences is formidable and may be calculated by the following equation:

$$\pi = CRT \qquad (9.1)$$

where π is osmotic pressure in atmospheres, C is concentration of all osmotically active solutes in the solution (in moles per liter), R is gas constant (0.08206 liter-atm/mole-degree), and T is temperature in degrees Kelvin (° K).

BOX 9.1 Calculate the Osmolarity of a 0.9% Solution of Saline

Fact: The molecular weight of NaCl is 58.43 g/mol.

Fact: A 0.9% solution of NaCl contains 9 g of NaCl per 1000 mL of solution.

The first step is to calculate the molarity of the 0.9% solution. To do this, we divide 9 g/L by 58.43 g/mol, which equals 0.154 mol/L or a 154 mmol/L solution of NaCl. Because each molecule of NaCl disassociates in water into a Na^+ and a Cl^- ion, we multiply the molar value by two to get an osmolarity of 308 mOsm/L. This value corresponds to the osmolarity listed on any container of 0.9% saline.

BOX 9.2 Calculation of Osmotic Pressure

Calculate the osmotic pressure generated by a 1 mOsm difference in osmolarity at body temperature and express the results in millimeters of mercury.

Formula for calculation of osmotic pressure is as follows:

$$\pi = CRT$$

where:

$C = 0.001$ mol/L (ie, 1 mOsm/L)

$R = 0.08206$

$T = 273° K + 36° K = 309° K$ (body temperature)

Therefore:

$$\pi = 0.001 \times 0.08206 \times 309° = 0.02535 \text{ atm}$$

or 19.27 mmHg

Table 9.1 Osmolarity of Commonly Used Intravenous Fluids

Fluid	Osmolarity (mOsm/L)	Oncotic Pressure (mmHg)
Lactated Ringer's solution	>273	0
D_5 lactated Ringer's solution	525	0
0.9% saline	308	0
D_5 0.45% saline	406	0
0.45% saline	154	0
20% mannitol	1098	0
Hetastarch (6%)	310	31[2]
Dextran 40 (10%)	≈300	169[3]
Dextran 70 (6%)	≈300	69[3]
Albumin (5%)	290	19
Plasma	295	26

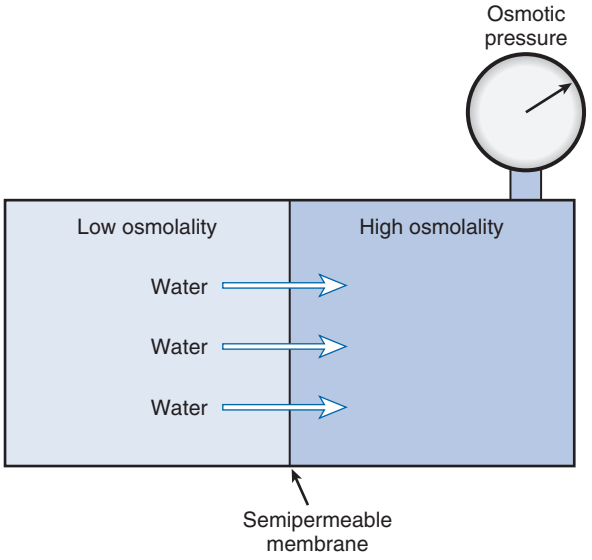


Fig. 9.1 When solutions of unequal osmolality are separated by a semipermeable membrane, water moves from the solution of lower osmolality through the membrane and into the more concentrated solution. This process continues until the solutions are of equal osmolality or the osmotic pressure reaches the point that no further net flux of water across the membrane is possible.

On the basis of this formula, a pressure of more than 19 mmHg is generated for each milliosmole difference across a semipermeable membrane (see Box 9.2). Thus, osmolar differences can provide a potent driving force for the movement of water between the intracellular and extracellular spaces and, as seen later, across the blood–brain barrier. Although osmolar gradients can be produced by administering hypo-osmolar or hyperosmolar fluids, these gradients are fleeting; and water moves from one compartment to another so that all body fluids are again of equal osmolarity.

Oncotic Pressure

Oncotic pressure is the osmotic pressure generated by solutes larger than an arbitrary limit (usually 30,000 molecular weight [MW]). Albumin (69,000 approximate MW), hetastarch (480,000 mean MW), dextran 40 (40,000 mean MW), and dextran 70 (70,000 mean MW) are compounds of clinical

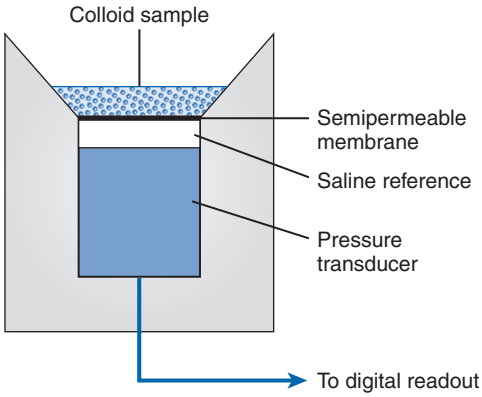


Fig. 9.2 Oncotic pressure of various fluids can be measured with the use of a simple device constructed from a pressure transducer and semipermeable membrane. The chamber containing a saline reference is positioned above the pressure transducer and is separated from the sample well by a semipermeable membrane. The colloidal fluid being tested is placed in the sample well. Oncotic pressure of the colloidal fluid draws a small volume of saline across the semipermeable membrane, thereby creating a negative pressure above the pressure transducer. This pressure, which is digitally displayed, represents the oncotic pressure of the colloidal sample.

interest that are capable of exerting oncotic pressure. Reported values for the oncotic pressures of plasma, mannitol, albumin, and hetastarch are listed in Table 9.1.[2,3] The oncotic pressure produced by all plasma proteins (eg, albumin, globulins, fibrinogen) accounts for less than 0.5% of total plasma osmotic pressure. The oncotic pressure of various solutions can be easily measured with an electronic pressure transducer and a membrane that is freely permeable to low-molecular-weight (LMW) solutes but that prevents the passage of particles greater than 30,000 MW (Fig. 9.2).

Determinants of Fluid Movement between Vasculature and Tissues

Nearly 100 years ago, Ernest Starling described the forces that determine the movement of water between tissues and the intravascular space.[4] This description was subsequently formalized in what is now known as the Starling equation, as follows:[5]

$$Q_f = K_f S\left[\left(Pc - Pt\right) - \sigma\left(\pi_c - \pi_t\right)\right] \qquad (9.2)$$

where Q_f is the net amount of fluid that moves between the capillary lumen and the surrounding extracellular space (interstitium), K_f is the filtration coefficient for the membrane, S is the surface area of the capillary membrane, P_c is the hydrostatic pressure in the capillary lumen, P_t is the hydrostatic pressure (usually negative) in the extracellular space of the surrounding tissue, σ is the coefficient of reflection—this number, which can range from 1 (no movement of the solute across the membrane) to 0 (free diffusion of the solute across the membrane), quantitates the "leakiness" of the capillary and is different for vessels in the brain and those in peripheral tissues, π_c is the oncotic pressure of the plasma, and π_t is the oncotic pressure of the fluid in the extracellular space.[5]

Capillary pressure, tissue pressure (negative in nonedematous tissues), and tissue oncotic pressure all act to draw fluid from the capillaries and into the extracellular space of the tissue (Fig. 9.3). In peripheral tissues, the only factor that serves to maintain intravascular volume is the plasma oncotic pressure, which is produced predominantly by albumin and to a lesser extent by immunoglobulins, fibrinogen, and other high-molecular-weight (HMW) plasma proteins (see Fig. 9.3).

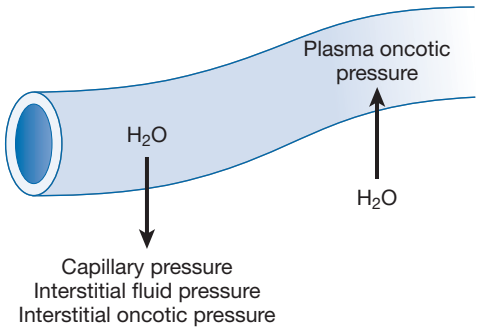


Fig. 9.3 In peripheral tissues, four forces act on intravascular water: capillary hydrostatic pressure, interstitial fluid pressure (negative in most tissues), and interstitial oncotic pressure (exerted by proteins in the interstitial space) act to draw water from the intravascular space into the interstitium. The only force that acts to maintain intravascular volume is plasma oncotic pressure. This last force is produced by the presence in plasma of high-molecular-weight proteins that cannot cross the capillary wall.

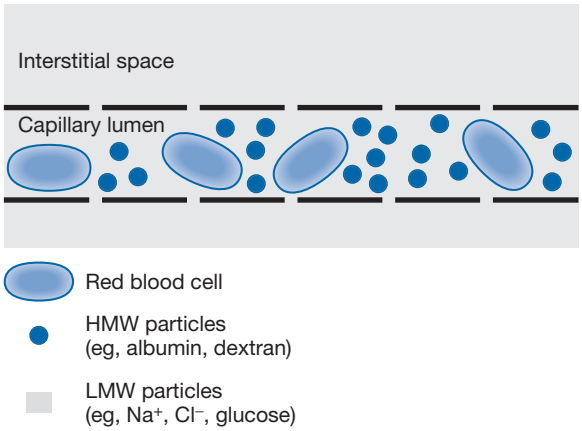


Fig. 9.4 In peripheral capillaries, free movement of most low-molecular-weight (LMW) particles (including sodium and chloride ions, glucose, and mannitol) occurs between the capillary lumen and the interstitial space. Intravenous administration of LMW solutes cannot affect the movement of water between the interstitium and vasculature because no osmotic gradient can be established. In contrast, a rise in plasma oncotic pressure from the administration of concentrated albumin, hetastarch, or dextran may draw water from the interstitium into the vessels because these high-molecular-weight (HMW) particles are precluded from passing through the capillary wall. Hypertonic saline solutions create an osmotic gradient across cell membranes and thus transfer fluid from the intracellular to the extracellular compartment, including the intravascular space.

Under most circumstances, the sum of the forces results in a Q_f value that is slightly greater than zero, indicating a net outward flux of fluid from the vessels into the tissue extracellular space. This fluid is cleared from the tissue by the lymphatic system, thereby preventing the development of edema (Fig. 9.4).

The clinical effects of altering one or more of the variables in the Starling equation may frequently be observed in the operating room. Many patients who have been resuscitated from hemorrhagic hypovolemia with large volumes of crystalloid solutions demonstrate pitting edema, caused by a dilution of plasma proteins. This results in a decrease in intravascular oncotic pressure (π_c). In the presence of relatively unchanged capillary hydrostatic pressure, an increased movement of fluid from the vasculature into the tissues occurs. When this fluid flux exceeds the drainage capacity of the lymphatics, clinically apparent edema results.

Another example of the Starling equation in action is the facial edema that is often seen in patients who have been placed in the Trendelenburg position for prolonged periods. In this case, the edema is due not to a decrease in plasma oncotic pressure but rather to an increase in the capillary hydrostatic pressure (P_c), favoring an increased transudation of fluid into the tissue.

Fluid Movement between Capillaries and the Brain

The Starling equation describes the factors that govern fluid movement between the intravascular and peripheral extracellular spaces (eg, the interstitium of lung, bowel, and muscle). However, the brain and spinal cord are unlike most other tissues in the body in that they are isolated from the intravascular compartment by the blood–brain barrier. Morphologically, this barrier is now thought to be composed of endothelial cells that form tight junctions in the capillaries supplying the brain and spinal cord. Endothelial cells are surrounded by the layer of pericytes delineated by the foot processes of glial cells. In the normal brain, these tight junctions severely limit the diffusion of molecules between the intravascular space and the brain. By measuring the movement of water out of the central nervous system after abrupt changes in plasma osmolality, Fenstermacher and Johnson[6] calculated the effective pore radius for the blood–brain barrier to be only 7 to 9 Å. This small pore size of the blood–brain barrier prevents movement not only of plasma proteins but also of sodium, chloride, and potassium ions between the intravascular compartment and the brain's extracellular space (Fig. 9.5). In effect, the blood–brain barrier acts like the semipermeable membrane of an osmometer, and movement of water across this membrane is determined by the relative concentrations of impermeable solutes.

This situation is markedly different in peripheral tissues, where endothelial cells do not form tight junctions and pore sizes in the capillaries may be as much as several orders of magnitude greater. Although these pores are small enough to preclude the movement of most protein components of plasma, electrolytes pass freely from the capillary lumen into the extracellular space. Thus, in peripheral tissues, movement of water between the intravascular space and the extravascular space is governed by the plasma concentration of large macromolecules (oncotic gradient) as defined by the Starling equation. In

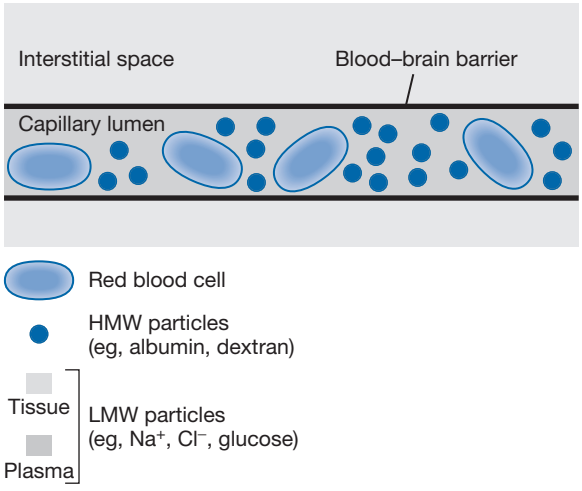


Fig. 9.5 In cerebral capillaries, the blood–brain barrier (estimated pore size of 7–9 Å) prevents movement of even very small particles between the capillary lumen and the brain's interstitial space. Increasing plasma osmolality by intravenous infusion of mannitol or hypertonic saline can, therefore, establish an osmotic gradient between the brain and intravascular space that acts to move water from the brain into capillaries. HMW, high-molecular-weight; LMW, low-molecular-weight.

contrast, fluid moves in and out of the central nervous system according to the *osmolar* gradient (determined by relative concentrations of all osmotically active particles, including most electrolytes) between the plasma and the extracellular fluid. This difference in the determinants of fluid flux explains why the administration of large volumes of iso-osmolar crystalloid results in peripheral edema caused by dilutional reduction of plasma protein content, but does not increase brain water content or intracranial pressure (ICP).

There can be little doubt that osmolarity is the primary determinant of water movement across the intact blood–brain barrier.[7] The administration of excess free water (either iatrogenically or as a result of psychogenic polydipsia) can result in an increased ICP and an edematous brain.[8] Conversely, the intravenous administration of markedly hyperosmolar crystalloids (eg, mannitol) to increase plasma osmolarity results in a decrease in brain water content and ICP. Hyperosmolar solutions are used as standard therapeutic agents to treat intracranial hypertension.

In the presence of an intact blood–brain barrier, plasma osmolarity is the key determinant of water movement between the central nervous system and the intravascular space. However, what occurs when the brain is injured with disruption of the barrier? If the blood–brain barrier is partially disrupted, will blood vessels in the brain start to act more like peripheral capillaries? Experimental evidence is not conclusive, but if the injury is of sufficient severity to allow extravasation of plasma proteins into the interstitial space (ie, capillaries have become "leaky"), plasma oncotic pressure does not affect water movement, because no oncotic gradient between the plasma and the brain interstitial space can be produced (ie, the proteins leak out of the capillaries and into the brain tissue) (Fig. 9.6). In an animal study using a cryogenic lesion as a model of acute brain injury, a 50% decrease in plasma oncotic pressure had no effect on regional water content or ICP.[9] These results were confirmed in a subsequent study that demonstrated that reducing the plasma oncotic pressure from approximately 21 mmHg to 10 mmHg for 8 hours had no effect on ICP or brain water content in animals with a cryogenic brain injury despite the fact that the anticipated increase in water content was documented in peripheral tissues (muscle and jejunum).[10]

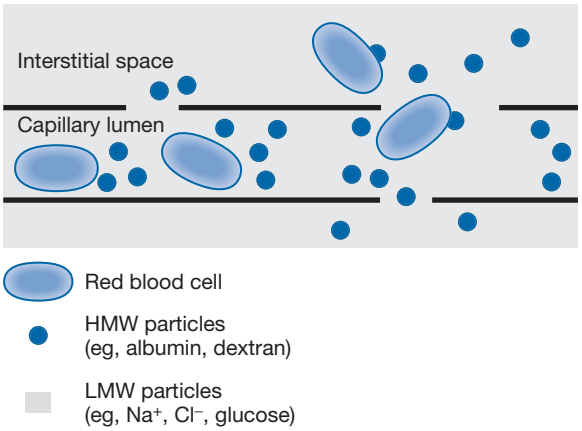


Fig. 9.6 After a variety of brain injuries (eg, ischemia, contusion), breakdown of the blood–brain barrier may occur, allowing both low-molecular-weight (LMW) and high-molecular-weight (HMW) particles to escape from the capillary lumen (ie, the capillaries become "leaky"). In severe cases, extravasation of red blood cells into the interstitium may even occur. In this situation, neither hyperosmolar nor hyperoncotic solutions will help reduce edema formation in the area of the injury. Hyperosmolar solutions may still be beneficial in areas remote from the injury, where the blood–brain barrier remains intact.

Despite a lack of convincing experimental evidence that iso-osmolar crystalloids are detrimental, the neurosurgical literature is filled with admonitions to restrict the use of crystalloids in patients at risk for intracranial hypertension.[11] In the case of the intact blood–brain barrier, neither theoretical nor experimental evidence suggests that colloids are more beneficial than crystalloids for either brain water content or ICP. The crystalloid-colloid question has been addressed in animal models of cerebral injury, with varying and sometimes conflicting results. Warner and Boehland[12] studied the effects of hemodilution with either saline or 6% hetastarch in rats subjected to 10 minutes of severe forebrain ischemia. Despite an approximately 50% reduction in plasma oncotic pressure in the saline group (from 17.2 ± 0.8 to 9 ± 0.6 mmHg), no beneficial effect in terms of decreased edema formation was demonstrated in the hetastarch group. Similarly, in a study that used a cryogenic lesion as a model of cerebral injury, Zornow and colleagues[9] found no differences in regional water content or ICP between animals that received saline, those that received 6% hetastarch, and those that received albumin.

In contrast, Korosue and associates[13] found a smaller infarct volume and better neurologic status in dogs undergoing hemodilution with a colloid (LMW dextran) than in animals undergoing hemodilution with lactated Ringer's solution after ligation of the middle cerebral artery. The researchers speculated (but did not provide evidence) that this beneficial effect was due to decreased edema formation in the ischemic zone. They further speculated that, in this model of moderate ischemic injury, the blood–brain barrier may become selectively permeable to ions with preservation of its impermeability to HMW compounds (eg, dextran and proteins). If this is the case, then the brain tissue in the ischemic region may act very much like tissues in the periphery (ie, decreases in plasma oncotic pressure result in increased water movement into the tissue). A study by Drummond and coworkers[14] suggests that a similar situation may occur after traumatic brain injury (TBI). They subjected anesthetized rats to a 2.7 atm fluid percussion injury and then hemodilution with normal saline or a colloid. Brain water content was increased in the animals that received the normal saline. Thus, although the osmolality of the infused solution is the primary determinant of water movement between the vasculature and brain tissue in the noninjured state, apparently in cases of ischemic or traumatic injury, colloids may or may not be beneficial, depending on the severity and extent of the injury as well as the time at which brain water content is measured.

Beneficial effects of hypertonic solutions in cases of localized brain injury with disruption of the blood–brain barrier appear to be derived primarily from the ability of hypertonic solutions to cause a fluid flux out of brain tissue where the blood–brain barrier remains intact. In effect, the normal brain is dehydrated to compensate for the edema that forms in the vicinity of the lesion.[15] The most likely mechanism for this beneficial effect is a decrease in brain water content in regions remote from the lesion.

SOLUTIONS FOR INTRAVENOUS USE

The anesthesiologist may choose from among a variety of fluids suitable for intravenous administration. These fluids may be categorized conveniently on the basis of osmolality, oncotic pressure, and dextrose content. The term *crystalloid* is commonly applied to solutions that do not contain HMW compounds and thus have an oncotic pressure of zero. Crystalloids

may be hyperosmolar, hypo-osmolar, or iso-osmolar and may or may not contain dextrose. Some commonly used crystalloid solutions are listed in Table 9.1. Crystalloids may be made hyperosmolar by the inclusion of electrolytes (eg, Na^+ and Cl^-, as in hypertonic saline) or LMW solutes, such as mannitol (182 MW), glycerol (92 MW), glucose (180 MW), or urea (60 MW). Urea and glycerol are now rarely used because over time they penetrate the blood–brain barrier and may cause worsening of intracranial hypertension hours after their initial beneficial effect.[16] Intravenous administration of mannitol has also been associated with the leakage into white matter near gliomas possibly due to the changes in blood–brain barrier permeability near tumors. Mannitol leak may exacerbate peritumoral edema and lead to ICP rebound.[17]

The term *colloid* denotes solutions containing insoluble macromolecules, which do not pass through semipermeable membranes or capillary walls under normal conditions. Some colloid solutions have oncotic pressure similar to that of plasma (see Table 9.1). The examples of colloids are 6% hetastarch (Hespan), 5% and 25% albumin, the dextrans (40 and 70), and plasma. Dextran and hetastarch are dissolved in normal saline, so the osmolarity of the solution is approximately 290 to 310 mOsm/L with a sodium and chloride ion content of about 145 mEq/L.

Hyperosmolar Solutions

Hyperosmotic fluids have been successfully used as a resuscitation fluid in hemorrhagic hypovolemia as well as an osmotherapeutic agent reducing brain edema or elevated ICP. The reputed advantages of such solutions include a more rapid resuscitation with smaller infused volumes, improved cardiac output, decreased peripheral resistance, and lower ICP.[18] The benefits of using a variety of hypertonic solutions in lowering ICP and improving cerebral blood flow have been demonstrated in a number of animal models.[15,19–22] Clearly, these solutions exert at least part of their beneficial effects by osmotically shifting water from the interstitial and intracellular spaces of the central nervous system to the intravascular space. Additional benefit may be derived from a reported reduction in cerebrospinal fluid production.[23]

Although an acute beneficial effect has been demonstrated, the longer-term (24–48 hours) effect of such hyperosmotic fluid therapy remains unknown. One primary area of concern is the hypernatremia that results from many of these solutions. Although survival has been reported with serum sodium levels as high as 202 mEq/L, acute increases to values that exceed 170 mEq/L are likely to result in a depressed level of consciousness or seizures.[24] Even with the administration of relatively small volumes (4.5 L) of moderately hypertonic saline (Na, 250 mEq/L; osmolarity, 514 mOsm/L), Shackford and coworkers[25,26] reported that serum sodium levels peaked at over 155 mEq/L in the postoperative period.

Several studies have reported a beneficial effect of hypertonic saline solutions in patients with intracranial hypertension. In one report, the administration of small volumes of markedly hypertonic saline in two patients resulted in a striking and sustained diminution in ICP. Both patients had suffered closed-head injuries with ICPs in the range of 30 to 50 mmHg. After conventional therapy with repeated doses of mannitol and hyperventilation had failed, 100 to 250 mmol of hypertonic saline was administered, resulting in prompt control of the intracranial hypertension.[27] In a second study involving eight patients with a total of 20 episodes of intracranial hypertension that was resistant to standard forms of management (including hyperventilation and mannitol), 30 mL of 23.4% saline brought prompt and sustained decreases in ICP.[28] In 80% of the cases, ICP dropped by more than 50% of the pretreatment value within 21 ± 10 minutes. Associated with this decrease in ICP was a significant rise in cerebral perfusion pressure from 64 ± 19 to 85 ± 18 mmHg 1 hour after hypertonic saline administration. In a controlled animal study designed to directly compare the cerebral effects of mannitol (20%) and hypertonic saline (3.2%), rabbits were randomly allocated to receive an equiosmolar load of one of these two solutions (10 mL/kg). Plasma osmolality increased to a similar extent in both groups, and no differences in ICP reduction or regional water content were identified (Fig. 9.7).[29]

Hypertonic saline can be administered as a bolus[30–32] or continuous infusion and the dose can be titrated according to serum sodium levels and/or serum osmolality.[33,34] Frequent serum sodium checks every 4–6 hours are recommended

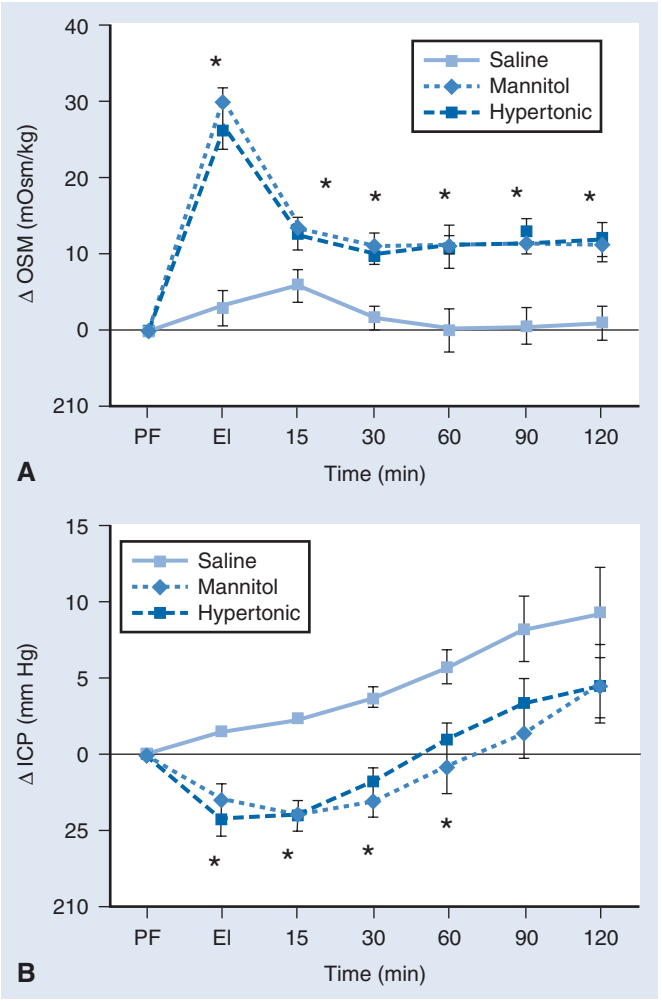


Fig. 9.7 **A,** Changes in plasma osmolality after intravenous administration of 0.9% saline or 11 mOsm/kg of either 20% mannitol or 3.2% (hypertonic) saline (Hypertonic). Note the prompt and equal increase (approximately 29 mOsm/kg) in plasma osmolality after administration of either of these two osmotic agents. No differences in plasma osmolality were noted between the hypertonic saline and mannitol groups at any time during the study. **B,** Effect of hypertonic saline and mannitol on intracranial pressure. Both of these osmotic agents produced transient decreases in intracranial pressure when compared with an equal volume of 0.9% saline. Δ ICP, change in ICP from PF value; Δ OSM, change in OSM from PF value; EI, end of infusion of 0.9% saline, mannitol, or hypertonic saline; PF, 45 minutes after induction of a cryogenic brain lesion; *, $p < 0.05$ mannitol and hypertonic saline groups vs. 0.9% saline group.) *(From Scheller MS, Zornow MH, Oh YS: A comparison of the cerebral and hemodynamic effects of mannitol and hypertonic saline in a rabbit model of acute cryogenic brain injury. J Neurosurg Anesth 1991;3:291-296.)*

when hypertonic saline is used as a continuous infusion or with repeated boluses. Another concern is the route of administration. Hypertonic saline infused via peripheral vein may lead to phlebitis. Alternatively central venous catheter placement may be required.

The possible benefit of adding furosemide to treatment with hypertonic solutions is controversial. In rats subjected to a closed-head injury, Mayzler and colleagues[35] demonstrated an additional decrease in brain water content when furosemide was added to treatment with 3% hypertonic saline. However, this additional benefit was not seen when furosemide was added to treatment with mannitol.[36] Although the protocols for these two studies differed in both the timing and the type of osmotic solutions administered, the findings suggest that the benefit of furosemide for a given patient is likely to be small, if it exists at all.

In a prospective controlled trial in children with head trauma, patients received a bolus (approximately 10 mL/kg) of either 0.9% or 3% saline. Baseline ICP values were similar in both groups (20 mmHg). No significant change in ICP was demonstrated in patients who received 0.9% saline. However, after a bolus of 3% saline, ICP decreased significantly and averaged 15.8 mmHg for the next 2 hours. In patients who received 3% saline, serum sodium concentrations increased from a mean of 147 mEq/L to 151 mEq/L.[37]

Most recent clinical studies suggest that, compared to mannitol, hypertonic saline may achieve similar if not better brain relaxation conditions in patients undergoing craniotomy. Rozet and associates[38] compared the effect of 5 mL/kg of 20% mannitol (1 g/kg) with that of an equiosmolar volume of 5 mL/kg of 3% hypertonic saline on brain relaxation in patients undergoing elective or urgent craniotomy for various neurosurgical procedures including tumor resection and cerebral aneurysm clipping. Both mannitol and hypertonic saline resulted in a similar increase in serum and CSF osmolalities and achieved a comparable degree of brain relaxation as assessed by the surgeon. Compared with 3% hypertonic saline, mannitol caused more diuresis ($P < .03$) with less pronounced positive fluid balance at 3 hours (hypertonic saline group, 3230 ± 1543 mL; mannitol group, 1638 ± 1620 mL; $P < .004$); however, fluid balance values were not statistically different at 6 hours.

In a prospective randomized study, Dostal and associates compared the effects of intravenous mannitol and hypertonic saline on brain relaxation and postoperative complications in patients undergoing elective intracranial tumor surgery.[39] Patients who received 3.75 mL/kg of 3.2% hypertonic saline had better brain relaxation conditions than those receiving 3.75 mL/kg equiosmolar 20% mannitol. Mannitol resulted in more pronounced diuresis, lower central venous pressures and natremia levels at the end of surgery. The authors did not find any significant differences in postoperative complications or lengths of hospital stay between the groups.

The studies by Rozet and Dostal suggest that hypertonic saline may be considered as an alternative to mannitol for brain relaxation in patients undergoing craniotomy, especially those who are hypovolemic or hemodynamically unstable.[38] It must be noted, however, that both of these studies may have been insufficiently powered to allow direct comparison of adverse events, which are infrequent.[40] Extensive review of Mortazavi and associates suggested that hypertonic saline offers better control of ICP than mannitol.[41] The sodium load and consequent hypernatremia may be a concern in patients with neurologic injury who are at risk for seizures and who may have altered mental status due to an underlying injury.

In summary, hypertonic saline can exert a beneficial effect on intracranial hypertension while providing rapid volume resuscitation. It appears to be equivalent to mannitol. Whether it provides significant advantages over mannitol awaits further investigation.

Dextrose Solutions and Hyperglycemia

It is now fairly well established that hyperglycemia before or during ischemia worsens neurologic outcome. Several independent investigators using a variety of animal models have reached this conclusion. Worsened neurologic outcome has been repeatedly demonstrated after global ischemia of either the brain or the spinal cord. Elevations in plasma glucose do not have to be marked to produce a significant worsening of neurologic outcome. In an early study using a primate model, Lanier and associates[42] showed that dextrose infusions (50 mL of 5% dextrose in 0.45% saline) markedly worsened the neurologic score after 17 minutes of global cerebral ischemia. Although plasma glucose levels were slightly higher in animals that received the dextrose infusion (181 ± 19 vs. 140 ± 6 mg/dL), this elevation did not even reach statistical significance. Drummond and Moore[43] demonstrated a similar detrimental effect of hyperglycemia on spinal cord function after transient ischemia.

Although the apparent consensus is that hyperglycemia during transient global ischemia is detrimental, both beneficial and adverse effects of glucose have been shown in models of focal ischemia. Ginsberg and colleagues[44] have demonstrated a decrease in infarct volume in rats made hyperglycemic before the ischemic event. Even greater beneficial effects (approximately 50% reduction in ischemic area) have been reported in a short-term study of hyperglycemia in cats after ligation of the middle cerebral artery.[45] The significance of these findings is uncertain because in a long-term cat study (survival time of 14 days), the hyperglycemic animals sustained infarcts twice the size of normoglycemic controls.[46]

The mechanism by which hyperglycemia worsens neurologic outcome is not clear. One hypothesis is that the glucose loading that occurs in central nervous system tissue during periods of hyperglycemia provides additional substrate for the production of lactic acid during the ischemic period. This increase in intracellular lactate is postulated to have a neurotoxic effect resulting in neuronal death. Although there is little doubt that lactate production increases in brains of hyperglycemic animals, the neurotoxic effect is less firmly established. Indeed, in neuronal cell cultures, lactic acidosis has been shown to be neuroprotective.[47,48] Another mechanism by which hyperglycemia may exacerbate neuronal injury is by enhancing glutamate release in the neocortex, but probably not in the hippocampus.[49,50]

In clinical studies, hyperglycemia has been associated with worsened neurologic outcome and/or mortality after TBI,[51] acute ischemic stroke (AIS),[52–54] subarachnoid hemorrhage (SAH)[55] and intracerebral hemorrhage (ICH).[56,57]

Whether hyperglycemia directly causes worsened neurologic outcome or rather reflects the severity of tissue injury and its parallel stress response has been the subject of debate.[58,59] More recently, Schlenk showed that blood glucose levels >140 mg/dL independently predicted unfavorable outcome and mortality at 12 months in patients with SAH besides age, Fisher and WFNS (World Federation of Neurosurgical Societies) grades.[57] After adding a logistic regression model, authors stated that hyperglycemia >140 mg/dL was independently predicting delayed ischemic neurological deficit. Cerebral glucose measured by microdialysis increased only

at blood glucose levels higher than 140 mg/dL. The metabolic derangements, measured as lactate concentration and lactate/pyruvate ratio, were slightly elevated compared to patients with lower glucose levels but the difference was not statistically significant.

A post hoc analysis of data from the IHAST study showed that patients with glucose levels > 129 mg/dL at the time of aneurysm clipping had more cognitive impairment defined by neuropsychological function composite scoring at 3 months compared to normoglycemic patients. Patients with glucose > 152 mg/dL had significantly greater neurologic impairment defined by NIHSS (National Institute of Health Stroke Scale).[60]

A recent retrospective observational study of Kurtz and associates evaluated the role of serum glucose variability in predicting cerebral metabolic distress and mortality.[61] Plasma glucose variability was expressed daily as standard deviation (SD) of all serum glucose measurements per total monitoring period. Increased serum glucose variability SD of greater than 1.4 mmol/L (25.2 mg/dL) per day was associated with an increased risk of developing metabolic distress (lactate/pyruvate ration > 40) independently of GCS and brain glucose. Daily glucose SD greater than 1.4 mmol/L was also independently associated with hospital mortality. Davis and associates studied the effect of preoperative hyperglycemia on the risk of complications and length of ICU and hospital stay.[62] Authors studied 918 craniotomy and spine-related neurosurgical cases and concluded that even mild preoperative hyperglycemia (>120 mg/dL) was associated with an increased risk of a wide range of postoperative complications and prolonged length of stay.

The previously discussed studies show that hyperglycemia and glucose variability are associated with worse neurologic outcome, mortality, complication rate and increased hospital/ICU stay depending on the patient population studied. So, does treating hyperglycemia indeed make a difference in morbidity and mortality? A frequently cited study by Van den Berghe,[63] demonstrating reduced morbidity and mortality in postoperative patients managed with "tight" (80–110 mg/dL) versus conventional (180–200 mg/dL) glucose control, stimulated interest in a more aggressive approach to treating hyperglycemia in the perioperative period. However, several subsequent studies examining intensive glucose control in broader ICU patient population raised concerns about the efficacy and safety of such an approach.[64–67] In the NICE-SUGAR trial,[67] 6104 ICU patients were randomized to undergo either intensive glucose control (target blood glucose levels 81–108 mg/dL) or conventional glucose control (target blood glucose levels ≤180 mg/dL). Mortality at 90 days was higher in the intensive-control group (27.5%) compared to the conventional-control group (24.9), and the treatment effect did not differ between medical and surgical patients. The incidence of severe hypoglycemia (glucose ≤40 mg/dL) was also higher in patients assigned to intensive glucose control. New single or multiple organ failure and hospital or ICU lengths of stay were no different between the groups. It is important to note that the median glucose level for intensive glucose control was 107 mg/dL vs. 142 mg/dL in conventional control, and the mean time-weighted blood glucose level 115 ± 18 vs. 144 ± 23 mg/dL, respectively.[67]

Tight glucose control may carry a significant risk of hypoglycemic events and reduced survival, at least in the critically ill; and the question becomes how to minimize the very real risks associated with the treatment of hyperglycemia while maximizing the potential benefits. In many cases, the answer to this question is institution-specific and depends on the staffing and resources available to provide safe and effective care. Krinsely[68] compared outcomes in 800 patients with intensive glucose management (target plasma glucose <140 mg/dL) who were consecutively admitted to a medical-surgical ICU to outcomes in a historical control group of 800 ICU patients without standardized glycemic control. The incidence of hypoglycemia was similar in the two groups of patients. However, hospital mortality decreased 29.3% in the protocol group. Although the study was not adequately powered to allow a robust subgroup analysis, the decrease in mortality was especially marked in the neurologic patients.[68] The weaknesses of this study are all those associated with nonrandomized clinical trials using historical controls.

Ooi and associates conducted a meta-analysis of studies reporting outcomes in neurological and neurosurgical patients and the role of glucose levels and insulin protocols.[69] The authors compared intensive vs. conventional insulin therapy. Intensive insulin therapy involved intravenous administration of insulin via infusion pump for glucose target 80–110 mg/dL or looser; conventional therapy referred to subcutaneous insulin per sliding scale targeting glucose 180–220 mg/dL. The review showed that neurological and neurosurgical patients who received intensive insulin therapy had better neurological outcome and lower risk of infections than conventional therapy; mortality was not different.[69] In contrast, Cinotti in his recent subgroup analysis of a randomized controlled CGAOREA (Contrôle Glycémique Assisté par Ordinateur) study did not find that tight glycemic control improved 28-day mortality or neurologic recovery of patients with severe brain injury.[70] It is important to note that the study evaluated neurological outcomes of patients with a variety of pathological states and mechanisms including TBI, SAH, ICH, cardiac arrest, brain tumor, brain abscess, and central nervous system infection.[70]

Multiple studies have addressed glycemic control in aneurysmal SAH patients. Hyperglycemia on admission as well as during hospitalization has been associated with poor outcome.[57] Some studies suggest that patients with SAH may benefit from stricter glycemic control than concluded by the NICE-SUGAR trial (<180 mg/dL). Study of Latorre, which included 332 SAH patients from a prospective intensive care unit database, demonstrated that patients with good glycemic control managed by an aggressive hyperglycemia protocol targeting glucose levels 80–140 mg/dL resulted in reduction of poor neurological outcome at 3 and 6 months.[71] Furthermore, a randomized prospective pilot trial on the effect of intensive insulin therapy in patients after intracranial aneurysm clipping with acute SAH showed reduced infection rates (27% vs. 42%, resp.) when glucose was maintained in a range of 80 to 120 mg/dL than a range of 80–220 mg/dL.[72] However, the study was not intended to be sufficiently powered to address questions about the incidence of vasospasm, overall mortality, and neurologic outcome.

Treatment of hyperglycemia did not lead to improved outcome in a large multicenter randomized control trial of patients with acute stroke. In the GIST-UK trial, stroke patients who presented within 24 hours of symptoms onset and with initial plasma glucose 6–17 mmol/L (108–306 mg/dL) were randomized to either receive continuous infusion of variable dose insulin and potassium (GKI) to aim for capillary glucose level 4–7 mmol/L (72–126 mg/dL) or to receive normal saline infusion with no glycemic control for 24 hours. Excluded patient categories comprised those with SAH and insulin treated diabetes mellitus. The level of hyperglycemia on admission was moderate in the majority of patients, with mean level of 8.43 mmol/L (159 mg/mL). The study was stopped due to slow

enrollment after entering 933 patients instead of the planned 2355 and hence was underpowered. The authors did not find difference in 90 day mortality or neurologic outcome between the study groups; however, a post hoc safety analysis showed increased mortality in those patients treated with GKI who had the greatest reductions in glucose levels (decrease of >2 mmol/L).[73]

In summary, hyperglycemia should be avoided in patients who are at risk for an ischemic event. Dextrose solutions should not be infused in the patient undergoing a neurosurgical procedure unless they are needed for the treatment or prevention of hypoglycemia. A more complex question is how to proceed when a patient enters the operating room with hyperglycemia. Although normalizing this patient's plasma glucose level with insulin infusion is tempting, the effect of this intervention in reducing the risk of adverse outcome in a patient with neurologic injury is not clear.

The preceding evidence suggests that intensive glucose control (target <110 mg/dL) carries a definite risk of hypoglycemia and may be harmful in the critically ill patient. The NICE-SUGAR trial set a reasonable glucose goal <180 mg/dL in the general ICU patient population, with the caveat that the median glucose level in patients managed with conventional protocol was <142 mg/dL.[72] Bilotta's review, focusing on glucose management in neurosurgical patients, leans toward the recommendation of moderate glucose management with the goal of 140–180 mg/dL.[74] Evidence is accumulating, however, that tighter glucose control may improve neurologic outcome and lower risk of infections, especially in patients with SAH.[69,71] More prospective studies are needed to address optimal glucose management targets for patients with a specific type of neurologic injury or neurosurgical procedures.

FLUID ADMINISTRATION DURING CRANIOTOMY

Preoperative Deficits

The preoperative intravascular volume deficit of neurosurgical patients may be estimated in a manner similar to that used for patients undergoing other types of surgical procedures. For the nonfebrile adult patient, daily water loss averages approximately 100 mL/h (Table 9.2) and occurs by evaporation from the skin and airways (insensible losses) and in urine, sweat, and feces.[75]

In addition to these obligatory losses, fluid loss caused by nasogastric suction, diarrhea, emesis, and phlebotomy must be considered. Patients who have undergone angiographic studies with intravenous contrast agents have excessive urinary losses from the diuresis produced by these hyperosmotic agents. Respiratory and insensible losses are higher in patients who are febrile from any cause in the preoperative period. To determine the net deficit, one must add whatever fluids have been administered to the patient. These usually consist of intravenous intake or intake by mouth. Consideration of these values, in combination with physical examination, gives an estimate of the net volume deficit for a given patient.

Table 9.2 Daily Water Loss for an Adult

Type/Location	Amount (mL/day)
Insensible losses:	
Skin	350
Lungs	350
Urine	1400
Sweat	100
Feces	200
TOTAL	2400

Intraoperative Fluids

Crystalloids

Intraoperative maintenance fluid administration usually consists of normal saline and lactated Ringer's solution. As stated previously, these fluids are crystalloids and are approximately equiosmolar to normal plasma (see Table 9.1). Iso-osmolar crystalloids are given at a rate sufficient to replace the patient's urine output and insensible losses milliliter for milliliter. As a general rule, alternating between normal saline and lactated Ringer's solutions is advised to avoid hyperchloremic metabolic acidosis with larger volumes of the former and a relative hypo-osmolar state with the latter, especially in patients who have received osmotherapy. Hypo-osmolar solutions and dextrose-containing solutions should be avoided. Blood loss is replaced at about a 3:1 ratio (crystalloid/blood) down to a hematocrit value of approximately 25–30%, depending on the rate of hemorrhage and the patient's physical status. During procedures in which marked brain swelling is present, requests are often made to keep the patient "dry" in the unsubstantiated belief that fluid restriction lessens brain edema formation. Complete water restriction in dogs for 72 hours, however, results in an 8% loss of body weight but only a 1% decrease in brain water content.[76] Such severe water restriction imposes severe physiologic stress, and the benefit of the minimal decrease in brain water content is unwarranted. Under no circumstances should iso-osmolar fluids be withheld to the point that the patient manifests hemodynamic instability caused by hypovolemia. Furthermore, patients with SAH are more likely to suffer from cerebral infarction if their intravascular volume and sodium are not adequately replaced, ostensibly for the mistaken belief that hyponatremia attendant with SAH is due to SIADH only, while discounting the contributory effect of cerebral salt wasting.[77,78]

Ideally, sufficient intravenous fluids should be administered to maintain an adequate cardiac output but should avoid excessive fluid resuscitation. A great deal of evidence has accumulated in the critical care literature showing that the "dynamic" hemodynamic parameters (eg, changes in stroke volume, arterial pulse pressure [Fig. 9.8], and delta down [Fig. 9.9] during positive-pressure ventilation) provide a more accurate picture of volume status and responsiveness to fluid expansion than static hemodynamic parameters (eg, right atrial pressure or pulmonary artery occlusion pressure, right-ventricular end-diastolic volume, and left ventricular end-diastolic area).[79–82]

Furthermore, evidence suggests using thresholds of 13% for arterial pulse pressure variation (or delta pulse pressure) and 5 mmHg for delta down during positive-pressure ventilation for the administration of additional volume.[80–83]

Whether perioperative goal-directed hemodynamic optimization, which fluid therapy is part of, will ultimately improve outcome awaits further investigation. Multiple studies, summarized in a recent review by Navarro, have shown fewer postoperative complications and shorter hospital length of stay in a variety of surgical patient populations.[84] However, a recent large prospective randomized POEMAS trial (PeriOperative

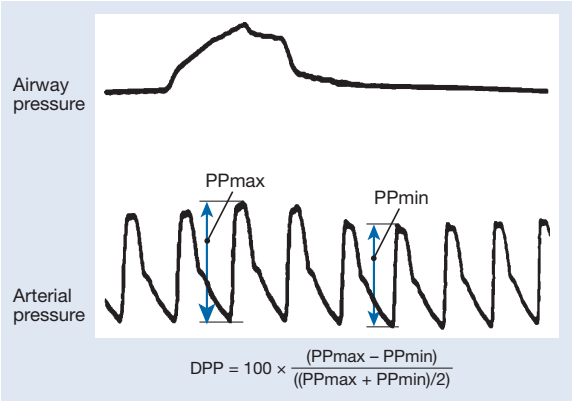


Fig. 9.8 Illustration of delta pulse pressure measurement from arterial blood pressure tracing during positive-pressure ventilation. *Delta pulse pressure* (DPP) is the difference between the maximal (PPmax) and minimal (PPmin) pulse pressures during one breath cycle, divided by the mean. *(From Deflandre E, Bonhomme V, Hans P: Delta down compared with delta pulse pressure as an indicator of volaemia during intracranial surgery. Br J Anaesth 2008;100:245-250. By permission of Oxford University Press/British Journal of Anaesthesia.)*

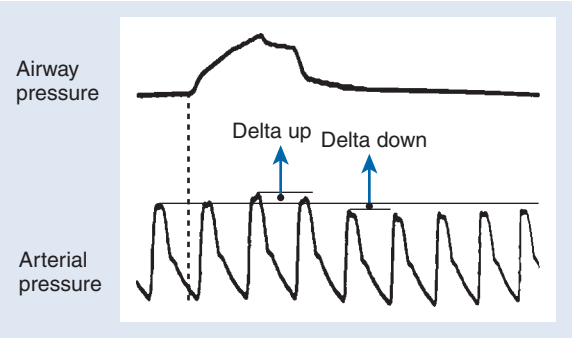


Fig. 9.9 Illustration of delta down measurement from arterial blood pressure tracing during positive-pressure ventilation. *Delta down* is the difference between baseline apneic systolic blood pressure and minimum systolic blood pressure. Delta up, the difference between baseline apneic systolic blood pressure and maximal systolic blood pressure during one mechanical respiratory cycle. *(Illustration from Deflandre E, Bonhomme V, Hans P: Delta down compared with delta pulse pressure as an indicator of volaemia during intracranial surgery. Br J Anaesth 2008;100:245-250. By permission of Oxford University Press/British Journal of Anaesthesia.)*

goal-directed thErapy in Major Abdominal Surgery) did not find a difference in overall complications rate or length of stay between patients treated with hemodynamic protocol guided by a noninvasive cardiac output monitor compared to the institutional standard practice.[85]

Mannitol

Mannitol, a six-carbon sugar alcohol derived from flowering ash plant with an MW of 182, is the most commonly administered hyperosmolar solution. It is available in 20% and 25% solutions with osmolalities of 1098 and 1372, respectively. Mannitol is often administered when significant brain swelling occurs or when it becomes necessary to decrease brain volume to facilitate exposure and thereby reduce brain retractor ischemia. It should be given only after other potential causes of increased brain volume have been considered (eg, hypercapnia, vasodilators, obstruction to venous outflow). Mannitol is commonly administered as a rapid intravenous infusion in doses of 0.25 to 1 g/kg. Manninen and coworkers[86] examined the effects of 1- and 2-g/kg doses on serum electrolytes and plasma osmolality in neurosurgical patients. In addition to the anticipated transient increase in plasma osmolality, these researchers observed an associated decrease in serum sodium and bicarbonate concentrations, probably due to osmotically induced expansion of the extracellular volume. Patients who received the high dose of mannitol (ie, 2 g/kg) also manifested a marked increase in serum potassium concentration (maximum mean increase of 1.5 mmol/L). Possible explanations include solvent drag (ie, as water leaves the intracellular compartment, potassium is carried with it) and hemolysis of red cells near the tip of the infusion catheter caused by the locally high concentration of mannitol. Although transient, the hyperkalemia is reportedly associated with characteristic electrocardiographic changes.[87] The use of mannitol is contraindicated in patients with end-stage renal disease or severe congestive heart failure patients. Mannitol may have a biphasic effect on ICP. Concomitant with the infusion, ICP may transiently increase, presumably because of vasodilation of cerebral vessels in response to the sudden increase in plasma osmolality.[16] A subsequent reduction in ICP is achieved by the movement of water from the brain's interstitial and intracellular spaces into the vasculature.

The effect of a single bolus of 20% mannitol on hemodynamic parameters in neurosurgical patients undergoing elective supratentorial craniotomy was recently evaluated by Chatterjee with the use of transesophageal echocardiography.[88] The authors observed that 1 g/kg of 20% mannitol infused over 15 minutes caused a significant rise in left ventricular preload (at 5 minutes) and cardiac output (at 5 and 15 minutes), with a decline in systemic vascular resistance (at 5 and 15 minutes) but without concomitant changes in mean arterial pressure and heart rate.

Results of studies comparing the effects of 20% mannitol to equiosmolar amount of hypertonic saline on surgical brain relaxation suggest that hypertonic saline may provide equivalent, if not superior, brain relaxation to mannitol.[38,39] See above, the section on hyperosmolar solutions in "Solutions for Intravenous Use" for more detail (p. 156).

Colloids

Hetastarch

The non-blood-derived colloids available for infusion are hetastarch, dextran 40, and dextran 70. Hetastarch (Hespan) is a 6% solution of hydroxyethyl starch (HES) in normal (0.9%) saline. HES is an enzymatically hydrolyzed amylopectin, which is chemically modified by hydroxyethylation of glucose subunits at carbon positions C2, C3 or C6. The metabolism and plasma clearance of HES is determined by the molecular weight (MW), degree of molar hydroxyethyl substitution (number of moles of hydroxyethyl groups present per mole of glucose subunits) and the pattern of this substitution (C2/C6 ratio). HES with lower MW, molar substitution, and C2/C6 ratio are degraded faster, resulting in faster renal elimination, shorter volume effect, and fewer adverse effects on coagulation.[89]

Recently published data from several randomized trials have raised serious concerns about the adverse effects of HES products on renal function[90–92] and ICU patient survival.[93,94] An extensive review of randomized controlled trials by Zarychanski concluded that hydroxyethyl starch significantly increased the risk of mortality and acute renal injury in the critically ill.[95] In contrast, a recent large randomized clinical trial, the CRISTAL, evaluated the effect of colloid compared to crystalloid fluid resuscitation in critically ill patients in hypovolemic shock. The authors found no significant difference in

28 day mortality or in renal replacement therapy.[96] However, various colloid and crystalloid fluids were combined in the trial.

As a result of this accumulating evidence, the European Medicines Agency decided in 2013 that: "HES solutions must no longer be used to treat patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality." HES solutions may still be used for fluid resuscitation in addition to crystalloids in patients with acute blood loss; their use should be limited to 24 hours with renal function monitoring.[97] The United States Food and Drug Administration (FDA) added a boxed warning to the use of HES regarding mortality and renal replacement therapy risks and recommended that HES products not be used in critically ill patients or in patients with pre-existing renal dysfunction.[98]

In summary, based on the evidence presented above, the use of hydroxyethyl starch solutions cannot be recommended until it is clearly demonstrated that such products provide benefit in the neurosurgical patient and do not cause harm when infused in limited volumes.

Dextrans

Dextran solutions are colloids composed of glucose polymers with predominantly 1–6 glycosidic linkages. Although dextran 70 has an oncotic pressure about twice that of plasma, the oncotic pressure of dextran 40 is significantly greater; thus, infusion of dextran 40 can actually draw water from the interstitial space into the intravascular compartment.[99]

Dextrans are associated with a variety of adverse effects that have limited their clinical use. In a manner analogous to the effect of hetastarch, dextrans interfere with normal blood coagulation, and are associated with allergic and pseudoallergic reactions.[100]

Dextran may also interfere with blood typing and cross-matching[101] and with a number of clinical laboratory tests, including blood glucose, bilirubin, and protein measurements. Finally, acute renal failure was reported following the overzealous administration of dextran 40 that resulted in a hyperoncotic state (plasma oncotic pressure 33.1 mmHg).[102]

Albumin

Human albumin is available for infusion in 5% and 25% solutions. These solutions do not contain any of the clotting factors found in fresh whole blood or fresh plasma. Because all of the isoagglutinins are also removed in the processing, albumin may be given without regard to the patient's blood type. The albumin is derived from the plasma of volunteer donors, pooled, heat-treated at 60° C for 10 hours to inactivate possible viral contamination, and finally sterilized by ultrafiltration. Albumin has an MW of approximately 69,000 and constitutes 50% of the total plasma proteins by weight. Intravenously infused albumin has a plasma half-life of 16 hours in nonedematous patients.

The use of albumin compared to normal saline was evaluated by SAFE trial multicenter randomized controlled study.[103] 6997 critically ill patients were randomized to receive 4% albumin or 0.9% normal saline as a resuscitation fluid for 28 days. Studied subgroups were trauma, severe sepsis and ARDS patients. 28-day all-cause mortality was no different in the study groups, with the exception of higher mortality seen with albumin in the TBI subgroup. Post hoc follow-up analysis of TBI patients showed that only patients with severe TBI (GCS 3–8) accounted for increased mortality and that elevated ICP within the first week of injury may play a role.[104]

Reduced infarction size with albumin has been demonstrated in animal models of global and focal cerebral ischemia.[105,106] The neuroprotective effect of albumin is multifactorial.[106] Albumin has been shown to improve perfusion to the ischemic penumbra,[107] augment collateral perfusion,[108] and have a positive effect on microvascular hemodynamics.[109]

The potentially neuroprotective properties of albumin in animal studies have been investigated by several controlled studies in patients with ischemic stroke and SAH. ALIAS, a multicenter randomized controlled trial, was designed to evaluate the effect of 25% albumin on outcome in AIS patients 5 hours within symptom onset.[110] The infused volume of albumin was 8 mL/kg with maximum dose of 750 mL. The trial was stopped early for futility due to a higher risk of hemorrhagic conversion and more medical complications in the albumin group. A pilot clinical trial ALISAH investigated the therapeutic effect and safety of different doses of 25% albumin administered for 7 days to patients with SAH.[111] Results showed a dose-dependent reduction in vasospasm, delayed cerebral ischemia and infarction. However, the study was halted early due to severe cardiovascular side effects associated with higher albumin doses (1.875 g/kg/d).

Based on the evidence presented above, the utility of albumin in patients with neurological injury remains questionable. The ALISAH trial, albeit terminated early, showed reduced incidence of vasospasm and infarction in SAH patients receiving 25% albumin at 1.25/kg/d x 7 days—a dosage that the authors stated was well tolerated.[111] Whether 25% albumin will prove to be indeed neuroprotective in a patient with SAH awaits further investigation.

Plasma and Red Blood Cells

Greater professional and public awareness of the hazards associated with infusing blood products has markedly curtailed their use. Currently, red blood cells (RBCs) should be given only to keep hematocrit at a "safe" level. This level varies from patient to patient; and even in a specific circumstance, it may be difficult to objectively define what constitutes "safe." In vitro studies have shown that oxygen delivery to the tissues is maximal at a hematocrit of approximately 30%. At higher hematocrits, oxygen delivery is compromised by increased viscosity of the blood, whereas at hematocrits much below 25%, delivery decreases because of reduced oxygen carrying capacity of the blood.

Healthy individuals show signs of cognitive impairment with hemoglobin below 7 g/dL[112,113] and may tolerate low levels of hematocrit (20–25%) without complications when undergoing elective surgery. Evidence from studies of patients who are critically ill but without serious cardiac disease, supports a restrictive transfusion strategy (hemoglobin ~ 7 g/dL).[114,115]

As of now transfusion thresholds have not been well established for patients with acute brain injury or when oxygen delivery is impaired. There is a large variability in transfusion triggers for patients with TBI, AIS, ICH and SAH.[113,116–118] Studies show that both anemia and RBC transfusion may negatively influence outcome,[113] even though leukoreduction of RBC products has made RBC transfusion safer with fewer adverse effects.[119] Most of the developed nations adopted the practice of using leukoreduced blood products as of 2008 or earlier; however, such practice has not been universally accepted in the United States.[120]

Studies of patients with spontaneous ICH demonstrated that anemia has been an independent predictor of hematoma size[121] and was associated with poor outcomes.[122] Anemia in

ischemic stroke was linked with stroke deterioration and poor outcome.[123] Prospective study of 1176 AIS patients showed that admission anemia was an independent predictor of mortality.[124]

Several studies have examined the effect of anemia on the outcome of patients with SAH. Anemia has been associated with a worse outcome regardless of WFNS, modified Fisher score or vasospasm.[125] In a prospective study of high-grade SAH patients, hemoglobin <9 g/dL carried a risk of increased brain hypoxia, cell energy dysfunction and impaired autoregulation.[116] Multiple studies show a relationship between higher hemoglobin levels and a decreased risk of cerebral infarction and improved functional outcome in SAH patients.[126,127] Patients with higher mean hemoglobin (11.7 ± 1.5 vs. 10.9 ± 1.2, $p < 0.001$) and nadir (9.9 ± 2.1 vs. 8.6 ± 1.8, $p < 0.001$) had improved neurological outcome at discharge and at 14 days.[127]

Anemia is a known deleterious factor but the effect of RBC transfusion is still not fully elucidated. RBC transfusion has been linked with worse outcome in multiple studies of SAH patients.[128–130] However, in a prospective study of eight SAH patients that compared the effect of fluid bolus, induced hypertension and RBC transfusion, Dhar and associates showed a significant improvement in global CBF and oxygen delivery after RBC transfusion (general threshold hemoglobin <7, vasospasm patients hemoglobin <10 g/dL).[131]

Large randomized clinical trials of TBI patients have found that admission anemia predicted worse outcome (hemoglobin 14.3 vs. 10.8 g/dL),[132,133] but the effects of RBC transfusion and transfusion thresholds in this patient population remain unclear. Duanes' study of isolated TBI patients showed that anemia and administration of total RBC products were associated with increased mortality. They noticed that the effect was stronger with hemoglobin <8 g/dL.[134]

In conclusion, anemia is associated with a worse outcome in patients with neurologic injury; however, whether transfusing RBCs improves outcome is not clear. Results of recent studies suggest that patients with acute brain injury do better with higher hemoglobin levels but solid evidence for optimal transfusion triggers is lacking. The individual practitioner has to use his/her clinical judgment and guidance from any institution-specific protocols.

Plasma should be administered only in an attempt to correct a coagulation defect caused by a deficiency of one or more of the coagulation factors. Volume expansion is no longer considered an appropriate use of this blood product. Coagulation defects may arise in neurosurgical patients for a variety of reasons. In one study, an abnormality in the prothrombin time, partial thromboplastin time, or platelet count at admission was present in 55% of patients with head injuries and computed tomography evidence of new or progressive lesions.[135] Victims of traumatic injury may require massive fluid resuscitation because of hemorrhagic hypovolemia. If this initial fluid resuscitation is achieved with asanguinous fluids, a dilutional coagulopathy may aggravate a preexisting clotting disorder.

SUMMARY

The movement of water between the vasculature and the brain's extracellular space is driven primarily by the presence of osmotic gradients. Clinically, these gradients can be established by administration of either hyperosmolar (eg, mannitol) or hypo-osmolar (eg, 5% dextrose in water) solutions. In the brain (unlike peripheral tissues), plasma oncotic pressure has little impact on cerebral edema formation. Attempts to minimize cerebral edema formation by fluid restriction are unlikely to be successful and, if overzealously pursued, may lead to hemodynamic instability. Although no single intravenous solution is best suited for the neurosurgical patient who is at risk for intracranial hypertension, the use of iso-osmolar crystalloids is widely accepted and can be justified on a scientific basis.

ACKNOWLEDGMENT

The authors wish to thank Dr. Michael M. Todd for the inspiration for Figs. 9.4, 9.5, and 9.6 and Dr. Mark Zornow for permission to use Figs. 9.7 A and B.

REFERENCES

1. Bevan DR, Osmometry I. Terminology and principles of measurement. *Anaesthesia*. 1978;33(9):794–800.
2. Haupt MT, Rackow EC. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin, and saline solutions. *Crit Care Med*. 1982;10(3):159–162.
3. Marty AT, Zweifach BW. The high oncotic pressure effects of dextrans. *Arch Surg*. 1970;101(3):421–424.
4. Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol*. 1896;19(4):312–326.
5. Peters RM, Hargens AR. Protein vs. electrolytes and all of the Starling forces. *Arch Surg*. 1981;116(10):1293–1298.
6. Fenstermacher JD, Johnson JA. Filtration and reflection coefficients of the rabbit blood-brain barrier. *Am J Physiol*. 1966;211(2):341–346.
7. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *Anesthesiology*. 1987;67(6):936–941.
8. Dodge PR, Crawford JD, Probst JH. Studies in experimental water intoxication. *Arch Neurol*. 1960;3:513–529.
9. Zornow MH, Scheller MS, Todd MM, et al. Acute cerebral effects of isotonic crystalloid and colloid solutions following cryogenic brain injury in the rabbit. *Anesthesiology*. 1988;69(2):180–184.
10. Kaieda R, Todd MM, Warner DS. Prolonged reduction in colloid oncotic pressure does not increase brain edema following cryogenic injury in rabbits. *Anesthesiology*. 1989;71(4):554–560.
11. Shenkin HA, Bezier HS, Bouzarth W. Restricted fluid intake: Rational management of the neurosurgical patient. *J Neurosurg*. 1976;45(4):432–436.
12. Warner DS, Boehland LA. Effects of iso-osmolal intravenous fluid therapy on post-ischemic brain water content in the rat. *Anesthesiology*. 1988;68(1):86–91.
13. Korosue K, Heros RC, Ogilvy CS, et al. Comparison of crystalloids and colloids for hemodilution in a model of focal cerebral ischemia. *J Neurosurg*. 1990;73(4):576–584.
14. Drummond JC, Patel PM, Cole DJ, et al. The effect of the reduction of colloid oncotic pressure, with and without reduction of osmolality, on posttraumatic cerebral edema. *Anesthesiology*. 1998;88(4):993–1002.
15. Zornow MH, Scheller MS, Shackford SR. Effect of a hypertonic lactated Ringer's solution on intracranial pressure and cerebral water content in a model of traumatic brain injury. *J Trauma*. 1989;29(4):484–488.
16. Shenkin HA, Goluboff B, Haft H. Further observations on the effects of abruptly increased osmotic pressure of plasma on cerebrospinal-fluid pressure in man. *J Neurosurg*. 1964;22(6):563–568.
17. Palma L, Bruni G. Fiaschi Al, et al. Passage of mannitol into the brain around gliomas: A potential cause of rebound phenomenon. A study on 21 patients. *J Neurosurg Sci*. 2006;50(3):63–66.
18. Kien ND, Kramer GC, White DA. Acute hypotension caused by rapid hyper-tonic saline infusion in anesthetized dogs. *Anesth Analg*. 1991;73(5):597–602.
19. Gunnar W, Jonasson O, Merlotti G, et al. Head injury and hemorrhagic shock: Studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. *Surgery*. 1988;103(4):398–407.
20. Gunnar WP, Merlotti GJ, Jonasson O, et al. Resuscitation from hemorrhagic shock: Alterations of the intracranial pressure after normal saline, 3% saline and Dextran-40. *Ann Surg*. 1986;204(6):686–692.
21. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: Effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. *J Neurosurg*. 1992;76(1):91–98.
22. Todd MM, Tommasino C, Moore S. Cerebral effects of isovolemic hemo-dilution with a hypertonic saline solution. *J Neurosurg*. 1985;63(6):944–948.

23. Sahar A, Tsiptstein E. Effects of mannitol and furosemide on the rate of formation of cerebrospinal fluid. *Exp Neurol*. 1978;60(3):584–591.
24. Sotos JF, Dodge PR, Meara P, et al. Studies in experimental hypertonicity I: Pathogenesis of the clinical syndrome, biochemical abnormalities and cause of death. *Pediatrics*. 1960;26:925–938.
25. Shackford SR, Fortlage DA, Peters RM, et al. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. *Surg Gynecol Obstet*. 1987;164(2):127–136.
26. Shackford SR, Sise MJ, Fridlund PH, et al. Hypertonic sodium lactate versus lactated Ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery*. 1983;94(1):41–51.
27. Worthley LIG, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. *J Neurosurg*. 1988;68(3):478–481.
28. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26(6): 1118–1122.
29. Scheller MS, Zornow MH, Oh YS. A comparison of the cerebral and hemodynamic effects of mannitol and hypertonic saline in a rabbit model of acute cryogenic brain injury. *J Neurosurg Anesthesiol*. 1991;3(4):291–296.
30. Ichai C, Armando G, Orban JC, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med*. 2009;35(3):471–479.
31. Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med*. 2003;31(6):1683–1687.
32. Al-Rawi PG, Tseng MY, Richards HK, et al. Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. *Stroke*. 2010;41(1):122–128.
33. Peterson B, Khanna S, Fisher B, et al. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med*. 2000;28(4):1136–1143.
34. Qureshi AI, Suarez JI, Bhardwaj A, et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. *Crit Care Med*. 1998;26(3):440–446.
35. Mayzler O, Leon A, Eilig I, et al. The effect of hypertonic (3%) saline with and without furosemide on plasma osmolality, sodium concentration, and brain water content after closed head trauma in rats. *J Neurosurg Anesthesiol*. 2006;18(1):24–31.
36. Todd MM, Cutkomp J, Brian JE. Influence of mannitol and furosemide, alone and in combination, on brain water content after fluid percussion injury. *Anesthesiology*. 2006;105(6):1176–1181.
37. Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intra-cranial pressure in children after head trauma. *J Neurosurg Anesthesiol*. 1992;4(1):4–10.
38. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology*. 2007;107(5):697–704.
39. Dostal P, Dostalova V, Schreiberova J, et al. A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation in patients undergoing elective intracranial tumor surgery: A randomized clinical trial. *J Neurosurg Anesthesiol*. 2015;27(1):51–56.
40. McDonagh DL, Warner DS. Hypertonic saline for craniotomy? *Anesthesiology*. 2007;107(5):91–689.
41. Mortazavi MM, Romeo AK, Deep A, et al. Hypertonic saline for treating raised intracranial pressure: Literature review with meta-analysis. *J Neurosurg*. 2012;116(1):210–221.
42. Lanier WL, Stangland KJ, Scheithauer BW, et al. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. *Anesthesiology*. 1987;66(1):39–48.
43. Drummond J, Moore S. The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. *Anesthesiology*. 1989;70(1):64–70.
44. Ginsberg MD, Prado R, Dietrich WD, et al. Hyperglycemia reduces the extent of cerebral infarction in rats. *Stroke*. 1987;18(3):570–574.
45. Zasslow MA, Pearl RG, Shuer LM, et al. Hyperglycemia decreases acute neuronal ischemic changes after middle cerebral artery occlusion in cats. *Stroke*. 1989;20(4):519–523.
46. De Courten-Meyers G, Myers RE, Schoolfield L. Hyperglycemia enlarges infarct size in cerebrovascular occlusion in cats. *Stroke*. 1988;19(5):623–630.
47. Choi DW, Monyer H, Giffard RG, et al. Acute brain injury, NMDA receptors, and hydrogen ions: Observations in cortical cell cultures. *Adv Exp Med Biol*. 1990;268:501–504.
48. Giffard RG, Monyer H, Christine CW, et al. Acidosis reduces NMDA receptor activation, glutamate neurotoxicity, and oxygen-glucose deprivation neuronal injury in cortical cultures. *Brain Res*. 1990;506(2):339–342.
49. Ping-An L, Shuaib A, Miyashita H, et al. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. *Stroke*. 2000;31(1):183–192.
50. Choi KT, Illievich UM, Zornow MH, et al. Effect of hyperglycemia on peri-ischemic neurotransmitter levels in the rabbit hippocampus. *Brain Res*. 1994;642(1-2):104–110.
51. Lam AM, Winn RH, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75(4): 545–551.
52. Bruno A, Biller J, Adams HP, et al. Acute blood glucose level and outcome from ischemic stroke. *Neurology*. 1999;52(2):280–284.
53. Weir CJ, Murray GD, Dyker AG, et al. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. *BMJ*. 1997;314(7090):1303–1306.
54. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients. *Stroke*. 2001;32(10):2426–2432.
55. Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH, predictors, associated complications, and impact on outcome. *Stroke*. 2006;37(1):199–203.
56. Kimura K, Iguchi Y, Inoue T, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci*. 2007;255(1-2):90–94.
57. Schlenk F, Vajkoczy P, Sarrafzadech. Inpatient hyperglycemia following aneurysmal subarachnoid hemorrhage: Relation to cerebral metabolism and outcome. *Neurocrit Care*. 2009;11(1):56–63.
58. Murros K, Fogelholm R, Kettunen S, et al. Blood glucose, glycosylated haemoglobin, and outcome of ischemic brain infarction. *J Neurol Sci*. 1992;111(1):59–64.
59. Tracey F, Crawford VLS, Lawson JT, et al. Hyperglycaemia and mortality from acute stroke. *Q J Med*. 1993;86(7):439–446.
60. Pasternak JJ, McGregor DG, Schroeder DR, et al. Hyperglycemia in patients undergoing cerebral aneurysm surgery: Its association with long-term gross neurologic and neuropsychological function. *Mayo Clin Proc*. 2008;83(4):406–417.
61. Kurtz P, Claassen J, Helbok R, et al. Systemic glucose variability predicts cerebral metabolic distress and mortality after subarachnoid hemorrhage: A retrospective observational study. *Crit Care*. 2014;18(3):R89.
62. Davis MC, Ziewacz JE, Sullivan SE, et al. Preoperative hyperglycemia and complication risk following neurosurgical intervention: A study of 918 consecutive cases. *Surg Neurol Int*. 2012;3:49.
63. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359–1367.
64. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery. *Ann Intern Med*. 2007;146(4):233–243.
65 National Institutes of Health: Glucontrol study: A multi-center study comparing the effects of two glucose control regimens by insulin in intensive care unit patients available at http://www.clinicaltrials.gov/ct/gui/show/NCT00107601.
66. Devos P, Preiser J-C. Current controversies around tight glucose control in critically ill patients. *Curr Opin Clin Nutr Metab Care*. 2007;10(2):206–209.
67. Finfer S, Chittock DR, Su SY, et al. The NICE-SUGAR study investigators: Intensive verus conventional glucose control in critically III patients. *N Engl J Med*. 2009;360(13):1283–1297.
68. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*. 2004;79(8):992–1000.
69. Ooi YC, Dagi TF, Maltenfort M, et al. Tight glycemic control reduces infection and improves neurological outcome in critically ill neurosurgical and neurological patients. *Neurosurgery*. 2012;71(3):692–702.
70. Cinotti R, Ichai C, Orban JC, et al. Effects of tight computerized glucose control on neurological outcome in severely brain injured patients: A multicenter sub-group analysis of the randomized-controlled open-label CGAO-REA study. *Crit Care*. 2014;18(5):498.
71. Latorre JG, Chou SH, Nogueira RG, et al. Effective glycemic control with aggressive hyperglycemia management is associated with improved outcome in aneurysmal subarachnoid hemorrhage. *Stroke*. 2009;40(5):1644–1652.
72. Bilotta F, Spinelli A, Giovanninni F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: A randomized prospective pilot trial. *J Neurosurg Anesthesiol*. 2007;19(3):156–160.
73. Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: The UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6(5):397–406.

74. Bilotta F, Rosa G. Glucose management in the neurosurgical patient: Are we yet any closer? *Curr Opin Anaesthesiol*. 2010;23(5):539–543.
75. Guyton AC. *Textbook of Medical Physiology*. ed 5. Philadelphia: WB Saunders; 1976.
76. Jelsma LF, McQueen JD. Effect of experimental water restriction on brain water. *J Neurosurg*. 1967;26(1):35–40.
77. Tisdall M, Crocker M, Watkiss J, et al. Disturbances of sodium in critically ill adult neurologic patients: A clinical review. *J Neurosurg Anesthesiol*. 2006;18(1):57–63.
78. Sherlock M, O`Sullivan E, Agha A, et al. The incidence of pathophysiology of hyponatraemia after subarachnoid haermorrhage. *Clin Endocrinol (Oxf)*. 2006;64(3):250–254.
79. Berkenstadt H, Margalit N, Hadani M, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg*. 2001;92(4):984–989.
80. Michard F, Teboul J-L. Predicting fluid responsiveness in ICU patients: A critical analysis of the evidence. *Chest*. 2002;121(6):2000–2008.
81. Tavernier B, Makhotine O, Lebuffe G, et al. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*. 1998;89(6):1313–1321.
82. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med*. 2000;162(1):134–138.
83. Defandre E, Bonhomme V, Hans P. Delta down compared with delta pulse pressure as an indicator of volaemia during intracranial surgery. *Br J Anaesth*. 2008;100(2):245–250.
84. Navarro LH, Bloomstone JA, Auler Jr JO, et al. Perioperative fluid therapy: A statement from the international Fluid Optimization Group. *Perioper Med (Lond)*. 2015;10(4):3.
85. Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: A prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). *Anesth Analg*. 2014;119(3):579–587.
86. Manninen PH, Lam AM, Gelb AW, et al. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. *Can J Anaesth*. 1987;34(5):442–446.
87. Moreno M, Murphy C, Goldsmith C. Increase in serum potassium resulting from the administration of hypertonic mannitol and other solutions. *J Lab Clin Med*. 1969;73(2):291–298.
88. Chatterjee N, Koshy T, Misra S, et al. Changes in left ventricular preload, afterload, and cardiac output in response to a single dose of mannitol in neurosurgical patients undergoing craniotomy: A transesophageal echocardiographic study. *J Neurosurg Anesthesiol*. 2012;24(1):25–29.
89. Treib J, Baron J-F, Grauer MT, et al. An international view of hydroxy-ethyl starches. *Intensive Care Med*. 1999;25(3):258–268.
90. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125–139.
91. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124–134.
92. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901–1911.
93. Nolan JP, Mythen MG. Hydroxyethyl starch: here today, gone tomorrow. *Br J Anaesth*. 2013;111(3):321–324.
94. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013;2:CD000567.
95. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. *JAMA*. 2013;309(7):678–688.
96. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. *JAMA*. 2013;310(17):1809–1817.
97. Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients. *European Medicines Agency*; 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Solutions_for_infusion_containing_hydroxyethyl_starch/European_Commission_final_decision/WC500162361.pdf.
98. FDA Safety Communication. Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings; 2013. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm.
99. Nearman HS, Herman ML. Toxic effects of colloids in the intensive care unit. *Crit Care Clin*. 1991;7(3):713–723.
100. Lacy Ch, Armstrong L, Goldman M, Lance L, eds. Dextran. In: *Drug Information Handbook*. 17th Edition. Hudson: Lexi-comp; 2008:445.
101. Lutz H, Georgieff M. Effects and side effects of colloid plasma substitutes as compared to albumin. *Curr Stud Hematol Blood Transfus*. 1986;53:145–154.
102. Moran M, Kapsner C. Acute renal failure associated with elevated plasma oncotic pressure. *N Engl J Med*. 1987;317(3):150–153.
103. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.
104. Cooper DJ, Myburgh J, Heritier S, et al. Albumin resuscitation for traumatic brain injury: Is intracranial hypertension the cause of increased mortality? *J Neurotrauma*. 2013;30(7):512–518.
105. Belayev L, Saul I, Huh PW, et al. Neuroprotective effect of high-dose albumin therapy against global ischemic brain injury in rats. *Brain Res*. 1999;845(1):107–111.
106. Belayev L, Liu Y, Zhao W, et al. Human albumin therapy of acute ischemic stroke: Marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. *Stroke*. 2001;32(2):553–560.
107. Huh PW, Belayev L, Zhao W, et al. The effect of high-dose albumin therapy on local cerebral perfusion after transient focal cerebral ischemia in rats. *Brain Res*. 1998;804(1):105–113.
108. Defazio RA, Zhao W, Deng X, et al. Albumin therapy enhances collateral perfusion after laser-induced middle cerebral artery branch occlusion: A laser speckle contrast flow study. *J Cereb Blood Flow Metab*. 2012;32(11):2012–2022.
109. Nimmagadda A, Park HP, Prado R, et al. Albumin therapy improves local vascular dynamics in a rat model of primary microvascular thrombosis: A two-photon laser-scanning microscopy study. *Stroke*. 2008;39(1):198–204.
110. Ginsberg MD, Palesch YY, Hill MD, et al. High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: A randomised, double-blind, phase 3, placebo-controlled trial. *Lancet Neurol*. 2013;12(11):1049–1058.
111. Suarez JI, Martin RH, Calvillo E, et al. Effect of human albumin on TCD vasospasm, DCI, and cerebral infarction in subarachnoid hemorrhage: The ALISAH Study. *Acta Neurochir Suppl*. 2015;120:287–290.
112. Weiskopf RB, Kramer JH, Viele M, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology*. 2000;92(6):1646–1652.
113. LeRoux P. Haemoglobin management in acute brain injury. *Curr Opin Crit Care*. 2013;19(2):83–91.
114. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2012;4:CD002042.
115. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: A clinical practice guideline from the AABB*. *Ann Intern Med*. 2012;157(1):49–58.
116. Oddo M, Milby A, Chen I, et al. Hemoglobin concentration and cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2009;40(4):1275–1281.
117. Kramer AH, Diringer MN, Suarez JI, et al. Red blood cell transfusion in patients with subarachnoid hemorrhage: A multidisciplinary North American survey. *Crit Care*. 2011;15(1):R30.
118. Utter GH, Shahlaie K, Zwienenberg-Lee M, et al. Anemia in the setting of traumatic brain injury: The arguments for and against liberal transfusion. *J Neurotrauma*. 2011;28(1):155–165.
119. Blumberg N, Zhao H, Wang H, et al. The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. *Transfusion*. 2007;47(4):573–581.
120 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. Guidance for industry: Pre-storage leukocyte reduction of whole blood and blood components intended for transfusion. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm320636.htm.
121. Kumar MA, Rost NS, Snider RW, et al. Anemia and hematoma volume in acute intracerebral hemorrhage. *Crit Care Med*. 2009;37(4):1442–1447.
122. Diedler J, Sykora M, Hahn P, et al. Low hemoglobin is associated with poor functional outcome after non-traumatic, supratentorial intracerebral hemorrhage. *Crit Care*. 2010;14(2):R63.
123. Kellert L, Martin E, Sykora M, et al. Cerebral oxygen transport failure?: Decreasing hemoglobin and hematocrit levels after ischemic stroke predict poor outcome and mortality: STroke: RelevAnt Impact of hemoGlobin, Hematocrit and Transfusion (STRAIGHT) – an observational study. *Stroke*. 2011;42(10):2832–2837.
124. Hao Z, Wu B, Wang D, et al. A cohort study of patients with anemia on admission and fatality after acute ischemic stroke. *J Clin Neurosci*. 2013;20(1):37–42.
125. Kramer AH, Zygun DA, Bleck TP, et al. Relationship between hemoglobin concentrations and outcomes across subgroups of patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2009;10(2):157–165.

126. Naidech AM, Drescher J, Ault ML, et al. Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. *Neurosurgery*. 2006;59(4):775–779.
127. Naidech AM, Jovanovic B, Wartenberg KE, et al. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. *Crit Care Med*. 2007;35(10):2383–2389.
128. Festic E, Rabinstein AA, Freeman WD, et al. Blood transfusion is an important predictor of hospital mortality among patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2013;18(2):209–215.
129. Kramer AH, Gurka MJ, Nathan B, et al. Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med*. 2008;36(7):2070–2075.
130. Levine J, Kofke A, Cen L, et al. Red blood cell transfusion is associated with infection and extracerebral complications after subarachnoid hemorrhage. *Neurosurgery*. 2010;66(2):312–318.
131. Dhar R, Zazulia AR, Videen TO, et al. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke*. 2009;40(9):3039–3044.
132. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS*. 2008;5(8).
133. Van Beek JG, Mushkudiani NA, Steyerberg EW, et al. Prognostic value of admission laboratory parameters in traumatic brain injury: Results from the IMPACT study. *J Neurotrauma*. 2007;24(2):315–328.
134. Duane TM, Mayglothling J, Grandhi R, et al. The effect of anemia and blood transfusions on mortality in closed head injury patients. *J Surg Res*. 2008;147(2):163–167.
135. Stein SC, Young GS, Talucci RC, et al. Delayed brain injury after head trauma: Significance of coagulopathy. *Neurosurgery*. 1992;30(2):160–165.

10 Care of the Acutely Unstable Patient

R. Kutteruf • I. Rozet • K.B. Domino

Most neurologic emergencies that require the intervention of an anesthesiologist are caused by head and spine trauma, leading to traumatic brain injury (TBI) and traumatic spinal cord injury (SCI). NonTBIs which can cause acute patient instability include nontraumatic intracranial hemorrhage, ruptured cerebral aneurysms or arteriovenous malformations, acute arterial hypertension, or chronic anticoagulation therapy; acute hydrocephalus; intracranial tumors with impending brain herniation; and ischemic stroke. Likewise, tumors or hematomas compressing the spinal cord may cause acute spinal cord injury.

The aims of the acute care of patients with either brain injury or SCI are stabilization of the patient and prevention of secondary neurologic injury. Secondary insults to other organs and systems as a result of the primary neurologic injury and coexisting injuries in patients with trauma contribute to development of the secondary injury of the neurologic system, adversely affecting outcome.

This chapter focuses on the acute care of the neurologically unstable patient with brain and spinal cord injuries, regardless of the cause. We discuss the initial neurologic evaluation, the evaluation of other organ systems, and the goals of the acute care of the unstable patient.

BRAIN INJURY

Initial Evaluation

Every patient with trauma should be approached in accordance with the basic Advanced Trauma Life Support (ATLS) principles that prioritize systems assessment in an order of ABCD: A—airway, B—breathing, C—circulation, D—disability/neurologic assessment, E—exposure.

A *basic neurological assessment,* known by the mnemonic AVPU (Alert, Verbal stimuli response, Painful stimuli response, or Unresponsive), should be performed with the primary survey of patients' assessment.

A more detailed neurological evaluation is performed at the end of the primary survey and involves assessment of level of consciousness, pupil size and reaction, lateralizing signs, and spinal cord injury level.

The Glasgow Coma Scale (GCS) is a quick method to determine the level of consciousness. An altered level of consciousness requires an immediate re-evaluation of the patient's oxygenation, ventilation, and perfusion. If factors such as drugs, including alcohol and hypoglycemia, are excluded, a decrease in the level of consciousness should be considered to be due to TBI until proven otherwise.

Every patient with an acute onset of focal neurological deficit, on the other hand, should be considered to have a cerebral vascular accident, until proven otherwise.[1]

Assessment of breathing and circulation with basic vital signs measures should be done concomitantly with the initial assessment of consciousness.

Detailed Neurologic Evaluation

The Glasgow Coma Scale (GCS)[2] score (Box 10.1) comprises the best verbal response, the best motor response, and the presence of eye opening, using a scale from 3 to 15. The scaling system is effective because it is easy to use, has good interobserver reliability, helps guide diagnosis and therapy, and has prognostic significance. Morbidity and mortality are closely related to the initial GCS score, with lower scores predicting a worse outcome, irrespective of the cause of the brain injury.[3] Another factor that predicts the prognosis of the brain injury is age, with a better prognosis noted among pediatric patients, and worse prognosis in adults older than 40 years. Pupillary responses and gag reflexes should be evaluated in the initial neurologic examination. In the acute setting, examination of the size and reactivity of the pupils is particularly important (Box 10.2). A dilated, unresponsive ("blown") pupil may be a sign of ipsilateral uncal herniation, in which the medial aspect of the temporal lobe (uncus) herniates through the tentorium, thereby compressing the midbrain and nucleus of the third cranial nerve.[4] Bilateral pupillary dilation may be due to bilateral uncal herniation or injury (eg, ischemic or metabolic) to the midbrain. Local eye trauma or third nerve compression may cause a dilated, nonreactive pupil in the absence of a brain injury. In head-injured patients with systolic blood pressure (SBP) greater than 60 mmHg, clinical signs of tentorial herniation or upper brainstem dysfunction are valid

BOX 10.1 Neurologic Evaluation of the Brain-Injured Patient

- Glasgow Coma scale score (points):
  - Eye opening:
    - Spontaneous (4)
    - To speech (3)
    - To pain (2)
    - None (1)
  - Best verbal response:
    - Oriented (5)
    - Confused (4)
    - Inappropriate (3)
    - Incomprehensible (2)
    - None (1)
  - Best motor response:
    - Obeys commands (6)
    - Localizes pain (5)
    - Withdraws (4)
    - Flexion to pain (3)
    - Extension to pain (2)
    - None (1)
- Pupillary size and reactivity
- CT scan:
  - Mass lesion
  - Cerebral edema
  - Midline shift/absent basal cisterns

BOX 10.2 Pupillary Assessment in the Patient with Brain Injury

1. The pupil is considered "dilated" if pupillary diameter is >4 mm.
2. The pupil is considered "fixed" in the absence of constrictor response to bright light.
3. Bilateral pupillary light reflex should be assessed and used as a prognostic factor.
4. The duration of pupillary dilation and fixation should be documented.
5. Any asymmetry of pupils should be documented.
6. Hypotension and hypoxia should be corrected before pupillary assessment.
7. Orbital trauma should be excluded.
8. Pupils should be reassessed after surgical intervention (eg, evacuation of hematoma).

Modified from The Brain Trauma Foundation, The American Association of Neurological Surgeons, The Joint Section on Neurotrauma and Critical Care: Pupillary diameter and light reflex. J Neurotrauma 2000;17:583–590.

indicators of possible mechanical compression.[5] However, in patients with SBP less than 60 mmHg or with cardiac arrest, pupillary signs are unreliable indicators of mechanical compression.[5]

If the patient is comatose (eg, no eye opening, verbal response, or ability to follow commands), after an initial radiologic evaluation is completed, evaluation of midbrain and brainstem reflexes (eg, pupillary response, corneal reflexes, oculomotor movements, and gag reflex) may aid in localization of the injury.

Neuroimaging

After clinical neurologic evaluation and initial stabilization, radiologic evaluation with computed tomography (CT) is performed to diagnose the underlying disease process. If the patient is hemodynamically unstable with intra-abdominal or intrathoracic bleeding, the head CT scan is delayed until the life-threatening surgical bleeding is controlled. If the physical examination indicates a high likelihood of a brain injury, an intracranial pressure (ICP) monitor may be placed concurrently with the laparotomy or thoracotomy. Intracranial mass lesions that require rapid surgical treatment, such as epidural, subdural, or large intracerebral hemorrhages, are readily identified on CT scan (Figs. 10.1 and 10.2). Nonsurgical lesions, such as cerebral edema and hemorrhagic contusion, are also identified (Fig. 10.3). Diffuse cerebral swelling may develop after head trauma, especially in children. The severity of the

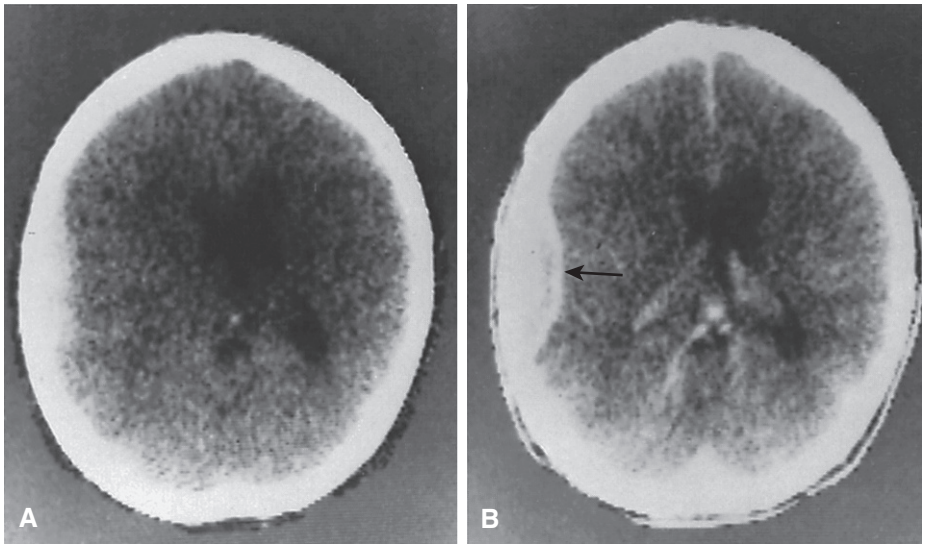


Fig. 10.1 Computed tomography (CT) of epidural hematoma. **A,** Plain CT scan shows parietal epidural hematoma. **B,** Contrast-enhanced CT scan shows enhancing dural rim (*arrow*). *(From Haaga JR, Alfidi RJ [eds]: Computed Tomography of the Whole Body, Vol 1. St. Louis, Mosby, 1983, p 185.)*

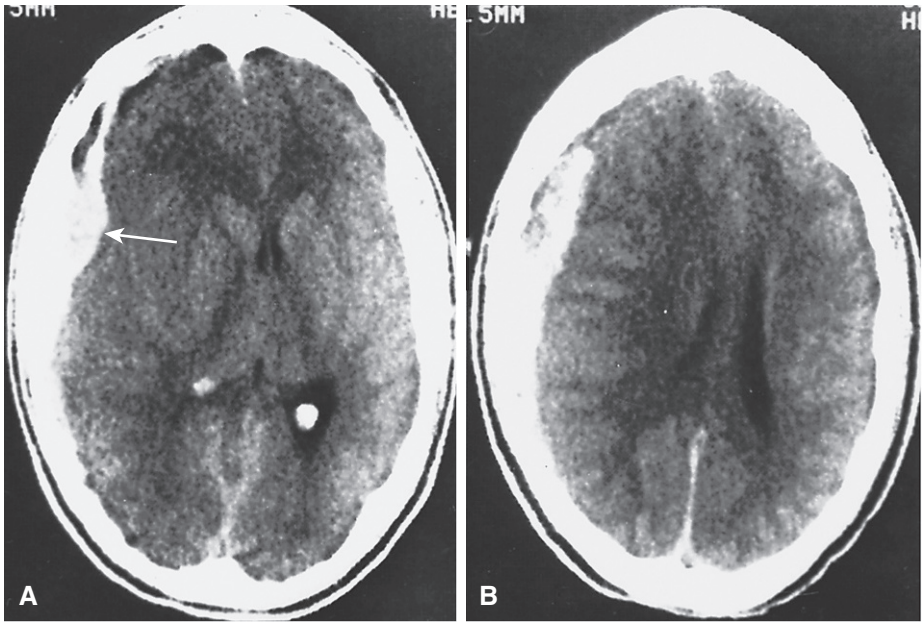


Fig. 10.2 Computed tomography of subdural hematoma. **A,** Acute subdural hematoma can be seen (*arrow*). **B,** Note the marked midline shift, with displacement of lateral ventricles toward the left. *(From Haaga JR, Alfidi RJ [eds]: Computed Tomography of the Whole Body, Vol 1. St. Louis, Mosby, 1983, p 187.)*

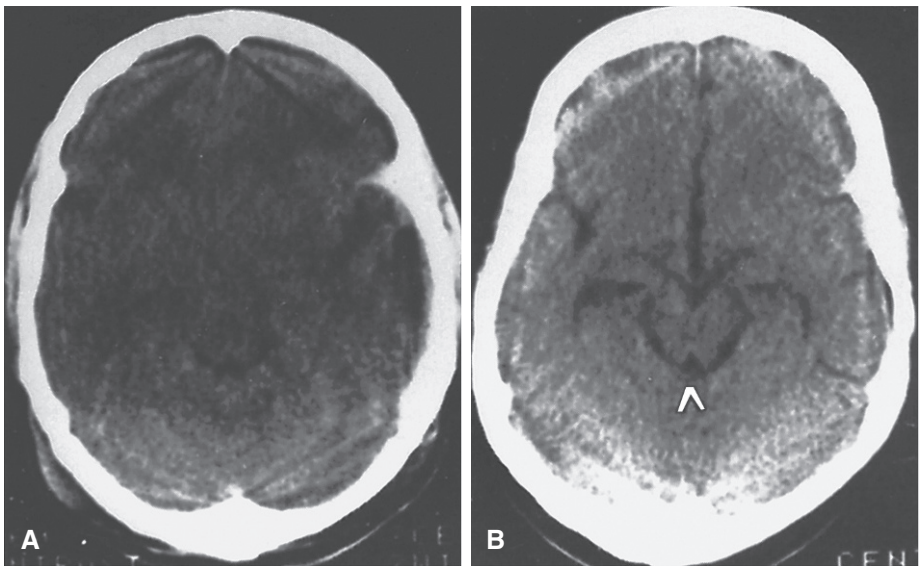


Fig. 10.3 Computed tomography scans showing compressed basal cisterns **(A)** and normal basal cisterns (**B,** *arrow*). The presence of compressed basal cisterns after head trauma increases the risk of poor outcome. *(From Toutant SM, Klauber MR, Marshall LF, et al: Absent or compressed basal cisterns on first CT scan: Ominous predictors of outcome in severe head injury. J Neurosurg 1984;61:691-694.)*

brain injury can be correlated with the magnitude of the midline shift (see Fig. 10.2) and compression of the basal cisterns (see Fig. 10.3).[6] In one study, patients with GCS scores of 6 to 8 in whom initial CT scan showed compression of the basal cisterns had a fourfold higher risk of poor outcome than those with normal cisterns.[6] Because patients may often have delayed neurologic deterioration, a repeat CT scan is indicated after any deterioration in neurologic status. Of patients whose conditions deteriorated after a mild head injury, 80% had a mass lesion that potentially required surgery.[6] In contrast, cerebral swelling is more likely to be the cause of deterioration in patients with severe head injury. Occasionally, manifestation of an intracerebral hematoma after TBI is delayed.

Patients with stroke might require an emergency brain MRI to differentiate brain ischemia from bleeding, and subsequent CT angiography, contrast-enhanced CT or MRI to identify brain lesions.[1]

Evaluation of Other Organ Systems

In addition to the neurologic evaluation, an evaluation of other organ systems should be performed (Box 10.3).

Respiratory System

Following assessment of the pattern of breathing and auscultation of the lungs, chest radiography should be performed soon after the trauma patient arrives in the emergency department and in patients with hypoxemia. Many patients with brain injuries are hypoxemic regardless of the mechanism of injury, and an increased degree of pulmonary shunting is associated with a worsened neurologic outcome.[7] Hypoxemia may be due to airway obstruction, hypoventilation, atelectasis, aspiration, and associated lung injuries in trauma patients such as pneumothorax, or pulmonary contusion. On rare occasions, neurogenic pulmonary edema may occur, often in the more devastating injuries. Neurogenic pulmonary edema has been reported after a variety of central nervous system insults, including subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), TBI, spinal cord trauma, acute hydrocephalus, colloid cyst of the third ventricle, seizures, and hypothalamic lesions. An acute rise in ICP often, but not always, accompanies the development of pulmonary edema. Increases in ICP may elicit only the sympathetic activation and cardiopulmonary responses that are essential for the development of edema. The mechanism of neurogenic pulmonary edema is not completely understood.[8] Marked sympathetic activation at the time of the injury may damage the pulmonary capillary endothelium by both hydrostatic and increased permeability mechanisms.[8] Increased pulmonary shunting may also be observed in patients with head trauma in the absence of distinct pulmonary edema or pathologic condition.[9] The increased alveolar-arterial oxygen tension gradient in these patients may be related to airway closure caused by a decreased functional residual capacity in a comatose patient or by neurogenic alterations in ventilation–perfusion matching.[10]

BOX 10.3 Brain Injury: Effects on Other Organ Systems

1. Respiratory system:
   a. Upper airway obstruction, inability to protect airway.
   b. Increased pulmonary shunting.
   c. Neurogenic pulmonary edema.
   d. Associated pulmonary injuries: atelectasis, aspiration, pneumothorax, hemothorax, flail chest, pulmonary contusion.
2. Cardiovascular system:
   a. Sympathetic nervous system overactivity.
   b. Hemorrhagic shock.
   c. Cushing response (hypertension, bradycardia).
   d. Hypotension (another cause should be sought).
3. Musculoskeletal system:
   a. Cervical spine injury in 10% of cases.
   b. Long bone or pelvic fractures.
4. Gastrointestinal system:
   a. "Full stomach."
   b. Blood alcohol levels.
   c. Possible intra-abdominal injury.
5. Other systems:
   a. Disseminated intravascular coagulation.
   b. Hypokalemia.
   c. Hyperglycemia.
   d. Diabetes insipidus.
   e. Hyponatremia.

Cardiovascular System

Severe brain injury activates the autonomic nervous system and causes a hyperdynamic cardiovascular response consisting of hypertension, tachycardia, increased cardiac output, and electrocardiogram changes that may mimic myocardial ischemia.[11]

A Cushing response, in which bradycardia accompanies the hypertension, may occur.[12] This response is thought to occur

because marked intracranial hypertension causes medullary ischemia as a result of decreased cerebral perfusion pressure (CPP) and brainstem distortion, resulting in activation of medullary sympathetic and vagal centers.[12] Although bradycardia accompanies the hypertension in a classic Cushing response, the presence of a relative tachycardia in a patient with a "blown" pupil may indicate that the patient is hypovolemic. If the patient has outright hypotension, other sources of blood loss (eg, pelvic, thoracic, abdominal) should be sought. An isolated, mild-to-moderate TBI is not generally associated with hypotension because the blood loss from the head wound is usually insufficient to cause hypotension in adults.

Acute brain injury may lead to development of a Takotsubo stress cardiomyopathy (stunned myocardium) characterized by an acute transient ST-elevation left ventricle dysfunction, not related to coronary artery disease, and may be easily confused with an acute myocardial infarction. Transthoracic echocardiography (TTE) should be urgently performed to differentiate from coronary artery disease as it demonstrates classical left ventricular dysfunction with akynesis of apex (ballooning) and hypokynesis of other left ventricle segments. Although the pathophysiology of the phenomenon is not exactly clear, it is believed that dramatic catecholamine release with stress, pain or intracranial bleeding lead to so-called "catecholamine cardiac toxicity," and, possibly, transient coronary spasm, leading subsequently to global, but transient, heart dysfunction. Most frequently (in about 90% of cases) Takotsubo cardiomyopathy is observed in middle-aged female patients with SAH. On occasion, it can also develop in a variety of CNS injuries such as TBI, ICH, ischemic stroke, and epilepsy. Awake patients may present with classic chest pain and shortness of breath, cardiac enzyme elevation, and ST-segment elevations and negative T waves in anterolateral wall on the EKG. Takotsubo cardiomyopathy can be complicated by profound hypotension, arrhythmias including torsade de pointes, heart failure and ventricular rupture and should be treated symptomatically.[13] Usually, an acute cardiomyopathy resolves within a few weeks, echocardiogram normalizes in 6 weeks and ECG in 10 weeks.[14]

Musculoskeletal System

Lateral cervical spine (C-spine) radiography should be performed immediately because approximately 10% of patients with head injuries have associated cervical spine injuries. The lateral cervical spine film picks up approximately 80% of cervical spine fractures[15] and can display lethal injuries such as atlanto-occipital separation. The remainder of the spine series that is required to "clear the neck" (confirm absence of vertebral injuries) should be performed later, after complete evaluation of the head injury. Many patients with head trauma also have long-bone or pelvic fractures that may cause significant blood loss or fat emboli.

Gastrointestinal System

Every patient with a neurosurgical emergency should be assumed to have a full stomach and to be at risk for aspiration. Patients with acute head trauma may also have intra-abdominal injuries. Delayed gastric emptying may persist for several weeks after severe head injury.[16] Significant blood alcohol levels have been found in more than 50% of head-injured patients.[17]

Coagulation

Patients with head trauma may also have disseminated intravascular coagulation, possibly caused by release of brain thromboplastin into the systemic circulation.[18] Outcome is poorer in patients in whom the condition develops.[18] An increase in fibrin split products may identify patients with head injury who are at high risk for adult respiratory distress syndrome.[19] Coagulation factor levels should be checked in the emergency department, and aggressive replacement of platelets and clotting factors may be required. Use of recombinant factor VII has been advocated in patients with polytrauma that includes TBI[20,21] and with spontaneous intracranial hemorrhages.[22] However, data are inconsistent regarding mortality benefit, reduction in transfusion requirements, and associated complications from the use of this agent.[23–25] Given the serious risk of thromboembolic events, recombinant factor VII cannot be recommended as prophylactic therapy in patients without acute bleeding.[26] Prothrombin complex concentrate (PCC), consisting of factors II, VII, IX, and X, and proteins C and S, is a newer agent that has demonstrated superiority to FFP in the rapid reversal of warfarin-associated coagulopathy.[27,28] Its use has been expanded beyond warfarin reversal and has been shown to be effective in treating both acquired and induced coagulopathy in patients with TBI.[29] Additionally, PCC offers significant cost savings over recombinant factor VII[27,29] and should be considered as a viable alternative for the treatment of coagulopathy in the setting of TBI.

According to the recently issued by ASA/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (ICH), patients with severe anticoagulation factor deficiency or thrombocytopenia should receive appropriate replacements of factors or platelets.[1] An effect on outcome of platelet transfusion in patients receiving anti-platelet medications, particularly dual antiplatelet medications combining aspirin with P_2Y_{12}-ADP inhibitors (clopidogrel, prasugrel, ticagrelor), is not clear and considered a Class IIB recommendation. In cases of oral anticoagulant-associated intracranial hemorrhage, normalization of coagulation by reversing anticoagulant should be performed as soon as possible. In patients receiving warfarin, intravenous vitamin K (5–10 mg) should be given along with FFP (20 mL/kg) or PCC (20–40 IU/kg) to normalize prothrombin time. Administration of PCC (either 3 or 4 factors) may be advantageous in patients in whom fluid overload should be avoided (eg, patients with heart failure) as about 1 liter of FFP is required to normalize coagulation (10–15 mL/kg of FFP raises level of factors by 10–20%).[1] Patients receiving direct thrombin inhibitor dabigatran or factor Xa inhibitors (rivaroxaban and apixaban) may be treated similarly to patients on warfarin with FFP or PCC[30] as there are no reversal agents available. An antibody fragment idarucizumab has been recently advocated for the effective reversal of dabigatran;[31] its safety in neurosurgical patients, however, needs to be proven.

Electrolyte Imbalance

The patient may demonstrate hypokalemia and hyperglycemia in response to stress and trauma.[32] β-Adrenergic receptor stimulation from epinephrine (adrenaline) causes a decrease in serum potassium by driving potassium into the cells. Similarly, when pH is elevated, as is common in the brain-injured patient in whom hyperventilation is used to reduce ICP, potassium is driven into cells as hydrogen ions are released. Decreases in serum potassium values associated with acute hyperventilation and stress do not need to be treated, because total body potassium is unchanged. However, diuretic-induced renal losses of potassium do require replacement to avoid complications of acute intracellular potassium depletion, including potentiation of neuromuscular blockade

and cardiac dysrhythmias. Often, in the acutely brain-injured patient, the cause of hypokalemia is multifactorial. Initiation of treatment depends on the predominant clinical circumstances.

Diabetes insipidus may occur in the patient with basilar skull fracture or severe head injury involving the hypothalamus or posterior pituitary. Antidiuretic hormone (ADH) is synthesized in the hypothalamus and secreted by the posterior pituitary. ADH enhances the permeability of free H_2O in the distal convoluted tubule and collecting duct of the kidney. Patients with diabetes insipidus can lose large volumes (25 L/day) of dilute urine, resulting in marked increases in serum sodium and osmolality.

Diabetes insipidus should be considered in the differential diagnosis of polyuria in any patient with head trauma or pituitary and hypothalamic lesions. The differential diagnosis of intraoperative polyuria includes excessive fluid administration, osmotic agents (eg, hyperglycemia with serum glucose level greater than 180 mg/dL, mannitol), diuretics, paradoxic diuresis in patients with brain tumor,[33] and nephrogenic and central diabetes insipidus. Diabetes insipidus is diagnosed intraoperatively by the ruling out of iatrogenic causes and hyperglycemia, and through a demonstration of marked increases in serum sodium and osmolality with low urine osmolality.

Treatment of diabetes insipidus involves adequate fluid replacement with half-normal (0.45%) saline and administration of ADH. Five percent dextrose in water may alternatively be used; however, caution should be applied to avoid hyperglycemia. Aqueous vasopressin may be given subcutaneously or intramuscularly (5 to 10 U) every 6 hours or as a slow intravenous infusion (up to 0.01 U/kg/h) for rapid control of intraoperative or postoperative diabetes insipidus.[34] Larger doses may cause hypertension. For less frequent dosage, desmopressin (DDAVP) 1 to 4 µg intravenously or subcutaneously every 12 hours may be administered. Desmopressin may be given more frequently if the diabetes insipidus is not controlled. This agent has less vasopressor activity than aqueous vasopressin and is preferable to vasopressin in patients with coronary artery disease and hypertension.

Hyponatremia may also occur in the acutely brain-injured patient. Hyponatremia may be associated with diminished (eg, diuretic usage, adrenal insufficiency, salt-losing nephritis), expanded (eg, congestive heart failure, renal failure), or normal (eg, hypothyroidism, syndrome of inappropriate ADH secretion) extracellular fluid volumes. Rapid reduction of the serum sodium value to less than 125 to 130 mEq/L may cause changes in mental status and seizures. The first step in diagnosis is to establish the category to which the patient belongs. Although many clinicians are quick to suggest syndrome of inappropriate ADH secretion in patients with brain injury, this diagnosis should be made only after exclusion of other possible causes. In neurosurgical patients, hyponatremia is most commonly associated with intravascular volume depletion caused by diuretic administration or a loss of sodium via the kidney. After SAH, patients may have a primary natriuresis ("cerebral salt wasting"), which, unlike syndrome of inappropriate ADH secretion, is associated with a decreased intravascular volume.[35] Aggressive fluid therapy is required in patients with SAH to maintain a normal intravascular volume.

Blood toxicology screen is indicated in patients with impaired neurological status as alcohol, cocaine and other sympathomimetic drugs are associated with both TBI and spontaneous ICH. Pregnancy test should be performed in women of childbearing age.

Management of the Brain-Injured Patient

Airway

Patients with a GCS score of 8 or less or uncooperative patients who require sedation for neuroimaging require intubation, because patients with suspected head injury should not be sedated without an endotracheal tube in place and control of ventilation ensured. Trauma patients should be assumed to have a cervical spine injury until proven otherwise. Nasal intubation should be avoided in patients with suspected basilar skull fractures and sinus injuries.

The patient's airway and hemodynamic status should be quickly assessed before a plan for endotracheal intubation is chosen (Fig. 10.4). Rapid sequence induction with cricoid pressure is a standard technique for establishing a definitive airway in the neurologically compromised patient. Comatose patients may not require sedation or paralysis for direct laryngoscopy and endotracheal intubation. In trauma patients, in-line stabilization of the neck should be utilized. Newer airway equipment, such as optical and video laryngoscopes (eg, AirTraq, GlideScope®, McGrath®) and stylets (Shikani Seeing Stylet), may be utilized to improve visualization of the glottic opening. However, fiberoptic laryngoscopy is still considered the "gold standard" for management of the difficult airway, especially if concomitant cervical spine injury is suspected. In some cases, a cricothyroidotomy may be required.

If the airway appears normal, a muscle relaxant should be given to facilitate glottic exposure and reduce coughing. The prevention of the cough by the prior administration of a muscle relaxant appears to be most important in preventing significant increases in ICP with endotracheal intubation. Nondepolarizing neuromuscular blockers have been shown to prevent increases in ICP during tracheal stimulation.[36] Additionally, White and colleagues[37] found that succinylcholine, but not thiopental, fentanyl, or lidocaine, prevented marked rises in ICP with endotracheal suctioning in comatose head-injured patients, because of the greater reduction in coughing after administration of succinylcholine. However, barbiturates and lidocaine were effective in attenuating the increase in ICP due to tracheal stimulation in patients who also received a muscle relaxant.[38,39] These drugs and narcotics may also be necessary to prevent increases in mean arterial pressure and ICP with endotracheal intubation.

One should assess the patient's hemodynamic status to choose an anesthesia induction agent that reduces the increase in ICP that accompanies endotracheal intubation. The primary goal is to maintain adequate cerebral perfusion pressure (CPP) by ensuring hemodynamic stability while reducing ICP. Severe hypotension from the inappropriate administration of a large dose of propofol in a hypovolemic patient may be worse for the patient than the transient rise in ICP that accompanies endotracheal intubation. If the patient is hypertensive or hemodynamically stable, a rapid-sequence induction with head and neck stabilization, defasciculation, cricoid pressure, and administration of propofol, lidocaine, and succinylcholine can be used. To avoid hypoxemia and excessive increases in $PaCO_2$, the patient may be manually hyperventilated while cricoid pressure is maintained before intubation. If the patient is hypertensive, administration of narcotics (such as fentanyl), antihypertensive agents, or both may be necessary to prevent

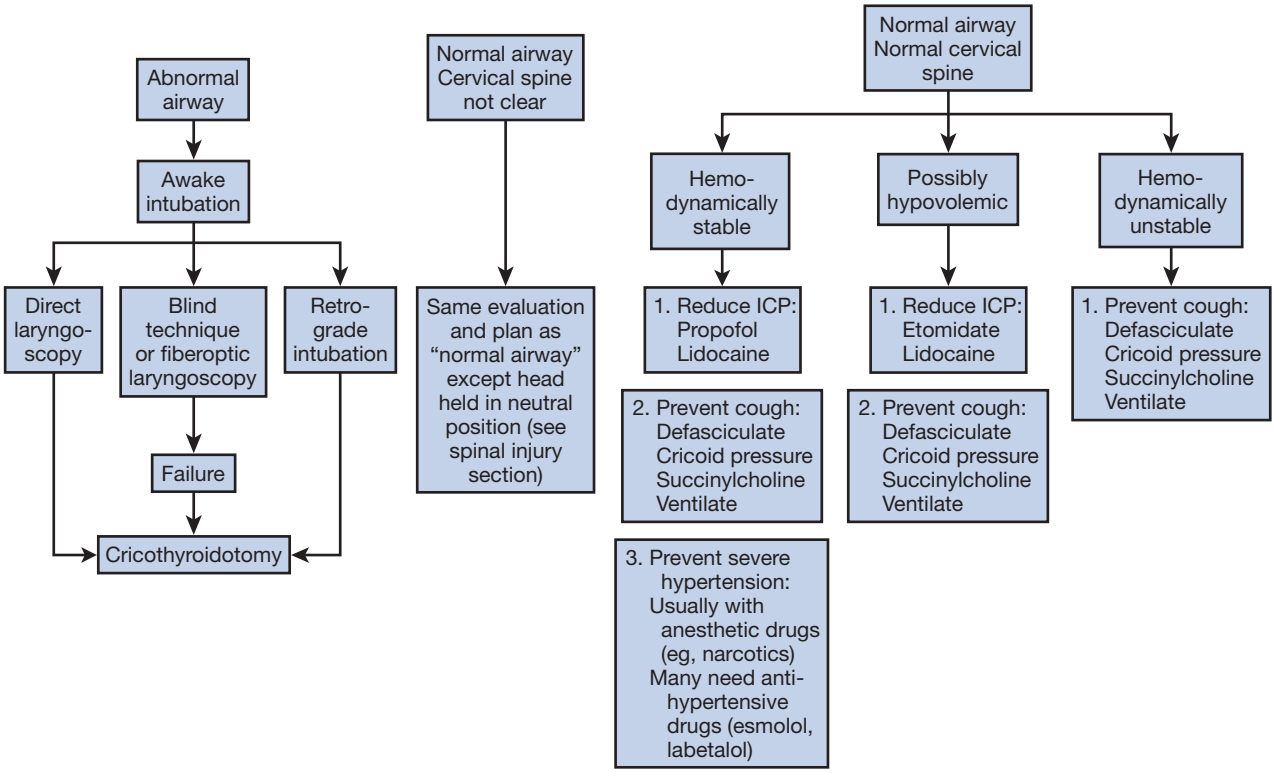


Fig. 10.4 Airway management of the brain-injured patient. ICP, intracranial pressure.

severe hypertension and increases in ICP with endotracheal intubation, but extreme caution is required to prevent untoward reductions in CPP in this setting. Esmolol and labetalol have less potential to raise ICP than sodium nitroprusside, which is a marked cerebrovasodilator.[40] Calcium channel blockers nicardipine and clevidipine are potent and safe antihypertensive medications which are widely used, particularly in patients with ICH.[41,42] If the patient is somewhat hypovolemic (as is common in the patient with multiple injuries), etomidate (0.2–0.4 mg/kg) may be used as an alternative to propofol because it is effective in reducing cerebral blood flow (CBF) and ICP.[42]

There is a renewed interest in ketamine as an induction agent in patients with brain injury. A recent randomized controlled trial proved safety of ketamine (2 mg/kg) while providing similar intubating conditions compared to etomidate in 655 patients with brain injury requiring emergency intubation.[43] If hypertension and tachycardia are of concern, another option would be a mixture of ketamine 0.75 mg/kg and propofol, which provides more stable hemodynamics compared to induction with propofol only.[44] Ketamine (1 mg/kg) was shown to decrease intracranial pressure in adults during anesthesia[45] and recently in ICU children with increased ICP (ketamine 1–1.5 mg/kg).[46]

Although succinylcholine may transiently increase ICP because of greater CO_2 production or cerebral stimulation from the fasciculations,[47] succinylcholine is the muscle relaxant of choice in emergent endotracheal intubation because of its fast onset of action, short duration, and excellent intubating conditions, unless it is contraindicated. Whether pretreatment with a "defasciculating" dose of nondepolarizing muscle relaxant is effective preventing succinylcholine-induced increase in ICP is not clear.[48] The benefits of rapid intubation and hyperventilation, if required, outweigh the disadvantages of brisk ICP increase during intubation in the acutely injured patient. Succinylcholine can potentially cause hyperkalemia. Rocuronium (0.6–1.2 mg/kg) should be chosen in this circumstance, assuming that the airway is not difficult.

Goals in the Acute Care of the Brain-Injured Patient

The principal aim in the acute medical management of the brain-injured patient is to prevent secondary neurologic injury. Over the last 30 years, an understanding of the pathophysiology and goals of an early treatment of the potential causes of secondary neurologic injury led to a significant decrease in mortality of patients with severe TBI, from 50% to 25–30%.[49]

Secondary brain injury is an important determinant of outcome from severe TBI. Factors contributing to the development of secondary neurologic injury include hypoxia, hypercapnia, hypotension, intracranial hypertension, and transtentorial or cerebellar herniation. Durations of systemic hypotension with systolic blood pressure (SBP) 90 mmHg or lower, hypoxia with arterial O_2 saturation (SaO_2) 90% or lower, and pyrexia with core temperature 38°C or higher have been found to be strongly associated with mortality after TBI.[50] Many of these factors are potentially treatable. Both CPP greater than 90 mmHg and higher GCS scores correlated with better neurologic outcome,[51] whereas CPP lower than 50 mmHg is independently associated with poor outcome after TBI.[50] Box 10.4 summarizes the aims in the acute care of patients with TBI injuries.

High-dose steroids do not reduce ICP in TBI[52] and do not affect outcome from severe head injury.[53] They are therefore not recommended for the treatment of acute TBI. Steroids may be useful in reducing edema in the rare patient who presents with impending brain herniation from a brain tumor.[54] In such a patient, clinical improvement occurs within hours of the initiation of steroid therapy.

BOX 10.4 Major Goals in the Acute Care of the Brain-Injured Patient

A. Prevention of hypoxemia—maintain PaO_2 > 60 mmHg or SaO_2 > 90%:
   1. Increase inspired oxygen tension.
   2. Treat pulmonary pathologic condition.
   3. Consider positive end-expiratory pressure (10 cm H_2O or less).
B. Maintenance of blood pressure:
   1. Prevent hypotension—maintain systolic blood pressure (SBP) >90 mmHg:
      a. Avoid glucose-containing solutions.
      b. Maintain intravascular volume status—aim for euvolemia.
   2. Treat hypertension:
      a. Sympathetic nervous system overactivity.
      b. Increased intracranial pressure.
      c. Light anesthesia.
C. Reduction in intracranial pressure:
   1. Head position.
   2. Brief periods of hyperventilation.
   3. Hyperosmolar therapy.
   4. Sedation.
   5. Hypothermia.
   6. Surgical procedures: drainage of cerebrospinal fluid and evacuation of hematoma.

Prevention of Hypoxemia

Prompt and aggressive treatment of hypoxemia in TBI patients is imperative because hypoxemia is associated with the development of secondary brain injury, worsening neurologic outcome,[7] and increasing mortality, especially when associated with systemic hypotension.[55] According to a study of 717 cases in the Traumatic Coma Data Bank, hypoxemia was identified in 22.4% patients with severe TBI and was associated with increases in morbidity and mortality.[55]

Every patient with brain injury should be assessed according to general "ABC" principles of trauma management (airway, breathing, circulation), which is initiated with provision of an adequate airway and breathing/ventilation. Every brain-injured patient should receive supplemental oxygen regardless of initial GCS score. Oxygenation should be monitored whenever possible with pulse oximeter or by measurement of arterial blood gas levels. The minimum goal of oxygenation in patients with brain injury should be to maintain SaO_2 at 90% or higher or PaO_2 at 60 mmHg or higher.[56] Patients with severe brain injury should be intubated and ventilated with 100% oxygen until adequate oxygenation is verified.

The possibility has been raised that positive end-expiratory pressure (PEEP) may increase ICP in the brain-injured patient because it may increase cerebral venous volume by reducing cerebral venous outflow. However, 10 cm H_2O PEEP improves oxygenation and usually results in clinically inconsequential increases in ICP in patients with severe head trauma.[57] PEEP may affect ICP less in patients with the stiffest lungs, who are presumably the ones who need PEEP the most.

Maintenance of Hemodynamic Stability

Hypotension

When systemic hypotension is defined as SBP less than 90 mmHg, even a single recorded prehospital episode has been shown to correlate with higher morbidity and mortality in patients with TBI.[55] While patients are in the intensive care unit, the duration of hypotension (SBP < 90 mmHg) strongly correlates with worsening of neurologic outcome as assessed by the GCS and with an increase in mortality.[50] Blood pressure should be monitored and SBP should be kept higher than 90 mmHg.[56]

The most common hemodynamic problem in the patient with head trauma and multiple injuries is hypovolemia caused by blood loss, profound diuresis from mannitol, and inappropriate attempts to restrict fluid intake. Because the damaged brain tolerates hypotension poorly, intravenous fluids should be administered in sufficient quantities to rapidly restore intravascular volume and CBF. Intraoperative blood loss may be severe in vascular injuries and skull fractures. Massive volume replacement may be required intraoperatively if a dural sinus is injured. In addition, blood loss may be difficult to quantify because it spills on the drapes and on the floor. Patients with large intracranial hemorrhages, with normal blood pressures in the lower range (SBP 100–120 mmHg), or with relative tachycardia (heartbeat >100 beats/min), should be considered to be hypovolemic unless proven otherwise. The hypovolemia may manifest as severe hypotension when the brain is decompressed. With the acute reduction of ICP, sympathetic tone and systemic vascular resistance are diminished, unmasking profound intravascular volume depletion. Vasopressors may be helpful in restoring blood pressure while fluid is being given to restore intravascular volume. However, overzealous fluid administration that elevates cerebral venous pressure may exacerbate brain edema.

The presence of hypovolemia is best assessed from clinical signs such as hypotension, tachycardia, an inability to tolerate anesthetic agents, and SBP variations with positive-pressure ventilation. A drop in SBP greater than 10 mmHg with positive-pressure ventilation is a sensitive indicator of a 10% reduction in blood volume (Fig. 10.5).[58] This decrease in SBP is a significantly better indicator than the central venous pressure.

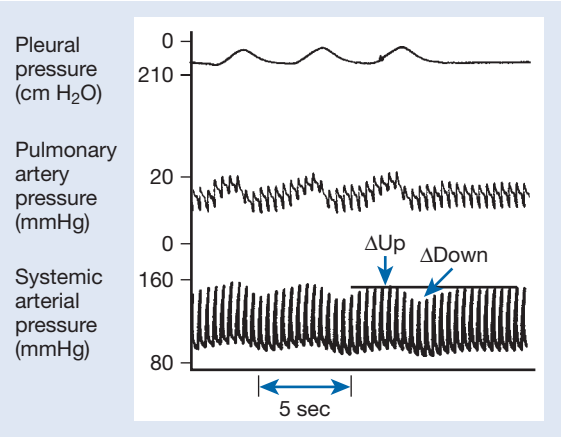


Fig. 10.5 Continuous record from mechanically ventilated dog after hemorrhage of 10% of blood volume. Pleural, pulmonary arterial, and systemic pressures are shown. Note the fluctuation in systolic blood pressure with positive-pressure ventilation. The difference between maximum and minimum systolic blood pressure is divided into delta up (ΔUp) and delta down (ΔDown) components. The delta up component is the difference between maximum systolic and end-expiratory systolic blood pressure during a 5-second period of apnea; the delta down component is the difference between end-expiratory and minimum systolic blood pressures. The systolic blood pressure variation and delta up and delta down components correlate with the severity of hypovolemia better than central venous pressure. *(From Perel A, Pizov R, Cotev S: Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 1987;67:498-502.)*

The variation in SBP correlates well with the degree of hemorrhage in dogs and humans. However, placement of a central venous line may be helpful in the acute setting, especially to prevent overhydration, and should ultimately be performed to help guide fluid replacement. Timely evacuation of the brain mass must be accomplished first, with placement of central line later, after surgery has begun and the patient has been stabilized.

Hypertension

Patients are often hypertensive after an isolated brain injury, because of an increase in catecholamines from stress-induced activation of the sympathetic nervous system.[11] Because autoregulation may be impaired after head trauma,[59] hypertension may cause brain hyperemia, promote the development of vasogenic edema, and further increase ICP. However, before immediate treatment of the blood pressure elevation with an antihypertensive agent, other causes of hypertension (such as increased ICP and inadequate anesthesia) should be first eliminated. Ensuring adequate oxygenation and ventilation, placing the head up slightly in neutral position, preventing coughing, or administering propofol alone or together with narcotics may help reduce ICP and provide greater anesthesia. Usually these measures are effective to control blood pressure in the acute management of the brain-injured patient. However, in the patient with preexisting hypertension or the severely hyperdynamic patient, control of hypertension with β-adrenergic antagonists (eg, metoprolol, labetalol, esmolol) may also be indicated. These drugs specifically treat the cause of hypertension (eg, sympathetic overactivity), and they are not cerebral vasodilators. Prophylactic β-adrenergic receptor blockade may also be useful in reducing supraventricular tachycardia, ST-segment and T-wave changes, and myocardial necrosis associated with severe head injury. Calcium channel blockers such as nicardipine and clevidipine are also suitable to control hypertension. Systemic vasodilators, such as sodium nitroprusside, nitroglycerin, and hydralazine, may increase ICP and should be avoided.[40,60,61]

In nontrauma patients, vomiting, hypertension of systolic blood pressure >200 mmHg, along with severe headache and fast progression of neurological deficit, are highly suspicious for ICH. Arterial hypertension in patients with ICH contributes to enlargement of hematoma, rebleeding and brain edema. Rapid diagnostic neuroimaging and aggressive gradual control of blood pressure with continuous intravenous antihypertensive medication is required, while maintaining cerebral perfusion pressure not less than 60 mmHg.[1] Recently, a rapid, within 1 hour, decrease in blood pressure lower than 140 mmHg was shown to be safe;[42] however, whether it is beneficial to outcome is not clear yet. There is currently an on-going multicenter study which might clarify this question (http://atach2.com/). Calcium channel blockers nicardipine and clevidipine,[62] along with alpha- and beta-blockers and other medications, can be safely used for blood pressure control utilized.

Fluid Management (see Chapter 9)

Iso-osmolar crystalloid solutions should be used to replace intravascular volume. These include Plasma-Lyte, Normosol-R, and 0.9% normal saline. Although use of any of these solutions may considerably raise ICP after resuscitation from shock,[63] ICP would be higher after inadequate resuscitation because of the development of cytotoxic edema from cerebral ischemia. The blood–brain barrier may be damaged by head trauma, allowing all fluids to cross the blood–brain barrier. Overhydration, causing increases in central venous pressure, should be avoided. Therefore, the aim of fluid management is to maintain a euvolemic patient. Less urgent procedures (eg, orthopedic surgeries) that entail significant blood loss should be delayed as long as the brain injury has stabilized (eg, ICP is within normal limits). Lactated Ringer's solution should be avoided because of its hypo-osmolarity.

The choice between *colloid* and *crystalloid* solutions for fluid replacement remains controversial. Water movement across the blood–brain barrier depends primarily on the difference in osmolality between plasma and brain. Decreases in oncotic pressure may not affect brain water content much because oncotic pressure makes only a small contribution to total plasma osmolality. Most experimental studies suggest that brain water content and ICP are no different whether isotonic colloid or crystalloid solutions are administered. Although there is experimental evidence that colloids may result in less brain edema in a model of head trauma,[64] this finding has not been supported by human studies. Investigators of the SAFE (Saline versus Albumin Fluid Evaluation) trial[65] analyzed results from a subgroup of 460 patients with TBI who were randomized to receive albumin or 0.9% saline for the initial fluid resuscitation.[66] The authors demonstrated a strong association of albumin administration with poor neurologic outcome (52.7% in albumin versus 39.4% in saline group) and death (33.2% in albumin versus 20.4% in saline group) at 24 months after TBI.[66] Significantly higher morbidity and mortality with albumin than with saline was found for patients with severe TBI, with GCS score 3 to 8 at admission, but not with moderate TBI. The mechanism of such a dramatic influence of albumin on the outcome after TBI is not clear; however, aggravation of brain edema following movement of albumin across the disrupted blood–brain barrier has been hypothesized.[66] This theory is also supported by another randomized clinical trial,[67] in which 90 patients with TBI were randomly assigned to receive initial fluid resuscitation with either fresh frozen plasma or 0.9% saline, which demonstrated a higher incidence of intracerebral hematoma formation and an increased 1-month mortality after the use of fresh frozen plasma.[67]

Hydroxyethyl starch (HES) was once the most commonly administered colloid in the treatment of critically ill patients.[68] However, practitioners are now shying away from the use of HES due to its association with severe complications, including coagulopathy and renal failure. HES prolongs the partial thromboplastin time (PTT) through a decrease in factor VIII coagulant activity and von Willebrand factor level, and volumes in excess of 500 mL may put the patient at increased risk for an intracranial hematoma.[69] Several studies have examined the use of 6% HES in critically ill patients and found a significant increase in the incidence of kidney injury, the need for renal replacement therapy, and the incidence of adverse events compared to 0.9% saline.[68,70–72] The impact on mortality is less clear. The European Society of Intensive Care Medicine released a consensus statement in 2012 recommending against the use of HES in organ donors and in patients with severe sepsis, head injury, or at risk for acute kidney injury.[73] In 2013, the United States Food and Drug Administration recommended that HES solutions not be used in critically ill adult patients and mandated that a boxed warning regarding the increased risk of mortality, severe renal injury, and excessive bleeding be included in the package insert for HES products.[74] Based on this evidence, it is prudent to avoid the use of HES in the management of patients with acute brain injury.

Hypertonic saline (HS) solutions have a potential advantage over other solutions in the resuscitation of hypotensive

brain-injured patients because of their ability to reduce brain water content and ICP[63,75] and to stabilize blood pressure. Small-volume (bolus of 250 mL) resuscitation with 7.5% HS in hypotensive patients with multiple trauma and TBI has been shown to be safe[76] and tends to better stabilize blood pressure and to improve in-hospital survival in patients with severe TBI (GCS score <8) than lactated Ringer's solution.[77,78] However, when the same regimens of fluid resuscitation were compared in patients with GCS scores less than 9 and SBP lower than 100 mmHg, the neurologic outcome at 6 months after injury in patients who received HS did not differ from that in the patients who received lactated Ringer's solution.[79]

There are no current data about an optimal concentration and volume of HS that can be recommended for fluid resuscitation. However, with safety and potential benefits taken into account, use of HS for fluid resuscitation in a hemodynamically unstable patient with brain injury represents one of the reasonable options. Other concentrations of HS—1.6%[80] or 3%[81] —may be used as well. Because the osmolality values of 3% HS and 20% mannitol are close, 5 mL/kg of 3% HS will provide the same osmolar load as 1 g/kg of 20% mannitol. To date, there are very few clinical situations in which the use of HS is of major concern. Although rapid correction of sodium in a patient with chronic hyponatremia may potentially predispose to the development of central pontine myelinolysis,[82] the latest literature does not reveal any cases of central pontine myelinolysis after resuscitation with HS, even after repeated boluses. On the other hand, continuous administration of HS in patients with a syndrome of inappropriate ADH secretion may potentially aggravate hyponatremia owing to accumulation of fluid, so HS should not be used as a first-line drug; it should be given only after water restriction and a diuretic regimen have been initiated.

In summary, iso-osmotic solutions (eg, Plasma-Lyte and 0.9% saline) are recommended for initial fluid resuscitation after brain injury. Choice of fluid should be adjusted to levels of blood electrolytes. Prophylactic administration of fresh frozen plasma is not recommended and should be used judiciously in patients with signs of coagulopathy.

Blood Glucose Control

In critically ill neurologic patients stress-induced hyperglycemia is common, and has been strongly associated with increased morbidity and mortality after stroke,[83,84] SAH,[85] TBI,[86,87] and cardiac arrest.[88] In these human studies, whether the hyperglycemia was the cause or the result of the increased severity of the neurologic damage is unclear.

Although cellular mechanisms of hyperglycemia, such as an impaired immunity and an increased risk of infection, mitochondrial damage, intracellular acidosis, endothelial injury, and inflammation, have been described, the exact mechanisms for the enhanced neurologic damage are unclear. How glucose administration affects outcome after brain injury also is not known. In a rat model of head trauma, glucose administration did not alter neurologic outcome or the formation of brain edema.[89]

The exact threshold level of blood glucose value above which ischemic neurologic damage is increased is also not known; however, it appears to be less than 200 mg/dL. On the other hand, tight glycemic control (maintenance of a blood glucose level at 80–100 mg/dL) using intensive insulin therapy, which has been broadly advocated in the surgical critically ill population,[90] has been recently shown to be detrimental.[91] Tight glycemic control may be particularly dangerous in patients who had experienced some degree of brain injury, such as after cardiac arrest[92] or SAH,[93] because of high incidence of hypoglycemia, lack of benefit, or worsening of outcome. Glucose is the main energy source of the brain, and due to its limited capacity for glycogen storage, the brain has limited compensatory capacity against hypoglycemia. Additionally, the acutely injured brain has a higher metabolic demand than under physiologic conditions and is thus prone to glucose shortage.[94]

Glucose-containing solutions should not be administered acutely to the brain-injured patient because they may exacerbate neurologic damage. Numerous animal studies provide convincing evidence that glucose administration, with or without marked hyperglycemia, enlarges infarct size and augments neurologic damage from global and regional cerebral ischemia.[95]

Part of the difficulty in determining a "safe" level of blood glucose in patients is that blood glucose levels may not accurately reflect brain glucose levels during periods of transient hyperglycemia. Brain glucose values remain elevated after glucose infusion, whereas blood glucose values decrease in response to insulin. Meta-analysis of 16 randomized controlled studies (1248 patients) of the last decade demonstrated that, although tight glycemic control of blood glucose between 70 and 140 mg/dL had no impact on mortality in patients with an acute neurologic injury (TBI, stroke, CNS infections and SCI) compared to conventional glycemic control maintaining blood glucose between 144 and 300 mg/dL, it worsened neurological outcome.[96] These data suggest that maintaining blood glucose between 140 and 180 mg/dL would be an appropriate strategy of glycemic control in patients with acute CNS injury. However, the actual benefits and risks of acute reductions of blood glucose in patients with acute and chronic hyperglycemia are unclear.

Temperature Control

Hyperthermia (temperature >38° C) is known to be detrimental for patients with brain injury and is strongly associated with worsening neurologic outcome and increasing mortality in patients with TBI,[50] SAH,[97] and stroke.[98] Undoubtedly, hyperpyrexia in patients with brain injury should be avoided and treated. Aggressive warming up of patients with traumatic brain injury who were hypothermic at arrival has been shown to be detrimental;[99] therefore, fast infusion of warmed fluids should be performed cautiously, especially in the operating room setting in cases of hypovolemia and hemorrhage, with the danger of hyperpyrexia in mind.

Treatment options to reduce temperature in patients with acute brain injury include (1) antipyretic medications (aspirin, acetaminophen, ibuprofen, diclofenac), which can be used in patients with stroke but not in those with TBI because of potential worsening of coagulation, (2) external devices such as cooling blankets, which are the most safe and useful tools, and (3) internal cooling such as an intravenous infusion of cold saline and, in resistant hyperpyrexia, endovascular cooling. Currently, there are no data available demonstrating the optimal treatment of the febrile patient with acute neurologic injury, so the treatment approach should be specifically chosen for each patient.

From the physiologic point of view, induction of hypothermia in the patient with brain injury offers the potential benefit of reducing the cerebral metabolic rate of oxygen. Currently there are not sufficient data for a strong recommendation of inducing mild hypothermia in brain-injured patients. Based on the analysis of six randomized control trials[99–104] performed during the last 15 years (target cooling temperature between

32° and 35° C), Brain Trauma Foundation 2007 guidelines suggested that moderate hypothermia may potentially improve outcome after TBI, suggesting that initiation of hypothermia targeted to 32° to 33° C should be induced and maintained for at least 48 hours after injury to decrease the mortality rate.[105] However, concomitant use of barbiturates and hypothermia can significantly raise the incidence of pneumonia, and, therefore, in patients with increased ICP, the conventional treatment including barbiturates should be applied first, before hypothermia is considered.

Monitoring and Treatment of Intracranial Hypertension

A major goal in the acute treatment of the brain-injured patient is to reduce ICP, which may be accomplished through head position, hyperventilation, hyperosmotic solutions and diuretics, barbiturates and other IV anesthetics such as propofol, and surgical treatment. Monitoring of ICP, CPP, oxygen saturation in the jugular bulb (SjO_2), and brain tissue oxygen (PbO_2) are useful tools for the bedside assessment of patients with brain injury.

Head Position

A slightly head-up position (up to 30-degree head-up tilt) with the neck in neutral position promotes cerebral venous drainage and reduces ICP if the cerebrospinal fluid pathways are still patent.[106] Lateral turning of the head, tight endotracheal or tracheostomy tube ties around the neck, and the Trendelenburg position may dramatically raise ICP because they restrict venous return from the brain. The patient's respiratory muscles should be paralyzed to prevent coughing and bucking on the endotracheal tube, which also increases ICP. On the other hand, marked elevation of the head in a hypovolemic patient, if it diminishes mean arterial pressure, may cause decreased brain perfusion and cerebral ischemia.

Hyperventilation

Hyperventilation-induced hypocapnia is a powerful therapeutic tool in treatment of intracranial hypertension. Although hypocapnia may acutely lower ICP by causing an extracellular alkalosis and cerebral vasoconstriction, it may increase cerebral ischemia.[107] Excessive hyperventilation causes profound cerebral vasoconstriction and a decrease in CBF, which may be detrimental if CBF was already impaired as a result of brain injury. Taking into account that a majority of brain-injured patients suffer a dramatic decrease in CBF to less than 50% of normal in the first 24 to 48 hours after injury,[108,109] the Brain Trauma Foundation's 2007 guidelines recommend avoiding hyperventilation in the first 24 hours after brain injury and avoiding prophylactic hyperventilation.[110]

A randomized, controlled trial of prophylactic hyperventilation therapy for 5 days after severe TBI also found that outcome was worse in the hyperventilated group, but only in patients with relatively intact motor function.[111] This result may reflect the ability of hypocapnic vasoconstriction to exacerbate cerebral ischemia in the injured brain. Global CBF and regional CBF are severely reduced and metabolism is increased during the first few hours and days after brain injury. Focal cerebral ischemia is common after TBI.[112] Hyperventilation causes a further drop in CBF, often without a decrease in ICP, which may further exacerbate cerebral ischemia.

Hyperventilation may have significant adverse cardiopulmonary effects. It may lower systemic blood pressure by reducing venous return, sympathetic stimulation, and cardiac output. It results in a leftward shift of the oxyhemoglobin dissociation curve, causing lower mixed venous and arterial oxygen tension values for any given oxygen saturation. Hypocapnia inhibits hypoxic pulmonary vasoconstriction and causes bronchoconstriction. Increases in pulmonary shunt may occur in hyperventilated patients.[113]

Because of these concerns, $PaCO_2$ generally should be kept at normocapnic levels in the patient with TBI. Brief periods of hypocapnia may be useful and have not been shown to be harmful in the acutely decompensating patient until definitive surgical treatment takes place. According to the Brain Injury Foundation's guidelines for the management of severe traumatic brain injury,[110] if hyperventilation is considered for treatment, a jugular venous bulb catheter should be inserted for monitoring of SjO_2. Jugular desaturation is common after head injury and traumatic intracranial hematoma, and it may be exacerbated by hyperventilation.[112] High interpersonal variability in normal levels of SjO_2 (55–75%) may make interpretation of the parameter difficult in the brain-injured patient. However, the majority of experts believe that a decrease in SjO_2 to less than 50% reflects a decrease in CBF, which could potentially lead to brain ischemia and should be avoided.

Hyperosmolar Therapy

Mannitol decreases brain water content and ICP primarily by increasing plasma osmolality, thereby creating an osmotic gradient across the intact blood–brain barrier. The amount of water that can be withdrawn from the brain depends on the magnitude of the osmotic gradient, the total time the gradient exists, and the integrity of the blood–brain barrier. Mannitol is less effective with larger lesions because with damaged blood–brain barriers, mannitol moves down its concentration gradient into the brain. This movement may account for a rebound increase in ICP occasionally seen after mannitol infusion.

Administration of mannitol may cause a triphasic hemodynamic response. Transient (1 to 2 minutes) hypotension may occur after rapid administration of mannitol. Mannitol then increases blood volume, cardiac index, and pulmonary capillary wedge pressure, with a maximum increase shortly after termination of the infusion.[114] ICP may rise transiently because of increases in cerebral blood volume and CBF.[115] ICP increases are attenuated by slow infusion of mannitol. Transient rises in ICP are uncommon in the patient with elevated ICP.[116] At 30 minutes after mannitol administration, blood volume returns to normal, and pulmonary capillary wedge pressure and cardiac index drop to below normal levels because of peripheral vascular pooling.[114]

Mannitol reduces blood viscosity and red blood cell rigidity, which may enhance perfusion of the brain microcirculation. This agent transiently reduces hematocrit and increases serum osmolality. It also causes hyponatremia, hyperkalemia, and decreases in pH caused by HCO_3 dilution. Prolonged and marked hyperosmolality with hyponatremia can occur in patients with acute or chronic renal failure.[117]

Doses of mannitol from 0.25 to 2 g/kg are usually administered; a typical dose is 1 g/kg. Lower doses are effective in reducing ICP acutely and cause fewer electrolyte abnormalities; however, they must be given more frequently. Rapid administration of mannitol causes a more profound reduction in ICP but may transiently cause hypotension and more marked increases in intravascular and cerebral blood volumes. The benefits and disadvantages of a particular dose and speed of administration must be weighed carefully in any patient. Giving more mannitol when the patient's serum osmolality value is higher than 330 mOsm/L is seldom effective.

Mechanisms of action of *hypertonic saline* on the cerebral physiology resemble those of mannitol. Equiosmolar boluses of HS and mannitol have been shown to have similar effects on brain shrinkage in patients undergoing craniotomy with and without SAH[81] as well as on the decrease in ICP in patients with TBI.[118] However, HS does not cause as profound a diuresis or as negative a fluid balance as mannitol does. Therefore, administration of HS can be beneficial and should be considered in hemodynamically unstable or hypovolemic patients or patients with heart disease. Boluses of HS may be administered intravenously over 15 to 20 minutes. No exact bolus volume or concentration of HS solution can be strongly recommended. A wide range of HS solution concentrations, between 1.6% and 7.5%, have been successfully administered peripherally without significant complications. Administration of 5 mL/kg of 3% HS will provide the same osmolar load as 1 g/kg of 20% mannitol.

Diuretics

Furosemide has been reported to lower ICP and brain water content when used alone in large (1 mg/kg) doses[119] or in combination with mannitol in smaller doses.[120] In contrast to mannitol, furosemide alone did not reduce ICP. Clinical impressions are that mannitol produces a better reduction of brain bulk than furosemide. Furosemide may be advantageous to patients with heart and renal diseases because, unlike mannitol, it does not increase blood volume or ICP.

The mechanism of furosemide's action on reducing ICP is unknown. It is not related to the agent's diuretic effect. Furosemide may reduce cerebrospinal fluid formation and water and ion penetration across the blood–brain barrier. It also potentiates mannitol by sustaining the increase in serum osmolality induced by mannitol. Therefore, reductions in ICP and brain shrinkage are consistently greater and longer in duration with mannitol and furosemide than with either agent alone.[120] However, hyponatremia, hypokalemia, hypochloremia, hyperosmolality, and a significantly greater rate of water and electrolyte excretion occur with this combination of diuretics. Water excretions of up to 42 mL/min have been reported with the combination of drugs, compared with 17 mL/min with mannitol alone.

Low doses of furosemide (5–20 mg) added to mannitol (0.25–1 g/kg) are very effective in reducing brain bulk. Larger doses of furosemide may be required to produce the same effect in the patient who had been undergoing long-term diuretic therapy. Mannitol-induced increases in blood volume and ICP may also be attenuated when furosemide is administered before mannitol. However, with administration of combined diuretics, vigorous intravascular fluid and electrolyte replacement are required. A urine loss of 2–3 L over 2 hours is common with combined diuretic therapy.

Barbiturates and Other Sedatives and Analgesics

Barbiturates reduce cerebral metabolism, CBF, cerebral blood volume, and ICP. Due to a lack of availability of short-acting barbiturates in the United States, barbiturate administration is infrequent and primarily reserved for treatment in the intensive care unit. High-dose barbiturates have been used successfully to reduce ICP in patients with TBI refractory to other treatments and are considered the gold standard for sedation in patients with refractory intracranial hypertension.[121] However, barbiturate therapy probably does not affect long-term outcome after TBI.[122]

Although barbiturates may aid in the acute control of ICP, their use is limited by the fact that they may cause cardiac depression as well as reduce arterial blood pressure and CPP. Because hypotension is a definite risk factor for worsened neurologic outcome in the brain-injured patient, maintaining a normal blood pressure is particularly important. Thus barbiturates should be carefully titrated, and blood pressure supported with vasopressors or inotropic agents as necessary. Barbiturates should not be administered to hypovolemic or hypotensive patients. High doses of barbiturates should be administered with caution before the surgical evacuation of an intracranial mass, because blood pressure may decrease with the reduction in sympathetic tone that accompanies brain decompression. Pentobarbital is the most useful barbiturate for the control of ICP. The classic regimen, which was recommended for inducing barbiturate coma, consisted of a loading dose of pentobarbital, 10 mg/kg over 30 minutes, followed by 5 mg/kg/hour for 3 hours, followed by a maintenance infusion of 1 mg/kg/hour.[123] However, other regimens may be successfully used, especially if burst suppression is controlled by EEG. Given the instability of the acutely injured patient, high doses of barbiturates are best reserved for use in the intensive care unit.

Propofol is useful for sedation and control of ICP.[121] Like barbiturates, propofol may cause a decrease in blood pressure; however, the major advantage of propofol is the fast recovery from its effect, which provides favorable conditions for neurologic examination. The dose of propofol required for the burst suppression is high (about 200 µg/kg/min) and therefore provides a high lipid load to the patient. Long-term high-dose (>5 mg/kg/hour for >48 hours) propofol sedation has the potential for the development of the fatal propofol-infusion syndrome. This condition is characterized by lactic acidosis, rhabdomyolysis, renal failure, lipidemia, fatty infiltration of liver, and fatal cardiac failure.[124–126] Propofol infusion syndrome has been more commonly reported in children, and its use is not advised for long-term infusion for children in the intensive care unit. It has been shown to have a strong association with neurologic disease, particularly TBI. The onset of propofol-infusion syndrome may be short—less than 24 hours—so when a patient is in the intensive care unit, the choice of sedative agent should be reconsidered daily.

Midazolam reduces cerebral metabolism, blood flow and blood volume, but preserves cerebral autoregulation and can be successfully used for sedation. Usually, continuous infusion of midazolam (2–4 mg/hour) is combined with opioids (morphine sulfate 4 mg/hour, fentanyl 2–5 µg/kg/h, or sufentanil 0.05–2 µg/kg/h). Because opioids generally do not affect cerebral metabolism and blood flow and do provide hemodynamic stability, these regimens are well tolerated. However, slow recovery after cessation of infusion makes midazolam-opioid sedation less desirable for patients with brain injury. Reversal of benzodiazepine effects with flumazenil can lead to increases in ICP and seizure activity.[127]

Surgical Treatment

Surgical treatment may be required to lower ICP acutely. Placement of a ventriculostomy catheter may be difficult because the extent of brain swelling may prevent localization of the ventricles.

Prompt removal of an acute subdural, epidural, or large solitary intracerebral hematoma is indicated. Mortality and morbidity are reduced by prompt diagnosis and surgical treatment of an epidural hematoma, especially if performed before signs of tentorial herniation occur. In addition, mortality from an acute subdural hematoma is reduced by rapid diagnosis and surgical treatment. Seelig and colleagues[128] reported that

patients who underwent surgery within 4 hours of injury had a 30% mortality rate, compared with 90% mortality for those who had surgery after 4 hours.

SPINAL CORD INJURY

Spinal injuries occur in 5–10% of major trauma cases. The National Emergency X-Radiography Utilization Study (NEXUS) group, which prospectively enrolled 34,069 patients with blunt trauma who underwent cervical spine radiography at admission in 21 institutions, found an incidence of cervical spine injuries of 2.4%.[129] Risk factors for cervical spine injury included (1) male gender, (2) age older than 65 years, and (3) ethnicity (white, and "other" ethnicity, non-Hispanic, non-black).[130] Motor vehicle accidents are the most common cause of injury, followed by falls, sports injuries, and gunshot or stab wounds. People experiencing head-first falls and unrestrained (by seatbelts) drivers or passengers in high-speed, front-end motor vehicle accidents are at particularly high risk (6– 10%) for cervical spine injury.[131] At moderate risk (1–3%) are drivers or passengers (unrestrained by seatbelts) in lower-speed motor vehicle accidents and people with blunt head trauma or with side-first or foot-first falls. Totally alert patients without any neck pain or tenderness are generally not at risk for spinal injury,[132] because a significant association is found between neck pain or tenderness and cervical injury. However, if a patient has even minimal spinal tenderness, has other painful injuries, or is intoxicated, the cervical spine should be considered unstable and should be fully evaluated.

Only about 5% of all spinal cord injuries are observed in children. In childhood, fractures are less common because spine mobility is greater than that in adulthood as a result of ligamentous laxity and incompletely ossified wedge-shaped vertebrae.[133] However, these anatomic features make children prone to extremely high cervical lesions and increase the incidence of SCI without radiographic abnormality.[134]

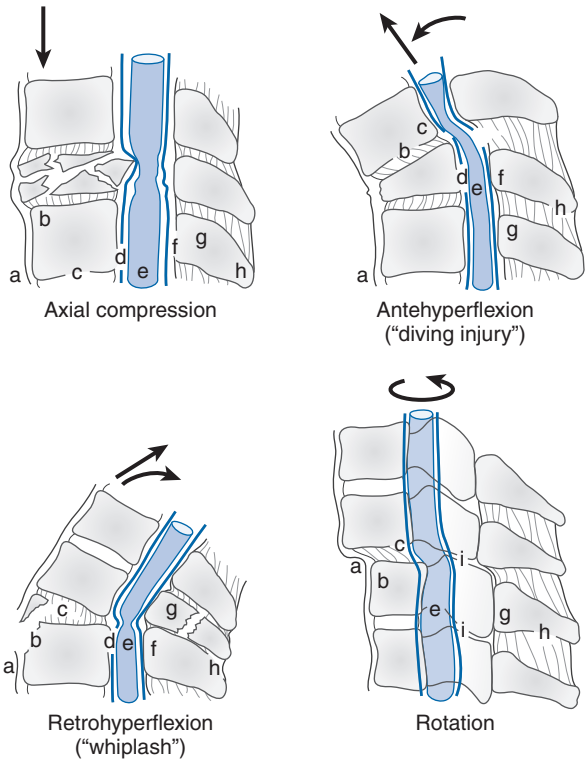


Fig. 10.6 Mechanisms of spinal cord injury: axial compression, antehyperflexion (flexion injury), retrohyperflexion (extension injury), and rotation. The arrows show the direction of compression, flexion, or rotation injury to the spinal cord. a, Anterior spinal ligament; b, vertebral body; c, intervertebral disk; d, posterior spinal ligament; e, spinal cord; f, ligamentum flavum; g, spinal process; h, interspinous ligaments; i, intervertebral facet joint. Note compression of the anterior elements in flexion injury and compression of the posterior elements in extension injuries. *(From Fraser A, Edmonds-Seal J: Spinal cord injuries: A review of the problems facing the anaesthetist. Anesthesia 1982;37:1084-1098.)*

Neurologic Evaluation

Evaluation of the Extent of Spinal Cord Injury

A convenient way to visualize the structure of the vertebral column uses the three-column concept.[135] The anterior column contains the anterior longitudinal ligament and the anterior two-thirds of the vertebral body and annulus fibrosus. The middle column contains the posterior one-third of the vertebral body, annulus fibrosus, and posterior longitudinal ligament. The posterior column consists of the posterior neural arch, spinous processes, articular facet processes, and their corresponding posterior ligamentous column. The three-column concept is useful in localizing spinal injury, depending on the mechanism of injury.

Injuries to the spine may be classified as extension, flexion, compression, rotation, or some combination of these four basic mechanisms (Fig. 10.6). Extension injuries, such as those from blows under the chin or whiplash, mostly disrupt the posterior column. Flexion injuries, such as a diving injury, mostly disrupt the anterior column. The stability of the injured spine is variable and ranges from stable (eg, burst fracture or wedge of a vertebral body) to very unstable (eg, hangman's fracture). The primary factor that determines the stability of the injury is the integrity of the ligaments, intervertebral disks, and osseous articulators.[136] In addition, the spinal cord may or may not be injured. With a complete SCI, there is loss of all motor or sensory function below the level of the injury. With incomplete injuries, there is some preservation of function. Incomplete lesions may result in several syndromes (Table 10.1). Of patients with significant SCI, 30–70% have neurologic deficits.[137] About 70% of cervical spine injuries are considered potentially unstable or to be associated with clinically significant SCI.[129] Vertebrae C5 to C7 constitute the most vulnerable segment of cervical spine, and fractures, dislocations, or bony injuries in this segment are most likely to result in SCI. However, the degree of SCI cannot be correlated with the stability of the spine.

Extension injuries are twice as common as flexion injuries.[136] One-third of extension injuries involve the atlantoaxial joint. Hyperextension with compression may cause fracture–dislocation disruption of both anterior and posterior columns and is highly unstable. A hangman's fracture, which occurs with violent hyperextension, fractures the pedicles of C2, causes anterior subluxation of C2 or C3, and is also highly unstable, with a variable severity of spinal cord damage. Flexion injuries may result in wedge fractures of the vertebral body without ligamentous injuries. These are often stable, except in severe injuries, in which greater disruption of the anterior and posterior columns may occur. The most severe flexion injury is a teardrop fracture, which is highly unstable. Compression injuries may cause burst fractures, and posterior displacement of vertebral body fragments may cause SCI despite the relative stability of the fracture.

Spine Immobilization

Because patients with high-speed multiple trauma and head injury are at increased risk for SCI, their cervical spines

Table 10.1 Spinal Cord Injury Syndromes

Syndrome	Signs
Complete neurologic injury	Loss of all motor and sensory function below the level of injury
Incomplete neurologic injury:	
Central cord	Motor loss (arms greater than legs) Bladder dysfunction Variable sensory loss
Brown-Séquard syndrome	Ipsilateral paralysis Ipsilateral loss of proprioception, touch, and vibration Contralateral loss of pain and temperature
Anterior cord syndrome	Bilateral motor loss Bilateral loss of pain and temperature Preservation of proprioception, touch, and vibration
Posterior cord syndrome	Loss of touch and temperature Motor function intact Proprioception and vibration intact

should be immobilized, and they should be moved using the logroll technique until evaluation reveals no injury. The best way to immobilize the neck in the acute setting is with use of a rigid collar, sandbags on either side of the neck, and tape across the forehead.[138] Soft collars do not effectively limit neck motion; they actually permit 96% of normal flexion and 73% of normal extension, and they do not restrict motion in the lateral or rotational directions.[139] Thus soft collars serve only as a reminder of the possibility of cervical spine injury. Rigid collars (eg, Philadelphia collar, extrication collar) still allow about 30% of neck extension and flexion, and about 45% of normal rotation or lateral movement. The Philadelphia collar is preferred because it is a two-piece collar that is easy to place without significantly moving the patient. In contrast, lateral sandbags and forehead tape effectively prevent flexion, reducing lateral and rotary motions to 5% of normal and extension to 35% of normal. After the initial diagnosis and work-up are completed, tong or halo fixation devices can be applied. These devices dramatically reduce neck motion, allowing only 4% of flexion or extension and 1% of normal rotation.[138]

Radiologic Evaluation

The standard radiologic evaluation of the cervical spine involves obtaining cross-table lateral, anteroposterior, and odontoid (open-mouth) radiographs of the cervical spine. Because 20% of all spinal fractures occur at C7,[129] all seven cervical vertebrae must be evident on the lateral spine film.[15,139] The cross-table lateral film (Fig. 10.7) allows evaluation of the alignment of the vertebrae, the bony structure of each vertebra, and the width of the prevertebral and intervertebral spaces.[139] A lordotic alignment should be present on each of the four anatomic lines on the cervical spine (ie, along the anterior and posterior margins of the vertebral border, the spinolaminar line, and the posterior margins of the spinous process; Fig. 10.8). The bony structure of each vertebra is examined for the structure of the vertebral body and spinous processes, the size of the intervertebral

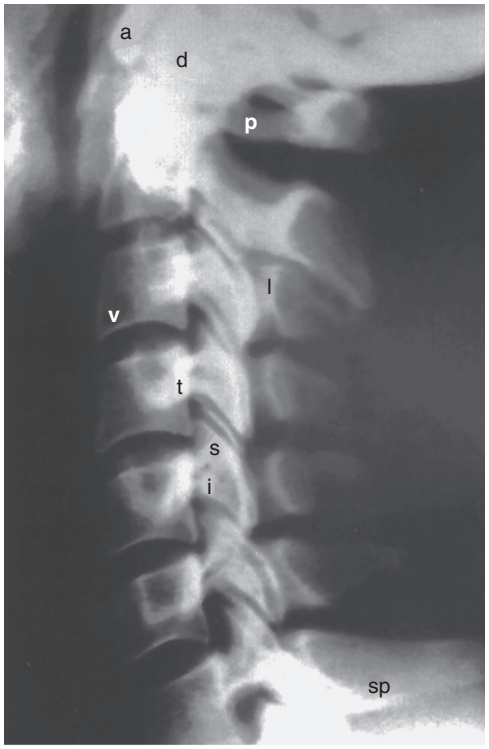


Fig. 10.7 Cross-table radiograph of normal cervical spine. a, Anterior arch of C1; d, posterior arch of C1; i, inferior articulating facet of C5; l, lamina of C3; s, superior articulating facet of C5; sp, spinous process of C7; t, transverse process of C4; v, vertebral body of C3. *(From Ovassapian A: Fiberoptic Airway Endoscopy in Anesthesia and Critical Care. New York, Raven Press, 1990.)*

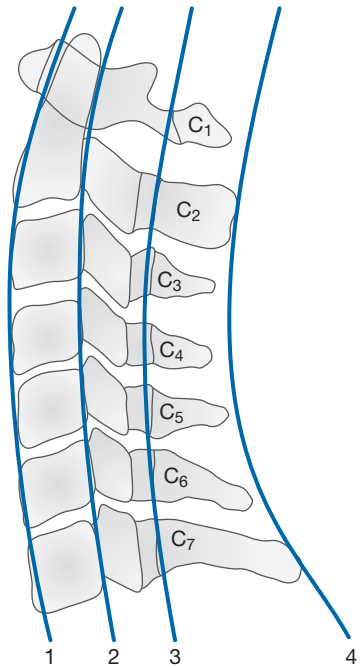


Fig. 10.8 Diagram of the lateral view of the cervical spine demonstrating normal alignment. The "ABCs" of interpretation involve alignment, bones, cartilage, and soft tissue spaces. Four smooth, lordotic curves are drawn along the anterior margins of the vertebral border (1), the posterior margins (2), the junction between the lamina and the spinous processes (3), and the tips of the spinous process (4). Lines 2 and 3 are the approximate borders of the spinal canal. *(From Williams CF, Bernstein TW, Jalenko C: Essentiality of the lateral cervical spine radiograph. Ann Emerg Med 1981;10:198.)*

disk space, the relationship of the articular facet and joints, and the interspinous process distance.[139] Widening of the prevertebral space may indicate the presence of a severe and unstable spine injury, even on an otherwise normal C-spine radiograph, or it may be associated with airway obstruction (Fig. 10.9).[140,141] About 15–20% of cervical spine fractures are not identified on the cross-table lateral radiograph.[139] Therefore, if a lateral film alone has been taken in a high-risk patient, the neck should continue to be treated as injured and potentially unstable. The sensitivity of the radiographs can be increased to 93% by adding an anteroposterior view and an odontoid view.[139] The anteroposterior view (Fig. 10.10) demonstrates the vertical alignment of the spinous and articular process and abnormalities in disk and joint spaces, such as disk space enlargement, which may indicate a severe ligamentous injury.[136] The open-mouth or odontoid view (Fig. 10.11) visualizes the atlanto-occipital and atlantoaxial joints and the odontoid process. Supplemental films, such as oblique and flexion-extension views, may be required for further detail.

CT may be used to rule out cervical spine injury when the plain radiograph findings are suspicious, equivocal, or negative in the patient with clinical signs of SCI. This modality is also used to evaluate the cervical spine in patients who cannot open their mouths (such as intubated patients). It is superior to the plain radiographs in diagnosing cervical spine trauma, especially at C1 or C2; however, ligamentous injuries may be missed on a CT scan.[137] In rare cases, magnetic resonance imaging or myelography may be required to determine the extent of spine injury.

It is important to identify and to differentiate cervical spine injuries that are not associated with clinical instability. Two large multicenter studies, performed by the National Emergency X-Radiography Utilization Study (NEXUS) group and the Canadian CT Head and Cervical Spine Study group, have identified the radiographic signs of clinically insignificant cervical spine injuries (Table 10.2).[129,142]

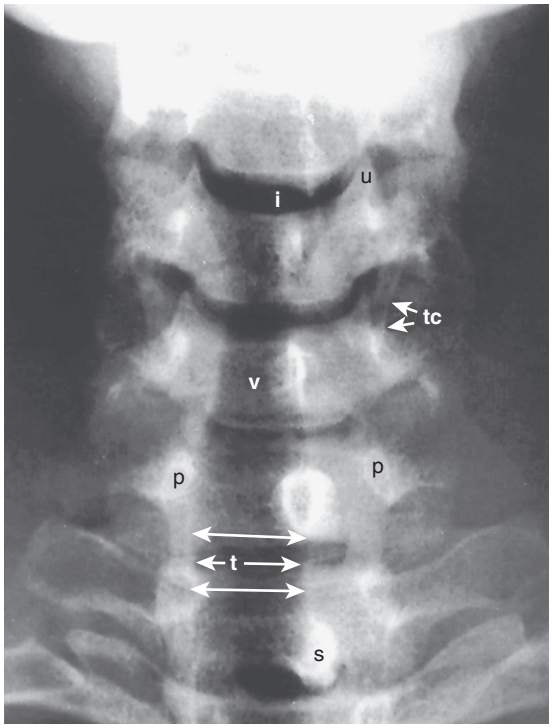


Fig. 10.10 Anteroposterior radiograph of the normal cervical spine. i, Intervertebral foramen of C3–C4; p, pedicle of C6; s, spinous process of C7; t, trachea (*arrows*); tc, thyroid cartilage; u, uncinate process of C4; v, vertebral body of C5. *(From Ovassapian A: Fiberoptic Airway Endoscopy in Anesthesia and Critical Care. New York, Raven Press, 1990, p 37.)*

Evaluation of Other Organ Systems

Respiratory System

Respiratory complications represent the most common (80% in some studies) and serious complications in patients with SCI, significantly contributing to morbidity and mortality. The pathophysiologic changes of the breathing process and

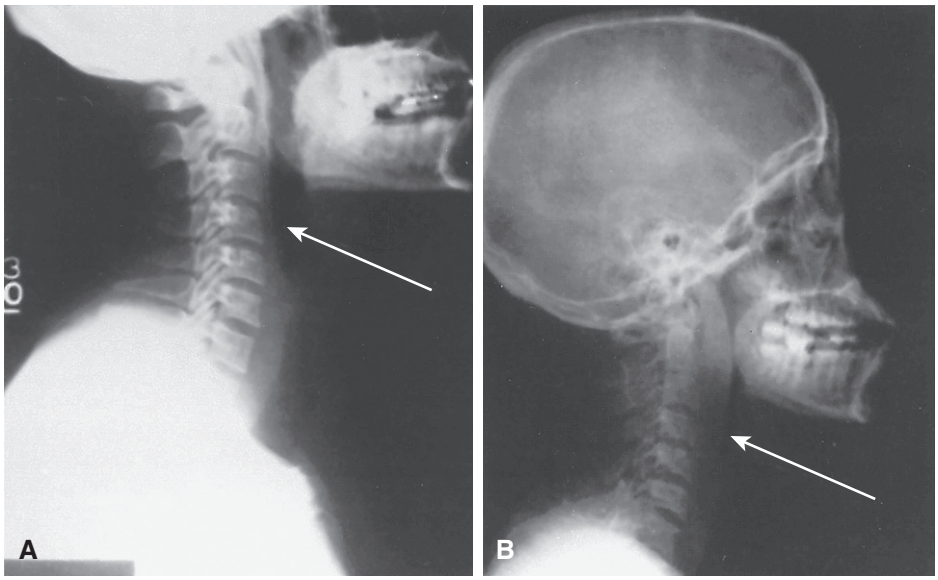


Fig. 10.9 Example of severe prevertebral soft tissue swelling secondary to a whiplash injury. **A,** Radiograph illustrates lateral cervical spine in a normal patient. *Arrow* points to the prevertebral plane, which has a width of 3.2 mm at C2. **B,** Radiograph illustrates a patient with marked widening of the prevertebral plane (*arrow*), which measures 11 mm at C2. This patient presented with airway obstruction requiring endotracheal intubation with a fiberoptic technique. *(From Biby L., Santora AH: Prevertebral hematoma secondary to whiplash injury necessitating emergency intubation. Anesth Analg 1990;70:112.)*

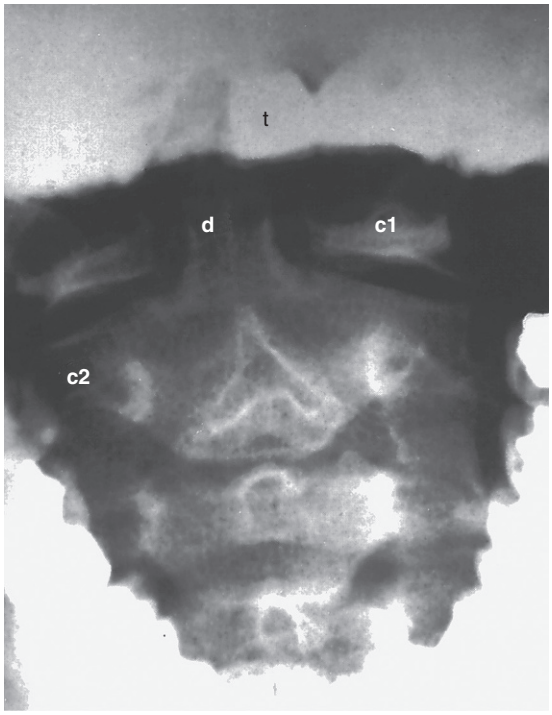


Fig. 10.11 Open-mouth or odontoid radiograph of normal cervical spine. c1, Anterior arch of C1; c2, body of C2; D, Dens axis (C2); t, teeth. *(From Ovassapian A: Fiberoptic Airway Endoscopy in Anesthesia and Critical Care. New York, Raven Press, 1990, p 37.)*

TABLE 10.2 Radiologic Signs of Clinically Insignificant Cervical Spine Injuries

From the National Emergency X-Radiography Utilization Study (NEXUS) (21 hospitals; 34,069 patients)[134]	Spinous process fracture Wedge compression fractures with loss of ≤25% of vertebral body height Isolated osteophyte fractures Isolated transverse process fractures End-plate fractures Type 1 odontoid fracture Trabecular fractures Isolated avulsion fractures without ligament injury
From the Canadian CT Head and Cervical Spine Study (CCTHCSS) (10 hospitals; 8,924 patients)[143]	Spinous process fracture Compression fractures with loss of ≤25% of vertebral body height Simple osteophyte fractures Isolated transverse process fractures

BOX 10.5 Spinal Cord Injury: Effects on Other Organ Systems

1. Respiratory system:
   a. Decreased ability to ventilate, depending on level of injury.
   b. Associated pulmonary injuries: atelectasis, aspiration, pulmonary contusion, pneumothorax, neurogenic or non-neurogenic pulmonary edema.
2. Cardiovascular system:
   a. Initial sympathetic nervous system overactivity.
   b. Spinal shock: hypotension, bradycardia.
   c. Severe bradycardia (or asystole) with airway instrumentation.
3. Temperature control: poikilothermia.
4. Other systems: possible orthopedic, intrathoracic, intra-abdominal, or head injuries.

Table 10.3 Effects of Spinal Cord Injury on Respiratory Function

Damaged Cord Segment	Severity of Respiratory Compromise
C3–C5	Decrease in vital capacity to 20–25% of normal or lower
	Paradoxical respiration
	Use of accessory muscles
	Variable loss of phrenic nerve function and paralysis of diaphragm
	Loss of intercostal and abdominal muscles
	Ventilatory support required
C5–C8	Decrease in vital capacity to 30% of normal
	Paradoxical respiration
	Use of accessory muscles
	No cough
	Ventilation improved in supine position
	Loss of intercostal and abdominal muscles
T1–T6	Variable intercostal muscle functions
	Partial loss of diaphragm effectiveness
	Weak cough
T6–T12	Weak cough
	Variable abdominal muscle strength

lung injury secondary to SCI occur early after SCI. Forced vital capacity and functional residual capacity are reduced in patients with SCIs, with the greatest respiratory impairment observed with cervical lesions (Box 10.5 and Table 10.3).[144] The diaphragm, which contributes 60% to normal vital capacity, is innervated by the phrenic nerve (C3 to C5). Lesions above this level cause total diaphragmatic paralysis and inability to ventilate (see Table 10.3). The patient with a lesion below C6 has an intact diaphragm but variable loss of intercostal and abdominal muscle function. Patients with C6 lesions have a significant decrease in vital capacity to 30% of predicted, associated with a reduction in functional residual capacity, caused primarily by loss of expiratory reserve volume. Paradoxical ventilation (chest retraction on inspiration and chest expansion during expiration), relaxation of the abdominal wall that interferes with the normal position and movement of the diaphragm, loss of cough, reduced ability to handle secretions, and associated chest injuries also contribute to respiratory compromise. Vital capacity is higher in the supine than in the head-up or prone position because of diaphragmatic mechanics. In addition to impaired ventilation, other pulmonary injuries, such as atelectasis, aspiration, pulmonary contusion, hemothorax, pneumothorax, and neurogenic or non-neurogenic pulmonary edema, may contribute to respiratory failure in the acute setting. Like patients with head injury, patients with spinal cord trauma are at a particular risk for the development of neurogenic pulmonary edema.

Although a patient's ventilation may be adequate on initial presentation, progressive atelectasis and pneumonia caused by inability to cough and clear secretions, sedative and

narcotic administration, gastric atony and dilation, and spinal cord edema may contribute to the subsequent development of respiratory failure. Ledsome and Sharp[144] found that patients with an injury at the C4 to C5 level had a vital capacity of 25% of predicted on admission, and required ventilatory support 1 to 5 days after injury. Loss of sympathetic control may contribute to hypersecretion of bronchial mucus, which can occur just 1 hour after acute SCI with tetraplegia,[145] and also contributes to formation of plugs, atelectasis, and pneumonia. In the acute phase of SCI, neurogenic pulmonary edema can occur owing to systemic and pulmonary vasoconstriction with subsequent ventilation–perfusion mismatch and left heart failure.

Cardiovascular System

At the time of primary spinal cord injury, intense sympathetic nervous system activation causes a brief period of severe hypertension.[146] The excessive sympathetic discharge may cause ST-segment and T-wave changes that may mimic myocardial ischemia or dysrhythmias or may result in neurogenic pulmonary edema.

Currently a four-phase model of the *spinal shock* development has been proposed.[147] Phase 1, called "hyporeflexive," usually manifests during the first 24 hours after injury. It is characterized by areflexia or hyporeflexia due to loss of the descending pathways, causing flaccid paralysis, loss of deep tendon reflexes below the level of the lesion and autonomic dysfunction. This is followed by phase 2, which is characterized by some return of the initial reflexes and denervation supersensitivity. One week later, phase 2 transforms into phase 3, with the symptoms of the "initial" hyperreflexia, which is explained by the axon-related growth of synapses. Synaptic endings from axotomized neurons below the injury degenerate over days after initial insult, followed by slow replacement by terminal sprouting from other neurons, which takes weeks to months. Phase 3 usually takes a month and is followed by phase 4, or "final hyperreflexia," with the underlying process of the soma-related growth of synapses.

If phase 1 of spinal shock is associated with profound peripheral vasodilatation and systemic hypotension, it is called *neurogenic shock*. The loss of sympathetic tone results in a decrease in systemic vascular resistance, an increase in venous capacitance with venous pooling, a reduced ability for vasoconstriction in response to changes in position and hypovolemia, and a poor hemodynamic response to surgical stimulation. Unopposed vagal tone with loss of cardioaccelerator fibers (T1 to T4) contributes to the bradycardia. Severe reflex bradycardia and asystole may occur in response to airway instrumentation and may be prevented by prophylactic administration of atropine. Patients with high cervical injuries (C1–C5) or patients with complete motor deficit below the injury tend to have lower systolic blood pressure at admission than patients with C6–C7 injury or with mild or moderate motor deficit. When neurogenic shock is defined as systolic blood pressure lower than 90 mmHg, there is an association between neurogenic shock and a delay in surgical intervention.[143]

Treatment of neurogenic shock involves the careful administration of isotonic fluids and possibly the administration of vasopressors to maintain spinal cord perfusion pressure. Some writers suggest using pulmonary artery catheters to gauge fluid requirements in all quadriplegic patients because even previously healthy patients may be susceptible to pulmonary edema and myocardial dysfunction.[148] In most patients, judicious fluid replacement alone is enough to raise blood pressure moderately in order to improve spinal cord perfusion. A pulmonary artery catheter may be placed in the patient who requires large volumes of fluid or vasopressors. Ephedrine, phenylephrine, and dopamine are commonly used as vasopressors, with the choice of drug depending on heart rate, cardiac output, and vascular resistance.

Temperature Control

There is a loss of thermoregulatory ability below the level of the lesion. Patients with injury above T6 tend to become poikilothermic, assuming the temperature of their surroundings. Careful monitoring of temperature and warming efforts are required.

Associated Injuries

As with head trauma, multiple organ systems (eg, orthopedic, intrathoracic, intra-abdominal, head) may be affected by the injury. Patients are assumed to have a full stomach (ie, to be at risk for aspiration). Intravenous access should be established, and Foley catheters and a nasal gastric tube should be placed. Long-bone fractures should be immobilized.

Airway Management of the Patient with Suspected Cervical Spine Injury

The goal of the anesthesiologist is to establish endotracheal intubation without causing further injury to the spinal cord. Unfortunately, there are few data on the safety of the various airway maneuvers and intubation techniques.[149] Overall incidence of the development of secondary neurologic injury after cervical spine injury ranges between 2% and 10%.[149,150] Direct laryngoscopy (DL) without neck stabilization can result in quadriplegia or death.[137,151] However, no studies have elucidated the actual risk of airway management techniques in patients with cervical spine injuries when standard cervical spine precautions, including in-line stabilization, are used.[151] Because of the lack of outcome data, no consensus has been reached regarding which technique for endotracheal intubation is safest in patients with suspected cervical spine injuries. Therefore, the optimal technique must be chosen by the anesthesiologist, depending on the particular patient's medical condition, the urgency with which the airway must be secured, the patient's level of cooperation, and the anesthesiologist's skills.

Effects of Various Airway Maneuvers on Cervical Spine Mobility

Basic Airway Maneuvers

Many airway maneuvers may increase distraction and subluxation at the site of a cervical spine injury.[149] However, no outcome studies are available to determine whether these maneuvers are, in fact, dangerous to living patients.[149] Chin lift and jaw thrust in a cadaver model with an unstable C5 to C6 ligamentous injury causes a greater than 5-mm widening of the disk space,[152] which is not prevented by a Philadelphia collar. Single-handed cricoid pressure, with "manual in-line stabilization" of the neck but without posterior neck support, also caused a vertical displacement of the neck between 4.6 and 5 mm (range of 0 to 9 mm).[153] It is not known whether support to the posterior part of the neck with a hard collar or a second hand would also allow this posterior displacement. Head tilt, insertion of an oral airway, or insertion of a nasopharyngeal airway resulted in a minimal change in the disk space.[152] Both the intubating laryngeal mask airway (LMA) and the regular LMA exert greater pressures against the cervical vertebrae than other intubation techniques and may produce posterior displacement of the cervical spine.[154] The rigid intubating

LMA tube also compresses the posterior pharynx and has resulted in severe pharyngeal edema in patients undergoing anterior cervical spine fixation.[155] However, outcome data are not available.

"Manual in-line traction" to stabilize the neck, depending on the force of the traction and integrity of the surrounding tissues, may by itself cause significant subluxation and distraction of the disk space.[156] Whether traction may cause neurologic damage is not clear; however, deterioration of neurologic function has been reported in association with excessive traction during cervical spine stabilization procedures. Therefore, only "manual in-line stabilization" should be used, and traction should not be performed.

Techniques for Urgent Airway Control

Direct Laryngoscopy

To secure the airway quickly, a rapid-sequence induction with direct laryngoscopy (DL) may be required. Unfortunately, DL is associated with cervical spine movement in normal anesthetized volunteers[157–159] as well as in cadavers with unstable spines.[152,156] Regardless of the curve of the blade (either a straight or curved blade), DL caused a 3- to 4-mm widening of the C5 to C6 disk space in the cadaver model of an unstable C5 to C6 injury.[152] Extension of the cervical spine movement was not prevented by a Philadelphia collar; however, it was reduced by 60% when in-line stabilization was provided by an assistant.[152,157]

Although DL does result in motion of the cervical spine, the actual risk of exacerbating neurologic damage associated with DL is not known. The available evidence suggests that neurologic deterioration after oral intubation with neck stabilization is very rare.[137,138,149,160–165] The widespread use of DL with in-line stabilization in the trauma setting suggests that the 95% confidence interval for neurologic deterioration is small (2% or less). In case reports, neurologic deterioration with DL has occurred in the absence of precautions taken for spine injury.[166,167]

Immobilization of the cervical spine also may make visualization of the larynx more difficult.[168,169] A poor view is obtained on laryngoscopy (grade 3 or 4) in 22% of patients with manual in-line stabilization[169] and in 64% of patients with a rigid neck collar with tape across the forehead or sandbags on either side of the neck. Because the main limitation to laryngoscopy with a rigid collar is a reduction in mouth opening, the front portion of the cervical collar may be removed before laryngoscopy. The posterior portion should remain in place to provide neck support for cricoid pressure. The view at laryngoscopy can often be improved by application of *b*ackward pressure on the thyroid cartilage and by the addition of *u*pward and slightly *r*ightward *p*ressure on the thyroid cartilage (BURP maneuver).[170]

Bullard laryngoscope, McCoy laryngoscope blade (Macintosh blade with hinged tip) light wand stylet and GlideScope® have been advocated for use in the cervical spine-injured patient.[171–173]

Cricothyroidotomy

Cricothyroidotomy has been suggested as an alternative to direct laryngoscopy for rapidly securing the airway. In theory, cricothyroidotomy might avoid neck motion. In reality, lack of spinal motion has not been documented because radiographic studies on the risk of cervical spine motion during cricothyroidotomy and neurologic outcome studies have not been performed. In addition, the complication rate for cricothyroidotomy is fairly high. When performed in the field or the emergency department, cricothyroidotomy has been shown to have a very high immediate complication rate (32%),[174] including a longer execution time (13%), incidences of unsuccessful tracheostomy tube placement (8% to 25%), and significant hemorrhage (5%). Long-term complications, such as infection and damage to the larynx, may also occur (2%). Cricothyroidotomy may also make definitive repair of the cervical spine by an anterior approach difficult because of the presence of the contaminated wound in the surgical field. Many of the complications can be attributed to the inexperience of the physician performing the procedure. However, the lack of documentation of any beneficial effect on neurologic outcome; the relative inexperience of most anesthesiologists, emergency department physicians, and surgeons in using the technique; and the often high complication rate suggest that use of cricothyroidotomy should be reserved to secure the airway quickly in selected patients in whom direct laryngoscopy has failed or is anticipated to fail.

Transtracheal Jet Ventilation

Transtracheal jet ventilation may be used to temporarily oxygenate the patient during difficult direct laryngoscopy, cricothyroidotomy, or fiberoptic laryngoscopy. Use of a 14-gauge catheter placed through the cricothyroid membrane and connected to a high-pressure source of oxygen may provide adequate oxygenation and ventilation; however, it does not protect against aspiration, and it may be associated with barotrauma (10%) and catheter dislodgment.

Techniques for Elective Airway Control

The following sections discuss techniques for elective airway control.

Awake Intubation (Blind Nasal, Light Wand, or Fiberoptic Laryngoscopy)

Awake nasotracheal or orotracheal intubation has been advocated as a safer technique for endotracheal intubation in the patient with an unstable cervical spine.[136,149] Meschino and coworkers[175] reported that using awake tracheal intubation in patients with cervical spine injuries did not change neurologic outcomes in the 136 patients who required endotracheal intubation from those in 233 patients who did not require intubation. However, the report did not supply details of how the intubations were performed, how the neurologic examination was assessed, and the location and degree of instability of the injury.

Although awake intubation is often appropriate, it may not secure the airway quickly enough if rapid intubation is required, as in the hypoxemic, hemodynamically unstable, or head-injured patient. Nasal intubation should be avoided in the patient with a midface or basilar skull fracture, in whom it might allow entry of bacteria and foreign materials into the cranial cavity.[176] It also may induce epistaxis, which is aggravated in the multiple-trauma victim by dilutional coagulopathy and which, with long-term intubation, may cause paranasal sinusitis and sepsis.[177] In uncooperative, inebriated, or head-injured patients neck motion may be greater, with potential cervical spine damage, than if direct laryngoscopy were performed with the use of general anesthesia. Ovassapian and colleagues[178] found that blind nasotracheal intubation required multiple attempts in 70–90% of patients.

Fiberoptic laryngoscopy has often been recommended for intubation in the patient with an unstable cervical spine because it allows intubation under direct vision without much neck motion. Fiberoptic laryngoscopy may be difficult in the acutely injured patient because of excessive salivation, airway bleeding, and edema in the pharyngeal space. It requires a cooperative

patient and adequate topical anesthesia of the supraglottic and infraglottic regions to prevent gagging. Anesthetizing the area below the vocal cords is controversial. Although this step may prevent severe coughing and bucking (which potentially may exacerbate neurologic damage), it might increase the likelihood of aspiration. Ovassapian and colleagues,[178] however, found no evidence of aspiration 24 hours after fiberoptic intubation performed with laryngeal anesthesia in 105 patients at risk for aspiration. There is also no evidence that coughing raises the neurologic risk to the spinal cord.

Retrograde Tracheal Intubation

Retrograde tracheal intubation is a technique of tracheal intubation over a guide wire which is passed through the cricothyroid membrane retrogradely to the mouth, and is a technique that is advocated to minimize neck motion in the patient with trauma.[179] A large-scale assessment of the reliability and safety of this technique as the primary means to secure the airway is not available.

Management of Endotracheal Intubation

No consensus has been reached regarding the relative safety of the various techniques to achieve endotracheal intubation.[149] The specific choice of technique often depends on the particular anesthesiologist's skills. The possible risk of secondary damage to the spinal cord with laryngoscopy (which varies with stability of the injuries) must be balanced by other considerations, such as the degree of urgency for achieving intubation, associated medical conditions (TBI, airway trauma or pathologic condition, hypoxemia, and cardiovascular instability), and level of patient cooperation.

The first step of the airway management plan involves determination of the degree of urgency for securing the airway (Fig. 10.12). Immediate endotracheal intubation is required in patients with cardiovascular instability, hypoxemia, or elevated ICP. Oxygenation and ventilation are initially provided with bag and mask, with an airway or jaw thrust, as required, to open the airway. If the patient has an anatomically normal airway (ie, one in which endotracheal intubation is expected to be easily achieved with the head and neck secured in neutral position), a modified rapid-sequence induction should be performed. The front half of the Philadelphia collar may be removed before laryngoscopy because it interferes with mouth opening. To prevent aspiration, cricoid pressure may be applied, although this pressure may cause a posterior subluxation of the cervical cord.[153] Succinylcholine is the muscle relaxant of choice if the injury is less than 48 hours old, because hyperkalemia does not occur until later.[180] Ventilation should continue with cricoid pressure in place until the intubation is complete. During laryngoscopy, an assistant should stabilize the head in a neutral position without applying traction. Neck flexion should be avoided, and the minimum of neck extension necessary to visualize the glottis should be used. If conventional methods to place the endotracheal tube fail, an intubating LMA can be inserted and an endotracheal tube passed with or without fiberoptic guidance through the airway.[181]

Ventilation using a supraglottic device may be required as a temporary measure if ventilation by bag and mask is difficult. If immediate control of the airway is required and the airway is anatomically abnormal, a cricothyroidotomy may be performed to secure the airway. Patients with severe facial fractures, soft tissue swelling or injuries, marked obesity, or airway obstruction due to massive prevertebral hematoma, in whom endotracheal intubation appears to be, or is, impossible, should be managed with cricothyroidotomy.

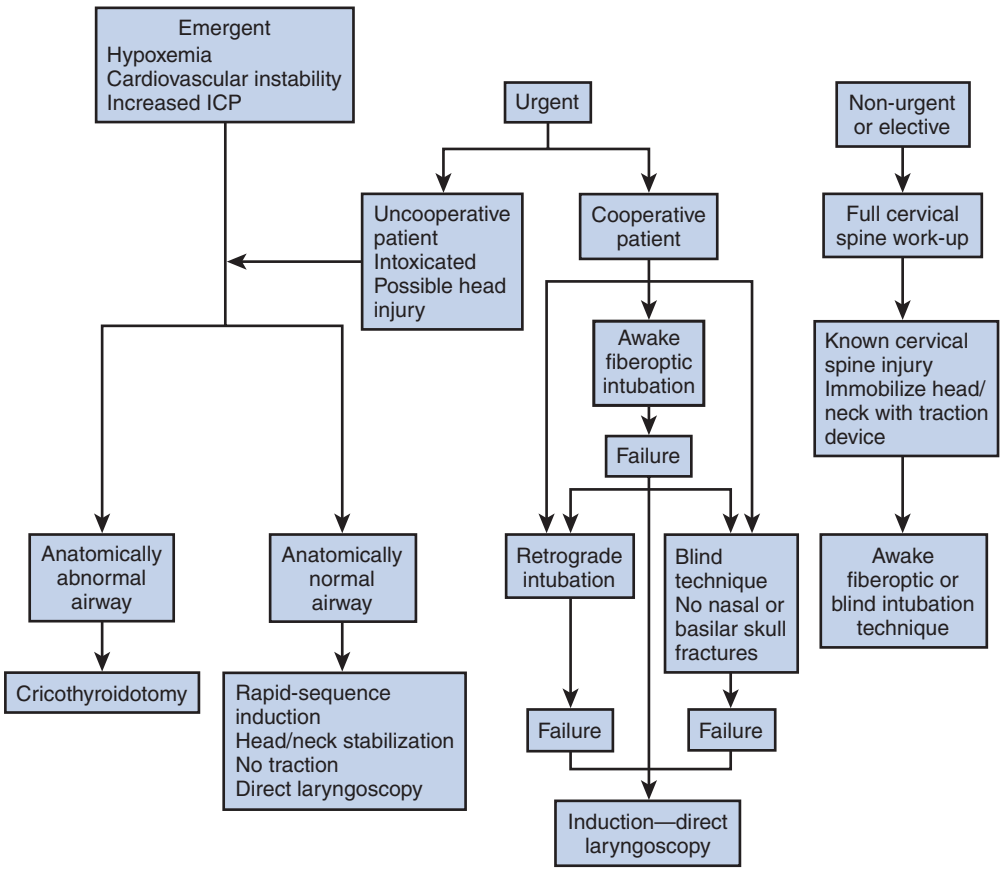


Fig. 10.12 Endotracheal intubation in the patient with suspected cervical spine injury. ICP, intracranial pressure.

If the airway must be secured urgently, but not immediately, the other techniques for endotracheal intubation may be useful. The key point in the decision for urgent endotracheal intubation is whether the patient is cooperative (see Fig. 10.12). If the patient is uncooperative or inebriated or has a possible significant TBI, the steps listed for emergent intubation should be performed. In a cooperative patient, awake fiberoptic intubation or blind technique may be chosen.

In the non-urgent elective setting, such as requiring anesthesia for the repair of orthopedic or facial injuries, the patient should first undergo a full evaluation of the cervical spine.

Goals in the Acute Care of the Spinal Cord-Injured Patient

As for patients with head trauma, the primary aim in the management of patients with SCI is to prevent secondary cord injury (Box 10.6). The principal way to prevent additional injury is immobilization of the spine. Treatment, therefore, has consisted of anatomic realignment and stabilization with or without surgery for decompression and stabilization.

Prevention of secondary neurologic damage by treating hypoxemia and maintaining spinal cord perfusion is important in the acute management of these patients. Spinal cord blood flow is autoregulated in a fashion similar to blood flow in the brain,[182] and autoregulation may be impaired several hours after injury.[183] Maintenance of spinal cord perfusion pressure at greater than 60 mmHg is advised to improve spinal cord blood flow after injury; this, however, is a vague recommendation because the pressure around injured segment of the spinal cord is not measured, unlike ICP in head injury. Current recommendations of the American Association of Neurosurgeons include maintaining mean arterial pressure at 85–90 mmHg, while there are no clear treatment recommendations.[184,185] In an experimental model of spinal injury, spinal cord blood flow was increased by infusion of phenylephrine but not of mannitol or hetastarch, although neurologic function was not improved.[186] However, the control of blood pressure was at 80 mmHg, suggesting that elevation of blood pressure beyond a minimum of 60 mmHg is not helpful. In addition, hypertension may cause hemorrhage and increase edema formation. Recently, Werndle and colleagues[187] reported on a novel technique for the successful measurement of intraspinal pressure via dural hole at the level of injury in adult patients with traumatic SCI. This promising technique may permit the calculation of an actual spinal cord perfusion pressure.

No evidence has shown that hyperventilation to reduce $PaCO_2$ or hyperosmolar fluids (and theoretically to decompress the spinal cord) improve outcome in patients with SCI. Hyperglycemia should be avoided immediately after SCI. Drummond and Moore[188] found that minimally increased blood glucose levels (177 mg/dL), associated with intravenous infusions of glucose before experimentally induced spinal cord ischemia, worsened neurologic outcome.[189] Reduction of blood glucose by insulin has also been found to improve recovery of electrophysiologic function after experimentally induced spinal cord ischemia.[189] These results suggest that infusion of glucose-containing solutions within the first 24 hours of injury should be avoided. In addition, hyperglycemia should be treated; the glucose level at which treatment should be initiated and the targeted glucose level have not yet been defined. Most practitioners, however, begin treatment if blood glucose levels increase beyond the range of 140–180 mg/gl.

The effectiveness of previously reported large doses of methylprednisolone (30 mg/kg followed by a continuous infusion of 5.4 mg/kg/h for 23 hours) to improve neurologic outcome in patients with complete and incomplete lesions,[190] however, has been recently questioned.[191–193] Subsequently, the number of surgeons who report using high-dose steroids in the treatment of acute spinal cord injuries has significantly decreased since 2006.[194] Currently, the use of steroids in the acute SCI may be considered as optional, but not standard care.

BOX 10.6 Aims in Acute Care of Spinal Cord Injury

1. Immobilize the spine.
2. Prevent subsequent damage associated with hypoxemia and decreased spinal cord perfusion pressure.
3. Treat hyperglycemia and avoid glucose-containing solutions in first 24 hours of the injury.

SUMMARY

The care of the acutely unstable patient involves neurologic and radiologic examination, evaluation of other organ systems, appropriate airway management, and treatment of associated problems. Brain and spinal cord injuries are both accompanied by physiologic derangements in other bodily functions, challenges in airway control, and the primary management goal of prevention of secondary injury and further neurologic damage.

REFERENCES

1. Morgenstern LB, Hemphill 3rd JC, Anderson C, et al. American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108–2129.
2. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet*. 1974;2(7872):81–84.
3. Choi SC, Muizelaar JP, Barnes TY, et al. Prediction tree for severely head-injured patients. *J Neurosurg*. 1991;75:251–255.
4. Jennett WB, Stern WE. Tentorial herniation, the midbrain and the pupil: Experimental studies in brain compression. *J Neurosurg*. 1960;17:598–609.
5. Bedford RF, Persing JA, Pobereskin L, et al. Lidocaine or thiopental for rapid control of intracranial hypertension? *Anesth Analg*. 1980;59:435–437.
6. Toutant SM, Klauber MR, Marshall LF, et al. Absent or compressed basal cisterns on first CT scan: Ominous predictors of outcome in severe head injury. *J Neurosurg*. 1984;61:691–694.
7. Frost EAM, Arancibia CU, Shulman K. Pulmonary shunt as a prognostic indicator in head injury. *J Neurosurg*. 1979;50:768–772.
8. Malik AB. Mechanisms of neurogenic pulmonary edema. *Circ Res*. 1985;57:1–18.
9. Popp AJ, Shah DM, Berman RA, et al. Delayed pulmonary dysfunction in head-injured patients. *J Neurosurg*. 1982;57:784–790.
10. Cooper KR, Boswell PA. Reduced functional residual capacity and abnormal oxygenation in patients with severe head injury. *Chest*. 1983;84:29–35.
11. Clifton GL, Robertson CS, Kyper K, et al. Cardiovascular response to severe head injury. *J Neurosurg*. 1983;59:447–454.
12. Cushing H. Concerning a definite regulatory mechanism of the vasomotor center which controls blood pressure during cerebral compression. *Johns Hopkins Hosp Bull*. 1901;12:290.
13. Komamura K, Fukui M, Iwasaku T, et al. Takatsubo cardiomyopathy: Pathophysiology, diagnosis and treatment. *World J Cardiol*. 2014;6(7):602–609.
14. Finsterer J, Wahbi K. CNS disease triggering Takotsubo stress cardiomyopathy. *Int J Cardiol*. 2014;177(2):322–329.
15. Ross SE, Schwab CW, David ET, et al. Clearing the cervical spine: Initial radiologic evaluation. *J Trauma*. 1987;27:1055–1060.
16. Ott L, Young B, Phillips R, et al. Altered gastric emptying in the head-injured patient: Relationship to feeding intolerance. *J Neurosurg*. 1991;74:738–742.

17. Kraus JF, Morgenstern H, Fife D, et al. Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *Am J Public Health*. 1989;79:294–299.
18. Becker P, Zieger S, Rother U, et al. Complement activation following head and brain trauma. *Anaesthesist*. 1987;36:301–365.
19. Crone KR, Lee KS, Kelly Jr DL. Correlation of admission fibrin degradation products with outcome and respiratory failure in patients with severe head injury. *Neurosurgery*. 1987;21:532–536.
20. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: Two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59:8–15.
21. Kluger Y, Riou B, Rossaint R, et al. Safety of rFVIIa in hemodynamically unstable polytrauma patients with traumatic brain injury: Post hoc analysis of 30 patients from a prospective, randomized, placebo-controlled, double-blind clinical trial. *Crit Care*. 2007;11:R85.
22. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785.
23. Brophy GM, Candeloro CL, Robles JR, et al. Recombinant activated factor VII use in critically ill patients: Clinical outcomes and thromboembolic events. *Ann Pharmocother*. 2013;47:447–454.
24. DeLaoughery EP, Lenfesty B, DeLoughery TG. The use of recombinant factor VIIa in warfarin patients with traumatic brain injury: A retrospective case-control study. *Blood Coagul Fibrinolysis*. 2013;24:317–320.
25. Brown CVR, Foulkrod KH, Lopez D, et al. Recombinant factor VIIa for the correction of coagulopathy before emergent craniotomy in blunt trauma patients. *J Trauma*. 2010;68:348–352.
26. Pickard JD, Kirkpatrick PJ, Melsen T, et al. Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagul Fibrinolysis*. 2000;11(suppl 1):S117–S120.
27. Woo CH, Patel N, Conell C, et al. Rapid warfarin reversal in the setting of intracranial hemorrhage: A comparison of plasma, recombinant activated factor VII, and prothrombin complex concentrate. *World Neurosurg*. 2014;81:110–115.
28. Yanamadala V, Walcott BP, Fecci PE, et al. Reversal of warfarin associated coagulopathy with 4-factor prothrombin complex concentrate in traumatic brain injury and intracranial hemorrhage. *J Clin Neurosci*. 2014;21:1881–1884.
29. Joseph B, Hadjizacharia P, Aziz H, et al. Prothrombin complex concentrate: An effective therapy in reversing the coagulopathy of traumatic brain injury. *J Trauma Acute Care Surg*. 2013;74:248–253.
30. Rybinnik I, Mullen MT, Messe S, et al. Treatment of acute stroke in patients on dabigatran: A survey of US stroke specialists. *J Stroke Cerebrovasc Dis*. 2013;22(8):1312–1316.
31. Pollack Jr CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511–520.
32. Shin B, Mackenzie CF, Helrich M. Hypokalemia in trauma patients. *Anesthesiology*. 1986;65:90–92.
33. Mehta MP, Gergis SD, Sokoll M. Paradoxical diuresis in some neuro-surgical patients under balanced anesthesia. *Anesthesiology*. 1983;59:585–587.
34. Harris AS. Clinical experience with desmopressin. Efficacy and safety in central diabetes insipidus and other conditions. *J Pediatr*. 1989;114:711–718.
35. Nelson PB, Seif S, Gutai J, et al. Hyponatremia and natriuresis following subarachnoid hemorrhage in a monkey model. *J Neurosurg*. 1984;60:233–237.
36. Sanfilippo F, Santonocito C, Veenith T, et al. The role of neuromuscular blockade in patients with traumatic brain injury: A systematic review. *Neurocrit Care*. 2015;22:325–334.
37. White PF, Schlobohm RM, Pitts LH, et al. A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. *Anesthesiology*. 1982;57:242–244.
38. Donegan MF, Bedford RF. Intravenously administered lidocaine prevents intracranial hypertension during endotracheal suctioning. *Anesthesiology*. 1980;52:516–518.
39. Unni VKN, Johnston RA, Young HSA, et al. Prevention of intracranial hypertension during laryngoscopy and endotracheal intubation: Use of a second dose of thiopentone. *Br J Anaesth*. 1984;56:1219–1223.
40. Cottrell JE, Patel K, Turndorf H, et al. Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. *J Neurosurg*. 1978;48:329–331.
41. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med*. 2010;38(2):637–648.
42. Anderson CS, Heeley E, Huang Y, et al, INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355–2365.
43. Jabre P, Combes X, Lapostolle F, et al, KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet*. 2009;374(9686):293–300.
44. Smischney NJ, Beach ML, Loftus RW, et al. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: A randomized, controlled trial. *J Trauma Acute Care Surg*. 2012;73(1):94–101.
45. Mayberg TS, Lam AM, Matta BF, et al. Ketamine does not increase cerebral blood flow velocityor intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. *Anesth Analg*. 1995;81(1):84–89.
46. Bar-Joseph G, Guilburd Y, Tamir A, et al. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr*. 2009;4(1):4–6.
47. Lanier WL, Milde JH, Michenfielder JD. Cerebral stimulation following succinylcholine in dogs. *Anesthesiology*. 1986;64:551–559.
48. Clancy M, Halford S, Walls R, et al. In patients with head injuries who undergo rapid sequence intubation using succinylcholine, does pretreatment with a competitive neuromuscular blocking agent improve outcome? A literature review. *Emerg Med J*. 2001;18:373–375.
49. Brain Trauma Foundation: American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Carney NA, Ghajar J. Guidelines for the management of severe traumatic brain injury. *Introduction*. *J Neurotrauma*. 2007;24(suppl 1):S1–S2.
50. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol*. 1994;6:4–14.
51. Changaris DG, McGraw CP, Richardson JD, et al. Correlation of cerebral perfusion pressure and Glasgow Coma Scale to outcome. *J Trauma*. 1987;27:1007–1013.
52. Gudeman SK, Miller JD, Becker DP. Failure of high-dose steroid therapy to influence intracranial pressure in patients with severe head injury. *J Neurosurg*. 1979;51:301–306.
53. Dearden NM, Gibson JS, McDowall DG, et al. Effect of high-dose dexamethasone on outcome from severe head injury. *J Neurosurg*. 1986;64:81–88.
54. Miller JD, Sakalas R, Ward JD, et al. Methylprednisolone treatment in patients with brain tumors. *Neurosurgery*. 1977;1:114–117.
55. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34:216–222.
56. Bratton SL, Chestnut RM, Ghajar J, et al, Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. I: Blood pressure and oxygenation. *J Neurotrauma*. 2007;24(suppl 1):S7–S13.
57. Cooper KR, Boswell PA, Choi SC. Safe use of PEEP in patients with severe head injury. *J Neurosurg*. 1985;63:525–552.
58. Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology*. 1987;67:498–502.
59. Enevoldsen EM, Jensen FT. Autoregulation and CO2 responses of cerebral blood flow in patients with acute severe head injury. *J Neurosurg*. 1978;48:689–703.
60. Cottrell JE, Gupta B, Rappaport H, et al. Intracranial pressure during nitroglycerin-induced hypotension. *J Neurosurg*. 1980;53:309–311.
61. James DJ, Bedford RF. Hydralazine for controlled hypotension during neurosurgical operations. *Anesth Analg*. 1982;61:1016–1019.
62. Graffagnino C, Bergese S, Love J, et al. Clevidipine rapidly and safely reduces blood pressure in acute intracerebral hemorrhage: The ACCELERATE trial. *Cerebrovasc Dis*. 2013;36(3):173–180.
63. Gunnar W, Jonasson O, Merlotti G, et al. Head injury and hemorrhagic shock: Studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. *Surgery*. 1988;103:398–407.
64. Drummond JC, Patel PM, Cole DJ, et al. The effect of the reduction of colloid oncotic pressure, with and without reduction of osmolality, on post-traumatic cerebral edema. *Anesthesiology*. 1998;88:993–1002.
65. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
66. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874–884.
67. Etemadrezaie H, Baharvahdat H, Shariati Z, et al. The effect of fresh frozen plasma in severe closed head injury. *Clin Neurol Neurosurg*. 2007;109:166–171.

68. Bagshaw SM, Chawla LS. Hydroxyethyl starch for fluid resuscitation in critically ill patients. *Can J Anesth*. 2013;60:709–713.
69. Culley MD, Larson Jr CP, Silverberg GD. Hetastarch coagulopathy in a neurosurgical patient. *Anesthesiology*. 1987;66:706–707.
70. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
71. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2013;7: http://dx.doi.org/10.1002/14651858.CD007594.pub3. CD007594.
72. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. *JAMA*. 2013;309:678–688.
73. Reinhart K, Perner A, Sprung CL. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med*. 2012;38:368–383.
74. Food and Drug Administration. Hydroxyethyl starch solutions: FDA safety communication—boxed warning on increased mortality and severe renal injury and risk of bleeding. June 6, 2013.
75. Todd MM, Tommasino C, Moore S. Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. *J Neurosurg*. 1985;63:944–948.
76. Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. *Arch Surg*. 1990;125:1309–1315.
77. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. *Arch Surg*. 1991;126:1065–1072.
78. Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride: The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Arch Surg*. 1993;128:1003–1011.
79. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: A randomized controlled trial. *JAMA*. 2004;291:1350–1357.
80. Shackford SR, Bourguignon PR, Wald SL, et al. Hypertonic saline resuscitation of patients with head injury: A prospective, randomized clinical trial. *J Trauma*. 1998;44:50–58.
81. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology*. 2007;107:697–704.
82. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: Relation to central pontine myelinolysis. *Science*. 1981;211:1068–1070.
83. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59:669–674.
84. Danaei G, Lawes CM, Vander Hoorn S, et al. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: Comparative risk assessment. *Lancet*. 2006;368:1651–1659.
85. Badjatia N, Topcuoglu MA, Buonanno FS, et al. Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. *Crit Care Med*. 2005;33:1603–1609.
86. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75:545–551.
87. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery*. 2000;46:335–342.
88. Longstreth Jr WT, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. *Ann Neurol*. 1984;15:59–63.
89. Shapira Y, Artru AA, Cotev S, et al. Brain edema and neurologic status following head trauma in the rat: No effect from large volumes of isotonic or hypertonic intravenous fluids, with or without glucose. *Anesthesiology*. 1992;77:79–85.
90. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
91. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
92. Oksanen T, Skrifvars MB, Varpula T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Med*. 2007;33:2093–2100.
93. Bilotta F, Spinelli A, Giovannini F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: A randomized prospective pilot trial. *J Neurosurg Anesthesiol*. 2007;19:156–160.
94. Jauch-Chara K, Oltmanns KM. Glycemic control after brain injury: Boon and bane for the brain. *Neuroscience*. 2014;283:202–209.
95. de Courten-Myers G, Myers RE, Schoolfield L. Hyperglycemia enlarges infarct size in cerebrovascular occlusion in cats. *Stroke*. 1988;19:623–630.
96. Kramer AH, Roberts DJ. Zygun DA Optimal glycemic control in neurocritical care patients: A systematic review and meta-analysis. *Crit Care*. 2012;16(5):R203.
97. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: Relationship to vasospasm and outcome. *Neurology*. 2001;56:1299–1304.
98. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422–425.
99. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. 2001;344:556–563.
100. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med*. 1997;336:540–546.
101. Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma*. 1993;10:263–271.
102. Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. *Crit Care Med*. 2000;28:3902–3906.
103. Jiang J, Yu M, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg*. 2000;93:546–549.
104. Qiu WS, Liu WG, Shen H, et al. Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chin J Traumatol*. 2005;8:27–32.
105. Bratton SL, Chestnut RM, Ghajar J, et al, Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury. III: Prophylactic hypothermia. *J Neurotrauma*. 2007;24(suppl 1): S21–S25.
106. Kenning JA, Toutant SM, Saunders RL. Upright patient positioning in the management of intracranial hypertension. *Surg Neurol*. 1981;15:148–152.
107. Harp JR, Wollman H. Cerebral metabolic effects of hyperventilation and deliberate hypotension. *Br J Anaesth*. 1973;45:256–262.
108. Bouma GJ, Muizelaar JP, Stringer WA, et al. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *J Neurosurg*. 1992;77:360–368.
109. Sioutos PJ, Orozco JA, Carter LP, et al. Continuous regional cerebral cortical blood flow monitoring in head-injured patients. *Neurosurgery*. 1995;36:943–949.
110. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIV: Hyperventilation. *J Neurotrauma*. 2007;24(suppl 1): S87–S90.
111. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg*. 1991;75:731–739.
112. Gopinath SP, Robertson CS, Contant CF, et al. Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psychiatry*. 1994;57:717–723.
113. Michenfielder JD, Fowler WS, Theye RA. CO2 levels and pulmonary shunting in anesthetized man. *J Appl Physiol*. 1966;21:1471–1476.
114. Rudehill A, Lagerkranser M, Lindquist C, et al. Effects of mannitol on blood volume and central hemodynamics in patients undergoing cerebral aneurysm surgery. *Anesth Analg*. 1983;62:875–880.
115. Ravussin P, Archer DP, Tyler JL, et al. Effects of rapid mannitol infusion on cerebral blood volume: A positron emission tomographic study in dogs and man. *J Neurosurg*. 1986;64:104–113.
116. Ravussin P, Abou-Madi M, Archer D, et al. Changes in CSF pressure after mannitol in patients with and without elevated CSF pressure. *J Neurosurg*. 1988;69:869–876.
117. Berry AJ, Peterson ML. Hyponatremia after mannitol administration in the presence of renal failure. *Anesth Analg*. 1981;60:165–167.
118. Francony G, Fauvage B, Falcon D, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. *Crit Care Med*. 2008;36:795–800.
119. Cottrell JE, Robustelli A, Post K, et al. Furosemide- and mannitol-induced changes in intracranial pressure and serum osmolality and electrolytes. *Anesthesiology*. 1977;47:28–30.
120. Schettini A, Stahurski B, Young HF. Osmotic and osmotic-loop diuresis in brain surgery: Effects on plasma and CSF electrolytes and ion excretion. *J Neurosurg*. 1982;56:679–684.
121. Bratton SL, Chestnut RM, Ghajar J, et al, Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic

brain injury. XI: Anesthetics, analgesics, and sedatives. *J Neurotrauma*. 2007;24(suppl 1):S71–S76.
122. Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. *J Neurosurg*. 1985;62:383–388.
123. Eisenberg HM, Frankowsky RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg*. 1988;69:15–23.
124. Kang TM. Propofol infusion syndrome in critically ill patients. *Ann Pharmacother*. 2002;36:1453–1456.
125. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: A simple name for a complex syndrome. *Intensive Care Med*. 2003;29:1417–1425.
126. Wysowski DK, Pollock ML. Reports of death with use of propofol (Diprivan) for nonprocedural (long-term) sedation and literature review. *Anesthesiology*. 2006;105:1047–1051.
127. Chiolero RL, Ravussin P, Anderes JP, et al. The effects of midazolam reversal by RO 15-1788 on cerebral perfusion pressure in patients with severe head injury. *Intensive Care Med*. 1988;14:196–200.
128. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma: Major mortality reduction in comatose patients treated within four hours. *N Engl J Med*. 1981;304:1511–1518.
129. Goldberg W, Mueller C, Panacek E, et al. NEXUS Group: Distribution and patterns of blunt traumatic cervical spine injury. *Ann Emerg Med*. 2001;38:17–22.
130. Lowery DW, Wald MM, Browne BJ, et al. Epidemiology of cervical spine injury victims. *Ann Emerg Med*. 2001;38:12–16.
131. Kreipke DL, Gillespie KR, McCarthy MC, et al. Reliability of indications for cervical spine films in trauma patients. *J Trauma*. 1989;29:1438–1439.
132. Roberge RJ, Wears RC, Kelly M, et al. Selective application of cervical spine radiography in alert victims of blunt trauma: A prospective study. *J Trauma*. 1988;28:784–788.
133. Fesmire FM, Luten RC. The pediatric cervical spine: Developmental anatomy and clinical aspects. *J Emerg Med*. 1989;7:133–142.
134. Hadley MN, Zabramski JM, Browner CM, et al. Pediatric spinal trauma: Review of 122 cases of spinal cord and vertebral column injuries. *J Neurosurg*. 1988;68:18–24.
135. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. *Spine*. 1983;8:817–831.
136. Crosby ET, Lui A. The adult cervical spine: Implications for airway management. *Can J Anaesth*. 1990;37:77–93.
137. Hastings RH, Marks JD. Airway management for trauma patients with potential cervical spine injuries. *Anesth Analg*. 1991;73:471–482.
138. Podolsky S, Baraff LJ, Simon RR, et al. Efficacy of cervical spine immobilization methods. *J Trauma*. 1983;23:461–465.
139. Williams CF, Bernstein TW, Jelenko III C. Essentiality of the lateral cervical spine radiograph. *Ann Emerg Med*. 1981;10:198–204.
140. Biby L, Santora AH. Prevertebral hematoma secondary to whiplash injury necessitating emergency intubation. *Anesth Analg*. 1990;70:112–114.
141. Meakem TD, Meakem TJ, Rappaport W. Airway compromise from prevertebral soft tissue swelling during placement of halo-traction for cervical spine injury. *Anesthesiology*. 1990;73:775–776.
142. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. *JAMA*. 2001;286:1841–1848.
143. Tuli S, Tuli J, Coleman WP, et al. Hemodynamic parameters and timing of surgical decompression in acute cervical spinal cord injury. *J Spinal Cord Med*. 2007;30:482–490.
144. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. *Am Rev Respir Dis*. 1981;124:41–44.
145. Lanig IS, Peterson WP. The respiratory system in spinal cord injury. *Phys Med Rehabil Clin N Am*. 2000;11:29–43.
146. Piepmeier JM, Lehmann KB, Lane JG. Cardiovascular instability following acute cervical spinal cord trauma. *Cent Nerv Syst Trauma*. 1985;2:153–160.
147. Ditunno JF, Little JW, Tessler A, et al. Spinal shock revisited: A four-phase model. *Spinal Cord*. 2004;42:383–395.
148. Mackenzie CF, Shin B, Krishnaprasad D, et al. Assessment of cardiac and respiratory function during surgery on patients with acute quadriplegia. *J Neurosurg*. 1985;62:843–849.
149. Crosby ET. Airway management in adults after cervical spine trauma. *Anesthesiology*. 2006;104:1293–1318.
150. Reid DC, Henderson R, Saboe L, et al. Etiology and clinical course of missed spine fractures. *J Trauma*. 1987;27:980–986.
151. Muckart DJJ, Bhagwanjee S, van der Merwe R. Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. *Anesthesiology*. 1997;87:418–420.
152. Aprahamian C, Thompson BM, Finger WA, et al. Experimental cervical spine injury model: Evaluation of airway management and splinting techniques. *Ann Emerg Med*. 1984;13:584–587.
153. Gabbott DA. The effect of single-handed cricoid pressure on neck movement after applying manual inline stabilization. *Anaesthesia*. 1997;52:586–588.
154. Keller C, Brimacombe J, Keller K. Pressures exerted against the cervical vertebrae by the standard and intubating laryngeal mask airways: A randomized, controlled, cross-over study in fresh cadavers. *Anesth Analg*. 1999;89:1296–1300.
155. Nakazawa K, Tanaka N, Ishikawa S, et al. Using the intubating laryngeal mask airway (LMA-Fastrach™) for blind endotracheal intubation in patients undergoing cervical spine operation. *Anesth Analg*. 1999;89:1319–1321.
156. Bivins HG, Ford S, Bezmalinovic Z, et al. The effect of axial traction during orotracheal intubation of the trauma victim with an unstable cervical spine. *Ann Emerg Med*. 1988;17:25–29.
157. Majernick TG, Bieniek R, Houston JB, et al. Cervical spine movement during orotracheal intubation. *Ann Emerg Med*. 1986;15:417–420.
158. Horton WA, Fahy L, Charters P. Disposition of cervical vertebrae, atlanto-axial joint, hyoid and mandible during X-ray laryngoscopy. *Br J Anaesth*. 1989;63:435–438.
159. Sawin PD, Todd MM, Traynelis VC, et al. Cervical spine motion with direct laryngoscopy and orotracheal intubation: An in vivo cinefluoroscopic study of subjects without cervical abnormality. *Anesthesiology*. 1996;85:26–36.
160. Doolan LA, O'Brien JF. Safe intubation in cervical spine injury. *Anaesth Intensive Care*. 1985;13:319–324.
161. Rhee KJ, Green W, Holcroft JW, et al. Oral intubation in the multiply injured patient: The risk of exacerbating spinal cord damage. *Ann Emerg Med*. 1990;19:511–514.
162. Shatney CH, Brunner RD, Nguyen TQ. The safety of orotracheal intubation in patients with unstable cervical spine fracture or high spinal cord injury. *Am J Surg*. 1995;170:676–679.
163. Talucci RC, Shaikh KA, Schwab CW. Rapid sequence induction with oral endotracheal intubation in the multiple injured patient. *Am Surg*. 1988;54:185–187.
164. Smith CE. Cervical spine injury and tracheal intubation: A never-ending conflict. *Trauma Care*. 2000;10:20–26.
165. Hindman BJ, Palecek JP, Posner KL, et al. Cervical spinal cord, root, and bony spine injuries: A closed claims analysis. *Anesthesiology*. 2011;114:782–795.
166. Muckart DJ, Bhagwanjee S, van der Merwe R. Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. *Anesthesiology*. 1997;87:418–420.
167. Hastings RH, Kelley SD. Neurologic deterioration associated with airway management in a cervical spine-injured patient. *Anesthesiology*. 1993;78:580–583.
168. Hastings RH, Wood PR. Head extension and laryngeal view during laryngoscopy with cervical spine stabilization maneuvers. *Anesthesiology*. 1994;80:825–831.
169. Nolan JP, Wilson ME. Orotracheal intubation in patients with potential cervical spine injuries: An indication for the gum elastic bougie. *Anaesthesia*. 1993;48:630–633.
170. Knill RL. Difficult laryngoscopy made easy with a "BURP". *Can J Anaesth*. 1993;40:279–282.
171. Cohn AI, Zornow MH. Awake endotracheal intubation in patients with cervical spine disease: A comparison of the Bullard laryngoscope and the fiberoptic bronchoscope. *Anesth Analg*. 1995;81:1283–1286.
172. Turkstra TP, Craen RA, Pelz DM, et al. Cervical spine motion: A fluoroscopic comparison during intubation with lighted stylet, Glide-scope, and Macintosh laryngoscope. *Anesth Analg*. 2005;101:910–915.
173. Wendling AL, Tighe PJ, Conrad BP, et al. A comparison of 4 airway devices on cervical spine alignment in cadaver models of global ligamentous instability at C1-2. *Anesth Analg*. 2013;117:126–132.
174. McGill J, Clinton JE, Ruiz E. Cricothyrotomy in the emergency department. *Ann Emerg Med*. 1982;11:361–364.
175. Meschino A, Devitt JH, Koch JP, et al. The safety of awake tracheal intubation in cervical spine injury. *Can J Anaesth*. 1992;39:114–117.
176. Seebacher J, Nozik D, Mathieu A. Inadvertent intracranial introduction of a nasogastric tube, a complication of severe maxillofacial trauma. *Anesthesiology*. 1975;42:100–102.
177. Grindlinger GA, Niehoff J, Hughes SL, et al. Acute paranasal sinusitis related to nasotracheal intubation of head-injured patients. *Crit Care Med*. 1987;15:214–217.
178. Ovassapian A, Krejcie TC, Yelich SJ, et al. Awake fiberoptic intubation in the patient at high risk of aspiration. *Br J Anaesth*. 1989;62:13–16.
179. Barriot P, Riou B. Retrograde technique for tracheal intubation in trauma patients. *Crit Care Med*. 1988;16:712–713.
180. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology*. 1975;43:89–99.
181. Pennant JH, Pace NA, Gajraj NM. Role of the laryngeal mask airway in the immobile cervical spine. *J Clin Anesth*. 1993;226–230.

182. Hickey R, Albin MS, Bunegin L, et al. Autoregulation of spinal cord blood flow: Is the cord a microcosm of the brain? *Stroke*. 1986;17:1183–1189.
183. Senter HJ, Venes JL. Loss of autoregulation and posttraumatic ischemia following experimental spinal cord trauma. *J Neurosurg*. 1979;50:198–206.
184. No authors. Blood pressure management after acute spinal cord injury. *Neurosurgery*. 2002;50(3 suppl):S58–S62.
185. U.K. National Spinal Cord Injury Strategy Board website. The initial management of adults with spinal cord injuries: advice for major trauma networks and SCI centres on the development of joint protocols. With advice for clinicians in acute hospitals. Available at: http://www.mascip.co.uk/wp-content/uploads/2015/03/The-Initial-Management-of-Adults-with-SCI.-NSCISB.pdf.
186. Dyste GN, Hitchon PW, Girton RA, et al. Effect of hetastarch, mannitol, and phenylephrine on spinal cord blood flow following experimental spinal injury. *Neurosurgery*. 1989;24:228–235.
187. Werndle MC, Saadoun S, Phang I, et al. Monitoring of spinal cord perfusion pressure in acute spinal cord injury: Initial findings of the injured spinal cord pressure evaluation study. *Crit Care Med*. 2014;42(3):646–655.
188. Drummond JC, Moore SS. The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. *Anesthesiology*. 1989;70:64–70.
189. Robertson CS, Grossman RG. Protection against spinal cord ischemia with insulin-induced hypoglycemia. *J Neurosurg*. 1987;67:739–744.
190. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury: Results of the second National Acute Spinal Cord Injury Study. *N Engl J Med*. 1990;322:1405–1411.
191. Rozet I. Methylprednisolone in acute spinal cord injury: Is there any other ethical choice? *J Neurosurg Anesthesiol*. 2008;20:137–139.
192. Miller SM. Methylprednisolone in acute spinal cord injury: A tarnished standard. *J Neurosurg Anesthesiol*. 2008;20:140–142.
193. Bydon M, Lin J, Macki M, et al. The current role of steroids in acute spinal cord injury. *World Neurosurg*. 2014;82:848–854.
194. Schroeder GD, Kwon BK, Eck JC, et al. Survey of cervical spine research society members on the use of high-dose steroids for acute spinal cord injuries. *Spine*. 2014;39:971–977.

Supratentorial Masses: Anesthetic Considerations

11

N.J. Bruder • P. Ravussin • P. Schoettker

EPIDEMIOLOGY

According to the Central Brain Tumor Registry of the United States (CBTRUS) for the years 2007–2011, the incidence of primary brain and central nervous system (CNS) tumors is 21.42/100,000 per year. For children and adolescents 0–19 years of age, the incidence is 5.42/100,000. The incidence is 27.85/100,000 for adults (>20 years). For the year 2015, the estimate is 68,470 primary brain and CNS new cases. The overall mortality rate is 4.26/100,000. Approximately 34% of the tumors are malignant. The most common tumor is meningioma (36%) followed by glioblastoma (15%). The broad category glioma represents 28% of all tumors. The 5-years survival rate for malignant brain and CNS tumors is 34%, but only 5% for glioblastoma.[1] The majority of tumors (>80%) are supratentorial. For all primary brain tumors, the median age of diagnosis is 59 years. From 1985 to 1999, the incidence of primary brain tumors rose modestly (1.1% per year).[2] The exact incidence of brain metastases is unknown but certainly underestimated. In about 25% of patients who die from cancer, central nervous system metastases are detected at autopsy. For the five most common sources of brain metastases (breast, colorectal, kidney, lung, and melanoma), 6% of the patients suffer this complication within 1 year of diagnosis of the primary cancer.[3] Thus, these five cancers probably cause approximately 37,000 cases of brain metastases per year in the United States. Conversely, about 10% of patients with lung cancer present to the physician with symptoms from a brain metastasis.

General Considerations

For patients the problems associated with supratentorial tumors result from local and generalized pressure, whereas for surgeons the difficulties arise during surgical exposure because the brain is particularly susceptible to damage from retraction and mobilization. Anesthesia for supratentorial tumors thus requires an understanding of the pathophysiology of localized or generalized rising intracranial pressure (ICP); the regulation and maintenance of intracerebral perfusion; how to avoid secondary systemic insults to the brain[4,5] (Box 11.1); the effects of anesthesia on ICP, perfusion, and metabolism; and the therapeutic options available for decreasing ICP, brain bulk, and tension perioperatively. Specific problems include massive intraoperative hemorrhage, seizures, and air embolism in the head-elevated or sitting position or if venous sinuses are traversed. Further questions are how to monitor the brain's function and environment, and whether to aim for rapid anesthesia emergence or for prolonged postoperative sedation and ventilation. Finally, the concurrence of various intracranial and extracranial pathologic conditions should not be forgotten, such as the presence of cardiovascular or pulmonary disease or—in the case of metastases—the existence of paraneoplastic phenomena and the effects of chemotherapy or radiotherapy. This concept can be summarized as follows:

The anesthetic goal:	To preserve brain from secondary insult
The anesthetic risk factors:	Hypoxemia, hypercapnia, anemia, hypotension
The anesthetic actions:	Conserve cerebral autoregulation and CO_2 responsiveness Maximize brain elastance to decrease retractor pressure

Pathophysiology of Rising Intracranial Pressure

The main normal intracranial components of the brain (tissue, intravascular blood, cerebrospinal fluid [CSF]) are contained in an unyielding skull. Hence any increase in their volume—or the addition of an abnormal mass—must be compensated by a concurrent reduction in volume of one or more of these components, mainly CSF or blood (the brain is largely incompressible) (Fig. 11.1). The ability of these homeostatic mechanisms to compensate depends not only on the volume of the mass but also on the speed at which it arises: for rapidly expanding masses, the ICP volume curve shifts markedly to the left. Early but limited homeostasis is provided by extracranial shifts of intracranial blood, followed by larger-capacity displacement of CSF—which is ineffective if CSF flow is obstructed. Once these compensatory mechanisms are exhausted, ICP rises rapidly, which is followed by impairment of cerebral circulation[6] and, ultimately, by brain herniation; generally subfalcine ("midline shift") or

BOX 11.1 Secondary Insults to the Already Injured Brain

Intracranial
- Increased intracranial pressure
- Midline shift: tearing of the cerebral vessels
- Herniation: falx, transtentorial, trans-foramen magnum, transcraniotomy
- Epilepsy
- Vasospasm

Systemic
- Hypercapnia
- Hypoxemia
- Hypotension or hypertension
- Hypo-osmolality or hyperosmolality
- Hypoglycemia
- Hyperglycemia
- Low cardiac output
- Hyperthermia

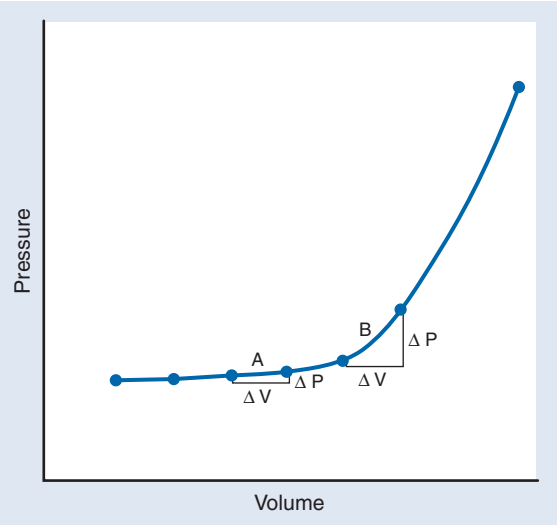


Fig. 11.1 Idealized hyperbolic intracranial pressure–volume curve. **A,** high intracranial compliance: a change in volume produces minimal change in pressure; **B,** low intracranial compliance: a same change in volume as that in A produces a large change in intracranial pressure; ΔP, change in pressure; ΔV, change in volume.

transtentorial, the end stage of compensation. This concept can be summarized as follows:

The cornerstone of neuroanesthesia:	Intracranial pressure–volume relationship
The main goal of neuroanesthesia:	Avoiding intracranial compartment volume increase, especially for cerebral blood volume (anesthetics, mean arterial pressure autoregulation, CO_2)
Anesthetic risk factor:	Administration of hypotonic fluids Medications that affect cerebral autoregulation

Volume Effects of Intracranial Tumors

The intracranial volume effects of tumors are due not only to the mass of the tumor itself but also to the surrounding vasogenic brain edema.[7,8] Such edema, commonly seen on preoperative computed tomography (CT) or magnetic resonance imaging, apparently results from secretory factors that increase vascular permeability in the nearby brain.[8] Peritumoral edema is particularly marked around fast-growing tumors, generally responds well to corticosteroid therapy, and can persist or even rebound after surgery for excision of the tumor. Thus the areas surrounding large tumors suffer from ischemia resulting from compression (cerebral blood flow [CBF]) in peritumoral tissue may be decreased by up to one-third compared with normal tissue).[9] Treatment with steroids such as dexamethasone usually results in dramatic decreases in surrounding brain edema. The emergency and preoperative treatment of peritumoral vasogenic edema is the only good indication for steroid therapy in this context.

The Blood–Brain Barrier and Edema

The blood–brain barrier is also affected by intracranial pathologic conditions. Normally the blood–brain barrier is impermeable to large or polar molecules and variably permeable to ions and small hydrophilic nonelectrolytes. Thus any disruption of the blood–brain barrier permits water, electrolytes, and large hydrophilic molecules to enter perivascular brain tissues, leading to vasogenic brain edema. In this case, leakage—and the resulting brain edema—is directly proportional to the cerebral perfusion pressure (CPP). Vasogenic edema should be differentiated from osmotic edema (caused by a drop in serum osmolality) and cytotoxic edema (secondary to ischemia). Blood osmolality is a critical determinant of cerebral edema because a 19-mmHg pressure gradient across the blood–brain barrier is generated for every milliosmole. In contrast, oncotic pressure plays a minor role. Neuroimaging shows disruption of the blood–brain barrier in many tumors. New strategies are being investigated to improve drug delivery to brain tumors. In the future, it is possible that new treatments to augment blood–brain barrier permeability (osmotic blood–brain barrier disruption, intra-arterial chemotherapy) will interfere with perioperative management.[10]

Intracerebral Perfusion and Cerebral Blood Flow

CBF is regulated at the level of the cerebral arteriole. It depends on the pressure gradient across the vessel wall (which in turn is the result of CPP) and $PaCO_2$ value (which depends on ventilation) (Fig. 11.2). CBF autoregulation, dominant to ICP homeostasis, keeps CBF constant in the face of changes in CPP or mean arterial pressure (MAP). It does this through alterations in cerebral vasomotor tone (i.e., cerebrovascular resistance [CVR]). Autoregulation is normally functional for CPP values of 50 to 150 mmHg and is impaired by many intracranial (e.g., blood in CSF, trauma, tumors) and extracranial (e.g., chronic systemic hypertension) pathologic conditions. It is also affected by drugs used in anesthesia.

If CPP is inadequate, tissue perfusion will decrease when the lower limit of autoregulation is less than 50 mmHg (if autoregulation is intact). Ischemia results at levels of CBF below 20 mL/100 g/min unless CPP is restored (by increasing MAP or decreasing ICP) or cerebral metabolic demand is reduced (through deepened anesthesia or hypothermia). Increased ICP resulting in reduced CPP is met by cerebral arteriolar relaxation; in parallel, MAP is increased via the systemic autonomic response. As a result, a vicious cycle can be established, particularly in the presence of impaired intracranial homeostasis, as cerebral vessel relaxation increases cerebral blood volume (CBV), thus further raising ICP. In addition, an acute reduction in CPP or MAP tends to acutely increase ICP (the so-called vasodilatory cascade[11]). Reductions in $PaCO_2$ induce vasoconstriction,[12] reducing CBF, CBV, and thus ICP. Conversely, hypercapnia increases ICP and should be prevented in the perioperative period. This makes hyperventilation a useful

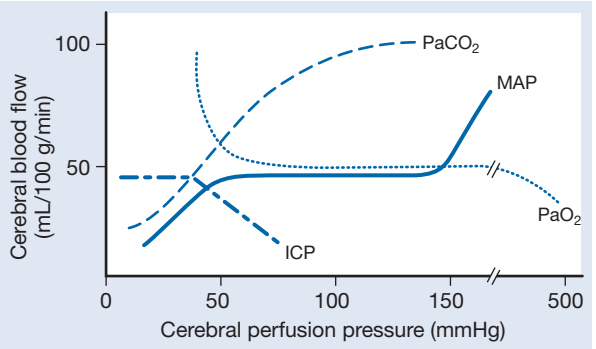


Fig. 11.2 Cerebral blood flow (CBF) autoregulation: for a cerebral perfusion pressure (CPP) value between 50 and 150 mmHg, CBF is maintained at 50 mL/100 g/min (__ MAP). There is a linear relationship between $PaCO_2$ (20–80 mmHg) and CBF (--- $PaCO_2$). Hypoxemia increases CBF and hyperoxia decreases CBF (…. PaO_2). If arterial pressure remains constant, CBF decreases when ICP increases (_ - _ - ICP). MAP mean arterial (blood) pressure.

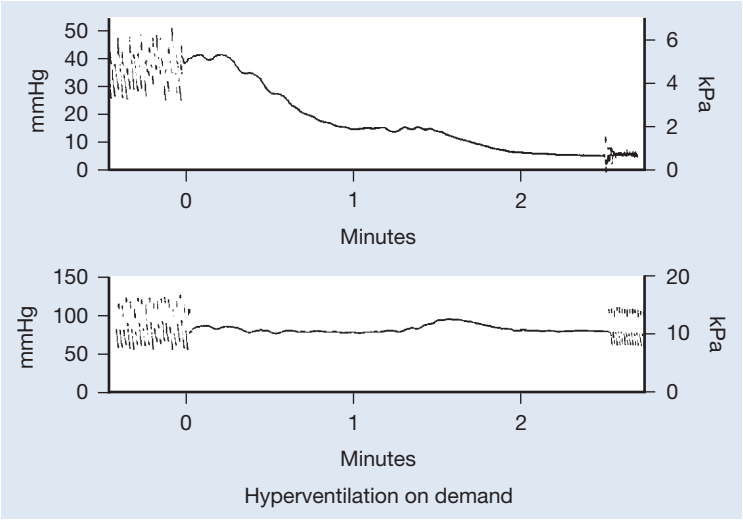


Fig. 11.3 Beneficial effect of voluntary hyperventilation on intracranial pressure before anesthesia induction. The upper trace is the ICP trend. The bottom trace shows the stability of the mean arterial pressure. *(Courtesy R Chiolero, MD)*

tool for the acute control of intracerebral hyperemia and elevated ICP (Fig. 11.3), as summarized here:

The anesthetic goal:	Hemodynamic stability
The reason:	Autoregulation takes 30 to 120 seconds to be established; thus sharp MAP fluctuations entrain undesirable CBF, CBV, and ICP changes
The formulas:	CBF = CPP/CVR CPP = MAP – ICP Normally, ICP < CVP

Anesthesia and Intracerebral Pressure, Perfusion, and Metabolism

Anesthesia exerts major effects on the intracranial environment through a variety of drug and nondrug effects. These effects are sensitive to the state of the intracranial and extracranial environment (e.g., cerebral compliance, presence or absence of intracranial pathologic condition, general volemic state).

Intravenous Anesthetics

Intravenous anesthetics include barbiturates, propofol, etomidate and ketamine. Apart from anesthesia induction, propofol is being increasingly used for maintenance as a continuous intravenous infusion (often computer controlled).[13] All the intravenous drugs mentioned are cerebral vasoconstrictors that act by depression of cerebral metabolic rate (CMR), except ketamine.[14–19] Ketamine increases whole brain CBF without changing CMR in healthy volunteers.[20] At subanesthetic doses, ketamine increases regional glucose metabolic rate and CBF.[21] The other agents decrease CBF, CBV, and ICP while leaving autoregulation and vessel reactivity to $PaCO_2$ intact (see Fig. 11.3).[17,22–25] CMR reduction reflects brain activity[26] and is mediated through the electrical but not the basal metabolic activity of the neurons. Hence there is a ceiling effect for CMR reduction at electroencephalogram (EEG) burst suppression (Fig. 11.4). In contrast to volatile anesthetics, propofol has been shown capable of suppressing the cerebrostimulatory effects of nitrous oxide.[22] Etomidate directly inhibits adrenal cortisol secretion for 24 to 48 hours even after a single injection,[27] and its use is often associated with myoclonic (not epileptic) movements.

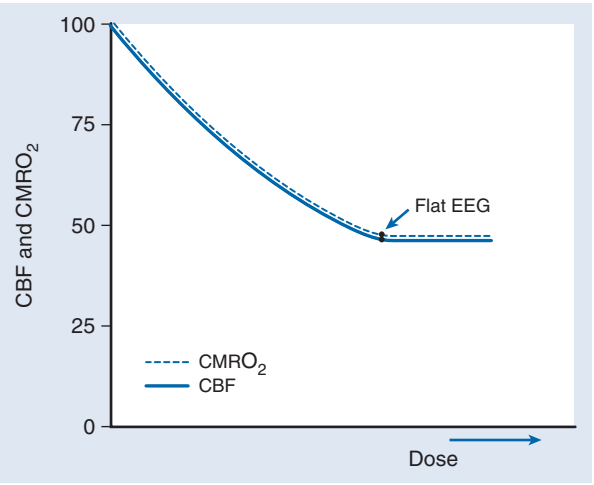


Fig. 11.4 Parallel decrease in cerebral blood flow (CBF) and cerebral metabolic rate of O_2 ($CMRO_2$) produced by an intravenous agent. Change is dose dependent until the electroencephalogram (EEG) becomes isoelectric (flat).

Volatile Anesthetics

All volatile anesthetics are cerebral vasodilators,[28,29] but isoflurane, sevoflurane, and desflurane also reduce CMR. A flat EEG is obtained with these three agents at around 2 minimum alveolar concentrations (2 MAC), a concentration at which maximum metabolic depression is achieved. The response of cerebral metabolism to rising concentrations of volatile anesthetics is not linear. The decrease in CMR is steep from 0 to 0.5 MAC and then more gradual up to 2 MAC.[30] The effect of volatile anesthetics on CBF is the result of their vasodilatory properties and flow-metabolism coupling. At low concentrations (<1 MAC), CBF is lower than in the awake person.[31] But CBV is unchanged with isoflurane and decreased with propofol at comparable concentrations.[15] Among the volatile anesthetics, sevoflurane is the least vasodilating and desflurane the most.[32,33] The effects of xenon are more complex. This agent decreases CBF in gray matter, particularly in specific brain areas such as the thalamus, the cerebellum, the cingulated gyrus, and the hippocampus, and increases CBF in white matter.[34] It does not impair flow-metabolism coupling.

For the normal brain and volatile concentrations below 1 MAC, $PaCO_2$ reactivity remains intact, permitting control of

vasodilation by hypocapnia.[22,25,35] (However, the presence of a pathologic brain condition or use of a high-MAC volatile anesthetic may impair or even abolish $PaCO_2$ reactivity and autoregulation.)[36,37]

Nitrous Oxide

Nitrous oxide is cerebrostimulatory, increasing CBF, CMR, and sometimes ICP. Its effect is not uniform throughout the brain but is limited to selected brain regions (basal ganglia, thalamus, insula), changing the regional distribution of CBF.[38,39] If substituted for an equipotent concentration of a volatile anesthetic agent, nitrous oxide increases CBF.[40,41] For the normal brain, the resulting cerebral vasodilation can be controlled by hypocapnia or the addition of an intravenous anesthetic. However, volatile agents have no such attenuating effect;[42] CMR and CBF are higher during 1 MAC anesthesia produced by a nitrous oxide-volatile anesthetic combination than that produced only by a volatile anesthetic.[42,43] This effect is especially deleterious in the actual or potential presence of brain ischemia. Particularly for repeat craniotomy, the potential of nitrous oxide, which is poorly soluble, to diffuse into and hence expand hollow spaces must be remembered as it could cause tension pneumocephalus in patients with intracranial air (repeat neurosurgery or head trauma).[44–46]

Opioids

Opioids have been associated with short-term increases in ICP,[47–50] particularly sufentanil or alfentanil. Reflex cerebral vasodilation after decreases in MAP and hence in CPP is the underlying mechanism for the transient increases in ICP,[42,51–54] although a direct modest cerebral vasodilator effect has been demonstrated.[48] This effect demonstrates the sensitivity of intracerebral drug effects to the intracranial and extracranial environment and the importance of maintaining normovolemia for ICP stability. Generally, opioids modestly reduce CMR and do not affect flow-metabolism coupling, autoregulation, or the carbon dioxide sensitivity of the cerebral vessels. Remifentanil has been extensively studied. Its cerebral effects are comparable to those of other opioids, and its use in neuroanesthesia has been validated in clinical trials.[11,55–58]

Other Drugs

Vasodilating antihypertensive agents such as nitroglycerine, nitroprusside, and nicardipine increase ICP and should be avoided.[59,60] Cerebral vasodilation may result from a normal autoregulation response or direct arterial vasodilation. For example, sodium nitroprusside increases ICP,[61] but intracarotid injection of nitroprusside does not change CBF.[62] Conversely, verapamil decreases cerebrovascular resistance in humans by inducing direct cerebral vasodilation.[63] Theophylline constricts cerebral vessels but increases CSF production and is a potent central nervous system (CNS) stimulant, raising the risk of convulsions. Most β-adrenergic blockers, especially esmolol, do not interfere with cerebral blood flow or metabolism.[64]

Reducing Intracranial Pressure, Brain Bulk, and Tension

The anesthesiologist possesses a number of instruments to achieve ICP reduction and brain relaxation (Box 11.2), and thus to improve the quality of surgical exposure and to reduce retractor pressure. The effectiveness of these instruments depends on intact intracerebral homeostatic mechanisms.

BOX 11.2 Management of Intracranial Hypertension and Brain Bulging

Prevention

- Euvolemia
- Sedation, analgesia, anxiolysis
- No noxious stimulus applied without sedation and local anesthesia
- Head-up position, no compression of the jugular veins, head straight
- Osmotic agents: mannitol, hypertonic saline
- β-Blockers or clonidine or lidocaine
- Steroids, if a tumor is present
- Adequate hemodynamics: mean arterial blood pressure, central venous pressure, pulmonary capillary wedge pressure, heart rate
- Adequate ventilation: $PaO_2 > 100$ mmHg, $PaCO_2$ 35 mmHg
- Intrathoracic pressure as low as possible
- Hyperventilation on demand before induction
- Use of intravenous anesthetic agents for induction and maintenance in case of tensed brain

Treatment

- Cerebrospinal fluid drainage if ventricular or lumbar catheter in situ
- Osmotic agents
- Hyperventilation
- Augmentation of anesthesia with intravenous anesthetic agents: propofol, thiopentone, etomidate
- Muscle relaxants
- Venous drainage: head up, no positive end-expiratory pressure, reduction of inspiratory time
- Mild controlled hypertension if autoregulation present

Intravenous Anesthetics

Intravenous anesthetics reduce CMR, CBF, and hence CBV and ICP, leading to a diminution of brain bulk, as discussed previously. Cerebral vasoconstriction depends on intact flow-metabolism coupling (Figs. 11.4 and 11.5) and is dose related up to neuronal electrical silence (EEG burst suppression). Like autoregulation, flow-metabolism coupling is impaired by brain contusion and other intracerebral pathologic conditions.

Hyperventilation

Hyperventilation results in hypocapnia and subsequent cerebral vasoconstriction. In the context of intact autoregulation, CBF is roughly linearly related to $PaCO_2$ between 20 and

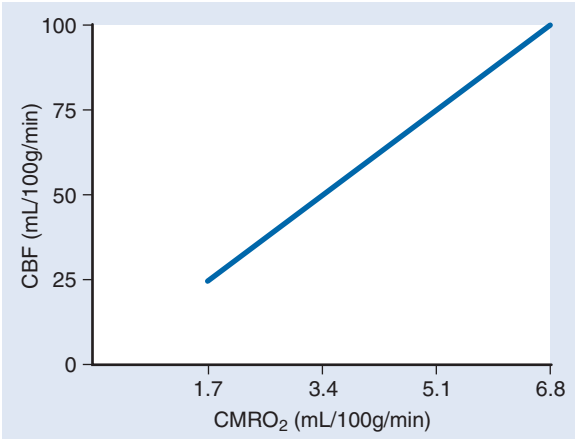


Fig. 11.5 Coupling between cerebral blood flow (CBF) and cerebral metabolic rate of O_2 production ($CMRO_2$) coupling (flow-metabolism coupling). Normally, a $CMRO_2$ of 4 mL/100 g/min is coupled to a CBF of 50 mL/100 g/min.

70 mmHg.[12] However, the carbon dioxide reactivity of cerebral vessels may be impaired or abolished in the presence of head injury or other intracerebral pathologic conditions, by high inspired concentrations of volatile anesthetics, or, particularly if the vessels are already dilated, by nitrous oxide. The CBF-, CBV-, and ICP-reducing effects of hypocapnia are acute and apparent for less than 24 hours.[65] A typical value to aim for is a $PaCO_2$ of 30 to 35 mmHg; arterial blood gas analysis rather than end-tidal CO_2 ($ETCO_2$) should be used as a controlling variable because of the possibility of large arterioalveolar CO_2 gradients in neurosurgical patients. The effectiveness of hyperventilation ($PaCO_2$ at 25 ± 2 mmHg) for controlling brain bulk in the patient under either isoflurane or propofol anesthesia has been demonstrated.[66]

The main complication associated with hyperventilation is reduction of CBF, which gives rise to cerebral ischemia.[67] Thus, the anesthesiologist must balance the benefit of brain relaxation against the risk of cerebral hypoperfusion. Other side effects are linear reduction in coronary artery flow, reduced cardiac venous return, hypokalemia, and potentiation of the brain's response to opioids.[68]

Diuretics and Osmotic agents

Osmotic diuretics such as mannitol and hyperosmotic saline increase blood osmolality acutely, thus reducing brain water content (mainly in healthy brain tissue with an intact blood–brain barrier) and hence brain bulk and ICP.[69] This response improves brain deformability and thereby facilitates surgical exposure. A further beneficial effect is improvement in blood rheology[70] as a result of the reduction in edema of vascular endothelium and erythrocytes (increasing erythrocyte deformability)—the basis of mannitol's classic "antisludge" effect.[71] A typical regimen is to give 0.5 to 1 g/kg mannitol (150–400 mL 20% mannitol) intravenously, split between a more rapid pre-craniotomy dose and a slower infusion, until brain dissection is complete. The ICP effect is prompt,[72] removes about 90 mL of brain water at peak effect,[73] and lasts for 2 to 3 hours. Theoretically, equiosmolar infusions of hypertonic saline or mannitol should have the same effect for reducing brain water content. One study showed slightly better results with hypertonic saline than mannitol on intraoperative brain relaxation.[74] Normally the aim is to keep osmolality at less than 320 mOsm/kg. Problems with the use of osmotic diuretics include hypernatremia, hypokalemia, and acute hypervolemia, which could be deleterious in patients with congestive heart failure. There is no additional benefit to using loop diuretics such as furosemide, which induces hypovolemia and does not reduce brain water content except that it may limit rebound edema formation.[75] On the contrary, serum saline should be infused to replace urinary losses in order to avoid hypovolemia and maintain blood pressure.

Cerebrospinal Fluid Drainage

CSF drainage is achieved either by intraoperative direct puncture of the lateral ventricle or through a lumbar spinal catheter placed preoperatively. The latter is effective only if there is no caudal block to CSF outflow. Because of the risk of causing acute brain herniation, lumbar CSF drainage should be used cautiously and only when the dura is open. The patient should receive at least mild hyperventilation when CSF is drained. Normally removal of 10–20 mL of CSF is very effective in reducing brain tension. Up to 50 mL can be drained if necessary.

Other Factors

Other factors causing cerebral vasodilation and that can be corrected by the anesthesiologist include hypovolemia and hypoxia. The position of the patient (head down, extreme turning of the neck) also influences brain volume because of impaired venous drainage of the brain.[76] This should be kept in mind when brain swelling is observed without any obvious reason after the dura is opened. Repositioning of the head to avoid excessive rotation and compression of the jugular vein may be the solution.

Vasoconstrictive Cascade

Finally, the anesthesiologist can use the vasoconstrictive cascade[77] by mildly increasing MAP, thus increasing CPP and decreasing CBV and ICP (Fig. 11.6).

General Anesthetic Management

Preoperative Assessment

Determination of anesthetic strategy for a given neurosurgical intervention depends on thorough knowledge of the neurologic and general state of the patient, the planned intervention, and holistic integration of these factors. The patient and the planned intervention should be discussed with the neurosurgeon involved.

Neurologic State of Patient

A major aim in evaluating neurologic status is to estimate how much ICP is raised, the extent of impairment of intracranial compliance and autoregulation, the localization of the tumor and how much homeostatic reserve for ICP and CBF remains before brain ischemia and neurologic impairment occur. The goal is also to assess how much permanent and reversible neurologic damage is already present. Typical pointers to these elements in the patient history, physical examination, and technical examinations are listed in Box 11.3. The minimum examination should involve a neurologic mini-mental status assessment, comprising the patient's ability to follow commands, the patient's degree of orientation, the presence or

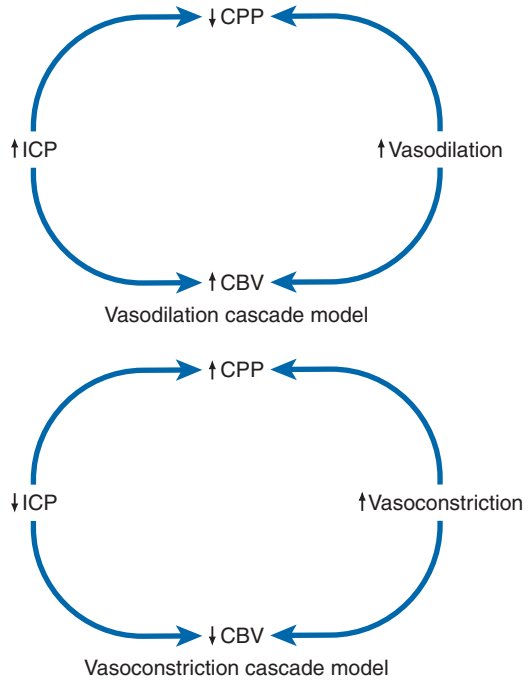


Fig. 11.6 Vasodilatory cascade model proposes that a decrease (↓) in cerebral perfusion pressure (CPP) can lead to cerebral vasodilation with subsequent increases (↑) in cerebral blood volume (CBV) and intracranial pressure (ICP). In contrast, the vasoconstriction cascade model suggests that an increase in CPP can reduce CBV and thus ICP. *(Modified from Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. J Trauma 1990;30:933–940.).*

BOX 11.3 Preoperative Neurologic Evaluation

History
- Seizure (type, frequency, treatment)
- Increased intracranial pressure (ICP): headache, nausea, vomiting, blurred vision
- Decreased level of consciousness, somnolence
- Focal neurologic signs: hemiparesis, sensory deficits, cranial nerve deficits, etc.
- Paraneoplastic syndromes, including presence of thrombosis

Physical Evaluation
- Mental status
- Papilledema (increased ICP)
- Signs of Cushing's response: hypertensive bradycardia
- Pupil size, speech deficit, Glasgow Coma Scale score, focal signs

Medication
- Steroids
- Antiepileptic drugs

Technical Examination (Computed Tomography or Magnetic Resonance Imaging)
- Size and location of the tumor: silent or eloquent area, near a major vessel, etc.
- Intracranial mass effect: midline shift, decreased size of the ventricles, temporal lobe hernia
- Intracranial mass effect: hydrocephalus, cerebrospinal fluid space around brainstem
- Others: edema, brainstem involvement, pneumocephalus (repeat craniotomy)

Evaluation of Hydration Status
- Fever; infection
- Duration of bed rest
- Fluid intake
- Diuretics
- Inappropriate secretion of antidiuretic hormone

Neurologic Working Diagnosis
- Tissue type of tumor

absence of speech deficit, the pupil symmetry and the Glasgow Coma Scale score. Elucidating what medication the patient is receiving and for how long is important because this medication may also affect intracranial compliance, perfusion, and reserves, as well as modify the pharmacokinetics and dynamics of anesthetic drugs.

The patient's CT scan or magnetic resonance image should be examined for the size and localization of the tumor and for signs of increased ICP. The latter include effacement of the lateral ventricle by tumor mass, lateral ventricle extension resulting from obstructive hydrocephalus, and midline shift (midline shift > 5 mm).[78,79] The presence of such signs warns that the ICP-volume curve is close to decompensation (the "knee" of the hyperbolic ICP-volume curve; see Fig. 11.1), with small increases in intracranial volume leading to disproportionate ICP increases and brain swelling. The preoperative treatment of brain edema with steroids should not mislead the neuroanesthetist into thinking that the patient is no longer at risk for perioperative intracranial hypertension. Any patient who has presented with symptoms and signs of elevated ICP should be regarded as being at risk for perioperative intracranial hypertension even if the presenting clinical tableau is no longer present.

General State of Patient

Cardiovascular and respiratory functions are important because brain perfusion and oxygenation ultimately depend on them; their function should therefore be optimized preoperatively. Some intracranial pathologic conditions alter cardiovascular function (e.g., effects of raised ICP on cardiac conduction). Supratentorial surgery (particularly for meningiomas, metastasis) can be associated with significant blood loss, and hypovolemia and hypotension have detrimental effects in the neurosurgical context. The neuroanesthetist should note that both hyperventilation—often used to control ICP, CBF, CBV, and brain tension—and the operative position make additional demands on the respiratory and cardiovascular systems. Finally, especially in neurosurgery for metastases, the primary tumor can itself impair cardiorespiratory function (e.g., 40% of brain metastases originate from the lung[80]) as can anticancer chemotherapy or radiotherapy. Examples are cardiomyopathy and doxorubicin (Adriamycin) or cyclophosphamide (Cytoxan) therapy and inhibition of plasma cholinesterase activity.[81]

Further problems associated with malignant tumors include coagulation disorders, which are associated with an increased risk of thromboembolism, as high as 21% in the first year after surgery.[82] Thus, despite the risk of bleeding, low-molecular-weight heparin may be indicated after craniotomy to prevent venous thromboembolism in high-risk patients.[83]

Other systems interacting with neuroanesthesia are the renal system (e.g., diuretics and subsequent changes in plasma electrolytes, diabetes insipidus, decreased fluid intake), the endocrine system (altered by the intracranial disease process, such as pituitary adenoma, or by therapeutic drugs, such as the effect of glucocorticosteroids on hyperglycemia and cerebral ischemia), and the gastrointestinal tract (e.g., mucosal effects of steroids, motility effects of raised ICP). Hypercalcemia should be ruled out when brain tumors are associated with bone metastasis. A thorough history, supplemented by appropriate physical and technical examinations, is important for the elucidation and definition of these problems. It is important to remember that elderly patients (especially those with impaired cardiac and pulmonary function) pose particular challenges for anesthetic and perioperative management in this context.

Planned Operative Intervention

For a planned operative intervention, the important points to clarify include the size and position of the tumor, the tissue diagnosis, the surgical approach, the structures in proximity and the likelihood of their involvement by surgery, and whether the tumor is to be removed radically. Knowing whether the mass to be resected is a tumor, a hematoma (acute or chronic), an abscess, a metastasis, or something else is useful information. The surgical approach determines the positioning of the patient; common approaches to supratentorial masses are either pterional or temporal and frontal craniotomies. In a bifrontal approach, the sagittal venous sinus is traversed, thereby raising the risk of bleeding and venous air embolism.

When the tissue diagnosis is meningioma, the anesthesiologist should anticipate an operation with the goal of complete excision, which is generally curative.[84] Meningiomas can grow quite large, particularly in neurologically silent areas such as the frontal region, because they often grow slowly. They are often in difficult locations because of either surrounding structures or problematic access (e.g., sagittal sinus, optic nerve sheath, clivus, tentorial notch, ventricles, bone invasion). The combination of large size, difficult location, and the desire for radical excision makes for long and technically demanding operations. Such procedures are often accompanied by significant bleeding (from surrounding structures and because meningiomas are often highly vascular) and require maximal reduction of brain tension to facilitate surgical access. Preoperative embolization may reduce intraoperative

bleeding during meningioma resection. Intraoperative blood salvage and autotransfusion may limit homologous transfusion in about 15% of patients.[85] In contrast, glioma resections are often easy debulking operations, of simple surgical access and low propensity to stimulate bleeding.

Colloid cysts of the third ventricle and epidermoid tumors arising in the basal cisterns are the most common nonpituitary supratentorial lesions. Colloid cysts of the third ventricle may be accompanied by obstructive hydrocephalus and thus high ICP at anesthesia induction. The relatively deep location of colloid cysts, epidermoid tumors of the basal cisterns, and pituitary tumors (if operated transcranially) make the provision of excellent brain relaxation for their exposure at the skull base the major anesthesiologic challenge during resection. Transsphenoidal resection of a pituitary adenoma is an essentially extracranial operation.

Determination of Anesthetic Strategy

After consideration of the preceding factors, the following issues are addressed:

Vascular access: Consider risk of bleeding and venous air embolism, need for hemodynamic and metabolic monitoring, and requirements for infusion of anesthesia (TCI), vasoactive and other substances.

Fluid therapy: Aim for normovolemia and normotension, avoid hypo-osmolar fluids (lactated Ringer's solution), and avoid glucose-containing solutions in order to prevent hyperglycemia, which exacerbates ischemic brain injury.

Anesthetic regimen: Use (1) volatile agent-based anesthesia for "simple" procedures with low risk of ICP problems, ischemia, and need for brain relaxation and (2) total intravenous anesthesia for more complex procedures with anticipation of ICP problems, significant risk of cerebral ischemia, and need for excellent brain relaxation.

Ventilatory regimen: Aim for normocapnia or mild hypocapnia, mild hyperoxia, and low intrathoracic pressures (to improve cerebral venous return).

Extracranial monitoring: Assess cardiovascular and renal function (anticipate the management of venous air embolism). Monitor bleeding with point-of-care devices such as ROTEM®. TEG® and Multiplate®.

Intracranial monitoring: Check general intracranial environment versus specific functions or pathways, for example, neurophysiologic (EEG, evoked potentials), metabolic (jugular venous bulb oxygenation, transcranial oximetry), and functional (transcranial Doppler ultrasonography).

Special techniques: Take into account surgical needs that may modify anesthetic management (brain stimulation and use of muscle relaxants, for example).

Preoperative Preparation

Premedication

Sedation carries the risk of hypercapnia, hypoxemia, and partial upper airway obstruction, all of which are detrimental in the context of increased ICP. However, avoiding stress (increased CMR, CBF) and hypertension (increased CBF, possibly vasogenic edema with impaired autoregulation) is also desirable.[86] Thus analgesia and sedation (e.g., midazolam 0.5 to 2 mg or other benzodiazepines and/or fentanyl 25 to 100 µg or sufentanil 5 to 20 µg) may be provided during the placement of preoperative vascular access and monitoring devices by small, titrated, and intravenous increments under the direct and continuing control and observation of the anesthesiologist. The patient must never be left unsupervised in this context; respiratory support should be provided as necessary. However, in patients with tumors with no clinical or other signs of increased ICP (no shift, etc.), a small dose of benzodiazepine can help decrease the level of anxiety while keeping in mind to use medications allowing proper postoperative assessment. Small doses of benzodiazepines or narcotics can unmask or worsen a preexisting compensated neurologic deficit.[87,88] This event may be difficult to distinguish from rapid worsening of mass effect and intracranial hypertension.

Steroids should be continued on the morning of the operation (methylprednisolone or dexamethasone). Histamine (H_2) blockers and gastric prokinetic agents should be considered to counteract the reduced gastric emptying and greater acid secretion associated with increased ICP and steroid therapy, particularly in patients with cranial nerve (IX, X) palsies (impairment or absence of gag reflexes). Other regular medication, particularly anticonvulsants,[89–91] as well as antihypertensive and other cardiac medications, should be continued, although drug interactions may occur with phenytoin. Perioperative fluctuations in antiepileptic medications may occur, contributing to perioperative development of seizures.[90,91] Monitoring of plasma levels or temporary augmentation of dosage of such medications may be necessary.

Vascular Access

Two large-bore peripheral intravenous lines are usually placed for a full craniotomy; one line should suffice for stereotactic biopsy. Central venous access, currently less systematically inserted, is indicated if a clinically significant risk of venous air embolism exists, if substantial bleeding is anticipated (e.g., a large vascular tumor, proximity to major arteries or venous sinuses, or extensive bone resection), if major cardiovascular compromise is evident or suspected, and if vasoactive drugs are to be infused continuously. We recommend the internal jugular approach with a meticulous cannulation technique and minimization of head-down positioning and neck rotation. Such positioning and neck rotation, together with the inevitable element of patient discomfort, can increase ICP. Thus in a stable patient, consideration can be given to putting these lines in once the patient is asleep. If the central line is placed for the management of venous air embolism, its position must be carefully controlled radiographically (tip at transition between vena cava and right atrium) or with the use of an electrocardiography lead.

Neuroanesthesia for full craniotomy with arterial cannulation is recommended, because of the need for very tight monitoring and control of CPP (obtainable by transducing arterial pressure at the mid-ear level of the circle of Willis and using the formula CPP = MAP − ICP). After the dura is opened, ICP equals the atmospheric pressure, so CPP equals MAP. In addition, frequent blood sampling is necessary for measurements of $PaCO_2$, particularly if the patient is hyperventilated, is elderly, or has chronic obstructive pulmonary disease,[92,93] and for plasma glucose, potassium, osmolality, and other measurements. Monitoring of $ETCO_2$ is no substitute for $PaCO_2$ measurement because the two often correlate poorly, especially with impaired ventilation–perfusion matching as occurs in chronic obstructive pulmonary disease, in elderly patients, or with long procedures.

The monitoring of jugular venous bulb oxygen saturation via a catheter placed by retrograde cannulation of the internal jugular vein, permits continuous monitoring of cerebral oxygen extraction and hemoglobin oxygen saturation in jugular venous bulb blood ($SjvO_2$). Under the assumption that CMR is constant, or through observation of its alteration by EEG monitoring, conclusions can be drawn about the global adequacy of cerebral perfusion (Fig. 11.7).[94]

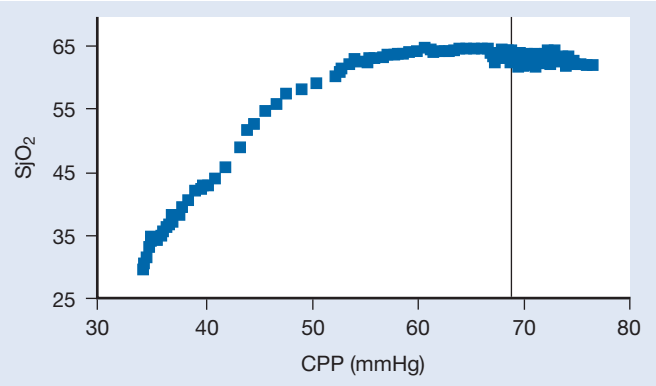


Fig. 11.7 Jugular venous bulb oxygen saturation (SjO_2) versus cerebral perfusion pressure (CPP) during administration of a methoxamine bolus for hypotension. SjO_2 starts to decline. *(Courtesy Andrews PJD, Wang FC, Miller JD, unpublished data.)*

Monitoring

As already noted, close hemodynamic monitoring is fundamental during neurosurgery. This includes beat-to-beat monitoring of arterial blood pressure and the electrocardiogram for the diagnosis of myocardial ischemia and arrhythmias. Pulse oximetry (for the detection of systemic hypoxia), $ETCO_2$ (as a *trend* monitor for $PaCO_2$ and to help in the detection of venous air metabolism), and temperature monitoring (eg, esophageal or urinary bladder) represent standard monitoring. A urinary catheter is placed to monitor urine output.

The occurrence of air embolism[95] is best detected by transesophageal echocardiography or precordial Doppler ultrasonography, the most sensitive monitor (together with transesophageal echocardiography) for air bubbles in the venous circulation. If myorelaxants are necessary during the operation, neuromuscular block should be monitored. However, neuromuscular transmission should not be monitored on hemiplegic extremities because the greater acetylcholine receptor density of lower motor neuron units innervated by dysfunctional or nonfunctional upper motor neurons leads to resistance to nondepolarizing myorelaxants. If myorelaxant dosing is based on peripheral nerve stimulation of a hemiplegic extremity, overdosing of normal neuromuscular units will result.[96] In this context hemiparesis is probably not associated with hyperkalemia as appears in paraplegic or burn patients, and the use of succinylcholine is therefore not contraindicated from this point of view.[97] Because general anesthesia and steroid therapy both raise blood glucose levels and because brain retraction is often associated with at least some focal cerebral ischemia,[98] blood glucose levels should be monitored regularly; hyperglycemia worsens neuronal damage during ischemia.[99–102] In this context, monitoring plasma electrolytes (particularly potassium) and osmolality (particularly if mannitol or hypertonic saline is used) would also appear to be prudent, as would hemoglobin and hematocrit determinations in the context of bleeding.

Particular attention must be paid to the monitoring of coagulation and hemostasis disorders. Primary or metastatic brain tumors may result in vascular perturbations that are thought to contribute to the progression of underlying diseases, such as thrombosis and hemorrhage.[103] Endothelial injury, ischemia and secondary inflammatory reactions trigger the release of brain thromboplastins, thrombin, and iron while degradation products of lysed red blood cells will lead to hemostatic perturbations.

Increased expression of tissue factor, for example, may be related to astrocytic tumors,[104] while specific brain tumors have a direct effect on fibrinolysis[105,106] or enhance plasmatic coagulation.[107] Moreover, the use of antiepileptic drugs has been related to hemostatic disorders, such as platelet dysfunction,[108] hypofibrinogenemia[109] or lowered factor XIII.[110]

In addition to the routine coagulation parameters, point-of care (POC) viscoelastic assays (ROTEM® or TEG®) or whole-blood impedance aggregometry (Multiplate®) can provide an overall understanding of the coagulation status and platelet function.[111] They are performed in whole blood and provide clinically relevant data, such as the speed and quality of clot formation, clot firmness, the presence of hyperfibrinolysis or the effect of aspirin, clopidrogel and GP IIb/IIIA receptor blockers.[112] First reports of their use in neurosurgical cases are published.[113,114] The availability of rapid POC tests can guide intraoperative therapeutic management and allow goal-directed hemostatic therapy in neurosurgical patients.

Monitoring of the intracranial environment or cerebral function is increasingly practiced during neurosurgery. For some operations, monitoring of evoked potentials is helpful in observing the intactness of specific central nervous pathways. The surgical treatment of tumors located near eloquent brain areas carries a high risk of worsening neurologic deficits. Intraoperative electrostimulation (IES) has been developed to optimize the benefit–risk ratio of surgery. Motor mapping with the patient under general anesthesia or conscious sedation is being increasingly used to localize motor cortex adequately and improve the quality of surgical tumor or of an epileptic zone removal (see Chapter 17). Compared with general anesthesia, conscious sedation improved the chance of achieving successful stimulation.[115]

Preoperative ICP monitoring for elective supratentorial tumor surgery is rarely used today because of the impact of corticosteroids on preoperative ICP reduction and the ability of modern anesthetic techniques to control ICP during induction. This does not apply to neurotraumatology, in which ICP monitoring is vital for therapy from the patient's entry in the emergency department onward. With the advent of relatively safe and simple-to-use catheter-tip ICP monitoring, there is, however, a trend toward more use of postoperative ICP monitoring, particularly for patients at risk (especially for removal of large tumors with extensive surrounding edema or for emergency surgery in patients with intracranial hypertension and altered consciousness). Intracranial hypertension develops in up to 20% of patients in the immediate postoperative period from brain swelling or hematoma formation, and such patients benefit from prompt therapeutic intervention.[116] Postoperative ICP monitoring may also help with the differential diagnosis in patients who do not emerge from anesthesia after operation. For all of these uses, looking at the shape of the ICP curve is important to ensure that the pressures displayed are reliable.

In some specific cases, if lumbar CSF drainage is used, it can provide a reflection of ICP as long as the CSF pathways are not blocked. This approach can be tested by determining whether compression of the jugular veins increases lumbar CSF pressure (Queckenstedt maneuver). The lumbar CSF pressure can then be used to provide information to the surgeon and anesthesiologist about the influence of positioning, anesthesia, and surgery on potential brain perfusion pressure.

Transcranial Doppler ultrasonography (TCD) is being increasingly used in anesthesia and intensive care for monitoring blood flow velocity (FV) (see Chapter 7). TCD allows estimation of pressure autoregulation and CO_2 reactivity.[117] In addition, TCD is the only convenient noninvasive method both to detect intracranial complications that lead to increased ICP and to assess cerebral perfusion in anesthetized

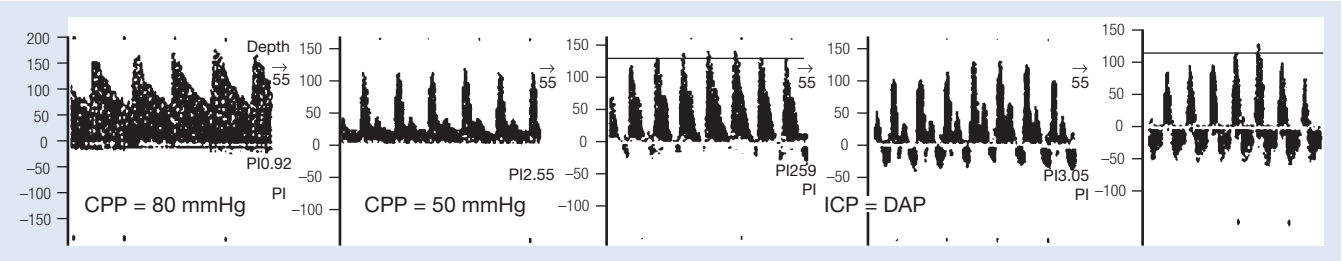


Fig. 11.8 Changes seen on transcranial Doppler ultrasonography with decreasing cerebral perfusion pressure (CPP). Cerebral diastolic velocities decrease to zero when intracranial pressure (ICP) reaches diastolic arterial pressure (DAP). Ultimately, a reverse flow pattern with upward flow during systole and downward flow during diastole indicates cerebral circulatory arrest. PI, xx.

patients (Fig. 11.8).[118] During emergence from anesthesia, FV monitoring can detect cerebral hyperemia.[119] Although the implications of this physiologic change are not clear, cerebral hemorrhage after severe cerebral hyperemia has been reported.[120] Intraoperative Doppler monitoring in the surgical field, by means of a microvascular ultrasonic flow probe, has been used mostly in aneurysm surgery.[121] It may be used in tumor surgery to assess vessel patency during difficult dissection from the tumor.

Induction of Anesthesia

Goals and Drugs

The major factors to be considered for anesthesia induction for elective supratentorial neurosurgery are avoidance of secondary brain injuries. Therefore, ventilatory control (avoidance of hypercapnia and hypoxemia), sympathetic and thus blood pressure control (ie, adequate depth of anesthesia and antinociception to prevent CNS arousal), and prevention of cranial venous outflow obstruction (head positioning) are essential. Attention to these details improves the patient's intracranial pressure–volume curve status, ensures the adequacy of cerebral perfusion, helps prevent untoward increases in ICP, and decreases brain perfusion pressure. A typical scheme for achieving these goals is detailed in Box 11.4, with propofol or thiopental given as a "starter," and an opioid, together with gentle hyperventilation, administered before intubation. For induction in more frail or elderly patients, etomidate (0.2 to 0.4 mg/kg) may be used instead of propofol.

BOX 11.4 Suggested Anesthesia Induction Sequence for Intracranial Surgery

1. Adequate anxiolysis in the anesthetic room. Adequate fluid loading (5 to 7 mL/kg of NaCl 0.9%). Electrocardiogram leads in place; capnometer, pulse oximeter, and noninvasive blood pressure monitors. Insertion of intravenous and arterial lines under local anesthesia.
2. Induction of general anesthesia. Fentanyl 1 to 2 µg/kg or sufentanil or remifentanil. Preoxygenation and voluntary hyperventilation propofol 1.25 to 2.5 mg/kg or thiopentone 3 to 6 mg/kg for induction. Nondepolarizing muscle relaxant: vecuronium, rocuronium, or cisatracurium. Controlled ventilation at $PaCO_2$ of 35 mmHg propofol 50 to 150 µg/kg/min or isoflurane 0.5% to 1.5% (or sevoflurane or desflurane) for maintenance and fentanyl (or alfentanil, sufentanil, or remifentanil) 1 to 2 µg/kg/h (or bolus) for analgesia.
3. Intubation.
4. Local anesthesia or intravenous remifentanil 0.5 to 1 µg/kg for skull-pin head-holder placement and skin incision.
5. Adequate head-up positioning; no compression of the jugular veins.
6. Brain relaxation. Mannitol 0.5 to 0.75 g/kg if needed. Insertion of a lumbar drain if needed. Normovolemia with the use of NaCl 0.9% or starch 6%—no lactated Ringer's solution.

Fentanyl may be replaced by alfentanil (5 to 10 µg/kg followed by infusion at 5 to 10 µg/kg/h), by sufentanil (0.5 to 1.5 µg/kg followed by infusion at 0.1 to 0.3 µg/kg/h) for smoother hemodynamic control, or by remifentanil (0.25 to 0.5 µg/kg followed by infusion at 0.1 to 0.2 µg/kg/h) for rapid awakening and early neurologic assessment independent of the duration of anesthesia.[58,122,123]

Muscle Relaxants

Modern nondepolarizing myorelaxants have minimal effects on intracerebral hemodynamics. It is thought that the use of succinylcholine should be reserved for patients with possible intubation difficulties or when rapid-sequence induction is absolutely unavoidable. Succinylcholine can cause transient increases in CMR, CBF, and ICP, although such increases usually can be controlled by hyperventilation or deepened anesthesia and are of consequence mainly in patients who have precariously elevated ICP.

We strongly recommend avoiding longer-acting myorelaxants, such as pancuronium, and prefer the use of middle- to short-acting myorelaxants, such as vecuronium, cisatracurium, mivacurium, and rocuronium. Our recommendation is based on the fact that neurosurgical patients are particularly susceptible to the effects of myorelaxant hangover (difficult to detect with manual assessment of peripheral nerve stimulation). In this context, the interaction (need for up to 50% to 60% higher doses) between long-term phenytoin[89,124] or carbamazepine treatment[125] (>7 days) and pancuronium, vecuronium, atracurium, or cisatracurium[126,127] should be noted, as should the need to monitor neuromuscular transmission on nonhemiplegic extremities (as discussed previously). The anesthesiologist should keep in mind, however, that immobility of the patient must be guaranteed during the procedure.

Patient Positioning

Pin holder application is a maximal nociceptive stimulus. It must be adequately blocked by deepening of analgesia (bolus of remifentanil 0.25 to 1 µg/kg) or anesthesia (e.g., intravenous bolus of propofol 0.5 mg/kg), preferably in conjunction with local anesthetic infiltration of the pin site to prevent undesirable CNS arousal and hemodynamic activation.[128] Alternatively, hemodynamic control can be achieved with antihypertensive agents such as esmolol (1 mg/kg) and labetalol (0.5 to 1 mg/kg). Scalp blockade, ideally before pinning, improves intraoperative hemodynamic stability and provides some degree of postoperative analgesia.[129] *Pin insertion can be associated in very rare cases with venous air embolism in head-up positioned patients.*

Patient positioning must be closely surveyed by both the anesthesiologist and the surgeon, with extreme positioning being avoided. Careful attention should be paid to padding or fixing of regions susceptible to injury by pressure, abrasion, or movement, such as falling extremities. A mild head-up

position helps venous drainage. Severe lateral extension or flexion of the head on the neck should be prevented (there should be at least two fingers' space between chin and nearest bone) to avoid endotracheal tube kinking, postoperative airway swelling and compromise, and impairment of cerebral venous drainage (brain swelling). The knees should be mildly flexed to avoid lumbosacral injury. If the head is turned laterally (e.g., for pterional or frontotemporal craniotomy), the contralateral shoulder should be elevated (with a wedge or roll) to prevent brachial plexus stretch injury. The lateral and sitting positions have their own specific positioning precautions. The endotracheal tube must be fixed and packed securely to prevent accidental extubation or abrasions resulting from movement and must be accessible intraoperatively (note: there is increased dead space if extension tubing is used distal to the Y-piece). Finally, the eyes should be taped closed to prevent corneal damage from exposure or irrigation with antiseptic or other fluids.

Maintenance of Anesthesia

Goals

The main anesthetic aims during supratentorial surgery are (1) control of brain tension via control of CBF and CMR (the so-called chemical brain retractor concept [Box 11.5]) and (2) neuroprotection through maintenance of an optimal intracranial environment. The first goal depends on the prevention of CNS arousal; it is achieved through good depth of anesthesia and antinociception (Fig. 11.9), antiepileptic prophylaxis, as well as control of the consequences of CNS arousal should it occur (with antihypertensives, sympatholytics). The second goal depends on maintaining a good match between cerebral substrate demand and supply, as well as attempts at specific neuroprotection if mismatch occurs (note: ischemia occurs under the retractor in 5% to 10% of patients).[98] Some anesthesiologists use modest passive hypothermia (35 °C) to provide neuroprotection, on the basis of the abundant experimental literature demonstrating its efficacy after brain injury. However, clinical studies have not demonstrated any beneficial effect of hypothermia in neurosurgical patients.[130] In addition, hypothermia impairs platelet function and the coagulation cascade. Consequently, even mild hypothermia (<1 °C) may increase blood loss and the risk for transfusion.[131] Although a higher risk of cerebral bleeding due to hypothermia has not been demonstrated during neurosurgery, this theoretical effect should be considered in the risk–benefit analysis of inducing hypothermia. Other complications of hypothermia are surgical wound infection,[132] adverse myocardial outcomes,[133] prolonged recovery, and shivering.[134] Thus, normothermia should be a major goal of neuroanesthetic management. Hypothermia should be considered only in cases with a major risk of cerebral ischemic injury.

BOX 11.5 Chemical Brain Retractor Concept

Mild hyperosmolality (use NaCl 0.9% [304 mOsm/kg] as baseline infusion; give 20% mannitol [1245 mOsm/kg] 0.5 to 0.75 g/kg or hypertonic saline [7.5%, 2498 mOsm/kg] 2 to 4 mL/kg before bone flap removal)
Intravenous anesthetic agent (propofol), adequate depth of anesthesia
Mild hyperventilation, mild hyperoxygenation
Mild controlled hypertension: mean arterial blood pressure maintained around 100 mmHg in order to decrease cerebral blood volume and intracranial pressure
Normovolemia; no vasodilators
Mild hyperoxia

Together with:

- Head-up positioning with unimpeded cerebral venous drainage; no compression of the jugular veins
- Minimal positive end-expiratory pressure
- Adequate anesthetic depth or muscle relaxant to prevent bucking on ventilator
- Lumbar drainage
- Avoidance of brain retractors

Choice of Technique

There has been long-standing controversy surrounding the use of intravenous versus volatile anesthetics for intracranial procedures. So far, no study comparing intravenous with volatile agent-based neuroanesthesia has been able to demonstrate major outcome differences.[79,135]

At present, the major argument for the still extensive and successful use of volatile agent-based techniques remains controllability, predictability, and the attainability of early awakening.[136] However, volatile anesthetics are otherwise far from ideal agents for neuroanesthesia because of their ability to increase CBF, ICP, and brain bulk.[15,16] In a prospective randomized study comparing propofol-fentanyl, isoflurane-fentanyl, and sevoflurane-fentanyl anesthesia in normocapnic patients, the rate of ICP and cerebral swelling was lower in the propofol-fentanyl group.[135] However, in a study of patients

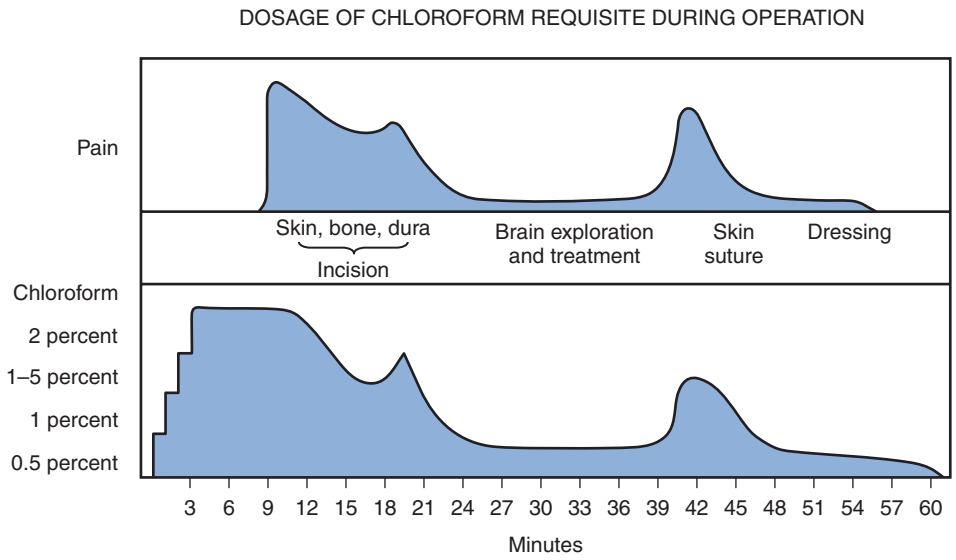


Fig. 11.9 Nociception and depth of anesthesia as illustrated by this graph of chloroform requirements during various levels of operative nociception. *(From Horsley V: On the technique of operations on the central nervous system: Address in surgery. Lancet 1906; ii; 484.)*

with no evidence of midline shift on a preoperative CT scan, neither isoflurane nor desflurane was shown to have induced a significant variation in ICP.[137] Similarly, there was no difference in the surgeon's assessment of brain swelling between patients anesthetized with isoflurane and those anesthetized with propofol.[66] Thus, despite evidence that ICP is lower with total intravenous techniques, the clinical impact of this technique in patients with elevated ICP has yet to be evaluated.[138] Although intravenous agents offer good control of CBF, ICP, and brain bulk,[16,135,138] prolonged or unpredictable awakening remains the main concern with intravenous techniques, with possible resulting difficulties in the differential diagnosis of delayed awakening and the need for emergency CT to rule out surgical complications. This problem is increasingly mitigated by the use of computer-controlled infusion schemes (target-controlled infusion pumps) and the availability of short-acting or infusion duration-insensitive drugs, such as propofol and remifentanil.

At this time, we would consider intravenous techniques to be most clearly indicated for the problem neurosurgical patient (high risk of ICP problems and brain swelling), whereas volatile techniques are best used for the uncomplicated neurosurgical case. The concurrent use of nitrous oxide and volatile anesthetics is best avoided in the problem patient because of their synergistic effects in increasing cerebral metabolism and blood flow, as discussed previously.[15,22,41–43,139] Clearly, if measures to control brain bulk (hyperventilation, osmotic diuretics, blood pressure control, positioning, lumbar drainage) are unsuccessful during anesthesia with volatile agents, consideration should be given to converting to a total intravenous anesthetic technique (see Box 11.2).

If undesirable CNS arousal and hemodynamic activation occur despite an adequate depth of anesthesia and analgesia, these problems may be controlled by an antisympathetic drug such as esmolol (initial dose of 1 mg/kg), labetalol (initial dose of 0.5 to 1 mg/kg), or clonidine (initial dose of 0.5 to 1 µg/kg).

Management of Increases in Intracranial Pressure and Brain Bulk

Details of prevention and treatment of increases in ICP and brain bulk are shown in Box 11.2. The occurrence of brain protrusion requires *immediate* intervention, which should include deepening anesthesia with intravenous agents (the capnogram curve should be checked to rule out "fighting" against the ventilator), increasing hyperventilation, performing CSF drainage, and changing to head-up positioning without delay.

Intraoperative ventilation

Lung-protective ventilation including low tidal volumes and positive end-expiratory pressure (PEEP) have been associated with improved outcome in patients at intermediate or high risk of pulmonary complications after major surgery.[140] Patients with intracranial disease are at high risk of pulmonary complication[141] and may benefit from lung-protective ventilation. Unfortunately, neurosurgical patients were not included in the trials on intraoperative ventilation, making the risk–benefit ratio difficult to assess. However, several studies have demonstrated minimal effects on CBF or ICP for levels of PEEP less than 10 cm H_2O in neurosurgical patients.[142] A German observational study showed that intraoperative tidal volume nearly halved from years 1995 to 2010, demonstrating that neurosurgical anesthesiologists take into account lung protective strategies.[143] During intracranial surgery, the effect of increasing PEEP on the brain can be observed directly. In all instances, the effect of ventilation changes on $PaCO_2$ has to be monitored.

Fluid Therapy

The practice of maintaining normovolemia and normotension during intracranial surgery is now well-established. Hyperglycemia (glycemia >10 mmol/L), which worsens the consequences of cerebral ischemia,[99,100] and hypo-osmolality (target osmolality, 290 to 320 mOsm/kg), which can increase brain edema, should be avoided. Colloid oncotic pressure plays an unclear role in brain edema. Glucose-containing or hypo-osmolar solutions (e.g., lactated Ringer's solution, 254 mOsm/kg) should be avoided. Suitable choices for infusion liquids during intracranial surgery include isotonic crystalloids and colloids to replace blood losses. In one retrospective study, flurbiprofen and perioperative hypertension, but not the intraoperative infusion of hydroxyethyl starch, were associated with post-craniotomy hemorrhage.[144] The hematocrit should be kept above 28%. Fluids should be warmed at the end of the procedure to ensure normothermia for emergence from anesthesia.

Emergence from Anesthesia

Emergence from anesthesia has respiratory, cardiovascular, metabolic-endocrine, and neurologic consequences.[145,146] In the early postoperative period after elective craniotomy, autoregulation is often impaired, with 20% of patients demonstrating raised ICP.[116] Particularly in the neurosurgical context, extubation criteria must be strictly observed: respiratory drive and airway protection are likely to be impaired after brain surgery, and both hypercapnia and hypoxia carry the risk of causing additional systemic secondary brain damage (see Box 11.1). Awakening and extubation after anesthesia are associated with hemodynamic arousal lasting 10 to 25 minutes[145] and only weakly correlating to rises in oxygen consumption (Fig. 11.10). This activation is partially mediated by elevations in catecholamine levels and partially by nociceptive stimuli. A link between perioperative hypertension and intracranial hemorrhage after craniotomy has been demonstrated.[144,147] In the study, patients with postoperative intracranial hemorrhage were 3.6 times more likely to be hypertensive than their matched controls. The very strong association of intracranial hemorrhage with the pattern of blood pressure remaining in the normal range intraoperatively but hypertension occurring during emergence from anesthesia suggested that loose surgical hemostasis achieved at a low blood pressure may result in bleeding at a higher one.

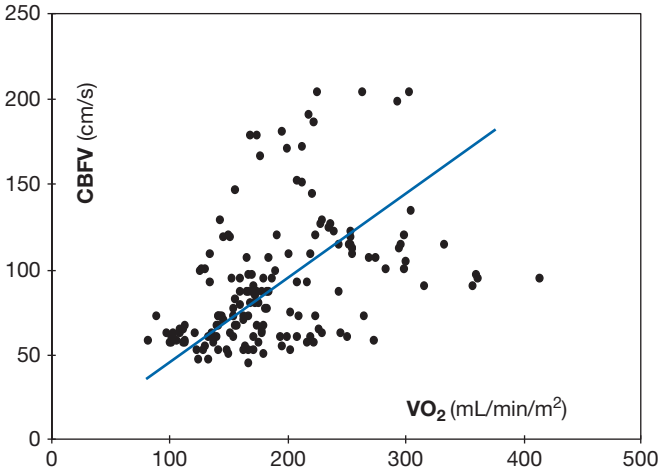


Fig. 11.10 Relationship between body oxygen consumption and cerebral hemodynamic activation assessed by transcranial cerebral blood flow velocity (CBFV) at extubation (N Bruder, P Ravussin, unpublished data).

Changes in the cerebral circulation may also contribute to postoperative cerebral complications (hemorrhage or edema). Tracheal extubation is associated with a 60–80% increase in cerebral blood flow velocity from preinduction baseline value with an increase in $SjvO_2$.[119] It seems clear that the association of arterial hypertension and postoperative cerebral hyperemia may be dangerous for the patients. Analgesia, the prevention of hypothermia and shivering, and timely tracheal extubation to avoid fighting of the patient against the tube are required to limit catecholamine release and hemodynamic changes. β-Adrenergic blocking agents improve hemodynamic stability during emergence and mitigate CBF changes.[148] Esmolol, a short-acting beta-blocker (half-life 9 minutes), may be used as a bolus (1 mg/kg) followed by a continuous infusion (100 to 300 µg/kg/min) for 15 to 30 minutes after tracheal extubation.

Extubation under a continuous low dose of remifentanil has been shown to blunt the hemodynamic responses due to tube withdrawal[149,150] but attention should be paid to avoid respiratory depression and hypercapnia.

Aims of Emergence After Neurosurgery

The main aim during emergence from anesthesia after neurosurgery is maintenance of intracranial and extracranial homeostasis, particularly of the following parameters: MAP, CBF, ICP, $PaCO_2$, PaO_2, CMR, and temperature (Box 11.6). Factors likely to cause intracranial bleeding or to affect CBF or ICP, such as coughing, fighting against the ventilator, hypertension, and airway overpressure, should be avoided. The patient should be responsive to verbal commands, calm, and cooperative soon after emergence. The most common signs of deterioration after intracranial surgery are a decrease in the level of consciousness and clinical signs of focal neurologic deficit. The most feared postoperative complication, cerebral hemorrhage, occurs most often in the first 6 hours after surgery, justifying close clinical monitoring in the first postoperative hours.[151] In a retrospective analysis, factors associated with postoperative complications were tumor severity score (combining tumor location, mass effect, and midline shift), estimated blood loss and intraoperative fluids volume, duration of surgery more than 7 hours, and postoperative ventilation. The shortage in intensive care unit resources may justify a prolonged stay in a postanesthesia care unit and return to the neurosurgical ward by bypassing the intensive care unit only for patients at low risk of cerebral complications. But one postoperative catastrophe may far outweigh the potential cost saving needing to establish clear postoperative protocols in case of neurologic worsening.[152]

BOX 11.6 Neurosurgical Awakening

Neurosurgical awakening should maintain:
- Stable arterial blood pressure and thus cerebral blood flow and intracranial pressure
- Stable oxygenation and carbon dioxide tension
- Stable $CMRO_2$
- Normothermia

Neurosurgical awakening should avoid:
- Coughing
- Tracheal suctioning
- Airway overpressure during extubation
- Patient-ventilator dyssynchrony

Early versus Late Emergence

Ideally, patients recovering from neurosurgery should emerge rapidly from anesthesia to permit immediate assessment of the results of surgery and to provide a baseline for continuing postoperative neurologic follow-up. However, there are still some categories of patients for whom early emergence is not appropriate. Advantages and disadvantages of early versus late emergence are summarized in Table 11.1.

Indications for Late Emergence

If the patient had obtunded consciousness or inadequate airway control preoperatively, the problem is not likely to improve postoperatively, making successful early extubation unlikely. If there is a high postoperative risk of brain edema, raised ICP, or deranged intracerebral hemostasis or homeostasis, early awakening is not appropriate. Such a risk is increased after long (>6 hours) and extensive surgery (particularly if associated with bleeding), repeat surgery, major glioblastoma surgery, surgery involving or close to vital brain areas, and surgery associated with significant brain ischemia (e.g., long vascular clipping times, extensive retractor pressure). If delayed emergence is chosen, adequate sedation and analgesia should be ensured, preferably with short-acting drugs.

Preconditions for Early Emergence

Early emergence from anesthesia necessitates planning. It entails an anesthetic technique pharmacologically adequate to permit early awakening and requires meticulous attention to the detail of intraoperative systemic and brain homeostasis

Table 11.1 Pros and Cons: Early versus Delayed Awakening

	Early Awakening	Delayed Awakening
Advantages	Earlier neurologic examination and reintervention if necessary Easier transfer to intensive care unit (ICU) Earlier indications for further investigations Setting of neurologic scene for following hours (baseline for further clinical assessment) Less hypertension, less catecholamine burst Performed by anesthetist who knows patient: brain tightness, bleeding, surgery, etc. Potential lower costs	Less risk of hypoxemia or hypercapnia Better late hemostasis Stabilization period in same position as during surgery
Disadvantage(s)	Greater risk of hypoxemia, hypercapnia Larger hemodynamic changes Difficult respiratory monitoring during transfer to ICU	Less neurologic monitoring

BOX 11.7 Preconditions for Early Emergence from Anesthesia: Homeostasis

Systemic Homeostasis

Normovolemia, normothermia
Normotension (mean arterial blood pressure 80 mmHg)
Mild hypocapnia ($PaCO_2$ 35 mmHg)
Normoglycemia (serum glucose 4 to 6 mmol/L)
Mild hyperosmolality (285 ± 5 mOsm/kg)
Hematocrit approximately 30%

Brain Homeostasis

Normal cerebral metabolic rate, cerebral blood flow, and intracranial pressure
Antiepileptic prophylaxis
Adequate head-up position

(preservation of normal oxygenation, temperature, intravascular volume, blood pressure, cardiovascular function, and CNS metabolism) (Box 11.7). To avoid the trauma of mechanical brain retraction, ICP and brain bulk should be controlled pharmacologically during the operation (see Box 11.5). The neurosurgeon contributes by minimizing blood loss via obsessive hemostasis and reduction of surgical invasiveness with the use of microsurgery and small operative fields. If these conditions are fulfilled, early emergence can be associated with less metabolic, hemodynamic, and endocrine activation than delayed emergence (Fig. 11.11).[145]

Conduct of Early Emergence

The essentials of conducting a patient's early emergence from anesthesia are listed in Box 11.8. The cardinal prerequisite for a "soft landing" is careful titration of anesthetics and analgesics at the end of the procedure. This goal is achieved with the use of small "top-up" doses of intravenous anesthetics or

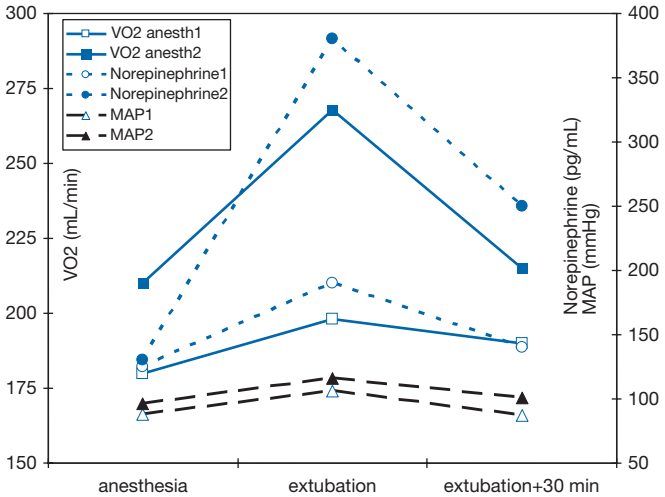


Fig. 11.11 Early versus delayed recovery after neurosurgery: differences in body oxygen consumption (VO2, squares left axis), norepinephrine blood concentration (circles right axis), and mean arterial pressure (MAP, triangles right axis). The measures were recorded during anesthesia, at extubation and 30 minutes after extubation (x-axis). In this study, patients were divided into two groups, those extubated in the operating room (group 1) and those extubated more than 2 hours later in the intensive care unit (group 2). Despite similar changes in blood pressure, patients in group 2 had higher VO2 and catecholamine blood level at extubation. *(Modified from Bruder N, Stordeur JM, Ravussin P: Metabolic and hemodynamic changes during recovery and tracheal extubation in neurosurgical patients: immediate versus delayed recovery. Anesth Analg 1999; 89:674-678)*

BOX 11.8 Conduct of Early Emergence from Anesthesia after Intracranial Surgery

Checklist before Attempting an Early "Landing"

Adequate preoperative state of consciousness
Limited brain surgery, no major brain laceration
No extensive posterior fossa surgery involving cranial nerves IX to XII
No major arteriovenous malformation resection, which may give rise to malignant postoperative edema
Normal body temperature and oxygenation; cardiovascular stability

Suggested Awakening Sequence

1. Discontinue long-lasting opioids (fentanyl or sufentanil) approximately 60 minutes before planned emergence or remifentanil at the end of skin closure
2. Allow progressive rise of $PaCO_2$ to normoventilation
3. Let neuromuscular block decrease to two twitches (TOF) if myorelaxation is used
4. Treat blood pressure bursts resulting from nociception with boluses of intravenous agents or high-concentration volatile bursts; if hypertension persists, consider sympatholytics
5. Stop anesthetic administration during skin closure (syringe of intravenous agent ready or hand on vaporizer)
6. Remove head pins as early as possible—esmolol or lidocaine 1.5 mg/kg for short-term hemodynamic control
7. Stop nitrous oxide if used (antagonize myorelaxants if necessary—should be avoided if possible)
8. Try for spontaneous ventilation as soon as possible. Remove packing, perform adequate suctioning before extubation
9. Keep blood pressure in the preoperative range by quickly treating arterial hypertension
10. Perform brief, targeted neurologic status examination.
11. Transfer patient to postanesthetic care unit or intensive care unit.

analgesics (opioids, lidocaine) or, alternatively, a short burst of volatile agents, or both. The judicious use of sympatholytic agents may be indicated. Prevention of postoperative pain is mandatory, especially after remifentanil analgesia. The infusion of a single non-narcotic analgesic does not provide adequate analgesia in all patients. A combination of two non-narcotic analgesics, associated with small doses of morphine after extubation as needed, is recommended.[153] A scalp nerve block or bupivacaine infiltration of the wound provides adequate analgesia in the early postoperative period and should be considered.[154] Adequate antiepileptic prophylaxis relies mostly on a phenytoin (or fosphenytoin) loading dose during surgery, but other intravenous antiepileptic agents (valproate, levetiracetam, etc.) may be used. Prospective trials comparing various antiepileptic agents for early postoperative prophylaxis are lacking.

Differential Diagnosis of Unplanned Delayed Emergence

If the patient is not awake enough to obey simple verbal commands 20 to 30 minutes after pharmacologically adequate cessation of anesthesia, nonanesthetic causes of delayed emergence must be considered and ruled out (with CT or magnetic resonance imaging) or treated. The differential diagnosis includes seizure, cerebral edema, intracranial hematoma, pneumocephalus, vessel occlusion, and ischemia as well as metabolic or electrolyte disturbances. If opioid overdose is suspected, it is not unreasonable to try carefully titrated antagonization with small doses of naloxone or naltrexone.

Postoperative Care After Uncomplicated Surgery

Complications are frequent after neurosurgery. A large surgical database for the years 2006–2011 found complications in 23.6% of cranial procedures.[155] The 30-day mortality rate after surgery for intracranial tumor is around 2.2% .[156,157] This is the rationale for routine postoperative admission to the intensive care unit. However, ICU resources are scarce and direct admission to the ward in low risk patients has been proposed.[158,159] Risk factors for postoperative complications are Karnofsky performance scale score < 80 (meaning unable to carry on normal activity or work), lateral positioning of the patient during surgery, duration of surgery of more than 4 hours, failure to extubate the trachea in the operating room, and intraoperative blood loss >350 mL.[159,160] Routine admission to the ward in low-risk patients depends on adequate nurse and physician staffing, available monitoring, and the presence of a rapid response team in cases of neurological worsening.

Pain and Postoperative Nausea and Vomiting

Postcraniotomy pain is often moderate or severe and frequently undertreated.[161] The increasing use of remifentanil during anesthesia also requires an effective postoperative analgesic strategy. Scalp nerve blocks or wound infiltrations with local anesthetics provide some postoperative analgesia but the effect may be too short when the injection takes place before the surgical incision. Paracetamol alone does not provide pain relief.[153] The association with tramadol is effective, with no effect on ICP or CPP, but may give rise to nausea and vomiting.[162] Nefopam has antishivering and analgesic effects, but has been associated with a few cases of convulsions.[163] Opioid patient-controlled analgesia is safe, but the risk of somnolence, retention of CO_2 and increased intracranial pressure needs adequate postoperative monitoring. Nonsteroidal anti-inflammatory drugs (NSAID) are rarely used because they inhibit platelet aggregation and patients frequently receive corticosteroids. However, the risk of bleeding due to NSAID is probably very low and has not been demonstrated after neurosurgery.[164]

The frequency of nausea is 50% after craniotomy and vomiting occurs in approximately 40% of the patients.[165,166] Prophylaxis for postoperative nausea and vomiting is often indicated. Ondansetron is safe and has few side effects but is only partially effective.[167,168] Droperidol is more effective than ondansetron for preventing vomiting and does not induce sedation if the dose is less than 1 mg. Corticosteroids are also effective to prevent PONV.

Corticosteroids

Corticosteroids are very effective in decreasing vasogenic brain edema surrounding malignant tumors.[169] The most frequent complication related to their use in the postoperative period is hyperglycemia, but psychiatric disorders related to corticosteroid treatment are often overlooked. High postoperative corticosteroid doses should be tapered rapidly over a few days. Dexamethasone is the most commonly prescribed corticosteroid for the management of cerebral edema. However, other corticosteroids, for example methylprednisolone, may be used. Dexamethasone is approximately six times more potent than methylprednisolone suggesting a multiplication of doses by six from dexamethasone to methylprednisolone. The initial dexamethasone regimen is a bolus dose of 10 mg followed by 4 mg every 6 hours.[170] Much larger doses may be used immediately after surgery for a short time period.

Prevention of Seizures

Prophylactic use of antiepileptic drugs (phenytoin or levetiracetam) after intracerebral surgery is controversial because its effect on the prevalence of seizures is unclear and they have important side effects.[171,172] In 2000, a consensus statement from the Quality Standards Subcommittee of the American Academy of Neurology recommended not to use antiepileptic drugs routinely as prophylaxis in patients with brain tumors, and to withdraw these drugs in the first week after surgery if patients never present a seizure.[173] Although the current best available evidence is against the anticonvulsant prophylaxis after craniotomy,[174] a practice survey revealed that more than 70% of neurosurgeons routinely used prophylactic antiepileptic drugs in patients undergoing brain tumor resection.[175] Phenytoin is frequently used for seizure prophylaxis but levetiracetam is as effective with fewer side effects.[176,177] Preoperative antiepileptic treatments should not be interrupted in the perioperative period because it may give rise to breakthrough seizures.

Thromboprophylaxis

The risk of deep vein thrombosis (DVT) is high after intracranial surgery. Without prophylaxis, the frequency of DVT, diagnosed using ultrasonography or venography, is 20–35% and 2.3–6% for symptomatic events.[178] The intermittent pneumatic compression of the legs is recommended in all craniotomy patients, during, or as soon as possible after, surgery. In very high-risk patients (malignant tumor, prolonged surgery, hemiparesis and advanced age) unfractionated heparin or low molecular weight heparin should be added to mechanical thromboprophylaxis once adequate hemostasis is established (24–48 hours after surgery).[179]

Other treatments

Antibiotic prophylaxis is recommended for intracranial surgery. It reduces by half the rates of postoperative infections.[180] Its optimal duration is unknown but it has to be shorter than 24 hours in order to avoid the selection of antibiotic-resistant microorganisms. A first generation cephalosporin (cefazoline) is usually recommended.

Hormonal treatments may be necessary after pituitary or craniopharyngioma surgery. Cortisol replacement may be needed after treatment of Cushing's disease and is mandatory in patients with preoperative adrenal insufficiency. Hydrocortisone 50 mg q 6 hours is enough to prevent relative adrenal insufficiency in the first 24 hours. Diabetes insipidus (DI) is characterized by sudden polyuria and polydipsia but the polydipsia is often not seen in sedated postoperative patients. Monitoring of urine output and density is needed to avoid dehydration and hypernatremia. Increased diuresis from intraoperative fluids or residual effects of mannitol can occur but is usually limited to the early postoperative period. Urine output above 250 mL/hour for more than 2 hours with a density less than 1.005 (urine osmolality < 300 mOsm/kg) is an indication to give desmopressin (DDAVP). DDAVP can be given by oral, nasal, intravenous or subcutaneous route. In postoperative patients, parenteral administration is preferred (1–4 µg q 8–24 hours). Intravenous hypotonic fluid replacement may be necessary to limit hypernatremia.

Specific Anesthetic Management

Difficult Airway

The avoidance of hypoxia is more important than the prevention of ICP increases. The advances in technology and equipment, videolaryngoscopy and fiberoptic intubation techniques may

allow intubation in anesthetized patients with difficult airways where awake intubation was previously the preferred choice before brain tumor surgery. By allowing better visualization of the airway anatomy and endotracheal intubation, videolaryngoscopes have made their way in numerous difficult airway algorithms and reflect a better understanding of the science of airway management.[181] However, proper assessment of each situation must be performed, including the setting, the equipment and the competencies of the anesthetic team.[182,183] The choice of the device and technique (channeled device vs. stylet-assisted videolaryngoscopy), spontaneously breathing sedated patient (sevoflurane or remifentanil assisted), the physicians' preference or the patients' situation must be carefully weighted, taking into account advantages and contraindications. Videolaryngoscopy may allow intubation under general anesthesia for suspected difficult airway management, avoiding hypercapnia by quicker and easier tracheal intubation,[184] reducing sympathetic stimulation and hemodynamic instability by necessitating less force to expose the laryngeal inlet.[185]

Awake fiberoptic intubation must be carefully prepared. It begins with a good explanation of the procedure to the patient, continues with meticulous local anesthesia of the nasopharynx and airways, and is supplemented by judicious use of small doses of sedatives (midazolam, fentanyl or remifentanil or the use of a low-dose infusion of propofol). The cerebral consequences of deep sedation and hypercapnia should be kept in mind during this procedure. Hemodynamic activation should be treated promptly by antihypertensive agents (e.g., labetalol or esmolol).

Infectious Tumors (Abscess)

Brain abscesses form part of the differential diagnosis of supratentorial mass lesions, and their effects on the brain and ICP pressure are similar. Risk factors include contiguous infections (sinus, ear), right-to-left cardiac shunt, immunosuppression (extraneous or intrinsic), and intravenous drug abuse.[186] Brain abscess is often accompanied by a low-grade fever. If its presence is suspected, initial treatment includes antibiotics to control the infection and corticosteroids to try to control brain edema—sometimes in conjunction with diuretics. Definitive diagnosis and treatment are achieved with craniotomy or stereotaxy and aspiration of the abscess. The surgical and anesthetic management is similar to that for supratentorial neoplasms. If the patient is immunocompromised (e.g., acquired immunodeficiency syndrome [AIDS]), sterile technique and aseptic precautions must be adhered to with particular vigor. It is notable that human immunodeficiency virus (HIV) infection is associated with non-Hodgkin's lymphoma of the brain.

Craniofacial and Skull Base Surgery

Craniofacial and skull base surgery is an approach that is increasingly used for tumors near the posterior wall of the nasal sinuses, the orbits, and so on. These are complex operations requiring a multidisciplinary surgical approach and often involving sensory and motor neurophysiologic monitoring of cranial nerves. Because of the transfacial surgical approach, oral intubation or tracheostomy is often required. The extensive bony involvement of the procedure carries the potential for significant blood loss, hemorrhagic diathesis, and venous air embolism, particularly if the head is elevated. If cranial nerve monitoring (particularly of motor nerves) is performed, neuromuscular blockade should be avoided. For a second procedure of this type, skull base exposures involve extensive temporalis muscle mobilization and often result in mandibular pseudoankylosis with subsequent limitation of mouth opening and difficult intubation.[187–189]

Awake Craniotomy or Stereotactic Procedures

The most common indications for awake neurosurgery are stereotactic biopsies or procedures and the surgery of small lesions in close proximity to speech or motor areas (including epilepsy surgery). Retrospective studies have shown that intraoperative electrical stimulation reduced by approximately twofold the incidence of severe permanent neurologic deficits and markedly improved the completeness of surgical resection.[190] Motor mapping may be performed in a patient under general anesthesia, although the results of stimulation are better in conscious patients.[115] However, surgery of a tumor involving speech areas needs the intraoperative cooperation of a fully awake patient (see Chapter 17).

ANESTHESIA FOR INTRACRANIAL HEMATOMAS

General Considerations

Even more than with supratentorial tumors, the effects of intracranial hematomas on neurologic status and ICP depend on the speed with which they arise. At one end of the time spectrum, patients with chronic subdural hematomas show only subtle neurologic signs with small increases in ICP and can thus be anesthetized with a technique similar to that for supratentorial tumors. At the other extreme, acute epidural or subdural hematomas arise much more rapidly than tumors, with massive neurologic impairment and potentially acutely life-threatening ICP elevations.[191,192] In these patients, anesthetic management must entail aggressive reduction of ICP together with measures to preserve brain oxygenation and perfusion, followed by urgent surgical decompression.

Anesthetic Management of Acute Intracranial Hematoma

Induction

Ensuring oxygenation is paramount during induction of the patient with acute intracranial hematoma. It begins with securing of the airway and is followed by mild hyperventilation with 100% oxygen. In the context of head trauma, cervical spine fracture should be ruled out with preoperative CT if the patient's ventilatory state permits it. Intubation following hyperventilation by mask ideally should be swift, atraumatic, and associated with minimal ICP rise. Anesthesia must be deep enough to avoid coughing or arterial hypertension. However, compromises as to the depth of anesthesia are inevitable in the polytraumatized, hypovolemic, and possibly comatose patient with a full stomach (rapid-sequence induction with cricoid pressure). In the case of severe arterial hypertension due to intracranial hypertension (Cushing's response), thiopental 3 to 5 mg/kg is probably a good choice to decrease both arterial pressure and ICP, thus maintaining CPP before intubation. Judicious use of a sedative (e.g., etomidate 0.2 to 0.5 mg/kg, propofol 0.5 to 1 mg/kg) together with a myorelaxant is necessary for a semiconscious, struggling patient. The choice as to which myorelaxant procedure to use to achieve rapid-sequence induction in this context is still controversial. A modified rapid-sequence induction, where the patient is bag-mask ventilated during the time necessary for the suxamethonium to reach its peak effect, might help in keeping CO_2 in acceptable ranges.[193] A large dose of rocuronium, which permits intubation 1 minute later, may be a choice only if an

appropriate dosage of suggamadex (16 mg/kg) is immediately available.[194] In all of these cases, consideration should be given to aspiration prophylaxis in conscious patients (e.g., 50 mg ranitidine IV, if possible, 20 minutes before induction or, if the patient is cooperative, sodium citrate PO).

Once ventilation and the airway are controlled, thought should be given to early and continuing control of ICP and brain swelling. Typically, osmotic diuretics such as mannitol are given at this stage. Corticosteroids have not been shown to be effective for improving outcome for intracranial hematomas, either traumatic or primary, and they raise mortality risk in head-injured patients.[195,196] The use of myorelaxants is indicated even in comatose patients because increased muscle tone and shivering increase CO_2 production, complicating ICP control through hyperventilation.

Anesthesia Maintenance

The main aim of anesthesia for acute intracranial hematoma is to control ICP and brain swelling while maintaining adequate cerebral perfusion and oxygenation (i.e., matching CMR and CBF). Particular attention is required upon hematoma evacuation, which may result in rapid and severe hypotension (loss of Cushing's response). Vasopressors should be ready to use at this time. An epinephrine bolus (0.1 mg) may be necessary in some patients.

Monitoring

Patients with acute intracranial hematoma are often hemodynamically unstable (hypertension, hypovolemia). Invasive arterial pressure monitoring is used to permit close hemodynamic control and for repeated laboratory determinations (blood gas analysis, hematocrit, etc.). Arterial cannulation is commenced, preferably before induction, particularly in polytraumatized patients, except in case of impending brain herniation, when every minute counts. If a hematoma is to be evacuated, ICP monitoring is generally installed once evacuation has been performed. Electrocardiographic monitoring is particularly important in patients with multiple trauma because electrocardiogram changes can result from cerebral (e.g., blood in the CSF causing T-wave inversion) and cardiac (e.g., ST-segment change in cardiac contusion) causes. Blood gas analysis forms the basis for various interventions in acid–base balance, ventilation, and metabolic dysregulation. Blood glucose levels should be followed closely, and any hyperglycemia should be corrected, because it has been shown to worsen the effects of brain ischemia. Also of note is that brain tissue damage releases large quantities of thromboplastin into the circulation, adversely affecting blood coagulation, which should be checked regularly (coagulation status, activated partial thromboplastin time). If osmotic diuretics have been started (mannitol), their further use should be guided by determinations of blood osmolality (maximum, 320 mOsm/kg). More detail on the management and monitoring of head injury patients is given in Chapters, 10, 18 and 22.

Anesthetic Technique

Intravenous anesthetics that increase CVR, decrease CBF and CBV (brain relaxation), and reduce CMR are the mainstays of anesthesia for acute intracranial hematoma. The use of volatile anesthetics is not recommended because they can cause unacceptable rises in ICP and brain tension to the point of acute transtentorial or transcraniotomy herniation, even in the context of preexisting hypocapnia.

Arterial hypotension subsequent to the use of intravenous anesthetics or opioids must be avoided to prevent cerebral ischemia and because reductions in CPP can cause reflex cerebral vasodilation and consequent ICP increases not controlled by hypocapnia (see earlier). The management of controlled arterial hypertension in the context of acute intracranial hematoma is controversial and must carefully balance the maintenance of adequate CPP to areas of the brain ischemia caused by hematoma compression against the risks of producing more vasogenic brain edema and resuming hemorrhage. TCD just before or just after induction of anesthesia may help assess cerebral perfusion and determine the optimal blood pressure level. $SjvO_2$ monitoring may help in providing a global assessment of the adequacy of CPP;[197] however, globally adequate CPP does not rule out regional CPP inadequacies and thus regional brain ischemia. If a reduction in arterial hypertension is indicated, the first line of management should be improved analgesia (i.e., opioids) followed by an increased depth of anesthesia (propofol, barbiturates, etomidate).

Emergence from Anesthesia

In general, patients suffering from acute cerebral hematomas have suffered significant brain injury with significant actual and potential brain swelling. They should thus undergo slow weaning and delayed extubation in a neurointensive care unit (see Chapter 22) with all of the monitoring and therapeutic facilities it provides. Patients with chronic subdural hematomas often have minimal neurologic signs and impairment of consciousness preoperatively and can, therefore, usually be extubated immediately after surgery.

SUMMARY

The basis of neuroanesthesia for surgery of supratentorial masses is an understanding of the following:

- Pathophysiology of raised ICP
- Regulation and maintenance of cerebral perfusion
- Effects of anesthesia and surgery on ICP, cerebral perfusion, and intracerebral homeostasis
- Differences between the pathophysiology and management of rapidly expanding masses, such as acute hematomas, and slowly growing masses, such as brain tumors.

The main objectives of anesthesia for excision of a cerebral tumor are as follows:

1. The preservation during the procedure of the uninjured cerebral territories by global maintenance of cerebral homeostasis and protection by:
   - normovolemia and normotension
   - normoglycemia
   - mild hyperoxia
   - mild hyperosmolality.
2. The preservation of CBF autoregulation vs. MAP, as well as cerebral vasoreactivity to $PaCO_2$.
3. The minimization of the need for surgical retraction through the use of "chemical brain retraction," which consists of:
   - the control of $CMRO_2$, CBF, and CBV
   - moderate hyperventilation
   - strict maintenance of CPP
   - osmotherapy
   - CSF drainage
   - the use of intravenous anesthetics for tight brain.
4. The provision of early neurosurgical awakening, thus permitting:
   - adequate immediate postoperative neurologic assessment
   - continuing further postoperative evaluation

- diagnosis of complications by the neurologic team without delay
- immediate CT scanning or surgery if necessary.

5. Management of anesthesia and surgical recovery consists of:
   - adequate pain relief
   - prevention of postoperative nausea and vomiting
   - hemodynamic control.

The main objectives of anesthesia for acute cerebral hematoma are as follows:

- Aggressive control of ICP and brain swelling
- Adequate blood pressure to maintain CPP and limit cerebral hemorrhage or edema
- Time management in the context of impending brain herniation.

REFERENCES

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol*. 2014;16(Suppl 4):iv1–iv63.
2. Hoffman S, Propp JM, McCarthy BJ. Temporal trends in incidence of primary brain tumors in the United States, 1985-1999. *Neuro Oncol*. 2006;8:27–37.
3. Gavrilovic IT, Posner JB. Brain metastases: Epidemiology and pathophysiology. *J Neurooncol*. 2005;75:5–14.
4. Carrel M, Moeschler O, Ravussin P, et al. Prehospital air ambulance and systemic secondary cerebral damage in severe craniocerebral injuries. *Ann Fr Anesth Reanim*. 1994;13:326–335.
5. Chesnut RM, Marshall SB, Piek J, et al. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)*. 1993;59:121–125.
6. Langfitt TW, Weinstein JD, Kassell NF. Cerebral vasomotor paralysis produced by intracranial hypertension. *Neurology*. 1965;15:622–641.
7. Bell BA, Smith MA, Kean DM, et al. Brain water measured by magnetic resonance imaging. Correlation with direct estimation and changes after mannitol and dexamethasone. *Lancet*. 1987;1:66–69.
8. Bruce JN, Criscuolo GR, Merrill MJ, et al. Vascular permeability induced by protein product of malignant brain tumors: inhibition by dexamethasone. *J Neurosurg*. 1987;67:880–884.
9. Tatagiba M, Mirzai S, Samii M. Peritumoral blood flow in intracranial meningiomas. *Neurosurgery*. 1991;28:400–404.
10. Neuwelt E, Abbott NJ, Abrey L, et al. Strategies to advance translational research into brain barriers. *Lancet Neurol*. 2008;7:84–96.
11. Baker KZ, Ostapkovich N, Sisti MB, et al. Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. *J Neurosurg Anesthesiol*. 1997;9:134–140.
12. Grubb Jr RL, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO2 on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke*. 1974;5:630–639.
13. Nunes CS, Ferreira DA, Antunes L, Amorim P. Clinical variables related to propofol effect-site concentrations at recovery of consciousness after neurosurgical procedures. *J Neurosurg Anesthesiol*. 2005;17:110–114.
14. Bekker AY, Mistry A, Ritter AA, et al. Computer simulation of intracranial pressure changes during induction of anesthesia: Comparison of thiopental, propofol, and etomidate. *J Neurosurg Anesthesiol*. 1999;11:69–80.
15. Kaisti KK, Langsjo JW, Aalto S, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology*. 2003;99:603–613.
16. Kaisti KK, Metsahonkala L, Teras M, et al. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. *Anesthesiology*. 2002;96:1358–1370.
17. Renou AM, Vernhiet J, Macrez P, et al. Cerebral blood flow and metabolism during etomidate anaesthesia in man. *Br J Anaesth*. 1978;50:1047–1051.
18. Robertson SC, Brown 3rd P, Loftus CM. Effects of etomidate administration on cerebral collateral flow. *Neurosurgery*. 1998;43:317–323; discussion 23–24.
19. Todd MM, Weeks J. Comparative effects of propofol, pentobarbital, and isoflurane on cerebral blood flow and blood volume. *J Neurosurg Anesthesiol*. 1996;8:296–303.
20. Langsjo JW, Maksimow A, Salmi E, et al. S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology*. 2005;103:258–268.
21. Langsjo JW, Salmi E, Kaisti KK, et al. Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. *Anesthesiology*. 2004;100:1065–1071.
22. Eng C, Lam AM, Mayberg TS, et al. The influence of propofol with and without nitrous oxide on cerebral blood flow velocity and CO2 reactivity in humans. *Anesthesiology*. 1992;77:872–879.
23. Fox J, Gelb AW, Enns J, et al. The responsiveness of cerebral blood flow to changes in arterial carbon dioxide is maintained during propofol-nitrous oxide anesthesia in humans. *Anesthesiology*. 1992;77:453–456.
24. Johnston AJ, Steiner LA, Chatfield DA, et al. Effects of propofol on cerebral oxygenation and metabolism after head injury. *Br J Anaesth*. 2003;91:781–786.
25. Strebel S, Kaufmann M, Guardiola PM, Schaefer HG. Cerebral vasomotor responsiveness to carbon dioxide is preserved during propofol and midazolam anesthesia in humans. *Anesth Analg*. 1994;78:884–888.
26. Veselis RA, Feshchenko VA, Reinsel RA, et al. Propofol and thiopental do not interfere with regional cerebral blood flow response at sedative concentrations. *Anesthesiology*. 2005;102:26–34.
27. Vinclair M, Broux C, Faure P, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med*. 2008;34:714–719.
28. Adams RW, Cucchiara RF, Gronert GA, et al. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology*. 1981;54:97–99.
29. Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane, and desflurane during propofol-induced isoelectric electroencephalogram in humans. *Anesthesiology*. 1995;83:980–985; discussion 27A.
30. Stullken Jr EH, Milde JH, Michenfelder JD, Tinker JH. The nonlinear responses of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane, and thiopental. *Anesthesiology*. 1977;46:28–34.
31. Alkire MT. Quantitative EEG, correlations with brain glucose metabolic rate during anesthesia in volunteers. *Anesthesiology*. 1998;89:323–333.
32. Bedforth NM, Hardman JG, Nathanson MH. Cerebral hemodynamic response to the introduction of desflurane: a comparison with sevoflurane. *Anesth Analg*. 2000;91:152–155.
33. Holmstrom A, Akeson J. Cerebral blood flow at 0.5 and 1.0 minimal alveolar concentrations of desflurane or sevoflurane compared with isoflurane in normoventilated pigs. *J Neurosurg Anesthesiol*. 2003;15:90–97.
34. Laitio RM, Kaisti KK, Laangsjo JW, et al. Effects of xenon anesthesia on cerebral blood flow in humans: A positron emission tomography study. *Anesthesiology*. 2007;106:1128–1133.
35. Young WL, Prohovnik I, Correll JW, et al. A comparison of cerebral blood flow reactivity to CO2 during halothane versus isoflurane anesthesia for carotid endarterectomy. *Anesth Analg*. 1991;73:416–421.
36. Ringaert KR, Mutch WA. Regional cerebral blood flow and response to carbon dioxide during controlled hypotension with isoflurane anesthesia in the rat. *Anesth Analg*. 1988;67:383–388.
37. Strebel S, Lam AM, Matta BF, Newell DW. Impaired cerebral autoregulation after mild brain injury. *Surg Neurol*. 1997;47:128–131.
38. Reinstrup P, Ryding E, Algotsson L, et al. Effects of nitrous oxide on human regional cerebral blood flow and isolated pial arteries. *Anesthesiology*. 1994;81:396–402.
39. Reinstrup P, Ryding E, Ohlsson T, et al. Regional cerebral metabolic rate (positron emission tomography) during inhalation of nitrous oxide 50% in humans. *Br J Anaesth*. 2008;100:66–71.
40. Drummond JC, Scheller MS, Todd MM. The effect of nitrous oxide on cortical cerebral blood flow during anesthesia with halothane and isoflurane, with and without morphine, in the rabbit. *Anesth Analg*. 1987;66:1083–1089.
41. Drummond JC, Todd MM. The response of the feline cerebral circulation to PaCO2 during anesthesia with isoflurane and halothane and during sedation with nitrous oxide. *Anesthesiology*. 1985;62:268–273.
42. Jung R, Reinsel R, Marx W, et al. Isoflurane and nitrous oxide: Comparative impact on cerebrospinal fluid pressure in patients with brain tumors. *Anesth Analg*. 1992;75:724–728.
43. Lam AM, Mayberg TS, Eng CC, et al. Nitrous oxide-isoflurane anesthesia causes more cerebral vasodilation than an equipotent dose of isoflurane in humans. *Anesth Analg*. 1994;78:462–468.
44. Artru AA. Nitrous oxide plays a direct role in the development of tension pneumocephalus intraoperatively. *Anesthesiology*. 1982;57:59–61.
45. Goodie D, Traill R. Intraoperative subdural tension pneumocephalus arising after opening of the dura. *Anesthesiology*. 1991;74:193–195.
46. Yates H, Hamill M, Borel CO, Toung TJ. Incidence and perioperative management of tension pneumocephalus following craniofacial resection. *J Neurosurg Anesthesiol*. 1994;6:15–20.

47. Albanese J, Viviand X, Potie F, et al. Sufentanil, fentanyl, and alfentanil in head trauma patients: A study on cerebral hemodynamics. *Crit Care Med*. 1999;27:407–411.
48. de Nadal M, Munar F, Poca MA, et al. Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: Absence of correlation to cerebral autoregulation. *Anesthesiology*. 2000;92:11–19.
49. Engelhard K, Reeker W, Kochs E, Werner C. Effect of remifentanil on intracranial pressure and cerebral blood flow velocity in patients with head trauma. *Acta Anaesthesiol Scand*. 2004;48:396–399.
50. Jamali S, Ravussin P, Archer D, et al. The effects of bolus administration of opioids on cerebrospinal fluid pressure in patients with supratentorial lesions. *Anesth Analg*. 1996;82:600–606.
51. From RP, Warner DS, Todd MM, Sokoll MD. Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. *Anesthesiology*. 1990;73:896–904.
52. Hormann C, Langmayr J, Schalow S, Benzer A. Low-dose sufentanil increases cerebrospinal fluid pressure in human volunteers. *J Neurosurg Anesthesiol*. 1995;7:7–11.
53. Marx W, Shah N, Long C, et al. Sufentanil, alfentanil, and fentanyl: Impact on cerebrospinal fluid pressure in patients with brain tumors. *J Neurosurg Anesthesiol*. 1989;1:3–7.
54. Mayer N, Weinstabl C, Podreka I, Spiss CK. Sufentanil does not increase cerebral blood flow in healthy human volunteers. *Anesthesiology*. 1990;73:240–243.
55. Coles JP, Leary TS, Monteiro JN, et al. Propofol anesthesia for craniotomy: A double-blind comparison of remifentanil, alfentanil, and fentanyl. *J Neurosurg Anesthesiol*. 2000;12:15–20.
56. Ostapkovich ND, Baker KZ, Fogarty-Mack P, et al. Cerebral blood flow and CO2 reactivity is similar during remifentanil/N2O and fentanyl/N2O anesthesia. *Anesthesiology*. 1998;89:358–363.
57. Sneyd JR, Whaley A, Dimpel HL, Andrews CJ. An open, randomized comparison of alfentanil, remifentanil and alfentanil followed by remifentanil in anaesthesia for craniotomy. *Br J Anaesth*. 1998;81:361–364.
58. Warner DS. Experience with remifentanil in neurosurgical patients. *Anesth Analg*. 1999;89:S33–S39.
59. Nishikawa T, Omote K, Namiki A, Takahashi T. The effects of nicardipine on cerebrospinal fluid pressure in humans. *Anesth Analg*. 1986;65:507–510.
60. Pinaud M, Souron R, Lelausque JN, et al. Cerebral blood flow and cerebral oxygen consumption during nitroprusside-induced hypotension to less than 50 mmHg. *Anesthesiology*. 1989;70:255–260.
61. Griswold WR, Reznik V, Mendoza SA. Nitroprusside-induced intracranial hypertension. *JAMA*. 1981;246:2679–2680.
62. Joshi S, Young WL, Duong H, et al. Intracarotid nitroprusside does not augment cerebral blood flow in human subjects. *Anesthesiology*. 2002;96:60–66.
63. Joshi S, Meyers PM, Pile-Spellman J, et al. Intracarotid verapamil decreases both proximal and distal human cerebrovascular resistance. *Anesthesiology*. 2004;100:774–781.
64. Heinke W, Zysset S, Hund-Georgiadis M, et al. The effect of esmolol on cerebral blood flow, cerebral vasoreactivity, and cognitive performance: A functional magnetic resonance imaging study. *Anesthesiology*. 2005;102:41–50.
65. Albrecht RF, Miletich DJ, Ruttle M. Cerebral effects of extended hyperventilation in unanesthetized goats. *Stroke*. 1987;18:649–655.
66. Gelb AW, Craen RA, Rao GS, et al. Does hyperventilation improve operating condition during supratentorial craniotomy? A multicenter randomized crossover trial. *Anesth Analg*. 2008;106:585–594.
67. Coles JP, Fryer TD, Coleman MR, et al. Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism. *Crit Care Med*. 2007;35:568–578.
68. Matteo RS, Ornstein E, Schwartz AE, et al. Effects of hypocarbia on the pharmacodynamics of sufentanil in humans. *Anesth Analg*. 1992;75:186–192.
69. Muizelaar JP, Lutz 3rd HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg*. 1984;61:700–706.
70. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. *J Neurosurg*. 1983;59:822–828.
71. Burke AM, Quest DO, Chien S, Cerri C. The effects of mannitol on blood viscosity. *J Neurosurg*. 1981;55:550–553.
72. Ravussin P, Abou-Madi M, Archer D, et al. Changes in CSF pressure after mannitol in patients with and without elevated CSF pressure. *J Neurosurg*. 1988;69:869–876.
73. Cascino T, Baglivo J, Conti J, et al. Quantitative CT assessment of furosemide- and mannitol-induced changes in brain water content. *Neurology*. 1983;33:898–903.
74. Dostal P, Dostalova V, Schreiberova J, et al. A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation in patients undergoing elective intracranial tumor surgery: A randomized clinical trial. *J Neurosurg Anesthesiol*. 2015;27:51–56.
75. Todd MM, Cutkomp J, Brian JE. Influence of mannitol and furosemide, alone and in combination, on brain water content after fluid percussion injury. *Anesthesiology*. 2006;105:1176–1181.
76. Mavrocordatos P, Bissonnette B, Ravussin P. Effects of neck position and head elevation on intracranial pressure in anaesthetized neurosurgical patients: Preliminary results. *J Neurosurg Anesthesiol*. 2000;12:10–14.
77. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. *J Trauma*. 1990;30:933–940; discussion 40–41.
78. Bedford RF, Morris L, Jane JA. Intracranial hypertension during surgery for supratentorial tumor: Correlation with preoperative computed tomography scans. *Anesth Analg*. 1982;61:430–433.
79. Todd MM, Warner DS, Sokoll MD, et al. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. *Anesthesiology*. 1993;78:1005–1020.
80. Black PM. Brain tumors. Part 1. *N Engl J Med*. 1991;324:1471–1476.
81. Truong J, Yan AT, Cramarossa G, Chan KK. Chemotherapy-induced cardiotoxicity: Detection, prevention, and management. *Can J Cardiol*. 2014;30:869–878.
82. Brandes AA, Scelzi E, Salmistraro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: A prospective study. *Eur J Cancer*. 1997;33:1592–1596.
83. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med*. 1998;339:80–85.
84. Ayerbe J, Lobato RD, de la Cruz J, et al. Risk factors predicting recurrence in patients operated on for intracranial meningioma. A multivariate analysis. *Acta Neurochir (Wien)*. 1999;141:921–932.
85. Cataldi S, Bruder N, Dufour H, et al. Intraoperative autologous blood transfusion in intracranial surgery. *Neurosurgery*. 1997;40:765–771; discussion 71–72.
86. Lunn JK, Stanley TH, Webster LR, Bidwai AV. Arterial blood-pressure and pulse-rate responses to pulmonary and radial arterial catheterization prior to cardiac and major vascular operations. *Anesthesiology*. 1979;51:265–269.
87. Lazar RM, Fitzsimmons BF, Marshall RS, et al. Reemergence of stroke deficits with midazolam challenge. *Stroke*. 2002;33:283–285.
88. Thal GD, Szabo MD, Lopez-Bresnahan M, Crosby G. Exacerbation or unmasking of focal neurologic deficits by sedatives. *Anesthesiology*. 1996;85:21–25.
89. Ornstein E, Matteo RS, Schwartz AE, et al. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology*. 1987;67:191–196.
90. Paul F, Veauthier C, Fritz G, et al. Perioperative fluctuations of lamotrigine serum levels in patients undergoing epilepsy surgery. *Seizure*. 2007;16:479–484.
91. Yeh JS, Dhir JS, Green AL, et al. Changes in plasma phenytoin level following craniotomy. *Br J Neurosurg*. 2006;20:403–406.
92. Grenier B, Verchere E, Mesli A, et al. Capnography monitoring during neurosurgery: Reliability in relation to various intraoperative positions. *Anesth Analg*. 1999;88:43–48.
93. Whitesell R, Asiddao C, Gollman D, Jablonski J. Relationship between arterial and peak expired carbon dioxide pressure during anesthesia and factors influencing the difference. *Anesth Analg*. 1981;60:508–512.
94. Valadka AB, Furuya Y, Hlatky R, Robertson CS. Global and regional techniques for monitoring cerebral oxidative metabolism after severe traumatic brain injury. *Neurosurg Focus*. 2000;9:e3.
95. Ganslandt O, Merkel A, Schmitt H, et al. The sitting position in neurosurgery: Indications, complications and results. A single institution experience of 600 cases. *Acta Neurochir (Wien)*. 2013;155:1887–1893.
96. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. *Anesthesiology*. 1980;52:74–75.
97. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. *Anesthesiology*. 1986;65:165–169.
98. Andrews RJ, Bringas JR. A review of brain retraction and recommendations for minimizing intraoperative brain injury. *Neurosurgery*. 1993;33:1052–1063.
99. Kimura K, Iguchi Y, Inoue T, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci*. 2007;255:90–94.
100. McGirt MJ, Woodworth GF, Brooke BS, et al. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. *Neurosurgery*. 2006;58:1066–1073; discussion 1066–1073.
101. Ribo M, Molina CA, Delgado P, et al. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622.

102. Sonneville R, Vanhorebeek I, den Hertog HM, et al. Critical illness-induced dysglycemia and the brain. *Intensive Care Med*. 2015;41:192–202.
103. Magnus N, D'Asti E, Garnier D, et al. Brain neoplasms and coagulation. *Semin Thromb Hemost*. 2013;39:881–895.
104. Guan M, Su B, Lu Y. Quantitative reverse transcription-PCR measurement of tissue factor mRNA in glioma. *Mol Biotechnol*. 2002;20:123–129.
105. Goh KY, Tsoi WC, Feng CS, et al. Haemostatic changes during surgery for primary brain tumours. *J Neurol Neurosurg Psychiatry*. 1997;63:334–338.
106. Seifman MA, Lewis PM, Rosenfeld JV, Hwang PY. Postoperative intracranial haemorrhage: A review. *Neurosurg Rev*. 2011;34:393–407.
107. Nielsen VG, Lemole Jr GM, Matika RW, et al. Brain tumors enhance plasmatic coagulation: The role of hemeoxygenase-1. *Anesth Analg*. 2014;118:919–924.
108. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. *Crit Care Med*. 2010;38:S145–S154.
109. Gerstner T, Teich M, Bell N, et al. Valproate-associated coagulopathies are frequent and variable in children. *Epilepsia*. 2006;47:1136–1143.
110. Pan CF, Shen MY, Wu CJ, et al. Inhibitory mechanisms of gabapentin, an antiseizure drug, on platelet aggregation. *J Pharm Pharmacol*. 2007;59:1255–1261.
111. Abrahams JM, Torchia MB, McGarvey M, et al. Perioperative assessment of coagulability in neurosurgical patients using thromboelastography. *Surg Neurol*. 2002;58:5–11; discussion 11–12.
112. Skukalek SL, Winkler AM, Kang J, et al. Effect of antiplatelet therapy and platelet function testing on hemorrhagic and thrombotic complications in patients with cerebral aneurysms treated with the pipeline embolization device: A review and meta-analysis. *J Neurointervensional Surg*. 2014.
113. Figueiredo S, Vigue B, Benhamou D, Duranteau J. Emergency reversal of heparin overdose in a neurosurgical patient guided by thromboelastography. *Br J Anaesth*. 2013;111:303–304.
114. Neyens R, Bohm N, Cearley M, et al. Dabigatran-associated subdural hemorrhage: Using thromboelastography (TEG((R))) to guide decision-making. *J Thromb Thrombolysis*. 2014;37:80–83.
115. Vitaz TW, Marx W, Victor JD, Gutin PH. Comparison of conscious sedation and general anesthesia for motor mapping and resection of tumors located near motor cortex. *Neurosurg Focus*. 2003;15:E8.
116. Constantini S, Cotev S, Rappaport ZH, et al. Intracranial pressure monitoring after elective intracranial surgery. A retrospective study of 514 consecutive patients. *J Neurosurg*. 1988;69:540–544.
117. Moppett IK, Mahajan RP. Transcranial Doppler ultrasonography in anaesthesia and intensive care. *Br J Anaesth*. 2004;93:710–724.
118. Eng CC, Lam AM, Byrd S, Newell DW. The diagnosis and management of a perianesthetic cerebral aneurysmal rupture aided with transcranial Doppler ultrasonography. *Anesthesiology*. 1993;78:191–194.
119. Bruder N, Pellissier D, Grillot P, Gouin F. Cerebral hyperemia during recovery from general anesthesia in neurosurgical patients. *Anesth Analg*. 2002;94:650–654.
120. Meyers PM, Higashida RT, Phatouros CC, et al. Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. *Neurosurgery*. 2000;47:335–343; discussion 343–345.
121. Amin-Hanjani S, Meglio G, Gatto R, et al. The utility of intraoperative blood flow measurement during aneurysm surgery using an ultrasonic perivascular flow probe. *Neurosurgery*. 2008;62:1346–1353.
122. Bouillon T, Bruhn J, Radu-Radulescu L, et al. Non-steady state analysis of the pharmacokinetic interaction between propofol and remifentanil. *Anesthesiology*. 2002;97:1350–1362.
123. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74:53–63.
124. Wright PM, McCarthy G, Szenohradszky J, et al. Influence of chronic phenytoin administration on the pharmacokinetics and pharmacodynamics of vecuronium. *Anesthesiology*. 2004;100:626–633.
125. Spacek A, Neiger FX, Krenn CG, et al. Rocuronium-induced neuromuscular block is affected by chronic carbamazepine therapy. *Anesthesiology*. 1999;90:109–112.
126. Richard A, Girard F, Girard DC, et al. Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients. *Anesth Analg*. 2005;100:538–544.
127. Tempelhoff R, Modica PA, Jellish WS, Spitznagel EL. Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg*. 1990;71:665–669.
128. Bayer-Berger MM, Ravussin P, Fankhauser H, Freeman J. Effect of three pretreatment techniques on hemodynamic and CSFP responses to skull-pin head-holder application during thiopentone/isoflurane or propofol anesthesia. *J Neurosurg Anesthesiol*. 1989;1:227–232.
129. Papangelou A, Radzik BR, Smith T, Gottschalk A. A review of scalp blockade for cranial surgery. *J Clin Anesth*. 2013;25:150–159.
130. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
131. Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. *Anesthesiology*. 2008;108:71–77.
132. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med*. 1996;334:1209–1215.
133. Frank SM, Beattie C, Christopherson R, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology*. 1993;78:468–476.
134. Lenhardt R, Marker E, Goll V, et al. Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology*. 1997;87:1318–1323.
135. Petersen KD, Landsfeldt U, Cold GE, et al. Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: A randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. *Anesthesiology*. 2003;98:329–336.
136. Ravussin P, de Tribolet N, Wilder-Smith OH. Total intravenous anesthesia is best for neurological surgery. *J Neurosurg Anesthesiol*. 1994;6:285–289.
137. Fraga M, Rama-Maceiras P, Rodino S, et al. The effects of isoflurane and desflurane on intracranial pressure, cerebral perfusion pressure, and cerebral arteriovenous oxygen content difference in normocapnic patients with supratentorial brain tumors. *Anesthesiology*. 2003;98:1085–1090.
138. Cole CD, Gottfried ON, Gupta DK, Couldwell WT. Total intravenous anesthesia: advantages for intracranial surgery. *Neurosurgery*. 2007;61:369–377; discussion 377–378.
139. Hoffman WE, Charbel FT, Edelman G, et al. Nitrous oxide added to isoflurane increases brain artery blood flow and low frequency brain electrical activity. *J Neurosurg Anesthesiol*. 1995;7:82–88.
140. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369:428–437.
141. Sogame LC, Vidotto MC, Jardim JR, Faresin SM. Incidence and risk factors for postoperative pulmonary complications in elective intracranial surgery. *J Neurosurg*. 2008;109:222–227.
142. Lowe GJ, Ferguson ND. Lung-protective ventilation in neurosurgical patients. *Curr Opin Crit Care*. 2006;12:3–7.
143. Treschan TA, Schaefer MS, Subasi L, et al. Evolution of ventilator settings during general anaesthesia for neurosurgery: An observational study in a German centre over 15 years. *Eur J Anaesthesiol*. 2015;32:894–896.
144. Jian M, Li X, Wang A, et al. Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery. *Br J Anaesth*. 2014;113:832–839.
145. Bruder N, Ravussin P. Recovery from anesthesia and postoperative extubation of neurosurgical patients: A review. *J Neurosurg Anesthesiol*. 1999;11:282–293.
146. Muzzi DA, Black S, Losasso TJ, Cucchiara RF. Labetalol and esmolol in the control of hypertension after intracranial surgery. *Anesth Analg*. 1990;70:68–71.
147. Basali A, Mascha E, Kalfas I, Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. *Anesthesiology*. 2000;93:48–54.
148. Grillo P, Bruder N, Auquier P, et al. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. *Anesth Analg*. 2003;96:1145–1149. table of contents.
149. Lee JH, Choi SH, Choi YS, et al. Does the type of anesthetic agent affect remifentanil effect-site concentration for preventing endotracheal tube-induced cough during anesthetic emergence? Comparison of propofol, sevoflurane, and desflurane. *J Clin Anesth*. 2014;26:466–474.
150. Choi SH, Min KT, Lee JR, et al. Determination of EC95 of remifentanil for smooth emergence from propofol anesthesia in patients undergoing transsphenoidal surgery. *J Neurosurg Anesthesiol*. 2015;27:160–166.
151. Fabregas N, Bruder N. Recovery and neurological evaluation. *Best Pract Res Clin Anaesthesiol*. 2007;21:431–447.
152. Ziai WC, Varelas PN, Zeger SL, et al. Neurologic intensive care resource use after brain tumor surgery: An analysis of indications and alternative strategies. *Crit Care Med*. 2003;31:2782–2787.
153. Verchere E, Grenier B, Mesli A, et al. Postoperative pain management after supratentorial craniotomy. *J Neurosurg Anesthesiol*. 2002;14:96–101.
154. Ayoub C, Girard F, Boudreault D, et al. A comparison between scalp nerve block and morphine for transitional analgesia after remifentanil-based anesthesia in neurosurgery. *Anesth Analg*. 2006;103:1237–1240.
155. Rolston JD, Han SJ, Lau CY, et al. Frequency and predictors of complications in neurological surgery: National trends from 2006 to 2011. *J Neurosurg*. 2014;120:736–745.

156. Lassen B, Helseth E, Ronning P, et al. Surgical mortality at 30 days and complications leading to recraniotomy in 2630 consecutive craniotomies for intracranial tumors. *Neurosurgery*. 2011;68:1259–1268; discussion 1268–1269.
157. Solheim O, Jakola AS, Gulati S, Johannesen TB. Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: A national, population-based study. *J Neurosurg*. 2012;116:825–834.
158. Bui JQ, Mendis RL, van Gelder JM, et al. Is postoperative intensive care unit admission a prerequisite for elective craniotomy? *J Neurosurg*. 2011;115:1236–1241.
159. Rhondali O, Genty C, Halle C, et al. Do patients still require admission to an intensive care unit after elective craniotomy for brain surgery? *J Neurosurg Anesthesiol*. 2011;23:118–123.
160. Asano K, Nakano T, Takeda T, Ohkuma H. Risk factors for postoperative systemic complications in elderly patients with brain tumors. Clinical article. *J Neurosurg*. 2009;111:258–264.
161. Gottschalk A, Berkow LC, Stevens RD, et al. Prospective evaluation of pain and analgesic use following major elective intracranial surgery. *J Neurosurg*. 2007;106:210–216.
162. Jeffrey HM, Charlton P, Mellor DJ, et al. Analgesia after intracranial surgery: A double-blind, prospective comparison of codeine and tramadol. *Br J Anaesth*. 1999;83:245–249.
163. Durrieu G, Olivier P, Bagheri H, Montastruc JL. Overview of adverse reactions to nefopam: An analysis of the French Pharmacovigilance database. *Fundam Clin Pharmacol*. 2007;21:555–558.
164. Magni G, La Rosa I, Melillo G, et al. Intracranial hemorrhage requiring surgery in neurosurgical patients given ketorolac: A case-control study within a cohort (2001-2010). *Anesth Analg*. 2013;116:443–447.
165. Fabling JM, Gan TJ, Guy J, et al. Postoperative nausea and vomiting. A retrospective analysis in patients undergoing elective craniotomy. *J Neurosurg Anesthesiol*. 1997;9:308–312.
166. Kathirvel S, Shende D, Madan R. Comparison of anti-emetic effects of ondansetron, metoclopromide or a combination of both in children undergoing surgery for strabismus. *Eur J Anaesthesiol*. 1999;16:761–765.
167. Fabling JM, Gan TJ, El-Moalem HE, et al. A randomized, double-blinded comparison of ondansetron, droperidol, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. *Anesth Analg*. 2000;91:358–361.
168. Fabling JM, Gan TJ, El-Moalem HE, et al. A randomized, double-blind comparison of ondansetron versus placebo for prevention of nausea and vomiting after infratentorial craniotomy. *J Neurosurg Anesthesiol*. 2002;14:102–107.
169. Galicich JH, French LA, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. *Lancet*. 1961;81:46–53.
170. Hockey B, Leslie K, Williams D. Dexamethasone for intracranial neurosurgery and anaesthesia. *J Clin Neurosci*. 2009;16:1389–1393.
171. Komotar RJ, Raper DM, Starke RM, et al. Prophylactic antiepileptic drug therapy in patients undergoing supratentorial meningioma resection: A systematic analysis of efficacy. *J Neurosurg*. 2011;115:483–490.
172. Pulman J, Greenhalgh J, Marson AG. Antiepileptic drugs as prophylaxis for post-craniotomy seizures. *Cochrane Database Syst Rev*. 2013;2:CD007286.
173. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2000;54:1886–1893.
174. Sayegh ET, Fakurnejad S, Oh T, et al. Anticonvulsant prophylaxis for brain tumor surgery: Determining the current best available evidence. *J Neurosurg*. 2014;121:1139–1147.
175. Siomin V, Angelov L, Li L, Vogelbaum MA. Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in patients with brain tumors. *J Neurooncol*. 2005;74:211–215.
176. Lim DA, Tarapore P, Chang E, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: A randomized phase II pilot study. *J Neurooncol*. 2009;93:349–354.
177. Milligan TA, Hurwitz S, Bromfield EB. Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. *Neurology*. 2008;71:665–669.
178. Samama CM, Albaladejo P, Benhamou D, et al. Venous thromboembolism prevention in surgery and obstetrics: Clinical practice guidelines. *Eur J Anaesthesiol*. 2006;23:95–116.
179. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e227S–e277S.
180. Barker 2nd FG. Efficacy of prophylactic antibiotics against meningitis after craniotomy: A meta-analysis. *Neurosurgery*. 2007;60:887–894; discussion 887–894.
181. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:251–270.
182. Paolini JB, Donati F, Drolet P. Review article: Video-laryngoscopy: Another tool for difficult intubation or a new paradigm in airway management? *Can J Anaesth*. 2013;60:184–191.
183. Schmidt U, Eikermann M. Organizational aspects of difficult airway management: Think globally, act locally. *Anesthesiology*. 2011;114:3–6.
184. Ng I, Hill AL, Williams DL, et al. Randomized controlled trial comparing the McGrath videolaryngoscope with the C-MAC videolaryngoscope in intubating adult patients with potential difficult airways. *Br J Anaesth*. 2012;109:439–443.
185. Pieters B, Maassen R, van Eig E, et al. Indirect videolaryngoscopy using Macintosh blades in patients with non-anticipated difficult airways results in significantly lower forces exerted on teeth relative to classic direct laryngoscopy: A randomized crossover trial. *Minerva Anestesiol*. 2015;81:846–854.
186. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis*. 1997;25:763–779; quiz 780–781.
187. Coonan TJ, Hope CE, Howes WJ, et al. Ankylosis of the temporomandibular joint after temporal craniotomy: A cause of difficult intubation. *Can Anaesth Soc J*. 1985;32:158–160.
188. Kawaguchi M, Sakamoto T, Ohnishi H, et al. Do recently developed techniques for skull base surgery increase the risk of difficult airway management? Assessment of pseudoankylosis of the mandible following surgical manipulation of the temporalis muscle. *J Neurosurg Anesthesiol*. 1995;7:183–186.
189. Nitzan DW, Azaz B, Constantini S. Severe limitation in mouth opening following transtemporal neurosurgical procedures: Diagnosis, treatment, and prevention. *J Neurosurg*. 1992;76:623–625.
190. Duffau H, Lopes M, Arthuis F, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: A comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry*. 2005;76:845–851.
191. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *N Engl J Med*. 1986;314:953–958.
192. Ross DA, Olsen WL, Ross AM, et al. Brain shift, level of consciousness, and restoration of consciousness in patients with acute intracranial hematoma. *J Neurosurg*. 1989;71:498–502.
193. Ehrenfeld JM, Cassedy EA, Forbes VE, et al. Modified rapid sequence induction and intubation: A survey of United States current practice. *Anesth Analg*. 2012;115:95–101.
194. Sorensen MK, Bretlau C, Gatke MR, et al. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: A randomized trial. *Br J Anaesth*. 2012;108:682–689.
195. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet*. 2005;365:1957–1959.
196. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): Randomised placebo-controlled trial. *Lancet*. 2004;364:1321–1328.
197. Gopinath SP, Cormio M, Ziegler J, et al. Intraoperative jugular desaturation during surgery for traumatic intracranial hematomas. *Anesth Analg*. 1996;83:1014–1021.

Anesthetic Management for Posterior Fossa Surgery

12

R.A. Schlichter • D.S. Smith

The confines of the posterior fossa and the myriad of neuronal and vascular structures that traverse it create a challenge for the anesthesiologist, whose intraoperative goals are to facilitate surgical access, minimize nervous tissue trauma, and maintain respiratory and cardiovascular stability. This discussion focuses on the anesthetic considerations for posterior fossa surgery in adult patients; preoperative evaluation and preparation; general monitoring considerations; choice of surgical position; anesthetic considerations including the risks, prevention, detection, treatment, and complications of air embolism; and special monitoring issues.

PREOPERATIVE EVALUATION AND PREPARATION

Patient physical status, particularly in reference to cardiovascular and pulmonary stability and airway manageability, is a determinant of the choice of patient position for posterior fossa surgery. The efforts to obtain optimal operating conditions and maintain a stable perioperative course may sometimes be at cross-purposes. For example, patients with previous cerebrospinal fluid shunting procedures may be at greater risk for subdural pneumocephalus with surgery in the head-up position. Thus a thorough evaluation of previous operations and cardiopulmonary problems, current cardiac and respiratory status, evidence of cerebrovascular compromise, and suitability of vascular access for right atrial catheter placement are of particular importance in the patient undergoing posterior fossa surgery.

In patients with altered limits of cerebral autoregulation, impaired cerebral perfusion, or abnormal baroreceptor function resulting from hypertension, cardiovascular disease, cerebrovascular insufficiency, or prior carotid endarterectomy, the occurrence of hypotension during anesthesia in the head-up position may be especially detrimental.

Assessment of vascular access for right atrial catheter placement helps determine the most promising route. Patients who are obese, have poor vasculature due to disease or chronic intravenous cannulation, or have short, thick necks should be identified early so that necessary time may be allotted for catheter placement. Some authorities have advocated echocardiography to detect patent foramen ovale (PFO) in patients scheduled for surgery in the head-up position; the use of an alternative position for those who have PFO might reduce the occurrence of paradoxical air embolism (PAE).[1,2] A detection rate of 10% to 30% with use of echocardiography is comparable with the 20% to 30% incidence reported in autopsy findings.[3] The noninvasive nature of echocardiography makes it attractive for screening purposes; its specificity is reported to be 64% to 100%.[4–6] However, preoperative screening echocardiography lacks sensitivity (ie, nondetection of PFO does not guarantee its absence).[7,8] Transesophageal echocardiography (TEE) is used after induction of anesthesia in some institutions,[9] but it is not 100% sensitive for detection of PFO.[10] More recently, Feigl and associates[11] described their experience in 200 patients scheduled for posterior fossa surgery in the sitting position. After induction of anesthesia, transesophageal echocardiography was performed to check for PFO. Fifty-two patients (26%) had a detectable PFO with a venous air embolism (VAE) rate of 54%. Only one patient had significant clinical manifestations but was without neurologic sequelae.

GENERAL MONITORING ISSUES

The goals of monitoring are to ensure adequate central nervous system perfusion, maintain cardiorespiratory stability, and detect and treat air embolism. Box 12.1 lists the monitors used regardless of patient position; monitors not in routine use but that provide specialized information during certain procedures are noted with an asterisk. Not every "routine" monitor listed in the box is always used for every posterior fossa procedure.

For surgery on the head or neck, many clinicians prefer placement of central venous catheters in the forearm or the antecubital fossa, preferably via the basilic vein after induction of anesthesia. In patients with small veins, a modified Seldinger technique can be used for specialized right atrial catheters. Prolonged head-down position and head rotation for jugular vein catheter placement should be minimized because these maneuvers may reduce cerebral blood perfusion. Doppler ultrasound can be used to localize the jugular or subclavian vein before needle insertion.[12] Whenever catheters are placed via the neck or subclavian routes, the insertion sites should be sealed with bacteriostatic ointment and dressing to minimize air entrainment, especially for patients in head-up positions. Another precaution is to place and remove these central lines

BOX 12.1 Monitors for Posterior Fossa Surgery

Preinduction and Induction
Five-lead electrocardiogram
Blood pressure monitoring
Pulse oximetry
Precordial stethoscope
$ETCO_2$ monitoring
Electrophysiologic monitoring*

Postinduction
Central venous (right atrial, pulmonary artery) catheter
Precordial Doppler ultrasound probe
Esophageal stethoscope
Esophageal or nasopharyngeal temperature probe
$ETCO_2$
Transesophageal echocardiogram*

*Not routine but provides specialized information during certain procedures.

while the patient is flat, never in the head-up position, because air embolism has been reported with central line removal when a patient's head is elevated above the heart.

CHOICE OF PATIENT POSITION

Surgical access to the posterior fossa can be obtained through various patient positions, such as the sitting position and variants of the horizontal position, which include supine retrosigmoid, prone, three-quarter prone, and park bench lateral positions.

Sitting Position

To establish the sitting position, the patient's skull is most often secured in a three-pin head holder.[13] The arterial pressure transducer is zeroed at the skull base during positioning and throughout the procedure to make maintenance of adequate cerebral perfusion pressure (CPP) easier. Bony prominences should be well padded, the elbows supported by padding to avoid contact with the table or stretch on the brachial plexus, and the legs freed of pressure at the level of the common peroneal nerve just distal and lateral to the head of the fibula. Efforts to prevent cervical cord stretching and obstruction of venous drainage from the face and tongue include maintenance of at least a 2.5 cm space between chin and chest, avoidance of large oral airways or bite blocks in the pharynx, and avoidance of excessive neck rotation, especially in elderly patients. Abdominal compression, lower extremity ischemia, and sciatic nerve injury are prevented by avoidance of excessive flexion of the knees toward the chest.

A "lounge chair" modification of the sitting position, with the thoracic cage raised 30 to 45 degrees, may be used for lateral lesions. Access to more midline structures may be impeded by the degree of neck flexion required. Another modification, the lateral park bench, allows rapid head lowering to the left lateral decubitus position and continuation of the operation in the event of hypotension or persistent VAE.

For the anesthesiologist, the advantages of the sitting position include lower airway pressures, ease of diaphragmatic excursion and improved ability for hyperventilation; better access to the endotracheal tube and thorax for monitoring; improved access to the extremities for monitoring, fluid or blood administration and blood sampling; and better visualization of the face for observation of motor responses during cranial nerve stimulation.

Improved postoperative cranial nerve function has been reported in patients undergoing acoustic neuroma resection in the sitting position than in those operated on in horizontal positions.[14] Relative contraindications to the sitting position are known intracardiac septal defects, known pulmonary arteriovenous malformations, severe hypovolemia, cachexia, or severe hydrocephalus.

Physiologic Changes that occur with the Sitting Position

Head elevation above the right atrium reduces dural sinus pressure, which decreases venous bleeding, but raises the risk of VAE. Head elevation to the 90-degree sitting position produces decreases in dural sinus pressure of up to 10 mmHg.

Cardiovascular effects include increases in pulmonary and systemic vascular resistance and decreases in cardiac output, venous return, and CPP.[15,16] For each 1.25-cm movement of the head above the level of the heart, local arterial pressure is reduced by approximately 1 mmHg.[17] Dysrhythmias, such as bradycardia, tachycardia, premature ventricular contractions, and asystole, may result from manipulation or retraction of cranial nerves or the brainstem regardless of patient position.[18–20] The negative effects of dysrhythmias on cardiac output may be more pronounced for patients in the sitting position than in a horizontal position. Pulmonary vital capacity and functional residual capacity are improved in the sitting position, but hypovolemia may decrease perfusion of the upper lung, leading to ventilation or perfusion abnormalities. Nitrous oxide may increase the likelihood of transpulmonary passage of air in a dose-dependent manner,[21] a feature that influences the choice of anesthetic in the sitting position, as this should not be increased with inhaled ethers or intravenous anesthetics.

The use of nitrous oxide in the sitting position continues to be controversial. Nitrous oxide increases the size of intravascular air bubbles if air embolism occurs.[22] However, N_2O has not been determined to be a factor in perioperative morbidity in several series of patients undergoing posterior fossa surgery at different institutions, regardless of patient position and occurrence of VAE.[23,24]

Because N_2O raises pressure in a closed air space, some clinicians recommend discontinuation of its use before the dura is completely closed to prevent the buildup of gas pressure and possible neurologic deficit from tension pneumocephalus.[25,26] Others have demonstrated that continued use of N_2O until the end of the procedure actually promotes removal of the gas after the N_2O is discontinued, because of the gradient created between the gas space and blood, provided that circulation to that area is intact.[27] Discontinuation of N_2O has not been effective in preventing pneumocephalus.[28]

The incidence of pneumocephalus was reported to be 100% for intracranial procedures performed with patients in the sitting position, 72% for those in the "park-bench" (semiprone lateral) position, and 57% for those in the prone position.[29,30] Pneumocephalus is usually asymptomatic and resolves spontaneously. However, tension pneumocephalus may produce postoperative neurologic deficits.[31–33] It may be diagnosed intraoperatively from decreases in somatosensory evoked potentials (SSEPs) (if monitored)[34,35] and postoperatively on computed tomography. Treatment is supportive, consisting of 100% O_2 administration and, in severe cases, removal of gas by aspiration or reopening of the dura.

Prone Position

The prone position is associated with a lower incidence of VAE.[14,23] However, the patient's head is usually elevated above the heart to decrease venous bleeding, so the risk of VAE is not eliminated. Access to superior posterior fossa structures and ease of head manipulation is not as favorable as in the sitting position; the sitting position may also offer better operating conditions for high cervical decompression, in which neck flexion and weight-bearing on the head are detrimental.[36]

When the patient is in the head-elevated position, placement of the shoulders at or above the edge of the operating table back prevents the face from becoming compressed against the cephalad edge of the table when it is inclined. Eye compression can produce blindness from retinal artery thrombosis; this risk is greater for prone and lateral patient positions, particularly when a padded facial headrest is used. Conjunctival edema is a benign consequence of the prone position that resolves quickly. Visual loss from a variety of mechanisms, usually perioperative ischemic optic neuropathy, is a rare but catastrophic outcome of operative intervention and may be of particular relevance in spinal fusion procedures. Venous pooling sufficient to impair venous return can occur in the lower extremities when they lie below the right atrium.

Table 12.1 **Complications Associated with Surgical Position in Posterior Fossa Surgery**

Complication(s)	Sitting Position	Prone Position	Lateral, Three-Quarter Prone Position	Park-Bench, "Lounge" Position
Nervous System				
Cerebral ischemia	++	+	0	+
Cervical spine ischemia	++	+	0	+
Palsies				
Cranial nerve	+	++	++	
Brachial plexus	+	++	++	
Sciatic nerve	+	0	0	0
Peroneal nerve	+	0	?	
Airway				
Edema of face, tongue, neck (postoperative obstruction)	++	++	+	0
Endotrachael tube migration	++	++	+	+
Pulmonary				
Ventilation/perfusion abnormalities	+	+	+	+
Increased airway pressures	0	++	0-+	0
Tension pneumocephalus	+	+	0	0
Cardiovascular				
Hypotension	++	++	0	+
Dysrhythmias	++	++	±	++
Need for blood transfusion	+	++	±	+
Miscellaneous				
Eye compression	0	+++	++	+
"Compartment syndrome"	+	0	0	0
Venous air embolism	+++	++	+	++
Paradoxical air embolism	++	+	?	?

0, +, ++, ++ indicate relative probability from no risk to high risk.

Elderly, debilitated patients may not tolerate even a brief discontinuation of monitoring during the turn to the prone position without suffering severe hypotension. In these patients, monitoring cables and transducers should be oriented to allow uninterrupted electrocardiogram (ECG) and arterial blood pressure monitoring throughout the turn to the prone position and positioning adjustments.

Lateral, Three-Quarter Prone, and Park-Bench Positions

The lateral position is used for unilateral neurosurgical procedures in the upper posterior fossa. The three-quarter prone position, a modification of the prone and lateral positions, and the park-bench position are used for similar procedures to permit greater head rotation and access to more axial structures. The supine retrosigmoid position is often easier and quicker to perform. Although it provides inferior surgical exposure, it may be preferred because the time required for placing a patient in this position is less.

Risk–Benefit Analysis of Sitting Position Compared with Other Positions

The usefulness or appropriateness of the sitting surgical position for access to the posterior fossa is still a matter of debate among neurosurgeons and neuroanesthesiologists, because alternative positions can be used for posterior fossa access and the occurrence of VAE is more common and severe in posterior fossa procedures performed in the sitting position than in alternative positions. Investigators from different institutions have reported their experience with the sitting position, with particular emphasis placed on complications and outcome (Table 12.1).[18,24] Some of the reported complications might have been prevented or reduced if the sitting position had not been used (Table 12.2).

ANESTHETIC CONSIDERATIONS

The practical significance of theoretic considerations regarding the choice of anesthetic drugs for patients who undergo posterior fossa surgery remains to be determined. First is the question of the effects of inhalational versus intravenous anesthetic drugs on the lungs' ability to retain air that enters the venous circulation, thus preventing its passage to the arterial circulation. Transpulmonary air passage occurs in humans and is supported by reports of cerebral air emboli in the absence of an intracardiac defect,[37] as well as detection of left-sided heart air on echocardiogram without demonstration of an intracardiac defect.[5] The intravenous anesthetics thiopental, fentanyl, and ketamine maintain a higher threshold for trapping air

Table 12.2 Posterior Fossa Craniotomy: Intraoperative Surgical Problems by Patient Position

Problem	Sitting Position*	Horizontal Position*
Total number of patients	333	246
Hypotension:		
With positioning	63 (19%)	60 (24%)
During procedure	86 (26%)	54 (22%)
Entire anesthetic	121 (36%)	94 (38%)
Without cardiac disease	101/297 (34%)	130/197 (34%)
With cardiac disease	30/36 (56%)	27/49 (55%)
Transfusion of > 2 units of blood	3%	13%†
Average blood replacement	359 mL	507 mL‡
Postoperative cranial nerve function:		
Improved	41 (12)	50 (20)§
Unchanged	218 (65)	112 (45)
Deteriorated	74 (22)	84 (34)

*Unless otherwise indicated, the first number is the number of patients affected, and the number in parentheses is the percentage of total patients.
†$P < .01$ (chi-square test).
‡$P < .05$ (Student t test).
§26% of patients in horizontal position had decompression for tic douloureux.
Adapted from Black S, Ockert DB, Oliver WC, et al: Outcome following posterior fossa craniotomy in patients in the sitting or horizontal positions. Anesthesiology 1988;69:49–56.

bubbles in the pulmonary circulation than inhaled agents.[21] Thus such agents may decrease the risk and severity of air emboli if they occur.

A second consideration is the maintenance of adequate CPP. Before surgical incision, administration of intravenous anesthetic drugs has been demonstrated to have less effect on cardiovascular function than inhalational anesthetics in patients placed in the sitting position.[38] Whether the relationship continues after the start of surgery has not been investigated.

A third issue is the potential benefit of preserving cardiovascular responsiveness to surgical manipulation of brainstem structures. In such instances, the avoidance of anticholinergic drugs or long-acting β-adrenergic blockers that would mask cardiovascular response may provide useful information to the surgeon and anesthesiologist.

An additional consideration surrounds the use of N_2O in cases in which the risk of VAE is increased. A prospective, randomized study of patients requiring posterior fossa exploration or cervical spine surgery demonstrated that 50% N_2O had no significant effect on the incidence or severity of VAE if the N_2O was discontinued when air was detected by Doppler ultrasonography. Its analgesic effect, rapid elimination and emergence characteristics, and facilitation of the postoperative neurologic assessment continue to make it a popular adjunct. However, fentanyl-based anesthesia with supplemental isoflurane has been administered with no difference in time to emergence from anesthesia between patients who received 50% N_2O and those who did not.[9]

Induction of Anesthesia

Direct arterial blood pressure monitoring established before induction of anesthesia allows tighter control of blood pressure and CPP during induction and intubation, especially in patients at risk for increased ICP. The use of a low-dose, narcotic-based (4 to 6 µg/kg fentanyl), muscle relaxant technique with 0.5 to 1.0 MAC volatile inhalational anesthetic after intravenous induction with thiopental or propofol affords adequate analgesia and amnesia, preservation of autonomic nervous system activity, and rapid awakening after discontinuation of the inhalational anesthetics, allowing an early postoperative neurologic examination if desired. Some anesthesiologists continue to use nitrous oxide in oxygen (typically 50%) unless air embolism occurs, but with agents such as desflurane, propofol, dexmedetomidine, remifentanil, and sufentanil there appears to be little advantage to nitrous oxide. A propofol infusion (50–100 µg/kg/min) often provides better surgical access than inhalational anesthetic alone. Remifentanil and sufentanil infusions have a MAC sparing effect on both propofol and inhaled agents. Moreover, they are effective as akinetic agents for unparalyzed patients (eg, cranial nerve monitoring). β-Adrenergic blocking drugs and direct-acting vasodilators may be used alone or in combination to treat increases in blood pressure (instead of anesthetics). Use of long-acting antihypertensive drugs is avoided until the patient has been placed in the operating position. The need for vasopressor administration may arise after induction of anesthesia or positioning, especially in chronically hypertensive or debilitated patients. Short-acting drugs, such as small boluses of ephedrine or phenylephrine, are usually effective. Rarely, after all correctable derangements such as hypovolemia have been ruled out, inotrope infusions may be required throughout the surgical procedure, but a cause for an underlying mechanism should be sought.

Verification of appropriate placement of the endotracheal tube after final positioning, but before surgical incision, is of utmost importance, regardless of the position employed. Intraoperative access to the airway is limited by virtue of the proximity of the operative site, and neck flexion or extension can produce caudad or cephalad displacement of the endotracheal tube, respectively, by as much as 2 cm. Palpation of the endotracheal tube cuff above the sternal notch is a useful maneuver to ensure that the tip of the endotracheal tube rises above the carina, though this is not possible with many types of endotracheal tubes.

Maintenance of Anesthesia

Controlled positive-pressure ventilation with paralysis has the following advantages:

- Maintenance of lighter levels of anesthesia
- Hyperventilation, which diminishes $PaCO_2$, thereby decreasing both sympathetic stimulation and blood pressure at any given depth of anesthesia
- Cerebral vasoconstriction
- Less bleeding
- Lower ICP
- Less cardiovascular depression because of decreased anesthetic depth
- Less likelihood of patient movement.

The MAC for desflurane (and presumably other anesthetic drugs) is not altered by the sitting position.[39] Excessive decreases in inhaled agent concentration as a strategy to combat hypotension may allow awareness. Intravenous anesthesia has been associated with smaller increases in CBF, and ICP, and less brain swelling, possibly improving surgical conditions.[40] Intraoperative hypothermia should be avoided. Glucose-containing solutions are not used because of the possible detrimental effects of hyperglycemia on areas of the brain at risk for cerebral ischemia.[41]

The administration of osmotic and loop diuretics for tumor resection and vascular procedures may predispose sitting patients to electrolyte disturbances or cardiovascular instability caused by hypovolemia.[42] Also, the size of the pneumocephalus may be increased.[30]

Emergence from Anesthesia

The anesthetic goals during emergence from anesthesia are to prevent abrupt rises in blood pressure, allow rapid awakening, return of motor strength, and minimize coughing and straining on the endotracheal tube. The feasibility of immediate postoperative extubation is determined by the nature and extent of surgery (eg, extensive brainstem manipulation with a greater likelihood of postoperative brainstem edema or brainstem injury caused by a difficult tumor resection) and the patient's preoperative neurologic condition.[43,44] If extensive manipulation of the medullary structures or significant edema is a factor, a secured airway should be maintained until the patient is awake, following commands, and demonstrating return of protective airway reflexes. Additional sedation may be required until this point of recovery is reached. Persistent postoperative hypertension and bradycardia in a previously normotensive patient should alert the anesthesiologist to possible brainstem compression, ischemia, or hematoma.

Postoperative nausea and vomiting (PONV) is a side effect of both anesthesia and surgery. Retching and vomiting can increase ICP and the risk of postoperative bleeding. The nonsedating antiemetics dexamethasone and ondansetron have been shown to reduce PONV by 25% each. Propofol has also been shown to reduce the incidence another 25%.[45]

VENOUS AIR EMBOLISM

Documentation of venous air embolism has existed for more than 100 years (Table 12.3). VAE is associated most often with posterior fossa procedures in the sitting position because of facilitation of air entry by subatmospheric pressure in an opened vein and the presence of noncollapsible venous channels such as diploic veins and dural sinuses. Cases in which air entered the venous circulation via burr holes or wounds from the skull head holder have also been reported, particularly when the head was elevated.[24,46,47] Often unappreciated is the potential for venous air embolism originating from the sites of central venous access. Air can be entrained around the site of catheter entry. Air embolism may also occur when central catheters are removed with the patient's head up.

Table 12.3 **Early Historical Perspective on Air Embolism**

Year(s)	Finding	Discoverer
1667	Death in animals when air enters vein	Redi
1681	Characteristic noise of air entrainment	Hardner
1683–1686	Right-heart dilation from air insufflation; mortality is rate- and dose-dependent	Camerarius, de Heyde
1800	First recorded case of air embolism during excision of a neck tumor (not realized until 30 years later)	Barlow
1811	Small air dose well tolerated; right ventricular distention is cause of death	Nysten
1818	Sudden death associated with hissing noise in young patient having clavicular tumor resection in sitting position	Bauchene
1821	Development of experimental surgery to investigate clinical findings	Magendie
1823	Treatment of air embolism during tumor resection by closing vein wound when hissing noise occurred	Wattmann
1832	Treatment for traumatic air embolism published (but overlooked)	Wattmann
1839	Establishment of conditions, treatment for venous air embolism in humans, including air aspiration	Amussat
1843	Approximately 40 cases of air embolism described	Various scientists
1845	Wattmann's work recognized	
1846	Concept and term "embolism" created	Virchow
1877	Paradoxical embolism associated with patent foramen ovale	Cohnheim
1885	Importance of head position in air entrainment	Senn

Compiled from Bedford RF: Semin Anesth 2:169-176, 1983; Lesky E: German Med Monthly 6:159-161, 1961; Senn N: Ann Surg 3:197-302, 1885 and Whitby JD: Anaesthesia 19:579-584, 1964.

VAE in neurosurgery is a subset of the larger problem of VAE in the medical population. Several reviews addressing this issue have been published.[48,49]

Pathophysiology

Review of the pathophysiologic effects of gas bubbles on the vascular endothelium suggests that a form of ischemia/reperfusion injury occurs that is common to all organs involved. During slow, continuous air entrainment, air is dissipated into the peripheral pulmonary circulation. The mechanical obstruction or local hypoxemia produced creates sympathetic reflex vasoconstriction. Microvascular bubbles can activate the endothelium, resulting in complement activation, cytokine release, and production of reactive O_2 molecules. Pulmonary manifestations include pulmonary hypertension, impairment of gas exchange and hypoxemia, CO_2 retention, increased pulmonary dead space, and decreased end-tidal CO_2 ($ETCO_2$).[50] Bronchoconstriction results in increased airway pressure. Reduced venous return leads to decreases in cardiac output and systemic arterial blood pressure.[51] Myocardial and cerebral ischemia may result from severe, persistent hypoxemia or hypotension.

A rapidly entrained air bolus may result in an air lock within the right side of the heart or a cumulative gas volume that exceeds pulmonary arterial capacity (estimated to be 5 mL/kg), blockage of the right ventricular outflow tract, air or blood layer formation with obstructed venous return, decreased cardiac output, acute right ventricular dilation and failure, myocardial and cerebral ischemia, dysrhythmias, and cardiovascular collapse.[51]

Morbidity and mortality are directly related to the amount and rate of air entry. The "symptomatic dose" of venous air is not well documented in humans, but in a review of the clinical manifestations of VAE,[52] more than 50 mL have been retrieved in patients manifesting clinical changes such as decreases in blood pressure, dysrhythmia, and ECG changes. This same review summarized a collection of 93 early case reports in which 37 of 40 (93%) untreated patients died, and the lethal dose of intravascular air in humans has been estimated to be greater than 300 mL. Factors contributing to the occurrence and severity of VAE include the surgical site, such as the posterior fossa, where venous channels are stented open by surrounding structures, and the extent of head elevation and negative pressure between the right atrium and the surgical site. VAE is more common and severe in posterior fossa craniotomies than in laminectomies.[24,53,54] The incidence is decreased by careful surgical dissection, hemostasis, and liberal use of bone wax. Hypovolemia lowers central venous pressure and increases the negative pressure gradient between the elevated head and the right side of the heart.

Incidence

A 1988 study reported the incidence of VAE to range from as low as 25% to as high as 60% in patients when the head is higher than the heart (Table 12.4).[55] Several later series have not changed this incidence but suggest that a higher incidence is detected when Doppler monitoring is used (43%) than with $ETCO_2$ monitoring (9–28%).[56–59] TEE is still the most sensitive (54%) detector of venous air.[11]

Table 12.4 Incidence of Venous Air Embolism in Posterior Fossa Surgery

Investigator(s)	Year Reported	Surgical Position	Incidence	Percentage of Patients with VAE	Method of Detection
Michenfelder et al.[60]	1969	Sitting	37/751	5	Right-atrial catheter, aspiration
Michenfelder et al.[61]	1972	Sitting	26/69	42	Right-atrial catheter, Doppler
Albin et al.[23]	1987	Sitting	100/400	25	Right-atrial catheter, Doppler
		Horizontal	13/118	11	Right-atrial catheter, Doppler
Marshall & Bedford[62]	1980	Sitting	20/52	38	Doppler only
			13/52	25	Doppler, ↑PAP, ↓$ETCO_2$
Voorhies et al.[63]	1983	Sitting	41/81	50	Doppler, PEEP (no right-atrial catheter)
Standefer et al.[64]	1984	Sitting	22/382	6	Right-atrial catheter, Doppler
Matjasko et al.[53]	1985	Sitting	130/554	23.5	Right-atrial catheter, Doppler ($ETCO_2$ in 94 pts)
Young et al.[54]	1986	Sitting	70/255	30	Right-atrial catheter, Doppler
Black et al.[14]*	1988	Sitting	150/333	45	Right-atrial catheter, Doppler
		Horizontal	30/246	12	Right-atrial catheter (33%), Doppler (30%)
Von Gösseln et al.[65]	1991	30- to 45-degree head elevation	46/704	6.5	Right-atrial catheter, Doppler, $ETCO_2$

*Mass spectroscopy after 1982.
Doppler, precordial Doppler ultrasonography; PAP, pulmonary artery pressure; PEEP, positive end-expiratory pressure; VAE, venous air embolism; ↑, increase; ↓, decrease.

Risks of Air Embolism

The greater the pressure gradient between cerebral veins and the right atrium and the lower the central venous pressures, the greater is the tendency for air to enter venous openings at the craniotomy site. The risk of catastrophic air embolism has been reduced dramatically by improved detection and prompt treatment of VAE.[60,66,67] More attention has been directed toward recognition and treatment of paradoxical air embolism (PAE).

Risks of Paradoxical Air Embolism

Clinical evidence of PAE in the perioperative period is less frequent than calculated estimates based on the incidence of VAE and the prevalence of PFO.[68] However, complications, such as myocardial or cerebral ischemia resulting from PAE, may be devastating.

The most likely mechanism of PAE in humans is right-to-left shunting through an intracardiac defect. A PFO is reported to exist in 20% to 30% of the population.[3] The likelihood of right-to-left shunt may be increased if the right atrial pressure exceeds left atrial pressure, and up to 50% of patients may experience reversal of an existing left-to-right atrial pressure gradient with the potential for PAE after 1 hour in the sitting position.

Although echocardiographic studies and numerous case reports describe its occurrence, the conditions under which PAE can occur through the pulmonary vascular bed in humans have not been well defined.[43,69,70] PAE to the cerebral circulation should be suspected in any patient who manifests an unexpected neurologic deficit after a surgical procedure known to be associated with a risk of air embolism, regardless of the intraoperative patient position.

Hypovolemia has been proposed as a predisposing factor to the occurrence of PAE as well as of VAE.[71] Intravenous fluid loading has been recommended to decrease the likelihood of right-to-left shunting and PAE in patients undergoing surgery in the sitting position.[72]

Use of Positive End-Expiratory Pressure

VAE and positive end-expiratory pressure (PEEP) may both increase right atrial pressure, and PEEP may raise cerebral venous pressure. PEEP has been proposed as a prophylactic measure against VAE.[73] However, it may impair surgical conditions, decrease venous return, and increase the chance that right atrial pressure will exceed left atrial pressure, thus predisposing an at-risk patient to PAE. Giebler and colleagues[74] found no reduction in the incidence of air embolism when they compared 10 cm PEEP with no PEEP in a prospective randomized study of patients operated on in the sitting position; these researchers suggested that the use of PEEP in sitting cases be abandoned. Jugular venous compression has been demonstrated to be effective in reducing air entry.[75,76]

Monitoring for Venous Air Embolism

Table 12.5 summarizes the monitors that may be used to detect VAE.

Doppler Ultrasound Transducer

The precordial Doppler ultrasound transducer is the most cost-effective sensitive device commonly available for the detection of air in the right atrium[77–79] (transesophageal echocardiography is more sensitive but also more invasive). Patient position influences air detection and retrieval.[80] Correct positioning of the Doppler probe over the right side of the heart may be difficult, especially in the morbidly obese.

The Doppler probe generates a 2.5-MHz continuous ultrasonic signal that is reflected by moving blood and cardiac

Table 12.5 Monitors for Detection of Venous Air Embolism

Monitor	Advantages	Disadvantages
Doppler	Most sensitive noninvasive monitor Earliest detector (before air enters pulmonary circulation)	Not quantitative May be difficult to place in obese patients, patients with chest wall deformity, or those in the prone/lateral positions False-negative result if air does not pass beneath ultrasonic beam (about 10% of cases); useless during electrocautery IV mannitol may mimic intravascular air
PA catheter	Quantitative, slightly more sensitive than $ETCO_2$ Widely available Placed with minimal difficulty in experienced hands Can detect right-atrial pressure greater than pulmonary capillary wedge pressure	Small lumen, less air aspirated than with right-atrial catheter Placement for optimal air aspiration may not allow pulmonary capillary wedge pressure measurement Nonspecific for air
$ETCO_2$	Noninvasive Sensitive Quantitative Widely available	Nonspecific for air Less sensitive than Doppler ultra, PA catheter Accuracy affected by tachypnea, low cardiac output, chronic obstructive pulmonary disease
TEE	Most sensitive detector of air Can detect air in left heart, aorta	Invasive, cumbersome Expensive Must be observed continuously Not quantitative May interfere with Doppler ultrasonography

Doppler, precordial Doppler ultrasonography; PA, pulmonary artery; TEE, transesophageal echocardiography.

structures,[61,81] and the frequency change between transmitted and reflected signal is electronically converted into a readily detectable audible sound. Small volumes of air are detected easily with the probe because air is a good acoustic reflector. The precordial probe is placed just to the right of the sternum and a few inches above the xiphoid, where maximal signal is detected. Position of the probe is confirmed by injection 5 mL of aerated saline[81,82] through a right atrial catheter and listening for the characteristic change in the Doppler tones.

Right Atrial Catheter

The right atrial catheter (RAC) is used to aspirate air entering the right side of the heart; air aspiration is therapeutic during episodes of VAE. This procedure is also useful in confirming the diagnosis of air embolism, particularly during electrocautery use, when the Doppler signal is obscured.[51,83] Optimal catheter placement requires that the orifice(s) be placed in or near the air–blood interface.[80,84,85]

The RAC is placed with a minimum of difficulty. Large-diameter catheters can retrieve large quantities of air, and aspiration of air has been demonstrated to be therapeutic when larger quantities have been entrained.[86] Disadvantages are that the catheter's position can change (especially after patient repositioning)[87] and that it may not retrieve all intravascular air. Multiple-orifice RACs are more effective than single-orifice catheters in aspirating air from the circulation.[23] There is greater air recovery with the tip at or 2 cm below the sinoatrial node. On the basis of modeling studies, with the RAC at an 80-degree atrial tilt, the proximal port should be located 1 to 3 cm above the sinoatrial node.[80]

Factors that influence air retrieval include catheter length and diameter, extent of patient inclination (retrieval is most efficient at 80%; retrieval at 60% is equal to that at 90%), number and size of orifices, and distance between orifices.[88–90] RAC positioning for optimal air aspiration can be accomplished with intravascular electrocardiography.[69,88] A method for ECG-guided catheter placement is performed as follows:

1. For the arm or neck, perform a venipuncture aseptically using a modified Seldinger technique.
2. Advance the catheter at least 20 cm via the arm or 15 cm via the neck.
3. Place a specially adapted conductive connector for ECG attachment (Arrow-Johans ECG adapter, Arrow International, Inc., Reading, PA) in the right atrial line next to the standard stopcock. Flushing the catheter with $NaHCO_3$ will reduce electrical impedance and improve the signal.
4. Set the ECG monitor for lead II and attach the right arm lead to the conductive connector. Some centers use lead V, which results in deflection of the P wave in the opposite direction.
5. Observe the ECG trace and pressure waveform on the monitor, and manipulate the catheter until the tip is in the right ventricle, and then withdraw it into the mid-right atrium to detect a biphasic P wave.
6. Withdraw the catheter until the P wave is approximately the height of the QRS complex (Fig. 12.1). Withdraw an additional centimeter, at which point the P wave should be slightly smaller than the QRS complex, and then secure the catheter.

The intracardiac ECG should be rechecked after the patient has been placed in the final position because sitting, as well as movement of the neck or the catheterized arm, may move the catheter.[87,88] Although a high incidence of catheter migration has been reported, the conductive connector should be removed after the patient is sitting and the catheter position has been reconfirmed in order to eliminate its electrical microshock hazard. The catheter tip should be withdrawn from the right atrium at the end of surgery to prevent atrial perforation.

Observation of the ECG configuration to confirm proper catheter placement in the right atrium is more precise than chest radiography. However, changes in the venous pressure waveform during pressure-wave transduction for catheter placement are reportedly as accurate as changes in the ECG waveform.[91] Pressure waveforms may be of greatest benefit in rechecking catheter position periodically throughout surgery. Schummer and colleagues[92] have questioned the accuracy of ECG configuration changes as a guide to central-line

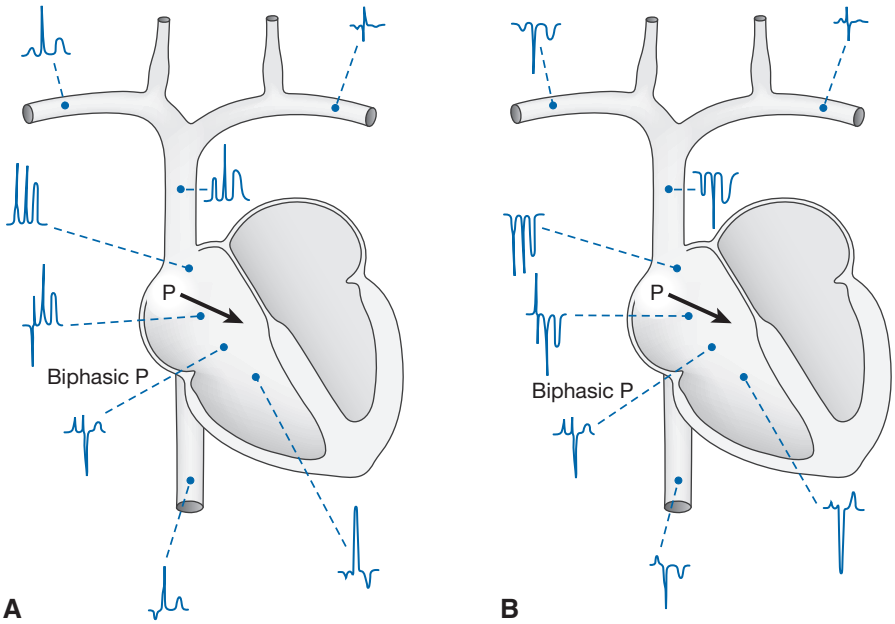


Fig. 12.1 Positioning a right atrial catheter. **A,** P wave changes seen with lead II as the sensing lead. **B,** P wave changes seen with lead V as the sensing lead. P represents the origin of the P wave vector at the sinoatrial node.

placement when the left internal jugular vein is used and suggested that the transesophageal echocardiograph or chest radiograph should be the final determinant of placement.

Pulmonary Artery Catheter

The PA catheter detects the pulmonary hypertension resulting from mechanical obstruction and reflex vasoconstriction from local hypoxemia caused by transpulmonary air.[93] PA pressure measurement is slightly more sensitive than capnography for detection of VAE; however, it is more invasive, and the PA catheter's lumen makes air aspiration more difficult than with larger catheters.

Capnography

Capnography ($ETCO_2$ monitoring) has a specific role in air embolism detection. Falls in $ETCO_2$ may suggest an increased arterial–to–end-tidal CO_2 gradient that occurs with the presence of intravascular air. Factors that may influence the capnograph's accuracy include rapid respiratory rate, low cardiac output, and chronic obstructive pulmonary disease.

Transesophageal Echocardiography

TEE detects air bubbles with a 3.5- to 5-MHz echocardiographic probe placed behind the heart; a visual image is produced with two-dimensional TEE[94,95] and, like Doppler ultrasonography, TEE detects air when it is still in the right side of the heart. A major advantage of TEE over other monitors currently available is that it can detect air in the left side of the heart and in the aorta. However, its detection of air bubbles is qualitative, not quantitative; and microbubbles can generate a dramatic image that may not be physiologically significant. The use of TEE in screening of anesthetized sitting patients for PFOs has been described.[10,11,96]

Complications Resulting from Venous Air Embolism

Table 12.6 summarizes the complications of venous air embolism in posterior fossa surgery.

Intraoperative Complications

Cardiovascular instability due to VAE may manifest in a number of ways. The most common dysrhythmia is premature ventricular contraction, but murmurs, tachycardia, bradycardia, and ventricular tachycardia may occur.[51,60,83] Hypertension and tachycardia may occur initially in response to air entry into the pulmonary microcirculation. Marked alterations in blood pressure and the characteristic changes in heart sounds usually do not appear until large emboli are present. Hypotension is most likely due to decreases in cardiac output associated with larger volumes of intravascular air.[51] However, the duration of changes in heart tones[97] may be brief (ie, < 5 minutes), although air is still present. ECG changes are generally too late to be useful diagnostically; however, evidence of transmural myocardial ischemia may indicate airflow into the coronary arteries.[98]

The extent of pulmonary dysfunction depends on the amount of air that reaches the pulmonary circulation.[99] Hypercapnia, hypoxemia, and pulmonary hypertension may be mild, moderate, or severe.

Pulmonary edema may follow both small and large air emboli. Its development is believed to involve mechanisms similar to those of clot emboli rather than neurogenic pulmonary edema. The association of pulmonary edema with elevations in pulmonary capillary wedge pressure can be used to distinguish it from neurogenic pulmonary edema, which after the acute sympathetic response is associated with a normal wedge pressure.[100,101] Damage to the pulmonary vascular endothelium may result from repeated bouts of pulmonary hypertension.[102] Perfusion defects similar to those found in instances of pulmonary clot emboli have been described after pulmonary air embolism.[103] Their distinguishing feature is the more rapid resolution of the defect.

Postoperative Complications

Complications arising from air embolism primarily involve the central nervous, cardiovascular, and pulmonary systems. Neurologic deficits, stroke, and coma may result from surgical manipulation, hypoxic or ischemic injury, or cerebral air embolism. Dose and rate of air entrainment appear to influence the clinical findings. Increases in ICP appear to be associated with more severe injury.

Available studies in humans have been unable to correlate morbidity and mortality with the volume of cerebral arterial air introduced. However, clear laboratory findings and clinical evidence have shown that cerebral air can produce brain injury.[104,105] Other studies have reported altered sensorium, seizures, hemiplegia, monoplegia, hemianesthesia, hemianopsia, nystagmus, strabismus, and respiratory disturbances. A case report described suspected arterial air embolism from an indeterminate volume of air flushed retrograde through a radial artery catheter.[106]

Table 12.6 **Complications of Venous Air Embolism**

Location	Intraoperative Complications	Postoperative Complications
Cardiovascular	Dysrhythmias	Myocardial ischemia
	Hypotension/hypertension	Right-ventricular failure
	Changes in heart sounds, murmurs	
	Electrocardiographic evidence of ischemia	
	Acute right-ventricular failure	
	Cardiac arrest	
Pulmonary	Hypercarbia	Perfusion defects
	Hypoxemia	
	Pulmonary hypertension	
	Pulmonary edema	
Central nervous system	Hyperemia Brain swelling	Neurologic deficits, stroke, coma

Potential postoperative cardiovascular complications resulting from VAE include right ventricular failure (from pulmonary hypertension) and myocardial ischemia (from coronary air embolism or right-sided heart strain). Postoperative pulmonary edema may produce chest radiograph abnormalities and perfusion defects, but it is usually self-limited and responsive to conservative therapy, such as supplemental O_2 or small doses of furosemide.[103,107]

Prevention of Air Embolism

No maneuver is 100% effective in preventing the occurrence of VAE if a gradient exists between the operative site and the right atrium, regardless of patient position. However, the incidence and severity can be decreased by the use of controlled positive-pressure ventilation, adequate hydration, positioning so that head elevation is the lowest possible while still providing good surgical exposure, meticulous surgical technique with careful dissection and liberal use of bone wax, avoidance of N_2O in patients with known intracardiac defects, and avoidance of drugs that may increase venous capacitance (eg, nitroglycerin).

Treatment of Venous Air Embolism

Box 12.2 summarizes the treatment of VAE.

Intraoperative Period

The intraoperative goals in the treatment of VAE are to stop further air entry, remove air already present, and correct hypotension, hypoxemia, and hypercapnia. If Doppler ultrasonography changes occur or $ETCO_2$ decreases more than 2 mmHg, the surgeon should be informed immediately.

Jugular compression has been shown to be effective in raising dural sinus pressure in patients in both the supine and sitting positions.[75] However, there is concern that the technique of jugular venous compression may cause the following:

- Cerebral venous outflow obstruction with a resulting decrease in cerebral blood flow
- Carotid artery compression or dislodgment of atherosclerotic plaques
- Venous engorgement, leading to brain swelling and cerebral edema
- Carotid sinus compression and bradycardia. Maintenance of CPP greater than 50 mmHg in normotensive patients should minimize the risk of cerebral hypoperfusion. Higher perfusion pressures should be maintained in patients with chronic hypertension.

BOX 12.2 Treatment of Venous Air Embolism

Intraoperative Goals

1. Inform surgeon immediately
2. Discontinue N_2O, increase O_2 flows
3. Modify the anesthetic
4. Have the surgeon flood the surgical field with fluids
5. Provide jugular vein compression
6. Aspirate the right atrial catheter
7. Provide cardiovascular support
8. Change the patient's position.

Postoperative Goals

1. Provide supplemental O_2
2. Perform electrocardiography, chest radiographs
3. Measure serial arterial blood gas levels
4. If arterial air emboli are suspected, provide hyperbaric oxygen compression if available.

Aspiration of the RAC should be initiated as quickly as possible after Doppler ultrasonography or TEE detection of intravascular air. This maneuver has been demonstrated as effective in reducing morbidity from VAE.[51,60,83,86]

Patient position should be changed to lower the head to heart level when feasible. Other measures include increasing intravenous fluid administration, vasopressors if hypotension occurs, antidysrhythmics, and modification of the anesthetic technique in the absence of N_2O with more anesthetic drugs. Intravenous anesthesia will not be affected by the V/Q mismatch. External cardiac massage has been shown to be effective in disrupting a large air lock in the event of cardiovascular collapse.[108] Changing the patient's position to left lateral decubitus to limit airflow through the pulmonary outflow tract is of limited benefit in the presence of a continuous stream of air. The surgeon should flood the field with saline. PEEP or Valsalva maneuver may increase the likelihood of PAE after VAE has occurred and should, therefore, be avoided.[1,5,6,74] On the basis of data from a porcine model of cerebral air embolism, hyperventilation is not helpful.[109,110]

Postoperative Period

Postoperative goals in the treatment of VAE include prevention of hypoxemia or other respiratory compromise, detection and treatment of myocardial ischemia, and treatment of clinical evidence of PAE. Air bubbles in the retinal vessels, seen through funduscopic examination, have been described as a diagnostic sign for cerebral air embolism. In patients with suspected cerebral air embolism, a CT scan may aid in the diagnosis. However, radiographic evidence of cerebral air may vary among patients, initial CT scans may be normal, and the findings may change over time.[111,112] The role of magnetic resonance imaging in the diagnosis of air embolism remains to be determined. Magnetic resonance imaging has been described as more sensitive than CT in detecting ischemic cerebral and diving-related spinal injuries.[113]

Annane and coworkers[114] demonstrated that experimental cerebral air embolism in beagles is cleared faster when the animals undergo mechanical ventilation with 100% oxygen than for spontaneous ventilation on room air. Because patients undergoing posterior fossa surgery are already intubated, this finding would not change practice; however, patients with suspected, neurologically significant cerebral air detected after extubation might benefit from reintubation.

Hyperbaric oxygen (HBO) therapy for the treatment of suspected cerebral air embolism is used when appropriate equipment is available. Rapid application of very high pressure reduces air bubble volume, which should speed elimination of dissolved gas and reduce cerebral edema.[115] Numerous reports, some dramatic, describe the benefits of HBO therapy for decompression sickness and arterial gas embolism.[116] In a review of 86 patients treated for iatrogenic air embolism between 1980 and 1999, Blanc and colleagues[117] found better neurologic outcome when therapy was started less than 6 hours from the time of insult. Thus, if HBO is to be used, treatment should be started as soon as possible.

Electrophysiologic Monitoring

Various forms of monitoring, such as raw or processed electroencephalogram (EEG), brainstem auditory evoked potentials (BAEPs), and somatosensory and motor nerve stimulation, are being used with increasing frequency to determine the integrity of cerebral function during posterior fossa surgery. Such monitoring is used in selected intracranial, spinal, and cerebrovascular procedures and is generally handled by experienced electrophysiologists. Bimodal or multimodal

measurements of EEG, BAEPs, SSEPs, and cranial nerves (CN) have been advocated as a more effective means of monitoring central nervous system function for posterior fossa surgery than single-modality monitoring.[118]

Brainstem Auditory Evoked Potentials

BAEPs are robust signals that are minimally influenced by the type or depth of anesthesia. Cranial nerve VIII monitoring during acoustic neuroma resection or microvascular decompression has been advocated to help preserve nerve VIII function.[119–121] Bilateral changes in BAEPs are indicative of brainstem compromise.[122,123] Normalization of BAEPs during emergency posterior fossa decompression has been used to guide postoperative management and timing of extubation.

Somatosensory Evoked Potentials

SSEPs may be of use in detecting morbidity from cerebral air embolism,[124] spinal cord ischemia caused by hypotension, stretch of the cord due to excessive neck flexion, and pneumocephalus.[125] Monitoring of short-latency SSEPs, which monitor subcortical components of central sensory pathways, has been advocated for surgery on the cervical cord and posterior fossa.[64] Long-latency components of SSEPs may be difficult to evaluate because of greater variability in both latency and amplitude. SSEPs have also been shown to help detect peripheral neuronal injury for long cases in the positions described earlier.[126]

Electroencephalogram

EEG signals provide information regarding depth of anesthesia because they are sensitive to both inhalational and intravenous anesthetics. Intraoperative EEG monitoring during posterior fossa surgery can detect decreased cortical responses resulting from deep anesthesia or ischemia. The information from the cortical components of SSEPs is similar to that from EEG signals.

Cranial Nerve Monitoring

Monitoring of cranial nerves (VII, IX, X and XII) may help reduce complications of surgical dissection and manipulation for resection of acoustic neuromas and microvascular decompression.[119] Muscle paralysis, which can interfere with the signal, should be significantly reduced or avoided when muscle stimulation is required. In the unparalyzed patient, CN monitoring may be useful in gauging the depth of anesthesia, preventing premature emergence, self-extubation, or movement in surgical frames resulting in serious injury.[127]

SUMMARY

The patient undergoing posterior fossa surgery poses challenges to the anesthesiologist in terms of preoperative evaluation, positioning, choice of anesthetic agents, and monitoring, particularly for prevention of air embolism and preservation of neurologic function. The goals of monitoring are maintenance of hemodynamic stability and early detection of air embolism. Active clinical and basic science investigations continue to improve the means by which these challenges may be met in optimal fashion.

REFERENCES

1. Cucchiara RF, Seward JB, Nishimura RA, et al. Identification of patent foramen ovale during sitting position craniotomy by transesophageal echocardiography with positive airway pressure. *Anesthesiology*. 1985;63:107–109.
2. Guggiari M, Lechat Ph, Garen-Colonne C, et al. Early detection of patent foramen ovale by two-dimensional contrast echocardiography for prevention of paradoxical air embolism during sitting position. *Anesth Analg*. 1988;67:192–194.
3. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59:17–23.
4. Banas JS, Meister SG, Gazzaniga AB, et al. A simple technique for detecting small defects in the atrial septum. *Am J Cardiol*. 1971;28:467–471.
5. Kronik G, Mosslacher H. Positive contrast echocardiography in patients with patent foramen ovale and normal right heart hemodynamics. *Am J Cardiol*. 1982;49:1806–1809.
6. Lynch JJ, Schuchard GH, Gross CM, et al. Prevalence of right-to-left atrial shunting in a healthy population: Detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol*. 1984;53:1478–1480.
7. Black S, Muzzi DA, Nishimura RA, et al. Preoperative and intraoperative echocardiography to detect right-to-left shunt in patients undergoing neurosurgical procedures in the sitting position. *Anesthesiology*. 1990;72:436–438.
8. Cucchiara RF, Nishimura RA, Black S. Failure of preoperative echo testing to prevent paradoxical air embolism: Report of two cases. *Anesthesiology*. 1989;71:604–607.
9. Losasso TJ, Muzzi DA, Dietz NM, et al. Fifty percent nitrous oxide does not increase the risk of venous air embolism in neurosurgical patients operated upon in the sitting position. *Anesthesiology*. 1992;77:21–30.
10. Papadopoulos G, Kuhly P, Brock M, et al. Venous and paradoxical air embolism in the sitting position: A prospective study with transesophageal echocardiography. *Acta Neurochir*. 1994;126:140–143.
11. Feigl GC, Decker K, et al. Neurosurgical procedures in the semisitting position: Evaluation of the risk of paradoxical venous air embolism in patients with a patent foramen ovale. *World Neurosurg*. 2014;81:159–164.
12. Troianos CA, Jobes DR, Ellison N. Ultrasound-guided cannulation of the internal jugular vein: A prospective, randomized study. *Anesth Analg*. 1991;72:823–826.
13. Colley PS, Dunn R. Prevention of blood pressure response to skull-pin head holder by local anesthesia. *Anesth Analg*. 1979;58:241–243.
14. Black S, Ockert DB, Oliver WC, et al. Outcome following posterior fossa craniotomy in patients in the sitting or horizontal positions. *Anesthesiology*. 1988;69:49–56.
15. Coonan TJ, Hope CE. Cardio-respiratory effects of change of body position. *Can Anaesth Soc J*. 1983;30:424–437.
16. Darymple DG, MacGowan SW, MacLeod GF. Cardiorespiratory effects of the sitting position in neurosurgery. *Br J Anaesth*. 1979;51:1079–1081.
17. Enderby GEH. Postural ischaemia and blood pressure. *Lancet*. 1954;266:185–187.
18. Albin MS, Babinski M, Maroon JC, et al. Anesthetic management of posterior fossa surgery in the sitting position. *Acta Anaesthesiol Scand*. 1976;20:117–128.
19. Millar RA. Neuroanesthesia in the sitting position. *Br J Anaesth*. 1972;44:495.
20. Whitby JD. Electrocardiography during posterior fossa operations. *Br J Anaesth*. 1963;35:624–630.
21. Butler BD, Leiman BC, Katz J. Arterial air embolism of venous origin in dogs: Effect of nitrous oxide in combination with halothane and pento-barbitone. *Can J Anaesth*. 1987;34:570–576.
22. Munson ES, Merrick HC. Effects of nitrous-oxide on venous air embolism. *Anesthesiology*. 1986;27:783–787.
23. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerning detection of venous air embolism. *Neurosurgery*. 1978;3:380–384.
24. Cabezudo JM, Gilsanz F, Vaquero J, et al. Air embolism from wounds from a pin-type head-holder as a complication of posterior fossa surgery in the sitting position. *J Neurosurg*. 1981;55:147–148.
25. Artru AA. Nitrous oxide plays a direct role in the development of tension pneumocephalus intraoperatively. *Anesthesiology*. 1982;57:59–61.
26. Artru AA. Breathing nitrous oxide during closure of the dura and cranium is not indicated. *Anesthesiology*. 1987;66:719.
27. Skahen S, Shapiro HM, Drummond JC, et al. Nitrous oxide withdrawal reduces intracranial pressure in the presence of pneumocephalus. *Anesthesiology*. 1986;65:192–196.
28. Friedman GA, Norfeet EA, Bedford RF. Discontinuance of nitrous oxide does not prevent pneumocephalus. *Anesth Analg*. 1981;60:57–58.
29. Di Lorenzo N, Caruso R, Floris R, et al. Pneumocephalus and tension pneumocephalus after posterior fossa surgery in the sitting position: A prospective study. *Acta Neurochir (Wien)*. 1986;83:112–115.
30. Toung TJK, McPherson RW, Ahn H, et al. Pneumocephalus: effects of patient position on the incidence and location of aerocele after posterior fossa and upper cervical cord surgery. *Anesth Analg*. 1986;65:65–70.
31. Kishan A, Naidu MR, Muralidhar K. Tension pneumocephalus following posterior fossa surgery in sitting position: A report of 2 cases. *Clin Neurol Neurosurg*. 1990;92:245–248.
32. Kitahata LM, Katz JD. Tension pneumocephalus after posterior fossa craniotomy: A complication of the sitting position. *Anesthesiology*. 1976;45:578.
33. MacGillivray RG. Pneumocephalus as a complication of posterior fossa surgery in the sitting position. *Anaesthesia*. 1982;37:722–725.

34. McPherson RW, Toung TJK, Johnson RM, et al. Intracranial subdural gas: A cause of false-positive change of intraoperative somatosensory evoked potential. *Anesthesiology*. 1985;62:816–819.
35. Schubert A, Zornow MH, Drummond JC, et al. Loss of cortical evoked responses due to intracranial gas during posterior fossa craniectomy in the seated position. *Anesth Analg*. 1986;65:203–206.
36. Rayport M. The head-elevated positions: neurosurgical aspects: Approaches to the occiput and cervical spine. In: Martin JT, ed. *Positioning in Anesthesia and Surgery*. ed 2. Philadelphia: WB Saunders; 1987.
37. Black M, Calvin J, Chan KL, et al. Paradoxic air embolism in the absence of an intracardiac defect. *Chest*. 1991;99:754–755.
38. Marshall WK, Bedford RF, Miller ED. Cardiovascular responses in the seated position: Impact of four anesthetic techniques. *Anesth Analg*. 1983;62:648–653.
39. Lin C-M, Wu C-T, Lee S-T, et al. Sitting position does not alter minimum alveolar concentration for desflurane. *Can J Anaesth*. 2007;54:523–530.
40. Cole CD, Gottfried OH, Gupta DK, et al. Total intravenous anesthesia: Advantages for intracranial surgery. *Neurosurgery*. 2007;61:369–377.
41. Sieber FE, Smith DS, Traystman RJ, et al. Glucose: A reevaluation of its intraoperative use. *Anesthesiology*. 1987;67:72–81.
42. Cottrell JE, Robustelli A, Post K, et al. Furosemide and mannitol-induced changes in intracranial pressure and serum osmolarity and electrolytes. *Anesthesiology*. 1977;47:28–30.
43. Artru AA, Cucchiara RF, Messick JM. Cardiorespiratory and cranial nerve sequelae of surgical procedures involving the posterior fossa. *Anesthesiology*. 1980;52:83–86.
44. Howard R, Mahoney A, Thurlow AC. Respiratory obstruction after posterior fossa surgery. *Anaesthesia*. 1990;45:222–224.
45. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of post operative nausea and vomiting. *N Engl J Med*. 2004;350:2441–2451.
46. Edelman JD, Wingard DW. Air embolism arising from burrholes. *Anesthesiology*. 1980;53:167–168.
47. Wilkins RH, Albin MS. An unusual entrance site of venous air embolism during operation in the sitting position. *Surg Neurol*. 1977;7:71.
48. Mirski MA, Lele AV, Fitzsimmons L, et al. Diagnosis and treatment of vascular air embolism. *Anesthesiology*. 2007;106:164–177.
49. Muth CM, Shank ES. Gas embolism. *N Engl J Med*. 2000;342:476–482.
50. Pftzner J, Petito SP, McLean AG. Hypoxaemia following sustained low-volume venous air embolism in sheep. *Anaesth Intensive Care*. 1988;16:164–170.
51. Adornato DC, Gildenberg PL, Ferrario CM, et al. Pathophysiology of intra venous air embolism in dogs. *Anesthesiology*. 1978;49:120–127.
52. Gottlieb JD, Ericsson JA, Sweet RB. Venous air embolism: A review. *Anesth Analg*. 1963;44:773–778.
53. Matjasko J, Petrozza P, Cohen M, et al. Anesthesia and surgery in the seated position: Analysis of 554 cases. *Neurosurgery*. 1985;17:695–702.
54. Young ML, Smith DS, Murtagh F, et al. Comparison of surgical and anesthetic complications in neurosurgical patients experiencing venous air embolism in the sitting position. *Neurosurgery*. 1986;18:157–161.
55. Gottdiener JS, Papademetriou V, Notargiacomo A, et al. Incidence and cardiac effects of systemic venous air embolism: Echocardiographic evidence of arterial embolization via noncardiac shunt. *Arch Intern Med*. 1988;148:795–800.
56. Domaingue CM. Neurosurgery in the sitting position: A case series. *Anaesth Intensive Care*. 2005;33:332–335.
57. Bithal PK, Pandia MP, Dash HH, et al. Comparative incidence of venous air embolism and associated hypotension in adults and children operated for neurosurgery in the sitting position. *Eur J Anaesthesiol*. 2004;21:517–522.
58. Rath GP, Bithal PK, Chaturvedi A, et al. Complications related to positioning in posterior fossa craniectomy. *J Clin Neurosci*. 2007;14:520–525.
59. Leslie K, Hui R, Kaye AH. Venous air embolism and the sitting position: A case series. *J Clin Neurosci*. 2006;13:419–422.
60. Michenfielder JD, Martin JT, Altenburg BM, et al. Air embolism during neurosurgery: An evaluation of right atrial catheters for diagnosis and treatment. *JAMA*. 1969;208:1353–1358.
61. Michenfielder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. *Anesthesiology*. 1972;36:164–168.
62. Marshall MK, Bedford RF. Use of a pulmonary-artery catheter for detection and treatment of venous air embolism: A prospective study in man. *Anesthesiology*. 1980;52:131–134.
63. Voorhies RM, Fraser RA, Van Poznak A. Prevention of air embolism with positive end expiratory pressure. *Neurosurgery*. 1983;12:503–506.
64. Standefer M, Bay JW, Trusso R. The sitting position in neurosurgery: A retrospective analysis of 488 cases. *Neurosurgery*. 1984;14:649–659.
65. Von Gösseln H, Samii M, Suhr D, et al. The lounging position for posterior fossa surgery: Anesthesiological considerations regarding air embolism. *Childs Nerv Syst*. 1991;7:568–574.
66. Bedford RF. Perioperative venous air embolism. *Semin Anesth*. 1987;6:163–170.
67. Michenfielder JD. The 27th Rovenstine Lecture: Neuroanesthesia and the achievement of professional respect. *Anesthesiology*. 1989;70:695–701.
68. Black S, Muzzi DA, Nishimura RA, et al. Preoperative and intraoperative echocardiography to detect right-to-left shunt in patients undergoing neurosurgical procedures in the sitting position. *Anesthesiology*. 1990;72:436–438.
69. Bowdle TA, Artru AA. Positioning the air aspiration pulmonary artery catheter introducer sheath by intravascular electrocardiography. *Anesthesiology*. 1988;69:276–279.
70. Marquez J, Sladen A, Gendell H, et al. Paradoxical cerebral air embolism without an intracardiac septal defect. *J Neurosurg*. 1981;55:997–999.
71. Pftzner J, McLean AG. Venous air embolism and active lung inflation at high and low CVP: A study in upright anesthetized sheep. *Anesth Analg*. 1987;66:1127–1134.
72. Colohan ART, Perkins NAK, Bedford RF, et al. Intravenous fluid loading as prophylaxis for paradoxical air embolism. *J Neurosurg*. 1985;62:839–842.
73. Perkins NAK, Bedford RF. Hemodynamic consequences of PEEP in seated neurosurgical patients: Implications for paradoxical air embolism. *Anesth Analg*. 1984;63:429–432.
74. Giebler R, Kollenberg B, Pohlen G, et al. Effect of positive end-expiratory pressure on the incidence of venous air embolism and on the cardiovascular response to the sitting position during neurosurgery. *Br J Anaesth*. 1998;80:30–35.
75. Grady MS, Bedford RF, Park TS. Changes in superior sagittal sinus pressure in children with head elevation, jugular venous compression and PEEP. *J Neurosurg*. 1986;65:199–202.
76. Toung TJK, Miyabe M, McShane AJ, et al. Effect of PEEP and jugular venous compression on canine cerebral blood flow and oxygen consumption in the head elevated position. *Anesthesiology*. 1988;68:53–58.
77. Edmonds-Seal J, Maroon JC. Air embolism diagnosed with ultrasound. *Anaesthesia*. 1969;24:438–440.
78. Edmonds-Seal J, Prys-Roberts C, Adams AP. Air embolism: A comparison of various methods of detection. *Anaesthesia*. 1971;26:202–208.
79. Gildenberg PL, O'Brien RP, Britt WJ, et al. The efficacy of Doppler monitoring for the detection of venous air embolism. *J Neurosurg*. 1981;54:75–78.
80. Bunegin L, Albin MS, Helsel PE, et al. Positioning the right atrial catheter: A model for reappraisal. *Anesthesiology*. 1981;55:343–348.
81. Maroon JC, Albin MS. Air embolism diagnosed by Doppler ultrasound. *Anesth Analg*. 1974;53:399–402.
82. Tinker JH, Gronert GA, Messick JM, et al. Detection of air embolism: A test for positioning of right atrial catheter and Doppler probe. *Anesthesiology*. 1975;43:104–105.
83. Alvaran SB, Toung JK, Graff TE, et al. Venous air embolism: Comparative merits of external cardiac massage, intracardiac aspiration, and left lateral decubitus position. *Anesth Analg*. 1978;57:166–170.
84. Bunegin L, Albin MS. Balloon catheter increases air capture. *Anesthesiology*. 1982;57:66–67.
85. Diaz PM. Balloon catheter should increase recovery of embolized air. *Anesthesiology*. 1982;57:66.
86. Colley PS, Artru AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in upright dogs. *Anesth Analg*. 1989;68:298–301.
87. Lee DS, Kuhn J, Shaffer MJ, et al. Migration of tips of central venous catheters in seated patients. *Anesth Analg*. 1984;63:949–952.
88. Colley PS, Artru AA. ECG-guided placement of Sorenson CVP catheters via arm veins. *Anesth Analg*. 1984;63:953–956.
89. Johans TG. Multi-orifced catheter placement with an intravascular electrocardiographic technique. *Anesthesiology*. 1986;64:411–413.
90. Warner DO, Cucchiara RF. Position of proximal orifce determines electrocardiogram recorded from multiorifced catheter. *Anesthesiology*. 1986;65:235–236.
91. Mongan P, Peterson RE, Culling RD. Pressure monitoring can accurately position catheters for air embolism aspiration. *J Clin Monit*. 1992;8:121–125.
92. Schummer W, Herrmann S, Schummer C, et al. Intra-atrial ECG is not a reliable method for positioning left internal jugular vein catheters. *Br J Anaesth*. 2003;91:481–486.
93. Munson ES, Paul WC, Perry JC, et al. Early detection of venous air embolism using a Swan-Ganz catheter. *Anesthesiology*. 1975;42:223–226.
94. Glenski JA, Cucchiara RF, Michenfielder JD. Transesophageal echocar-diography and transcutaneous O_2 and CO_2 monitoring for detection of venous air embolism. *Anesthesiology*. 1986;64:541–545.
95. Sato S, Toya S, Ohira T, et al. Echocardiographic detection and treatment of intraoperative air embolism. *J Neurosurg*. 1986;64:440–444.
96. Mammoto T, Hayashi Y, Osnishi Y, et al. Incidence of venous and paradoxical air embolism in neurosurgical patients in the sitting position:

Detection by transesophageal echocardiography. *Acta Anaesthesiol Scand*. 1998;42:643–647.
97. Whitby JD. Early cases of air embolism. *Anaesthesia*. 1964;19:579–584.
98. Durant TM, Oppenheimer MJ, Webster MR, et al. Arterial air embolism. *Am Heart J*. 1949;38:481–500.
99. Lesky E. Notes on the history of air embolism. *German Med Monthly*. 1961;6:159–161.
100. Chandler WF, Dimsheff DG, Taren JA. Acute pulmonary edema following venous air embolism during a neurosurgical procedure. *J Neurosurg*. 1974;40:400–404.
101. Peterson BT, Petrini MF, Hyde RW, et al. Pulmonary tissue volume in dogs during pulmonary edema. *J Appl Physiol*. 1978;44:782–795.
102. Ohkuda K, Nakahara K, Binder A, et al. Venous air emboli in sheep: Reversible increase in lung microvascular permeability. *J Appl Physiol*. 1981;51:887–894.
103. Sessler CN, Kiser PE, Raval V. Transient pulmonary perfusion scintigraphic abnormalities in pulmonary air embolism. *Chest*. 1989;95:910–912.
104. Gronert GA, Messick JM, Cucchiara RF, et al. Paradoxical air embolism from a patent foramen ovale. *Anesthesiology*. 1979;50:548–549.
105. Mills NL, Ochsner JL. Massive air embolism during cardiopulmonary bypass: Causes, prevention, and management. *J Thorac Cardiovasc Surg*. 1980;80:708–717.
106. Chang C, Dughi J, Shitabata P, et al. Air embolism and the radial arterial line. *Crit Care Med*. 1988;16:141–143.
107. Perschau RA, Munson ES, Chapin JC. Pulmonary interstitial edema after multiple venous air emboli. *Anesthesiology*. 1976;45:364–366.
108. Ericsson JA, Gottlieb JD, Sweet RB. Closed-chest cardiac massage in the treatment of venous air embolism. *N Engl J Med*. 1964;270:1353–1354.
109. Hirabuki N, Miura T, Mitomo M, et al. Changes of cerebral air embolism shown by computed tomography. *Br J Radiol*. 1988;61:252–255.
110. Muth C-M, Shank ES. Cerebral arterial gas embolism: Should we hyperventilate these patients? *Intensive Care Med*. 2004;30:742–743.
111. van Hulst RA, Haitsma JJ, Lameris TW, et al. Hyperventilation impairs brain function in acute cerebral air embolism in pigs. *Intensive Care Med*. 2004;30:944–950.
112. Jensen ME, Lipper MH. CT in iatrogenic cerebral air embolism. *AJNR Am J Neuroradiol*. 1986;7:823–827.
113. Warren Jr LP, Djang WT, Moon RE, et al. Neuroimaging of scuba diving injuries to the CNS. *Am J Roentgenol*. 1988;151:1003–1008.
114. Annane D, Troche G, Delisle F, et al. Effects of mechanical ventilation with normobaric oxygen therapy on the rate of air removal from cerebral arteries. *Crit Care Med*. 1994;22:851–857.
115. Dutka AJ. A review of the pathophysiology and potential application of experimental therapies for cerebral ischemia to the treatment of cerebral arterial gas embolism. *Undersea Biomed Res*. 1985;12:403–421.
116. Dutka AJ. Air or gas embolism. In: Camporesi EM, Barker AC, eds. *Hyperbaric Oxygen Therapy: A Critical Review*. Bethesda: Undersea and Hyperbaric Medical Society; 1991:1–10.
117. Blanc P, Boussuges A, Henriette K, et al. Iatrogenic cerebral air embolism: importance of an early hyperbaric oxygenation. *Intensive Care Med*. 2002;28:559–563.
118. Schramm J, Watanabe E, Strauss C, et al. Neurophysiologic monitoring in posterior fossa surgery. I: Technical principles, applicability and limitations. *Acta Neurochir (Wien)*. 1989;98:9–18.
119. Linden RD, Tator CH, Benedict D, et al. Electrophysiological monitoring during acoustic neuroma and other posterior fossa surgery. *Can J Neurol Sci*. 1988;15:73–81.
120. Radtke RA, Erwin CW, Wilkins RH. Intraoperative brainstem auditory evoked potentials: Signifcant decrease in postoperative morbidity. *Neurology*. 1989;39:187–191.
121. Watanabe E, Schramm J, Strauss C, et al. Neurophysiologic monitoring in posterior fossa surgery. II: BAEP waves I and V and preservation of hearing. *Acta Neurochir (Wien)*. 1989;98:118–128.
122. Grundy BL, Linda A, Procopio PT, et al. Reversible evoked potential changes with retraction of the eighth cranial nerve. *Anesth Analg*. 1981;60:835–838.
123. Radtke RA, Erwin CW. Intraoperative monitoring of auditory and brain-stem function. *Neurol Clin*. 1988;6:899–915.
124. Reasoner DK, Dexter F, Hindman BJ, et al. Somatosensory evoked potentials correlate with neurological outcome in rabbits undergoing cerebral air embolism. *Stroke*. 1996;27:1859–1864.
125. Sloan T. The incidence, volume, absorption, and timing of supratentorial pneumocephalus during posterior fossa neurosurgery conducted in the sitting position. *J Neurosurg Anesthesiol*. 2010;22:59–66.
126. Anastasian ZH, Ramnath B, Komotar RJ, et al. Evoked potential monitoring identifies possible neurological injury during positioning for craniotomy. *Anesth Analg*. 2009;109:817–821.
127. Prell J, Rampp S, Ache J, et al. The potential of quantified lower cranial nerve EMG for monitoring of anesthetic depth. *J Neurosurg Anesthesiol*. 2012;24:139–145.

Anesthetic Management of Cerebral Aneurysm Surgery

13

R.P. Pong • A.M. Lam

Although it is simplistic, the statement by the British neurosurgeon J. Gillingham that "in the early years anesthetists spent their time pushing the brain out of the skull while in recent times they have been sucking it back in"[1] underscores the importance and contribution of neuroanesthesia to the improved results of the surgical treatment of cerebral aneurysms. Other advances are the improvements in microsurgical instrumentation such as the operating microscope, neuroradiology, neurophysiologic monitoring, and the development of specialized centers with surgeons and anesthesiologists dedicated to the treatment of patients with cerebral aneurysms. However, data published from the International Cooperative Study on the Timing of Aneurysm Surgery (Cooperative Study) in 1990 indicated that overall surgical mortality was high, at approximately 20%.[2,3] To a certain extent these results might have been biased because of the trend toward early operative intervention in high-risk patients who were previously considered unsuitable for surgery. Nonetheless, even patients admitted in good condition with a level of consciousness score equivalent to Hunt and Hess grades I and II (see later discussion) have a "good" recovery rate of only 58% and a mortality rate of 26%.[2] Thus, much room exists for improvement in all aspects of cerebral aneurysm treatment. Efforts at improving outcome and mortality seem to be making some progress: in 2002 mortality rates were about 8%; however, the rates for those with a good outcome remained about the same at 64–75%.[4] Considerable variations in mortality and morbidity exist among centers of the Cooperative Study, the reasons for which are not apparent. The leading causes of death and disability were, in descending order, vasospasm, the direct effects of the initial bleed (massive subarachnoid, subdural, or intracerebral hematoma, permanent ischemic effects of increased intracranial pressure [ICP]), rebleeding, and surgical complications.[2] Successful anesthetic management of patients with cerebral aneurysms requires a thorough understanding of the natural history, pathophysiology, and surgical requirements of the procedures.

Endovascular treatment using thrombogenic coils is an alternative to surgical treatment. The results of the International Subarachnoid Trial (ISAT) showed that when an aneurysm is amenable to either endovascular coiling or surgical clipping, outcomes favor the coiling.[4,5] Longer term follow-up studies have questioned this result and have raised questions as to which modality is superior,[6,7]and there is interest in establishing in which cohort one treatment is favored over the other. Multiple factors must be evaluated, including aneurysm factors such as location and anatomy, and patient factors such as age, comorbidities, and patient wishes.[6]

PREOPERATIVE CONSIDERATIONS

The main steps in preoperative evaluation are as follows:

1. Assessment of the patient's neurologic condition and clinical grading of the subarachnoid hemorrhage (SAH)
2. A review of the patient's intracranial pathologic condition, including the performing of computed tomography (CT) and angiograms
3. Monitoring of ICP and transcranial Doppler ultrasonography (TCD) if available
4. Evaluation of other systemic functions, premorbid as well as current condition, with emphasis on systems affected by SAH
5. Communication with the neurosurgeon regarding positioning, anticipated difficulty/technique to clip and special monitoring requirements
6. Optimization of the patient's condition by correcting any existing biochemical and physiologic disturbances.

The preoperative assessment allows appropriate planning of an anesthetic regimen with consideration of the pathophysiology of all organ systems as well as the surgical and monitoring requirements. This approach facilitates the goals of smooth anesthesia for an uncomplicated aneurysm and ensures a heightened level of preparedness for a complicated one.

The Central Nervous System

To allow better assessment of surgical risk and prognosis, Botterell and colleagues in 1956 first proposed the grading of subarachnoid hemorrhage,[8] which was later modified by Hunt and Hess (Table 13.1).[9] In the 1980s a grading scale based on the Glasgow Coma Scale was introduced by the World Federation of Neurological Surgeons (Table 13.2).[10] In the World Federation classification, the most important correlate with outcome is the preoperative level of consciousness.[2] These clinical grading schemes allow evaluation of operative risk, communication among physicians about a patient's condition, and conduct of comparative studies of therapy on outcome. The modified Hunt and Hess grading scale is still the most commonly used, because of both familiarity and ease of application.

Despite successful surgical treatment, delayed ischemic neurologic deficits (DIND) resulting in permanent neurologic injury or death can occur in patients in whom the complication vasospasm develops. Because the incidence and severity of vasospasm is related to the amount of subarachnoid blood present, computed tomography (CT) findings are often graded according to the Fisher's grading system (Table 13.3a and b).[11] Despite criticisms of Fisher grading[12] and proposed modifications,[13] it remains the primary method of describing the CT findings with regard to clot burden and the risk of vasospasm in aneurysmal SAH.

Although the surgical mortality and morbidity vary with different institutions, patients in good preoperative condition (assigned to clinical grades I and II) can be expected to do well; patients with grade V status have a high mortality and morbidity, but aggressive management has resulted in substantial improvement (Table 13.4).[14] The clinical grade also

Table 13.1 Modified Hunt and Hess Clinical Grades for Patients with Subarachnoid Hemorrhage*

Grades	Criteria
0	Unruptured aneurysm
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, but no neurologic deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, mild or severe hemiparesis, possible early decerebrate rigidity, vegetative disturbance
V	Deep coma, decerebrate rigidity, moribund appearance

*Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography result in assignment of the patient to the next less favorable category.

Table 13.2 World Federation of Neurological Surgeons' Grades for Patients with Subarachnoid Hemorrhage

Grade	Glasgow Coma Scale Score	Motor Deficit
I	15	Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	6–3	Present or absent

(Data from Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg 1988;68:985–986.)

Table 13.3a Fisher Grades for Computed Tomography Findings in Subarachnoid Hemorrhage

Grade	CT Finding(s)
1	No blood detected
2	Diffuse thin layer of subarachnoid blood (vertical layers < 1 mm thick)
3	Localized clot or thick layer of subarachnoid blood (vertical layers ≥ 1 mm thick)
4	Intracerebral or intraventricular blood with diffuse or no subarachnoid blood

CT, computed tomography.
(Data from Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 6:1–9, 1980.)

Table 13.3b Modified Fisher Grades for CT Findings in Subarachnoid Hemorrhage

	No SAH	Focal or diffuse thin SAH	Focal or diffuse thick SAH	IVH	
0	+	-	-	-	No subarachnoid hemorrhage (SAH); no intraventricular blood
1	-	+	-	-	Thin diffuse or focal subarachnoid blood but no intraventricular blood
2	-	+	-	+	Thin diffuse or local subarachnoid blood with intraventricular blood
3	-	-	+	-	Thick focal or diffuse subarachnoid blood but no intraventricular blood
4	-	-	+	+	Thick local or diffuse subarachnoid blood with intraventricular blood

(From Frontera JA, Claasen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified Fisher scale. Neurosurgery 58: 21–27, 2006.)

Table 13.4 Surgical Mortality and Major Morbidity of Subarachnoid Hemorrhage According to Clinical Grades*

Grade (Hunt and Hess)	Mortality (%)	Morbidity (%)
0	0–2	0–2
I	2–5	0–2
II	5–10	7
III	5–10	25
IV	20–30	25
V	30–40	35–40

*Pooled from the literature and experience in the author's (A.M.L.) institution.

indicates the severity of associated cerebral pathophysiology. The higher the clinical grade, the more likely the occurrence of vasospasm, elevated ICP,[15,16] impairment of cerebral autoregulation,[17,18] and a disordered cerebrovascular response to hypocapnia.[17] A worse clinical grade is also associated with a higher incidence of cardiac arrhythmia and myocardial dysfunction.[19,20]

Patients with worse clinical grades have a tendency to become hypovolemic and hyponatremic.[21,22] Thus, understanding the grading scale allows the anesthesiologist to communicate effectively with other physicians and facilitates assessment of pathophysiologic derangements and the planning of perioperative anesthetic management.

Intracranial Pressure

ICP increases rapidly after an SAH and may approach the levels of the systemic blood pressure. This phase lasts minutes and is thought to limit the amount of blood leakage through the ruptured aneurysm. With recurrent rupture of the aneurysm, ICP increases further from mass effect (clot), cerebral edema, or hydrocephalus due to a blocked aqueduct. ICP that reaches at least 20 mmHg is present in 36–67% of patients.[23,24]

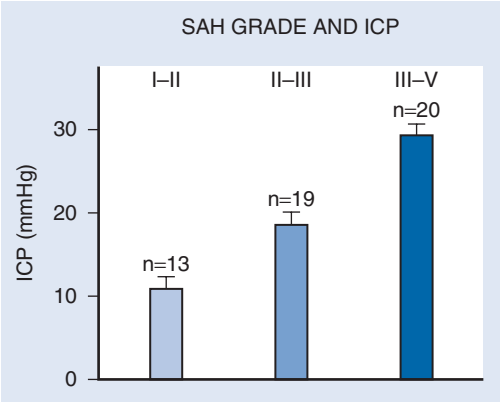


Fig. 13.1 The relationship between grade of subarachnoid hemorrhage (SAH) (Hunt and Hess) and intracranial pressure (ICP). *(Data From Voldby B, Enevoldsen EM: Intracranial pressure changes following aneurysm rupture. Part 1: Clinical and angiographic correlations. J Neurosurg 1982;56:186–196.)*

ICP correlates well with clinical grade. It is generally normal in patients with grade I and II status but is elevated in those with grade IV and V status (Fig. 13.1). However, a normal ICP does not necessarily imply normal intracranial compliance (elastance). It is important not to normalize the ICP too rapidly, because doing so may increase the transmural pressure (TMP) gradient across the aneurysm wall and cause further hemorrhage. A cerebral perfusion pressure (CPP) value of 60 to 80 mmHg is a reasonable goal.[25]

A communicating hydrocephalus may later develop because of arachnoidal adhesions from the extravascular blood that interferes with reabsorption of cerebrospinal fluid (CSF). In several large studies the incidence of hydrocephalus ranged from 15%[2] to 41%.[23] Clinically, hydrocephalus is characterized by progressive obtundation and nonreactive small pupils. The clinical features are present in only about 50% of cases, and therefore radiologic diagnosis is essential. Elevated ICP with hypovolemia may increase the likelihood of delayed cerebral ischemia and infarction.[26] Patients with SAH generally have decreased cerebral blood flow (CBF) and cerebral metabolic rate.[27,28] The development of vasospasm can also exacerbate a rise in ICP because the reduction in CBF resulting from vasoconstriction of large conductance vessels is accompanied by vasodilation in the distal vessels, leading to an increase in cerebral blood volume (CBV) and a subsequent rise in ICP. Another factor that would contribute to increases in ICP is an intracerebral (17%) or intraventricular (17%) hematoma.[2] It is possible that there is a causal relationship between acute hydrocephalus[29] and delayed cerebral ischemia, but this remains to be established.[26]

Impairment of Autoregulation and Carbon Dioxide Reactivity

Patients with SAH have both an impairment of autoregulatory capacity[30] and a rightward shift in the lower limit of autoregulation. The severity of autoregulatory impairment correlates directly with the clinical grade.[17,18,30] Nornes and colleagues[31] observed that the lower limit of autoregulation was significantly higher in patients with clinical grade III than in those with clinical grade I and II during intracranial surgery. The development of impaired autoregulation closely correlates with the occurrence of vasospasm.[32] This impaired autoregulation in the presence of vasospasm predicts delayed ischemic deficits[33–35] and is associated with an unfavorable outcome.[36]

If neurologic deterioration occurs, it is vital to review the hemodynamic measurements for any associated relationship. Many well-documented cases describe patients with SAH in whom a new neurologic deficit developed in association with a decrease in blood pressure and a subsequent reversal of the deficit with a pharmacologically induced increase in blood pressure.[37] Thus, the anesthesiologist must not allow the perfusion pressure to decrease below this lower limit perioperatively. This situation represents a relative contraindication to induced hypotension during surgery, as discussed later. One study looked at outcome in relation to the incidence and magnitude of decrease in blood pressure and failed to find any difference in poor outcomes.[38] While seemingly tolerated, induced hypotension may predispose to inadequate CPP values as well as exacerbate elevated ICP, and so is best avoided.

The cerebrovascular response to hyperventilation is generally preserved after SAH.[17,18] Although impairment of autoregulation may occur in patients assigned relatively good clinical grades, a decline in CO_2 reactivity does not occur until there is severe damage.[18] Thus, hyperventilation remains effective in reducing CBF and CBV during perioperative management for most patients and potentially could improve autoregulation in those compromised by the SAH.[39]

Systemic Effects

Intravascular Volume Status and Hyponatremia

The intravascular volume status has been found to be abnormally low in 36% to 100% of patients with SAH, and the level of hypovolemia correlates with the clinical grade.[22,40] Moreover, patients with signs of increased ICP on CT scan have a greater likelihood of systemic hypovolemia.[22] The reasons are multifactorial and probably include bed rest, supine diuresis, negative nitrogen balance, decreased erythropoiesis, and iatrogenic blood loss. Hypovolemia may exacerbate the clinical effects of vasospasm and is associated with cerebral ischemia and infarction.[22,40,41]

Paradoxically, hypovolemia has often been observed to be associated with hyponatremia, which occurs in approximately 30–57%[41–43] of cases of SAH. The etiology of hyponatremia is still a matter of debate.[44] The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been implicated,[43] treatment for which consists of fluid restriction. An alternative etiology is cerebral salt wasting syndrome (CSWS),[45] which involves natriuretic peptides being released from the walls of the myocardium[46] or from the hypothalamus in response to hydrocephalus, which causes distention of the cerebral ventricles.[21] The release of brain natriuretic peptide has been correlated with cerebral vasospasm and hyponatremia[47,48] as well as cerebral infarction independent of vasospasm.[49] What distinguishes CSWS from SIADH is the difference in intravascular volume, which is relatively low with the former and high in the latter. As hypovolemia can aggravate vasospasm, it is probably safer to err on the hypervolemic side, although normovolemia should be the goal. Hypertonic saline is the treatment of choice for both conditions.

Other significant electrolyte abnormalities are hypokalemia and hypocalcemia. In a series of 406 patients with SAH, both hypokalemia (serum K^+ value < 3.4 mmol/L) and hypocalcemia (serum Ca^{2+} value 2.2 mmol/L) were noted (in 41% and 74% of cases, respectively).[50]

Cardiac Effects

The effects of SAH on the myocardium can range from alterations in the electrocardiogram, to leakage of cardiac troponins, to wall motion abnormalities evident on

echocardiography. Preexisting coronary artery disease in the setting of the profound stress induced by SAH may result in myocardial ischemia. However, the majority of patients with cardiac dysfunction secondary to SAH have normal coronary artery anatomy and suffer from a neurogenic stressed myocardium.[51]

Electrocardiographic Changes

Electrocardiographic (ECG) abnormalities occur in 40–100% of patients with SAH.[52] These abnormalities include sinus bradycardia, sinus tachycardia, atrioventricular dissociation, and bradycardia-tachycardia, in addition to more serious and potentially life-threatening rhythms such as ventricular tachycardia and fibrillation. Morphologic changes in the ECG tracing include T-wave inversion, depression of the ST segment, the appearance of U waves, prolonged QT interval, and, rarely, Q waves.[53] A prolonged QT interval may occur in 20–41% of patients predisposing them to dangerous ventricular arrhythmias. Atrial arrhythmias including fibrillation and flutter occur in 4% of patients and have been found to be associated with a higher risk of severe disability and death.[54] The incidence of ECG changes correlates with the amount of intracranial blood, and patients with Fisher grades 3 and 4 CT findings having more abnormalities.[55] Potassium and calcium abnormalities may contribute to the ECG changes.

Myocardial Function

After SAH, damage to the myocardium can be indicated by an increase in circulating levels of cardiac troponin I (cTi) found in 17% to 68% of patients.[56,57] This cTi elevation following SAH-induced myocardial insult is much less than that related to myocardial infarction.[58] Elevation of cTi has been found to be associated with regional wall motion abnormalities and left ventricular dysfunction,[57] as well as hypotension, delayed cerebral ischemia from vasospasm, and death and disability at 90 days.[57,59]

Echocardiography of patients with SAH has shown depressed left ventricular function and regional wall motion abnormalities in 13–18% of cases.[20,60] Predictors of ventricular dysfunction include elevated cTi,[20,57,58] poor clinical grade (Hunt and Hess III to V),[20,60] and female gender.[60]

The mechanism of myocardial dysfunction has garnered much attention lately, leading to the proposal of several mechanisms.[51] The arterial supply to the heart has been implicated. Multivessel coronary artery spasm seems unlikely, given that the available coronary angiographic studies demonstrate normal coronary structure even in the presence of ongoing ECG and echocardiographic evidence of myocardial dysfunction.[61,62] Currently the favored mechanism is increased release of localized catecholamines in the myocardium.[63] This intense stimulation leads to contraction band necrosis and subsequent myocardial dysfunction. The fact that regional wall motion abnormalities span the myocardium in a pattern outside the territories of known coronary artery distributions lends credence to this theory.[64]

Takotsubo cardiomyopathy (TTC) has been reported in aneurysmal subarachnoid hemorrhage,[65] but typically, ventricular dysfunction secondary to SAH is associated with apical sparing.[64] In a multicenter study on patients with SAH, neurogenic stress cardiomyopathy consistent with TTC was observed in 10% of the cases.[66] Although the prognosis of SAH-induced ventricular dysfunction is good and generally considered reversible,[67] it is associated with increased risk for delayed cerebral ischemia and poor outcome in this study.

Anesthetic Implications

Patients with prolonged QT interval, T-wave abnormalities, and Q waves should undergo prompt correction of electrolyte disturbances. Experimentally, pharmacologic or surgical blockade of the sympathetic nervous system prevents or abolishes these ECG changes. However, no evidence exists that the prophylactic administration of a β-adrenergic or other autonomic antagonist significantly alters the outcome in such patients, and the use of these agents for this purpose is probably not warranted.[68]

Q waves and other ECG evidence of ischemia are always worrisome and, when observed in a patient with SAH, pose a diagnostic dilemma. Although most ECG abnormalities after SAH appear to be neurogenic rather than cardiogenic in nature, diagnostic difficulty has on occasion led to a delay in surgery. Moreover, microscopic hemorrhages and myocytolysis have been observed in a postmortem study, although other studies have reported no signs of myocardial damage.

The three possibilities for ECG abnormalities consistent with infarction are: (1) coincidental acute myocardial infarction, (2) SAH-induced myocardial infarction, and (3) ECG changes without infarction. Cardiac enzyme measurements and echocardiography should be obtained in suspicious cases. As with any surgical procedure, the decision to proceed with surgery should be based on a risk–benefit analysis and, therefore, depends on the urgency of the situation. Because of the risk of rebleeding, surgical therapy of a ruptured aneurysm is almost always considered urgent.

In summary, ECG changes are prevalent after SAH and likely represent hyperactivity of the sympathetic system with increased levels of norepinephrine. Although in some patients there is no myocardial pathologic condition, in others there may be ventricular dysfunction, and in rare cases necrosis and other myopathology can occur. In suspicious cases, serial cTi measurements should be obtained. Because the electrocardiographic changes reflect the severity of neurologic damage and have not been shown to materially contribute to perioperative mortality or morbidity,[69] the decision to operate should not be influenced by these ECG changes. These considerations, however, may influence the decision about the choice of invasive monitoring. The various ECG changes and their potential correlation with ventricular dysfunction and pathology are summarized in Table 13.5.

Respiratory System

Pulmonary edema has been observed to accompany SAH in 8% to 28% of cases[70,71] leading to an acute lung injury (PaO2-FiO2 ration <300) in 27%.[72] This may be due to pulmonary congestion from myocardial dysfunction or directly mediated at the lung via a sympathetic mechanism, and an inflammatory component has also been implicated.[73] Parallel to myocardial dysfunction, the incidence of pulmonary edema is correlated closely with clinical grade.[70] Aspiration and hydrostatic pneumonia are other potential complications.

Other Major Medical Problems

On the basis of the findings of the Cooperative Study, other major medical problems associated with SAH are systemic hypertension (21%), heart disease (3%), and diabetes mellitus (2%).[2]

Concurrent Medical Treatments

Patients receiving diuretic therapy for chronic hypertension may have preexisting fluid and electrolyte problems before SAH.

Table 13.5 Electrocardiography and Myocardial Dysfunctions seen in Subarachnoid Hemorrhage*

Benign changes	Sinus bradycardia Sinus tachycardia Atrioventricular dissociation Premature ventricular contractions Nonspecific ST segment depression T wave inversion U wave
Possible and actual wall motion abnormalities	Symmetrical T wave inversion[217,218] Prolonged QT interval > 500 msec[218] ST segment elevation[219] Left ventricular dysfunction with apical sparing[49] Regional wall motion abnormalities[19]
Possible and actual myocardial injury	Q wave ST segment elevation Elevated myocardial enzyme values Elevated troponin I value

*Superscript numbers are chapter references.

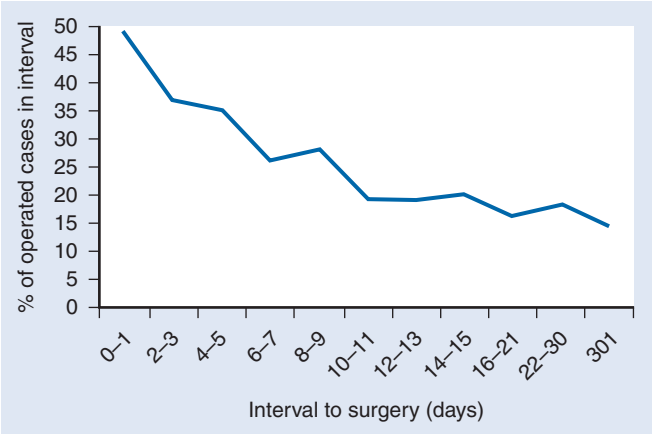


Fig. 13.2 The percentage of patients with a "tight" brain during surgical exposure correlated with the number of day(s) after subarachnoid hemorrhage that the operation was performed. *(From Kassell NF, Torner JC, Haley EC Jr, et al: The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg 1990;73:18–36.)*

Anticonvulsant medications such as phenytoin and carbamazepine antagonize the actions of nondepolarizing agents such as pancuronium and vecuronium (and atracurium to a lesser extent) as well as fentanyl requirements. A higher dose requirement and shortened duration of action for these drugs might be anticipated if the anticonvulsant therapy has been greater than 7 days in duration. The effect of the newer anticonvulsants lamotrigine and levetiracetam on nondepolarizing agents has not been rigorously studied. However, preliminary data indicate that higher doses are not needed and shortened duration of neuromuscular blockade does not occur.[74]

Antifibrinolytic agents such as ε-aminocaproic acid and tranexamic acid to prevent rebleeding while the patient is waiting for surgery have been evaluated. Although these agents have been found to decrease the risk of rebleeding, they are associated with an increased risk of cerebral ischemia, and no overall benefit has been shown for their use.[75] The anesthesiologist should be aware that patients on antifibrinolytics may have a greater incidence of vasospasm and hydrocephalus, and have a higher incidence of venous thrombosis and pulmonary embolism. Thus, the usage of antifibrinolytics cannot be recommended.[76] Use of recombinant factor VII (rFVIIIa) to decrease the incidence of rebleeding has been deterred by the occurrence of critical thrombosis in an early trial.[77]

Calcium channel antagonists (usually oral nimodipine) should be routinely administered for vasospasm prophylaxis. This therapy has specific anesthetic implications that are discussed later in the chapter.

Timing of Surgery

The two major complications contributing to significant morbidity and mortality after SAH are rebleeding and vasospasm, with each accounting for about 7% of mortality.[2] Because the brain is acutely swollen with fresh clots following SAH, it was generally believed that early operation increases the incidence of postoperative vasospasm. The Cooperative Study data influenced most surgeons to wait 7–10 days for the acute inflammatory process to subside before any operative intervention. Indeed, results from the Cooperative Study indicate that the brain was considered "tight" in 50% of cases with early surgery (same day as SAH), but in only 20% of cases undergoing operation after 10 days (Fig. 13.2).[3] Although delaying surgery does allow brain swelling to decrease, both rebleeding and vasospasm can occur during this waiting period. When surgery was delayed, antifibrinolytic agents were usually given to prevent lysis of the clot and rebleeding from the rent of the aneurysm. However, randomized clinical trials showed that, although these agents are effective in reducing the incidence of rebleeding, the incidence of vasospasm increases, leaving the overall morbidity and mortality unchanged.

Outcome studies to guide practice in timing of surgery are lacking.[78] While observational studies favor earlier surgery—with poor grade patients seemingly having the most benefit from early surgery[79,80] there is variation in when patients with poor clinical grade are taken to surgery. In an attempt to improve the overall outcome, there is a growing trend toward early operation, so that the risk of rebleeding can be eliminated and any vasospasm more aggressively treated. However, the results from the Cooperative Study showed that the overall management results for early (3 days or sooner) and late (after 10 days) surgery are not significantly different, although the results were the worst when surgery was performed between 7 and 10 days.[2] A subsequent analysis of data derived from only North American centers varied from the overall findings and indicated that the best results were achieved when surgery was planned within 3 days of SAH, therefore arguing strongly in favor of early surgery.[81] Although they should never be the primary consideration, substantial economic savings are also realized with early surgery. The trend toward early operation will probably continue, and patients in less-than-ideal condition for surgery will be coming to the operating room.

Rebleeding

Previous studies suggest that rebleeding following the initial SAH peaks at the end of the first week. The Cooperative Study data indicate that rebleeding peaks at 4% during the first 24 hours and then levels off at 1.5% per day on subsequent days. The overall incidence is 11%,[6,81] which accounts for 8% of the mortality and disability.[2] The incidence is lower in patients receiving antifibrinolytic agents.[2] Rebleeding remains a major threat in hospitals where delayed surgery is the standard practice. With the trend toward early operation, the risk of rebleeding

is reduced but not eliminated.[82] A combination of antifibrinolytic therapy for rebleeding and a calcium channel blocker for vasospasm has been suggested as a possible remedy.[83]

Vasospasm

Incidence

In patients who initially survive a SAH, cerebral vasospasm causing ischemia or infarction remains an important cause of morbidity and mortality. In the Cooperative Study, vasospasm accounted for 13.5% of the overall mortality and major morbidity.[2] Not all patients with SAH have vasospasm, and the severity, time course, and prognosis of vasospasm are largely unpredictable. The incidence and severity of delayed cerebral vasospasm have been shown to correlate with the amount and location of blood in the basal cisterns. The frequency of occurrence as determined by angiography is estimated to be 40–60%. However, clinically significant and symptomatic vasospasm occurs at a lower frequency (20–30%). The difference may be explained by the varying severity of vasospasm. Significant narrowing of the major blood vessels can occur without an overall reduction in distal perfusion. Furthermore, CBF can be reduced significantly by 20–25% without compromising normal brain function. Thus, considerable reduction in CBF can occur from vasospasm without clinical symptoms. Of the patients in whom symptomatic vasospasm develops, approximately 50% die or are left with a serious residual neurologic deficit. Typically, angiographically detectable vasospasm is not seen until 72 hours after SAH, the incidence peaks 7 days after SAH, and the problem is seldom seen after 2 weeks. When comparing endovascular aneurysm therapy and surgical clipping of the aneurysm with regards to vasospasm—endovascular therapy appears to have either the same[84] or reduced[85] incidence of vasospasm.

Pathogenesis

The vasospastic artery has structural and pathologic changes within the vessel wall, such as swelling and necrosis of the smooth muscle cells. Although the exact mechanism and cause of spasm have not been completely elucidated, a reasonable hypothesis is that one or more vasoactive substances contained in the blood in the basal cisterns induce inflammatory changes in the cerebral arteries to cause severe constriction.[86] The component in the blood implicated in the pathogenesis of vasospasm is currently thought to be oxyhemoglobin.[87] The normal cerebrovascular tone is regulated by a balance between vasodilating and vasoconstricting factors. The suppressive interaction of oxyhemoglobin with endothelium-derived relaxing factor or nitric oxide (potent vasodilator) coupled with stimulated production of endothelin (potent vasoconstrictor) is the postulated cause of cerebral vasospasm. In experimental vasospasm, the rise in perivascular concentrations of oxyhemoglobin and deoxyhemoglobin parallel the time course of vasospasm.[88] The presence of hemoglobin in the extravascular space incites an inflammatory reaction including such molecules as free radicals, haptoglobin, cell-adhesion molecules, cytokines which act to recruit macrophages and leukocytes into the extravascular areas containing blood.[89]

Clinical Manifestations

Delayed cerebral ischemia from vasospasm after SAH is a multivascular or diffuse process in most patients. The clinical manifestations of vasospasm include a decrease in the level of consciousness, new onset of focal signs, and mutism. In a prospective study, Hijdra and associates[90] found that the majority of patients with delayed cerebral ischemia from vasospasm had a decrease in level of consciousness that was sometimes accompanied, but never preceded, by focal signs. Clinical manifestations most commonly appear gradually but may also occur abruptly.

Diagnosis

After the appearance of new focal signs or a decrease in level of consciousness, the diagnosis of cerebral vasospasm is confirmed by angiography. A CT scan may show hypodense lesions in brain areas that are consistent with the clinical signs; however, these have been found to be not sensitive and potentially unreliable.[91] The diagnosis of vasospasm may also be predicted or made before the onset of clinical vasospasm with the use of transcranial Doppler ultrasonography (TCD). With vasospasm and narrowing of the conductance arteries of the circle of Willis, cerebral artery flow velocities increase,[92] although confirmation with angiography is definitive. The noninvasive technology of TCD also allows continual evaluation of the patient in vasospasm without resorting to frequent angiographic investigations. However, in patients treated with hypertensive therapy, increase in flow velocity may represent increase in local cerebral blood flow instead of worsening vasospasm.[93,94] Radiologic confirmation with angiography, single-photon emission CT (SPECT), CT perfusion, or MR perfusion studies may be necessary. CT angiography and MR angiography have also been used to diagnose vasospasm, but the sensitivity and specificity have not been established. Digital subtraction angiography remains the gold standard for diagnosis of vasospasm.

Treatment

Pharmacologic

Numerous drugs have been investigated for the prevention or treatment of vasospasm, but most are ineffective. Calcium channel blockers, of which nimodipine has been most extensively studied, are the only class of drugs that have been shown to consistently reduce the morbidity and mortality from vasospasm. Depending on the study, the incidence of poor outcome is reduced by 40–70%.[95] Interestingly, none of these studies with favorable results for calcium channel blocker prophylaxis was able to demonstrate any significant change in the incidence or severity of vasospasm, suggesting that the beneficial effects of nimodipine may be occurring at either a distal vessel site or a cellular level. The only study that demonstrated a significant improvement in angiographic vasospasm with a calcium channel blocker used fasudil hydrochloride (not approved for use in the United States). Its use has yielded clinical outcomes similar to those for nimodipine.[96] High-dose intravenous nicardipine has been investigated for the prevention of vasospasm. Although the incidence of symptomatic vasospasm was reduced from 38% to 25%, there was no difference in outcome at 3 months, presumably because hypervolemic hypertensive therapy is effective in ameliorating the ischemic deficits from vasospasm.[97]

Because cerebral vasospasm is frequently the cause of poor outcomes after successful surgical or endovascular treatment, there are many investigations looking for new pharmacologic therapies. Magnesium sulfate is thought to be a cerebral vasodilator by way of blocking voltage-dependent calcium channels. This property, paired with its ability to antagonize *N*-methyl-D-aspartate receptors, thereby limiting the damaging excitatory glutamate stimulation, has led to many preliminary studies. So far, magnesium sulfate has shown a similar efficacy in replacing nimodipine,[98] and use of these two agents in conjunction has led to positive results in decreasing

vasospasm and improving outcome.[99] The enthusiasm, however, must be tempered by the concern for hypotension and hypocalcemia that accompany its use[100] and studies have not supported its use.[101] The endothelin receptor antagonists clazosentan has been shown to be effective in the prevention as well as he treatment of established vasospasm. However, a multicenter clinical trial failed to demonstrate a significant effect on mortality or morbidity, mainly secondary to an increase in lung complications, anemia and hypotension.[102] The use of statins to increase endothelial nitric oxide and thus treat vasospasm has received interest. A meta-analysis of trials to date[103] suggests that statins may reduce the incidence of delayed ischemic deficits but does not seem to have an effect on long-term outcome.

Several other medications have shown early promise but subsequently failed to be adopted into clinical use. Of these, tirilazad, a potent lipid peroxidation inhibitor, initially showed promise, but further studies and a meta-analysis failed to show benefit.[104] Nicaraven, a hydroxyl radical scavenger, afforded a 35% reduction in the incidence of delayed ischemic deficits at 1 month; however, the results were no longer favorable at 3 months.[105]

Nonpharmacologic

Surgical. The presence of subarachnoid blood is related to the occurrence of vasospasm both qualitatively and quantitatively. By operating on patients with SAH within 48 hours of hemorrhage, Taneda reduced the incidence of delayed ischemic deficits from 25% (11 of 44 patients who underwent surgery 10 days or more after the hemorrhage) to 11% (11 of 101 patients).[106] Thus, early operation with extensive irrigation of the cisterns may have lowered the incidence or severity of vasospasm.

Reduction of Intracranial Pressure. If the patient has elevated ICP, cerebral perfusion may be improved by lowering of the ICP. Improvement in neurologic status with this treatment alone has been reported.

Hypervolemic, Hypertensive, and Hemodilution Therapy. Historically the most consistently effective regimen available to treat ischemic neurologic deficits due to cerebral vasospasm uses hypervolemia, hypertension, and hemodilution (triple-H therapy). The rationale behind induced hypervolemia and hypertension is that in SAH the ischemic areas of the brain have impaired autoregulation and thus CBF depends on perfusion pressure, which partly depends on the intravascular volume and mean arterial blood pressure.[107,108] Although the triple H therapy may still be practiced in some centers, the latest guideline essentially focuses solely on the hypertensive therapy as repeated studies suggest that hypervolemia provides no additional benefit and might increase the risk of pulmonary dysfunction.[109]

This classic triple H-therapy or, currently, hypertensive therapy, is most successful if instituted early, when the neurologic deficits are mild and before the onset of infarction.[37] However, prophylactic treatment initiated before aneurysm clipping is associated with a significant risk of rebleeding (19% in one series). Other concerns are worsening of cerebral edema, increasing ICP, and hemorrhage into an infarcted area. With early surgery there is less likelihood of rebleeding from the hypervolemic, hypertensive therapy.[110] Other systemic complications are pulmonary edema (7–17%), myocardial infarction (2%), dilutional hyponatremia (3–35%), and coagulopathy (3%).[37]

To optimize therapy and minimize the potential cardiovascular and pulmonary complications, the use of invasive blood pressure monitoring is essential. Central venous pressure (CVP) or pulmonary artery catheter (PAC) was once commonplace but is increasingly being replaced by less invasive equivalents, including transpulmonary thermodilution monitoring[111] as well as algorithmic-based derivations of stroke volume variation and cardiac output.[112] Because a growing number of studies have implicated PACs as increasing complication rates with no improvement in outcome,[113] it is rare to place a PAC to guide triple-H therapy. Select cases where neurogenic cardiac stunning may complicate triple-H therapy may warrant the addition of a PAC to guide fluid therapy, although hypervolemia is no longer the goal.

Hypervolemia or, more appropriately, normovolemia is generally achieved with infusions of crystalloids or colloids when indicated (e.g., 5% albumin). Hetastarch and dextran solutions probably should not be used because of the potential complication of coagulopathy through interference with platelets and factor VIII.[114,115] Trumble and colleagues[116] examined the use of hetastarch for hypervolemic treatment of vasospasm and reported the occurrence of coagulation abnormalities in all patients. Thus they were unable to formulate any dose guideline for its safe use. The lower-molecular-weight (LMW) dextran (pentastarch) appears to be associated with fewer coagulation problems.[117] Although intravenous fluid loading alone is often effective, it is at times insufficient to raise the blood pressure or reverse ischemic symptoms; vasopressors are then initiated to induce hypertension. The most widely used vasopressors are dopamine, dobutamine, norepinephrine (noradrenaline), and phenylephrine. The hypertensive therapy may induce a vagal response as well as a profound diuresis, requiring administration of large amounts of intravenous fluids. Atropine (1 mg intramuscularly every 3 to 4 hours) may be given to maintain the heart rate between 80 and 120 beats/min, and aqueous vasopressin (Pitressin) (5 units intramuscularly) may be administered to maintain the urine output at less than 200 mL/h. With this regimen, often only small amounts of vasopressor drugs are required.[37] The blood pressure is titrated to a level necessary to reverse the signs and symptoms of vasospasm or to a maximum of 160 to 200 mmHg systolic in the patient whose aneurysm has been clipped.[37] If the aneurysm has not been clipped, the systolic blood pressure is increased to only 120 to 160 mmHg. Blood pressure management should not be affected by the presence of incidental unruptured aneurysms, as the risk of hemorrhage from unsecured, unruptured aneurysms during hypertensive therapy is very low.[118] The elevated blood pressure must be maintained until the vasospasm resolves, usually in 3 to 7 days. Response to therapy can now be monitored noninvasively with TCD. Improvement in vasospasm is generally clinically evident, and may or may not be associated with a decrease in flow velocity and, more importantly, a decrease in the Lindegaard ratio (MCA to extracranial ICA flow velocity ratio). Hemodilution, the last component of the traditional triple-H therapy, is based on the correlation of hematocrit and whole blood viscosity. As the hematocrit and viscosity diminish, the cerebrovascular resistance correspondingly decreases and CBF increases. One argument against hemodilution is that oxygen-carrying capacity is also reduced. Experimental studies have suggested that a hematocrit of 33% provides an optimal balance between viscosity and oxygen-carrying capacity, and this value has been applied clinically. With the growing concern about increased morbidity and mortality related to blood transfusion, this value is now often revised downwards to between 25% and 30%. Active hemodilution is currently seldom used, as most patients are at the target concentration at the onset of vasospasm.

Transluminal Angioplasty. In all major vessels that are accessible, transluminal angioplasty has been used in patients with vasospasm refractory to conventional treatment,[119] with reversal of deficits being achieved in 65% of the patients treated.[120] The time frame within which to institute angioplastic therapy has not yet been established, but prophylaxis is not warranted because of the small but inherent risk of rupture. In distal vessels that are not accessible for angioplasty, the administration of vasodilators (nicardipine, verapamil, papaverine, milrinone) via superselective intra-arterial infusion has been shown to be effective.[121–124]

Improvement in cerebral venous oxygen saturation and metabolic profile with this treatment has been demonstrated.[125] However, studies have failed to show a definitive difference between angioplasty and papaverine injection.[126] Although rare, complications from intra-arterial papaverine infusion include severe thrombocytopenia,[127] increase in ICP,[128] and transient brainstem dysfunction (when infused into the posterior circulation).[124] Intraoperative cisternal injection of papaverine to reduce the risk of vasospasm has also been reported to cause transient pupillary dysfunction, which may interfere with neurologic assessment.[129] The newer vasodilators used for intra-arterial injection seem to decrease these side effects, with nicardipine showing better results than verapamil.[126] A reduction in systemic blood pressure has been reported with the use of nicardipine, milrinone,[121] and verapamil[130] Intraventricular use of nicardipine[131] and intrathecal nimodipine[132] in initial studies has shown some benefit in the treatment of vasospasm. Intraventricular administration of sodium nitroprusside has also been reported to reverse vasospasm refractory to conventional triple-H therapy.[133] However, none of this is currently considered to be accepted therapy.

Anesthetic Considerations

Hypertensive Therapy

The anesthetic management of patients who have or are at risk for vasospasm requires an understanding of the natural course of vasospasm, concurrent therapy, the importance of intravascular volume status, the changes in electrolyte concentration that occur with the treatment of vasospasm, and which hemodynamic variables are associated with vasospasm. Although it is generally believed that early surgery raises the risk of vasospasm, there are no substantiating data, and some data suggest otherwise.[2,110] Further investigations suggest that the interplay of vasospasm and surgical timing might account for the severity of the bleeding.[134]

Asymptomatic patients at risk for vasospasm include all patients who undergo surgery before the onset of vasospasm. Although it is not possible to predict the occurrence of postoperative vasospasm, patients with good SAH grades and low Fisher grade tend to have a lower incidence. These patients should be kept in a normovolemic state, with volume loading initiated toward the end of the operation, after the aneurysm has been clipped. Intraoperatively, controlled hypotension can be provided safely, if so requested by the surgeon.[135] Treatment of postoperative hypertension should not be too aggressive.

Some physicians consider patients who are symptomatic of vasospasm as being at high risk and not eligible for surgery. Many other surgeons, however, believe the most effective treatment of vasospasm is immediate clipping of the aneurysm so that aggressive hypertensive and hypervolemic therapy can be implemented. Symptomatic patients presenting for emergency clipping of aneurysms should be treated aggressively, and normovolemia should be maintained and guided with invasive or noninvasive monitoring. For patients who have already been treated with hypertensive therapy, the threshold blood pressure below which the patient becomes symptomatic must be noted, and the blood pressure should not be allowed to fall below this value. Buckland and coworkers[136] have advocated intraoperative induced hypertension as a prophylactic measure. This approach, however, must be balanced against the risk of re-rupture of the aneurysm as well as increased brain swelling and difficulty with intraoperative brain retraction. Because the main aim must be to maintain adequate CPP, induced hypotension is contraindicated in these patients.

With respect to asymptomatic patients who undergo operation on a delayed basis, vasospasm seldom occurs more than 12 days after SAH. Therefore patients who have surgery later than 10 to 12 days after SAH have a low risk of vasospasm and can be managed in a normal fashion.

Calcium Channel Antagonists

Calcium channel antagonists have a proven efficacy in reducing the neurologic complications of vasospasm. In most institutions, all patients with SAH are prophylactically treated with nimodipine. Clinical experience suggests that these drugs do not present any difficulty for anesthetic management, although 5% of the patients who receive nimodipine and 23% of the patients who receive intravenous nicardipine demonstrate mild hypotension as a result of systemic vasodilation. A similar tendency toward lower systemic blood pressure was also observed intraoperatively, and there was a reduced demand for hypotensive agents when controlled hypotension was used.

Premedication

To allow accurate assessment of the patient's immediate preoperative neurologic condition and clinical grade, preoperative medications are best omitted. A proper preoperative visit by the anesthesiologist with a thorough explanation usually obviates any need for preoperative medication. However, an anxious patient may become hypertensive, with greater risk of rebleeding. On the other hand, premedications such as barbiturates and narcotics may cause respiratory depression, resulting in an increase in CBF and CBV; therefore such medication must be used judiciously in patients with elevated ICP. Premedication should be individualized. Patients with a good clinical grade may receive fentanyl, 50–150 μg or morphine, 1–5 mg, and/or midazolam, 1–5 mg, intravenously for sedation. In general, premedication should be conservative, and narcotics are preferable to benzodiazepines. The best results are achieved when administration is titrated incrementally. Patients already treated with mechanical ventilation may receive higher doses (fentanyl 250–500 μg or morphine, 10–20 mg; midazolam, 5–10 mg) if hemodynamic stability is maintained. Muscle relaxants may also be required for transport of intubated patients. Patients should continue to receive their regular doses of nimodipine and dexamethasone.

INTRAOPERATIVE CONSIDERATIONS AND INDUCTION OF ANESTHESIA

The incidence of aneurysm rupture during induction of anesthesia, although rare (reported to be 2% in one series but probably less than 1% with modern anesthetic techniques), is usually precipitated by a sudden rise in blood pressure during tracheal intubation and is associated with a high mortality. Therefore the goal during induction of anesthesia for aneurysm surgery is to reduce the risk of aneurysm rupture by

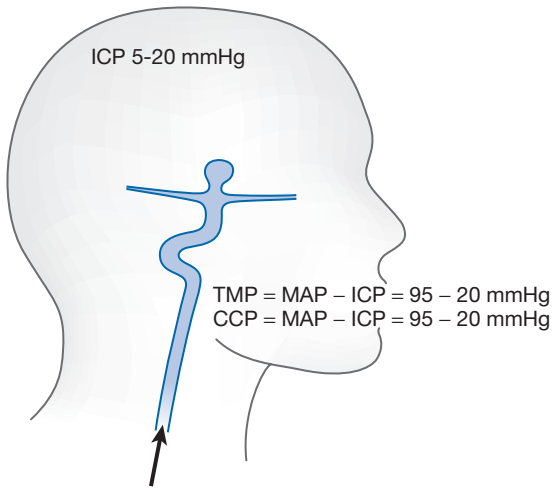


Fig. 13.3 Determinants of transmural pressure (TMP) and cerebral perfusion pressure (CPP). Both are determined by the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) and are therefore numerically identical.

minimizing the TMP while simultaneously maintaining an adequate CPP. As illustrated in Fig. 13.3, both TMP and CPP are determined by the same equation, mean arterial blood pressure (MAP) minus ICP (MAP − ICP). Therefore these goals represent opposite objectives. Ideally, the TMP or CPP should be kept at the preoperative value throughout the induction period, particularly in patients with good SAH grades; however, this is not always possible.

As a general principle, the patient's blood pressure should be reduced to 20–25% below the baseline value, and prophylaxis for the normal hypertensive response to intubation should be instituted before tracheal intubation is attempted. Another useful approach is to balance the risk of ischemia from a reduction in CPP against the benefit of a reduced chance of aneurysmal rupture from a decrease in TMP, taking into consideration the patient's clinical grade. Patients with SAH grades 0, I, and II generally have normal ICP and are not experiencing acute ischemia.[15] Therefore, these patients will tolerate a bigger transient decrease in blood pressure (30–35%, or systolic blood pressure at about 100 mmHg). In contrast, patients with poor clinical grades frequently have increased ICP,[15] low CPP, and ischemia. The elevated ICP decreases the TMP and partially protects the aneurysm from re-rupture. These patients may not tolerate transient hypotension as well, and the duration and magnitude of blood pressure decrease should be moderated. The same consideration applies to the use of hyperventilation. Patients with a good clinical grade should not be hyperventilated, because the reduction in CBF will lead to a reduction in ICP and, consequently, an increase in TMP. Conversely, patients with poor clinical grades should be managed with moderate hyperventilation to improve cerebral perfusion. To reduce the risk of aneurysm rupture or ischemia, the change in TMP or CPP should always be gradual, not abrupt.

If these principles and objectives are adhered to, a variety of anesthetic agents and techniques can be used successfully. Irrespective of the technique used, vigilant monitoring of blood pressure is required, which may be achieved by direct intra-arterial blood pressure monitoring.

Conceptually, it is convenient to think of the induction phase as consisting of two parts: (1) induction to achieve loss of consciousness and (2) prophylaxis to prevent a rise in blood pressure in response to laryngoscopy and intubation.

Induction

Achieve Loss of Consciousness

Propofol (1.5–2 mg/kg) or thiopental (3–5 mg/kg) in combination with fentanyl (3–5 μg/kg) or sufentanil (0.3–0.5 μg/kg) is suitable. Propofol has superseded thiopental, which is no longer available in North America, and remifentanil or fentanyl are the preferred narcotics. Other alternatives are etomidate (0.3–0.4 mg/kg) and midazolam (0.1–0.2 mg/kg). Propofol is similar in action to thiopental. It reduces CBF and metabolic rate,[137] and with careful titration (1.5–2.5 mg/kg) it can be used without compromising cerebral perfusion.

Regarding the use of narcotics, Marx and associates[138] observed that sufentanil may cause an increase in ICP in patients with supratentorial tumors and suggested that this increase may be secondary to cerebral vasodilation. However, both fentanyl and sufentanil have been shown to raise ICP in patients with head trauma,[139] and Trindle and colleagues[140] reported that both agents increase CBF velocity. Other investigators, however, were unable to document either an increase in flow or a change in ICP with sufentanil.[141,142] Similarly, Mayberg and coworkers did not observe an increase in flow velocity or ICP with alfentanil.[143] In view of these studies, the mechanism of the rise in ICP remains unclear and may be related to the simultaneous decrease in systemic blood pressure resulting in autoregulation-mediated compensatory vasodilation. The study by Werner and associates[144] in patients with head injury supports this possibility; they observed an increase in ICP only in the patient group in whom systemic hypotension developed after sufentanil administration. This mechanism has been questioned by de Nadal and colleagues,[145] who found that autoregulatory status was not predictive of ICP changes induced with opioids in head-injured patients.

These studies leave the mechanism of ICP change with opioids in question, although the importance of maintaining normotension with administration of synthetic narcotics cannot be neglected. When used in combination with a vasoconstrictive agent such as propofol, these narcotics should be safe for use in patients with SAH, although mild hyperventilation should be instituted in patients with elevated ICP. The action of the most recently introduced narcotic remifentanil appears to be similar to that of fentanyl,[146–148] with the exception that the context-sensitive half-life is very short at 3 minutes after a 3-hour infusion.[149] This ultra-short-acting narcotic facilitates the emergence of the patient from anesthesia and allows immediate assessment of neurologic function. It is often used in combination with propofol infusion as part of total intravenous anesthesia regimen.

Intubation

Prophylaxis against a Rise in Blood Pressure during Laryngoscopy

The aforementioned regimen deals only with the induction of unconsciousness, and other agents are required before tracheal intubation is attempted. Many anesthetic adjuncts have been used successfully to prevent the rise in blood pressure that occurs with laryngoscopy and tracheal intubation. They include the use of high-dose narcotics (e.g., fentanyl, 5–10 μg/kg, sufentanil, 0.5–1.0 μg/kg or remifentanil, 1–1.5 μg/kg), β-adrenergic antagonists (e.g., esmolol, 0.5 mg/kg), labetalol (10–20 mg), intravenous or topical lidocaine (1.5–2.0 mg/kg), a second dose of propofol (0.5–1 mg/kg), or a deep level of an inhalation anesthetic such as isoflurane or sevoflurane. Intravenous adjuncts are preferred in patients with poor SAH grade, whereas deep inhalation anesthetics are appropriate for patients with good SAH grades, but should be avoided in patients with increased ICP.

Choice of Muscle Relaxant

Although succinylcholine has been reported to increase ICP,[150] it has been used successfully in many aneurysm patients with no known sequelae. Moreover, this increase in ICP is not seen when the patients are sedated, or have suffered neurologic injury,[151] or when succinylcholine is preceded by a defasciculating dose of a nondepolarizing agent. Another potential concern with succinylcholine is the possibility of potassium release. An early study reported potassium release to be a significant complication, but this observation was not confirmed by a later investigation.[152] In all likelihood, succinylcholine is probably safe to use in the patient with acute SAH but should be avoided in patients with motor deficits in the subacute stages.

In view of these potential complications, many anesthesiologists prefer to use a nondepolarizing agent. Rocuronim or cisatracurium are both suitable agents that do not cause hypertension or tachycardia. Vecuronium is also associated with hemodynamic stability. Rocuronium, given at 1.2 mg/kg, is similar in onset time to succinylcholine and may be the nondepolarizing muscle relaxant of choice in neurosurgical anesthesia. Overall, the choice of muscle relaxant depends on the anesthesiologist's preference as well as the nature of other drugs being administered at the time of induction. For subsequent neuromuscular blockade, any of the nondepolarizing agents can be used. If neurophysiologic monitoring (specifically motor evoked potential [MEP] monitoring) is employed, subsequent doses of muscle relaxants may interfere with optimal monitoring.[153]

To avoid coughing, the neuromuscular junction should be monitored, and tracheal intubation should be attempted only when muscle paralysis is complete. The blood pressure should also be watched closely during laryngoscopy. If the blood pressure begins to rise unexpectedly (above the preinduction value), the intubation attempt must cease, and additional anesthetic agents or adjuncts should be given.

The Patient with a Full Stomach

If the patient has a full stomach, the anesthesiologist must balance the risk of aneurysm rupture against the risk of aspiration. One approach is to treat the patient like any patient at risk of regurgitation and aspiration, using a rapid-sequence induction with cricoid pressure. To obtund the hypertensive response to tracheal intubation, fentanyl 5–10 µg/kg, sufentanil 0.1 µg/kg or remifentanil 1 µg/kg[154] should be used in combination with propofol. Either succinylcholine (1.5–2.0 mg/kg, preceded by defasciculation) or rocuronium (1.0–1.2 mg/kg) can be used for muscle relaxation. Without the ability to titrate the drugs to response, this technique is associated with a risk of systemic hypotension. An alternative approach is to accept the small risk of regurgitation and to titrate in the appropriate amount of narcotics and hypnotics as indicated by the blood pressure response while maintaining oxygenation and ventilation with mask and cricoid pressure. With either approach, if the blood pressure starts to rise with laryngeal stimulation, the anesthesiologist should abort the laryngoscopy, maintain ventilation with cricoid pressure, and increase the depth of anesthesia before another attempt at tracheal intubation. Esmolol (0.5 mg/kg) given intravenously may be a useful adjunct in this situation. Labetalol, 10–30 mg in 5-mg increments, is also effective.

The Patient with a Potentially Difficult Airway

The potential risk of aneurysm rupture is increased in patients with a difficult airway.

When a difficult airway is anticipated awake fiberoptic intubation traditionally is the method of choice. Videolaryngoscopy, however, is increasingly displacing fiberoptic intubation as the preferred method, particularly if difficulty with ventilation is not anticipated and the patient can therefore be safely anesthetized. Because translaryngeal injection may cause coughing and hypertension, it is preferable in the patient with a difficult airway to provide topical anesthesia by inhalation of nebulized lidocaine (4%). Sufficient time (20 to 30 minutes), however, must be allowed for this method to be effective. Intravenous fentanyl and midazolam in 50-µg and 1-mg increments, respectively, may be administered judiciously, provided that the patient does not have elevated ICP. Alternatively, after appropriate sedation as outlined previously, translaryngeal injection through the cricothyroid membrane of lidocaine (2.5–3.0 mL of 4% lidocaine) can be performed. After obtundation of the cough reflex with intravenous narcotics, the cough response to the translaryngeal injection should be brief and attenuated. To anesthetize the upper pharynx and laryngopharynx, nebulized lidocaine can be used. Other authorities advocate supplementation with bilateral superior laryngeal nerve block by injecting 0.75 mL lidocaine (2%) subcutaneously on either side of the hyoid arch. We have found the combination of nebulized lidocaine and translaryngeal injection satisfactory.

If there is an unexpectedly difficult airway but ventilation is adequate and tracheal intubation is impossible, the patient should be kept anesthetized with either intravenous or inhalation agents. The usual approach to a difficult intubation with adequate mask ventilation should be employed, utilizing adjunctive measures such as a videolaryngoacope, a fiberoptic bronchoscope or intubating laryngeal mask airway. Attention must simultaneously be directed to control of systemic blood pressure. If neither ventilation nor intubation is possible, transtracheal jet ventilation should be implemented and oxygenation maintained while fiberoptic intubation is attempted. Cricothyroidotomy or tracheostomy may be necessary. The availability of the laryngeal mask airway has improved safety under these conditions.

After Intubation

Monitoring Requirements

Following induction of anesthesia and tracheal intubation, additional monitors and catheters are placed. In addition to standard ASA monitors including ECG, noninvasive blood pressure, pulse oximetry, and end-tidal capnography, a neuromuscular blockade monitor, urinary catheter, and temperature monitor should be used. Monitoring for aneurysm surgery should also include direct intra-arterial blood pressure measurement, preferably instituted before laryngoscopy or induction of anesthesia. Adequate intravenous access is important, and at least one 16-G or well running 18-G peripheral catheter should be inserted in addition to other venous access (see below). To accurately reflect the CPP, the arterial transducer should be placed at the level of the base of the skull and adjusted with any change in the patient's position. Intermittent blood sampling for determination of hematocrit, blood gas, glucose, osmolarity, and electrolyte values is also important. Osmolarity measurement helps determine the efficacy of additional mannitol when the brain is judged "tight"; if serum osmolarity exceeds 320 mOsm, additional mannitol may cause renal dysfunction. Patients placed in the seated position have other requirements, which are discussed in other chapters.

It has been well demonstrated that hyperglycemia can exacerbate cellular injury during cerebral ischemia.[155,156] There has now been a movement toward tight glycemic control utilizing intensive insulin therapy to achieve this goal. Although avoiding very high levels of glucose is important, the rigidity with which such control is achieved may lead to hypoglycemic events and equally devastating neurologic injury.[157] Blood glucose values exceeding 200 mg/dL should be judiciously treated with insulin.

Once the patient is positioned for surgery insertion of the pins for the Mayfield or other pin fixation device can begin; this represents a very noxious stimulus and can raise the blood pressure dramatically if the patient is not pretreated. Infiltration with local anesthesia[158] and administration of additional propofol, or narcotics is an effective regimen. Alternatively, esmolol (0.5 mg/kg) or labetalol (10 to 20 mg) can be used.

Central Venous Pressure Catheter versus Pulmonary Artery Catheter

Consideration for central venous access in patients undergoing craniotomy for aneurysm surgery includes: (1) the prevalence of preexisting hypovolemia, (2) the large intraoperative fluid shift with the use of osmotic and loop diuretics, (3) the potential risk of aneurysm rupture, necessitating blood and fluid resuscitation, and (4) the possible presence of myocardial dysfunction, (5) the need to administer vasoactive medication via a central route. There is a great deal of institutional variability concerning central line placement.[159,160] A PAC can be considered when the patient (1) has known coronary artery disease or ventricular dysfunction, (2) has symptomatic vasospasm necessitating preoperative hypertensive therapy, or (3) has a poor clinical grade and is at high risk of postoperative vasospasm, and intravascular volume expansion is planned. Despite these considerations, it is seldom used in clinical practice because of its inherent risk and the availability of other noninvasive methods based on arterial waveform analysis or esophageal Doppler.

Site of Central Venous Catheter and Pulmonary Artery Catheter Placement

Central venous access can be established via the internal jugular vein, the subclavian vein, or the antecubital vein. Each route has advantages and disadvantages. The internal jugular vein is readily accessible and easy to locate, but some neurosurgeons are concerned about potential venous obstruction. We have not found this possibility to be a problem, and it is our method of choice. For subtemporal incisions, as well as in procedures in which the extracranial internal carotid artery may be temporarily occluded, we place the catheter on the contralateral side to avoid interference with the surgical field. With the advent of the routine use of ultrasound, insertion of a central venous catheter into the internal jugular vein carries a very low risk of complications. However, the intraoperative monitoring of central venous pressure for patient management remains a controversial issue.

The subclavian route does not interfere with cerebral venous drainage but is associated with a significant risk of pneumothorax. The antecubital approach is the least invasive, but has a lower success rate, which can be improved, however, with ECG guidance.

Although it is customary to place the patient in Trendelenburg position to facilitate placement of the central venous catheter, this practice is potentially dangerous in patients with elevated ICP. We generally do not use more than a 5–10% tilt, and for patients with known elevated ICP, we prefer to attempt placement in the neutral supine position.

Because of the potential risk of intraoperative aneurysm rupture, blood should have been typed and crossmatched for the patient and should be available at the time of surgical incision.

Other Monitoring

Other monitoring includes jugular bulb oxygen saturation, noninvasive cerebral oximetry, and TCD.

Placement of a catheter (continuous fiberoptic oximetry or intermittent sampling) in the jugular bulb allows monitoring of the cerebral venous oxygen saturation ($SjvO_2$). Because the cerebral metabolic rate for oxygen is equal to the product of CBF and arteriovenous oxygen content difference—assuming 100% arterial oxygen saturation—$SjvO_2$ reflects the balance between cerebral metabolic supply and demand. This approach is analogous to the monitoring of mixed venous oxygen saturation as an index of the balance between systemic metabolic requirement and cardiac output. The use of jugular venous oximetry in the intensive care of head-injured patients is relatively well established. Its use in the intraoperative management of patients undergoing cerebral aneurysm surgery, however, remains investigative rather than routine. Matta and colleagues[161] reported on the feasibility and safety of the use of retrograde catheters in a variety of neurosurgical procedures. Although the outcome is not addressed in their report, they observed that venous oximetry monitoring in patients undergoing aneurysm surgery allows optimization of ventilation with fine-tuning of $PaCO_2$ to avoid potential cerebral ischemia. Moss and colleagues[162] determined that jugular venous oximetry may facilitate intraoperative blood pressure management, whereas Clavier and associates[163] observed that it can be used to diagnose hyperemia or luxury perfusion. Acute decrease in jugular venous oxygen saturation during intraoperative aneurysm rupture has also been described.[164]

Regional cerebral oximetry uses optical spectroscopy to measure brain vascular hemoglobin saturation in a noninvasive manner to provide similar information. At present, however, it is not reliable enough to be used clinically. Continuous TCD monitoring may improve the safety of induced hypotension by correlating the blood velocity change with the decline in blood pressure. It has also been used perioperatively to confirm the diagnosis of aneurysmal rupture,[165] but its routine use in this regard is impractical.

Positioning of the Patient

The location and the size of the aneurysm generally determine the position of the patient for the surgical procedure. Preoperative review of the angiogram and CT scan will facilitate proper positioning of the patient. Anterior circulation aneurysms are usually approached through a frontal temporal (pterional) incision with the patient in the supine position. Basilar tip aneurysms are approached through a subtemporal incision with the patient in the lateral position or an incision allowing the patient to remain supine. Vertebral and basilar trunk aneurysms are often approached through a suboccipital incision, with the patient either in the seated position or the "park-bench" (semiprone lateral) position. The risk of air embolism is always present, although it is significantly higher in the seated position than in the supine position. As a general principle, because of the duration of these surgical procedures, all bony prominences must be well padded and all extremities well supported before the surgical procedure begins. Equally important before draping is a final inspection of the head and neck position in relationship to the body and palpation of the neck to ensure that jugular venous obstruction does not occur. Failure to make this inspection is a common cause of unexplained intraoperative cerebral swelling. Therefore, it is generally advisable to secure the tracheal tube with tapes rather than a tie because a tie may slip and tighten around the neck. Although not proven, partial venous obstruction may contribute to reported postoperative tongue swelling and airway obstruction in posterior fossa procedures.[166,167] For this reason a soft bite block is preferable to an oropharyngeal airway.

After final positioning, the lung fields should be auscultated to rule out bronchial intubation. Flexion of the head tends to advance the endotracheal tube, whereas extension of the head has the opposite effect. Careful initial placement of the endotracheal tube, ensuring that it measures between 20 and 24 cm

at the teeth (in the average-sized adult), will diminish but not eliminate the possibility of bronchial intubation with flexing of the patient's head.

Maintenance of Anesthesia

The goals during maintenance of anesthesia are to (1) provide a relaxed or "slack" brain that will allow minimal retraction pressure, (2) maintain adequate perfusion to the brain, (3) reduce TMP if necessary during dissection of the aneurysm and final clipping, (4) provide adjunct therapy as needed (this may include induced hypothermia, metabolic suppression, induced hypotension, or adenosine-induced transient cardiac standstill), and (5) allow prompt awakening and assessment of patients with good SAH grades.

With early surgery, the anesthesiologist can expect to see more difficult conditions in which maximal brain "relaxation" therapy is required. Because no data exist about the influence of anesthetic drugs on the outcome of aneurysm surgery, the choice should be based on both the brain condition and the overall management plan, with the patient's preoperative clinical grade taken into consideration. In general, a patient with SAH grades I, II, or III undergoing an uneventful aneurysm clipping should be allowed to awaken and should be extubated in the operating room. Either an intravenous or an inhalation anesthetic, or a combination of both, can be used to provide such conditions.

Nitrous oxide is a cerebral vasodilator when used in combination with a potent inhaled anesthetic.[168,169] It has also been reported to cause cerebral stimulation with an increase in cerebral metabolic rate.[169] Although no outcome studies suggest that nitrous oxide may have a detrimental effect[170] there is little or no advantage in using it with a potent inhaled anesthetic. On the other hand, the vasodilatory properties of nitrous oxide are attenuated when it is used in combination with an intravenous anesthetic agent.[137] Generally, nitrous oxide is omitted when isoflurane or sevoflurane is used, but it may be combined with propofol and fentanyl/remifentanil infusion.

With regard to narcotic agents, fentanyl or sufentanil given either in bolus (50–100 µg and 5–10 µg, respectively) in response to hemodynamic changes or in continuous infusion (1–2 µg/kg/h or 0.1K0.2 µg/kg/h, respectively) or remifentanil as a continuous infusion (0.1–0.3 µg/kg/min), when combined with isoflurane or sevoflurane (0.5–1.0 MAC) provides excellent surgical conditions for most patients in good condition. Desflurane (4–6%), which appears to be similar in cerebrovascular effects to those of isoflurane, could be used as an alternative. Its low blood gas solubility is a theoretical advantage. However, in high concentration it can cause sympathetic stimulation. Sevoflurane has a slightly higher blood-gas solubility, but has a better hemodynamic profile. Although its cardiovascular and cerebrovascular properties appear to be similar to those of other inhaled anesthetics,[171,172] it is unique in that autoregulation appears to be preserved at all concentrations of sevoflurane, whereas other inhaled anesthetics impair the autoregulatory capacity in a dose-related manner.[173,174]

Fentanyl and sufentanil infusions should be discontinued approximately 1 hour before the surgical dressing is applied. The ultra-short-acting remifentanil, used at a rate of 0.1–0.3 µg/kg/min, can be infused until about 5 minutes before the end of dressing application. Systemic hypotension is a potential complication with remifentanil. For the other narcotics, the total dosage should not exceed 10 µg/kg for fentanyl and 2 µg/kg for sufentanil, to allow awakening and immediate neurologic assessment.

No differences among the narcotic drugs have been found with respect to observed brain "tightness"[175] or the amount of retractor pressure required for intraoperative brain retraction. Fentanyl and alfentanil exhibit no significant clinical differences with respect to emergence from anesthesia.[176] Total intravenous anesthesia with propofol and alfentanil infusion has also been used successfully. High-dose narcotics (fentanyl 20–50 µg/kg; sufentanil 2–5 µg/kg), however, will prolong recovery and are unsuitable if rapid awakening and assessment are desired. For patients with poor preoperative SAH grades, extubation of the trachea at the end of the surgical procedure is not planned, and an intravenous anesthetic-based technique may be more appropriate (fentanyl or sufentanil with propofol). In difficult cases in which the brain remains tight, continuous propofol infusion at 150–200 µg/kg/min should be considered. Irrespective of the anesthetic technique used, an important factor to recognize is that the surgical stimulus during cerebral aneurysm surgery varies at different times. Noxious stimuli begin with insertion of the pins of the head holder and intensify with the raising of the bone flap; once the dura is open there is little or no surgical stimulation. The anesthetic plan must, therefore, take this process into consideration to avoid wide fluctuations in CPP or dangerous increases in blood pressure. Of note is the fact that retraction of cranial nerves and the brainstem (posterior fossa aneurysms) may be associated with sudden increases in blood pressure or heart rate. Thus a deeper level of anesthesia must be maintained with these circumstances.

Brain Relaxation

Various maneuvers and adjuncts are used to relax the brain. Although the details of practice vary, they are all directed at the components of the intracranial vault: brain tissue volume, CSF volume, and blood volume.

Patient position can have a profound impact on ICP and brain relaxation. Tankisi and associates[177] found that 10 degrees of reverse Trendelenburg positioning had a favorable effect on ICP while maintaining CPP.

To reduce brain tissue volume, 20% mannitol (0.5–2 g/kg) is usually given over 30 minutes to effect osmotic free water movement from the brain and subsequent diuresis. The usual dose is 1 g/kg; an additional dose is given when indicated by the brain conditions. A total dose of 2 g/kg is frequently given when temporary artery occlusion is planned (also see the section on temporary occlusion). Mannitol's action begins within 4 to 5 minutes and peaks in about 30 to 45 minutes. Although the classic mechanism is believed to be movement of intracellular water into the intravascular volume along the osmotic gradient (the osmolarity of 20% mannitol is 1098 mOsm/L), some evidence exists that the rapid action of mannitol can be mediated by decreased production of CSF.[178] The cardiovascular and cerebrovascular actions of mannitol can be considered to be triphasic: transient, delayed, and late. Because of mannitol's high osmolarity, it transiently increases CBF, CBV, and ICP, which are followed by decreases in CBV and ICP.[179] Systemically, an acute decrease in peripheral vascular resistance occurs, particularly when mannitol is given quickly (<10 minutes). This may result in transient hypotension, followed by a marked rise in CVP, PAWP, and cardiac output. Therefore, the full dose of mannitol should be given over 30 minutes. It also transiently reduces hematocrit, increases serum osmolarity, and causes hyponatremia, hypochloremia, and at high doses, hyperkalemia.[180] Potential complications from the delayed effects therefore include fluid overload and pulmonary edema in patients with poor cardiac function. Within 45 minutes the cardiovascular effects have dissipated, and with the onset of full diuresis the intravascular volume may start to contract. Theoretically mannitol should not be given before the dura is open to minimize fluctuation in ICP. Shrinkage of the brain may also cause tearing

of the bridging veins. In clinical practice, slow mannitol infusion (100–200 mL/h) is frequently begun after final positioning of the patient, and the infusion rate increased after the bone flap has been raised (400–500 mL/hr). Some practitioners routinely use furosemide (0.1– 0.5 mg/kg) to augment the action of mannitol. Additional mannitol, to a total of 2 g/kg, because of its potential brain-protective effect, is often administered before temporary occlusion of major feeding arteries to reduce the risk of aneurysm rupture.[180]

Hypertonic saline is a reasonable alternative to mannitol for brain relaxation. An investigation comparing 20% mannitol with 3% hypertonic saline found no difference between them in the extent of brain relaxation.[181] Volume shift and fluid requirement were lower in the hypertonic saline group.

Reducing the volume of the CSF compartment by drainage of CSF with a lumbar subarachnoid catheter facilitates surgical exposure; the average adult has approximately 150 mL of CSF. Extreme care should be exercised during insertion of the subarachnoid drain to minimize CSF loss and a sudden decrease in ICP, so as to avoid an abrupt increase in TMP predisposing to a rebleed. Because of the risk of brainstem herniation, lumbar drainage of CSF is contraindicated in patients with intracerebral hematoma. In theory, free drainage of CSF should be allowed only after the dura is open to minimize the risk of rebleeding; in practice, however, 20–30 mL of CSF is usually drained just before dural opening to facilitate dural incision. Rapid drainage can cause sudden reflex hypertension, presumably from downward movement of the brainstem, not unlike herniation. Barker has suggested that the drainage rate should not exceed 5 mL/min.[182] The drain is usually left open during the procedure, until the aneurysm is clipped or until the beginning of dural closure.

The equipment used for subarachnoid lumbar drainage varies among different hospitals, and some neurosurgeons prefer not to use CSF drainage, relying on mannitol and hyperventilation instead. We use a standard commercially available kit (Lumbar Catheter Accessory Kit, Cordis Corporation, Miami, FL), which essentially consists of a 14-gauge Touhy needle and a soft flexible catheter having multiple orifices at the end. In essence the subarachnoid drain differs from a subarachnoid catheter inserted for continuous spinal analgesia only in size. Regular lumbar epidural kits designed for epidural anesthesia are generally not satisfactory because the size of the catheter is too small with only one orifice on the distal tip. In patients with acute SAH, blood clots frequently block the drainage. Pediatric feeding catheters have also been used with success, but the stiffness of these catheters increases the risk of potential spinal cord damage. On the other hand, caution must be exercised with the insertion and removal of the soft, flexible catheters. Withdrawal of the catheter through the needle and the use of guidewires increase the risk of catheter shearing.[183] Because the catheter is placed with the patient in the flexed position but often is removed with the patient in the extended or neutral position, the catheter has been known to break off at the site of compression between the vertebral bodies.[183] The patient should, therefore, be placed in the flexed position whenever difficulty with catheter removal is encountered. To avoid the difficulty with insertion and removal of these catheters, some hospitals use malleable spinal needles and simply bend the needle to the patient's contour after placement. This approach is most suited to patients who have been placed in the lateral position for surgery.

CBV can be reduced. Within the physiologic range of $PaCO_2$ (20–70 mmHg) CBF bears an almost linear relationship to arterial $PaCO_2$, changing 2–3% for each 1 mmHg change in $PaCO_2$. Controlled hyperventilation, therefore, can be used to decrease the CBV, which probably changes by about 1% for each 1 mmHg change in $PaCO_2$. Anesthetic agents may influence the response to CO_2, but the changes are clinically insignificant and CO_2 reactivity is generally well preserved. CO_2 reactivity is normal in patients with good SAH grades, but may be impaired in those with poor SAH grades. Although it is generally safe to maintain $PaCO_2$ in the range of 30–35 mmHg, it should be individualized according to the operating conditions. A reasonable approach is to institute mild hypocapnia (30–35 mmHg) before the dura is open, moderate hypocapnia (25–30 mmHg) after the dura is open, and relative normocapnia during induced hypotension (if used) and after the aneurysm is clipped. The advantages of extreme hypocapnia in reducing CBV should always be balanced against the risk of potential cerebral ischemia.[184] Because the objective is to relax the brain without causing ischemia, the efficacy of hyperventilation should be continuously assessed by observing the intraoperative brain relaxation in order to achieve the optimal $PaCO_2$.

In difficult situations, brain relaxation may remain unsatisfactory and refractory to the regimen just described. If this occurs, the anesthesiologist should:

1. make sure that there is no hypoxemia or systemic hypertension
2. check the patient's head and neck position to rule out venous obstruction
3. inspect the subarachnoid drain to ensure patency and proper drainage of CSF
4. discontinue nitrous oxide, since nitrous oxide is a cerebral vasodilator when used in conjunction with an inhaled anesthetic[168].
5. implement a head-up tilt to facilitate venous blood and CSF drainage, after communication with the surgeon[177]
6. give a test dose of propofol bolus (100 to 200 mg) and, if brain relaxation improves, start a continuous infusion (150–200 µg/kg/min). This will usually, but not always, produce a prolonged recovery from anesthesia.

Occasionally, uncontrolled intraoperative swelling may be due to an intracerebral hematoma.

Fluid and Electrolyte Balance

Fluid should be administered according to the patient's need and guided by intraoperative blood loss, urine output, and CVP, if present, or other dynamic index of volume status such as pulse pressure variation.[185] Intravenous fluid should not be withheld if induced hypotension is planned, because hypovolemic hypotension is detrimental to organ perfusion. The aim is to maintain normovolemia before aneurysm clipping and slight hypervolemia after clipping. Electrolytes should be replaced as needed. Glucose-containing solutions should not be given, because evidence exists that hyperglycemia may aggravate both focal and global transient cerebral ischemia.[155,156] Because lactated Ringer's solution is relatively hypo-osmolar, a more physiologic solution, such as Plasma-Lyte, Normo-sol, or normal saline, is preferred. Some practitioners use 5% albumin after clipping of the aneurysm, but the advantages of this protocol have not been documented. On the other hand, hetastarch probably should not be used or should be used sparingly (less than 500 mL) because of the risk of intracranial bleeding.[114,115]

Other Considerations

Controlled Hypotension versus Temporary Occlusion

Because of the enlargement of the aneurysmal sac, the wall stress increases proportionately to increases in blood pressure, as dictated by the law of Laplace, as follows:

$$T = R \times P/2 \qquad (13.1)$$

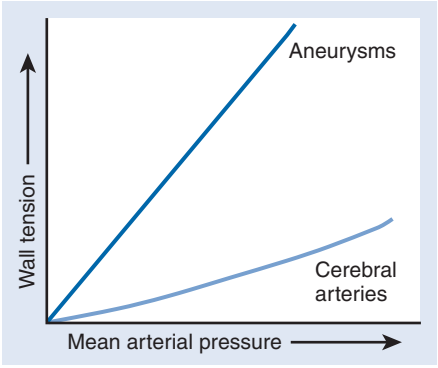


Fig. 13.4 The relationship between wall tension and mean arterial pressure (intracranial pressure is 0 when the dura is open). For any given pressure, wall stress, and therefore the tendency to rupture, is higher in an aneurysmal sac than in a normal cerebral artery. *(From Ferguson GG: The rationale for controlled hypotension. In Varkey GP [ed]: Anesthetic Considerations in the Surgical Repair of Intracranial Aneurysms. Boston, Little, Brown, 1982.)*

where T is wall tension, P is mean blood pressure, and R is the radius of the aneurysm (Fig. 13.4); hence, large aneurysms are more likely to rupture than small ones. Therefore, the blood pressure is traditionally lowered during microscopic dissection of the aneurysm, particularly during clip placement, to reduce the risk of rupture. Hypotension also reduces bleeding, allowing better visualization of the anatomy of the aneurysm and the perforating vessels. Although the risk of hypotension-induced global cerebral ischemia always exists, deliberate hypotension has been used successfully for many years without apparent ill effects. However, the demonstration of impairment of autoregulatory capacity after SAH,[17,18] the unpredictable cerebrovascular response to induced hypotension, increased risk of vasospasm,[135] and reported poorer outcomes[135,186] have rendered the use of deliberate hypotension an exceedingly rare event. Patients with vasospasm, as evidenced by angiography or symptoms, are particularly at risk of ischemia during hypotension.

To reduce the risk of aneurysm rupture without using hypotension, many surgeons are now using temporary occlusion of the major feeding artery[187–190] (Fig. 13.5; modified from 190). The potential risks of temporary occlusion include focal cerebral ischemia and subsequent infarction, as well as damage to the feeding artery from the occlusion. With the improved design of temporary clips, the latter complication is now of less concern. The risk of cerebral infarction remains, however, and is determined by the duration of the temporary occlusion as well as the state of the collateral circulation.

Table 13.6 Temporary Arterial Occlusion versus Controlled Hypotension during Cerebral Aneurysm Surgery

Temporary Occlusion	Controlled Hypotension
Normotension or hypertension	Systemic hypotension
Temporary cessation of flow	Uninterrupted flow
Regional ischemia	Global ischemia
Short duration (10–20 min)	Longer duration
Dependent on collateral vessels	Independent of collateral vessels
Potential vessel damage	No vessel damage
Possibly complete control	Lack of complete control

The anesthetic management of patients during induced hypotension clearly differs from their management during temporary occlusion. The major differences are summarized in Table 13.6.

Controlled Hypotension

The major concerns with controlled hypotension are avoidance of cerebral ischemia and maintenance of organ perfusion. No ideal hypotensive agent exists, but many hypotensive drugs and techniques have been used successfully and are discussed in detail elsewhere in this book.

Temporary Occlusion

Because the tolerable duration of temporary occlusion varies with different arteries as well as among individuals, it is difficult to predict the upper time limit in any given situation. Occlusion for 5 to 7 minutes with prompt reperfusion is usually well tolerated, but this time period is generally insufficient for clipping difficult or giant aneurysms. Although no randomized

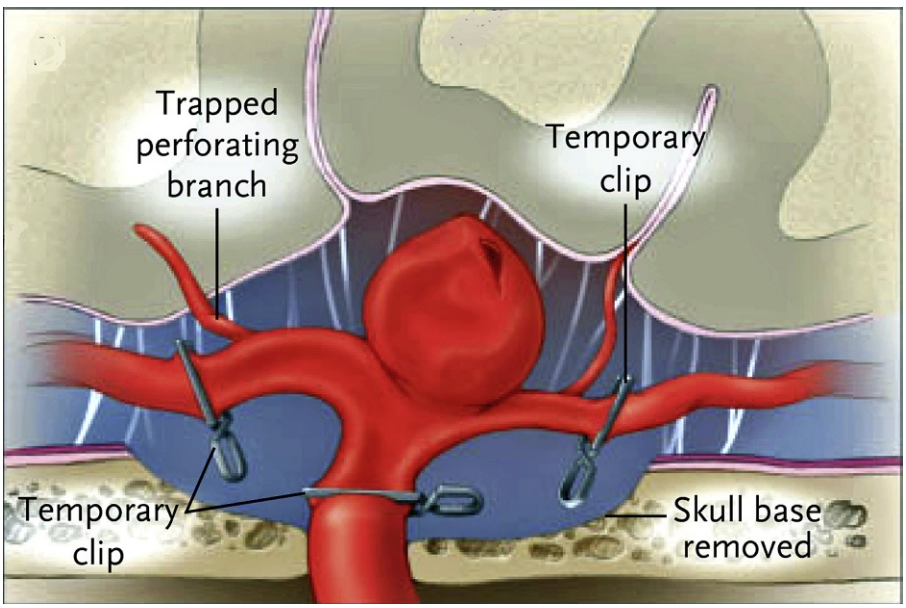


Fig. 13.5 To reduce the risk of rupture of the aneurysm during surgical repair, temporary clips can be placed on the proximal artery as well as on the distal arteries to reduce the pressure inside the aneurysmal sac.

clinical trials have been conducted, a number of regimens have been used to extend the occlusion duration. Suzuki[191] introduced the technique of high-dose mannitol (2 g/kg) for temporary arterial occlusion, and experimental studies have supported a brain-protective role for mannitol. Because neuronal damage may be mediated by the production of free radicals, Suzuki[191] advocates a combination of mannitol (500 mL of a 20% solution, or 100 g), vitamin E (500 mg), and dexamethasone (50 mg), often referred to as the "Sendai cocktail," for temporary arterial occlusion. Up to 60 minutes of temporary arterial occlusion has been obtained with use of this regimen without apparent postoperative neurologic deficits. In general, however, 15 to 20 minutes is considered to be the upper limit of safety[192] with occlusion time of less than 20 minutes being associated with better chances of a good outcome.[193]

Other surgeons use pharmacologic metabolic suppression, theorizing that decreasing cerebral metabolic rate enables the tissues distal to the occlusion to tolerate a longer period of ischemia. Thiopental, etomidate, and propofol have been used for this purpose.[194] Administration of any of these agents prior to temporary clipping generally aims to achieve the endpoint of burst suppression, as indicated by EEG monitoring, in 2 to 3 minutes. Additional doses may be given as indicated by EEG. However, the additional doses may not be effective if collateral circulation is inadequate for delivery of the agent. On the other hand, in this situation the agent that has been given would also stay in the ischemic area longer because of the diminished blood flow for washout. Although there have been no controlled clinical studies, good results have been reported whether thiopental,[195] etomidate,[194] or mannitol[192] was used for cerebral protection. Theoretically, because there is less associated systemic hypotension, etomidate may be preferable to propofol. However, some studies suggest that etomidate, despite reducing global cerebral metabolic rate, may cause cerebral tissue hypoxia during temporary occlusion, as determined with brain oxygen tension measurements.[196] On the other hand, Lavine and associates[194] reported their results comparing patients who received intravenous brain-protective therapy (barbiturates or etomidate) with those who did not (inhalation anesthetics only) during temporary occlusion; they concluded that brain protective therapy can extend the occlusion duration from 12 minutes to 19 minutes without cerebral infarction.

In general, if the temporary occlusion time is kept below 10 minutes, the risk of infarction is low irrespective of anesthetic agents used. In an earlier series, Samson and colleagues[197] reported that patients older than 61 years and in poor condition (Hunt and Hess grades III to V) did not tolerate temporary occlusion as well as patients who were younger and in better neurologic condition. In this series all patients in whom occlusion time exceeded 31 minutes had cerebral infarction. Traditionally, to use pharmacologic protection efficiently, it is necessary to monitor the EEG to define the endpoint, because no further metabolic benefits can be derived with doses greater than those needed to produce burst suppression or electrical silence. Warner and coworkers observed in experimental ischemia that maximal protection with barbiturates need not occur at burst suppression, and such findings have raised questions about this practice.[198] In the absence of clinical data to support this observation, it remains prudent to use burst suppression as the endpoint. Although the data from IHAST trial suggests that metabolic suppression may improve outcome in patients undergoing temporary occlusion >20 min,[199] currently pharmacologic neuroprotection does not have sufficient data to support its routine use, and in each situation the potential risks must be weighed against the sought benefit.[200]

Cardiac Standstill Using Adenosine (Transient Cardiac Pause)

To facilitate clipping of a large aneurysm with a broad neck and reduce the risk of rupture, transient cardiac arrest can be induced with a bolus of adenosine. There is some concern for hypotension and reduced cerebral perfusion; however, in one case series, those that received adenosine had no difference in neurological or cardiac outcome from a control group.[201,202] After a dose response has been established with the use of two to three incremental doses of adenosine between 6 and 18 mg,[203] a duration of approximately 30 seconds of asystole can be induced with an average dose of 30 to 36 mg of adenosine. Recovery of cardiac rhythm is spontaneous and may be followed by rebound tachycardia and hypertension. This technique is contraindicated in patients with preexisting cardiac conduction abnormalities or severe asthma.

Electrophysiologic monitoring can also be used to determine the upper limit of occlusion duration, thus allowing the surgeon to proceed without haste as long as the monitoring suggests normal function. This approach allows the anesthesiologist to recognize the need for brief periods of reperfusion when the monitoring indicates deterioration. EEG or evoked potentials, including MEPs and SSEPs, are increasingly being used for such purposes. It is important to realize the limitations of these modalities: the deep levels of anesthesia given to obtain burst suppression can affect signal quality for the monitoring modalities. Some surgeons use mild hypotension during dissection and then apply temporary arterial occlusion during actual placement of the clip. It is important to restore the blood pressure to normal before the placement of the temporary clips to maximize collateral blood flow.

Moderate Hypothermia and Neuroprotection

Moderate hypothermia (28–32 °C) has also been used in the past to extend the duration of tolerable occlusion.[191] Because experimental studies in cerebral ischemia have demonstrated that even mild hypothermia can exert significant cerebroprotective effects by suppressing release of excitotoxic amino acids,[204,205] the practice of maintaining the body temperature between 33° and 35 °C during the periods when the patient is considered to be at risk for cerebral ischemia was quite routine. Although it is clear that metabolic suppression is achieved, potential complications include ventricular arrhythmia, myocardial depression, coagulopathy, and postoperative shivering. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) evaluated the effects of mild hypothermia (33.5 °C) and found no effect on neurologic outcome in patients with favorable clinical grade aneurysms.[199] No significant complications were noted in the hypothermia group and, specifically, no coagulopathy was observed. The protective effects of moderate hypothermia in patients with poor clinical grade and those with prolonged temporary occlusion, however, have not been studied. Consequently, considering that the cerebroprotective effect of moderate hypothermia following global ischemia has been documented with respect to ventricular fibrillation,[206,207] the intraoperative use of this maneuver for aneurysm surgery in patients at high risk for infarction due to prolonged temporary occlusion needs further evaluation.

Improvements in cardiopulmonary bypass technology and coagulation management have led to a revival of interest in the use of profound hypothermia and circulatory arrest for complex or giant aneurysms (Box 13.1).[208]

In corollary to hypothermia, any increase in body temperature above normal must be vigorously treated. The site of temperature monitoring should reflect the temperature in the brain. Clearly, the temperatures at the surface and deeper part

BOX 13.1 Protocol for Circulatory Arrest

1. Place intra-arterial and large-bore intravenous catheters before induction of anesthesia. The usual precautions for induction of anesthesia in patients with a cerebral aneurysm apply.
2. Once anesthesia is induced and the trachea intubated, place the following devices:
   - Either a central venous line or PAC
   - A second intra-arterial catheter to allow phlebotomy
   - A lumbar subarachnoid drain
   - Electrophysiologic monitors (EEG and/or somatosensory evoked potentials)
   - Both nasopharyngeal and esophageal temperature probes.

   Anticipate periods of stimulation, such as during tracheal intubation, head pinning, and periosteal retraction, which can cause hypertension.
3. Begin surface cooling by using a cooling blanket and lowering the room temperature. The rate of decrease should proceed at approximately 0.2 °C/min.
4. If barbiturates are to be used, administer a 3–5 mg/kg bolus of thiopental to induce either a burst suppression pattern at a 1:5 ratio (i.e., time period in burst relative to electrical silence, or a burst suppression ratio of 80%) or an isoelectric EEG. This can be followed by a continuous infusion of thiopental at 0.1–0.5 mg/kg/min. Once cooling begins, continue the infusion at this rate for the entire period of cardiopulmonary bypass.
5. Perform hemodilution to a hematocrit of 28– 30% by collecting blood into an anticoagulant solution kept at room temperature. Maintain intravascular volume with up to 4 L of cold intravenous saline containing potassium chloride (4–6 mEq/L).
6. After the aneurysm is dissected and hemostasis obtained, begin extracorporeal circulation via femoral artery–femoral vein bypass when the patient's temperature reaches 34 °C. Just before initiation of bypass, ensure surgical hemostasis and then give heparin, 300 to 400 IU/kg, to maintain the ACT between 450 and 480 seconds.
7. Cool the patient to between 15° and 18 °C. Be aware of electrocardiographic changes; at 28 °C, the myocardium is extremely irritable and may fibrillate continuously. Fibrillation should be stopped with 40 to 80 mEq of potassium chloride, but if fibrillation is persistent, defibrillator should be used at 100 to 250 watts/sec. Administer additional doses of potassium chloride as needed.
8. Circulatory arrest occurs between 15° and 18 °C and should be limited to the period of clip application. The EEG should be isoelectric before arrest. If barbiturates were not used earlier, they may be added at this point to achieve a silent EEG. Elevate the patient's head slightly to facilitate venous drainage, keeping in mind that this position increases the potential risk of air embolism and no-reflow phenomenon in small vessels.
9. The circulatory arrest time should be limited to less than 60 minutes for optimal results. This arrest time can be further minimized with intermittent perfusion with or dissection under low flow until the clip is ready to be placed.
10. Once the aneurysm is clipped, bypass is reestablished and the patient is rewarmed at a rate of 0.2° to 0.5 °C/min. Too-rapid rewarming can cause tissue acidosis and hypoxia. Sodium nitroprusside may be used to allow a more homogeneous rewarming.
11. With rewarming, the heart will fibrillate. Perform cardioversion with 200 to 400 joules through external defibrillating pads. Antiarrhythmic drugs may be required to restore a normal sinus rhythm. In addition, the patient may require inotropic support.
12. Discontinue extracorporeal circulation when the patient's temperature is 34 °C and the heart can maintain a normal cardiac output and sinus rhythm. An after-drop in temperature can be expected, and it is important to use other ancillary devices, such as forced warm air, to keep the patient warm.
13. Correct the ACT to 100 and 150 seconds with protamine sulfate. Transfuse the autologous blood containing platelet-rich plasma. Other blood products may be necessary to restore hemostasis.

ACT, activated clotting time; EEG, electroencephalogram.

of the brain may be different,[209] but in general, nasopharyngeal and tympanic membrane temperature closely approximates that of the deep brain structures.[210]

Pharmacologic metabolic suppression or use of mannitol appears to provide some brain protection without the complications of hypothermia. In some centers the routine practice is to use additional mannitol to a total of 2 g/kg just before the proximal vessel occlusion. In patients in whom the collateral circulation has been demonstrated to be poor or nonexistent angiographically and yet temporary occlusion is deemed necessary, we would induce burst suppression with propofol in addition to the use of mannitol. Prior communication between the neurosurgeon and the anesthesiologist is clearly needed for the successful management of these patients. The placement of EEG electrodes must not interfere with the surgical field and the electrodes must be well shielded and protected from both preparation solution and blood to allow proper intraoperative monitoring of EEG. Fortunately, a simple bihemispheric fronto-occipital montage suffices. It can be accomplished by placing surface gel electrodes with appropriate occlusive dressing or needle electrodes over the forehead just above the eyes, which are then referenced to the respective electrodes placed over the ipsilateral mastoid processes.

Electrophysiologic Monitoring

Electrophysiologic monitoring such as EEG and evoked potentials may allow intraoperative detection of cerebral ischemia, leading to a change in surgical technique that improves perfusion. Although there are no randomized clinical trials on the efficacy of evoked potential monitoring, this technique is increasingly used as routine monitoring during aneurysm surgery. Optimal monitoring of SSEPs and MEPs usually necessitates the use of total intravenous anesthesia and the omission of muscle relaxants.

EEG has been used to determine the lowest blood pressure tolerable during induced hypotension, but the results are inconsistent. This is not surprising because a significant decrease in EEG activity can be compatible with normal neurologic recovery. EEG monitoring may be indicated when temporary occlusion is planned, either to determine the duration of tolerance or for titration of anesthetic agents when pharmacologic metabolic suppression is desired.

SSEP monitoring has been investigated for use during procedures on both anterior and posterior circulation aneurysms, whereas brainstem auditory evoked potential (BAEP) monitoring has been investigated primarily for use during procedures on vertebrobasilar aneurysms. Both monitors are probably most useful when temporary or permanent vessel occlusion is planned. Evoked potentials can be recorded even when the EEG signal is suppressed with high-dose barbiturates or propofol and, therefore, represent the only electrophysiologic monitoring technique available when maximal pharmacologic metabolic suppression is used. Similar to other types of electrophysiologic monitoring, even during

temporary occlusion, SSEP monitoring lacks specificity, and a significant false-alarm rate can be expected. The false-negative rate (SSEP unchanged but neurologic deficit occurs) is lower, but remains significant in most series. The implementation of MEP monitoring has improved both sensitivity and specificity, and several case series have reported on positive predictive values on postoperative neurologic deficits. However, there are no studies on the impact of electrophysiologic monitoring on the overall outcome of aneurysm surgery. Table 13.7 summarizes the reported series on the use of SSEPs during temporary arterial occlusion as well as later series on MEPs. Most studies report a high false-positive rate as well as a considerable false-negative rate for SSEPs.[188,189,211–216] Despite these results, routine use of evoked potential monitoring is growing. In selected cases for which permanent occlusion of a major vessel is anticipated, SSEP or BAEP monitoring may be useful. In a series examining the use of both SSEPs and BAEPs in posterior circulation aneurysms, neither modality was superior in predicting neurologic deficits, but the combination reduced the false-positive and false-negative rates to 13% and 20%, respectively.[211] These results are better than reported by most other studies.

Monitoring of MEPs has now been added to multimodality monitoring during intracranial aneurysm surgery. With the significant false-negative rate for SSEP monitoring, the addition of MEPs was sought to improve both the sensitivity and specificity for ischemia resulting in postoperative deficit, particularly that secondary to ischemia of subcortical structures.[217] Several case series[218–222] have shown promising results with better sensitivity than SSEP in both anterior[222] and posterior circulation aneurysms.[223] The proliferation of MEP monitoring for aneurysm surgery may dictate a change in anesthetic plan with regard to the use of inhaled anesthetics as well as neuromuscular blocking agents, both of which have been shown to preclude adequate MEP recording.[224] One must also consider the profound depressive effects that pharmacologic burst suppression has on MEP signal quality. The effect can be so pronounced that MEP signal may be lost completely (authors' unpublished data).

Spontaneous breathing has been used in the past as an indicator of brainstem function, particularly when extreme hypotension is used. It is seldom used today, because optimal brain relaxation is difficult to achieve and extreme hypotension is no longer used. However, with aneurysms involving the low basilar artery and the vertebral arteries, where temporary or permanent occlusion of the feeding vessel is contemplated, spontaneous breathing may provide additional and more specific information than cardiovascular monitoring. Disturbances ranging from tachypnea to apnea have been observed.[211] Spontaneous ventilation has been compared with BAEP as a monitor of brainstem function during vertebrobasilar aneurysm surgery, and its complementary efficacy demonstrated.[225] Fortunately, these situations are extremely rare.

Intraoperative Aneurysm Rupture

The incidence of aneurysm rupture varies with the size and the anatomic location of the aneurysm, larger arteries, posteroinferior cerebellar arteries, and anterior and posterior communicating arteries being more likely to rupture.[226] There also appear to be differences between institutions. In the Cooperative Study, an intraoperative aneurysm leak occurred in about 6% of patients, whereas frank rupture occurred in 13%,[2] for a combined incidence of 19%. In a later series, the rate of rupture was down to 3.8% for frank rupture and 7.9% for all ruptures, including leaks.[226] These findings are similar to those reported by Batjer and Samson.[227] In approximately 8% of the cases reported by the Cooperative Study, the rupture resulted in frank hemorrhagic shock.[2] In Batjer and Samson's series,[227] 7% of the ruptures occurred before dissection of the aneurysm, 48% during dissection, and 45% during clip application. Mortality and morbidity are higher with intraoperative aneurysm rupture. A multicenter study examining intraprocedure rupture of aneurysms similarly reported an incidence of 19% with clipping, and 31% of these cases were associated with death or disability.[228]

Management of aneurysm rupture during surgery partially depends on the ability to maintain the blood volume during the rupture. If the leak is small and dissection is complete,

Table 13.7 Monitoring of SSEPs and MEPs in Temporary Arterial Occlusion for Cerebral Aneurysm Surgery

Study*	No. of Patients	Temporary Occlusion	False-Positive Results	False-Negative Results
MEP monitoring:				
Takebayashi et al. (2014)[218]	50	?	0%	13%
Yeon et al. (2010)[219]	98	98	0%	0%
Irie et al. (2010)[220]	110	0	67%	6%
Szelenyi et al. (2006)[221]	119	71	4%	7%
Horiuchi et al. (2005)[222]	53	?	6%	0
SSEP monitoring:				
Manninen et al. (1994)[211]	70	52	11%	47
Mizoi et al. (1993)[212]	124	97	57%	25
Schramm et al. (1990)[213]	113	34	40%	34%
Manninen et al. (1990)[214]	157	97	43%	14%
Mooij et al. (1987)[187]	5	5	?	0%
Momma et al. (1987)[188]	40	40	60%	5%
Kidooka et al. (1987)[215]	31	15	38%	22%
Symon et al. (1984)[216]	34	15	40%	7%

MEP, motor evoked potential; SSEP, somatosensory evoked potential.
*Superscript numbers indicate chapter references.

the surgeon can gain control with suction and then apply the permanent clip to the neck of the aneurysm. Alternatively, temporary clips can be applied proximally and distally to the aneurysm to gain control. The keys to anesthetic management are good communication with the surgeon and close monitoring of the patient's vital signs as well as the surgical conditions. Video monitors allowing the anesthesiologist to view the surgical field greatly facilitate patient care during this acute, rapidly changing situation. If temporary occlusion is not planned or not possible and blood loss is not significant, the MAP should be decreased transiently to 50 mmHg or even lower to facilitate surgical control. Proximal and distal temporary occlusion, however, is the preferred method. Propofol or etomidate may be given to provide some protection before placement of the temporary clip. If frank hemorrhage occurs, aggressive fluid resuscitation and blood transfusion must begin immediately. Administration of a cerebroprotective agent may not be possible because of its associated hemodynamic effects. Induced hypotension under these circumstances may not be possible, because the intravascular volume must be restored first. During temporary occlusion, normotension must be maintained to maximize collateral perfusion. Excellent results have been achieved by Batjer and Samson[227] with the use of temporary occlusion for intraoperative aneurysm rupture.

Intraoperative Catheter Angiography and Indocyanine Green Videoangiography

Many surgeons routinely perform intraoperative contrast angiography to confirm the proper placement of the clip and patency of the vessels. This practice requires the use of special radiolucent operating room table attachments and the prior placement of intra-arterial sheath for catheter angiography. Near-infrared indocyanine green (ICG) videoangiography has now been introduced,[229] and is routine in many institutions. Injection of 25 mg of ICG as the contrast agent and use of a microscope equipped with the special camera allows the anatomy of the aneurysm and the associated arteries to be visualized. While this is much simpler, and it works efficiently for simple aneurysms, this might not hold true for complex aneurysms, as false-negatives may occur.[230] For difficult aneurysms with complex anatomy intraoperative catheter angiography remains the gold standard.[231]

Emergence and Recovery

Communication between the surgeon and the anesthesiologist is again essential for optimal management of the patient's emergence from anesthesia. If the surgical procedure is uneventful, patients with preoperative SAH grade I or II should be allowed to awaken, and their tracheas may be extubated in the operating room. To minimize coughing, particularly during movement of the head when the surgical dressing is applied, intravenous lidocaine, 1.5 mg/kg, is effective, but its duration of action is only about 3 to 5 minutes. It can be safely repeated if necessary. Because hypertensive therapy is effective in reversing delayed cerebral ischemia from vasospasm, modest levels of postoperative hypertension (<180 mmHg systolic) are not aggressively treated. Nonetheless, severe hypertension (>200 mmHg systolic) may cause increased swelling or cerebral hemorrhage. Labetalol and esmolol are both effective in controlling emergence hypertension. Labetalol is usually given in 5–10-mg increments, and esmolol in 0.1–0.5-mg/kg increments, until blood pressure is controlled. Other hypotensive drugs, including sodium nitroprusside, nitroglycerin, hydralazine, and nicardipine, can also be used. However, these drugs may cause cerebral vasodilation and increase ICP. In institutions where ICP monitors are placed routinely at the end of the surgical procedure and ICP is monitored postoperatively, it is safe to use these vasodilators for control of blood pressure. They are equally safe in patients who are awake and whose neurologic signs are being monitored continually.

Depending on preoperative ventilatory status and the duration and difficulty of the surgical procedure, the patient with preoperative SAH grade III may or may not undergo tracheal extubation in the operating room. In general, one should err on the side of caution. Only when the surgical procedure is uneventful, brain relaxation has not been a problem, and the patient can maintain adequate ventilation with intact laryngeal reflexes, should extubation of the trachea be considered. Patients with preoperative SAH grade IV or V usually require postoperative ventilatory support and continuous neurointensive care. In patients with multiple aneurysms, systemic blood pressure must continue under strict control (within 20% of their normal blood pressure) to prevent rupture of unclipped aneurysms during emergence and recovery from anesthesia.

Patients who have experienced intraoperative aneurysm rupture and patients with vertebrobasilar aneurysms must be considered individually irrespective of their preoperative clinical SAH grade. In both groups the recovery may be slow, and immediate tracheal extubation may not be possible. In the former group, intraoperative cerebral ischemia may have occurred, and in the latter, transient or permanent cranial nerve dysfunction may have resulted from perforator vessel occlusion or brainstem retraction.

POSTOPERATIVE CONSIDERATIONS

In the immediate postoperative period, the anesthesiologist should assess the patient who has undergone cerebral aneurysm surgery to ensure that the recovery is satisfactory and consistent with the anesthetic given. The time of recovery clearly depends on the type and dose of anesthetic given as well as the patient's sensitivity to drugs given. The preoperative condition and intraoperative events must also be taken into consideration. There is no hard-and-fast rule to discriminate between anesthetic effects and surgical complications. Nevertheless, distinguishing residual anesthesia from surgical complications, such as development of subdural or epidural hematomas, is important. The following general guidelines are useful:

1. Anesthesia causes global depression, and any new focal neurologic deficit should be assumed to be a surgical cause, although sedatives and analgesics have been reported to exacerbate or unmask focal neurologic findings in patients with previous strokes.[232]
2. The effect of potent inhaled anesthetics should have largely dissipated after 30–60 minutes.
3. Patients whose pupils are mid-sized and reactive to light and whose respiration is not depressed are unlikely to be experiencing narcotic overdose.
4. The postoperative presence of unequal pupils in a patient without this sign before operation always suggests a surgical event.
5. The patient's neurologic status should be assessed every 15 minutes in the recovery room or intensive care unit, and in some patients an immediate CT scan or angiogram may be necessary.

GIANT ANEURYSMS

Giant cerebral aneurysms are defined as those greater than 2.5 cm in diameter, representing a subset of cerebral aneurysms that may present technical difficulty because of their size or lack of an anatomic neck. They often have perforating

vessels originating in, or probably more typically, adherent to the wall of the aneurysm, as well as a high likelihood of atheromatous changes. The incidence of giant aneurysm is 2% of all patients in the Cooperative Study.[2] Most giant aneurysms manifest as symptoms of a mass lesion, such as headache, visual disturbance, and cranial nerve palsies.

The surgical treatment of these aneurysms is associated with significant perioperative morbidity and mortality. In a series of 174 patients with giant aneurysms who underwent standard surgical treatment, Drake[233] reported that 71.5% of the patients had good outcomes, 13% were severely disabled, and 15.5% died. The series of 174 included 73 patients with giant basilar aneurysms that were associated with a complication rate of near 50% (23% had poor outcome and 25% died). A more recent series of 59 giant aneurysms by a single surgeon had approximately 18% poor outcome and 10% mortality.[234] Surgery for giant aneurysm remains a formidable challenge, and some neurosurgeons advise their patients against operative intervention unless immediate life-threatening risks are present.[235] The introduction of new endovascular technique including pipeline embolization devices may obviate the need for surgical treatment of unruptured giant aneurysms.[236]

Two surgical techniques are used for the management of giant aneurysms considered otherwise inoperable: (1) the use of proximal and distal temporary occlusion to collapse the aneurysm and (2) the use of circulatory arrest with profound hypothermia.[237] Although the former approach has been advocated by some surgeons,[238] it is not considered uniformly applicable. The latter approach had been used as a general approach for all cerebral aneurysms, but fell into disfavor as improvements in microsurgical technique and neuroanesthesia allowed conventional approaches to achieve better results. However, interest in using hypothermic circulatory arrest for giant aneurysms has been revived, with several groups reporting good results and a mortality ranging from 0% to 25%. The main advantages of hypothermic circulatory arrest for giant aneurysm are (1) decompression of the aneurysmal sac, (2) better visualization of the anatomy, (3) a totally bloodless field, and (4) greater ease in placement of the clip across a large or anatomically complicated aneurysm neck. Circulatory arrest can be performed with use of closed-chest femoral vein-femoral artery bypass or through an open chest with median sternotomy and ventricular venting. The closed-chest method is associated with lower morbidity and is preferred.

The anesthetic management of temporary occlusion has already been described; therefore only circulatory arrest under profound hypothermia is discussed here. The major issues concern brain protection and the complications of cardiopulmonary bypass. For details on physiology and management of cardiopulmonary bypass, the reader should consult a standard textbook on cardiovascular anesthesia.

Brain Protection in Circulatory Arrest

Cerebral hypoxia and ischemia are the factors that limit the duration of the circulatory arrest. The metabolic oxygen consumption of the brain may be divided into an active component, which can be regarded as any neuronal activity, and a basal component, which is related to maintenance of cellular integrity. Pharmacologic and nonpharmacologic methods that reduce metabolic oxygen consumption increase the duration of arrest tolerated. At present, these include the use of barbiturates or propofol and profound hypothermia. A number of investigators have reported good results with giant aneurysm surgery utilizing the combination of barbiturate therapy and profound hypothermia during circulatory arrest.[235,238–241] High-dose propofol has also been used to achieve a similar purpose. However, similar results have also been obtained with profound hypothermia alone.[242]

Barbiturates

Barbiturates can reduce the cerebral metabolic rate for oxygen ($CMRO_2$) attributed to the active component to zero and, therefore, reduce the overall $CMRO_2$ to a maximum of 50%. Additional barbiturate administration beyond what is required to cause electrical silence in the EEG will not decrease the metabolic rate further. However, barbiturates may have other actions, including free radical scavenging and membrane stabilization.[239] Therefore, barbiturates may provide additional cerebral protection even during profound hypothermia, although this notion remains controversial. Barbiturate therapy is most effective in preventing cerebral injury secondary to temporary focal ischemia. It is less well established in the situation of temporary global ischemia.

Two modes of administering barbiturates (primarily, sodium thiopental) before cooling and arrest are used, a single bolus and a continuous infusion. In studies in which a single dose of thiopental was given, the amount ranged from 30 to 40 mg/kg administered over 30 minutes.[238,240,243] Thiopental is no longer available in North America, and must be substituted with pentobarbital or propofol. In most of the reported studies, however, EEG monitoring was not used to determine the endpoint. Monitoring the EEG allows the anesthesiologist to titrate the loading dose and the maintenance infusion to achieve EEG burst suppression throughout the procedure.[239,241] A simple bihemispheric two-channel EEG device will suffice. Burst suppression may be accomplished with an initial loading dose of thiopental, 3–5 mg/kg, followed by a continuous infusion varying from 0.1 to 0.5 mg/kg/min for the entire period of cardiopulmonary bypass. With profound hypothermia at temperatures below 18 °C, the EEG is rendered isoelectric even without pharmacologic suppression (in contrast, evoked responses are abolished between 15° and 18 °C). It is recommended that the thiopental infusion rate established during normothermia be maintained during circulatory arrest.[239] In patients with heart disease, thiopental loading may lead to severe myocardial dysfunction, preventing separation of the patient from cardiopulmonary bypass after the aneurysm is clipped. Several small studies examining the cardiac performance in patients undergoing profound hypothermia for cerebral aneurysm surgery demonstrated that cardiac function was only minimally impaired. Similar observations were made with the use of high-dose propofol.[244]

Hypothermia

Hypothermia (Table 13.8), a nonpharmacologic method of reducing the $CMRO_2$, is different from barbiturates in that it reduces not only the active component but also the basal component of the $CMRO_2$. Hypothermia causes a significant reduction in cerebral oxygen consumption and has been demonstrated to protect the brain during anoxic conditions. The period of circulatory arrest tolerated at normothermia is only 4 to 5 minutes, but it doubles for every 8 °C in temperature reduction. Thus, the $CMRO_2$ value drops to 50% of normal with hypothermia at 30 °C, to 25% of normal at 25 °C, 15% of normal at 20 °C, and to 10% of normal at 15 °C. At 15 °C, continuous circulatory arrest can be tolerated for 32 to 40 minutes. The maximum time of deep hypothermic arrest has not been definitively established, but in clinical practice the maneuver has been safely used for up to 60 minutes.[242]

Table 13.8 Hypothermia for Treatment of Giant Cerebral Aneurysms

Body Temperature (°C)	Percentage of Normal Cerebral Metabolic Rate	Period of Tolerated Circulatory Arrest (min)
38	100	4–5
30	50	8–10
25	25	16–20
20	15	32–40
10	10	64–80

Because substantial gradients in temperature can develop between the brain and the periphery during cooling and rewarming, it is important to monitor the brain temperature accurately before circulatory arrest. Williams and associates[242] reported close correlation of brain temperatures measured with esophageal, tympanic membrane, and nasopharyngeal sensors. In contrast, rectal temperatures were unreliable and bladder temperature reliability varied among studies.[245] Direct brain temperature monitoring has also been advocated.[209] To improve safety, at least two temperature monitoring sites should be used.

The depth of hypothermia and the duration of circulatory arrest reported in various studies for treatment of giant aneurysms are summarized in Table 13.9. Note that the amount of time necessary for the clipping is usually less than the tolerable safe limit at the temperature used. Compared to early experience, the mortality and morbidity have declined substantially. The more recent series suggest that temperature should be decreased to 15°–18 °C, since the series with the highest mortality (25%) was associated with circulatory arrest at 25 °C.[246]

Cardiovascular Effects of Profound Hypothermia

Hypothermia induces characteristic cardiovascular changes. As temperature decreases, systemic vascular resistance increases while cardiac output decreases. To allow high pump flow to facilitate rapid cooling and subsequent rewarming, use of vasodilators such as sodium nitroprusside may be necessary. Progressive bradycardia occurs as the temperature approaches 30 °C, and the atrium frequently begins to develop flutter or fibrillation below 30 °C. The ventricles usually fibrillate below 28 °C. Because continuous ventricular fibrillation may cause ischemic injury to the heart, electrical activity should be terminated with administration of 40 to 80 mEq of potassium chloride to the pump or with cardioversion (100 to 250 watts/sec).

Table 13.9 Reports of Circulatory Arrest for Treatment of Giant Cerebral Aneurysms

Study*	No. of Cases	Body Temperature (°C)	Duration of Arrest (min)		Rate of Major Morbidity (%)	Rate of Mortality (%)
			Median	Range		
Schebesch et al. (2010)[247]	26	19.6	23.4 (mean)	3–102	15	11.5
Ponce et al. (2011)[248]	105	17.2	21.8 (mean)	2–72	18	14
Mack et al. (2007)[208]	66	17.6	26.2	6–77	31	12
Levati et al. (2007)[241†]	12	14.1	26.5	9–54	25	0
Lawton et al. (1998)[249‡]	60	9–19	23	2–72	13.3	8.3
Greene et al. (1994)[250§]	2	15–18	40,70	40–70	0	0
Ausman et al. (1993)[251]	9	17–18	20	12–37	22	33
Williams et al. (1991)[242]	10[¶¶]	8.4–13.7	25	1.25–60	20	10
Solomon et al. (1991)[235†]	14	15–22.5	22	8-51	50	0
Thomas et al. (1990)[240†]	1	15.4	35	—	0	0
Spetzler et al. (1988)[239†]	7	17.5–21	11	7–53	29	14
Gonski et al. (1986)[252†]	40	25	10	0–35	23	25
Baumgartner et al. (1983)[238†]	15[¶]	16–21.5	19	0–51	20	0
McMurtry et al. (1974)[253]	12[**]	28–29	9	1–28	50	8
Sundt et al. (1972)[254]	1	13	30	—	100	0
Drake et al. (1964)[237]	10	13–17	14	2–18	40	30
Michenfelder et al. (1964)[255]	15	13–16	17	0–39	40	20
Patterson & Ray (1962)[246]	7	14–17	25	9–43	0	30
Woodhall et al. (1960)[256]	1[††]	12	30	—	100	0

?, means unknown (not reported); —, information not available from the reference.
*Superscript numbers indicate chapter references.
†Barbiturate therapy was also used.
‡Includes patients from previously published series.
§Pediatric cases.
¶¶Only 4 out of 10 are giant aneurysms. The patient who died had an arteriovenous malformation (AVM); the patients with morbidity included 1 with AVM and 1 with aneurysm.
¶Two of 15 are patients with medullary hemangioblastoma.
**One of 12 with AVM.
††Patient with metastatic bronchogenic carcinoma.

Hematologic Effects of Profound Hypothermia

The coagulation system is severely perturbed by hypothermia, and the problem is compounded by inadequate surgical hemostasis or incomplete reversal of heparin with protamine.[238,239,242] Hypothermia-induced coagulopathy is caused by a multitude of factors, including (1) reduction of the platelet count, probably from splenic sequestration, (2) a reversible platelet dysfunction through a decrease in adhesiveness, (3) slowing down of the enzyme-mediated steps in the coagulation cascade, and (4) decrease in the metabolism of heparin. The dilutional effect of priming solutions with cardiopulmonary bypass on coagulation factors I, II, V, VII, and XIII also contributes to difficulty with hemostasis.

Hypothermia also causes an increase in viscosity, leading to sludging of the red blood cells. However, this problem can be effectively treated through a deliberate lowering of the hematocrit with phlebotomy and simultaneously, replacement of the blood volume with a crystalloid solution. The phlebotomy not only decreases the hematocrit but also preserves platelet-rich autologous blood for subsequent transfusion during the rewarming phase. The lower hematocrit reduces oxygen-carrying capacity, but this effect is partially compensated for by the greater amount of dissolved oxygen, which results from the higher oxygen solubility that occurs with hypothermia. The hemoglobin-oxygen dissociation curve, however, is also shifted to the left and may reduce unloading of oxygen in ischemic tissue.

Hyperglycemia

Hypothermia prevents proper utilization and metabolism of glucose and may cause hyperglycemia. As mentioned previously, hyperglycemia may exacerbate neuronal damage during ischemia[141,142] and, therefore, should be treated with insulin. Frequent monitoring of serum glucose and electrolyte concentrations in addition to acid–base balance is, therefore, essential.

Anesthetic Considerations

In addition to the normal evaluation of the patient with SAH, preoperative consideration of patients scheduled for hypothermic circulatory arrest must include special emphasis on coexisting cardiac, pulmonary, hematologic, or neurologic disorders that may require modification of this form of therapy or exclude the patient from undergoing it. For example, patients with aortic valve insufficiency may require the open-chest method of cardiopulmonary bypass to prevent ventricular distention. On the other hand, patients with poor ventricular function, existing coagulopathy, or significant carotid artery disease may be considered unsuitable for the procedure.

Although induction of anesthesia is similar to what has been covered previously regarding monitors, blood pressure control, and intubation, several additional monitors should be considered. These include EEG, SSEP and BAEP monitoring, transesophageal echocardiography, and TCD. The EEG monitors cortical activity and is necessary as an endpoint for barbiturate-induced burst suppression when barbiturates are used for added protection. SSEP monitoring, on the other hand, is a measure of the sensory conduction to the cortex and can be recorded even during a barbiturate-induced silent EEG. The BAEP reflects the function of the auditory pathway through the brainstem and so its monitoring may be useful during procedures on vertebrobasilar aneurysms.[249] During profound hypothermia at 15° to 18°C, all electrophysiologic activity is abolished; nevertheless, SSEP monitoring may allow assessment of neurologic function during cooling as well as rewarming and may have prognostic value. Transesophageal echocardiography allows visualization of the cardiac chambers and assessment of ventricular function and is useful in the management of patients with cardiac disease.[235] In addition, TCD has been used during these procedures,[235] presumably to monitor CBF velocity and emboli, although its value has not been established.

The overall management necessitates a team effort requiring effective communication from all participants. To administer anesthesia safely for hypothermic circulatory arrest, a thorough understanding of the cardiovascular and hematologic perturbations in response to hypothermia must be appreciated. The technique also demands knowledge of the use of the various electrophysiologic monitors that guide efforts to provide cerebral protection. Although the actual practice varies among different institutions, a suggested protocol is appended.

The major and most feared postoperative complication associated with hypothermic cardiac arrest for aneurysm surgery is coagulopathy leading to cerebral hemorrhage. A small leak at the operative site can be disastrous. To reduce this risk, the surgeon should complete the dissection of the aneurysm and verify absolute hemostasis before initiating hypothermic circulatory arrest. Heparinization should be evaluated and followed with the activated clotting time, which should be maintained within 400 to 450 seconds. Once rewarming has occurred and the patient no longer requires bypass, protamine sulfate is titrated to reverse the effect of heparin until the activated clotting time is between 100 and 150 seconds. The phlebotomized blood removed earlier is transfused back, and additional blood products, such as fresh frozen plasma, cryoprecipitate, and platelets, are often required. Meticulous achievement of surgical hemostasis is again necessary before dural closure begins.

The anesthesiologist must also watch for any cardiovascular complications associated with cardiopulmonary bypass, including hypotension, low cardiac output, and hypertension, and must correct any rhythm abnormalities during the cooling or rewarming phase. The patient may also require inotropic support during warming and the immediate postoperative course. With or without additional barbiturate protection, the patient is generally transferred directly to the intensive care unit for continued care. Extubation of the trachea and assessment of neurologic function can usually be accomplished within 12 to 24 hours postoperatively.

SUMMARY

Because of the associated systemic effects and the surgical requirements, patients with cerebral aneurysms present a unique challenge to the anesthesiologist. This chapter has highlighted the major considerations and suggested rational approaches. The important steps are the following:

1. A thorough understanding of the patient's pathophysiology in relation to the subarachnoid hemorrhage as well as other related systemic effects
2. Communication with the neurosurgeon to clarify the surgical approach and the necessity for any specific monitoring
3. Outline of the anesthetic objectives
4. Formulation of anesthetic plan to meet the objectives, taking into consideration one's knowledge of anesthetic drugs and clinical experience (this should also include planning for untoward events intraoperatively such as rupture of the aneurysm)
5. Implementation of the plan.

There will always be patients who, despite our best efforts, fail to benefit from the surgical procedure. It is hoped, however, that with proper planning, optimal results can be achieved.

REFERENCES

1. Drake CG. Aneurysm surgery: past, present, and future. In: Varkey GP, ed. *Anesthetic Considerations in the Surgical Repair of Intracranial Aneurysms*. Boston: Little, Brown; 1982.
2. Kassell NF, Torner JC, Haley Jr EC, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. *J Neurosurg*. 1990;73:18–36.
3. Kassell NF, Torner JC, Jane JA, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. *J Neurosurg*. 1990;73:37–47.
4. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised trial. *Lancet*. 2002;360:1267–1274.
5. Molyneux AJ, Kerr RS, Yu LM, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366:809–817.
6. Campi A, Ramzi N, Molyneux AJ, et al. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). *Stroke*. 2007;38:1538–1544.
7. Spetzler RF, McDougall CG, Albuquerque FC, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. *J Neurosurg*. 2013;119:146–157.
8. Botterell EH, Lougheed WM, Scott JW, Vandewater SL. Hypothermia, and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. *J Neurosurg*. 1956;13:1–42.
9. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28:14–20.
10. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. *J Neurosurg*. 1988;68:985–986.
11. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to sub-arachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery*. 1980;6:1–9.
12. Smith ML, Abrahams JM, Chandela S, et al. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: The Fisher grade revisited. *Surg Neurol*. 2005;63:229–234; discussion 234–235.
13. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modifed Fisher scale. *Neurosurgery*. 2006;59:21–27.
14. Le Roux PD, Elliott JP, Newell DW, et al. Predicting outcome in poor-grade patients with subarachnoid hemorrhage: A retrospective review of 159 aggressively managed cases [see comments]. *J Neurosurg*. 1996;85:39–49.
15. Voldby B, Enevoldsen EM. Intracranial pressure changes following aneurysm rupture. Part 1: Clinical and angiographic correlations. *J Neurosurg*. 1982;56:186–196.
16. Heuer GG, Smith MJ, Elliott JP, et al. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal sub-arachnoid hemorrhage. *J Neurosurg*. 2004;101:408–416.
17. Dernbach PD, Little JR, Jones SC, Ebrahim ZY. Altered cerebral autoregulation and CO_2 reactivity after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1988;22:822–826.
18. Tenjin H, Hirakawa K, Mizukawa N, et al. Dysautoregulation in patients with ruptured aneurysms: Cerebral blood flow measurements obtained during surgery by a temperature-controlled thermoelectrical method. *Neurosurgery*. 1988;23:705–709.
19. Davies KR, Gelb AW, Manninen PH, et al. Cardiac function in aneurysmal subarachnoid haemorrhage: A study of electrocardiographic and echocardiographic abnormalities. *Br J Anaesth*. 1991;67:58–63.
20. Kothavale A, Banki NM, Kopelnik A, et al. Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage. *Neurocrit Care*. 2006;4:199–205.
21. Diringer MN, Lim JS, Kirsch JR, Hanley DF. Suprasellar and intraventricular blood predict elevated plasma atrial natriuretic factor in sub-arachnoid hemorrhage. *Stroke*. 1991;22:577–581.
22. Nelson RJ, Roberts J, Rubin C, et al. Association of hypovolemia after subarachnoid hemorrhage with computed tomographic scan evidence of raised intracranial pressure. *Neurosurgery*. 1991;29:178–182.
23. Zoerle T, Lombardo A, Colombo A, et al. Intracranial pressure after subarachnoid hemorrhage. *Crit Care Med*. 2015;43(1):168–176.
24. Wang X, Chen JX, Mao Q, et al. Relationship between intracranial pressure and aneurysmal subarachnoid hemorrhage grades. *J Neurol Sci*. 2014;346(1-2):284–287.
25. Shapiro HM. Intracranial hypertension: Therapeutic and anesthetic considerations. *Anesthesiology*. 1975;43:445–471.
26. Bakker AM, Dorhout Mees SM, Algra A. Rinkel GJ: Extent of acute hydrocephalus after aneurysmal subarachnoid hemorrhage as a risk factor for delayed cerebral infarction. *Stroke*. 2007;38:2496–2499.
27. Carpenter DA, Grubb Jr RL, Tempel LW, Powers WJ. Cerebral oxygen metabolism after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 1991;11:837–844.
28. Jakobsen M, Enevoldsen E, Bjerre P. Cerebral blood flow and metabolism following subarachnoid haemorrhage: Cerebral oxygen uptake and global blood flow during the acute period in patients with SAH. *Acta Neurol Scand*. 1990;82:174–182.
29. Fugate JE, Rabinstein AA. Aggressive CSF diversion reverses delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a case report. *Neurocrit Care*. 2012;17:112–116.
30. Schmieder K, Moller F, Engelhardt M, et al. Dynamic cerebral autoregulation in patients with ruptured and unruptured aneurysms after induction of general anesthesia. *Zentralbl Neurochir*. 2006;67:81–87.
31. Nornes H, Knutzen HB, Wikeby P. Cerebral arterial blood flow and aneurysm surgery. Part 2: Induced hypotension and autoregulatory capacity. *J Neurosurg*. 1977;47:819–827.
32. Voldby B, Enevoldsen EM, Jensen FT. Cerebrovascular reactivity in patients with ruptured intracranial aneurysms. *J Neurosurg*. 1985;62:59–67.
33. Lam JM, Smielewski P, Czosnyka M, et al. Predicting delayed is chemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. *Neurosurgery*. 2000;47:819–825; discussion 825–826.
34. Jaeger M, Schuhmann MU, Soehle M, et al. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke*. 2007;38:981–986.
35. Budohoski KP1, Czosnyka M, Smielewski P, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: A prospective observational study. *Stroke*. 2012;43(12):3230–3237.
36. Jaeger M1, Soehle M, Schuhmann MU, et al. Clinical significance of impaired cerebrovascular autoregulation after severe aneurysmal subarachnoid hemorrhage. *Stroke*. 2012;43(8):2097–2101.
37. Kassell NF, Peerless SJ, Durward QJ, et al. Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery*. 1982;11:337–343.
38. Hoff RG, Vand GW, Mettes S, et al. Hypotension in anaesthetized patients during aneurysm clipping: Not as bad as expected? *Acta Anaesthesiol Scand*. 2008;52:1006–1011.
39. Ma X, Willumsen L, Hauerberg J, et al. Effects of graded hyperventilation on cerebral blood flow autoregulation in experimental subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2000;20:718–725.
40. Wijdicks EF, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: Is fluid restriction harmful? *Ann Neurol*. 1985;17:137–140.
41. Hasan D, Wijdicks EF, Vermeulen M. Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. *Ann Neurol*. 1990;27:106–108.
42. Betjes MG. Hyponatremia in acute brain disease: The cerebral salt wasting syndrome. *Eur J Intern Med*. 2002;13:9–14.
43. Sherlock M, O'Sullivan E, Agha A, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol (Oxf)*. 2006;64:250–254.
44. Hannon MJ, Behan LA, O'Brien MM, et al. Hyponatremia following mild/moderate subarachnoid hemorrhage is due to SIAD and glucocorticoid deficiency and not cerebral salt wasting. *J Clin Endocrinol Metab*. 2014;99(1):291–298.
45. Harrigan MR. Cerebral salt wasting syndrome: A review. *Neurosurgery*. 1996;38:152–160.
46. Tung PP, Olmsted E, Kopelnik A, et al. Plasma B-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. *Stroke*. 2005;36:1567–1569.
47. Sviri GE, Shik V, Raz B, Soustiel JF. Role of brain natriuretic peptide in cerebral vasospasm. *Acta Neurochir (Wien)*. 2003;145:851–860.
48. McGirt MJ, Blessing R, Nimjee SM, et al. Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. *Neurosurgery*. 2004;54:1369–1373.
49. Taub PR, Fields JD, Wu AHB, et al. Elevated BNP is associated with vasospasm-independent cerebral infarction following aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2011;15:13–18.
50. Rudehill A, Gordon E, Sundqvist K, et al. A study of ECG abnormalities and myocardial specific enzymes in patients with subarachnoid haemorrhage. *Acta Anaesthesiol Scand*. 1982;26:344–350.
51. Lee VH, Oh JK, Mulvagh SL, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2006;5:243–249.

52. Sakr YL, Ghosn I, Vincent JL. Cardiac manifestations after subarachnoid hemorrhage: A systematic review of the literature. *Proc Cardiovasc Dis*. 2002;45:67–80.
53. Lanzino G, Kongable GL, Kassell NF. Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 1994;6:156–162.
54. Frontera JA, Parra A, Shimbo D, et al. Cardiac arrhythmias after sub-arachnoid hemorrhage: Risk factors and impact on outcome. *Cerebrovasc Dis*. 2008;26:71–78.
55. Manninen PH, Ayra B, Gelb AW, Pelz D. Association between electrocardiographic abnormalities and intracranial blood in patients following acute subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 1995;7:12–16.
56. Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. *Acta Neurochir*. 1998;140:87–93.
57. Naidech AM, Kreiter KT, Janjua N, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. *Circulation*. 2005;112:2851–2856.
58. Bulsara KR, McGirt MJ, Liao L, et al. Use of the peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2003;98:524–528.
59. Yarlagadda S, Rajendran P, Miss JC, et al. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. *Neurocrit Care*. 2006;5:102–107.
60. Mayer SA, Lin J, Homma S, et al. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke*. 1999;30:780–786.
61. Zaroff JG, Rordorf GA, Titus JS, et al. Regional myocardial perfusion after experimental subarachnoid hemorrhage. *Stroke*. 2000;31:1136–1143.
62. de Chazal I, Parham 3rd WM, Liopyris P, Wijdicks EF. Delayed cardiogenic shock and acute lung injury after aneurysmal subarachnoid hemorrhage. *Anesth Analg*. 2005;100:1147–1149.
63. Salem R, Vallee F, Depret F, et al. Subarachnoid hemorrhage induces an early and reversible cardiac injury associated with catecholamine release: One-week follow-up study. *Crit Care*. 2014;18:558.
64. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: Evidence for neurally mediated cardiac injury. *J Am Soc Echocardiogr*. 2000;13:774–779.
65. Lee VH, Connolly HM, Fulgham JR, et al. Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: An underappreciated ventricular dysfunction. *J Neurosurg*. 2006;105:264–270.
66. van der Bilt I, Hasan D, van den Brink R, et al. Cardiac dysfunction after aneurysmal subarachnoid hemorrhage. Relationship with outcome. *Neurology*. 2014;82:351–358.
67. Banki N, Kopelnik A, Tung P, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. *J Neurosurg*. 2006;105:15–20.
68. Grad A, Kiauta T, Osredkar J. Effect of elevated plasma norepinephrine on electrocardiographic changes in subarachnoid hemorrhage. *Stroke*. 1991;22:746–749.
69. Zaroff JG, Rordorf GA, Newell JB, et al. Cardiac outcome in patients with subarachnoid hemorrhage and electrocardiographic abnormalities. *Neurosurgery*. 1999;44:34–39; discussion 39–40.
70. Muroi C, Keller M, Pangalu A, et al. Neurogenic pulmonary edema in patients with subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2008;20:188–192.
71. McLaughlin N, Bojanowski MW, Girard F, Denault A. Pulmonary edema and cardiac dysfunction following subarachnoid hemorrhage. *Can J Neurol Sci*. 2005;32:178–185.
72. Kahn JM, Caldwell EC, Deem S, et al. Acute lung injury in patients with subarachnoid hemorrhage: Incidence, risk factors, and outcome. *Crit Care Med*. 2006;34:196–202.
73. Baumann A, Audibert G, McDonnell J, Mertes PM. Neurogenic pulmonary edema. *Acta Anaesthesiol Scand*. 2007;51:447–455.
74. Audu P, Kim LI, Mehta MY, Kim J. Newer anti-epileptic drugs do not cause resistance to non-depolarizing neuromuscular blockade. *Anesthesiology*. 2006;105:A115.
75. Roos YB, Rinkel GJ, Vermeulen M, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2003;(2). CD001245.
76. Baharoglu MI, Germans MR, Rinkel GH, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2013;30(8).
77. Pickard JD, Kirkpatrick PJ, Melsen T, et al. Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagul Fibrinolysis*. 2000;11(Suppl 1):S117–S120.
78. Whitfield PC, Kirkpatrick P. Timing of surgery for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2001;(2). CD001697.
79. Nieuwkamp DJ, de Gans K, Algra A, et al. Timing of aneurysm surgery in subarachnoid haemorrhage – An observational study in the Netherlands. *Acta Neurochir (Wien)*. 2005;147:815–821.
80. de Gans K, Nieuwkamp DJ, Rinkel GJE, et al. Timing of aneurysm surgery in subarachnoid hemorrhage: A systematic review of the literature. *Neurosurgery*. 2002;50(2):336–340.
81. Haley Jr EC, Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery: The North American experience. *Stroke*. 1992;23:205–214.
82. Park J, Woo H, Kang DH, et al. Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. *J Neurosurg*. 2014;18:1–9.
83. Chwajol M, Starke RM, Kim GH, et al. Antifbrinolytic therapy to prevent early rebleeding after subarachnoid hemorrhage. *Neurocrit Care*. 2008;8:418–426.
84. de Oliveira JG, Beck J, Ulrich C, et al. Comparison between clipping and coiling on the incidence of cerebral vasospasm after aneurysmal sub-arachnoid hemorrhage: A systematic review and meta-analysis. *Neurosurg Rev*. 2007;30:22–30.
85. Dumont AS, Crowley RW, Monteith SJ, et al. Endovascular treatment or neurosurgical clipping of ruptured intracranial aneurysms: Effect on angiographic vasospasm, delayed ischemic neurological deficit, cerebral infarction, and clinical outcome. *Stroke*. 2010;41:2519–2524.
86. Carr KR, Zuckerman SL, Mocco J. Inflammation, cerebral vasospasm, and evolving theories of delayed cerebral ischemia. *Neurol Res International*. 2013;2013:1–12.
87. Macdonald RL, Weir BK. A review of hemoglobin and the pathogenesis of cerebral vasospasm. *Stroke*. 1991;22:971–982.
88. Pluta RM, Afshar JK, Boock RJ, Oldfield EH. Temporal changes in perivascular concentrations of oxyhemoglobin, deoxyhemoglobin, and methemoglobin after subarachnoid hemorrhage. *J Neurosurg*. 1998;88:557–561.
89. Carr KR, Zuckerman SL, Mocco J. Inflammation, cerebral vasospasm, and evolving theories of delayed cerebral ischemia. *Neurol Res International*. 2013;2013:1–12.
90. Hijdra A, Van Gijn J, Stefanko S, et al. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Clinicoanatomic correlations. *Neurology*. 1986;36:329–333.
91. Ibrahim GM, Weidauer S, Vatter H, et al. Attributing hypodensities on CT to angiographic vasospasm is not sensitive and unreliable. *Stroke*. 2012;43:109–112.
92. Seiler RW, Grolimund P, Aaslid R, et al. Cerebral vasospasm evaluated by transcranial ultrasound correlated with clinical grade and CT-visualized subarachnoid hemorrhage. *J Neurosurg*. 1986;64:594–600.
93. Clyde BL, Resnick DK, Yonas H, et al. The relationship of blood velocity as measured by transcranial Doppler ultrasonography to cerebral blood flow as determined by stable xenon computed tomographic studies after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1996;38:896–904.
94. Manno EM, Gress DR, Schwamm LH, et al. Effects of induced hypertension on transcranial Doppler ultrasound velocities in patients after subarachnoid hemorrhage. *Stroke*. 1998;29:422–428.
95. Dorhout Mees SM, Rinkel GJ, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;(3) CD000277.
96. Zhao J, Zhou D, Guo J, et al. Efficacy and safety of fasudil in patients with subarachnoid hemorrhage: Final results of a randomised trial of fasudil versus nimodipine. *Neurol Med Chir (Tokyo)*. 2011;51(10):679–683.
97. Haley Jr EC, Kassell NF, Torner JC. A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage: A report of the Cooperative Aneurysm Study. *J Neurosurg*. 1993;78:537–547.
98. Schmid-Elsaesser R, Kunz M, Zausinger S, et al. Intravenous magnesium versus nimodipine in the treatment of patients with aneurysmal subarachnoid hemorrhage: A randomized study. *Neurosurgery*. 2006;58:1054–1065.
99. van den Bergh WM, Algra A, van Kooten F, et al. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: A randomized controlled trial. *Stroke*. 2005;36:1011–1015.
100. Muroi C, Terzic A, Fortunati M, et al. Magnesium sulfate in the management of patients with aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, dose-adapted trial. *Surg Neurol*. 2008;69:33–39.
101. Suarez JI. Magnesium sulfate administration in subarachnoid hemorrhage. *Neurocrit Care*. 2011;15:302–307.
102. Macdonald RL, Higashida RT, Keller E. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: A randomized, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011;10:618–625.

103. Kramer AH, Fletcher JJ. Statins in the management of patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Neurocrit Care*. 2010;12:285–296.
104. Zhang S, Wang L, Liu M, et al. Tirilazad for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2010;17(2).
105. Asano T, Takakura K, Sano K, et al. Effects of a hydroxyl radical scavenger on delayed ischemic neurological deficits following aneurysmal subarachnoid hemorrhage: Results of a multicenter, placebo-controlled double-blind trial. *J Neurosurg*. 1996;84:792–803.
106. Taneda M. Effect of early operation for ruptured aneurysms on prevention of delayed ischemic symptoms. *J Neurosurg*. 1982;57:622–628.
107. Levy ML, Rabb CH, Zelman V, Giannotta SL. Cardiac performance enhancement from dobutamine in patients refractory to hypervolemic therapy for cerebral vasospasm. *J Neurosurg*. 1993;79:494–499.
108. Levy ML, Giannotta SL. Cardiac performance indices during hypervolemic therapy for cerebral vasospasm. *J Neurosurg*. 1991;75:27–31.
109. Treggiari MM, et al. Hemodynamic management of subarachnoid hemorrhage. *Neurocrit Care*. 2011;15(2):329–335.
110. Solomon RA, Fink ME, Lennihan L. Early aneurysm surgery and prophylactic hypervolemic hypertensive therapy for the treatment of aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1988;23:699–704.
111. Mutoh T, Kazumata K, Ishikawa T, et al. Performance of bedside transpulmonary thermodilution monitoring for goal-directed hemodynamic management after subarachnoid hemorrhage. *Stroke*. 2009;40:2368–2374.
112. Mutoh T, Ishikawa T, Nishino K, et al. Evaluation of the FloTrac uncalibrated continuous cardiac output system for perioperative hemodynamic monitoring after subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2009;21:218–225.
113. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348:5–14.
114. Cully MD, Larson Jr CP, Silverberg GD. Hetastarch coagulopathy in a neurosurgical patient. *Anesthesiology*. 1987;66:706–707.
115. Damon L, Adams M, Stricker RB, Ries C. Intracranial bleeding during treatment with hydroxyethyl starch. *N Engl J Med*. 1987;317:964–965.
116. Trumble ER, Muizelaar JP, Myseros JS, et al. Coagulopathy with the use of hetastarch in the treatment of vasospasm. *J Neurosurg*. 1995;82:44–47.
117. Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost*. 1997;78:974–983.
118. Hoh BL, Carter BS, Ogilvy CS. Risk of hemorrhage from unsecured, unruptured aneurysms during and after hypertensive hypervolemic therapy. *Neurosurg*. 2002;50:1207–1212.
119. Elliott JP, Newell DW, Lam DJ, et al. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1998;88:277–284.
120. Komotar RJ, Zacharia BE, Otten ML, et al. Controversies in the endovascular management of cerebral vasospasm after intracranial aneurysm rupture and future directions for therapeutic approaches. *Neurosurgery*. 2008;62:897–905.
121. Schmidt U, Bittner E, Pivi S, et al. Hemodynamic management and outcome of patients treated for cerebral vasospasm with intraar-terial nicardipine and/or milrinone. *Anesth Analg*. 2010;110:895–902.
122. Keuskamp J, Murali R, Chao KH. High-dose intraarterial verapamil in the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2008;108:458–463.
123. Fraticelli AT, Cholley BP, Losser MR, et al. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2008;39:893–898.
124. Mathis JM, DeNardo A, Jensen ME, et al. Transient neurologic events associated with intraarterial papaverine infusion for subarachnoid hemorrhage-induced vasospasm. *AJNR Am J Neuroradiol*. 1994;15:1671–1674.
125. Fandino J, Kaku Y, Schuknecht B, et al. Improvement of cerebral oxygenation patterns and metabolic validation of superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm. *J Neurosurg*. 1998;89:93–100.
126. Kimball MM, Velat GJ, Hoh BL. Critical care guidelines on the endovascular management of cerebral vasospasm. *Neurocrit Care*. 2011;15:336–341.
127. Miller JA, Cross DT, Moran CJ, et al. Severe thrombocytopenia following intraarterial papaverine administration for treatment of vasospasm. *J Neurosurg*. 1995;83:435–437.
128. McAuliffe W, Townsend M, Eskridge JM, et al. Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. *J Neurosurg*. 1995;83:430–434.
129. Pritz MB. Pupillary changes after intracisternal injection of papaverine. *Surg Neurol*. 1994;41:281–282.
130. Stuart RM, Helbok R, Kurtz P, et al. High-dose intra-arterial verapamil for the treatment of cerebral vasospasm after subarachnoid hemorrhage: Prolonged effects on hemodynamic parameters and brain metabolism. *Neurosurgery*. 2011;68:337–345.
131. Goodson K, Lapointe M, Monroe T, Chalela JA. Intraventricular nicardipine for refractory cerebral vasospasm after subarachnoid hemorrhage. *Neurocrit Care*. 2008;8:247–252.
132. Hanggi D, Beseoglu K, Turowski B, Steiger HJ. Feasibility and safety of intrathecal nimodipine on posthaemorrhagic cerebral vasospasm refractory to medical and endovascular therapy. *Clin Neurol Neurosurg*. 2008;110:784–790.
133. Thomas JE, Rosenwasser RH, Armonda RA, et al. Safety of intrathecal sodium nitroprusside for the treatment and prevention of refractory cerebral vasospasm and ischemia in humans. *Stroke*. 1999;30:1409–1416.
134. Jarus-Dziedzic K, Zub W, Warzecha A, et al. Early cerebral hemodynamic alternations in patients operated on the first, second and third day after aneurysmal subarachnoid hemorrhage. *Neurol Res*. 2008;30:307–312.
135. Chang HS, Hongo K, Nakagawa H. Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. *J Neurosurg*. 2000;92:971–975.
136. Buckland MR, Batjer HH, Giesecke AH. Anesthesia for cerebral aneurysm surgery: Use of induced hypertension in patients with symptomatic vasospasm. *Anesthesiology*. 1988;69:116–119.
137. Van Hemelrijck J, Fitch W, Mattheussen M, et al. Effect of propofol on cerebral circulation and autoregulation in the baboon. *Anesth Analg*. 1990;71:49–54.
138. Marx W, Shah N, Long C, et al. Sufentanil, alfentanil, and fentanyl: Impact on cerebrospinal fluid pressure in patients with brain tumors. *J Neurosurg Anesthesiol*. 1989;1:3–7.
139. Sperry RJ, Bailey PL, Reichman MV, et al. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. *Anesthesiology*. 1992;77:416–420.
140. Trindle MR, Dodson BA, Rampil IJ. Effects of fentanyl versus sufentanil in equianesthetic doses on middle cerebral artery blood flow velocity. *Anesthesiology*. 1993;78:454–460.
141. Mayer N, Weinstabl C, Podreka I, Spiss CK. Sufentanil does not increase cerebral blood flow in healthy human volunteers. *Anesthesiology*. 1990;73:240–243.
142. Weinstabl C, Mayer N, Richling B, et al. Effect of sufentanil on intracranial pressure in neurosurgical patients. *Anaesthesia*. 1991;46:837–840.
143. Mayberg TS, Lam AM, Eng CC, et al. The effect of alfentanil on cerebral blood flow velocity and intracranial pressure during isoflurane-nitrous oxide anesthesia in humans. *Anesthesiology*. 1993;78:288–294.
144. Werner C, Kochs E, Bause H, et al. Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. *Anesthesiology*. 1995;83:721–726.
145. de Nadal M, Munar F, Poca MA, et al. Cerebral hemodynamic effects of morphine and fentanyl in patients with severe head injury: Absence of correlation to cerebral autoregulation. *Anesthesiology*. 2000;92:11–19.
146. Baker KZ, Ostapkovich N, Sisti MB, et al. Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. *J Neurosurg Anesthesiol*. 1997;9:134–140.
147. Warner DS, Hindman BJ, Todd MM, et al. Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg*. 1996;83:348–353.
148. Guy J, Hindman BJ, Baker KZ, et al. Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. *Anesthesiology*. 1997;86:514–524.
149. Kapila A, Glass PS, Jacobs JR, et al. Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology*. 1995;83:968–975.
150. Lanier WL, Milde JH, Michenfielder JD. Cerebral stimulation following succinylcholine in dogs. *Anesthesiology*. 1986;64:551–559.
151. Kovarik WD, Mayberg TS, Lam AM, et al. Succinylcholine does not change intracranial pressure, cerebral blood flow velocity, or the electroencephalogram in patients with neurologic injury. *Anesth Analg*. 1994;78:469–473.
152. Manninen PH, Mahendran B, Gelb AW, Merchant RN. Succinylcholine does not increase serum potassium levels in patients with acutely ruptured cerebral aneurysms. *Anesth Analg*. 1990;70:172–175.
153. Lotto ML, Banoub M, Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. *J Neurosurg Anesthesiol*. 2004;16:32–42.
154. Min JH, Chai HS, Kim YH, et al. Attenuation of hemodynamic responses to laryngoscopy and tracheal intubation during rapid sequence induction: Remifentanil vs. lidocaine with esmolol. *Minerva Anestesiol*. 2010;76(3):188–192.

155. Lanier WL, Stangland KJ, Scheithauer BW, et al. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. *Anesthesiology*. 1987;66:39–48.
156. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75:545–551.
157. Prakash A, Matta BF. Hyperglycaemia and neurological injury. *Curr Opin Anaesthesiol*. 2008;21:565–569.
158. Levin R, Hesselvik JF, Kourtopoulos H, Vavruch L. Local anesthesia prevents hypertension following application of the Mayfield skull-pin head holder. *Acta Anaesthesiol Scand*. 1989;33:277–279.
159. Mills SJ, Tomlinson AA. The use of central venous cannulae in neuroanaesthesia. *Anaesthesia*. 2001;56(5):465–470.
160. O'Hare K, Jackson S. Central lines and cerebral aneurysm surgery. *Anaesthesia*. 2002;57:90.
161. Matta BF, Lam AM, Mayberg TS, et al. A critique of the intraoperative use of jugular venous bulb catheters during neurosurgical procedures. *Anesth Analg*. 1994;79:745–750.
162. Moss E, Dearden NM, Berridge JC. Effects of changes in mean arterial pressure on SjO_2 during cerebral aneurysm surgery. *Br J Anaesth*. 1995;75:527–530.
163. Clavier N, Schurando P, Ragguneau JL, Payen DM. Continuous jugular bulb venous oxygen saturation validation and variations during intracranial aneurysm surgery. *J Crit Care*. 1997;12:112–119.
164. Rozet I, Newell DW, Lam AM. Intraoperative jugular bulb desaturation during acute aneurysmal rupture. *Can J Anaesth*. 2006;53:97–100.
165. Eng CC, Lam AM, Byrd S, Newell DW. The diagnosis and management of a perianesthetic cerebral aneurysmal rupture aided with transcranial Doppler ultrasonography. *Anesthesiology*. 1993;78:191–194.
166. Moore JK, Chaudhri S, Moore AP, Easton J. Macroglossia and posterior fossa disease. *Anaesthesia*. 1988;43:382–385.
167. Lam AM, Vavilala MS. Macroglossia: Compartment syndrome of the tongue? *Anesthesiology*. 2000;92:1832–1835.
168. Lam AM, Mayberg TS, Eng CC, et al. Nitrous oxide-isoflurane anesthesia causes more cerebral vasodilation than an equipotent dose of isoflurane in humans. *Anesth Analg*. 1994;78:462–468.
169. Roald OK, Forsman M, Heier MS, Steen PA. Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. *Anesth Analg*. 1991;72:75–79.
170. Pasternak JJ, Lanier WL. Is nitrous oxide use appropriate in neurosurgical and neurologically at-risk patients? *Curr Opin Anaesthesiol*. 2010;23(5):544–550.
171. Artru AA, Lam AM, Johnson JO, Sperry RJ. Intracranial pressure, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane. *Anesth Analg*. 1997;85:587–592.
172. Kuroda Y, Murakami M, Tsuruta J, et al. Blood flow velocity of middle cerebral artery during prolonged anesthesia with halothane, isoflurane, and sevoflurane in humans. *Anesthesiology*. 1997;87:527–532.
173. Cho S, Fujigaki T, Uchiyama Y, et al. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation: Transcranial Doppler study. *Anesthesiology*. 1996;85:755–760.
174. Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *Br J Anaesth*. 1997;79:469–742.
175. From RP, Warner DS, Todd MM, Sokoll MD. Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. *Anesthesiology*. 1990;73:896–904.
176. Mutch WA, Ringaert KR, Ewert FJ, et al. Continuous opioid infusions for neurosurgical procedures: A double-blind comparison of alfentanil and fentanyl. *Can J Anaesth*. 1991;38:710–716.
177. Tankisi A, Rasmussen M, Juul N, Cold GE. The effects of 10 degrees reverse Trendelenburg position on subdural intracranial pressure and cerebral perfusion pressure in patients subjected to craniotomy for cerebral aneurysm. *J Neurosurg Anesthesiol*. 2006;18:11–17.
178. Sahar A, Tsipstein E. Effects of mannitol and furosemide on the rate of formation of cerebrospinal fluid. *Exp Neurol*. 1978;60:584–591.
179. Ravussin P, Archer DP, Tyler JL, et al. Effects of rapid mannitol infusion on cerebral blood volume: A positron emission tomographic study in dogs and man. *J Neurosurg*. 1986;64:104–113.
180. Manninen PH, Lam AM, Gelb AW, Brown SC. The effect of high-dose mannitol on serum and urine electrolytes and osmolality in neurosurgical patients. *Can J Anaesth*. 1987;34:442–446.
181. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology*. 2007;107:697–704.
182. Barker J. An anaesthetic technique for intracranial aneurysms [letter]. *Anaesthesia*. 1975;30:557–558.
183. Olivar H, Bramhall JS, Rozet I, et al. Subarachnoid lumbar drains: A case series of fractured catheters and a near miss. *Can J Anaesth*. 2007;54:829–834.
184. Grüne F1, Kazmaier S, Sonntag H, et al. Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux. *Anesthesiology*. 2014;120(2):335–342. Feb.
185. Qiao H, Zhang J, Liang WM. Validity of pulse pressure and systolic blood pressure variation data obtained from a Datex Ohmeda S/5 monitor for predicting fluid responsiveness during surgery. *J Neurosurg Anesthesiol*. 2010;22(4):316–322.
186. Hitchcock ER, Tsementzis SA, Dow AA. Short- and long-term prognosis of patients with a subarachnoid haemorrhage in relation to intra-operative period of hypotension. *Acta Neurochir (Wien)*. 1984;70:235–242.
187. Jabre A, Symon L. Temporary vascular occlusion during aneurysm surgery. *Surg Neurol*. 1987;27:47–63.
188. Momma F, Wang AD, Symon L. Effects of temporary arterial occlusion on somatosensory evoked responses in aneurysm surgery. *Surg Neurol*. 1987;27:343–352.
189. Mooij JJ, Buchthal A, Belopavlovic M. Somatosensory evoked potential monitoring of temporary middle cerebral artery occlusion during aneurysm operation. *Neurosurgery*. 1987;21:492–496.
190. Ellegala DB, Day AL. Ruptured cerebral aneurysms. *N Engl J Med*. 2005;352:121–124.
191. Suzuki J. Temporary occlusion of trunk arteries of the brain during surgery. *Treatment of Cerebral Infection: Experimental and Clinical Study*. New York: Springer-Verlag; 1987.
192. Ogilvy CS, Carter BS, Kaplan S, et al. Temporary vessel occlusion for aneurysm surgery: Risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. *J Neurosurg*. 1996;84:785–791.
193. Dhandapani S, Pal SS, Gupta SK, et al. Does the impact of elective temporary clipping on intraoperative rupture really influence neurological outcome after surgery for ruptured anterior circulation aneurysms?—A prospective multivariate study. *Acta Neuro-chir (Wien)*. 2013;155:237–246.
194. Lavine SD, Masri LS, Levy ML, Giannotta SL. Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: Time limitation and advantage of brain protection. *J Neurosurg*. 1997;87:817–824.
195. Taylor CL, Selman WR, Kiefer SP, Ratcheson RA. Temporary vessel occlusion during intracranial aneurysm repair. *Neurosurgery*. 1996;39:893–905.
196. Edelman GJ, Hoffman WE, Charbel FT. Cerebral hypoxia after etomidate administration and temporary cerebral artery occlusion. *Anesth Analg*. 1997;85:821–825.
197. Samson D, Batjer HH, Bowman G, et al. A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. *Neurosurgery*. 1994;34:22–28.
198. Warner DS, Takaoka S, Wu B, et al. Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. *Anesthesiology*. 1996;84:1475–1484.
199. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
200. Connolly ES, Rabinstein AA, Carhuapoma, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke*. 2012;43:1711–1737.
201. Bebawy JF, Zeeni C, Sharma S, et al. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation does not worsen neurologic outcome. *Anesth Analg*. 2013;117:1205–1210.
202. Groff MW, Adams DC, Kahn RA, et al. Adenosine-induced transient asystole for management of a basilar artery aneurysm: Case report. *J Neurosurg*. 1999;91:687–690.
203. Hashimoto T, Young WL, Aagaard BD, et al. Adenosine-induced ventricular asystole to induce transient profound systemic hypotension in patients undergoing endovascular therapy: Dose-response characteristics. *Anesthesiology*. 2000;93:998–1001.
204. Minamisawa H, Nordstrom CH, Smith ML, Siesjo BK. The influence of mild body and brain hypothermia on ischemic brain damage. *J Cereb Blood Flow Metab*. 1990;10:365–374.
205. Busto R, Dietrich WD, Globus MY, Ginsberg MD. The importance of brain temperature in cerebral ischemic injury. *Stroke*. 1989;20:1113–1114.
206. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
207. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.

208. Mack WJ, Ducruet AF, Angevine PD, et al. Deep hypothermic circulatory arrest for complex cerebral aneurysms: Lessons learned. *Neurosurgery*. 2007;60:815–827.
209. Stone JG, Goodman RR, Baker KZ, et al. Direct intraoperative measurement of human brain temperature. *Neurosurgery*. 1997;41:20–24.
210. Crowder CM, Tempelhoff R, Theard MA, et al. Jugular bulb temperature: Comparison with brain surface and core temperatures in neurosurgical patients during mild hypothermia. *J Neurosurg*. 1996;85:98–103.
211. Manninen PH, Patterson S, Lam AM, et al. Evoked potential monitoring during posterior fossa aneurysm surgery: A comparison of two modalities. *Can J Anaesth*. 1994;41:92–97.
212. Mizoi K, Yoshimoto T. Permissible temporary occlusion time in aneurysm surgery as evaluated by evoked potential monitoring. *Neurosurgery*. 1993;33:434–440.
213. Schramm J, Koht A, Schmidt G, et al. Surgical and electrophysiological observations during clipping of 134 aneurysms with evoked potential monitoring. *Neurosurgery*. 1990;26:61–70.
214. Manninen PH, Lam AM, Nantau WE. Monitoring of somatosensory evoked potentials during temporary arterial occlusion in cerebral aneurysm surgery. *J Neurosurg Anesthesiol*. 1990;2:97–104.
215. Kidooka M, Nakasu Y, Watanabe K, et al. Monitoring of somatosensory-evoked potentials during aneurysm surgery. *Surg Neurol*. 1987;27:69–76.
216. Symon L, Wang AD, Costa e Silva IE, Gentili F. Perioperative use of somatosensory evoked responses in aneurysm surgery. *J Neurosurg*. 1984;60:269–275.
217. Neuloh G, Schramm J. Monitoring of motor evoked potentials compared with somatosensory evoked potentials and microvascular Doppler ultrasonography in cerebral aneurysm surgery. *J Neurosurg*. 2004;100:389–399.
218. Takebayashi S, Kamiyama H, Takizawa K, et al. The significance of intraoperative monitoring of muscle motor evoked potentials during unruptured large and giant cerebral aneurysm surgery. *Neurol Med Chir(Tokyo)*. 2014;54:180–188.
219. Yeon JY, Seo D-W, Hong S-C, et al. Transcranial motor evoked potential monitoring during the surgical clipping of unruptured intracranial aneurysms. *J Neurol Sci*. 2010;293:29–34.
220. Irie T, Yoshitani K, Ohnishi Y, et al. The efficacy of motor-evoked potentials on cerebral aneurysm surgery and new-onset postoperative motor deficits. *J Neurosurg Anesthesiol*. 2010;22:247–251.
221. Szelenyi A, Langer D, Kothbauer K, et al. Monitoring of muscle motor evoked potentials during cerebral aneurysm surgery: Intraoperative changes and postoperative outcome. *J Neurosurg*. 2006;105:675–681.
222. Horiuchi K, Suzuki K, Sasaki T, et al. Intraoperative monitoring of blood flow insuffciency during surgery of middle cerebral artery aneurysms. *J Neurosurg*. 2005;103:275–283.
223. Quinones-Hinojosa A, Alam M, et al. Transcranial motor evoked potentials during basilar artery aneurysm surgery: Technique application for 30 consecutive patients. *Neurosurgery*. 2004;54:916–924.
224. Sekimoto K, Nishikawa K, Ishizeki J, et al. The effects of volatile anesthetics on intraoperative monitoring of myogenic motor-evoked potentials to transcranial electrical stimulation and on partial neuromuscular blockade during propofol/fentanyl/nitrous oxide anesthesia in humans. *J Neurosurg Anesthesiol*. 2006;18:106–111.
225. Manninen PH, Cuillerier DJ, Nantau WE, Gelb AW. Monitoring of brainstem function during vertebral basilar aneurysm surgery: The use of spontaneous ventilation. *Anesthesiology*. 1992;77:681–685.
226. Leipzig TJ, Morgan J, Horner TG, et al. Analysis of intraoperative rupture in the surgical treatment of 1694 saccular aneurysms. *Neurosurgery*. 2005;56:455–468.
227. Batjer H, Samson D. Intraoperative aneurysmal rupture: Incidence, outcome, and suggestions for surgical management. *Neurosurgery*. 1986;18:701–707.
228. Elijovich L, Higashida RT, Lawton MT, et al. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: The CARAT study. *Stroke*. 2008;39:1501–1506.
229. Raabe A, Nakaji P, Beck J, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. *J Neurosurg*. 2005;103:982–989.
230. Kulwin C, Cohen-Gadol AA. False-negative indocyanine green videoangiography among complex unruptured middle cerebral artery aneurysms: The importance of further aneurysm inspection. *Br J Neurosurg*. 2014;28(5):658. -62, 2014.
231. Imizu S, Kato Y, Sangli A, et al. Assessment of incomplete clipping of aneurysms intraoperatively by a near-infrared indocyanine green-video angiography (Niicg-Va) integrated microscope. *Minim Invasive Neurosurg*. 2008;51:199–203.
232. Thal GD, Szabo MD, Lopez-Bresnahan M, Crosby G. Exacerbation or unmasking of focal neurologic deficits by sedatives. *Anesthesiology*. 1996;85:21–25.
233. Drake CG. Giant intracranial aneurysms: Experience with surgical treatment in 174 patients. *Clin Neurosurg*. 1979;26:12–95.
234. Nanda A, Sonig A, Banerjee AD, et al. Microsurgical management of giant intracranial aneurysms: A single surgeon experience from Louisiana State University, Shreveport. *World Neurosurg*. 2014;81(5-6):752–764.
235. Solomon RA, Smith CR, Raps EC, et al. Deep hypothermic circulatory arrest for the management of complex anterior and posterior circulation aneurysms. *Neurosurgery*. 1991;29:732–737.
236. Murthy SB, Shah S, Venkatasubba Rao CP, Bershad EM, Suarez JI. Treatment of unruptured intracranial aneurysms with the pipeline embolization device. *J Clin Neurosci*. 2014;21(1):6–11.
237. Drake CG, Barr HW, Coles JC, Gergely NF. The use of extracorporeal circulation and profound hypothermia in the treatment of ruptured intracranial aneurysm. *J Neurosurg*. 1964;21:575–581.
238. Baumgartner WA, Silverberg GD, Ream AK, et al. Reappraisal of cardiopulmonary bypass with deep hypothermia and circulatory arrest for complex neurosurgical operations. *Surgery*. 1983;94:242–249.
239. Spetzler RF, Hadley MN, Rigamonti D, et al. Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. *J Neurosurg*. 1988;68:868–879.
240. Thomas AN, Anderton JM, Harper NJ. Anaesthesia for the treatment of a giant cerebral aneurysm under hypothermic circulatory arrest. *Anaesthesia*. 1990;45:383–385.
241. Levati A, Tommasino C, Moretti MP, et al. Giant intracranial aneurysms treated with deep hypothermia and circulatory arrest. *J Neurosurg Anesthesiol*. 2007;19:25–30.
242. Williams MD, Rainer WG, Fieger Jr. HG, et al. Cardiopulmonary bypass, profound hypothermia, and circulatory arrest for neurosurgery. *Ann Thorac Surg*. 1991;52:1069–1074.
243. Silverberg GD, Reitz BA, Ream AK. Hypothermia and cardiac arrest in the treatment of giant aneurysms of the cerebral circulation and hemangioblastoma of the medulla. *J Neurosurg*. 1981;55:337–346.
244. Stone JG, Young WL, Marans ZS, et al. Consequences of electroencephalographic-suppressive doses of propofol in conjunction with deep hypothermic circulatory arrest. *Anesthesiology*. 1996;85:497–501.
245. Camboni D, Philipp A, Schebesch KM, Schmid C. Accuracy of core temperature measurement in deep hypothermic circulatory arrest. *Interact Cardiovasc Thorac Surg*. 2008;7:922–924.
246. Patterson Jr. RH, Ray BS. Profound hypothermia for intracranial surgery: Laboratory and clinical experiences with extracorporeal circulation by peripheral cannulation. *Ann Surg*. 1962;156:377–393.
247. Schebesch KM, Proescholdt M, Ullrich OW, et al. Circulatory arrest and deep hypothermia for the treatment of complex intracranial aneurysms—Results from a single European center. *Acta Neurochir (Wien)*. 2010;152(5):783–792.
248. Ponce FA, Spetzler RF, Han PP, et al. Cardiac standstill for cerebral aneurysms in 103 patients: an update on the experience at the Barrow Neurological Institute. *J Neurosurg*. 2011;113(3):877–884.
249. Lawton MT, Raudzens PA, Zabramski JM, Spetzler RF. Hypothermic circulatory arrest in neurovascular surgery: Evolving indications and predictors of patient outcome. *Neurosurgery*. 1998;43:10–20.
250. Greene KA, Marciano FF, Hamilton MG, et al. Cardiopulmonary bypass, hypothermic circulatory arrest and barbiturate cerebral protection for the treatment of giant vertebrobasilar aneurysms in children. *Pediatr Neurosurg*. 1994;21:124–133.
251. Ausman JI, Malik GM, Tomecek FJ, et al. Hypothermic circulatory arrest and the management of giant and large cerebral aneurysms. *Surg Neurol*. 1993;40:289–298.
252. Gonski A, Acedillo AT, Stacey RB. Profound hypothermia in the treatment of intracranial aneurysms. *Aust N Z J Surg*. 1986;56:639–643.
253. McMurtry JG, Housepian EM, Bowman Jr. FO, Matteo RS. Surgical treatment of basilar artery aneurysms: Elective circulatory arrest with thoracotomy in 12 cases. *J Neurosurg*. 1974;40:486–494.
254. Sundt Jr. TM, Pluth JR, Gronert GA. Excision of giant basilar aneurysm under profound hypothermia: Report of case. *Mayo Clin Proc*. 1972;47:631–634.
255. Michenfielder JD, Kirklin JW, Uihlein A, et al. Clinical experience with a closed-chest method of producing profound hypothermia and total circulatory arrest in Neurosurgery. *Ann Surg*. 1964;159:125–131.
256. Woodhall B, Sealy WC, Hall KD, Floyd WL. Craniotomy under conditions of quinidine-protected cardioplegia and profound hypothermia. *Ann Surg*. 1960;152:37–44.

Interventional Neuroradiology Anesthetic Management

14

P.O. Talke • C.F. Dowd • C.Z. Lee

Interventional neuroradiology (INR) is the discipline that uses endovascular procedures to treat vascular conditions of the central nervous system. Other names for the field are neurointerventional surgery, surgical neuroangiography, and endovascular neurosurgery. INR is firmly established in the management of cerebrovascular disease, a watershed event perhaps being the International Subarachnoid Aneurysm Trial, which provided level 1 evidence that aneurysm coiling has advantages over surgical clipping of intracranial aneurysms.[1]

The discussion in this chapter emphasizes perioperative and anesthetic management strategies to optimize conditions for therapeutic interventions, to prevent complications and to minimize their effects if they occur. We further assume that the primary imaging technology is catheter angiography, although magnetic resonance imaging may one day augment this practice.[2] Planning of the anesthetic and perioperative management is predicated on an understanding of the goals of the therapeutic intervention and anticipation of potential problems.

The anesthetic concerns of particular importance for INR procedures are (1) maintaining the patient's immobility during the procedure to facilitate imaging and to prevent intervention-related complications; (2) either enabling rapid recovery from anesthesia at the end of the operation to facilitate neurologic examination and monitoring or providing for intermittent evaluation of neurologic function during the procedure; (3) managing anticoagulation; (4) treating and managing sudden unexpected procedure-specific complications during the procedure, such as hemorrhage or vascular occlusion, which may involve manipulating systemic blood pressure; (5) guiding the medical management of critical care patients during transport to and from radiology suites; and (6) recognizing self-protection issues related to radiation safety.[3,4]

PREOPERATIVE PLANNING AND PATIENT PREPARATION

Patients for NIR procedures range from healthy outpatients coming for diagnostic NIR procedures to the critically ill, unresponsive patients from the intensive care unit with devastating intracranial bleeds. Procedures may be elective or emergent, such as treatment of acute ischemic strokes. Thus, the preoperative planning may vary significantly from patient to patient.

Baseline blood pressure and cardiovascular reserve should be assessed carefully. This almost axiomatic statement is particularly important for several reasons. Blood pressure manipulation is commonly required, and treatment-related perturbations should be anticipated. Therefore, a clear sense of the patient's baseline blood pressure needs to be established. One must keep in mind that "autoregulation" as presented in the textbooks is a description of a population; individual patients are likely to vary considerably, a concept based on the historical observations that underlie our modern notions of autoregulatory behavior.[5,6] To state the issue another way: when looking at the usual autoregulation curve, one should bear in mind that each point on that curve has a 95% confidence interval (CI) associated with it in both x and y directions. For most procedures, beat-to-beat blood pressure monitoring is useful, considering the rapid time constants in this setting for changes in systemic or cerebral hemodynamics.

Preoperative administration of calcium channel blockers for prophylaxis for cerebral ischemia may be used and can affect hemodynamic management. In addition, these agents or transdermal nitroglycerin are sometimes used to lower the chance of catheter-induced vasospasm.

Radiologic contrast media are well known to cause allergic reactions.[7] There seems to be no difference between the older and newer agents in their propensity to cause anaphylactoid reactions. However, newer agents provide a much lower osmolar load and, therefore, preserve intravascular volume in the event of an allergic crisis. The newer agents are also less neurotoxic than the older, high osmolar contrast agents.

The patient's previous experience with radiologic imaging that may have included administration of contrast agents should be inquired about. As intraprocedural systemic heparinization is commonly used in INR, protamine sulfate is also often used to reverse the anticoagulant effect of heparin. Protamine is also known to cause allergic reactions. In the history, items of interest include prior anticoagulation, coagulation disorders, protamine allergy (related items include protamine insulin use, fish allergy, and prior vasectomy), recent steroid use, and contrast agent reactions (including general atopy and iodine/shellfish allergies).

Patients who give a history of significant contrast agent reactions can be treated with steroids, antihistamines and H2 blockers prior to the procedure. The treatment of severe allergic response is reviewed in general textbooks and prominently features use of adrenergic agonists, such as epinephrine (adrenaline).

The patient's renal function should be evaluated before the procedure due to nephrotoxicity of the contrast agents.

Patients coming from intensive care units may be intubated, mechanically ventilated and have an intra-arterial catheter and/or an extra ventricular device (EVD) in place. Hemodynamic, ventilator and EVD management of these patients should be clearly discussed with the ICU team before the procedure.

A number of considerations regarding the anesthetizing location should be borne in mind. Both wall and tank oxygen should be available. All the usual anesthetizing location considerations should be provided, including adequate lighting, electrical power, and ready access to a phone line (dedicated if at all possible). The access to emergency equipment must be proximate and immediate. One configuration of a modern neuroradiology suite and associated images is shown in Fig. 14.1. Magnetic resonance imaging and conventional

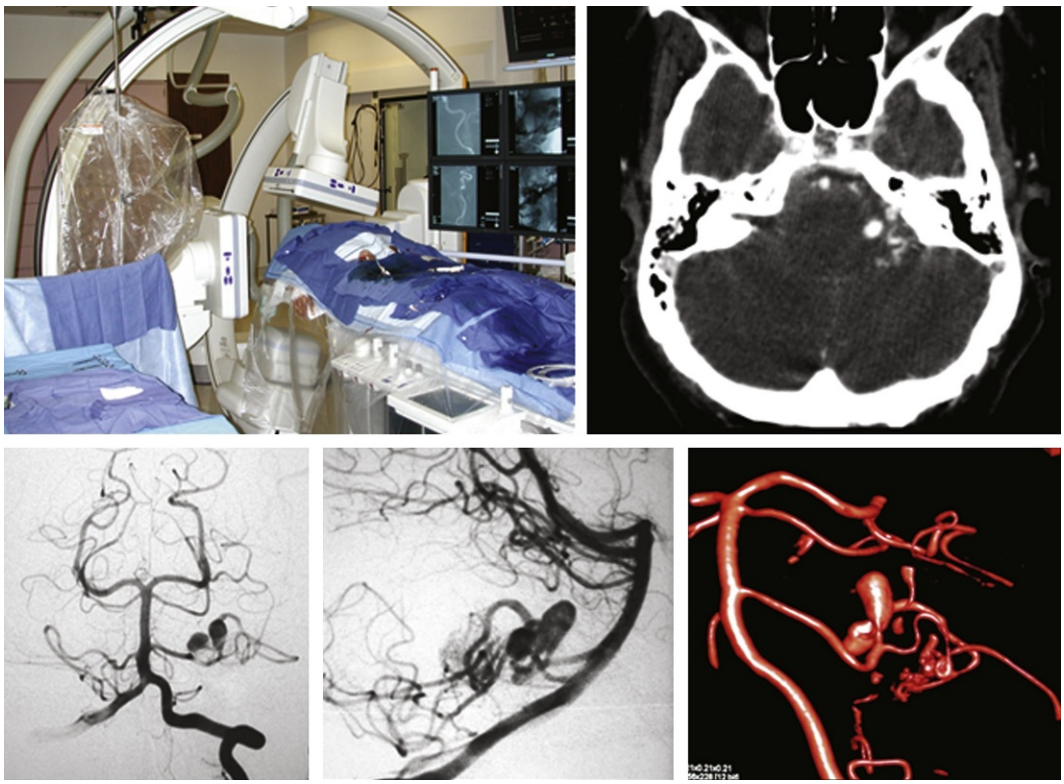


Fig. 14.1 State-of-the-art neuroangiography suite (top left) has the capability to perform computed tomography (top right), biplane angiography (bottom left and middle), and three-dimensional reconstructed rotational angiography (bottom right). These views show a small cerebellar arteriovenous malformation with recently ruptured feeding artery aneurysms (see Fig. 14.6).

Fig. 14.2 Photograph of an interventional radiology suite that combines rotational angiography with MRI capability, allowing immediate transfer of the patient from one modality to the other. The image intensifier for the angiography unit is seen in the foreground; the bore of the magnet and MR gantry is seen in the background. *(Courtesy of Alastair Martin, PhD.)*

angiography units are sometimes combined in one setting (Fig. 14.2).

A fundamental knowledge of radiation safety is essential for all staff members working in an INR suite as well as a critical part of preoperative planning. It is reasonable to assume that the X-ray machine is always on. There are three sources of radiation in the INR suite: *direct radiation* from the X-ray tube, *leakage* (through the collimators' protective shielding), and *scatter radiation* (reflected from the patients and the area surrounding the body part to be imaged). The amount of exposure decreases proportionally to the inverse of the square of the distance from the source of radiation (inverse square law). Digital subtraction angiography delivers considerably more radiation than fluoroscopy.

Optimal protection involves the use of lead aprons, thyroid shields, eye protection, and radiation exposure badges. The lead aprons should be periodically evaluated for any cracks in the lead lining that may allow accidental radiation exposure. Movable lead glass screens may provide additional protection for the anesthesia team. Clear communication between the INR and anesthesia teams is also crucial for limiting radiation exposure. With proper precautions, the anesthesia team should be exposed to far less than the annual recommended limit for health care workers.

Anesthetic Technique

Choice of Anesthetic Technique

The choice of anesthetic technique varies among centers, with no clear superior method, and generally follows the dictates of the well-described considerations for operative neuroanesthesia. At UCSF we typically provide monitored anesthesia care (MAC, sedation) to patients undergoing diagnostic angiography as long as the patients are cooperative and can remain still during image acquisition. Patients receiving therapeutic intervention involving intracranial blood vessels and patients undergoing spinal angiography typically receive general anesthesia (GA).

Secure intravenous (IV) access should be available with adequate extension tubing to allow drug and fluid administration at maximal distance from the image intensifier during fluoroscopy. Access to intravenous or arterial catheters and EVDs can be difficult when the patient is draped with the arms restrained at the sides. Primary anesthetic or vasoactive agent infusions should be given through proximal ports with minimal dead space.

Monitoring

In addition to the standard monitors specified by the American Society of Anesthesiologists, capnography sampling via the sampling port of the nasal cannula is used during IV sedation.

For intracranial procedures and postoperative care, beat-to-beat arterial pressure monitoring and blood sampling can be facilitated by the placement of an intra-arterial catheter. A side port of the femoral artery introducer sheath can also be used, but the sheath is usually removed immediately after the procedure. In a patient who requires continuous blood pressure monitoring or frequent blood sampling postoperatively, it is convenient to have a separate radial arterial catheter. Electrophysiologic monitoring is not commonly used.

With a coaxial or triaxial catheter system, arterial pressure at the carotid artery, the vertebral artery, and the distal cerebral circulation can be measured. Pressures in these distal catheters usually underestimate systolic and overestimate diastolic pressure; however, mean pressures are reliable. Bladder catheters assist in fluid management as well as patient comfort; a significant volume of heparinized flush solution and radiographic contrast agent may be used. Sodium bicarbonate infusions are used to reduce potential renal injury, especially in patients with abnormal renal function. The infusion is typically started before the procedure, and continued till after the end of procedure.

EVDs should be monitored and drained as discussed with the primary care team.

General Anesthesia

The primary reasons for employing general anesthesia in INR are to minimize motion artifacts, to improve the quality of the image and to reduce catheter-induced complications. Normocapnia or modest hypocapnia consistent with the safe conduct of positive-pressure ventilation should be maintained, unless intracranial pressure is a concern. The specific choice of anesthesia may be guided primarily by other cardiovascular and cerebrovascular considerations and typically follow general neuroanesthesia principles. There is no clear superiority of one modern anesthetic over another in terms of pharmacologic protection against neuronal injury. Total intravenous anesthetic techniques, or combinations of inhalational and intravenous methods, may optimize rapid emergence. An argument could be made for avoiding nitrous oxide because of the possibility of introducing air emboli into the cerebral circulation and also because of reports that this agent worsens outcome after experimental brain injury.

It is important to distinguish between the two general settings in which hyperventilation is used in anesthetic practice. First, it is used to treat intracranial hypertension. Hyperventilation is an important mainstay in the management of an intracranial catastrophe to acutely reduce cerebral blood volume (Box 14.1). $PaCO_2$ management should aim at normocapnia or mild hypocapnia to the extent consistent with the safe conduct of positive-pressure ventilation. If a patient has increased intracranial pressure, prophylactic mild hypocapnia may be indicated during the induction and maintenance of anesthesia. Patients who have been hyperventilated in the ICU before the procedure, and patients who may be spontaneously hyperventilating secondary to cerebral injury should have their pCO_2 maintained at or below pre-procedure levels.

Intravenous Sedation

For cases managed with an unsecured airway, routine evaluation of the potential ease of laryngoscopy in an emergency situation should take into account that direct access to the airway may be limited by table or room logistics. Recent pterional craniotomy can sometimes result in impairment of temporomandibular joint mobility.

For IV sedation cases, careful padding of pressure points and working with the patient to obtain a final comfortable positioning may assist in the patient's ability to tolerate a long period of lying supine and motionless, decreasing the requirement for sedation, anxiolysis, and analgesia. The possibility of pregnancy in women and a history of adverse reactions to radiographic contrast agents should be explored.

Intravenous sedation in aneurysm management is used most often for patients coming for diagnostic angiography or interim follow-up angiography to assess the necessity for re-treatment after primary coiling. If further treatment is indicated or the patient is not able to stay still during image acquisition, the technique can be converted to general anesthesia. The goals of anesthetic choice for intravenous sedation are to alleviate pain, anxiety, and discomfort, and allow rapid recovery. There may be some discomfort associated with injection of contrast media into the cerebral arteries (burning) and with distention or traction on them (headache). A long period of lying motionless can also cause significant discomfort.

A variety of sedation regimens is available, and specific choices are based on the experience of the practitioner and the goals of anesthetic management. Common to all intravenous sedation techniques is the potential for upper airway obstruction. However, light levels of sedation that provide anxiolysis are usually optimal as the patients need to stay still and hold their breath during image acquisition. At UCSF we frequently use small doses of midazolam and fentanyl for sedation during NIR procedures. Placement of a nasopharyngeal airway may cause troublesome bleeding in anticoagulated patients and is generally avoided.

Dexmedetomidine is a newer agent that may have applicability in the INR setting. It is a potent, selective alpha2 adrenoceptor agonist with sedative, anxiolytic, and analgesic properties. Dexmedetomidine is especially noteworthy for its ability to produce a state of patient tranquility without depressing respiration. However, like other sedatives, dexmedetomidine-induced sedation may cause upper airway obstruction. More importantly, there is a tendency for patients managed with dexmedetomidine to have relatively low blood

BOX 14.1 Management of Intracranial Catastrophes[*]

Initial Resuscitation

Communicate with endovascular therapy team. Assess the need for assistance; call for assistance. Secure the airway and ventilate with 100% O_2.

Determine whether the problem is hemorrhagic or occlusive:

Hemorrhagic: Immediate heparin reversal (1 mg protamine for each 100 units of heparin given) and low normal mean arterial pressure.

Occlusive: Deliberate hypertension, titrated to findings of neurologic examination, angiography, or physiologic imaging studies or to clinical context.

Further Resuscitation

$PaCO_2$ manipulation consistent with clinical setting; otherwise normocapnia. Mannitol 0.5 g/kg, rapid IV infusion.

Titrate IV agent to electroencephalographic burst suppression.

Consider ventriculostomy for treatment or monitoring of increased intracranial pressure. Consider anticonvulsant.

*These are only general recommendations and drug doses. They must be adapted to specific clinical situations and in accordance with a patient's preexisting medical condition. In some cases of asymptomatic or minor vessel puncture or occlusion, less aggressive management may be appropriate.

There are some special circumstances for which induced *hypercapnia* may be indicated, such as embolization of extracranial vascular malformations, which drain into the intracranial venous system. In these cases, induction of hypercapnia can promote high venous outflow from the cerebral venous system and help minimize the risk of inadvertent movement of embolic material into the intracranial compartment (discussed later).

pressure in the postoperative recovery period.[8] Because patients with aneurysmal subarachnoid hemorrhage (SAH) may be critically dependent on the adequacy of collateral perfusion pressure, regimens that may result in blood pressure decreases should be used with great caution.

Anticoagulation

Heparin

Careful management of coagulation is required to prevent thromboembolic complications during and after the procedure. Generally, after a baseline activated clotting time is obtained, intravenous heparin (approximately 70 units/kg) is given to a target prolongation of 2 to 3 times the baseline value. Then heparin can be given continuously or as an intermittent bolus with hourly monitoring of activated clotting time. For the occasional case of refractoriness, adequate anticoagulation, switching from bovine to porcine heparin, or vice versa, should be considered. If antithrombin III deficiency is suspected, administration of fresh frozen plasma may be necessary.

Direct Thrombin Inhibitors

Heparin-induced thrombocytopenia is a rare but important adverse event in heparin anticoagulation. Development of heparin-dependent antibodies after initial exposure leads to a prothrombotic syndrome. In high-risk patients, direct thrombin inhibitors can be applied, with the realization that adverse events are inherent to their use, such as anaphylaxis. Direct thrombin inhibitors inhibit free and clot-bound thrombin, and their effect can be monitored by either an activated partial thromboplastin time or activated clotting time. Lepirudin and bivalirudin, a synthetic derivative, have half-lives of 40 to 120 minutes and about 25 minutes, respectively. Because these drugs undergo renal elimination, dose adjustments may be needed in patients with renal dysfunction. Argatroban is an alternative agent that undergoes primarily hepatic metabolism. One report has described bivalirudin as a potential alternative to heparin during INR procedures for intravenous anticoagulation and intra-arterial thrombolysis.[9]

Antiplatelet Agents

Although still controversial in the acute setting,[10] antiplatelet agents (aspirin, the glycoprotein IIb/IIIa receptor antagonists, and the thienopyridine derivatives) are increasingly being used for cerebrovascular disease management[11] and may be of use for acute treatment of thromboembolic complications.[12] Abciximab (ReoPro) has been used to treat thromboembolic complications. Activation of the platelet membrane glycoprotein IIb/IIIa leads to fibrinogen binding and is a final common pathway for platelet aggregation. Abciximab, eptifibatide, and tirofiban are glycoprotein IIb/IIla receptor antagonists. The long duration and potent effect of abciximab also increase the likelihood of major bleeding. The smaller-molecule agents, eptifibatide and tirofiban, are competitive blockers with shorter half-lives of about 2 hours. Thienopyridine derivatives (ticlopidine and clopidogrel) bind to the platelet's adenosine diphosphate receptor, permanently altering the receptor; therefore, the duration of action is the lifespan of the platelet. Clopidogrel is commonly added to the antiplatelet regimen for procedures that require placement of devices (eg, stents, coiling or stent-assisted coiling) primarily in patients who have not had an acute event, such as those with unruptured aneurysms. Patients who are expected to receive stents, should be pretreated with antiplatelet agents, because of the potential risk of thrombus formation on the stent.

Reversal of Anticoagulation

At the end of the procedure or at occurrence of hemorrhagic complication, heparin anticoagulation may be reversed with protamine. Because there is no specific antidote for the direct thrombin inhibitors or the antiplatelet agents should reversal be indicated, biologic half-life is one of the major considerations in drug choice, and platelet transfusion is a nonspecific therapy. There is no currently available accurate test to measure platelet function in patients taking the newer antiplatelet drugs. Desmopressin (DDAVP) has been reported to shorten the prolonged bleeding time of individuals taking antiplatelet agents, such as aspirin and ticlopidine. There are also increasingly more reports on the use of specific clotting factors, such as recombinant factor VIIa and factor IX complex, to rescue severe life-threatening bleeding, including intracranial hemorrhage uncontrolled by standard transfusion therapy. The safety and efficacy of these coagulation factors remain to be investigated.

DELIBERATE HYPERTENSION

During acute arterial occlusion or vasospasm, the only practical way to increase collateral blood flow may be an augmentation of the collateral perfusion pressure by raising the systemic blood pressure. The circle of Willis is a primary collateral pathway in cerebral circulation. However, in as many as 21% of otherwise normal subjects, the circle may not be complete. There are also secondary collateral channels that bridge adjacent major vascular territories, most importantly for the long circumferential arteries that supply the hemispheric convexities. These pathways are known as the pial-to-pial collateral or leptomeningeal pathways.

The extent to which the blood pressure has to be raised depends on the condition of the patient and the nature of the disease. Typically, during deliberate hypertension, the systemic blood pressure is raised by 30% to 40% above baseline in the absence of some direct outcome measure, such as resolution of ischemic symptoms or imaging evidence of improved perfusion. Phenylephrine, usually the first-line agent for deliberate hypertension, is titrated to achieve the desired level of blood pressure. Norepinephrine (noradrenaline) and vasopressin are used occasionally when phenylephrine is not sufficient to increase blood pressure. The electrocardiogram and ST segment monitor should be carefully inspected for signs of myocardial ischemia. Intra-arterial blood pressure monitoring should be used during use of deliberate hypertension.

The risk of causing hemorrhage into an ischemic area must be weighed against the benefits of improving perfusion, but augmentation of blood pressure in the presence of acute cerebral ischemia is probably protective in most settings. There is also a risk of rupturing an aneurysm or arteriovenous malformation (AVM) with induction of hypertension. There are no data that deal with this risk directly, other than older case series that report rupture during anesthetic induction in the range of about 1% that was presumably due to acute hypertension. For AVMs, cautious extrapolation of observations for head-frame application suggests the rarity of AVM rupture from acute blood pressure increases. Szabo and colleagues[13] measured blood pressure changes noninvasively in 56 conscious, unpremedicated patients undergoing local anesthetic injection and pin insertion; the maximum mean arterial pressure was 118 ± 7 mmHg, representing an increase of 37% from baseline. These researchers concluded that since none of their 56 patients, nor any of the more than 1000 patients treated in similar fashion, suffered a hemorrhage, moderate arterial hypertension does not cause spontaneous AVM hemorrhage.[13]

DELIBERATE HYPOTENSION

The two primary indications for induced hypotension are (1) to test cerebrovascular reserve in patients undergoing carotid test occlusion and (2) to slow flow in a feeding artery of a brain AVM before injecting glue (sometimes termed "flow arrest"). The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while keeping the patient physiologically stable, and, if the patient is awake, not to interfere with neurologic assessment.

The choice of agent should be determined by the experience of the practitioner, the patient's medical condition, and the goals of the blood pressure reduction in a particular clinical setting. We typically use nicardipine or sodium nitroprusside infusions to induce hypotension. Intravenous adenosine has been used during aneurysm surgery to induce transient cardiac pause and may be a viable method of partial flow arrest.[14] Direct intra-arterial blood pressure monitoring should be used during deliberate hypotension.

MANAGEMENT OF NEUROLOGIC AND PROCEDURAL CRISES

A well thought-out plan, coupled with rapid and effective communication between the anesthesia and radiology teams, is critical for good outcomes in INR. The primary responsibility of the anesthesia team is to preserve gas exchange and stable hemodynamics, and, if indicated, secure the airway. Simultaneous with airway management, the first branch in the decision-making algorithm is for the anesthesiologist to communicate with the INR team and determine whether the problem is hemorrhagic or occlusive.

In the setting of vascular occlusion, the goal is to increase distal perfusion by means of blood pressure augmentation with or without direct thrombolysis. If the problem is hemorrhagic, immediate cessation of heparin and reversal of anticoagulation with protamine is indicated. As an emergency reversal dose, 1 mg protamine can be given for each 100 units of initial heparin dosage that resulted in therapeutic anticoagulation. The activated clotting time can then be used to fine-tune the final protamine dose. Complications of protamine administration include hypotension, true anaphylaxis, and pulmonary hypertension. With the advent of newer long-acting direct thrombin inhibitors, such as bivalirudin, new strategies for emergency reversal of anticoagulation need to be developed.

Bleeding catastrophes are usually heralded by headache, nausea, vomiting, and vascular pain related to the area of perforation. Sudden loss of consciousness is not always due to intracranial hemorrhage. Seizures, due to contrast media reaction or transient ischemia, and the resulting postictal state, can also result in an obtunded patient. In the anesthetized or comatose patient, the sudden onset of bradycardia and hypertension (Cushing response) or the endovascular therapist's diagnosis of extravasation of contrast agent may be the only clues to a developing hemorrhage. Most cases of vascular rupture can be managed in the angiography suite. The INR team can attempt to seal the rupture site endovascularly and abort the procedure; a ventriculostomy catheter may be placed emergently in the angiography suite. Some authorities suggest that ventriculostomy catheters should be placed prior to the procedure in selected high-risk patients, for example, those with ventricomegaly.[15] After the procedure, the patient with suspected rupture requires evaluation with computed tomography, but emergency craniotomy is usually not indicated. Some of the newer angiographic C-arm image acquisition systems are capable of producing CT images, although these are often of lesser quality than could be obtained by standard CT scanners.

SPECIFIC PROCEDURES

Table 14.1 summarizes representative procedures in INR.

Intracranial Aneurysm Ablation

Patients undergoing intracranial aneurysm ablation may have ruptured or unruptured aneurysms. They may have multiple aneurysms. Patients may come from home or from the ICU. They may be neurologically normal or devastated. Many patients have multiple comorbidities.

The two basic approaches for INR therapy of cerebral aneurysms are occlusion of proximal parent arteries and obliteration of the aneurysmal sac. With the publication of the International Subarachnoid Aneurysm Trial,[16] coil embolization

Table 14.1 Interventional Neuroradiologic Procedures and Primary Anesthetic Considerations

Procedure	Possible Anesthetic Considerations
Therapeutic embolization of vascular malformation:	
Intracranial AVM	Deliberate hypotension, postprocedure NPPB
Dural arteriovenous fistula	Existence of venous hypertension; deliberate hypercapnia
Extracranial AVM	Deliberate hypercapnia
Carotid cavernous fistula	Deliberate hypercapnia, postprocedure NPPB
Cerebral aneurysms	Aneurysmal rupture, blood pressure control[*]
Ethanol sclerotherapy of arteriovenous or venous malformations	Brain swelling, airway swelling, hypoxemia, hypoglycemia, intoxication from ethanol, cardiorespiratory arrest
Balloon angioplasty and stenting of occlusive cerebrovascular disease	Cerebral ischemia, deliberate hypertension, concomitant coronary artery disease, bradycardia, hypotension
Balloon angioplasty of cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage	Cerebral ischemia, blood pressure control[*]
Therapeutic carotid occlusion for giant aneurysms and skull base tumors	Cerebral ischemia, blood pressure control[*]
Thrombolysis of acute thromboembolic stroke	Postprocedure intracranial hemorrhage (NPPB), concomitant coronary artery disease, blood pressure control[*]
Intra-arterial chemotherapy of head and neck tumors	Airway swelling, intracranial hypertension
Embolization for epistaxis	Airway control

AVM, arteriovenous malformation; NPPB, normal perfusion pressure breakthrough.
*Blood pressure control refers to deliberate hypotension or hypertension.

of intracranial aneurysms has become a routine first-choice therapy for many lesions (Fig. 14.3). Inflation of a temporary balloon catheter (balloon assisted coiling) or stents (stent assisted coiling) may be used to aid in placement of coils in selected cases (Fig. 14.4). Patients for whom stent placement is contemplated may be started on antiplatelet agents preoperatively.

There is great interest in the development of stent-assisted coiling methods (Fig. 14.5). Placement of embolic coils within a target aneurysm may be difficult if the aneurysm has a wide neck. Stent-supported coiling is designed to provide a scaffold for the containment of the coils within the aneurysm sac and to provide continued patency of the parent artery. Aggressive antiplatelet therapy, currently using both aspirin and clopidogrel, must accompany the performance of stent-assisted coiling procedures owing to the risk of thromboembolic complications. Stent placement requires more instrumentation and manipulation, probably increasing the ever-present intraprocedural risk of parent vessel occlusion, thromboembolism, or vascular rupture.

Anesthetic management should proceed with the usual considerations employed in the care of a patient with an intracranial aneurysm.[17] Patients with aneurysmal SAH often have either increased intracranial pressure or decreased intracranial compliance, secondary to the mass of SAH, parenchymal injury from ischemia or hydrocephalus.

The anesthesiologist should be prepared for aneurysmal rupture and acute SAH at all times, from spontaneous rupture of a leaky sac to direct injury of the aneurysm wall by the vascular manipulation, perianeurysmal thrombus formation, or arterial branch occlusion. The morbidity and mortality of intraprocedural rupture is high. One report found that, in the 5% of the studied coiling cases, 63% of patients with intraprocedural rupture had periprocedural death or disability compared with 15% of those without intraprocedural rupture.[18]

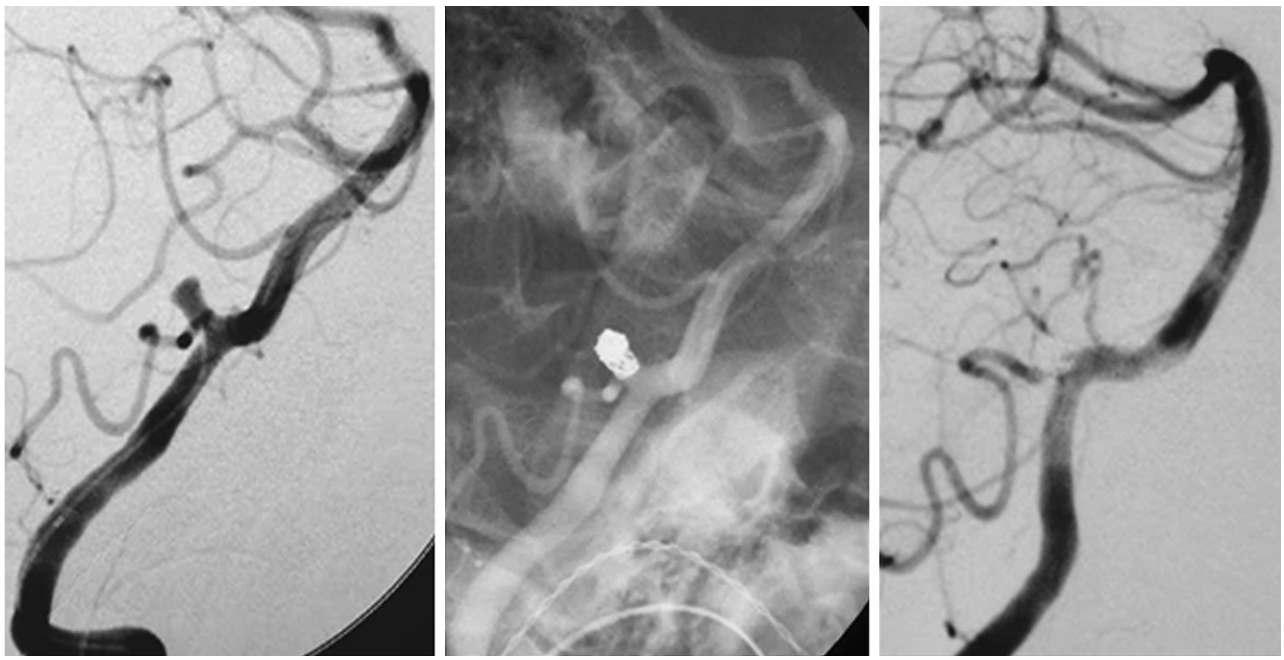


Fig. 14.3 Small ruptured posterior inferior cerebellar artery (PICA) aneurysm, before (left) and after (middle and right) successful endovascular treatment with detachable platinum coils, with preservation of the parent PICA. The left and right views show subtracted images. The middle view shows an unsubtracted image to demonstrate coil mass.

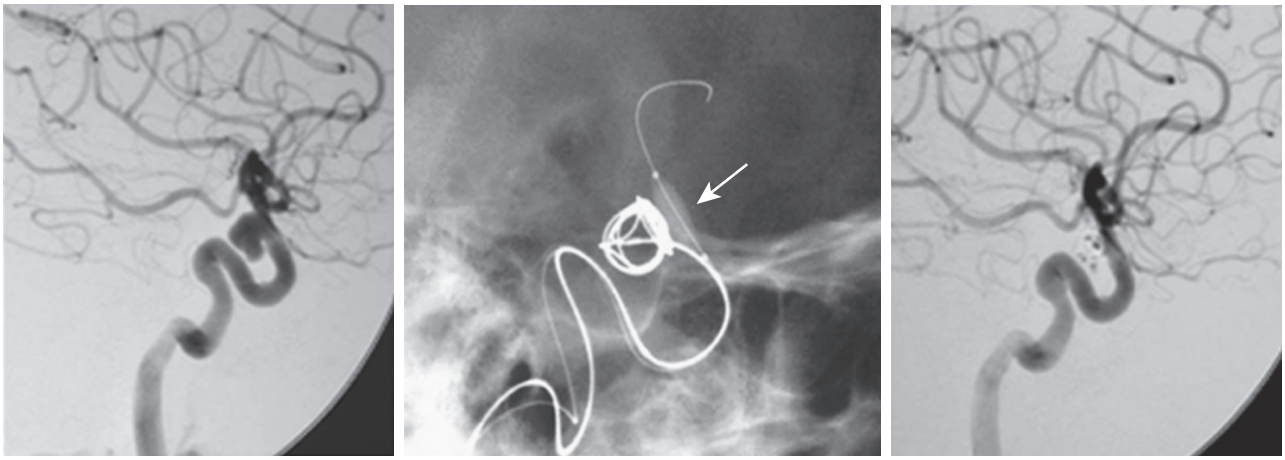


Fig. 14.4 Wide-necked supraclinoid internal carotid artery aneurysm (left) successfully treated using temporary placement of a balloon (arrow middle) to support placement of coils properly within the aneurysm sac (right). There are two catheters in the vascular lumen, one to deliver the coils and one to temporarily inflate the balloon.

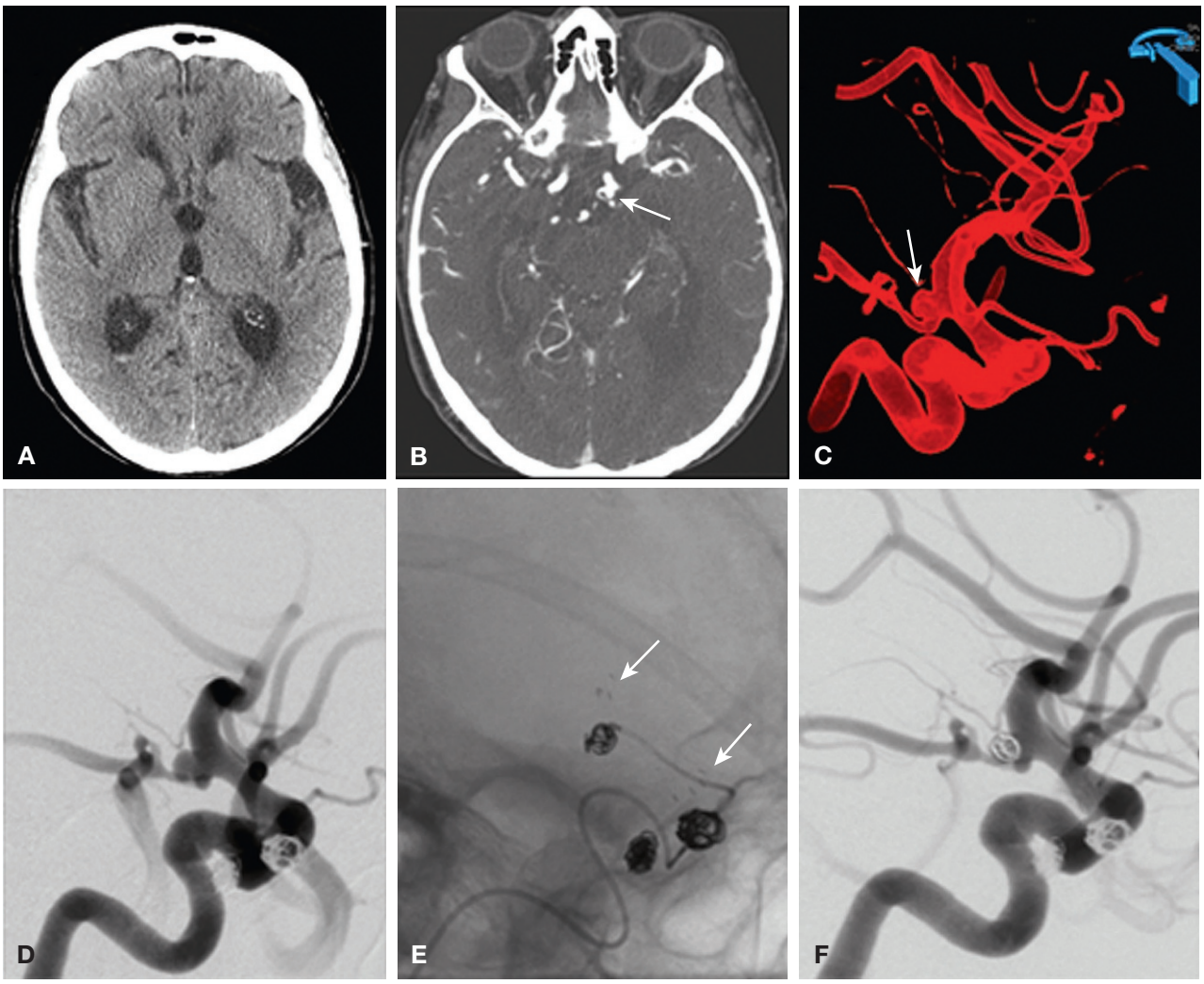


Fig. 14.5 The patient is an elderly woman with a recent small subarachnoid hemorrhage. CT scans without **(A)** and with **(B)** contrast agent demonstrate blood layering in the occipital horn of the right lateral ventricle and a small, wide-necked aneurysm at the origin of the left posterior communicating (PComm) artery (arrow). **C,** Three-dimensional reconstruction of a rotational angiogram shows the aneurysm at the PComm origin (arrow). **D, E,** and **F,** Lateral views of a left internal carotid angiogram show successful treatment of the PComm aneurysm using stent-supported coiling. (Note that two contralateral internal carotid aneurysms had already been treated with endovascular coiling.) In E, the ends of the stent (arrows) are radiodense.

If a rupture occurs, anticoagulation must be immediately reversed, and cerebral perfusion pressure should be maintained at adequate levels. A Cushing response (hypertension and bradycardia) may be one of the first signs of an aneurysm rupture. Sudden increases in blood pressure or decreases in heart rate should be immediately communicated with the interventionalists. Emergency placement of a ventriculostomy should be considered, and an emergency computed tomography scan should be obtained to assess for sequelae of the perforation or rupture.

Angioplasty of Cerebral Vasospasm from Aneurysmal Subarachnoid Hemorrhage

Roughly one out of four patients with SAH has symptomatic vasospasm. Angioplasty, either mechanical (balloon) or pharmacologic (intra-arterial vasodilators), may be used as a treatment.[19] Angioplasty is ideally done in patients in whom the ruptured aneurysm has already been coiled or surgically clipped and for patients in the early course of symptomatic ischemia in order to prevent hemorrhagic transformation of an ischemic region.

Balloon angioplasty is a treatment option only for the more proximal cerebral arteries. It is also possible to perform a "pharmacologic" angioplasty by direct intra-arterial infusion of vasodilators. Historically, papaverine was the first widely used agent, but there has been growing appreciation that it may have serious toxic central nervous system effects.[20,21] In few occasions, selective cerebral intra-arterial papaverive injections have caused cerebral tissue damage (infarctions) resulting in serious brain injury.[20] Calcium channel or entry blockers (CCB/CEBs), such as nicardipine and verapamil, are now being used.[22–26] Use of intravenous nimodipine has also been reported.[27,28] Intra-arterial vasodilators may have systemic effects (bradycardia and hypotension) that may be profound and may work at cross-purposes with the goals of maintaining adequate perfusion pressure.[29,30] Because the CCB/CEBs also vasodilate the pulmonary circulation, a loss of hypoxic pulmonary vasoconstriction may worsen oxygenation in susceptible patients.[31,32] Seizure activity is a potential complication of the intra-arterial injection of CCB/CEBs.[33]

The topic of endovascular vasospasm and its treatment is reviewed in depth in Chapter 1.

Carotid Test Occlusion and Therapeutic Carotid Occlusion

Large fusiform aneurysms of the cavernous segment of the internal carotid artery (ICA) may be treated by proximal vessel occlusion. Also, some aggressive skull-base tumors may

encase the ICA, and preoperative intentional, controlled ICA occlusion may help the surgeon provide optimal resection. To assess the consequences of carotid occlusion in anticipation of surgery, the surgeon may schedule the patient for a carotid test occlusion, in which cerebrovascular reserve is evaluated in several ways. A multimodal combination of angiographic, clinical, and physiologic tests can be used to arrive at the safest course of action for a given patient's clinical circumstances. The judicious use of deliberate hypotension can improve the sensitivity of the test.[34] The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure. The choice of agent should be determined by the experience of the practitioner, the patient's medical condition, and the goals of the blood pressure reduction in a particular clinical setting. To facilitate neurological testing during carotid test occlusion, only mild levels of sedation are used.

Brain Arteriovenous Malformations

Also called cerebral or pial AVMs, brain AVMs (BAVMs) occur in 0.02% of adults, and are typically large, complex lesions made up of a tangle of abnormal vessels (called the *nidus)* frequently containing several discrete fistulas served by multiple feeding arteries and draining veins. The goal of therapeutic embolization is to obliterate as many of the fistulas and their respective feeding arteries as possible (Figs. 14.6 and 14.7). BAVM embolization is usually an adjunct to surgery or radiotherapy. The primary reason to treat a BAVM is to prevent future spontaneous hemorrhage. Those patients with BAVMs that have not previously ruptured may have a low risk of bleeding[35,36] and may be at a higher risk for invasive treatment.[37,38] A randomized controlled trial sponsored by the National Institute of Neurological Disorders and Stroke studied the long-term benefit of treating unruptured BAVMs. [39,40] The Randomized Trial of Brain Unruptured AVMs (ARUBA) randomized patients with unruptured brain AVMs that were suitable for treatment to either medical management or invasive therapy, which included embolization and/or surgery. The study was terminated early after a planned interim analysis found superiority for the medical arm of the study. The interim results showed an increased risk of major neurological deficits in the invasive therapy arm of the study. The study also provided valuable natural history data of unruptured brain AVMs.[41]

The cyanoacrylate glues offer relatively "permanent" closure of abnormal vessels. N-Butyl cyanoacrylate (NBCA) is a low-viscosity liquid monomer that polymerizes to a solid form upon contact with ionic solutions, including blood and saline, but not 5% dextrose in water. Passage of glue into a draining vein can result in acute hemorrhage; in smaller patients, pulmonary embolism of glue can be symptomatic. For these reasons, deliberate hypotension may increase safety of glue delivery. There is no compelling reason to choose any particular

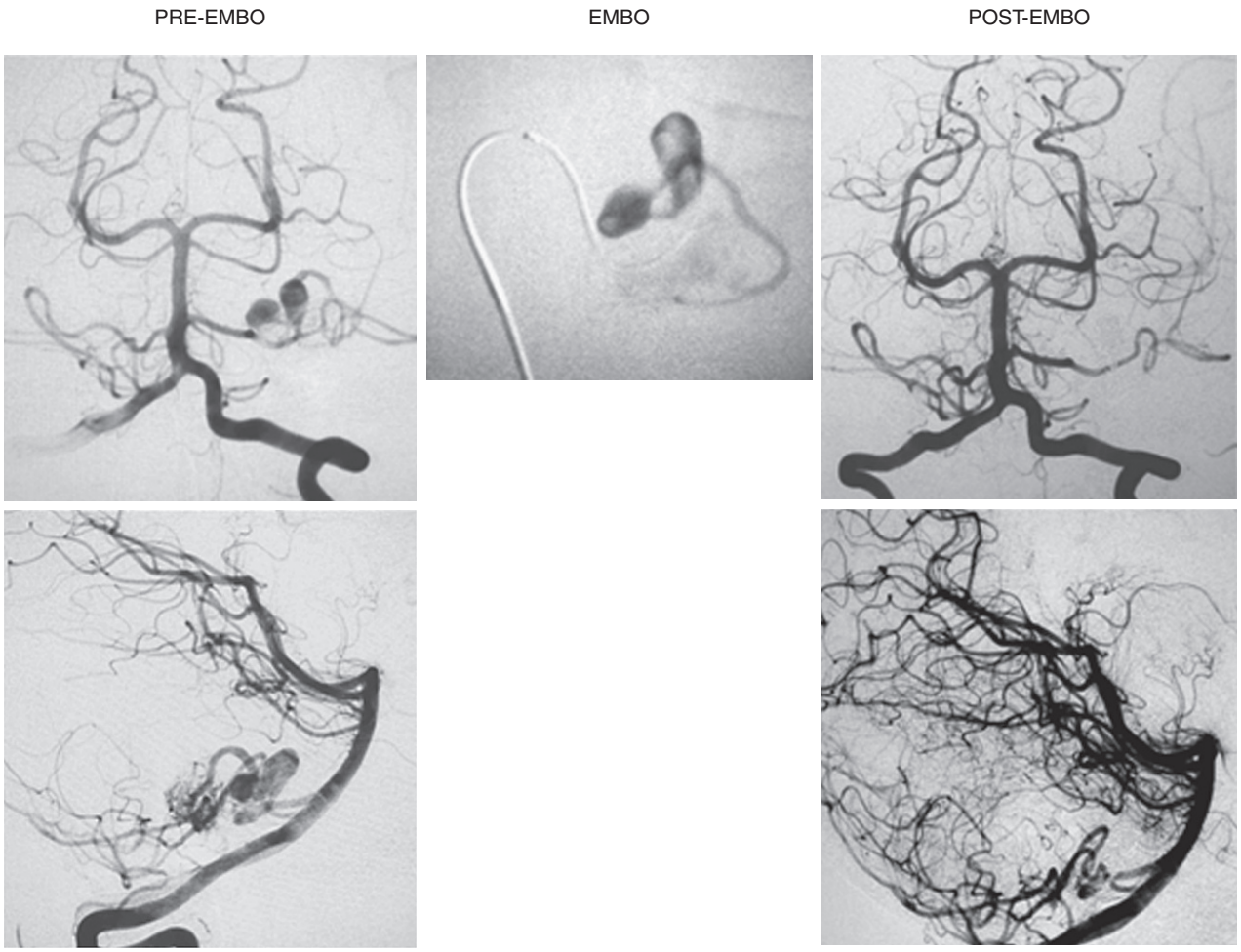


Fig. 14.6 Embolization of the cerebellar arteriovenous malformation shown in Fig. 14.1. Left, Pre-embolization angiography shows anteroposterior (top) and lateral (bottom) projections. Middle, Slightly magnified view of microcatheter placement through the left anterior inferior cerebellar artery into the proximal feeding artery aneurysm sac, with subsequent elimination of the aneurysm complex after placement of detachable platinum coils. Right, Postembolization views.

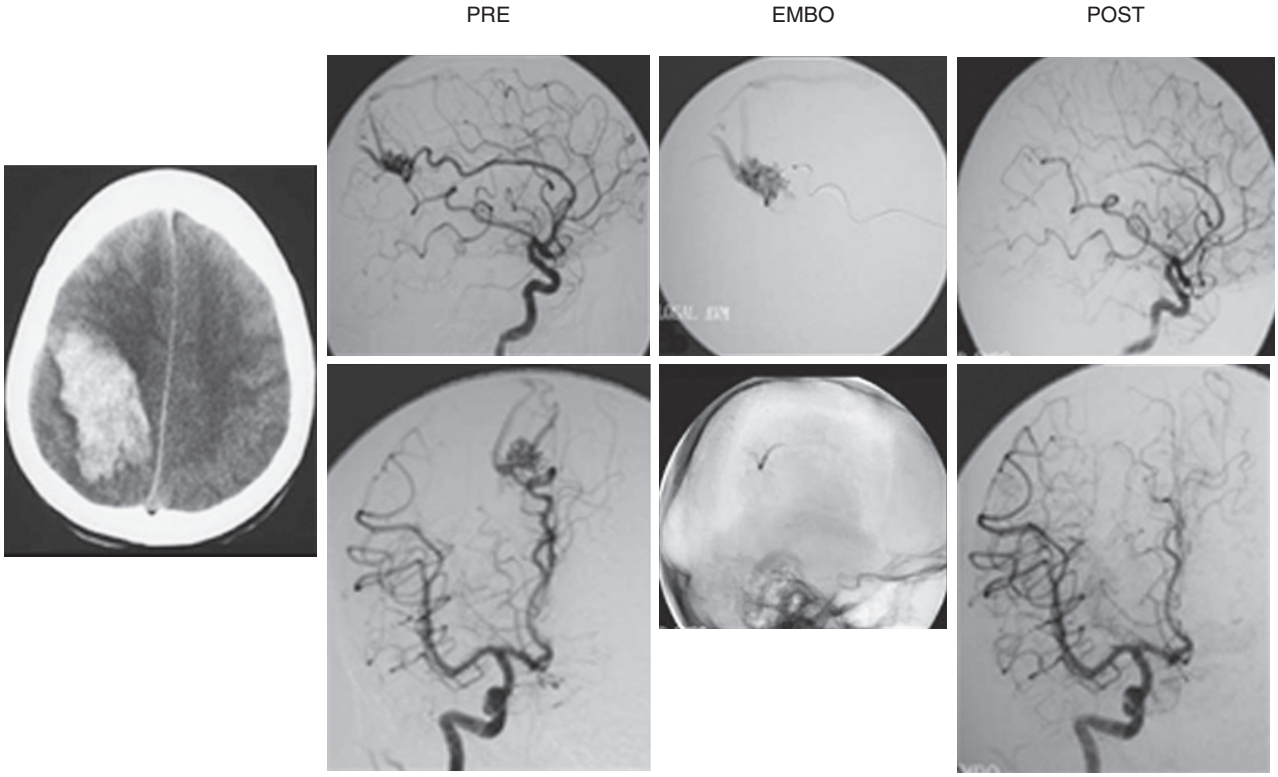


Fig. 14.7 Endovascular treatment of a ruptured right parietal arteriovenous malformation (AVM). Left, CT scan shows acute parenchymal hemorrhage. Pre-embolization (PRE), mid-embolization (EMBO), and post-embolization (POST) angiographs show placement of a flow-directed microcatheter into the feeding artery and embolization using cyanoacrylate glue, with complete eradication of the AVM. Pre and post-embolization images are lateral (top) and anteroposterior (bottom) projections. Middle views show the microcatheter in the AVM during progressive occlusion; both are lateral projections.

method to achieve the hypotension. The flow through the fistula is a pressure-dependent phenomenon.[42]

A major drawback to the use of N-butyl cyanoacrylate is that it is adhesive, with the potential to inadvertently glue the catheter to the injected polymer. Onyx Liquid Embolic System (ev3, Inc., Plymouth, MN), a new, nonadhesive liquid embolic agent consisting of ethylene-vinyl alcohol copolymer and tantalum powder in a dimethyl sulfoxide solvent, theoretically may reduce the overall complication rates for use of N-butyl cyanoacrylate,[43,44] although aggressive therapy may have intrinsic risks. The agent or its vehicle, dimethyl sulfoxide, may have unusual adverse effects;[45] dimethyl sulfoxide can cause a garlic-like taste and odor on the breath and skin that may last several hours and may be alarming to the patient.

Although less durable, polyvinyl alcohol microsphere embolization is also commonly used. If surgery is planned within days after polyvinyl alcohol embolization, the rate of recanalization is low. Because the BAVMs have high flow shunts, some of the embolic material may pass through the BAVMs and dislodge in the lungs increasing VQ mismatching. Ethanol has also been used as an agent but has many untoward effects, including induction of brain edema (see later).[46]

Even in the absence of clinically detectable deficits, subclinical injury can result from BAVM embolization. There is a high incidence of abnormal findings that are detectable on postprocedure magnetic resonance imaging examination; for example, 22% of patients showed ischemic lesions on postprocedure images in one series.[47] Intraoperative management should take this trend into consideration.

For AVM evaluation, some centers use superselective Wada testing prior to therapeutic embolization to test the eloquence of regions adjacent to the lesion. It is important to consider using a sedation regimen for such cases that will minimally affect cognitive or motor findings. The purpose of such testing is to establish treatment risk in individual patients. Interestingly, Wada testing, functional imaging studies, and intrasurgical cortical mapping have shown redistribution of language and memory to unpredictable regions.[48,49] Further, developmental cognitive history in these patients indicates that most will have had at least some learning problems during their school-age years with varying severity,[50] reflecting a time when brain reorganization may have been occurring.

Some centers may measure feeding artery or draining vein pressures to assist in evaluating the risk of future hemorrhage, if the lesion is not treated.[3,51,52] High pressure is associated with hemorrhagic presentation. Delayed transit of contrast media might be a surrogate for high intranidal pressure.[53,54]

Dural Arteriovenous Fistulas

A dural arteriovenous fistula (DAVF) is an acquired arteriovenous shunt in the wall of a dural venous sinus. The etiology of DAVFs is unclear, although some believe that many DAVFs result from venous dural sinus stenosis or occlusion, opening of potential arteriovenous shunts, and subsequent recanalization. Intracranial DAVF accounts for about 10% to 15% of all intracranial vascular malformations. Symptoms vary according to the sinus involved. Venous hypertension of pial veins is a risk factor for intracranial hemorrhage. DAVFs may be fed by multiple meningeal vessels, and, therefore, multistaged embolization is often necessary. Dural arteriovenous fistulas can induce markedly raised venous pressure and diminished net cerebral perfusion pressure. Therefore, the presence of venous hypertension should be factored into management of systemic arterial and cerebral perfusion pressure. This is a critical aspect of DAVF perioperative management. It is often assumed that the venous hypertension induces the angiogenic phenotype

by acting through its cause, cerebral ischemia, but newer evidence suggests that venous hypertension may be a direct stimulus for angiogenesis,[55] DAVFs are unique in that there are promising animal models of their pathogenesis,[56,57] unlike for most other hemorrhagic brain diseases. DAVFs can be embolized using detachable coils or liquid embolic agents such as Onyx. DAVFs may be extensive and require long procedures.

Vein of Galen Malformations

Vein of Galen malformation is a special case of an intracranial arteriovenous shunt that is beyond the scope of this review.[58,59] The malformations are relatively uncommon but complicated lesions that are present in infants and require a multidisciplinary approach. Patients may have intractable congestive heart failure, intractable seizures, hydrocephalus, and mental retardation. Several approaches have been attempted, both transarterial and transvenous. In infants with high-output failure, preexisting right-to-left shunts, and pulmonary hypertension, a relatively small pulmonary glue embolism can be fatal.

Craniofacial Venous Malformations

A craniofacial venous malformation is a congenital disorder of venous maldevelopment. In addition to causing significant cosmetic deformities, it may impinge on the upper airway and interfere with swallowing. Many of these lesions are resistant to conventional surgery, cryosurgery, or laser surgery. In the INR procedure, sclerosing agents, such as USP grade 95% ethanol opacified with contrast agent, is injected percutaneously into the lesion under fluoroscopic guidance, resulting in a chemical burn to the lesion and eventually shrinking it. Sclerotherapy alone may be adequate treatment or may be combined with surgery.[60]

This therapy has several inter-reactions with anesthetic management.[3] Because marked swelling occurs immediately after ethanol injection, the ability of the patient to maintain a patent airway postoperatively must be carefully considered.[60] Desaturation is frequently noted on the pulse oximeter after the injection. Cardiopulmonary arrest has been reported[46] One theory is that ethanol induces severe pulmonary precapillary vasospasm, but the relationship between this and the more common hypoxemic response is not clear. The predictable intoxication and other side effects of ethanol may be evident after emergence from anesthesia, particularly post-emergence agitation in children.

Venous malformations of the face or dural fistulas have the potential to drain into intracerebral veins or sinuses. If the $PaCO_2$ is raised to 50–60 mmHg, cerebral venous outflow will greatly exceed extracranial venous outflow, and the pressure gradient will favor movement of a sclerosing agent, chemotherapeutic agent, or glue away from vital intracranial drainage pathways. Although actual pressure gradients have never been studied, increased intracranial outflow is readily demonstrable in clinical practice with angiography. Addition of CO_2 gas to the inspired gas mixture is the easiest and safest way to achieve hypercapnia. Airway collapse and atelectasis are prevented by maintaining adequate tidal volume. However, hypoventilation may be employed if CO_2 gas is not available.

Angioplasty and Stenting for Atherosclerotic Lesions

Angioplasty and stenting for treatment of atherosclerotic stenosis of the cervical, vertebral, and intracranial arteries represent alternatives to endarterectomy or other surgical management (Fig. 14.8).[61,62] Risk of distal thromboembolism is a potential complication of this procedure. Intravascular filters and balloons, collectively called "distal protection devices," have been developed to theoretically prevent distal intracranial embolization of thrombus or plaque that may become dislodged during deployment of the stent or angioplasty balloon at the carotid bifurcation. These distal protection devices have come into common use for carotid stenting, although the procedure-related complications of the use of such protection devices (carotid dissection or occlusion, device-induced arterial spasm, thrombus formation) have not been well studied. There are multiple ongoing trials to compare the utility of stenting with that of carotid endarterectomy for extracranial carotid disease. Well-defined criteria are used to determine which patients are eligible for carotid artery stenting. These criteria are in part driven by CMS reimbursement guidelines.

Preparation for anesthetic management in the patient undergoing angioplasty and stenting may include placement of transcutaneous pacing leads, in case of severe bradycardia or asystole from carotid body stimulation during angioplasty. Intravenous atropine or glycopyrrolate may also be used in an attempt to mitigate bradycardia, which almost invariably occurs to some extent with inflation of the balloon. This powerful chronotropic response may be difficult or impossible to prevent or control by conventional means. Adverse effects of increasing myocardial oxygen demand need to be considered in antibradycardia interventions.

Potential complications of the procedure include vessel occlusion, perforation, dissection, spasm, thromboemboli, occlusion of adjacent vessels, transient ischemic episodes, and stroke. As with carotid endarterectomy, there is about a 5% risk of symptomatic cerebral hemorrhage or brain swelling after carotid angioplasty.[63] Although the etiology of this syndrome is unknown, it has been associated with cerebral hyperperfusion, and it may be related to poor postoperative blood pressure control.

Thrombolysis and Thrombectomy of Acute Thromboembolic Stroke

In acute occlusive stroke, it is possible to recanalize the occluded vessel by intra-arterial thrombectomy, chemical and/or mechanical. Thrombolytic agents can be delivered in high concentrations through a microcatheter navigated close to the clot (Fig. 14.9). Neurologic deficits may be reversed with minimal risk of secondary hemorrhage if treatment is completed within several hours from the onset of ischemia in the carotid territory, and somewhat longer for ischemia in the vertebrobasilar territory. Intra-arterial thrombolysis is currently an "off-label" use of these agents.

A newer and promising approach is the use of mechanical retrieval devices to physically remove the offending thromboembolic material from the intracranial vessel.[64,65] Devices including corkscrew-shaped Merci retrievers, nondetachable stents ("stentrievers"), and suction/aspiration catheters appear to be efficacious in recanalizing occluded vessels, and early restoration of flow appears to reduce the volume of infarcted brain (Fig. 14.10). For additional discussion on treatments for cerebral ischemia, please read the section on "Reperfusion Strategies" in Chapter 1.

Both tissue plasminogen activator and mechanical retrieval have an inherent risk of promoting hemorrhagic transformation, just as in the case of IV thrombolysis. This is an important area for investigation because hemorrhagic transformation, or its threat, has great impact on clinical practice.

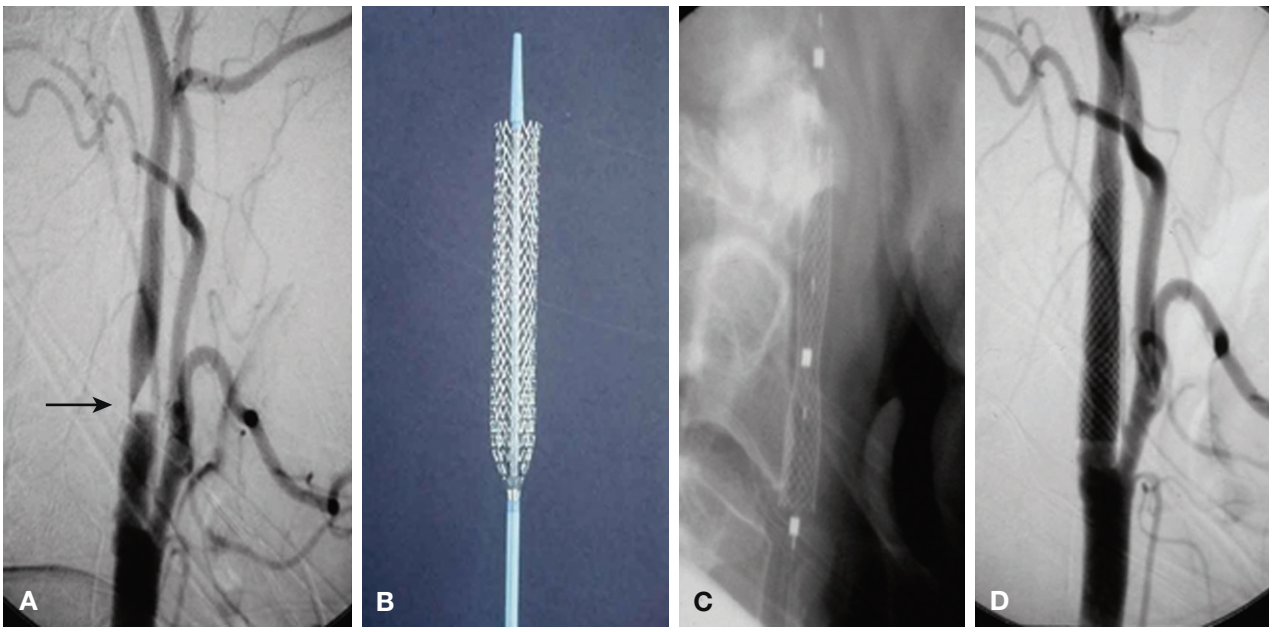


Fig. 14.8 Use of a carotid artery stent restores normal luminal diameter to an internal carotid artery origin narrowed by atherosclerosis. **A,** Stenosis at arrow. **B,** Stent before deployment on catheter system. **C,** Stent expanded in situ. **D,** Catheter removed; luminal diameter is now restored.

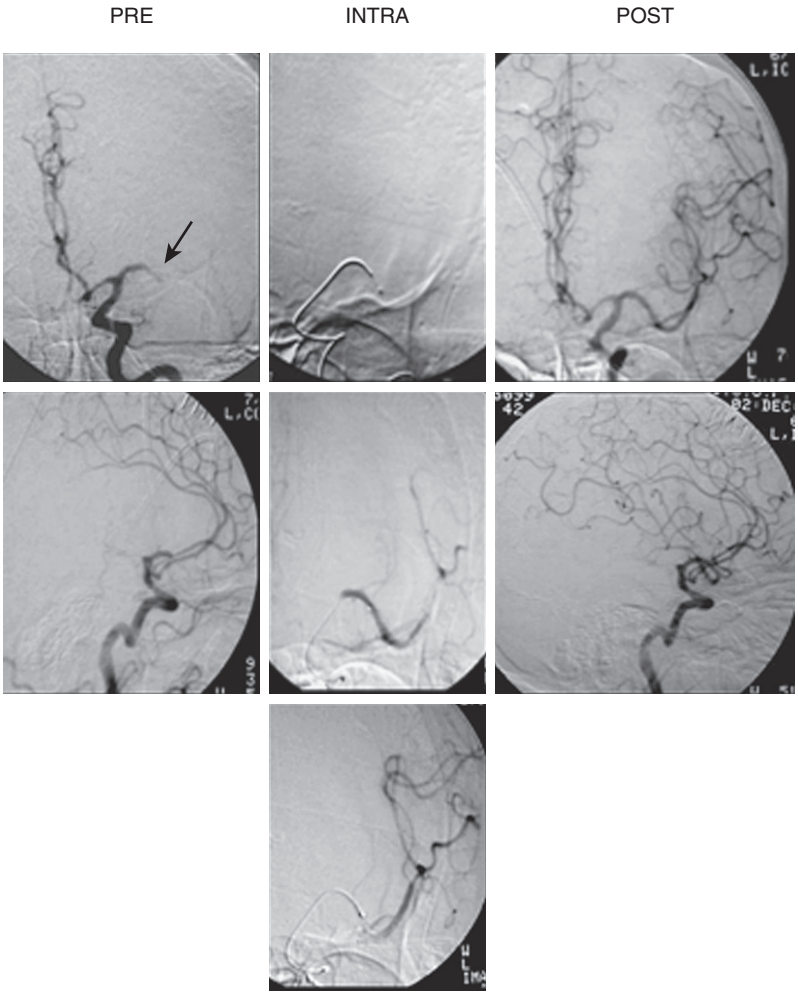


Fig. 14.9 Patient with an acute left middle cerebral artery occlusion (arrow in top left view) caused by an iatrogenic embolus during angiography. Left, Left internal carotid angiography is shown (PRE); top is anteroposterior projection, and bottom is lateral projection. Middle, Immediate microcatheter placement into the clot allowed successful thrombolysis using tissue plasminogen activator (TPA) (INTRA). Top image shows microcatheter in position; middle and bottom images show contrast injection during course of thrombolysis. Right, Corresponding left internal carotid artery after successful TPA thrombolysis and restoration of arterial flow to the left middle cerebral territory.

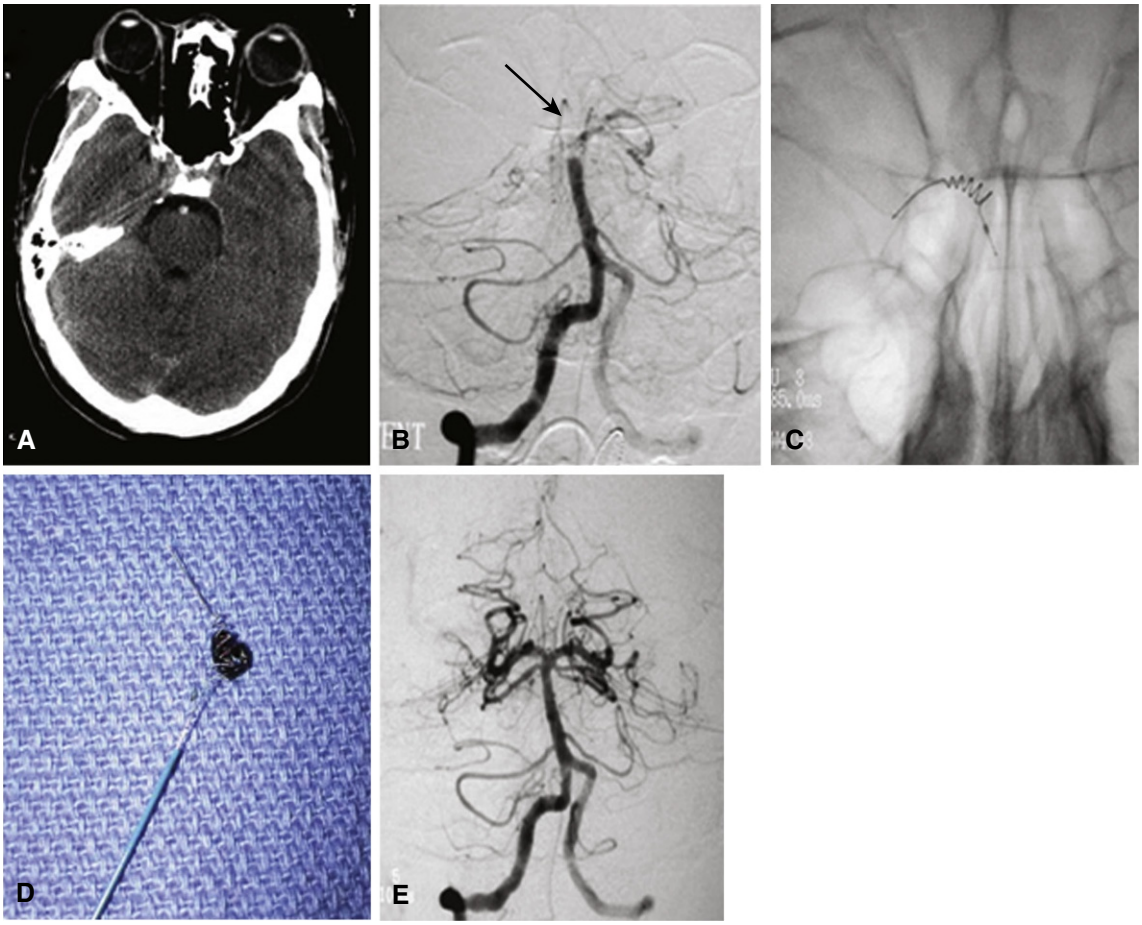


Fig. 14.10 Acute basilar artery occlusion from an embolus caused by a traumatic dissection of the vertebral artery. **A,** Computed tomography scan demonstrates only a dense basilar artery, indicating its occlusion. **B,** The thrombus obstructs flow at the top of the basilar artery (arrow). **C,** Corkscrew-shaped clot retrieval device is seen in place on unsubtracted anteroposterior image. **D,** Clot was removed by means of this retrieval device. **E,** Flow is restored to the basilar artery, leaving the patient without neurologic deficit.

Comprehensive details of anesthetic management of endovascular treatment for acute ischemic stroke are reviewed elsewhere.[66] Briefly, there are a number of challenges in care of a patient population that is generally elderly and has common medical comorbidities, especially if little knowledge of patient history is available prior to treatment. The choice of sedation or general anesthesia is controversial and often depends on local practices. It is clear that time is of the essence during endovascular treatment of acute ischemic stroke to achieve the best possible outcome and endovascular procedures should be performed as soon as possible. Anesthesia-related delays should be minimized. Regardless of anesthetic techniques, good blood pressure control is pivotal to provide maximal collateral blood flow. Three randomized, controlled studies have questioned the efficacy of endovascular treatment of acute ischemic stroke.[67–69] Most recently, another randomized trial of patients with acute ischemic stroke concluded that intra-arterial treatment increased functional independence of the patients without increasing morbidity or mortality.[30] Due to the ongoing development of new thrombectomy devices and techniques, future studies will need to verify the efficacy of these treatments.

POSTOPERATIVE MANAGEMENT

After endovascular procedures, patients may recover in the postanesthesia care unit or ICU depending on their condition and the procedure. Patients will be watched for signs of hemodynamic instability or neurologic deterioration. Some patients may remain intubated after the procedure. Control of blood pressure (eg, induced hypertension, if indicated) may be necessary during transport and postoperative recovery. In particular, patients who have received treatment of extracranial carotid disease are prone to postprocedural hemodynamic instability, like patients who have undergone carotid endartectomy.[70]

Abrupt restoration of normal systemic pressure to a chronically hypotensive (ischemic) vascular bed may overwhelm autoregulatory capacity and result in hemorrhage or swelling, this is termed normal perfusion pressure breakthrough.[63,71–74] The pathogenetic mechanism is unclear, but it is probably not simply a hemodynamic effect, and the loss of neurovascular unit integrity is probably related to the pathways involved in post-reperfusion hemorrhage in the setting of acute stroke (described previously).

Nonetheless, cerebral hyperemia is probably exacerbated by uncontrolled increases in systemic arterial blood pressure. In the absence of collateral perfusion pressure inadequacy, fastidious attention to preventing hypertension is warranted. Patients with complicated situations may first be sent for computed tomography or some other kind of tomographic imaging; critical care management may have to be extended during transport and imaging. Symptomatic hyperemic complications are more uncommon than "silent" hyperemic states; with the greater use of more sensitive magnetic resonance imaging, ischemic events are probably more common than previously suspected.[47]

FUTURE DIRECTIONS

For the overall management approach to the patient with cerebrovascular disease, there is accelerating interest in and discussion of the appropriate management of asymptomatic or unruptured lesions. Anesthesiologists are not traditionally caught on the horns of these management dilemmas—at least directly. However, optimal provision of perioperative care and effective resource allocation would benefit from active involvement of all practitioners involved in the management of patients with such conditions. The literature is practically silent on optimal anesthetic management strategies during endovascular neuroradiology procedures, providing future investigators with ample opportunities.

The indications for invasive therapy for unruptured AVMs[39] and aneurysms[75,76] are currently undergoing critical discussion. Although it is generally agreed that ruptured lesions need treatment, the aggregate risks for treating all patients with unruptured lesions may exceed the potential benefit from protecting against future hemorrhage. For example, the previously described international multicenter randomized controlled trial sponsored by the National Institute of Neurological Disorders and Stroke known as A Randomized Trial of Unruptured Brain Arteriovenous Malformations, was terminated early because medical therapy was found superior during interim analysis.[41] Similarly, the International Study of Unruptured Intracranial Aneurysms (ISUIA) is a longstanding effort to document the natural history and treatment outcomes for unruptured lesions.[75,77]

Future research directions for vascular disease of the brain present opportunities for neuroanesthesia, perioperative management, and neurocritical care. Basic or translational questions include the effect of the interaction of angiogenesis and vascular remodeling on pathogenesis and clinical course. Growing evidence suggests that some of these lesions undergo active angiogenesis and vascular remodeling during the patient's adult life. This new concept—active angiogenesis and vascular remodeling in intracranial vascular malformations—may generate new clinical paradigms in which pharmacologic interventions are proposed to stabilize these abnormal blood vessels and prevent further growth or hemorrhage. Research on intracranial vascular malformations has been focusing on identifying the roles of angiogenic and anti-angiogenic factors in the pathophysiology.[78]

Abnormal vascular remodeling mediated by inflammatory cells has been identified as a key pathologic component of various vascular diseases, including abdominal aortic aneurysms, brain arteriovenous malformations and atherosclerosis.[79–82] This concept may provide a new treatment strategy utilizing agents to inhibit inflammation or cytokines produced by inflammatory cells such as matrix metalloproteinases. On the basis of findings of observational studies that analyzed human intracranial aneurysms and of experimental studies that utilized animal models, an emerging concept suggests that a key component of the pathophysiology of intracranial aneurysms is sustained abnormal vascular remodeling coupled with inflammation.[83–85]

Consistent with a background contribution of a ubiquitous process, such as inflammation, aneurysmal disease may be better conceived of as a process, rather than an event. For example, the long-term durability of aneurysm treatment is often assumed. There is a growing appreciation of the idea that our traditional notion of "disease treatment" should not necessarily be construed as a "cure," although it may be in many cases. Although treatment clearly reduces new rupture rates, there is a measurable rebleeding rate after treatment (surgery or coiling).[1] The risk of further hemorrhage continues for up to 30 years after SAH.[86] Taken together with observations that a significant fraction of aneurysms enlarge over time,[86–88] this finding indicates that aneurysmal disease may be a process characterized by generalized vascular dysfunction rather than a sporadic focal event.

Pro-inflammatory influence on disease susceptibility[89,90] and clinical course[91–93] appears to apply to AVMs as well. Tissue interleukin-6 (IL-6) expression is associated with IL-6-174G > C genotype and linked to downstream targets involved in angiogenesis and vascular instability.[94] Further, interleukin-6 was found to induce MMP-3 and MMP-9 expression and activity in the mouse brain and to increase proliferation and migration of cerebral endothelial cells. Taken together, such observations are consistent with the hypothesis that inflammatory processes influence angiogenic and proteolytic activity, thus contributing to the pathogenesis of intracranial hemorrhage.

In the future, identification of genetic risk factors has the potential to help predict new intracranial hemorrhage in the natural course after presentation,[91,92] or to be used in risk stratification for postoperative complications.[95] Genetic variation can also potentially provide information related to the risk of development of post-intracranial hemorrhage complications, particularly vasospasm after SAH.[96,97] Genetic variation or plasma biomarker assays[98–100] have the developmental potential to affect multiple aspects of perioperative management.

ACKNOWLEDGMENTS

The authors would like to thank their colleague William Young MD who was responsible for much of the original text of this chapter.

REFERENCES

1. Molyneux AJ, Kerr RS, Yu LM, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366:809–817.
2. Omary RA, Unal 0, Koscielski DS, et al. Real-time MR imaging-guided passive catheter tracking with use of gadolinium-filled catheters. *J Vasc lntervent Radiol*. 2000;11:1079–1085.
3. Young WL, Pile-Spellman J. Anesthetic considerations for interventional neuroradiology. *Anesthesiology*. 1994;80:427–456.
4. Young WL, Pile-Spellman J, Hacein-Bey L, Joshi S. Invasive neuroradiologic procedures for cerebrovascular abnormalities: Anesthetic considerations. *Anesthesiol Clin N Am*. 1997;15:631–653.
5. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *BMJ*. 1973;1(5852):507–510.
6. Drummond JC. The lower limit of autoregulation: Time to revise our thinking? *Anesthesiology*. 1997;86:1431–1433.
7. Goldberg M. Systemic reactions to intravascular contrast media: A guide for the anesthesiologist. *Anesthesiology*. 1984;60:46–56.
8. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg*. 2002;95:461–466.
9. Harrigan MR, Levy El, Bendok BR, Hopkins LN. Bivalirudin for endovascular intervention in acute ischemic stroke: Case report. *Neurosurgery*. 2004;54:218–222.
10. Ciccone A, Abraha 1, Santilli 1. Glycoprotein IIb-Illa inhibitors for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2006. CD005208.
11. Hashimoto T, Gupta DK, Young WL. Interventional neuroradiology-anesthetic considerations. *Anesthesiol Clin N Am*. 2002;20:347–359. vi.
12. Fiorella D, Albuquerque FC, Han P, McDougall CG. Strategies for the management of intraprocedural thromboembolic complications with abciximab (ReoPro). *Neurosurgery*. 2004;54:1089–1097.
13. Szabo MD, Crosby G, Sundaram P, et al. Hypertension does not cause spontaneous hemorrhage of intracranial arteriovenous malformations. *Anesthesiology*. 1989;70:761–763.

14. Hashimoto T, Young WL, Aagaard BD, et al. Adenosine-induced ventricular asystole to induce transient profound systemic hypotension in patients undergoing endovascular therapy: Dose-response characteristics. *Anesthesiology*. 2000;93:998–1001.
15. Connolly Jr. ES, Lavine SD, Meyers PM, et al. Intensive care unit management of interventional neuroradiology patients. *Neurosurg Clin N Am*. 2005;16:541–545. vi.
16. Molyneux A, Kerr R. Stratton 1, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomized trial. *Lancet*. 2002;360:1267–1274.
17. Drummond JC, Patel PM. Neurosurgical anesthesia. In: Miller RD, 5th ed. *Anesthesia. . .* Vol. 2. New York: Churchill Livingstone; 2000:1895–1933.
18. Elijovich L, Higashida RT, Lawton MT, et al. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: The CARAT study. *Stroke*. 2008;39:1501–1506.
19. Newell DW, Eskridge JM, Mayberg MR, et al. Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage. *J Neurosurg*. 1989;71:654–660.
20. Smith WS, Dowd CF, Johnston SC, et al. Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2004;35:2518–2522.
21. Fogarty-Mack P, Pile-Spellman J, Hacein-Bey L, et al. Superselective intra-arterial papaverine administration: Effect on regional cerebral blood flow in patients with arteriovenous malformations. *J Neurosurg*. 1996;85:395–402.
22. Feng L, Fitzsimmons BF, Young WL, et al. Intra-arterially administered verapamil as adjunct therapy for cerebral vasospasm: Safety and 2-year experience. *AJNR Am J Neuroradiol*. 2002;23:1284–1290.
23. Tejada JG, Taylor RA, Ugurel MS, et al. Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: Initial clinical experience with high-dose infusions. *AJNR Am J Neuroradiol*. 2007;28:844–848.
24. Avitsian R, Fiorella D, Soliman MM, Mascha E. Anesthetic considerations of selective intra-arterial nicardipine injection for intracranial vasospasm: A case series. *J Neurosurg Anesthesiol*. 2007;19:125–129.
25. Badjatia N, Topcuoglu MA, Pryor JC, et al. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *AJNR Am J Neuroradiol*. 2004;25:819–826.
26. Mazumdar A, Rivet DJ, Derdeyn CP, et al. Effect of intra-arterial verapamil on the diameter of vasospastic intracranial arteries in patients with cerebral vasospasm. *Neurosurg Focus*. 2006;21:E15.
27. Biondi A, Ricciardi GK, Puybasset L, et al. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: Preliminary results. *AJNR Am J Neuroradiol*. 2004;25:1067–1076.
28. Hui C, Lau KP. Efficacy of intra-arterial nimodipine in the treatment of cerebral vasospasm complicating subarachnoid haemorrhage. *Clin Radiol*. 2005;60:1030–1036.
29. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. MR CLEAN Investigators. *N Engl J Med*. 2015;372:11–20.
30. Flexman AM, Ryerson CJ, Talke PO. Hemodynamic stability after intraarterial injection of verapamil for cerebral vasospasm. *Anesth Analg*. 2012;114:1292–1296.
31. Stiefel MF, Heuer GG, Abrahams JM, et al. The effect of nimodipine on cerebral oxygenation in patients with poor-grade subarachnoid hemorrhage. *J Neurosurg*. 2004;101:594–599.
32. Devlin JW, Coplin WM, Murry KR, et al. Nimodipine-induced acute hypoxemia: Case report. *Neurosurgery*. 2000;47:1243–1246.
33. Westhout FD, Nwagwu CI. Intra-arterial verapamil-induced seizures: Case report and review of the literature. *Surg Neurol*. 2007;67:483–486.
34. Marshall RS, Lazar RM, Pile-Spellman J, et al. Recovery of brain function during induced cerebral hypoperfusion. *Brain*. 2001;124:1208–1217.
35. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66:1350–1355.
36. Kim H, Sidney S, McCulloch CE, et al. Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. *Stroke*. 2007;38:2430–2437.
37. Wedderburn CJ, van Beijnum J, Bhattacharya JJ, et al. Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: A prospective, population-based cohort study. *Lancet Neurol*. 2008;7:223–230.
38. Lawton MT, Du R, Tran M, et al. Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. *Neurosurgery*. 2005;56:485–493.
39. Stapf C, Mohr JP, Choi JH, et al. Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy. *Curr Opin Neurol*. 2006;19:63–68.
40. National Institute of Neurological Disorders and Stroke (NINDS): A Randomized Trial of Unruptured Brain AVMs (ARUBA), 2007. Information available at http://clinicaltrials.gov/ct2/show/NCT00389181?term=brain+malformation&rank=6.
41. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. International ARUBA investigators. *Lancet*. 2014;383:614–621.
42. Gao E, Young WL, Pile-Spellman J, et al. Deliberate systemic hypotension to facilitate endovascular therapy of cerebral arteriovenous malformations: A computer modeling study. *Neurosurg Focus*. 1997;2:e3.
43. van Rooij WJ, Sluzewski M, Beute GN. Brain AVM embolization with Onyx. *AJNR Am J Neuroradiol*. 2007;28:172–177.
44. Linfante I, Wakhloo AK. Brain aneurysms and arteriovenous malformations: Advancements and emerging treatments in endovascular embolization. *Stroke*. 2007;38:1411–1417.
45. Murugesan C, Saravanan S, Rajkumar J, et al. Severe pulmonary oedema following therapeutic embolization with Onyx for cerebral arteriovenous malformation. *Neuroradiology*. 2008;50:439–442.
46. Yakes WF, Rossi P, Odink H. How I do it: Arteriovenous malformation management. *Cardiovasc Intervent Radiol*. 1996;19:65–71.
47. Cronqvist M, Wirestam R, Ramgren B, et al. Endovascular treatment of intracerebral arteriovenous malformations: Procedural safety, complications, and results evaluated by MR imaging, including diffusion and perfusion imaging. *AJNR Am J Neuroradiol*. 2006;27:162–176.
48. Lazar RM, Marshall RS, Pile-Spellman J, et al. Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. *Neuropsychologia*. 2000;38:1325–1332.
49. Lazar RM, Marshall RS, Pile-Spellman J, et al. Anterior translocation of language in patients with left cerebral arteriovenous malformations. *Neurology*. 1997;49:802–808.
50. Lazar RM, Connaire K, Marshall RS, et al. Developmental deficits in adult patients with arteriovenous malformations. *Arch Neurol*. 1999;56:103–106.
51. Henkes H, Gotwald TF, Brew S, et al. Intravascular pressure measurements in feeding pedicles of brain arteriovenous malformations. *Neuroradiology*. 2006;48:182–189.
52. Duong DH, Young WL, Vang MC, et al. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. *Stroke*. 1998;29:1167–1176.
53. Todaka T, Hamada J, Kai Y, et al. Analysis of mean transit time of contrast medium in ruptured and unruptured arteriovenous malformations: A digital subtraction angiographic study. *Stroke*. 2003;34:2410–2414.
54. Norris JS, Valiante TA, Wallace MC, et al. A simple relationship between radiological arteriovenous malformation hemodynamics and clinical presentation: A prospective, blinded analysis of 31 cases. *J Neurosurg*. 1999;90:673–679.
55. Zhu Y, Lawton MT, Du R, et al. Expression of hypoxia-inducible factor-1 and vascular endothelial growth factor in response to venous hypertension. *Neurosurgery*. 2006;59:687–696.
56. Lawton MT, Jacobowitz R, Spetzler RF. Redefined role of angiogenesis in the pathogenesis of dural arteriovenous malformations. *J Neurosurg*. 1997;87:267–274.
57. Terada T, Higashida RT, Halbach VV, et al. Development of acquired arteriovenous fistulas in rats due to venous hypertension. *J Neurosurg*. 1994;80:884–889.
58. Fullerton HJ, Aminoff AR, Ferriera DM, et al. Neurodevelopmental outcome after endovascular treatment of vein of Galen malformations. *Neurology*. 2003;61:1386–1390.
59. Lasjaunias PL, Chng SM, Sachet M, et al. The management of vein of Galen aneurysmal malformations. *Neurosurgery*. 2006;59:S184–S194; discussion S183-S113.
60. Lasjaunias P, Berenstein A. Endovascular treatment of the craniofacial lesions. In: Golzarian J, Sun S, Sharafuddin MJ, eds. *Surgical Neuroangiography*; Vol. 2. Heidelberg: Springer Verlag; 1987:389–397.
61. Higashida RT, Meyers PM, Connors 3rd. JJ, et al. American Society of Interventional and Therapeutic Neuroradiology; Society of Interventional Radiology; American Society of Neuroradiology: Intracranial angioplasty and stenting for cerebral atherosclerosis: A position statement of the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, and the American Society of Neuroradiology. *AJNR Am J Neuroradiol*. 2005;26:2323–2327.
62. Goodney PP, Schermerhorn ML, Powell RJ. Current status of carotid artery stenting. *J Vasc Surg*. 2006;43:406–411.
63. Meyers PM, Higashida RT, Phatouros CC, et al. Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. *Neurosurgery*. 2000;47:335–343.
64. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR Am J Neuroradiol*. 2006;27:1177–1182.

65. Smith WS, Sung G, Starkman S, et al. MERCI Trial Investigators: Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. *Stroke*. 2005;36:1432–1438.
66. Talke PO, Sharma D, Heyer EJ, et al. Republished: Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: Anesthetic management of endovascular treatment for acute ischemic stroke. *Stroke*. 2014;45:138–150.
67. Broderick JP, Palesch YY, Demchuk AM, et al. Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368:893–903.
68. Ciccone A, Valvassori L, Nichelatti M, et al. SYNTHESIS Expansion Investigators Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368:904–913.
69. Kidwell CS, Jahan R, Gornbein J, et al. MR RESCUE Investigators A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914–923.
70. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. *Stroke*. 1999;30:2086–2093.
71. Young WL, Kader A, Ornstein E, et al. Cerebral hyperemia after arteriovenous malformation resection is related to "breakthrough" complications but not to feeding artery pressure. Columbia University AVM Study Project. *Neurosurgery*. 1996;38:1085–1093.
72. Abou-Chebl A, Yadav JS, Reginelli JP, et al. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: Risk factors, prevention, and treatment. *J Am Coll Cardiol*. 2004;43:1596–1601.
73. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. *Cathet Cardiovasc lnterv*. 2007;69:690–696.
74. Kang HS, Han MH, Kwon OK, et al. Intracranial hemorrhage after carotid angioplasty: A pooled analysis. *J Endovasc Ther*. 2007;14:77–85.
75. Wiebers D, Whisnant JP, Huston 3rd. J, et al. Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103–110.
76. Wiebers DO. Patients with small, asymptomatic, unruptured intracranial aneurysms and no history of subarachnoid hemorrhage should generally be treated conservatively. *Stroke*. 2005;36:408–409.
77. Unruptured intracranial aneurysms-risk of rupture and risks of surgical intervention: International Study of Unruptured Intracranial Aneurysms Investigators. *N Engl J Med*. 1998;339:1725–1733.
78. Hashimoto T, Young WL. Roles of angiogenesis and vascular remodeling in brain vascular malformations. *Semin Cerebrovasc Dis Stroke*. 2004;4:217–225.
79. Hashimoto T, Wen G, Lawton MT, et al. Abnormal expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in brain arteriovenous malformations. *Stroke*. 2003;34:925–931.
80. Knox JB, Sukhova GK, Whittemore AD, Libby P. Evidence for altered balance between matrix metalloproteinases and their inhibitors in human aortic diseases. *Circulation*. 1997;95:205–212.
81. Goodall S, Crowther M, Hemingway DM, et al. Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. *Circulation*. 2001;104:304–309.
82. Loftus IM, Naylor AR, Goodall S, et al. Increased matrix metalloproteinase-9 activity in unstable carotid plaques: A potential role in acute plaque disruption. *Stroke*. 2000;31:40–47.
83. Chyatte D, Bruno G, Desai S, Todor DR. Inflammation and intracranial aneurysms. *Neurosurgery*. 1999;45:1137–1146.
84. Frosen J, Piippo A, Paetau A, et al. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: Histological analysis of 24 unruptured and 42 ruptured cases. *Stroke*. 2004;35:2287–2293.
85. Hashimoto T, Meng H, Young WL. Intracranial aneurysms: Links between inflammation, hemodynamics and vascular remodeling. *Neural Res*. 2006;28:372–380.
86. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: Probability of and risk factors for aneurysm rupture. *J Neurosurg*. 2000;93:379–387.
87. Wermer MJ, van der Schaaf IC, Velthuis BKASTRA. Study Group, et al. Follow-up screening after subarachnoid haemorrhage: Frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain*. 2005;128:2421–2429.
88. Mangrum Wl, Huston 3rd. J, Link MJ, et al. Enlarging vertebrobasilar nonsaccular intracranial aneurysms: Frequency, predictors, and clinical outcome of growth. *J Neurosurg*. 2005;102:72–79.
89. Simon M, Franke D, Ludwig M, et al. Association of a polymorphism of the ACVRL1 gene with sporadic arteriovenous malformations of the central nervous system. *J Neurosurg*. 2006;104:945–949.
90. Pawlikowska L, Tran MN, Achrol AS, et al. Polymorphisms in transforming growth factor-related genes ALK1 and ENG are associated with sporadic brain arteriovenous malformations. *Stroke*. 2005;36:2278–2280.
91. Achrol AS, Pawlikowska L, McCulloch CE, et al. Tumor necrosis factor-alpha-238G > A promoter polymorphism is associated with increased risk of new hemorrhage in the natural course of patients with brain arteriovenous malformations. *Stroke*. 2006;37:231–234.
92. Pawlikowska L, Poon KY, Achrol AS, et al. Apoliprotein E epsilon2 is associated with new hemorrhage risk in brain arteriovenous malformation. *Neurosurgery*. 2006;58:838–843.
93. Kim H, Hysi PG, Pawlikowska L, et al. Common variants in interleukin-1-beta gene are associated with intracranial hemorrhage and susceptibility to brain arteriovenous malformation. *Cerebrovasc Dis*. 2009;27:176–182.
94. Chen Y, Pawlikowska L, Yao JS, et al. lnterleukin-6 involvement in brain arteriovenous malformations. *Ann Neurol*. 2006;59:72–80.
95. Achrol AS, Kim H, Pawlikowska L, et al. TNF-alpha polymorphism is associated with intracranial hemorrhage (ICH) after arteriovenous malformation (AVM) treatment [abstract]. *Stroke*. 2007;38:597–598.
96. Starke RM, Kim GH, Komotar RJ, et al. Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2008;28:1204–1211.
97. Ko NU, Rajendran P, Kim H, et al. Endothelial nitric oxide synthase polymorphism (-786 T--- + C) and increased risk of angiographic vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2008;39:1103–1108.
98. Sanchez-Pena P, Pereira AR, Sourour NA, et al. S1008 as an additional prognostic marker in subarachnoid aneurysmal hemorrhage. *Crit Care Med*. 2008;36:2267–2273.
99. Castellanos M, Leira R, Serena J, et al. Plasma metalloproteinase-9 concentration predicts hemorrhagic transformation in acute ischemic stroke. *Stroke*. 2003;34:40–46.
100. Tung PP, Olmsted EA, Kopelnik A, et al. Plasma 8-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. *Stroke*. 2005;36:1567–1569.

Anesthetic Considerations for Surgical Resection of Brain Arteriovenous Malformations

15

C.Z. Lee • P.O. Talke • M.T. Lawton

Surgical management of brain arteriovenous malformations (AVMs) is one of the most challenging in neurosurgery and, despite the relative rarity of the disease, the subject of a disproportionally large fraction of the literature on surgical cerebrovascular disease. Perioperative and anesthetic management is optimal when the anesthesiologist has familiarity with the strategic goals of therapy and familiarity with AVM pathophysiology. This chapter will summarize these topics and discuss specific neuroanesthetic issues regarding care of these patients. While the fundamentals of providing perioperative care are similar to other neurovascular conditions, there are some important considerations unique to AVMs.

CLINICAL BEHAVIOR

Brain AVMs are a relatively infrequent, but important source of neurological morbidity in young adults.[1] The basic morphology is of a vascular mass, called the nidus, that directly shunts blood between the arterial and venous circulations without a true capillary bed. Hemodynamic alterations include variable degrees of high flow through the feeding arteries, nidus and draining veins, as well as venous hypertension.[2] The nidus is a complex tangle of abnormal, dilated channels, not clearly artery or vein, with intervening gliosis.

AVMs may exert a deleterious effect on brain function by several mechanisms, including mass effects (e.g., hematoma, edema or gradually expanding abnormal vascular structures such as venous aneurysms), metabolic depression (diaschisis) and seizure activity. The most common presentation and source of morbidity, however, is spontaneous intracranial hemorrhage (ICH) from rupture, occurring in about one-half of all patients.

The risk of spontaneous ICH without treatment is commonly estimated to be approximately 2–4% per year for all patients,[3] but the rate varies widely depending on what ICH risk factors are present. The best studied risk factors are a presentation with ICH, deep location, and venous drainage pattern.[4,5] Factors such as small size of lesion and advanced age are less robust; others, such as presence of aneurysms, are harder to accurately define.[6,7] High intranidal pressure, as measured with direct puncture of feeding arteries or during superselective angiography, is associated with hemorrhage presentation.[8]

Clinical presentation with ICH appears to be the strongest risk factor for future hemorrhage.[5] There are a number of reports concerning other risk factors,[1,9–15] but few that have prospectively assessed future hemorrhage risk.[4,5,16–19] The risk of spontaneous ICH has been estimated in retrospective and prospective observational studies to range from 2% to 4% per year.[5] However, depending on a number of risk factors, the range of yearly bleeding risk varies widely, estimated to range from under 1% to over 30% per year.[4]

Approximately 10% of patients with AVMs also harbor intracranial aneurysms. Note that the converse is not true; the detection rate of AVMs in aneurysm patients is closer to the detection rate of AVMs in the general population. Intracerebral hemorrhage from aneurysms is usually associated with subarachnoid hemorrhage, whereas AVMs more commonly bleed into the ventricle or into parenchyma. This probably accounts for why the occurrence of vasospasm is uncommon in AVM cases. Spontaneous hemorrhage during the perioperative period as a result of variations in systemic blood pressure is probably less likely as well, due to a "buffering" capacity of the fistula on changes in systemic pressure.[20]

The morbidity of spontaneous AVM hemorrhage is controversial,[21,22] but estimates run from very low to as high as 25–50%.[22–32] The most recent prospective, longitudinal study data suggest that earlier estimates may be overestimates, and that hemorrhage, either at initial presentation or during follow-up of untreated AVM patients, appears to carry a lower morbidity than ICH from other causes.[33]

Consistent with the risk factors described above, the primary reason to treat a patient with an AVM is to protect him or her against future spontaneous intracranial hemorrhage, although more rarely, treatment may be undertaken for control of progressive neurological deficits or intractable seizures. Lacking any specific medical therapies for this purpose, treatment options are currently limited to three modes for treatment of AVMs: endovascular embolization, radiosurgery, and microsurgical excision. Treatment strategies, especially for complex lesions, frequently involve more than one modality. In general, endovascular therapy is performed as a preparatory adjunct to surgery. Using various glues or other embolic materials like Onyx, the blood supply to the fistula can be reduced, sometimes in several stages. This has the theoretical advantage of allowing surrounding brain regions to adapt to the circulatory changes. As a preoperative adjunct, embolization is thought to facilitate operative removal with less bleeding and seems to be associated with better surgical outcome. Embolization also can eliminate deep vascular pedicles that might be difficult to control surgically.

The **risks of invasive therapy** can be estimated using scales adapted for different treatment modalities, most importantly for surgery and radiotherapy.[34,35] Neurosurgeons are confident in their recommendations for **microsurgical resection** with most low-grade AVMs (Spetzler-Martin grade I–III), based on numerous reports detailing excellent results.[36] However, all treatment modalities—endovascular therapy, surgical and radiosurgical—continue to be reported as carrying a substantial risk of disability.[22,37–41]

For example, a meta-analysis of 2,425 patients from 25 sources undergoing invasive treatment[40] described an aggregate mortality of 3.3% with permanent morbidity of 8.6%, ranging from 1.5% to 18.7%.[40] Protection from spontaneous ICH by partial, non-curative **endovascular embolization** therapy has been suggested[42] but does not have rigorous support.[18,43] Pre-surgical embolization, thought to enhance

safety of surgical resection, has its own inherent morbidity varying from 4% to 9%.[40,44] A recent multicenter overview on endovascular AVM therapy (commissioned by the 2005 World Federation of Interventional and Therapeutic Neuroradiology meeting) revealed stable frequencies of self-reported treatment-related complications in numerous well-established international centers, in the range 9–12%,[45–51] but going as high as 22%.[52]

It is worthwhile noting that those risk factors that increase the risk of leaving the lesion untreated (i.e., increase the risk of spontaneous hemorrhage) do overlap with those characteristics that increase risk of surgical intervention, but they are not the same. The most widely used surgical risk score is the Spetzler-Martin scheme.[53] Any deep venous drainage increases surgical risk, but only exclusively deep venous drainage appears to influence rupture risk.[11] Larger size is an important component of increased surgical risk,[54] but does not affect natural history risk or may even represent a protective effect owing to low intranidal pressure with high flow lesions. Eloquence, an important attribute of where the AVM is located, strongly influences surgical risk, but has no effect on natural history risk. The point here is that when one is discussing "high risk lesions," it is important to specify whether one is talking about natural history or treatment risk.

Radiosurgical treatment offers a means to treat surgically inaccessible lesions and appears to be useful for smaller lesions. It is less efficacious for lesions >2–3 cm.[55–58] Further, patients who have received radiosurgical treatment are still exposed to the risk of new bleeding until the AVM is obliterated, usually after a course of 2–3 years, termed the *latency period*.[1] During the latency period, risk for ICH may decrease in patients who presented with hemorrhage, but not in those who were unruptured at presentation.[59] The frequency of neurological complications from radiotherapy of brain AVMs is generally similar to the complication rate from surgical and endovascular treatment. The Randomized Trial of Brain Unruptured AVMs (ARUBA) investigators[60] performed a systematic review of the literature from 1990 or later of prospective studies with at least 30 patients, and yielded 16 studies on 3,854 patients undergoing radiosurgery and a mean rate of treatment-related permanent neurological deficits in the range of 6–7%; obliteration rates, completeness and type of follow-up varied greatly.

The most controversial aspect of treatment is offering potentially high-risk invasive therapy for those who have not yet ruptured. Patients with unruptured lesions are at the highest risk for postoperative deficits.[54] The presenting hemorrhage may, in effect, perform some of the dissection, in that the hemorrhage cavity is an attractive approach to the lesion. Further, patients who are recovering from a hemorrhage-induced deficit may not have reached the final level of spontaneous recovery that may continue into the postoperative period, thus masking operative injury. One of the most important studies of recent times is the ARUBA trial,[61] an international randomized controlled trial (RCT) to test whether it is best medical therapy or procedural intervention that results in superior outcomes. The mean follow-up was 33.3 months in 223 patients, including 114 assigned to interventional therapy and 109 to medical management,[62] to compare the risk of death and symptomatic stroke. The superiority of the medical management group was demonstrated based on the incidences of strokes or death in 11 (10.1%) of the medical management group compared with 35 (30.7%) of the interventional therapy group. While the ARUBA trial suggests that medical management alone is superior for the prevention of death or stroke in patients with unruptured brain AVMs, there are ongoing debates about the applicability to all patients, given the heterogeneity of the disease and the small sample sizes, short follow-up, and poor participation of American centers in the trial.

ETIOLOGY AND PATHOGENESIS

The genesis of AVMs has been enigmatic. Unlike the association of antecedent head trauma or other injuries with the pathogenesis of dural arteriovenous fistulae (DAVF), environmental risk factors for AVMs are lacking. There is remarkably little evidence for the common assertion that AVMs are congenital lesions as a result of embryonic maldevelopment during the 4th to 8th week, considering high utilization of prenatal ultrasound (vein of Galen lesions are not true AVMs). Further, there have been multiple reports of AVMs that grow or regress, including de novo AVM formation.[63] Inciting event(s) might include the sequelae of even relatively modest injury from an otherwise unremarkable episode of trauma, infection, inflammation, irradiation, compression, or some underlying structural defect.[64] In susceptible individuals, one might posit some degree of localized venous hypertension[65] from microvascular thrombosis, perhaps associated with a state of relative thrombophilia.[66] All of these events may synergize and involve some underlying development defect that otherwise does not come to clinical attention. The scarce data available on longitudinal assessment of AVM growth suggest that approximately 50% of cases display interval growth.[67] Consistent with growth is the many-fold higher endothelial proliferation rate in AVM surgical specimens, compared to the control brain.[67]

Available evidence points towards an active angiogenic and inflammatory lesional phenotype rather than a static congenital anomaly. There are a host of abnormal signals present in the lesional tissue.[68,69] A prominent feature of the AVM phenotype is relative overexpression of VEGF-A, at both the mRNA and protein level. VEGF may contribute to the hemorrhagic tendency of AVMs, extrapolating from animal models.[70] Other upstream factors that may contribute to AVM formation might include Homeobox genes, such as excess pro-angiogenic Hox D3 or deficient anti-angiogenic Hox A5.[71] The vascular phenotype of AVM tissue may be explained, in part, by inadequate recruitment of periendothelial support structure, which is mediated by angiopoietins and Tie-2 signaling. For example, angiopoietin-2 (Ang-2), which allows loosening of cell-to-cell contacts, is overexpressed in the perivascular region in AVM vascular channels.[72]

Vascular remodeling is facilitated by proteases and is necessary to form the enlarged vascular elements in the nidus. A key downstream consequence of VEGF and other angiogenic activity is MMP expression. MMP-9 is of particular interest and is an order of magnitude higher in AVM than control tissue.[73,74] Inflammatory markers that are overexpressed include myeloperoxidase (MPO) and IL-6,[75] as well as higher immunoglobulin levels than control the brain, perhaps suggesting lymphocytic contributions.[76] The presence of T-lymphocytes in BAVMs also suggest the possibility of an independent cell-mediated immunological mechanism in AVM pathogenesis.[77]

Brain AVMs are usually sporadic, but sometimes familial.[78] The most promising candidate genes/pathways for brain AVM pathogenesis relate to hereditary hemorrhagic

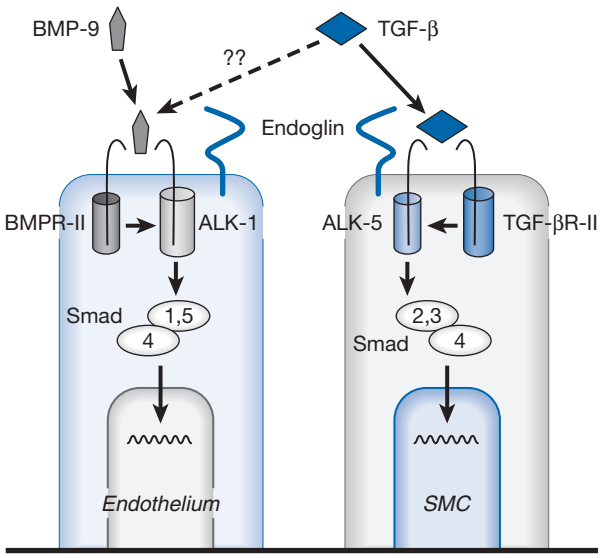


Fig. 15.1 Transforming growth factor-ß (TGF-ß) superfamily signaling may be an important aspect of sporadic arteriovenous malformation (AVM) pathogenesis. TGF-ß signals through a complex, tissue-specific set of receptors and intracellular signals. Loss-of-function mutations in at least two of these receptor proteins (endoglin and activing receptor-like kinase-1 [ALK-1]) result in hereditary hemorrhagic telangiectasia, with a high prevalence of solid-organ AVMs, including those in the brain. The relative roles of bone morphogenetic protein (BMP-9) and TGF-ß, and their cell type specificity, are currently controversial. Smad, proteins that modulate the activity of TGFs; SMC, smooth muscle cell; TGF-ßR-II, TGF-ß receptor 2. *(Adapted from Young WL: Clinical Neuroscience Lectures. Munster, IN, Cathenart Publishing, 2007.)*

telangiectasia (HHT), an autosomal dominant disorder of mucocutaneous fragility and AVMs in various organs including the brain. There are now at least five genes associated with HHT,[79–81] but the two main subtypes of HHT (HHT1 and 2) are caused by loss-of-function mutations in two genes originally implicated in TGF-β signaling pathways (Fig. 15.1).[82] The first is endoglin (ENG), which codes for an accessory protein of TGF-β receptor complexes. The second is activin-like kinase 1 (*ALK1*, or *ACVLR1*), which codes for a transmembrane kinase also thought to participate in TGF-β signaling. Recent data suggest that ALK1 may also signal through BMP-9, and that ENG can potentiate the signal.[83,84]

As a class, the inherited AVMs in HHT have some distinguishing morphological features, such as smaller size, multiplicity and more superficial location, but are generally similar to the sporadic lesions and cannot be distinguished individually on the basis of their angioarchitecture.[85,86] Together, about 10% of HHT1 and HHT2 patients display brain AVMs. This 10% figure is some 1000 times more frequent than the prevalence of brain AVM in the normal population (about 10/100,000 or .01%).[87] Therefore, one could view frank mutations in ALK1 and ENG as "hyper-risk" factors for the brain AVM phenotype.

Such a greatly elevated risk of brain AVM development in the Mendelian disorders raises the possibility that germline *sequence variants* of these and other genes may likewise pose a significant risk for *sporadic* brain AVM development. An intronic SNP in ALK1 has been associated with a two-fold elevated risk of the developing sporadic brain AVM,[88] a finding replicated in an independent cohort.[89,90] This SNP probably causes in-frame exon skipping, and may result in an ALK1 protein variant that lacks a transmembrane domain. An intriguing but unproven mechanism would be excess soluble receptor in the extracellular matrix that binds ligand and prevents it from normal signaling.

It is highly unlikely that a single polymorphic gene is responsible for AVM formation. Rather, it is mostly likely some combination of (a) an inciting event or developmental defect, (b) some genetic alteration in either ALK1 or ENG signaling or a closely related pathway, and (c) a set of modifier genes or conditions. For example, there are multiple genetic loci that appear to control VEGF factor-induced angiogenesis.[91,92] Such a conspiracy of factors is suggested by the observation that ENG-deficient mice spontaneously form vascular dysplasia,[93] and that the response can be amplified using viral transduction to overexpress VEGF in the mouse brain.[94] Recent advances in genetic mutation, in combination with angiogenic stimulation, have made it possible to establish testable adult mouse brain AVM models. Mutation of ALK1 and ENG genes in different vascular cell types can mimic many phenotypes of human brain AVM and can thus be used for studying brain AVM pathogenesis and testing new therapies.[95–97]

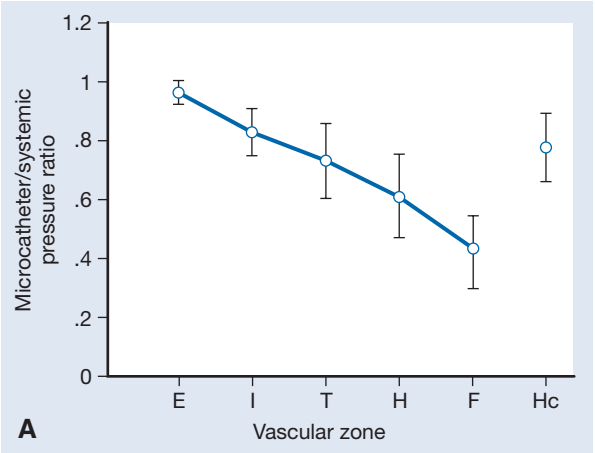
CEREBRAL CIRCULATORY CHANGES IN PATIENTS WITH ARTERIOVENOUS MALFORMATIONS

There are two primary characteristics of the cerebral circulatory changes brought about by AVMs. Rapid shunt flow results in an increased total amount of bulk flow through the AVMs. This increased flow results in cerebral arterial hypotension along the path of the shunt. Patients with AVMs have a progressive decrease in cerebral arterial pressure that proceeds from the circle of Willis to AVMs nidus (Fig. 15.2).[98] The corollary of this observation is that circulatory beds in parallel with the shunt system will be perfused at lower-than-normal pressures, even if flow remains relatively normal.

In patients with large, high flow AVMs, there may be normal brain regions in which cerebral arterial hypotension is below the range of normal autoregulation. Despite significant cerebral arterial hypotension, a majority of patients are free from ischemic symptoms. Hypotensive normal brain regions can be demonstrated to have normal rates of tissue perfusion, implying some adaptive change in total cerebrovascular resistance.

This phenomenon may be explained by "adaptive autoregulatory displacement."[100] In vascular territories adjacent to AVMs, the lower limit of the autoregulation curve appears to be shifted to the left, which is opposite of the effect of chronic systemic (essential) arterial hypertension on the cerebral autoregulation curve.[101] This adaptive shift to the left places the lower limit at a level considerably lower than the lower limit postulated for the normal brain (50 or 60 mmHg).[102,103] Therefore, the presence of chronic hypotension does not necessarily result in vasoparalysis in the arteriolar resistance bed. There is generally a preserved responsiveness to CO_2 pre- and post-surgical resection, which lends further support to the notion of intact autoregulatory capacity.[101]

Historically, it has been believed that it is not the AVM itself but rather decreased perfusion pressure in adjacent, functional tissue that is responsible for both pre-treatment *ischemic* and post-treatment *hyperemic* symptoms, namely "cerebral steal"



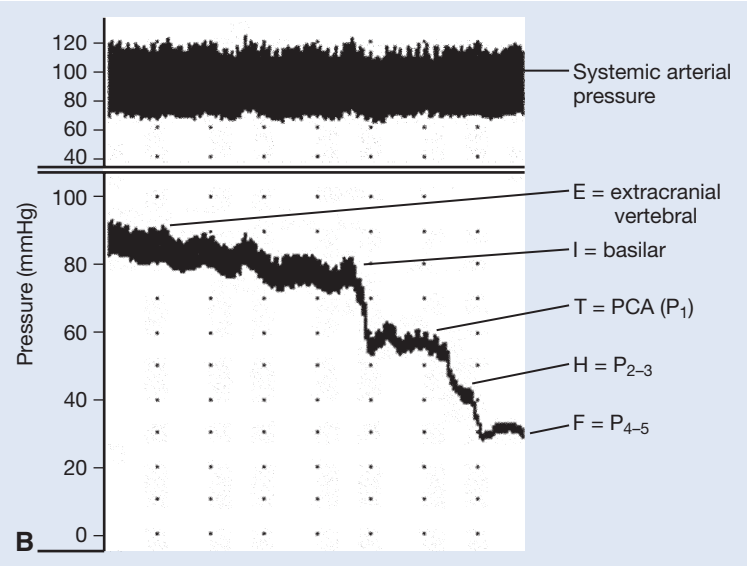


Fig. 15.2 **A,** Pressure ratios in zones E, I, T, H, F and Hc compared with clinical observations (see Table 15.1). The predicted values of our model for the medium arteriovenous malformation are close to the mean values of the experimental observations of Fogarty-Mack and colleagues.[99] E, extracranial: systemic pressure at level of coaxial catheter in extracranial vertebral artery or internal carotid artery; I, intracranial: supraclinoid internal carotid artery or basilar artery; T, transcranial Doppler insonation site: A_1, M_1, or P_1; H, halfway: arbitrarily "halfway" between T and the feeding artery; F, feeder in this model; Hc, contralateral distal arterial pressure. **B,** The continuous pressure tracing in a 40-year-old man who presented with seizures and had a left-sided, 3.5 x 2.5 x 7.0 cm temporal-occipital AVM fed by branches of the middle cerebral artery and the posterior cerebral artery (PCA). This tracing documents the pressure in the vertebral artery (E), basilar artery (I), P1 segment of the PCA (T), P2–P3 segment (H), and P4–P5 segment (F). Note the gradual decline in pressure, which is accentuated at major branch points. Further, all areas distal to the P1 (zone T), which irrigates a large area of normal, eloquent tissue, are relatively hypotensive. *(Adapted from Fogarty-Mack P, Pile-Spellman J, Hacein-Bey L, et al: The effect of arteriovenous malformations on the distribution of intracerebral arterial pressures. AJNR Am J Neuroradiol 1996;17:1443–1449.)*

and "normal perfusion pressure breakthrough" (NPPB). These widely discussed concepts have limited anecdotal evidence to support their existence.

Cerebral steal has been suggested as an explanation for focal neurologic deficits in AVM patients; "steal" is assumed to be attributable, by inference, to local hypotension and hypoperfusion. It has been postulated that arteriolar vascular resistance in territories adjacent to AVMs is at or near a state of maximal vasodilation, and, therefore, "steal" ensues if perfusion pressure decreases. Although cerebral arterial hypotension in normal brain areas is common in AVM patients, clinical presentations with focal neurological deficits are rare (10%). Moreover, there is no relation between local hypotension and focal neurologic deficits.[104] It is likely that local mass effects from the abnormal vessels of the AVMs are more important than local "hemodynamic failure" to account for symptomatic focal neurologic deficit unrelated to intracerebral hemorrhage or seizure activity.

The intraoperative appearance of diffuse bleeding from the operative site or brain swelling, and the postoperative occurrence of hemorrhage or swelling have been attributed to NPPB or "hyperemic" complications. There are difficulties in studying NPPB-type complications. First, there appear to be very heterogeneous sets of criteria used by different authors. Second, the incidence of this type of postoperative complication is probably lower than 5%.[105] The increase in global CBF after AVM resection appears to be associated with NPPB-type complications, but there is no relationship with preoperative regional arterial hypotension.[105] NPPB is attributed to cerebral hyperemia due to repressurization of previously hypotensive regions. This theory assumes that the chronic dilatation of vessels in the hypotensive/ischemic territory leads to a loss

of autoregulation.[102] However, there are several observations contradicting this theory. First, cerebral hyperemia after an AVM resection is global and not limited to the ipsilateral side of the AVM.[105] Second, there is no relationship between CBF changes after resection and the degree of arterial hypotension induced by AVM shunts.[105] Third, in hypotensive regions, autoregulatory response is not impaired, but intact and shifted to the left.[101] Finally, cerebrovascular reactivity to carbon dioxide is preserved after AVM resection,[106] suggesting that the vessels in previously hypotensive territories are not "paralyzed." All of these considerations notwithstanding, postoperative brain swelling and hemorrhage will be favored by uncontrolled systemic blood pressure. Although the mechanisms are still unclear, it seems reasonable to hypothesize that barrier integrity in the circulation is compromised by excessive protease activity or growth factor elaboration, as is probably the case in the setting of post-reperfusion hemorrhage after ischemic stroke.[107]

The states of "steal" and "normal perfusion pressure breakthrough" probably do exist in some minority of cases, but if they exist, they are the exception rather than the rule. As regards perioperative management, the diagnosis of NPPB should be a diagnosis of exclusion after all other correctable causes for malignant brain swelling or bleeding have been excluded. In addition to other supportive and resuscitative measures, preventing postoperative hypertension may be useful in preventing and treating this syndrome.

PERIOPERATIVE ANESTHETIC MANAGEMENT

Patients with AVMs often undergo several diagnostic (CT, MRI, PET) and therapeutic (interventional neuroradiology, radiosurgery, neurosurgery) procedures that may require anesthesia. Anesthetic management of these patients follows general goals of neuroanesthesia to maintain adequate CPP and to prevent increases in ICP, and focuses on preventing and managing serious perioperative complications, such as intracranial bleeding and NPPB. The following discussion of perioperative anesthetic management will concentrate on anesthesia for neuroradiologic and intraoperative procedures.

Preoperative Management

AVM resection is rarely emergent, unless there is a need for immediate surgical evacuation of an intracranial hematoma. Thus, a careful review of the patient's preoperative status and assessment of potential intraoperative difficulties should be possible. Most patients present with intracranial hemorrhage, new seizures or neurological deficits. Preexisting medical conditions should be optimized. The impact of any neurologic dysfunction, possible use of anti-seizure medications, the location (eloquent areas) and size of the AVM (possibility for significant blood loss), and intraoperative neurophysiologic monitoring should be factored into the anesthetic management plan regarding the choice of monitoring, vascular access, anesthetic agents, vasoactive drugs, muscle relaxants, and perioperative airway control.

Intraoperative Management

Monitoring

In addition to routine monitors—EKG, pulse oximeter, end-tidal CO_2 and temperature—central venous catheters may be considered for use during resection of large AVMs when there is a high risk for significant intraoperative blood loss. Intra-arterial catheters are routinely used during AVM resection for continuous, direct blood pressure monitoring and arterial blood sampling. Since hypertensive episodes are not commonly associated with AVM rupture, intra-arterial catheters are often placed after induction of anesthesia.[108] During AVM embolization, continuous intra-arterial blood pressure monitoring will help in the diagnosis and treatment of AVM rupture. Fortunately, these potentially devastating complications are rare (1–2%).[109]

Unfortunately, our ability to routinely monitor the central nervous system lags far behind our ability to monitor other systems, and the development of suitable technologies is still in its infancy. SSEP, MEP, and EEG monitoring may be used intraoperatively, and direct cerebral blood flow monitoring has been proposed by several groups. At present, this is an institution-specific endeavor and is not routinely performed. Jugular venous saturation monitoring has been proposed as index of throttling the shunt fraction through the fistula.[110]

Transduction of intravascular pressures in the operative field may aid the surgeon in differentiating arterial and venous structures. In certain cases, it may assist in the decision of whether a draining vein interfering with surgical access to the nidus can be sacrificed. Proximal arterial pressure is measured during a temporary occlusion of the vein; if the pressure does not change, it implies that alternate venous pathways are sufficient to prevent distention of the nidus and rupture. Technically, direct puncture of feeding arteries and draining veins in the operative field using 26-g needles is a simple procedure with minimal risk.

Vascular Access

The likelihood for significant intraoperative blood loss should be discussed preoperatively with the neurosurgeon. Multiple large-bore intravenous access for rapid blood administration and the availability of appropriate blood products are mandatory. Preoperative planning may include consideration of a central venous catheter if there is potential for significant intraoperative blood loss.

Anesthetic Technique

Choice of Agents

Scientific literature provides minimal guidance regarding anesthetic management of patients with AVMs. The choice of anesthetic agents varies widely among institutions and is made largely to follow basic neuroanesthesia principles and co-existing diseases. The most commonly used neuroanesthesia techniques at UCSF can be found on our website at neuroanesthesia.ucsf.edu.

Intracranial pressure control, which is often discussed with regards to the anesthetic care of neurosurgical patients, is usually not an issue with the AVM patient coming for elective resection, as the lesion does not displace, but rather replaces normal brain structures. Nonetheless, these patients may have decreased intracranial compliance, especially if significant venous hypertension is present, so the usual caveat about avoiding an anesthetic technique that results in significant cerebral vasodilation is a reasonable choice.

Patients having their AVM embolized at our institution routinely receive a general anesthetic. During embolization procedures, the anesthetic goals are to maintain an immobile patient with adequate CPP and to plan for immediate post-procedure neurologic examination. In addition to these

goals, during AVM resection, the anesthetic technique should minimize brain volume in order to reduce retractor-induced cerebral ischemia. For both procedures, there should also be a plan in place for the treatment of potential complications, such as intracerebral hemorrhage during embolization and significant bleeding and/or brain swelling during and after surgery (see below).

Neurologically intact patients may be premedicated with benzodiazepines (midazolam). Propofol, thiopental or etomidate can be used to induce anesthesia, propofol being most commonly used. Maintenance of anesthesia can be achieved with varying combinations of propofol/narcotic/inhalation anesthetic. Total intravenous anesthetic techniques or combinations of inhalational and intravenous methods may optimize rapid emergence from anesthesia and allow for SSEP and MEP monitoring. There is no evidence that the choice of an inhalation anesthetic, narcotic or muscle relaxant has an intrinsic, independent effect on outcome.

Some centers traditionally use barbiturate loading during the resection of AVM for metabolic suppression to afford additional protection against cerebral ischemia, resulting in, perhaps, a greater degree of brain relaxation and protection against acute hyperemia.[111] Barbiturates can be titrated to an EEG-endpoint of burst-suppression. The main price to be paid for barbiturate use is delayed emergence and forgoing an early postoperative neurologic exam. There is no evidence that outcome is affected. Other intravenous anesthetic agents, such as propofol and etomidate, can also be titrated to the effect of burst suppression.[112,113]

Nonpharmacologic Cerebral Protection

The goals of modern neuroanesthesia should optimize brain protective therapy. There are a number of basic considerations that will maximize nonpharmacologic cerebral protection (summarized in Table 15.1). There are two general types of damage towards which protective efforts are guided: neurosurgical (anatomic) and anesthetic (physiologic) trespass. Possible mechanisms of injury from the neurosurgeon include brain retraction, direct vascular injury (ischemia, thrombosis, venous occlusion), and mechanical disruption of neuronal tissue or white matter tracts. Anesthetic injury may result from systemic hypo- or hypertension, decreased O_2 content, hypo-osmolarity or hyperglycemia. It must be stressed that mechanisms of damage are interactive. For example, modest amounts of brain retraction coupled with a modest reduction of systemic blood pressure may have synergistic effects on neurologic outcome.

Management goals should include provision for a relaxed brain (to reduce retractor-induced ischemia), controlled systemic and cerebral hemodynamics, avoidance of hypotonicity, hyperglycemia and hyperthermia, and timely emergence from anesthesia without significant hypertension, tachycardia or coughing.

Table 15.1 **Nonpharmacologic Brain Protection**
Relaxed Brain
Good head position
Cerebrospinal fluid drainage
Diuretics/osmotherapy
Avoidance of excessive cerebral vasodilators
Modest hypocapnia
Controlled Systemic and Cerebral Hemodynamics
Euvolemia
Optimal cerebral perfusion pressure
Fluid and Electrolyte Management
Isotonicity
Euglycemia
Temperature Management
Toleration of modest hypothermia intraoperatively
Postoperative prevention of hyperthermia
Controlled Emergence
Tailored awakening
Autonomic control

Brain Relaxation during Surgery

Interventions that reduce brain volume may help in reducing retractor-induced ischemia. Adequate brain relaxation begins with good head position to promote intracranial venous drainage. The least amount of flexion and rotation necessary for the operative approach should be planned with the surgeon. A rule of thumb might be given as two-finger breadths between the mandible and clavicle (not the sternum) after the head is positioned in rigid pin fixation. The head of the table should be elevated slightly to prevent venous engorgement.

Cerebral spinal fluid removal is an effective means of brain relaxation, obtained by inserting a lumbar intrathecal catheter or ventricular drainage. Osmotic diuretic therapy with mannitol (0.5–1.0 gm/kg) with or without furosemide is widely applied. The most important consideration for anesthetic choice intraoperatively is the avoidance of cerebral vasodilators (moderate to high dose inhalation anesthetics). Modest hypocapnia should be used sparingly as an adjunct to brain relaxation, and $PaCO_2$ levels below 30 mmHg should have a specific indication.

Fluid Management and Glucose Control

There is a convincing body of evidence that serum osmolarity strongly influences water movement into both the normal and damaged brain.[114] Even mildly hypotonic fluids such as lactated Ringer's solution (without mannitol), if given in sufficient quantity, may aggravate brain swelling more than isotonic crystalloids or colloids. Isotonic fluid replacement with blood, saline or hetastarch after forebrain ischemia in the rat appears to yield similar results in terms of cerebral edema formation.[115] In clinical practice, many authorities recommend isotonic fluid replacement during neurosurgical procedures. Although some anesthesiologists do use limited amounts of hetastarch, its use in neuroanesthesia is controversial due to its potential to induce coagulopathy. In 2013 the U.S. Food and Drug Administration (FDA) approved the warnings about the risk of mortality and renal injury, as well as advising other precautions, in the use of hydroethyl starch (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability). Serum osmolarity can be easily monitored if large volumes of crystalloid are administered. The influence of colloid oncotic pressure on the formation of brain edema is still a controversial topic.[116–118] A recent experimental study indicated that a reduction of colloid oncotic pressure without decreased osmolarity may exacerbate

post-traumatic brain edema.[116] Aggressive administration of isotonic crystalloids may worsen brain edema by decreasing colloid oncotic pressure.[116] Although there are no perioperative outcome data to support the use of one fluid over another, based on available data it is advisable to avoid perioperative hypo-osmolarity.

There is considerable evidence that glucose aggravates cerebral injury not only in animals but also in humans.[119–122] Perioperative stress and the use of steroids may contribute to intraoperative and postoperative hyperglycemia. In fact, evidence for the use of steroids for cerebrovascular surgery is lacking, although many teams continue to use them.

In the absence of clear guidelines, the most rational approach is to avoid glucose-containing fluids, unless there is a specific indication. One such indication would be a diabetic patient receiving insulin therapy. In this case, "tight" rather than "loose" control of serum glucose seems reasonable. Despite the compelling animal data, the lack of specific clinical outcome data would suggest that over-aggressive lowering of glucose is not worth risking hypoglycemia in an anesthetized patient. A reasonable but arbitrary target might be to prevent renal spillage of glucose in the range of 180 mg per 100 mL. This is supported by a large international randomized trial showing that a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter, suggesting intensive glucose control increased mortality among adults in the ICU.[123]

Controlled Systemic and Cerebral Hemodynamics

Blood Pressure Control

Control of cerebral hemodynamics begins with control of systemic arterial pressure, which in turn is predicated on adequate cardiac preload (euvolemia). The most important point is that fluid should never be withheld at the expense of a stable cardiovascular status. Indeed, in the setting where there is the potential for rapid, significant intraoperative hemorrhage, it is clearly deleterious. A large amount of shunting blood through the AVM reduces blood pressure of the feeding and adjacent arteries. Marginally perfused areas may be critically dependent on collateral perfusion pressure. Maintenance of low blood pressure may be inadequate and result in infarction if unrecognized.

During manipulation of the intracranial contents or their vascular supply, the anesthesiologist should strive to maintain the "optimal CPP," that is, the highest clinically acceptable blood pressure for the particular clinical circumstance. We achieve this with a low-dose phenylephrine infusion when necessary. Brain relaxation is probably also served by maintenance of normal arterial pressure (cerebral blood volume is kept to a minimum by autoregulatory vasoconstriction).[124]

Anesthesiologists have a major role in preventing and/or treating retractor-related cerebral ischemia, cerebral ischemia secondary to poor cerebral perfusion, intraoperative hemorrhage and postoperative edema. There may be marginally perfused areas adjacent to an AVM that are critically dependent on collateral perfusion pressure. Although this may be secondary to the hemodynamic effects of the shunt, they are more likely due to mass effect from the vascular structures of the nidus or the residua of a prior hemorrhage. The cause notwithstanding, prolonged systemic hypotension might result in infarction, if unrecognized. Thus, CPP should be maintained at close to normal values unless there is an indication for inducing hypotension to control hemorrhage.

Induced Hypotension

In contrast to the current trend for maintaining normotension during intracranial aneurysm clipping, induced hypotension may be useful during AVM resection in cases of significant intraoperative bleeding. This is especially pertinent to large AVMs that have a deep arterial supply. Bleeding from these small, deep-feeding vessels may be difficult to control and decreasing arterial pressure facilitates surgical hemostasis. The subject of induced hypotension is discussed extensively in the neuroanesthesia literature.

During uncontrolled bleeding the surgeons may be forced to place clips blindly in an attempt to stem hemorrhage. In this event, deepening the anesthesia plane with intravenous agents may be indicated and could be used as a means of, or as an adjunct to, inducing mild or moderate temporary arterial blood pressure reduction until bleeding is brought under control. Induction of systemic hypotension with a pure vasodilator has theoretical disadvantages. In the setting of emergent intracranial vascular occlusion to control hemorrhage, the distal perfusion field of the occluded artery will have little or no opportunity to recruit collateral flow from neighboring (relatively vasodilated) normal arterial supply regions. However, the clinician should use whatever means indicated by the clinical situation that he or she is comfortable with and adept at to expeditiously reduce blood pressure.

Use of Hypothermia

Mild hypothermia (with core temperature decreases as little as 1.5–3 °C) has been shown to offer dramatic cerebral protection against ischemic insult in animal models.[125] This protective effect is greater than what would be expected from metabolic suppression alone, and may be related to a decrease in excitatory neurotransmitter release from ischemic cells.[126] Although RCTs have shown favorable results from mild hypothermia in patients with severe traumatic brain injury and in in-hospital cardiac arrest, the benefit was not certain in later targeted temperature controlled hypothermia trials on patients suffering out-of-hospital cardiac arrest.[127–130] Similarly, the efficacy of prophylactic mild hypothermia during craniotomy has not been validated.[131–133]

Anesthetized patients can be easily cooled to 33–34 °C, although complete intraoperative rewarming may be difficult to achieve.[134] Even mild degrees of hypothermia are not without potential risk.[135] Passive rewarming is associated with peripheral vasoconstriction, shivering, and subsequent increases in oxygen consumption and myocardial work. Drug metabolism is decreased, prolonging the effect of even short-acting anesthetic drugs. Moderate hypothermia (<33 °C) has other well-documented potential effects, including increased susceptibility to infection, cardiac arrhythmias and ischemia, hypercoagulability, thrombocytopenia, impaired platelet aggregation, and activation of fibrinolysis, all of which reverse with rewarming.[134,136] Most of these adverse effects have been observed in patients leaving the operating room while still hypothermic. It is unclear whether the potential benefits of cerebral protection gained from mild hypothermia and partial rewarming are offset by the hypothermia-induced systemic physiologic stress, particularly if shivering occurs upon emergence. Postoperative shivering can be significantly attenuated by intraoperative administration of meperidine or alpha-2 agonists (clonidine, dexmedetomidine).[137]

A conservative recommendation would be mild body temperature reduction (35–36 °C) until closure is imminent, followed by active rewarming. Careful temperature monitoring should continue throughout the perioperative period; hyperthermia must be avoided, as it potentiates ischemic damage.[138]

Emergence from Anesthesia and Initial Recovery

A particularly challenging aspect of perioperative care of patients with AVMs is emergence from anesthesia and initial recovery. A moderate phenylephrine-induced blood pressure augmentation (20–30% above normal mean arterial pressure) may be needed during drying of the operative bed to inspect for hemostasis. After hemostasis is achieved and anesthetic agents are reduced/discontinued, antihypertensive agents such as labetolol can be used to ensure the patient's blood pressure does not drop further than 10% below the patient's baseline values. Control of systemic hemodynamics is of critical importance during the emergence phase as the patient makes the transition from the anesthetized to the conscious state.[139] Administration of alpha-2 agonists (clonidine, dexmedetomidine) before the end of anesthesia can attenuate an emergence-induced stress response (hypertension, tachycardia).[140]

We would emphasize that, without firm outcome data indicating the superiority of one drug regimen over another, the choice of agent for manipulation of blood pressure must be placed in the context of the clinical situation (e.g., avoiding beta adrenergic blockers with bronchospastic airway disease or use of nitroglycerin with coronary artery disease) and the experience of the practitioner.

The most sensitive monitor of cerebral function remains the neurologic examination. A prompt emergence from anesthesia will ensure that drug residua will neither be confused with nor obscure focal neurologic damage. Delayed emergence may require emergent CT examination to rule out brain swelling or bleeding. However, long procedures with massive fluid resuscitation, complicated intraoperative courses, and situations where patients have pre-existing neurological deficits may be indications for postoperative sedation and mechanical ventilation. There is no ideal regimen to maintain postoperative sedation and blood pressure control. Use of dexmedetomidine has gained popularity due to its sympatholytic and sedative effects while the patient remains arousable to allow postoperative neurologic examination.

OPERATIVE CONSIDERATIONS FOR AVOIDING COMPLICATIONS

Intraoperative complications with AVMs challenge the neurosurgeon like no other lesion in the brain. Bleeding can erupt quickly to fill the surgical field, obscure critical anatomy, and impede microdissection. Bleeding arteries can be difficult to control, particularly when they are thin, friable perforating arteries resisting coagulation with bipolar cautery. Hemorrhage into the brain can damage it and compromise patient outcomes. Worst of all, uncontrollable bleeding can force dangerous or hasty maneuvers. Bleeding demands reactions from the anesthesiologist to replace volume, transfuse blood, maintain blood pressure, and sometimes correct coagulation disturbances.

Surgical complications are best avoided with judicious patient selection. The combination of AVM size, deep venous drainage, and eloquence of the adjacent brain that comprises the Spetzler-Martin grading scale provides a preliminary assessment of surgical risks,[34] with low-grade AVMs (grade I–III) having acceptably low morbidity rates and high-grade AVMs (grade IV–V) having unacceptably high morbidity and mortality rates. As helpful as this simple grading scale is, it is crude at best and demands more thorough assessment of other factors: grade III subtype, patient presentation, age, deep perforating artery supply, diffuseness, and functional eloquence. The Lawton-Young AVM grading system, which combines age, hemorrhagic presentation, and nidal compactness in a numbering system analogous to the Spetzler-Martin system, has been developed to supplement the well-established Spetzler-Martin grading system.[141] This supplementary grading scale has shown high predictive accuracy on its own and stratifies surgical risk more evenly for better prediction of neurologic outcomes after AVM surgery.[142] The sum of the Spetzler-Martin and Lawton-Young scores, otherwise referred to as the supplemented Spetzler-Martin score, is the best predictor of surgical morbidity and can be used to define limits of AVM operability, with a supplemented score less than or equal to 6 considered operable.

The dividing line between operability and nonoperability probably does not run cleanly between Spetzler-Martin grades III and IV, but rather between subtypes of the third grade.[143] Our experience has demonstrated that medium-sized AVMs (3–6 cm diameter) in eloquent locations have morbidity rates that resemble grade IV AVMs more than other grade III AVMs. In contrast, small-sized AVMs (less than 3 cm diameter) with deep venous drainage and in eloquent locations, as well as other medium-sized AVMs away from eloquent locations, have morbidity rates that are expected for grade III lesions. Therefore, the surgeon must beware of grade III AVMs that are larger in size and eloquent, and perhaps manage them more conservatively.

Presentation with hemorrhage is an important factor because it not only indicates AVMs with high risk of rehemorrhage, but also facilitates surgery.[54] Hematomas help separate an AVM from adjacent brain, completing some of the neurosurgeon's dissection preoperatively. Evacuation of hematoma also creates working space around the AVM that can minimize transgression of the normal brain to reach the nidus, or access a deep nidus that might otherwise have been unreachable. Hemorrhage can also obliterate some of the AVM's arterial supply, reducing its flow and the risk of bleeding during resection. Hemorrhage can be damaging to brain tissue, and young age and plasticity can enhance a patient's ability to recover neurological function. Even with unruptured AVMs, youth can enhance recovery from deficits caused by surgery.

Other anatomical features predict the likelihood of intraoperative bleeding and neurological outcomes. For example, compact AVMs with tightly woven arteries and veins often have distinct borders that separate cleanly from the adjacent brain, whereas diffuse AVMs with ragged borders and intermixed brain force the neurosurgeon to establish a dissection plane that can extend into the normal brain. Deep perforating arteries are thin, fragile, and difficult to occlude with cautery. Bleeding during surgery can escape into deep white matter tracts and cause significant deficits. These clues to intraoperative bleeding can be found on angiography, and used during the selection process.

The Spetzler-Martin grading scale defines eloquence as anatomical locations whose injury would result in a discrete

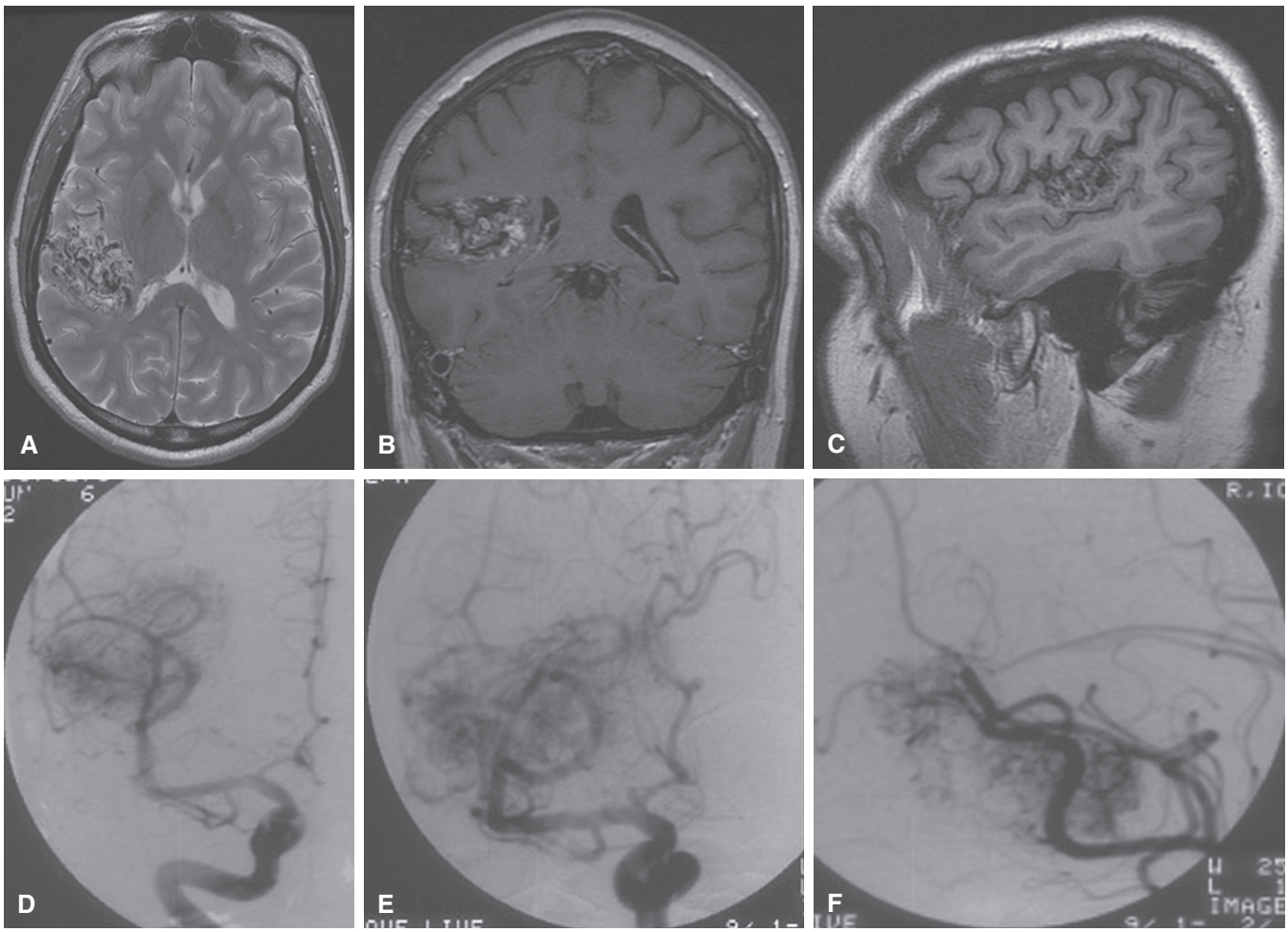


Fig. 15.3 **A–C,** Preoperative magnetic resonance imaging (MRI) demonstrates an arteriovenous malformation (AVM) in the posterior insular and superior temporal cortex. **A,** T2-weighted axial MRI; **B,** T1-weighted coronal image with gadolinium enhancement; **C,** T1-weighted sagittal image. **D–F,** Preoperative angiography shows this Spetzler-Martin grade III AVM with feeding arteries originating from insular branches of the middle cerebral artery. Right internal carotid artery injection, anteroposterior view **(D)**, anterior oblique view **(E)**, and lateral view **(F)**.

neurological deficit, such as the motor and somatosensory strips, visual cortex, speech areas, thalamus, and brainstem. However, structural anatomy does not always indicate functional anatomy with AVMs, because the brain often relocates functions if they lie too close to an AVM. For example, the presence of an AVM in the central sulcus may relocate motor function anteriorly from the precentral gyrus into premotor cortex. In more dramatic cases, left hemispheric functions such as speech can be moved to the opposite hemisphere or rearranged in the ipsilateral hemisphere.[144,145] Therefore, we have found that preoperative imaging with functional MRI (fMRI) more precisely localizes neurological function, allowing us to replace anatomical eloquence with individualized functional eloquence. These radiological adjuncts better define the surgical risks and refine patient selection. An example is shown in Figs. 15.3–15.6.

Even in the most carefully selected patients, intraoperative complications and catastrophes occur. Stroke from occlusion of an artery to the normal brain is one that occurs silently, unless detected on intraoperative neurophysiological monitoring. This complication can happen when an artery feeding the nidus is occluded too early, compromising branches to the normal brain that originate between the point of occlusion and the AVM. En passage arteries transmit branches to the AVM and distal branches to the brain downstream. These en passage arteries must be skeletonized or pruned to occlude only those that supply the AVM while preserving distal perfusion. Uninvolved arteries can also be mistaken for AVM feeding arteries. The neurosurgeon must rely on thorough analysis of the preoperative angiograms, thorough inspection of subtle anatomical features, and precise arterial occlusion at the point of entry into the nidus. Unexpected brain swelling during a long case may be an indication of an evolving stroke.

Bleeding is encountered most frequently along the deep plane of dissection, after the nidus has been dissected circumferentially. The deep penetrating arteries are typically encountered along this border and can resist coagulation with bipolar cautery. Visualization of these deep feeding arteries is often compromised by the overlying bulk of the nidus, and with stereotypical cone-shaped AVMs, this final plane is often deep below the cortical surface. The tip of the nidus can reach the ventricle, and bleeding from ventricular arteries can be difficult to identify, rapidly fill the ventricle, and cause the brain to herniate outward. With all these hazards along this deep plane, the neurosurgeon must approach this last stage of the dissection with the utmost concentration. The nidus is dissected completely on all sides before

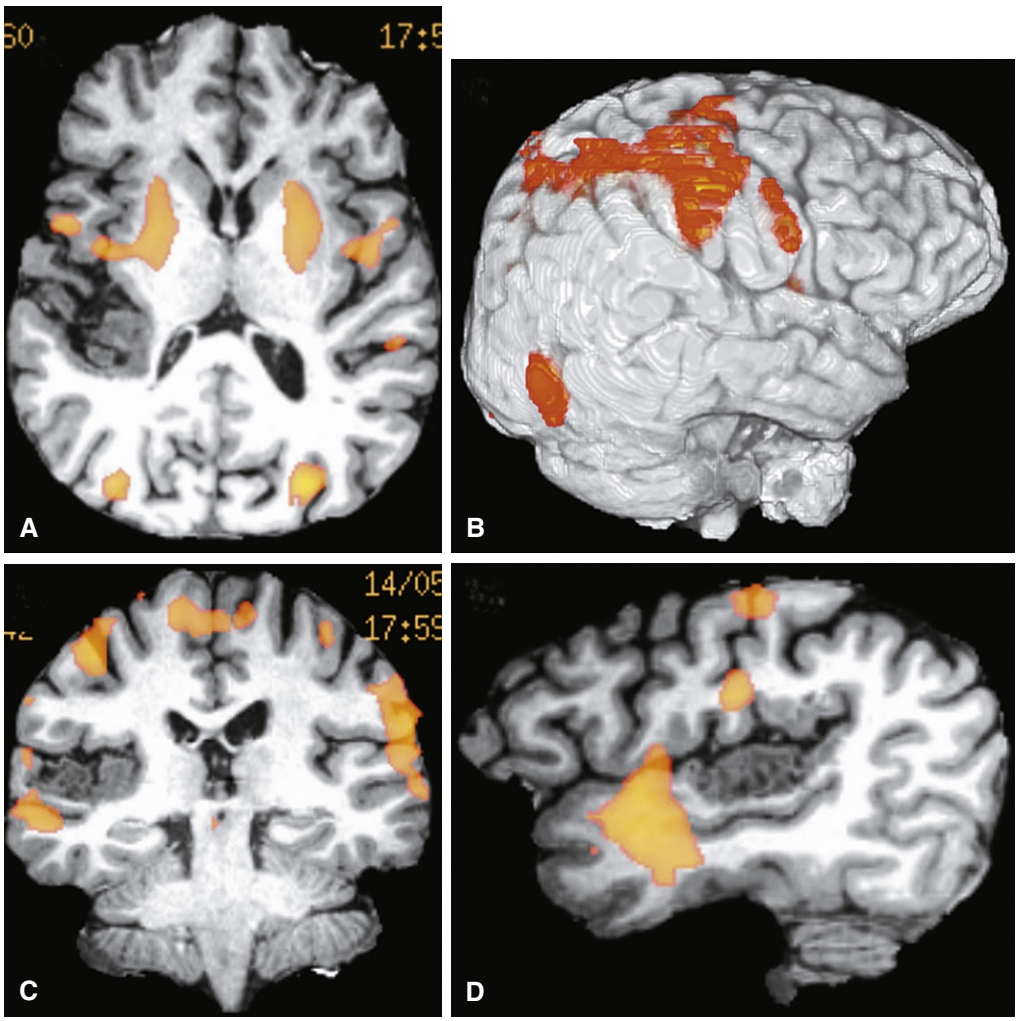


Fig. 15.4 **A** and **B,** Functional magnetic resonance imaging (MRI) localizes left-hand motor function by acquiring images with the patient tapping the left fingers. Activated parts of the brain are shown in Axial **(A)** and three-dimensional reconstructed **(B)** images. **C** and **D,** Functional MRI localizes tongue motor function by acquiring images with the patient moving the tongue. Activated parts of the cortex are shown in Coronal **(C)** and sagittal **(D)** views. Even though this AVM was considered eloquent by its anatomical location, fMRI demonstrated some separation from these motor functions and facilitated the decision to resect it.

proceeding to the deep plane; arteries resisting cautery are occluded with microclips; ventricular tips of AVMs are encircled to make sure that feeding arteries are effectively closed; and any bleeding is meticulously controlled before proceeding with the dissection.

In addition to bleeding along the deep plane, frank rupture of the AVM can also occur. One of the tenets of AVM surgery is to dissect circumferentially, encircling the AVM but never violating it. AVM rupture can occur when the plane of dissection is too close. Bleeding is brisk, and the nidus cannot be cauterized like a feeding artery. The rupture site is tamponaded with hemostatic agents to control the bleeding and enable the neurosurgeon to continue working. If the dissection plane is too tight, a portion of the nidus can be separated from the AVM as a remnant. These remnants typically have arterial input but lack venous outflow, which predisposes them to rupturing either during surgery or shortly thereafter. An area that is unusually bloody may be a sign of retained AVM, and a wider path of dissection must be established around this area. Another tenet of AVM surgery is to occlude all the feeding arteries before occluding the draining vein. Occasionally, an arterialized draining vein may be mistaken for a feeding artery and occluded early, compromising venous outflow, pressuring the AVM, and precipitating rupture. The neurosurgeon must recognize this dangerous state and quickly remove the AVM. A ruptured, bleeding AVM is less tense and angry, and the neurosurgeon has a limited time window to continue working through the bleeding. The anesthesiologist must keep pace with this blood loss during these situations.

Significant intra- or postoperative brain swelling may occur after AVM resection, as discussed above. If there is no identifiable cause, for example, undiagnosed rupture or obstructed venous drainage from thrombosis or occlusion, treatment is symptomatic with such maneuvers as hyperventilation, mannitol and tight blood pressure control.

The threat of bleeding and catastrophe is ever present in AVM surgery. Intraoperative excitement is rarely associated with good outcomes. The best AVM surgery is steady and meticulous for the neurosurgeon, and quiet and unexciting for the anesthesiologist. The neurosurgeon and the anesthesiologist must make preparations to deal with the worst of complications, while working continuously to avoid them.

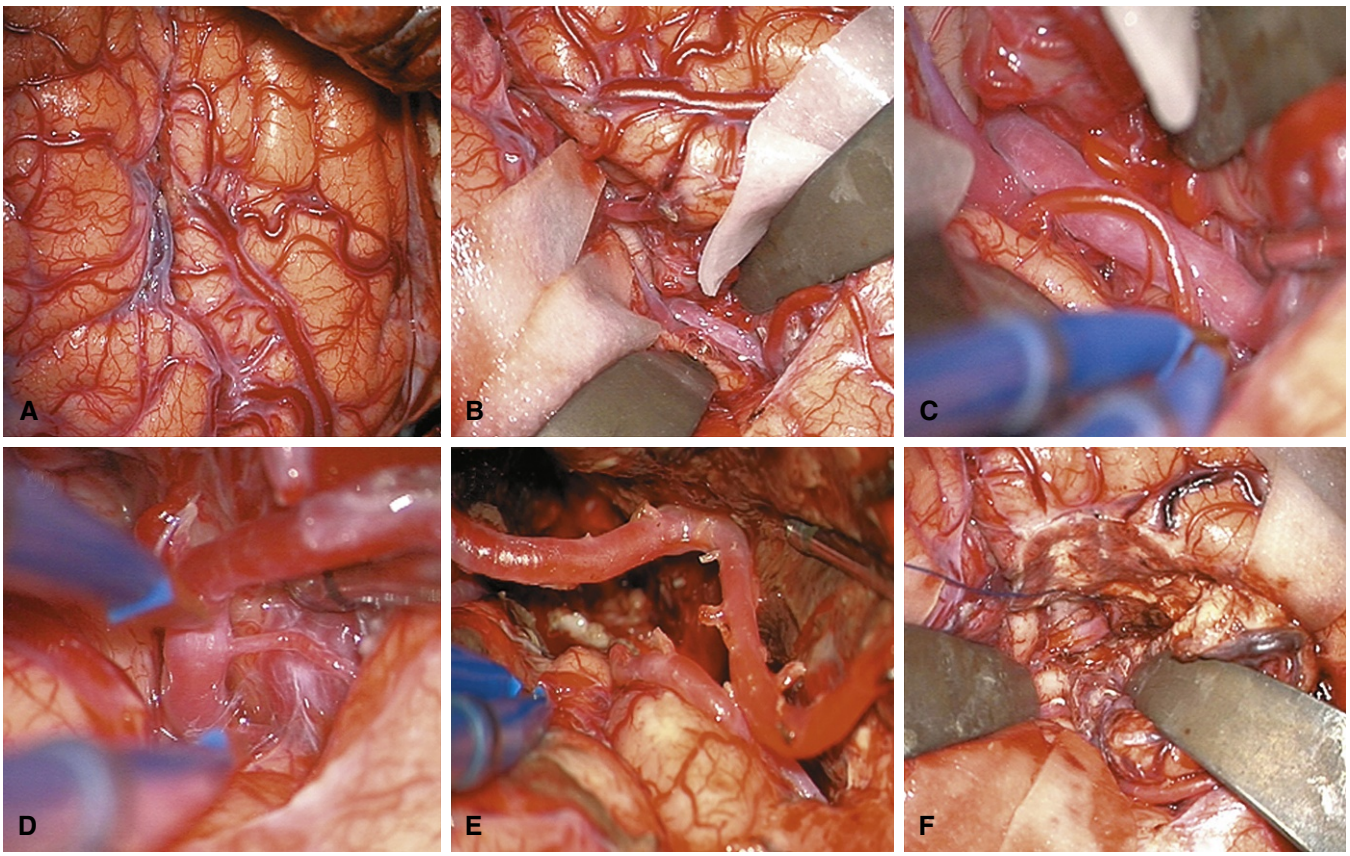


Fig. 15.5 **A,** Intraoperative photograph shows that the arteriovenous malformation (AVM) does not reach the brain surface. Wide splitting of the distal Sylvian fissure revealed the feeding middle cerebral arteries **(B)**, with the AVM located on the temporal side of the fissure (**C,** superior). Feeding arteries were branches from the middle cerebral artery **(D)**, which was pruned or skeletonized to preserve distal blood flow to angular cortex **(E)**. After devascularizing of the AVM, its deep plane was dissected **(F)** and the nidus was removed.

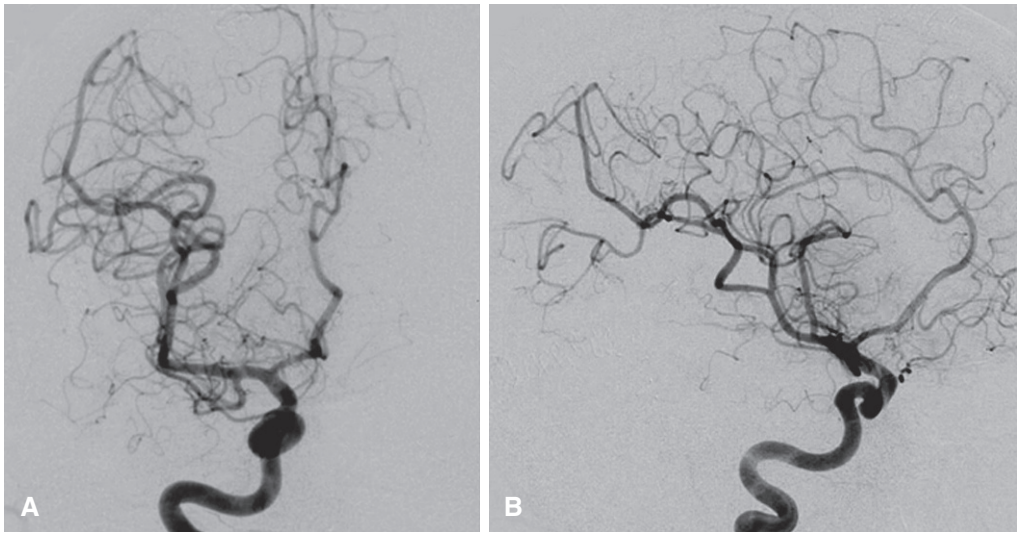


Fig. 15.6 Postoperative angiography shows complete resection of the arteriovenous malformation, with preservation of *en passage* arteries. Right internal carotid artery injection, anteroposterior **(A)** and lateral **(B)** views.

REFERENCES

1. Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. *N Engl J Med*. 1999;340:1812–1818.
2. Young WL. Intracranial arteriovenous malformations: Pathophysiology and hemodynamics (Chapter 6). In: Jafar JJ, Awad IA, Rosenwasser RH, eds. *Vascular Malformations of the Central Nervous System*. New York: Lippincott Williams & Wilkins; 1999:95–126.
3. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. *Lancet Neurol*. 2005;4:299–308.
4. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66:1350–1355.
5. Kim H, Sidney S, McCulloch CE, et al. Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. *Stroke*. 2007;38:2430–2437.
6. Kim H, Al-Shahi Salman R, McCulloch CE, et al. Untreated brain arteriovenous malformation: Patient level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83:590–597.

7. Stapf C, Mohr JP, Pile-Spellman J, et al. The effect of concurrent arterial aneurysms on the risk of hemorrhagic presentation in brain arteriovenous malformations [Abstract]. *Stroke*. 2001;32:337-c.
8. Duong DH, Young WL, Vang MC, et al. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. *Stroke*. 1998;29:1167–1176.
9. Spetzler RF, Hargraves RW, McCormick PW, et al. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. *J Neurosurg*. 1992;76:918–923.
10. Miyasaka Y, Kurata A, Tokiwa K, et al. Draining vein pressure increases and hemorrhage in patients with arteriovenous malformation. *Stroke*. 1994;25:504–507.
11. Kader A, Young WL, Pile-Spellman J, et al. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. *Neurosurgery*. 1994;34:801–807; discussion 807–808.
12. Brown Jr. RD, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: Frequency of intracranial hemorrhage and relationship of lesions. *J Neurosurg*. 1990;73:859–863.
13. Marks MP, Steinberg GK, Norbash AM, et al. Characteristics predictive of hemorrhage in AVMs [Abstract]. *Stroke*. 1993;24:184.
14. Marks MP, Lane B, Steinberg GK, et al. Hemorrhage in intracerebral arteriovenous malformations: Angiographic determinants. *Radiology*. 1990;176:807–813.
15. Batjer H, Suss RA, Samson D. Intracranial arteriovenous malformations associated with aneurysms. *Neurosurgery*. 1986;18:29–35.
16. Mast H, Young WL, Koennecke HC, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. *Lancet*. 1997;350:1065–1068.
17. Halim AX, Johnston SC, Singh V, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke*. 2004;35:1697–1702.
18. Stefani MA, Porter PJ, terBrugge KG, et al. Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. *Stroke*. 2002;33:1220–1224.
19. Kim H, Sidney S, Johnston SC, et al. Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients [Abstract]. *Stroke*. 2007;38:468.
20. Gao E, Young WL, Pile-Spellman J, et al. Cerebral arteriovenous malformation feeding artery aneurysms: A theoretical model of intravascular pressure changes after treatment. *Neurosurgery*. 1997;41:1345–1356. discussion 1356-1348.
21. Fleetwood IG, Steinberg GK. Arteriovenous malformations. *Lancet*. 2002;359:863–873.
22. Hartmann A, Mast H, Mohr JP, et al. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. *Stroke*. 1998;29:931–934.
23. Forster DM, Steiner L, Hakanson S. Arteriovenous malformations of the brain. A long-term clinical study. *J Neurosurg*. 1972;37:562–570.
24. Ondra SL, Troupp H, George ED, et al. The natural history of symptomatic arteriovenous malformations of the brain: A 24-year follow-up assessment. *J Neurosurg*. 1990;73:387–391.
25. Svien HJ, McRae JA. Arteriovenous anomalies of the brain. Fate of patients not having definitive surgery. *J Neurosurg*. 1965;23:23–28.
26. Waltimo O. The change in size of intracranial arteriovenous malformations. *J Neurol Sci*. 1973;19:21–27.
27. Fults D, Kelly Jr. DL. Natural history of arteriovenous malformations of the brain: A clinical study. *Neurosurgery*. 1984;15:658–662.
28. Luessenhop AJ, Rosa L. Cerebral arteriovenous malformations: Indications for and results of surgery, and the role of intravascular techniques. *J Neurosurg*. 1984;60:14–22.
29. Brown Jr. RD, Wiebers DO, Forbes G, et al. The natural history of unruptured intracranial arteriovenous malformations. *J Neurosurg*. 1988;68:352–357.
30. Perret G, Nishioka H. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI. Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the cooperative study. *J Neurosurg*. 1966;25:467–490.
31. Perret G. The epidemiology and clinical course of arteriovenous malformations (Chapter II: Clinical Aspects). In: Pia HW, Gleave JRW, Grote E, et al., eds. *Cerebral Angiomas: Advances in Diagnosis and Therapy*. New York: *Springer-Verlag*; 1975:21–26.
32. Graf CJ, Nibbelink DW. Cooperative study of intracranial aneurysms and subarachnoid hemorrhage: Report on randomized treatment study: Intracranial surgery. *Stroke*. 1974;5:559–561.
33. Choi JH, Mast H, Sciacca RR, et al. Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. *Stroke*. 2006;37:1243–1247.
34. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65:476–483.
35. Pollock BE, Flickinger JC. A proposed radiosurgery-based grading system for arteriovenous malformations. *J Neurosurg*. 2002;96:79–85.
36. Lawton MT, Hamilton MG, Spetzler RF. Multimodality treatment of deep arteriovenous malformations: Thalamus, basal ganglia, and brain stem. *Neurosurgery*. 1995;37:29–36.
37. Hartmann A, Stapf C, Hofmeister C, et al. Determinants of neurological outcome after surgery for brain arteriovenous malformation. *Stroke*. 2000;31:2361–2364.
38. Hartmann A, Pile-Spellman J, Stapf C, et al. Risk of endovascular treatment of brain arteriovenous malformations. *Stroke*. 2002;33:1816–1820.
39. ApSimon HT, Reef H, Phadke RV, et al. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. *Stroke*. 2002;33:2794–2800.
40. Castel JP, Kantor G. Postoperative morbidity and mortality after microsurgical exclusion of cerebral arteriovenous malformations. Current data and analysis of recent literature. *Neurochirurgie*. 2001;47:369–383.
41. Morgan MK, Rochford AM, Tsahtsarlis A, et al. Surgical risks associated with the management of Grade I and II brain arteriovenous malformations. *Neurosurgery*. 2004;54:832–837. discussion 837-839.
42. Meisel HJ, Mansmann U, Alvarez H, et al. Effect of partial targeted N-butyl-cyano-acrylate embolization in brain AVM. *Acta Neurochir (Wien)*. 2002;144:879–887; discussion 888.
43. Wikholm G, Lundqvist C, Svendsen P. The Goteborg cohort of embolized cerebral arteriovenous malformations: A 6-year follow-up. *Neurosurgery*. 2001;49:799–806.
44. Taylor CL, Dutton K, Rappard G, et al. Complications of preoperative embolization of cerebral arteriovenous malformations. *J Neurosurg*. 2004;100:810–812.
45. Goto K. Ectatic and occlusive diseases of the 95 venous drainage system of cerebral arteriovenous malformations (AVMs) with emphasis on specutacular shrinking neurological deficits after embolization. *Interv Neuroradiol*. 2005;11(Sup 1):95–118.
46. Bhattacharya J, Jenkins S, Zampakis P, et al. Endovascular treatment of AVMs in Glasgow. *Interv Neuroradiol*. 2005;11(Sup 1):73–80.
47. Campos J, Biscoito P, Sequeira P, et al. Intra-arterial embolization in the analysis of five years (2000-2004) in the treatment of brain arteriovenous malformations. *Interv Neuroradiol*. 2005;11(Sup 1):81–94.
48. Vinuela F, Duckwiler G, Jahan R, et al. Therapeutic management of cerebral arteriovenous malformations. Present role of interventional neuroradiology. *Interv Neuroradiol*. 2005;11(Sup 1):13–29.
49. Ozanne A, Alvarez H, Rodesch G, et al. Management of brain AVMs at Bicêtre: A comparison of two patient cohorts treated in 1985-1995 and 1996-2005. *Interv Neuroradiol*. 2005;11(Sup 1):31–36.
50. Klurfan P, Gunnarsson T, Haw C, et al. Endovascular treatment of brain arteriovenous malformations: The Toronto experience. *Interv Neuroradiol*. 2005;11(Sup 1):51–56.
51. Beltramello A, Zampieri P, Ricciardi G, et al. Combined treatment of brain AVMs: Analysis of five years (2000-2004) in the Verona experience. *Interv Neuroradiol*. 2005;11(Suppl 1):63–72.
52. Raymond J, Iancu D, Weill A, et al. Embolization as one modality in a combined strategy for the management of cerebral arteriovenous malformations. *Interv Neuroradiol*. 2005;11(Sup 1):57–62.
53. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. 1986. *J Neurosurg*. 2008;108:186–193.
54. Lawton MT, Du R, Tran M, et al. Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. *Neurosurgery*. 2005;56:485–493.
55. Pollock BE, Flickinger JC, Lunsford LD, et al. Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. *Neurosurgery*. 1996;38:652–659. discussion 659-661.
56. Pollock BE, Flickinger JC, Lunsford LD, et al. Factors that predict the bleeding risk of cerebral arteriovenous malformations. *Stroke*. 1996;27:1–6.
57. Pollock BE, Flickinger JC, Lunsford LD, et al. Factors associated with successful arteriovenous malformation radiosurgery. *Neurosurgery*. 1998;42:1239–1244; discussion 1244–1237.
58. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. *Int J Radiat Oncol Biol Phys*. 1999;44:67–74.
59. Maruyama K, Kawahara N, Shin M, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. *N Engl J Med*. 2005;352:146–153.
60. Hartmann A, Marx P, Schilling AM, et al. Neurologic complications following radiosurgical treatment of brain arteriovenous malformations [Abstract]. In: *12th European Stroke Conference;* Valencia, Spain; 2003.
61. National Institute of Neurological Disorders and Stroke (NINDS). *A randomized trial of unruptured brain AVMs (ARUBA)*; 2007. Available at http://clinicaltrials.gov/ct/show/NCT00389181.

62. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. *Lancet*. 2014;383:614–621.
63. Du R, Hashimoto T, Tihan T, et al. Growth and regression of an arteriovenous malformation in a patient with hereditary hemorrhagic telangiectasia: Case report. *J Neurosurg*. 2007;106:470–477.
64. Mullan S, Mojtahedi S, Johnson DL, et al. Embryological basis of some aspects of cerebral vascular fistulas and malformations. *J Neurosurg*. 1996;85:1–8.
65. Lawton MT, Jacobowitz R, Spetzler RF. Redefined role of angiogenesis in the pathogenesis of dural arteriovenous malformations. *J Neurosurg*. 1997;87:267–274.
66. Singh V, Smith WS, Lawton MT, et al. Thrombophilic mutation as a new high-risk feature in DAVF patients [Abstract]. *Ann Neurol*. 2006;60:S30.
67. Hashimoto T, Mesa-Tejada R, Quick CM, et al. Evidence of increased endothelial cell turnover in brain arteriovenous malformations. *Neurosurgery*. 2001;49:124–131; discussion 131–132.
68. Hashimoto T, Young WL. Roles of angiogenesis and vascular remodeling in brain vascular malformations. *Semin Cerebrovasc Dis Stroke*. 2004;4:217–225.
69. Hashimoto T, Lawton MT, Wen G, et al. Gene microarray analysis of human brain arteriovenous malformations. *Neurosurgery*. 2004;54:410–423; discussion 423–425.
70. Lee CZ, Xue Z, Zhu Y, et al. Matrix metalloproteinase-9 inhibition attenuates vascular endothelial growth factor-induced intracranial hemorrhage. *Stroke*. 2007;38:2563–2568.
71. Chen Y, Xu B, Arderiu G, et al. Retroviral delivery of homeobox d3 gene induces cerebral angiogenesis in mice. *J Cereb Blood Flow Metab*. 2004;24:1280–1287.
72. Hashimoto T, Lam T, Boudreau NJ, et al. Abnormal balance in the angiopoietin-tie2 system in human brain arteriovenous malformations. *Circ Res*. 2001;89:111–113.
73. Hashimoto T, Wen G, Lawton MT, et al. Abnormal expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in brain arteriovenous malformations. *Stroke*. 2003;34:925–931.
74. Chen Y, Fan Y, Poon KY, et al. MMP-9 expression is associated with leukocytic but not endothelial markers in brain arteriovenous malformations. *Front Biosci*. 2006;11:3121–3128.
75. Chen Y, Zhu W, Bollen AW, et al. Evidence of inflammatory cell involvement in brain arteriovenous malformations. *Neurosurgery*. 2008;62:1340–1349.
76. Shenkar R, Shi C, Check IJ, et al. Concepts and hypotheses: Inflammatory hypothesis in the pathogenesis of cerebral cavernous malformations. *Neurosurgery*. 2007;61:693–702; discussion 702–703.
77. Guo Y, Tihan T, Lawton MT, et al. Distinctive distribution of lymphocytes in unruptured and previously untreated brain arterviovenous malformation. *Neuroimmunol Neuroinflamm*. 2014;1:147–152.
78. Inoue S, Liu W, Inoue K, et al. Combination of linkage and association studies for brain arteriovenous malformation. *Stroke*. 2007;38:1368–1370.
79. Gallione CJ, Richards JA, Letteboer TG, et al. SMAD4 Mutations found in unselected HHT patients. *J Med Genet*. 2006;43:793–797.
80. Bayrak-Toydemir P, McDonald J, Akarsu N, et al. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. *Am J Med Genet A*. 2006;140:2155–2162.
81. Cole SG, Begbie ME, Wallace GM, et al. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. *J Med Genet*. 2005;42:577–582.
82. Marchuk DA, Srinivasan S, Squire TL, et al. Vascular morphogenesis: Tales of two syndromes. *Hum Mol Genet*. 2003;12:R97–R112.
83. Scharpfenecker M, van Dinther M, Liu Z, et al. BMP-9 signals via ALK1 and inhibits bFGF-induced endothelial cell proliferation and VEGF-stimulated angiogenesis. *J Cell Sci*. 2007;120:964–972.
84. David L, Mallet C, Mazerbourg S, et al. Identification of BMP9 and BMP10 as functional activators of the orphan activin receptor-like kinase 1 (ALK1) in endothelial cells. *Blood*. 2007;109:1953–1961.
85. Matsubara S, Mandzia JL, ter Brugge K, et al. Angiographic and clinical characteristics of patients with cerebral arteriovenous malformations associated with hereditary hemorrhagic telangiectasia. *AJNR Am J Neuroradiol*. 2000;21:1016–1020.
86. Maher CO, Piepgras DG, Brown Jr RD, et al. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. *Stroke*. 2001;32:877–882.
87. Berman MF, Sciacca RR, Pile-Spellman J, et al. The epidemiology of brain arteriovenous malformations. *Neurosurgery*. 2000;47:389–396; discussion 397.
88. Pawlikowska L, Tran MN, Achrol AS, et al. Polymorphisms in transforming growth factor-beta-related genes ALK1 and ENG are associated with sporadic brain arteriovenous malformations. *Stroke*. 2005;36:2278–2280.
89. Simon M, Franke D, Ludwig M, et al. Association of a polymorphism of the ACVRL1 gene with sporadic arteriovenous malformations of the central nervous system. *J Neurosurg*. 2006;104:945–949.
90. Simon M, Schramm J, Ludwig M, et al. Author reply to letter by Young WL et al, Arteriovenous malformation. *J Neurosurg*. 2007;106:732–733.
91. Rogers MS, D'Amato RJ. The effect of genetic diversity on angiogenesis. *Exp Cell Res*. 2006;312:561–574.
92. Shaked Y, Bertolini F, Man S, et al. Genetic heterogeneity of the vasculogenic phenotype parallels angiogenesis: Implications for cellular surrogate marker analysis of antiangiogenesis. *Cancer Cell*. 2005;7:101–111.
93. Satomi J, Mount RJ, Toporsian M, et al. Cerebral vascular abnormalities in a murine model of hereditary hemorrhagic telangiectasia. *Stroke*. 2003;34:783–789.
94. Xu B, Wu YQ, Huey M, et al. Vascular endothelial growth factor induces abnormal microvasculature in the endoglin heterozygous mouse brain. *J Cereb Blood Flow Metab*. 2004;24:237–244.
95. Walker EJ, Su H, Shen F, et al. Arteriovenous malformation in the adult mouse brain resembling the human disease. *Ann Neurol*. 2011;69:954–962.
96. Chen W, Sun Z, Han Z, et al. De novo cerebrovascular malformation in the adult mouse after endothelial Alk1 deletion and angiogenic stimulation. *Stroke*. 2014;45:900–902.
97. Choi EJ, Chen W, Jun K, et al. Novel brain arteriovenous malformation mouse models for type 1 hereditary hemorrhagic telangiectasia. *PLoS One*. 2014;9:e88511.
98. Fogarty-Mack P, Pile-Spellman J, Hacein-Bey L, et al. The effect of arteriovenous malformations on the distribution of intracerebral arterial pressures. *AJNR Am J Neuroradiol*. 1996;17:1443–1449.
99. Fogarty-Mack P, Pile-Spellman J, Hacein-Bey L, et al. Superselective intraarterial papaverine administration: Effect on regional cerebral blood flow in patients with arteriovenous malformations. *J Neurosurg*. 1996;85:395–402.
100. Kader A, Young WL. The effects of intracranial arteriovenous malformations on cerebral hemodynamics. *Neurosurg Clin N Am*. 1996;7:767–781.
101. Young WL, Pile-Spellman J, Prohovnik I, et al. Evidence for adaptive autoregulatory displacement in hypotensive cortical territories adjacent to arteriovenous malformations. *Neurosurgery*. 1994;34:601–610; discussion 610–611.
102. Spetzler RF, Wilson CB, Weinstein P, et al. Normal perfusion pressure breakthrough theory. *Clin Neurosurg*. 1978;25:651–672.
103. Nornes H, Grip A. Hemodynamic aspects of cerebral arteriovenous malformations. *J Neurosurg*. 1980;53:456–464.
104. Mast H, Mohr JP, Osipov A, et al. "Steal" is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. *Stroke*. 1995;26:1215–1220.
105. Young WL, Kader A, Ornstein E, et al. Cerebral hyperemia after arteriovenous malformation resection is related to "breakthrough" complications but not to feeding artery pressure. Columbia University AVM Study Project. *Neurosurgery*. 1996;38:1085–1093; discussion 1093–1085.
106. Young WL, Prohovnik I, Ornstein E, et al. The effect of arteriovenous malformation resection on cerebrovascular reactivity to carbon dioxide. *Neurosurgery*. 1990;27:257–267.
107. Rosell A, Lo EH. Multiphasic roles for matrix metalloproteinases after stroke. *Curr Opin Pharmacol*. 2008;8:82–89.
108. Szabo MD, Crosby G, Sundaram P, et al. Hypertension does not cause spontaneous hemorrhage of intracranial arteriovenous malformations. *Anesthesiology*. 1989;70:761–763.
109. Jayaraman MV, Marcellus ML, Hamilton S, et al. Neurologic complications of arteriovenous malformation embolization using liquid embolic agents. *AJNR Am J Neuroradiol*. 2008;29:242–246.
110. Katayama Y, Tsubokawa T, Hirayiama T, et al. Continuous monitoring of jugular bulb oxygen saturation as a measure of the shunt flow of cerebral arteriovenous malformations. *J Neurosurg*. 1994;80:826–833.
111. Spetzler RF, Martin NA, Carter LP, et al. Surgical management of large AVM's by staged embolization and operative excision. *J Neurosurg*. 1987;67:17–28.
112. Shanechi MM, Chemali JJ, Liberman M, et al. A brain-machine interface for control of medically-induced coma. *PLoS Comput Biol*. 2013;9:e1003284.
113. Ching S, Liberman MY, Chemali JJ, et al. Real-time closed-loop control in a rodent model of medically induced coma using burst suppression. *Anesthesiology*. 2013;119:848–860.
114. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *Anesthesiology*. 1987;67:936–941.
115. Warner DS, Boehland LA. The effects of iso-osmolal hemodilution on post-ischemic brain water content in the rat. *Anesthesiology*. 1988;68:86–91.
116. Drummond JC, Patel PM, Cole DJ, et al. The effect of the reduction of colloid oncotic pressure, with and without reduction of osmolality, on post-traumatic cerebral edema. *Anesthesiology*. 1998;88:993–1002.

117. Kaieda R, Todd MM, Warner DS. Prolonged reduction in colloid oncotic pressure does not increase brain edema following cryogenic injury in rabbits. *Anesthesiology*. 1989;71:554–560.
118. Kaieda R, Todd MM, Cook LN, et al. Acute effects of changing plasma osmolality and colloid oncotic pressure on the formation of brain edema after cryogenic injury. *Neurosurgery*. 1989;24:671–678.
119. Lanier WL. Glucose management during cardiopulmonary bypass: Cardiovascular and neurologic implications. *Anesth Analg*. 1991;72:423–427.
120. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75:545–551.
121. Godoy DA, Pinero GR, Svampa S, et al. Hyperglycemia and short-term outcome in patients with spontaneous intracerebral hemorrhage. *Neurocrit Care*. 2008;9:217–229.
122. Meynaar IA, Eslami S, Abu-Hanna A, et al. Blood glucose amplitude variability as predictor for mortality in surgical and medical intensive care unit patients: A multicenter cohort study. *J Crit Care*. 2012;27:119–124.
123. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
124. Rosner MJ. Cerebral perfusion pressure: Link between intracranial pressure and systemic circulation (Chapter 27). In: Wood JH, ed. *Cerebral Blood Flow: Physiologic and Clinical Aspects*. New York: McGraw-Hill; 1987:425–448.
125. Busto R, Dietrich WD, Globus MY-T, et al. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab*. 1987;7:729–738.
126. Busto R, Dietrich WD, Globus MY-T, et al. The importance of brain temperature in cerebral ischemic injury. *Stroke*. 1989;20:1113–1114.
127. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. *JAMA*. 2014;311:45–52.
128. Kim F, Bravo PE, Nichol G. What is the use of hypothermia for neuroprotection after out-of-hospital cardiac arrest? *Stroke*. 2015;46:592–597.
129. Cronberg T, Lilja G, Horn J, et al. Neurologic function and health-related quality of life in patients following targeted temperature management at 33 degrees C vs 36 degrees C after out-of-hospital cardiac arrest: A randomized clinical trial. *JAMA Neurol*. 2015;72:634–641.
130. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369:2197–2206.
131. Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma*. 1993;10:263–271; discussion 273.
132. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med*. 1997;336:540–546.
133. Todd MM, Hindman BJ, Clarke WR, et al. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
134. Baker KZ, Young WL, Stone JG, et al. Deliberate mild intraoperative hypothermia for craniotomy. *Anesthesiology*. 1994;81:361–367.
135. Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology*. 2001;95:531–543.
136. Frank SM, Beattie C, Christopherson R, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology*. 1993;78:468–476.
137. Stapelfeldt C, Lobo EP, Brown R, et al. Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg*. 2005;100:226–232.
138. Chen H, Chopp M. Effect of mild hyperthermia on the ischemic infarct volume after middle cerebral artery occlusion in the rat. *Neurology*. 1991;41:1133–1135.
139. Morgan MK, Sekhon LH, Finfer S, et al. Delayed neurological deterioration following resection of arteriovenous malformations of the brain. *J Neurosurg*. 1999;90:695–701.
140. Talke P, Chen R, Thomas B, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg*. 2000;90:834–839.
141. Lawton MT, Kim H, McCulloch CE, et al. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. *Neurosurgery*. 2010;66:702–713; discussion 713.
142. Kim H, Pourmohamad T, Westbroek EM, et al. Evaluating performance of the Spetzler-Martin supplemented model in selecting patients with arteriovenous malformation patients for surgery. *Stroke*. 2012;43:2497–2499.
143. Lawton MT. UCSF AVM study project: Spetzler-Martin Grade III arteriovenous malformations: Surgical results and a modification of the grading scale. *Neurosurgery*. 2003;52:740–748; discussion 748–749.
144. Lazar RM, Marshall RS, Pile-Spellman J, et al. Anterior translocation of language in patients with left cerebral arteriovenous malformations. *Neurology*. 1997;49:802–808.
145. Lazar RM, Marshall RS, Pile-Spellman J, et al. Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. *Neuropsychologia*. 2000;38:1325–1332.

Occlusive Cerebrovascular Disease: Anesthetic Considerations

16

I.A. Herrick • J. Chui • R.T. Higashida • A.W. Gelb

Carotid endarterectomy (CEA) was initially introduced in the early 1950s. An intuitively appealing procedure, the number of procedures rose steadily until 1985, when CEA was ranked the third most common operation performed in the United States.[1] Its popularity shifted over the subsequent years as questions arose regarding its efficacy and the wide variation in reported morbidity and mortality associated with the procedure. However, several large, well-designed, randomized trials[2–4] have confirmed the benefit of this procedure in selected patients and current guidelines for CEA[5–7] define an important role for this operation, combined with best medical therapy, in the prevention of stroke.

CEA remains the gold standard surgical procedure for the prevention of stroke. However, over the past two decades considerable interest has accompanied the emergence of carotid angioplasty and stenting (CAS) procedures for treating extracranial, as well as intracranial, occlusive vascular disease.[8–10] Based on the results of several well-designed, prospective trials, current guidelines identify CAS as an alternative to CEA in appropriately selected patients.[6,7,11a,11b,12a]

Both CEA and CAS will remain important treatments for the prevention of stroke. Both these operations are directed at patients with advanced cerebrovascular disease and represent challenging procedures from the anesthesiologist's perspective because many of the patients are elderly and have significant coexisting disease. This chapter reviews the anesthetic considerations for, and management of, patients undergoing CEA and explores the roles for CEA and CAS procedures for the prevention of stroke.

PHYSIOLOGIC CONSIDERATIONS

Carotid revascularization procedures involve the manipulation of the blood supply to the brain. As a consequence, the rationale and recommendations for the management of patients undergoing these procedures are founded on an understanding of neurovascular anatomy and physiology.

The brain is highly active metabolically but is essentially devoid of oxygen and glucose reserves, making it dependent on the continuous delivery of oxygen and glucose by the cerebral circulation. Cerebral blood flow (CBF) is provided by the internal carotid arteries (approximately 80%) and the vertebral arteries (approximately 20%). These major arteries anastomose at the base of the brain to form the circle of Willis, which provides the primary collateral vascular channel between the cerebral hemispheres. However, other collateral channels between the intracranial and extracranial circulations (e.g., through the orbit) may become well developed in patients with occlusive disease of the internal carotid artery.

CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR) according to the following equation:

$$CBF = CPP / CVR \quad (16.1)$$

where *CPP* represents the difference between mean arterial blood pressure and intracranial pressure or central venous pressure, whichever is greater, and *CVR* is a function of blood viscosity and the diameter of the cerebral vessels. Normally CBF is autoregulated in response to cerebral metabolic requirements, a process common to many specialized vascular beds. During CEA, however, optimization of CBF is hampered by the fact that the only factors readily amenable to intraoperative manipulation are arterial blood pressure and arterial carbon dioxide tension ($PaCO_2$), which affect CPP and CVR, respectively. Confounding this situation, our current understanding of the physiology of CBF is incomplete. For example, much of our understanding of cerebral hemodynamic changes during anesthesia is based on the assessment of changes that occur in larger vessels using techniques such as computed tomography (single-photon emission computed tomography [SPECT]) or transcranial Doppler ultrasonography (TCD) studies.[12b–14] However, work using orthogonal polarization spectral imaging of the sublingual microcirculation[15] suggests that the flow observed in larger vessels after the induction of anesthesia may not parallel changes in flow observed in the capillary network. These findings raise questions about our ability to predict microvascular perfusion consistently on the basis of the dynamic behavior of large vessels.

Carbon Dioxide Tension

CBF is exquisitely sensitive and directly related to $PaCO_2$. CBF changes 1 to 2 mL/100 g/min for every 1-mmHg change in $PaCO_2$ within the range of 20–80 mmHg. The most appropriate level of $PaCO_2$ during CEA has not been definitively established. Hypocapnia has been advocated on the premise that vasoconstriction in areas of normal (CO_2-responsive) brain will potentially divert blood flow toward ischemic regions, the "Robin Hood" effect.[16,17] Conversely, deliberate hypercapnia has been postulated to increase global CBF and as a consequence may improve perfusion to potentially ischemic regions.[18] However, both concepts have been criticized on the grounds that studies of regional cerebral blood flow during carotid cross-clamping have demonstrated that the regional CBF response to changes in $PaCO_2$ is not entirely predictable.[19] Cerebral autoregulation has been reported to be completely lost during carotid cross-clamping under hypercapnic conditions and partially lost during hypocapnia, illustrating the relatively greater importance of blood pressure control during CEA. Furthermore, increasing $PaCO_2$ causes vasodilation in normal brain and has been reported to result in a potential steal of blood flow from ischemic zones in up to 23% of patients.[19] A similar steal phenomenon has also been reported during CEA in association with cerebral vasodilatation that accompanies the administration of volatile anesthetic drugs such as sevoflurane.[20]

A recent review of the scant clinical literature pertaining to the influence of carbon dioxide on cerebral autoregulation concluded that hypercapnia is likely to be associated with relative cerebral hyperperfusion but that there is insufficient published evidence to delineate the underlying cerebrovascular response to this condition at the microvascular level. In contrast, hypocapnia is associated with a decrease in cerebral blood flow that is compounded by concommittant hypotension irrespective of whether it is produced by hemorrhage or anesthetic drugs. The authors caution that these conditions could be associated with ischemia and emphasize that wide inter-individual variability around the lower limit of autoregulation compromises the reliability of this parameter to consistently reflect the adequacy of cerebral perfusion in individual patients.[21]

Further confounding decisions regarding the appropriate management of $PaCO_2$ during CEA is the fact that other disease processes also may alter the response to changes in arterial carbon dioxide tension. For example, patients with diabetes mellitus, a common condition among patients presenting for CEA, have been reported to display impairment of cerebrovascular responsiveness to hypercapnia during anesthesia with propofol, sevoflurane, or isoflurane.[22,23] Although the level of impairment was observed to be related to the severity of the diabetes (i.e., glycosylated hemoglobin value and extent of retinopathy), the level of impairment observed among individual patients was not consistently predictable.

In the absence of a clear clinical benefit associated with either hypercapnia or hypocapnia, or a readily available means to titrate either to a cerebrovascular effect, the most prudent approach to the ventilatory management of patients undergoing CEA is maintenance of normocapnia. This is accomplished by reference to preoperative arterial blood gas measurements or, if these are not available, by ventilating to a $PaCO_2$ value that produces a normal pH in a patient who does not have a coexisting metabolic acidosis. This approach attempts to achieve a balance between the optimization of CBF and the avoidance of cerebral steal.

Blood Pressure

Traditionally, many textbooks report that CBF is maintained relatively constant within the range of mean arterial blood pressure (MAP), from approximately 50 to 150 mmHg. Beyond this range the limit of vasomotor activity is exceeded and CBF becomes directly dependent on changes in CPP. In patients with preexisting chronic hypertension, both the upper and lower limits of autoregulation are shifted toward higher pressures. However, several investigators have noted that most available evidence suggests that, based on MAP, the lower limit of autoregulation in humans is substantially higher on average than 50 mmHg (at least 70 mmHg) and subject to large inter-individual variation.[21,24] As a consequence, as noted previously, caution is advised when using these traditional values to guide blood pressure management at the lower limit of autoregulation.

A deliberate increase in intraoperative blood pressure has been advocated during CEA based on the premise that autoregulation will maintain normal CBF in areas of healthy brain while flow will be increased in areas of the brain that are hypoperfused owing to vasomotor paralysis or atherosclerotic narrowing.[18] The CBF response to changes in $PaCO_2$ is depressed in patients with cerebrovascular disease as well as during carotid cross-clamping (as discussed previously), suggesting that blood vessels distal to regions of atherosclerotic narrowing are operating near the limits of autoregulatory vasodilation.[25] Under these conditions, improvement in CBF is likely to depend on increases in CPP. Higher stump pressures and reversal of ischemic changes on the electroencephalogram (EEG) have been reported in response to induced hypertension during cross-clamping.[16,26] The use of deliberate hypertension during carotid cross-clamping continues to be advocated by some investigators. Routine phenylephrine-induced systolic hypertension to 200 mmHg (and selectively up to 240 mmHg for persistent cross-clamp intolerance) during the period of cross-clamp application has been reported to reduce the need for intraoperative shunting during CEA performed under regional anesthesia in low-risk patients. While the incidence of cross-clamp intolerance was reported to be reduced, the potential for cardiac ischemic events (a risk reported to accompany the use of pharmacologically induced hypertension during these procedures) was not specifically evaluated.[27]

Deliberate hypertension is not devoid of risk. Excessive increases in CPP may cause cerebral hemorrhage or edema formation in regions of the brain that have lost autoregulation ability. In addition, patients most at risk for the development of cerebral ischemia—those with inadequate collateral blood flow—have been shown to be the least responsive to induced hypertension.[28] However, these patients are most in need of safe maneuvering, including judiciously induced hypertension that may increase flow to the ischemic region. In patients with ischemic heart disease, systemic vasoconstriction may lead to an adverse myocardial oxygen balance. The incidence of myocardial ischemia has been reported to be higher among patients who receive phenylephrine infusions or metaraminol to increase blood pressure during CEA.[29,30]

On the basis of the available evidence, the routine intraoperative elevation of blood pressure above the patient's normal level is not recommended. Instead, the extent and patency of the collateral circulation should be discussed prior to induction of anesthesia. In patients with patent collateral vessels, careful maintenance of blood pressure within the normal preoperative range is recommended. Spontaneous increases in systolic blood pressure of up to 20% above normal at the time of cross-clamping are acceptable. In patients with poor collaterals, blood pressure may be cautiously increased up to about 20% to 30% above baseline, with consideration of the concerns previously described. Excessive spontaneous increases may reflect cerebral ischemia, a possibility that should be considered before the increase in blood pressure is controlled pharmacologically.

PREOPERATIVE CONSIDERATIONS

Carotid endarterectomy and carotid stenting procedures are interventions designed to reduce the risk of stroke among patients with advanced cerebrovascular disease. Most patients presenting for these procedures are elderly with a variety of comorbidities including, coronary artery disease, arterial hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes mellitus, renal insufficiency, or a combination of such conditions Based on the medical characteristics of the patients included in NASCET[31] (1991) and the GALA study[32] (2008), published 17 years apart, the burden of these conditions remains substantial among patients presenting for CEA (Table 16.1). As a consequence of these conditions, it is not surprising that CEA and CAS procedures also carry a substantial risk of death or serious morbidity. The benefit of these procedures resides in the fact that for the majority of patients with advanced disease, the risk of stroke or

Table 16.1 Comparative Medical Characteristics of Patients Eligible for Inclusion in NASCET (1991) and the GALA (2008) Trial

	Proportion of Patients (%)	
	NASCET[a]	GALA[b]
Medical Condition	(n = 2256)	(n = 3526)
Angina	24	
Previous myocardial infarction	20	
Coronary artery disease		36
Hypertension	60	77
Peripheral vascular disease	14	25
Smoker (current or previous)	77	80
Diabetes mellitus	19	25

NASCET, North American Symptomatic Carotid Endarterectomy Trial;GALA, General Anaesthesia versus Local Anaesthesia for Carotid Surgery

(a. Adapted from North American Symptomatic Carotid Endarterectomy Trial Steering Committee. Methods, patient characteristics, and progress. Stroke 1991;22:711–720; b. Adapted from GALA Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008;372:2132–42.)

death without intervention is higher than the risk associated with the procedure. Hence, appropriate selection and optimization of candidates for these procedures represent important opportunities to mitigate perioperative risk.

Patient Selection

Overwhelming evidence supports the efficacy of CEA combined with best medical therapy for the prevention of stroke among appropriately selected patients. Three large multicenter randomized trials conducted in North America[2,33] and Europe[3] over two decades ago validated the role of CEA in the treatment of patients with symptomatic high-grade carotid disease. Current American Heart Association (AHA) guidelines recommend CEA in symptomatic patients with carotid stenosis of 50% to 99% if the risk of perioperative stroke or death is less than 6%.[6,7] Pooled data from the major CEA trials involving symptomatic patients with stenosis greater than 50% support these recommendations and show that the number of patients needed to treat (NNT) to prevent one stroke over a 2-year period is nine for men and 36 for women.[34] Benefit is also greater in older rather than younger patients, particularly those older than 75 years, with an NNT value of 5.

For asymptomatic patients the data are less robust. The risk of stroke is lower in asymptomatic patients than in patients with symptomatic disease and, as a consequence, the benefit of surgical intervention is realized only if the procedure can be performed with a lower 30-day risk of stroke and death. AHA guidelines[5,35] recommend CEA for asymptomatic patients with carotid stenosis of 60% to 99% if the perioperative risk of stroke or death is less than 3%.

It is noteworthy in relation to perioperative risk that many studies that support the preceeding recommendations included exclusion criteria that eliminated patients with significant comorbid conditions and many also required that participating surgeons performed a suitable volume of procedures. Consequently, current recommendations for CEA are also influenced by clinical factors that may modify the risk and the potential for benefit (stroke prevention), such as life expectancy, age, gender, the presence of coexisting medical conditions, and the outcome performance of the surgeon and surgical team who perform the procedure.[36–38] It has been noted that published outcomes following CEA as well as CAS procedures, particularly the 30-day incidence of stroke, have been progressively improving over the past two decades,[5,7] an observation that has been attributed to recognition of the important impact of surgical training and case volume on outcome as well as to the evolution of medical therapy including better management of comorbid conditions such as hypertension, dyslipidemia and diabetes.

The Role for Carotid Angioplasty and Stenting

Over the past three decades there has been an exponential increase in interest in and use of endovascular approaches for the treatment of carotid artery stenosis. This increase has paralleled the growth in the use of these techniques in other vascular specialties, especially in the coronary and peripheral vascular beds. Further impetus has come from advances in catheter, balloon, stent, and endovascular emboli trapping device development and has been encouraged by recognition of the many potential advantages of endovascular approaches, particularly in high-risk patients (Table 16.2). The benefits of an endovascular approach include: it is "minimally invasive"; it avoids surgical wounds and their complications; and endovascular procedures can generally be accomplished with local anesthesia and sedation.

The technique employs standard endovascular approaches from a transfemoral arterial approach. Patients are routinely pre-medicated with ASA 325 mg and clopidogrel 75 mg 3–5 days prior to the procedure. A diagnostic catheter is advanced under fluoroscopic guidance and the vascular anatomy of the aorta, neck, and head are imaged. Once the vessel to be treated is fully defined, an 8.0 F guiding catheter or 6.0 F long sheath is placed from the femoral artery and proximal to the lesion in the mid-low cervical common carotid artery. After systemic heparinization is given (70–100 units/kg) and an activated clotting time (ACT) is confirmed to be increased by two times the baseline, a fine (e.g., 0.014") steerable guide wire, in combination with a distal filter protection device, is advanced across the stenosis and deployed 2–4 cm distal to the lesion to be treated. The distal filter devices are expandable umbrella-like devices that are deployed distal to the stenosis

Table 16.2 Potential Indications for Carotid Angioplasty-Stent

Previous carotid endarterectomy
Contralateral carotid artery occlusion
Previous radical neck dissection or radiation therapy to neck region
Target lesion above C2 (level of jaw) or low cervical carotid lesions
Carotid dissection
Tandem lesions with ≥70% stenosis, intracranial stenosis, or occlusion
Significant cardiorespiratory comorbidity
Requires concurrent major cardiac or aortic surgery
Inability to extend neck
Contralateral laryngeal nerve palsy
At risk for wound infection (e.g., immunosuppressed, tracheostomy)

to trap emboli that may be released during the angioplasty and stent deployment. The appropriate size (e.g., 2.5–4 mm × 20–40 mm) angioplasty balloon is then placed across the stenosis, and once positioned it is inflated to high pressure (up to 8–12 atm) for 60–120 seconds to pre-dilate the stenotic lesion. Aggressive balloon dilation may increase the risk of complications with vessel dissection and/or embolization of the plaque, and residual stenosis is mostly related to calcification, which does not resolve with repeated dilations. Thereafter a nitinol or stainless steel self-expanding stent of appropriate length (2–4 cm) and diameter (4–10 mm) is then deployed across the lesion to completely bridge and cover the plaque in both the cervical internal and/or common carotid arteries. Following stent deployment, a larger angioplasty balloon, which matches the normal luminal diameter of the cervical internal carotid and/or the common carotid arteries are then used to dilate the lesion to >80–100% of the normal lumen, to ensure maximal restoration to normal vessel size is achieved.

Following final balloon angioplasty across the stented lesion, the distal filter protection device is then recaptured, and withdrawn. A post-stent angiogram is then performed to insure restoration of normal luminal diameter, full patency of the stent, and normal filling of the more distal intracranial blood vessels are maintained. The patient is then rechecked neurologically, and in most instances, a femoral arterial closure device is placed to ensure hemostasis. Patients are usually monitored in the neuro ICU or another high-dependency monitoring environment for 24 hours and, if stable, discharged home on ASA 325 mg indefinitely and clopidogrel 75 mg for at least 6–12 weeks post stenting.

Major Randomized Trials Comparing Carotid Artery Stenting versus Carotid Endarterectomy

The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial[39] was a non-inferiority randomized controlled clinical trial in which 334 patients, judged to be at high risk for CEA, and who were either symptomatic (transient ischemic attack (TIA) or stroke) with a >50% stenosis or asymptomatic with a >80% stenosis were randomized to CEA (n = 167) or CAS (n = 167). The primary endpoint was a composite of death, stroke, or myocardial infarction (MI) within 30 days or ipsilateral stroke and/or death from 31 days to 1 year. There was no statistical difference between CAS versus CEA at 30 days (cumulative incidence 20.1%; absolute difference, −7.9%; p = 0.004 for non-inferiority). At 1 year, carotid restenosis requiring treatment was less for CAS than CEA (cumulative incidence, 0.6% vs. 4.3%; p = 0.04). In symptomatic patients at 1 year, the primary endpoint for CAS was 16.8% vs. CEA was 16.5% (p = 0.95). For asymptomatic patients at 1 year, the primary endpoint for CAS was 9.9% vs. CEA was 21.5% (p = 0.02).

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy (SPACE) trial[40–42] was a non-inferiority study comparing CAS vs. CEA in symptomatic patients. A total of 1200 patients, were randomly assigned to CAS (n = 605) versus CEA (n = 595) within 180 days of a TIA or stroke. The primary endpoint was ipsilateral ischemic stroke or death at 30 days post procedure. For CAS, the endpoint was 6.84% vs. CEA of 6.34% (absolute difference, 0.51%; 95% confidence interval; p = 0.09 for non-inferiority). Embolic protection devices were only used in a small percent of cases. At 30 days and 2 years, the outcomes between the two groups were comparable.

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial[43] was a multicenter non-inferiority randomized controlled trial comparing CAS vs. CEA in asymptomatic patients with a stenosis >60%. The primary endpoint was the incidence of any stroke or death within 30 days. At 6-month follow-up, the incidence of any stroke or death for CAS was 11.7% vs. CEA 6.1% (p = 0.02). The trial was stopped prematurely after 527 of the 872 intended patients were enrolled, for safety and futility. Major criticisms of this study were that embolic protection devices were not required in the CAS arm, and that many of the CAS operators lacked adequate training. At the 4-year follow-up, the death or stroke rate still favored CEA, driven by the 30-day event rate. However, beyond 30 days, no difference in adverse outcomes between CAS and CEA was observed.

The largest randomized controlled trial to date was the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[44] A total of 2502 patients, both symptomatic and asymptomatic, with a >70% stenosis by ultrasound were randomized at 108 centers. Training standards, experience, and competency levels were established prior to enrollment, and an embolic protection system was required in CAS cases.[45] The primary endpoint was a composite of stroke, MI, or death of any cause up to 30 days post procedure, or any ipsilateral stroke during the 4-year follow-up. The primary composite endpoint over a median follow-up period of 2.5 years for CAS was 7.2% vs. CEA 6.8% (Hazard Ratio (HR) = 1.11; 95% CI 0.81–1.51; p = 0.51) and demonstrated no difference. There was no significant difference in the frequency of the primary endpoint between symptomatic and asymptomatic patients. The periprocedure mortality rates were similar, but there were significantly different rates of stroke between CAS of 4.1% vs. CEA 2.3% (p = 0.01) and MI (CAS 1.1% vs. CEA 2.3% [p = 0.03]). The 4-year rate of any ipsilateral stroke for CAS was 2.0% vs. CEA of 2.4% (p = 0.85). The 4-year rate of death alone was similar for CAS of 11.3% vs. CEA of 12.6% (p = 0.45). In terms of quality of life, major and minor strokes had a greater negative impact on quality of life scores (–15.8 points) than did MI (–4.5 points). There was no difference in the primary endpoint rate between men and women with either treatment. Long-term (10-year) results for CREST[12a] have been published recently and reported no significant difference in risk between patients who underwent stenting versus endarterectomy in relation to the composite outcomes of peri-procedural stroke, myocardial infarction, or death and for subsequent ipsilateral stroke. Individually, consistent with the 4-year follow-up results, the rate of peri-procedural stroke remained higher among patients who underwent stenting and the rate of peri-procedural myocardial infarction was higher in patients who underwent CEA. The rate of postprocedural ipsilateral stroke did not differ between groups.

The International Carotid Stenting Study (ICSS)[46] was a multicenter randomized controlled trial which enrolled 1713 symptomatic patients with carotid stenosis. The primary endpoint was the long-term rate of any fatal or disabling stroke. An interim safety analysis showed the 120 day rate of stroke, death, or procedure MI for CAS was 8.5% versus CEA of 5.2% (HR: 1.69; 95% confidence intervals (CI) 1.16–2.45; p = 0.006). The incidence of disabling stroke or death at 120 days did not differ between CAS of 4.0% and CEA of 3.2%, but there was an excess of overall strokes in the CAS group (HR: 1.92, 95% CI 1.27–2.89; p = 0.002). The use of an embolic protection device was not mandated. The final results demonstrated that the 5-year risk incidence of a fatal or disabling stroke did not differ between CAS of 6.4% and CEA of 6.5%.[47] Beyond 30 days following carotid artery treatment, there was no difference in the rates of ipsilateral stroke for CAS, which was 4.7% vs. CEA of 3.4% (HR: 1.29, 95% CI 0.74–2.24). There was an excess number of strokes in the CAS patients that persisted, with a

5-year cumulative risk of 15.2% vs. CEA of 9.4% (HR: 1.71, 95% CI 1.28–2.30; $p < 0.001$), although this did not translate into differences in functional disability and quality of life, as assessed by the modified Rankin scale and EQ-5D questionnaire. In this trial, various stents and protection devices were used for CAS patients at the discretion of the interventionist with only 72% of patients receiving distal protection during the index stent procedure. The study concluded that long-term functional outcome and the risk of fatal or disabling stroke are similar for CAS and CEA for symptomatic carotid stenosis.

A meta-analysis of randomized controlled trials which included 3754 patients treated with CAS vs. 3723 patients undergoing CEA showed that at 30 days, CAS was associated with a significant elevated risk of stroke (Odds Ratio (OR): 1.53, 95% CI 1.23–1.91; $p < 0.001$), death or stroke (OR: 1.54, 95% CI 1.25–1.89; $p < 0.001$), while MI (OR: 0.48, 95% CI 0.29–0.78; $p = 0.003$) and cranial nerve injuries (OR: 0.09, 95% CI 0.05, 0.16; $p < 0.001$) were significantly reduced compared to CEA.[48] Beyond 30 days, the efficacy of the CAS group vs. CEA for ipsilateral stroke prevention, restenosis rates and the need for repeat revascularization was comparable in all trials.

A retrospective study analyzed data on 22,516 Medicare patients with a mean age of 76.3 years from the Centers for Medicare & Medicaid Services (CMS) database who underwent CAS with embolic protection between 2005 and 2009.[49] Approximately half of the patients were symptomatic, 91.2% were at high surgical risk, and 97.4% had carotid stenosis >70%. Overall, patients had high medical comorbidities which included ischemic heart disease, heart failure, diabetes, and peripheral arterial disease. Approximately 25% had undergone coronary artery bypass graft (CABG) during the prior year, and 27.8% were admitted nonelectively for CAS. At 30 days the mortality was 1.7% with stroke or TIA in 3.3%. From 30 days to 4 years of follow-up, the mortality rate was 32.0% and the stroke or TIA rate was 9.1%. Periprocedure mortality and stroke/TIA risks were highest for patients who were symptomatic, >80 years of age, treated nonelectively with CAS, and at high surgical risk with a symptomatic stenosis >50%. The mortality risk exceeded one-third for patients who were >80 years old, symptomatic, at high surgical risk with symptomatic carotid stenosis >50% and admitted nonelectively. This paper suggested that the benefits of treatment seen in randomized controlled trials may not apply to the wider population, especially for patients who are older, >80 years of age, and with a high burden of comorbidities.

The ACT 1 clinical trial[11b] published in 2016, compared carotid artery stenting with embolic protection and carotid endarterectomy in patients <79 years of age who had severe carotid stenosis and were asymptomatic without a prior stroke, TIA, or amaurosis fugax in the 180 days before enrollment, and who were not considered to be at high risk for surgical complications. The trial was designed to enroll 1658 patients but was halted early, after only 1453 patients underwent randomization, because of slow enrollment. Patients were followed up to 5 years. The primary composite end point of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within 1 year was tested at a non-inferiority margin of 3%. Stenting was non-inferior to endarterectomy with regard to the primary composite end point (event rate, 3.8% and 3.4% respectively; $P = 0.01$ for non-inferiority). The rate of stroke or death within 30 days was 2.9% in the stent group vs. 1.7% in the CEA group ($P = 0.33$). From 30 days to 5 years after the procedure, the rate of freedom from ipsilateral stroke was 97.8% in the stent group vs. 97.3% in the CEA group. In conclusion, for asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was non-inferior to CEA with regard to the rate of the primary composite end point at 1 year. At 5 years of follow up, there were no significant differences between the study groups in the rates of non-procedure-related stroke, all stroke, and survival.

In summary, although carotid angioplasty and stenting has become integrated into many clinical practices, additional ongoing clinical trials will further define the most suitable patients, the long-term patency, and the benefits of embolic protection devices and other endovascular techniques such as flow reversal, proximal and distal balloon protection, proximal cerebral protection, and direct puncture of the common carotid artery combined with carotid artery stenting.[50] Current clinical trials[11b,12a] indicate that carotid stenting for both symptomatic patients and for patients with asymptomatic severe carotid stenosis who were not at high risk for surgical complications is non-inferior to CEA both in the peri-procedure period and at long term follow up. Additional clinical trials are still on-going regarding randomizing asymptomatic patients with severe carotid stenosis to best medical treatment vs. stenting vs. CEA.

Preanesthesia Assessment

The aims of preoperative assessment of CEA include: (1) risk stratification, (2) evaluation of the benefits and risks of revascularization to guide the decision to either proceed to CEA or alternative therapy such as carotid stenting, (3) optimization of preexisting medical conditions, (4) identification of occult cardiac conditions or risk factors that warrant immediate and/or long-term management, and (5) formulation of an anesthetic plan, particularly in relation to the choice of anesthetic techniques and intraoperative neurological monitoring. However, achieving all these aims is challenging because current evidence suggests that outcomes are improved by timely access to surgery. On the basis of a combined 5-year analysis of symptomatic patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST), the benefit of CEA is highest (greatest risk reduction for perioperative stroke or death) when the procedure is performed within 2 weeks of the ischemic event.[51] These investigators report that the NNT is 5 if patients were randomly assigned to therapy within 2 weeks of the index event and 125 if they were randomly assigned more than 12 weeks after the index event. Furthermore, the benefit from surgery declines more rapidly in women than in men.

Despite the clear benefit of timely surgery, many centers are challenged to perform surgeries within 2 weeks of the onset of symptoms.[52,53] Current AHA guidelines for symptomatic patients suggest it is reasonable to proceed to revascularization (CEA or CAS) within 2 weeks of the index event when there are no contraindications to early intervention.[7] Preoperative assessment, investigation and optimization should be conducted in an efficient and timely manner with special consideration of the rapid decline of treatment benefits in symptomatic CEA patients.

The preoperative visit should include an assessment of the patient's state of health based on history, pertinent physical examination, and chart review. The head and neck should be examined to identify potential airway problems or evidence of positional ischemia. Catheter angiography or magnetic resonance angiography should also be reviewed to identify patients at higher risk due to high-grade contralateral carotid disease or poor collateral circulation. Special attention should be directed toward the assessment of coexisting disease.

A variety of indices have been proposed over the years to identify patients at risk of perioperative stroke or death. The risk stratification scheme for patients undergoing CEA that

was proposed and validated by Sundt and colleagues[54,55] combines medical, neurologic, and radiologic risk factors to determine the risks of postoperative morbidity (neurologic and cardiac) and mortality (Tables 16.3 and 16.4). This scheme has been in widespread use in the neurosurgical field since the mid-1970s and continues to provide a helpful overview of some factors that contribute to perioperative complications.

Two relatively newer indices were developed from large population-based cohorts addressing the perioperative risks of stroke and death associated with CEA—the Halm index was proposed in 2005[56] and revisited in 2009[57] and the Tu index proposed in 2003[58] (Table 16.5). As expected, the performance of two these indices is heavily affected by the characteristics of the study population from which the cohorts were derived. The Tu index was derived from a study of Canadian patients with a substantially higher burden of symptomatic carotid disease (69% of study population) and lower incidence of coronary artery disease (CAD), whereas, the Halm index was derived from an American population that included more asymptomatic CEA patients (71% of study population) with a much higher incidence of underlying CAD. It is unclear whether the Tu index[58] represents a more reliable predictor in circumstances in which the majority of patients presenting for CEA have symptomatic disease and the Halm index represents a better model for asymptomatic patients. Despite the fact that these two large cohorts were derived from two substantially different populations, they share many common factors. The presence of significant heart disease (especially a history of coronary artery disease, congestive heart failure and atrial fibrillation), the presence of significant contralateral carotid occlusion, and a history of recent TIA or stroke as the indication of surgery are associated with higher risks of perioperative stroke or death. Similarly, consistent with the risk factors identified by Sundt and colleagues,[54,55] Halm and coworkers found the patients presenting with acute stroke or unstable ischemic neurologic symptoms (e.g., crescendo TIAs and stroke-in-evolution), face a particularly ominous prognosis in relation to CEA, with combined rates of death and stroke of 28.6% and 57.1%, respectively, on the basis of this study experience.[56]

Table 16.3 Preoperative Risk Stratification for Patients Undergoing Carotid Endarterectomy

Risk Group	Characteristics	Total Morbidity and Mortality (%)
1	Neurologically stable, no major medical or angiographic risk	1
2	Neurologically stable, significant angiographic risk, no major medical risk	2
3	Neurologically stable, major medical risk, major angiographic risk	7
4	Neurologically unstable, major medical or angiographic risk	10

(Adapted from Sundt TM Jr, Sandok BA, Whisnant JP: Carotid endarterectomy: Complications and preoperative assessment of risk. Mayo Clinic Proc 1975;50:301–306 (with permission).)

Table 16.4 Risk Factors Used in Risk Stratification for Patients Undergoing Carotid Endarterectomy

Type of Risk	Risk Factors
Medical risk	Angina
	Myocardial infarction (<6 months)
	Congestive heart failure
	Severe hypertension (>180/110 mmHg)
	Chronic obstructive lung disease
	Age >70 years
	Severe obesity
Neurologic risk	Progressing deficit
	New deficit (<24 hours)
	Frequent daily transient ischemic attacks
	Multiple cerebral infarcts
Angiographic risk	Contralateral carotid artery occlusion
	Internal carotid artery siphon stenosis
	Proximal or distal plaque extension
	High carotid bifurcation
	Presence of soft thrombus

(Adapted from Sundt TM Jr, Sandok BA, Whisnant JP: Carotid endarterectomy: Complications and preoperative assessment of risk. Mayo Clinic Proc 1975;50:301–306.)

Table 16.5 Multivariate Odds Ratios for Complications after Carotid Endarterectomy

	Odds Ratio for Death and Stroke (95% CI)*	Odds Ratio for Fatal and Nonfatal Stroke (95% CI)
Halm Index (n = 9308)		
Stroke as indication for sugery	2.4 (1.74–3.31	2.54 (1.79–3.59)
Active coronary artery disease	1.51 (1.2–1.91)	1.38 (1.08–1.75)
Contralateral stenosis (>50%)	1.44 (1.15–1.79)	1.42 (1.11–1.80)
Tu Index (n = 6038)		
History of stroke and transient ischemic attack(s) (<6 months)	1.75 (1.39–2.20)	1.84 (1.42–2.39)
Contralateral carotic occlusion	1.72 (1.25–2.38)	Not applicable
History of atrial fibrillation	1.89 (1.29–2.76)	1.83 (1.18–2.83)
History of congestive heart failure	1.80 (1.15–2.81)	1.86 (1.12–3.08)
History of diabetes	1.28 (1.01–1.63)	Not applicable

CI, confidence interval; OR, odds ratio.
*"Death and stroke" indicates the rate of death and nonfatal stroke combined within 30 days.

(Data adapted from Halm EA, Tuhrim S, Wang JJ, et al. Risk factors for perioperative death and stroke after carotid endarterectomy: results of the New York Carotid Artery Surgery Study. Stroke 2009;40(1):221–229 (with permission); and Tu JV, Wang H, Bowyer B, et al. Risk factors for death or stroke after carotid endarterectomy: Observations from the Ontario Carotid Endarterectomy Registry. Stroke 2003;34:2568–2573 (with permission).)

Cardiac complications have been reported to be a primary source of mortality associated with CEA and CAS.[30,49,59,60] There are several widely used risk stratification schemes that have been developed over the past few decades to predict the perioperative risk of major cardiac events in patients undergoing noncardiac surgery (not specific to CEA), these include the American Society of Anesthesiologists Physical Status Classification system (ASA Classification),[61] the index proposed by Goldman and colleagues,[62] the index proposed by Detsky and associates,[63] and the Revised Cardiac Risk Index (RCRI) (Table 16.6).[64] In addition, the American College of Surgeons (ACS) has recently developed two new risk assessment tools that are based on prospective data derived from more than 1 million operations (not including CEA) across more than 525 hospitals in the United States.

The ACS National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest (MICA) tool provides an estimate of the risk of perioperative myocardial infarction or cardiac arrest based on an assessment of functional status, creatinine level, ASA Classification, age and surgical site. The authors[65] report that the MICA tool has higher discriminative power for predicting major cardiac events than RCRI in non-cardiac vascular surgery (http://www.surgicalriskcalculator.com/miorcardiacarrest).

The ACS NSQIP Surgical Risk Calculator[66] uses 21 patient characteristics and comorbid disease factors to estimate procedure specific risk for 11 different perioperative outcomes including pneumonia, cardiac complications, surgical site infection, venous thromboembolism, renal failure, reoperation, discharge to a high dependency facility and death. The risk stratification indices in current common clinical use (i.e., the ASA Physical Status Classification and the Goldman, Detsky and RCR indices) appear to perform similarly as predictors of postoperative cardiac complications in patients presenting for CEA with one comparative study, using patient data collected originally to derive the Halm index, reporting areas under the ROC curve ranging from 0.58 to 0.66.[67] Each of the four indices also performed similarly as predictors of noncardiac medical complications. Multivariate odds ratios for predicting postoperative cardiac complications following CEA using the RCRI are presented in Table 16.6. The role of the ACS NSQIP MICA tool or Surgical Risk Calculator for risk stratification for patients presenting for CEA is yet to be evaluated.

Table 16.6 Multivariate Odds Ratios for Complications after Carotid Endarterectomy based on the Revised Cardiac Risk Index

Revised Cardiac Risk Index (n = 2893)	OR for Major Cardiac Complications (95% CI)*
1. High-risk type of surgery	2.8 (1.6–4.9)
2. Ischemic heart disease	2.4 (1.3–4.2)
3. History of congestive heart failure	1.9 (1.1–3.5)
4. History of cerebrovascular disease	3.2 (1.8–6.0)
5. Insulin therapy for diabetes mellitus	3.0 (1.3–7.1)
6. Preoperative serum creatinine level (>2.0 mg/dL)	3.0 (1.4–6.8)

CI, confidence interval; OR, odds ratio; RCRI, revised cardiac risk index.
(*Data from Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100: 1043–1049 (with permission).)

The presence of extracranial cerebrovacular disease has been reported to be a strong predictor for CAD.[68,69] As a consequence, it is not surprising that patients undergoing CEA are known to have a high incidence of CAD. According to data from Halm's study, 61% of patients were known to have CAD, 9.4% of patients had a history of congestive heart failure and 4% of patients had active coronary diseases. The incidence of coronary artery disease or previous MI among patients enrolled in the NASCET[2] or the GALA trial[32] was lower but still substantial at 44% and 36%, respectively (see Table 16.1). Some investigators have advocated routine coronary angiography[60] prior to CEA to screen for occult CAD; however, little evidence supports the premise that routine preoperative coronary angiography, and consequent prophylactic coronary revascularization, improves cardiac outcome in patients with stable CAD.[70,71] It seems more reasonable to assume that all patients presenting for CEA have atherosclerotic heart disease and to evaluate perioperative risk in relation to each patient's functional status. Current AHA guidelines support the consideration of additional noninvasive testing, such as exercise stress testing, dobutamine stress echocardiography, and dipyridamole myocardial perfusion imaging, in patients scheduled for CEA (elevated risk surgery) with poor or unknown functional capacity.[52,70] Testing should be directed toward patients for whom the results are likely to influence perioperative management in light of the time-sensitive nature of CEA in symptomatic patients. Patients with other coexisting cardiac conditions, such as congestive heart failure, arrhythmias and conduction disorders, valvular heart disease or adult congenital heart disease, have significantly higher risks of perioperative cardiac complications and require specific preoperative evaluation and treatment.[52]

Patients with concomitant carotid stenosis and severe CAD may be considered for staged or combined carotid revascularization and CABG procedures. Since the patients with either symptomatic or asymptomatic carotid stenosis undergoing CABG have a significantly higher risk of perioperative stroke, the 2011 AHA guidelines[7] on the management of patients with extracranial carotid and vertebral artery disease recommends that preoperative carotid duplex ultrasound screening is reasonable if any of the following are present: carotid bruit, age >65 years, peripheral arterial disease, history of TIA or stroke, cigarette smoking, or left main coronary artery disease. Patients with severe carotid stenosis (greater than 80%) who have been symptomatic within the preceding 6 months could be considered for either a staged carotid revascularization procedure (CEA or CAS) prior to CABG or concomitant myocardial and carotid revascularization. However, the benefit of carotid revascularization combined with myocardial revascularization, whether staged or concurrent, for patients with asymptomatic carotid stenosis, including stenotic lesions classified as severe, is not convincing.[7] CABG alone is reasonable for patients with severe asymptomatic carotid stenosis.

Available evidence remains inadequate, due to insufficient prospective data, to allow definitive conclusions to be drawn regarding the staging of CEA with CABG surgery. Some studies have found staged operations are associated with lower risk of perioperative stroke, but with higher risk of myocardial ischemia. In contrast, some case series have reported combined operations are associated with lower risks of MI, stroke, and death than staged operations in patients with symptomatic carotid stenosis. If the procedures are to be staged, complication rates are lower when carotid revascularization precedes

CABG. Reviews of the national experiences with CABG alone and combined CEA and CABG operations from the United States[72] and Canada[73] found combined operations have a higher procedural risk of stroke (9.5% and 13%, respectively) compared to CABG surgery alone; however, the overall mortality rates of combined operations in both studies were similar to the rates for CABG alone. Reflecting the state of the literature, a Cochrane systematic review focused on outcome following prophylactic CEA combined with best medical care (versus best medical care alone) in patients undergoing CABG failed to identify any suitably constructed prospective, randomized trials for inclusion and as a consequence was unable to draw any meaningful conclusion.[74]

Carotid angioplasty and stenting is an intuitively less invasive, but unproven option for treating patients requiring carotid revascularization prior to coronary revascularization. In one nonrandomized cohort study,[75] carotid stenting prior to CABG was found to be associated with a lower incidence of stroke (2.4% vs. 3.9%), but similar in-hospital mortality, compared to CEA prior to CABG. More patients with acute coronary syndrome, renal failure, chronic lung disease and hypertension were selected to undergo CAS prior CABG in this cohort, which reflects a clinical preference to use CAS over CEA in patients with multiple comorbidities and the selection bias of this study. In contrast, two systematic reviews reported 30-day outcomes for composite stroke or death following staged CAS and CABG procedures of 9.1% and 12.3% in study populations that were predominantly asymptomatic.[76,77] As a consequence, similar to CEA, there is little rigorous published evidence supporting the use of CAS for revascularization prior to, or concomitant with, CABG particularly in neurologically asymptomatic patients.

In addition to the preceding considerations, CAS patients are treated with the platelet-inhibitor clopidogrel for at least 1 month following the procedure to prevent stent thrombosis and stroke but, if continued preoperatively, this treatment would significantly increase the bleeding risk during a subsequent CABG procedure. For patients who can defer CABG for 4–5 weeks, awaiting the completion of antiplatelet therapy is a reasonable option. Alternatively, intravenous heparin therapy may be used to bridge the period between the CAS procedure and proceeding to coronary revascularization.[7]

Over the past decade, considerable interest has also focused on pharmacologic interventions that may reduce the risk of perioperative cardiac events in high-risk patient groups. The aim of therapy is to mitigate perioperative conditions that lead to myocardial supply–demand imbalances or to promote stabilization of the coronary plaque and thereby reduce the incidence of ischemic events. β-Blockers, statins, and aspirin are the most prominent drugs used in this manner.

β-Blockers have attracted widespread interest, with numerous small studies reporting a reduction in the risk of perioperative myocardial infarction with their use. However, many were also heavily criticized for methodologic inadequacies including inadequate power and selection bias. The Perioperative Ischemic Evaluation (POISE)[78,79] study was a large-scale multicenter trial designed to address these concerns and reported that the perioperative administration of extended-release metoprolol (100 mg administered orally commencing 2–4 hours preoperatively) to high-risk patients undergoing noncardiac surgery (including major vascular procedures but excluding CEA) reduced the incidence of perioperative myocardial infarction, but was associated with a higher incidence of death, nonfatal stroke, and clinically significant hypotension and bradycardia compared to patients receiving placebo therapy. The 2014 AHA guidelines for the perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery recommends the perioperative continuation of β-blockers for patients taking long-term β-blocker therapy for established indications, such as the treatment of myocardial infarction, because preoperative discontinuation of established β-blocker treatment has been shown to be associated with increased risk.[52,80,81] These guidelines[52] also suggest that it may be appropriate to initiate β-blocker therapy for patients undergoing surgery with elevated cardiac risk due to documented cardiac ischemia by preoperative testing and for those with three of more RCRI risk factors prior to surgery. When β-blocker therapy is initiated preoperatively, it is preferable to commence treatment at least 2 to 7 days prior to surgery. β-Blocker treatment should not be initiated on the day of surgery. Notably, although patients undergoing CEA were not included in many previous studies, including the POISE study, the foregoing recommendations regarding the initiation of β-blocker therapy would seem particularly prudent for patients scheduled for CEA, given the nature of the procedure and the attendant risk of stroke. Until further evidence is available to clarify the issue in this group of patients, β-blocker therapy should be only used very cautiously.

The use of statins in the perioperative period has garnered considerable interest over the past decade. While abundant evidence links statin use to primary and secondary prevention of cardiovascular events and stroke in high-risk populations, evidence demonstrating similar benefits in the perioperative setting, particularly among patients undergoing CEA, has been less robust. A recent Cochrane meta-analysis of perioperative statin use for CABG surgery[82] reported a reduction in perioperative atrial fibrillation and length of ICU and total hospital stay as well as a trend toward a lower incidence of myocardial infarction, but no differences in the incidence of death or stroke in this population. However, a similar meta-analysis involving studies that included patients undergoing vascular surgery,[83] including CEA, was unable to draw conclusions due to inadequate evidence. This study reported trends favoring statin use for all-cause mortality and perioperative nonfatal MI (within 30 days), but the trends did not achieve statistical significance. A very recent systematic review of statin use in patients undergoing vascular surgery or endovascular procedures[84] (including CEA and CAS procedures) evaluated data from four randomized controlled trials (RCTs) and 20 observational cohort or case-control studies. The randomized studies contributed 675 patients, and the observational studies contributed 22,861 patients to the analysis. Statin therapy was associated with a lower risk of all-cause mortality, myocardial infarction, stroke, and the composite outcomes of myocardial infarction, stroke, and death. However, these benefits were not reflected in analyses that included only data from the RCTs.

The current AHA guideline for the perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery support the continuation of statin therapy in patients who are taking these medications prior to surgery.[52] The guidelines also recommend that preoperative initiation of statin therapy would be reasonable for patients undergoing vascular surgery or for patients with indications that support the use of statins who are undergoing an elevated-risk procedure. Perioperative cardiac benefits are believed to relate to plaque-stabilizing properties as well as antioxidant and anti-inflammatory effects. Similar effects have been reported in relation to carotid plaque.[85]

Most patients who present for CEA are currently taking low-dose ASA as medical therapy for the prevention of stroke. Although data from observational studies suggest that preoperative ASA withdrawal increases the risk of adverse cardiac events and thrombotic complications,[86] the POISE-2 trial,[87] which did not include CEA patients, failed to demonstrate any benefit from 200 mg of ASA compared to placebo for major cardiac events or death. In view of its well-established beneficial effects in relation to stroke prevention, most surgeons performing CEA prefer that patients continue low-dose ASA throughout the perioperative period.

Several studies have reported that uncontrolled or inadequately controlled preoperative arterial hypertension (systolic blood pressure >150–170 mmHg) increases the risk of postoperative hypertension and adverse neurologic outcome after CEA.[88,89] Aggressive perioperative control of blood pressure in patients undergoing CEA, including adequate preoperative treatment of hypertension, has been associated with improved outcome.[90] A review of the patient's blood pressure record to establish a baseline blood pressure range often provides a useful aid to intraoperative hemodynamic management.

For patients with diabetes mellitus, blood glucose levels should be carefully managed throughout the perioperative period to avoid both hypo- and hyperglycemia. Following acute stroke, current clinical and experimental evidence suggests that hyperglycemia lowers the neuronal ischemic threshold, may increase ischemic volume, and is associated with higher morbidity and mortality.[70,91,92] Similar findings have also been reported specifically in association with CEA; higher risks for stroke, myocardial infarction, and death have been associated with the presence of hyperglycemia—defined as a blood glucose level greater than 200 mg/dL (11.1 mmol/L)—at the time of surgery.[93]

Hypoglycemia also represents a deleterious condition for the brain. It has also been noted that the development of hypoglycemia is a significant risk when aggressive glycemic control is adopted.[94,95] In view of these concerns, perioperative management of blood glucose levels in diabetic patients presenting for CEA should probably be more conservative, in keeping with the recommendations of the AHA guidelines for the management of acute stroke, with blood glucose levels maintained in the range of 140 to 185 mg/dL (7.8–10.3 mmol/L).[70]

ANESTHETIC MANAGEMENT

Intraoperative Monitoring

In view of the high incidence of coronary artery disease in patients undergoing CEA, the electrocardiogram (ECG) is monitored with an emphasis on the detection of ischemia. Use of a five-lead ECG with continuous monitoring of leads II and V_5 is common practice, and automated ST segment monitoring is a useful adjunct. A study of postoperative cardiac ischemic events among 185 patients who had vascular surgery reported that lead V_3 or V_4 detects ischemic changes more consistently than V_5.[96] These investigators suggest that the use of lead V_4 may be preferable for detecting perioperative ischemia because its signal is more commonly isoelectric on baseline recordings. Furthermore, they advocate the use of multiple-lead monitoring in the perioperative period for patients at risk for cardiac ischemia, on the basis of the observation that monitoring two precordial leads (V_3 and V_4, V_3 and V_5, or V_4 and V_5) improved the sensitivity for detecting cardiac ischemia to more than 90%, compared with 66% with the use of lead V_5 alone.

An intra-arterial cannula placed with the use of local analgesia before the induction of anesthesia (regional or general) permits continuous monitoring of blood pressure throughout the perioperative period and facilitates sampling of arterial blood for blood gas analyses. Alternatively, in low-risk patients, a rapidly cycling (1-minute intervals) noninvasive blood pressure device can be used during induction, and the arterial cannula can be placed before commencement of surgery. Central venous pressure, pulmonary capillary wedge pressure, cardiac output, transesophageal echocardiography and urine output are not routinely monitored, but monitoring can be considered for high-risk patients. Evidence from a small prospective trial suggests that pulse pressure variability and stroke volume variability, indices derived from arterial waveform analysis, are useful predictors of cardiac preload/fluid responsiveness during CEA.[97] These indicies, increasingly popular as guides to fluid management in a variety of procedures, may be well suited to CEA procedures in view of the high incidence of coexisting cardiac disease and the widespread use of perioperative arterial blood pressure measurement.

Oxygenation is monitored continuously with a pulse oximeter. Placement of an esophageal stethoscope after induction of general anesthesia facilitates monitoring of core temperature as well as ventilation, because the chest is not readily accessible during surgery. End-tidal CO_2 monitoring, validated relative to an arterial blood gas sample, facilitates the continuous maintenance of $PaCO_2$ within the patient's normal range. For patients who undergo CEA under regional anesthesia or local infiltration, the use of nasal prongs with a CO_2 sampling port allows the provision of supplemental oxygen and the measurement of expired CO_2. The CO_2 measurements obtained in this manner do not consistently correlate with end tidal CO_2 values, but do provide a useful aid in monitoring respiratory rate and rhythm in situations in which the patient's face and chest may be partially obscured by surgical drapes.

Choice of Anesthetic Technique

CEA can be performed safely with use of either general anesthesia or regional anesthesia (including local anesthetic infiltration). General anesthesia represents the most popular anesthetic technique for CEA.[98–101]

Advocates of general anesthesia cite patient comfort, airway security, and the more expedient management of ventilation, autonomic reflexes, and potential intraoperative complications as prominent advantages. However, general anesthesia is typically more expensive in terms of anesthetic agents used than regional anesthesia, and its use forfeits the ability to monitor neurologic status in the awake patient. Regional anesthesia is popular in some centers, and extensive experience has been reported with its use.[102] Advocates of regional anesthesia endorse the superior neurologic monitoring afforded by an awake patient as a major advantage. The technique is generally less expensive than general anesthesia, and some studies report shorter length of hospital stay and lower risk of complications in association with regional anesthesia and awake monitoring. Performing major surgery with use of regional anesthesia requires the focus of the entire operating room team being committed to the needs of the awake patient; airway and ventilation are not readily controlled, and the management of intraoperative complications, such as stroke, seizure, airway obstruction, hypoventilation, and confusion or agitation, can be more challenging, including intraoperative conversion to general anesthesia.

Despite the relative merits of the two techniques and enthusiastic advocates for each, there is little evidence, from the results of the large randomized trials, to suggest that outcome following CEA is substantially affected by the choice of regional versus general anesthesia. Subgroup analysis of patients enrolled in the NASCET[98] and the ECST[99] revealed no difference in outcome associated with the use of local or regional anesthesia, although the number of patients who underwent CEA under regional block was small in both studies (7% and 3.4%, respectively).

The largest prospective trial evaluating the relative benefits of regional anesthesia compared to general anesthesia was the General Anesthesia versus Local Anesthesia for carotid surgery (GALA) trial published in 2008.[32] This study included 3526 patients recruited by 95 centers across 24 countries and reported no difference in outcome for the composite primary events (stroke, myocardial infarction and death within 30 days of the procedure) with an incidence of 4.8% and 4.5% respectively for the general anesthetic group versus the local anesthetic group (Table 16.7). Similarly, there was no difference in outcome for ipsilateral stroke, MI or death independently between the groups who had CEA performed under general anesthesia or local anesthesia. Ninety-three percent of the patients in the local anesthesia group received a cervical plexus block with or without supplemental local anesthetic infiltration by the anesthesiologist or surgeon. Secondary outcome evaluation suggested that performing CEA under local anesthesia was less expensive and was associated with better neurocognitive performance in the early postoperative period among patients who underwent CEA under local anesthesia compared to general anesthesia. A trend favoring local anesthesia was also noted in the subgroup of patients with contralateral carotid occlusion reflected in a lower incidence of neurologic events; however, the analysis failed to achieve statistical significance. The report concludes that there is no difference in primary outcomes for stroke, myocardial infarction or death, for CEA performed under general anesthesia or local anesthesia and that the decision regarding the most appropriate anesthetic choice should be made by the anesthesiologist and surgeon, in consultation with the patient, on an individual basis.[32]

Table 16.7 **GALA Trial[a] Outcomes Following Carotid Endarterectomy Performed Under General or Local Anesthesia (30 Days Following Surgery)**

Outcome	General Anesthesia (n = 1752)	Local Anesthesia (n = 1771)
All strokes	70 (4.0%)	66 (3.7%)
Ipsilateral stroke	54 (3.1%)	57 (3.2%)
Contralateral stroke	15 (0.9%)	7 (0.4%)
Myocardial infarction	4 (0.2%)	9 (0.5%)
Death (any cause)	26 (1.5%)	19 (1.1%)
Stroke or death	81 (4.6%)	74 (4.2%)
Stroke, myocardial infarction or death	84 (4.8%)	80 (4.5%)

Number of patients and proportion (%).

None of the outcome measures were statistically significant between treatment groups.

(Adapted from GALA Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008; 372:2132–2142 (with permission).)

Similar results were reported by a recent Cochrane systematic review update that compared outcome for CEA performed under general or local anesthesia.[102] The review pooled data from 14 randomized studies with 4596 patients and reported no difference in outcome for stroke or stroke and death at 30 days following surgery. Many of the studies were noted to be small and the GALA study contributed a substantial portion of the patients included in the data pool (3526 of 4596 patients).

Given these results, it seems appropriate to conclude that outcome following CEA is likely more dependent on patient selection, preoperative optimization of comorbid conditions, and an experienced and committed surgical team than on the choice of anesthetic technique. Supporting this premise, Calligaro and colleagues[103] described their experience converting from general to regional anesthesia for CEA. Reporting on the results of 401 carotid endarterectomies (216 general anesthesia, 185 cervical plexus block) performed over a 6-year period in which a conversion from general to regional anesthesia was performed; these investigators reported a similar stroke mortality rate (<2%) with each technique. Interestingly, they also commented that a satisfactory surgical environment for performing CEA with regional anesthesia was intimately dependent on a committed group of anesthesiologists who provided a consistent and standardized approach to managing the patient.

Regional Anesthesia

Superficial cervical plexus block is the most common regional anesthetic technique for CEA. The superficial cervical plexus block is performed by injection of local anesthetic subcutaneously along the posterior border of the sternocleidomastoid muscle, where the cutaneous branches of the plexus fan out to innervate the skin of the lateral neck.

The deep cervical plexus block is a paravertebral block of the C2–C4 nerve roots that continues to be used by some anesthesiologists for CEA. The technique involves injecting local anesthetic at the vertebral foramina (transverse processes) of the C2, C3, and C4 vertebrae to block neck muscles, fascia, and the greater occipital nerve. A 2007 review of the published experience with deep and superficial cervical plexus blocks for CEA since 1974 reported that, although the absolute incidence of block-related serious (life-threatening) complications is very low, essentially all serious complications were associated with the deep component of the block.[104] In addition, conversion to general anesthesia as a consequence of inadequate block was five times more common when a deep cervical block technique was used. The investigators in this review suggest that the use of the superficial cervical block technique is safer and technically less challenging and should be the preferred regional anesthetic option for CEA, citing evidence from two randomized comparisons that the two techniques are equally effective.[105,106] Similar findings were reported in a systematic review of complications associated with superficial versus deep cervical plexus blocks. The authors reviewed 69 papers describing a total of 7558 deep blocks and 2533 superficial blocks and report that deep cervical plexus blocks are associated with a higher incidence of serious complications and a higher incidence of conversion to general anesthesia.[107]

Some interest has been developing in relation to the use of ultrasound to guide placement of cervical plexus blocks.[108,109] Initial evidence would suggest that the technique does not contribute substantively to the safety or success rate for superficial blocks compared to a landmark-based approach.[110]

Insufficient experience is available to determine the potential contribution that ultrasound imaging may make to enhancing the safety and success rate associated with intermediate and deep cervical plexus blockade. Cervical plexus blocks have been described in detail[111] and should be reviewed before they are performed.

Monitors during regional anesthesia should include continuous electrocardiography, pulse oximetry, capnography, and an arterial cannula placed with use of local anesthesia. Supplemental oxygen should be provided with a mask or nasal prongs positioned to avoid the site of surgery. Traditionally, carefully titrated sedation using small, repeated, intravenous doses of fentanyl (10–25 μg), midazolam (0.5–2 mg), or both represents a popular and well-established approach to ensuring that the patient is comfortable and cooperative during the operation. Propofol, a reasonable alternative to midazolam, is typically administered as a low-dose continuous infusion (20–60 μg/kg/min). Provisions should be available to convert to general anesthesia if intraoperative conditions warrant.

The use of sedating central α_2 receptor agonists, such as clonidine and dexmedetomidine, during CEA with regional anesthesia has also been reported. Both drugs provide effective sedation and modest analgesia with minimal respiratory depression. Limited published experience with these drugs in the context of CEA has generally been favorable, with marked attenuation of sympathetic stress responses and variably beneficial effects on intraoperative hemodynamic control (e.g., reduced need for intervention for hypertension or tachycardia).[112–114] Based on a systematic review that identified four studies, dexmedetomidine has been reported to provide satisfactory sedation with a lower risk of respiratory complications compared to sedation using remifentanil for CEA performed under regional anesthesia.[115] However, a higher incidence of postoperative hypotension requiring intervention has been noted,[112] and transient hypertension, hypotension, and bradycardia have been described in association with the infusion of dexmedetomidine in other settings.[116,117]

General Anesthesia

Traditionally, a variety of drugs has been used satisfactorily to induce general anesthesia for CEA, including thiopental, midazolam, propofol, and etomidate. As is the case in most other areas of anesthetic practice, propofol is likely the most popular induction drug at present. A supplemental opioid such as fentanyl (2–5 μg/kg) or sufentanil (0.5–1.0 μg/kg), administered intravenously, is often included in the induction sequence. Remifentanil is also a suitable opioid to supplement anesthesia induction. Whether this agent is administered as a bolus (0.2–0.5 μg/kg) or as an infusion (0.05–0.2 μg/kg/min), its short half-life facilitates titration of anesthesia during the relatively unstimulating period of surgical preparation and draping that follows intubation.

Tracheal intubation is usually performed after the administration of a nondepolarizing neuromuscular blocking drug. Because many of the currently popular neuromuscular blocking drugs possess favorable hemodynamic profiles, the choice of drug is rarely a clinically important issue. Succinylcholine is a reasonable alternative in most circumstances, although it is contraindicated in patients who have experienced a recent paretic cerebral infarct. The hemodynamic response to tracheal intubation can be attenuated by the administration of intravenous lidocaine (1–1.5 mg/kg), additional opioid, or supplemental hypnotic drug, or the addition of a volatile anesthetic before intubation. An armored endotracheal tube, although not essential, may be of benefit because its flexibility facilitates its positioning without impinging on the surgical field.

Anesthesia is typically maintained with a volatile anesthetic supplemented with an opioid. Alternatively, total intravenous anesthesia (TIVA) using a propofol infusion combined with a supplemental opioid such as remifentanil or fentanyl is also popular for maintenance anesthesia. Any of the currently available vapors, isoflurane, desflurane, or sevoflurane, may be used. The agents used and doses will be influenced by the use of electrophysiologic monitoring, because evoked potentials may become depressed as the hypnotic dose increases.

The limited literature available comparing anesthetic drugs that are used during CEA is composed largely of small clinical studies comparing combinations of these drugs in relatively small numbers of patients. At present there is no clear basis to support a strong preference among the drug options in terms of outcome. Intraoperative hemodynamic stability and cardiac status have been reported to be similar during isoflurane, desflurane, and sevoflurane anesthesia.[118] The use of remifentanil and sevoflurane or desflurane is reported to be associated with earlier emergence from anesthesia than the use of fentanyl and isoflurane, but the difference extends only into the immediate postoperative period (e.g., 15–30 minutes).[118,119] Remifentanil combined with propofol appears to be associated with fewer episodes of intraoperative hypertension than fentanyl combined with propofol,[120] but reviews of published experience with remifentanil suggest that, although patients receiving remifentanil have a lower incidence of intraoperative hypertension, they are more prone to hypotension and bradycardia.[121,122] Finally, the question has been raised whether the modest benefits reported to favor remifentanil-propofol anesthesia over isoflurane-fentanyl anesthesia for CEA justify the substantially higher cost of anesthesia using the former agents.[123]

Nitrous oxide has been popular as a supplemental anesthetic for CEA for many years. The favorable hemodynamic profile associated with nitrous oxide permits a reduction in the dose of other anesthetic drugs with less favorable hemodynamic characteristics, particularly during periods with minimal surgical stimulation, and its low solubility coefficient facilitates a prompt emergence at the conclusion of surgery. Nitrous oxide continues to be used by some anesthesiologists during CEA, although its popularity is declining as a consequence of the availability of other short-acting anesthetic drugs such as sevoflurane, desflurane, and remifentanil as well as reports that its use during major surgical procedures is associated with a higher incidence of other postoperative complications, including postoperative fever, wound infection, pneumonia, pulmonary atelectasis, and severe nausea or vomiting[124] and conflicting data, largely from animal model studies, that it may cause an increase in CBF and cerebral metabolic rate.[125–127] However, a detrimental effect of nitrous oxide on neurologic outcome in humans, particularly following CEA, has been difficult to establish. Later evidence suggests that nitrous oxide may be neuroprotective in the rat at low inspired concentrations (50%)[128] and that it does not cause a significant increase in cerebral blood volume or global cerebral metabolic rate in human volunteers.[129] In addition, the use of nitrous oxide during aneurysm surgery, in a population at high risk for ischemic sequelae, was not associated with a higher risk of ischemic complications.[130,131]

In relation to CEA, subgroup analysis of the GALA trial data included a comparison of primary outcome events among patients who received nitrous oxide during general anesthesia for CEA versus those who were not administered nitrous

oxide.[132] The use of nitrous oxide was at the discretion of the attending anesthesiologist and 671 patients received nitrous oxide versus 944 patients who did not. The subgroup analysis reported no difference in outcome for stroke, myocardial infarction or death at 30 days with a composite incidence of 5.2% in the nitrous oxide group vs. 4.7% in the group who did not receive nitrous oxide. Comorbidities among the patients who received nitrous oxide were more likely to include coronary artery disease, peripheral vascular disease, and atrial fibrillation, suggesting that the use of nitrous oxide does not appear to adversely affect outcome for patients undergoing CEA.

Irrespective of the specific choice of anesthetic drugs, the anesthetic goal during CEA is to provide a relatively light level of general anesthesia because the procedure is typically not highly stimulating. Some surgeons routinely infiltrate the wound with local anesthetic at the beginning of the operation, further reducing the depth of general anesthesia needed. Neuromuscular blockade is often maintained throughout the procedure and, as discussed, mechanical ventilation is adjusted to maintain end tidal CO_2 at normocapnic levels.

Hypertension most often arises in response to visceral pain associated with traction or distortion of the carotid artery or surrounding structures and typically responds to local anesthetic infiltration of the carotid sheath or deepening of the level of anesthesia. When this measure is inadequate, blood pressure should be controlled with an intravenous antihypertensive drug, such as esmolol or labetalol.

Hypotension, bradycardia, or both may also accompany traction on the carotid artery during surgical dissection. These responses represent the parasympathetic output of the baroreflex, where the traction is "misinterpreted" as an increase in blood pressure. This response can usually be attenuated by local anesthetic blockade of the carotid sinus nerve. Episodes of hypotension during other phases of the operation are treated by reduction of the depth of anesthesia, infusion of intravenous fluid or, if necessary, administration of a vasopressor such as phenylephrine (0.5–1.0 μg/kg) to maintain blood pressure. Ephedrine (5–10 mg IV) is a reasonable alternative to phenylephrine, particularly for hypotension associated with bradycardia.

Before carotid cross-clamping, heparin (75–100 units/kg) is administered intravenously. Application of the carotid clamps is often associated with a rise in blood pressure, a baroreflex due to loss of stretch of the vessel wall. Mild increases in arterial pressure are acceptable (up to approximately 20% above preoperative levels), but excessive increases should be controlled. Excessive increases may also indicate inadequate cerebral perfusion.

Intravenous fluids are administered according to maintenance requirements. Blood loss during CEA is typically minimal, although the potential for hemorrhage exists. Because temporary cerebral ischemia may be aggravated by hyperglycemia or hypoglycemia, as discussed previously, intraoperative glycemic management should include the judicious use of glucose-containing solutions and intraoperative glucose monitoring for patients at risk for these complications.

Carotid Angioplasty and Stenting Procedures

For CAS procedures, which are typically performed under light conscious sedation with monitored anesthesia care, maintenance of hemodynamic stability, continuing neurological assessment, management of procedural anticoagulation (typically using unfractionated heparin to achieve a doubling of the activated clotting time (ACT) above baseline) and management of comorbid conditions that require intraprocedural intervention are key considerations. Baroreceptor manipulation during CAS procedures can be associated with hemodynamic instability including hypotension, bradycardia and vasovagal reactions. Continuous ECG and blood pressure monitoring is routine. These barorecptor-mediated reflexes are reported to occur in 5–10% of patients,[7] arise most commonly during angioplasty and stent deployment when the carotid sinus is distorted and are typically transient, although baroreceptor dysfunction frequently persists into the postoperative period[133] (see later, Postoperative Care). A recent meta-analysis[134] reported that hemodynamic events associated with carotid sinus manipulation during CAS procedures (bradycardia and/or hypotension) occurred with a pooled incidence of of 39.4%. Bradycardia and hypotension independently or in combination occurred with an incidence of approximately 12% each.

Persistent or profound bradycardia can be treated with atropine 0.5–1.0 mg or glycopyrrolate 0.2–0.4 mg administered intravenously (sometimes given prophylactically in advance of balloon/stent deployment). Occasionally, a temporary transvenous or transthoracic pacemaker is used to treat refractory bradycardia.[134] Hypotension alone or accompanied by bradycardia can be treated by infusion of intravenous fluid and/or the administration of phenylephrine or ephedrine, in a similar manner to the management of baroreceptor-mediated hypotension arising during CEA. Hypertension develops occasionally during CAS procedures[7] and, similar to the considerations during CEA, is treated pharmacologically as needed to maintain systolic blood pressure below 180 mmHg to reduce the risk of hyperperfusion syndrome, intracranial hemorrhage or postoperative bleeding from the arterial access site.

Cerebral Protection

Interest in elucidating putative neuroprotective properties associated with many drugs used in anesthesia spans several decades. Most drugs used to induce anesthesia, including barbiturates, lidocaine, benzodiazepines, etomidate, propofol, ketamine, and the volatile agents, have been investigated in a variety of animal models and under a wide range of experimental conditions of global and regional ischemia. All of these drugs have been reported to bestow a modest degree of protection under appropriate experimental conditions,[135,136] but evidence that these benefits translate to the clinical environment is scarce.

A recent systematic review[137] of the literature identified 25 methodologically appropriate, randomized, controlled trials (n = 3274 patients) assessing pharmacologic brain protection in the perioperative period. Eighty-eight percent of these studies were performed in patients undergoing cardiac surgery. A range of drugs were evaluated, but most were represented in the analysis by a single study. The authors concluded that, of the 17 drugs tested, evidence suggested that only atorvastatin (represented by 1 study in vascular surgery patients) and magnesium sulfate (represented by two studies, vascular surgery and cardiac surgery) may be associated with a lower incidence of new postoperative neurological deficits. None of the drugs reduced the mortality rate.

Similarly, a recent review of the conceptual role of preconditioning or postconditioning techniques for anesthetic neuroprotection during CEA reported a paucity of clinical evidence of benefit, although the authors report that preclinical animal studies suggest the techniques have merit.[138] Patients undergoing CEA are at risk for development of cerebral ischemia; hence, it is appealing to speculate that an additional margin

of safety may be achieved by administering anesthetic drugs that protect the brain from ischemic injury. Although some anesthesiologists prefer to administer additional intravenous anesthetic drugs, or to increase the depth of anesthesia, before carotid cross-clamping on the basis of the assumption that some degree of protection may be realized,[139,140] there is no current evidence to suggest that this practice influences outcome in the context of CEA. A recent survey of anesthetic practices in the United States[101] suggests that the most common anesthesia strategies used to protect the brain at the time of cross-clamping were increasing blood pressure (60.9% of respondents), administering 100% oxygen (34%) and no neuroprotection (32.6%). Among those who administered additional anesthetic drugs prior to cross-clamping, propofol was the most common choice (9.6%).

Neurologic Monitoring

A reliable means of monitoring the patient's intraoperative neurologic status has long been considered to be a key facet of intraoperative care during CEA to enable the identification of intraoperative embolic complications and, more importantly, to evaluate neurologic tolerance to carotid cross-clamping. Neurologic monitoring during CEA is based on the following premises: (1) the monitor is able to accurately identify patients at risk for development of intraoperative cerebral ischemia and (2) with identification, interventions can be instituted (e.g., placement of an internal shunt, increase CPP to prevent irreversible neuronal injury or administer a neuroprotective substance and thereby improve outcome). Despite intense interest, both premises remain controversial.[141–143]

There seems little doubt that an awake, cooperative patient provides a highly sensitive and specific means of monitoring intraoperative neurologic status. Many surgeons who prefer to perform CEA with local anesthesia cite the ability to validate management decisions at the time of cross-clamping on the basis of the patient's objective neurologic response as a key advantage associated with the technique. In contrast, the broad popularity of general anesthesia for CEA has generated enthusiasm for evaluating other monitoring techniques that can identify patients at risk of neurologic injury during general anesthesia. Many primary studies over the decades have evaluated the accuracy of various neurological monitors and combinations of techniques for identifying conditions that will lead to cerebral injury. Such studies frequently rely on different cut-off values to predict postoperative neurological outcome or compare results to awake neurological testing during carotid cross-clamping. As a result, the reported diagnostic accuracies are very heterogeneous. A recent meta-analysis reviewed studies comparing the diagnostic accuracy of individual neurological monitoring techniques versus awake testing during carotid cross-clamping (Table 16.8). The authors suggested that the combination of stump pressure combined with either TCD or EEG achieved the best post-test probability of accurately predicting hemodynamic intolerance during carotid cross-clamping.[144]Traditionally, the EEG has been the most extensively used monitor of neurologic function during CEA,[145,146] although recent evidence, based on a survey of US anesthesiologists suggests that, in the United States at least, EEG is now second in popularity (23.7% of respondents) after cerebral oximetry. Extensive evidence generated over several decades of clinical use during CEA supports a strong correlation between EEG changes and critical alterations in CBF.[147–149] The EEG is sensitive to adverse hemodynamic and embolic complications associated with CEA, and most patients who experience an adverse neurologic event will be identified (low false-negative rate).[150,151] However, the few prospective studies available in which intervention was not initiated in response to EEG changes[152,153] suggest that many patients experience intraoperative EEG changes that do not correlate with neurologic outcome, which is the clinically relevant endpoint (high false-positive rate). Nevertheless, EEG remains a popular technique for monitoring neurologic function during CEA, but its routine use requires expertise for technical support and real-time interpretation.

TCD is a well-established technology for assessing intraoperative cerebral blood flow in large intracranial vessels (see Chapter 7). During CEA, changes in velocity are generally considered to reflect similar changes in blood flow, provided that the arterial $PaCO_2$ remains constant.[154,155] The unique

Table 16.8 Diagnostic Accuracy of Different Types of Intraoperative Neuromonitoring Techniques for Predicting Hemodynamic Intolerance During Carotid Cross-clamping Compared with Awake Testing

Monitor	No of studies	Sensitivity (95% CI; heterogeneity)	Specificity (95% CI; heterogeneity)	AUC (SE;Q)	DOR (95% CI; heterogeneity)	Cut-off values
TCD	8	0.88 (0.79–0.94; 30%)	0.92 (0.9–0.94; 80.4%)	0.945 (0.023; 0.884)	73.9 (36.41–149.85; 0%)	↓ 48–70%
EEG	5	0.7 (0.58–0.8; 13.1%)	0.96 (0.94–0.97; 85.8%)	0.864 (0.06; 0.795)	65.27 (20.51–207.71; 56.8%)	NA
NIRS	5	0.84 (0.7–0.93; 63.7%)	0.89 (0.84–0.92; 84%)	0.943 (0.075; 0.881)	40.25 (6.46–250.74; 69%)	↓ 15–20%
Stump pressure	15	0.76 (0.71–0.8; 85.5%)	0.88 (0.87–0.9; 89.5%)	0.935 (0.019; 0.871)	37.14 (19.82–69.57; 46%)	25–50 mmHg
Evoked potentials	3	0.85 (0.7–0.94; 0%)	0.84 (0.77–0.9; 93.3%)	0.907 (0.036; 0.839)	35.14 (4.52–273.1; 69.3%)	↓0–50% of amplitude of N20/P25
Jugular venous saturation	2	0.82 (0.57–0.96; 57.4%)	0.86 (0.71–0.91; 0%)	NA	18.73 (4.63–75.78; 0%)	≤55%

AUC, area under the curve; CI, confidence interval; EEG, electroencephalography; DOR, diagnostic odds ratio; TCD, transcranial Doppler; NA, not available due to insufficient number of studies; NIRS, near infared spectroscopy.

(Adapted from Guay J, Kopp S. Cerebral monitors versus regional anesthesia to detect cerebral ischemia in patients undergoing carotid endarterectomy: a meta-analysis. Can J Anaesth. 2013;60(3):266–279 (with permission).)

perspective on the cerebral circulation made available noninvasively with TCD makes it an appealing technique for monitoring CBF during CEA. However, TCD does not directly measure cerebral function or ischemia, the equipment tends to be cumbersome, and the results are operator dependent. TCD has also been used to detect shunt malfunction during CEA.[156]

In addition to measuring flow velocity, TCD is a sensitive method for detecting cerebral emboli that may accompany carotid manipulation, cross-clamping, and shunt insertion and can aid in the etiologic distinction between hemodynamic and embolic causes of neurologic deterioration at the time of cross-clamping. In addition, prospective studies have reported a correlation between the number of emboli detected during carotid dissection and the risk of adverse neurologic outcome and radiologic evidence of cerebral injury.[157,158] Several investigators have extended the application of TCD monitoring into the postoperative period and have reported a high incidence of microemboli originating in the ipsilateral carotid artery in the hours following CEA. Microemboli have been linked to a higher incidence of stroke among patients with symptomatic and asymptomatic carotid stenosis,[159,160] and some evidence suggests that a high incidence of microemboli after CEA (more than 50 embolic signals per hour) is associated with increased risk for subsequent stroke.[161–163] The administration of antiplatelet agents (Dextran-40[162,164,165] and, more recently, the selective platelet glycoprotein IIb/IIIa receptor antagonist such as tirofiban[166,167] or clopidogrel[168]) in the perioperative period has been reported to substantially reduce the number of microembolic events identified with TCD in high-risk patients.

Carotid stump pressure (CSP) is the mean arterial pressure measured in the carotid stump (the internal carotid artery cephalad to the common carotid cross-clamp) after cross-clamping of the common and external carotid arteries. This measurement reflects pressure transmitted in a retrograde fashion through the ipsilateral carotid artery and has been postulated to provide a useful indicator of the adequacy of collateral circulation. Moore and associates[169,170] initially reported that CSP values less than 25 mmHg correlated with cross-clamp intolerance and suggested that this level of CSP represented the threshold for adequate cerebral perfusion. However, despite the conceptual appeal and technical simplicity of the technique, CSP measurements are generally not popular as a sole index of the adequacy of cerebral perfusion, for the following reasons: (1) inadequate validation as a useful predictor of outcome, (2) controversy related to the level of stump pressure that reflects inadequate collateral circulation, and (3) evidence that the pressure measurements are influenced by the choice of anesthetic.[171–173]

Investigators continue to study CSP as a means of assessing the adequacy of cerebral perfusion after cross-clamping, but the studies continue to yield conflicting results. Moritz and colleagues,[174] for example, found a CSP of 40 mmHg to have a sensitivity of 100% and a specificity of 75% for identifying cross-clamp intolerance among patients undergoing CEA under regional anesthesia (awake neurologic assessment). In contrast, Hans and Jareunpoon[175] reported a sensitivity of 57% and a specificity of 97% using a CSP value of 40 mmHg under similar clinical conditions (CEA performed with regional anesthesia) and concluded that CSP monitoring lacked adequate sensitivity to reliably identify patients who require shunt placement. As a result of this continuing controversy, CSP monitoring is used in some centers, but primarily as an adjuvant technique combined with another modality, such as EEG.

Cerebral near-infrared spectroscopy (NIRS) is a relatively new neurologic monitoring technique in relation to CEA that uses infrared spectrometry to estimate cerebral oxyhemoglobin saturation. Although the technology for in vivo measurement of cerebral oxygenation has been available for many years, its application during CEA has become popular more recently.[101,176] Like the familiar pulse oximeter, the cerebral oximeter emits light in the near-infrared range that penetrates the scalp and cranium. Because oxyhemoglobin and deoxyhemoglobin have distinct infrared absorption spectra, their relative proportions can be measured. In contrast to pulse oximeters, which use pulse-gated changes in optical density to measure arterial oxygen saturation, cerebral oximeters emit light continuously and measure the oxygen saturation of arterial, venous, and capillary hemoglobin in the superficial cerebral cortex. Because 75% of cortical blood volume is venous, cerebral oximetry reflects predominantly venous hemoglobin saturation.[176–178]

NIRS provides a convenient, portable, noninvasive measurement of regional cerebral venous oxyhemoglobin saturation (rSO_2) based on monitoring of a small sample of cortical vessels typically over the frontal lobe(s). However, it is unclear whether such regional measurements consistently reflect physiologic changes in other areas of the brain. Measurements are influenced by small changes in sensor placement, patient age, hemoglobin concentration, and some contribution from nonbrain sources; also, the technique is subject to high interpatient variability.[179,180] In addition, an ischemic threshold value for rSO_2 monitoring has not been established to date in relation to CEA. To compensate for these limitations, the technique is typically used to monitor trends in rSO_2, and several investigators have reported that during CEA, a change in rSO_2 value of 20% from baseline is associated with a negative predictive value of 97% and a positive predictive value of 35% for cerebral ischemic complications.[181,182] These data suggest that the technique provides reassurance when cross-clamping is not accompanied by a significant change in regional oxygenation but does not consistently identify patients at risk of ischemic injury when measurements decline in excess of 20%. Despite these concerns, NIRS has been identified as the preferred neuromonitoring technique among anesthesiologists (28% of respondents) during CEA, followed by EEG (24%), and awake testing (23%) in a US-based survey of anesthesia practices during CEA.[101]

Evoked potentials, especially somatosensory evoked potentials (SSEPs), have been used during CEA and some are now using motor evoked potentials as well. The measurement of SSEPs during CEA remains inadequately validated as a means of identifying patients at risk for adverse neurologic outcome, with many conflicting reports concerning its reliability for this application. However, a recent systematic review[183] of 4577 patients from 15 studies reported that intraoperative SSEP changes have a pooled mean sensitivity of 58% and pooled mean specificity of 91%. The study reported that the pooled diagnostic odds ratio for observing an SSEP change among those with neurologic deficits was 14 times higher than in individuals without a neurologic deficit. The authors conclude that intraoperative SSEP monitoring is a highly specific test for predicting neurological outcome following CEA and attribute the low sensitivity to interventions such as increasing blood pressure that improved CBF and prevented progression to neurologic injury. These considerations notwithstanding, the low pooled mean sensitivity associated with SSEP monitoring is concerning and suggests that this technique is unreliable for predicting neurologic outcome associated with carotid cross-clamping. In addition, compared with EEG monitoring, most evidence would suggest that SSEP monitoring

does not improve accuracy and is less robust during general anesthesia.[184]

Although each of these monitoring techniques can identify conditions that are associated with a higher risk of ischemic complications during CEA (ie, reductions in cerebral blood flow or oxygenation, disturbances in neuronal metabolic activity), a completely reliable method for accurately predicting neurologic outcome following CEA has yet to be identified. Since reliable pharmacological neuroprotection is not yet available (as discussed), the options that are available to intervene when the intraoperative neurological monitor(s) identifies evidence of hemodynamic cross-clamp intolerance include, (1) raising CPP by administering systemic vasopressor drugs such as phenylephrine, and (2) protecting the brain by restoring internal carotid blood flow through placement of a carotid shunt. However, most intraoperative strokes are thromboembolic in origin and can arise as a complication of intraluminal shunt insertion. In addition, only 1–5% of patients develop hemodynamic intolerance during carotid cross-clamping. Although many surgeons continue to use selective, or routine, shunting during CEA, there is little adequately validated evidence that the use of shunting, with or without any type of intraoperative neuromonitoring technique, improves outcome.[185,186] As a consequence, the use of carotid artery shunting and the choice of intraoperative monitoring technique largely depends on the preference and experience of the individual surgeon and the expertise of the surgical team.

Emergence from Anesthesia

Heparin is often not reversed after closure of the arteriotomy. If hemostasis is inadequate at the time of wound closure, a small dose of protamine (0.5 mg/kg) may be given intravenously. Depth of anesthesia is adjusted so that the patient can be promptly extubated at the end of surgery to avoid prolonged coughing and straining. A small dose of opioid (eg, fentanyl (0.5–1.0 µg/kg), remifentanil (0.2–0.5 µg/kg) or the continuation of a remifentanil infusion at very low dose), or lidocaine (1 to 1.5 mg/kg) given before emergence from anesthesia often attenuates coughing but temporarily deepens the level of anesthesia. Hemodynamic responses associated with emergence and extubation should be anticipated and treated. Drugs such as esmolol and nitroglycerine offer short durations of action, which can be useful for controlling hemodynamic changes during emergence and in the early postoperative period. Longer-acting antihypertensives such as labetalol, hydralazine, and metoprolol can be used effectively to control hypertension that persists in the postanesthesia care unit.

Postoperative Care

The intra-arterial cannula is maintained during the initial postoperative period to permit continuous blood pressure monitoring and blood sampling for arterial blood gas analyses. All patients receive supplemental oxygen, and the adequacy of oxygenation is monitored by pulse oximetry. Bilateral CEA, which is a high-neurologic-risk procedure not often performed, is associated with changes in the chemical control of ventilation.[187] Resting $PaCO_2$ increases by about 5 mmHg, and the ventilatory and cardiovascular responses to hypoxemia are abolished. Provision of supplemental oxygen and close monitoring of ventilatory status is particularly important in patients undergoing this procedure.

Carotid sinus baroreceptor function has been reported to be impaired in patients with extracranial carotid stenosis. Short-term effects associated with CEA procedures are variable, probably reflecting a variety of competing factors such as changes in baroreceptor sensitivity associated with removal of the plaque and enhanced exposure to intra-arterial pressure, mechanical injury to the receptors at the time of surgery or use of a technique that preserves or sacrifices innervation to the sinus (surgical distruption or injection with local anesthetic).[188,189] Evidence suggests that baroreceptor function is also disturbed by carotid stenting procedures which are postulated to potentially distort or alter pressure in the carotid sinus with stent deployment potentially triggering acute hypotension and/or severe bradycardia. These changes in receptor function persist into the early postoperative period but appear to resolve eventually as evidence suggests that long-term (evaluation at 8–114 months following CAS) baroreceptor dysfunction following carotid stenting procedures remains similar to patients with nonstented extracranial carotid atherosclerosis.[133]

Long-term changes in baroreceptor function following CEA are less clear. A study evaluating baroreceptor sensitivity at 4 months following surgery reported some improvement in baroreceptor function compared to preoperative performance.[190] However, other investigators, evaluating baroreceptor fuction at 6 months to 11 years following CAS procedures reported persistently attenuated reflex control of heart rate, but with no significant persistent effect on blood pressure lability.[191]

As a consequence of these changes, early postoperative hemodynamic instability is common after CEA. Determining the exact incidence is confounded by differing definitions used in the studies. Hypotension occurs in approximately 10% and hypertension in up to 50% of patients who have undergone CEA.[192] CEA performed with a technique that spares the carotid sinus nerve is associated with a higher incidence of postoperative hypotension, postulated to be due to increased exposure of the carotid sinus to the higher arterial pressure following removal of the atheromatous plaque.[193,194] This hypotension is associated with a marked decrease in systemic vascular resistance and is treated with intravenous fluid administration or, if necessary, the administration of vasopressor drugs, such as phenylephrine.[195] Intraoperative local anesthetic blockade of the carotid sinus nerve has been advocated to prevent, or attenuate, hypotension after CEA, but the effectiveness of this treatment is controversial.[193,194,196]

Hypertension after CEA is less well understood and has been reported to be more common in patients with preoperative hypertension, particularly poorly controlled or uncontrolled hypertension, and to occur more often after procedures in which the carotid sinus is denervated (surgical division or local anesthetic blockade).[89,188,196] Hypertension after sinus nerve-sparing CEA has been postulated to be caused by temporary dysfunction of the baroreceptor or nerve due to intraoperative trauma.[188] Mild rises in postoperative blood pressure are acceptable (up to approximately 20% above preoperative normotensive levels), but marked increases should be treated with antihypertensive drugs.

Other causes of hemodynamic instability after CEA are myocardial ischemia or infarction, dysrhythmias such as atrial fibrillation, hypoxia, hypercarbia, pneumothorax, pain, confusion, stroke, and distention of the urinary bladder.

Complications

Major postoperative complications after CEA are stroke, myocardial infarction (MI), death, and the hyperperfusion syndrome. The incidence of major complications, particularly stroke and MI, following CEA and CAS procedures, is

declining. While operator volume and training have been shown to influence outcome associated with CEA and CAS, it is likely that a significant proportion of the trend favoring outcome is related to advances in medical management. Improved surgical outcome has been outstripped by medical treatment aimed at reducing the risk of stroke. More consistent management of hypertension and diabetes combined with the introduction and widespread use of statins and antiplatelet drugs and enhanced emphasis on modifying lifestyle factors that contribute to stroke risk (eg, smoking, obesity, diet, activity) have reduced the risk of stroke in medically managed patients to levels that approach, or exceed, the risk associated with surgical intervention—especially for asymptomatic patients.[5,197]

Stroke

The majority of strokes complicating CEA have been reported to be related primarily to technical factors resulting in carotid occlusion (thrombosis or intimal flap) or emboli originating at the surgical site rather than to hemodynamic factors.[198–200] Most intraoperative strokes occur during carotid manipulation or cross-clamping and are embolic in nature. For example, a review of 2024 carotid endarterectomies[201] found 13% of strokes manifesting within the first 24 hours to be related to clamping ischemia and 63% to be thromboembolic (in addition, intracerebral hemorrhage contributed to 13% of perioperative strokes, and 11% had no relationship to the operated artery). Similarly, other investigators[202] reporting experience with 2365 patients undergoing CEA identified cross-clamp related ischemia as the cause of injury in 15% of patients who suffered a perioperative stroke. Of these events, only 3% were related to hemodynamic factors such as hypotension or hemodynamically significant bradycardia during cross-clamping. Additionally, 42% of perioperative strokes in this series of patients were reported to arise as a consequence of thrombotic or embolic events and 18% were the consequence of intracerebral hemorrhage. Thus, very few intraoperative strokes are hemodynamic in origin. Intraoperative neurologic function monitoring is directed toward the identification of the relatively small group of patients in whom potentially reversible, hemodynamically induced ischemia develops.

Myocardial Infarction

Given the high incidence of concomitant coronary artery disease in patients undergoing CEA, it is not surprising that myocardial infarction represents an important cause of morbidity and mortality after CEA. The North America based CREST study[44] prospectively studied 2502 symptomatic and asymptomatic patients undergoing CEA and CAS procedures and reported an incidence of perioperative myocardial infarction of 2.3% following CEA (1.1% following CAS procedures). In contrast, the European-based ICSS trial[46] also evaluated outcome following CAS and CEA procedures, and reported a low incidence of myocardial infarction (within 30 days) at 0.4% for CAS and 0.6% for CEA procedures—an incidence that is substantially lower than the North American experience. A recent Cochrane systematic review update (2013)[102] included data from 14 studies that compared outcome following CEA performed under general vs. local anesthesia. Eleven of 14 studies reported the incidence of postoperative myocardial infarction (within 30 days of surgery). Based on a mixed cohort of symptomatic and asymptomatic patients drawn from 11 studies and 4357 CEA procedures, this review reported a perioperative rate of myocardial infarction of 0.6% and 0.4% in the local and general anesthesia groups respectively. These data would suggest, like stroke, the incidence of perioperative MI is declining following CEA, perhaps as a consequence of improvements in assessment and management, as many of the medical therapies directed at the prevention of stroke are also advocated for the perioperative management of patients with coronary artery disease.[52] However, one should not be complacent, because a rise in cardiac troponin level of more than 0.5 ng/mL has been found in 13% of patients undergoing CEA.[203]

Death

Stroke and myocardial infarction represent the major causes of perioperative mortality associated with CEA. As emphasized previously, operative risk is affected by patient selection, the experience of the surgeon, and the institution where the surgery is performed.[37,38] Outcome is also influenced by concomitant best medical care. The American Heart Association guidelines for CEA recommend that the combined risk for death or stroke associated with CEA should not exceed 3% for asymptomatic patients and 6% for symptomatic patients.[5–7] These recommendations, with a durability spanning more than two decades of analysis and review, remain the gold standard against which other surgical interventions, such as CAS, are compared. However, as noted, many current studies of CEA and CAS report outcomes, including death and stroke, that are superior to these recommendations.[44,46] Indeed, best medical care for patients with cerebrovascular disease is now also reported to achieve, or exceed, these recommendations, particularly for asymptomatic patients.[197]

Hyperperfusion Syndrome

An increase in CBF has been reported to occur frequently after CEA and has been reported after CAS procedures as well.[204–206] Typically the magnitude of this increase is relatively small (less than 35%); however, in severe cases, rises in CBF can exceed 200% of preoperative levels and can be associated with greater morbidity and mortality.[148,207–209] There is no accepted definition of what absolute level of CBF increase should be considered "hyperperfusion" as knowledge of the underlying metabolic rate would be necessary to understand relative "excess" flow states. However, many investigators define an increase of 100% above baseline (preoperative) CBF as hyperperfusion. Clinically, hyperperfusion syndrome (HS) would be diagnosed in patients with all or part of the clinical triad ipsilateral headache, seizures, and focal neurologic symptoms that arise in the absence of cerebral ischemia. Features of hyperperfusion syndrome include headache (usually unilateral), face and eye pain, cerebral edema, seizures, and intracerebral hemorrhage.[207,208,210] A recent review of published experience with HS between 2003 and 2008 identified 13 studies (4689 patients) and reported a pooled incidence of 1.9% (range 0.4–14%) following CEA.[210] The incidence of intracranial hemorrhage (ICH) associated with HS was 0.37% (range 0.2–1%). A similar review[210] following CAS procedures identified nine studies (4446 patients) over the same 5-year period and reported pooled incidences of 1.16% (range 0.44–11.7%) and 0.74% (range 0–11.7%) respectively for HS and ICH.

The syndrome is postulated to occur after perfusion is restored to an area of the brain that has lost its autoregulation ability because of chronically decreased CBF and is typically accompanied by postoperative hypertension. Patients at greatest risk include those with reduced preoperative hemispheric CBF (eg, those with bilateral high-grade carotid stenoses, unilateral high-grade carotid stenosis with poor collateral cross-flow, or unilateral carotid occlusion with contralateral high-grade stenosis) and those with poorly controlled postoperative hypertension.[210] A recent systematic review[211] of studies reporting postoperative hypertension and HS following

CEA identified 36 papers (34,833 procedures) and reported an incidence of severe postoperative hypertension (systolic BP >180 mmHg) in 19% of patients. Hyperperfusion syndrome was reported with an incidence of 1%, ICH occurred with an incidence of 0.5% and mortality following ICH was 51%. The authors noted that 81% of patients at the time of presentation with HS had severe hypertension and that the risk of developing HS increased progressively with systolic blood pressure (SBP) measurements in excess of 140 mmHg. No cases of HS were identified in patients with SBP below 135 mmHg.

Histologically, the hyperperfusion syndrome has features very similar to those of hypertensive encephalopathy. Patients at risk for this syndrome should be monitored closely in the perioperative period, and blood pressure should be meticulously controlled, at normal or slightly below normal levels, until autoregulation is reestablished, typically over a period of several days. Adhiyaman and Alexander[207] have suggested that blood pressure should preferably be reduced using drugs such as labetalol and clonidine, which do not increase CBF, rather than angiotensin-converting enzyme inhibitors, calcium channel blockers, or direct vasodilators such as nitroprusside and nitroglycerine, but they acknowledge that there is no evidence favoring any particular drug.

Other Complications

Other complications associated with CEA are hematoma formation and cranial nerve palsies. Postoperatively, patients should be monitored carefully for evidence of wound hematoma (i.e., neck swelling), which may progress rapidly to airway obstruction and death. From analysis of NASCET surgical outcome data, the incidence of postoperative wound hematoma has been reported to be 7% (approximately 45% of hematomas are classified as moderate to severe, involving delayed discharge and/or reoperation), and the occurrence of wound hematoma has been reported to represent a significant risk factor for perioperative stroke and death.[98] Evidence of an expanding wound hematoma should be managed as an emergency with reintubation and surgical exploration. Experience with airway management among patients returning to the operating room for evacuation of a wound hematoma following CEA was recently reported.[212] The incidence of wound hematoma was 1.4%. Reintubation was performed prior to induction in 64% of patients and following induction of anesthesia in 36%. Awake fiberoptic intubation following topicalization (most common technique) was successful 75% of the time. Direct laryngoscopy as the primary technique was performed awake following topicalization in 17% of patients and following induction of anesthesia in 36% with a success rate of 71% and 87% respectively. Awake tracheostomy was performed in one patient and successful direct laryngoscopy and intubation followed hematoma decompression in three patients. These data suggest that successful airway management can be accomplished by several approaches and that none of the techniques were immune to failure. An appropriate approach to airway management must be made on the basis of the individual patient and in the context of the patient's level of consciousness, degree of airway compromise and physiological stability.

The incidence of cranial nerve palsies following CEA has been reported to be 5% to 12%.[98,213,214] On the basis of NASCET[98] and ECST[99] results, the hypoglossal nerve, vagus nerve, and branches of the facial nerve are the most common cranial nerves injured during CEA, and their injury may manifest as dysphagia. Most events are thought to be related to traction injury, and increasing duration of the surgical procedure (>2 hours) has been reported to raise the risk of cranial nerve injury.[213] The GALA trial reported no difference in the incidence of cranial nerve injuries during CEA procedures performed under general versus local anesthesia (10.5% vs. 12.0%, respectively).[32] The incidence of cranial nerve injury is reported to be higher following CEA procedures compared to CAS procedures. The International Carotid Stenting Study (ICSS) reported an incidence of cranial nerve injury of 5.3% with all injuries arising in the CEA group (actually one injury was attributed to the CAS group, but occurred in association with CEA performed within 30 days of the endovascular procedure).[46]

Injuries to laryngeal nerves (recurrent or superior laryngeal nerves) have also been reported. When these deficits were specifically assessed with postoperative laryngoscopic examination, vocal cord dysfunction (reduction or absence of unilateral vocal cord movement) was reported in 4% of patients after CEA; this complication typically manifests as hoarseness.[214] Although cranial nerve injuries rarely lead to airway compromise following CEA, anesthesiologists should be cognizant that vocal cord dysfunction and swallowing difficulties are not uncommon after these procedures. Cranial nerve palsies following CEA are typically temporary, resolving within several months. Of the cranial nerve injuries reported in the ECST, 92% resolved within 4 months of surgery and 8% were permanent (persisting beyond 2 years).[213] Prolonged resolution of recurrent laryngeal nerve injuries has been reported, with recovery of full function occurring up to 36 months after surgery.[214]

SUMMARY

Evidence derived from several large prospective trials completed over the past 5–10 years has continued to refine our understanding of the roles of CEA and CAS for the prevention of stroke and the patients most likely to benefit from these procedures. CEA remains the gold standard for the surgical treatment of cerebrovascular occlusive disease, although CAS will continue to offer an alternative treatment option for some subgroups—particularly symptomatic high-risk patients.

Anesthesiologists will continue to be challenged to provide care for this elderly population of patients, who commonly present with multiple comorbid conditions. The preoperative assessment and optimization of comorbidities is increasingly recognized as the foundation for achieving best outcome. Best medical therapy directed at reducing the risk of stroke and myocardial infarction has contributed substantially to improving outcomes attributed to CEA and CAS procedures. The role of the anesthesiologist in the care of these patients will undoubtedly continue to expand as opportunities to mitigate perioperative risk evolve.

REFERENCES

1. Alpert JN. Extracranial carotid artery—current concepts of diagnosis and management. *Tex Heart Inst J*. 1991;18:93–97.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
3. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative. *Lancet*. 1991;337:1235–1243.
4. Endarterectomy for asymptomatic carotid artery stenosis: Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273:1421–1428.
5. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke. A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832.

6. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236.
7. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA Guideline on the management of patients with extracranial carotid and vertebral artery disease. *Stroke*. 2011;42:e464–e540.
8. Naylor AR, London NJM, Bell PRF. Carotid endarterectomy versus carotid angioplasty. *Lancet*. 1997;349:203–204.
9. Coward LJ, Featherstone RL, Brown MM. Safety and efficacy of endo-vascular treatment of carotid artery stenosis compared with carotid end-arterectomy: A Cochrane systematic review of the randomized evidence. *Stroke*. 2005;36:905–911.
10. van der Vaart MG, Meerwaldt R, Reijnen MM, et al. Endarterectomy or carotid artery stenting: The quest continues. *Am J Surg*. 2008;95:259–269.

11a. Powers CJ, Hirsch JA, Hussain MS, et al. Standards of practice and reporting standards for carotid artery angioplasty and stenting. *J Neurointerv Surg*. 2014;6:87–90.

11b. Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med*. 2016;374(11):1011–1020.

12a. Cenic A, Craen RA, Lee TY, Gelb AW. Cerebral blood volume and blood flow responses to hyperventilation in brain tumors during isoflurane or propofol anesthesia. *Anesth Analg*. 2002;94:661–666.

12b. Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med*. 2016;374(11):1021–1031.

13. Ohmori S, Iwama H. An induction dose of propofol does not alter cerebral blood flow determined by single-photon-emission computed tomography. *J Anesth*. 2000;14:61–67.
14. Conti A, Iacopino DG, Fodale V, et al. Cerebral hemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia. Transcranial Doppler study under bispectral index monitoring. *Br J Anaesth*. 2006;97:333–339.
15. Koch M, De Backer D, Vincent JL, et al. Effects of propofol on human microcirculation. *Br J Anaesth*. 2008;101:473–478.
16. Fourcade HE, Larson P, Ehrenfield WK, et al. The effects of CO_2 and systemic hypertension on cerebral perfusion pressure during carotid endarterectomy. *Anesthesiology*. 1970;33:383–390.
17. Lassen NA, Palvolgyi R. Cerebral steal during hypercapnia and the inverse reaction during hypocapnia observed by the 133xenon technique in man. *Scand J Lab Clin Invest*. 1968;22(S102):13D.
18. Wells BA, Keats AS, Cooley DA. Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. *Surgery*. 1963;54:216–223.
19. Boysen G, Ladegaard-Pedersen HJ, Henriksen H, et al. The effects of $Paco_2$ on regional cerebral blood flow and internal carotid arterial pressure during carotid clamping. *Anesthesiology*. 1971;35:286–300.
20. McCulloch TJ, Thompson CL, Turner MJ. A randomized crossover comparison of the effects of propofol and sevoflurane on cerebral hemodynamics during carotid endarterectomy. *Anesthesiology*. 2007;106:56–64.
21. Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. *Anesthesiology*. 2015;122:196–205.
22. Kadoi Y, Hinohara H, Kunimoto F, et al. Diabetic patients have an impaired cerebral vasodilatory response to hypercapnia under propofol anesthesia. *Stroke*. 2003;34:2399–2403.
23. Kadoi Y, Takahashi K, Saito S, Goto F. The comparative effects of sevoflurane versus isoflurane on cerebrovascular carbon dioxide reactivity in patients with diabetes mellitus. *Anesth Analg*. 2006;103:168–172.
24. Drummond JC. The lower limit of autoregulation: Time to revise our thinking? *Anesthesiology*. 1997;86:1431–1433.
25. Yamamoto M, Meyer JS, Sakai F, et al. Aging and cerebral vasodilator responses to hypercarbia. Responses in normal aging and in persons with risk factors for stroke. *Arch Neurol*. 1980;37:489–496.
26. Hansebout RR, Blomquist G, Gloor P, et al. Use of hypertension and electroencephalographic monitoring during carotid endarterectomy. *Can J Surg*. 1981;24:304–307.
27. LeSar CJ, Sprouse LR, Harris WB. Permissive hypertension during awake eversion carotid endarterectomy: A physiologic approach for cerebral protection. *J Am Coll Surg*. 2014;218(4):760–766.
28. Boysen G, Engell HC, Henriksen H. The effect of induced hypertension on internal carotid artery pressure and regional cerebral blood flow during temporary carotid clamping for endarterectomy. *Neurology*. 1972;22:1133–1144.
29. Smith JS, Roizen MF, Cahalan MK, et al. Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: Effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. *Anesthesiology*. 1988;69:846–855.
30. Riles TS, Kopelman I, Imparato AM. Myocardial infarction following carotid endarterectomy: A review of 683 operations. *Surgery*. 1979;85:249–252.
31. North American Symptomatic Carotid Endarterectomy Trial Collaborators. North American Symptomatic Carotid Endarterectomy Trial: Methods, patient characteristics, and progress. *Stroke*. 1991;22:711–720.
32. GALA Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): A multicentre, randomised controlled trial. *Lancet*. 2008;372:2132–2142.
33. Mayberg MR, Wilson SE, Yatsu F, et al. Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA*. 1991;266:3289–3294.
34. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.
35. Chambers BR, Donnan G. Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database Syst Rev*. 2005;(4). CD001923.
36. Nazarian SM, Yenokyan G, Thompson RE, et al. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. *J Vasc Surg*. 2008;48:343–350.
37. Holt PJ, Poloniecki JD, Loftus IM, Thompson MM. Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy. *Eur J Vasc Endovasc Surg*. 2007;33:645–651.
38. Killeen SD, Andrews EJ, Redmond HP, Fulton GJ. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures. *J Vasc Surg*. 2007;45:615–626.
39. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351(15):1493–1501.
40. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: A randomised non-inferiority trial. *Lancet*. 2006;368(9543):1239–1247.
41. Ringleb PA, Hennerici M, Hacke W. Stent protected angioplasty of symptomatic carotid artery stenoses. The European point of view. *Int J Stroke*. 2006;1(2):94–96.
42. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: A multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7(10):893–902.
43. Mas JL, Trinquart L, Leys D, et al. Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial: Results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7(10):885–892.
44. Brott TG, Hobson 2nd. RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363(1):11–23.
45. Hopkins LN, Roubin GS, Chakhtoura EY, et al. The Carotid Revascularization Endarterectomy versus Stenting Trial: Credentialing of interventionalists and final results of lead-in phase. *J Stroke Cerebrovasc Dis*. 2010;19(2):153–162.
46. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): An interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985–997.
47. Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: The International Carotid Stenting Study (ICSS) randomised trial. *Lancet*. 2015;385:529–538.
48. Economopoulos KP, Sergentanis TN, Tsivgoulis G, et al. Carotid artery stenting versus carotid endarterectomy: A comprehensive meta-analysis of short-term and long-term outcomes. *Stroke*. 2011;42(3):687–692.
49. Jalbert JJ, Nguyen LL, Gerhard-Herman MD, et al. Outcomes after carotid artery stenting in Medicare beneficiaries, 2005 to 2009. Published online: *JAMA Neurol*. 2015;72:276–286.
50. Cremonesi A, Castriota F, Secco GG, et al. Carotid artery stenting: An update. *Eur Heart J*. 2015;36(1):13–21.
51. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924.
52. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64(22):e77–e137.

53. Gladstone DJ, Oh J, Fang J, et al. Urgency of carotid endarterectomy for secondary stroke prevention: Results from the Registry of the Canadian Stroke Network. *Stroke*. 2009;40(8):2776–2782.
54. Sundt Jr. TM, Sandok BA, Whisnant JP. Carotid endarterectomy. Complications and preoperative assessment of risk. *Mayo Clin Proc*. 1975;50:301–306.
55. Sundt Jr TM, Whisnant JP, Houser OW, et al. Prospective study of the effectiveness and durability of carotid endarterectomy. *Mayo Clin Proc*. 1990;65:625–635.
56. Halm EA, Hannan EL, Rojas M, et al. Clinical and operative predictors of outcomes of carotid endarterectomy. *J Vasc Surg*. 2005;42:420–428.
57. Halm EA, Tuhrim S, Wang JJ, et al. Risk factors for perioperative death and stroke after carotid endarterectomy: Results of the New York Carotid Artery Surgery study. *Stroke*. 2009;40(1):221–229.
58. Tu JV, Wang H, Bowyer B, et al. Risk factors for death or stroke after carotid endarterectomy: Observations from the Ontario Carotid Endarterectomy Registry. *Stroke*. 2003;34:2568–2573.
59. Hertzer NR, Lees CD. Fatal myocardial infarction following carotid endarterectomy. *Ann Surg*. 1981;194:212–218.
60. Towne JB, Weiss DG, Hobson RW. First phase report of cooperative Veterans Administration asymptomatic carotid stenosis study—Operative morbidity and mortality. *J Vasc Surg*. 1990;11:252–259.
61. American Society of Anesthesiologists. New classifcation of physical status. *Anesthesiology*. 1963;24:111.
62. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845–850.
63. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery: A multifactorial clinical risk index. *Arch Intern Med*. 1986;146:2131–2134.
64. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
65. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for the prediction of cardiac risk after surgery. *Circulation*. 2011;124:381–387.
66. The American College of Surgeons, National Surgical Quality Improvement Program. *Surgical Risk Calculator*. http://www.riskcalculator.facs.org/ last accessed 07.02.15.
67. Press MJ, Chassin MR, Wang J, et al. Predicting medical and surgical complications of carotid endarterectomy: Comparing the risk indexes. *Arch Intern Med*. 2006;166(8):914–920.
68. Gongora-Rivera F, Labreuche J, Jaramillo A, et al. Autopsy prevalence of coronary atherosclerosis in patients with fatal stroke. *Stroke*. 2007;38:1203–1210.
69. Sirimarco G, Amarenco P, Labreuche J, et al. Carotid atherosclerosis and risk of subsequent coronary event in outpatients with atherothrombosis. *Stroke*. 2013;44:373–379.
70. Adams HP, del Zoppo G, Alberts MJ, et al. AHA/ASA guidelines for the early management of adults with ischemic stroke. *Stroke*. 2007;38:1655–1711.
71. Olympio MA. The preoperative evaluation for symptomatic carotid endarterectomy: A debated issue. *J Neurosurg Anesthesiol*. 1996;8:310–313.
72. Dubinsky RM, Lai SM. Mortality from combined carotid endarterectomy and coronary artery bypass surgery in the US. *Neurology*. 2007;68:195–197.
73. Hill MD, Shrive FM, Kennedy J, et al. Simultaneous carotid endarterectomy and coronary bypass surgery in Canada. *Neurology*. 2005;64:1435–1437.
74. Mortaz HS, Mostafazadeh DB, Sahraian MA. Carotid endarterectomy for carotid stenosis in patients selected for coronary artery bypass graft surgery. *Cochrane Database Syst Rev*. 2009;4. CD006074.
75. Timaran CH, Rosero EB, Smith ST, et al. Trends and outcomes of concurrent carotid revascularization and coronary bypass. *J Vasc Surg*. 2008;48:355–360.
76. Naylor AR, Mehta Z, Rothwell PM. A systematic review and meta-analysis of 30-day outcomes following staged carotid stenting and coronary bypass. *Eur J Vasc Endovasc Surg*. 2009;37:379–387.
77. Guzman LA, Costa MA, Angiolillo DJ, et al. A systematic review of outcomes in patients with staged carotid artery stenting and coronary artery bypass graft surgery. *Stroke*. 2008;39:361–365.
78. Devereaux PJ, Yang H, Guyatt GH, et al. Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) trial: A randomised controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. *Am Heart J*. 2006;152:223–230.
79. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomized controlled trial. *Lancet*. 2008;371:1839–1847.
80. Sear JW, Giles JW, Howard-Alpe G, Foex P. Perioperative beta-blockade, 2008: What does POISE tell us, and was our earlier caution justified? *Br J Anaesth*. 2008;101:135–138.
81. Fleisher LA, Poldermans D. Perioperative β blockade: Where do we go from here? *Lancet*. 2008;371:1813–1814.
82. Liakopoulos OJ, Kuhn EW, Slottosch I, et al. Preoperative statin therapy for patients undergoing cardiac surgery. *Cochrane Database Syst Rev*. 2012;4. CD008493.
83. Sanders RD, Nicholson A, Lewis SR, et al. Perioperative statin therapy for improving outcomes during and after noncardiac vascular surgery. *Cochrane Database Syst Rev*. 2013;7. CD009971.
84. Antoniou GA, Hajibandeh S, Hajibandeh S, et al. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. *J Vasc Surg*. 2015;61:519–532.
85. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, et al. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: Implications for plaque stabilization. *Circulation*. 2001;103:926–933.
86. Burger W. Low dose aspirin for secondary cardiovascular prevention. *J Intern Med*. 2005;257:399–414.
87. Garg AX, Kurz A, Sessler DI, et al. Perioperative aspirin and clonidine and risk of acute kidney injury: A randomized clinical trial. *JAMA*. 2014;312(21):2254–2264.
88. Gelb AW, Herrick IA. Preoperative hypertension does predict post-carotid endarterectomy hypertension. *Can J Neurol Sci*. 1990;17:95–96.
89. Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. *Surgery*. 1980;88:575–580.
90. Skudlarick JL, Mooring SL. Systolic hypertension and complications of carotid endarterectomy. *South Med J*. 1982;75:1563–1565.
91. Baird TA, Parsons MW, Phanh T, Butcher KS, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
92. McCormick MT, Muir KW, Gray CS, Walters MR. Management of hyperglycemia in acute stroke: How, when, and for whom? *Stroke*. 2008;39:2177–2185.
93. McGirt MJ, Woodworth GF, Brooke BS, et al. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction and death after carotid endarterectomy. *Neurosurgery*. 2006;58:1066–1073.
94. Varghese P, Gleason V, et al. Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. *J Hosp Med*. 2007;2:234–240.
95. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. *JAMA*. 2008;300:933–944.
96. Landesberg G, Mosseri M, Wolf Y, et al. Perioperative myocardial ischemia and infarction: Identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. *Anesthesiology*. 2002;96:264–270.
97. Kim KM, Gwak MS, Choi SJ, Kim MH, Park MH, Heo BY. Pulse pressure variation and stroke volume variation to predict fluid responsiveness in patients undergoing carotid endarterectomy. *Korean J Anesthesiol*. 2013;65(3):237–243.
98. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: Surgical results in 1415 patients. *Stroke*. 1999;30:1751–1758.
99. Bond R, Warlow CP, Naylor AR, et al. Variation in surgical and anaesthetic technique and associations with operative risk in the European carotid surgery trial: Implications for trials of ancillary techniques. *Eur J Vasc Endovasc Surg*. 2002;23:117–126.
100. Cheng MA, Theard MA, Tempelhoff R. Anesthesia for carotid endarterectomy: A survey. *J Neurosurg Anesthesiol*. 1997;9:211–216.
101. Greene NH, Minhaj MM, Zaky AF, et al. Perioperative management of carotid endarterectomy: A survey of clinicians' backgrounds and practices. *J Cardiothorac Vasc Anesth*. 2014;28:1002–1005.
102. Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database Syst Rev*. 2013. (12):http://dx.doi.org/10.1002/14651858.CD000126.pub4. CD000126.
103. Calligaro KD, Dougherty MJ, Lombardi J, et al. Converting from general anesthesia to cervical block anesthesia for carotid endarterectomy. *Vasc Surg*. 2001;35:103–106.
104. Pandit JJ, Satya-Krishna R, Gration P. Superfcial or deep cervical plexus block for carotid endarterectomy: A systematic review of complications. *Br J Anaesth*. 2007;99:159–169.
105. Pandit JJ, Bree S, Dillon P, et al. A comparison of superfcial versus combined (superfcial and deep) cervical plexus block for carotid endarterectomy: A prospective, randomized study. *Anesth Analg*. 2000;91:781–786.
106. Stoneham MD, Doyle AR, Knighton JD, et al. Prospective, randomized comparison of deep or superfcial cervical plexus block for carotid end-arterectomy surgery. *Anesthesiology*. 1998;89:907–912.

107. Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: A systematic review of complications. *Br J Anaesth*. 2007;99:159–169.
108. Usui Y, Kobayashi T, Kakinuma H, et al. An anatomic basis for blocking of the deep cervical plexus and cervical sympathetic tract using an ultrasound-guided technique. *Anesth Analg*. 2010;110:964–968.
109. Sandeman DJ, Griffiths MJ, Lennox AF. Ultrasound guided deep cervical plexus block. *Anaesth Intensive Care*. 2006;34:240–244.
110. Tran De QH, Dugani S, Finlayson RJ. A randomized comparison between ultrasound-guided and landmark-based superficial cervical plexus block. *Reg Anesth Pain Med*. 2010;35:539–543.
111. Suresh S, Jagannathan N. Somatic blockade of the head and neck. In: Cousins MJ, Carr DB, Horlocker TT, Bridenbaugh PO, eds. *Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine*. 4th ed.Philadelphia: Lippincott Williams & Wilkins; 2009.
112. McCutcheon CA, Orme RM, Scott DA, et al. A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anesthesia. *Anesth Analg*. 2006;102:668–675.
113. Schneemilch CE, Bachmann H, Ulrich A, et al. Clonidine decreases stress response in patients undergoing carotid endarterectomy under regional anesthesia: A prospective, randomized, double-blinded, placebo-controlled study. *Anesth Analg*. 2006;103:297–302.
114. Bekker AY, Basile J, Gold M, et al. Dexmedetomidine for awake carotid endarterectomy: Efficacy, hemodynamic profle, and side effects. *J Neurosurg Anesthesiol*. 2004;16:126–135.
115. Carter R, Richardson A, Santoro J, et al. Is dexmedetomidine more effective than remifentanil for neurologic outcomes in patients undergoing CEA surgery using regional anesthesia? *J Perianesth Nurs*. 2014;29:466–474.
116. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: A review of clinical applications. *Curr Opin Anaesthesiol*. 2008;21:457–461.
117. Gerlach AT, Dasta JF. Dexmedetomidine: An updated review. *Ann Pharmacother*. 2007;41:245–252.
118. Umbrain V, Keeris J, D'Haese J, et al. Isoflurane, desflurane and sevoflurane for carotid endarterectomy. *Anaesthesia*. 2000;55(11):1052–1057.
119. Wilhelm W, Schlaich N, Harrer J, et al. Recovery and neurological examination after remifentanil-desflurane or fentanyl-desflurane anaesthesia for carotid artery surgery. *Br J Anaesth*. 2001;86(1):44–49.
120. Kostopanagiotou G, Markantonis SL, Polydorou M, et al. Recovery and cognitive function after fentanyl or remifentanil administration for carotid endarterectomy. *J Clin Anesth*. 2005;17:16–20.
121. Komatsu R, Turan AM, Orhan-Sungur M, et al. Remifentanil for general anaesthesia: A systematic review. *Anaesthesia*. 2007;62:1266–1280.
122. Fodale V, Schifflitid D, Pratico C, Santamaria LB. Remifentanil and the brain. *Acta Anaesthesiol Scand*. 2008;52:319–326.
123. Jellish WS, Sheikh T, Baker WH, et al. Hemodynamic stability, myocardial ischemia, and perioperative outcome after carotid surgery with remifentanil/propofol or isoflurane/fentanyl anesthesia. *J Neurosurg Anesthesiol*. 2003;15:176–184.
124. Myles PS, Leslie K, Chan MTV, et al. Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. *Anesthesiology*. 2007;107:221–231.
125. Algotsson L, Messeter K, Rosen I, et al. Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. *Acta Anaesthesiol Scand*. 1992;36:46–52.
126. Hansen TD, Warner DS, Todd MM, et al. Effects of nitrous oxide and volatile anesthetics on cerebral blood flow. *Br J Anaesth*. 1989;63:290–295.
127. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. *Anesthesiology*. 1984;60:405–412.
128. Haelewyn B, David HN, Rouillon C, et al. Neuroprotection by nitrous oxide: Facts and evidence. *Crit Care Med*. 2008;36:2651–2659.
129. Reinstrup P, Ryding E, Ohlsson T, et al. Regional cerebral metabolic rate (positron emission tomography) during inhalation of nitrous oxide 50% in humans. *Br J Anaesth*. 2008;100:66–71.
130. McGregor DG, Lanier WL, Pasternak JJ, et al. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. *Anesthesiology*. 2008;108:568–579.
131. Culley DJ, Crosby G. Nitrous oxide in neuroanesthesia. *Anesthesiology*. 2008;108:553–554.
132. Sanders RD, Graham C, Lewis SC, et al. Nitrous oxide exposure does not seem to be associated with increased mortality, stroke, and myocardial infarction: A non-randomized subgroup analysis of the General Anaesthesia compared with Local Anaesthesia for carotid surgery (GALA) trial. *Br J Anaesth*. 2012;109:361–367.
133. Huang C-C, Wu Y-S, Chen T, et al. Long-term effects of baroreceptor function after stenting in patients with carotid artery stenosis. *Auton Neurosci*. 2010;158:100–104.
134. Mylonas SN, Moulakakis KG, Antonopoulos CN, et al. Carotid artery stenting-induced hemodynamic instability. *J Endovasc Ther*. 2013;20:48–60.
135. Head BP, Patel P. Anesthetics and brain protection. *Curr Opin Anaesthesiol*. 2007;20:395–399.
136. Koerner IP, Brambrink AM. Brain protection by anesthetic agents. *Curr Opin Anaesthesiol*. 2006;19:481–486.
137. Bilotta F, Gelb AW, Stazi E, et al. Pharmacological perioperative brain neuroprotection: A qualitative review of randomized clinical trials. *Br J Anaesth*. 2013;110:113–120.
138. Jovic M, Unic-Stojanovic D, Isenovic E, et al. Anesthetics and cerebral protection in patients undergoing carotid endarterectomy. *J Cardiothorac Vasc Anesth*. 2015;29:178–184.
139. Melgar MA, Mariwalla N, Madhusudan H, Weinand M. Carotid endarterectomy without shunt: The role of cerebral metabolic protection. *Neurol Res*. 2005;27:850–856.
140. Durward QJ, Ragnarsson TS, Reeder RF, et al. Carotid endarterectomy in nonagenarians. *Arch Surg*. 2005;140:625–628.
141. Drader KS, Herrick IA. Carotid endarterectomy: Monitoring and its effect on outcome. *Anesthesiol Clin N Am*. 1997;15:613–629.
142. Craen RA, Gelb AW, Eliasziw M, et al. Anesthesia monitoring and neurologic outcome in carotid endarterectomy: NASCET results. *J Neurosurg Anesthesiol*. 1993;5:303.
143. Guarracino F. Cerebral monitoring during cardiovascular surgery. *Curr Opin Anaesthesiol*. 2008;21:50–54.
144. Guay J, Kopp S. Cerebral monitors versus regional anesthesia to detect cerebral ischemia in patients undergoing carotid endarterectomy: A meta-analysis. *Can J Anaesth*. 2013;60(3):266–279.
145. Cheng MA, Theard MA, Tempelhoff R. Anesthesia for carotid endarterectomy: A survey. *J Neurosurg Anesthesiol*. 1997;9:211–216.
146. Craen RA, Gelb AW, Eliasziw M, et al. Anesthesia for carotid endarterectomy: The North American practice at 50 centres. *NASCET Study Results Anesth Analg*. 1993;76:S61.
147. Sundt Jr TM, Sharbrough FW, Anderson RE, et al. Cerebral blood flow measurements and electroencephalograms during carotid endarterectomy. *J Neurosurg*. 1974;41:310–320.
148. Sundt Jr TM, Sharbrough FW, Piepgras DG, et al. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: With results of surgery and hemodynamics of cerebral ischemia. *Mayo Clin Proc*. 1981;56:533–543.
149. Sundt Jr TM. The ischemic tolerance of neural tissue and need for monitoring and selective shunting during carotid endarterectomy. *Stroke*. 1983;14:93–98.
150. Redekop G, Ferguson GG. Correlation of contralateral stenosis and intraoperative electroencephalogram change with risk of stroke during carotid endarterectomy. *Neurosurgery*. 1992;30:191–194.
151. Plestis KA, Loubser P, Mizrahi EM, et al. Continuous electroencephalographic monitoring and selective shunting reduces neurologic morbidity rates in carotid endarterectomy. *J Vasc Surg*. 1997;25:620–628.
152. Morawetz RB, Zeiger HE, McDowell Jr HA, et al. Correlation of cerebral blood flow and EEG during carotid occlusion for endarterectomy (without shunting) and neurologic outcome. *Surgery*. 1984;96:184–189.
153. Zampella E, Morawetz RB, McDowell HA, et al. The importance of cerebral ischemia during carotid endarterectomy. *Neurosurgery*. 1991;29:727–731.
154. Murkin JM, Lee DH. Noninvasive measurement of cerebral blood flow: Techniques and limitations. *Can J Anaesth*. 1991;38:805–808.
155. Markwalder TM, Grolimund P, Seiler RW, et al. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure—A transcranial ultrasound Doppler study. *J Cereb Blood Flow Metab*. 1984;4:368–372.
156. Naylor AR, Wildsmith JA, McClure J, et al. Transcranial Doppler monitoring during carotid endarterectomy. *Br J Surg*. 1991;78:1264–1268.
157. Jansen C, Ramos LM, van Heesewijk JP, et al. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. *Stroke*. 1994;25:992–997.
158. Ackerstaff RG, Jansen C, Moll FL, et al. The significance of microemboli detection by means of transcranial Doppler ultrasonography monitoring in carotid endarterectomy. *J Vasc Surg*. 1995;21:963–969.
159. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. *Stroke*. 1999;30:1440–1443.
160. Siebler M, Kleinschmidt A, Sitzer M, et al. Cerebral microembolism in symptomatic and asymptomatic high-grade internal carotid artery stenosis. *Neurology*. 1994;44:615–618.
161. Levi CR, O'Malley HM, Fell G, et al. Transcranial Doppler detected cerebral microembolism following carotid endarterectomy: High microembolic signal loads predict postoperative cerebral ischaemia. *Brain*. 1997;120:621–629.

162. Lennard N, Smith J, Dumville J, et al. Prevention of postoperative thrombotic stroke after carotid endarterectomy: The role of transcranial Doppler ultrasound. *J Vasc Surg*. 1997;26:579–584.
163. van der Schaaf IC, Horn J, Moll FL, Ackerstaff RG. Transcranial Doppler monitoring after carotid endarterectomy. *Ann Vasc Surg*. 2005;19:19–24.
164. Levi CR, Stork JL, Chambers BR, et al. Dextran reduces embolic signals after carotid endarterectomy. *Ann Neurol*. 2001;50:544–547.
165. Robless PA, Tegos TJ, Okonko D, et al. Platelet activation during carotid endarterectomy and the antiplatelet effect of Dextran 40. *Platelets*. 2002;13:231–239.
166. Junghans U, Siebler M. Cerebral microembolism is blocked by tirofban, a selective nonpeptide platelet glycoprotein IIb/IIIa receptor antagonist. *Circulation*. 2003;107:2717–2721.
167. van Dellen D, Tiivas CA, Jarvi K, et al. Transcranial Doppler ultrasonography-directed intravenous glycoprotein IIb/IIIa receptor antagonist therapy to control transient cerebral microemboli before and after carotid endarterectomy. *Br J Surg*. 2008;95:709–713.
168. Tsivgoulis G, Kerasnoudis A, Krogias C, et al. Clopidogrel load for emboli reduction in patients with symptomatic carotid stenosis undergoing urgent carotid endarterectomy. *Stroke*. 2012;43(7):1957–1960.
169. Moore WS, Hall AD. Carotid artery back pressure: A test of cerebral tolerance to temporary carotid occlusion. *Arch Surg*. 1969;99:702–710.
170. Moore WS, Yee JM, Hall AD. Collateral cerebral blood pressure: An index of tolerance to temporary carotid occlusion. *Arch Surg*. 1973;106:521–523.
171. McKay RD, Sundt TM, Michenfielder JD, et al. Internal carotid artery stump pressure and cerebral blood flow during carotid endarterectomy: Modification by halothane, enflurane and Innovar. *Anesthesiology*. 1976;45:390–399.
172. Modica PA, Tempelhoff R. A comparison of computerized EEG with internal carotid artery stump pressure for detection of ischemia during carotid endarterectomy. *J Neurosurg Anesthesiol*. 1989;1:211–218.
173. Whitley D, Cherry KJ. Predictive value of carotid artery stump pressures during carotid endarterectomy. *Neurosurg Clin N Am*. 1996;7:723–732.
174. Moritz S, Kasprzak P, Arlt M, et al. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. *Anesthesiology*. 2007;107:563–569.
175. Hans SS, Jareunpoon O. Prospective evaluation of electroencephalography, carotid artery stump pressure, and neurologic changes during 314 consecutive carotid endarterectomies performed in awake patients. *J Vasc Surg*. 2007;45:511–515.
176. Wolf M, Ferrari M, Quaresima V. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J Biomed Opt*. 2007;12:062104.
177. McCormick PW, Stewart M, Goetting MG, et al. Regional cerebrovascular oxygen saturation measured by optical spectroscopy in humans. *Stroke*. 1991;22:596–602.
178. Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. *Can J Appl Physiol*. 2004;29:463–487.
179. Lam JM, Smielewski P, al-Rawi P, et al. Internal and external carotid contributions to near-infrared spectroscopy during carotid endarterectomy. *Stroke*. 1997;28:906–911.
180. Kishi K, Kawaguchi M, Yoshitani K, et al. Influence of patient variables and sensor location on regional cerebral oxygen saturation measured by INVOS 4100 near-infrared spectrophotometers. *J Neurosurg Anesthesiol*. 2003;15:302–306.
181. Samra SK, Dy EA, Welch K, et al. Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. *Anesthesiology*. 2000;93:964–970.
182. Mille T, Tachimiri ME, Klersy C, et al. Near infrared spectroscopy monitoring during carotid endarterectomy: Which threshold value is critical? *Eur J Vasc Endovasc Surg*. 2004;27:646–650.
183. Nwachuku EL, Balzer JR, Yabes JG, et al. Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: A systematic review and meta-analysis. *JAMA Neurol*. 2015;72(1):73–80.
184. Whiten C, Gunning P. Carotid endarterectomy. Intraoperative monitoring of cerebral perfusion. *Curr Anaesth Crit Care*. 2009;20:42–45.
185. Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev*. 2014;6. CD000190.
186. Sloan MA. Prevention of ischemic neurologic injury with intraoperative monitoring of selected cardiovascular and cerebrovascular procedures: Roles of electroencephalography, somatosensory evoked potentials, transcranial Doppler, and near-infrared spectroscopy. *Neurol Clin*. 2006;24:631–645.
187. Wade JG, Larson CP, Hickey RF, et al. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. *N Engl J Med*. 1970;15:823–829.
188. Bove EL, Fry WJ, Gross WS, et al. Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. *Surgery*. 1979;85:633–637.
189. Nouraei SA, Al-Rawi PG, Sigaudo-Roussel D, et al. Carotid endarterectomy impairs blood pressure homeostasis by reducing the physiologic baroreflex reserve. *J Vasc Surg*. 2005;41:631–637.
190. Vecchia LD, Barbic F, Galli A, et al. Favorable effects of carotid endarterectomy on baroreceptor sensitivity and cardiovascular neural modulation: A 4-month follow-up. *Am J Physiol Regul Integr Comp Physiol*. 2013;304:R1114–R1120.
191. Timmers HJLM, Buskens FGM, Wieling W, et al. Long-term effects of unilateral carotid endarterectomy on arterial baroreflex function. *Clin Auton Res*. 2004;14:72–79.
192. O'Connor CJ, Tuman KJ. Anesthetic considerations for carotid artery surgery. In: Kaplan JA, Lake CL, Murray MJ, eds. *Vascular Anesthesia*. 2nd ed.St. Louis: Churchill Livingstone; 2004.
193. Cafferata HT, Merchant RF, DePalma RG. Avoidance of postcarotid endarterectomy hypertension. *Ann Surg*. 1982;196:465–472.
194. Pine R, Avellone JC, Hoffman M, et al. Control of postcarotid endarterectomy hypotension with baroreceptor blockade. *Am J Surg*. 1984;147:763–765.
195. Prough DS, Scuderi PE, McWhorter JM, et al. Hemodynamic status following regional and general anesthesia for carotid endarterectomy. *J Neurosurg Anesthesiol*. 1989;1:35–40.
196. Gottlieb A, Satariano-Hayden P, Schoenwald P, et al. The effect of carotid sinus nerve blockade on hemodynamic stability after carotid endarterectomy. *J Cardiothorac Vasc Anesth*. 1997;11:67–71.
197. Constantinou J, Jayia P, Hamilton G. Best evidence for medical therapy for carotid artery stenosis. *J Vasc Surg*. 2013;58:1129–1139.
198. Krul JMJ, van Gijn J, Ackerstaff RGA, et al. Site and pathogenesis of infarcts associated with carotid endarterectomy. *Stroke*. 1989;20:324–328.
199. Steed DL, Peitzman AB, Grundy BL, et al. Causes of stroke in carotid endarterectomy. *Surgery*. 1982;92:634–641.
200. Radak D, Popovic AD, Radicevic S, et al. Immediate reoperation for perioperative stroke after 2250 carotid endarterectomies: Differences between intraoperative and early postoperative stroke. *J Vasc Surg*. 1999;30:245–251.
201. Rockman CB, Jacobowitz GR, Lamparello PJ, et al. Immediate reexploration for the perioperative neurologic event after carotid endarterectomy: Is it worthwhile? *J Vasc Surg*. 2000;32:1062–1070.
202. Riles TS, Imparato AM, Jacobowitz GR, et al. The cause of perioperative stroke after carotid endarterectomy. *J Vasc Surg*. 1994;1994:206–216.
203. Motamed C, Motamed-Kazerounian G, Merle JC, et al. Cardiac troponin I assessment and late cardiac complications after carotid stenting or endarterectomy. *J Vasc Surg*. 2005;41:769–774.
204. Rijbroek A, Boellaard R, Vermeulen EG, et al. Hemodynamic changes in ipsi- and contralateral cerebral arterial territories after carotid endarterectomy using positron emission tomography. *Surg Neurol*. 2009;71:668–676; discussion 676.
205. Abou-Chebl A, Yadav JS, Reginelli JP, et al. Intracranial haemorrhage and hyperperfusion syndrome following carotid artery stenting. *J Am Coll Cardiol*. 2004;43:1596–1601.
206. Buczek J, Karlinski M, Kobayashi A, et al. Hyperperfusion syndrome after carotid endarterectomy and carotid stenting. *Cerebrovasc Dis*. 2013;35:531–537.
207. Adhiyaman V, Alexander S. Cerebral hyperperfusion syndrome following carotid endarterectomy. *Q J Med*. 2007;100:239–244.
208. Schroeder T, Sillesen H, Sorensen O, et al. Cerebral hyperperfusion following carotid endarterectomy. *J Neurosurg*. 1987;66:824–829.
209. Schroeder T. Hemodynamic significance of internal carotid artery disease. *Acta Neurol Scand*. 1998;77:353–372.
210. Moulakakis KG, Mylonas SN, Sfyroeras GS, Andrikopoulos V. Hyperfusion syndrome after carotid revascularization. *J Vasc Surg*. 2009;49:1060–1068.
211. Bouri S, Thapar A, Shalhoub G, et al. Hypertension and post-carotid endarterectomy cerebral hyperperfusion syndrome. *Eur J Vasc Endovasc Surg*. 2011;41:229–237.
212. Shakespeare WA, Lanier WL, Perkins WJ, Pasternak JJ. Airway management in patients who develop neck hematomas after carotid endarterectomy. *Anesth Analg*. 2010;110:588–593.
213. Cunningham EJ, Bond R, Mayberg MR, et al. Risk of persistent cranial nerve injury after carotid endarterectomy. *J Neurosurg*. 2004;101:445–448.
214. Ballotta E, Da Giau G, Renon L, et al. Cranial and cervical nerve injuries after carotid endarterectomy: A prospective study. *Surgery*. 1999;125:85–91.

Awake Craniotomy, Epilepsy, Minimally Invasive and Robotic Surgery

17

L. Emory • A. Schubert

AWAKE CRANIOTOMY

Awake craniotomy refers to surgery that is performed on the brain while the patient is in a state of awareness and that allows for cooperation with functional testing of the cortex. It is usually performed when eloquent cortical tissue—tissue that is involved in motor, visual, or language function—is located in close proximity to the area to be resected. This may include resection of tumor or ictal foci in patients with epilepsy. The patient's awake state allows for the mapping of the brain near the area to be resected, which avoids morbidity related to resection of the eloquent tissue and can reduce anesthetic interference with brain mapping.

Awake craniotomy has been shown to reduce the size of the resection, surgery time, postoperative neurologic deficits, early postoperative nausea and vomiting, and hospital stay.[1] Vasopressor use and hypertension during head pinning are also decreased.[2] Hospital stays have been reported to be as short as 1 day for patients with good functional status and uncomplicated tumors.[3,4] Lower post-intensive care unit inpatient costs were found in patients undergoing glioma resection under sedation versus general endotracheal anesthesia.[5] Awake craniotomy has even been studied as a potential outpatient procedure with no reported adverse outcomes.[6] This technique has been shown to have better patient acceptance.[7] Despite the most common complaints about pain from the head holder, inadequate local anesthesia, and uncomfortable position,[8] patients report better postoperative pain scores and use less opioids in recovery.

The anesthetic technique for awake craniotomy varies. The common goal is to ensure the best possible resection by keeping patients comfortable and safe with sedation and anesthesia before and after the awake interval, and by monitoring and guiding patients through conscious mapping and testing. General anesthesia—using a laryngeal mask airway (LMA),[9] endotracheal intubation, or varying degrees of sedation—with discontinuation of anesthesia for the period of speech, memory, or motor testing, or a combination of these techniques, has been described[10,11] and found to be safe.[12]

Approach to the Awake Craniotomy

Appropriate patient selection and preparation are the most important factors in the success of anesthesia for awake craniotomy. In the selection process, the following should be considered: age and maturity; anxiety, claustrophobia, or other psychiatric disorders; a patent airway; and a history of reflux or nausea and vomiting. Literature and experience suggest that hypertension, alcohol abuse, and lack of maturity may be risk factors for sedation failure.[13] We recommend that children younger than 14 years not be considered, although the developmental status of the individual should be assessed.[14] Furthermore, a patient with a potentially difficult airway or who demonstrates that there is a likelihood that they will obstruct under sedation is a poor candidate for awake craniotomy. Because the patient's head will be in pins and positioned by the surgeon, sudden conversion to endotracheal intubation may be difficult. A plan must exist between the anesthesia and surgical teams for the management of the airway should patency be lost. Patients with a history of obstructive sleep apnea (OSA), difficult ventilation, or difficult intubation may be considered as higher risk for adverse outcomes, although current evidence does not support OSA as an independent risk factor for failure of awake craniotomy.

Preoperative consultation is essential. The anesthesiologist should clearly outline for the patient what to expect during the procedure, including the varying states of sedation and awareness, the positioning, the possible discomfort, and the testing process. A strong rapport between the patient and the anesthesiologist should be established prior to the procedure, and comfortable patient positioning, scalp block, proper anesthetic selection, and communication are paramount. The anesthesiologist must keep in mind the psychological state of the patient and attempt to alleviate anxiety and discomfort as much as possible to ensure the success of the technique and the surgery.

Positioning

Patient comfort and access during the awake period is important in a successful awake craniotomy. Lateral or semi-lateral positioning is commonly used to allow for patient comfort and to offer the anesthesia team ideal access to the patient. Adequate padding and pillows should be provided and pressure points carefully checked. The patient should confirm an acceptable level of comfort prior to sedation, as he or she will be in pins upon emergence from sedation and must remain still during the period when repositioning is not feasible. The patient must also be positioned and draped for ideal access by the anesthesia team who need to speak with the patient to test motor and sensation. Tenting the drapes upward from the patient on the side of the anesthesia team provides an area of access and may also reduce the patient's sense of claustrophobia. Fig. 17.1 shows a configuration for setup in the operating room. The patient's position is stabilized with the use of a deflatable beanbag or a backrest fixed to the operating table, and the patient is taped to the table.

Scalp Block

Performance of a reliable blockade of the innervation of the scalp is essential to the successful performance of an awake craniotomy. The technique for local scalp block for craniotomy is well-described.[15,16] Individually blocking the auriculotemporal, zygomaticotemporal, supraorbital, supratrochlear, lesser occipital, and greater occipital nerves is necessary to provide complete analgesia of the scalp. Ropivacaine and levobupivacaine can be safely used up to doses of 4.5 mg/kg[17] and 2.5 mg/kg, respectively.[18] Mepivacaine may also be used adjunctively if a faster setup is required. These blocks achieve

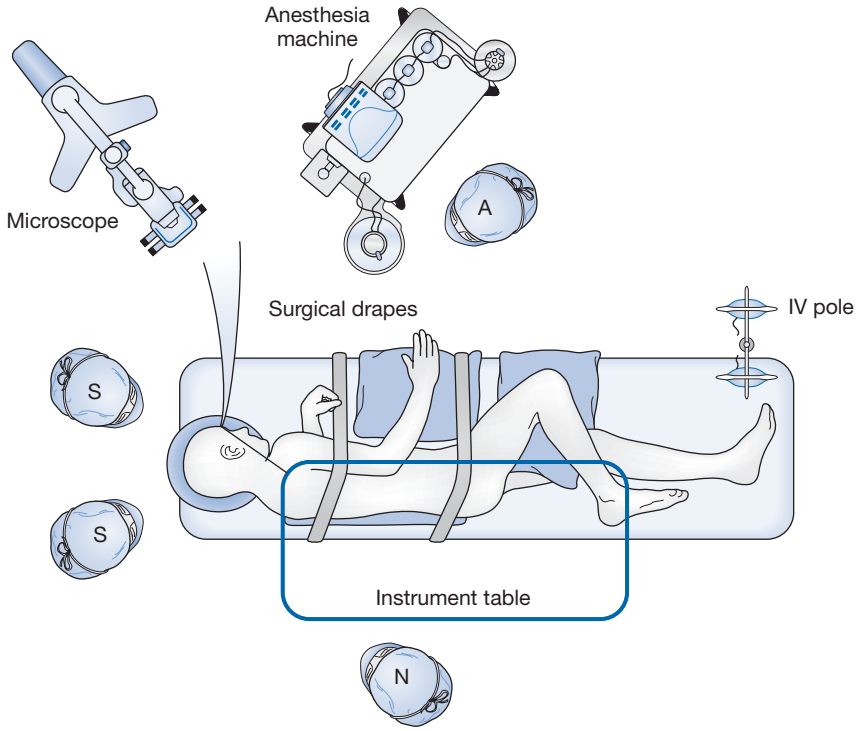


Fig. 17.1 Operating room setup for right-sided craniotomy performed for the awake patient. Note the arrangement of the surgical drapes, which ensures access to the patient's face. The pin holder is not shown. **A,** anesthesiologist; **N,** nurse; **S,** surgeon. *(From Schubert A: Epilepsy Surgery. Clinical Neuroanesthesia, 2nd ed. Cleveland, OH, Cleveland Clinic Press, 2006, p 66.)*

peak plasma concentrations approximately 15 minutes after injection. Severe bradycardia after scalp block has been reported.[19]

If general anesthesia is performed for the initial asleep period, necessary access, invasive monitors, and urinary catheters may be placed after induction. However, if sedation is selected, it should be deep enough for the patient to comfortably tolerate these invasive measures with minimal recall. Scalp block may also be performed at this time. The success of the scalp block is likely not known until the placement of head pins begins. Obvious physical response in the sedated patient or an increase in heart rate and blood pressure in the general anesthesia patient would indicate block failure. Boluses of propofol may be necessary to temporarily rescue the inadequately sedated patient.

Anesthetic Options

A number of different anesthetic techniques may be useful for awake craniotomy. Some providers may choose varying levels of sedation as tolerated by the patient. Others may choose a general anesthetic, with or without endotracheal intubation, in what is referred to as the asleep-awake-asleep technique.

One may choose to perform a general anesthetic from induction to completion of exposure and awaken the patient for neurocognitive and neurofunctional testing. If this method is chosen, it is important to remember that the patient will be emerging in head pins and bucking must be avoided to prevent patient morbidity. Conversely, one may choose sedation during the exposure period, keeping in mind that airway reflexes should be preserved.

Propofol, dexmedetomidine, and opioid infusions have been safely and successfully used for awake craniotomy. Volatile anesthetics have been used for general anesthesia during the asleep portion of the procedure. While the patient is in head pins, the provider should be aware of the danger of laryngospasm during emergence and extubation or LMA removal.

Total intravenous anesthesia (TIVA) is a viable choice for awake craniotomy.[20] Propofol-only anesthesia with spontaneously breathing patients has been described as safe. Propofol is begun with a bolus of 0.5 mg/kg and continued at a rate of 75–250 μg/kg/min.[12] Practitioners have safely and successfully used a combination of propofol or dexmedetomidine with an opioid such as remifentanil, sufentanil, or boluses of fentanyl. The rapid clearance of remifentanil makes it an appealing choice for quickly achieving the awake state. However, remifentanil may cause hypopnea in the spontaneously ventilating patient. A dose range of 0.01–0.1 μg/kg/min[21] has been described, although when used alone, we have found efficacy as high as 0.2 μg/kg/min. In Manninen and colleagues' 2006 study, propofol infusion combined with intermittent fentanyl yielded similar patient satisfaction, recall, and intraoperative complications to remifentanil, with a slightly higher rate of respiratory depression in the propofol and fentanyl group.[22] Emergence from remifentanil-propofol has been described as approximately 9 minutes.[23] Sedation with remifentanil infusion alone is performed in some centers, although no data have been published at this time. Alfentanil is known to induce epileptiform discharges in the hippocampal area and should be used with caution in patients with complex partial epilepsy.[24] For patient comfort, an opioid infusion may be continued at a low dose during testing, titrated to effective patient cooperation. Longer-acting analgesia may be necessary prior to emergence, although emergence on low-dose opioid infusion continued to recovery may be used.

The alpha-2-agonist dexmedetomidine also may be used and has been recommended, due to its lack of interference with electrophysiologic testing, sedation with minimal respiratory effects,[25,26] and anxiolytic and analgesic qualities. A loading dose of 1 μg/kg is delivered over 10–15 minutes with an infusion rate of 0.1–0.6 μg/kg/h. Doses are higher in children. Dexmedetomidine use as a lone sedating agent has been described, as well as a combined anesthetic with propofol or opioids, or both.[27] The use of remifentanil combined with dexmedetomidine has also been reported.[28] Like remifentanil, dexmedetomidine may be continued at low doses during brain mapping and functional testing if needed for patient comfort. Dexmedetomidine is known to have a significant synergistic effect when used in combination with other sedative agents.[29]

Droperidol and fentanyl were commonly used in the past, but neuroleptanalgesia has given way to faster acting and more quickly eliminated regimens.

Brain Mapping and Cognitive Testing

As patients emerge from deep sedation or anesthesia, the anesthesiologist must take responsibility for safely re-orienting the patient, providing a calming influence, and guiding him or her through the brain mapping and cognitive testing phase. The use of bispectral-index monitoring to shorten emergence has been described and may be useful.[30] The patient may be disoriented for a brief period after sedation. Again, preoperative preparation becomes essential during this phase. As the patient is guided through the process, he or she must be reassured that involuntary movements and speech patterns may occur as a result of cortical stimulation by the surgical team. The anesthesia team must be prepared to address any anxiety and discomfort that may occur. Motor, sensory, cognitive, and speech testing may be performed during this time. The patient may be asked to verbally identify objects or pictures, read passages aloud, perform specific motor tasks, or identify paresthesias or other sensations. Cortical evoked potentials and electrocorticography (ECoG) may be used to identify functional tissue and seizure foci. The results of this testing will guide the surgeon in removing pathologic tissue with minimal disruption to eloquent tissue in order to reduce patient morbidity. Surgical resection then proceeds while the patient completes verbal tasks (speech area assessment) or performs motor tasks (motor area assessment). Seizure activity is also possible during this phase, and the anesthesiologist must be prepared for prompt treatment, possible airway intervention, and conversion to general endotracheal anesthesia.

When brain mapping and functional testing are complete, the patient should be sedated once more for closure of the dura, calvarium, and scalp. This period can be very stimulating to the patient and adequate sedation can usually be achieved with remifentanil, propofol, dexmedetomidine, or a combination of these agents, as has been described.

Adverse Events and Management

Seizures, respiratory depression, nausea, vomiting, anxiety, discomfort, and agitation may occur during awake craniotomy. As is commonly the case with sedation, airway obstruction, hypercarbia, and hypoxemia are all possible, and careful preoperative assessment of the airway is vital. We have also experienced laryngospasm with LMA during the asleep portion of the asleep-awake-asleep technique. An extensive review of anesthetic complications of awake craniotomies showed an 18.4% rate of hypoxemic events for patients undergoing sedation for the procedure compared to merely 1% in patients who received endotracheal intubation. Airway or ventilation complications occurred in just 2% when patients received propofol-only sedation.[12] The rate of conversion to general anesthesia has been reported to be 2%.[10] Dexmedetomidine appears significantly better than propofol for rate of respiratory depression.[10] Dexmedetomidine has been described for rescue of a patient unable to tolerate awake brain mapping after a propofol-remifentanil sedation regimen,[31] and is now used more commonly as a primary sedative. Airway-assist maneuvers and the use of oral or nasal airways are common in patients undergoing sedation and should be expected to treat transient obstruction.

Vomiting and aspiration are possible in the sedated patient. As the airway will be unprotected using this technique, administration of prophylactic antiemetics is advisable, and rapid treatment should be provided if nausea occurs. The incidence of nausea and vomiting is 4% for mixed sedation techniques[32] and even less for the use of propofol.[12] Once symptoms occur, they can be controlled with a hydroxytryptamine-3 receptor (HT-3) antagonist, such as metoclopramide 10 mg. Nausea can also result from inadequate analgesia of dural attachments and meningeal vessels. Additional local anesthetic should be administered by the surgeon and supplemental sedation administered by anesthesia.

Sedation with spontaneous ventilation may pose the problem of brain swelling, particularly when mass-effect already exists, due to hypopnea or periods of apnea and concomitant increase in $PaCO_2$. However, spontaneous ventilation also may assist in keeping the brain relaxed due to maintenance of negative intrathoracic pressure and promotion of cerebral venous outflow. Mannitol or furosemide administration may be necessary to reduce swelling and improve the surgical field. Patient movement—with the head in pins or during craniotomy—can have morbid outcomes, including scalp and soft tissue injury, brain swelling from straining, and placing the cervical spine at risk. It is critical to anticipate possible patient movement—during times like emergence from sedation or as a result of seizure initiated during mapping or delirium—and control the movement quickly. Deepening sedation with propofol boluses may be effective, and conversion to general anesthesia must be considered if necessary. It is important to be aware that deepening sedation may result in hypopnea or apnea, and the anesthetic team must be prepared to take control of the airway.

Seizures may occur from electrical stimulation during brain mapping or from a patient's underlying condition. Vigilance is critical because the untreated seizure while in head pins could be catastrophic. Seizure activity can be treated with propofol (0.75–1.25 mg/kg) or benzodiazepines, depending on the need for subsequent electroencephalograph (EEG) recording. A 4.9% incidence of seizures was reported with cortical mapping in an unselected series of 610 awake craniotomies.[3] At the end of the procedure, benzodiazepines and phenytoin may also be used more freely.

EPILEPSY SURGERY

Epilepsy is a disease of the brain characterized by: two unprovoked seizures greater than 24 hours apart; one unprovoked seizure; and a probability of seizures similar to the general recurrence risk after two unprovoked seizures occurring over the next 10 years, or diagnosis of an epilepsy syndrome.[33] It is present in 0.5–2.2% of the general population.[34] Because 30–40% of epileptics do not respond adequately to pharmacologic intervention,[35] more than 400,000 people still have medically uncontrolled epilepsy in the United States. However, only 10–30% of patients with seizures refractory to medical management are appropriate candidates for seizure surgery, and only 1% eventually undergo the procedure.

Epilepsy is classified as partial, generalized, or psychogenic nonepileptiform seizures (PNES). Partial seizures are characterized by electrical disturbances localized to one area of one cerebral hemisphere. Simple partial seizures are not associated with a loss of consciousness, and generally last 1 minute or less. Complex partial seizures are characterized by a loss of consciousness or awareness and spread from their localized focus to other regions. Complex partial seizures may spread to become generalized. Generalized seizures have no demonstrated focal onset, although they may evolve from focal seizures, affect both hemispheres of the brain, and are characterized by a loss of consciousness. They are sub-categorized as

generalized tonic-clonic (grand mal), tonic, myoclonic, absence (petit mal), and atonic. PNES are psychogenic episodes that may be characterized by seizure-like physical manifestations but have no corresponding epileptiform activity on EEG and are considered conversion reactions.

Surgical management of epilepsy may be an option for patients with intractable epilepsy refractory to medical treatment. With successful surgical intervention, lifestyle improves, although most patients continue anticonvulsant therapy. Chin et al.[36] reported that the rate of employment improved only modestly in their group of 375 patients, from 39.5% fully employed status preoperatively to 42.8% postoperatively; however, the rate of part-time employment nearly doubled, from 6.9 to 12.4%.[36]

Anesthetic regimens have a significant effect on cortical mapping for epilepsy and may reduce or improve the effectiveness of testing and surgery. While many anesthetic agents have anticonvulsant properties, many also have varying profiles of proconvulsant or pharmacoactivating properties that can be useful in intraoperative localization of epileptogenic foci. Alternately, other agents may confound ECoG testing and lead to poor localization and less effective outcomes. Pharmacologic interactions between anticonvulsant medications and anesthetic drugs must also be taken into account. Pharmacoactivation of interictal epileptiform activities (IEAs) can be necessary in patients who do not demonstrate spontaneous interictal discharges during ECoG. The goals of the anesthetic regimen should be discussed with the neurosurgeon, neurologist, or neurophysiologist to determine if pharmacoactivation will be required. This may change during the procedure if the patient fails to generate IEAs spontaneously or under electrical stimulation. A goal-oriented anesthetic plan in concert with the neurosurgical team and knowledge of the activating properties of various anesthetic agents are essential.

Pharmacology of Anesthetic Agents

Proper sedation can be achieved through the use of a variety of anesthetic plans. In many cases, a general endotracheal anesthetic is preferred. In others, an awake craniotomy is performed for better functional testing and identification of seizure activity. Visualization of seizure activity that is similar to the patient's typical seizures can be very helpful in identifying the true epileptogenic focus. Iatrogenic activation of IEAs may be achieved with administration of proconvulsant anesthetics and awareness of their anticonvulsant activities. EEG recordings support altering the activation and inhibition of the cerebral cortex with administration of anesthetic agents. For example, during light sedation, cortical activation with higher-frequency beta activity predominates, which progresses to slow-wave activity as sedative or anesthetic depth increases.[37]

Sedative-Hypnotic Agents

As a group, sedative-hypnotic agents have the greatest variation and most confusing profile regarding effects on epileptogenic activity. Most agents can generate neuroexcitatory effects when used at low doses and neurodepressive effects when used at higher doses. Several induction agents, such as propofol and thiopental, can induce myoclonic movements not associated with EEG excitatory activity; whereas others, such as etomidate and methohexital, have been shown to generate both myoclonus and EEG-documented epileptiform activity in patients.[38,39] Motor stimulatory phenomena, such as myoclonus, opisthotonus, and tonic-clonic activity, may occur with varying frequency in both epileptic and nonepileptic patients during induction with these agents, but only a few agents actually produce cortical electrical activity suggestive of seizures.

Barbiturates and benzodiazepines have substantiated anticonvulsive properties and are recommended for treatment of refractory status epilepticus.[40]

Propofol is among the most commonly used induction and maintenance agents in general anesthesia for epilepsy surgery and awake craniotomy. Propofol has been shown to depress ECoG recordings, decrease the frequency of spike activity, and produce a minimal effect on spontaneous IEAs. Propofol decreases the frequency of epileptogenic spikes and quiets existing seizure foci, particularly in the lateral and mesial temporal areas.[41] One study demonstrated spike activation with low-dose propofol.[42] There have been reported cases of tonic-clonic seizures with propofol, and myoclonic activity not related to excitatory EEG activity may be seen. Propofol may obscure spike wave activity for up to 20 minutes after termination of infusion and should be discontinued prior to ECoG testing.

Etomidate has been shown to activate EEG seizure activity at induction doses in patients with a history of epilepsy and may also generate myoclonic activity. It has been shown to have a high activation rate and demonstrates successful spike activation during intracranial electrode testing. At higher doses, etomidate may produce burst suppression and break status epilepticus.[43,44] To date, its use in intraoperative ECoG has not been studied.[45]

Methohexital has been shown to activate EEG seizure activity in patients with epilepsy and may assist with activation of ictal foci during ECoG. It is associated with a high percentage of spike activation (50–85%),[46] although with questionable specificity, showing up to 43% inappropriate activation in one study.[47]

Dexmedetomidine may be a favorable agent for awake craniotomy due to its effects of sedation, analgesia, and anxiolysis; the absence of motor stimulatory effects; and the lack of respiratory depression. Dexmedetomidine does not affect background ECoG activity or IEAs and may be the best alternative for awake craniotomy.[28,48,27]

Ketamine may induce nonspecific activation of IEAs, especially in the limbic structure, and can activate seizure activity in patients with epilepsy.[49,50] It has been used to assist with activation of ictal foci during intraoperative ECoG.[51–54] Ketamine appears to have a dose-dependent threshold for seizure generation, with most reported cases of clinical seizure activity occurring when doses larger than 4 mg/kg are administered.[55,56]

Opioids

Synthetic opioids such as alfentanil, fentanyl, sufentanil, and remifentanil are commonly used in neurosurgical anesthesia because of their short duration of action and their ability to minimize cortical effects through continuous infusion. High doses of synthetic opioids have proepileptic properties. Standard maintenance doses of these agents do not significantly increase the risk of perioperative seizures or effects on ECoG. However, bolus doses of synthetic opioids, such as alfentanil and remifentanil, increase spike wave activity in the interictal foci of patients undergoing intraoperative ECoG.[57,58] Due to their high effectiveness and specificity, bolus doses of these agents are used to facilitate location of the ictal cortex through stimulation of spike wave phenomenon with concomitant depression of background EEG. Alfentanil has been shown to be the most effective and specific synthetic opioid for pharmacoactivation.[59] Fentanyl has been associated with epileptiform electrical activity in subcortical nonictal cortical

tissue and has been shown to be associated with contralateral activity.[60] The clinical history of the use of synthetic opioids in large numbers of epileptic patients undergoing ablative procedures suggests that synthetic opioids can be used safely in this patient population without a significant increase in the risk of perioperative seizures. Morphine and hydromorphone used at clinically relevant doses do not appear to have significant proconvulsant activity.[61]

Volatile Inhalational Agents and Nitrous Oxide

The epileptogenic potential of isoflurane, desflurane, and halothane appears low, and there have been no reported seizures when used in isolation.[62] However, there are rare reports of myoclonic activity with a normal EEG. Convulsions with spike and wave activity on EEG have been reported with combinations of isoflurane and nitrous oxide (N_2O).[63,64] Although N_2O has been associated with seizure generation when used to supplement other agents, it appears to be fairly inert in both the development and the treatment of seizure activity in humans.[61] Both N_2O and isoflurane have been used for many years at multiple institutions with a good safety record in epileptic patients.

Enflurane, used with or without N_2O, has been the most common offender, with reports of intraoperative and postoperative myoclonus and EEG-demonstrated epileptiform activity in both epileptic and nonepileptic patient populations.[16,46,50,51,61] The incidence of EEG spike wave production with enflurane appears to be dose dependent. The end-tidal concentration that triggers maximum epileptiform activity is reduced during hypocapnia. Enflurane has fallen out of favor as new inhalational agents have become available, and it is now rarely used clinically in the United States. Enflurane should be avoided in patients with epilepsy unless the desired effect is to trigger seizures during ECoG.

Sevoflurane (not desflurane)[62] has been reported to generate convulsions as well as electrical spike waves in both epileptic and nonepileptic patients.[65,66] The frequency of spike wave activity with sevoflurane increases with dose escalation and hyperventilation (Fig. 17.2).[62,67] Hisada and colleagues[68] reported that widespread neuroexcitatory activity associated with sevoflurane did not facilitate seizure focus localization in patients with temporal lobe epilepsy.[68] Hyperventilation decreases the prediction specificity of leads with ictal spikes and should be employed cautiously during ECoG.[69]

Muscle Relaxants

Long-term anticonvulsant therapy with phenytoin, carbamazepine, or both, is associated with resistance to the effect of nondepolarizing neuromuscular blockers, including pancuronium, vecuronium,[70–72] metocurine, cisatracurium, and rocuronium, but less so with atracurium.[73,74] The etiology of this phenomenon is likely both pharmacodynamic and pharmacokinetic.[75,76]

Anesthetic Management

Goals

Preoperative assessment of the patient's neurologic condition, as well as comorbidities, is essential. Careful attention should be paid to anti-seizure medications. Intraoperative goals include maintenance of appropriate cerebral blood flood and perfusion, control of brain bulk, and rapid emergence from anesthesia for postoperative neurologic evaluation. In the event that seizure induction is desired, the goals of the anesthesiologist include selection of effective inducing agents and avoidance of patient injury. Careful postoperative monitoring of the patient's neurologic status is required, and postoperative seizure control may be necessary.

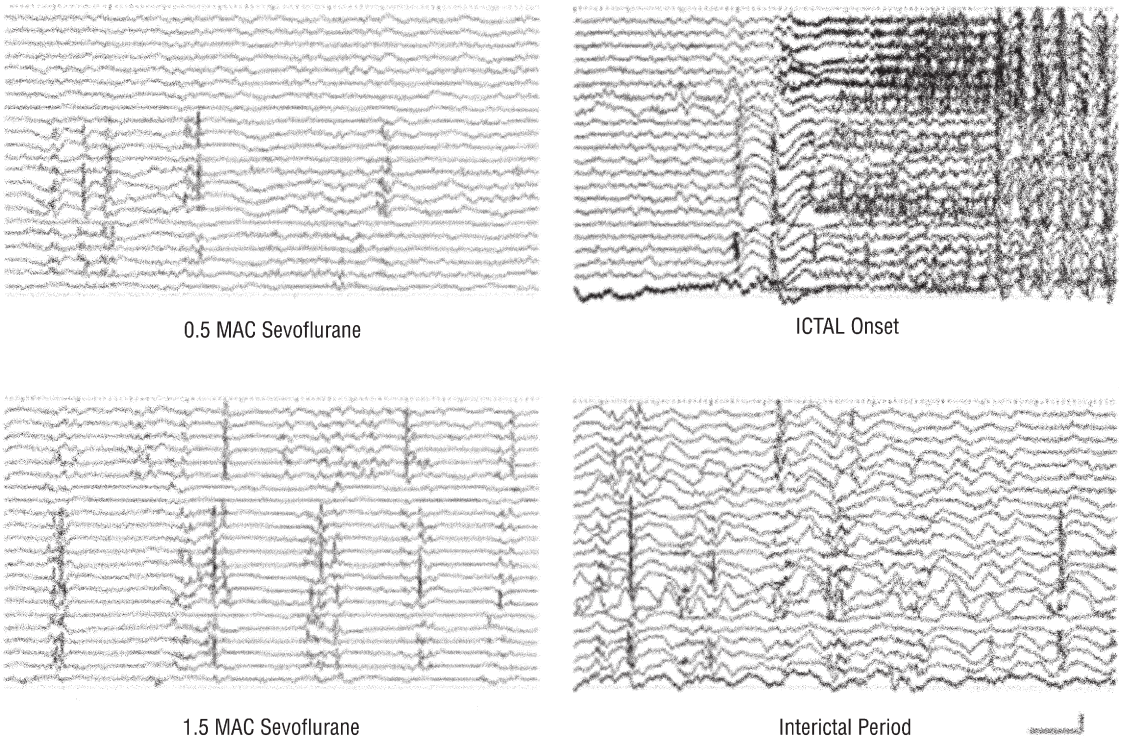


Fig. 17.2 Effect of sevoflurane on electroencephalogram (EEG). At 0.5 minimum alveolar concentration (MAC) sevoflurane, EEG is comparable to preictal awake EEG. At 1.5 MAC sevoflurane, EEG is similar to interictal periods before anesthesia. *(From Kurita N, Kawaguchi M, Hoshida T, et al: The effects of sevoflurane and hyperventilation on electrocorticogram spike activity in patients with refractory epilepsy. Anesth Analg 2005;101:517–523.)*

Preoperative Evaluation

Neurologic History

The patient's seizure history should be thoroughly understood prior to surgery. It may be difficult to discriminate seizure activity in the perioperative period from prolonged emergence or emergence delirium. Knowledge of the patient's known seizure patterns may help to determine postoperative intervention. Prolonged emergence, characteristic motor activity, and poor responsiveness should raise suspicion for perioperative seizure activity.

The anesthesiologist should be vigilant for a number of medical conditions associated with epilepsy. Neurofibromatosis, also known as Von Recklinghausen's disease, is an inherited condition that leads to tumor growth on nerve tissue. Variable expressivity means that the severity of this condition is wide ranging, from benign, asymptomatic tumors, to acoustic neuromas, significant intracranial lesions, and peripheral lesions. These tumors may involve cranial nerves or respiratory tract tumors leading to airway and respiratory compromise, including chronic aspiration, pulmonary fibrosing alveolitis, pulmonary hypertension, and cor pulmonale. Tuberous sclerosis is a disease causing widespread benign tumor growth in the brain, heart, lungs, kidneys, skin, and eyes. While it is less common than neurofibromatosis, tumors may lead to blockage of intraventricular cerebrospinal fluid (CSF) flow with hydrocephalus, cardiac dysrhythmias, intracardiac tumors, cerebral embolization, renal dysfunction, and arterial aneurysms. Intracardiac tumors, known as rhabdomyomas, are found in approximately 32.8–48% of tuberous sclerosis patients on echocardiography.[77,78] These patients should undergo a full preoperative cardiac evaluation. Down syndrome, Angelman syndrome, and Sturge–Weber syndrome are also associated with epileptiform activity. Open craniotomy is considered a moderate-risk procedure (indicating a less than 5% risk of cardiac events) with regard to its taxing effects on the cardiovascular system of the patient.[79] Due to possible significant pneumocephalus up to 1 month after craniotomy,[80] N_2O should be avoided in patients who have undergone recent intracranial electrode placement.

Medication History

Medications for patients with epilepsy may present significant anesthetic considerations. Certain anticonvulsants significantly elevate dose requirements for both nondepolarizing muscle blockers[75] and opioids.[81] Both phenytoin and carbamazepine are associated with resistance to nondepolarizing neuromuscular blockade and elevated liver function parameters. The direct relationship between the number of anticonvulsants a patient receives and the dose of fentanyl required for intraoperative anesthetic maintenance[81] further suggests that anticonvulsant therapy predisposes to opioid resistance. Elevated liver enzymes seen on liver function tests are commonly associated with anticonvulsant medications.[82] Sedation and lethargy are common side effects of many antiepileptic agents, including newer agents such as lamotrigine and oxcarbazepine, and may potentiate the central nervous system-depressant effects of anesthetics. Chronic topiramate intake has been associated with intraoperative metabolic acidosis.[83] Topiramate is associated with an asymptomatic non-anion-gap acidosis.[84] Carbamazepine may cause a severe depression of the hematopoietic system and cardiac toxicity in rare cases. This drug's metabolism is materially slowed by erythromycin and cimetidine, drugs that may be administered perioperatively. Likewise, a ketogenic diet, sometimes used as an adjunct anticonvulsant therapy, predisposes patients to metabolic acidosis. Valproic acid therapy results in dose-related thrombocytopenia and platelet dysfunction.[85] However, additional bleeding risk during surgery is likely to be low in a patient taking valproic acid.[86]

Patient Preparation

Regardless of the anesthetic approach selected, intraoperative awareness during ECoG is a possibility, due to reduced dosing of certain agents or the use of awake techniques. The patient should be reassured that this experience is usually described as a painless awareness. Careful explanation and reassurance to the patient and family of this and other risks, such as perioperative seizure, nausea, vomiting, and airway compromise, is essential. Neuropsychological impairment is commonly associated with epilepsy and psychiatric disorders, and impaired cognition is increased in this population.[87] The anesthesiologist must be aware of these issues when selecting and preparing a patient for an awake technique.

Diagnostic Surgical Procedures for Intractable Epilepsy

Subdural grid electrodes may be placed for identification of epileptogenic foci in preparation for resection. A craniotomy is performed and the grid electrodes are placed under general anesthesia. Usual anesthetic concerns for craniotomy should be observed. Hyperventilation to relax the brain during exposure may be efficacious, but should be considered carefully against the risk of precipitating seizure activity in the epileptic patient. Hyperventilation may be less effective in patients with complex partial seizures, who may have lower CO_2 reactivity of cerebral blood flow than normal patients.[88] Arterial line placement for blood gases and accurate blood pressure monitoring as well as adequate IV access are indicated. Since intraoperative testing is not performed, anesthetic techniques may be used without regard to their effect on EEG. As always, rapid emergence from anesthesia for neurologic assessment is preferred.

Placement of epidural ("peg") electrodes may be used to include recording from deeper structures. It requires multiple burr holes and can be a lengthy procedure, depending on the number of electrodes to be placed. "Depth" electrodes for exploring subcortical regions of the brain require stereotactic placement. The procedure usually is uneventful and not associated with significant bleeding. A general anesthetic is most frequently used. Unless further monitoring is indicated for a medical comorbidity, only routine noninvasive monitoring is employed.

Resection of Epileptogenic Brain Regions under General Anesthesia

Anesthetic planning for epileptogenic brain resection procedures depends greatly on the need for intraoperative brain mapping for seizure foci localization. In some cases, resection of epileptogenic foci is performed without brain mapping under general anesthesia. In such cases, the anesthetic goals are much like those of most open craniotomy procedures. If EEG is not planned, benzodiazepines may be given preoperatively for patient comfort. Monitoring should include direct arterial blood pressure monitoring and IV access should be adequate to replace rapid blood loss from dural sinuses. Brain relaxation is desirable to facilitate surgical exposure and resection. Maintenance of adequate cerebral perfusion without brain engorgement is an essential feature. As always, immobility is critical to the safety of the patient, as is adequate anesthesia to avoid patient awareness and pain. The anesthesiologist should always be prepared to control intraoperative seizures. Neurological evaluation in the immediate postoperative

period is highly desirable. Therefore, the plan should consider anesthetic management that will allow for rapid emergence. This may include the use of the ultra-short-acting narcotic remifentanil, which allows for rapid emergence and early neurologic examination when compared to other opioids.[89–92] However, addition of a longer acting opioid in the immediate postoperative period will be required. TIVA with propofol and remifentanil may be considered. Propofol's property of better brain relaxation than isoflurane or sevoflurane at greater than half-monitored anesthesia care (MAC) in patients with mass lesions[93] suggests its efficacy in craniotomies. However, these benefits may be less clinically significant when lower MAC doses of such volatile agents are used.[94] Prospective studies have not been sufficiently powered to allow determination of the impact of anesthetic technique on neurologic and functional outcome after craniotomy as of this time. Antihistamines can activate seizure foci in patients with epilepsy and should be avoided as premedicants.

By contrast, when intraoperative brain mapping is anticipated, additional anesthetic goals and planning need to be considered. As described above, many anesthetic agents may promote or suppress epileptiform activity. The anesthesiologist must take care that medications administered to the patient will not interfere with intraoperative monitoring and the mapping of ictal foci. Likewise, it may be desirable in some instances to administer agents that will promote epileptiform discharges and improve mapping.

Barbiturate and benzodiazepine premedication should be avoided because it may elevate the seizure threshold, making ECoG recording of epileptogenic activity more difficult. An intubation dose of short-acting barbiturate during anesthesia induction is not contraindicated, but barbiturates should be avoided later in the procedure, as should intravenous lidocaine. Despite an isolated report of N_2O-related diminution of epileptic foci during intraoperative ECoG,[88] N_2O can be used for these procedures. Ebrahim and colleagues[95] recommended that propofol administration be stopped 20–30 minutes prior to ECoG, because it elicits high-frequency beta EEG activity (Fig. 17.3) for as long as 30 minutes after discontinuation, although other investigators have reported that this type of EEG activity did not prevent ECoG interpretation.[96] The use of low concentrations of isoflurane or desflurane is permissible when ECoG recording is planned, provided that these agents can be eliminated well before the start of corticography. Isoflurane may decrease the frequency and spatial distribution of epileptogenic spikes, although it is unclear whether this effect persists at low concentrations.[97] Low-dose sevoflurane would be preferred, given its mild proconvulsant properties and short duration of action. When no potent inhaled anesthetics are in use, scopolamine, droperidol, and increased opioid dosing can be substituted to prevent intraoperative recall with virtually no effect on the EEG. Mild-to-moderate hypocapnia ($PaCO_2$ 30–35 mmHg), however, is often necessary to assist in brain volume control and brain relaxation. If hyperventilation must be initiated during sevoflurane anesthesia, the anesthesiologist should be aware that the specificity of ictal lead prediction may diminish.[69]

If cortical motor area stimulation is necessary for the surgeon to accomplish safe resection, particular attention must be paid to the management and dosage of neuromuscular blocking agents. As a general rule, neuromuscular blockade should be minimal to allow motor stimulation. If moderate residual neuromuscular block persists, a small dose of anticholinesterase can be administered to achieve its complete reversal.

Cortical stimulation for localization as well as light anesthesia and brain manipulation may lead to intraoperative seizures. Treatment of seizure activity during ongoing intraoperative ECoG, therefore, requires the use of short-acting anticonvulsants (such as methohexital) as one weighs the therapeutic goals of gross seizure control against the potential for interference with critical electrocortical monitoring. An alternative and highly effective means of suppressing seizures is irrigation of the cortical surface with cold saline.

When intraoperative EEG recordings fail to reveal seizure spikes, and in consultation with the surgeon and the electroencephalographer, the anesthesiologist administers anesthetics known to promote epileptiform discharges. These include methohexital (25–50 mg),[46,51] alfentanil (20 µg/kg),[24,98] and etomidate (0.2 mg/kg),[50] all of which may be administered to help activate dormant foci. Alfentanil is the most effective of these agents, provoking abnormal EEG spike activity in 83% of patients, compared with 50% for methohexital.[24] However, controversy exists over the correlation of pharmacologically elicited seizure spikes with the patients' native epileptogenic foci.[47] Severe bradycardia has been reported during amygdalahippocampectomy that is not seen during routine anterior

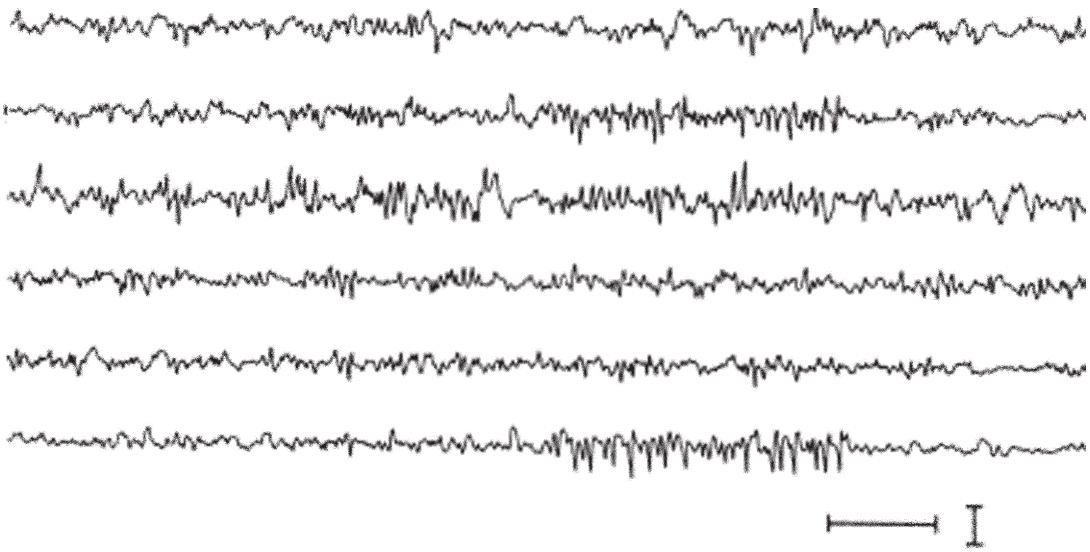


Fig. 17.3 β-Electroencelographic activation 10 minutes after propofol injection (right temporal and central convexity). *(From Ebrahim ZY, Schubert A, Van Ness P, et al: The effect of propofol on the electroencephalogram of patients with epilepsy. Anesth Analg 1994;78:275–279.)*

temporal lobe resection. This problem is thought to be the result of surgical limbic system stimulation resulting in enhanced neural vagal activity.[99,100]

Cerebral Hemispherectomy

On occasion, the seizure foci are so diffuse as to require resection of substantial portions of an entire cerebral hemisphere. Frequently, this procedure is performed in children and can be associated with significant morbidity and mortality related to massive blood loss, electrolyte and metabolic disturbances, coagulopathy, cerebral hemorrhage, and seizures. Hemispherectomy requires a very large craniectomy, which increases the chance of bleeding and tearing of dural sinuses. Air embolism has also been reported and may lead to serious morbidity. Kofke and associates[101] compared three different surgical techniques (anatomical, functional, and lateral) for hemispherectomy. Lateral hemispherectomy was associated with the lowest intraoperative blood loss, the shortest intensive care stay, and the lowest complication rate. Functional hemispherectomy had the highest rate of reoperation, whereas patients undergoing anatomical hemispherectomy had the longest hospital stays, greatest requirement for CSF diversion, and highest postoperative fever. Patients with cortical dysplasia had the largest intraoperative blood loss.[101]

Continuous monitoring of blood pressure by arterial catheter is required, as is central venous access and monitoring of cardiac filling pressure. In addition, pressor and inotropic infusions should be readily available to combat low cardiac output states.[84] Brian et al.[102] report a series of 10 patients, aged 3 months to 12 years, whose intraoperative blood replacement amounted to 1.5 blood volumes on average. In seven patients, a coagulopathy developed intraoperatively and required administration of platelets, fresh frozen plasma, or both. Progressive hypokalemia requiring replacement occurred in four patients. Hypothermia and metabolic acidosis was observed in five patients. Urine output was a poor indicator of volume status because of frequent massive glycosuria. Zuckerberg and colleagues[103] report several children younger than 5 years in whom severe decreases in cardiac index, bradycardia, increased systemic vascular resistance, and an alveolar-to-arterial gradient suggestive of neurogenic pulmonary edema developed after hemispherectomy with extensive subcortical resection. Removal of the endotracheal tube at the conclusion of procedures with large-volume resuscitation and with a high potential for postoperative complications would, therefore, seem unwise. Postoperative hemodynamic instability is common, and the airway may be compromised by seizure activity. Early postoperative recovery is best accomplished in an intensive care environment. As has been reported in adults,[104] children undergoing major brain resection become hypercoagulable as early as during dural closure.[105] Although the clinical significance of this finding is debated, thrombotic complications should be anticipated.

Vagal Nerve Stimulator Placement

Vagal nerve stimulation is a nonpharmacological intervention for patients with refractory epilepsy. A device based on cardiac pacemakers, the vagal nerve stimulator (VNS) emits electrical pulses from a generator, through an implanted wire, to an electrode wrapped around the left vagus nerve to modulate cerebral neuronal excitativity.[106] It has been demonstrated to reduce seizure frequency. Proposed mechanisms of action include activation of the limbic system, locus ceruleus, and amygdala.[107]

The VNS is placed on the left side to avoid the vagal fibers that affect the sinoatrial node associated with the right vagus nerve and to reduce the likelihood of clinically significant bradycardia. The patient is positioned supine with the head turned to the right. The left vagus nerve is exposed, taking care not to injure the left carotid and jugular that flank the nerve within the carotid sheath. The generator pocket is created above the left pectoralis muscle. A tunnel is created, and the connecting wire from the generator is advanced through the tunnel to the nerve. The electrode array is attached to the nerve. The generator is connected, and the unit is tested before it is sewn into the pocket.

VNS placement is usually performed under general endotracheal anesthesia. Standard American Society of Anesthesiologists (ASA) induction monitors are used. Additional monitoring should be based on the patient's comorbid status. Perioperative complications may include seizures; bradycardia; vocal cord paralysis or hoarseness from recurrent and superior laryngeal nerve injury or activation; and hematoma. Unilateral vocal cord paralysis has been reported as well, as has a predisposition to chronic pulmonary aspiration.[108] Complete atrioventricular block and ventricular asystole have also been reported.[109] If cardiac dysrhythmias occur, stimulation of the vagal nerve should be stopped immediately and additional rescue measures may be necessary.

Anesthetic management with regard to the patient's seizure disorder is the same as has been described for other procedures under general anesthesia without mapping. It is recommended that patients take their seizure medications as scheduled prior to the procedure, and the anesthesiologist should be aware of interactions and effects with regard to anesthetic agents. Management of intraoperative and postoperative seizures may be necessary.

Emergence from Anesthesia and Postoperative Management

As with most intracranial procedures, rapid emergence from anesthesia is helpful for postoperative neurologic assessment. However, patients with seizure disorders and a long history of anticonvulsant use may experience lethargy and slower emergence from anesthesia. Intraoperative loading of phenytoin for treatment of seizures may increase the risk of delayed emergence from general anesthesia. Coughing and bucking on emergence are undesirable as they may increase the risk of intracranial bleeding and CSF leak. Hypertension should be avoided. If short-acting narcotic agents were used, postoperative pain control with longer acting agents may be necessary. The anesthesiologist should remain vigilant for changes in the patient's mental status in the recovery phase that may indicate seizure activity, bleeding, or hematoma formation. Minor postoperative complications occur in 5.1–10.9% of patients undergoing surgical procedures for epilepsy.[110] CSF leak was the most common minor complication. Neurologic complications involving speech, visual, motor, and memory deficits may occur. Cerebral edema may occur in patients with temporary subdural grid electrode implants. Nausea and vomiting occur in 38% of intracranial neurosurgical cases.[111] Prophylactic administration of antinauseants is effective[112] and advisable.

If patients have tapered or discontinued anticonvulsant medications prior to surgery, the anesthesiologist must be especially vigilant for postoperative seizures. Benzodiazepines and propofol may be administered to control seizure activity, and the airway may need to be secured. Administration of anticonvulsants such as phenytoin also may be necessary and is begun at 50 mg/min to a total dose of 20 mg/kg, assuming the patient has not previously been treated with phenytoin.

MINIMALLY INVASIVE CRANIAL NEUROSURGERY

Background and Anesthetic Goals

The evolution of minimally invasive neurosurgery (MIN) has led to improved patient safety, decreased morbidity, decreased intraoperative blood loss, and shorter hospital stays compared to open procedures for certain conditions. Improvements in fiberoptic technology and digital imaging have allowed greater access to surgical sites with less disruption of nontarget tissue. However, MIN comes with its own set of considerations and concerns that must be anticipated by the anesthesiologist. In step with technological advances in imaging, computing, and optics, the field of MIN has evolved rapidly with regard to indications and applications. The potential benefit of MIN results from enhanced patient safety, shorter hospital stay, reduced invasiveness, and lower postoperative morbidity compared to open surgical procedures. Table 17.1 describes the most common indications for cranial disease. General goals for anesthetic management are to (1) keep the patient immobile; (2) ensure safe, rapid emergence from anesthesia for prompt neurologic assessment; (3) minimize postoperative complications; (4) facilitate intraoperative neurophysiologic monitoring techniques; and (5) collaborate in the management of intracranial pressure (ICP).

Whether the procedure requires general anesthesia or MAC, preoperative evaluation should be as thorough and comprehensive as for other surgical procedures. Immobility is crucial to the success of minimally invasive procedures. The choice of neuromuscular blocking drugs and the methods for monitoring their effects are critically important, because immobilization must be complete yet also rapidly reversible. Head fixation is required for some procedures, and movement during use of head pins must be scrupulously avoided. Procedures are of variable duration, depending on the neuropathology being treated. It is generally more difficult for the anesthesiologist to keep track of surgical progress in MIN procedures than during conventional craniotomy. The anesthesia team must maintain a dialogue with surgical team members about the progress of the procedure while also closely observing the surgical video screens, the surgical field, and neurologic and anesthetic monitoring systems.

Table 17.1 Indications for Minimally Invasive Surgery on the Central Nervous System*

Diagnosis	Intervention
Hydrocephalus	Third ventriculostomy for aqueductal stenosis,[113] fourth ventricular outlet obstruction,[114] or pineal neoplasm[115] Septostomy[116] Endoscopic ventriculoperitoneal shunts[117,118]
Colloid cysts	Endoscopic removal[119]
Arachnoid cysts	Fenestration[120]
Hematoma	Endoscopic drainage for subdural,[121] intracerebral[122]
Brain abscess	Endoscopic drainage[123] Image-guided stereotactic drainage[124]
Pituitary tumor	Endoscopic transnasal hypophysectomy[125]
Periventricular tumor	Biopsy[126]
Cranial synostosis	Endoscopic strip craniectomy[127]
Cerebral aneurysm	Endoscope-assisted microsurgery[128]
Acoustic neuroma	Endoscope-assisted microsurgery[129]
Arteriovenous malformation	Endoscope-assisted surgery[130,131]
Parkinson's disease,[132] behavioral disorders,[133,134] essential tremor[135]	Deep brain stimulation (uses stereotaxis)
Spinal disease (syringomyelia, palmar hyperhidrosis, disk herniation, spine deformities, instability, tumors)	Syringostomy[136] Transthoracic endoscopic sympathectomy[137] Arthroscopic microdiskectomy[138] Lumbar diskectomy[139] Video-assisted thoracoscopic surgery[140,141] Kyphoplasty[142] Spinal fusion[143] Tumor resection[144–146] Spine trauma[147]

*Superscript numbers refer to references in this chapter.

Neuroendoscopy

Neuroendoscopic surgical procedures may be indicated for the treatment of hydrocephalus and intraventricular or periventricular pathologies, including tumors, hemorrhage, hematomas, and cysts. Other uses include craniosynostosis, trigeminal nerve procedures, and CSF leaks. Visualization of the surgical site is achieved with only burr-hole access instead of open craniotomy. The endoscope is passed through the burr hole and the frontal cortex to reach the ventricle, as shown in Fig. 17.4. However, the use of saline or lactated Ringer solution and the direct and indirect pressure of irrigation present their own challenges. Neuroendoscopy is most commonly used for treatment of noncommunicating hydrocephalus in the form of endoscopic third ventriculostomy (ETV). During ETV, the floor of the third ventricle is fenestrated to create flow between the ventricle and the subarachnoid space (see Fig. 17.4). The surgical risk of ETV is approximately 5% for significant morbidity,[148] with an overall success rate of 60–90%.[149,150] Intraoperative mortality is reported at 0–1% for neuroendoscopy in general. However, the incidence of intraoperative and postoperative complications ranges widely from 5% to 30%.[151–153]

Preoperative Issues

It is common to see patients presenting with signs of increased intracranial pressure for neuroendoscopic procedures.

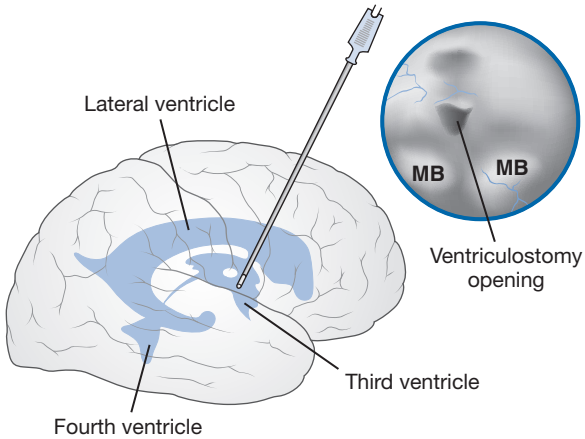


Fig. 17.4 Endoscopic third ventriculostomy and endoscopic view of the floor of the third ventricle. MB, mammillary body.

Depressed mental status, confusion, headache, nausea, and vomiting are all common in patients with hydrocephalus. Nausea and vomiting present obvious aspiration concerns, as well as regarding the possibility of metabolic derangements. Preoperative investigation should include the taking of a history and a physical examination focusing on signs and symptoms of increased intracranial pressure or other neurologic sequelae and chemistry for electrolyte abnormalities. Preoperative sedation should be carefully considered, as patients may already have an altered or depressed mental status. Ventricular shunt revision is commonly performed to relieve hydrocephalus in patients with prior shunt placements. If central venous access is planned, knowledge of the location of these shunts and tubing is essential to avoid puncture during central line placement.

Intraoperative Concerns

Despite the minimally invasive nature of neuroendoscopy, general anesthesia remains strongly advocated to ensure immobility, although local anesthetic with sedation has been described.[154] After induction, the patient may be positioned in neurosurgical head pins or a "horseshoe" headrest. A common operating room configuration is shown in Fig. 17.5. Invasive arterial pressure monitoring is strongly advised due to possible perturbations of hemodynamics during neuroendoscopy and potential rupture of the basilar or perforating artery.[155–157] Delayed emergence has been reported to occur in up to 15% of patients undergoing neuroendoscopy.[152]

The provider must be aware of the possibility of expansion pneumocephalus with the use of N_2O and avoid its use unless absolutely necessary. Burr hole incision sites are small and are often injected with local anesthetic by the surgeon so postoperative pain is not a significant problem.

Despite the minimal brain penetration required with the use of an endoscope, a number of potentially serious complications are presented. The pressure generated by the continuous irrigation system can create significant intraoperative events owing to intracranial circulatory insufficiency.[158] Mean arterial pressure should be carefully monitored to ensure adequate cerebral perfusion pressure. Measurement of intracranial pressure through the endoscope or other methods is recommended as it has been shown to correlate with ICP and cerebral perfusion pressure.[152,158] Hemodynamic effects of neuroendoscopy may range from mild, transient, dysrhythmias and hypotension to cardiac arrest. Cardiovascular instability, bradyarrhythmias, and ventricular irritability are most commonly reported, occurring in 28–32% of patients,[152,153] with bradyarrhythmias occurring in as many as 41%.[159] Significant increases in intracranial pressure and direct stimulation or damage to the hypothalamus by the irrigating jet may explain these phenomena. These events usually improve with the release of the increased intracranial pressure or temporary stoppage of irrigation and drainage of the irrigant. However, severe bradycardia leading to cardiac arrest requiring cardiopulmonary resuscitation has also been reported.[160,161] Stimulation of the hypothalamus posteriorly causes an increase in heart

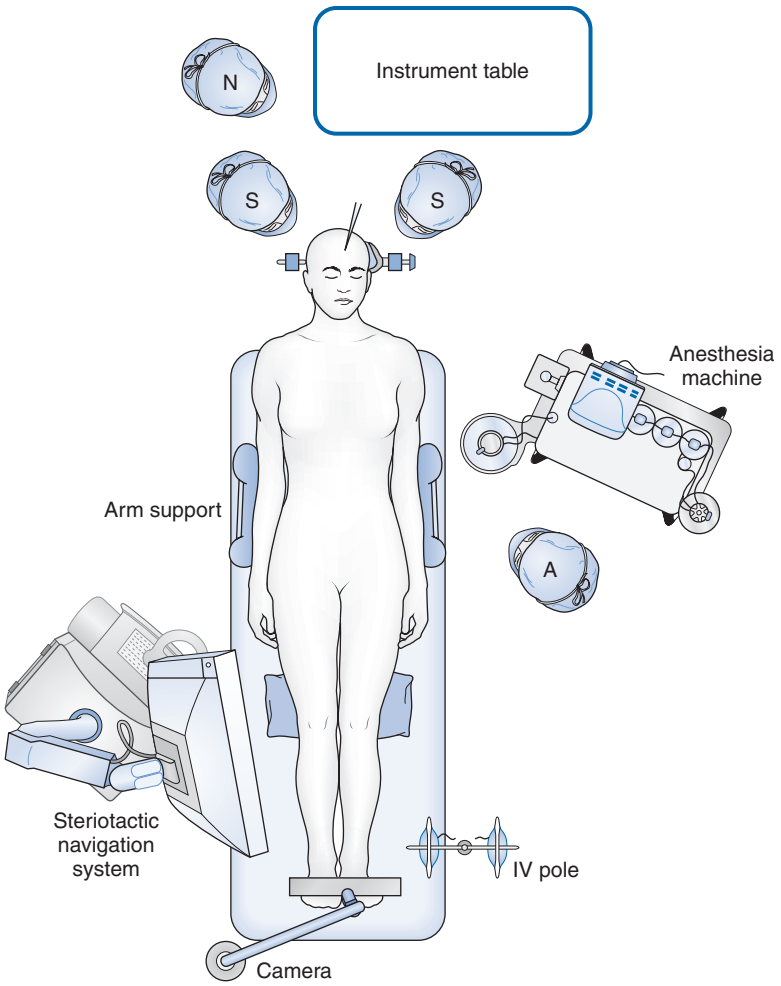


Fig. 17.5 Operating room setup for functional neurosurgery procedures. **A,** Anesthesiologist; **N,** nurse; **S,** surgeon.

rate and blood pressure as opposed to stimulation in the preoptic area, which decreases heart rate and blood pressure. Posterior hypothalamic stimulation and traction, as well as significant increases in ICP, may be the cause of bradycardia during ETV.[162] Hypothalamic injury can occur and may lead to syndrome of inappropriate antidiuretic hormone secretion (SIADH) or diabetes insipidus.

The type and volume of irrigating solution can have significant effects on CSF composition. Warmed lactated Ringer solution has been most commonly used, although it has been shown to result in hyperkalemia.[162] Warmed normal saline irrigation has been advocated,[163] but may cause CSF acidosis, with a pH reduction greater than 0.2, at volumes larger than 500 mL.[164] Hypothermia has been described in small children due to the exchange of CSF and irrigating fluid as well as surface temperature loss due to wet drapes from drained irrigation.[153] Intraoperative bleeding may occur and obfuscate the operative field, and basilar and perforating artery injuries have resulted in intraoperative death.[151,165] The anesthesiologist should always be prepared for conversion to open craniotomy. In two series, venous air embolism occurred in 0.35–4% of patients. None of the earlier reported episodes of venous air embolism in the minimally invasive surgery cases resulted in hemodynamic compromise.[157,166] Pneumocephalus and transient herniation syndromes due to CSF drainage and irrigation have also been reported.[148] A preexisting patent ventriculoatrial shunt could theoretically predispose to venous air embolism if pneumocephalus were to develop after endoscopy.

Postoperative Concerns

Patients undergoing neuroendoscopic procedures should be monitored closely in the postoperative period for complications associated with increased intracranial pressure, hypothalamic injury, and metabolic derangements. Delayed emergence is commonly seen. The most common postoperative complication is transient neurologic deficit, which occurs in 8–38% of patients.[151,152] Hyperkalemia,[162] confusion, transient pupillary dysfunction, transient hemiplegia, and memory loss[151,152,167] are also common complications. High pressure levels inside the endoscope are reportedly associated with delayed arousal and a higher rate of postoperative complications.[152] Careful control of irrigating pressure may reduce postoperative risk and avoid delayed emergence. Respiratory arrest has been reported in infants during the first hours after neuroendoscopy, necessitating the use of apnea monitors.[168] Postoperative monitoring of serum electrolyte levels is warranted because diabetes insipidus and hypothalamic dysfunction have been reported in multiple series of patients undergoing endoscopic surgery.[151,167,169] Late infectious complications, such as meningitis and ventriculitis, have significantly contributed to morbidity, so patients should be monitored for signs of central nervous system infection.[151,153]

Endoscopic Transsphenoidal Hypophysectomy

Anesthetic and surgical considerations for hypophysectomy are discussed in Chapter 28.

Endoscopic Strip Craniectomy

The development of endoscopic surgery has advanced markedly, especially for the treatment of craniosynostosis in infants. The concept of using minimally invasive surgery to remold the skull is not new, and dates back to the early part of the twentieth century, when neurosurgeons performed strip craniectomies to remove abnormal, premature suture fusions. Today, the endoscopic cranial vault remodeling technique involves more than a simple strip craniectomy through a small endoscopic port. It is a wide sutural excision combined with lateral osteotomies and osteoectomies that allow for normalization of the cranial skeleton.

Endoscopic strip craniectomy is a minimally invasive method of remolding the cranial vault in children with craniosynostosis, a premature fusion of one or more cranial sutures. It is most commonly used to treat sagittal synostosis and performed on children under 6 months of age, although other suture fusions may also be treated. The stenotic suture is excised from within the cranial vault under endoscopic visualization, parietal "barrel stave" osteotomies are created, and incisions are closed. Postoperatively, an orthotic molding helmet is used to promote normal development of the calvarium.

Endoscopic cranial vault remodeling has several distinct advantages over conventional reconstruction techniques. The endoscopic approach reduces scarring and alopecia risks, operative time, blood loss, and hospital stay. Mean operative time is less than 1 hour, compared with approximately 3 hours for the conventional open approach. Instead of a typical 5-day postoperative course with an intensive care admission, patients undergoing endoscopic surgery may be discharged on the first postoperative day.[170] More than 90% of patients undergoing open calvarial surgery require transfusion,[171] compared with 10% of those receiving endoscopic surgery.[170] A shorter operative time and reduced hospital stay, in addition to the use of fewer blood products, and the elimination of internal plating systems all add up to a decrease in overall cost of the procedure.

One disadvantage of endoscopic procedures is that the surgery needs to be performed at a young age, preferably before 4 months. The reason is that the cranial bones in children this young are thin enough to allow osteotomies with endoscopic shears. In addition, there is less bleeding associated with the bone cutting owing to the underdevelopment of the cancellous space between the two cortices of the skull. Lastly, endoscopic cranial vault remodeling involves the added expense of the cranial orthotic molding helmet as well as the prolonged and frequent postoperative follow-up (8–15 months) to ensure that cranial form is normalizing.

Preoperative Concerns

Patients presenting for endoscopic strip craniectomy are usually younger than 6 months. Ideally, the surgery should be scheduled past the physiologic nadir of the infant's hematocrit value, which occurs between the second and third month of life, to reduce the need for transfusion. Some centers give recombinant erythropoietin at a dose of 600 IU/kg/wk for 3 weeks prior to surgery to increase the preoperative hematocrit.[172] Preoperative laboratory analysis should include a baseline complete blood count. Although blood loss and blood transfusions are significantly decreased with endoscopic surgery, there is always the risk of significant blood loss due to injury of the sagittal sinus. A blood specimen for type and screen can be sent on the day of surgery after the placement of an intravenous cannula. If the patient has received previous blood transfusions and has potential antibody formation, a blood cross-match should be obtained before the start of surgery.

Craniofacial anomalies may be associated with cardiac and other congenital or chromosomal abnormalities, including Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Saethre–Chotzen syndrome, and Muenke syndrome.[173] Awareness of coexisting congenital anomalies is important for appropriate intraoperative management. Patients may have a difficult airway, cervical spine abnormalities, cardiovascular problems, altered respiratory mechanics, gastroesophageal

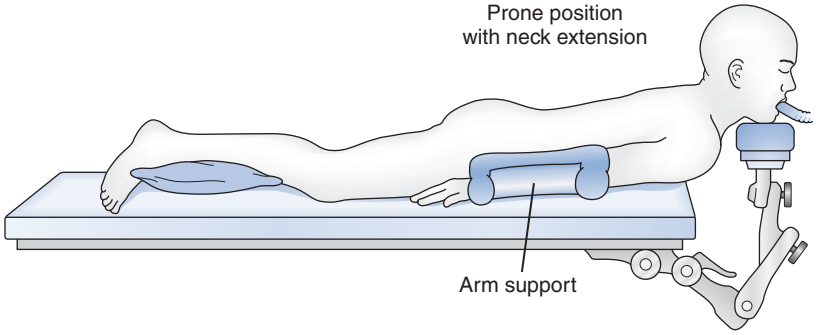


Fig. 17.6 Positioning for endoscopic strip craniectomy.

reflux, and other organ involvement. Undiagnosed OSA syndrome might coexist and add to the perioperative morbidity in these children.[174] Butler and associates[175] provide an excellent review of complications with recommended presedation evaluations and a checklist of potential problems for common and uncommon genetic disorders. Associated cervical spine abnormalities are of particular importance, as patients may be in the "sphinx" or "sea-lion" position for endoscopic strip craniectomies. This is a modified prone position (Fig. 17.6) with the neck extended and supported by an inflatable bag. This position may be contraindicated in patients with cervical spine anomalies. If a difficult airway is anticipated, fiberoptic intubation equipment and the LMA should be available. Pretreatment with glycopyrrolate (6–10 µg/kg) as an anti-sialagogue may be indicated. Patients receiving anticonvulsants or other therapeutic agents should continue to take them during the perioperative period. Anticonvulsant levels should be checked for optimal dosing.

Intraoperative Concerns

Issues of greatest importance in strip craniectomy include airway control, patient positioning, venous air embolism, and possible rapid blood loss. Although minimal blood loss is expected in these procedures, injury to the dural sinus or emissary vein could lead to significant intraoperative bleeding. Preoperative hemoglobin and hematocrit values, type and cross-match, and availability of packed red blood cells are, therefore, indicated. Inhalation induction is usually performed and intravenous access is obtained. After endotracheal tube placement, it is important to be aware of possible tube repositioning with extension of the neck during positioning. Endobronchial intubation or accidental extubation during positioning are possible.[176] One can advance the endotracheal tube into the right mainstem bronchus and then pull back until bilateral breath sounds are appreciated. Endotracheal tube depth and bilateral breath sounds should be noted prior to positioning and rechecked when the patient is in the final surgical position. Appropriate intravenous access should be achieved with the understanding that the anesthesiologist's access to the patient is limited. Arterial line placement is at the discretion of the anesthesiologist due to the short duration and minimal hemodynamic changes anticipated in this procedure. Pressure points must be padded, and pressure must not be placed on bony prominences or vital structures such as the eyes. Owing to the small size of the infant, minimal shifting of the position can cause significant changes in pressure points. In two series, venous air embolism occurred in 0.35–4% of patients. None of the earlier reported episodes of venous air embolism in the minimally invasive surgery cases resulted in hemodynamic compromise.[157,166] Patients should be monitored with a precordial Doppler ultrasonography probe throughout the case.

Postoperative Concerns

No infections, dural sinus tears, CSF leaks, or neurologic injuries were reported in a representative series of patients undergoing endoscopic strip craniectomy.[170] Although careful monitoring is needed in the immediate postoperative period, many patients are discharged within 24 hours.

Functional Neurosurgery and Deep Brain Stimulation

Surgical and anesthetic considerations for deep brain stimulation are discussed in Chapter 18.

MINIMALLY INVASIVE SPINE SURGERY

Minimally invasive spine surgery encompasses a large group of procedures that offer an alternative to open reconstructive surgery, in an effort to reduce surgical trauma and improve outcomes. Continued advancements in microsurgery, endoscopy, and percutaneous techniques have diversified the possible approaches to the treatment of a number of spinal pathologies with a goal to reduce treatment morbidity. Common indications are listed in Table 17.1. Transluminal, percutaneous, and "key-hole" approaches have continued to evolve, allowing safer and less invasive access to surgical sites. Smaller incisions are possible through the extensive use of operating microscope, fluoroscopic guidance, stereotactic neuronavigation, and special instruments such as tubular retractors, disk space dilators, and special cage devices for structural support.[143] Endoscopic approaches reduce the amount of muscle dissection required for access to the spine and thereby decrease postoperative pain, recovery time, and hospital stay.[177]

Neuraxial and general anesthesia are both commonly used and studied for spine surgery. Spinal anesthesia for lumbar spine surgery is virtually free of the risk of post-dural-puncture headache and reduces postprocedure pain, nausea, and bleeding.[178] In one study,[179] shorter operative times, less nausea and use of opioids, and less urinary retention were demonstrated in patients undergoing lumbar spine surgery. Another study, published in 2012,[180] demonstrated less use of opioids and less nausea in epidural and combined spinal epidural than with spinal anesthesia alone. However, motor examination cannot be readily or reliably performed with electrophysiologic or gross monitoring under neuraxial anesthesia. Contraindications to neuraxial anesthesia would include coagulopathy, patient refusal, and lesion at the site. Currently, both regional and general anesthesia should be considered safe and effective for lumbar spine surgery and regional anesthesia may be a better choice in patients at higher risk for complications of general anesthesia.[181]

Video-Assisted Thoracoscopic Surgery

Video-assisted thoracoscopic surgery (VATS) is used for intrathoracic procedures of the lung and surrounding tissue. In some centers it may also be applied for treatment of thoracic disc disease,[182a] spondylitis,[182b,183] anterior thoracic spine release, fusion for scoliosis/kyphosis or spine trauma,[182b,184] and for thoracic sympathetic ganglionectomy for hyperhidrosis.[140] The advantages of the minimally invasive approach to the spine are less surgical time,[185] less acute postoperative pain, improved postoperative respiratory function, and a faster functional recovery compared with conventional procedures.[186] Table 17.2 compares VATS with open thoracotomy. Recently, robotic-assisted thoracic surgery (RATS) techniques have been introduced that may offer improved surgical precision.[187]

Table 17.2 Comparison of Video-Assisted Thoracoscopic Surgery with Open Thoracotomy

	VATS	Thoracotomy
Operating time (min)	205 (80–542)	268 (210–690)
Blood loss (mL)	327 (125–1500)	683 (250–1200)
Chest tube (days)	1.5 (0–6)	3.5 (2.8–9.1)
Narcotics (mg/day)	3.7 (1.5–15)	20.4 (5–60)
Hospital stay (days)	6.5 (2–24)	16.2 (5–34)
Pulmonary dysfunction	7%	33%
Neurological deterioration	16%	50%

(From Rosenthal D, Dickman CA: Thoracoscopic microsurgical excision of herniated thoracic discs. J Neurosurg 1998;89:224–235.)

Preoperative Concerns

The term minimally invasive surgery does not inherently confer low perioperative risk. Blood loss, perioperative physiologic stress, and postoperative complications vary significantly with the type of minimally invasive spinal surgery performed and with the patient's comorbid status. Thoracoscopically and laparoscopically assisted scoliosis correction, multilevel spinal fusions, and thoracic corpectomies should still be considered intermediate- to high-risk procedures. Should VATS be selected for the surgical approach, patients must be evaluated and prepared for one-lung ventilation. In patients with chronic kyphoscoliosis restrictive lung disease and associated congenital anomalies may be present and should be thoroughly evaluated. Some neuromuscular diseases predispose to a higher risk of malignant hyperthermia. Coagulation abnormalities, fibrotic lung disease, pulmonary hypertension, and cervical spine pathology may be seen in patients with spine disorders related to connective tissue diseases.

Intraoperative Concerns

Patients are usually placed in the lateral position for transthoracic spinal surgery. The operating room arrangement for VATS is shown in Fig. 17.7. Because the lower extremities are positioned below the level of the heart, venous return may be restricted, predisposing to hypotension. One-lung ventilation facilitates the surgeons' view through the endoscope, which would otherwise be obliterated by the nondeflated lung. The possibility of prolonged one-lung ventilation should be anticipated during anterior release and multiple level fusions. Nitrous oxide is avoided. Either a double-lumen endotracheal tube or a bronchial blocker can be used to isolate and deflate the nondependent lung. Double-lumen tubes may be difficult to place in patients with significant thoracic kyphosis because of tracheobronchial distortion.

Combined anterior–posterior fusions may require changing the double-lumen tube to a single-lumen tube prior to placing the patient in the prone position. This position change creates an inherent risk of loss of the secured airway. The alternative is to withdraw the bronchial portion of the double lumen tube into the trachea, but has the disadvantage of potential tube malposition during prone ventilation. We, therefore, prefer to use a bronchial blocker or change to a single-lumen tube using a tube exchanger. Anesthetic and muscle relaxant restrictions required for somatosensory and motor evoked potential monitoring[188,189] can make it difficult to avoid patient coughing from carinal stimulation due to the double-lumen tube. Remifentanil has been show to improve depth of anesthesia and tolerance of the endotracheal tube[190] and to prevent patient movement in the absence of neuromuscular blockade.[191] The risk of patient movement during VATS or RATS must be balanced against the gain from neurophysiologic monitoring; it may be possible to reduce risk of movement by restricting avoidance of neuromuscular blockade

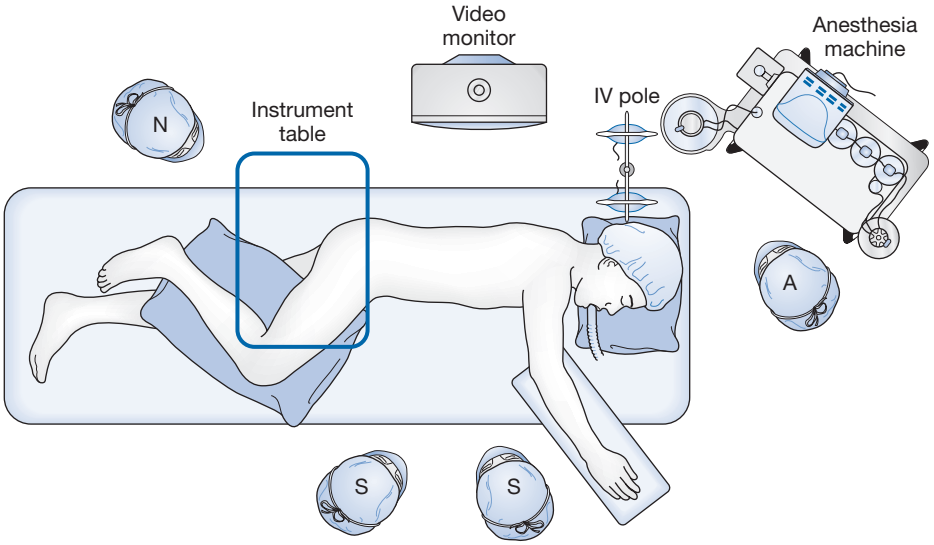


Fig. 17.7 Operating room setup for video-assisted thorascopic spine surgery. **A,** Anesthesiologist; **N,** nurse; **S,** surgeon.

only for critical monitoring periods. The anesthetic and surgical teams must be prepared for unintended surgical injury to large intrathoracic vessels. The prophylactic placement of arterial and venous access lines is advocated, and blood should be available. Risk of blood loss with various VATS procedures is described in Table 17.3.

Table 17.3 Risk of Blood Loss in Video-Assisted Thoracoscopic Surgery*

Author	Blood Loss	Indication
Singh et al[183]	418 +/- 191 mL	Tubercular spondylitis
Liu et al[192]	50–200 mL	Anterior spine release (scoliosis)
Kapoor et al[193]	497 +/- 302 mL	Tubercular spondylitis
Liu and Kit[182b]	258 mL	Thoracic spine disease

*Superscript numbers refer to references in this chapter.

An alternative procedure involves a combined posterior and lateral chest approach in the prone position.[194] This technique entails surgical preparation of the right chest as well as the back for optimal surgical access. Lung isolation is not necessary because the lung falls away from the surgical endoscope, aided either by an atmospheric pneumothorax or by mild tension pneumothorax induced by low-pressure insufflation with carbon dioxide. Insufflation should be performed slowly to avoid sudden decreases of venous return to the thorax.[187] Advantages include shorter procedure times, because placement of double-lumen tracheal tube and confirmatory bronchoscopy are avoided, as is the repositioning from the lateral to the prone position. Furthermore, a lower rate of pulmonary complications has been observed.[195]

Postoperative Concerns

Intercostal neuralgia, pneumothorax, and Horner's syndrome have been reported after thoracoscopic procedures.[196] Pulmonary complications such as atelectasis may be sufficiently severe to prolong hospitalization.[197] Proper attention should be directed to appropriate chest-tube management and assurance of good pulmonary toilet. Chylothorax, hemidiaphragm and pericardial penetration, tension pneumothorax and long thoracic nerve injury have also been reported.[182b]

Kyphoplasty and Vertebroplasty

Kyphoplasty and vertebroplasty are similar minimally invasive percutaneous procedures that have shown short-term benefits in pain relief[198] in patients with osteoporotic and osteolytic fractures of the thoracic and lumbar vertebrae. The procedures reduce pain through cementing of the fractured vertebrae with polymethylmethacrylate cement to reduce movement of bony fragments. Kyphoplasty is slightly more invasive than vertebroplasty in that it uses balloon tamps to reexpand the vertebrae to their original height and to create a potential space prior to cement application.

Preoperative Concerns

While these procedures may present low surgical risks, significant comorbidities associated with these pathologies may still pose anesthetic risks. The elderly patient population often associated with these procedures may present with a broad spectrum of advanced illnesses as well as specifically associated pathologies such as metastatic cancer, steroid-dependent pulmonary or inflammatory diseases, and severe osteoporosis. Careful preoperative evaluation and preparation are, as always, recommended. In patients with pulmonary inflammatory disease, pulmonary function should be optimized prior to surgery and stress-dose steroids may be required. Chronic pain is a common comorbidity in many of these patients and opioid tolerance should be considered and adequate intraoperative and postoperative pain-control measures planned.

Intraoperative Concerns

Kyphoplasty and vertebroplasty may be performed under MAC or general anesthesia. Considerations for the choice of anesthetic include the patient's ability to tolerate the prone position for the duration of the procedure, tolerance of limb position in patients with osteoarthritis or rheumatoid arthritis, whether the patient is a good candidate for monitored sedation, and access to the patient's airway. Additionally, positive pressure ventilation may reduce cement leakage.[199,200]

Padding and gentle positioning are crucial in patients with severe osteoporosis. Skin lacerations and rib fractures have been reported in these patients during prone positioning.[198] The procedures require only a minimal incision and are generally well tolerated despite the acute illness level of this patient population. Arterial oxygenation decreases during vertebroplasty under sedation; the decrement in partial pressure of oxygen is related to the number of spinal segments treated.[201] It is not clear whether this relationship is the result of higher sedative doses or a greater amount of cement used.

Rare occurrences of symptomatic pulmonary embolism and intraoperative death have been reported during vertebroplasty.[202,203] A light anesthesia regimen using short-acting anesthetic agents is appropriate, aiming at rapid recovery to facilitate same-day discharge.

Postoperative Concerns

Patients are commonly discharged on the day of surgery; however, those with end-stage pulmonary disease or severe perioperative pain may warrant closer monitoring and a hospital stay of up to 24 hours.

Endoscopic Cervical Diskectomy and Foraminotomy

Anterior microforaminotomy has long been in use for radiculopathic conditions, and has now been advocated to replace anterior vertebrectomy for removal of tumors located anterior to the spinal cord. Minimally invasive endoscopic cervical foraminotomy (MEF) is being increasingly used for cervical root decompression and results in less blood loss, shorter hospitalizations, and a much lower postoperative pain medication requirement than open cervical laminoforaminotomy.[204] Postoperative pain is minimal. Neither bony fusion nor a cervical brace are needed, and patients undergoing MEF are kept in the hospital only overnight.[144]

The prone or sitting position may be used for posterior cervical MEF. The sitting position decreases epidural venous engorgement and has been shown to entail less blood loss than MEF performed in the prone position,[205] but obviously confers the potential risk of venous air embolism. Other potential complications of MEF include the risk of dural puncture or nerve root injury with guidewires.[206] Injury to the sympathetic chain causing postoperative Horner's syndrome can occur during anterior cervical foraminotomy. However, the intraoperative complication of most concern with this approach is injury to the vertebral artery during drilling of the uncovertebral joint.[144] The risk of arterial injury is highest

at the level of C6–C7. Vertebral artery injury requires intraoperative control of bleeding and postoperative angiographic assessment to assess for dissection or pseudoaneurysm formation.[206]

Microdiskectomy and Percutaneous Disk Space Treatment

Both general anesthesia and neuraxial techniques may be used for open lumbar microdiskectomy.[207] As noted above, spinal anesthesia for lumbar spine surgery has been studied and shown to have shorter operative times; less bleeding, postprocedure pain, opioid use, and nausea; and no postdural puncture headache risk. Less opioid use and nausea were also seen in epidural and combined spine epidural techniques than with just spinal anesthesia. Coagulopathy, a lesion at the intended site, or patient refusal are contraindications to a neuraxial technique. Motor examination cannot be reliably performed under neuraxial anesthesia. Isobaric bupivacaine (0.5%) with epinephrine and fentanyl has been used successfully with minimal cardiovascular effect.

Postoperative pain requirements after microdiskectomy depend significantly on preoperative pain severity.[208] A combination of anesthetic techniques, utilizing spinal anesthesia with supplemental epidural clonidine in combination with incision site subcutaneous bupivacaine,[209] may be of further benefit through improving postoperative pain control in these patients.

Percutaneous hemonucleolysis with the use of papain as well as blind nucleotomy and laser disk decompression have largely fallen out of favor because of allergic complications, neurovascular injury, and transverse myelitis.[210] Instead, arthroscopic technology, using instruments that can be visualized, and endoscopic fiberoptic techniques are being developed and show considerably greater promise.

Minimally Invasive Spinal Fusion

Minimally invasive techniques for spinal fusion include transforaminal lumbar interbody fusion (TLIF), extreme lateral interbody fusion (XLIF), and the less commonly used anterior lumbar interbody fusion (ALIF) and axial lumbar interbody fusion (AxiaLIF).

TLIF procedures are usually performed in the prone position. The incision is small, facilitated by microscopic technique, computer or precise fluoroscopic localization, and tubular retractors. The surgeon begins by performing a total facetectomy, after which annulotomy and diskectomy are accomplished. After the disk space is freed up, it is filled with morselized cancellous bone or a metal cage for structural support. Autologous bone from the iliac crest may be harvested. Stabilization may be augmented through the use of limited open or percutaneous pedicle screw fixation.[143]

Extreme lateral interbody fusion (XLIF) is performed in the lateral position with the operating table flexed at the interspace of interest. The surgical approach entails risk of injury to the peritoneal cavity, pleural cavity, great vessels, and lumbosacral plexus. To deal with the latter, intraoperative electromyographic monitoring may be used, which limits the use of neuromuscular blockade. If the interspace to be treated is thoracic, the potential for development of intraoperative pneumothorax should be considered.

Transperitoneal or retroperitoneal laparoscopic approaches may still be used to access the lumbar spine.[139] They have been used successfully for both lumbar diskectomy and ALIF. The laparoscopic approach to the lumbar spine requires steep head-down positioning and the use of shoulder braces, which can cause brachial neurapraxia if they are placed too medially. The patient's arms may need to be crossed and placed on the anterior chest. The usual precautions for laparoscopic procedures must be followed, and potential problems anticipated, such as pulmonary barotrauma, CO_2 embolism, hypercapnia, and right main-stem intubation. The bifurcation of the iliac vessels occurs around the level of the L4–L5 interspace; thus, an anterior laparoscopic approach to the lower lumbar disk spaces requires the mobilization of these vessels, raising the risk of laceration. Iatrogenic injury to bowel and superior hypogastric plexus has also been reported. Surgeons have reported prolonged surgical times, which has led some to prefer a mini-open procedure to laparoscopic assistance.[211] These procedures have become less favorable.

Newer developments have made an axial approach to the lower lumbar spine possible. Axial approaches to spinal fusion are thought to have substantial biomechanical advantages.[143] This approach affords the surgeon access to the spine via the presacral space through a keyhole incision, avoiding the risks of body cavity, ligamentous, muscle, and neural plexus injury inherent in ALIF, TLIF, and XLIF. The patient is positioned prone, and extensive use of fluoroscopy and special instrumentation are required.

Robotic-Assisted Spine Surgery

Robotic-assisted surgery represents another major technological advancement that may significantly alter the field of neurosurgery. It has been employed for screw and rod insertion in spinal surgery, vertebroplasty, tumor resection, and for anesthetic nerve blocks. The most important proposed feature of robotic-assisted neurosurgery is improved accuracy, which decreases the likelihood of collateral damage to structures adjacent to the target site and less-than-optimal hardware placement. In addition, shorter surgical times, reduced exposure to radiation, and a decrease in surgeon fatigue may be achieved. Faster workflow is also anticipated, but well-trained teams will have to develop to realize this goal. The development of more robotic-guided tools should allow for expansion of the practice. Robotic-assisted neurosurgery is a growing field, but one that lacks a clear consensus on efficacy.

SUMMARY

Awake craniotomy is a safe, effective technique for treatment of certain lesions that reduces morbidity and length of stay and may provide better overall patient outcomes when eloquent cortex is involved. Anesthetic techniques for awake craniotomy vary among institutions, but generally feature a period of sedation or general anesthesia followed by an awake phase for mapping and in some cases resection, after which the patient is sedated again for the remainder of the procedure. Awake craniotomy may be used for tumor resection, epilepsy surgery, as well as DBS placement. In the case of DBS insertion, the patient is sedated only when absolutely necessary so that awake testing for optimal lead-placement can be performed.

Minimally invasive techniques have continued to improve variables such as recovery periods, operative time, length of stay, and patient discomfort. Continuing advances in technology and technique allow for a variety of procedures that may be performed with minimally invasive surgery. Anesthetic management will vary by procedure and patient, but the anesthesiologist contributes to the outcome for the patient through an awareness of the patient's condition and comorbidities, an understanding of the procedure and its possible

complications, and a working knowledge of currently accepted techniques. Further technological advances in visualization and tools will likely continue to advance and evolve this field in the coming years.

REFERENCES

1. Brown T, Shah AH, Bregy A, et al. Awake craniotomy for brain tumor resection: The rule rather than the exception? *J Neurosurg Anesthesiol*. 2013;25(3):240–247.
2. Rajan S, Cata JP, Nada E, Weil R, Pal R, Avitsian R. Asleep-awake-asleep craniotomy: A comparison with general anesthesia for resection of supratentorial tumors. *J Clin Neurosci*. 2013;20(8):1068–1073.
3. Serletis D, Bernstein M. Prospective study of awake craniotomy used routinely and nonselectively for supratentorial tumors. *J Neurosurg*. 2007;107:1–6.
4. Blanshard HJ, Chung F, Manninen PH, et al. Awake craniotomy for removal of intracranial tumor: Considerations for early discharge. *Anesth Analg*. 2001;92:89–94.
5. Peruzzi P, Bergese SD, Viloria A, Puente EG, Abdel-Rasoul M, Chiocca EA. A retrospective cohort-matched comparison of conscious sedation versus general anesthesia for supratentorial glioma resection. *J Neurosurg*. 2011;114(3):633–639.
6. Purzner T, Purzner J, Massicotte EM, Bernstein M. Outpatient brain tumor surgery and spinal decompression: A prospective study of 1003 patients. *Neurosurgery*. 2011;69(1):119–126.
7. Wrede KH, Stieglitz LH, Fiferna A, et al. Patient acceptance of awake craniotomy. *Clin Neurol Neurosurg*. 2011;113(10):880–884.
8. Whittle IR, Midgley S, Georges H, et al. Patient perceptions of "awake" brain tumour surgery. *Acta Neurochir (Wien)*. 2005;147:275–277.
9. Hagberg CA, Gollas A, Berry JM. The laryngeal mask airway for awake craniotomy in the pediatric patient: Report of three cases. *J Clin Anesth*. 2004;16:43–47.
10. Archer DP, McKenna JM, Morin L, Ravussin P. Conscious-sedation analgesia during craniotomy for intractable epilepsy: A review of 354 consecutive cases. *Can J Anaesth*. 1988;35:338–344.
11. Sarang A, Dinsmore J. Anaesthesia for awake craniotomy—Evolution of a technique that facilitates awake neurological testing. *Br J Anaesth*. 2003;90:161–165.
12. Skucas AP, Artru AA. Anesthetic complications of awake craniotomies for epilepsy surgery. *Anesth Analg*. 2006;102:882–887.
13. Senel FC, Buchanan Jr JM, Senel AC, Obeid G. Evaluation of sedation failure in the outpatient oral and maxillofacial surgery clinic. *J Oral Maxillofac Surg*. 2007;65:645–650.
14. Klimek M, Verbrugge SJ, Roubos S, et al. Awake craniotomy for glioblastoma in a 9-year-old child. *Anaesthesia*. 2004;59:607–609.
15. Drummond JC, Iragui-Madoz VJ, Alksne JF, Kalkman CJ. Masking of epileptiform activity by propofol during seizure surgery. *Anesthesiology*. 1992;76:652–654.
16. Girvin JP. Neurosurgical considerations and general methods for craniotomy under local anesthesia. *Int Anesthesiol Clin*. 1986;24:80–114.
17. Costello TG, Cormack JR, Hoy C, et al. Plasma ropivacaine levels following scalp block for awake craniotomy. *J Neurosurg Anesthesiol*. 2004;16:147–150.
18. Costello TG, Cormack JR, Mather LE, et al. Plasma levobupivacaine concentrations following scalp block in patients undergoing awake craniotomy. *Br J Anaesth*. 2005;94:848–851.
19. Chowdhury T, Baron K, Cappellani RB. Severe bradycardia during scalp nerve block in patient undergoing awake craniotomy. *Saudi J Anaesth*. 2013;7(3):356–357.
20. Silbergeld DL, Mueller WM, Colley PS, et al. Use of propofol (Diprivan) for awake craniotomies: Technical note. *Surg Neurol*. 1992;38:271–272.
21. Berkenstadt H, Perel A, Hadani M, et al. Monitored anesthesia care using remifentanil and propofol for awake craniotomy. *J Neurosurg Anesthesiol*. 2001;13:246–249.
22. Manninen PH, Balki M, Lukitto K, Bernstein M. Patient satisfaction with awake craniotomy for tumor surgery: A comparison of remifentanil and fentanyl in conjunction with propofol. *Anesth Analg*. 2006;102:237–242.
23. Keifer JC, Dentchev D, Little K, et al. A retrospective analysis of a remifentanil/propofol general anesthetic for craniotomy before awake functional brain mapping. *Anesth Analg*. 2005;101:502–508.
24. Keene DL, Roberts D, Splinter WM, et al. Alfentanil mediated activation of epileptiform activity in the electrocorticogram during resection of epileptogenic foci. *Can J Neurol Sci*. 1997;24:37–39.
25. Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care*. 2001;7:221–226.
26. Rozet I. Anesthesia for functional neurosurgery: The role of dexmedetomidine. *Curr Opin Anaesthesiol*. 2008;21(5):537–543.
27. Souter MJ, Rozet I, Ojemann JG, et al. Dexmedetomidine sedation during awake craniotomy for seizure resection: Effects on electrocorticography. *J Neurosurg Anesthesiol*. 2007;19:38–44.
28. Bekker AY, Kaufman B, Samir H, et al. The use of dexmedetomidine infusion for awake craniotomy. *Anesth Analg*. 2001;92:1251–1253.
29. Bustillo MA, Lazar RM, Finck AD, et al. Dexmedetomidine may impair cognitive testing during endovascular embolization of cerebral arteriovenous malformations: A retrospective case report series. *J Neurosurg Anesthesiol*. 2002;14:209–212.
30. Conte V, L´Acqua C, Rotelli S, Stocchetti N. Bispectral index during asleep-awake craniotomies. *J Neurosurg Anesthesiol*. 2013;25(3):279–284.
31. Moore TA, Markert JM, Knowlton RC. Dexmedetomidine as rescue drug during awake craniotomy for cortical motor mapping and tumor resection. *Anesth Analg*. 2006;102:1556–1558.
32. Manninen PH, Tan TK. Postoperative nausea and vomiting after craniotomy for tumor surgery: A comparison between awake craniotomy and general anesthesia. *J Clin Anesth*. 2002;14:279–283.
33. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.
34. Kelvin EA, Hesdorffer DC, Bagiella E, et al. Prevalence of self-reported epilepsy in a multiracial and multiethnic community in New York City. *Epilepsy Res*. 2007;77:141–150.
35. Bazil CW. Comprehensive care of the epilepsy patient-controlled, comorbidity, and cost. *Epilepsia*. 2004;45:3–12.
36. Chin PS, Berg AT, Spencer SS, et al. Employment outcomes following resective epilepsy surgery. *Epilepsia*. 2007;48:2253–2257.
37. Kiersey DK, Bickford RG, Faulconer Jr A. Electro-encephalographic patterns produced by thiopental sodium during surgical operations: Description and classification. *Br J Anaesth*. 1951;23:141–152.
38. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (part II). *Anesth Analg*. 1990;70:433–444.
39. Reddy RV, Moorthy SS, Dierdorf SF, et al. Excitatory effects and electroencephalographic correlation of etomidate, thiopental, methohexital, and propofol. *Anesth Analg*. 1993;77:1008–1011.
40. Walker M. Status epilepticus: An evidence based guide. *BMJ*. 2005;331:673–677.
41. Rampil IJ, Lopez CE, Laxer KD, Barbaro NM. Propofol sedation may disrupt interictal epileptiform activity from a seizure focus. *Anesth Analg*. 1993;77:1071–1073.
42. Smith M, Smith SJ, Scott CA, Harkness WF. Activation of the electrocorticogram by propofol during surgery for epilepsy. *Br J Anaesth*. 1996;76(4):499–502.
43. Opitz A, Marschall M, Degan R, et al. General anesthesia in patients with epilepsy and status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, eds. *Advances in Neurology: Status Epilepticus, Mechanisms of Brain Damage and Treatment*. New York: Raven Press; 1983:531–535.
44. Yeoman P, Hutchinson A, Byrne A, et al. Etomidate infusions for the control of refractory status epilepticus. *Intensive Care Med*. 1989;15:255–259.
45. Chui J, Manninen P, Valiante T, Venkatraghavan L. The anesthetic considerations of intraoperative electrocorticography during epilepsy surgery. *Anesth Analg*. 2013;117(2):479–486.
46. Wyler AR, Ritchey ET, Atkinson RA, Hermann BP. Methohexital activation of epileptogenic foci during acute electrocorticography. *Epilepsia*. 1987;28:490–494.
47. Fiol ME, Torres F, Gates JR, Maxwell R. Methohexital (Brevital) effect on electrocorticogram may be misleading. *Epilepsia*. 1990;31:524–528.
48. Talke P, Stapelfeldt C, Garcia P. Dexmedetomidine does not reduce epileptiform discharges in adults with epilepsy. *J Neurosurg Anesthesiol*. 2007;19(3):195–199.
49. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. *Anesthesiology*. 1981;54:333–335.
50. Ebrahim ZY, DeBoer GE, Luders H, et al. Effect of etomidate on the electroencephalogram of patients with epilepsy. *Anesth Analg*. 1986;65:1004–1006.
51. Hufnagel A, Burr W, Elger CE, et al. Localization of the epileptic focus during methohexital-induced anesthesia. *Epilepsia*. 1992;33:271–284.
52. Rysz A, Bachanski M, Bidzinski J, Bacia T. The comparison of ketamine with methohexital and thiopental in the intraoperative EEG in drug-resistant epilepsy. *Neurol Neurochir Pol*. 1998;32:237–245.
53. Hansen HC, Drenck NE. Generalised seizures after etomidate anaesthesia. *Anaesthesia*. 1988;43:805–806.
54. Nicoll K, Callender J. Etomidate-induced convulsion prior to electroconvulsive therapy. *Br J Psychiatry*. 2000;177:373.
55. Bennett DR, Madsen JA, Jordan WS, et al. Ketamine anesthesia in brain-damaged epileptics: Electroencephalographic and clinical observations. *Neurology*. 1973;23:449–460.
56. Kugler J, Doenicke A. Ketamine—Anticonvulsive and proconvulsive actions. *Anaesthetist*. 1994;43:S2–S7.

57. Wass CT, Grady RE, Fessler AJ. The effects of remifentanil on epileptiform discharges during intraoperative electrocorticography in patients undergoing epilepsy surgery. *Epilepsia*. 2001;42:1340–1344.
58. Cascino GD, So EL, Sharbrough FW, et al. Alfentanil-induced epileptiform activity in patients with partial epilepsy. *J Clin Neurophysiol*. 1993;10:520–525.
59. McGuire G, El-Beheiry H, Manninen P, et al. Activation of electrocorticographic activity with remifentanil and alfentanil during neurosurgical excision of epileptogenic focus. *Br J Anaesth*. 2003;91:651–655.
60. Tempelhoff R, Modica PA, Bernardo KL, Edwards I. Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. *J Neurosurg*. 1992;77:201–208.
61. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (part I). *Anesth Analg*. 1990;70:303–315.
62. Vakkuri AP, Seitsonen ER, Jantti VH, et al. A rapid increase in the inspired concentration of desflurane is not associated with epileptiform encephalogram. *Anesth Analg*. 2005;101:396–400.
63. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg*. 1985;101:396–400.
64. Harrison JL. Postoperative seizures after isoflurane anesthesia. *Anesth Analg*. 1986;64:367–368.
65. Schultz B, Schultz A, Grouven U, Korsch G. Epileptiform EEG activity: Occurrence under sevoflurane and not during propofol application. *Anaesthetist*. 2001;50:43–45.
66. Woodforth IJ, Hicks RG, Crawford MR, et al. Electroencephalographic evidence of seizure activity under deep sevoflurane anesthesia in a non-epileptic patient. *Anesthesiology*. 1997;87:1579–1582.
67. Watts AD, Herrick IA, McLachlan RS, et al. The effect of sevoflurane and isoflurane anesthesia on interictal spike activity among patients with refractory epilepsy. *Anesth Analg*. 1999;89:1275–1281.
68. Hisada K, Morioka T, Fukui K, et al. Effects of sevoflurane and isoflurane on electrocorticographic activities in patients with temporal lobe epilepsy. *J Neurosurg Anesthesiol*. 2001;13:333–337.
69. Kurita N, Kawaguchi M, Hoshida T, et al. The effects of sevoflurane and hyperventilation on electrocorticogram spike activity in patients with refractory epilepsy. *Anesth Analg*. 2005;101:517–523.
70. Koenig HM, Hoffman WE. The effect of anticonvulsant therapy on two doses of rocuronium-induced neuromuscular blockade. *J Neurosurg Anesthesiol*. 1999;11:86–89.
71. Richard A, Girard F, Girard DC, et al. Cisatracurium-induced neuromuscular blockade is affected by chronic phenytoin or carbamazepine treatment in neurosurgical patients. *Anesthesiology*. 2005;100:538–544.
72. Ornstein E, Matteo RS, Young WL, Diaz J. Resistance to metocurine-induced neuromuscular blockade in patients receiving phenytoin. *Anesthesiology*. 1985;63:294–298.
73. Spacek A, Neiger FX, Spiss CK, Kress HG. Atracurium-induced neuromuscular block is not affected by chronic anticonvulsant therapy with carbamazepine. *Acta Anaesthesiol Scand*. 1997;41:1308–1311.
74. Tempelhoff R, Modica PA, Jellish WS, Spitznagel Jr EL. Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg*. 1990;71:665–669.
75. Ornstein E, Matteo RS, Schwartz AE, et al. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology*. 1987;67:191–196.
76. Alloul K, Whalley DG, Shutway F, et al. Pharmacokinetic origin of carbamazepine-induced resistance to vecuronium neuromuscular blockade in anesthetized patients. *Anesthesiology*. 1996;84:330–339.
77. Isaacs H. Perinatal (fetal and neonatal) tuberous sclerosis: A review. *Am J Perinatol*. 2009;26(10):755–760.
78. Jóźwiak S, Kotulska K, Kasprzyk-Obara J, et al. Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. *Pediatrics*. 2006;118(4):e1146–e1151.
79. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation*. 2002;105:1257–1267.
80. Reasoner DK, Todd MM, Scamman FL, et al. The incidence of pneumocephalus after supratentorial craniotomy: Observations on the disappearance of intracranial air. *Anesthesiology*. 1994;80:1008–1012.
81. Tempelhoff R, Modica PA, Spitznagel Jr EL. Anticonvulsant therapy increases fentanyl requirements during anaesthesia for craniotomy. *Can J Anaesth*. 1990;37:327–332.
82. Wall M, Baird-Lambert J, Buchanan N, et al. Liver function tests in persons receiving anticonvulsant medications. *Seizure*. 1992;1:187–190.
83. Rodriguez L, Valero R, Fabregas N. Intraoperative metabolic acidosis induced by chronic topiramate intake in neurosurgical patients. *J Neurosurg Anesthesiol*. 2008;20:67–68.
84. Soriano SG, Bozza P. Anesthesia for epilepsy surgery in children. *Childs Nerv Syst*. 2006;22:834–843.
85. Gidal B, Spencer N, Maly M, et al. Valproate-mediated disturbance of hemostasis: Relationship to dose and plasma concentration. *Neurology*. 1994;44:1418–1422.
86. Anderson GD, Lin YX, Berge C, Ojemann GA. Absence of bleeding complications in patients undergoing cortical surgery while receiving valproate treatment. *J Neurosurg*. 1997;87:252–256.
87. Seidenberg M, Pulsipher DT, Hermann B. Association of epilepsy and comorbid conditions. *Future Neurol*. 2009;4(5):663–668.
88. Artru AA, Lettich E, Colley PS, et al. Nitrous oxide: Suppression of focal epileptiform activity during inhalation and spreading of seizure activity following withdrawal. *J Neurosurg Anesthesiol*. 1990;2:189–193.
89. Coles JP, Leary TS, Monteiro JN, et al. Propofol anesthesia for craniotomy: A double-blind comparison of remifentanil, alfentanil, and fentanyl. *J Neurosurg Anesthesiol*. 2000;12:15–20.
90. Balakrishnan G, Raudzens P, Samra SK, et al. A comparison of remifentanil and fentanyl in patients undergoing surgery for intracranial mass lesions. *Anesth Analg*. 2000;91:163–169.
91. Gerlach K, Uhlig T, Huppe M, et al. Remifentanil-propofol versus sufentanil-propofol anaesthesia for supratentorial craniotomy: A randomized trial. *Eur J Anaesthesiol*. 2003;20:813–820.
92. Sneyd JR, Whaley A, Dimpel HL, et al. An open, randomized comparison of alfentanil, remifentanil and alfentanil followed by remifentanil in anaesthesia for craniotomy. *Br J Anaesth*. 1998;81:361–364.
93. Peterson KD, Landsfeldt U, Cold GE, et al. Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: A randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. *Anesthesiology*. 2003;98:329–336.
94. Todd MM, Warner DS, Sokoll MD, et al. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. *Anesthesiology*. 1993;78:1005–1020.
95. Ebrahim ZY, Schubert A, Van Ness P, et al. The effect of propofol on the electroencephalogram of patients with epilepsy. *Anesth Analg*. 1994;78:275–279.
96. Herrick IA, Craen RA, Gelb AW, et al. Propofol sedation during awake craniotomy for seizures: Patient-controlled administration versus neurolept analgesia. *Anesth Analg*. 1997;84:1285–1291.
97. Ito BM, Sato S, Kufta CV, et al. Effect of isoflurane and enflurane on the electrocorticogram of epileptic patients. *Neurology*. 1988;38:924–928.
98. Cascino GD, Sharbrough FW, So EL, et al. Intraoperative alfentanil hydrochloride in temporal lobe epilepsy: Correlation with MRI-based volume studies. *Epilepsia*. 1992;33:85.
99. Sato K, Shamoto H, Yoshimoto T. Severe bradycardia during epilepsy surgery. *J Neurosurg Anesthesiol*. 2001;13:329–332.
100. Sinha PK, Neema PK, Manikandan S, et al. Bradycardia and sinus arrest following saline irrigation of the brain during epilepsy surgery. *J Neurosurg Anesthesiol*. 2004;16:160–163.
101. Kofke WA, Tempelhoff R, Dasheiff RM. Anesthesia for epileptic patients and for epilepsy surgery. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery*. St. Louis: Mosby; 1994:495–524.
102. Brian Jr JE, Deshpande JK, McPerson RW. Management of cerebral hemispherectomy in children. *J Clin Anesth*. 1990;2:91–95.
103. Zuckerberg AL, Tobin JR, Fleisher L, et al. The physiopathological consequences of cerebral hemispherectomy in children. *Anesthesiology*. 1993;79:A1187.
104. Abrahams JM, Torchia MB, McGarvey M, et al. Perioperative assessment of coagulability in neurosurgical patients using thromboelastography. *Surg Neurol*. 2002;58:5–11.
105. Goobie SM, Soriano SG, Zurakowski D, et al. Hemostatic changes in pediatric neurosurgical patients as evaluated by thrombelastograph. *Anesth Analg*. 2001;93:887–892.
106. Hatton KW, McLarney JT, Pittman T, Fahy BG. Vagal nerve stimulation: Overview and implications for anesthesiologists. *Anesth Analg*. 2006;103(5):1241–1249.
107. Ramani R. Vagus nerve stimulation therapy for seizures. *J Neurosurg Anesthesiol*. 2008;20:29–35.
108. Zalvan C, Sulica L, Wolf S, et al. Laryngopharyngeal dysfunction from the implant vagal nerve stimulator. *Laryngoscope*. 2003;113:221–225.
109. Tatum 4th WO, Moore DB, Stecker MM, et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology*. 1999;52(6):1267–1269.
110. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery: A systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia*. 2013;54(5):840–847.

111. Manninen PH, Raman SK, Boyle K, et al. Early postoperative complications following neurosurgical procedures. *Can J Anaesth*. 1999;46:7–14.
112. Madenoglu H, Yildiz K, Dogru K, et al. Randomized, double-blinded comparison of tropisetron and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. *J Neurosurg Anesthesiol*. 2003;15:82–86.
113. Feng H, Huang G, Liao X, et al. Endoscopic third ventriculostomy in the management of obstructive hydrocephalus: An outcome analysis. *J Neurosurg*. 2004;100:626–633.
114. Mohanty A, Anandh B, Kolluri V, Praharaj SS. Neuroendoscopic third ventriculostomy in the management of fourth ventricular outlet obstruction. *Minim Invasive Neurosurg*. 1999;42:18–21.
115. Robinson S, Cohen AR. The role of neuroendoscopy in the treatment of pineal region tumors. *Surg Neurol*. 1997;48:360–365.
116. Hamada H, Hayashi N, Kurimoto M, et al. Neuroendoscopic septostomy for isolated lateral ventricle. *Neurol Med Chir*. 2003;43:582–587.
117. Kestle JR, Drake JM, Cochrane DD, et al. Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: A multicenter randomized trial. *J Neurosurg*. 2003;98:284–290.
118. Villavicencio AT, Leveque JC, McGirt MJ, et al. Comparison of revision rates following endoscopically versus nonendoscopically placed ventricular shunt catheters. *Surg Neurol*. 2003;59:375–379.
119. Lewis AI. Endoscopic management of colloid cysts. *Neurosurgery*. 1999;44:232.
120. Levy ML, Wang M, Aryan HE, et al. Microsurgical keyhole approach for middle fossa arachnoid cyst fenestration. *Neurosurgery*. 2003;53:1138–1144.
121. Rodziewicz GS, Chuang WC. Endoscopic removal of organized chronic subdural hematoma. *Surg Neurol*. 1995;43:569–572.
122. Karakhan VB, Khodnevich AA. Endoscopic surgery of traumatic intracranial haemorrhages. *Acta Neurochir Suppl (Wien)*. 1994;61:84–91.
123. Fritsch M, Manwaring KH. Endoscopic treatment of brain abscess in children. *Minim Invasive Neurosurg*. 1997;40:103–106.
124. Boviatsis EJ, Kouyialis AT, Stranjalis G, et al. CT-guided stereotactic biopsies of brain stem lesions: Personal experience and literature review. *Neurol Sci*. 2003;24:97–102.
125. An H, Wang L, Liu Y. Endoscopic transnasal sphenoidal approach in hypophysectomy. *Zhonghua Er Bi Yan Hou Ke Za Zhi*. 2000;35:367–368.
126. Yurtseven T, Ersahin Y, Demirtas E, Mutluer S. Neuroendoscopic biopsy for intraventricular tumors. *Minim Invasive Neurosurg*. 2003;46:293–299.
127. Cartwright CC, Jimenez DF, Barone CM, Baker L. Endoscopic strip craniectomy: A minimally invasive treatment for early correction of craniosynostosis. *J Neurosci Nurs*. 2003;35:130–138.
128. Kalavakonda C, Sekhar LN, Ramachandran P, Hechl P. Endoscope-assisted microsurgery for intracranial aneurysms. *Neurosurgery*. 2002;51:1119–1126.
129. Tan C, Brookes GB. The endoscopic technique utilized in removal process of acoustic neuroma by retrosigmoid approach. *Lin Chuang Er Bi Yan Hou Ke Za Zhi*. 2003;17:25–26.
130. Yamada S, Iacono RP, Mandybur GT, et al. Endoscopic procedures for resection of arteriovenous malformations. *Surg Neurol*. 1999;51:641–649.
131. Otsuki T, Jokura H, Nakasato N, Yoshimoto T. Stereotactic endoscopic resection of angiographically occult vascular malformations. *Acta Neurochir Suppl (Wien)*. 1994;61:98–101.
132. Benabid AL. Deep brain stimulation for Parkinson's disease. *Curr Opin Neurobiol*. 2003;13:696–706.
133. Cosyns P, Gabriels L, Nuttin B. Deep brain stimulation in treatment refractory obsessive compulsive disorder. *Verh K Acad Geneeskd Belg*. 2003;65:385–399.
134. Temel Y, Visser-Vandewalle V. Surgery in Tourette syndrome. *Mov Disord*. 2004;19:3–14.
135. Rehncrona S, Johnels B, Widner H, et al. Long-term efficacy of thalamic deep brain stimulation for tremor: Double-blind assessments. *Mov Disord*. 2003;18:163–170.
136. Huewel N, Perneczky A, Urban V, Fries G. Neuroendoscopic technique for the operative treatment of septated syringomyelia. *Acta Neurochir Suppl (Wien)*. 1992;54:59–62.
137. Fredman B, Olsfanger D, Jedeikin R. Thorascopic sympathectomy in the treatment of palmar hyperhidrosis: Anaesthetic implications. *Br J Anaesth*. 1997;79:113–119.
138. Heikkinen ER. Whole body stereotaxy: Application of stereotactic endoscopy to operations of herniated lumbar discs. *Acta Neurochir Suppl (Wien)*. 1992;54:89–92.
139. Henry LG, Cattey RP, Stoll JE, Robbins S. Laparoscopically assisted spinal surgery. *JSLS*. 1997;1:341–344.
140. Ng CS, Yeung EC, Wong RH, Kwok MW. Single-port sympathectomy for palmar hyperhidrosis with Vasoview Hemopro 2 endoscopic vein harvesting device. *J Thorac Cardiovasc Surg*. 2012;144(5):1256–1257.
141. Anand N, Regan JJ. Video-assisted thoracoscopic surgery for thoracic disc disease: Classification and outcome study of 100 consecutive cases with a 2-year minimum follow-up period. *Spine*. 2002;27:871–879.
142. Krasna MJ, Jiao X, Eslami A, et al. Thoracoscopic approach for spine deformities. *J Am Coll Surg*. 2003;197:777–779.
143. Shen FH, Samartzis D, Khanna AJ, Anderson DG. Minimally invasive techniques for lumbar interbody fusions. *Orthop Clin North Am*. 2007;38:373–386.
144. Jho HD, Ha HG. Anterolateral approach for cervical spinal cord tumors via an anterior microforaminotomy: Technical note. *Minim Invasive Neurosurg*. 1999;42:1–5.
145. McLain RF. Spinal cord decompression: An endoscopically assisted approach for metastatic tumors. *Spinal Cord*. 2001;39:482–487.
146. Rosenthal D, Marquardt G, Lorenz R, Nichtweiss M. Anterior decompression and stabilization using a microsurgical endoscopic technique for metastatic tumors of the thoracic spine. *J Neurosurg*. 1996;84:565–572.
147. Khoo LT, Beisse R, Potulski M. Thoracoscopic-assisted treatment of thoracic and lumbar fractures: A series of 371 consecutive cases. *Neurosurgery*. 2002;51:104–117.
148. Brockmeyer D, Abtin K, Carey L, Walker ML. Endoscopic third ventriculostomy: An outcome analysis. *Pediatr Neurosurg*. 1998;28:236–240.
149. Cinalli G, Salazar C, Mallucci C, et al. The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery*. 1998;43:1323–1327.
150. Hopf NJ, Grunert P, Fries G, et al. Endoscopic third ventriculostomy: Outcome analysis of 100 consecutive procedures. *Neurosurgery*. 1999;44:795–804.
151. Schroeder HW, Niendorf WR, Gaab MR. Complications of endoscopic third ventriculostomy. *J Neurosurg*. 2002;96:1032–1040.
152. Fabregas N, Lopez A, Valero R, et al. Anesthetic management of surgical neuroendoscopies: Usefulness of monitoring the pressure inside the neuroendoscope. *J Neurosurg Anesthesiol*. 2000;12:21–28.
153. Ambesh SP, Kumar R. Neuroendoscopic procedures: Anesthetic considerations for a growing trend: A review. *J Neurosurg Anesthesiol*. 2000;12:262–270.
154. Longatti PL, Barzoi G, Paccagnella F, et al. A simplified endoscopic third ventriculostomy under local anesthesia. *Minim Invasive Neurosurg*. 2004;47:90–92.
155. van Aken J, Struys M, Verplancke T, et al. Cardiovascular changes during endoscopic third ventriculostomy. *Minim Invasive Neurosurg*. 2003;46:198–201.
156. Ganjoo P, Sethi S, Tandon MS, Chawla R, Singh D. Incidence and pattern of intraoperative hemodynamic response to endoscopic third ventriculostomy. *Neurol India*. 2009;57(2):162–165.
157. Ganjoo P, Sethi S, Tandon MS, Singh D, Pandey BC. Perioperative complications of intraventricular neuroendoscopy: A 7-year experience. *Turk Neurosurg*. 2010;20(1):33–38.
158. Fabregas N, Valero R, Carrero E, et al. Episodic high irrigation pressure during surgical neuroendoscopy may cause intermittent intracranial circulatory insufficiency. *J Neurosurg Anesthesiol*. 2001;13:152–157.
159. El Dawlatly AA, Murshid WR, Elshimy A, et al. The incidence of bradycardia during endoscopic third ventriculostomy. *Anesth Analg*. 2000;91:1142–1144.
160. Fukuhara T, Vorster S, Luciano M. Risk factors for failure of endoscopic third ventriculostomy for obstructive hydrocephalus. *Neurosurgery*. 2000;46:1100–1109.
161. Handler M, Abbott III R, Lee M. A near-fatal complication of endoscopic third ventriculostomy: Case report. *Neurosurgery*. 1994;33:525–527.
162. Anandh B, Madhusudan Reddy KR, Mohanty A, et al. Intraoperative bradycardia and postoperative hyperkalemia in patients undergoing endoscopic third ventriculostomy. *Minim Invasive Neurosurg*. 2002;45:154–157.
163. El Dawlatly AA. Blood biochemistry following endoscopic third ventriculostomy. *Minim Invasive Neurosurg*. 2004;47:47–48.
164. Salvador L, Valero R, Carrero E, et al. Cerebrospinal fluid composition modification after neuroendoscopic procedures. *Minim Invasive Neurosurg*. 2007;50:51–55.
165. McLaughlin MR, Wahlig JB, Kaufmann AM, Albright AL. Traumatic basilar aneurysm after endoscopic third ventriculostomy: Case report. *Neurosurgery*. 1997;41:1400–1403.
166. Fàbregas N. Neurological monitoring in anesthesiology. Where are we and where are we going? [Spanish]. *Rev Esp Anestesiol Reanim*. 2000;47(10):439–441.
167. Choi J, Kim D, Kim S. Endoscopic surgery for obstructive hydrocephalus. *Yonsei Med J*. 1999;40:600–607.
168. Enya S, Masuda Y, Terui K. Respiratory arrest after a ventriculoscopic surgery in infants: Two case reports. *Masui*. 1997;46:416–420.
169. Teo C, Jones R. Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg*. 1996;25:57–63.

170. Jimenez DF, Barone CM, Cartwright CC, Baker L. Early management of craniosynostosis using endoscopic-assisted strip craniectomies and cranial orthotic molding therapy. *Pediatrics*. 2002;110:97–104.
171. Faberowski LW, Black S, Mickle JP. Blood loss and transfusion practice in the perioperative management of craniosynostosis repair. *J Neurosurg Anesthesiol*. 1999;11:167–172.
172. Helfaer MA, Carson BS, James CS, et al. Increased hematocrit and decreased transfusion requirements in children given erythropoietin before undergoing craniofacial surgery. *J Neurosurg*. 1998;88:704–708.
173. Bermejo E, Felix V, Lapunzina P, Galan E, et al. Craniofacial dyssynostosis: Description of the first four Spanish cases and review. *Am J Med Genet A*. 2005;132:41–48.
174. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. *J Craniofac Surg*. 2004;15:670–674.
175. Butler MG, Hayes BG, Hathaway MM, Begleiter ML. Specific genetic diseases at risk for sedation/anesthesia complications. *Anesth Analg*. 2000;91:837–855.
176. Sugiyama K, Yokoyama K. Displacement of the endotracheal tube caused by change of head position in pediatric anesthesia: Evaluation by fiberoptic bronchoscopy. *Anesth Analg*. 1996;82:251–253.
177. Regan JJ, Yuan H, McAfee PC. Laparoscopic fusion of the lumbar spine: Minimally invasive spine surgery: A prospective multicenter study evaluating open and laparoscopic lumbar fusion. *Spine*. 1999;24:402–411.
178. Tetzlaff JE, Dilger JA, Kodsy M, et al. Spinal anesthesia for elective lumbar spine surgery. *J Clin Anesth*. 1998;10:666–669.
179. McLain RF, Kalfas I, Bell GR, Tetzlaff JE, Yoon HJ, Rana M. Comparison of spinal and general anesthesia in lumbar laminectomy surgery: A case-controlled analysis of 400 patients. *J Neurosurg Spine*. 2005;2(1):17–22.
180. Düger C, Gürsoy S, Karadağ O, et al. Anesthetic and analgesic effects in patients undergoing a lumbar laminectomy of spinal, epidural or a combined spinal-epidural block with the addition of morphine. *J Clin Neurosci*. 2012;19(3):406–410.
181. De Rojas JO, Syre P, Welch WC. Regional anesthesia versus general anesthesia for surgery on the lumbar spine: A review of the modern literature. *Clin Neurol Neurosurg*. 2014;119:39–43.
182a. Rosenthal D, Dickman CA. Thoracoscopic microsurgical excision of herniated thoracic discs. *J Neurosurg*. 1998;89:224–235.
182b. Liu GK, Kit WH. Video assisted thoracoscopic surgery for spinal conditions. *Neurol India*. 2005;53(4):489–498.
183. Singh R, Gogna P, Parshad S, Karwasra RK, Karwasra PK, Kaur K. Video-assisted thoracic surgery for tubercular spondylitis. *Minim Invasive Surg*. 2014.
184. Lile A, Lenfant F, Tapie MC, et al. Anesthesia for video-assisted surgery of the thoracic and lumbar spine: A survey of 44 patients [French]. *Neurochirurgie*. 2007;53(1):18–22.
185. Huang EY, Acosta JM, Gardocki RJ, et al. Thoracoscopic anterior spinal release and fusion: Evolution of a faster, improved approach. *J Pediatr Surg*. 2002;37:1732–1735.
186. Kokoska ER, Gabriel KR, Silen ML. Minimally invasive anterior spinal exposure and release in children with scoliosis. *JSLS*. 1998;2:255–258.
187. Steenwyk B, Lyerly 3rd R. Advancements in robotic-assisted thoracic surgery. *Anesthesiol Clin*. 2012;30(4):699–708.
188. Banoub M, Tetzlaff JE, Schubert A. Pharmacologic and physiologic influences affecting sensory evoked potentials. *Anesthesiology*. 2003;99:716–737.
189. Lotto ML, Banoub M, Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. *J Neurosurg Anesthesiol*. 2004;16:32–42.
190. Boulesteix G, Simon L, Lamit X, et al. Intratracheal intubation without muscle relaxant with the use of remifentanil-propofol. *Ann Fr Anesth Reanim*. 1999;18:393–397.
191. Maurtua M, Deogaonkar A, Katz E, et al. Does remifentanil prevent movement during neurosurgical stimulation in the absence of neuromuscular blockade? Preliminary results from a randomized trial. *J Neurosurg Anesthesiol*. 2004;16:363. 126.
192. Liu L, Song Y, Li T. Releasing anterior part of spine under video-assisted thoracoscope for treatment of adolescent idiopathic scoliosis [Chinese]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2007;21:825–828.
193. Kapoor SK, Agarwal PN, Jain Jr BK, Kumar R. Video-assisted thoracoscopic decompression of tubercular spondylitis: Clinical evaluation. *Spine (Phila PA 1976)*. 2005;30:E605–E610.
194. Engum SA. Minimal access thoracic surgery in the pediatric population. *Semin Pediatr Surg*. 2007;16:14–26.
195. Sucato DJ, Elerson E. A comparison between the prone and lateral position for performing a thoracoscopic anterior release and fusion for pediatric spinal deformity. *Spine*. 2003;28:2176–2180.
196. Lai YT, Yang LH, Chio CC, Chen HH. Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. *Neurosurgery*. 1997;41:110–113.
197. McAfee PC, Regan JR, Zdeblick T, et al. The incidence of complications in endoscopic anterior thoracolumbar spinal reconstructive surgery: A prospective multicenter study comprising the first 100 consecutive cases. *Spine*. 1995;20:1624–1632.
198. Coumans JV, Reinhardt MK, Lieberman IH. Kyphoplasty for vertebral compression fractures: 1-year clinical outcomes from a prospective study. *J Neurosurg Spine*. 2003;99:44–50.
199. Katonis P, Hadjipavlou A, Souvatzis X, Tzermiadianos M, Alpantaki K, Simmons JW. Respiratory effects, hemodynamic changes and cement leakage during multilevel cement balloon kyphoplasty. *Eur Spine J*. 2012;21(9):1860–1866.
200. Groen RJ, du Toit DF, Phillips FM, et al. Anatomical and pathological considerations in percutaneous vertebroplasty and kyphoplasty: A reappraisal of the vertebral venous system. *Spine (Phila Pa 1976)*. 2004;29(13):1465–1471. 1.
201. Uemura A, Numaguchi Y, Matsusako M, et al. Effect on partial pressure of oxygen in arterial blood in percutaneous vertebroplasty. *AJNR Am J Neuroradiol*. 2007;28:567–569.
202. Childers Jr JC. Cardiovascular collapse and death during vertebroplasty. *Radiology*. 2003;228:902–903.
203. Yoo KY, Jeong SW, Yoon W, Lee J. Acute respiratory distress syndrome associated with pulmonary cement embolism following percutaneous vertebroplasty with polymethylmethacrylate. *Spine*. 2004;29: E294–E297.
204. Fessler RG, Khoo LT. Minimally invasive cervical microendoscopic foraminotomy: An initial clinical experience. *Neurosurgery*. 2002;51:37–45.
205. King AG, Mills TE, Loe Jr WA, et al. Video-assisted thoracoscopic surgery in the prone position. *Spine*. 2000;25:2403–2406.
206. Perez-Cruet MJ, Fessler RG, Perin NI. Review: Complications of minimally invasive spinal surgery. *Neurosurgery*. 2002;51:26–36.
207. Dagher C, Narchi P, Naccache N, et al. Regional anesthesia for lumbar disc surgery. *Anesthesiology*. 1998;89.
208. Fogarty P, Abalos A, Haas D, et al. Postoperative narcotic requirement following lumbar microdiscectomy is related to pre-operative pain, not to intraoperative ketorolac or bupivacaine. *Anesth Analg*. 1998;86:314.
209. Jellish WS, Thalji Z, Stevenson K, Shea J. A prospective randomized study comparing short- and intermediate-term perioperative outcome variables after spinal or general anesthesia for lumbar disk and laminectomy surgery. *Anesth Analg*. 1996;83:559–564.
210. Mathews HH, Long BH. Minimally invasive techniques for the treatment of intervertebral disk herniation. *J Am Acad Orthop Surg*. 2002;10:80–85.
211. Liu JC, Ondra SL, Angelos P, et al. Is laparoscopic anterior lumbar interbody fusion a useful minimally invasive procedure? *Neurosurgery*. 2002;51:155–158.

Stereotactic Surgery, Deep Brain Stimulation, Brain Biopsy, and Gene Therapies

18

P.H. Manninen • L. Venkatraghavan

INTRODUCTION

Stereotactic surgery is a minimally invasive surgical intervention used for the treatment of functional disorders and in the diagnosis of intracranial lesions. The anesthesiologist plays a key role in the management of patients undergoing stereotactic surgery. The techniques of anesthesia will vary depending on the patient and the traditions and requirements of each institution performing these procedures. The purpose of this chapter is to familiarize the anesthesiologist with the surgical techniques for the insertion of deep brain stimulation (DBS), the influences of anesthesia agents on this procedure, and the anesthetic management of these patients. New developments in this field, as well as in the management of patients for other stereotactic procedures such as brain biopsy and radiosurgery, will also be discussed.

STEREOTACTIC SURGERY

Stereotactic surgery requires a planning system with multimodality neurological imaging and calculation of coordinates of an intracranial location or lesion. This can be performed with either a frame-based or a frameless system. A stereotactic headframe system such as Cosman-Roberts-Wells or Leksell uses a three-dimensional coordinate's frame and a multipurpose stereotactic arc that locates small targets inside the brain.[1] Computerized tomography (CT) or magnetic resonance imaging (MRI) with or without angiography is used to identify the targeted lesion in relation to the distance from the lesion to reference points on the external frame. Surgical apparatus such as an electrode guide or biopsy needle is attached to the headframe and adjusted according to the three-dimensional coordinates of the target. Frameless stereotactic surgery avoids the invasive placement of the headframe and uses external fiducial scalp markers for reference. The relationship of the surgical instrument is then displayed over a previously obtained image of the brain. After imaging and the calculation of coordinates, the patient is transferred to the operating room for surgery.

DEEP BRAIN STIMULATION

Introduction

Deep brain stimulation is used for the treatment of patients with neurological disorders that have an alteration of function that is not usually accompanied by gross structural or anatomical changes, such as Parkinson's disease.[2] The aim of this procedure is to improve the quality of life of the patient. The overall procedure for the insertion of a DBS includes the placement of electrodes into deep brain structures for microelectrode recordings (MER) and macrostimulation for clinical testing of the patient and then the connection of the DBS to an implanted pulse generator.

History

Historically, surgical procedures for functional neurological disorders, such as Parkinson's disease, consisted of making a lesion in deep brain structures with procedures such as thalamotomy, pallidotomy and cingulotomy.[2,3] These procedures are irreversible and may be associated with permanent side effects. In 1987 the use of DBS was first described as an alternative treatment to ablative procedures to reduce the symptoms of patients with Parkinson's disease.[4] The DBS system has advantages over surgical ablation because it is nondestructive, reversible, and adjustable. The safety and long-term benefits of DBS are well documented. The DBS used today provides multiple programmable options, which allow for long-term control of symptoms.[5]

Indications

Following the initial success of DBS therapy in patients with Parkinson's disease, the indications and applications have expanded to include many other disorders. Movement disorders treated with DBS include Parkinson's disease, dystonia, essential tremor, and Tourette's syndrome, and psychiatric disorders include depression, obsessive compulsive disorder, and anorexia. Other indications are chronic pain, epilepsy, Alzheimer's disease, and dementia. With future advances in research in DBS, the list of indications will continue to be modified and extended.[6]

Mechanism and Targets

The exact mechanism of the DBS is not fully understood and may well differ depending on the site of stimulation.[2] The primary target sites vary with the patient's symptoms and include the subthalamic nuclei (STN), globus pallidus pars interna (GPi), and the ventralis intermedius nucleus of the thalamus (Vim). The effects of stimulation on the various nuclei differ. Stimulation of the STN causes hyperpolarization or "neuronal jamming" and this action results in the inhibition of its activity.[7] Stimulation of the GPi nuclei may result in activation of gamma amino butyric acid (GABA)ergic axons, which in turn inhibits GPi neurons. In contrast, stimulation of the Vim nucleus of the thalamus activates output to neurons in the reticular nucleus, which results in an inhibitory signal being sent to thalamic nuclei. The inhibition of these targeted nuclei will then result in improvements of the patient's symptoms (Fig. 18.1).

The most common target for DBS in Parkinson's disease is the STN, as this ameliorates the cardinal symptoms like bradykinesia, rigidity, and tremor.[6] The effective target for stimulation in patients with generalized dystonia and cervical dystonia is the GPi nuclei. Stimulation of the GPi is also used in patients with Parkinson's disease with severe dyskinesia. Stimulation of the Vim nuclei is effective for essential tremors and tremor-dominant Parkinson's disease. Subcallosal cingulate gyrus

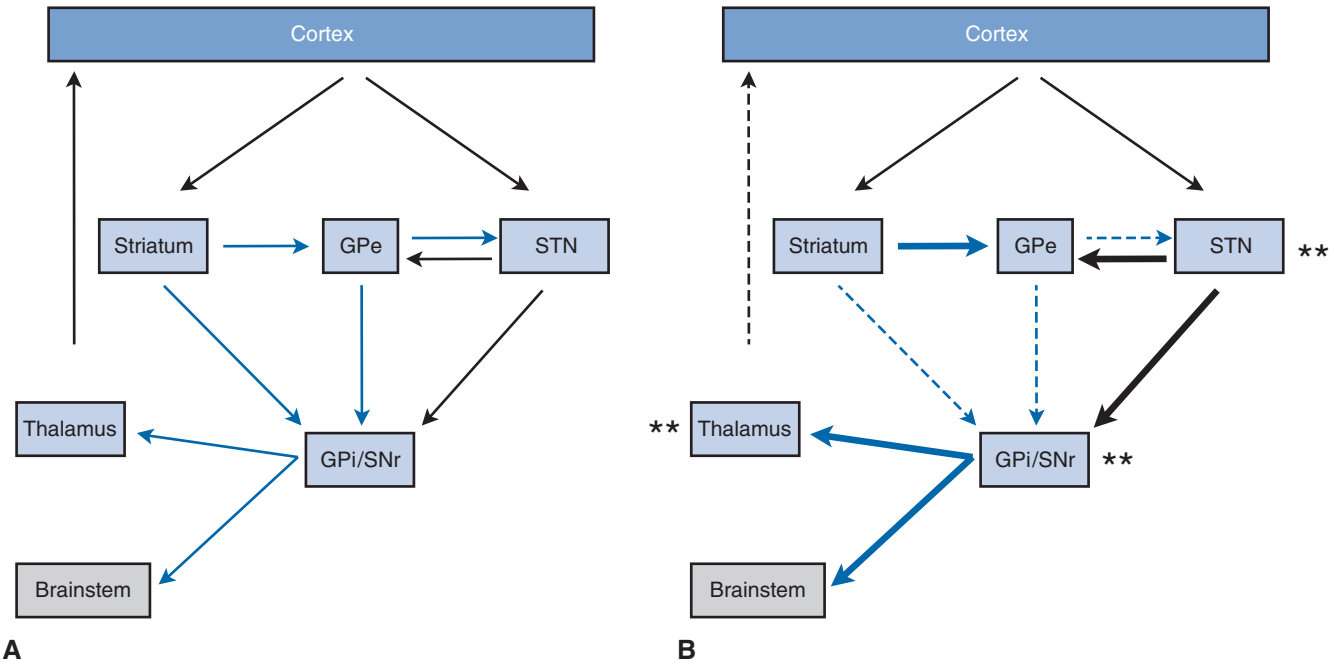


Fig. 18.1 Basal ganglia motor circuitry and targets for deep brain stimulation (DBS) insertion. A simplified motor circuitry of basal ganglia in **(A)** the normal state and in **(B)** Parkinson's disease. In Parkinson's disease (PD), there is an increased activity in both the subthalamic nuclei (STN) and the globus pallidus pars interna (GPi). The output from STN is excitatory to GPi, substantia niagra (SNr) and the global pallidus pars external (GPe). The output from GPi is inhibitory to ventral thalamus and brainstem. This abnormal pathological activity in the STN and GPi and the transmission to the thalamocortical and to the brainstem motor systems are responsible for motor symptoms of Parkinson's disease. Hence, the STN, GPi and the thalamus are the targets for the deep brain stimulation. Stimulation at these sites improves the motor functions in PD by blocking these pathological activities. ➔ (Blue arrows) Inhibitory gamma amino butyric acid (GABA)ergic pathways. ➔ (Black Arrows) Excitatory glutaminergic pathways. Pathways with increased activity are shown in bold and the pathways with decreased activity in PD are shown as dotted line. * * – Targets for DBS insertion. *(Adapted from Lozano AM, Dostrovsky J, Chen R, Ashby P. Deep brain stimulation for Parkinson's disease: disrupting the disruption. Lancet Neurol. 2002;1:225–231.)*

(Cg25), anterior limb of internal capsule (AIC), and the nucleus accumbens (NAcc) are the common target areas in patients with depression and obsessive compulsive disorders. Other targets for stimulation include anterior thalamus (epilepsy), centromedian–parafascicular thalamic nuclei (Tourette syndrome), fornix, and hypothalamus (dementia).[6]

Deep Brain Stimulator Device

The DBS system consists of three components: the intracranial electrode, an extension cable and an implanted pulse generator. The electrode is a coiled wire insulated in polyurethane with four platinum iridium electrodes for implantation in the target neural tissue. The lead is connected by an extension cable to the implanted pulse generator which is a battery-powered programmable single- or dual-channel internal pulse generator (IPG) with a battery unit encased in a titanium housing that sends electrical pulses to stimulate the target site. It is placed subcutaneously below the clavicle or in the abdomen and can be programmed to optimize symptom suppression and control side effects.

Surgical Techniques

The therapeutic effectiveness of DBS depends on the placement of the stimulating electrodes in close proximity to the target nuclei. The target nuclei are deep seated and small in size, requiring innovative methods to increase the accuracy of placement. This includes the use of imaging techniques to visualize and establish coordinates to the target nuclei, intraoperative electrophysiological guidance using MER, and macrostimulation testing of an awake patient to verify that the stimulation of the electrode improves the symptoms with minimal side effects. The procedure begins with placement of the headframe to the patient's skull followed by imaging. Usually MRI is performed to identify target nuclei, although, alternatively, CT can be used if MRI is not possible or is contraindicated. The patient is transferred to the operating room and positioned in a sitting or semi-sitting position with the headframe fixed to the operating room table. The incision and burr hole(s) are made to allow for the placement of an electrode guide and then the DBS electrode(s) into the vicinity of the planned target. Many centers utilize MER to further fine-tune localization of the target sites by detecting and amplifying the activity of individual neurons. The MER electrode is usually inserted 10–15 mm above the target site and then advanced in steps of 0.5–1 mm with a micro driver along the trajectory toward the target nuclei while spontaneous neuronal discharges are recorded. Specific brain structures can be identified based on their unique patterns of firing. Using these variations in spontaneous firing rates between specific nuclei, as well as changes in the firing rates related to patient movement, the neurophysiology team is able to localize the specific brain target (Fig. 18.2). This allows feedback along the entire trajectory and fine adjustments of position before inserting the final electrode. Macrostimulation, which involves the clinical testing of the patient's movements, is used to verify that the stimulation of the electrode at this location will improve their symptoms and not cause any side effects. Radiological confirmation of the electrode placement is obtained and then it is secured and the wound closed. Imaging techniques using 3 Tesla MRI will also improve the accuracy of target localization.[8] Successful insertion of a MRI guided STN-DBS has been used in patients with Parkinson's disease.[9]

Internalization of the Electrodes and Implantation of Pulse Generator

The second stage, the internalization, is performed by tunneling the electrode(s) and connecting extension cable

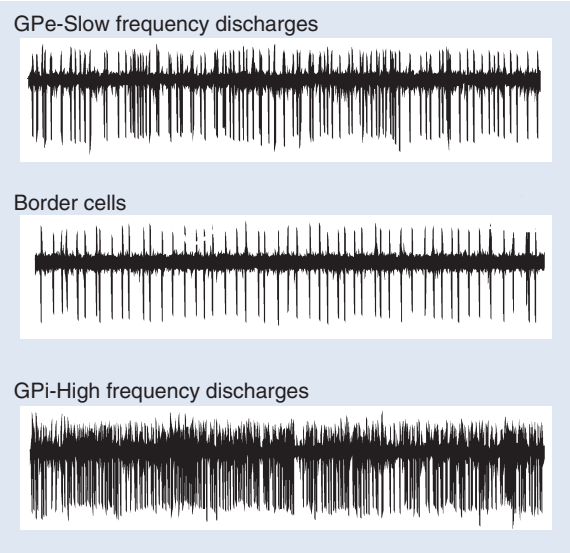


Fig. 18.2 Microelectrode recording during localization of globus pallidus pars interna nuclei (GPi). Changes in neuronal firing are shown as the electrode travels from globus pallidus externa (GPe) through border cells into the GPi.

through the scalp and then subcutaneously tunneling down the side of the neck to where it is connected to the internal pulse generator and battery unit, which is usually implanted in the infraclavicular region of the chest. This procedure may be performed on the same day as insertion of the DBS or maybe delayed for 3 days up to 2 weeks post initial procedure. There is no evidence to favor the best timing of the second stage. The timing depends on the duration of the initial procedure and on patient cooperation. Another reason for delaying is the development of a "microlesion" effect due to edema around the freshly implanted electrode. This effect may cause improvement of the patient's symptoms without any stimulation, which impairs the ability to check for stimulation-induced benefits.[10]

The Effects of Anesthetic Agents on Neuromonitoring for Target Localization

Microelectrode Recordings

The MER are the direct measurements of both spontaneous and stimulus-evoked cellular activity. They help to distinguish the areas that are populated by neurons from the axonal tracts, which are devoid of any action potential activity. The MER are obtained as the microelectrode is passed along the trajectories to the target nuclei. Precise localization can be achieved with a single trajectory pass but multiple passes may be needed. Accurate localization of the target nuclei depends on the individual cellular activity as well as the background neuronal discharges. There are differences in the rate and the pattern of neuronal discharges among the various target cells. Anesthetic agents have been shown to affect both the background activity and the neuronal spike activity.[11]

The effect of anesthetic agents on the MER varies with both target nuclei and also within the same nuclei with different disease processes, such as Parkinson's disease and dystonia.[12] The ability to obtain MER from the STN nuclei during anesthesia has been more successful.[13–15] The anesthetic techniques used have varied from conscious sedation with propofol and dexmedetomidine to general anesthesia with either intravenous or inhalation techniques. Propofol has been shown to affect the background neuronal discharges and both propofol and remifentanil have been shown to produce only minor alterations of STN discharge activity.[11,16] Similarly, dexmedetomidine has been shown to have minimal effect on the MER from the STN. The degree of MER suppression is related to the level of sedation.[17]

The MER from the GPi is often difficult to obtain under general anesthesia. Anesthetic agents have minimal effect on MER from the GPi in patients with Parkinson's disease.[12,18] By contrast, the firing rates in the GPi are substantially decreased in patients with dystonia under general anesthesia with propofol compared to patients with no sedation.[12] The differences in the anesthetic effects on the various target nuclei (STN versus GPi) may be explained by the amount of their GABA input. Neurons from the GPi predominantly receive gamma-amino butyric acid (GABA) input from putamen and GPe and hence they are more suppressed by propofol. Successful target localization in patients with dystonia is possible using balanced anesthesia with low-dose propofol in combination with low level of sevoflurane and/or desflurane.[12,18]

Macrostimulation Testing

Macrostimulation testing of the patient is another complimentary technique for target localization, but requires an awake and cooperative patient. By stimulating the target areas, the clinical benefit of DBS can be assessed by observing the improvement in clinical symptoms such as tremors and rigidity. With stimulation of adjacent structures (internal capsule, medial lemniscus), the patient can report subjective symptoms such as paresthesia or abnormal motor activity. The electrode position can be adjusted to minimize any side effects. When sedation is provided, short-acting agents should be used and all sedation stopped well before the testing. General anesthesia interferes with the evaluation of clinical benefits of DBS by the suppression of clinical symptoms such as tremors and rigidity.[19,20] Also, the patient cannot report subjective effects such as paresthesia or abnormal motor activity associated with stimulation of adjacent structures. Some centers that routinely perform DBS insertion under general anesthesia do not conduct any form of stimulation testing in the operating room but confirm the location of implanted DBS electrode with MRI.[21] Currently, there are no data to show the differences in adverse effects with this approach.

Anesthesia for Deep Brain Stimulation

Goals

The goals of anesthesia during insertion of DBS include providing optimal surgical conditions and patient comfort during the procedure, facilitating intraoperative monitoring and target localization, and rapid diagnoses and treatment of any complications. Considerations for the choice of anesthetic agents and techniques used for each patient include the specific patient population and the specific DBS target.[19,20,22,23] The anesthetic techniques vary according to the institutional practice and have included monitored anesthesia care or conscious sedation with local anesthesia, and general anesthesia. Currently, none of the anesthetic techniques has proven to be superior to others, although awake or sedation techniques are popular as they facilitate intraoperative neurophysiological monitoring.[24,25]

Preoperative Evaluation and Preparation

Successful treatment with DBS is dependent upon appropriate patient selection and evaluation by a multidisciplinary team of neurologists, neurosurgeons, neurophysiologists, and psychiatrists. This includes assessment of the patient

BOX 18.1 Considerations for the Management of Anesthesia

1. Preoperative preparation and reassurance of patient
   a. Appropriate patient selection for anesthesia technique (awake, general anesthesia)
   b. Long procedure – positioning, neurological testing
2. Patient-related concerns
   a. Primary disease (Parkinson's, dystonia)
   b. Comorbidities (cardiac, respiratory, diabetes)
   c. Age (elderly, children)
3. Medications
   a. Polypharmacy, altered pharmacokinetics and dynamics
   b. Medication "off state" – worsening of symptoms
   c. Continuation of medications
4. Procedure and intraoperative considerations
   a. Multiple locations for procedure and transporting between (radiology, operating room)
5. Stereotactic frame
   a. Airway considerations
6. Positioning
   a. Sitting, semi-sitting
   b. Complications (venous air embolism, hypovolemia)
7. Blood pressure control
   a. Treatment of hypertension
8. Anesthetic effects on microelectrode recordings
9. Stimulation testing of patient
   a. Need cooperative, alert patient
10. Postoperative considerations
    a. Slow emergence
    b. Postoperative cognitive problems

with respect to diagnosis, cognitive and psychiatric status, access to care, and expectations by the patient, and the patient's response to medical treatment.[26,27] All patients should also be seen by the anesthesiology team prior to surgery. This includes the routine preoperative assessment and preparation of any patient for a neurosurgical procedure. The considerations for the anesthetic management of patients are shown in Box 18.1. Many patients may have comorbidities related to the disease processes for which the DBS is indicated (Box 18.2).[19,20] Patients who will be awake need good psychological preparation and information on what to expect during the procedure. Instructions for the continuation of disease-specific drugs should be done in conjunction with the neurosurgical team, as some patients need to be in a "drug-off" state to facilitate MER and clinical testing. If the patient's symptoms, especially in Parkinson's disease, worsen during the "drug-off" state a reduced dose of their regular medication can be administered.

Remote Location

The initial part of this procedure, placement of the headframe, may be performed outside of the main operating room, such as in the radiology suite, depending on the institution's practice. In most adults, local anesthesia is used for infiltration of pin sites or a regional scalp block. If anesthesia, general or sedation, is required and is administered in a remote site, all anesthesia equipment, monitors, and drugs should be readily available at the site and for transporting of the patient. If sedation or general anesthesia is required during MRI all precautions and appropriate MRI compatible equipment need to be considered. After imaging the patient is transported to the operating room. Imaging may also be repeated after the procedure to confirm correct placement of the electrode(s).

BOX 18.2 Disease-related Considerations

1. Parkinson's disease:
   a. Pharyngeal, laryngeal dysfunction with increased risk of aspiration pneumonia and of laryngospasm
   b. Hemodynamic instability with autonomic dysfunction, orthostatic hypotension, hypovolemia
   c. Difficulty with monitoring and positioning
   d. Potential drug interactions and adverse effects with anti-Parkinson's medications
   e. Symptoms may get worse in the "off drug" state
2. Dystonia:
   a. Constant movement and deformities may result in difficulties with positioning
   b. Difficult airway with cervical dystonia (spasmodic torticollis)
   c. Laryngeal dystonia increases the risk of laryngospasm and spasmodic dysphonia may lead to difficult communication
3. Essential tremors:
   a. Difficulty in positioning and monitoring
   b. Bradycardia and cardiac arrhythmias from treatment with beta blockers
4. Epilepsy:
   a. Frequent seizures
   b. May have developmental delay which compromises ability to cooperate
   c. Antiepileptic medications may alter pharmacokinetics and dynamics, and result in drug interactions
5. Tourette's syndrome:
   a. Severe movements will make positioning and monitoring difficult
6. Psychiatric patients:
   a. Present with behavioral problems such as severe anxiety, obsessive compulsive
   b. Interactions between psychiatric medications and anesthetic agents
7. Chronic pain:
   a. Opioid resistance
   b. Difficult perioperative pain management
8. Dementia, Alzheimer's:
   a. Communication and cooperation for procedure will be difficult
   b. Postoperative delirium and agitation
9. Anorexia;
   a. Poor nutrition – electrolyte abnormalities and arrhythmias
   b. Altered pharmacokinetics with low albumin

Monitoring and Positioning

Standard monitors include an electrocardiogram, noninvasive blood pressure, oxygen saturation, and end-tidal CO_2. In patients with severe movement disorders and spasticity, monitoring may be technically difficult. Invasive blood pressure monitoring may be considered for patients with severe comorbidities and to guide administration of vasoactive drug in patients with labile blood pressure. Supplemental oxygen is delivered via nasal prongs or a mask with an outlet for end-tidal CO_2 and respiratory rate monitoring. Omission of the urinary catheter will be more comfortable for the awake patient. Vigilant monitoring of fluid administration is necessary to minimize bladder distention, but hypovolemia should also be avoided. The usefulness of depth of anesthesia monitors during DBS insertion is uncertain. Bispectral index monitoring may offer advantages with respect to arousal time, total propofol consumption, and cardiopulmonary stability.[17,28]

Proper positioning of patients on the operating table is important to ensure maximum comfort and cooperativeness for awake patients. The head and neck should be positioned with

some degree of flexion at the lower cervical spine and extension at the atlanto-occipital junction. This helps to make the patient's airway patent and to make it possible to secure the airway in an emergency. The legs should be flexed and supported under the knees to maintain stability when the patient is elevated to a sitting position. Patients with obstructive sleep apnea may need continuous positive airway pressure therapy. Use of clear plastic drapes will make it easier to maintain verbal and eye contact with the patient. Frequent communication with the patient is necessary, to provide reassurance and motivation.

Local Anesthesia

Local anesthesia (bupivacaine, ropivacaine, and lidocaine with and without epinephrine) is used for infiltration or for scalp blocks for the insertion of pins for the headframe and for the surgical incision in patients who will be awake for some part of the procedure. Additional infiltration may be required for closure with prolonged procedures.

Monitored Anesthesia Care

In some centers, and with specific patients, the choice of the surgeon and neurophysiologist may be to have no sedative drugs administered to the patient during the most of the procedure.[24] This is to avoid any influence of sedative drugs on the MER and macrostimulation testing. After the completion of all testing, analgesic and sedative agents may be given to the patient for pain relief during the closure.

Conscious Sedation

Conscious sedation is the most commonly used anesthetic technique during DBS implantation. This allows for patient comfort during the opening and closure. Residual sedative effects can be minimized prior to MER and macrostimulation testing if short-acting agents are used and then stopped prior to any mapping.[22] The use of conscious sedation is particularly appropriate in patients with dystonia or essential tremor who may not be able to lie still for the procedure, but where MER and macrostimulation testing are needed to localize GPi and/or Vim nuclei.[23] With the use of conscious sedation there may be less postoperative nausea and vomiting and therapeutic drugs to treat disorders such as Parkinson's disease can be resumed earlier.

An ideal sedative agent should have no effect or a reversible effect on subcortical activity for good MER and macrostimulation testing. Subcortical areas are extremely sensitive to GABA receptor-mediated medications and will affect the quality of MER. Commonly used agents include propofol, opioids (fentanyl or remifentanil), and dexmedetomidine.[14,24,25] Generally benzodiazepines are avoided as these drugs can abolish the MER. Propofol infusion (50 mcg/kg/min) is commonly used either alone or in combination with opioids, especially for DBS insertion in the STN.[19,25] Propofol is known to cause dyskinesia and abolish tremor, but the extent to which it interferes with MER localization is not fully understood.[25] Short-acting opioids have minimal effect on MER, but with higher doses they may cause worsening of rigidity.[16,25] Dexmedetomidine at low dose infusion rates (0.3–0.6 μg/kg/h) may be a better choice due to its nonGABA-mediated mechanism of action, which allows for MER and not the ameliorating clinical signs of Parkinson's disease.[14,17] Dexmedetomidine also attenuates the hemodynamic responses to anxiety and surgery, reducing the need for antihypertensive medication. This drug is now the sedative agent of choice in many centers. The effects of sedation from any of the anesthetic agent may be more profound in patients undergoing DBS insertion. Delayed awakening in patients with dystonia may occur with propofol as the Gpi neurons receive higher GABA input than STN neurons and these patients have low baseline pallidal activity.[21]

General Anesthesia

Although general anesthesia provides the highest degree of patient comfort and greater control of physiologic parameters, many of the available intraoperative neurophysiological testing procedures are difficult or impossible to perform during general anesthesia. A general anesthetic may provide a higher level of acceptance for DBS surgery by some patients, but it is also necessary in specific groups of patients, such as those who fear being awake, have chronic pain syndromes, have severe "off-medication" movements, have severe dystonia or choreoathetosis, and children.[13] In patients with Parkinson's disease, DBS for the STN can be done safely and effectively under general anesthesia with or without MER.[15,29–31] However, though many different anesthetic agents have been used, there is limited information as to the best agents for general anesthesia. These procedures are also performed under general anesthesia with direct image guidance using intraoperative real-time imaging, which eliminates the need for physiological recordings and patient cooperation.[9,32]

Anesthesia for Second Stage

Anesthesia for internalization of DBS electrodes and implantation of the pulse generator is usually performed under general anesthesia. Though the generator is often implanted in the pectoral area, similar to a cardiac pacemaker, the leads from the DBS system must be tunneled from the site of the burr hole through the neck, which is painful. At this time there are no specific anesthetic drug considerations. However, as head position is often manipulated during this procedure, the seal of a laryngeal mask airway might be unpredictable, thus, endotracheal intubation is usually preferred.

Battery Replacement

The life of the pulse generator battery is about 2 to 5 years. Thus, these patients will be returning for short surgical procedures to replace the battery. The DBS generator should be turned off prior to the procedure but can be restarted immediately after. The patient is positioned supine and infiltration of local anesthesia to the site can be used for intraoperative and postoperative pain. These procedures can be performed with conscious sedation or with general anesthesia using a laryngeal mask.

Complications

During the insertion of DBS with any technique of anesthesia there is the potential for perioperative complications, which demands vigilance in rapid recognition and treatment by the anesthesiologist. Overall, intraprocedure complications have been reported to occur in 12–16% of patients.[24,25]

Surgery-Related Complications

The rate of surgical complications associated with DBS surgery has been decreasing.[33] Intracranial hemorrhage, seizures, and venous air embolism (VAE) are the important perioperative emergencies.[34] Other complications include problems related to the hardware used. Early diagnosis and treatment are important determinants of successful outcome.

Intracranial Bleed

The occurrence of an intracranial hemorrhage is rare but can be devastating. In an awake patient, this is suspected when there is a sudden change in mental status, occurrence of a focal neurological deficit, or sudden onset of hypertension. The diagnosis is usually confirmed by CT or MRI. The incidence of hemorrhage varies from 0.6% to 3.3%.[25,35,36] The presence of hypertension is the only consistent factor associated with the occurrence of a hematoma.[37] A sudden loss of consciousness may require rapid treatment with securing the airway, control of blood pressure, and possible transfer of the patient for CT.

Seizures

Seizures occur in 0.8–4.5 % of patients during insertion of DBS.[24,25] Most periprocedural seizures occur during macrostimulation testing, and are often self-limited and focal in nature. The role of perioperative anticonvulsant therapy in such cases is not clear. Occasionally a generalized tonic clonic seizure may occur and should be treated with small doses of propofol (20 mg). If seizures are controlled, the procedure may be continued as long the patient has recovered and is stable.

Postoperative Cognitive Problems

Postoperative behavioral and cognitive problems are common after DBS insertion.[38] The management of these should include a multidisciplinary approach and assessment of potential underlying causes, such as medications or hemorrhage. Restless or violent patients in the postoperative period may require urgent care. Selective dopamine blockers (clozapine, quetiapine) may be administered safely for the treatment of postoperative behavioral complications (hallucination/delusions) though nonselective blockers (olanzapine, haloperidol) should be avoided.[38]

Anesthesia-Related Complications

Respiratory and Airway

Respiratory and airway complications occur in 1.6–2.2% of patients.[24,25] In the awake patient respiratory depression or loss of airway may result from oversedation or intracranial events, such as seizures or hemorrhage with decreased level of consciousness. When general anesthesia is used, induction of anesthesia and intubation may take place prior to placement of the headframe. But once in the operating room the patient's head is further immobilized as the stereotactic headframe is fixed to the operating room table. If intubation of the trachea is required at any time after this, conventional laryngoscopy may be awkward or difficult as the headframe often restricts neck movement and may cover some or all of the patient's mouth and nose. In an emergency situation the prompt insertion of a laryngeal mask airway may be the most appropriate option. Acute airway obstruction may also occur when a restless, awake patient moves the body but the head remains fixed to the bed.[24,25] Equipment that is necessary to release the headframe from the operating table and to remove the headframe from the patient should be immediately available. If possible, one should attempt to secure the airway without the removal of the patient's headframe, so surgery can be continued if indicated. Other perioperative respiratory complications may be related to comorbid diseases, especially in patients with Parkinson's disease (see Box 18.2).[19,20] Respiratory insufficiency may also occur due to the absence of anti-Parkinson medications in the postoperative period.

Cardiovascular

Overall incidence of cardiac complications is low (0.4–0.6%) during DBS insertion.[25] Hypertension during the procedure, especially with insertion of electrode(s), has been associated with increased risk of intracerebral hemorrhage.[25,35,36] The hypertension may be related to poor preoperative blood pressure control or due to the anxiety and discomfort in an awake patient. The optimal level of blood pressure is not well defined. An acceptable practice is to keep systolic pressure less than 140 mmHg; an increase in blood pressure greater than 20% of the patient's baseline pressure may warrant treatment. Agents such as labetalol, hydralazine, nitroglycerine, sodium nitroprusside, or esmolol may be used. In patients with Parkinson's disease orthostatic hypotension may result from autonomic dysfunction, medications, or preoperative hypovolemia. Administration of a vasoconstrictor agent such as ephedrine or phenylephrine may be necessary.

Venous Air Embolism

Venous air embolism is a potential complication with an incidence of 4.5% mostly due to the sitting position and possible hypovolemia.[39] It frequently occurs during the creation of the burr hole(s). In awake patients, sudden vigorous coughing, chest discomfort, hypoxia, and hypotension may be signs of VAE. Early detection may be possible with precordial Doppler monitoring. If a VAE does occur, the initial treatment includes flooding of the surgical site with fluid and placing the head in a down position. Tension pneumocephalus may also occur during DBS insertion.

Postoperative Care

After surgery patients will be cared for and monitored in a post anesthetic care unit, neurosurgical observation or intensive care unit according routine institutional practice. Frequent assessment of neurological status, respiratory status, control of blood pressure, and prompt treatment of any pain or nausea are important considerations. Any change in neurological status should be immediately related to the neurosurgical team. If therapeutic medications for Parkinson's disease have been withheld, these should be resumed as soon as possible to avoid deterioration in neurological and respiratory function. Further care and activation of the DBS will be performed by the appropriate personnel.

Pediatric Procedures

For pediatric patients with movement disorders such as dystonia, treatment with DBS is highly effective.[40] Children who are very young, have developmental delay, or other congenital problems may not tolerate awake procedures and may require general anesthesia. Some children who are more mature will tolerate conscious sedation or an asleep awake asleep technique. Various sedation techniques have been reported including the use of dexmedetomidine, propofol, ketamine, and remifentanil.[33,40] Real-time interventional MRI guidance in conjunction with a skull mounted aiming device has also been used in children under general anesthesia.[41]

Pre-existing Deep Brain Stimulation for Other Surgery

Patients with pre-existing DBS may present for unrelated surgery. Many concerns of perioperative management are similar to those for patients with cardiac pacemakers and automatic defibrillator devices, although there are specific differences.[27,42] For example, in contrast to cardiac pacemakers, patients can turn off some of the DBS devices. During preoperative

preparation, the information obtained from the patient needs to include an identification of the device and the severity of the patient's symptoms when the DBS system is turned off. If deactivation of the device results in severe symptoms, oral medication should be started before turning the device off. Intraoperative considerations are the adverse interactions between the DBS device and other monitoring and therapeutic equipment. The DBS systems may produce artifacts and interfere with the recording of the electrocardiogram.[19,20] The use of intraoperative electrocautery has the potential to burn neural tissue around the stimulator or to reprogram the device.[43] Turning the device off may decrease possible damage to the stimulator and should be done whenever electrocautery is required. Use of bipolar electrocautery is safer, but if monopolar cautery is absolutely required, the return electrode should be placed as far away as possible from the generator, and the lowest possible source of energy used in short irregular pulses. Short-wave diathermy modalities should not be used as they produce radiofrequency currents and heating of electrodes.[43] The safe use of external and internal cardiac defibrillators has not been established in patients with DBS systems. If cardioversion or defibrillation is required, the paddles must be positioned as far away as possible from the generator and the lowest clinically appropriate energy output should be used. The function of the generator must be checked after such treatments. Electroconvulsive therapy, radiofrequency neuroablation, and peripheral nerve stimulation have been reported to be safe if the stimulator is turned off and the probes are placed far away from the generator.[42] Some patients with a DBS system may need MRI. Generally, MRI is possible in patients, as long as the manufacturer guidelines are followed and scan time is minimized.[44]

ADVANCES

Biological Therapies

Biological therapies aimed to modify degenerated neural circuitry have been explored recently as an alternative therapy in patients with movement disorders. They consist of gene therapy, cell-based therapies or direct infusion of trophic factors.[45] Gene therapy is a technique of providing the long-term production of a therapeutic protein in a target region. In brief, DNA that encodes a therapeutic protein is inserted into a viral vector that can be engineered to specific target cell types (dopaminergic neurons). This viral vector is then injected directly into the target region, which infects the desired cells and transfers the DNA into the host genome. This new DNA then continues to produce the therapeutic protein leading to therapeutic benefit.[46] There are published trials showing promising results in patients with Parkinson's disease.[46]

Magnetic Resonance Image-guided Focused Ultrasound

Prior to the use of DBS, the standard treatment for Parkinson's disease and essential tremors was the production of lesions in the basal ganglia structures.[3] The development of DBS has decreased the use of these procedures, but implanted neurostimulators are expensive, labor intensive, and require continuous maintenance with replacement of pulse generators every 2–6 years. In addition, there is a risk of infection and other hardware-related complications.[33] Recently, transcranial MRI guided focused ultrasound (MRgFUS) has emerged as a novel modality for thermal ablation of the soft tissue.[47] In contrast to traditional ablation procedures, MRgFUS is noninvasive and uses focused ultrasound energy, which is transmitted stereotactically through an array of 1024 ultrasound transducers to produce the ablative lesions. Targeting is done with stereotactically guided high-precision MRI with continuous temperature measurements at and around the target in real time with MR thermometry. The procedure is done entirely inside the MRI unit, with monitored anesthesia care with or without sedation. After its initial success in the treatment for essential tremors and neuropathic pain, this technique is now being considered in patients with Parkinson's disease and other movement disorders.[48] Finally, since no device is implanted into the brain or the body, there is no restriction to future diagnostic work-up with MRI.

Stereotactic Biopsy of Intracranial Lesions

Intracranial lesions that are deep or difficult to access are biopsied for diagnostic purposes. These procedures are usually performed with stereotactic surgery either with a frame-based or frameless system. The overall management of these procedures is similar to that described for DBS insertion. For frame-based procedures the frame is placed on the patient initially, followed by imaging for coordinates and then the surgical biopsy in the operating room. Frameless stereotaxy is less cumbersome as the headframe is not required. However, in the operating room the patient's head will still be fixed with a headclamp to allow for immobilization for neuronavigation-guided placement of the biopsy needle.[49] Further developments with frameless stereotaxy include the use of intraoperative MRI-guided biopsy. Anesthesia for stereotactic biopsies may be with monitored anesthesia care, conscious sedation or general anesthesia, similar to that described for DBS insertion without the mapping considerations. However, continuous vigilance is needed to diagnosis and treat complications quickly, especially in the awake or sedated patient. A change in neurological status may be result of intracranial bleeding or neurological injury.

Therapeutic Stereotactic Radiosurgery

Therapeutic stereotactic radiosurgery procedures include different systems that deliver high-dose radiation beams to various lesions, such as brain tumors and arteriovenous malformations, and to the trigeminal ganglion for the treatment of neuralgia. Some of the systems used are the Gamma Knife, Linear Accelerator, and Cyber Knife. Most stereotactic radiosurgery procedures in adults are performed without anesthesia. However, general anesthesia is frequently required in young children and in some uncooperative adults. The administration of anesthesia requires coordination of the departments of radiology, radiation therapy, neurosurgery, and anesthesiology. As the overall procedure is conducted in several steps and at different locations, all appropriate anesthesia equipment, monitors, and drugs must be ready for use at each site and during transportation. Due to the prolonged procedure, general anesthesia is usually required. At many sites both total intravenous anesthesia (TIVA) and inhalation can be used, but during transport from site to site TIVA is required. Radiation therapy units may not be set up for general anesthesia, for example lack of gas evacuation, making TIVA the only option. An example is Gamma Knife radiotherapy in a young child with general anesthesia.[50] This is often a whole-day procedure, which begins in the radiology suite with the securing of a stereotactic headframe to the cranium. The imaging studies may include CT, MRI, and angiography followed by a planning session. In the Gamma Knife suite, due to the presence of high radiation, monitoring of the patient will take place via cameras directed at the patient, monitors,

gas machine and/or pumps with the video monitors placed at the control desk. After the therapy session is completed, the patient is transferred to a monitored suite, which may be a holding area or post anesthetic care unit for emergence and postoperative care.

SUMMARY

Stereotactic surgery is often a complex procedure involving interactions of multiple specialty teams (neurosurgery, neurology, neurophysiology, neuroradiology, and anesthesiology). The implantation of DBS systems has been shown to be effective in the treatment of many functional disorders and will continue to increase in popularity as new indications emerge. There will also be new developments in surgical, imaging, and monitoring techniques as well as a better understanding of the effects of drugs on the MER. This will help to reduce some of the difficulties and complications of these procedures. Thus, the anesthetic management of these patients will also continue to evolve and to be a challenge for the anesthesiologist. Even though the techniques of anesthesia will continue to differ amongst various centers and may include monitored anesthesia care, conscious sedation and general anesthesia, the general principles of anesthesia care remain the same. The anesthesiologist needs to be aware of the unique requirements of these patients and of these procedures. Continuous monitoring and extreme vigilance are key to early diagnosis and rapid treatment of complications.

REFERENCES

1. Ondo WG, Bronte-Stewart H. The North American survey of placement and adjustment strategies for deep brain stimulation. *Sterotact Funct Neurosurg*. 2005;83:142–147.
2. Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. *JAMA Neurol*. 2013;70:163–171.
3. Lozano AM, Lang AE. Pallidotomy for Parkinson's disease. *Arch Neurol*. 2005;62:1377–1381.
4. Benabid AL, Pollak P, Louveau A, et al. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol*. 1987;50:344–346.
5. Shah RS, Chang SY, Min HK, et al. Deep brain stimulation: technology at the cutting Edge. *J Clin Neurol*. 2010;10:167–182.
6. Venkatraghavan L, Manninen P. Anesthesia for deep brain stimulation. *Curr Opin Anaesthesiol*. 2011;24:495–499.
7. Lozano AM, Dostrovsky J, Chen R, Ashby P. Deep brain stimulation for Parkinson's disease: Disrupting the disruption. *Lancet Neurol*. 2002;1:225–231.
8. Slavin KV, Thulborn KR, Wess C, Nersesyan H. Direct visualization of the human subthalamic nucleus with 3 T MR imaging. *AJNR Am J Neuroradiol*. 2006;27:80–84.
9. Starr PA, Martin AJ, Ostrem JL, et al. Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: Technique and application accuracy. *J Neurosurg*. 2010;112:479–490.
10. Rezai AR, Kopell BH, Gross RE, et al. Deep brain stimulation for Parkinson's disease: Surgical issues. *Mov Disord*. 2006;21:S197–S218.
11. Raz A, Eimerls D, Zaidel A, et al. Propofol decreases neuronal spiking activity in the subthalamic nucleus of Parkinsonian patients. *Anesth Analg*. 2010;111:1285–1289.
12. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: Implications for models of dystonia. *Ann Neurol*. 2003;53:480–488.
13. Maltête D, Navarro S, Welter ML, et al. Subthalamic stimulation in Parkinson disease: With or without anesthesia? *Arch Neurol*. 2004;61:390–392.
14. Rozet I, Muangman S, Vavilala MS, et al. Clinical experience with dexmedetomidine for implantation of deep brain stimulators in Parkinson's disease. *Anesth Analg*. 2006;103:1224–1228.
15. Chen SY, Tsai ST, Lin SH, et al. Subthalamic deep brain stimulation in Parkinson's disease under different anesthetic modalities: A comparative cohort study. *Stereotact Funct Neurosurg*. 2011;89:372–80.
16. Maciver MB, Bronte-Stewart HM, Henderson JM, et al. Human subthalamic neuron spiking exhibits subtle responses to sedatives. *Anesthesiology*. 2011;115:254–264.
17. Elias WJ, Durieux ME, Huss D, Frysinger RC. Dexmedetomidine and arousal effect of subthalamic neurons. *Mov Disord*. 2008; 23:1317–1320.
18. Sanghera MK, Grossman RG, Kalhorn CG, et al. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. *Neurosurgery*. 2003;52:1358–1373.
19. Deiner S, Hagen J. Parkinson's disease and deep brain stimulator placement. *Anesthesiol Clin*. 2009;29:391–415.
20. Frost EA, Osborn I. Deep brain stimulation – surgery for movement disorders and Parkinson's disease. *Int Anesthesiol Clin*. 2009;47:57–68.
21. Foltynie T, Zrinzo L, Martinez-Torres I, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: Efficacy and safety. *J Neurol Neurosurg Psychiatry*. 2011;82:358–363.
22. Venkatraghavan L, Luciano M, Manninen P. Anesthetic management of patients undergoing deep brain stimulation insertion. *Anesth Analg*. 2010;110:1138–1145.
23. Sebeo J, Deiner SG, Alterman RL, Osborn IP. Anesthesia for pediatric deep brain stimulation. *Anesthesiol Res Pract*. 2010;2010. pii: 401419.
24. Khatib R, Ebrahim Z, Rezai A, et al. Perioperative events during deep brain stimulation: The experience at Cleveland Clinic. *J Neurosurg Anesthesiol*. 2008;20:36–40.
25. Venkatraghavan L, Manninen P, Mak P, et al. Anesthesia for functional neurosurgery. Review of complications. *J Neurosurg Anesthesiol*. 2006;18:64–67.
26. Rodriguez RL, Fernandez HH, Haq I, Okun MS. Pearls in patient selection for deep brain stimulation. *Neurologist*. 2007;13:253–260.
27. Poon CCM, Irvin MG. Anaesthesia for deep brain stimulation and in patients with implanted neurostimulator devices. *Br J Anaesth*. 2009;103:152–165.
28. Schulz U, Keh D, Barner C, et al. Bispectral Index Monitoring does not improve anesthesia performance in patients with movement disorders undergoing deep brain stimulating electrode implantation. *Anesth Analg*. 2007;104:1481–1487.
29. Trombetta C, Deogaonkar A, Deogaonkar M, et al. Delayed awakening in dystonia patients undergoing deep brain stimulation surgery. *J Clin Neurosci*. 2010;17:865–868.
30. Harries AM, Kausar J, Roberts SA, et al. Deep brain stimulation of the subthalamic nucleus for advanced Parkinson disease using general anesthesia: Long-term results. *J Neurosurg*. 2012;116:107–113.
31. Kinfe TM, Vesper J. The impact of multichannel microelectrode recording (MER) in deep brain stimulation of the basal ganglia. *Acta Neurochir Suppl*. 2013;117:27–33.
32. Nakajima T, Zrinzo L, Foltynie T, et al. MRI-guided subthalamic nucleus deep brain stimulation without microelectrode recording: Can we dispense with surgery under local anaesthesia? *Stereotact Funct Neurosurg*. 2011;89(5):318–325.
33. Hu X, Jiang X, Zhou X, et al. Avoidance and management of surgical and hardware-related complications of deep brain stimulation. *Stereotact Funct Neurosurg*. 2010;88:296–303.
34. Fenoy FJ, Simpson Jr. RK. Risks of common complications in deep brain stimulation surgery: Management and avoidance. *J Neurosurg*. 2014;120:132–139.
35. Binder DK, Rau GM, Starr PA. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery*. 2005;56:722–732.
36. Gorgulho A, De Salles AA, Frighetto L, Behnke E. Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and microelectrodes in functional neurosurgery. *J Neurosurg*. 2005;102:888–896.
37. Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: A large case series and systematic literature review. *J Neurosurg*. 2012;116:84–94.
38. Poston EM, Frucht SJ. Movement disorder emergencies. *J Neurol*. 2008;255:2–13.
39. Hooper AK, Okun MS, Foote KD, et al. Venous air embolism in deep brain stimulation. *Stereotact Funct Neurosurg*. 2008;87:25–30.
40. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: Experience and technical pearls. *J Neurosurg Pediatr*. 2011;8(6):566–574.
41. Starr PA, Markun LC, Larson PS, et al. Interventional MRI-guided deep brain stimulation in pediatric dystonia: First experience with the ClearPoint system. *J Neurosurg Pediatr*. 2014;14:400–408.

42. Venkatraghavan L, Chinnapa V, Peng P, Brull R. Non-cardiac implantable electrical devices: Brief review and implications for anesthesiologists. *Can J Anaesth*. 2009;56:320–326.
43. Nutt JG, Anderson VC, Peacock JH, et al. DBS and diathermy interaction induces severe CNS damage. *Neurology*. 2001;56:1384–1386.
44. Larson PS, Richardson RM, Starr PA, Martin AJ. Magnetic resonance imaging of implanted deep brain stimulators: Experience in a large series. *Stereotact Funct Neurosurg*. 2008;86:92–100.
45. Remy P. Biotherapies for Parkinson disease. *Rev Neurol (Paris)*. 2014;170(12):763–769.
46. Olanow CW. Gene theapy for Parkinson disease – a hope, or a dream? *Nat Rev Neurol*. 2014;10:9186–9187.
47. Bauer R, Martin E, Haegele-Link S, et al. Noninvasive functional neurosurgery using transcranial MR imaging-guided focused ultrasound. *Parkinsonism Relat Disord*. 2014;20:S197–S199.
48. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: A proof-of-concept study. *Lancet Neurol*. 2013;12:462–468.
49. Dorwald NL, Paleologos TS, Alberti O, Thomas DGT. The advantages of frameless sterotactic biopsy over frame-based biopsy. *Br J Neurosurg*. 2002;16:110–118.
50. Elder A. Special considerations for stereotactic radiosurgery in children. *J Clin Anesth*. 2007;19:616–618.

Perioperative Management of Adult Patients with Severe Head Injury

19

R.D. Phan • A.A. Bendo

EPIDEMIOLOGY OF HEAD INJURY

A *traumatic brain injury* (TBI) is defined as a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain. TBI is one of the most serious, life-threatening conditions in trauma victims. It is a leading cause of disability and death in children and adults. An estimated 1.5 million people sustain TBIs every year in the United States.[1] Of these, more than 50,000 die annually as a result of TBI, and another 80,000 become impaired or disabled for life. TBI is a leading cause of disability in the United States, affecting approximately 5.3 million people. TBI-related disability has a devastating effect on the lives of the injured individuals and their families and results in a tremendous cost to hospital systems and society in terms of the rehabilitation and chronic care of these individuals.

Head injury occurs most often in adolescents, young adults, and people older than 75 years. In all age groups, males are affected two times more often than females and are more likely to sustain severe head injury. The leading causes of TBI are falls, motor vehicle crashes, and assaults.[1] Blasts are a leading cause of TBI among active duty military personnel in war zones.[1] On April 28, 2008, the 110th United States Congress passed a bill to provide for the expansion and improvement of TBI programs (Public Law 110-206), such as research funding for therapeutic interventions and development of practice guidelines for rehabilitation.

HEAD INJURY GUIDELINES

In 1995, recognizing the need to standardize care to improve the outcome for head-injured patients, the Brain Trauma Foundation approved guidelines for the initial resuscitation of the patient with severe head injury and the treatment of intracranial hypertension.[2] A task force was formed in 1998 to review and update the scientific evidence for the guidelines. These evidence-based guidelines for the management of severe TBI were published in 2000[3,4] and then updated in 2007 (Box 19.1).[5] This extensive review of the literature recommends only three standards based on Class I evidence and several guidelines based on Class II evidence. Adherence to these guidelines has remained variable across the trauma centers. However, studies have shown a causal relationship between adherence to the guidelines and improved outcomes. In a study with 22 New York State trauma centers, increased guideline adherence for intracranial pressure monitoring and cerebral perfusion pressure management resulted in significant reductions in mortality over 9 years. [6]

Results of the Corticosteroid Randomization After Significant Head Injury (CRASH) trial, which studied the effect of early administration of methylprednisolone on outcome after head injury in 10,008 adults, were published in 2005.[7] This was an international randomized, placebo-controlled trial on the effect of early administration of 48-hour infusion of methylprednisolone on the risk of death and disability after head injury. The CRASH trial revealed a higher risk of death within 2 weeks of injury in the group receiving corticosteroids than in the group receiving placebo, as well as a higher risk of death or severe disability.[7] The trial investigators concluded that "corticosteroids should not be used routinely in the treatment of head injury."[7]

Evidence-based guidelines for prehospital management of TBI[8,9] and for pediatric brain injury[10] have also been published, and in March 2006, surgical management guidelines were published.[11] However, unlike the writers of the severe TBI management guidelines,[3,5] the writers of the surgical management guidelines report no controlled clinical trials in the literature to support different forms of surgical management or surgical versus conservative therapy. As with the other published guidelines for the management of severe TBI, they state that "this is a document in evolution," and revisions will be made as new knowledge is gained.[11]

CLASSIFICATION OF HEAD INJURY

Classification of severe head injury is based on the Glasgow Coma Scale (GCS) (Table 19.1), which defines neurologic impairment in terms of eye opening, speech, and motor function.[12,13] The total score that can be obtained is 15, and severe head injury is determined by a score of 8 or less persisting for 6 hours or more. The GCS and Glasgow Outcome Scale permit comparison between series of traumatically head-injured patients on the basis of initial clinical presentation and eventual outcome.[14] The prognosis after head injury depends on the type of lesion sustained, the age of the patient, and the severity of the injury as defined by the GCS. In general, mortality is closely related to the initial score on the GCS. For any given lesion and score, however, the elderly have a poorer outcome than do younger patients.[15,16]

Following head trauma, the primary injury results from the biomechanical effect of forces applied to the skull and brain at the time of the insult and are manifested within milliseconds. Currently, there is no treatment for the primary injury. However, primary injuries continue to evolve over the hours after impact and the cascade of injury leading to cell death may be modified. Secondary injury begins within minutes, hours, or days after the impact and represents complicating processes initiated by the primary injury, such as ischemia, brain swelling and edema, intracranial hemorrhage, intracranial hypertension, and herniation. The common denominator of secondary injury is cerebral hypoxia and ischemia (Box 19.2). Factors that aggravate the initial injury include hypoxia, hypercarbia, hypotension, anemia, and hyperglycemia. These contributing factors to secondary injury are preventable. Seizures, infection, and sepsis that may occur hours to days after injury can further aggravate brain damage and must also be prevented or treated promptly.

BOX 19.1 Recommendations from Guidelines for the Management of Severe Traumatic Brain Injury

Standards Based on Class I Evidence

- If intracranial pressure (ICP) is normal, avoid prolonged hyperventilation therapy ($PaCO_2 < 25$ mmHg).
- The use of steroids is not recommended for improving outcome or reducing ICP.
- Prophylactic use of anticonvulsants does not prevent late post-traumatic seizures.

Guidelines Based on Class II Evidence

- All regions should have an organized trauma care system.
- Avoid or immediately correct hypotension (systolic blood pressure <90 mmHg) and hypoxia ($SaO_2 < 90\%$ or $PaO_2 < 60$ mmHg).
- Indications for ICP monitoring include Glasgow Coma Scale score of 3–8 with abnormal computed tomography findings or two or more of the following adverse features: age >40 years, motor posturing, and systolic blood pressure <90 mmHg.
- Initiate treatment for ICP at an upper threshold above 20 mmHg.
- The cerebral perfusion pressure (CPP) value to target lies within the range of 50–70 mmHg. Aggressive attempts to maintain CPP above 70 mmHg should be avoided because of the risk of acute respiratory distress syndrome.
- Avoid using prophylactic hyperventilation ($PaCO_2 \leq 25$ mmHg) therapy during the first 24 hours after severe traumatic brain injury (TBI).
- Mannitol is effective for controlling raised ICP after severe TBI, in doses ranging from 0.25 to 1 g/kg.
- High-dose barbiturate therapy may be considered in hemodynamically stable, salvageable patients who have severe TBI and whose intracranial hypertension is refractory to maximal medical and surgical ICP-lowering therapy.
- Provide nutritional support (140% of resting energy expenditure in patients without respiratory paralysis and 100% of resting energy expenditure in patients with it), using enteral or parenteral formulas containing at least 15% of calories as protein by day 7 after injury.

(Adapted from Bullock RM, Chesnut RM, Clifton GL, et al: Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000;17:449-554; Robertson CS: Management of cerebral perfusion pressure after traumatic brain injury. Anesthesiology 2001;95:1513–1517; and Guidelines for the management of severe traumatic brain injury, 3rd ed. The Brain Trauma Foundation, American Association of Neurological Surgeons; Congress of Neurological Surgeons. J Neurotrauma 2007;24:S1–106.)

Table 19.1 **Modified Glasgow Coma Scale***

Feature	Point(s)
Eye Opening	
Spontaneously	4
To verbal command	3
To pain	2
None	1
Best Verbal Response	
Oriented, conversing	5
Disoriented, conversing	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best Motor Response	
Obeys verbal commands	6
Localizes to pain	5
Flexion or withdrawal	4
Abnormal flexion (decorticate)	3
Extension (decerebrate)	2
No response (flaccid)	1

*Total scores: mild head injury = 13–15 points; moderate = 9–12 points; severe ≤8 points.
(Adapted from Teasdale G, Jennett B: Assessment of coma and impaired consciousness: A practical scale. Lancet 1974;2:81; and Jennett B: Assessment of the severity of head injury. J Neurol Neurosurg Psychiatry 1976;39:647.)

BOX 19.2 Secondary Insults that Can Contribute to Hypoxic and/or Ischemic Brain Damage

Systemic

- Hypoxemia
- Hypotension
- Anemia
- Hypocarbia
- Hypercarbia
- Pyrexia
- Hyponatremia
- Hypoglycemia
- Hyperglycemia

Intracranial

- Hematoma
- Raised intracranial pressure
- Edema
- Seizures
- Infection
- Vasospasm
- Metabolic and ionic changes
- Neurochemical changes
- Inflammatory changes

Secondary insults complicate the course of more than 50% of head-injured patients.[5] An outcome study using data from the Traumatic Coma Data Bank revealed that hypotension occurring after head injury is profoundly detrimental, with more than 70% of patients with hypotension experiencing significant morbidity and mortality (Table 19.2).[15] Furthermore, the combination of hypoxia and hypotension is significantly more detrimental than that of hypotension alone; more than 90% of patients who had both of these experienced a severe outcome or died. These findings confirm the importance of avoiding hypovolemic shock in head-injured patients. The management goal in head-injured patients is to initiate timely and appropriate therapy to prevent secondary brain injury. When the initial injury is not fatal, subsequent neurologic damage and systemic complications should be preventable in most patients.

Primary injury or biomechanical trauma to brain parenchyma consists of concussion, contusion, laceration, and hematoma. Not all severely head-injured patients require surgery. Generalized brain injury with edema or contusion is a common finding, whether or not a surgically correctable mass lesion is present. *Diffuse cerebral swelling* occurs because of sudden intracerebral congestion and hyperemia. Twenty-four

Table 19.2 **Impact of Hypoxia and Hypotension* on Outcome after Severe Head Injury (Defined as Glasgow Coma Scale Score ≤ 8)**

Secondary Insults	Number of Patients	Outcome (% of Patients)		
		Good or Moderate	Severe or Vegetative	Dead
Total number of cases	699	43	21	37
Neither insult	456	51	22	27
Hypoxia (PaO_2 < 60 mmHg)	78	45	22	33
Hypotension (systemic blood pressure <90 mmHg)	113	26	14	60
Both	52	6	19	75

*At time of hospital arrival.
(Data adapted from Moppett IK: Traumatic brain injury: Assessment, resuscitation and early management. Br J Anaesth 2007;99:18-31.)

hours or more after the initial insult, cerebral edema develops in the extracellular spaces of the white matter. Nonoperative treatment of diffuse cerebral swelling involves hyperventilation, diuresis with mannitol and/or furosemide, and barbiturates in conjunction with intracranial pressure (ICP) monitoring. With hyperventilation of $PaCO_2$ < 30 mmHg, oxygen saturation in the jugular bulb (SJO_2), arterio-jugular differences of oxygen ($AVDO_2$) and/or CBF monitoring is recommended. Aggressive hyperventilation ($PaCO_2$ ≤ 25 mmHg) should be avoided because reductions in cerebral blood flow can potentially exaccerbate cerebral hypoxia and ischemia.

Depressed skull fractures and acute epidural, subdural, and intracerebral hematomas usually require craniotomy. Chronic subdural hematomas are often evacuated through burr holes. *Depressed skull fractures* under lacerations should be elevated and debrided within 24 hours to minimize the risk of infection. Bony fragments and penetrating objects should not be manipulated in the emergency department (ED), because they may be tamponading a lacerated vessel or dural sinus.

Traumatic epidural hematoma is an infrequent complication of head injury, usually the result of a motor vehicle accident. The initial injury tears middle meningeal vessels or dural sinuses and causes unconsciousness. When a spasm and clot occur in the vessel(s), the bleeding stops and the patient recovers, experiencing a lucid interval. Over the next several hours, the vessel bleeds and the patient rapidly deteriorates (especially with arterial bleeding). In rapidly deteriorating conditions, treatment should not be delayed to await radiologic evaluation; emergency evacuation is necessary. Venous epidural hematomas develop more slowly, and there may be time for diagnostic testing.

The clinical presentation of *acute subdural hematomas* ranges from minimal deficits to unconsciousness and signs of a mass lesion (hemiparesis, unilateral decerebration, and pupillary enlargement). A lucid interval may occur. The most common cause of subdural hematoma is trauma, but it may occur spontaneously and is associated with coagulopathies, aneurysms, and neoplasms. The severity of injury to the underlying brain is greater with subdural hematomas than with epidural hematomas. It is considered acute if the patient becomes symptomatic within 72 hours, subacute if symptoms appear between 3 and 15 days, and chronic with symptoms after 2 weeks. *Subacute or chronic subdural hematoma* is usually observed in patients older than 50 years. There may be no history of head trauma. The clinical presentation in these patients may vary from focal signs of brain dysfunction to a depressed level of consciousness or development of an organic brain syndrome. Intracranial hypertension is usually associated with acute subdural hematoma. Intensive medical therapy to correct elevated ICP and control brain edema and swelling may be required before, during, and after hematoma evacuation.

In patients with *intracerebral hematomas*, the clinical picture may vary from minimal neurologic deficits to deep coma. Large, solitary intracerebral hematomas should be evacuated. Lesions causing delayed neurologic deterioration from fresh hemorrhage are also evacuated but carry a poor prognosis. Depending on the extent of cerebral injury, patients with intracerebral hematomas may require intensive medical therapy to control intracranial hypertension and cerebral edema. *Coup and contrecoup injuries* usually cause cerebral contusion and intracerebral hemorrhage. In general, contused brain tissue is not removed; occasionally, however, contused tissue over the frontal or temporal poles may be removed to control edema formation and prevent herniation.

EMERGENCY THERAPY

Perioperative management of the head-injured patient focuses on aggressive stabilization of the patient and avoidance of systemic and intracranial insults that cause secondary neuronal injury (see Box 19.2). Secondary brain injury complicates the course of the majority of head-injured patients, adversely influencing outcome. The need to improve care of these patients in the field and ED has been recognized with the development of guidelines, improvement of emergency response services, and better training of providers.[8] The goals of emergency therapy in the field and ED are to prevent and treat all secondary insults and, ultimately, to improve outcome in patients with TBI.

Prehospital Management

Emergency therapy should begin at the site of the accident and in the ambulance. According to the Brain Trauma Foundation's guidelines for prehospital management of traumatic brain injury,[8] emergency medical service (EMS) providers should be trained to follow an established algorithm for the assessment and treatment of TBI. The first priority is initiation of a basic resuscitation protocol that prioritizes the CABs (circulation, airway, and breathing), assessment, and treatment. The patient's airway is maintained, and blood pressure is supported. The EMS provider performs an assessment for appropriate triage of the patient and all necessary therapy to stabilize the patient prior to transport. It is recommended that the severely injured patient (GCS score <9) be taken directly to a level I trauma center "with 24 hour scanning capability, operating room, prompt neurosurgical care and the ability to monitor

intracranial pressure and treat intracranial hypertension as delineated in the Guidelines for the Management of Severe Head Injury."[8] Optimal results for patients with intracranial hematomas require surgical evacuation within 2 to 4 hours of the injury.[17] Therefore, direct transport to a neurosurgical center is crucial for such patients.

The prehospital management guidelines published in 2002[8] and 2008[9] are accepted as the standard for management by prehospital and ED clinicians. Currently, there are insufficient data to support any standard recommendations for prehospital assessment, treatment, transport, and destination. Subsequent to the initial publication of these guidelines, the results of several studies have questioned whether outcome is improved by following them.[18,19] These studies support the direct transfer of patients with severe TBI to a level I or level II trauma center, but controversy remains regarding whether patient outcome is improved by paramedic endotracheal intubation in the field and the mode of transport. The Ontario Prehospital Advanced Life Support (OPALS) Major Trauma Study has shown that a delay for advanced life support, especially on-scene endotracheal intubation, is associated with increased mortality among patients with suspected severe head injuries.[19] This makes it unclear as to which elements of airway management should be revised or reserved for a controlled hospital setting, especially given regional variations in infrastructure and EMS experience.

A prospective, randomized controlled study conducted in New South Wales, Australia known as the Head Injury Retrieval Trial (HIRT) attempted to address the efficacy of advanced prehospital intervention. The goal of the study was to evaluate physician-led prehospital teams compared to paramedic-only teams. The trial results suggests a potential reduction in 30-day mortality for patients with GCS < 9 who received prehospital physician care. [20] The study's conclusion, however, was obscured by the significant crossover where many patients received care they were not intended to receive; that is, changes in prehospital treatment policy during the recruitment period caused a higher rate of dispatched physicians than intended. Therefore, additional studies are needed to confirm these findings.

BOX 19.3 Computed Tomography Scanning Rules for Minor Head Injury

Canadian Rules[21]

High risk (for neurological intervention):
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture
- Vomiting ≥ two episodes
- Age ≥ 65 years

Medium risk (for brain injury on CT):
- Amnesia before impact >30 min
- High-risk mechanism of injury

New Orleans Rules[22]

Short-term memory deficits (persistent anterograde amnesia with GCS score 15)
Intoxication (drug alcohol)
Physical evidence of trauma above the clavicles
Age >60 years
Seizure (suspected or witnessed)
Headache
Vomiting
Coagulopathy

Emergency Department Management

All patients with head injury require full diagnostic evaluation with complete history and neurologic examination. Not all patients require radiologic examination. Two comprehensive studies have resulted in the development of two slightly different sets of rules for determining whether or not a patient with minor head injury must undergo computed tomography (CT) scanning.[21,22] These are the Canadian and New Orleans CT scanning rules for minor head injury (Box 19.3). An unenhanced CT scan is the radiologic procedure of choice in acute TBI. A spiral CT of the head and craniocervical junction is useful in the patients with more severe TBI and potential high cervical spine injuries. Ongoing research is being performed to determine whether or not S100B, a biomarker for blood–brain barrier permeability and CNS injury, may assist in screening patients with minor head injuries.[23]

The majority of head-injured patients seen in the ED are classified as having *mild head injuries* (GCS score 13–15). Most of these patients recover without incident or may have neuropsychological sequelae. These patients are sent home with a caregiver and instructions only, if they have had no history of loss of consciousness, no vomiting or amnesia, normal neurologic findings, and minimal, if any, subgaleal swelling. A small percentage of patients with a GCS score of 13 to 15 on arrival deteriorate and require neurosurgical intervention (for additional references, see Gopinath and colleagues[17]).

Implementation of ED protocols and the use of the Canadian or New Orleans CT scanning rules for minor head injury should help identify the subgroup of patients at risk of deterioration.[21,22] Patients with *moderate head injury* (GCS score 9–12) are able to follow simple commands in the ED, but they can deteriorate rapidly. These patients require emergency CT scanning and admission for observation with serial neurologic examinations, even if the initial CT scan is normal. Patients with *severe head injury* (GCS score ≤ 8) require full advanced trauma life support (ATLS) resuscitation and stabilization in the ED, CT scanning of the head and cervical spine, and, often, surgical management.

Emergency Therapy for Severe Traumatic Brain Injury

The neurologic status and concomitant injuries of patients with severe TBI should be assessed prior to tracheal intubation. These patients are intubated to protect the airway from aspiration and to ensure adequate ventilation and avoidance of hypoxia, hypocapnia, and hypercarbia. The incidence of cervical spine injuries in surviving victims of head injury is 1–3% in adults and 0.5% in children.[24,25] Victims of head-first falls or high-speed motor vehicle accidents have a 10% or greater chance of cervical spine fractures. Radiographic evaluation with a cross-table lateral view can miss 20% of cervical spine fractures.[25] Anteroposterior and odontoid views, in addition to a lateral view, miss only 7% of fractures.[24] Therefore, a CT cervical spine scan will assist in a definitive diagnosis. When a cervical spine fracture has not been excluded by radiographic evaluation, cervical alignment with in-line stabilization is recommended during emergency intubation.[25–28]

In several studies involving the normal and abnormal cervical spine of patients and cadaver models, all airway interventions (e.g., chin lift, cricoid pressure, oral airway placement) were found to cause some degree of cervical spine movement.[26] The literature does not strongly favor the use of any one particular strategy for airway management over another.[26]

Nevertheless, meticulous and prompt attention must be exercised during all stages of patient care starting with prehospital management and throughout the perioperative period, including airway manipulation and surgical positioning. If available, multimodal neuromonitoring (e.g., somatosensory evoked potentials, transcranial electrical motor evoked potentials) should be applied to assess the integrity of the spinal cord during the perioperative period.[26]

When facial fractures and soft tissue edema prevent direct visualization of the larynx, a fiberoptic intubation or intubation with an illuminated stylet or intubating laryngeal mask airway may be attempted. In the patient with severe facial and/or laryngeal injuries, a cricothyrotomy may be required. Nasal intubations are avoided in the patient with suspected basal skull fracture, severe facial fractures, or bleeding diathesis. Basal skull fractures are strongly suspected when the patient has tympanic cavity hemorrhage, otorrhea, petechiae on the mastoid process (Battle's sign), and petechiae around the eyes (panda sign). Nasal intubation of a patient with basal skull fractures can introduce contaminated material directly into the brain and so is best avoided.

For patients with facial injuries, the simplest and most expeditious approach to intubation is preoxygenation, followed by rapid-sequence anesthesia induction with cricoid pressure and maintenance of in-line stabilization. All head-injured patients are assumed to have a full stomach. Awake, oral intubation without anesthetic agents may be possible in the severely injured patient, but it is difficult in the awake or uncooperative, combative patient. Depending on the patient's cardiovascular status, virtually any of the intravenous anesthesia induction agents can be used. The choice of muscle relaxants for emergency intubation in a neurosurgical patient has been the subject of controversial discussion for many years. Succinylcholine can increase ICP. However, in the setting of acute airway compromise, full stomach, and the need to perform subsequent neurologic examinations, the benefits of rapid onset and elimination of succinylcholine may outweigh the risk of transiently increasing ICP.[29]

After control of the airway has been achieved in the head-injured patient, attention should focus on resuscitation of the cardiovascular system. Transient hypotension after head injury is not uncommon, but sustained hypotension usually results from hemorrhage secondary to other systemic injuries. These injuries must be sought and aggressively treated with fluids, blood, and inotropic and vasopressor drugs, when necessary.

When multiple traumas complicate head injury, there is no ideal crystalloid resuscitation fluid. A major concern during resuscitation is the development of cerebral edema. Animal investigations reveal that total serum osmolality is a key factor in brain edema formation.[30,31] When serum osmolality is reduced, cerebral edema develops in normal and abnormal brain. This occurs because the blood–brain barrier is relatively impermeable to sodium. Solutions containing sodium in concentrations lower than that in serum cause water movement into the brain, increasing brain water. Thus, hypo-osmolar solutions (0.45% NaCl and lactated Ringer's solution) are more likely than iso-osmolar fluids (0.9% saline) to increase brain water content. Large-volume fluid resuscitation with iso-osmolar crystalloids reduces colloid oncotic pressure and increases peripheral tissue edema. However, in animal investigations, the brain behaves differently from other tissues, and profound lowering of colloid oncotic pressure with maintenance of serum osmolality does not result in edema in normal brain[30] or in some head-injury models.[31] These results can be explained by the unique structure of the blood–brain barrier and the fact that colloid oncotic pressure gradients generate weak forces in comparison to osmolar gradients.[30]

Some doubt has been cast on the applicability of these laboratory findings to clinical practice. The cryogenic injury model used in these experiments may not be equivalent to head injury in patients. In head-injured patients, the capillary permeability of the brain may be rendered similar to that of peripheral tissues when the blood–brain barrier is damaged. In addition, the time course of these experiments did not allow observation of edema developing 24–48 hours after initial resuscitation, which occurs in head-injured patients. An investigation using the percussive head injury model in rats has shown that reduction in colloid oncotic pressure can aggravate cerebral edema under certain conditions.[32] Therefore, it seems reasonable in clinical practice to avoid a profound reduction in colloid oncotic pressure. Iso-osmolar colloid solutions, such as 5% albumin and 6% hetastarch, have been recommended to maintain oncotic pressure and intravascular volume. However, fresh whole blood, when available, is the ideal colloid resuscitation fluid for hypovolemic patients with TBI and ongoing blood loss.

There is continuing controversy about the selection of resuscitation fluids in patients with TBI after the report of the post hoc follow-up study on the Saline versus Albumin Fluid Evaluation (SAFE) study.[33] This randomized, controlled trial compared 4% albumin with 0.9% saline for fluid management in critically ill trauma patients. The subset of patients with TBI who received albumin resuscitation had substantially worse outcomes than patients with TBI who received saline resuscitation. A more recent post hoc follow-up study corroborated this by finding that albumin resuscitation is associated with elevated ICP, an increased need for additional interventions to treat increased ICP, and increased mortality.[34] Because of these findings the conclusion that colloids worsen the severity of TBI was made. However, analysis of the physico-chemical properties of Albumex 4%, the colloid that was used in the SAFE trial, showed that it is hypo-osmolar. According to Van Aken and co-authors, Albumex 4% has a "theoretical osmolarity of 274.4 mOsm/L, resulting in a nominal osmolality of only 250 mOsm/kg."[35] Considering normal plasma osmolality is 285 mOsm/kg, this finding may explain the increase in brain volume, ICP, and mortality seen from using Albumex 4% in the SAFE trial. Therefore, the authors state that a more appropriate conclusion to the SAFE study may be that hypo-osmolar resuscitation should be avoided in TBI.[35]

Hypertonic saline solutions (3%, 7.5%) can be very useful for low-volume resuscitation in the head-injured patient because they lower ICP, raise blood pressure, and may improve regional cerebral blood flow (CBF).[36,37] Hypertonic saline produces an osmotic diuretic effect on the brain that is similar to that of other hyperosmolar solutions (e.g., mannitol). However, a randomized controlled trial demonstrated that among patients with severe TBI not in hypovolemic shock, initial resuscitation with hypertonic saline did not result in improved 6 month neurologic outcome or survival when compared to normal saline.[38] Therefore, hypertonic saline for prehospital management of TBI patients has not been shown to be more effective in improving outcome than iso-osmolar fluids.[38]

During fluid resuscitation of the head-injured patient, the goals are to maintain serum osmolality, avoid profound reduction in colloid oncotic pressure, and restore circulating blood volume. Immediate therapy is directed at preventing hypotension and maintaining cerebral perfusion pressure (CPP) between 50 and 70 mmHg.[5] When indicated, an ICP monitor is inserted to guide fluid resuscitation and prevent

severe elevations in ICP. The current recommendation is to restore circulating blood volume to normovolemia with glucose-free isotonic crystalloids. Glucose-containing solutions are avoided to enhance perioperative glycemic control. In both animal and human studies, evidence suggests that hyperglycemia at the time of cerebral ischemia worsens outcome.[39,40] Substantial blood loss requires transfusion with crossmatched or fresh whole blood. A minimum hematocrit value between 30% and 33% is recommended to maximize oxygen transport.

Hypertension, tachycardia, and increased cardiac output often develop in patients with isolated head trauma, especially young adults. Electrocardiographic abnormalities and fatal arrhythmias have been reported. The hyperdynamic circulatory responses and electrocardiographic changes may result from a surge in epinephrine (adrenaline) that accompanies head injury. Either labetalol or esmolol can be used to control hypertension and tachycardia in this situation.

In some patients, severe intracranial hypertension precipitates reflex arterial hypertension and bradycardia (Cushing's triad). In such cases, a reduction of ICP by opening the dura or inserting a ventricular drain will interrupt this reflex response. A reduction in systemic blood pressure in these patients can further aggravate cerebral ischemia by reducing CPP. Systemic blood pressure must be lowered cautiously when intracranial hypertension is severe. Systemic vasodilators (e.g., hydralazine, nitroprusside, and sodium nitroglycerin), calcium channel blockers, and volatile anesthetic agents should be avoided as they may increase ICP. If necessary, hypertension is best controlled by anti-hypertensive agents (e.g., esmolol) that reduce CMR and ICP.

During stabilization of head-injured patients, including control of airway and systemic blood pressure, therapeutic interventions to control intracranial hypertension are instituted (Box 19.4). Management of intracranial hypertension is crucial because CPP is directly related to both mean arterial pressure and ICP. The following measures are instituted to acutely reduce intracranial hypertension:

1. The head is elevated 15 degrees and kept in a neutral position to facilitate cerebral venous and cerebrospinal fluid drainage.
2. Mannitol (0.25–1 g/kg) is administered to lower ICP acutely. Alternatively, hypertonic saline may be administered.[41-42]
3. After tracheal intubation, the patient is given a muscle relaxant and mechanically ventilated to a $PaCO_2$ value of 35 mmHg. When there is evidence of transtentorial herniation, hyperventilation to a $PaCO_2$ value of 30 mmHg should be instituted because hyperventilation can rapidly and effectively reduce ICP. Hyperventilation to a $PaCO_2$ lower than 30 mmHg, barbiturate therapy, and cerebrospinal fluid drainage may be considered when other measures have failed.[2,3,5]
4. Appropriate monitoring must be instituted, and hypotension must be avoided.

Mechanical hyperventilation to a $PaCO_2$ value of 25 to 30 mmHg was routinely employed in head-injured patients on the basis of an assumption that hyperventilation, by reducing CBF, would reduce ICP, thereby preserving CPP and CBF. Clinical investigations suggest that head-injured patients are ischemic within the first 24 hours of injury.[43–45] In these patients, hyperventilation may further diminish CBF and aggravate cerebral ischemia.[46] Published guidelines for the management of severe traumatic brain injury no longer recommend hyperventilation to a $PaCO_2$ of 25–30 mmHg as a first-tier therapy.[3,5] In fact, current guidelines recommend avoiding the use of prophylactic hyperventilation ($PaCO_2 \leq 35$ mmHg) therapy during the first 24 hours after severe TBI.[3,5] When hyperventilation is initiated for control of intracranial hypertension, the $PaCO_2$ value should be maintained in the range of 30–35 mmHg in order to accomplish ICP control while minimizing the associated risk of ischemia. Hyperventilation to $PaCO_2$ values less than 30 mmHg should be considered only when second-tier therapy of refractory intracranial hypertension is required. Continuous measurement of jugular bulb oxygen saturation or CBF monitoring is recommended during hyperventilation to guide therapy.[3,5] In emergency situations, hyperventilation should continue in patients in whom the clinical control of intracranial hypertension is the primary concern. However, when the clinical situation no longer requires it or there is evidence of cerebral ischemia, normocapnic ventilation should be instituted.

Mannitol is considered the standard for hyperosmolar therapy and is recommended as a first-tier therapy for treating increased ICP. However, a 2007 Cochrane systematic review found "insufficient reliable evidence to make recommendations on the use of mannitol in the management of patients with traumatic brain injury."[47] After publication of this review, a meta-analysis of 18 studies was conducted to analyze the dose–response relationship between mannitol and ICP.[48] This meta-analysis revealed a significant difference in ICP reduction between patients in whom the initial ICP was higher than 30 mmHg and those in whom it was lower, but it did not provide specific information regarding the mannitol dose–response curve. There was only a weak linear relationship between the change in ICP and mannitol dose. The investigators attributed this weakness to variation in protocols and patients within and among studies and highlighted the need for definitive well-designed studies to answer this important question.[48]

BOX 19.4 Treatment of Intracranial Hypertension in Severe Traumatic Brain Injury (Glasgow Coma Scale Score ≤8)

1. Insert intracranial pressure monitor
2. Maintain cerebral perfusion pressure between 50 and 70 mmHg

First-Tier Therapy

- Ventricular drainage (if available)
- Mannitol 0.25–1 g/kg IV (may repeat if serum osmolarity < 320 mOsm/L and patient is euvolemic)
- Hyperventilation to achieve $PaCO_2$ value of 30–35 mmHg

Second Tier-Therapy

- Hyperventilation to $PaCO_2 < 30$ mmHg (SJO_2, $AVDO_2$ and/or CBF monitoring is recommended)
- High-dose barbiturate therapy
- Consider hypothermia
- Consider hypertensive therapy
- Consider decompressive craniectomy

(Adapted from Bullock R, Chesnut R, Clifton G, et al: Guidelines for the management of severe head injury. The Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. J Neurotrauma 1996;13:641-734; Bullock RM, Chesnut RM, Clifton GL, et al: Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000;17:449–554; and Guidelines for the management of severe traumatic brain injury, 3rd ed. The Brain Trauma Foundation, American Association of Neurological Surgeons; Congress of Neurological Surgeons. J Neurotrauma 2007;24:S1–S106.)

Anesthetic Management

A management priority for all head-injured patients is the rapid diagnosis with CT of an expanding mass lesion that requires immediate surgical evacuation. Intracranial mass lesions such as acute extradural hematoma, subdural hematoma, intracerebral hematoma, and hemorrhagic contusion are surgically evacuated by craniotomy as soon as possible, but preferably no more than 4 hours after injury. When these patients are brought to the operating room, there is usually minimal time available for preanesthetic assessment. Information that should be obtained preoperatively is described in Box 19.5. Anesthetic management is a continuation of the initial resuscitation, including airway management, fluid and electrolyte balance, and ICP control. The routine monitors used for major neurosurgical procedures are applied.

The major goals of anesthetic management are to improve cerebral perfusion and oxygenation, to avoid secondary damage, and to provide adequate surgical conditions. CPP (which is equal to mean arterial pressure [MAP] minus ICP) should be maintained between 50 and 70 mmHg, especially prior to surgical opening of the dura. If ICP rises to a greater extent than mean arterial pressure, CPP is reduced, and the brain becomes ischemic. Uncontrolled increases in ICP can result in herniation and death. Therefore, drugs and techniques that raise ICP are avoided in these patients.

The choice of anesthetic agents depends on the condition of the patient. In the hemodynamically stable patient with severe intracranial hypertension, narcotics in conjunction with a thiopental infusion (2 to 3 mg/kg/h) and a nondepolarizing muscle relaxant can be administered with oxygen and air. Given limited availability of thiopental, most centers are now using pentobarbital. However, thiopental administration has been shown to be more effective than pentobarbital in managing refractory intracranial hypertension.[49]

In patients with less severe intracranial hypertension, anesthesia can be maintained with various combinations of benzodiazepines, narcotics, and a sub-minimum alveolar concentration (sub-MAC) concentration of a potent inhalation agent. Anesthetic management is directed at avoidance of secondary brain injury. Intraoperative hypotension secondary to blood loss or precipitated by anesthetic drugs must be avoided with appropriate volume expansion. Because the brain's response to injury in the first 24 hours is more often hypoperfusion, aggressive hyperventilation and drugs that can exacerbate cerebral ischemia should also be avoided. Propofol may reduce cerebral blood flow more than cerebral metabolism and thereby can produce ischemia under certain conditions, especially during hyperventilation.[50,51] Throughout intraoperative management, the anesthesiologist enhances cerebral homeostasis by maintaining oxygen delivery (hematocrit 30–35% and normal cardiac output), serum glucose level (144–180 mg/dL is recommended[52]), and normal electrolyte balance and by implementing temperature management.

Intraoperative brain swelling or herniation from the operative site may complicate hematoma decompression. Such causes as improper patient positioning, contralateral intracerebral hematoma, venous drainage obstruction from packing, and acute hydrocephalus from intraventricular hemorrhage must be eliminated. In this setting, the adequacy of hyperventilation must also be verified. A large alveolar-arterial CO_2 gradient may exist, so that end-tidal CO_2 may not reflect arterial CO_2. The respiratory system and equipment should be reviewed to ensure normal peak inspiratory and expiratory pressures. Hemopneumothorax, high intra-abdominal pressures, a kinked endotracheal or expiratory tube, or a stuck expiratory valve can produce marked peak inspiratory or expiratory pressures as well as hypoxemia and hypercarbia. Fluid and electrolyte balance must be re-evaluated in patients with cerebral swelling. Mannitol loses its effect after 1 to 3 hours, so a second mannitol bolus to increase osmolarity may be necessary. Volume overload and hyponatremia may also cause cerebral swelling and must be corrected. If cerebral swelling persists, the anesthetic should be converted to opioid and thiopental infusions with oxygen and air. Thiopental may be given in a series of boluses over 5–10 minutes to a total dose of 5–25 mg/kg, followed by an infusion of 4–10 mg/kg/h. To avoid barbiturate-induced myocardial depression and hypotension, it may be necessary to increase preload and add a vasopressor or inotrope such as phenylephrine or dopamine. Malignant brain swelling may require removal of brain tissue and temporary scalp closure with a loose dural patch to minimize ICP after closure.

Emergence of a patient with TBI from anesthesia usually involves transporting an intubated, ventilated, and anesthetized patient to the critical care unit. Even in an uncomplicated craniotomy for evacuation of hematoma, a period of postoperative ventilation is recommended because brain swelling is maximal 12–72 hours after injury. Hypertension and coughing or bucking of the patient on the endotracheal tube should be avoided because either can lead to significant intracranial bleeding. Labetalol or esmolol can be used to treat hypertension, and supplemental barbiturates are given to sedate the patient.

BOX 19.5 Preanesthesia Assessment of the Head-Injured Patient

Airway (cervical spine)
Breathing: ventilation and oxygenation
Circulatory status
Associated injuries
Neurologic status (Glasgow Coma Scale)
Preexisting chronic illness
Circumstances of the injury:
- Time of injury
- Duration of unconsciousness
- Associated alcohol or drug use

(Data from Bendo AA, Kass IS, Hartung J, Cottrell JE: Anesthesia for neurosurgery. In Barash PG, Cullen BF, Stoelting RK (eds): Clinical Anesthesia, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, pp. 746–789.)

Cerebral Protection

Reducing the cerebral metabolic rate for oxygen ($CMRO_2$) is the mainstay of pharmacologic brain protection, and barbiturate administration is the only such intervention that has proved useful in humans. However, level II evidence does not support the use of prophylactic barbiturate administration to achieve electroencephalographic burst suppression. High-dose barbiturate administration (e.g., thiopental and pentobarbital) has been recommended to control elevated ICP refractory to maximum medical and surgical treatment, but should be administered only in hemodynamically stable patients. However, a 2012 Cochrane systematic review of the use of barbiturates in reducing ICP, morbidity, and mortality in TBI patients did not find evidence that barbiturates improve outcome.[53] The review also concluded that one out of every four patients with severe brain injury will develop hypotension from barbiturate therapy that will offset its ICP lowering effect on CPP.[53]

When ischemia reduces supply, hypothermia remains the *sine qua non* for reducing oxygen demand. A reduction of body temperature to 33–35 °C may confer cerebral protection. Although results of earlier clinical trials of moderate hypothermia after head injury have been encouraging, a more recent phase III trial was not able to confirm the utility of hypothermia as a neuroproective strategy.[54] This study, a randomized, multicenter trial, showed no difference in mortality between hypothermic and normothermic treatments, and that hypothermic patients experienced more medical complications. However, a review of clinical trials of hypothermia in TBI has indicated its usefulness in the management of refractory intracranial hypertension.[55,56] It remains unclear whether there is a therapeutic window of opportunity for inducing protective post injury hypothermia. When induction of hypothermia is elected, meticulous care is necessary to avoid adverse side effects such as hypotension, cardiac arrhythmias, coagulopathies, and infections. Rewarming should be carried out slowly over 24 hours to prevent rebound cerebral edema.[56] In this population, there is no doubt that hyperthermia is strongly associated with poor outcome.[56]

CRITICAL CARE

In the critical care unit, the main objectives are to improve recovery from primary brain injury by preventing secondary injury and maintaining cerebral homeostasis. This requires provision of optimal systemic support for cerebral energy metabolism and adequate CPP, and normalizing of ICP for the injured brain. Prompt recognition and treatment of systemic complications that contribute to secondary injury are essential to management of the head-injured patient.[57]

Cerebral Monitoring

A variety of cerebral monitoring techniques have been shown to be increasingly useful in the management of secondary brain injury and the examination of an individual's response to therapeutic interventions.[58,59] Of these, ICP and CPP monitoring have become a cornerstone in neurocritical care. Substantial evidence has been collected indicating that ICP monitoring and management is associated with improved outcomes.[60] Current guidelines for ICP management include level II recommendations that ICP greater than 20 mmHg should be treated. [5] However, a randomized controlled trial conducted in Bolivia and Ecuador found that care focused on maintaining intraparenchymal ICP less than 20 mmHg was not superior to care based on imaging and clinical examination. Six-month mortality and median ICU length of stay were comparable between the two groups.[61] Nevertheless, the authors of the study do not argue against the use of ICP monitors. It also remains unclear whether these findings can be generalized to wealthier countries, where there are superior pre-hospital care and rehabilitation services available.[34]

CPP is an approximate for cerebral blood flow and through adjustments in systemic blood pressure and ICP, may be optimized to theoretically avoid cerebral ischemia and meet metabolic needs of the injured brain. Currently, the Brain Trauma Foundation level II recommendations for CPP target lies within the range of 50–70 mmHg. Although some recent studies have proposed a CPP threshold greater than 70 mmHg, a larger body of evidence has not shown that a higher threshold is associated with improved patient outcome, but has demonstrated that it is linked to serious systemic complications. This includes a five-fold increase in risk of acute respiratory distress syndrome (ARDS) and possible worsening cerebral edema.[62,63] The evidence from current literature does not support a single CPP threshold generalizable to all TBI cases. This underscores the importance of multimodal cerebral monitoring in determining an "optimal" CPP that is patient-, time-, and pathology-specific.[64] These multimodal cerebral monitors include measures of brain oxygenation (i.e., jugular venous oximetry, brain tissue oxygen tension), cerebral autoregulation, cerebral microdialysis, and continuous electroencephalogram.[64] There is controversy concerning the best management protocol for improving outcome in patients with TBI. Most likely, management based on individualized assessment and a multi-targeted approach to provide therapy and reduce the risk of iatrogenic injuries would benefit TBI patients.

Refractory Intracranial Hypertension

Hypertonic saline therapy may be more effective than other diuretics in certain clinical conditions. Examples include patients with refractory intracranial hypertension, and those who require maintenance of intravascular volume.[65,66] Two recent meta-analyses suggest that hypertonic saline is more effective than mannitol in the treatment of increased ICP.[67,68] Both analyses, however, did not include a study by Sakellaridis et al. which found no differences in the reduction of ICP nor duration of action when comparing mannitol to hypertonic saline of similar osmotic load.[69] Therefore, a larger multicenter randomized trial is still needed to establish the first-line medical therapy for intracranial hypertension and to determine dose–response curves and the safety and efficacy of these solutions. With long-term use of hypertonic sodium, there is concern about the physiologic implications of elevated serum sodium values, such as a depressed level of consciousness and seizures.

Decompressive craniectomy is an advanced treatment option for ICP control in patients with diffuse brain swelling refractory to maximal medical management. It decreases ICP by reducing volume constraints on the cranial contents. A wide bilateral frontotemporal craniectomy, duratomy, and duraplasty may be performed. Although decompressive craniectomy decreases ICP, it may not improve neurologic outcome and remains controversial. The DECRA Trial: Early Decompressive Craniectomy in Patients With Severe Traumatic Brain Injury in Australia showed a significantly worse outcome at 6 months in patients who underwent bifrontotemporoparietal decompressive craniectomy than those with maximal medical treatment.[70] Currently ongoing, the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure (RESCUEicp) is a study with different selection criteria for craniectomy. RESCUEicp includes patients with mass lesions, unilateral or bilateral decompressive crancienctomy, and uses a higher ICP threshold for decompressive craniectomy than the DECRA trial.[71] Pending the findings of this study, the indications for and timing of decompressive craniectomy in the treatment of refractory intracranial hypertension may be clarified.

Post-traumatic Seizure

The incidence of post-traumatic seizures (PTS) varies between 10% and 30% after severe TBI and up to 50% in penetrating TBI.[5] PTS occurring within the first 7 days of brain injury are classified as early and those occurring after 7 days are known as late. PTS may lead to cerebral metabolic derangements, increases in ICP, and worsening secondary brain injuries. Thus, prevention and prompt treatment is essential in the management of TBI. Incidence of early PTS has been shown to decrease with the use of phenytoin (gold standard). Another

agent, intravenous levetiracetam, has shown promise in the prevention of early PTS with a lower risk profile; however, it is currently not recommended as first-line therapy, given the need for further studies.[72] Prophylactic anticonvulsants are not recommended in the prevention of late PTS because evidence has not shown a reduction in incidence of late PTS.[5] Late PTS should be treated as new onset seizures.

Systemic Sequelae

The systemic effects of head injury are diverse and can complicate management. They include cardiopulmonary problems (airway obstruction, hypoxemia, shock, acute respiratory distress syndrome, neurogenic pulmonary edema, electrocardiographic changes), hematologic problems (disseminated intravascular coagulation), endocrine problems (pituitary dysfunction, e.g., diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion), metabolic problems (nonketotic hyperosmolar hyperglycemic coma), and gastrointestinal problems (stress ulcers, hemorrhage).

Aspiration pneumonia, fluid overload, and trauma-related acute respiratory distress syndrome are common causes of pulmonary dysfunction in head-injured patients. A fulminant pulmonary edema may also occur. Neurogenic pulmonary edema is characterized by marked pulmonary vascular congestion, intra-alveolar hemorrhage, and a protein-rich edema fluid. Specific features of this syndrome are its rapid onset, its relationship to hypothalamic lesions, and the ability to prevent or attenuate it by α-blockers and central nervous system depressants. Neurogenic pulmonary edema is thought to result from a massive sympathetic discharge from the injured brain secondary to intracranial hypertension. Traditional therapy for pulmonary edema of cardiac origin is ineffective, and the outcome is often fatal. Therapy consists of immediate pharmacologic or surgical relief of intracranial hypertension, supportive respiratory care, and careful fluid management.

Anterior pituitary insufficiency after head injury is a rare occurrence. However, patients exhibiting post-traumatic diabetes insipidus may have a delayed impairment of anterior pituitary hormones, requiring replacement therapy. Posterior pituitary dysfunction occurs more frequently after head trauma. Diabetes insipidus may occur after craniofacial trauma and basal skull fracture. Its clinical presentation involves polyuria, polydipsia, hypernatremia, high serum osmolality, and dilute urine. Commonly, post-traumatic diabetes insipidus is transient, and treatment is based on water replacement. If the patient cannot maintain fluid balance, exogenous vasopressin may be administered. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is associated with euvolumic or hypervolemic hyponatremia, serum and extracellular fluid hypo-osmolality, renal excretion of sodium, urine osmolality greater than serum osmolality, and normal renal and adrenal function. The patient has symptoms and signs of water intoxication (anorexia, nausea, vomiting, irritability, personality changes, and neurologic abnormalities). This syndrome usually begins 3–15 days after trauma, lasting no more than 10–15 days with appropriate therapy. Treatment includes water restriction with or without hypertonic saline. Cerebral salt wasting syndrome, while less common than SIADH, is characterized by hypovolemic hyponatremia with signs and symptoms of dehydration, serum hypo-osmalality, and a primary renal loss of sodium. Treatment involves adequate volume resuscitation and repletion of sodium slowly so as to avoid central pontine myelinolysis.

Many factors in neurosurgical patients predispose to nonketotic hyperosmolar hyperglycemic coma, such as steroids, prolonged mannitol therapy, hyperosmolar tube feedings, phenytoin, and limited water replacement. Diagnostic criteria for nonketotic hyperosmolar hyperglycemic coma are hyperglycemia, glucosuria, absence of ketosis, plasma osmolality greater than 330 mOsm/kg, dehydration, and central nervous system dysfunction. Hypovolemia and hypertonicity are the immediate threats to life. Serum sodium levels may be high, normal, or low, depending on the state of hydration. The serum potassium level is low. Serial laboratory tests are essential. Once sodium deficits are replaced and blood pressure and urine output are stable, water deficits are replaced with 0.45% saline. Hyperglycemia, which worsens secondary cerebral ischemia, should be treated with a "moderate" target range of 144–180 mg/dL, to avoid cerebral hypoglycemia.[52] Continuous insulin infusions, starting at a low dose, are preferable to insulin bolus in order to minimize large changes in glycemic levels.[73]

Coagulopathy

Traumatic brain injury, in the absence of extracranial injury, has been associated with hemostatic derangements, both hypocoagulable and hypercoagulable states. The incidence of TBI-related coagulopathy has been estimated at 20–35% for patients upon admission and nearly doubles within 72 hours post trauma.[74,75] Early detection and hemostatic monitoring have been reported to minimize secondary brain injury and improve patient outcome. In addition to PT, aPPT, INR, and platelet values, newer laboratory studies including rotational thromboelastometry or thromboelastography have shown promise in the detection and guidance of therapy.[76] The Brain Trauma Foundation's guidelines currently do not include recommendations for coagulopathy other than deep venous thrombosis prophylaxis.

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial assessed the effects of tranexamic acid (TXA) in reducing hemorrhage in trauma patients. A subgroup analysis, randomized control trial within the study, known as CRASH-2 Intracranial Bleeding Study, examined the effects of TXA on intracranial hemorrhage in TBI.[77] This study found that, although "neither moderate benefits nor moderate harmful effects can be excluded," early administration (within 3 hours of initial injury) might still improve outcome after TBI.[77] The CRASH-2 Intracranial Bleeding Study may be limited by the cofounding variable of extracranial hemorrhage in the study population. The effects of TXA may differ in cases with isolated TBI, which is currently being investigated by the ongoing CRASH-3 trial.[78]

SUMMARY

Guidelines for the management of patients with severe TBI were published by the Brain Trauma Foundation in 1996.[2] Revisions to the guidelines were published in 2000 in a document that discusses various management protocols and treatments in light of supporting evidence.[3] Management updates are being published on the World Wide Web as new information is made available and the guidelines are revised.[5] Publication of these recommendations, guidelines, and standards by the Brain Trauma Foundation reflects an ongoing effort to improve outcome in this high-risk population through evidence-based management and standardized care.

However, several management recommendations are based only on level II or III evidence, and not all recommendations, when implemented, have improved outcome. Therefore, to address these unresolved clinical concerns, large multicenter

randomized trials are under way or being planned. There is no doubt that the growing awareness of perioperative risk and prevention of secondary injury in this population from the time of injury through critical care has the potential to improve outcome. The challenge is to reduce both mortality and disability in this vulnerable patient population.

REFERENCES

1. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. CDC Fact Sheet, revised and updated, March 21, 2014.
2. Bullock R, Chesnut R, Clifton G, et al. Guidelines for the management of severe traumatic brain injury. The Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. *J Neurotrauma*. 1996;13:641–734.
3. Bullock RM, Chesnut RM, Clifton GL, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2000;17:449–554.
4. Robertson CS. Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology*. 2001;95:1513–1517.
5. The Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury, 3rd ed. *J Neurotrauma*. 2007;24:S1–S106.
6. Gerber LM, Chiu Y, Carney N, Hartl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. *J Neurosurg*. 2013;119:1583–1590.
7. Edwards P, Arango M, Balica L, et al. Crash Trial Collaborators. Final results of MRC CRASH, a randomized placebo controlled trial of intravenous corticosteroid in adults with head injury—Outcomes at 6 months. *Lancet*. 2005;365:1957–1959.
8. Gabriel EJ, Ghajar J, Jagoda A, et al. Brain Trauma Foundation. Guidelines for prehospital management of traumatic brain injury. *J Neurotrauma*. 2002;19:111–174.
9. Badjatia N, Carney N, Crocco TJ, et al. Brain Trauma Foundation, BTF Center for Guidelines Management. Guidelines for prehospital management of traumatic brain injury, 2nd ed. *Prehosp Emerg Care*. 2008;12:S1–S52.
10. Adelson PD, Bratton SL, Carney NA, et al. American Association for Surgery of Trauma, Child Neurology Society, International Society for Pediatric Neurosurgery, International Trauma Anesthesia and Critical Care Society, Society of Critical Care Medicine, World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. *Pediatr Crit Care Med*. 2003;4(suppl):S1–S75.
11. Bullock MR, Chesnut R, Ghajar J, et al. The Brain Trauma Foundation and the Congress of Neurological Surgeons. Guidelines for the surgical management of traumatic brain injury. *Neurosurg Suppl*. 2006;58:S2–S21. S2–S62.
12. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet*. 1974;2(7872):81.
13. Jennett B. Assessment of the severity of head injury. *J Neurol Neurosurg Psychiatry*. 1976;39:647.
14. Jennett B, Bond MR. Assessment of outcome after severe brain damage. *Lancet*. 1975;1(7905):480.
15. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34:216–222.
16. Moppett IK. Traumatic brain injury: Assessment, resuscitation and early management. *Br J Anaesth*. 2007;99:18–31.
17. Gopinath SP, Robertson CS. Management of severe head injury. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery*. 4th ed. St. Louis, MO: Mosby; 2001:663–691.
18. Härtl R, Gerber LM, Iacono L, et al. Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. *J Trauma*. 2006;60:1250–1256.
19. Stiell IG, Nesbitt LP, Pickett W, et al. OPALS Study Group. The OPALS Major Trauma Study: Impact of advanced life-support on survival and morbidity. *CMAJ*. 2008;178:1141–1152.
20. Garner AA, Mann KP, Fearnside M, et al. The Head Injury Retrieval Trial (HIRT): A single centre randomised controlled trial of physician prehospital management of severe blunt head injury compared with management by paramedics only. *Emerg Med J*. 2015;1–7. http://dx.doi.org/10.1136/emermed-2014-204390.
21. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT head rule for patients with minor head injury. *Lancet*. 2001;357:1391–1396.
22. Haydel MJ, Preton CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. *N Engl J Med*. 2000;343:100–105.
23. Zongo D, Ribéreau-Gayon R, Masson F, et al. S100-B protein as a screening tool for the early assessment of minor head injury. *Ann Emerg Med*. 2012;59(1):209–218.
24. Hastings RH, Marks JD. Airway management for trauma patients with potential cervical spine injuries. *Anesth Analg*. 1991;73:471–482.
25. Crosby ET. Airway management in adults after cervical spine trauma. *Anesthesiology*. 2006;104:1293–1318.
26. Hung O, Zhang JB. Breaking down silos to protect the spinal cord [editorial]. *Anesth Analg*. 2013;117:6–9.
27. Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. *N Engl J Med*. 2000;343:94.
28. Lennarson PJ, Smith D, Todd MM, et al. Segmental cervical spinal motion during orotracheal intubation of the intact and injured spine with and without external stabilization. *J Neurosurg*. 2000;92(Spine 2):201–206.
29. Bendo AA, Kass IS, Hartung J, Cottrell JE. Anesthesia for neurosurgery. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:746–789.
30. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *Anesthesiology*. 1987;67:936.
31. Kaieda R, Todd MM, Cook LN, et al. Acute effects of changing plasma osmolality and colloid oncotic pressure on the formation of brain edema after cryogenic injury. *Neurosurgery*. 1989;24:671.
32. Drummond JC, Patel PM, Cole DJ, et al. The effect of the reduction of colloid oncotic pressure, with and without reduction of osmolality, on post-traumatic cerebral edema. *Anesthesiology*. 1998;88:993.
33. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with hypotension and severe traumatic brain injury. *N Engl J Med*. 2007;357:874–884.
34. Cooper DJ, Myburgh J, Heritier S, et al. Albumin resuscitation for traumatic brain injury: Is intracranial hypertension the cause of increased mortality? *J Neurotrauma*. 2013;30:512–518.
35. Van Aken HK, Kampmeier TG, Ertmer C, Westphal M. Fluid resuscitation in patients with traumatic brain injury: What is a SAFE approach? *Curr Opin Anaesthesiol*. 2012;25:563–565.
36. Vassar MJ, Fischer RP, O'Brien RE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. *Arch Surg*. 1993;128:1003.
37. Prough DS, Whitley JM, Taylor CL, et al. Regional cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic saline. *Anesthesiology*. 1991;75:319.
38. Bulger EM, May S, Kerby JD, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: A randomized, placebo controlled trial. *Ann Surg*. 2011;253:431–441.
39. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: Review and clinical recommendations. *Mayo Clin Proc*. 1996;71:801–812.
40. Bilotta F, Giovannini F, Caramia R, Rosa G. Glycemia management in neurocritical care patients: A review. *J Neurosurg Anesthesiol*. 2009;20:2–9.
41. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg*. 2006;102:1836.
42. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology*. 2007;107:697.
43. Orbits WD, Linguist TW, Jaggy JL, et al. Cerebral blood flow and metabolism in comatose patients with acute head injury: Relationship to intracranial hypertension. *J Neurosurg*. 1984;61:241.
44. Mislead JP, Marabou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg*. 1991;75:731.
45. Martin NA, Patwardhan RV, Alexander MJ, et al. Characterization of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. *J Neurosurg*. 1997;87:9.
46. Stringer WA, Hasso AN, Thompson JR, et al. Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: Demonstration by xenon-enhanced CT. *AJNR Am J Neuroradiol*. 1993;14:475.
47. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2007;(1). CD001049.
48. Sorani MD, Manley GT. Dose-response relationship of mannitol and intracranial pressure: A meta-analysis. *J Neurosurg*. 2008;108:80–87.
49. Perez-Barcena J, Llompart-Pou JA, et al. Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: A randomized controlled trial. *Crit Care*. 2008;12:R112.

50. Cenic A, Craen RA, Lee TY, Gelb AW. Cerebral blood volume and blood flow responses to hyperventilation in brain tumors during isoflurane or propofol anesthesia. *Anesth Analg*. 2002;94:661–666.
51. Adembri C, Venturi L, Pellegrini-Giampietro DE. Neuroprotective effects of propofol in acute cerebral injury. *CNS Drug Rev*. 2007;13:333–351.
52. Kramer AH, Roberts DJ, Zygun DA. Optimal glycemic control in neurocritical care patients: A systematic review and meta-analysis. *Crit Care*. 2012;16:R203.
53. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Update in *Cochrane Database Syst Rev*. 2012;12.
54. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): A randomised trial. *Lancet Neurol*. 2011;10:131–139.
55 Clifton GL. Therapeutic hypothermia and temperature management. 2011;1(3):143–149.
56. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurologic injuries. *Lancet*. 2008;371:1955.
57. Mazzeo AT, Kunene NK, Choi S, et al. Quantification of ischemic events after severe traumatic brain injury in humans: A simple scoring system. *J Neurosurg Anesthesiol*. 2006;18:170.
58. Tisdall MM, Smith M. Multimodal monitoring in traumatic brain injury: Current status and future directions. *Br J Anaesth*. 2007;99:61–67.
59. Oddo M, Villa F, Citerio G. Brain multimodality monitoring: An update. *Curr Opin Crit Care*. 2012;18:111–118.
60. Stein SC, Georgoff P, Meghan S, et al. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. *J Neurosurg*. 2010;112:1105–1112.
61. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;367: 2471–2481.
62. Constant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: A complication of induced hypertension after severe head injury. *J Neurosurg*. 2001;95:560–568.
63. Robertson CS. Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology*. 2001;95:1513–1517.
64. Kirkman MA, Smith M. Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/CPP guided therapy: A standard of care or optional extra after brain injury? *Br J Anaesth*. 2014;112:35–46.
65. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med*. 2000;28:3301.
66. Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 ml/kg 7% saline is more effective than 2 ml/kg 20% mannitol. *Crit Care Med*. 2003;31:1683.
67. Kamel H, Navi BB, Nakagawa K, Hemphill 3rd. JC, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials. *Crit Care Med*. 2011;39:554–559.
68. Mortazavi MM, Romeo AK, Deep A, et al. Hypertonic saline for treating raised intracranial pressure: Literature review with meta-analysis. *J Neurosurg*. 2012;116:210–221.
69. Sakellaridis N, Pavlou E, Karatzas S, et al. Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries. *J Neurosurg*. 2011;114:545–548.
70. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364:1493–1502.
71 Hutchinson PJ. The RESCUEicp Study: Randomised evaluation of surgery with craniectomy for uncontrollable elevation of intra-cranial pressure. http://www.rescueicp.com; 2011.
72. Kirmani BF, Mungall D, Ling G. Role of intravenous levetiracetam in seizure prophylaxis of severe traumatic brain injury patients. *Front Neurol*. 2013;4:170.
73. Bilotta F, Rosa G. Optimal glycemic control in neurocritical care patients. *Crit Care*. 2012;16:163.
74. Franschman G, Boer C, Andriessen T, et al. Multicenter evaluation of the course of coagulopathy in patients with isolated traumatic brain injury: Relation to CT characteristics and outcome. *J Neurotrauma*. 2012;29:128–136.
75. Greuters S, van der Berg A, Franschman G, et al. Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. *Crit Care*. 2011;15:R2.
76. Boer C, Franschman G, Loer SA. Prehospital management of severe traumatic brain injury: Concepts and ongoing controversies. *Curr Opin Anaesthesiol*. 2012;25(5):556–562.
77. CRASH-2 Collaborators: Intracranial Bleeding Study. Effect of tranexamic and acid in traumatic brain injury: A nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011;343:d3795.
78. Dewan Y, Komolafe EO, Mejía-Mantilla JH, et al. On behalf CRASH-3 Collaborators. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: Study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials*. 2012;13:87.

Pediatric Neuroanesthesia and Critical Care

20

S.G. Soriano III • M.L. McManus

Neurosurgical lesions in infants and children have distinct manifestations and management issues. Age-related differences in the surgical lesions, anatomy and physiological responses to surgery and anesthesia underlie the clinically relevant differences between pediatric patients and their adult counterparts. Technical advances in neurosurgery and subspecialization in pediatric neurosurgery, anesthesiology and critical care have dramatically improved the outcome in pediatric patients with surgical lesions of the central nervous system (CNS).[1] The perioperative management should be based on the developmental stage of the patient with the caveat that neonates may be vulnerable to iatrogenic CNS injury.[2] The aim of this chapter is to highlight these age-dependent differences and their effects on the management of the pediatric neurosurgical patient during the perioperative period.

DEVELOPMENTAL CONSIDERATIONS

Differences in cerebrovascular physiology and cranial bone development distinguish infants and children from adults. Cerebral blood flow (CBF) is coupled tightly to metabolic demand, and both increase proportionally immediately after birth. CBF varies with the age of the patient. Computed tomography perfusion scans show that CBF peaks between 2 and 4 years and settles at 7–8 years (Fig. 20.1).[3] These changes mirror those in neuroanatomical development. The idealized autoregulatory range of blood pressure in a normal newborn is between 20 and 60 mmHg, which reflects the relatively low cerebral metabolic requirements and blood pressure during the perinatal period. More importantly, the slope of the autoregulatory curve drops and rises significantly at the lower and upper limits of the curve, respectively (Fig. 20.2).

Cerebral autoregulation is intact in healthy full-term neonates.[4] However, critically ill premature neonates have a linear correlation between CBF and systemic blood pressure.[5] This pattern of CBF pressure-passivity occurs in premature neonates with low gestational age and birth weight, and systemic hypotension. It should be noted that systolic arterial blood pressure is a poor surrogate of cerebral perfusion pressure in premature infants. An assessment of the diastolic blood pressure and CBF velocity may be a better marker of cerebral perfusion pressure in this population.[6] Therefore, tight blood pressure control is essential in the management of neonates to minimize both cerebral ischemia and intraventricular hemorrhage.

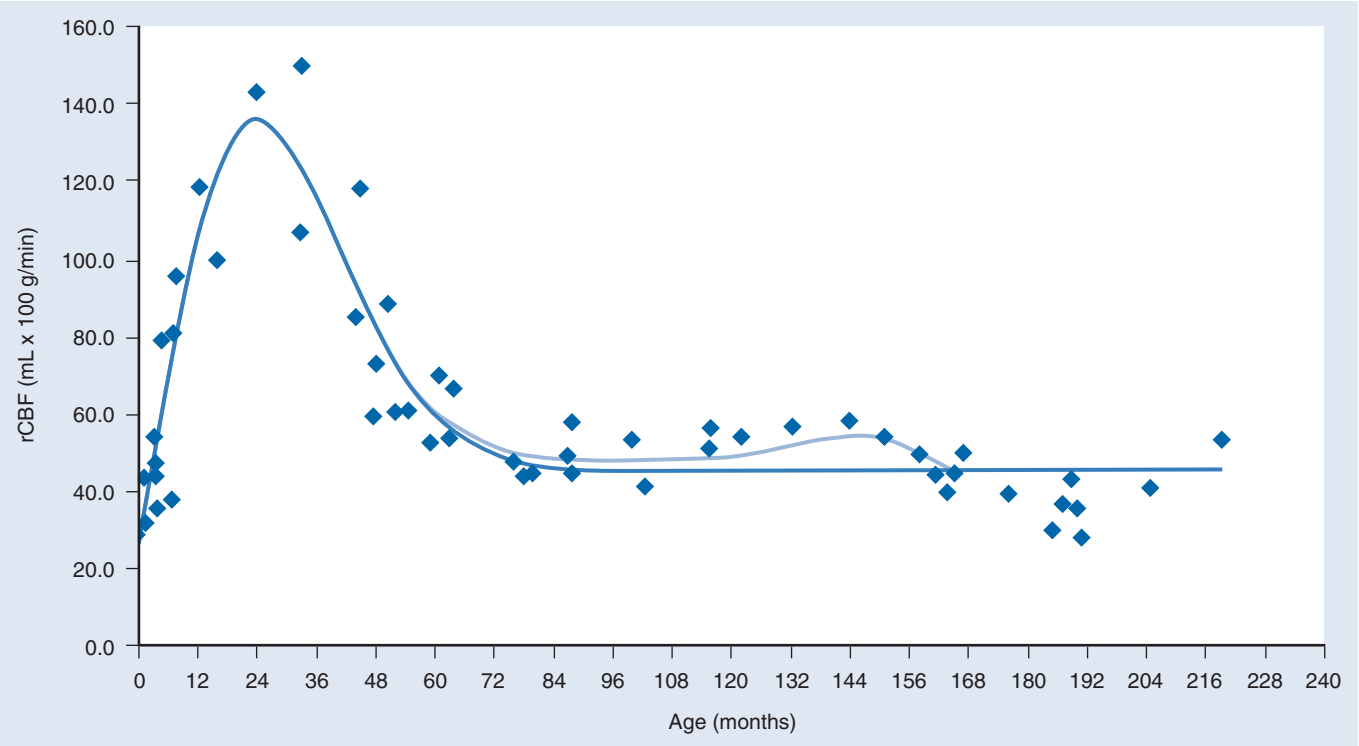


Fig. 20.1 Age-related evolution of global average regional cerebral blood flow (rCBF) values. *(From Wintermark M, Lepori D, Cotting J, et al: Brain perfusion in children: evolution with age assessed by quantitative perfusion computed tomography. Pediatrics 2004;113:1642–1652.)*

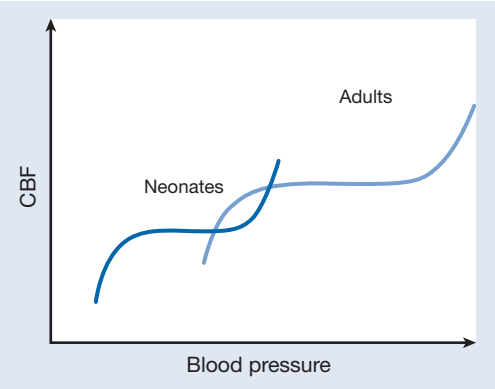


Fig. 20.2 Autoregulation of cerebral blood flow (CBF) in children. The slope of the autoregulatory curve drops and rises significantly at the lower and upper limits of the curve, respectively, and is shifted to the left in the neonate and small child.

Transcranial Doppler studies demonstrated that the lower limit of cerebral autoregulation was equivalent among older and younger children.[7] These observations suggest that children younger than 2 years may have lower autoregulatory reserve because of their relatively low baseline mean arterial pressures and may be at greater risk of cerebral ischemia. Multimodal analysis of cerebral perfusion in infants and children undergoing cardiopulmonary bypass surgery reveal a wide range of lower limits of autoregulation.[8] This observation demonstrates variability in pediatric patients and highlights the limitations of current monitors to optimize cerebral perfusion.[9]

Adults and infants differ in the percentage of cardiac output directed to the brain. CBF is 10–20% of the cardiac output during the first 6 months and peaks at 55% between the second and fourth years.[3] CBF settles to the adult levels of 15% by 7–8 years. The head of the infant and child also accounts for a large percentage of the body surface area and blood volume (Fig. 20.3). This feature places the young child at risk for significant hemodynamic instability during neurosurgical procedures.

The infant cranial vault is also in a state of flux. Open fontanels and cranial sutures result in a compliant intracranial space (Fig. 20.4). The mass effect of a slow-growing tumor or insidious hemorrhage is often masked in an infant by a compensatory distended fontanel and widening of the cranial sutures. However, acute increases in cranial volume due to massive hemorrhage or an obstructed ventricular system cannot be attenuated by expansion of the immature cranial vault and often result in life-threatening intracranial hypertension.

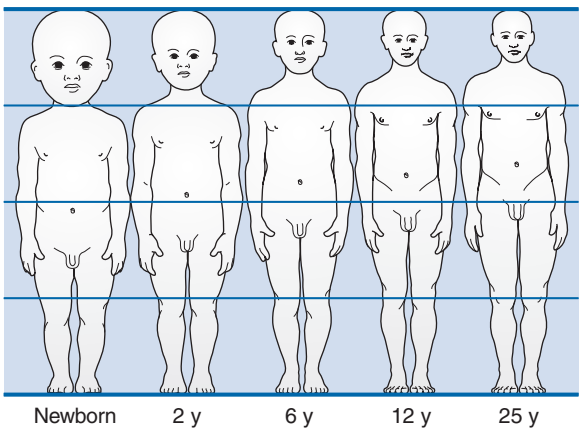


Fig. 20.3 The head size and surface area is proportionately greater in infants than in adults. y, years.

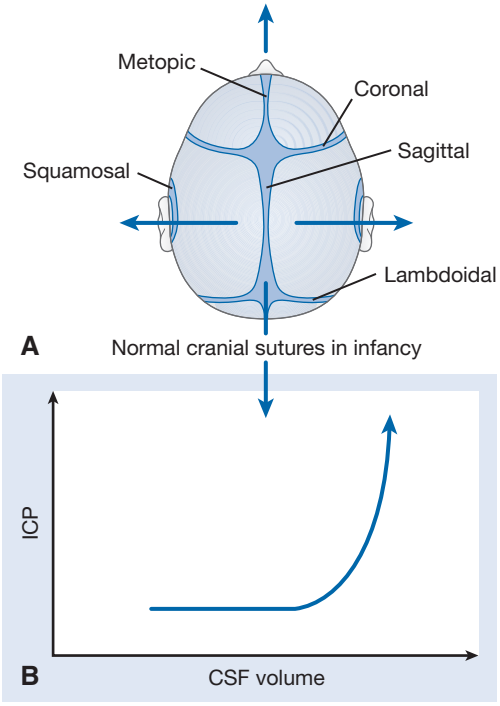


Fig. 20.4 Effect of cranial sutures and fontanel in neonates and infants. **A,** The open fontanelles and cranial sutures permit slow expansion of the intracranial volume. **B,** Initially the compliant skull of the neonate minimizes insidious increases in intracranial volume. However, acute increases in intracranial volume (hemorrhage and obstructed ventriculoperitoneal shunt) lead to rapid rises in intracranial pressure (ICP). CSF, cerebrospinal fluid.

Neonates and infants have functionally immature organ systems. The neonatal renal system is characterized by a decreased glomerular filtration rate and concentrating ability. These changes result in diminished excretion of saline and water, and limit the neonate's ability to compensate for fluctuations in fluid and solute loads. Drugs that are renally excreted may have a prolonged half-life. Hepatic function is also diminished in neonates, and the metabolism of drugs may be delayed owing to decreased activity of hepatic enzymes. Total body water drops from 85% in premature infants to 65% in adults, whereas body fat content increases from less than 1% in premature infants to 15% in term infants and 35% in adults. The total protein level follows a similar trend. Therefore, hydrophilic drugs have more binding sites, and hydrophobic drugs fewer, in infants. The constellation of these factors should prompt the clinician generally to decrease the weight-adjusted dose and frequency of administration of drugs given to the newborn.

PREOPERATIVE EVALUATION AND PREPARATION

Given the systemic effects of general anesthesia and the physiologic stress of surgery, an organ system review is essential for identifying coexisting disease, and anticipating potential physiologic derangements that increase the risk of perioperative complications. General perioperative concerns in infants and children are listed in Table 20.1. Preoperative laboratory tests should be tailored to the proposed neurosurgical procedure. Given the risk of significant blood loss associated with surgery,

Table 20.1 General Perioperative Concerns in Infants and Children

Condition	Anesthetic Implications
Congenital heart disease	Hypoxia, arrhythmias, and cardiovascular instability; paradoxical air emboli
Prematurity	Postoperative apnea
Gastrointestinal reflux	Aspiration pneumonia
Upper respiratory tract infection	Laryngospasm, bronchospasm, hypoxia, pneumonia
Craniofacial abnormality	Difficulty with airway management

Table 20.2 Common Perioperative Concerns for Infants and Children with Coexisting Neurologic Diseases

Condition	Anesthetic Implications
Denervation injuries	Hyperkalemia after succinylcholine Resistance to nondepolarizing muscle relaxants, abnormal response to nerve stimulation
Long-term anticonvulsant therapy	Hepatic and hematologic abnormalities Increased metabolism of anesthetic agents
Arteriovenous malformation	Potential congestive heart failure
Neuromuscular disease	Malignant hyperthermia Respiratory failure Sudden cardiac death
Chiari malformation	Apnea Aspiration pneumonia
Hypothalamic or pituitary lesions	Diabetes insipidus Hypothyroidism Adrenal insufficiency

the hematocrit, prothrombin time, and partial thromboplastin time should be measured to uncover any insidious hematologic disorder. Patients with suprasellar pathology should undergo an endocrinology evaluation. Table 20.2 matches special concerns in pediatric patients with neurologic problems.

Closed-claim analysis studies have revealed that neonates and infants are at higher risk for perioperative morbidity and mortality than other age groups.[10,11] Respiratory and cardiac-related events account for a majority of these complications. Given the urgent nature of many pediatric neurosurgical procedures, a thorough preoperative evaluation may be difficult. A complete airway examination is essential, since some craniofacial anomalies may require specialized techniques to secure the airway. Congenital heart disease may not be apparent immediately after birth and may complicate the perioperative course of the neonate undergoing an emergency neurosurgical procedure. Therefore, echocardiography can be helpful in the assessment of the heart, especially in the neonate, and a pediatric cardiologist should evaluate a patient with suspected cardiac problems in order to optimize cardiac function prior to surgery.

Perioperative anxiety plays a significant role in the care of the pediatric neurosurgical patient. These issues are related to the cognitive development and age of the child (Table 20.3). Preoperative sedatives given prior to the induction of anesthesia can ease the transition from the preoperative holding area to the operating room.[12] Midazolam administered orally is particularly effective in relieving anxiety and producing amnesia. If an indwelling intravenous catheter is in place, midazolam can be slowly titrated to achieve sedation.

Preoperative fasting regimens have dramatically evolved over the years and vary according to local preferences. The purpose of limiting oral intake is to minimize the risk of pulmonary aspiration of gastric contents. However, prolonged fasting periods can potentially result in both hypovolemia and hypoglycemia, which in turn can lead to hemodynamic and metabolic instability during anesthesia. Although the scientific validity of many recommendations has not been investigated, a common guideline is provided in Table 20.4.

INTRAOPERATIVE MANAGEMENT

Induction of Anesthesia

The patient's preoperative status dictates the appropriate technique and drugs for induction of anesthesia. General anesthesia can be induced with sevoflurane and nitrous oxide with oxygen. A nondepolarizing muscle relaxant is then administered after intravenous (IV) access has been established to facilitate intubation of the trachea. If the patient already has an IV catheter, anesthesia can be induced with a sedative-hypnotic drug such as propofol (2–4 mg/kg). It should be noted that neonates are vulnerable to propofol-induced hypotension that can persist for 30 minutes, especially when there is no surgical stimulation.[13] Patients who are vomiting or have recently ingested food or fluids are at risk for aspiration pneumonitis and so should undergo rapid-sequence induction of anesthesia with propofol, followed immediately with a rapid-acting muscle relaxant and cricoid pressure.

Table 20.3 Developmental Factors Affecting the Pediatric Patient in the Perioperative Period

Age Group	Concerns
Infants (0–9 months)	None; will separate easily from parents
Preschoolers (9 months–5 years)	Stranger anxiety; difficulty with separation from parents
Grade schoolers (6–12 years)	Fear of needles/pain
Adolescence (>12 years)	Anxiety about surgery and self-image

Table 20.4 Common Fasting Guidelines For Pediatric Patients

Fasting Time (Hours)	Substance to be Withheld
2	Clear liquids
4	Breast milk
6	Formula
8	Solid food

Airway Management

Developmental changes in airway anatomy have a significant effect on the management of the pediatric airway. The infant's larynx is funnel-shaped, being narrowest at the level of the cricoid ring. This feature puts the infant at risk for subglottic obstruction secondary to mucosal swelling after prolonged endotracheal intubation with a tight-fitting endotracheal tube. Cuffed endotracheal tubes can be used, but the cuff pressure should be checked frequently and adjusted to minimize tracheal injury. Since the infant's trachea is relatively short, an endotracheal tube can easily migrate into a mainstem bronchus when the head is flexed, as it will be for a suboccipital approach to the posterior fossa or the cervical spine (Fig. 20.5). Therefore, great care should be devoted to ensuring proper position of the endotracheal tube during tracheal intubation, and the anesthesiologist should auscultate both lung fields to rule out inadvertent intubation of a mainstem bronchus after final positioning of the patient. Nasotracheal tubes are best suited for the patient in the prone position, because they are easier to secure, less likely to kink at the base of the tongue when the head is a flexed and prevent pressure injury to the tongue.

Timing of tracheal extubation sometimes presents a challenge after neurosurgical procedures. Patients with Chiari malformation and brainstem surgery may exhibit intermittent postoperative apnea, vocal cord paralysis, or other irregularities before resuming a stable respiratory pattern. Significant airway edema and postoperative obstruction can complicate prone procedures or operations involving significant blood losses and large volume replacement. Preexisting pulmonary dysfunction, as in infants with bronchopulmonary dysplasia or older children with neuromuscular disease, may force delays in extubation because of respiratory insufficiency. In these cases, standard tracheal extubation criteria and the presence of an endotracheal tube air leak less than 20 cm H_2O can assist the clinician in appropriate decision-making. Lingual or supraglottic swelling can cause airway obstruction and can be diagnosed by direct laryngoscopy. When swelling is significant, postoperative lung ventilation in the intensive care unit, head-up positioning and gentle forced diuresis lead to improved conditions within 24 hours.

Positioning

The diminutive size of the neonate or infant requires careful preoperative planning to allow adequate access to the patient for both the neurosurgeon and anesthesiologist (Table 20.5).

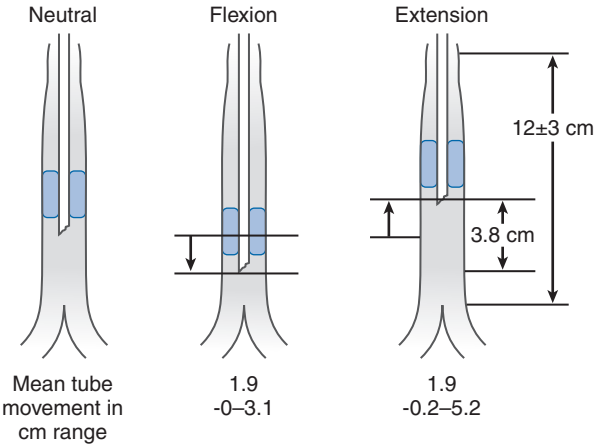


Fig. 20.5 Effect of head flexion and extension on endotracheal tube position. Note that flexion of the neck causes the endotracheal tube to migrate toward a mainstem bronchus, while neck extension can lead to dislodgement of the endotracheal tube from the trachea.

Table 20.5 Physiologic Effects of Positioning in All Patients

Position	Physiologic Effect
Head elevated	Enhanced cerebral venous drainage Decreased cerebral perfusion pressure (potential cerebral blood flow decrease) Increased venous pooling in lower extremities Postural hypotension
Head down	Increased cerebral venous and intracranial pressure Decreased functional residual capacity (lung function) Decreased lung compliance
Prone	Venous congestion of face, tongue, and neck Decreased lung compliance Increased abdominal pressure can lead to compression of the vena cava
Lateral decubitus	Decreased compliance of down-side lung

Skull fixation with a Mayfield frame is standard practice in craniotomies and cervical spine surgery. However, infants and small children have thin skulls and are at increased risk for fractures and epidural hemorrhage.[14] Therefore, age-appropriate fixation pins and tensions should be utilized. The prone position is commonly used for posterior fossa and spinal cord surgery. Although the sitting position has been used less often in pediatric patients, it may be appropriate for obese patients, who may be difficult to ventilate in the prone position. In addition to the physiologic sequelae of the prone position, a whole spectrum of compression and stretch injuries has been reported. Padding under the chest and pelvis can support the torso. It is important to ensure free abdominal wall motion because greater intra-abdominal pressure can impair ventilation, cause compression of the vena cava, and increase epidural venous pressure and bleeding. Soft rolls are generally used to elevate and support the lateral chest wall and hips to minimize the increases in abdominal and thoracic pressure. In addition, a Doppler probe can be applied to the chest without causing pressure sores.

Many neurosurgical procedures are performed with the head slightly elevated to facilitate venous and cerebrospinal fluid drainage from the surgical site. However, superior sagittal sinus pressures decrease with increasing head elevation and increase the likelihood of venous air embolism (VAE). Extreme head flexion can cause brainstem compression in patients with posterior fossa pathology, such as a mass lesion or Chiari malformation. Furthermore, significant rotation of the head can compress the jugular vein, which in turn impedes venous return leading to impairment of cerebral perfusion and increases in ICP and venous bleeding.

Vascular Access

Optimal intravenous access is mandatory prior to the start of surgery because access to the infant and small child during neurosurgical procedures can be limited. Typically two large-bore venous cannulas are sufficient for most craniotomies. Should initial attempts fail, central venous cannulation may be necessary. Cannulation of the femoral vein avoids the risk of pneumothorax associated with subclavian catheters and does not affect cerebral venous return. Furthermore, femoral catheters are more accessible during operations on the head.

Since significant blood loss and hemodynamic instability can occur during craniotomies, an arterial catheter would provide direct blood pressure monitoring and sampling for blood gas analysis.

Maintenance of Anesthesia

Sevoflurane is the principal anesthetic for induction of anesthesia in infants and children followed by opioid and low-dose (0.2–0.5%) isoflurane. The incidence of awareness under anesthesia has been reported to be 0.8% in children, a value higher than in adults.[15] Deep neuromuscular blockade with a nondepolarizing muscle relaxant is maintained to avoid patient movement and minimize the amounts of anesthetic agents needed. Patients who have undergone long-term anticonvulsant therapy will require larger doses of muscle relaxants and narcotics because of the enzymatic metabolism induced by these agents (Fig. 20.6).[16] Muscle relaxants should be withheld or their effects permitted to wear off when assessment of motor function during neurosurgery is planned.

Anesthetic-induced developmental neurotoxicity has been fully substantiated in preclinical reports, but the retrospective clinical studies have been inconclusive.[17] It is well known that extremely and very low-birth-weight survivors have poor neurological and cognitive outcomes.[18] Cerebral injury due to cerebral hypoperfusion, metabolic derangements, coexisting disease and surgery have the potential to worsen neurological outcomes in neonates and infants.[19] Therefore, intraoperative hypotension, hypocarbia, oxygenation, glycemia and temperature control should be aggressively managed in these vulnerable patients.[2]

Intraoperative Fluid and Electrolyte Management

Hemodynamic stability during intracranial surgery requires careful maintenance of intravascular volume and electrolytes. Sudden blood loss or venous air embolus can rapidly deteriorate to cardiovascular collapse. Therefore, normovolemia should be maintained throughout the procedure. Estimation of the patient's blood volume is essential in determining the amount of allowable blood loss and the time to transfuse blood. Blood volume depends on the age and size of the patient, as delineated in Table 20.6. Normal saline is commonly used as the maintenance fluid during neurosurgery because it is mildly hyperosmolar and should minimize cerebral edema.

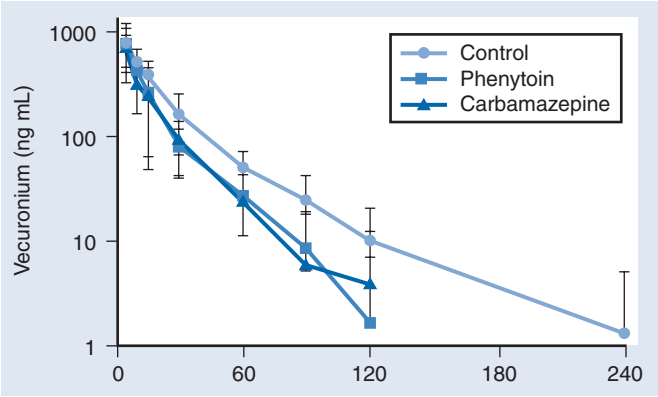


Fig. 20.6 Effect of long-term therapy with anticonvulsants (phenytoin, carbamazepine) on the half-life of the muscle relaxant vecuronium. Vecuronium plasma concentrations are plotted against time after a single bolus dose of vecuronium (0.15 mg/kg). Mean ± SD values are plotted for groups taking both anticonvulsants and the control group.

Table 20.6 Estimated Blood Volume in Children

Age	Estimated Blood Volume (mL/kg)
Preterm neonate	100
Full-term neonate	90
≤1 year	80
1–12 years	75
Adolescents and adults	70

Table 20.7 Rate of Maintenance Fluid Administration

Weight (kg)	Rate
≤10	4 mL/kg/h
10–20	40 mL + 2 mL/kg/h for every kg over 10 kg
≥20	60 mL + 1 mL/kg/h for every kg over 20 kg

However, rapid infusion of large quantities of normal saline (>60 mL/kg) can be associated with hyperchloremic acidosis.[20] Given the relatively large blood volume of the neonate or infant, the maintenance rate of fluid administration depends on the weight of the patient (Table 20.7). Significant blood loss is likely in most craniotomies in infants and children, so the maximum allowable blood loss should be determined in advance so the anesthesiologist will know when blood should be transfused to the patient. However, there are no guidelines for threshold in transfusing blood and the decision to transfuse should be dictated by the type of surgery, underlying medical condition of the patient, and potential for additional blood loss, both intraoperative and postoperative. Hematocrit values of 21–25% should provide some impetus for blood transfusion. Packed red blood cells (10 mL/kg) will raise the hematocrit by 10%. Initially, blood losses should be replaced with 3 mL of normal saline for each 1 mL of lost blood or a colloid solution, such as 5% albumin, equal to the blood loss. Depending on the extent and length of the surgical procedure and exposure of vascular beds, additional fluid administration at 3–10 mL/kg/h may be necessary.

Pediatric patients, particularly infants, are at particular risk for hypoglycemia. Small premature infants, who have limited reserves of glycogen and limited gluconeogenesis, require continuous infusions of glucose at 5–6 mg/kg/min to maintain serum levels. Surgery elicits a stress response, and children are generally able to maintain normal serum glucose levels without exogenous glucose administration.[21] Since inadvertent hypoglycemia occurs in fasted infants and children, frequent glucose measurements are recommended. Limited evidence now suggests that tight glycemic control may reduce postoperative infections but still carry undue risk of hypoglycemia.[22,23]

Brain edema can be managed initially with hyperventilation and elevation of the head above the heart. Should these maneuvers fail, mannitol can be given at a dose of 0.25–1.0 g/kg IV. This agent will transiently alter cerebral hemodynamics and raise serum osmolality by 10–20 mOsm/kg.[24] However, repeated dosing of mannitol can lead to extreme hyperosmolality, renal failure, and further brain edema.[25] Furosemide is a useful adjunct to mannitol for decreasing acute cerebral edema and has been shown in vitro to prevent the rebound swelling due to mannitol. All diuretics interfere with the ability to use urine output as a guide to intravascular volume status.

Monitoring

Hemodynamic Monitoring

Patients undergoing major craniotomies and spine surgery are at risk of sudden hemodynamic instability due to hemorrhage, VAE, herniation syndromes, or manipulation of cranial nerves. The potential for cerebral hypoperfusion generally warrants placement of an arterial cannula for continuous blood pressure monitoring. The utility of central venous catheterization remains controversial. Cannulation of the jugular or subclavian vein with multiple-orifice catheters in adults is often preferred, particularly when VAE is anticipated. However, these multiple-orifice catheters are too large for infants and most small children, and are not used in pediatric settings. Furthermore, monitoring of the central venous pressure may not accurately reflect intravascular volume in small children.[26] Therefore, the risks of a central venous catheter may outweigh its benefits. Even when VAE occurs, a single-orifice catheter is not often successful for aspirating air, presumably because of the high resistance of the small-gauge catheters used in these patients.[27]

Venous air emboli have been detected during many craniotomies in infants and children, primarily because the head of a small child is large in relation to the rest of the body and rests above the heart in either the prone or supine position (Fig. 20.7). Standard neurosurgical positioning often includes elevation of the patient's head to optimize cerebral venous drainage. However, this maneuver can increase the risk for air entrainment into the venous system through open venous channels in bone and sinuses. Patients with cardiac defects and the potential for right-to-left shunting, such as patent foramen ovale and patent ductus arteriosus, are at risk for paradoxical air emboli, leading to cerebral and myocardial infarction. A precordial Doppler ultrasound device can detect minute VAE and should be routinely used in conjunction with an end-tidal carbon dioxide analyzer and arterial catheter in all craniotomies in order to detect VAE early, before significant hemodynamic instability develops. The Doppler probe is best positioned on the anterior chest, usually just over or to the right of the sternum at the fourth intercostal space (i.e., the nipple line). An alternative site on the posterior thorax can be used in infants in the prone position who weigh approximately 6 kg or less.[28] In addition to the characteristic changes in Doppler sounds, sudden decreases in end-tidal CO_2, dysrhythmias, ischemic changes in the electrocardiogram, or a combination of these, can occur with VAE.

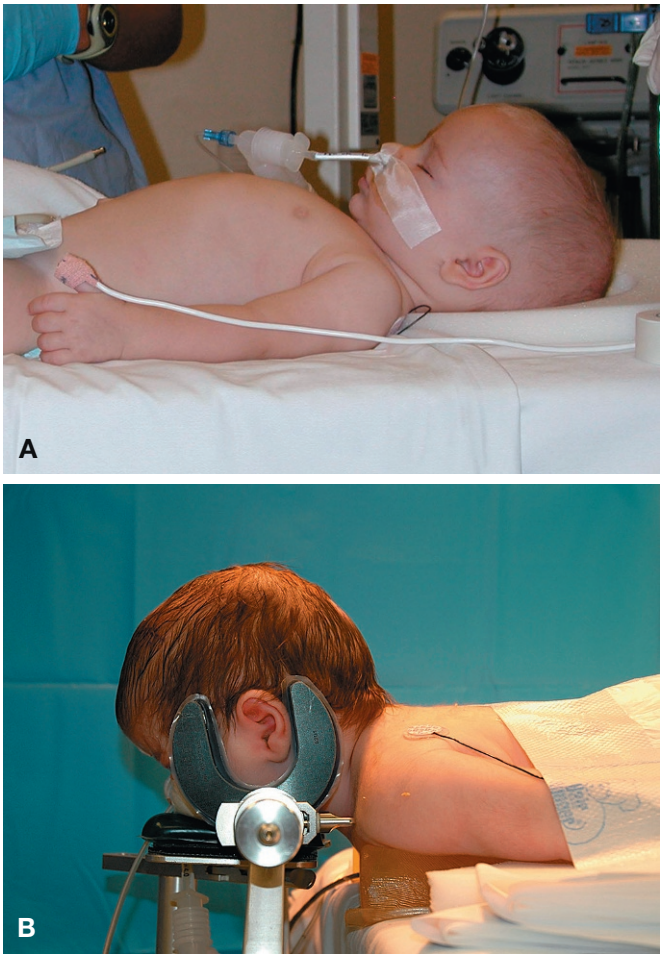


Fig. 20.7 Supine **(A)** and prone **(B)** positioning for an infant. Note that the infant's head lies at a higher plane than the rest of the body. This feature increases the likelihood of venous air embolism during craniotomy.

Neurophysiologic Monitoring

Advances in neurophysiologic monitoring have enhanced the ability to safely perform more definitive neurosurgical resections in functional areas of the brain and spinal cord.[29] However, the depressant effects of many anesthetic agents limit the utility of these monitors. A major part of preoperative planning should include a thorough discussion of the modality and type of neurophysiologic monitoring during the perioperative period.

Detection of Seizure Foci

Electrocorticography (ECoG) is typically recorded continuously on a polygraph via grid and strip electrodes placed on the surface of the brain after the dura is opened. Some epileptogenic foci are in close proximity to cortical areas controlling speech, memory, motor, or sensory function, so monitoring of the patient and electrophysiological responses is frequently utilized to minimize iatrogenic injury to these areas.[30,31] Cortical stimulation of the motor strip in a child under general anesthesia requires either electromyography (EMG) or direct visualization of muscle movement. Neuromuscular blockade should be discontinued. Cortical stimulation using a dual-channel stimulator is possible. Epileptogenic activity may be evident from either clearly documented electrographic seizures or spike activity, which consists of either interictal spikes of 50–80 msec or sharp waves of 80–200 msec. During anesthesia, the use of low concentrations of volatile anesthetics and opioids alone should not depress these signals.

Awake Craniotomy

Surgical resections of epileptogenic foci in functional areas of the brain can lead to significant neurologic deficits in patients under general anesthesia. Neural function is always best assessed in an awake and cooperative patient. Positioning of the patient is critical for the success of this technique. The patient should be in a semilateral position to allow patient comfort as well as providing surgical and airway access (Fig. 20.8). Motor and sensory cortices are localized by induction of motor movements or sensory changes with cortical stimulation. Language function is tested by eliciting speech arrest with cortical stimulation. Verbal memory is tested by stimulating the hippocampus or lateral temporal cortex. In children undergoing craniotomy with local anesthesia and propofol, and fentanyl for sedation and analgesia during resections in eloquent areas of the brain, discontinuing propofol 20 minutes before monitoring did not interfere with the ECoG and cooperative

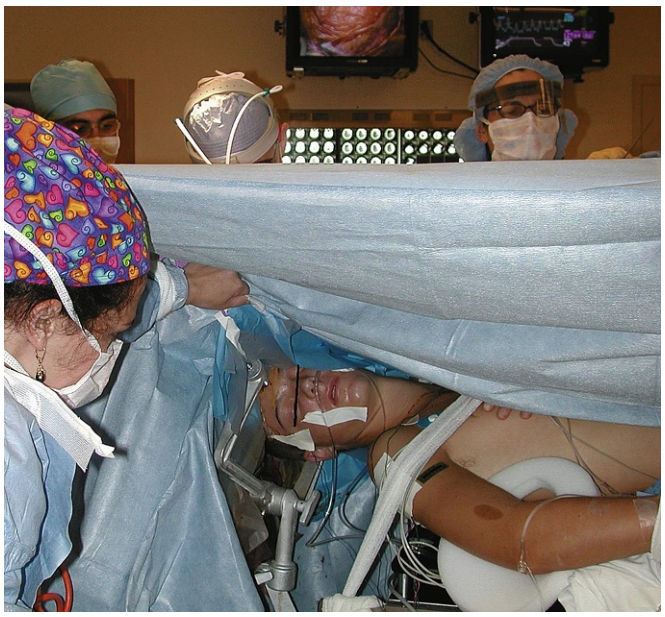


Fig. 20.8 Positioning the patient for an awake craniotomy. Note that there is clear access to the patient to facilitate neuropsychological testing.

children older than 10 years were able to withstand the procedure without incident.[32] Sedation with remifentanil-propofol and dexmedetomidine can also be used in children. However, it is imperative that for an awake craniotomy the child must be mature and psychologically prepared to participate in this procedure. Therefore, patients who are developmentally delayed or have a severe anxiety or psychiatric disorders are not candidates for an awake craniotomy. Very young patients cannot be expected to cooperate for these procedures and usually require general anesthesia with extensive neurophysiologic monitoring to minimize inadvertent resection of the eloquent cortex.

Monitoring Spinal Cord and Nerve Root Integrity

Surgery on the spinal cord and nerve roots exposes the patient to ischemic and traumatic injury. The risk for the development of a neural injury during the resection of a spinal cord or nerve root tumor can be difficult to assess, but can be exacerbated by compression of the vascular supply of the cord and resection of the tumor itself. Similarly, brainstem surgery places vital nuclei and spinal pathways at risk of ischemia and direct damage. These factors justify the need for intraoperative neurologic monitoring.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) primarily assess the integrity of the dorsal (sensory) pathways of the spinal cord. SSEP monitoring provides real-time examination of spinal tracts at risk during surgical manipulation of the spinal cord. SSEP monitoring in children undergoing orthopedic and neurosurgical procedures appear to be more sensitive to the depressant effects of general anesthesia. Cortical responses were less reliable in children younger than 10 years and in those with myelodysplasia or cerebral palsy. Although the SSEPs obtained from these patients demonstrated attenuated cortical responses, relatively robust signals were recorded from the cervical spine.

Motor Evoked Potentials

Integrity of the corticospinal tracks can be accessed by the motor evoked potential, which uses magnetic or electrical stimulation of the motor cortex and detection of the action potential in the corresponding muscle groups. All volatile anesthetic agents, including nitrous oxide, have a dose-dependent depressant effect on motor evoked potentials. Ketamine, propofol, or etomidate infusions appear to preserve the motor evoked potential and have been used routinely. Infants and small children require a greater stimulating threshold voltage and longer pulse trains in order to obtain adequate motor responses.[33]

Nerve Root Monitoring

Neurosurgical procedures for tethered spinal cord syndrome and spasticity often employ EMG monitoring during identification and dissection of the nerve roots. Tethered spinal cord syndrome due to spinal dysraphism is associated with conditions such as myelomeningocele, lipoma of the filum terminalis, spina bifida occulta, and adhesions from prior spinal surgery. Visualization and identification of functional nerve roots may be difficult and may result in an inadvertent injury during the surgical dissection. EMG monitoring can be helpful for identifying functional nerve roots. Placement of the EMG electrodes in the external anal and urethral (in girls) sphincter allows continuous monitoring of the nerve roots supplying the pudendal nerves (S2–S4). Inserting a balloon manometer into the bladder and recording changes in pressure during stimulation can assess detrusor muscle function. Movement and evoked action potentials of the anterior tibialis and sural muscles can also be detected visually and by EMG. Muscle contractions can be readily observed with the use of clear sterile plastic drapes. Muscle relaxation must be discontinued to enable detection of motor activity. Volatile anesthetics and opioids do not appear to interfere with muscle action potentials, and the patient should be deeply anesthetized for this monitoring because direct nerve root stimulation often elicits a significant sympathetic response and pain.

SPECIAL ISSUES

Neonatal Emergencies

Neonatal surgery is primarily performed on an emergency basis, thereby increasing morbidity in the perioperative period due to undiagnosed congenital anomalies and persistence of the transitional circulation in premature neonates. Congestive heart failure can occur in neonates with large cerebral arteriovenous malformations, and this condition requires aggressive hemodynamic support. More commonly, intracardiac right to left shunting occurs through a patent ductus arteriosus or foramen ovale that has not yet closed. Management of the neonatal respiratory system may be difficult because of the diminutive size of the airway, craniofacial anomalies, laryngotracheal lesions, and acute (hyaline membrane disease, retained amniotic fluid) or chronic (bronchopulmonary dysplasia) disease. Because these conditions are in a state of flux, they should be addressed preoperatively so as to minimize perioperative morbidity.

The neonatal central nervous system is capable of sensing pain and mounting a stress response after a surgical stimulus, and premature infants require anesthesia for painful procedures.[34] However, immature neonatal organ systems are highly sensitive to anesthetic agents. Neonatal myocardial function is particularly sensitive to both inhaled and intravenous anesthetics, and these agents must be administered judiciously to block the surgical stress response without causing myocardial depression. An opioid-based anesthetic is generally the most stable hemodynamic technique for neonates. However, neonatal hepatic and renal systems are not fully developed,

so neonates anesthetized with a narcotic technique often have delayed emergence from anesthesia and may require postoperative mechanical ventilation.

Closure of a myelomeningocele or encephalocele presents special problems. Positioning the patient for tracheal intubation may rupture the membranes covering the spinal cord or brain. Careful padding of the lesion by elevation of the neonate on top of soft supports with a hollow center minimizes the chance of rupture of the fragile membranes. In some cases intubation of the neonate's trachea in the left lateral decubitus position may be necessary. General anesthesia should be provided to optimize surgical condition and minimize pain. The use of spinal anesthesia for closure of small myelomeningoceles has been advocated by a highly specialized group who have integrated regional anesthesia in neonatal surgery,[35] but this practice has not been universally accepted. Most surgical closures of simple myelomeningoceles have relatively minimal blood loss. Large lesions may require significant dissection of cutaneous tissue to cover the defect, however, posing larger risks for blood loss and hemodynamic instability. Advances in the management of myelomeningoceles have led to early intervention in the intrauterine period. The management of the fetus and mother during fetal surgery has been reviewed extensively elsewhere.[36]

Craniosynostosis

Surgical treatment of craniosynostosis is likely to have the best result if done early in life.[37] However, the procedure can be associated with loss of a significant percentage of an infant's blood volume, with greater losses occurring when more sutures are involved. VAE often occurs and should be minimized by maintenance of adequate intravascular blood volume. Early detection with continuous precordial Doppler ultrasonography can enable treatment to be instituted before large amounts of air are entrained. When hemodynamic instability does occur, the operating table can be placed in the Trendelenburg position. This maneuver will augment the patient's blood pressure and prevent further entrainment of intravascular air. Special risks exist in neonates and young infants, in whom potential right-to-left cardiac mixing lesions can result in arterial emboli. Because neuroendoscopic techniques are designed to minimize surgical incision, dissection, and blood loss, less aggressive fluid replacement and invasive hemodynamic monitoring is becoming the norm. The application of endoscopic techniques for craniosynostosis repair has resulted in significantly less morbidity. Endoscopic strip craniectomy involves insertion of an endoscope through a small scalp incision and resection of the fused cranial sutures. This minimally invasive approach is associated with decreased blood loss, less surgical time, and improved postoperative recovery in neonates and infants.[38] There is a lower incidence of VAE during endoscopic strip craniectomy in comparison with the open procedure.[39] However, this approach is indicated only for infants.

Hydrocephalus

Hydrocephalus is the most common condition confronting the pediatric neurosurgical team. Hemorrhage (intraventricular or subarachnoid hemorrhage in the neonate), congenital problems (aqueductal stenosis) trauma, infection, or tumors (especially in the posterior fossa) lead to hydrocephalus. Anesthesia should be established with a rapid-sequence induction technique and tracheal intubation with cricoid pressure. If intravenous access cannot be established, an inhalation induction with sevoflurane and gentle cricoid pressure may be an alternative, though less desirable, method of induction. Unless the etiology of the hydrocephalus can be definitively treated, management entails surgical placement of a ventricular drain or ventriculoperitoneal shunt. Occasionally the distal end of the shunt must be placed in the right atrium or pleural cavity, usually because of inability of the peritoneal cavity to absorb cerebrospinal fluid. The possibility of VAE during placement of the distal end of a ventriculo-atrial shunt should always be kept in mind. Postoperatively, patients should be observed carefully because altered mental status and recent peritoneal incision put them at high risk for pulmonary aspiration once feedings are begun. Acute obstruction of these shunts should be treated urgently to avoid a lethal rise in ICP in the relatively small cranial vault of the infant and child.

Endoscopic third ventriculostomy combined with choroid plexus cautery, which curtails the source of CSF production, is a viable and efficacious alternative to ventricular shunts.[40] A fenestration is created on the floor of the third ventricle posterior to the infundibular recess into order to restore CSF flow, thus circumventing the need for the placement of a ventricular shunt. Despite the relative safety of this procedure, bleeding, hypertension, arrhythmias and neurogenic pulmonary edema have been reported in conjunction with acute intracranial hypertension due to lack of egress of irrigation fluids and/or manipulation of the floor of the third ventricle.

Tumors

The majority of intracranial tumors in children occur in the posterior fossa. These lesions create a mass effect, which obstructs cerebrospinal fluid flow leading to intracranial hypertension and hydrocephalus. Most neurosurgeons approach this region with the child in the prone position. The patient's head is generally secured with a Mayfield head frame, although pins used in small children can cause severe skin lacerations, skull fractures, dural tears, and intracranial hematomas.[14] Elevation of the bone flap can result in sinus tears, massive blood loss, or VAE. Surgical resection of tumors in the posterior fossa can also lead to brainstem or cranial nerve damage. Table 20.8 lists some of the signs of encroachment on these structures. Damage to the respiratory centers and cranial nerves can lead to apnea and airway obstruction after extubation of the patient's trachea, necessitating close postoperative observation.

Craniopharyngiomas are the most common perisellar tumors in children and adolescents, and may be associated with hypothalamic and pituitary dysfunction. Steroid replacement therapy (with dexamethasone or hydrocortisone) is generally

Table 20.8 Effect of Surgical Brainstem Manipulation

Brainstem Area	Signs	Changes Seen on Monitoring
Cranial nerve (CN) V	Hypertension, bradycardia	Arterial pressure, electrocardiography (ECG)
CN VII	Facial muscle movement	Electromyography
CN X	Hypotension, bradycardia	Arterial pressure, ECG
Pons, medulla	Arrhythmias, hypotension/ hypertension, tachycardia/bradycardia, irregular breathing pattern	ECG, arterial pressure, end-tidal carbon dioxide monitor

administered because the integrity of the hypothalamic–pituitary–adrenal axis may be uncertain. In addition, diabetes insipidus occurs preoperatively in some patients and the subsequent hypovolemia and electrolyte abnormalities should be managed prior to induction of anesthesia. If diabetes insipidus does not exist preoperatively, it usually does not develop until the postoperative period. However, the incidence of DI in adults is variable, but probably lies in the ~5–20% range after transphenoidal pituitary surgery.[41] Most of this is transient, but may complicate the postoperative course of the patient. This is because there appears to be an adequate reserve of antidiuretic hormone in the posterior pituitary gland capable of functioning for many hours, even when the hypothalamic–pituitary stalk is damaged. Surgical exposure to the sella is performed between the frontal lobes in infants and young children, and transnasally in the adolescent. Although diabetes insipidus occurs primarily after surgery, serum electrolytes should be frequently measured to detect its development.

Epilepsy

Surgical treatment has become a viable option for infants and children with medically intractable epilepsy. Two major considerations should be kept in mind. First, long-term administration of anticonvulsant drugs, such as phenytoin and carbamazepine, induces rapid metabolism and clearance of several classes of anesthetic agents, including neuromuscular blockers and opioids.[16] Therefore, the anesthetic requirements for these drugs are increased. Second, general anesthetics can compromise the sensitivity of the intraoperative neurophysiologic monitors used to guide the resection of the epileptogenic focus. Furthermore, if cortical stimulation is used to mimic the seizure pattern or identify areas on the motor strip, neuromuscular blockade should be antagonized. Implantable ECoG leads, grids and strips, are placed on the cortical surface in order to detect and localize the seizure focus.

After emergence from anesthesia, patients undergoing epilepsy surgery are typically monitored in a specialized EEG unit, and the seizure focus is mapped out. A second craniotomy is necessary for the removal of ECoG grids and strips used for invasive EEG monitoring and subsequent resection of the seizure focus. It is important to avoid administration of nitrous oxide until the dura is opened, because intracranial air can persist up to 3 weeks after a craniotomy, and nitrous oxide can cause rapid expansion of air cavities and result in tension pneumocephalus.[42]

Vascular Anomalies

Vascular anomalies are rare in infants and children. Most of these conditions are congenital lesions that manifest early in life. Large cerebral arteriovenous shunts in neonates may require ionotropic support to counter the progressive high-output congestive heart failure that often coexists with these lesions. They are usually vein of Galen malformations, but are sometimes true pial arteriovenous malformations. Initial treatment of a high-flow fistula often consists of intravascular embolization in the radiologic suite.[43] Surgical resection of these vascular lesions is associated with massive blood loss and requires several IV access sites, as well as invasive hemodynamic monitoring. Acute interruption of any sort of intracranial fistula or shunt may lead to dramatic hemodynamic changes, including sudden hypertension with hyperemic cerebral edema. Vasodilators such as labetalol and nitroprusside may be necessary to control a hypertensive crisis.

Moyamoya syndrome is a rare chronic vaso-occlusive disorder of the internal carotid arteries that manifests as transient ischemic attacks, recurrent strokes, or both in childhood. The etiology is unknown, but the syndrome can be associated with prior intracranial irradiation, neurofibromatosis, Down syndrome, and a variety of hematologic disorders. The anesthetic management of patients with this syndrome is directed at optimizing cerebral perfusion.[44] It includes ensuring generous preoperative hydration and maintaining the blood pressure within the patient's preoperative levels. Maintenance of normocapnia is essential as well, because hypercapnia can lead to steal phenomenon from the ischemic region and further aggravate cerebral ischemia, although the pathophysiology of "steal" is largely speculative. Hypocapnia-induced vasoconstriction can significantly reduce CBF in the compromised region of the brain. Intraoperative EEG monitoring may be utilized during surgery to detect cerebral ischemia. An opioid-based anesthetic technique provides a stable level of anesthesia for the patient with moyamoya syndrome and is compatible with intraoperative EEG monitoring.[45] Once the patient emerges from anesthesia, the same maneuvers that optimize cerebral perfusion should be extended into the postoperative period. The patient should receive IV fluids to maintain adequate cerebral perfusion and should be given adequate narcotics to avoid hyperventilation induced by pain and crying.

Trauma

Pediatric head trauma requires a multiple-organ approach to minimizing morbidity and mortality. A small child's head is often the point of impact in injuries, but other organs can also be damaged. Basic life-support algorithms should be immediately applied to ensure a patent airway and adequate respiration and circulation. Preservation of age-appropriate blood pressure (Table 20.9) is essential for minimizing mortality.[46] Since the head-to-torso ratio is great in infants and younger children, acceleration-deceleration injuries are more common in the pediatric population and lead to more diffuse brain and upper cervical spine injuries. Immobilization of the cervical spine is important to avoid secondary spinal cord injury with manipulation of the patient's airway until radiographs confirm absence of cervical spine injury. An unstable cervical spine should be immobilized with cervical traction during laryngoscopy for tracheal intubation. Blunt abdominal trauma and long bone fractures often occur with head injury and can be major sources of blood loss. To ensure tissue perfusion during the operative period, the patient's blood volume should be restored with crystalloid solutions or blood products.[47] Ongoing blood loss can lead to coagulopathies and should be treated with specific blood components.

Nonaccidental head injury in infants often presents with a myriad of chronic and acute subdural hematomas.[49] The presence of other coexisting injuries, fractures, and abdominal trauma should be identified. Small children undergoing

Table 20.9 **Normative Awake Blood Pressures on Pediatric Patients**[48]

Age	Systolic (mmHg)	Diastolic (mmHg)
Pre-term neonate	50–60	40
Full-term neonate	70	40
1 year	85	40
5 years	95	55
10 years	100	60
15 years	110	65

craniotomy for the evacuation of either epidural or subdural hematoma are at risk for significant blood loss and VAE. Postoperative treatment includes the management of intracranial hypertension and, in the most severe cases, determination of brain death.

Pediatric head injury management is currently based on few randomized trials and draws heavily from data derived from adult series; evidence-based management is still evolving in this area. Therefore, fundamental knowledge of age-related differences in cerebrovascular physiology and anatomy is essential in the application of adult-based head trauma protocols in pediatric patients. In 2012, a multispecialty group of pediatric neurosurgeons and intensivists published: *Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents*.[50] This document is a comprehensive evidence-based review of controversial management issues in the care of the head-injured pediatric patient.

Spine Surgery

Spinal dysraphism is the primary indication for laminectomies in pediatric patients. Many of these patients have a history of a meningomyelocele closure followed by several corrective operations. Latex allergy has been associated with this group and can manifest as a severe anaphylactic reaction, heralded by hypotension and wheezing with or without a rash. Fortunately, this complication is rare because most operating rooms are latex-free environments. Anaphylaxis should be rapidly treated by removal of the source of latex and administration of fluid and vasopressors.[51]

Tethered cord release entails EMG monitoring to help identify functional nerve roots. EMG of the anal sphincter and muscles of the lower extremities is performed to minimize inadvertent injury to nerves innervating these muscle groups.[52] Neuromuscular blockade should be discontinued or antagonized to allow accurate EMG monitoring. Insertion of an epidural catheter by the surgeon under direct vision can provide a conduit for the administration of local anesthetics and opioids for the management of postoperative pain. Severe spasticity associated with cerebral palsy can be surgically alleviated by a selective dorsal rhizotomy, which reduces spasticity by surgically dividing dorsal rootlets to diminish the afferent input to motor neurons in the spinal cord, thus decreasing the hyperactive reflexes associated with spastic diplegia. Pathologic rootlets are identified by direct stimulation and noting the corresponding muscle action potential with EMG. Exaggerated action potentials can be elicited in innervated as well as other distal muscle groups. These abnormal rootlets are partially sectioned to decrease afferent nerve conduction. However, these rootlets can potentially contain sensory and proprioceptive fibers.

Neuroendoscopy

Technological advances in minimally invasive endoscopic surgery have entered the pediatric neurosurgical arena.[53] The anesthetic considerations for these evolving techniques are the same as for any other neurosurgical procedures, as discussed in this chapter. Endoscopic third ventriculoscopy and choroid plexus coagulation is an accepted procedure for the treatment of obstructive hydrocephalus in infants and children.[40] Despite the relative safety of this procedure, arrhythmias and neurogenic pulmonary edema have been reported in conjunction with acute intracranial hypertension due to manipulation of the floor of the third ventricle and lack of egress of irrigation fluids.[54,55]

Neuroradiology

Advances in imaging technology have introduced a variety of diagnostic and therapeutic interventions for the treatment of lesions in the central nervous system. Since infants and most children do not have the ability to tolerate procedures in the radiology suite, sedation or general anesthesia is necessary. Most neuroradiology studies, such as computed tomography and magnetic resonance imaging, can be accomplished with use of light sedation. Recommendations published by consensus groups of anesthesiologists and pediatricians can serve as guidelines for managing patients undergoing neuroradiology procedures.[56] General anesthesia is typically used in patients who are uncooperative or have coexisting medical problems, to minimize motion artifact, and for potentially painful procedures, such as intravascular embolization of vascular lesions.[57] The advent of hybrid procedures consisting of pre- or postoperative angiography, embolization, and surgical resection requires a multidisciplinary team approach because of the transfer of care between the radiologist, neurosurgeons and intensivists. A well-delineated crisis management plan should be in place, since these procedures occur outside the operating room suites and intensive care unit.

POSTOPERATIVE CARE

General Considerations

Pediatric neurocritical care is rapidly emerging as a highly specialized clinical discipline.[58] Although a few selected patients may be safely managed in alternative settings, neurosurgical patients generally require postoperative treatment in an intensive care unit until cardiorespiratory stability and neurologic recovery are ensured. In high-volume centers, specialized neurocritical care teams can improve patient outcomes for children. Once the patient is in the intensive care unit, optimal care begins with a clear delineation of responsibilities and thorough "handoff" from the neurosurgical and anesthesia teams to the responsible intensive care professionals. Clear communication regarding patient history, medications, operative events, and anticipated course is essential.

All new arrivals require physiologic and neurologic assessment to ensure normal awakening from anesthesia. Although tracheal extubation and initial neurologic assessment are ideally accomplished in the operating room, this approach may not be possible in unstable patients who are slow to awaken, have large fluid shifts, or have significant comorbidities. In these settings, intermittent lightening of sedation and frequent neurological examinations are the norm.

Respiratory Support

Postoperative mechanical ventilation aims to support alveolar gas exchange while permitting ongoing neurologic assessment. In most cases, a triggered mode, which allows continuous assessment of respiratory drive, is preferable over controlled ventilation. Pressure support ventilation, even in neonates, offers a convenient means of providing needed support without losing respiratory control as a marker of neurologic function. In young infants, in whom fontanels and sutures are open, there is little or no association between mean airway and intracranial pressures. Finally, although heavy sedation, controlled ventilation, and neuromuscular blockade are employed more often in children than adults, the impact of this practice in the setting of intracranial hypertension is unknown.

Hemodynamic Support

Hemodynamic support aims to avoid hypotension, maintain adequate cerebral perfusion pressure, and minimize injury from transient changes in pressure. Even in very-low-birth-weight infants, both dopamine and epinephrine are effective in supporting systemic pressure and restoring CBF.[59] Critical cerebral perfusion pressure for preschool children (2–6 years) with intracranial hypertension is approximately 50 mmHg, rising to 55–60 mmHg in older children. Although lower levels are powerful predictors of poor outcome, intentional increases beyond these levels are controversial because complications of therapy (fluid overload, acute respiratory distress syndrome) may begin to negate any benefits.[60] When cerebral perfusion pressure is low and ICP remains high despite all medical management, decompressive craniectomy may have a more favorable outcome in children.[61]

Fluid Management

Meticulous fluid management is critical in the care of neurosurgical patients. Nonosmotic secretion of antidiuretic hormone makes hyponatremia common after neurosurgery, despite the intraoperative use of fluids that are high in sodium and isotonic or slightly hypertonic. Overall, more than 10% of all children experience postoperative hyponatremia, and this fraction is likely much higher after neurosurgery.[62] Elevations of antidiuretic hormone can result from a variety of stimuli ranging from pain and nausea to fluid shifts and hypovolemia. Because sudden, unrecognized drops in serum sodium levels can provoke seizures, it is prudent to monitor electrolyte values closely throughout the perioperative period. When significant hyponatremia occurs, seizures may be treated with hypertonic saline and free water excesses addressed through fluid restriction and administration of diuretics. Administration of hypotonic solutions in the perioperative period is avoided in order to minimize the increase of hyponatremia.[63]

The syndrome of cerebral salt wasting is also common in children and can be seen after head trauma and neurosurgical procedures. It has been diagnosed with increasing frequency and reported in association with meningitis, calvarial remodeling, tumor resection, and even hydrocephalus. The syndrome can be easily confused with other entities, but a retrospective review put its incidence at 11.3 per 1000 procedures.[64] In affected patients, the mean duration of symptoms was 6 days, with a range of 1–5 days. Cerebral salt wasting, the result of excessively high levels of atrial or brain natriuretic peptide, is marked by hyponatremia, hypovolemia, and excessive urinary excretion of sodium. The classic treatment involves saline administration, but more rapid resolution has been achieved with fludocortisone.[65]

Diabetes insipidus is a well-known complication of surgical procedures involving or adjacent to the pituitary and hypothalamus. It is most commonly seen in association with craniopharyngioma. Diabetes insipidus is recognized from a rising serum sodium value (>150 mg/dL) accompanied by copious (>4 mL/kg/h) output of dilute urine. Urine output is unchecked, so severe dehydration and hypovolemia may result. Because there are a variety of successful approaches to DI management, a standardized protocol is helpful when postoperative care is multidisciplinary. Patients who are unconscious, who are unable to take oral fluids, or whose normal thirst mechanisms are impaired are best managed with a continuous infusion of arginine vasopressin. One effective protocol employs maximal antidiuresis and strict limitation of intravenous fluids (Fig. 20.9).[66] This strategy avoids the pitfalls of titrating drug dosage to urine output and recognizes that renal blood flow remains adequate in the normovolemic child receiving maximal antidiuresis. Because urine output is minimal (0.5 mL/kg/min), other clinical markers of volume status must be followed closely. After recovery from surgery and anesthesia, the awake and thirsty patient may be easily transitioned to oral fluids and desmopressin.

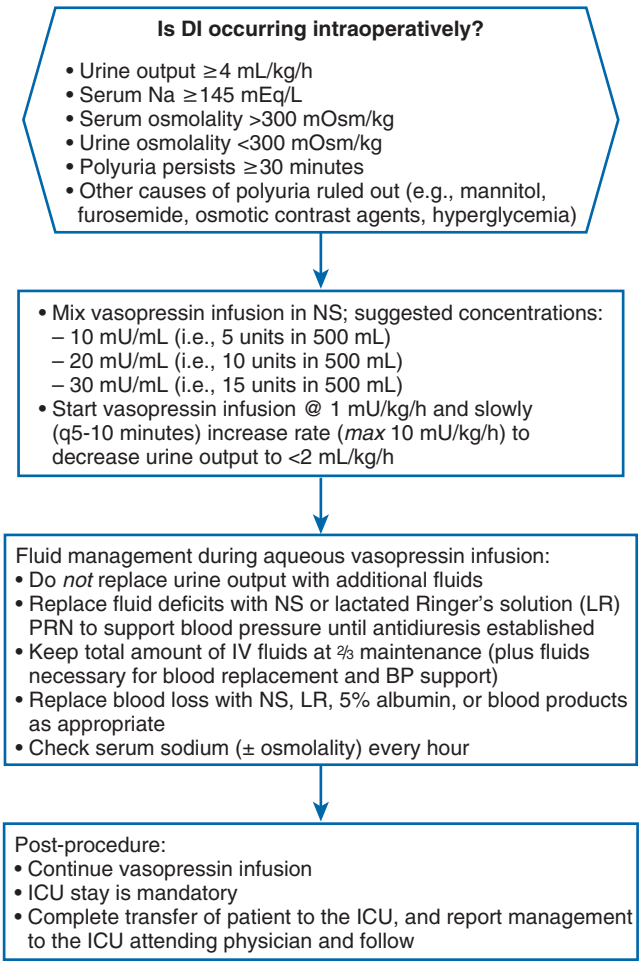


Fig. 20.9 Algorithm for perioperative management of diabetes insipidus (DI). BP, blood pressure; ICU, intensive care unit; NS, normal saline.

Sedation

Pain control and sedation present unique challenges in the pediatric intensive care unit.[67,68] Ideally, postoperative neurosurgical patients are comfortable, awake, and cooperative with their care. In pediatric patients, however, these goals can be mutually exclusive, and some level of sedation is often necessary to ensure a safe recovery. The ideal sedation regimen should employ short-acting or reversible agents that can be withdrawn intermittently to permit neurologic assessment. Propofol has limited utility because of its association with a fatal syndrome of bradycardia, rhabdomyolysis, metabolic acidosis, and multiple-organ failure when used over extended periods in small children.[69] Although the mechanism of this syndrome remains unclear, it appears related to both the duration of therapy and the cumulative dose.

Dexmedetomidine is a short-acting sedative that has advantages for pediatric intensive care unit patients.[70] It is not a respiratory depressant and maintains spontaneous ventilation. It has analgesic properties that decrease opioid and benzodiazepine requirements in postoperative pediatric patients.[71] Transient increases in blood pressure can be seen with bolus

administration, followed by hypotension and bradycardia as sedation deepens. In our experience, both hypotension and hypertension can occasionally be observed with long-term dexmedetomidine infusions, and a withdrawal syndrome results when extended infusions are discontinued. Further experience and vetting will be necessary to determine the proper place for this agent in the routine perioperative care of pediatric neurosurgical patients.

Given the limitations of propofol and dexmedetomidine, the mainstay of sedation in the pediatric intensive care unit remains a combination of narcotic and benzodiazepine administered via continuous infusion.[72] Titration to a validated sedation score is advised, and regular drug holidays help ensure that excessive sedation is avoided.[73] If chemical paralysis must be used to control ICP or facilitate mechanical ventilation, use of a neuromuscular blockade monitor helps avoid prolonged blockade and weakness. Infants and children receiving sedative infusions for more than 3–5 days are subject to tolerance and experience symptoms of withdrawal when infusions are discontinued.

Seizures

Seizures are a common manifestation of neurologic illness in pediatric patients. In the child with unexplained altered mental status, nonconvulsive status epilepticus should also be considered in the differential diagnosis. The incidence of perioperative seizures in pediatric neurosurgical patients is 7.4% with 4.4% of the whole cohort receiving prophylactic anticonvulsant drugs.[74] Independent factors associated with perioperative seizures include supratentorial tumor, age <2 years, and hyponatremia. Given the equivocal impact of prophylactic anticonvulsants, its routine use needs further investigation. For status epilepticus, lorazepam 0.1 mg/kg IV push over 2 minutes or diazepam 0.5 mg per kg per rectum are effective. Lorazepam may be repeated after 10 minutes and accompanied by fosphenytoin 20 mg phenytoin sodium equivalents per kg IV or intramuscularly if initial doses are ineffective. Though potentially compounding respiratory depression, phenobarbital 20 mg/kg is also an effective first-line antiepileptic drug.

Refractory status epilepticus continues to present a significant challenge, and no prospective study is available to inform management. Chemically induced coma remains the mainstay of care, with anticonvulsant drugs titrated to EEG burst suppression. In our institution, we typically employ pentobarbital, midazolam, or phenobarbital in bolus-infusion regimens with adjustments directed by continuous EEG monitoring. Mechanical ventilation is provided as outlined previously, and invasive monitoring is necessary because therapy usually results in hypotension and myocardial depression. Propofol is also effective in quenching seizures and inducing coma, but the propofol infusion syndrome limits its use in pediatrics.

The utility of seizure prophylaxis after pediatric head trauma continues to be controversial. Although some data suggest that children may benefit more than adults from routine prophylaxis, the overall risk of seizures is low after blunt injury. Thus, the added benefit of prophylaxis is small, and it remains a treatment option.[50]

Intracranial Pressure

ICP monitoring is desirable in trauma and in neurosurgical patients at risk for brain swelling or sudden expansion of a mass lesion. Symptoms of increased ICP are nonspecific in children, and intermittent apnea may be the first sign in infancy. Occasionally, increased ICP may be present even when computed tomography findings are normal. In babies, split sutures and bulging fontanels provide clinical evidence of rising ICP, but noninvasive quantitative measures are problematic. In our institution, intraventricular catheters are preferred for ICP monitoring because simultaneous cerebrospinal fluid drainage can provide significant therapeutic benefits.

Unfortunately, the treatment of increased ICP in infants and children is still largely driven by adult data. A notable exception, as discussed previously, is that target thresholds for mean arterial pressure and cerebral perfusion pressure vary with age. Although osmotherapy with 3% (hypertonic) saline is widely used in boluses or infusion to control ICP, it may lead to severe hypernatremia more rapidly in small children than in adults. Other elements of management extrapolated from adult data are avoidance of steroids, the preference of crystalloid over colloid resuscitation fluids, and the reluctance to employ hyperventilation. Regarding the last, it is particularly important to recognize that small children are subject to inadvertent hyperventilation and that cerebral ischemia can occur. Careful monitoring of blood gas tensions, minute ventilation, and end-tidal carbon dioxide tension values are therefore recommended.

SUMMARY

The perioperative management of pediatric neurosurgical patients presents many challenges to neurosurgeons, anesthesiologists, and intensivists. Many conditions are unique to small children. A basic understanding of age-dependent variables and of the interaction of anesthetic and surgical procedures is essential in minimizing perioperative morbidity and mortality at all stages of care.

REFERENCES

1. Chumas P, Kenny T, Stiller C. Subspecialisation in neurosurgery-does size matter? *Acta Neurochir (Wien)*. 2011;153:1231–1236.
2. McCann ME, Soriano SG. Perioperative central nervous system injury in neonates. *Br J Anaesth*. 2012;109(Suppl 1):i60–i67.
3. Wintermark M, Lepori D, Cotting J, et al. Brain perfusion in children: Evolution with age assessed by quantitative perfusion computed tomography. *Pediatrics*. 2004;113:1642–1652.
4. Pryds O. Control of cerebral circulation in the high-risk neonate. *Ann Neurol*. 1991;30:321–329.
5. Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*. 2000;106:625–632.
6. Rhee CJ, Fraser III CD, Kibler K, et al. The ontogeny of cerebrovascular pressure autoregulation in premature infants. *J Perinatol*. 2014;34:926–931.
7. Vavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. *J Neurosurg Anesthesiol*. 2003;15:307–312.
8. Brady KM, Mytar JO, Lee JK, et al. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke*. 2010;41:1957–1962.
9. Lee JK. Cerebral perfusion pressure: How low can we go? *Paediatr Anaesth*. 2014;24:647–648.
10. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth Analg*. 1990;70:160–167.
11. Bhananker SM, Ramamoorthy C, Geiduschek JM, et al. Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. *Anesth Analg*. 2007;105:344–350.
12. McCann ME, Kain ZN. The management of preoperative anxiety in children: An update. *Anesth Analg*. 2001;93:98–105.
13. Vanderhaegen J, Naulaers G, Van Huffel S, Vanhole C, Allegaert K. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. *Neonatology*. 2010;98:57–63.
14. McClain CD, Soriano SG, Goumnerova LC, Black PM, Rockoff MA. Detection of unanticipated intracranial hemorrhage during intraoperative magnetic resonance image-guided neurosurgery. Report of two cases. *J Neurosurg*. 2007;106:398–400.

15. Davidson AJ, Huang GH, Czarnecki C, et al. Awareness during anesthesia in children: A prospective cohort study. *Anesth Analg*. 2005;100:653–661. table of contents.
16. Soriano SG, Martyn JAJ. Antiepileptic-induced resistance to neuromuscular blockers: Mechanisms and clinical significance. *Clin Pharmacokinet*. 2004;43:71–81.
17. Jevtovic-Todorovic V, Absalom AR, Blomgren K, et al. Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth*. 2013;111:143–151.
18. Hintz SR, Kendrick DE, Stoll BJ, et al. Network NNR: Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. *Pediatrics*. 2005;115:696–703.
19. McCann ME, Schouten AN, Dobija N, et al. Infantile postoperative encephalopathy: Perioperative factors as a cause for concern. *Pediatrics*. 2014;133:e751–e757.
20. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90:1265–1270.
21. Sandstrom K, Nilsson K, Andreasson S, Niklasson A, Larsson LE. Metabolic consequences of different perioperative fluid therapies in the neonatal period. *Acta Anaesthesiol Scand*. 1993;37:170–175.
22. Agus MS. Tight glycemic control in children--is the target in sight? *N Engl J Med*. 2014;370:168–169.
23. Macrae D, Grieve R, Allen E, et al. A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med*. 2014;370:107–118.
24. Soriano SG, McManus ML, Sullivan LJ, Rockoff MA, Black PM, Burrows FA. Cerebral blood flow velocity after mannitol infusion in children. *Can J Anaesth*. 1996;43:461–466.
25. McManus ML, Soriano SG. Rebound swelling of astroglial cells exposed to hypertonic mannitol. *Anesthesiology*. 1998;88:1586–1591.
26. Stricker PA, Lin EE, Fiadjoe JE, et al. Evaluation of central venous pressure monitoring in children undergoing craniofacial reconstruction surgery. *Anesth Analg*. 2013;116:411–419.
27. Cucchiara RF, Bowers B. Air embolism in children undergoing suboccipital craniotomy. *Anesthesiology*. 1982;57:338–339.
28. Soriano SG, McManus ML, Sullivan LJ, Scott RM, Rockoff MA. Doppler sensor placement during neurosurgical procedures for children in the prone position. *J Neurosurg Anesthesiol*. 1994;6:153–155.
29. Busso VO, McAuliffe JJ. Intraoperative neurophysiological monitoring in pediatric neurosurgery. *Paediatr Anaesth*. 2014;24:690–697.
30. Ojemann SG, Berger MS, Lettich E, Ojemann GA. Localization of language function in children: Results of electrical stimulation mapping. *J Neurosurg*. 2003;98:465–470.
31. Adelson PD, Black PM, Madsen JR, et al. Use of subdural grids and strip electrodes to identify a seizure focus in children. *Pediatr Neurosurg*. 1995;22:174–180.
32. Soriano SG, Eldredge EA, Wang FK, et al. The effect of propofol on intraoperative electrocorticography and cortical stimulation during awake craniotomies in children. *Paediatr Anaesth*. 2000;10:29–34.
33. Lieberman JA, Lyon R, Feiner J, Diab M, Gregory GA. The effect of age on motor evoked potentials in children under propofol/isoflurane anesthesia. *Anesth Analg*. 2006;103:316–321.
34. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med*. 1987;317:1321–1329.
35. Viscomi CM, Abajian JC, Wald SL, Rathmell JP, Wilson JT. Spinal anesthesia for repair of meningomyelocele in neonates. *Anesth Analg*. 1995;81:492–495.
36. Lin EE, Tran KM. Anesthesia for fetal surgery. *Semin Pediatr Surg*. 2013;22:50–55.
37. Shillito Jr. J. A plea for early operation for craniosynostosis. *Surg Neurol*. 1992;37:182–188.
38. Meier PM, Goobie SM, Dinardo JA, Proctor MR, Zurakowski D, Soriano SG. Endoscopic strip craniectomy in early infancy: The initial five years of anesthesia experience. *Anesth Analg*. 2011;112:407–414.
39. Tobias JD, Johnson JO, Jimenez DF, Barone CM, McBride Jr. DS. Venous air embolism during endoscopic strip craniectomy for repair of craniosynostosis in infants. *Anesthesiology*. 2001;95:340–342.
40. Stone SS, Warf BC. Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment for infant hydrocephalus: A prospective North American series. *J Neurosurg Pediatr*. 2014;14:439–446.
41. Nemergut EC, Zuo Z, Jane Jr. JA, Laws Jr. ER. Predictors of diabetes insipidus after transsphenoidal surgery: A review of 881 patients. *J Neurosurg*. 2005;103:448–454.
42. Reasoner DK, Todd MM, Scamman FL, Warner DS. The incidence of pneumocephalus after supratentorial craniotomy. Observations on the disappearance of intracranial air. *Anesthesiology*. 1994;80:1008–1012.
43. Burrows PE, Robertson RL. Neonatal central nervous system vascular disorders. *Neurosurg Clin N Am*. 1998;9:155–180.
44. Soriano SG, Sethna NF, Scott RM. Anesthetic management of children with moyamoya syndrome. *Anesth Analg*. 1993;77:1066–1070.
45. Vendrame M, Kaleyias J, Loddenkemper T, et al. Electroencephalogram monitoring during intracranial surgery for moyamoya disease. *Pediatr Neurol*. 2011;44:427–432.
46. Vavilala MS, Bowen A, Lam AM, et al. Blood pressure and outcome after severe pediatric traumatic brain injury. *J Trauma*. 2003;55:1039–1044.
47. Fujita Y, Algarra NN, Vavilala MS, Prathep S, Prapruettham S, Sharma D. Intraoperative secondary insults during extracranial surgery in children with traumatic brain injury. *Childs Nerv Syst*. 2014;30:1201–1208.
48. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Report of the second task force on blood pressure control in children--1987. *Pediatrics*. 1987;79:1–25.
49. Matschke J, Voss J, Obi N, et al. Nonaccidental head injury is the most common cause of subdural bleeding in infants <1 year of age. *Pediatrics*. 2009;124:1587–1594.
50. Kochanek PM, Carney N, Adelson PD, et al. American Academy of Pediatrics-Section on Neurological S, American Association of Neurological Surgeons/Congress of Neurological S, Child Neurology S, European Society of P, Neonatal Intensive C, Neurocritical Care S, Pediatric Neurocritical Care Research G, Society of Critical Care M, Paediatric Intensive Care Society UK, Society for Neuroscience in A, Critical C, World Federation of Pediatric I, Critical Care S: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatr Crit Care Med*. 2012;13(Suppl 1):S1–S82.
51. Holzman RS. Clinical management of latex-allergic children. *Anesth Analg*. 1997;85:529–533.
52. Legatt AD, Schroeder CE, Gill B, Goodrich JT. Electrical stimulation and multichannel EMG recording for identification of functional neural tissue during cauda equina surgery. *Childs Nerv Syst*. 1992;8:185–189.
53. Meier PM, Guzman R, Erb TO. Endoscopic pediatric neurosurgery: Implications for anesthesia. *Paediatr Anaesth*. 2014;24:668–677.
54. El-Dawlatly AA, Murshid W, Alshimy A, Magboul MA, Samarkandi AH, Takrouri MS. Arrhythmias during neuroendoscopic procedures. *J Neurosurg Anesthesiol*. 2001;13:57–58.
55. Davidyuk G, Soriano SG, Goumnerova L, Mizrahi-Arnaud A. Acute intraoperative neurogenic pulmonary edema during endoscopic ventriculoperitoneal shunt revision. *Anesth Analg*. 2010;110:594–595.
56. American Academy of Pediatrics. American Academy of Pediatric Dentristry, Cote CJ, Wilson S, Work Group on Sedation: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. *Paediatr Anaesth*. 2008;18:9–10.
57. Landrigan-Ossar M, McClain CD. Anesthesia for interventional radiology. *Paediatr Anaesth*. 2014;24:698–702.
58. Tasker RC. Update on pediatric neurocritical care. *Paediatr Anaesth*. 2014;24:717–723.
59. Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. *Pediatrics*. 2004;114:1591–1596.
60. Chambers IR, Jones PA, Lo TY, et al. Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury. *J Neurol Neurosurg Psychiatry*. 2006;77:234–240.
61. Jagannathan J, Okonkwo DO, Dumont AS, et al. Outcome following decompressive craniectomy in children with severe traumatic brain injury: A 10-year single-center experience with long-term follow up. *J Neurosurg*. 2007;106:268–275.
62. Au AK, Ray PE, McBryde KD, Newman KD, Weinstein SL, Bell MJ. Incidence of postoperative hyponatremia and complications in critically-ill children treated with hypotonic and normotonic solutions. *J Pediatr*. 2008;152:33–38.
63. Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalised children: A systematic review. *Arch Dis Child*. 2006;91:828–835.
64. Jimenez R, Casado-Flores J, Nieto M, Garcia-Teresa MA. Cerebral salt wasting syndrome in children with acute central nervous system injury. *Pediatr Neurol*. 2006;35:261–263.
65. Taplin CE, Cowell CT, Silink M, Ambler GR. Fludrocortisone therapy in cerebral salt wasting. *Pediatrics*. 2006;118:e1904–e1908.
66. Wise-Faberowski L, Soriano SG, Ferrari L, et al. Perioperative management of diabetes insipidus in children. *J Neurosurg Anesthesiol*. 2004;16:220–225.
67. Shay JE, Kattail D, Morad A, Yaster M. The postoperative management of pain from intracranial surgery in pediatric neurosurgical patients. *Paediatr Anaesth*. 2014;24:724–733.
68. Nemergut ME, Yaster M, Colby CE. Sedation and analgesia to facilitate mechanical ventilation. *Clin Perinatol*. 2013;40:539–558.
69. Cray SH, Robinson BH, Cox PN. Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med*. 1998;26:2087–2092.

70. Carroll CL, Krieger D, Campbell M, Fisher DG, Comeau LL, Zucker AR. Use of dexmedetomidine for sedation of children hospitalized in the intensive care unit. *J Hosp Med*. 2008;3:142–147.
71. Whalen LD, Di Gennaro JL, Irby GA, Yanay O, Zimmerman JJ. Long-term dexmedetomidine use and safety profile among critically ill children and neonates. *Pediatr Crit Care Med*. 2014;15:706–714.
72. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: A wake-up call for the pediatric critical care community. *Crit Care Med*. 2014;42:1592–1600.
73. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. *Pediatr Crit Care Med*. 2005;6:58–63.
74. Hardesty DA, Sanborn MR, Parker WE, Storm PB. Perioperative seizure incidence and risk factors in 223 pediatric brain tumor patients without prior seizures. *J Neurosurg Pediatr*. 2011;7:609–615.

Neurosurgical Diseases and Trauma of the Spine and Spinal Cord: Anesthetic Considerations

21

G.R. Stier • F. Asgarzadie • D.J. Cole

The first descriptions of spine disorders were recorded nearly 4000 years ago in Egypt, when patients with such afflictions were left bedridden and death was considered unavoidable. One of the first extensive series on surgery of the spine was reported by Elsberg in 1925, in which the surgical treatment of spinal cord tumors was described.[1] Since those early reports, spine surgery has made remarkable advancements, particularly since the 1980s. As surgical techniques have matured, complex operations are being performed on spine diseases once thought incurable. Moreover, increasingly older patients with multiple comorbidities are presenting for spine procedures. Consequently, the anesthetic approach to patients scheduled for spine surgery must consider the following issues: a basic knowledge of spine anatomy and imaging modalities; an awareness of the specific spine disorder being treated and the surgical procedure planned; preoperative risk assessment and optimization; potential airway difficulties; patient positioning; anesthetic choices; intraoperative medical decision-making (blood replacement, blood salvage, hemodynamic goals, pulmonary function); postoperative airway concerns; and perioperative pain management. This chapter discusses these issues.

ANATOMY

The anatomy of the spine can be divided into that pertaining to the vertebral bony column and the contents of the vertebral canal.[2]

Vertebral Column

The vertebral column is composed of 33 vertebrae. In adult life this number is functionally reduced to 24 presacral vertebrae, the sacrum, and the coccyx. The presacral vertebrae consist of seven cervical, 12 thoracic, and five lumbar bones. The five sacral and four coccygeal vertebrae fuse early in development. The vertebral column normally exhibits four curves in the anteroposterior (AP) plane. The two forward curves, or lordoses, are in the cervical and lumbar areas, and the two posterior curves, or kyphoses, are in the thoracic and sacral areas. The combination of these curves gives the normal bony spine the characteristic S shape when viewed from the side (Fig. 21.1).

Each of the individual "standard" vertebrae that make up the vertebral column is a single bony structure consisting of a large body, bilateral pedicles, bilateral lamina, bilateral transverse processes, a spinous process, and four articular processes (Fig. 21.2). The two pedicles laterally, the two lamina posteriorly, and the body anteriorly together form the vertebral canal, in which lies the spinal cord. The segmental nerves exit between the vertebrae through the intervertebral foramina. The four articular processes mate with corresponding processes on the vertebrae above and below to form the facet joints. The facet joint articulations provide posterior stability, and the body articulations provide anterior and vertical stability. In addition, the facet joints provide flexion, extension, and lateral rotation of the spine.

The first two cervical vertebrae, C1 and C2, differ in structure from the standard vertebrae (Fig. 21.3). C1, the atlas, is ring-shaped and wider than the other vertebrae. The superior articular surfaces are configured to articulate with the two occipital condyles located at the base of the skull on either side of the foramen magnum. The atlas is composed of anterior and posterior arches, each possessing a tubercle while sharing lateral masses. The atlas has no spinous processes or body. C2, the axis, possesses a body that projects superiorly as the dens (odontoid process) (see Fig. 21.3), and a short bifid spinous process. The axis has two large flat superior articular facets. The transverse ligament of the atlas holds the dens in place, preventing horizontal movement of the atlas.

The anterior longitudinal ligament and the posterior longitudinal ligament (see Fig. 21.2) extend from the base of the skull and atlas to the sacrum. The anterior ligament is attached to the anterior surface of the vertebrae and intervertebral disks. The posterior ligament is attached to the posterior surface of the vertebrae and the intervertebral disks and lies within the vertebral canal. These two ligaments provide extension and flexion stability to the vertebral column. The supraspinal and interspinal ligaments join the spinous processes at each level, providing additional flexion stability. The ligamentum flavum unites the vertebral laminae at each level and forms part of the posterior border of the intervertebral foramen.

The intervertebral disks are fibrocartilaginous joints composed of an interior nucleus pulposus surrounded and enclosed by a tough anulus fibrosus (Fig. 21.4). Together, these two components provide a strong attachment between adjacent vertebrae but allow some movement. In addition, the disks act as very efficient shock absorbers.

The facet joints are synovial joints, which are paired and compose part of the posterior elements of the vertebral column. With the intervertebral disks they form the remaining articulations of the vertebrae with each other. As posterior elements, the facet joints allow flexion of the spine. The facet joints of the cervical region are less rigid, thus allowing greater flexion of the neck.

Spinal Cord

The spinal cord is contained within the confines of the vertebral canal. The anteroposterior (AP) diameter of the cervical cord constitutes about 40% of the diameter of the cervical canal, decreasing in diameter with neck extension. The spinal cord is contiguous with the brainstem at the foramen magnum, and in

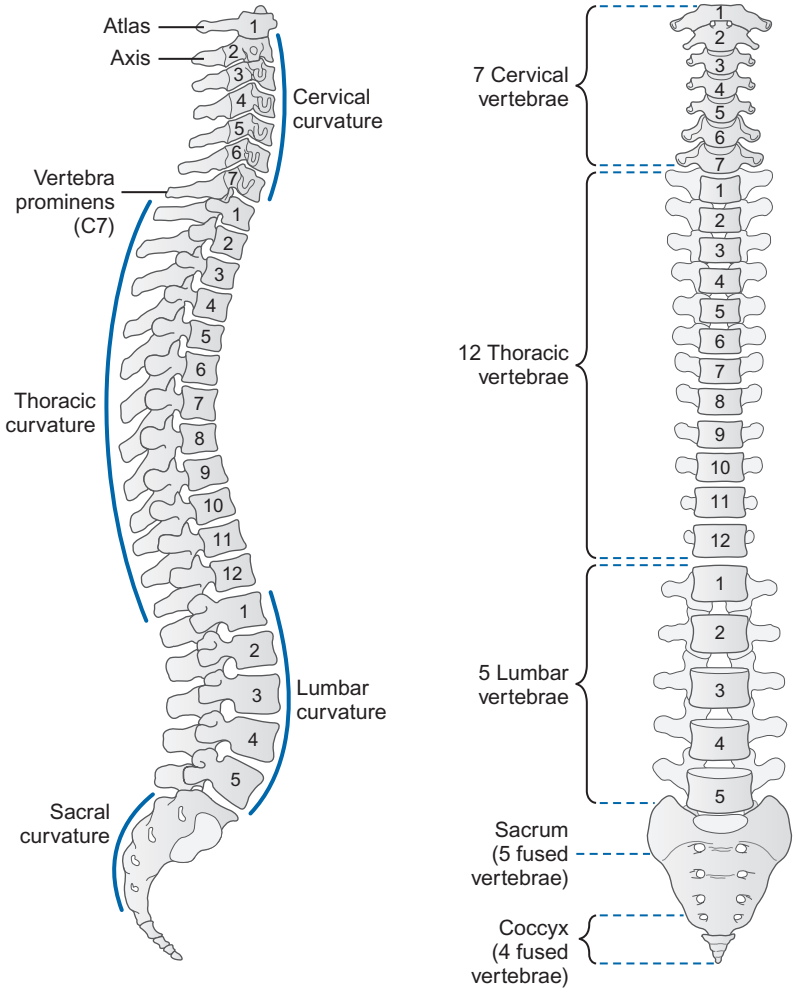


Fig. 21.1 Vertebral column showing 24 presacral vertebrae, sacrum, coccyx, and curvatures of the adult vertebral column. Note that the first coccygeal vertebra has fused with the sacrum. Most vertebral columns are 72–75 cm long; about one-fourth of this length is contributed by the fibrocartilaginous intervertebral disks. The vertebral column supports the skull and transmits the weight of the body through the pelvis to the lower limbs. *(From Moore KL: Clinically Oriented Anatomy, 2nd ed, Baltimore, Williams & Wilkins, 1985, p 566.).*

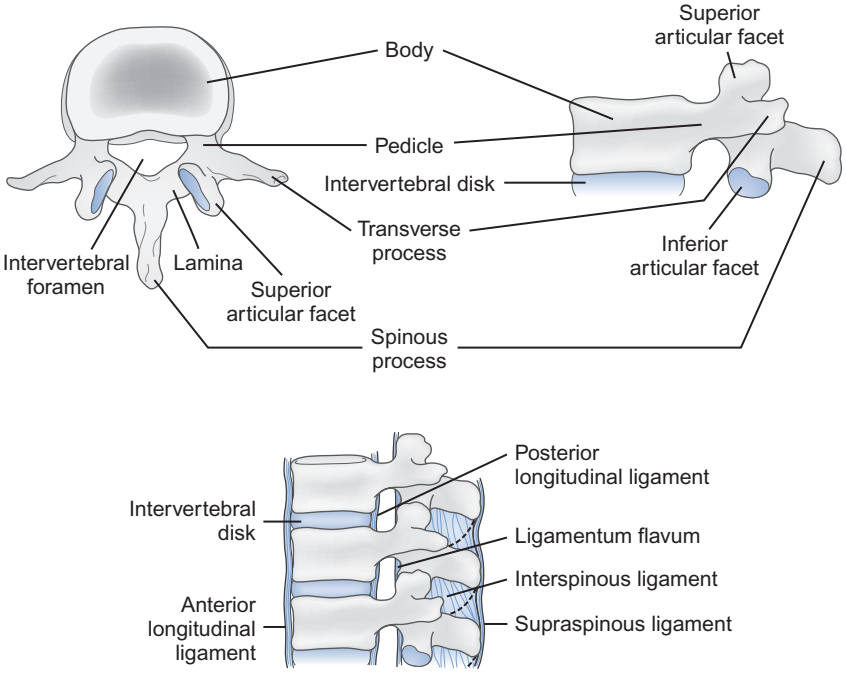


Fig. 21.2 Normal anatomic components of typical vertebrae and spinal column.

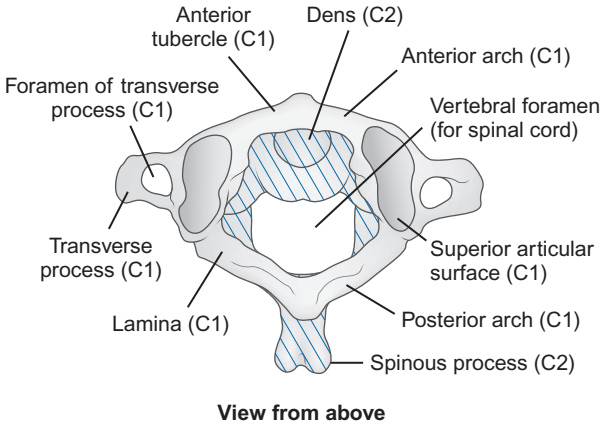


Fig. 21.3 C1 and C2 cervical vertebrae, viewed from above and in anterior view.

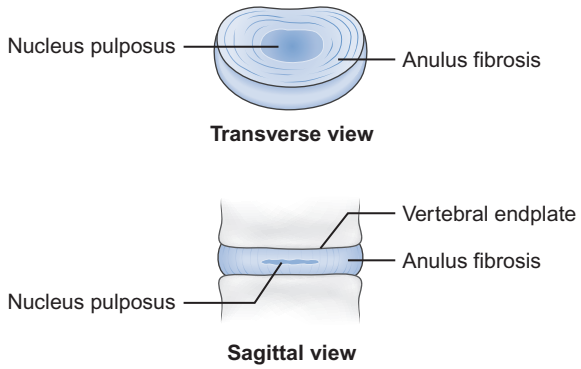


Fig. 21.4 Transverse and sagittal images of an intervertebral disk.

the adult it extends to the conus medullaris at about the level of the first or second lumbar vertebra. The filum terminale attaches the end of the conus to the first coccygeal segment of the bony spine. The cord exhibits two prominent bulges in the cervical and lumbar areas, which correspond to the origins of the nerves to the upper and lower extremities, respectively. A cross section of the cord reveals a mixture of white matter and gray matter (Fig. 21.5). The gray matter, in the shape of an H, surrounds the central canal and contains the cell bodies of the spinal neurons.

The dorsal horns are associated with sensory functions, including pain, position sense, touch, and temperature. The ventral horns contain neurons associated with motor functions and spinal reflexes. The surrounding white matter contains the myelinated and unmyelinated fibers that communicate with higher and lower centers, including the brainstem and cerebral cortex. The descending motor pathways travel in the white matter located in the lateral and ventral areas of the cord. The corticospinal tract conducts all primary motor impulses. The vestibulospinal and rubrospinal tracts also participate in motor function and are located in the ventral and lateral areas of white matter, respectively. The dorsal areas of white matter contain the dorsal column tracts, the spinothalamic tracts, and the spinoreticular tracts, among others. These pathways transmit sensory information to higher cord segments and the brain.

The sympathetic nervous system is also segmental and traverses the length of the vertebral column in two chains anterior to the bony spine (Fig. 21.6).[3] Segmental communication is accomplished at each spinal segment via the communicating ramus of each segmental spinal nerve. The segmental spinal nerves are made up of the confluence of a dorsal root and a ventral root at each level (see Fig. 21.6).

A nerve emerges from each side of the spinal cord; thus they are paired. The dorsal roots conduct sensory information, including pain. All nerve cell bodies of afferent axons are located in the dorsal root ganglion. The ventral roots conduct primarily motor and efferent information from the cord to the periphery. The two roots combine in the spinal nerve as they traverse the vertebral foramen. The nerve then divides into three rami: dorsal, ventral, and communicating. The ventral ramus continues as the primary spinal nerve, the dorsal ramus innervates the paraspinous muscles of the back and the facet joints at each level, and the communicating ramus provides segmental neuronal connections to the sympathetic chains.

The spinal nerves have a particular relationship to the respective spinal vertebrae (Fig. 21.7). The spinal nerves exit the vertebral canal via the intervertebral foramina. These foramina are formed by the juxtaposition of adjoining vertebrae in the spinal column.

Spinal Cord Blood Supply

The spinal cord is supplied with blood from the aorta via the vertebral and segmental or radicular arteries; the three main arteries of the spinal cord are the single anterior spinal artery in the anterior or ventral median sulcus and two posterior spinal arteries located in the area of the dorsal nerve rootlets (Fig. 21.8). These three arteries usually arise as branches of the vertebral arteries at the base of the brainstem and traverse the entire length of the cord (Fig. 21.9). The blood flow is augmented by multiple segmental radicular and medullary arteries that enter at the intervertebral foramen (see. Figs. 21.8 and 21.9).

The anterior spinal artery supplies the anterior two-thirds of the cord, and the posterior spinal arteries supply the posterior one-third. Below the level of the cervical cord segments, additional blood supply is provided by segmental or radicular arteries that arise as branches of the aorta and enter the cord arterial system. The most consistent of these arteries is the artery of Adamkiewicz, which is the largest segmental feeder in the thoracolumbar region of the cord. It usually enters as a single vessel between the ninth and the eleventh thoracic levels and arises on the left side of the aorta.[2] The artery of Adamkiewicz is thought to be the principal contributor to the arterial supply of the entire thoracic

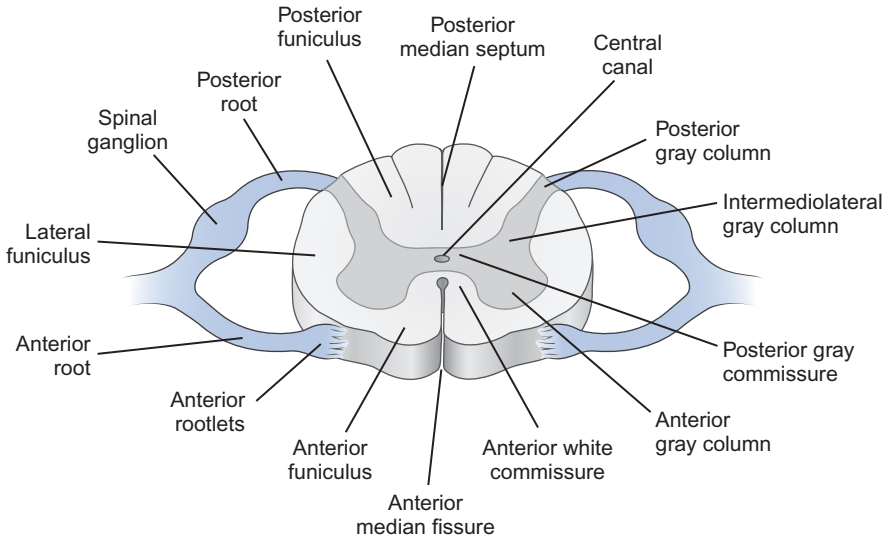


Fig. 21.5 Anatomy of the spinal cord.

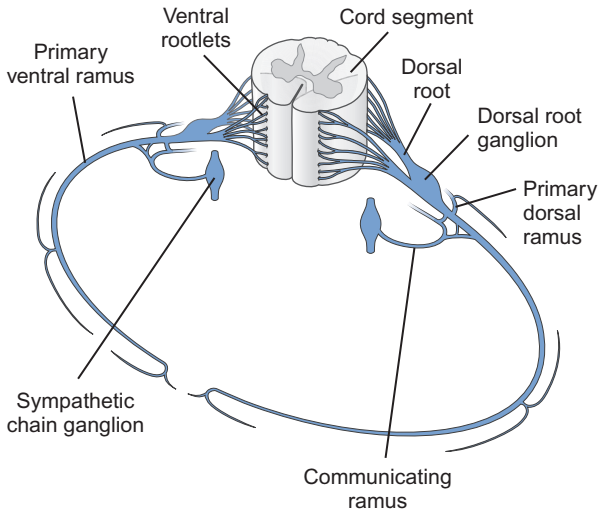


Fig. 21.6 Cord segment with its roots, ganglia, and branches.

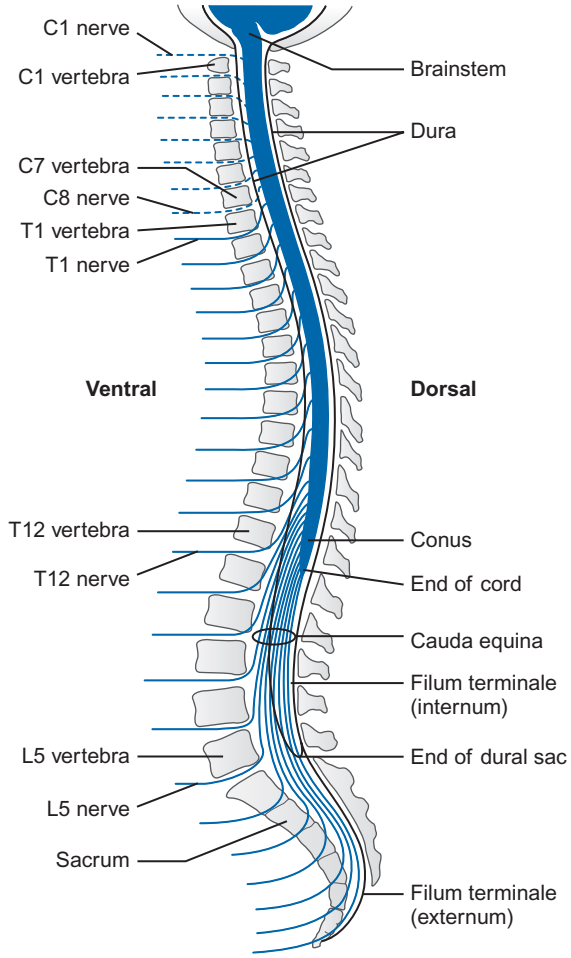


Fig. 21.7 Lateral view of the relationships among spinal cord, spinal nerves, and vertebral column. Termination of the dura (dura mater spinalis) and its continuation as the filum terminale externum are shown.

and lumbar cord distal to its entry. Loss of this artery after surgery or trauma to the aorta may produce paraplegia in the thoracic region.[4]

The arterial network of the three main blood vessels supplies blood to the interior of the cord through an extensive network of arterioles and capillaries. The density of the capillary bed reflects the metabolic demands of the different areas of the cord. Blood flow through these capillaries is very sensitive to compression of the cord, and ischemia may result.

Venous drainage of the spinal cord is through radial veins serving the parenchyma.[2] The veins feed into the coronal venous plexus or longitudinal veins on the surface of the cord, which are, in turn, drained by medullary veins that penetrate the dura adjacent to the dural penetration of the nerve roots to join the epidural venous plexus. The epidural or internal vertebral venous system drains into the external vertebral venous system, which communicates with the caval veins. The veins in the epidural system are valveless and, therefore, subject to engorgement in certain normal and disease states, such as pregnancy and obesity, in which there is an increase in the intra-abdominal pressure or obstruction to venous flow through the inferior vena cava.

PHYSIOLOGY

Blood Flow

Spinal cord blood flow (SCBF) has been studied extensively in animal models. The values and data obtained from these studies are consistent with values obtained for the brain; average

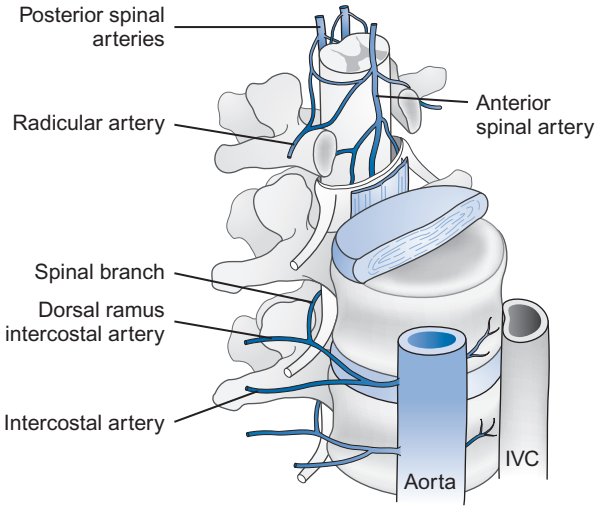


Fig. 21.8 Blood supply of the spinal cord illustrating the single anterior spinal artery, paired posterior arteries, and feeding radicular branches from the aorta. IVC, inferior vena cava.

SCBF is about 60 mL/100 g/min,[3] including a threefold to fourfold gray matter–white matter differential in blood flow.[4] Autoregulation in the cord mimics that in the brain, with flow well maintained between a mean arterial blood pressure (MAP) of 60 to 120 mm Hg.[4] Likewise, the effects of arterial blood gas tensions are similar to those in the brain; hypoxemia and hypercapnia cause vasodilation, and hypocapnia causes vasoconstriction (Fig. 21.10).

Injury to the spinal cord disturbs autoregulation of blood flow. Trauma to the cord results in a decrease in SCBF and loss of autoregulatory function.[5] The nature of the operative procedure itself may also have an effect on SCBF. This effect is well recognized with spinal distraction and instrumentation but may also occur during other operations, such as simple laminectomy.[6]

RADIOLOGIC CONSIDERATIONS

Imaging of the spine and spinal cord is an essential part of the diagnosis and treatment of spinal diseases. A variety of imaging modalities are available for the assessment of spinal pathology, the most common of which are plain radiography, computed tomography (CT), CT angiography, magnetic resonance imaging (MRI), MR angiography, bone scanning, single-photon emission computed tomography (SPECT), and positron emission tomography (PET). The choice of imaging modalities best suited for the patient depends on the history, physical findings, and differential diagnosis. A general review of the common imaging techniques used in spine disease can be found in the later section on traumatic spinal cord injury (SCI).

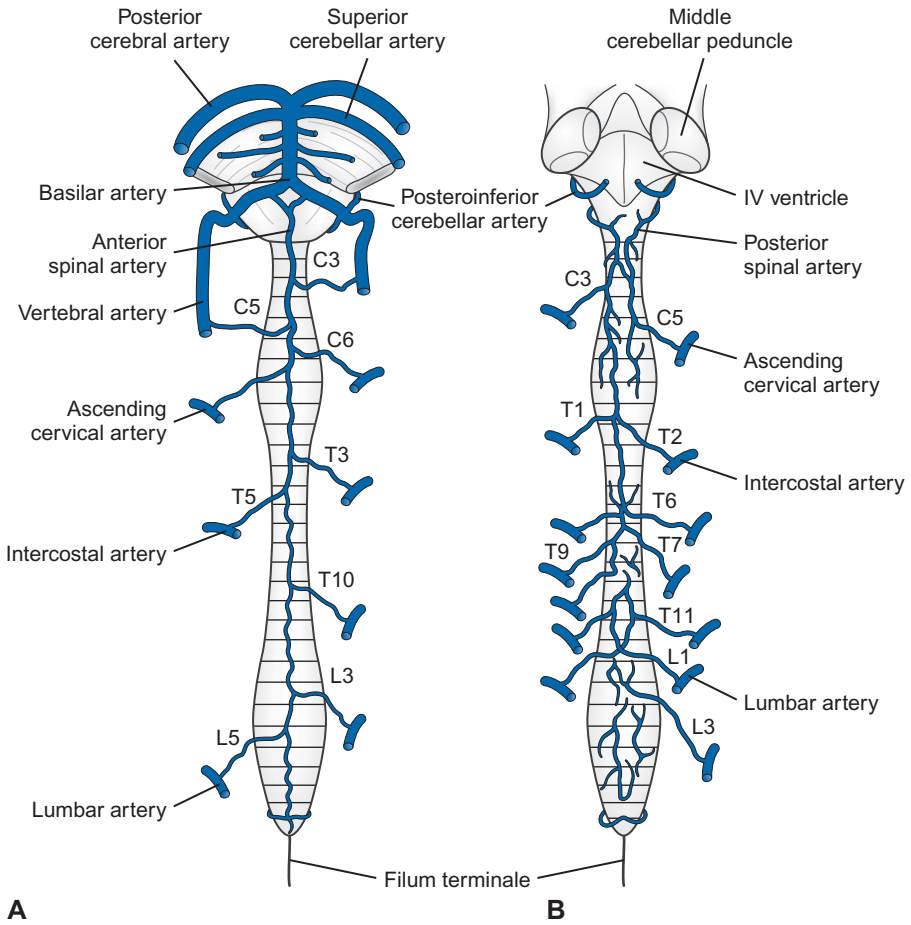


Fig. 21.9 Arteries of spinal cord. **A,** Ventral aspect. **B,** Dorsal aspect. Regions most vulnerable to vascular deprivation when the contributing arteries are injured are T3–T5 and T12–L2 for anterior spinal artery and C8–T4 for dorsal circulation. Levels of entry of common radicular branches are shown (e.g., C5 and T5). Note that the spinal cord is enlarged in two regions for innervation of the limbs. Cervical enlargement extends from C4 to T1, and lumbosacral enlargement extends from L2 to S3. *(From Moore KL: Clinically Oriented Anatomy, 2nd ed. Baltimore, Williams & Wilkins, 1985, p 613.)*

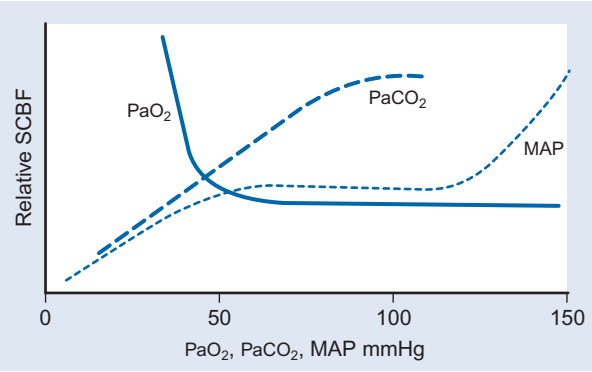


Fig. 21.10 Illustration of effect of changes in $PaCO_2$, PaO_2, and mean arterial pressure (MAP) on spinal cord blood flow (SCBF).

SURGICAL DISORDERS OF THE SPINE

Disorders of the Cervical Spine

Cervical Spondylosis

Degenerative disease of the cervical spine affects more than 90% of individuals older than 65 years. The term *cervical spondylosis* refers to the nonspecific degenerative process of the spine that may result in degenerative listhesis, spinal stenosis, as well as neural foraminal encroachment (Fig. 21.11).

In those individuals who eventually experience symptoms of cervical degenerative disease, radiculopathy is the most common. *Cervical radiculopathy* is defined as a neurologic condition characterized by dysfunction of a cervical spinal nerve, the nerve roots, or both.[7] It is most commonly caused by lateral disk herniation, osteophyte overgrowth with narrowing of the lateral foramen (termed the *lateral recess syndrome*), or cervical spinal instability caused by subluxation of a cervical vertebra (Fig. 21.12).

MRI is the imaging modality of choice in the diagnosis of cervical radiculopathy; however, MRI is not indicated in the initial stages of management because the findings will not alter treatment. In general, medical management is attempted for 4–6 weeks, and if the patient remains symptomatic, an MRI study is appropriate. CT is of value primarily for defining the bony anatomy and for helping to distinguish whether the stenosis is due to soft or calcified lesions. Surgical treatment for

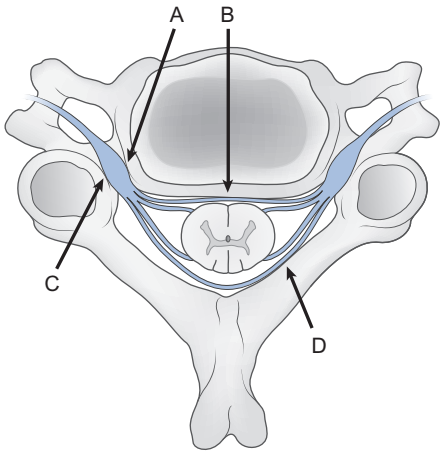


Fig. 21.11 Cervical spondylosis.[12] Common sites of pathology that may result in compression of the spinal cord or nerve root: **A,** Lateral disk herniation or osteophyte hypertrophy; **B,** central disk herniation or osteophyte formation; **C,** facet joint osteophyte; **D,** hypertrophy of the ligamentum flavum.

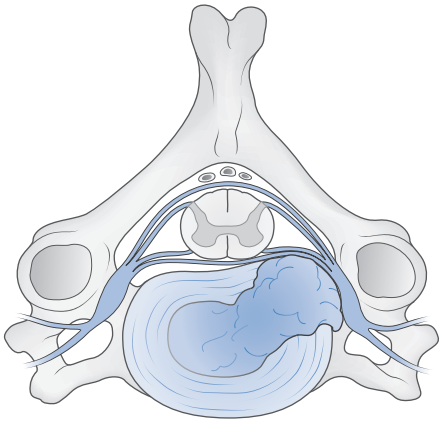


Fig. 21.12 Cervical radiculopathy caused by foraminal stenosis from a posterolateral herniation of the nucleus pulposus with compression of the exiting nerve root. *(From Won DS, Herkowitz HN: Cervical radiculopathy: Posterior surgical approach. In Herkowitz HN, Garfin SR, Eismont FJ, et al [eds], Rothman-Simeone: The Spine, 5th ed. Philadelphia, Saunders-Elsevier, 2006, p 842.)*

cervical radiculopathy is indicated for severe clinical symptoms that medical therapy has failed to control combined with a compatible MRI study demonstrating nerve compression; for the persistence of pain despite medical management for at least 6 weeks; and for the presence of an evolving neurologic deficit.[7]

Cervical Spondylotic Myelopathy

Cervical spondylotic myelopathy (CSM) is the most common type of spinal cord dysfunction in patients older than 55 years. Originally described more than 50 years ago, CSM is the result of narrowing of the cervical spinal canal due to a degenerative process or a congenital disorder. The primary pathophysiologic abnormality in CSM is a reduction in the sagittal diameter of spinal canal, with cervical myelopathy developing in nearly all patients in whom there is a greater than 30% reduction in the cross-sectional area of the cervical vertebral canal. Typical signs and symptoms of CSM are pain in the neck, shoulder, and subscapular areas; numbness or tingling in the upper extremities; motor weakness in the upper or lower extremities; sensory changes in the lower extremities; gait disturbances; bowel and bladder dysfunction; and spasticity, hyperreflexia, and clonus typical of an upper motor neuron lesion. The most common presentation of CSM is a spastic gait. Physical findings include atrophy of the muscles of the hand, hyperreflexia, electric-shock-like sensations down the arm or back after flexion of the neck (Lhermitte's sign), and sensory loss. Plain films often show evidence of osteophyte formation, kyphosis, and subluxation. MRI remains the imaging modality of choice, providing information about the spinal canal (demyelination, spinal cord atrophy, and edema), intervertebral disks, vertebral osteophytes, and ligaments. Treatment of CSM initially involves nonoperative therapy; however, early surgery is associated with significant improvement in the neurologic prognosis. If surgical intervention is chosen, treatment considerations include anterior cervical discectomy and fusion (ACD&F), anterior cervical fusion (ACF), cervical laminoplasty, and posterior cervical decompression and fusion.

The anesthetic management of patients with cervical spine instability or myelopathy should consider the specific technique most appropriate for securing the airway, choice of anesthetic agents, hemodynamic monitoring needs, use of vasoactive medications, and positioning. For patients with symptomatic spinal stenosis, an awake fiberoptic intubation is often suggested; however, initial induction of anesthesia

followed by fiberoptic intubation utilizing manual in-line stabilization with/without spinal cord monitoring is a viable option. The use of invasive (or advanced noninvasive) blood pressure monitoring is advocated to facilitate maintenance of an adequate spinal cord perfusion pressure (i.e., mean artery pressure ≥ 85 mm Hg) throughout the case. If electrophysiologic (EP) spinal cord monitoring is planned, the anesthetic strategy should select agents with minimal effects on the EP waveform potentials. The decision to extubate the patient following surgery should be made only in the absence of airway edema, neck hematoma, and depressed mental status.

Cervical Disk Herniation

Intervertebral disks are composed of a well-hydrated central nucleus pulposus surrounded by an outer anulus fibrosus. With age, the disks deteriorate, ultimately resulting in herniation when the anulus fibrosus breaks open or cracks, allowing the nucleus pulposus to extrude (see Fig. 21.12).

In the cervical spine, the most common location of the herniation is at C5–C6, followed by C6–C7, and herniation is most common in individuals older than 40 years. The symptoms of a cervical disk herniation are neck pain and radicular symptoms, which consist of shoulder, arm, or hand paresthesias or pain, and muscle weakness in a dermatomal nerve root distribution. Patients may also present with symptoms of a cervical myelopathy if the herniation is centrally located. In patients in whom a disk herniation is suspected, plain films may demonstrate a narrowed disk space, osteophytes, or subluxation of the vertebra. An MRI study is the radiologic imaging modality of choice for evaluation of a suspected herniated cervical disk (Fig. 21.13).

The primary treatment of a cervical disk herniation is medical management, at least initially. Cervical soft collars, anti-inflammatory agents, oral steroids, and physical therapy are all appropriate in the short term because more than 90% of patients with radiculopathic symptoms experience improvement with these measures. If nonsurgical therapy fails or the patient demonstrates progressive neurologic symptoms, surgical therapy is selected, typically an anterior cervical diskectomy and fusion (ACD&F), with or without anterior cervical plating.

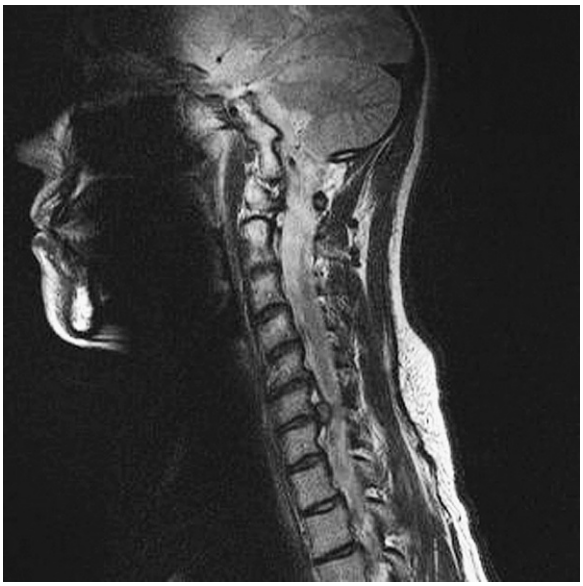


Fig. 21.13 Cervical disk herniation and anterior cervical diskectomy and fusion (ACD & F). A 41-year-old woman presented with pain in the neck that radiated to the left hand and fingers. This sagittal T2-weighted magnetic resonance image shows a 6-mm disk protrusion at C6–C7.

Complications of surgery include thoracic duct injury, cerebrospinal fluid (CSF) leak, spinal cord or nerve root injury, vertebral artery injury, perforation of the esophagus or trachea, recurrent laryngeal nerve injury (vocal cord paralysis), postoperative hematoma, and wound infection. In instances in which there is a significant postoperative hematoma, the airway should be left secured until the patient is fully awake, the hematoma is not enlarging, and there is a tracheal cuff leak.

Syringomyelia

Syringohydromyelia refers to the cystic cavitation of the spinal cord. Two main forms have been described: syringomyelia and hydromyelia. In hydromyelia, there is primary dilatation of the central canal that is often associated with abnormalities at the foramen magnum such as tonsillar herniation (Chiari malformation) and basal arachnoiditis. In true syringomyelia, a cyst arises within the cord substance itself and does not communicate with the central canal or subarachnoid space. Common causes of true syringomyelia include trauma (most common), neoplasm, and arachnoiditis. In the typical presentation, an adult between the ages of 20 and 50 years complains of sensory loss (similar to central cord syndrome) in a "cape" distribution, cervical or occipital pain, wasting in the hands, and painless arthropathies. MRI is the investigation of choice and should include images of the cervical and thoracic spinal cord as well as the brain. Treatment focuses upon reestablishing normal CSF flow across the site of the injury. Therapeutic choices include a posterior fossa decompression and C1 laminectomy (with or without expansile duroplasty) in the presence of a Chiari malformation, fenestration of associated arachnoidal cysts, resection of an associated neoplasm, or placement of a shunt with direct drainage of the cyst into the subarachnoid space or pleural cavity. The airway management of patients with syringomyelia should consider the neurologic deficits commonly associated with this disease. In patients in whom syringomyelia is associated with the Chiari malformation, limitation of neck flexion and extension is vital in preventing further compression of neuronal structures. The limitation of neck motion during intubation by the use of fiberoptic bronchoscopy (either awake or after induction) is an appropriate choice.

Disorders of the Thoracic and Lumbar Spine

Herniated Disk

Symptomatic thoracic disk herniations are rare, with an annual incidence of 1 per 1 million patients.[8] Thoracic disk herniations occur most commonly at T8–T12, with a peak incidence between the ages of 40 and 60 years (mean, 46 years). The majority of disk herniations are located centrolaterally (94%) or laterally (6%) and manifest a variety of symptoms and signs, including pain (localized, axial, or radicular), myelopathy, sensory disturbances, and bladder dysfunction. The radiographic diagnosis is made through a combination of CT and MRI imaging. The majority of symptomatic thoracic disk herniations are effectively managed with nonoperative therapy alone. Indications for surgery include failure of a 4– 6-week trial of medical treatment; severe, persistent radicular pain; and significant neurologic deficits, particularly if there is any progression of symptoms. Thoracic spine operations are typically lengthy procedures (≥3 hours), often with clinically significant blood loss. Major surgical complications are uncommon; they include death from cardiopulmonary compromise, spinal instability requiring further surgery, and worsening of neurologic deficits.

Unlike a thoracic disk herniation, a lumbar disk herniation is very common, occurring in 2% of the general population at some time in their lives.[9] Sciatica, resulting from a herniated lumbar disk, is the most common cause of radicular leg pain in the adult working population. Fortunately, the symptoms of sciatica typically resolve within 2 months from the onset in patients who are treated medically, and surgery is rarely necessary. The majority of lumbar herniations occur at the L4–L5 or L5–S1 spinal levels, most often posterolaterally, where the posterior longitudinal ligament is thinnest. The symptoms of a lumbar disk herniation range from lower back pain to radiculopathy with leg pain, weakness, and paresthesias. With a large centrally located disk herniation, the cauda equina syndrome may occur, resulting in lower back pain, bilateral lower extremity sensorimotor deficits, bladder dysfunction, sexual dysfunction, and perirectal sensory loss. The presence of cauda equina syndrome warrants urgent medical attention. MRI is the imaging modality of choice for suspected herniation of an intervertebral disk, as it clearly defines the local anatomy (Fig. 21.14).

The majority of patients with lumbar disk herniations are treated medically. With such treatments, more than 75% of patients recover within 6–8 weeks. Accepted indications for surgical therapy include the cauda equina syndrome; significant motor deficits; severe pain unresponsive to medical therapy; failure of conservative therapy after 2–3 months; and large extruded disk fragments. Surgical options include diskectomy only, diskectomy with spinal fusion, hemilaminotomy, and/or laminectomy. Anesthetic management should consider the presence of presurgical neurologic deficits, the requirement for a meticulous positioning technique, identification of comorbidities that may increase the risk of complications, and the amount of anticipated blood loss. Invasive blood pressure monitoring is appropriate in those patients with serious comorbidities; however, noninvasive blood pressure monitoring is usually adequate in otherwise healthy patients scheduled for a lumbar procedure for disk herniation.

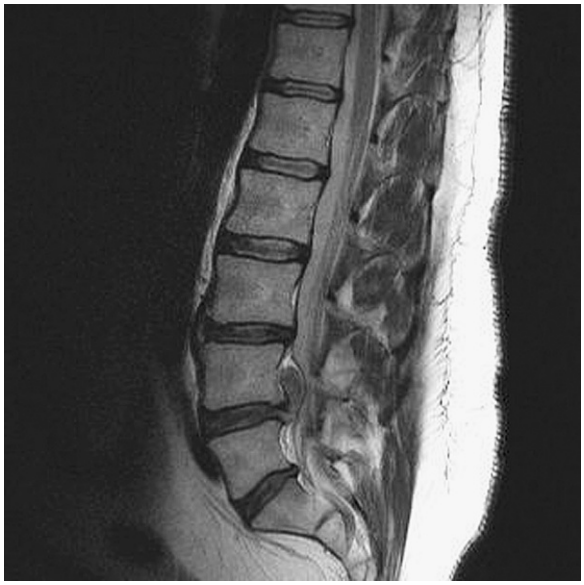


Fig. 21.14 Lumbar disk herniation. A 42-year-old man complained of low back pain with radiation to the left lower extremity. This sagittal T2-weighted magnetic resonance image shows a large disk herniation at L4–L5 with the nucleus pulposus extruding 2 cm cephalad into the ventral epidural space.

Lumbar Spondylosis

Lumbar spondylosis is a general term referring to changes in the vertebral joint characterized by progressive degeneration of the intervertebral disk, with subsequent changes in the bones and soft tissues. Disk degeneration, ligamentous and facet hypertrophy, spinal stenosis, and spondylolisthesis are the characteristic pathologic changes that result. The clinical spectrum of spondylosis includes spinal instability, spinal stenosis, and degenerative spondylolisthesis. Spinal stenosis, the most common of the spondylitic disorders, is a common indication for spinal surgery in adults older than 65 years.[10]

Lumbar Spinal Stenosis

The etiology of lumbar spinal stenosis may be congenital, acquired, or a combination of both. The patient with congenitally short pedicles typically has a shallow spinal canal that predisposes to spinal stenosis later in life as the typical degenerative changes in the spine occur, such as disk protrusion, facet joint degeneration and hypertrophy, ligamentous hypertrophy, and spondylolisthesis (Fig. 21.15).

Lumbar stenosis most commonly occurs at the L4–L5 spinal level, followed by the L3–L4 level. Clinical symptoms of lumbar spinal stenosis include the gradual onset of leg and buttock pain combined with lower extremity sensorineural deficits. These symptoms progress over a period of months. The initial diagnostic investigation should include AP, lateral, flexion, and extension plain films. Suggestive findings on plain films include disk space narrowing and erosion and sclerosis of the vertebral end plates. MRI, the imaging modality of choice in lumbar stenosis, typically shows degenerative changes such as facet joint and ligamentous hypertrophy, disk herniation, and nerve root impingement. The initial approach for patients with the symptoms of spinal stenosis is medical management. Surgical therapy is indicated in patients for whom conservative treatment has failed or who have severe and debilitating pain, significant motor deficits, or symptoms of myelopathy.

Degenerative Spondylolisthesis

Spondylolisthesis is a term referring to the anterior displacement of one vertebra on another associated with degenerative changes in the presence of an intact neural arch[11] (Fig. 21.16). Spondylolisthesis may be congenital or acquired. Degenerative spondylolisthesis is a common condition—particularly in individuals older than 50 years—with a reported incidence as high as 8.7%.[12] Women are affected four to six times more commonly than men. The development of spondylolisthesis is associated with the presence of degenerative intervertebral disks, laxity of ligaments, and facet joint pathology.[13]

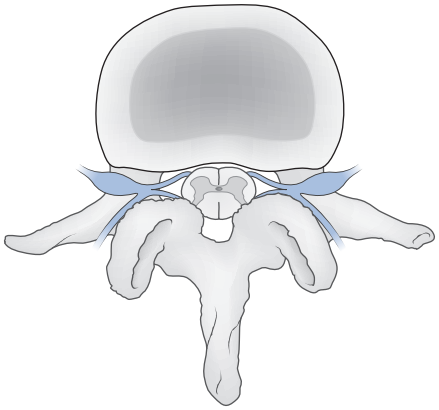


Fig. 21.15 Axial view of a lumbar vertebra. Characteristic hypertrophic degenerative changes can be seen in the central canal, facet joints, and lateral recesses.

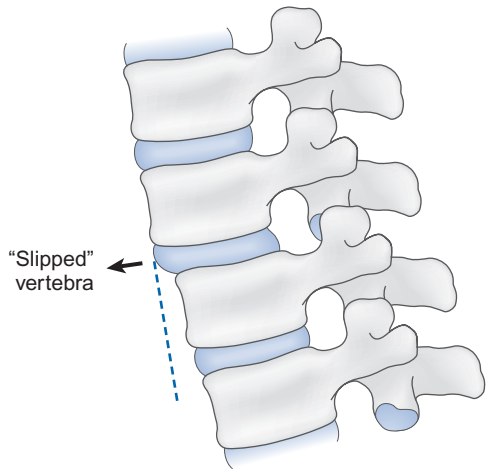


Fig. 21.16 Degenerative spondylolisthesis with anterior "slippage" of the cephalad vertebra over the vertebra below it.

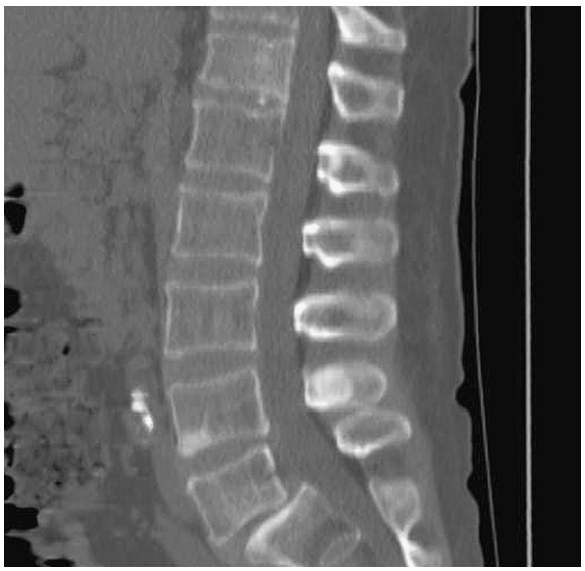


Fig. 21.17 Spondylolisthesis. A 48-year-old man presented with bilateral lower extremity numbness. This midsagittal computed tomography scan of the lumbar spine shows a 1-cm anterolisthesis of L5 on S1.

Spondylolisthesis is typically asymptomatic; however, clinical symptoms may develop and are related to the presence of spinal stenosis causing lower back pain, radiculopathy, and neurogenic claudication (lower extremity pain, paresthesias, and weakness associated with walking or standing). The evaluation of patients with spondylolisthesis incorporates clinical symptoms in combination with anatomic abnormalities detected on radiologic imaging studies, because stenosis is commonly present without symptoms.[11] The severity of spondylolisthesis is determined by evaluation of the extent of slip and the slip angle using plain films. The extent of slip is subsequently expressed as a percentage of anterior displacement of the inferior end plate of the vertebral body above with the superior end plate of the vertebral body below.[14] The slip angle is generally less than 30 degrees in patients with degenerative spondylolisthesis, but it may progress in about one-third of patients.

The initiating pathophysiologic event in the development of degenerative spondylolisthesis is deterioration of the intervertebral disk leading to a narrowing of the disk space, which in turn results in buckling of the ligamentum flavum with consequent microinstability of the motion segment.[15] Owing to the loss of normal ligamentous restriction, the vertebra develops an anterior listhesis (Fig. 21.17) or, occasionally, a posterior listhesis.

The diagnosis of degenerative spondylolisthesis is based on a combination of plain films and MRI.[11] MRI of the lumbosacral spine is indicated in the presence of neurologic signs and symptoms. MRI detects the presence of ligamentous hypertrophy, spinal cord compression, nerve root impingement, pathologic disk anatomy, and synovial cysts, all of which may be the source of back pain, neurologic deficits, or both.

Definitive therapy in patients with degenerative spondylolisthesis is based on the clinical signs and symptoms combined with the findings from imaging studies. In nearly all cases of lower back pain, with or without neurologic deficits, nonoperative therapy is preferred as the initial treatment for at least the first 4 to 6 weeks. If conservative therapy fails, a trial of epidural steroids and other pain management interventions is appropriate. The indications for surgery include: persistent or recurrent back or leg pain or neurogenic claudication that interferes with the daily activities of life and is unresponsive to 12 weeks of nonsurgical therapy; a progressive neurologic deficit; and symptoms of spinal stenosis. Surgical treatment considerations include the choice of surgical approach (anterior, posterior, or a combination approach) and the specific spine procedure. Surgical decompression with or without lumbar fusion and instrumentation is the usual procedure of choice.[11]

The anesthetic management of patients undergoing operations for lumbar spinal stenosis and degenerative spondylolisthesis must consider the specific surgical procedure and approach planned, the anticipated length of surgery, the anticipated blood loss, whether spinal cord monitoring will be utilized, and any associated comorbidities. Total intravenous anesthesia (TIVA) is often the preferred anesthetic technique, particularly if spinal cord monitoring of motor-evoked potentials is planned. Meticulous attention to patient positioning is important in reducing the incidence of postoperative complications (e.g., nerve injury, blindness).

Infections of the Spine

Osteomyelitis

Spinal infections may involve the vertebral body, the intervertebral disk, the neural arch, or the posterior elements. Vertebral osteomyelitis is the most common of the spinal infections, whereas epidural abscesses are relatively rare. Vertebral osteomyelitis preferentially involves the anterior and middle spinal columns. Although the treatment of vertebral osteomyelitis is usually nonsurgical, surgical intervention may at times be warranted.[16]

Clinically, the symptoms and laboratory findings in patients with vertebral osteomyelitis are nonspecific, with little evidence of a systemic process. The diagnosis relies upon a high index of clinical suspicion in combination with the results of radiologic, microbiologic and pathologic tests.[16–20] Bacteremic spread is the most likely route of vertebral osteomyelitis and is related to the rich arterial blood supply to the vertebral body, particularly near the longitudinal ligament. Vertebral osteomyelitis most commonly affects the lumbar spine, followed by the thoracic spine, cervical spine, and sacral spine. Patients often complain of localized back pain and paravertebral muscle spasms, with mild neurologic deficits reported in about one-third of patients; other patients demonstrate a severe neurologic deficit or an incomplete spinal cord syndrome. Laboratory tests reveal a leukocytosis in more than half of the patients, an elevation in the erythrocyte sedimentation rate

(ESR), and an increase in C-reactive protein (CRP) and procalcitonin levels;[18,19] the ESR and CRP are sensitive markers for infection, but nonspecific.[20]

The initial radiologic signs of osteomyelitis are usually absent; after several weeks, radiographic imaging reveals a reduction in disk height and vertebral end plate erosions, followed by the appearance of osteolytic areas, paravertebral soft tissue shadows, and eventual vertebral body collapse. The most sensitive early radiologic imaging technique is a nuclear bone scan using technetium Tc 99m MDP (methylene diphosphonate) with single-photon emission computed tomography.[17] MRI is the gold standard imaging modality for the diagnosis of osteomyelitis, providing accurate detail regarding the intervertebral disk, vertebral marrow, neurologic structures, and paraspinal soft tissue pathology.[18] Typical MRI findings in vertebral osteomyelitis and diskitis include loss of end-plate definition and decreased signal in the disk and adjacent vertebral bodies (Fig. 21.18).

Effective medical therapy begins after making an accurate and rapid diagnosis, followed by 4–6 weeks of a combination of intravenous and oral antibiotic therapy.[16,21,22] Surgical therapy is required for most cases of vertebral osteomyelitis;[23] the most common indications include: making a definitive identification of the causative organism; progressive neurologic deficits; spinal instability; progressive spinal deformity; and failure of medical therapy.

Epidural Abscess

Epidural abscesses are relatively rare infections, occurring in about 1 in 10,000 hospital admissions.[24] Local spread of bacteria into the epidural space is responsible for about one-third of cases, and bacteremic seeding of the epidural space occurs in about 50% of cases.[24] The clinical manifestations of an epidural abscess include back pain, fever, and neurologic deficits; half of patients with epidural abscesses are initially misdiagnosed at the time of presentation (range, 11–75%).[25] Neurologic deficits are late manifestations of the infection, and when present, require rapid treatment. As in vertebral osteomyelitis, laboratory findings are nonspecific, with a leukocytosis present in two-thirds of patients; however, blood culture results may be positive and patients may appear to be systemically septic.[26] Epidural abscesses are commonly located in the posterior regions of the thoracolumbar spine, and often involve multiple spinal segments.

Spinal epidural abscesses are diagnosed from clinical and radiologic findings in combination with results of culture of drainage material.[27,28] Plain radiographs provide diagnostic assistance in less than 20% of the cases, although there may be evidence of coexisting osteomyelitis.[28] MRI with gadolinium enhancement is the radiologic imaging test of choice. This modality can be used to identify the exact location and extension of the epidural infection and to detect spinal cord compression and surrounding edema. Once the diagnosis is confirmed, systemic antibiotic therapy is often combined with surgical drainage.[24,26] The most common surgical procedure performed for the treatment of a spinal epidural abscess is a posterior decompressive laminectomy with evacuation of the epidural abscess or phlegmon.[24] Neurologic outcome depends on the patient's preoperative neurologic condition and the provision of early surgical treatment.

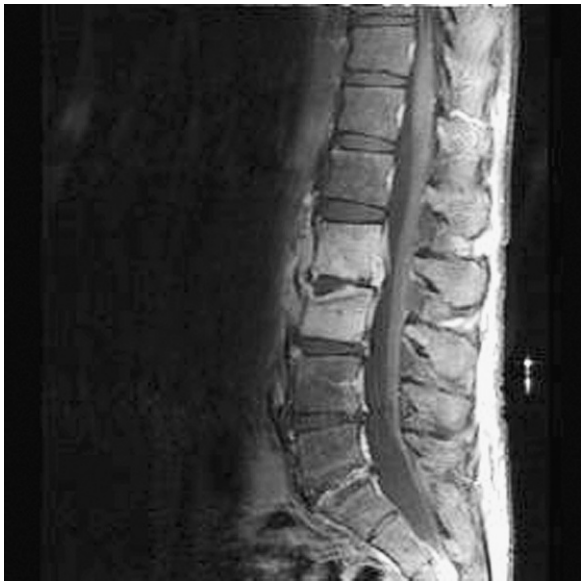


Fig. 21.18 Vertebral osteomyelitis. A 50-year-old male intravenous drug abuser presented with low back pain that had lasted for 1 month. This sagittal T1-weighted magnetic resonance image of the lumbar spine obtained after contrast administration shows edema and enhancement of the L2 and L3 vertebral body marrow and loss of height and signal in the L2–L3 disk space.

Spinal Tumors

Primary vertebral tumors are uncommon, accounting for less than 5% of spinal tumors; metastatic spinal tumors account for the vast majority of spinal neoplasms.[29] Clinically, the presentation of patients harboring spinal tumors includes pain, progressive spinal deformity, neurologic deficits, or a combination of all three. Radiologic imaging is invaluable in facilitating a diagnosis. For the diagnostic approach to spinal tumors, a simple anatomic classification divides the tumors into extradural, intradural extramedullary, and intramedullary categories (Box 21.1). Surgical biopsy is essential in making a definitive diagnosis; CT-guided fine needle aspirate biopsy is the most common method of diagnosis, with a tissue diagnosis made in 70–80% of biopsies. If the particular tumor type warrants surgical intervention, the specific surgical approach is influenced by the location and size of the tumor, the effect of the tumor on the biomechanical stability of the spine, and the involvement of surrounding tissues.[29,30]

Extradural spinal tumors account for 50% of all spinal tumors and most commonly originate in the vertebral body or the epidural space. Primary extradural tumors include Ewing's sarcoma (Fig. 21.19), chordomas, chondrosarcomas, osteoid osteomas, multiple myelomas, and osteosarcomas.

Most extradural tumors are malignant, representing metastatic disease from the lung, breast, prostate, or hematopoietic/lymphoid tissue. Indeed, the skeletal system is a common site of metastatic disease, ranking only behind the lungs and liver in the frequency of occurrence of metastases. As many as 30% of all patients with cancer have metastasis to the spine at autopsy.[31] Spinal metastasis typically involves the vertebral body and occurs through hematogenous seeding or direct extension of a paravertebral tumor. The thoracic spine is the most common location for spinal metastasis, with pain the presenting symptom in most cases. Neurologic deficits may vary from mild radicular symptoms to spinal cord dysfunction. The neurologic deficits may occur in response to pathologic vertebral body fractures or dislocations or to progressive neural compression from tumor growth.

Radiologic imaging is essential for the investigation of suspected extradural spinal metastasis. For highly vascular tumors (giant cell tumors, osteoblastoma, hypernephroma), preoperative angiography with tumor embolization may be used to minimize intraoperative blood loss during resection

BOX 21.1 Anatomic Classification of Spinal Tumors

Extradural
- Metastasis
- Chordoma
- Osteochondroma
- Osteoid osteoma
- Osteoblastoma
- Osteosarcoma
- Aneurysmal bone cyst
- Chondrosarcoma
- Neurofibroma
- Vertebral hemangioma
- Giant cell tumor
- Osteogenic sarcoma
- Plasmacytoma
- Multiple myeloma
- Ewing's sarcoma
- Angiolipoma

Intradural Extramedullary
- Spinal meningioma
- Schwannoma
- Neurofibroma
- Epidermoid/dermoid
- Lipoma
- Metastasis
- Arachnoid cyst

Intramedullary
- Astrocytoma
- Ependymoma
- Dermoid/epidermoid
- Malignant glioblastoma
- Teratoma
- Lipoma
- Neuroma
- Hemangioblastoma
- Ganglioglioma
- Oligodendroglioma
- Paraganglioma
- Cholesteatoma
- Metastases: melanoma, sarcoma, breast

(Data from Patel N: Surgical disorders of the thoracic and lumbar spine: A guide for neurologists. J Neurol Neurosurg Psychiatry 2002;73:42-48.)

of a particularly large tumor.[32–34] The treatment of metastatic disease to the spine involves primarily nonsurgical treatment, particularly in patients without neurologic compromise or spinal instability. These patients are best treated with palliative irradiation, chemotherapy, or both, depending on the tumor cell type. The indications for surgical therapy for extradural spinal disease include the need for tissue diagnosis in the setting of an unknown primary, progressive neurologic deficits, severe pain unresponsive to medical treatment, progressive spinal deformity or instability, radioresistant tumors, and solitary tumors not responding to nonsurgical treatments.

Intradural extramedullary tumors account for 40% of spinal tumors and are located within the dura, but outside the substance of the spinal cord. These tumors may involve the arachnoid tissue, circulating CSF, nerve sheaths, dentate ligaments, filum terminale, and vascular structures. Tumors that arise within this space are typically benign, and more than 90% are either nerve sheath tumors or meningiomas. The nerve sheath tumors can be located at any level of the spine and are usually schwannomas or neurofibromas, which tend to localize in the dorsal or sensory nerve roots. Malignant tumors in this region

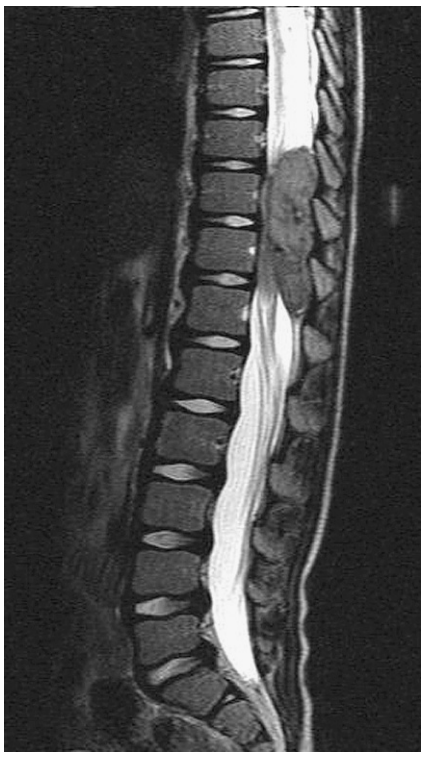


Fig. 21.19 Ewing's sarcoma. A sagittal pre-contrast T2-weighted magnetic resonance image shows a 5.4 cm long by 1.6 cm heterogeneously enhancing mass located in the dorsal epidural space from T9 to T12 that is severely compressing the spinal cord.

of the spine are much less common and usually originate from a primary brain tumor (e.g., ependymoma or medulloblastoma) or from meningeal spread secondary to metastatic disease. The thoracic spine is the most likely location for a meningioma (80%), followed by the cervical (10–20%) and lumbar (1–5%) regions.

The clinical presentation of a patient with an intradural extramedullary tumor usually involves the symptoms of myelopathy or radiculopathy. Although CT and MRI are both useful in suggesting the diagnosis, MRI is considered the imaging modality of choice. Surgery is warranted for the treatment of benign intradural extramedullary tumors such as schwannomas, meningiomas, and neurofibromas.

Intramedullary tumors account for 10% of spinal tumors and are located within the substance of the spinal cord. In adults, more than 80% of these tumors consist of astrocytomas and ependymomas. The typical clinical manifestations of intramedullary tumor consist of myelopathy and sensory disturbance below the level of the spinal tumor. When the tumor is located at the level of the conus medullaris, cauda equina syndrome may develop at very late stages. The primary treatment for an intramedullary tumor is surgical laminectomy, followed by tumor resection or biopsy.

Scoliosis

Adult scoliosis is defined as any curvature of the spine greater than 10 degrees in the coronal plane in a skeletally mature individual.[35] Adult scoliosis is divided into two groups: idiopathic and "de novo" scoliosis. In the first group, a curve develops during adolescence (idiopathic scoliosis) but is treated only in adulthood. In the second group, the curve first manifests after skeletal maturity (termed "de novo" scoliosis). Degenerative spine disease is the most common cause of de novo scoliosis, although scoliosis may occur after previous spinal surgery or in patients with osteoporosis.[36] Degenerative lumbar scoliosis

is a part of the normal aging process that adversely affects the vertebrae, intervertebral disks, spinal ligaments, facet joints, and muscles. This degenerative process leads to wedging of vertebral bodies and disks with progressive spinal rotation and translation, most commonly involving the upper lumbar and lower thoracolumbar spine. Degenerative scoliosis is common, with a prevalence reported to range from 6% to 68%[37] and increases with age, being observed in more than 30% of elderly patients without previous spinal abnormalities.[35,38] The initial clinical symptom is typically back pain. Although the incidence of back pain in adults with scoliosis is similar to that found in the general population, the most common indication for eventual surgery is persistent and clinically significant back pain, with 1% of patients undergoing scoliosis surgery.

Thoracic scoliotic curves have a much greater adverse effect on pulmonary function than curves located in other regions of the spine. There is a direct relationship between the magnitude of the curve and the reduction in lung volumes. With thoracic curves greater than 60 degrees, and particularly those greater than 100 degrees, the patient complains of shortness of breath and dyspnea, and spirometric testing shows progressive restrictive pulmonary disease with reductions in vital capacity, forced expiratory volume in 1 second (FEV_1), and PaO_2 with all abnormalities being in proportion to the severity of the scoliotic curve.

Most patients with scoliosis-related back pain are effectively treated with nonsurgical therapy. At present, the indications for surgery in the setting of scoliosis include persistent back pain refractory to medical therapy; progressive neurologic deficits; progressive spinal deformity, particularly in the setting of worsening pulmonary function; and postural imbalance related to muscle fatigue. The surgical goals are to correct deformity without creating spinal instability and to allow early patient mobilization. Adult scoliosis surgery is associated with a high complication rate. In studies investigating the incidence of complications following major spine surgery (with most studies including a significant percentage of patients with scoliosis), perioperative complications were noted to occur in over 20% of patients, with reported in-hospital mortality rates of 0.2– 0.5%.[39–41] Reported complications include infection, acute coronary syndrome, cerebrospinal fluid leak (CSF) leak, failure of the implant, paralytic ileus, deep venous thrombosis, urinary tract infection, and blindness.[35] Risk factors increasing the incidence of postoperative complications include age, pulmonary circulatory disease, heart failure, renal disease, liver disease, coagulopathy neurologic disease, and electrolyte disorders.[42] Pulmonary complications are common, with the highest incidence associated with anterior and anterior/posterior spine operations. Mortality rates are particularly high in patients who develop postoperative pulmonary complications.

An anesthetic plan well suited for major reconstructive spine surgery includes the use of a balanced general anesthetic technique, invasive hemodynamic monitoring, and large-bore intravenous catheters. The use of a TIVA technique may be indicated if neurophysiologic monitoring is planned.

Inflammatory Arthritides of the Spine

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common of the inflammatory diseases, affecting approximately 1% of the world's population. RA is characterized by a chronic, systemic, autoimmune inflammatory state resulting in symmetrical pain, heat, swelling, and destruction in synovial joints of the hands and feet, wrists, elbows, hips, knees, ankles, and the cervical spine.[43] The T cell-mediated inflammatory state of RA affects synovial tissues throughout the body, resulting in hypertrophy of joint tissue and erosion of articular cartilage and subchondral bone.[44] The cervical spine is often affected, with involvement of the synovial joints of the cervical spine, particularly those surrounding the C1–C2 articulation. The synovitis weakens the surrounding supportive structures, resulting in axial instability that may lead to subluxation of the C1–C2 articulation and spinal cord compression. Atlantoaxial subluxation affects as many as one-fourth of patients with RA and is the most common cervical spine manifestation of RA.

Clinically, patients with RA involving the cervical spine may complain of cervical neck pain, headaches, and limitation of neck movement. In severe disease, subaxial subluxation may cause progressive cervical myelopathy with spasticity of the legs, motor weakness, and incontinence, or symptoms of nerve root compression. The diagnosis of cervical spine involvement in RA relies upon typical radiologic findings, including atlantoaxial subluxation, narrowed disk spaces, erosion of vertebral end plates, apophyseal joint erosion with blurred facets, and spinal osteoporosis.[43] A CT scan is of value for detecting the extent of cervical spine bony destruction, whereas MRI is useful for identification of spinal cord pathology and soft tissue abnormalities.

Surgery is indicated in the presence of myelopathy; severe neck pain with a neurologic deficit; and excessive subluxation of C1–C2 with spinal canal stenosis, vertebral artery compromise, and spinal cord compression. Patients demonstrating symptoms of myelopathy, particularly in the presence of C1–C2 subluxation, require urgent posterior spinal decompression and instrumented fusion; current options may include C1 lateral mass screws in conjunction with C2 pedicle, pars or translaminar screws or C1–C2 transfacet screws and bone grafting. The presence of subaxial subluxation (C3–C7) warrants realignment and stabilization from a posterior approach, particularly when multiple levels are involved. An anterior approach may be appropriate as an alternative technique, especially in the case of significant kyphotic deformity. In select cases, a combined anterior and posterior approach may need to be utilized.[43]

The anesthetic approach for a patient undergoing surgery for RA should take into account the airway concerns unique to these patients, including limitation of neck and temporomandibular joint movement (limiting visualization of the larynx), arthritic involvement of the cricoarytenoid joints (preoperative hoarseness and stridor) with a narrowed tracheal inlet, atlantoaxial subluxation with potential vertebral artery compromise, basilar impression (from rostral advancement of the odontoid process with compression of the spinal cord or medulla), and instability of the lower cervical spine. Accordingly, an awake fiberoptic intubation or video-assisted laryngoscopy may be considered to minimize further neurologic injury during the induction of anesthesia and positioning of the patient.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is considered the prototypical seronegative spondyloarthropathy; it is characterized by a progressive inflammatory involvement of the spine and axial skeletal joints, which may result in severe spinal deformity (Fig. 21.20). The disease is three times more common in men than in women. In addition to axial skeletal disease, AS involves enthesopathy (inflammation at the sites of tendon and ligamentous insertions), the presence of human leukocyte antigen (HLA-B27), and the absence of rheumatoid nodules and rheumatoid factor in serum (seronegative).[43] The regions of the spine most often involved in AS are the sacroiliac,

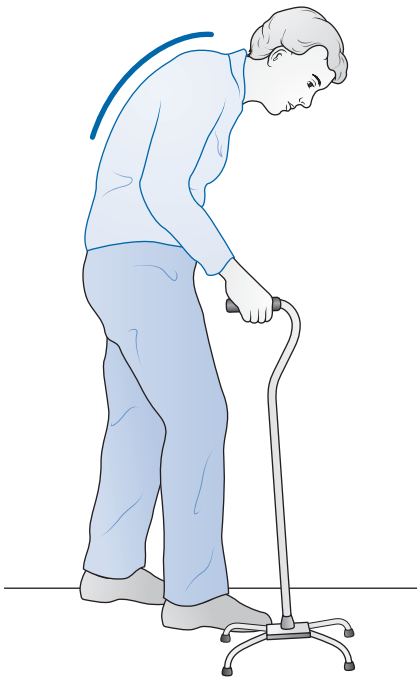


Fig. 21.20 In a patient with ankylosing spondylitis, a progressive spinal curvature may eventually develop, resulting in a stooped posture from vertebral fusion.

costovertebral, zygapophyseal, and discovertebral joints.[43] Ankylosing spondylitis-associated fractures are most commonly seen in the lower cervical spine (C6–C7), although they may also occur in the lumbar and thoracic segments. Diseases associated with AS include peripheral polyarthritis, C1–C2 subluxation, valvular heart disease, aortitis, restrictive pulmonary disease, upper lobe pulmonary fibrosis, colitis, renal amyloidosis, osteoporosis, psoriasis, uveitis, and iritis.

Surgery is indicated for individuals with severe spinal deformities that adversely affect normal activities and in patients who have spinal instability due to spondylodiskitis or spinal fracture.[45] In patients with AS who are scheduled for corrective spine surgery or for unrelated surgical procedures, careful preoperative assessment is essential. A thorough history should focus on the patient's habits, lifestyle, and medications (e.g., use of opioids, nonsteroidal anti-inflammatory agents). Areas of particular focus should include: kidney, pulmonary, gastrointestinal, and nutritional assessment. In addition; cervical spine flexibility and airway anatomy must be carefully evaluated in AS patients, as the potential for a difficult airway is increased. The presence and severity of cervical kyphosis should be noted as patients with marked neck flexion may mandate a fiberoptic airway approach or other advanced airway technique.

Osteoporosis

Osteoporosis is a metabolic bone disease characterized by a decrease in bone mineral density and disrupted microarchitecture that leads to a higher risk of fractures, particularly of the hip, spine, and wrists. The prevalence of primary osteoporosis affects approximately 10 million individuals in the United States, making it the most prevalent bone disease.[46] It is found most commonly in women after menopause (up to 30% are affected),[47] but may occur in men and premenopausal women in the presence of hormonal disorders or other chronic disease states, in which case it is termed secondary osteoporosis. Disease states associated with secondary osteoporosis include hyperthyroidism, gastrointestinal disorders, disorders of calcium balance, and chronic steroid use.

Fractures are common in osteoporosis. Vertebral compression fractures, one of the most frequent complications of osteoporosis, occur most often in the thoracic and lumbar spine.[48] In fact, the incidence of vertebral fractures has been estimated to occur in up to 25% of women at 50 years of age. Development of an acute fracture manifests as acute pain localized over the affected area or referred across the chest. After the fracture heals, the patient may complain of chronic back pain. In the thoracic spine, osteoporotic fractures are located primarily in the anterior aspect of the vertebral body, causing a compression fracture that appears as a wedge shape on plain films. The wedge-shaped vertebral body results in a dorsal kyphosis, particularly if fractures affect multiple spinal levels. In the lumbar spine, the vertebral fractures are located more evenly throughout the vertebral body, resulting in a compression fracture without the wedge shape.

The diagnosis of osteoporosis relies on a combination of clinical history, plain radiographs, bone mineral density (BMD) testing, and biochemical markers suggesting rapid bone turnover (bone-specific alkaline phosphatase). Osteoporosis is treated nonsurgically in the majority of cases. Surgical intervention is indicated in the setting of acute vertebral compression fractures associated with severe pain unresponsive to medical therapy, neurologic deficits, and in the presence of progressive spinal deformity and instability. The goals of surgical treatment for osteoporotic fractures include early mobilization and functional return to daily activities of life. The procedures most commonly performed for osteoporotic vertebral compression fractures include minimally invasive vertebroplasty and balloon kyphoplasty. Although the clinical efficacy of these procedures has been questioned,[49,50] recent reports support the general consensus that vertebroplasty and kyphoplasty are safe, efficacious, and durable procedures for the treatment of appropriate patients with pathologic fractures due to osteoporosis and neoplastic processes.[49–54]

TRAUMA OF THE SPINE AND SPINAL CORD

Among individuals suffering general traumatic injuries, the cervical spine is involved in 4.3% of cases, the thoracolumbar spine in 6.3% of cases, and the spinal cord in 1.3%.[55,56] The most common causes of spine trauma are motor vehicle accidents, falls, violence, and sports-related injuries (in that order). Spinal injuries have a predilection for the more mobile areas of the spine, which include the cervical spine (75% of cervical spine injuries are at C3–C7) and the thoracolumbar junction (16% of thoracolumbar injuries are at the L1 junction),[56] with as many as one-fifth of injuries to the spine occurring at multiple levels.

In general, the goals of management following spinal trauma are: prevention of further neurologic injury; enhancement of neurologic recovery if deficits exist; neurologic decompression; and the surgical correction of spinal malalignment or deformity. The initial evaluation and resuscitation of the trauma patient includes a detailed neurologic examination performed to detect the presence of neurologic deficits (see Fig. 21.25) combined with radiologic imaging of the spine; these actions complete the spine trauma assessment.

Biomechanical Considerations in Spinal Injury

An understanding of the biomechanics of spinal impact and resulting spinal injury is helpful in estimating the probability and severity of both the spinal column and SCI as well as the

planning of effective therapy. Traumatic spinal injuries most commonly occur after impact forces that result in the following seven basic types of spinal trauma: hyperflexion, hyperextension, compression, rotation, shear, avulsion injuries, and a combination of these types.[56] A mechanistic classification of cervical spinal injuries based on the original classification proposed by Allen and colleagues[56,67] is illustrated in Fig. 21.21. A summary table of selected traumatic spinal injuries, associated neurologic sequelae, and the common treatments are provided for reference (Table 21.1).

Hyperextension

Hyperextension injuries are most common in the cervical region and are a common cause of lower cervical neck injuries (Fig. 21.22). Hyperextension injuries may result from facial or frontal trauma, whereby the forces separate the vertebral body and the adjacent lower end of the intervertebral disk. Hyperextension injuries result in disruption of the anterior and middle spinal columns in tension, reducing the AP diameter of the spinal canal and compressing the spinal cord between the posterior aspect of the vertebral body and the ligamentum flavum and lamina. Elderly individuals with cervical spondylosis are particularly susceptible to hyperextension injuries, and even moderate hyperextension may produce cord injury. The vertebral arteries may be damaged in cervical extension injuries, particularly in people with severe spondylosis. Hyperextension injuries are typically unstable owing to the disruption of the stabilizing ligamentous elements and injury to the intervertebral disks.

Compression

Compression injuries occur after impact forces containing a significant axial load (e.g., falls on the occiput) and result in wedge compression fractures, burst fractures (Fig. 21.23), and ligamentous rupture. Wedge compression fractures, most common in the thoracolumbar region, result from pure flexion injury, whereby the posterior ligamentous complex remains intact. Compression injuries with burst fractures often cause serious neurologic damage from retropulsion of bone fragments, ligaments, and disk material into the spinal canal. Compression injuries associated with flexion may produce the so-called teardrop fracture, in which the vertebra is dislocated anteriorly, with an associated avulsion of the superior aspect of the vertebra and posterior longitudinal ligament damage, usually with significant neurologic damage.

Hyperflexion

Hyperflexion injuries may be divided into flexion–compression and flexion–distraction injuries. The direction of the applied load determines the particular injury pattern. Simple flexion–compression fractures results in wedge fractures of the vertebral body that cause a loss of anterior vertebral body height, creating a wedge shape. These injuries are typically stable, unless significant loss of vertebral body height results. Severe flexion–distraction injuries occur from a combination of flexion and distraction loads, with the center of rotation located anteriorly. This injury results in characteristic subluxations or dislocations (see Fig. 21.22) of the vertebral bodies with disruption of the posterior longitudinal ligament,

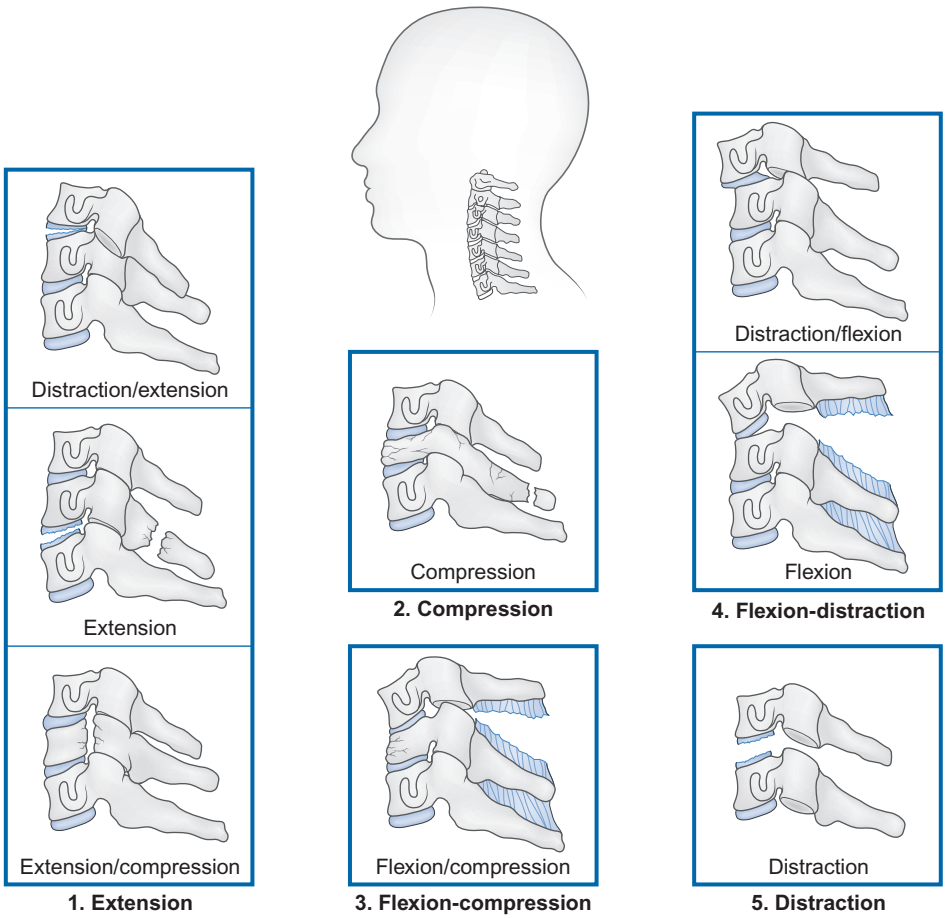


Fig. 21.21 Mechanistic classification of cervical spinal injuries. This illustration of the spectrum of cervical spine injuries is based on the mechanistic classification proposed by Allen and colleagues.[250] *(From Lindsey RW, Gugala Z, Pneumaticos SG: Injury to the vertebra and spinal cord. In Moore EE, Feliciano DV, Mattox KL [eds]: Trauma, 5th ed. New York, McGraw-Hill, 2004, pp 459–492.)*

Table 21.1 **Selected Spinal Injuries, Associated Clinical Findings, and Treatment**

Spinal Injury	Typical Clinical Findings	Treatment
Upper Cervical (C1–C2) Spine Injuries		
Atlanto-occipital dislocation	Unstable; commonly fatal; if patient survives there are neurologic deficits	Immediate halo vest vs. hard collar, then posterior occipitocervical fusion
Atlas burst fracture (Jefferson fracture)	Usually stable and neurologically intact; associated with head injuries and other cervical spine fractures	Cervical orthosis if nondisplaced; halo vest for 3 months vs. surgery if displaced; posterior C1–C2 fusion if instability persists after immobilization
Atlantoaxial dislocation/subluxation	Usually neurologically intact	Reduction and immobilization vs. posterior fusion
Isolated odontoid fracture: tip of dens (type I); base of the dens (type II); extension into the C2 body (type III)	Type I, stable; type II and III, usually unstable, with neurological deficits in 14% of type II and 8% type III	Type I, rigid cervical collar; type II and III, cervical immobilization, ± surgical posterior C1–C2 fusion
Axis fracture (hangman's fracture)—bilateral pars interarticularis (type I); bipedicular fracture (type II); severe displacement, uni- or bilateral facet dislocations (type III)	Usually neurologically intact (type I and II); type III very unstable, neurologic injuries	Type I, rigid cervical collar; type II, initial traction then halo vest vs. surgery; type III, open reduction and fusion
Subaxial Cervical (C3–C7) Spine Injuries		
Axial Compression		
Wedge compression fracture	May be stable; neurologically variable	Depends on severity of fracture: cervical collar or halo vest for stable fractures; if disruption of posterior longitudinal ligament, surgical stabilization-fusion
Burst fracture	Stability is variable, depending on ± involvement of the posterior ligamentous complex (PLC); neurologically variable	Cervical immobilization vs. surgical stabilization-fusion
Flexion–Compression		
Teardrop fracture	Usually unstable; neurologically variable	Immobilization vs. surgical stabilization-fusion
Flexion–distraction	Stability is variable, depending on ± posterior ligamentous injury; neurologically variable	Immobilization; ± surgical stabilization-fusion
Extension–Distraction		
Hyperextension, ± fracture ± dislocation:	Stability is variable, depending on ± posterior ligamentous injury; neurologically variable; seen in elderly patients with spinal stenosis; (central cord syndrome)	Immobilization; ± surgical decompression-fusion
With retrolisthesis	Unstable, neurologically variable	Surgical stabilization
Rotation–Flexion or Extension		
Isolated facet fracture without dislocation	Stable; usually neurologically intact	Cervical collar
Unilateral facet dislocation ± fracture	Often unstable; neurologically variable	Open or closed reduction; ± surgical stabilization and fusion
Bilateral facet dislocation ± fracture	Very unstable; disrupted posterior stabilizing elements; usually severe neurologic deficits	Open or closed reduction; surgical stabilization and fusion
Thoracolumbar Injuries		
Transverse process, spinous process, and articular process fractures	Stable; neurologically intact	Symptomatic; ± orthoses
Compression Fractures		
Wedge fracture	Usually stable and neurologically intact; unstable if severe compression (>50% loss of vertebral body height, >30° kyphosis deformity)	No orthosis vs. thoracolumbosacral orthosis (TLSO) if stable; surgical stabilization if unstable
Burst fracture	Stable if minimal posterior column disruption; unstable if neurologic deficits and/or posterior column disruption; neurologically variable	TLSO if stable and neurologically intact; surgical stabilization-fusion if unstable and/or neurologic deficits

(Continued)

Table 21.1 Selected Spinal Injuries, Associated Clinical Findings, and Treatment—cont'd

Flexion–Distraction		
Chance fracture (horizontal fracture through anterior-posterior bony elements)	Usually unstable; neurologic deficits in 10% to 15%	Surgical stabilization-fusion (rarely TLSO brace)
Fracture–dislocation	Highy unstable; neurologic deficits ≥ 75%	Early surgical reduction, stabilization-fusion
Extension–distraction	Rare (patients with metabolic bone disease); unstable; neurologic deficits common (≥75%)	Surgical stabilization-fusion
Penetrating missile injury	Neurologically variable; recovery poor	Symptomatic treatment; spinal orthoses if 2 to 3 spinal column involvement

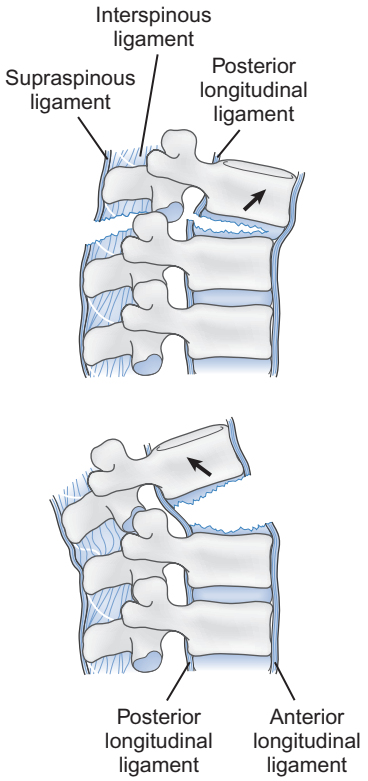


Fig. 21.22 *Top,* Distracted vertebral body with disrupted posterior longitudinal ligament occurring after hyperflexion injury. *Bottom,* Distracted vertebral body with disrupted anterior longitudinal ligament occurring after hyperextension injury (arrows show direction of forces).

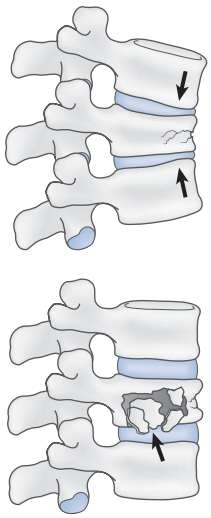


Fig. 21.23 *Top,* Vertebral compression fracture (arrow). *Bottom,* Vertebral burst fracture (arrow) with retropulsion of bone fragments posteriorly into the vertebral canal.

causing significant spinal instability. Herniation of the intervertebral disks is commonly seen after severe flexion injuries, as is dislocation of the facet joints, particularly if enough of a rotational component is involved.

Rotation

Flexion and extension injuries that include significant rotational forces may result in severe spinal injuries, including subluxation, dislocation, and fracture–dislocations. Serious injuries to the vertebral bodies and intervertebral disks are often involved in the process (Fig. 21.24).

Rotational spinal injuries often result in severe injuries to the spinal cord and cauda equina. In particular, hyperflexion–rotation forces associated with dislocation may produce either unilateral or bilateral locked facets. Bilateral facet dislocations (locked facets) are associated with major neurologic injury and often require surgical reduction and stabilization. These are most often seen in the lower cervical spine (C5–C7). Fractures of the vertebral peduncles may be associated with bilateral facet dislocations. Unilateral facet dislocations may be associated with no neurologic injury; however, they may be associated with nerve root compression or an incomplete SCI.

Shear

Some degree of spinal translation is involved in most spinal injuries, including spinal fractures and ligamentous tears. The shear mechanism typically involves all three columns of the spine and is associated with a higher incidence of facet dislocation.[56]

Avulsion

Avulsion injuries are typically stable injuries. Examples of avulsion injuries include the odontoid type 1 fracture, in which the tip of the odontoid process is fractured or chipped, and the hyperextension teardrop fracture.[56]

Combined

Combined injuries, resulting from various vectors of force such as axial loading, rotation, and flexion or extension, chiefly affect the cervical region and commonly produce ligamentous tears and distraction (an increase in distance between individual

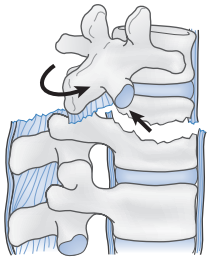


Fig. 21.24 Rotation injury showing dislocated articular facts (small arrow).

components of adjacent vertebrae. For example, a combined injury, or whiplash, involves rapid acceleration–deceleration forces resulting in extreme extension followed by flexion and is often associated with rotation, compression, and tearing forces. This kind of acceleration lesion distorts the spinal components, damaging the soft tissues of the neck, muscles, and anteroposterior ligaments, and sometimes involves nerve roots and disks.

Traumatic spondylolisthesis of the axis occurs with motor vehicle accidents when the driver's face or chin hits the steering wheel. The extreme hyperextension of the neck produces shear stresses on the C2–C3 vertebral units, resulting in fracture of the neural arches with dislocation between C2 and C3. However, the avulsed arches decompress the cervicomedullary junction, so patients seldom experience neurologic deficits and usually have a good prognosis.

Mid-thoracic to upper thoracic spinal injuries are much less common than injuries of the cervical or thoracolumbar regions, because of the protection and fixation of the thoracic area by the rib cage and sternum. The greater mobility of the vertebral column at the thoracolumbar junction contributes significantly to the frequency of spinal injuries in this region. Injury to the thoracolumbar spinal column can result in wedge fractures of the vertebrae, with destruction of the laminae, pedicles, and facets. Protrusion of the vertebral body or disk material into the spinal cord may occur. The addition of torque results in fracture–dislocations of the vertebral column. Lumbar fractures have been reported to occur much less often and are the result of flexion and compression forces. Neurologic injuries that involve only the cauda equina have a high potential for significant neurologic recovery.

Penetrating wounds of the spine may cause significant damage, including direct and indirect spinal cord injury through transmitted energy. Many of these injuries produce damage to both the spinal cord and nerve roots as a result of associated shear stress; compression and contusion of cord tissue by bony impingement, herniated disks, or intraparenchymal bone fragments; or ischemia caused by interruption of the vascular supply. However, no consistent relationship exists between actual trauma to supporting structures and injury to the spinal cord. Thus, a patient may present with a stable spine without bony or ligamentous injury and still sustain SCI or may have serious fractures and an unstable spine without neurologic deficits. In adults, the areas most susceptible to injury are the lower cervical spine (C5–C7) and the thoracolumbar junction (T12– L1), regions of the spine coinciding with the areas of greatest spinal column mobility.

Neurologic Assessment

In patients with spinal trauma, a neurologic examination is essential in establishing a baseline of neurologic function and in facilitating the decision matrix for specific radiologic testing. Following the primary trauma survey, the neurologic evaluation process includes an assessment of mental status, an examination of the spinal column, and an evaluation of the sensorimotor function of the extremities. Initially, the clinician palpates the spine in its entirety, specifically noting tenderness, evidence of hematoma, or spinal misalignment. During examination of the patient, it is important to maintain spinal precautions at all times (i.e., log rolling, maintaining neutral neck position). The neurologic examination should be accurately detailed in the medical record using the American Spinal Injury Association (ASIA) International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examination worksheet (Fig. 21.25).

The ASIA worksheet standardizes the neurologic evaluation process and facilitates the accuracy of the neurologic examination (see Fig. 21.25). In the ASIA system, the neurologic assessment includes the testing of key muscle groups and sensory points. For muscle testing, 10 groups are tested corresponding to 10-paired myotomes. The function of these muscles is graded on a 6-point scale, with 0 assigned for total paralysis and 5 points assigned for normal strength. In total, there are 100 points when the right and left sides are assessed.

The second part of the ASIA neurologic examination is the sensory score, which is based on the evaluation of 28 sensory dermatomes on the right and left sides of the body. At each of these key points, both the sensation to pinprick and light touch are tested and scored on a scale of 0 to 2 (0, absence of sensation; 1, impaired sensation; and 2, normal sensation). In addition to the testing of key muscles and sensory points, voluntary motor contraction of the external anal sphincter is tested by digital examination. Perirectal sensation is also tested; this sensation, along with the presence of the bulbocavernosus reflex or the anal-cutaneous reflex, is an important signal of the preservation of distal function (sacral sparing), indicating incomplete SCI and predicting a more favorable prognosis. The testing of proprioception (position sensation) is considered optional but is highly recommended.

Finally, an assessment should be made of the completeness of the neurologic injury as defined by the ASIA Impairment Scale (Table 21.2). In this scale (formerly called the Frankel scale), the neurologic injury is divided into one of five possible grades. The term *sensory level* or *motor level* is used to define the most caudal segment of the cord with normal sensory or motor function, respectively, on both sides of the body.

The diagnosis of SCI should be considered when the following signs or symptoms are present: motor signs, such as weakness or paralysis of the extremities or trunk muscles; sensory signs, such as the absence or alteration of sensation of the trunk or extremities; bowel or bladder incontinence; abrasions, lacerations, or deformities of the spine, neck, or head region; and tenderness or pain on palpation of the spine or neck. The patient's neck or back should not be moved to determine whether it is painful but should only be palpated. An unconscious patient must be considered to have an SCI until proved otherwise. An injury to other systems (e.g., head injury) may mask an SCI; conversely, an SCI may mask other system injuries (e.g., visceral rupture or fracture of long bones).

Radiologic Considerations

The goal of imaging after spinal trauma is to recognize and quantify spinal injury as well as to aid in determining prognosis (Table 21.3). The mechanism of injury combined with the clinical examination and the hemodynamic stability of the patient will guide the initial choices for spinal imaging. The results of radiologic tests and identification of neurologic deficits define the final pathologic state. For patients without clinical evidence of spinal cord injury, radiologic imaging of the cervical spine may not be necessary. In particular, the NEXUS decision tool or the Canadian Cervical Spine rule can be utilized to identify those individuals for whom spinal imaging is unnecessary.[57,58] The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recently published updated guidelines for the management of acute cervical spine and spinal cord injuries.[59] The guidelines state that for the awake, asymptomatic patient who is without neck pain or tenderness, has a normal neurological examination, is without an injury detracting from an accurate evaluation, and is able to complete a functional range of motion examination, radiographic evaluation of the cervical spine is not recommended.[60,61] For trauma patients considered

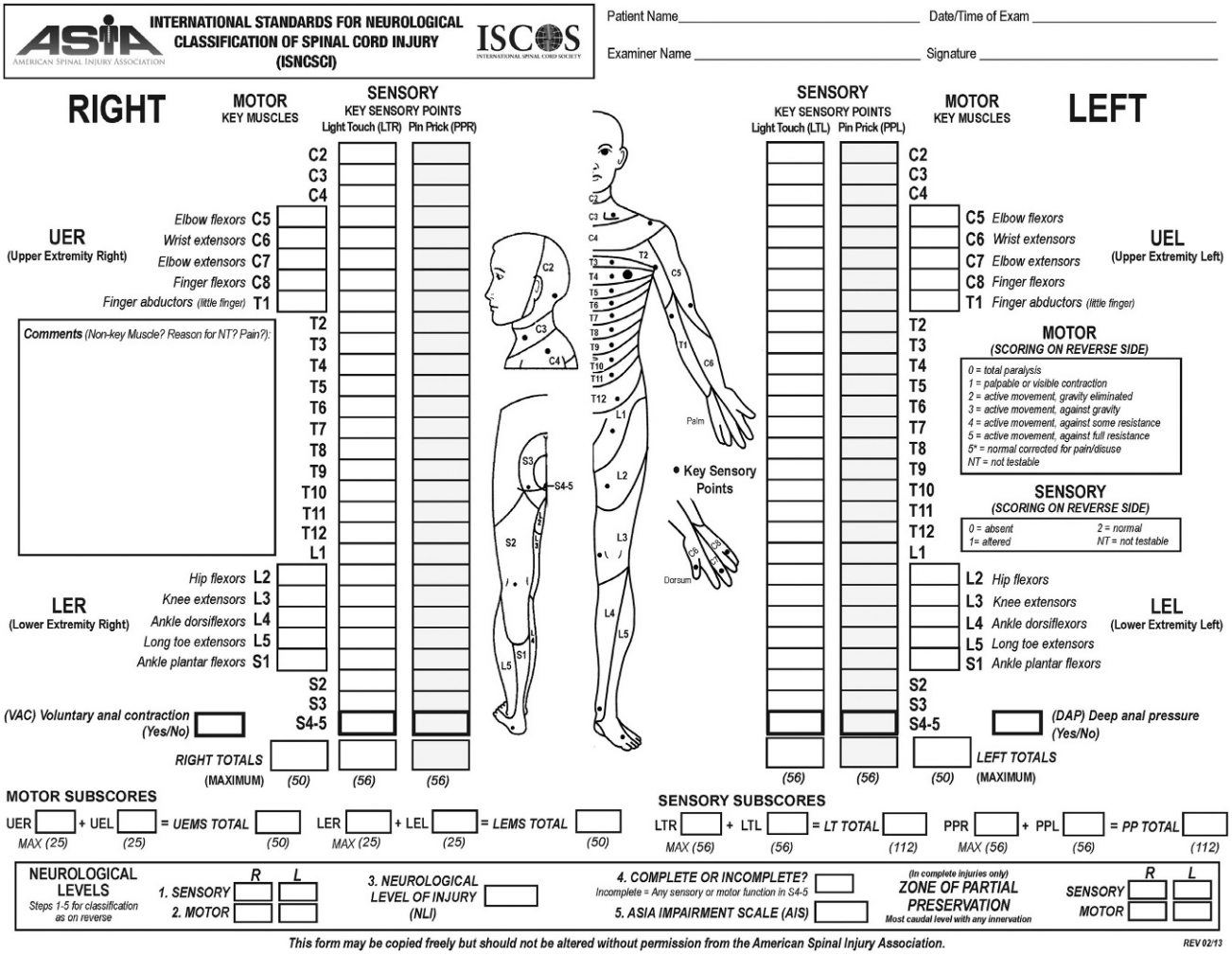


Fig. 21.25 American Spinal Injury Association (ASIA) International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examination worksheet demonstrating the comprehensive neurologic evaluation system for determining the extent of neurologic injury. *(Reproduced from the American Spinal Injury Association (2013), Atlanta, GA.)*

Table 21.2 American Spinal Injury Association (ASIA) Impairment Scale

ASIA Grade	Type of Injury	Definition of Type of Injury
A	Complete	No motor or sensory function
B	Incomplete	Sensory but not motor function is preserved below the level of the injury
C	Incomplete	Motor function is preserved, but majority of key muscles below the neurologic level have a muscle grade <3
D	Incomplete	Motor function is preserved, and majority of key muscles below the neurologic level have a muscle grade ≥3
E	Normal	Motor function and sensory function are normal

Table 21.3 Specificity of Spine Radiologic Evaluations

Category	Plain Radiograph	Computed Tomography	Magnetic Resonance Imaging
Bony anatomy	++	+++	++
Ligament injury	+	+	+++
Spinal canal size	0	+++	+++
Spinal cord compression	0	++	+++
Nerve root compression	0	++	+++
Hemorrhage and edema	0	+	+++
Syrinx formation	0	++	+++
Prediction of deficit	++	++	+++
Prediction of outcome	+	++	+++

0, no benefit; +, poor; ++, good; +++, very good.

to have, or be at risk for, cervical spine injuries, a CT scan is now considered the initial radiologic modality of choice. [62–66] Plain films of the cervical spine are regarded as a second line imaging choice, to be used if CT is unavailable.

Plain Radiographs

Plain radiographs can be obtained to identify spinal fractures, dislocations, and combination injuries. The most important cervical spine radiographs include an AP view, a lateral view, and an open-mouth view of the odontoid, referred to as the cervical "3-view series" (Fig. 21.26). The initial images must visualize the occipitocervical junction, all seven cervical vertebrae, and the C7–T1 junction. CT imaging should always supplement the 3-view series to further delineate areas that are questionable or not well visualized on plain films (e.g., C7/T1). For patients with a suspected thoracic or lumbosacral injury, AP and lateral films are appropriate.

Computed Tomography

Although plain films of the spine provide a rapid means of initial evaluation of spinal trauma, thin sliced CT scanning with coronal and sagittal reformatted images from the occiput to the cervicothoracic junction, with or without MRI is the recommended screening test of choice for the diagnosis of cervical fractures in most trauma centers.[62,63,66] CT imaging provides spatial resolution far superior to that of plain radiographs and offers an excellent means of imaging bone and properly evaluating the craniocervical junction and lower cervical areas, including the cervicothoracic junction (C7–T1). The axial format of CT provides better evaluation of the spinal canal, including measurements of spinal canal and neurofo-raminal diameters, details of the facet joints, identification of bone fragments in the canal or root foramen, detection of a unilateral jumped facet, identification of hematoma formation, and assessment of spinal stability.

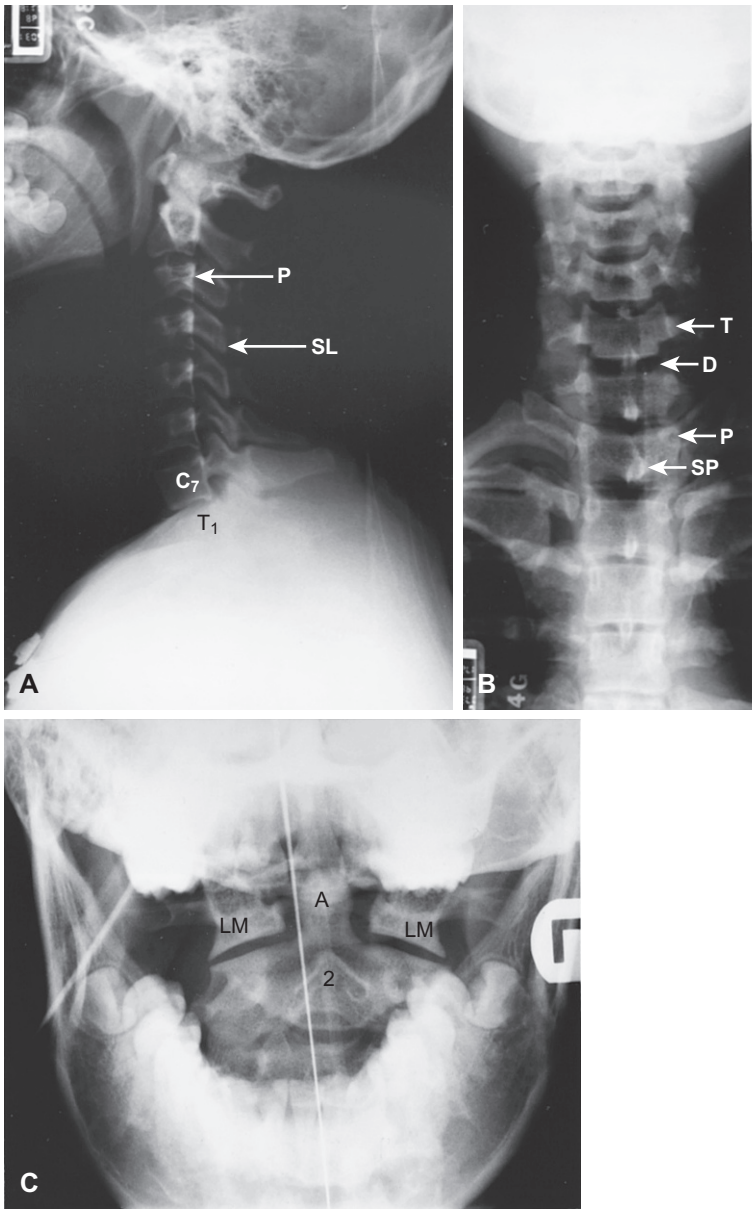


Fig. 21.26 Three-view cervical spinal radiographic series. **A,** Lateral view of cervical spine showing alignment of posterior aspects of the vertebral bodies (P) and spinolaminar junction (SL). All seven cervical vertebrae (including C7) and the upper border of T1 should be visualized. **B,** Anteroposterior view showing alignment of spinous processes (SP) and vertebral bodies. Note the uniformity of disk spaces (D). Also visualized are transverse processes (T) and pedicles (P). **C,** Open-mouth (odontoid) view showing the odontoid (A). The odontoid is normally centered between the lateral masses (LM) of C1. The body of C2 (2) should be clearly visualized.

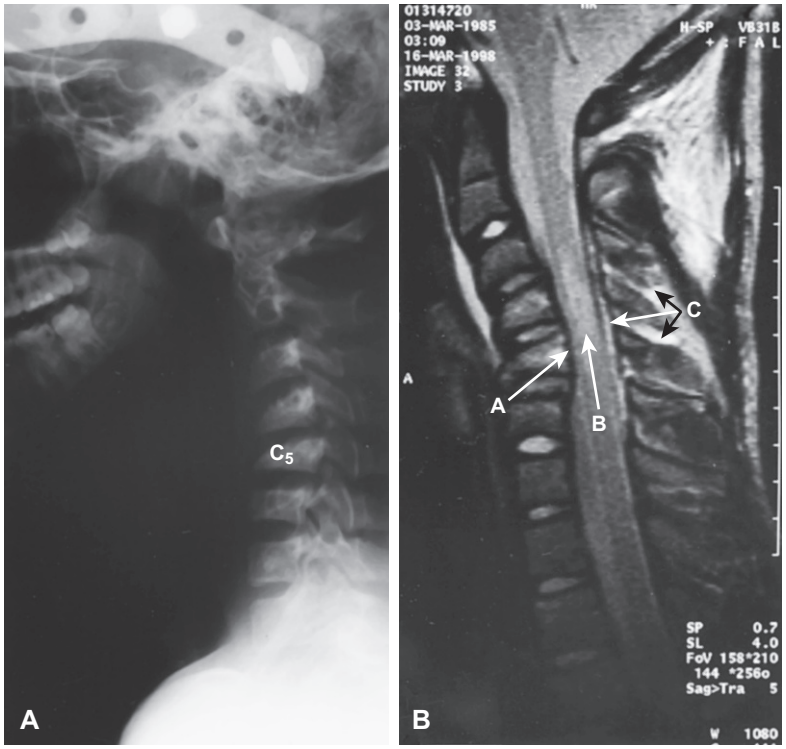


Fig. 21.27 **A,** Lateral cervical spine radiograph of a patient with a flexion injury involving C5 shows malaligned posterior vertebral body lines. **B,** T2-weighted sagittal magnetic resonance image of the same patient showing probable injury to the posterior longitudinal ligament *(A),* an increased signal within the spinal cord *(B)* consistent with spinal cord injury, and a hyperintense signal involving the posterior ligamentous complex *(C)*.

Magnetic Resonance Imaging

MRI has inherent advantages in the setting of spinal trauma, including the ability to image the spinal cord in any orientation and to visualize soft tissues. MRI is able to show the epidural and subarachnoid spaces, thereby providing exceptional ability to detect intraspinal ligament tears and disruptions (Fig. 21.27).

MRI is superior in the ability to directly image injury to spinal cord parenchyma, including edema, hemorrhage, myelomalacia, and lacerations. MRI also has a better capacity to evaluate the extent of spinal canal compromise from bone fragments, osteophytes, herniated disk material, or epidural hematomas. MRI is an excellent choice for directly imaging nerve root impingement in addition to detecting the presence of syrinx formation, scarring, or late compression of the cord. Although MRI can detect most vertebral fractures, it is not as sensitive as CT for this purpose. MRI is indicated in patients with incomplete neurologic deficits after traction, realignment, and immobilization of the spine and in patients who have cervical cord deficits after trauma but no demonstrated abnormalities on plain films or CT scans. MRI is indicated in a patient manifesting neurologic progression of a previously stable neurologic deficit as well as in a patient whose level of neurologic deficit appears to be above the level of apparent cervical spine injury. Finally, MRI has been demonstrated to be useful for prognostication of neurologic outcome following acute SCI.[68]

Summary

Patients at risk for SCI should undergo a neurologic evaluation followed by radiologic imaging to identify and quantify abnormalities suggested by history or examination (Table 21.4). Axial CT is the preferred imaging modality for suspected spinal trauma.[63,66] Plain radiographs are no longer recommended as the initial spinal trauma imaging modality of choice. Patients with SCI may benefit from an MRI study to detect intramedullary lesions, extrinsic spinal cord processes, and possible ligamentous injury. MRI is also of value in the prediction of recovery potential.[68]

Table 21.4 Summary of Appropriate Radiographic Evaluation of Cervical Spine Trauma

Clinical Status or Findings	Recommended Procedure
Asymptomatic; alert, with normal physical findings	Radiographs not needed
Symptomatic; signs and symptoms of cervical injury	Computed tomography; 3-view radiographic series
Ligamentous injury; normal plain film or CT findings, but with neck pain	Magnetic resonance imaging; radiologic flexion and extension views (patient awake; physician in attendance)
Neurologic deficit despite normal plain film findings	Magnetic resonance imaging
Plain films indicate craniovertebral injury involving occiput, C1, or C2	Computed tomography
Impaired sensorium; neurologic evaluation compromised	Computed tomography; 3-view radiographic series

Spinal Cord Injury

Epidemiology

The reported incidence of SCI in the United States is estimated at 56.4 cases per million population per year in the US, or about 12,500 new cases each year.[69,70] The prevalence of SCI in the US is estimated to be about 276,000 (range 240,000–337,000 persons).[69,70] Etiologic factors responsible

for SCI are motor vehicle accidents (38%), falls (30%), violence (14%), sports and recreational accidents (9%), and other causes (9%).[69,70] The average age at injury has increased over the last 40 years and is now 42 years.[69] Incidence rates of acute traumatic spinal cord injury are highest in elderly males (age ≥65 years), reaching more than 234 per million in the US in elderly males ≥85 years.[70] Traumatic spinal cord injury most commonly occurs in the cervical spine (55%), followed by the thoracic spine (30%), and the lumbar spine (15%). Of those individuals sustaining an SCI, incomplete tetraplegia (45%) is the most common, followed in descending order by incomplete paraplegia (21%), complete paraplegia (20%), and complete tetraplegia (14%).[69,70] Acute in-patient mortality is 7.5%, with a substantial increase in mortality in patients ≥65 years of age (in-patient mortality >9.5%).[70] After the first year, mortality rates decrease significantly with the 12-year survival rate at 85.1%.[71] Predictors of survival include the degree of consciousness; the level and severity of neurologic injury; presence of multiple injuries; need for respiratory assistance; age; and psychological, social, and vocational variables.[72] Leading causes of death in patients with SCI include respiratory and cardiac complications, septicemia, pulmonary embolism, and suicide.[71,73] The average length of stay for the acute intensive hospitalization phase of the patient with SCI is 7 days.[70] Lifetime costs ($2013) attributable to SCI are high, averaging $4,651,158 for a 25 year old with a high tetraplegic SCI to $2,274,396 for a paraplegic SCI.[69]

Terminology

In describing the severity of acute SCI, the use of correct terminology is essential. The term *pentaplegia* is used to describe high cervical spine injuries (C1) with paralysis of the lower cranial nerves and diaphragm and loss of motor and sensory function involving both upper and lower extremities. For SCI involving C3–C5, the term *tetraplegia* or *quadriplegia* is used; although facial and neck sensation and accessory muscle function remain intact at this level, the patient loses diaphragmatic function as well as motor and sensory function of the upper and lower extremities. For SCI involving C5–C6, the term *tetraplegia* is still used. In this lesion, patients retain diaphragmatic function and some proximal movement of the upper extremities but nothing else. For SCI involving the T1 level and below, the term *paraplegia* is used and is most commonly associated with loss of lower extremity function. Perineal paraplegia involves loss of sacral roots (S2–S5) only, with resulting dysfunction of the bowel, bladder, and sexual function.

Complete versus incomplete Spinal Cord Injury

Determining whether a patient has complete or incomplete SCI is vitally important in the prediction of outcome and in surgical planning. The diagnosis of a *complete SCI* (ASIA grade A) can be made only when there is absence of all motor and sensory function distal to the level of injury for more than 48 hours. An *incomplete neurologic injury* is defined by the ASIA as the presence of any sensory or motor function in the lowest sacral segment. Determining touch and pinprick sensations in the lowest sacral dermatomes (S4, S5), such as perianal sensation, and demonstrating voluntary rectal tone (rather than reflex rectal tone) is important, as there is a more favorable prognosis for subsequent neurologic improvement in patients with incomplete injuries.[74]

Incomplete SCI often manifests as a distinct constellation of neurologic abnormalities correlating with an involvement of a distinct lesion in the spinal cord (Fig. 21.28; Table 21.5). The type of neurologic syndrome depends on the level of injury as well as the force and vector of spinal impact. The common spinal cord syndromes are the cervicomedullary syndrome, central cord syndrome, anterior cord syndrome, posterior spinal cord syndrome, the Brown-Séquard syndrome, conus medullaris syndrome, and cauda equina syndrome (see Table 21.5). The *cervicomedullary syndrome* (cervical cord to medulla syndrome) involves the upper cervical cord and brainstem; it typically occurs from excessive traction or compression due to severe dislocation with AP spinal cord compression. The distinguishing feature is sensory loss over the face, so it is important to include an examination of facial sensation in all cervical spinal injuries. A perioral distribution

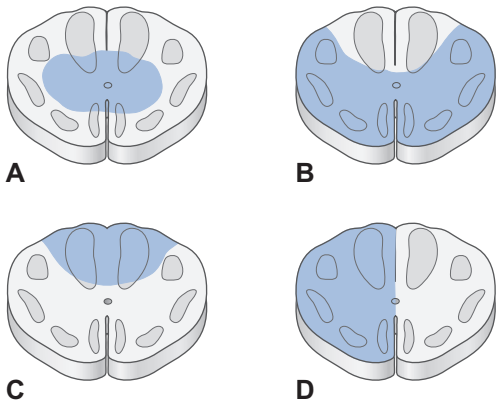


Fig. 21.28 Types of spinal cord injury (*shaded areas*) that produce the four main incomplete injury patterns seen clinically. **A,** Central cord syndrome; **B,** Anterior cord syndrome; **C,** Posterior cord syndrome; **D,** Brown-Séquard syndrome.

Table 21.5 **Incomplete Spinal Cord Injury Syndromes**

Syndrome	Clinical Findings
Conus medullans syndrome	Areflexia of bowel and bladder; variable motor and sensory loss in lower extremities; sacral sparing
Cauda equina syndrome	Areflexia of bowel and bladder; variable motor and sensory loss in lower extremities
Cervicomedullary syndrome tetraplegia	Respiratory arrest, hypotension, anesthesia below C1 Distinguishing feature is facial sensory loss Deficits may be greater in upper than in lower extremity
Anterior cord syndrome	Loss of motor, sensory, temperature, and pain sensations Vibration and position sensations intact
Central cord syndrome	Motor impairment of upper extremities more than lower extremities Alterations in pain and temperature sensations
Posterior cord syndrome	Loss of fine, vibratory, and position sensations Motor function preserved
Brown-Séquard syndrome	Ipsilateral paralysis, loss of proprioception, touch, and vibration sensations Contralateral loss of pain and temperature sensations

of sensory loss signifies a lesion in the medulla and upper cervical cord, whereas a more peripheral facial distribution of sensory loss, involving the forehead, ear, and chin, denotes a lesion in the cord at C3–C4. In addition to the facial sensory loss, there may be evidence of motor deficits with a greater loss of upper extremity function than lower extremity function (similar to the anterior cord syndrome).

The *central cord syndrome* is an acute central cervical spinal cord injury syndrome in which upper extremity weakness is greater than lower extremity weakness and there are alterations in pain and temperature sensations (as the fibers cross the midline). This syndrome is seen more often in elderly patients with cervical spinal stenosis who have extension-type injuries from falls, trauma, syringomyelia, or intrinsic cord tumor.

The *anterior cord syndrome* results from an injury to the spinal cord that spares the posterior columns. Motor and sensory functions and pain and temperature sensations are lost, but vibration and position sensation are preserved. The syndrome occurs more commonly in the cervical region and is characterized by lower motor neuron paralysis of the arms and upper motor neuron paralysis of the legs. The *posterior cord syndrome* is a rare type of incomplete syndrome that involves the posterior column primarily, resulting in loss of fine sensation and vibratory and position sensations, with preservation of pain sensation, temperature sensation, and motor function. The *Brown-Séquard syndrome* is relatively uncommon, appearing most often in the context of cervical spine injuries; it involves impairment of the lateral half of the spinal cord, sparing the other half. Clinically, there is motor paralysis and a loss of position sense ipsilateral to the lesion, with loss of sensory and temperature sensation opposite to the lesion. This syndrome is seen more often with hyperextension injuries but can be associated with flexion injuries, locked facets, compression fractures, herniated disks, and extrinsic tumors.

The *conus medullaris syndrome* involves a lesion at the level of the conus (T12–L1), where the spinal cord narrows and involves the sacral (and perhaps lumbar) cord segments. This syndrome is characterized by areflexia of the bowel and bladder, variable motor and sensory losses in the lower extremities, and sacral sensory sparing. The *cauda equina syndrome* occurs from SCI at or below the L1–L2 disk space and involves the lumbar and sacral nerve roots (L1–L5). Typical findings include variable lower motor neuron sensory and motor loss to the lower extremities and an areflexic bowel and/or bladder. The cauda equina syndrome is seen after acute central disk herniation, spinal trauma, and extrinsic neoplastic or infectious processes.

Anatomic and Physiologic Considerations

Autoregulation of SCBF is impaired following traumatic SCI; as a result, the presence of hypotension or hypoxia can further exacerbate the neurologic injury. Subsequent to the primary SCI event, there is an initial catecholamine release resulting in a pressor response that contributes to vasogenic edema.[75] After the initial hypertensive response, there is a phase of hypotension and reduced cardiac output. These hemodynamic changes are in part responsible for a reduction in SCBF that is observed as early as 30–60 minutes after injury, which preferentially affects gray matter and central white matter.[76] Blood flow may not return to preinjury levels for up to 24 hours. Finally, after SCI, there is a progressive decrease in oxygen tension and a loss of CO_2 responsiveness, which is correlated with neurologic outcome.[77]

Pathophysiology of Spinal Cord Injury

Primary and Secondary Injury (Fig. 21.29)

Primary injury results from direct tissue destruction from blunt or penetrating forces. Such trauma is observed following vertebral fracture or dislocation, burst fractures with retropulsion of bone fragments or disk material into the spinal cord, ligamentous injury with distraction and spinal cord compression, and gunshot and knife wounds. The term *secondary injury* is simply defined as a worsening of the original injury as a result of factors other than the mechanism of the original insult. Many mechanisms for secondary injury have been proposed (Box 21.2); the destructive processes are set in motion within minutes of the primary injury and may continue for days. These developments contribute to the ischemic zones observed in the gray matter and surrounding central white matter soon after SCI and explain the increases in tissue lactic acid and decreases in adenosine triphosphate (ATP) production observed.[78] Progressive ischemia is an etiologic factor in secondary degeneration; it may be worsened by edema, which reaches a maximum at 3 to 6 days and may persist for 2 weeks.

One of the first changes observed immediately after spinal injury is a loss of neurologic function (termed spinal cord concussion), which may occur in the absence of initial histologic changes. This effect is due in part to an efflux of K^+ into the extracellular space, which causes membrane depolarization as well as disturbances in metabolic and synaptic function.[79,80] Depolarization of the membrane stimulates the release of excitatory amino acids, which in turn facilitates further depolarization. In addition, the failure of transmembrane ionic pumps results in increases in intracellular Na^+, which stimulates the Na^+/Ca^{2+} pump to operate contrary to its normal function, that is, pumping Na^+ out of the cell and Ca^{2+} into the cell. Intracellular Ca^{2+} activates calcium-dependent proteases, phospholipases, and endonucleases, further facilitating cell damage. Free radical-induced lipid peroxidation of neuronal and vascular cell membranes and myelin is also involved in secondary injury.[81] Finally, the release of endogenous opioids after traumatic SCI has also been implicated in the pathophysiology of secondary injury.[82] However, although naloxone was not found to be useful in SCI in the original definitive clinical study,[83] subsequent reanalysis of the data did indicate some benefit from the use of naloxone.[84]

Spinal Cord-Protective Strategies

Minimizing secondary SCI is the most important aspect of medical therapy following any injury to the spinal cord. Early institution of pharmacologic therapies combined with surgical decompression and stabilization of the spine may result in the best outcome potential. The current use of both modalities is briefly reviewed.

Pharmacologic Therapies

Corticosteroids

Corticosteroids are believed to stabilize membranes, alter ionic-clearing mechanisms, improve blood flow, inhibit lipid peroxidation formation, and enhance Na^+/K^+-ATPase activity.[85] The membrane-stabilizing effects may prevent the release of lysosomes and excessive Ca^{2+} ionic fluxes into cells. Improvement in blood flow may be due to a reduction in tissue edema, the direct vasodilatory effects of steroids, and antioxidant properties. One of the first clinical studies of corticosteroid use in SCI was the first National Acute Spinal Cord Injury Study (NASCIS I).[86] This study failed to show any clinical benefit in neurologic recovery; however, the dose regimen was thought to be inadequate.

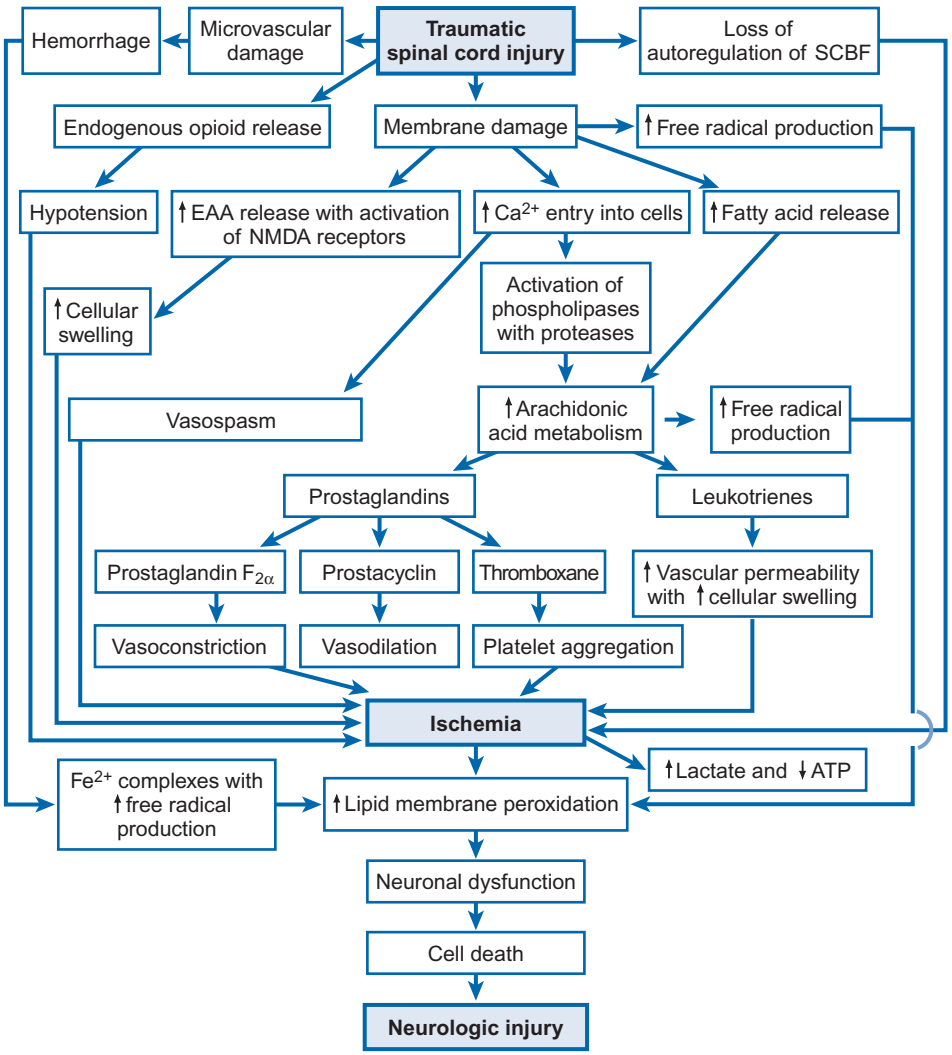


Fig. 21.29 Pathophysiologic cascade involved in secondary spinal cord injury. ATP, adenosine triphosphate; EAA, excitatory amino acids; NMDA, *N*-methyl-D-aspartate; SCBF, spinal cord blood flow; ↑, increase; ↓, decrease.

BOX 21.2 Secondary Mechanisms of Acute Spinal Cord Injury

Vascular	Cellular Dysfunction	Biochemical Aberrations
Hemorrhage	↑Extracellular K^+	↑Catecholamine release
Loss of autoregulation	↑Intracellular Ca^{2+}	↑Arachidonic acid metabolism
Arteriolar occlusion	↑Intracellular Na^+	Prostaglandins
Vasospasm	Inhibition of Na^+/K^+-ATPase	Thromboxanes
Edema	Lipid peroxidation	Leukotrienes
↑Vascular permeability	Increased intracellular edema	Free radicals
Hypotension	Mitochondrial failure	↑Endogenous opioid release
		↑Excitatory amino acid release
		↑Free radical formation
		↑Mitochondrial nitric oxide synthetase (NOS)
		Decompartmentalization of iron
		Hemoglobin extravasation
		Mitochondrial "leak"
		Activated neutrophils

The second National Acute Spinal Cord Injury Study (NASCIS II) was a multi-institutional, randomized, placebo-controlled, double-blind study that involved 487 patients entered into the study within 12 hours of injury.[83] The patients were randomly allocated to one of three treatment groups: (1) methylprednisolone (MP), 30 mg/kg, followed by 5.4 mg/kg/h for 23 hours; (2) naloxone, 5.4 mg/kg followed by 4 mg/kg/h for 23 hours; or (3) placebo. No meaningful improvement in neurologic function was seen between the groups, but when the methylprednisolone results were stratified according to the timing of administration, patients treated within 8 hours of injury showed significant improvement in motor and sensory function in comparison with those given the placebo. The NASCIS II results led to the common practice of administering methylprednisolone to patients within 8 hours of SCI.

NASCIS III compared the efficacy of MP administered for either 24 or 48 hours, and tirilazad mesylate administered for 48 hours.[85] A total of 499 patients received intravenous MP (30 mg/kg) within 8 hours of SCI followed by an infusion of MP at 5.4 mg/kg/h for either 24 hours or 48 hours. The tirilazad group received tirilazad mesylate at 2.5 mg/kg every 6 hours for 48 hours. Patients receiving treatment with MP between 3 hours and 8 hours after injury and continued on MP therapy for 48 hours showed greater motor recovery at 6 weeks and 6 months after injury than patients treated with the same agent for 24 hours. The conclusion from the NASCIS III trial was that patients with acute nonpenetrating SCI who received MP therapy within 3 hours of injury should remain on the treatment regimen for 24 hours; those in which MP therapy was initiated between 3 and 8 hours after injury, should receive treatment for 48 hours.

Despite the results of the NASCIS II and III trials, the standard use of MP after acute SCI is no longer recommended.[87] Reexamination of the studies has led to significant criticism about their results and conclusions; [88] consequently, it has been decided that both NASCIS II and III failed to demonstrate meaningful differences in neurologic recovery among treatment groups. Moreover, in patients receiving steroid treatments in the NASCIS II and III trials, and other studies in which patients received steroids for SCI, the complication rates were increased in comparison to placebo. [89–92] Thus, although some institutions may still consider the use of high-dose steroids to be a "treatment option,"[93] the general consensus is to avoid the use of steroids for the treatment of acute SCI.

Emerging Therapies

Investigations into the use of experimental treatments for SCI have targeted specific pathophysiologic processes occurring during specific time points following SCI (acute, subacute, chronic). During the acute phase of SCI, experimental pharmacologic therapies have included: anti-Nogo antibodies (inhibits myeline-associated inhibitors); riluzole (inhibits voltage-sensitive Na + channels); minocycline (anti-inflammatory, anti-apoptosis); magnesium-polyethylene glycol (anti-excitotoxicity, promotes repair of cellular membranes); granulocyte colony-stimulating factor (activates neuroprotective pathways); and FGF2 (promotes neuroprotection and neuroplasticity). Experimental therapies targeting the subacute and chronic stages of SCI include: transplantation of induced pluripotent stem cells, including human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs); skin-derived precursor cells; and electrical stimulation combined with neurorehabilitation. To date, only early surgical decompressive spine surgery offers proven clinical benefits.

Hypothermia

Hypothermia as a potential therapy for traumatic SCI has been investigated for many years. The protective effects of hypothermia are related to reductions in neuronal cell enzymatic activity and metabolism; other benefits include a reduction of extracellular glutamate levels, inhibition of apoptosis, and a decrease in inflammation. Animal models of traumatic SCI have consistently demonstrated a reduction in damage from secondary injury with the use of hypothermia, although improvements in functional outcome have been inconsistent, particularly in the setting of severe traumatic SCI. In clinical studies of traumatic SCI, insufficient evidence yet exists to conclusively demonstrate that hypothermic techniques can benefit patients with traumatic SCI, although some reports have demonstrated benefits.[94] A recent review of the use of hypothermia in the setting of acute SCI concluded that, although some clinical evidence existed to demonstrate the beneficial use of hypothermia in acute SCI, multicenter trials were needed to further study the utility of systemic hypothermia in this setting.[95] Given the scarcity of clinical evidence to date demonstrating consistent benefits of hypothermia, the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) has determined that there is insufficient evidence to recommend for or against the practice of either local or systemic therapeutic hypothermia in the routine clinical care of patients with acute SCI.[96]

Hypertension

Hypertension is advocated to improve perfusion in the post-traumatic patient with hypoperfusion of the spinal cord. Although definitive data are lacking, early and aggressive intervention to maintain a mean arterial blood pressure above 85 mm Hg for the first 7 days after injury is recommended to preserve neurologic function in the setting of impaired autoregulation.[93,97] Despite words of caution regarding maintaining higher blood pressure levels following spinal cord injury, no compelling evidence has yet been presented to associate aggressive blood pressure support and a clinically meaningful risk of further hemorrhage and edema.

Conclusion

Unfortunately, no clear benefit from any pharmacologic therapy has yet emerged to significantly reduce spinal cord damage following traumatic injury. Nonetheless, research into newer therapies focusing on neurologic regeneration and protection continues to receive much attention and may ultimately prove beneficial (Box 21.3).

Surgical Therapies

Early surgical therapy following SCI may reduce neurologic injury. The decision for surgical intervention following SCI involves many considerations including (1) neurologic and radiologic evaluation; (2) the initial success of closed reduction and decompression; (3) determination of the degree of spinal column stability; (4) determination of the benefit of early open surgical decompression and stabilization; and (5) choosing the particular surgical approach (Box 21.4).

Neurologic and Radiologic Evaluation

Surgical intervention following SCI is based on the detection of neurologic deterioration obtained from frequent neurologic assessments (every 12 hours) and the extent of spinal column abnormalities detected on initial radiographic studies.

Initial Closed Reduction and Decompression

Initial therapy after SCI is directed toward prevention of further neurologic injury, because up to 25% of SCIs occur after

BOX 21.3 Current Status of Treatment After Traumatic Spinal Cord Injury in Humans

Accepted Benefit
None

Potential Benefit
Early surgical decompression
Systemic or localized hypothermia
Minocycline
Prostacyclin analogs
NMDA-receptor antagonists (e.g., magnesium salts, gacyclidine)
Hypertonic saline
Platelet-activating factor antagonists
Capsase inhibitors
Neurite growth inhibitor antibodies
Antioxidants and free radical scavengers
Stem-cell transplantation
Gene therapy
Activated macrophage implantation
Receptor blockers or antibodies against inhibitory factors (e.g., anti-Nogo Ab)

Little or No Proven Benefit
Methylprednisolone
21-Aminosteroids
GM-1 gangliosides
Opioid antagonists
Thyrotropin-releasing hormone analogs
Arachidonic acid metabolite inhibitors
Dimethyl sulfoxide
Hyperbaric oxygen
ε-aminocaproic acid
Calcium antagonists

BOX 21.4 Indications for Surgical Intervention Following Traumatic Spinal Injury

- Progressive neurologic deterioration in an unstable spine, especially with spinal canal compromise
- Failure of closed reduction
- Unstable spine with dislocated bilateral "locked" facets
- Unstable spine where nonunion is likely (e.g., ligamentous injury)
- Uncooperative patient with unstable spine risking further neurologic injury
- Compression of conus medullaris or cauda equina
- Vertebral body fractures with bony encroachment of spinal canal without neurologic findings
- Incomplete SCI with dislocation successfully treated with closed reduction and immobilization
- Unstable spine with complete SCI (to facilitate "zonal root" recovery)
- Unstable spine with incomplete SCI (to prevent further deterioration)
- Unstable spine without neurologic deficits
- Thoracolumbar burst fractures with progressive pain, deformity or neurologic deficit

SCI, Spinal cord injury.

the initial insult, either during the transport process or early in the course of treatment. Spinal immobilization is initially carried out at the scene of the accident and is achieved by placing the patient on a spinal board, with immobilization of the head and neck using sandbags as well as adhesive tape on the forehead attached to each side of the board. Once the spine is immobilized, the patient should be rapidly transferred to a Level I trauma center for further management.

If radiographic images taken at the hospital reveal a possible spine injury, the spine should remain immobilized until further management decisions can be made. If imaging reveals a cervical spinal dislocation, urgent reduction for decompression of the neural structures is attempted, especially in the case of incomplete spinal cord injury. Reduction can be achieved in a closed fashion with the use of a traction device to align and immobilize the spine, or via an open surgical approach.[98,99] The intent of closed reduction is to realign and immobilize the spine, decompress neural structures, and prevent further neurologic injury. Any reduction of pressure on the spinal cord results in improved microvascular circulation, which may limit the degree of spinal cord edema and prevent a progressive neurologic deficit. Closed reduction is successful 73% to 97% of the time, with few reports of neurologic worsening during the procedure.[100,101] On occasion, facets joints may be "locked", preventing reduction even with extreme traction; in such instances, open surgical decompression is indicated. Another method utilized for spine immobilization is the halo vest orthosis. This device is utilized for treatment of unstable cervical and upper thoracic fractures and dislocations from C1 to T3. The halo orthosis provides greater motion restriction than other cervical orthoses. Patients with a halo orthosis presenting for surgical procedures pose significant anesthetic challenges, particularly with tracheal intubation as the neck is completely immobilized.

Determination of Spinal Stability

The determination of spinal stability following trauma is important in planning potential surgical treatment. *Spinal stability* has been defined as the means by which the vertebral structures maintain their cohesion in all physiologic positions.[102] Instability or loss of stability is a pathologic process that, if left untreated, can lead to progressive spinal deformity, neurologic loss, and chronic pain. In the setting of acute spine trauma, the clinical history, neurologic examination, and initial radiographic imaging should allow a reasonable determination of spinal stability.

For the upper cervical spine (C1–C2), the primary determinant of stability is the transverse atlantal ligament (TAL), which is assessed by plain radiographs and by CT and MRI. Any bony displacement beyond acceptable limits renders the spine unstable at that level.[103]

For the lower "subaxial" cervical spine (C3–C7), a variety of methods have been used to determine spinal stability; they include anatomic considerations that divide the spine into columns;[102,104,105] clinical considerations that correlate the magnitude of the neurologic injury with the likelihood of spinal instability;[106] and radiographic criteria that assess various measurements of spinal bony alignment, spinal canal dimensions, disk space size, and identification of the presence of major ligamentous injury,[102,104] and a combination of these methods.[107] Determination of major ligamentous injury is also important because adequate healing is unlikely in this setting, resulting in a chronically unstable spine with progressive kyphosis, neurologic deficits, or both.

Anatomic considerations used in the assessment of spinal stability after lower cervical spine injury may be viewed in the context of either a three-column[102,105] or a two-column approach.[104] The Denis three-column model is a well-described method of predicting spinal instability.[105] Originally described and most commonly used for assessing thoracolumbar trauma, it has been employed in cervical injuries as well. In this model, the spinal column is divided into three longitudinal columns (Fig. 21.30). The anterior column comprises the anterior longitudinal ligament, the anterior anulus fibrosis, and the anterior

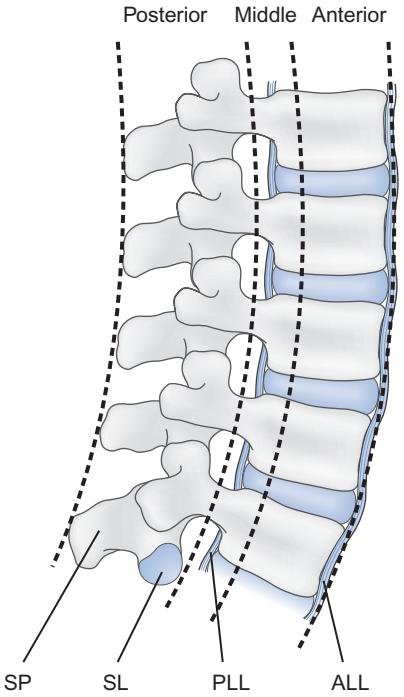


Fig. 21.30 Spinal column stability after traumatic injury is often based on a system that divides the spine into three columns. The anterior column comprises the anterior longitudinal ligament (ALL), the anterior anulus fibrosis, and the anterior half of the vertebral body. The middle column comprises the posterior half of the vertebral body, the posterior longitudinal ligament (PLL), and the posterior anulus fibrosis. The posterior column comprises the posterior bony arch, which includes the spinolaminar junction (SL), the spinous process (SP), and the posterior ligamentous complex. Disruption of two or more of these columns indicates spinal instability.

half of the vertebral body. The middle column comprises the posterior half of the vertebral body, the posterior longitudinal ligament, and the posterior anulus fibrosis. The posterior column comprises the posterior bony arch with the posterior ligamentous complex. The biomechanics of the injury combined with plain films and CT scans of the spine demonstrating failure of two or all columns renders the spinal unstable.

Clinical considerations used to predict cervical spine stability consider the presence of a neurologic deficit to imply that the cervical spinal trauma subjected the spinal cord or nerve roots to a vascular, mechanical, or chemical insult and that given such severe injury, the integrity of the supporting structures has been altered enough to permit further injury, thus representing an unstable spine.[103]

Radiographic considerations can be utilized for predicting lower cervical spine instability. Specifically, radiographic abnormalities demonstrating more than 11 degrees of sagittal plane translation and more than 3.5 mm of sagittal plane translation, more than 50% compression of the vertebral body, interspinous widening, loss of facet parallelism, and loss of normal cervical lordosis indicate spinal instability. Finally, both the clinical and radiologic findings may be combined and used as part of an instability checklist, as suggested by White and Panjabi.[103] The instability checklist assigns individual points to specific radiologic and clinical findings, and then the points are summated for a total score that is used to estimate the likelihood of spinal instability. This checklist approach is very useful and can be applied to a variety of clinical scenarios.

The Subaxial Injury Classification (SLIC) and Severity Scale is a more recent classification system employed in quantifying spinal stability and in determining the need for surgical therapy following traumatic spinal cord injury.[107–109] This method utilizes a standardized approach to estimating the degree of injury severity, as well as stability of the anterior and posterior motion segments of the cervical spine. In this scale, a weighted score is assigned to each of three parameters of spinal injury: morphology, discoligamentous complex (DLC), and neurological assessment. Depending upon the total score, conservative treatment (score, 1–3) or surgical management (score, ≥5) is suggested. The agreement regarding treatment strategies among surgeons utilizing this scoring system has been reported to be 74%.

For the assessment of thoracic and lumbar spinal injury, the evaluation is similar to the techniques described for assessing the cervical spine, often relying on the Denis three-column model, or an instability checklist similar to that described by White and Panjabi for cervical spinal injury.[103] In the lumbar region, the Denis three-column model is most frequently used. Ultimately, correlating neurologic findings with radiologic evidence of structural damage best guides treatment.

Early Surgical Therapy Following Spinal Injuries

The indications and timing of surgical therapy following spinal injuries are debated. Surgery is clearly indicated in any unstable spinal injury associated with evolving neurologic deficits, especially when such deficits are associated with radiologic evidence of acute spinal canal compromise. Surgery is also indicated for an unstable spine with dislocated bilateral "locked" facets, an unstable spine with significant ligamentous injury and vertebral body separation, and an unstable spine in an uncooperative patient who risks further neurologic injury. For other types of spinal injuries, the benefits and timing of surgical decompression and stabilization after SCI remain controversial. Experimental evidence strongly suggests that early decompression after SCI reduces secondary SCI and improves neurologic outcome.[110–112] Conversely, clinical studies have failed to clearly demonstrate the beneficial effects of early decompression so evident in the experimental models.[113] Nonetheless, the prevailing opinion is that early decompression may facilitate a more favorable neurologic outcome, particularly in patients with incomplete injuries.[114–119] For spinal decompression therapy to be most effective, evidence suggests that decompression must occur within 24 hours, particularly in incomplete neurologic injuries. In addition to improved neurologic outcome, proposed benefits of early surgical decompression include: reduced length of stay in the intensive care unit; reduced length of hospitalization; decrease in secondary complications of SCI; earlier mobilization and rehabilitation therapy; and decrease in overall costs of care. Late surgical decompression (>48 hours) offers no particular neurologic or economic benefits over early surgical decompression, and cannot be recommended as the preferred management option.

Surgical Approaches in Spinal Injury

Three basic surgical approaches are utilized to treat spine injuries: anterior, posterior, or a combination of the two methods. Anterior surgical approaches for spinal decompression and stabilization procedures are indicated for removal of disk material, bone, or ligamentous tissue compressing the spinal cord anteriorly. Anterior cervical instrumentation is typically used to treat unstable compression–flexion and distractive–flexion injuries, often in conjunction with a decompressive corpectomy (removal of vertebral body) if cord compression is present (Fig. 21.31).

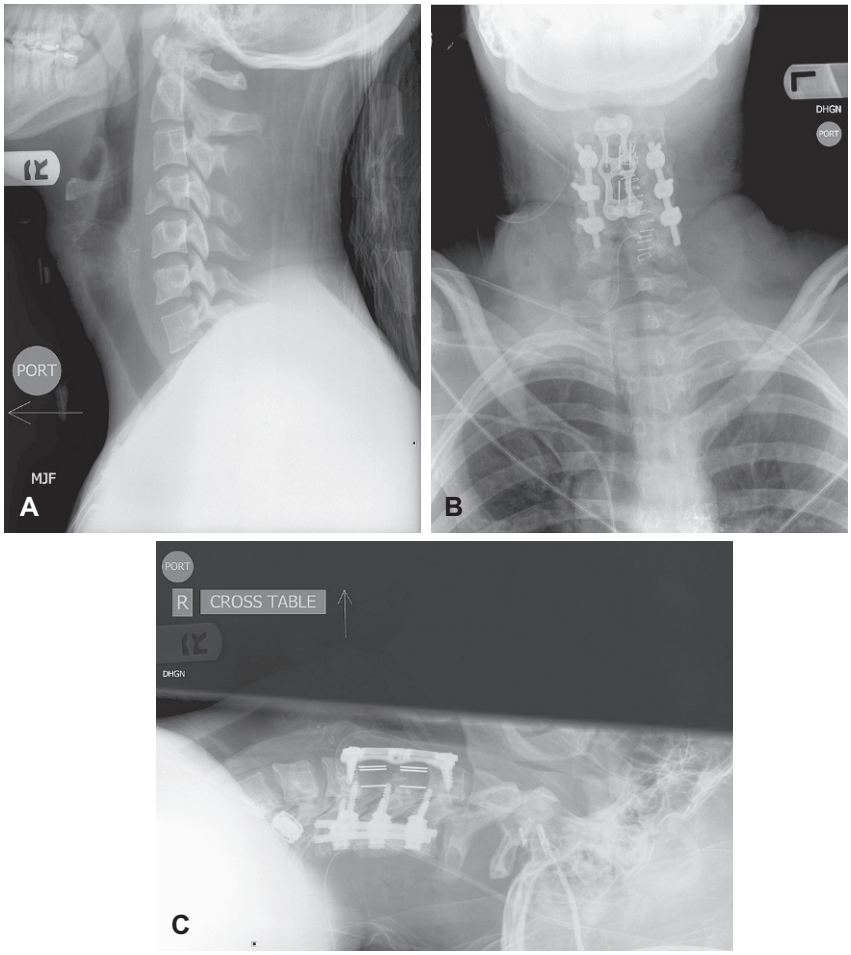


Fig. 21.31 Cervical spine teardrop fracture. **A,** A preoperative lateral cervical radiograph shows a teardrop fracture of the C4 vertebral body inferiorly. **B,** An anteroposterior radiograph shows anterior plate and screw fusion from C3 to C5 with prosthetic strut grafts and posterior fusion of the same levels with bilateral pedicle screws and rods. **C,** On this postoperative lateral radiograph, the anterior plate and screws are clearly visible.

Posterior surgical stabilization is indicated for significant disruption of the posterior bony or ligamentous structures of the cervical spine. Posterior fixation techniques are also used to treat instances of occipitocervical and atlantoaxial instability and for most cases of spinal instability caused by flexion injuries, including posterior ligamentous injury, anterior dislocation, bilateral facet dislocation, and simple wedge compression fractures. Flexion–rotation injuries causing unilateral facet dislocation may require a posterior cervical stabilization procedure, particularly if closed reduction is unsuccessful.

A combined anterior–posterior surgical approach is indicated for significant injuries involving both the anterior and posterior bony or ligamentous structures. Such injuries include extensive cervical injuries, such as flexion teardrop fractures, vertical compression burst fractures with significant posterior ligamentous injury, and bilateral facet dislocation with disk compression of the spinal cord.

Medical Management

Pulmonary System

Respiratory and pulmonary function may be significantly affected following cervical or thoracic SCI, with the level of SCI determining the magnitude of effect and the clinical course (Table 21.6; Box 21.5). Most abnormalities of lung function are related to the adverse effects of SCI on pulmonary lung volumes and pulmonary mechanics.

The normal muscles of respiration are composed of the intercostal muscles (supplied by the intercostal nerves originating from the thoracic spinal cord) and the diaphragm (supplied by cervical innervation originating from C3–C5). The diaphragm normally contributes about 65% of the vital capacity. Injuries to the cervical cord at or above C3 produce nearly complete respiratory muscle paralysis. Patients with injuries to this level of the spinal cord are not able to produce a tidal breath or to cough. Consequently, these patients require emergency assistance for breathing to prevent profound hypercapnia and hypoxemia. With cervical SCI involving levels below C3, the workload of breathing is highly dependent upon an effective contribution of the diaphragm. Although the use of the accessory muscles of breathing (cervical accessory muscles, scalene muscles, and the clavicular portion of the pectoralis major muscle) may temporarily augment respiratory mechanics, the persistent absence of intercostal muscle function and paralyzed abdominal muscles limits expiratory muscle use and significantly restricts the ability to cough effectively. Accordingly, these patients rapidly develop hypercarbia, hypoxemia, atelectasis, and inability to mobilize secretions. As a result, nearly all patients with a complete subaxial cervical SCI will require mechanical ventilatory support during the early phases of therapy.

Pulmonary mechanics are altered in cervical SCI, with significant reductions in lung compliance and resultant increases in the work of breathing. The adverse effects on lung compliance are related to changes in the mechanical properties of the lung, in addition to the reduction in lung volumes.

Table 21.6 Level of Spinal Cord Injury and Corresponding Respiratory Function*

Injury Level	Ventilatory Function	Cough	Relevant Comment(s)
Above C3	0	0	Paralysis of diaphragm and accessory muscles, resulting in apnea; lifelong ventilator dependence
C3–C5	0 to +	0	Partial to complete diaphragmatic paralysis; paralysis of accessory muscles; marked reduction in lung volumes with hypoxemia; recurrent atelectasis and pneumonia; prolonged mechanical ventilator dependence; probable tracheostomy; most patients will be weaned from mechanical ventilation
C5–C7	+ to ++	+ to ++	Paralysis of accessory muscles; marked reduction in volumes with hypoxemia; recurrent atelectasis and pneumonia; many patients need mechanical ventilation; possible tracheostomy
High thoracic	++	++	Partial paralysis of accessory muscles; reduction in lung volumes with atelectasis; increased incidence of pneumonia; possible need for mechanical ventilation

*Scale: 0 (no function) to +++ (normal).

BOX 21.5 Protocol for Reduction of Pulmonary Complications in Patients with Spinal Cord Injury

- Aggressive pulmonary hygiene
  - Frequent nasotracheal suctioning
  - Positional changes every 2 hours, best achieved with continuous lateral rotation beds
  - Chest percussion every 4 hours
  - Assisted coughing exercises every 4 hours (e.g., mechanical insufflation-exsufflation)
  - Deep breathing exercises every 4 hours
  - Incentive spirometry every 4 hours
- Bronchodilator therapy for assisting secretion clearance and bronchodilator effects
- Early use of fiberoptic bronchoscopy in cases of lobar atelectasis secondary to retained secretions
- Early institution of mechanical ventilation in those with progressive labored breathing, increasing respiratory failure (hypoxia or hypercapnia) and vital capacities <1000 mL
- Close monitoring of respiratory mechanics in patients receiving mechanical ventilation with optimal use PEEP therapy and limitation of plateau pressure to <30 cm Hg

Gastric distention secondary to gastric atony may also be a contributory factor to the adverse effects of SCI on pulmonary mechanics. As the spinal shock state resolves (2–5 weeks), progressive spasticity of chest wall and abdominal muscles will assist in improving pulmonary mechanics and lung function.

Lung volumes are considerably reduced following cervical SCI. Spirometric pulmonary function tests performed acutely after injury show significant reductions in tidal volume, forced vital capacity, and expiratory volume. In particular, vital capacity has been reported to be 30% of predicted with SCI at C5–C6, and worse if the level is at C4 and above. Conversely, residual volume increases to nearly twice the normal levels following acute SCI.[120] Positioning of the cervical SCI patient influences lung volumes. Patients demonstrate an improvement in vital capacity when assuming the supine position. The improvement in vital capacity is secondary to a reduction in the residual volume, which occurs in the supine position and is considered to be related to the effect of gravity on the abdominal contents in the presence of paralyzed abdominal musculature. Significant improvement in most lung volumes can be expected to occur after 3 weeks with substantial progress noted over the course of the first 4–5 months following injury.

Frequent clinical reassessment and close monitoring of diagnostic tests are imperative during the early period following acute cervical SCI. During the first 1 to 3 days, substantial declines in pulmonary reserve may occur before overt clinical signs are seen. Moreover, although SCI patients may be initially hospitalized with a functioning diaphragm, progressive cord edema may occur over the first 2 days, resulting in an ascending neurologic injury. This condition may cause a loss of diaphragmatic function with rapidly progressive respiratory failure and the need for tracheal intubation.

When mechanical ventilation is indicated, ventilator settings should be selected that limit the occurrence of ventilator-associated lung injury (VALI).[121–123] Typical settings include a volume-control mode of ventilation, a tidal volume of 6–8 mL/kg, positive end-expiratory pressure (PEEP) of 5, a ventilatory rate of 8 to 15 breaths/min, and an inspiratory plateau pressure of ≤30 mm Hg. In patients with cervical SCI below C4, eventual weaning from mechanical ventilation is to be expected and is facilitated when spinal shock resolves and the respiratory and abdominal muscles develop spasticity (2–3 weeks), leading to improvement in lung volumes and overall ventilatory ability. Nearly all patients with complete cervical SCI above C6 will require a tracheostomy because of the length of time on the ventilator and the difficulty with clearing secretions. In this setting, a tracheostomy should be placed early (3–7 days) from the time of injury, as little benefit is realized by delaying the procedure further.[124] The need for long-term ventilator support, weaning, and extubation in patients with SCI was reviewed by Kornblith and colleagues.[125] In this report, 361 patients with SCI from 14 major trauma centers were reviewed; 222 patients (64.5%) had cervical SCI (50% with complete injuries). Among these patients, 122 (81.9%) had a tracheostomy placed, with 62.6% of the patients ventilator-free by discharge. Studies investigating the use of diaphragmatic pacing in tetraplegic patients have shown promise in enhancing weaning from chronic ventilator dependence and this may become a valuable management strategy in the future.[126,127]

Pulmonary complications are common after cervical and upper thoracic SCI, and are the leading causes of morbidity and early mortality. Completeness of SCI, age, comorbidities, and tachypnea at admission are associated with the development of complications. The most frequent pulmonary complications include atelectasis, respiratory failure, and pneumonia. Pulmonary complications develop in over one-third of patients with SCI within the first 30 days of injury. Jackson and colleagues reported that 84% of patients with C1–C4 injuries, 60% of those with C5–C8 injuries, and 65% of those with T1–T12 injuries had respiratory complications.[128] Ventilatory failure and aspiration, in particular, occur early in patients with SCI (average, 4.5 days).[128,129] In one report,[130] all patients with complete SCI at the C5 level and above required mechanical

ventilation and tracheostomy. In those patients with SCI at C6 and below, 79% required mechanical ventilation and 50% required tracheostomy. Hassid et al.[131] reviewed 186 patients with traumatic acute SCI and recommended mandatory early intubation as the preferred approach to management of respiratory insufficiency due to SCI. Early tracheostomy also has advantages including: reductions in airway dead space and airway resistance; improved pulmonary toilet due to easier suctioning; earlier spontaneous breathing trials; more comfort for the patient; and a reduction in the incidence of ventilator-associated pneumonia (VAP). Frequent fiberoptic bronchoscopy may be needed during the first 2 weeks following acute cervical SCI to remove secretions that result in clinically significant lobar atelectasis or complete bronchus occlusion. Inadequate clearance of secretions is a leading risk factor for the development of pneumonia in acute SCI. If VAP is suspected, early and aggressive broad-spectrum antibiotic use is recommended.

Kinetic therapy (i.e., rotational bed) has been demonstrated to be effective in reducing the incidence of pulmonary complications, decreasing time on the ventilator, and shortening length of stay in the intensive care unit.[132–136] For best results, kinetic therapy should be started early following acute cervical spinal cord injury, and should achieve lateral rotation angles of >45 degrees. These strategies are effective in reducing hospital resource utilization as well as overall morbidity and mortality.

Cardiovascular System

SCI has a profound effect on the cardiovascular system, the magnitude of effect depending on the level of injury. In general, complete cervical SCI has the most pronounced physiologic effects, consisting of cardiovascular instability, cardiac dysrhythmias, and ventricular dysfunction, whereas SCI below T5 results in varying degrees of hypotension caused by the functional sympathectomy below the level of injury.

Hemodynamic changes noted after SCI have been observed consistently in experimental models of SCI and include a transient severe increase in blood pressure caused by an extensive sympathetic discharge at the time of injury[137]. This sympathetic discharge may be responsible for the noncardiogenic pulmonary edema reported to occur after SCI. Although the hypertensive response to SCI has been documented only in experimental models, it is generally believed to occur in humans at the time of injury and to resolve by the time medical treatment is undertaken.

Shortly after injury, hypotension becomes predominant, and is present in nearly all patients with complete cervical SCI. The hypotension is related to vasodilation of the vasculature, which arises secondary to the withdrawal of sympathetic neural outflow. When an SCI occurs in the cervical region, the sympathetic receptors lose their normal input and regulation, resulting in a functional sympathetic blockade. In contrast, the parasympathetic nervous system remains intact as the vagus nerve exits from the brainstem. Consequently, after an acute injury to the cervical or high thoracic spinal cord, the resulting autonomic imbalance between sympathetic and parasympathetic outflows leads to inadequate cardiac contraction, reduced stroke volume, and a loss of tonic vasoconstriction, with resulting hypotension, bradycardia, and hypothermia (termed *neurogenic shock*).[138]

Spinal shock describes the phenomenon seen with physiologic or anatomic transection, or near transection, of the spinal cord; it consists of the loss of somatic motor and sensory function below the level of injury, loss of voluntary rectal contraction, and loss of sympathetic autonomic function. The more severe the functional spinal cord transection and the higher the level of injury, the greater the severity and duration of spinal shock. If the loss of motor and sensory functions resulting from spinal shock lasts longer than 1 hour, pathologic injuries to the spinal cord, as opposed to a transient concussive injury, are assumed to exist.

Neurogenic shock is seen in 60% to 70% of patients following a complete cervical SCI.[138] The more cephalad the level of spinal injury, the more severe the physiologic derangements encountered. The most common cardiovascular abnormalities observed in patients after an acute cervical SCI are marked bradycardia (71%) and hypotension (68%). Bradycardia is present in virtually all patients with complete cervical SCI; however, it is less likely with SCI involving the thoracic and lumbar regions. Bradycardia results from the interruption of the sympathetic cardiac accelerator nerves (T1–T4), leaving an unopposed parasympathetic influence. Bradycardia usually resolves over a 3–5-week period after injury. More profound degrees of bradycardia, even cardiac arrest, may occur during stimulation of the patient, such as turning or tracheal suctioning. The cardiovascular derangements remain most problematic during the first 2 weeks after an acute cervical SCI. Preventive measures to avoid severe bradycardic episodes include sedation, 100% oxygen before suctioning, and limiting the time allowed for suctioning. Although most episodes are effectively treated with atropine, temporary pacemaker therapy may be required.

Hypotension, defined as a systolic blood pressure below 90 mm Hg or systolic blood pressure 30% below baseline, is seen in 60–80% of patients with an acute cervical SCI. Although the optimal treatment of hypotension after SCI has not been clearly established, it is recommended that the mean arterial pressure be maintained at ≥85 mm Hg for the first 7 days following acute SCI.[97,139] Because autoregulation is lost after SCI, judicious use of fluids and vasoactive medications are crucial for the correction of hypotension and optimal preservation of neurologic function. Although hypotension is initially treated with fluid therapy, caution should be exercised to limit the overall volume of fluid administered, because patients are prone to develop cardiogenic and noncardiogenic pulmonary edema. If hypotension persists despite adequate fluid administration, vasopressor or inotropic therapy should be promptly instituted. The institution of acute SCI management protocols have been associated with neurologic functional improvement, reduced ICU days, fewer hospital days, fewer ventilator days, and reduced complications.[140]

When utilizing vasopressors to treat hypotension in patients with neurogenic shock, potent intravenous α-agonist agents (norepinephrine, phenylephrine) are the agents of choice. Careful consideration of the clinical effects of vasopressor use is recommended, because substantial increases in cardiac afterload may impair cardiac output and precipitate left ventricular failure. Consequently, an inotropic agent can be added to optimize spinal cord perfusion. Invasive (or newer noninvasive) hemodynamic monitoring is recommended for guiding the treatment of persistent hypotension in the context of neurogenic shock. Evidence exists to support improvement in neurologic outcome in SCI patients in whom hemodynamics are managed aggressively during the first 3 to 6 days following injury when spinal cord edema is maximal.[97]

Isotonic crystalloid is the initial fluid of choice in the treatment of neurogenic shock. The use of hypertonic saline may have additional benefits in the initial resuscitation phase after SCI. Experimental data indicate that the administration of hypertonic saline after experimental SCI attenuates cord swelling and edema, improves SCBF, and preserves spinal cord function;[141] definitive clinical studies, however, are lacking.

Cardiac dysrhythmias are frequently observed following SCI in both experimental and clinical reports. In an experimental

model of extradural SCI,[142] sinus tachycardia was noted, followed by striking electrocardiographic changes consisting of sinus pauses, a shifting sinus pacemaker, nodal escape beats, brief runs of atrial fibrillation, multifocal ventricular premature contractions, ventricular premature contractions, ventricular tachycardia, and ST-T wave changes. Atropine or bilateral vagal nerve section abolished all ectopic atrial and ventricular rhythm abnormalities but did not alter the sinus tachycardia. Propranolol abolished the tachycardia and ST-T wave changes.

In a clinical report investigating the incidence of cardiovascular abnormalities in 71 consecutive patients with SCI,[138] persistent bradycardia was observed in all 31 patients with severe acute cervical SCI, in 6 of 17 (35.3%) patients with mild cervical SCI, and in 3 of 23 (13%) patients with thoracolumbar injury. Primary cardiac arrest requiring cardiopulmonary resuscitation occurred in 16% of the 31 patients with severe cervical SCI. The frequency of bradydysrhythmias was maximal on day 4 after injury, with all abnormalities resolving over a 14-day to 6-week period. The cardiac abnormalities are attributed to the acute autonomic imbalance resulting from a disruption of sympathetic pathways while the parasympathetic influences via the vagus nerve remain undisturbed. In patients with chronic SCI, the risk of cardiac dysrhythmias decreases with time from injury and eventually disappears.

Gastrointestinal System

Gastrointestinal complications are seen in up to 11% of patients after SCI and include ileus, gastric atony, bowel obstruction, constipation, abdominal bloating, fecal incontinence, pancreatitis and acalculous cholecystitis.[143] Excessive gastric dilation may occur after acute SCI, resulting in gastric distention that places the patient at risk for regurgitation and aspiration. Early placement of a nasogastric tube may help in limiting distention, reducing the risk of regurgitation and minimizing adverse effects on the diaphragm and pulmonary system. Gastric emptying rates are often decreased in patients with SCI; thus, patients should always be considered to be at increased risk of gastric regurgitation.

The incidences of gastritis, stress ulceration, and gastrointestinal hemorrhage are increased after SCI, particularly in patients requiring mechanical ventilation and those in whom high-dose corticosteroids have been administered. In response, therapy with either H_2 blockers or proton pump inhibitors are instituted as prophylactic treatment upon admission and continued for 4 weeks.[144]

Neurogenic bowel refers to the changes in gastric and intestinal motility that often occur in patients following tetraplegic SCI. Temporary loss of bowel reflex activity, increased colonic transit time, and alterations in anal sphincter tone that occur, combined with the use of narcotics and immobility, are contributory to the occurrence of ileus and constipation following SCI. Accordingly, an effective bowel program is essential in the management of neurogenic bowel.[145,146]

Genitourinary System

During the acute stages of SCI (spinal shock), abnormalities of bladder emptying (termed neurogenic bladder) are present; this period lasts about 3 weeks post injury. In response, early insertion of an indwelling urinary catheter (Foley catheter) facilitates bladder emptying and allows accurate recording of urinary output. Neurogenic bladder predisposes the patient to persistent urinary problems, which include recurrent urinary tract infections, bladder stones, nephrocalcinosis, and recurrent bouts of urosepsis.[147]

Temperature Control

The body temperatures of patients with complete SCI tend to approach that of the environment because of the inability to conserve heat in cold environments by vasoconstriction or to sweat in hot ambient conditions. Consequently, such patients are prone to hypothermia in situations in which the ambient temperatures are lower than normal body temperature. Although normal to mild hypothermia is the goal, hyperthermia should be aggressively treated.

Coagulation

Venous thromboembolism (VTE), a term referring to both DVT and pulmonary embolism, occurs commonly in SCI, arising in 0.5–4.6% of patients, with estimates as high as 8–10%;[148–150] VTE is the third leading cause of death in these patients.[150,151,153] VTE occurs more often with complete SCI and thoracic injury. Additional risk factors for VTE include advanced age, an associated lower extremity fracture, and inadequate thromboprophylaxis.[150] The diagnosis of VTE is made from clinical suspicion combined with support from a variety of diagnostic methods, including D-dimer levels, venography, color flow duplex imaging (CFDI), CT angiography, and pulmonary angiography. The high incidence of VTE in patients with SCI necessitates the institution of prophylactic treatment soon after injury (i.e., 72 hours), with continuation of therapy for a minimum of 3 months. Recommended prophylactic treatment for the prevention of VTE includes pharmacologic therapy (low-dose unfractionated heparin-LDUH or low-molecular weight heparin-LMWH) combined with mechanical prophylaxis using intermittent pneumatic compression devices.[150] An effective treatment plan can reduce the occurrence of VTE to 5%. Consensus recommendations on the prevention of VTE in patients with SCI have been recently published and serve to guide therapy.[150,152]

Hyperreflexic Syndromes

Hyperreflexic syndromes are caused by hyperactive spinal reflexes without the tempering effect of modulating cortical, brainstem, and cerebellar influences. This "mass reflex" may make the management of the unanesthetized patient difficult.

Autonomic Hyperreflexia

Autonomic hyperreflexia, which occurs in 85% of patients with spinal cord transections above T5 in whom the splanchnic outflow remains intact, is secondary to autonomic vascular reflexes, which usually begin to appear about 2–3 weeks after injury. Afferent impulses originating from bladder or bowel distention, childbirth, manipulations of the urinary tract, or surgical stimulation are transmitted along the pelvic, pudendal, or hypogastric nerves to the isolated spinal cord and elicit a massive sympathetic response from the adrenal medulla and sympathetic nervous system, which is no longer modulated by the normal inhibitory impulses arising from the brainstem and hypothalamus. Vasoconstriction occurs below the lesion; reflex activity of carotid and aortic baroreceptors produces vasodilation above the lesion, which is often accompanied by bradycardia, ventricular dysrhythmias, and even heart block. The hypertension may be treated with direct-acting vasodilators (e.g., sodium nitroprusside), β-blocking agents (e.g., labetalol, esmolol) in combination with alpha blockade, calcium channel blocking agents (nicardipine), or ganglionic blocking agents (e.g., trimethaphan). Sedation or topical anesthesia does not appear to attenuate the hypertensive response, but deep general, epidural, or spinal anesthesia is effective.

Infections

Infection is the leading cause of death in patients with SCI, with pneumonia and urosepsis the leading sources of serious infections. The overall incidence of pneumonia in SCI is reported to be 55%, with an incidence of 60–70% in complete, compared to 20–30% in incomplete cervical SCI.[154] Adequate pulmonary

secretion clearance, use of a rotational bed, institution of ventilator-associated pneumonia prevention strategies, and early use of broad-spectrum antibiotics in patients demonstrating the typical signs and symptoms of pneumonia will reduce morbidity and mortality. Urinary tract infections (UTIs) are another common complication in SCI, with catheter-associated UTI (CAUTI) and neurogenic bladder being the most common etiologic factors. Attention to a strict urinary catheter insertion process and early catheter removal will reduce the risk of infection.

Pressure Ulcers

Decubitus pressure ulcers readily develop in paralyzed patients as a result of direct pressure effects, reduced tissue perfusion, and limited mobility. The use of rotational beds, frequent patient turning, good skin care, foam padding of bony prominences, or air floatation beds can help prevent pressure ulcers. If a pressure ulcer is identified, early care is essential in healing.

Chronic Pain Syndromes

Pain following traumatic injury to the spinal cord is very common, with a prevalence of SCI-related chronic pain ranging from 66% to 79% of patients.[155,156] Chronic pain is defined as pain that persists for more than 6 months following SCI. The International Spinal Cord Injury Pain Classification (ISCIP) has been widely adopted as a common approach to the management of chronic SCI pain syndromes.[157] The ISCIP divides the pain type into nociceptive pain, neuropathic pain, other pain, and unknown pain types. Treatment is typically multimodal, utilizing a combination of pharmacologic medications, physical and occupational therapies, psychological treatments, and invasive therapies. Pharmacologic treatments may require a variety of medications, including opioids and neuropathic agents such as pregabalin. The underlying pathophysiologic mechanism helps to guide the treatment choice. Complete elimination of chronic pain is not to be expected; however, reasonable control of symptoms is achievable utilizing the management strategies mentioned.

Summary

The perioperative care of the patient with an acute SCI represents a complex challenge for anesthesiologists. A fundamental knowledge of the initial neurologic assessment and acute medical management strategies in the patient with SCI will facilitate the limitation of further neurologic deterioration (Box 21.6). Moreover, a familiarity with the complications associated with chronic SCI (Table 21.7) can facilitate better preoperative assessment and perioperative management approaches.

BOX 21.6 Summary of Medical Management Guidelines for Acute Spinal Cord Injury

Important General Points

- Any patient sustaining traumatic injuries resulting in significant head or facial injuries, severe penetrating injuries in proximity to the spine, multiple blunt trauma, crush injuries, or significant acceleration or deceleration injuries should be suspected of having an unstable spinal injury (SCI).
- Spinal injuries may occur at multiple levels. Immobilization of the head and neck should be performed until a spinal injury is excluded.

Initial Management Points

- Initial management involves limiting any further injury to the spine and spinal cord through careful immobilization of the spine. This is best accomplished initially by placing the patient on a spinal board with the neck in a neutral or slightly extended position, immobilizing the neck by placing sandbags on either side of the head, and securing the head to the spinal board by placing 3-inch adhesive tape over the forehead and attaching it to either side of the spinal board. A cervical collar also may be used but provides no further spinal protection.
- Respiratory failure should be identified rapidly, and any patient with obvious signs of respiratory distress, such as cyanosis, apnea, severe paradoxic breathing pattern, or airway obstruction, should have an oral airway placed with assisted or positive-pressure ventilation. This should be followed with endotracheal intubation via either an orotracheal or nasotracheal route stressing in-line manual immobilization (not traction). If endotracheal intubation is difficult and the patient is deteriorating, a laryngeal mask airway should be temporarily inserted until an emergency cricothyrotomy or tracheostomy can be performed.
- Hemodynamic instability is common in SCI because of the sympathectomy with resulting venous pooling. Hypotension should be identified and treated first with vasopressors, if needed, until further hemodynamic monitoring can guide therapy. As autoregulatory ability is lost after spinal cord injury, aggressive blood pressure control is essential with the goal of maintaining the blood pressure in the normal to slightly increased range (i.e., mean arterial pressure of ≥85 mm Hg). Patients with SCI are susceptible to fluid overload and pulmonary edema; thus indiscriminate administration of fluids for blood pressure support should be avoided. It is always important to consider hemorrhagic shock as the cause of hypotension and rule it out by appropriate examination and testing.
- Bradycardia is nearly universal in high spinal cord injuries and should be treated with atropine if associated with hypotension. Occasionally, a temporary pacemaker is needed.
- Gastric atony resulting in significant gastric distention is common in patients with SCI; thus a nasogastric tube for decompression is indicated early on to decrease the chances of regurgitation and to facilitate oxygenation.
- A physical examination, including a pointed neurologic examination, should focus on the patient's mental status, motor and sensory function (pinprick and light touch), and rectal tone. Frequent repeat neurologic examinations should be performed to detect deterioration in neurologic status. Following the new international standard for neurologic examination of the spinal cord-injured patient (American Spinal Injury Association grades and motor sensory scores) is important.
- Radiologic examination of the patient with potential spine injury should be carried out expeditiously. Computed tomography (CT) is the imaging test of choice for identification of bony spinal injuries, including spinal canal encroachment, facet joint dislocations, and occipital-C1 and C7–T1 vertebral injuries. A cervical 3-view radiographic series of films including a cross-table lateral (with visualization of C7–T1) anteroposterior (AP) and odontoid (open mouth) views of the cervical spine is appropriate in the absence of CT. Additional lateral and anterior–posterior (AP) plain films of the thoracic and lumbar spines are indicated for multiple trauma patients with a history and physical examination suggestive of thoracolumbar injury. Magnetic resonance imaging is often carried out after the initial stabilization of the patient and is superior for visualizing spinal cord parenchyma, longitudinal ligaments, nerve roots, and intervertebral disks.
- Steroid therapy is no longer recommended as treatment therapy in patients an acute spinal injury and neurologic abnormalities.
- Closed reduction of spinal dislocations, if present, is attempted using various traction devices as soon as the initial examination and radiologic testing are completed.

Table 21.7 Summary of Medical Problems in Patients with Chronic Spinal Cord Injury

System	Abnormality	Relevant Comment
Cardiovascular	Autonomic hyperreflexia, decreased blood volume, orthostatic hypotension	Patient is susceptible to hypertensive crisis if spinal cord injury level is above T5; positional changes and intrathoracic pressure may cause hypotension
Respiratory	Muscle weakness, decreased respiratory drive, decreased cough	Patient is susceptible to bacterial pneumonia and may be difficult to wean from mechanical ventilation
Muscular	Proliferation of acetylcholine receptors, spasticity	Hyperkalemia from succinylcholine
Genitourinary	Recurrent urinary tract infections, altered bladder emptying	May lead to renal insufficiency, pyelonephritis, sepsis, or amyloidosis
Gastrointestinal	Gastroparesis, ileus	Patient is susceptible to aspiration
Infectious	Urinary tract infection, pneumonia, decubitus ulcers, sepsis	Watch for subtle signs of infection and sepsis; questionable risk of seeding of an infection from invasive monitoring
Skin	Decubitus ulcers	Skin care essential; foam padding for bony prominences; frequent turning
Hematologic	Anemia, risk of deep vein thrombosis (DVT) or pulmonary embolism (VTE)	DVT prophylaxis; ≥3 months of anticoagulation if DVT/VTE diagnosed
Bone	Bone density	Osteoporosis, hypercalcemia, heterotopic ossification, and muscle calcification
Central nervous system	Postoperative pain, chronic pain	Perioperative pain difficult to manage; chronic pain syndromes common

ANESTHETIC CONSIDERATIONS IN SPINAL SURGERY

Preoperative Evaluation and Preparation

General

Preoperative considerations derive from the overall medical condition of the patient and the specific procedure that is planned. Patients presenting for surgery of the spine may manifest peripheral neuropathy, paraplegia, or spine instability, each with its attendant complications and anesthetic considerations. A comprehensive and coordinated anesthetic plan involving the surgeon and anesthesiologist that addresses the need for neurophysiologic or invasive monitoring (or both), the optimal approach to securing the airway, patient positioning, fluid requirements, special maneuvers such as an intraoperative "wake-up" test, and timing of tracheal extubation must be formulated in advance (Box 21.7).

Airway Evaluation

The airway of the patient presenting for elective spinal surgery requires meticulous assessment, perhaps more so than for any other operation. Particular attention should be paid to the range of motion of the neck and to the presence of any neurologic symptoms or pain during such movement.

The initial airway evaluation is made by means of a general survey of the patient's head and neck. Obvious problems such as morbid obesity, short neck, cervical collars, and any breathing difficulties (e.g., stridor) should be noted. The presence of any craniofacial abnormalities may suggest a potentially difficult airway. The presence of a full beard may make mask ventilation more difficult. Mouth opening, a function of the temporomandibular joint, should be assessed. The extent of mouth opening is often related to the ease of laryngoscopy. Limited mouth opening can make visualization of any laryngeal structures challenging. The presence of loose teeth

BOX 21.7 Anesthesia-Related Issues in the Management of the Acute Spinal Cord Injury Patient Undergoing Surgical Therapy

- Early surgical therapy for spine injuries focuses on the limitation of secondary spinal cord injury in patients with progressive neurologic deficits due to spinal instability or in patients with the failure of closed reduction.
- Anesthetic concerns should consider a technique of securing the airway that limits spine movement.
  - Manual in-line stabilization may be indicated with direct laryngoscopy.
  - An awake intubation may be the safest technique to limit neurologic injury.
- Anesthetic induction and maintenance techniques should select anesthetic agents and doses that support blood pressure and minimize cardiac depression.
- Hemodynamic monitoring is recommended for frequent determination of blood pressure, central venous pressure, arterial blood gas analysis, hemoglobin levels, and blood glucose.
- Meticulous attention to fluid management utilizing goal directed fluid therapy is recommended to avoid fluid overload.
- Bradycardia is treated with appropriate chronotropic agents (i.e., dopamine) and hypotension is treated with fluids, to a state of euvolemia, and then the use of vasoactive medications with alpha agonist properties.
- Following surgery, extubation should be carefully considered in the context of the level of spinal injury. Patients with a spine injury resulting in an acute cervical spinal cord injury should be left intubated and transferred to the intensive care unit for further treatment.

should be noted and documented on the record. Next, the oral pharynx is examined, with special notation made of the size of the tongue in relation to the mouth opening. During mouth opening, the ability to visualize the faucial pillars, soft palate, and base of the uvula with the tongue protruded maximally (Mallampati classification) has been shown to be an accurate predictor of difficulty with direct laryngoscopy and should be documented.

Patients with rheumatoid arthritis, cervical myelopathy, or spinal cord injury are at an increased risk for further neurologic injury if a controlled approach by an experienced anesthesiologist is not performed. Moreover, any patient with moderate-to-severe limitation caused by mechanical or neurologic restrictions should be considered for an awake intubation under local anesthesia to minimize movement of the head and neck. If an awake intubation is considered optimal, a detailed discussion should take place with the patient regarding the steps that will be required and in assuring the patient that care will be taken to minimize discomfort. Patients with only mild limitation of movement, in which a difficult intubation is not anticipated, may undergo anesthesia induction prior to laryngoscopy, depending on the comfort level of the anesthesiologist. However, it should always be brought to the patient's attention that the potential for further neurologic injury exists, and the option of performing an awake intubation should be offered.

For patients with spinal trauma who are presenting for urgent or elective surgery, the stability of the cervical spine injury should be determined prior to the performance of the surgical procedure and anesthetic induction. In the patient with cervical spine instability scheduled for emergency surgery, the spine should be immobilized before anesthetic induction. Several alternative means of intubating the trachea should be planned for and immediately available in the event that airway management becomes difficult.

Pulmonary Evaluation

Patients presenting for spine surgery may have significant pulmonary disease related to the specific spine abnormality or to other preexisting risk factors, including smoking, obesity, asthma, chronic obstructive lung disease (COPD), and pulmonary tumor. In the evaluation of the pulmonary system, a focused history and physical examination are important in eliciting evidence of pulmonary disease. A chest radiograph is indicated for any patient undergoing thoracotomy for spine surgery or for any patient with the signs and symptoms of acute pulmonary disease. Arterial blood gas analysis is reasonable in any patient with evidence of significant pulmonary dysfunction, with spinal deformity, or with morbid obesity.

Scoliosis may cause a significant restrictive lung defect; as such, pulmonary function should be optimized prior to surgical correction of scoliosis (or any major spine surgery). Preoperative baseline spirometric tests (pre- and post-bronchodilator) and arterial blood gas analysis are reasonable for any patient with serious pulmonary disease and in individuals with advanced scoliosis. Upper thoracic spine surgery has a greater impact on postoperative pulmonary function than lower thoracic or lumbar spine surgery; thus, optimization of pulmonary function is particularly vital for patients undergoing a planned upper thoracic procedure.

Cardiac Evaluation

Evaluation of the cardiac system should focus on identification of heart disease and the stability of the disease. A history and physical examination will identify most significant abnormalities. Cardiac risk assessment must consider the type of surgery (low, intermediate, or high risk), the level of activity, and, most importantly, the presence of key risk factors.[158]

The American College of Cardiology/American Heart Association (ACC/AHA) recently published updated guidelines on the perioperative cardiovascular evaluation and care for noncardiac surgery.[159] The Revised Cardiac Risk Index (RCRI), the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest (MICA) risk prediction tool, and the ACS NSQIP Surgical Risk Calculator are all included as part of the latest 2014 ACC/AHA algorithm for preoperative cardiovascular evaluation before noncardiac surgery.[158–161] The RCRI has been a part of preoperative cardiac risk assessment since Lee et al. published their landmark article in 1999.[159] The usefulness of the RCRI has been repeatedly validated in multiple studies and remains a common tool for cardiac risk stratification before noncardiac surgery. In instances in which the risk assessment tools indicate high perioperative ischemic risk, a discussion with the patient and the perioperative team can determine whether further testing will impact clinical decision-making. If so, then preoperative ischemic testing is appropriate. Otherwise, a strategy focusing upon perioperative heart rate control and utilization of goal-directed medical therapy is recommended.[159]

Patients with a history of heart failure or in whom heart failure is suspected on the basis of cardiomegaly seen on chest radiograph have very high perioperative morbidity and mortality. As such, these patients may benefit from a preoperative cardiac echocardiographic examination (if not performed within the past year) to better define the type of cardiac pathology and overall function.

Neurologic Evaluation

Patients presenting for spinal surgery should be carefully evaluated for a preexisting neurologic deficit. This assessment should be documented for comparison with the postoperative condition. The neurologic deficit, its duration, and its extent may influence other organ systems, as noted previously. If possible, the patient should demonstrate positions or describe conditions that exacerbate his or her neurologic symptoms; precautions should be taken to avoid these movements during surgery. The presence of neurologic deficits may affect the choice of anesthetic drugs and adjuncts, such as the use of muscle relaxants. Autonomic dysreflexia is likely in patients with SCI above T6 after 3 weeks of injury (sometimes sooner).

Laboratory Studies

The laboratory studies obtained for surgery are individualized to each patient. Although certain routine tests are applicable to all patients preparing to undergo a spine operation, additional studies may be indicated as guided by medical history and physical examination (Box 21.8). A 12-lead electrocardiogram (ECG) is appropriate for all healthy patients ≥50 years of age, and at any age if the patient has known cardiac disease or risk factors for it. Although age alone is no longer recommended as the sole determinant of the need for a preoperative ECG, particularly for low-risk surgical procedures, it has value in patients undergoing intermediate to high-risk spinal surgeries.[159]

Pharmacology

Medications administered to patients with an acute spinal injury must account for the presence of hypotension, predominant vagal tone with bradycardia, relative hypovolemia, altered cardiac rhythms, and left ventricular dysfunction. Additionally, opioid tolerance is often present in patients with

BOX 21.8 Preoperative Laboratory Values of Interest

Basic Laboratory Values
- Hematocrit
- Hemoglobin level
- White blood cell count
- Platelet count

Specific Laboratory Values
- Blood urea nitrogen
- Serum creatinine level
- Serum electrolytes
- Prothrombin time
- Partial thromboplastin time
- Fibrinogen
- Platelet count
- Electrocardiogram
- Chest X-ray film
- Arterial blood gases
- Pulmonary function tests (spirometry)

Intraoperative Monitoring Techniques for Spinal Surgery

Noninvasive Monitoring
- Electrocardiography
- Blood pressure measurement
- Pulse oximetry
- End-tidal carbon dioxide
- Temperature
- Brain-function monitor (e.g., bispectral index monitor)

Invasive Monitoring
- Urine output
- Arterial blood pressure
- Central venous pressure
- Pulmonary artery pressure
- Cardiac output
- Mixed venous oxygen saturation
- Neurophysiologic monitoring

spinal disorders and other neurologic conditions; this possibility should be considered in the administration of perioperative opioids (i.e., larger overall doses may be required). Chemoprophylaxis for DVT prevention is standard therapy for patients with SCI; the decision to use regional anesthetic techniques in this instance must be tempered by the slight risk of hematoma formation and spinal cord or nerve compression and injury.

An important anesthetic consideration in patients with a preexisting neurologic deficit is the effect of succinylcholine on denervated muscle. Succinylcholine normally causes a muscular depolarization with resultant relaxation. In denervated muscle, motor end plate receptors proliferate, and succinylcholine then produces an exaggerated response with a very large release of potassium into the circulation.[163] This acute increase in serum potassium may cause cardiac dysrhythmias, cardiac arrest, or death. Although it is generally agreed that succinylcholine can be administered to patients within the first 24 hours following an acute SCI, it is recommended that its use be avoided for up to 9 months after SCI.[163,164]

Finally, patients with chronic SCI may have altered pharmacokinetics with various medications; such patients generally demonstrate an increased ratio in the size of extravascular to intravascular albumin pools, decrease in total body water, and an increase in body fat content.[162] These factors should be considered when administering medications to patients with chronic SCI.

Premedication

The necessity for premedication and the drugs chosen depend largely on the perceived or stated level of anxiety of the patient, the medical condition of the patient, and aspects of the operation and anesthetic that may be affected. In general, premedication is optional and should be prescribed at the discretion of the anesthesiologist and the patient. A small dose of a potent intravenous benzodiazepine may be considered desirable if the patient is particularly anxious, and narcotic analgesics may be valuable if the patient is in pain.

Airway Management for Cervical Spine Surgery

Patients with disease of the cervical spine have an increased incidence of difficulty with laryngoscopy, approaching 20% in one report.[165] In particular, patients with occipito-atlanto-axial complex disease have a higher prevalence of difficulty than those with disease in the subaxial (C3–C7) cervical spine. The best single radiographic predictor of difficulty is reduced separation of the posterior elements of C1 and C2 on lateral views, whereas the Mallampati classification is the best single clinical predictor of a difficult airway.[165] For patients with symptomatic spinal stenosis (cervical myelopathy), initial airway management should consider the benefits of an awake fiberoptic intubation or induction of general anesthesia with the head stabilized and intubation performed under fiberoptic guidance with the use of spinal cord monitoring. For most other patients scheduled for cervical spine surgery who have a reasonable range of motion, the difficulty with intubation is no greater than with other types of surgery. For all patients with cervical spine disease, documentation of a preinduction mental status and neurologic examination is essential to ensure that further injury has not occurred during the intubation and positioning process.

One of the most challenging airways that anesthesiologists face is that of a patient with acute cervical spine injury. After a traumatic injury, patients who are awake, alert, and without neck pain or tenderness to palpation have minimal potential of cervical spine injury. However, a comatose or intoxicated patient is assumed to have a cervical spine injury until a full diagnostic evaluation can be completed and expertly reviewed. While secondary SCI resulting from airway management techniques is a valid concern, there are few case reports of neurologic injury following tracheal intubation in patients with unstable spine injuries.[166]

Although the indications for endotracheal intubation in the setting of a spine injury are well defined and often clinically apparent, there is a lack of general consensus regarding a superior intubation technique that will facilitate rapid airway securement while avoiding further neurologic injury. In this context, a basic knowledge of airway maneuvers and the effects that such maneuvers have on craniofacial structures and cervical spine motion is essential for avoiding airway mishaps that may worsen neurologic injury.[167,168] Since the current published literature does not clearly demonstrate a particular intubation technique to be better than another, the emphasis in airway management is upon the operator expertise and skill on a case-specific basis. Factors to consider in initial airway management of the potentially cervical spine-injured patient include urgency of airway intervention and whether there is time for adequate radiographic cervical spine evaluation; the presence of associated facial injuries or soft tissue injuries of the neck that may distort the normal airway anatomy and necessitate awake or surgical airway management; the presence of a basilar skull fracture or mid-face fracture that would contraindicate nasal tracheal intubation; whether the patient is awake and cooperative or possibly uncooperative as a

result of alcohol or drug use; head injury; and the expertise of the operator in the different airway management techniques, including direct laryngoscopy, nasal intubation, fiberoptic intubation, and surgical airway.

Maintaining a patent airway and adequate oxygenation in a patient with possible cervical spine injury may require bag-mask ventilation, an oral or nasal airway, chin lift or jaw thrust, and oral or nasotracheal intubation (which is often accomplished in a rapid-sequence manner with cricoid pressure). All of these modalities of airway support have the potential for moving the cervical spine even when a cervical collar is in place (Table 21.8).[169–171] The classic sniffing position requires flexion of the lower neck on the chest and extension of the head on the upper neck. The majority of cervical motion in anesthetized normal patients undergoing direct laryngoscopy with a Macintosh blade is extension produced at the occipitoatlantal and atlantoaxial (C1–C2) articulations. The subaxial cervical segments (C2–C5) are displaced only minimally so the risk of direct laryngoscopy may vary with the level of cervical spine injury.[171–173] By inference, the upper cervical spine is at greater risk for secondary injury with laryngoscopy than the lower cervical spine where the majority of traumatic injuries occur. Thus, patients with unstable C1 or C2 injuries might be the most vulnerable to neurologic damage from atlanto-occipital extension. However, the manner in which motion is distributed over segments adjacent to and remote from the level of cervical spine injury has not been fully studied.

An increased risk of cord injury may occur due to improper immobilization of the spine after trauma. However, immobilization techniques (Table 21.9) can easily become the primary focus in resuscitation of patients at risk for cervical spine injury, delaying airway assessment, making orotracheal intubation more difficult, and endangering patients subjected to the risks of inadequate ventilation.[175] Ensuring adequate oxygenation and ventilation is always the first priority in patients following major trauma and should receive the greatest focus.

Neck-stabilizing cervical orthotic devices, such as hard and soft collars (Fig. 21.32), are commonly placed on trauma patients until the cervical spine is confirmed to be free of injury. Although these devices provide some degree of spine immobilization and patient comfort, they do not prevent both neck flexion and extension and thus do little to eliminate cervical motion, particularly during laryngoscopy.[170] Moreover, the anterior portion of the collar interferes with mouth opening during orotracheal intubation and increases the incidence of difficult laryngoscopic views.[184,185] Accordingly, to facilitate tracheal intubation the removal of these devices is recommended in combination with manual in-line immobilization (MILI).[176]

Immobilization techniques are associated with difficult laryngoscopic views. Cervical collars, tape, and sandbags

Table 21.8 Airway Management Techniques and Their Effects on the Cervical Spine

Maneuver	Condition	Result
Laryngoscopy	Normal, anesthetized	• Extension at the occipitoatlantal and C1–C2 articulations • C2–C5 displaced only minimally • Sniffing position-flexing lower neck on the chest and extending the head on the upper neck
	Cadaver, C5–C6 instability	• 3–4 mm widening of the disk space at the level of injury
Straight vs. curved blade	Normal, anesthetized	• No difference in cervical spine movement
GlideScope®	Normal, anesthetized	• Overall spine movement reduced 50% at C2–C5 as compared to curved blade
Bullard laryngoscope	Normal, anesthetized, in-line stabilization	• Overall cervical spine movement reduced at C2–C5 • Less extension at occipitoatlantoaxial complex but similar occiput–C5 extension compared with direct laryngoscopy with Macintosh blade if no manual in-line immobilization
Augustine guide	Normal, healthy	• Less spine extension than with direct laryngoscopy
Rigid indirect laryngoscopy		• Cervical spine movements less than with direct laryngoscopy • Better visualization of the glottis than direct laryngoscopy
Intubating laryngeal mask airway		• Exerts high pressures against upper cervical vertebrae with insertion and manipulation • May produce posterior displacement of upper cervical spine • For insertion, C5 and superior spinal segments flexed <2°; during intubation, C4 and superior segments flexed <3°; little movement of the spine above C3
Cricoid pressure	Normal, anesthetized, in-line stabilization	• Single-handed cricoid pressure causes vertical displacement of neck ≈ 5 mm, but no spine movement
Blind nasotracheal	Cadaver, C5–C6 instability	• Up to 2 mm subluxation but no increase in disk space; intubation >5 mm subluxation when neck is stabilized anteriorly by hand pressure
Airway support		
Chin lift/jaw thrust	Cadaver, C5–C6 instability	• >5 mm widening disk space at level of injury
Oral/nasopharyngeal	Cadaver, C5–C6 instability	• ≈2 mm widening disk space at level of injury
Mask ventilation	Cadaver	• Significant anteroposterior translation displacement with maximal flexion and extension of the head

Table 21.9 Cervical Spine Immobilization Techniques

Technique	Effect on Spine Immobilization
Cervical collar, sandbags, backboard, head tape	• Very effective method of limiting flexion, extension, rotation, and lateral bending; recommended by the American College of Surgeons for effective C-spine immobilization; makes orotracheal intubation much more difficult if left in place at time of intubation
Hard and soft collar	• Little effect on spine immobilization; allows moderate amount of head and neck extension; does not effectively eliminate movement of the neck during tracheal intubation; anterior portion of collar interferes with mouth opening; increases incidence of grade III or IV laryngoscopic view; alerts medical personnel to possibility of C-spine injury
Manual in-line immobilization (MILI)	• Reduces neck movement during intubation; recommended method of reducing neck mobility during tracheal intubation; head held in neutral position without axial traction; better view of larynx when anterior aspect of collar, if present, is removed before laryngoscopy
Axial traction	• Excessive axial traction may cause distraction and subluxation
Halo brace	• Most rigid immobilization technique of all the spinal orthoses; highly effective for skeletal fixation and in limiting motion of the upper cervical spine; limits both flexion–extension and lateral bending movements of the cervical spine by 96% and axial rotation by 99%; utilized in the setting of an unstable cervical spine; does not allow any neck movement making direct laryngoscopy very difficult; fiberoptic intubation is recommended (awake or after induction)

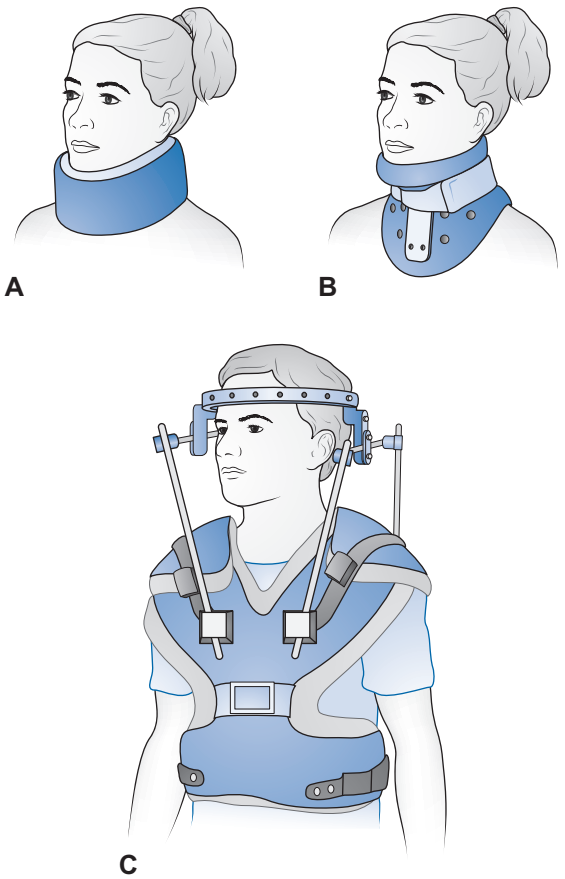


Fig. 21.32 Cervical orthoses. **A**, Soft cervical collar; **B,** Philadelphia-type reinforced cervical collar; **C,** halo brace.

result in a poor view of the larynx (grade III or IV) on laryngoscopy in more than half (64%) of patients immobilized in this manner.[175] MILI is a technique applied to patients with known or suspected cervical spine injury to limit movement of the head and neck during direct laryngoscopy or other similar procedures. MILI is carried out by having an assistant positioned at the head of the bed or just to the side of the patient providing immobilization of the head by placing the fingers on the mastoid processes and the hands holding the occiput steady.[168] In comparison to tracheal intubation with the collar, tape, and sandbags in place, MILI is associated with a better laryngoscopic view, mainly because of increased mouth opening.[172] MILI is associated with a grade 3 or 4 view in only 22% of patients, as compared with 64% in patients in whom collar, tape, and sandbags are in place.[175] Under normal conditions, the glottis is best visualized with 10 to 15 degrees of head extension (head tilt); with the use of MILI during laryngoscopy, head extension is limited an additional 4 to 5 degrees, which increases the difficulty of glottic visualization during direct laryngoscopy. Moreover, although MILI is effective in reducing neck motion during laryngoscopy, it does not totally eliminate spine movement.[170,175–180] Fortunately, the amount of airway movement during intubation utilizing MILI is small, and further neurologic injury is unlikely.[181,182]

As mentioned, all airway maneuvers cause some neck and cervical spine movement (see Table 21.8). Basic maneuvers, including the jaw thrust and chin lift, resulted in up to 5 mm of movement of the spine at the site of the cervical injury in a cadaver model with an unstable spine. In the same model, advanced maneuvers, including placement of an orotracheal tube using a straight or curved laryngoscope blade, an esophageal obturator airway, and a nasotracheal tube, produced 3–4 mm of disk space enlargement.[183] Hauswald et al.[184] examined the effect of basic airway maneuvers on cervical spine movement in traumatic arrest victims, observing that maximal cervical spine displacement was 2.93 mm for mask ventilation, 1.51 mm for oral intubation, and 1.20 mm for nasal intubation. Although mask ventilation resulted in more cervical spine movement than the other methods, the clinical significance of this finding is unclear.

Donaldson et al.[185] investigated spine motion during intubation in a cadaver model with an intact spine, and then following creation of an unstable C1–C2 segment. In the study, it was noted that the use of maximum neck flexion and extension maneuvers (as occurs with mask ventilation) narrowed the space available for the spinal cord (SAC) by 1.49 mm in the intact spine and by 6.06 mm in the unstable spine. Chin lift and jaw thrust reduced the SAC by 1.09 mm and 2.47 mm, respectively, and had the greatest effect in narrowing the SAC. Oral intubation and nasal intubation narrowed the SAC by 1.60 mm and 1.61 mm, respectively.[185] The researchers concluded that in an unstable C1–C2 spine injury, oral intubation had the same effect on

diminution of SAC as nasotracheal intubation and that the chin lift/jaw thrust maneuvers caused the most motion and hence the greatest effect on narrowing the SAC in the C1–C2 unstable spine.[185] Rigid indirect laryngoscopy is associated with less cervical spine movement and better glottic visualization than direct laryngoscopy, with the exception of the GlideScope device.

In general, cervical spine movement during laryngoscopy is associated with the greatest degree of movement in the upper cervical spine with superior rotation of the occiput and C1 and mild inferior rotation of C3–C5. The greatest motion is at the atlanto-occipital and atlantoaxial joints.[169] In contrast, the position of the cervical spine below C4 remains reasonably static during laryngoscopy.[174] Maximal movement of the spine during laryngoscopy is typically less than 5 mm with 2–3 mm of displacement. Such movements are very small and typically within physiologic ranges.[168] Specific blades available for direct laryngoscopy have minimal differences with respect to the effects on spine movement.[169,172,173,185–188] Video laryngoscopes, such as the GlideScope (Verathon, Inc., Bothell, WA) or the Airtraq (Prodol Ltd., Vizcaya, Spain) devices incorporate a digital camera in the tip of the blade that transmits images to a display monitor via a video cable. Compared with the curved Macintosh blade, the GlideScope improved the laryngeal view by one grade during laryngoscopy in normal patients wearing a cervical collar, while reducing spinal movement by 50%.[189] In another study, Robitalille et al.[190] found that the GlideScope did not significantly decrease movement of the nonpathologic cervical spine compared with direct laryngoscopy. Nevertheless, the use of a video laryngoscope remains an excellent laryngoscopic technique to use when limitation of spine movement is the goal; however, the time to intubation may be increased, so this must be kept in mind during emergency airway situations.[191]

Emergency Airway Management in the Cervical Spine-Injured Patient

For emergency situations, a variety of airway management plans are appropriate for patients with potential cervical spine injuries as no evidence has clearly demonstrated the superiority of any particular tracheal intubation technique over another. The urgency of the clinical situation is a primary factor in planning the airway management strategy. An updated management algorithm for the difficult airway has been published by the American Society of Anesthesiologists which can guide therapy;[192] a modified airway management algorithm for the patient with a suspected cervical spine injury is illustrated in Fig. 21.33.

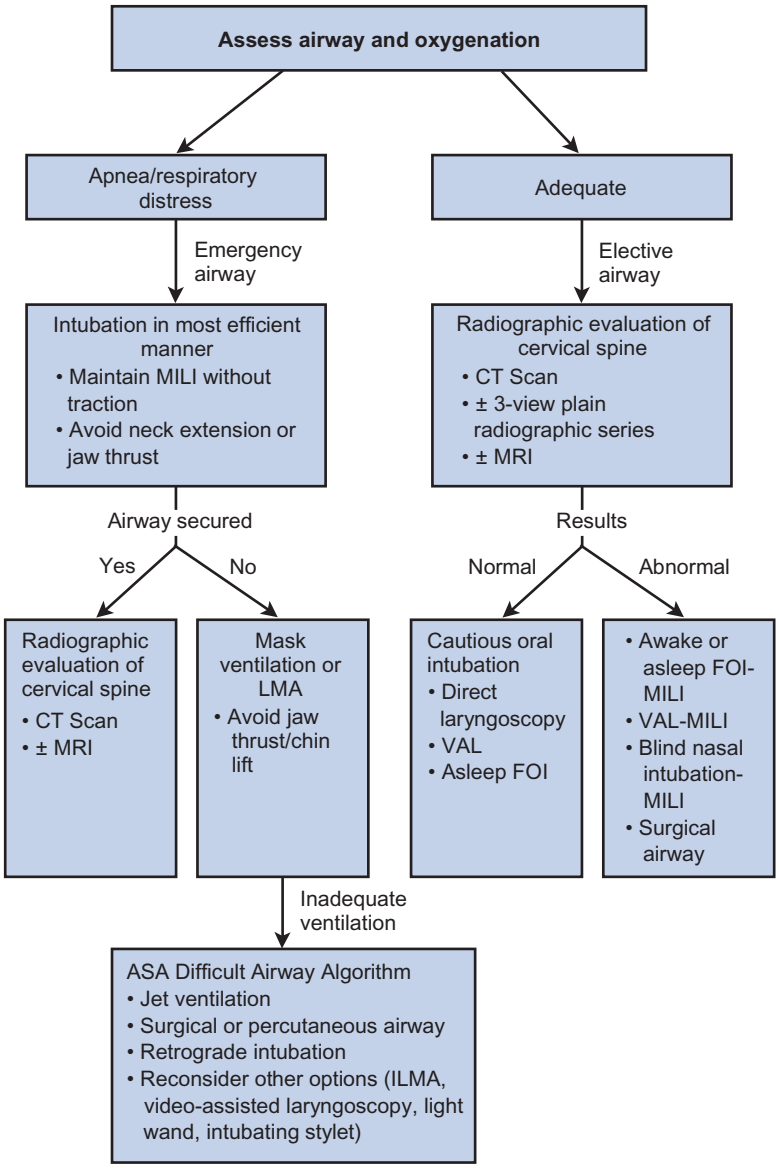


Fig. 21.33 Suggested airway management algorithm for a patient with a suspected cervical spine injury. ASA, American Society of Anesthesiologists; CT, computed tomography; LMA, laryngeal mask airway; MRI, magnetic resonance imaging; FOI, fiberoptic intubation; ILMA, intubating laryngeal mask airway.

Patients who need immediate airway control should initially receive oxygen by bag and mask with assisted ventilation. Although all of the techniques used to relieve airway obstruction have the potential of displacing the cervical spine (see Table 21.8), oxygenation and ventilation are a higher priority than the risk of neurologic injury. Succinylcholine may be used in emergency situations for muscular relaxation without apparent danger of hyperkalemia, if the spinal cord injury is less than 24 hours old.[163] The application of single- or double-handed cricoid pressure is appropriate to reduce the risk of pulmonary aspiration of gastric contents.[193,194] Depending on the force applied and whether the posterior aspect of the neck is stabilized, there is a risk of vertical displacement of the neck when bimanual application of cricoid pressure is used.[193] If direct laryngoscopy fails, the patient should be ventilated by mask, and a backup method for tracheal intubation should be attempted. Although many experts advocate direct laryngoscopy as the method of choice for immediate airway control in patients with actual or potential cervical spine injuries, others believe that selecting the airway technique with which the anesthesiologist has the most expertise is the preferred strategy.

As mentioned, head and neck stabilization techniques increase the difficulty of direct laryngoscopy and reduce visualization of the glottic structures. Moreover, facial edema and fractures, pharyngeal edema, and soft tissue injuries are common with cervical spine injuries, and fractures can cause hematoma and edema formation around the larynx, further increasing the difficulty of airway management. If laryngoscopy or other techniques fail and mask ventilation becomes inadequate, the practitioner should follow the American Society of Anesthesiologists (ASA) Difficult Airway Algorithm (see Fig. 21.33).[192] In the ASA algorithm, the laryngeal mask airway (LMA) is the initial intervention to be utilized in the event of a fail-to-intubate or fail-to-mask scenario. Although the safety of the laryngeal mask airway (LMA) in the cervical spine-injured patient has not been definitively determined, the presence of a cervical collar or use of MILI of the neck does not appear to interfere with placement of the LMA.[193] However, the LMA may be more difficult to position properly when MILI in combination with cricoid pressure is used. In one study,[195] not only was the LMA more difficult to place under these conditions, but also vocal cord identification through the LMA was not possible in many of the cases. This finding suggests that attempted tracheal intubation through the LMA, using a bougie or small endotracheal tube, may be extremely difficult. Ultimately, transtracheal ventilation, retrograde intubation, or cricothyrotomy may be required.

In situations where oxygenation and ventilation are initially assessed to be adequate, there is time to further assess the extent of injury to the cervical spine and to plan an elective method of airway management. If an unstable cervical spine injury is confirmed or suspected and tracheal intubation is necessary in a cooperative patient, an awake fiberoptic oral intubation, nasal intubation, or blind nasal intubation with topical anesthesia may be appropriate. However, awake intubation techniques are often unsuitable in traumatized, uncooperative patients who may be intoxicated or hemodynamically unstable. In this setting, a controlled oral intubation by an experienced laryngoscopist is appropriate.

If the patient is brought emergently to the operating room in a halo or traction device, any technique of tracheal intubation may be chosen as long as appropriate preparation for the potential difficult airway is assured. Because the halo or traction device prevents optimal airway positioning for direct laryngoscopy, an awake fiberoptic intubation in a cooperative patient, utilizing topical anesthesia and mild sedation (e.g., midazolam or dexmedetomidine), is safe and effective.

In summary, there is no clear evidence that any particular airway management technique enhances safety over other techniques in a patient with an unstable cervical spine. Although some authorities advocate an awake tracheal intubation in patients with an unstable spine injury to facilitate a neurologic evaluation before induction of general anesthesia, clinical evidence to support this approach is lacking.

Anesthesia Induction and Maintenance

Induction

Induction of anesthesia for spinal surgery involves many of the same considerations as those for any other general anesthetic. Concerns related to patient comorbidities should be addressed as appropriate. Another issue is often whether to induce anesthesia before or after positioning. Legitimate concerns arise regarding how best to ensure the protection of neurologic integrity during prone positioning when an area of the bony spine is unstable or there is another preexisting neurologic deficit. If spinal instability or disease is located in the cervical region and anesthesia is induced prior to positioning, it is important that every effort be made to keep the head and spine in a neutral position during the positioning of a patient. Another option is to perform an awake fiberoptic intubation with patient self-positioning to the prone position prior to anesthetic induction; this approach facilitates neurological examination and confirmation that no further neurologic injury has occurred during positioning.[196] Depolarizing muscle relaxants (succinylcholine) should only be used in the patient sustaining a spinal cord injury after consideration of the potential for a hyperkalemic response to drug administration. If nondepolarizing muscle relaxants are used for induction, short-acting agents are recommended in the instance in which spinal cord evoked response monitoring is planned.

Maintenance

The anesthetic technique chosen for the majority of surgical procedures on the spine should be based primarily on the patient's underlying medical condition, the anticipated intraoperative conditions, and the preference of the anesthetist. If neurophysiologic monitoring (e.g., spinal cord monitoring) is planned, an awareness of the effects of the various anesthetic agents on neurophysiologic testing is essential, and the anesthetic choices should be altered accordingly. Most importantly, a stable intraoperative anesthetic depth is essential so that any changes in evoked responses during spinal cord monitoring can be explained appropriately.

If an intraoperative wake-up test is desired, either a total intravenous anesthesia technique or a balanced technique consisting of low doses of a volatile agent together with opioids is effective. With the use of such regimens, the incidence of patient intraoperative awareness and recall of the awakening event is low.

Anesthetic Management of Patients with Acute Spinal Cord Injury

The level of SCI, severity of associated injuries, and preexisting medical conditions are factors to consider in selecting appropriate anesthetic agents and monitors for patients with acute SCI. The presence of neurogenic shock (hypotension, bradycardia), dysrhythmias, and myocardial dysfunction must be considered when choosing appropriate monitors; ensuring adequate spinal-cord perfusion is the most important goal.

The standard monitors recommended by the American Society of Anesthesiologists should be used; in addition, an arterial catheter, indwelling urinary catheter, and central venous or pulmonary artery catheter should be considered (see Box 21.7). The arterial catheter is particularly useful for intensive blood pressure management, following intraoperative arterial blood gases (ABG), and frequent monitoring of blood glucose and serum chemistries. Other useful monitors may include a cerebral hypnotic monitor and the precordial Doppler. Invasive hemodynamic monitoring devices that can follow cardiac output and mixed venous oxygenation saturation are particularly beneficial in patients with a high SCI and neurogenic shock.

Transesophageal echocardiography (TEE) may be selected to evaluate intraoperative myocardial function and anatomy. The decision to employ this modality must first consider several factors: the potential difficulty in placing the TEE probe with the cervical spine immobilized; the theoretical possibility of cervical spine movement when the relatively large transesophageal echocardiography probe is placed and moved in the esophagus to obtain views; and the potential for an associated esophageal injury in trauma patients with a high SCI.

Selecting the particular anesthetic technique for operations on the traumatized spine with acute SCI is of less importance than optimizing medical management during the procedure. To date, no evidence has been presented that conclusively favors one anesthetic agent or technique over another in the patient with acute SCI. However, maintenance of mean arterial blood pressure ≥85 mm Hg and an adequate cardiac output have been shown to prevent secondary injury to the spinal cord.[197] Adequate intravenous access is essential, particularly in patients undergoing a multilevel spinal fusion procedure, lengthy surgery (>4 hours), anticipated blood loss exceeding 1000 mL, and in the presence of multiple comorbidities.

Optimization of intraoperative cardiovascular function in patients with acute SCI is essential in avoiding further neurologic injury. Systemic arterial hypoxemia and hypotension (e.g., neurogenic shock) are common clinical sequelae of SCI. Loss of autoregulation coupled with hypotension and arterial hypoxemia may severely diminish spinal cord perfusion, leading to ischemia and secondary injury. Patients with a cervical SCI may be unusually sensitive to the myocardial depressant effects of anesthetics. Alpha-adrenergic agents, such as phenylephrine or norepinephrine (noradrenaline), are often utilized to support blood pressure; however, they may do so at the expense of increased afterload and a reduction in cardiac output. Careful consideration of these issues should be incorporated into the anesthetic plan.

Pulmonary dysfunction is common following acute cervical and upper thoracic SCI, and presents perioperative challenges. Patients have a predisposition to hypoxemia, typically require mechanical ventilation, and may have developed pneumonia. The incidence of neurogenic and cardiogenic pulmonary edema is increased and further aggravated by fluid overload, particularly during the early resuscitation period following injury (24–72 hours). Intraoperative ventilatory management should replicate the support required in the intensive care unit (ICU). If the preoperative level of ventilator support is high enough (PEEP ≥10 mm Hg), the patient may require the use of a specialized ICU ventilator during surgery; in such instances, TIVA will be required. Most patients with patients with cervical and high thoracic SCI should remain intubated after spine surgery as the ability to cough and maintain adequate ventilation is compromised; weaning from the ventilator can commence once full recovery from the anesthetic has been assured.

Meticulous fluid management is essential in patients with acute SCI undergoing spinal surgery. Effective fluid strategies include utilization of a goal-directed fluid therapy (GDFT) approach to limit excessive intraoperative fluid administration (≥3000 mL), avoidance of glucose-containing solutions, and the administration of isotonic balanced crystalloid solutions. The use of lactated Ringer's solution is not recommended as the relatively hypotonic solution (sodium, 130 mEq/L) may worsen spinal cord edema. Colloid solutions containing albumin are safe as part of the fluid strategy in patients with neurologic injury.[199,203,204]

Maintenance of intraoperative normoglycemia is imperative, as hyperglycemia in the setting of critical illness has been associated with an increase in morbidity and mortality. The blood glucose level above which neurologic risk is increased is unknown and likely varies among individuals; however, studies have demonstrated improved outcomes in critically ill patients with target blood glucose levels below 180 mg/dL.[205,206] Accordingly, the recommended strategy is to maintain intraoperative blood glucose levels below 180 mg/dL by the avoidance of glucose-containing intravenous solutions and frequent determination of blood glucose levels. In patients with persistent intraoperative hyperglycemia ≥180 mg/dL (i.e., two consecutive levels), a glucose-management strategy incorporating an insulin infusion is recommended with glucose levels monitored every hour.

Positioning

Spine surgery typically performed with the patient in one of three basic positions: supine, prone, or lateral decubitus. Each of these positions requires special considerations to prevent injury. Peripheral nerve injuries are one of the most common injuries encountered during spine operations in any of the positions. Avoidance of excessive arm abduction, preventing unnecessary pressure on nerves after proper positioning of the arms and lower extremities, appropriate padding of all pressure points including chest rolls for patients in the lateral decubitus position, neutral positions of the head and hips, properly functioning automated blood pressure equipment, and postoperative assessment for nerve injuries are recommended.

The lateral decubitus position is used for lateral approaches to the craniocervical junction, anterior approaches to the upper thoracic spine, and retroperitoneal approaches to the thoracolumbar junction and lumbar spine. In the lateral position, particular care must be directed to positioning of the dependent arm to prevent brachial plexus injury and vascular compression; the use of an axillary roll is thus recommended for most procedures in the lateral position. In addition, the nondependent arm is usually outstretched in front of the patient and should be supported on a pillow or padded armrest. The head should be positioned in a neutral position to avoid cerebral venous outflow and endotracheal tube obstruction, and it should be supported with a pillow or padded headrest.

The prone position is required for posterior spine surgery and is facilitated by the use of specialized surgical tables (Jackson Frame; Allen Advance Table), proning frames (Wilson Frame, Allen Bow Frame), and padding accessories (e.g., bolster supports, gel foam pads, chest rolls, prone head pillows) (Fig. 21.34). In general, the safety goals during prone positioning are to:

- provide adequate surgical exposure of the spine
- avoid abdominal compression, allowing for free movement of the abdomen and reducing vena caval pressure

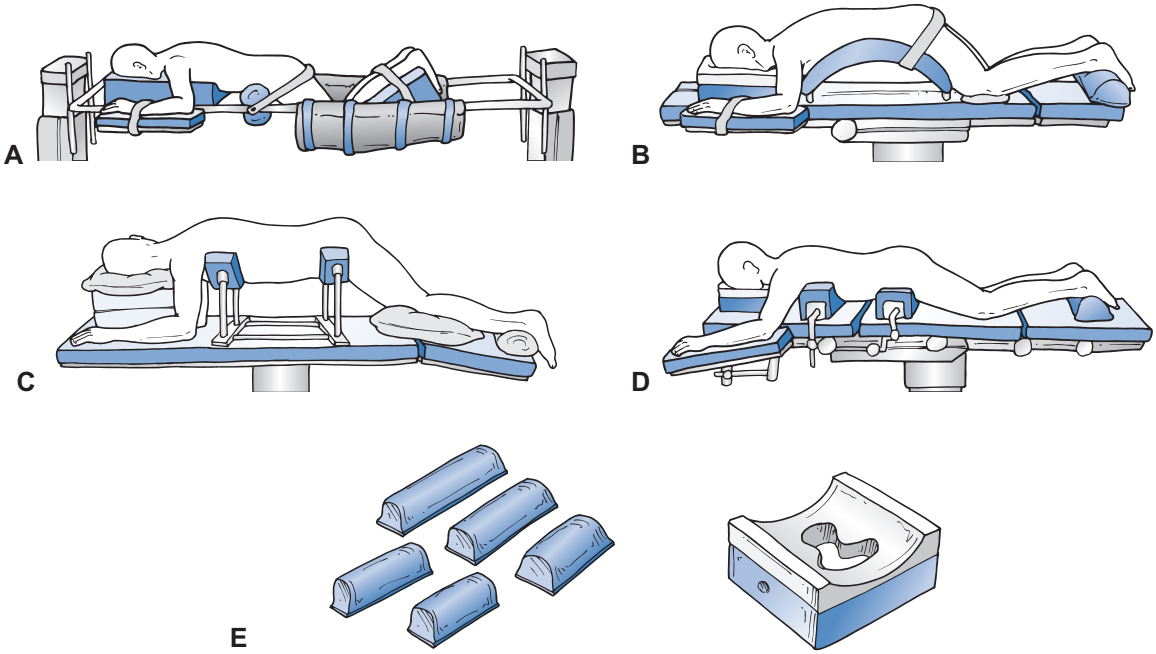


Fig. 21.34 Examples of equipment utilized for patients in the prone position undergoing spine surgery: **A,** Jackson frame; **B,** Wilson frame pad; **C,** Relton-Hall accessory frame; **D,** regular operating room table with bolster supports under sternum, iliac crest, and lower legs; **E,** gel foam pads and prone head pillows.

- avoid thoracic compression to facilitate easier ventilation and reduce excessive airway pressure, which may adversely affect cardiac output
- maintain normal positioning of the extremities to avoid compression or stretching of peripheral nerves
- provide adequate support for the head and face, reducing the potential for excessive nasal and ocular pressure
- provide liberal padding, thus avoiding pressure sores that otherwise may occur with long procedures.

Even with the safety goals in mind, potential complications inherent to the prone position include pressure necrosis and muscle breakdown (with myoglobinuria) from prolonged compression of tissues during lengthy operations, facial and airway edema, peripheral nerve injuries due to overstretch or pressure, visual loss, and inadvertent endotracheal tube malposition.

Head Position

Basic principles of head positioning include avoidance of hyperextension, hyperflexion, and extreme rotation of the cervical spine. Particular attention should always be directed to maintaining a neutral head position when placing a patient prone for spine surgery. For posterior approaches to the middle to lower thoracic, lumbar, or sacral spine, the head can be placed on soft foam or a gel pad with preconfigured cutouts or a horseshoe headrest that allows midline orientation of the face and head despite the prone position. The eyes should be carefully protected and undue ocular pressure avoided during surgery. In the prone position, the nose should be free from the surface of the table to avoid pressure-related sores.

During anterior cervical spine procedures, the surgeon may require traction on the head to distract the cervical vertebrae for placement of the bone graft for fusion. This maneuver should always be performed under the direct supervision of the surgeon, because excessive traction may result in stretching and ischemic damage to the cervical cord. Hyperflexion during cervical laminectomy using the posterior approach is a common occurrence, primarily because the surgeon must flex the head forward on the chest for adequate surgical exposure. This movement may put undue strain on the spine, in addition to restricting venous outflow from the head and face. Restriction of venous outflow from the face and head produces macroglossia and intracranial hypertension, respectively. In addition, sharp bending of the tracheal tube in the posterior pharynx during positioning may compromise the airway. To prevent this complication, sufficient space must be retained between the anterior angle of the mandible and the sternal notch. This space may be ascertained by the comfortable placement of at least two fingerbreadths in this space at peak inspiration after positioning.

Monitoring

Physiologic Monitoring

Surgical procedures on the spine are commonly associated with significant blood loss and extended operating times. Therefore, in addition to routine monitoring, anticipated hemodynamic conditions during an extensive surgery often require more intensive monitoring (see Box 21.8).

In general, invasive monitoring of arterial blood pressure is advisable for patients undergoing prolonged complex surgical procedures (>4 hours) in which moderate-to-heavy blood loss is anticipated; patients with significant cardiovascular and renal disease; and patients with serious pulmonary dysfunction or the intended use of intraoperative lung isolation techniques.

Some debate exists over the need to monitor patients for venous air embolism during spine surgery. The risk for venous air embolism is increased whenever the incision is elevated 5 cm or more above the level of the heart, and posterior spine approaches using the prone position result in a wound often located above that level. Venous air embolism has been reported during spine operations performed in the prone position, particularly during extensive surgical spine procedures associated with significant blood loss and bony dissections.[207–209] Accordingly, for spine procedures in which the surgical site is elevated above the level of the heart, and particularly when associated with the potential for substantial

blood loss, a central venous catheter and direct arterial pressure monitoring are suggested.[208,209]

Fluid Management and Blood Transfusion

Fluid management during spinal surgery reflects a balance between maintaining intravascular volume for adequate tissue perfusion and oxygenation of vital organs, and avoiding the venous congestion and interstitial edema that may occur with fluid overload. Surgery involving extensive exposure of the spine with denuding of bone, such as scoliosis repair or extensive spinal fusion and instrumentation procedures, may be associated with significant blood loss. Patients undergoing such procedures often receive large amounts of asanguineous fluid in addition to multiple blood products, with resulting increased lengths of stay in the intensive care unit. Utilization of a GDFT protocol, which defines and manages to intraoperative hemodynamic endpoints using dynamic and flow-based parameters (such as stroke volume variation, cardiac output, stroke volume), is associated with a reduction in total fluid administration and an improvement in outcome. Studies in patients undergoing high-risk surgical procedures indicate that GDFT is associated with reduced complications, including ileus, surgical site infections (SSI), acute kidney injury (AKI) urinary tract infection, respiratory dysfunction, and a reduced length of hospital stay.[210–213] In the context of spine surgery, GDFT is particularly beneficial in procedures involving a multilevel posterior spine decompression with fusion and segmental instrumentation, scoliosis spinal reconstruction, combined anterior and posterior multilevel spine operations, and in prolonged spine surgery in elderly patients with significant comorbidities; these factors appear to be the most significant in predicting length of hospital stay, operative time, intraoperative blood loss, and in the need for transfusion therapy.[214] Balanced isotonic crystalloid solutions, alone or in combination with colloid-containing fluids, are appropriate choices for intraoperative fluid therapy. In the resuscitation of critically ill patients, multiple studies comparing isotonic crystalloid versus colloid fluids have been unable to demonstrate worse outcomes in patients receiving albumin-containing colloids.[198–202] As such, fluid strategies that contain albumin solutions are appropriate in the setting of spine surgery, although recent evidence does strongly suggest that colloids containing hydroxyethyl starch should be avoided.[199,203,204] In the event that patients have received large amounts of intraoperative fluids, significant tissue edema is to be expected; thus, the safety of postoperative extubation should be carefully considered before the endotracheal tube is removed.

Significant intraoperative blood loss is a frequent occurrence during complex spine surgery. A predictive model of the potential need for blood transfusion during spine fusion operations has been reported.[215] In this model, important predictors of perioperative blood transfusion included preoperative hemoglobin levels, length of surgery, number of posterior spinal levels of instrumentation, and the surgical complexity of the spine procedure. Despite the known benefits of transfusion therapy in patients with hemorrhagic shock or profound anemic states, current studies have consistently identified an association between transfusion therapy and adverse reactions and immunomodulatory effects in both medical and surgical patient groups. In the setting of neurologic injury, the transfusion of red blood cells in patients without evidence of hemorrhagic shock has similarly demonstrated worsened outcomes, particularly when the hemoglobin is >10 g/dL.[216–218] A recent clinical practice guideline regarding red blood cell transfusion recommends adherence to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients, including those patients with preexisting cardiovascular disease.[219] In view of compelling scientific evidence indicating the dangers of red cell transfusion therapy, an appropriate perioperative strategy for patients undergoing spine stabilization surgery is the incorporation of a restrictive transfusion strategy with hemoglobin levels targeted at a range of 8–10 g/dL. This approach is prudent and scientifically sound, as long as the patient remains hemodynamically stable and frequent hemoglobin determinations are maintained throughout the procedure.[220]

Antifibrinolytic Agents

Antifibrinolytic medications (i.e., ε-aminocaproic acid, tranexamic acid) have been demonstrated to decrease intraoperative blood loss and transfusion requirements in numerous types of operations, including orthopedic spine surgery.[221–223] Antifibrinolytic agents function to decrease blood loss through blockage of clot degradation by a reversible interaction with plasminogen and the active protease, plasmin. The safety of these drugs has been repeatedly demonstrated in clinical studies with no increase in thromboembolic complications noted, although isolated case reports do exist. For spine procedures in which significant blood loss is anticipated to occur, the inclusion of antifibrinolytic agents into the perioperative medical plan has been demonstrated to be safe and should be considered.

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) involves the removal of blood from a patient immediately prior to surgery. The blood is removed into a collection bag containing an anticoagulant and is stored in the operating room at ambient temperature until it is reinfused into the patient at the conclusion of the operation once the majority of blood loss has occurred. The blood that has been removed from the patient is replaced with an appropriate volume of acellular fluid (crystalloid or colloid) to maintain euvolemia. The goal of ANH is to reduce the patient's hematocrit to 30% prior to surgery. Surgery is thus performed with a reduced red blood cell mass but a normal vascular volume. ANH is well tolerated in most patients because the reduced oxygen-carrying capacity of blood is compensated for by greater cardiac output and enhanced venous return owing to a reduction in viscosity. Moreover, oxygen delivery to the tissues is unaffected by hematocrit levels as low as 20%,[224] and cardiovascular stability does not deteriorate until hematocrit levels reach 15%.[225]

The decision to use ANH should consider the patient's underlying medical condition before the technique is implemented. Recommendations for the use of ANH have been previously published; they emphasize the use of ANH in the appropriately selected patient.[226] Patients who are considered good candidates for ANH have the following features: preoperative hemoglobin greater than 12 gm/dL; absence of clinically significant coronary, pulmonary, renal, or liver disease; absence of severe hypertension; and the absence of infection and the risk of bacteremia. Although the efficacy of ANH in reducing the use of allogeneic red blood cell transfusion is debated, a number of studies have demonstrated the usefulness of ANH in decreasing the use of allogeneic blood in cases associated with significant blood loss.[227,228]

Intraoperative Cell Salvage

Intraoperative cell salvage is a technique in which blood lost during surgery is collected via suction instruments, in which it is mixed with an anticoagulant (heparin or citrate) and then sent into a collection reservoir. After processing the salvaged blood, it is pumped back into the patient, with a final hematocrit approaching 60%. In comparison with other

methods of reducing allogeneic red cell transfusion, cell salvage offers the greatest flexibility and is the most cost effective method when blood loss is substantial (i.e., >2000 mL), as occurs in major reconstructive spine operations.[229] The disadvantages are that the reinfused red cells may cause a coagulopathy from residual anticoagulant and lack of coagulation factors or platelets. Clotting factors may need to be replaced if microvascular bleeding is noted in the surgical field. It is important to note that the washed blood is returned into a plastic bag that contains a significant amount of air; the use of a pressure device to accelerate transfusion of cell saver blood has led to massive air embolism. A "black box" warning recommends against the pressurization of the bag.

Postoperative Care

Extubation

The question whether or not to extubate the patient following spinal surgery depends largely on the particular surgical procedure performed and the clinical condition of the patient. In the majority of cases involving spinal surgery, extubation may be performed immediately upon awakening of the patient after demonstration of the usual criteria for extubation. Intubation may have to be maintained in certain cases of impaired ventilation caused by high cervical or thoracic lesions, preoperative pulmonary impairment, metabolic derangement, or persistent muscle weakness. Extubation is not necessarily imperative for the resumption of consciousness or ability to follow commands. In cases in which the operation was long (>6 hours) or the patient has significant facial edema, it is much safer to leave the patient intubated and to raise the head of the bed at least 45 degrees, and to extubate the patient in the recovery room or intensive care unit after the facial swelling has diminished.

Postoperative Pain Control

Major surgical operations on the spine result in significant postoperative pain.[229–236] Effective pain management is essential in order to facilitate early mobility, reduce postoperative pulmonary complications, shorten hospital length of stay, and enhance patient satisfaction. A variety of techniques are available to treat postoperative pain issues after spine surgery, with the particular surgical approach dictating the pain management method. In general, cervical spine surgery is associated with the least amount of postoperative pain, whereas spinal fusion and instrumentation procedures involving the thoracic and lumbar spine are associated with the most significant postoperative pain. Techniques of pain management that have been used vary widely and include: intermittent intravenous opioids; intravenous patient-controlled analgesia (PCA); central neuraxial (intrathecal, epidural); regional blocks; continuous wound installation of local anesthetics; and nonopioid analgesics, including intravenous acetaminophen (i.e., 1000 mg intravenously every 6 hours for eight total doses).[231–235] Multimodal analgesic regimens incorporating a variety of these pain techniques are the preferred pain management strategies for all surgical procedures, including orthopedic.[236–239] Multimodal pain protocols are the preferred perioperative pain management approach. The recent availability of intravenous acetaminophen has greatly enhanced the efficacy of the multimodal approach for perioperative pain management, particularly in the context of spine surgery.

Complications

Complications of spinal surgery may occur intraoperatively or postoperatively. Intraoperative complications include cardiac arrest from hypoxia while in the prone position and acute SCI from either direct trauma to the cord or distraction pressure during instrumentation, pneumothorax, and hemothorax. Postoperative complications include neurologic injury or deficit, visual loss, epidural hematoma, arachnoiditis, intravascular volume deficits, anemia, coagulopathy, CSF leak from an intraoperative dural tear, hypoxemia from atelectasis or pulmonary edema, urinary retention, ileus, atelectasis or pneumonia, and venous thrombosis. Complications specific to anterior cervical procedures include dysphagia, hoarseness, and airway obstruction from edema or neck hematoma.

Neurologic Deficit

Neurologic deficits following spinal surgery are uncommon events. In the ASA Closed Claims database, cervical cord, root, and bony spine injuries represented a very small percentage (<1%) of all general anesthesia malpractice claims.[240] When cervical injury did occur, it was often permanent. Factors increasing the risk of cervical cord injury include degenerative disease of the cervical spine, direct surgical complications, sitting position, intraoperative head/neck position during surgery, airway management (i.e., intubation), and arterial blood pressure (i.e., hypotension). In those patients undergoing complex spinal deformity operations, the incidence of neurologic deficits is significantly increased. In particular, the incidence of complications is highest with scoliosis repair in which spinal fusion and instrumentation is used.[240] Studies have reported the frequency of new neurologic deficits after corrective scoliosis repair at 0.45–7.5%; however, permanent neurologic deficits are reported to be <1%.[240–242] If a new neurologic deficit is identified during scoliosis surgery, removal of the instrumentation, alteration of the corrective angle within 3 hours of discovery of the neurologic deficit, or both is important. With the advent of neurophysiologic monitoring, neurologic deficits are now being detected intraoperatively, reducing the incidence of permanent injury.

Anterior Spinal Artery Syndrome

Anterior spinal artery syndrome results from anterior central cord ischemia in the distribution of the anterior spinal artery. This condition typically manifests as motor weakness that is greater than any sensory change and is due to the more central and ventral location of the motor tracts in the spinal cord, as opposed to the more dorsal and peripheral location of the sensory tracts. This syndrome results from obstruction of the feeder vessels to the anterior spinal artery, as occurs with aortic cross-clamping for repair of thoracolumbar aortic aneurysm or coarctation of the aorta. However, anterior spinal artery syndrome may also result from sustained hypoperfusion, correction of scoliosis, cervical spondylosis, disk herniation, and vertebral trauma. Treatment is aimed at relieving any existing contributory pathologic condition and providing general support.

Postoperative Visual Loss

Postoperative visual loss (POVL) is an uncommon but tragic complication that is associated with spine, cardiac, and head and neck operations. The reported estimates for blindness after spine surgery and cardiac surgery are 0.2% and 4.5%, respectively, with prevalence rates of POVL after spinal fusion of 0.0309%. [243,244] In a retrospective review of the Nationwide Inpatient Sample (NIS) of hospital care from 1996 to 2005, Shen et al.[244] studied the frequency and possible risk factors of POVL among eight commonly performed surgical operations. Risk factors that were found to increase the incidence of POVL in patients undergoing spine surgery in particular included age (>50 years), gender (male > female), preoperative

anemia, preexisting medical conditions, blood transfusion, and a posterior approach for spine surgery. Most cases of POVL involve ischemic optic neuropathy (ION), central retinal artery occlusion, or ischemic lesions in the cerebral cortex.[243,244] Although the etiology of POVL has not been clearly identified, the pathophysiologic mechanism considered most plausible in explaining the development of perioperative ION involves an elevation of venous pressure and the accumulation of interstitial edema, causing injury to the optic nerve by a combination of vascular compression, venous infarction, or mechanical compression.[245]

Two recent reports by the American Society of Anesthesiologists (ASA) identified risk factors for the development of ION in the setting of spine surgery. The members of the Postoperative Visual Loss Study Group utilized a multicenter case-control design to compare 80 adult patients with ION from the ASA Postoperative Visual Loss Registry with 315 adult control subjects without ION after spine fusion surgery.[246] In this report, risk factors for ION after spine fusion surgery were noted to include: male gender, obesity, anesthesia duration, Wilson frame use, estimated blood loss, and colloid as a percentage of total asanguinous fluid replacement. In the latest 2012 ASA Practice Advisory for Perioperative Visual Loss Associated with Spine Surgery,[247] the committee members were unable to conclusively identify preoperative patient characteristics that predispose a patient to ION; however, the task force did conclude that the risk of perioperative ION may be increased in patients who undergo prolonged spine procedures (>6 hours) in the prone position, have substantial blood loss (average loss, 44.7% of blood volume), or both. The important point is that, although these disorders *may* increase the risk of POVL, no direct evidence of any involvement of these conditions has ever been demonstrated to be clearly causative. Nonetheless, the ASA task force report on POVL does include advisory statements that should serve to guide perioperative management.[247]

In summary, POVL is uncommon after spine surgery but clearly does occur. Consequently, vision should be assessed after prolonged surgery once the patient is awake and alert. Any indication of deficit should be immediately followed by an ophthalmologic consultation to evaluate for possible causes. MRI should also be considered to evaluate for nonophthalmologic, intracranial causes of blindness.

Epidural Hematoma

Epidural hematomas may arise spontaneously as a result of a hypocoagulable state or trauma or from iatrogenic causes. The hematoma may exert a mass effect, with corresponding clinical neuropathy or focal deficit. If a pathologic epidural hematoma is suspected, an emergency spine MRI should be obtained.

Venous Thromboembolism

Venous thromboembolism (VTE) occurs with varying rates in orthopedic patients. Patients undergoing spine surgery appear to have a smaller risk of VTE than those who have lower extremity surgery;[150] nonetheless, the risk of developing postoperative VTE remains clinically relevant and must be actively addressed during the perioperative period. Deliberate hypotension, hypothermia, decreased cardiac output, and hypovolemia all may predispose to VTE, increasing the patient's risk for this complication. Recent studies have examined the risk of VTE in spinal surgery patients; in a report of patients undergoing spine surgery who did not have DVT prophylaxis, the rate of DVT was noted to be 2.3% for degenerative spine conditions, 6.0% for spine trauma, and 5.3% for spine deformity.[248] In a recent review of 14 studies, Sansone et al.[249] found that the pooled risks of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 1.09% and 0.06%, respectively. Advanced age and lumbar surgery appear to raise the postoperative risk for DVT.[230] Other proposed risk factors are anterior or combined anterior-posterior surgical approaches, surgery for tumors, multiple operative levels, prolonged operations, spinal cord injury, and decreased postoperative ambulation or activity.[230] Given the high rate of VTE following spine surgery, it is suggested that low-risk patients undergoing spinal operations receive mechanical prophylaxis (intermittent pneumatic compression-IPC) with or without pharmacologic prophylaxis (low-dose unfractionated heparin or low-molecular-weight heparin); for patients at high risk of VTE following spinal surgery (malignancy, spinal cord injury, combined anterior-posterior approach), IPC with pharmacologic prophylaxis should be administered once adequate hemostasis is obtained (preferably within 48 hours to 72 hours following surgery).[150,250]

Dural Tear

Interruption of the dura mater during spinal surgery is not uncommon and is often a necessary part of the operation, particularly in procedures on the cord itself. It also may occur unintentionally, especially when the surgeon is working in an area of a previous operation. The tear is usually repaired with no further sequelae. However, a CSF leak occasionally develops, which may result in a postoperative headache, fluid collections, or leaks. If drainage of CSF persists, CSF diversion or reoperation may be necessary.

SUMMARY

Patients undergoing surgery on the spine or spinal cord present a complex challenge to anesthesiologists. A fundamental knowledge of spine anatomy facilitates an appreciation of the scheduled surgical procedure and the particular approach used by the surgeon to complete the operation. A basic understanding of radiologic imaging in the context of spinal diseases, and the indications for such tests, enhances awareness of the importance of imaging in formulating a medical and surgical treatment strategy. General familiarity with the various surgical approaches to the spine greatly augments decisions about patient positions, hemodynamic monitoring, anesthetic choices, and the potential for perioperative complications. An awareness of the medical concerns related to the common surgical diseases of the spine assists the anesthesiologist in initiating medical discussions with the surgical team and also provides a degree of comfort with the appropriateness of the planned surgery. Spine diseases may present unique management challenges, such as the unstable cervical spine in a patient with severe rheumatoid arthritis or spinal cord impingement in a patient with spinal stenosis, and a more complete understanding of the pathology associated with such diseases directly affects the delivery of anesthetic care.

An in-depth comprehension of airway management in the context of spine diseases is a fundamental requirement for every anesthesiologist. Knowledge of airway manipulations and their effect on subsequent spine movement is important to facilitate better decision-making and reduce further neurologic injury, particularly in the setting of acute SCI. Following tracheal intubation, intraoperative anesthetic management of the spinal cord-injured patient should focus on maintaining adequate perfusion pressure and oxygenation. Vasoactive agents are appropriate only after ensuring adequate volume status and cardiac function. In the majority of spine operations, anesthesia induction and maintenance are achieved

using a variety of accepted techniques. In the setting of major spine surgery in which the potential for injury to the spinal cord is present (i.e., correction of spinal deformities, spinal stenosis, spine stabilization procedures), the use of neurophysiologic monitoring dictates the use of a limited number of acceptable anesthetic techniques. In this context, intravenous or balanced techniques are preferred.

Decisions regarding fluid management choices during spine surgery should focus more upon the maintenance of a euvolemic state and less upon the particular fluid type. Fluid overload is associated with an increase in morbidity, and thus invasive monitoring, combined with a GDFT strategy, may be appropriate in prolonged major spine operations to avoid excessive fluid administration. A sensible blood conservation strategy is facilitated by autologous blood predonation, lowering the transfusion triggers, preoperative acute normovolemic hemodilution, deliberate hypotension, and blood salvage techniques, whenever possible.

Postoperative pain control is important to increase patient satisfaction and reduce both the overall hospital length of stay and health care cost. A variety of techniques are appropriate in the postoperative setting, providing excellent pain control if started early and continued for 2–4 days postoperatively. Epidural techniques appear particularly efficacious, although other strategies are effective as well. Finally, the avoidance and early detection of perioperative complications is imperative in improving surgical outcome.

REFERENCES

1. Parsa AT, Miller JI. Neurosurgical diseases of the spine and spinal cord: Surgical considerations. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery*. 4th ed. St. Louis: Mosby; 2001:531–555.
2. Moore KL, Dalley II AF. *Clinically Oriented Anatomy*. Philadelphia: Lippincott Williams & Wilkins; 2006. 477–531.
3. Sandler AN, Tator CH. Effect of acute spinal cord compression injury on regional spinal cord blood flow in primates. *J Neurosurg*. 1976;45:660–676.
4. Hickey R, Albin MS, Bunegin L, et al. Autoregulation of spinal cord blood flow: Is the cord a microcosm of the brain? *Stroke*. 1986;17:1183–1189.
5. Guha A, Tator CH, Rochon J. Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. *Stroke*. 1989;20:372–377.
6. Anderson DK, Nicolosi GR, Means ED, et al. Effects of laminectomy on spinal cord blood flow. *J Neurosurg*. 1978;48:232–238.
7. Carette S, Fehlings MG. Cervical radiculopathy. *N Engl J Med*. 2005;353:392–399.
8. Rosen M, Beiner J, Kwon B, et al. Herniation of the nucleus pulposus in the cervical, thoracic, and lumbar spine. In: Vaccaro AR, ed. *Spine: Core Knowledge in Orthopaedics*. Philadelphia: Elsevier-Mosby; 2005:66–82.
9. Patel N. Surgical disorders of the thoracic and lumbar spine: A guide for neurologists. *J Neurol Neurosurg Psychiatry*. 2002;73:42–48.
10. Katz JN, Harris MB. Lumbar spinal stenosis. *N Engl J Med*. 2008;358:818–825.
11. Matz P, Meagher RJ, Lamer T, et al. *Diagnosis and Treatment of Degenerative Lumbar Spondylolisthesis: Evidenced-Based Clinical Guidelines for Multidisciplinary Spine Care*. North American Spine Society; 2014.
12. Iguchi T, Wakami T, Kurihara A, et al. Lumbar multilevel degenerative spondylolisthesis: Radiological evaluation and factors related to anterolisthesis and retrolisthesis. *J Spinal Disord Tech*. 2002;15:93–99.
13. Bell GR. Degenerative spondylolisthesis. In: Herkowitz HN, Garfn SR, et al., eds. *Rothman-Simeone: The Spine*. 6th ed. Philadelphia: Elsevier-Saunders; 2011:1101–1115.
14. Shaf B, Beiner JM, Grauer JN, et al. Lumbar spondylolisthesis. In: Vaccaro AR, ed. *Spine: Core Knowledge in Orthopaedics*. Philadelphia: Elsevier-Mosby; 2005:157–171.
15. Sengupta DK, Herkowitz HN. Degenerative spondylolisthesis: Review of current trends and controversies. *Spine*. 2005;30(suppl):S71–S81.
16. Berbari EF, Steckelberg JM, Osmon DR. Osteomyelitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Elsevier; 2015:1318–1327.
17. Basbarrini A, Bertoldi E, Mazzetti M, et al. Clinical features, diagnostic and therapeutic approaches to haematogenous vertebral osteomyelitis. *Eur Rev Med Pharmacol Sci*. 2005;9:53–66.
18. Tirrell S, Handa S. Spinal infections: Vertebral osteomyelitis, epidural abscess, diskitis. *Hosp Med Clin*. 2013;2:e509–e524.
19. Shen CJ, Wu MS, Lin KH, et al. The use of procalcitonin in the diagnosis of bone and joint infection: A systemic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2013;32:807–814.
20. Gok SE, Kaptanoglu E, Celikbas A, et al. Vertebral osteomyelitis: Clinical features and diagnosis. *Clin Microbiol Infect*. 2014;20:1055–1060.
21. Zimmerli W. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022–1029.
22. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: An open-label, non-inferiority, randomized controlled trial. *Lancet*. 2015;385:875–882.
23. Weissman S, Parker RD, Siddiqui W, et al. Vertebral osteomyelitis: Retrospective review of 11 years of experience. *Scand J Infect Dis*. 2014;46:193–199.
24. Darouiche RO. Spinal epidural abscess. *N Engl J Med*. 2006;355:2012–2020.
25. Patel AR, Alton TB, Bransford MD, et al. Spinal epidural abscesses: Risk factors, medical versus surgical management, a retrospective review of 128 cases. *Spine J*. 2014;14:326–330.
26. Curry Jr. WT, Hoh BL, Amin-Hanjani S, et al. Spinal epidural abscess: Clinical presentation, management, and outcome. *Surg Neurol*. 2005;63:364–371.
27. Tunkel AR. Subdural empyema, epidural abscess, and suppurative intracranial thrombophlebitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Elsevier; 2015:1177–1185.
28. Grewal S, Hocking G, Wildsmith JA. Epidural abscesses. *Br J Anaesth*. 2006;96:292–302.
29. Clarke MJ, Mendel E, Vrionis FD. Primary spine tumors: Diagnosis and treatment. *Cancer Control*. 2014;21:114–123.
30. Kaloostian PE, Zadnik PL, Etame AB, et al. Surgical management of primary and metastatic spinal tumors. *Cancer Control*. 2014;21:133–139.
31. Khan SN, Donthineni R. Surgical management of metastatic spine tumors. *Orthop Clin North Am*. 2006;37:99–104.
32. Rafiff JK, Cooper PR. Metastatic spine tumors. *South Med J*. 2004;97:246–253.
33. Ashour R, Aziz-Sultan A. Preoperative tumor embolization. *Neurosurg Clin N Am*. 2014;25:607–617.
34. Pikis S, Itshayek E, Barzilay Y, et al. Preoperative embolization of hypervascular spinal tumors: Current practice and center experience. *Neurol Res*. 2014;36:502–509.
35. Silva FE, Lenke LG. Adult degenerative scoliosis: Evaluation and management. *Neurosurg Focus*. 2010;28(3):E1. 1–10.
36. Hu SS. Adult scoliosis. In: Herkowitz HN, Garfn SR, et al., eds. *Rothman-Simeone: The Spine*. 5th ed. Philadelphia: Saunders-Elsevier; 2006:1046–1057.
37. Kobayashi T, Atsuta Y, Takemitsu M, et al. A prospective study of de novo scoliosis in a community based cohort. *Spine*. 2006;31:178–182.
38. Wang G, Hu J, Liu X, et al. Surgical treatments for degenerative lumbar scoliosis: A meta analysis. *Eur Spine J*. 2015;24:1792–1799.
39. Memtsoudis SG, Vougioukas VI, Ma Y, et al. Perioperative morbidity and mortality after anterior, posterior, and anterior/posterior spine fusion surgery. *Spine*. 2011;36:1867–1877.
40. Stundner O, Taher F, Pawar A, et al. Pulmonary complications after spine surgery. *World J Orthop*. 2012;3:156–161.
41. Pumberger M, Chiu YL, Ma Y, et al. National in-hospital morbidity and mortality trends after lumbar fusion surgery between 1998 and 2008. *J Bone Joint Surg Br*. 2012;94:359–364.
42. Guigui P, Blamoutier A, Groupe d'Etude de la Scoliose. Complications of surgical treatment of spinal deformities: A prospective multicentric study of 3311 patients. *Rev Chir Orthop Reparatrice Appar Mot*. 2005;91:314–327.
43. Borenstein D. Inflammatory arthritides of the spine: Surgical versus nonsurgical treatment. *Clin Orthop Rel Res*. 2006;443:208–221.
44. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365:2205–2219.
45. Szpalski M, Gunzburg R. What are the advances for surgical therapy of inflammatory disease of the spine? *Best Pract Clin Rheumatol*. 2002;16:141–154.
46. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol*. 2006;194(2 suppl):S3–S11.
47. Davies KM, Stegman MR, Heaney RP, et al. Prevalence and severity of vertebral fracture: The Saunders County Bone Quality Study. *Osteoporosis Int*. 1996;6:160–165.
48. Cole ZA, Dennison EM, Cooper C. Osteoporosis epidemiology update. *Curr Rheumatol Rep*. 2008;10:92–96.

49. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med*. 2009;361:557–568.
50. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*. 2009;361:569–579.
51. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine*. 2011;14:561–569.
52. Anderson PA, Froyshteter AB, Tontz WL. Meta-analysis of vertebral augmentation compared with conservative treatment for osteoporotic spinal fractures. *J Bone Miner Res*. 2013;28:372–382.
53. Savage JW, Schroeder GD, Anderson PA. Vertebroplasty and kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *J Am Acad Orthop Surg*. 2014;22:653–664.
54. Barr JD, Jensen ME, Hirsch JA, et al. Position statement on percutaneous vertebral augmentation: A consensus statement developed by the Society of Interventional Radiology (SIR), American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), American College of Radiology (ACR), American Society of Neuroradiology (ASSR), Canadian Interventional Radiology Association (CIRA), and the Society of Neurointerventional Surgery (SNIS). *J Vasc Interv Radiol*. 2014;25:171–181.
55. Holmes J, Miller P, Panacek E, et al. Epidemiology of thoracolumbar spine injury in blunt trauma. *Acad Emerg Med*. 2001;8:866–872.
56. Lindsey RW, Gugala Z, Pneumaticos SG. Injury to the vertebra and spinal cord. In: Moore EE, Feliciano DV, Mattox KL, eds. *Trauma*. 5th ed. New York: McGraw-Hill; 2004:459–492.
57. Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. *N Engl J Med*. 2000;343:94–99.
58. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. *JAMA*. 2001;286:1841–1848.
59. Hadley MN, Walter BC, Aarabi B, et al. Guidelines for the management of acute cervical spine and spinal cord injuries. AANS/CNS Joint Guidelines Committee. *Neurosurgery*. 2013;72(2 suppl):1–259.
60. Hadley MN, Walters BC. Introduction to the guidelines for the management of acute cervical spine and spinal cord injuries. *Neurosurgery*. 2013;72(2 suppl):5–16.
61. Walters BC, Hadley MN, Hurlbert RJ, et al. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 Update. *Clin Neurosurg*. 2013;60:82–91.
62. Munera F, Rivas LA, Nunez DB, et al. Imaging evaluation of adult spinal injuries: Emphasis on multidetector CT in cervical spine trauma. *Radiology*. 2012;263:645–660.
63. Como JJ, Diaz JJ, Dunham M, et al. Practice management guidelines for identification of cervical spine injuries following trauma: Update from the Eastern Association for the Surgery of Trauma Practice Management Guidelines Committee. *J Trauma*. 2009;67:651–659.
64. Bailitz J, Starr F, Beecroft M, et al. CT should replace three-view radiographs as the initial screening test in patients at high, moderate, and low risk for blunt cervical spine injury: A prospective comparison. *J Trauma*. 2009;66:1605–1609.
65. Como JJ, Leukhardt WH, Anderson JS, et al. Computed tomography alone may clear the cervical spine in obtunded blunt trauma patients: A prospective evaluation of a revised protocol. *J Trauma*. 2011;70:345–351.
66. Goldberg AL, Kershah SM. Advances in imaging of vertebral and spinal cord injury. *J Spinal Cord Med*. 2010;33:105–116.
67. Allen BL, Ferguson RL, Lehmann TR, et al. A mechanistic classification of closed indirect fractures and dislocations of the lower cervical spine. *Spine*. 1982;7:1–27.
68. Bozzo A, Marcoux J, Radhakrishna M, et al. The role of magnetic resonance imaging in the management of acute spinal cord injury. *J Neurotrauma*. 2011;28:1401–1411.
69. The National Spinal Cord Injury Statistical Center (NSCISC). *Facts and Figures at a Glance*. Birmingham, AL: University of Alabama at Birmingham; February 2014.
70. Jain NB, Ayers GD, Peterson EN, et al. Traumatic spinal cord injury in the United States, 1993–2012. *JAMA*. 2015;313:2236–2243.
71. DeVivo MJ, Stover SL, Black KJ. Prognostic factors for 12-year survival after spinal cord injury. *Arch Phys Med Rehabil*. 1992;73:156–162.
72. Al-Habib AF, Attabib N, Ball J, et al. Clinical predictors of recovery after blunt spinal cord trauma: Systematic review. *J Neurotrauma*. 2011;28:1431–1443.
73. Kruse JS, Kjorsvig JM. Mortality after spinal cord injury: A four-year prospective study. *Arch Phys Med Rehabil*. 1992;73:558–563.
74. Waters RL, Adkins RH, Yakura JS, et al. Motor and sensory recovery following incomplete tetraplegia. *Arch Phys Med Rehabil*. 1994;75:306–311.
75. Osterholm JL, Mathews GJ. Altered norepinephrine metabolism following experimental spinal cord injury. Part I: Relationship to hemorrhagic necrosis and post-wounding neurological deficits. *J Neurosurg*. 1972;36:386–394.
76. Griffiths IR. Spinal cord blood flow after acute experimental cord injury in dogs. *J Neurol Sci*. 1976;27:247–259.
77. Ducker TB, Saleman M, Perot PL, et al. Experimental spinal cord trauma. I: Correlation of blood flow, tissue oxygen and neurologic status in the dog. *Surg Neurol*. 1978;10:60–63.
78. Nemecek S. Morphological evidence of microcirculatory disturbances in experimental spinal cord trauma. *Adv Neurol*. 1978;20:395–405.
79. Zwimpfer TJ, Berstein M. Spinal cord concussion. *J Neurosurg*. 1990;72:894–900.
80. Chesler M, Young M, Hassan AZ, et al. Elevation and clearance of extracellular K^+ following graded contusion of the rat spinal cord. *Exp Neurol*. 1994;125:93–98.
81. Stys PK. Anoxic and ischemic injury of myelinated axons in CNS white matter: From mechanistic concepts to therapeutics. *J Cereb Blood Flow Metab*. 1998;18:2–25.
82. Faden AI, Molineaux CJ, Rosenberger JG, et al. Endogenous opioid immunoreactivity in rat spinal cord following traumatic injury. *Ann Neurol*. 1985;17:386–390.
83. Bracken MB, Shephard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone and naloxone in the treatment of acute spinal cord injury. *N Engl J Med*. 1990;322:1405–1411.
84. Bracken MB, Holford TR. Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function in NASCIS 2. *J Neurosurg*. 1993;79:500–507.
85. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA*. 1997;277:1597–1604.
86. Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. *JAMA*. 1984;251:45–52.
87. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. *Neurosurgery*. 2013;72:93–105.
88. Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: The myth challenged through a structured analysis of published literatures. *Spine J*. 2006;6:335–343.
89. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. *Spinal Cord*. 2000;38:71–76.
90. Lee HC, Cho DY, Lee WY, et al. Pitfalls in treatment of acute cervical spinal cord injury using high-dose methylprednisolone: A retrospect audit of 111 patients. *Surg Neurol*. 2007;68(suppl):37–42.
91. Suberviola B, Gonzalez-Castro A, Llorca J, et al. Early complications of high-dose methylprednisolone in acute spinal cord injury patients. *Injury*. 2008;39:748–752.
92. Ito Y, Sugimoto Y, Tomioka M, et al. Does high dose methylprednisolone sodium succinate really improve neurological status in patients with acute cervical cord injury? *Spine*. 2009;34:2121–2124.
93. Consortium for Spinal Cord Medicine. *Early Acute Management in Adults with Spinal Cord Injury: A Clinical Practice Guideline for HealthCare Providers*. Washington, DC: Paralyzed Veterans of America; 2007.
94. Levi A, Green B, Wang M, et al. Clinical application of modest hypothermia after spinal cord injury. *J Neurotrauma*. 2008;26:407–415.
95. Ahmad FU, Wang MY, Levi AD. Hypothermia for acute spinal cord injury: A review. *World Neurosurg*. 2014;82:207–214.
96. O'Toole JE, Wang MC, Kaiser MG. Hypothermia and human spinal cord injury: Updated position statement and evidence based recommendation from the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves and Neurotrauma and Critical Care, accessed at: http://www.spinesection.org; 2014.
97. Vale FL, Burns J, Jackson AB, et al. Combined medical and surgical treatment after acute spinal cord injury: Results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure measurement. *J Neurosurg*. 1997;87:239–246.
98. Gelb DE, Hadley MN, Aarabi B, et al. Initial closed reduction of cervical spinal fracture-dislocation injuries. *Neurosurgery*. 2013;72:73–83.
99. Gelb DE, Aarabi B, Dhall SS, et al. Treatment of subaxial cervical spine injuries. *Neurosurgery*. 2013;72:187–194.
100. Grant GA, Mirza SK, Chapman JR, et al. Risk of early closed reduction in cervical spine subluxation injuries. *J Neurosurg Spine*. 1999;90:13–18.
101. Lee AS, MacLean JC, Newton DA. Rapid traction for reduction of cervical spine dislocations. *J Bone Joint Surg Br*. 1994;76:352–356.
102. Louis R. Stability and instability of the cervical spine. In: Kehr P, Weidner A, eds. *Cervical Spine I*. New York: Springer-Verlag; 1987:21–27.

103. White III AA, Panjabi MM. The problem of clinical instability in the human spine: A systematic approach. In: White AA III, Panjabi MM, eds. *Clinical Biomechanics of the Spine*. 2nd ed. Philadelphia: Lippincott-Raven; 1990:277–378.
104. Holdsworth FW. Fractures, dislocations, and fracture-dislocations of the spine. *J Bone Joint Surg Br*. 1963;45:6–20.
105. Denis F. Spinal instability as defined by the three-column spine concept in acute spinal trauma. *Clin Orthop Rel Res*. 1984;189:65–76.
106. Bernhardt M, White AA, Panjabi MM. Biomechanical considerations of spinal stability. In: Herkowitz HN, Garfn SR, Eismont FJ, et al., eds. *Rothman-Simeone: The Spine*. 5th ed. Philadelphia: Saunders-Elsevier; 2006:132–156.
107. Aarabi B, Walters BC, Dhall SS, et al. Subaxial cervical spine injury classification systems. *Neurosurgery*. 2013;72:170–186.
108. Vaccaro AR, Hulbert J, Fisher C, et al. The Sub-axial Cervical Spine Injury Classification System (SLIC): A novel approach to recognize the importance of morphology, neurology and integrity of the discoligamentous complex. *Spine*. 2007;32:2365–2374.
109. Joaquim AF, Patel AA, Vaccaro AR. Cervical injuries scored according to the Subaxial Injury Classification system: An analysis of the literature. *J Craniovertebr Junction Spine*. 2014;5:65–70.
110. Guha A, Tator CH, Endrenyl L, et al. Decompression of the spinal cord improves recovery after acute experimental spinal cord compression injury. *Paraplegia*. 1987;25:324–339.
111. Carlson GD, Minato Y, Okada A, et al. Early time-dependent decompression for spinal cord injury: Vascular mechanisms of recovery. *J Neurotrauma*. 1997;14:951–962.
112. Delamarter RB, Sherman J, Carr JB. Pathophysiology of spinal cord injury: Recovery after immediate delayed decompression. *J Bone Joint Surg Am*. 1995;77:1042–1049.
113. Sacks GD, Panchmatia JR, Marino M, et al. The effect of operative timing on functional outcome after isolated spinal trauma. *J Trauma*. 2011;71:1668–1672.
114. Geisler F, Coleman W. Timing of surgical decompression for acute severe spinal injury: Retrospective results from a large multi-center clinical trial. *Spine J*. 2003;3:108S.
115. Fehlings MG, Perrin RG. The timing of surgical intervention in the treatment of spinal cord injury: A systematic review of recent clinical evidence. *Spine*. 2006;31:S28–S35.
116. La Rosa G, Conti A, Cardali S, et al. Does early decompression improve neurological outcome of spinal cord injured patients? Appraisal of the literature using a meta-analytical approach. *Spinal Cord*. 2004;42:503–512.
117. Ball JR, Sekhon HS. Timing of decompression and fixation after spinal cord injury: When is surgery optimal? *Crit Care Res*. 2006;8:56–63.
118. Furlan JC, Noonan V, Cadotte DW, et al. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: An evidence-based examination of preclinical and clinical studies. *J Neurotrauma*. 2011;28:1371–1399.
119. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One*. 2012;7:1–8.
120. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. *Am Rev Respir Dis*. 1981;124:41–44.
121. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med*. 2001;344:1986–1996.
122. Gajic O, Dara SI, Mendez JL, et al. Ventilator associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med*. 2004;32:1817–1824.
123. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress network. *N Engl J Med*. 2000;342:1301–1308.
124. Freeman BD, Morris PE. Tracheostomy practice in adults with acute respiratory failure. *Crit Care Med*. 2012;40:2890–2896.
125. Kornblith LZ, Kutcher ME, Callcut RA, et al. Mechanical ventilation weaning and extubation after spinal cord injury: A Western Trauma Association multicenter study. *J Trauma Acute Care Surg*. 2013;75:1060–1069.
126. Onders RP, Khansarinia S, Weiser T, et al. Multicenter analysis of diaphragm pacing in tetraplegics with cardiac pacemakers: Positive implications for ventilator weaning from intensive care units. *Surgery*. 2010;148:893–898.
127. Romero FJ, Gambarrutta C, Garcia-Forcada A, et al. Long-term evaluation of phrenic nerve pacing for respiratory failure due to high cervical spinal cord injury. *Spinal Cord*. 2012;50:895–898.
128. Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehabil*. 1994;75:270–275.
129. Reines HD, Harris RC. Pulmonary complications of acute spinal cord injuries. *Neurosurgery*. 1987;21:193–196.
130. Como JJ, Sutton ER, McCun M, et al. Characterizing the need for mechanical ventilation following cervical spinal cord injury with neurologic deficit. *J Trauma*. 2005;59:912–916.
131. Hassid VJ, Schinco MA, Tepas JJ, et al. Definitive establishment of airway control is critical for optimal outcome in lower cervical spinal cord injury. *J Trauma*. 2008;65:1328–1332.
132. Rechtine II GR. Nonoperative management and treatment of spinal injuries. *Spine*. 2006;31:S22–S27.
133. Pape HC, et al. Is early kinetic positioning beneficial for pulmonary function in multiple trauma patients? *Injury*. 1998;29:219–225.
134. Bein T, Reber A, Metz C, et al. Acute effects of continuous rotational therapy on ventilation-perfusion inequality in lung injury. *Intensive Care Med*. 1998;24:132–137.
135. Ahrens T, Kollef M, Stewart J, et al. Effect of kinetic therapy on pulmonary complications. *Am J Crit Care*. 2004;13:376–383.
136. Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305–313.
137. Eidelberg EE. Cardiovascular response to experimental spinal cord compression. *J Neurosurg*. 1973;38:326–331.
138. Lehmann KG, Lane JG, Piepmeier JM, et al. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: Incidence, time course, and severity. *J Am Coll Cardiol*. 1987;10:46–52.
139. Ryken TC, Hurlbert RJ, Hadley MN, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. *Neurosurgery*. 2013;72:84–93.
140. Vitaz TW, McIlvoy, Raque GH, et al. Development and implementation of a clinical pathway for spinal cord injuries. *J Spinal Disord*. 2001;14:271–276.
141. Nout YS, Mihal G, Tovar CA, et al. Hypertonic saline attenuates cord swelling and edema in experimental spinal cord injury: A study utilizing magnetic resonance imaging. *Crit Care Med*. 2009;37:2160–2166.
142. Greenhoot JH, Mauck HP. The effect of cervical cord injury or cardiac rhythm and conduction. *Am Heart J*. 1972;83:659–662.
143. Segal JL, Milne N, Brunnemann SR. Gastric emptying is impaired in patients with spinal cord injury. *Am J Gastroenterol*. 1995;90:466–470.
144. Wuermser L-A, Chester HH, Chiodo AE, et al. Spinal cord injury medicine: 2: Acute care management of traumatic and nontraumatic injury. *Arch Phys Med Rehabil*. 2007;88(1 suppl):S55–S61.
145. Sabharwal S. Neurogenic Bowel. In: *Essentials of Spinal Cord Medicine*. New York: Demos Medical Publishing; 2013:316–327.
146. Dhall SS, Hadley MN, Aarabi B, et al. Nutritional support after spinal cord injury. *Neurosurgery*. 2013;72:255–259.
147. Lensenmeyer TA. Neurogenic bladder following spinal cord injury. In: Kirshblum S, Campagnolo DI, eds. *Spinal Cord Medicine*. 2nd ed. Philadelphia: Wolters Kluwer-Lippincott Williams & Wilkins; 2011:211–241.
148. Rogers FB, Cipolle MD, Velmahos G, et al. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: The EAST Practice Management Guidelines Work Group. *J Trauma*. 2002;53:142–164.
149. Attia J, Ray JG, Cook DJ, et al. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med*. 2001;161:1268–1279.
150. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in non-orthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e227S–e277S.
151. Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: A randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. *J Trauma*. 2003;54:1116–1126.
152. Dhall SS, Hadley MN, Aarabi B, et al. Deep venous thrombosis and thromboembolism in patients with cervical spinal cord injuries. *Neurosurgery*. 2013;72:244–254.
153. Stawicki SP, Grossman MD, Cipolla J, et al. Deep venous thrombosis and pulmonary embolism in trauma patients: An overstatement of the problem? *Am Surg*. 2005;71:387–391.
154. Berney S, Bragge P, Granger C, et al. The acute respiratory management of cervical spinal cord injury in the first 6 weeks after injury: A systematic review. *Spinal Cord*. 2011;49:17–29.
155. Widerstrom-Noga EG. Neuropathic pain after spinal cord injury. In: Kirshblum S, Campagnolo D, eds. *Spinal Cord Medicine*. 2nd ed.Philadelphia: Lippincott Williams Wilkins; 2011:482–499.
156. Saulino M. Spinal cord injury pain. *Phys Med Rehabil Clin N Am*. 2014;25:397–410.
157. Bryce TN, Biering-Sorensen F, Finnerup NB, et al. International spinal cord injury pain classification: part 1. Background and description. *Spinal Cord*. 2012;50:413–417.
158. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.

159. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130: e278–e333.
160. Cohen ME, Ko CY, Bilimoria KY, et al. Optimizing ACS NSQIP modeling for evaluation of surgical quality and risk: Patient risk adjustment, procedure mix adjustment, shrinkage adjustment, and surgical focus. *J Am Coll Surg*. 2013;217:336–346.
161. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation*. 2011;124:381–387.
162. Segal JL, Brunnemann SR. Clinical pharmacokinetics in patients with spinal cord injuries. *Clin Pharmacokinet*. 1989;17:109–129.
163. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology*. 1975;43:4389–4399.
164. Dooney N, Dagal A. Anesthetic considerations in acute spinal cord trauma. *Int J Crit Illn Inj Sci*. 2011;1:36–43.
165. Calder I, Calder J, Crockard HA. Difficult direct laryngoscopy with cervical spine disease. *Anaesthesia*. 1995;50:756–763.
166. Hastings RH, Kelley SD. Neurologic deterioration associated with airway management in a cervical spine–injured patient. *Anesthesiology*. 1993;78:580–583.
167. Crosby ET. Considerations for airway management for cervical spine surgery in adults. *Anesthesiol Clin*. 2007;25:511–533.
168. Crosby ET. Airway management in adults after cervical spine trauma. *Anesthesiology*. 2006;104:1293–1318.
169. Sawin PD, Todd MM, Traynelis VC, et al. Cervical spine motion with direct laryngoscopy and orotracheal intubation. *Anesthesiology*. 1996;85:26–36.
170. Majernick T, Bieniek R, Houston J, et al. Cervical spine movement during orotracheal intubation. *Ann Emerg Med*. 1986;15:417–420.
171. Bivins H, Ford S, Bezmalinovic Z, et al. The effect of axial traction during orotracheal intubation of the trauma victim with an unstable cervical spine. *Ann Emerg Med*. 1988;17:25–29.
172. Hastings RH, Vigil AC, Hanna R, et al. Cervical spine movement during laryngoscopy with the Bullard, Macintosh, and Miller laryngoscopes. *Anesthesiology*. 1995;82:859–869.
173. Fitzgerald RD, Krafft P, Skrbensky G, et al. Excursions of the cervical spine during tracheal intubation: Blind oral intubation compared with direct laryngoscopy. *Anaesthesia*. 1994;49:111–115.
174. Horton WA, Fahy L, Charters P. Disposition of the cervical vertebrae, atlanto-axial joint, hyoid and mandible during X-ray laryngoscopy. *Br J Anaesth*. 1989;63:435–438.
175. Heath KJ. The effect of laryngoscopy on different cervical spine immobilization techniques. *Anaesthesia*. 1994;49:843–845.
176. Goutcher CM, Lochhead V. Reduction in mouth opening with semi-rigid cervical collars. *Br J Anaesth*. 2005;95:344–348.
177. Hastings RH, Wood PR. Head extension and laryngeal view during laryngoscopy with cervical spine stabilization maneuvers. *Anesthesiology*. 1994;80:825–831.
178. Watts AD, Gelb AW, Bach DB, et al. Comparison of Bullard and Macintosh laryngoscopes for endotracheal intubation of patients with a potential cervical spine injury. *Anesthesiology*. 1997;87:1335–1342.
179. Lennarson PJ, Smith DW, Sawin PD, et al. Cervical spinal motion during intubation: Efficacy of stabilization maneuvers in the setting of complete segmental instability. *J Neurosurg (Spine 2)*. 2001;94:265–270.
180. Santoni BG, Hindman BJ, Puttlitz CM, et al. Manual in-line stabilization increases pressures applied by the laryngoscope blade during direct laryngoscopy and orotracheal intubation. *Anesthesiology*. 2009;110:24–31.
181. Kolb JC, Summers RL, et al. Cervical collar-induced changes in intracranial pressure. *Am J Emerg Med*. 1999;17:135–137.
182. DeLorenzo RA, Olson JE, Boska M, et al. Optimal positioning for cervical immobilization. *Ann Emerg Med*. 1996;28:301–308.
183. Aprahamian C, Thompson BM, Finger WA, et al. Experimental cervical spine injury model: Examination of airway management and splinting techniques. *Ann Emerg Med*. 1984;13:584–587.
184. Hauswald M, Sklar DP, Tandberg D, et al. Cervical spine movement during airway management: Cinefuoroscopic appraisal in human cadavers. *Am J Emerg Med*. 1991;9:535–538.
185. Donaldson III WF, Heil BV, Donaldson VP, Silvagglo VJ. The effect of airway maneuvers on the unstable C1-C2 segment: A cadaver study. *Spine*. 1997;22:1215–1218.
186. Lennarson PJ, Smith D, Todd MM, et al. Segmental cervical spine motion during orotracheal intubation of the intact and injured spine with and without external stabilization. *J Neurosurg (Spine 2)*. 2000;92:201–206.
187. MacIntyre PR, McLeod AD, Hurley R, et al. Cervical spine movements during laryngoscopy: Comparison of the Macintosh and McCoy laryngoscope blades. *Anaesthesia*. 1999;54:413–418.
188. Gerling MC, Davis DP, Hamilton RS, et al. Effects of cervical spine immobilization technique and laryngoscope blade selection on an unstable cervical spine in a cadaver model of intubation. *Ann Emerg Med*. 2000;36:293–300.
189. Agro F, Barzoi G, Montechia F. Tracheal intubation using a Macintosh laryngoscope or a Glidescope® in 15 patients with cervical spine immobilization. *Br J Anaesth*. 2003;90:705–706.
190. Robitalille A, Williams SR, Tremblay M, et al. Cervical spine motion during tracheal intubation with manual in-line stabilization: Direct laryngoscopy versus GlideScope® videolaryngoscopy. *Anesth Analg*. 2008;106:935–941.
191. Turkstra TP, Craen RA, Pelz DM, et al. Cervical spine motion: A fluoroscopic comparison during intubation with lighted stylet, Glidescope®, and Macintosh laryngoscope. *Anesth Analg*. 2005;101:910–915.
192. Practice Guideline for Management of the Difficult Airway. An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:1–20.
193. Gabbott DA. The effect of single-handed cricoid pressure on neck movement after applying manual inline stabilization. *Anaesthesia*. 1997;52:586–588.
194. Hartley M. Cricoid pressure and potential spine injuries. *Anaesthesia*. 1993;48:1113.
195. Gabbott DA, Sasada MP. Laryngeal mask airway insertion using cricoid pressure and manual in-line neck stabilization. *Anaesthesia*. 1995;50:674–676.
196. Malcharek MJ, Rogos B, Watzlawek S, et al. Awake fiberoptic intubation and self-positioning in patients at risk of secondary cervical injury: A pilot study. *J Neurosurg Anesthesiol*. 2012;24:217–221.
197. Levi L, Wolf A, Belzberg H. Hemodynamic parameters in patients with acute cervical cord trauma: Description, intervention and prediction of outcome. *Neurosurgery*. 1993;33:1007–1016.
198. Finfer S, Bellomo R, Boycee N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit: The SAFE Study Investigators. *N Engl J Med*. 2004;350:2247–2256.
199. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
200. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs. crystalloids on mortality in critically ill patients presenting with hypovolemic shock: A CRISTAL randomized trial. *JAMA*. 2013;310:1809–1817.
201. Delaney AP, Dan A, McCaffrey J, et al. The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. *Crit Care Med*. 2011;39:386–391.
202. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2011;369:1243–1251. 2013.
203. Hartog CS, Bauer M, Reinhart K. The efficacy and safety of colloid resuscitation in the critically ill. *Anesth Analg*. 2011;112:156–164.
204. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:124–134.
205. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients: The NICE-SUGAR Study Investigators. *N Engl J Med*. 2009;360:1283–1297.
206. Egi M, Finfer S, Bellomo R. Glycemic control in the ICU. *Chest*. 2011;140:212–220.
207. Frankel AH, Holzman RS. Air embolism during posterior spinal fusion. *Can J Anaesth*. 1988;35:511–514.
208. McDouall SF, Shlugman D. Fatal venous air embolism during lumbar surgery: The tip of the iceberg? *Eur J Anaesth*. 2007;24:803–816.
209. Horlocker TT, Wedel DJ, Cucchiara RF. Venous air embolism during spinal instrumentation and fusion in the prone position. *Anesth Analg*. 1992;75:152–153.
210. Arulkumaran N, Corredor C, Hamilton MA, et al. Cardiac complications associated with goal-directed therapy in high-risk surgical patients: A meta-analysis. *Br J Anaesth*. 2014;112:648–659.
211. Ramsingh DS, Sanghvi C, Gamboa J, et al. Outcome impact of goal directed fluid therapy during high risk abdominal surgery in low to moderate risk patients: A randomized controlled trial. *J Clin Monit Comput*. 2013;27:249–257.
212. Donati A, Loggi S, Preiser JC, et al. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. *Chest*. 2007;132:1817–1824.
213. Grocott MP, Dushianthan A, Hamilton MA, et al. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: A Cochrane Systematic Review. *Br J Anaesth*. 2013;111:535–548.
214. Zheng F, Cammisa Jr. FP, Sandhu HS, et al. Factors predicting hospital stay, operative time, blood loss, and transfusion in patients undergoing revision posterior lumbar spine decompression, fusion, and segmental instrumentation. *Spine*. 2002;15:818–824.

215. Carabini LM, Zeeni C, Moreland NC, et al. Development and validation of a generalizable model for predicting major transfusion during spine fusion surgery. *J Neurosurg Anesthesiol*. 2014;26:205–215.
216. Elterman J, Brasel K, Brown S, et al. Transfusion of red blood cells in patients with a prehospital Glasgow Coma Score of 8 or less and no evidence of shock is associated with worse outcomes. *J Trauma Acute Care Surg*. 2013;75:8–14.
217. Warner MA, O'Keeffe T, Bhavsar P, et al. Transfusions and long-term functional outcomes in traumatic brain injury. *J Neurosurg*. 2010;113:539–546.
218. Robertson CS, Hannay J, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. *JAMA*. 2014;312:36–47.
219. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: A clinical practice guideline from the AABB. *Ann Intern Med*. 2012;157:49–58.
220. Kumar MA. Red cell transfusion in the neurological ICU. *Neurotherapeutics*. 2012;9:56–64.
221. Neilipovitz DT, Murto K, Hall L, et al. A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. *Anesth Analg*. 2001;93:82–87.
222. Elwatidy S, Jamjoom Z, Elgamal E, et al. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: A prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)*. 2008;33:2577–2580.
223. Wong J, El Beheiry H, Rampersaud YR, et al. Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. *Anesth Analg*. 2008;107:1479–1486.
224. Morisaki H, Sibbald WJ. Tissue oxygen delivery and the microcirculation. *Crit Care Clin*. 2004;20:213–223.
225. Martin E, Ott E. Extreme hemodilution in the Harrington procedure. *Bibl Haemat*. 1981;47:322–337.
226. Goodnough LT, Monk TG. Patient blood management: Autologous blood procurement, recombinant factor VIIa therapy, and blood utilization. In: Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier/Saunders; 2015:1881–1896.
227. Takayanag A, Masumori N, Kobayashi K, et al. Acute normovolemic hemdilution for radical retropubic prostatectomy and radical cystectomy. *Urology*. 2008;72:401–405.
228. Matot I, Scheinin O, Jurim O, et al. Effectiveness of acute normovolemic hemodilution to minimize allogeneic blood transfusion in major liver resections. *Anesthesiology*. 2002;97:794–800.
229. Waters JH. Red blood cell recovery and reinfusion. *Anesthesiol Clin North America*. 2005;23:283–294.
230. Oda T, Fuji T, Kato Y, et al. Deep venous thrombosis after posterior spinal surgery. *Spine*. 2000;25:2962–2967.
231. Fisher CG, Belanger L, Gofton EG, et al. Prospective randomized clinical trial comparing patient-controlled intravenous analgesia with patient-controlled epidural analgesia after lumbar spinal fusion. *Spine*. 2003;28:739–743.
232. Cohen BE, Hartman MB, Wade JT, et al. Postoperative pain control after lumbar spine fusion: Patient-controlled analgesia versus continuous epidural analgesia. *Spine*. 1997;22:1892–1897.
233. O'Neill P, Knickenberg C, Bogahalanda S, et al. Use of intrathecal morphine for postoperative pain relief following lumbar spine surgery. *J Neurosurg*. 1985;63:413–416.
234. Blackman RG, Reynolds J, Shively J. Intrathecal morphine: Dosage and efficacy in younger patients for control of postoperative pain following spinal fusion. *Orthopedics*. 1991;14:555–558.
235. Ross DA, Drasner K, Weinstein PR, et al. Use of intrathecally administered morphine in the treatment of postoperative pain after lumbar spine surgery: A prospective, double-blind, placebo-controlled study. *Neurosurgery*. 1991;28:700–704.
236. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesth Analg*. 2005;101:S5–S22.
237. Jebaraj B, Maitra S, Baidya K, et al. Intravenous paracetamol reduces postoperative opioid consumption after orthopedic surgery: A systematic review of clinical trials. *Pain Res Treat*. 2013;2013:402510.
238. Lachiewicz PF. The role of intravenous acetaminophen in multimodal pain protocols for perioperative orthopedic patients. *Orthopedics*. 2013;36(suppl):15–19.
239. Parvizi J, Bloomfield MR. Multimodal pain management in orthopedics: Implications for joint arthroplasty surgery. *Orthopedics*. 2013;36 (2 suppl):7–14.
240. Hindman BJ, Palecek JP, Posner KL, et al. Cervical spinal cord, root, and bony spine injuries: A closed claims analysis. *Anesthesiology*. 2011;114:782–795.
241. Divecha HM, Siddique I, Breakwell LM, et al. Complications in spinal deformity surgery in the United Kingdom: 5-year results of the annual British Scoliosis Society National Audit of Morbidity and Mortality. *Eur Spine J*. 2014;23(1 suppl):S55–S60.
242. Weiss H-R, Goodall D. Rate of complications in scoliosis surgery-a systematic review of the Pub Med literature. *Scoliosis*. 2008;3:9.
243. Stevens WR, Glazer PA, Kelley SD, et al. Opthalmic complications after spinal surgery. *Spine*. 1997;22:1319–1324.
244. Shen Y, Drum M, Roth S. The prevalence of perioperative visual loss in the United States: A 10-year study from 1996-2005 of spinal, orthopedic, cardiac, and general surgery. *Anesth Analg*. 2009;109:1534–1545.
245. Nickels TJ, Manlapaz MR, Farag E. Perioperative visual loss after spine surgery. *World J Orthop*. 2014;18:100–106.
246. Postoperative Visual Loss Study Group. Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. *Anesthesiology*. 2012;116:15–24.
247. Practice Advisory for Perioperative Visual Loss Associated with Spine Surgery. An updated report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss. *Anesthesiology*. 2012;116: 274–285.
248. Cheng JS, Arnold PM, Anderson PA, et al. Anticoagulation risk in spine surgery. *Spine*. 2010;35(9 suppl):S117–S124.
249. Sansone JM, del Rio AM, Anderson PA. The prevalence of and specific risk factors for venous thromboembolic disease following elective spine surgery. *J Bone Joint Surg Am*. 2010;92:304–313.
250. Christie S, Thibault-Halman G, Casha S. Acute pharmacological DVT prophylaxis after spinal cord injury. *J Neurotrauma*. 2011;28:1509–1514.

22 Neurologic Disease and Anesthesia

M.B. Friese • G. Crosby • D.J. Culley

HUNTINGTON'S DISEASE

Huntington's disease is a universally fatal neurodegenerative disorder affecting the central nervous system that results from an autosomal dominant mutation in the huntingtin gene.[1] It is characterized by movement and psychiatric disorders as well as dementia and occurs in 4–10 per 100,000 population.[1] The genetic defect is due to a mutation in the Huntingtin gene (HTT) on the short arm of chromosome 4, resulting in production of an abnormal form of huntingtin. Huntingtin is present ubiquitously in somatic tissues, and only recently have the pathological effects of mutant HTT been described outside of the CNS.[2,3] The mechanism by which the genetically altered protein induces the associated central nervous system changes is unknown, but prevailing theories suggest that huntingtin deposition enhances neuronal susceptibility to oxidative stress or glutamate mediated excitotoxicity.[1] The brain of a patient with Huntington's disease undergoes progressive atrophy and gliosis that is most prominent in the basal ganglia.[1] Interestingly, striatal atrophy becomes apparent with some MRI techniques more than a decade before onset of clinical symptoms.[1] These cerebral alterations, combined with loss of GABA-ergic neurons in the striatum, and skeletal muscle changes help explain the motor symptoms of Huntington's disease, but the pathophysiology of the cognitive and psychiatric alterations remains unknown.[4]

A patient with Huntington's disease can develop symptoms at any time after infancy, but they usually become evident in the late 30s or early 40s. As such, the diagnosis is often not established until after reproduction, but genetic testing now allows for earlier diagnosis and the option of genetic counseling. The motor symptoms of Huntington's disease typically begin with a lack of coordination and involuntary jerks. These uncontrollable, involuntary choreic movements (i.e., random jerking movements of the extremities, torso, face and truncal muscles) and athetosis (i.e., slower sinusoid writhing movements) peak after steady progression for 10 years and ultimately develop a rigid dystonic character. Dysphagia is common in advanced cases and most patients suffer from malnutrition at some stage.

All patients with Huntington's disease eventually develop dementia that spares long-term memory, but impairs executive functions. Other psychiatric and cognitive changes occur before, after, or at the same time as motor abnormalities and may include irritability, apathy, emotional instability, impulsiveness, and aggression. Depression is frequent, as is suicide, which occurs at a rate up to 10 times that of the general population.[5] Death usually occurs within 20 years of diagnosis due to falls, pneumonia, aspiration, malnutrition or suicide.[5]

There are no specific treatments that prevent, cure, or slow the progression of Huntington's disease. Symptomatic therapy aims to control the motor and psychiatric aspects of the disease. Drugs shown in clinical trials to be efficacious for the treatment of chorea include amantadine, remacemide, levetiracetam, and tetrabenazine. However, they can cause bradykinesia, rigidity, depression and sedation.[5] The affective disorders associated with Huntington's disease are often amenable to psychiatric treatment, such that polypharmacy is common in these patients. The prudent anesthesiologist will, therefore, be vigilant for the possibility of adverse drug interactions.[6]

Anesthetic management for a patient with Huntington's disease is driven mostly by theory because the literature is limited to anecdotal experiences and case reports. Because patients with Huntington's disease are at increased risk of pulmonary aspiration due to pharyngeal muscle abnormalities and dysphagia, aspiration prophylaxis and precautions seem warranted, but whether administration of anesthesia to these patients further increases the risk of aspiration pneumonitis is unknown. Patients with Huntington's disease are also alleged to be at risk for prolonged respiratory depression and delayed return to consciousness after general anesthesia and have reduced requirements for midazolam.[7] Whether this is related to altered pharmacokinetics due to nutritional depletion and altered protein binding, increased central nervous system sensitivity, or altered pharmacodynamics is unknown. In any event, most patients with Huntington's disease experience a normal anesthetic and postanesthetic course.[6,8,9]

Data concerning the response to muscle relaxants is similarly confusing. There is an increased incidence of abnormal plasma cholinesterase variants among patients with Huntington's disease and a case report of prolonged muscle relaxation following administration of succinylcholine, but succinylcholine has been used uneventfully in other cases.[10–13] There are, however, no case reports of succinylcholine-induced hyperkalemia. With respect to non-depolarizing muscle relaxants, both abnormal and normal responses have been reported.[11,13–15]

There are also reports of clinically significant, generalized, tonic muscle spasms related to shivering during emergence from anesthesia in patients with Huntington's disease,[13] suggesting maintenance of perioperative normothermia is especially important in these patients. Some authors even recommend avoiding inhalational anesthetics to decrease the risk of postoperative shivering, although the benefit of doing so is only theoretical and exacerbation of involuntary movements has been noted after propofol anesthesia. [8,16,17] Lastly, other than being technically difficult because of the continuous uncontrollable movements, there appears to be no contraindication to regional anesthesia in the patient with Huntington's disease.[9,18]

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a progressive, untreatable, degenerative disease of the central nervous system that involves both upper and lower motor neurons. The disease

affects 5–6 per 100,000 population with an average age at onset of 56 years.[19–21] ALS is marked by loss of motor neurons in the anterior horn of the spinal cord, brainstem nuclei of cranial nerves V, VII, IX, X, XII, and degeneration of the corticospinal tracts secondary to loss of cortical motor neurons. This degeneration produces symptoms that include asymmetric muscle atrophy and weakness and bulbar abnormalities, such as dysarthria, dysphagia, drooling, and an ineffective cough. The clinical course ultimately ends in paralysis, but the type depends upon whether upper or lower motor neuron lesions are most prominent. If upper motor neuron lesions predominate, the paralysis is spastic whereas lower motor neuron lesions result in flaccidity. Both evolve over months to years and affect all striated muscles except that of cardiac and ocular origin. The disease leads to a restrictive pulmonary defect, with progressive decreases in FVC and FEV1 as a result of muscle weakness and skeletal deformities. These changes can occur rapidly but typically are slowly progressive and lead to hypercarbia, atelectasis, and a predisposition to pneumonia.[22] Multiple studies suggest that survival and quality of life may be enhanced by the administration of riluzole, a glutamate release antagonist, and both respiratory and nutritional support in the form of noninvasive ventilation and placement of a gastrostomy tube.[22–24] Death usually occurs within 3–10 years of diagnosis due to respiratory complications, such as pneumonia, atelectasis, and/or aspiration.

There are no laboratory tests to confirm the diagnosis of ALS, which is usually made on the basis of both upper and lower motor neuron abnormalities in association with progressive motor dysfunction.[21,22] Supporting laboratory evidence includes spontaneous fibrillations, positive sharp waves, fasciculations and decreased recruitment of motor units on EMG. Nerve conduction studies are normal or reflect denervation of motor neurons without sensory involvement.

Genetics may play a role in the etiology of some cases of ALS as mutations in superoxide dismutase 1, TAR DNA-binding protein, fused in sarcoma, and ubiquitin 2 are associated with the development of ALS, but there are suggestions that environmental factors such as central nervous system trauma, bacteria, and cigarette smoke may be involved.[25] Ultrastructural changes in the motor neurons of patients with ALS include inclusion bodies and swelling in the proximal axon and cell body. Ultimately, these abnormal neurons are thought to undergo necrosis or apoptosis, leading to degeneration and neuronal cell loss.

Given the pathophysiology and clinical manifestations of ALS, anesthetic considerations include altered responses to muscle relaxants, ventilation impairment, bulbar dysfunction, and concerns about neurologic sequelae of regional anesthesia. Patients with ALS are predisposed to succinylcholine-induced hyperkalemia because of denervation and atrophy of skeletal muscles. Thus, succinylcholine is best avoided in these patients.[25–27] Patients with ALS may also have increased sensitivity to non-depolarizing muscle relaxants, suggesting either that relaxants be avoided altogether or that shorter acting relaxants be used.[25,27] Although not currently clinically available in the US, the administration of Sugammadex to a patient with ALS with residual neuromuscular weakness after reversal of neuromuscular blockade has been successfully reported.[28] Progressive impairment of ventilation is another serious problem and the degree of impairment is a useful predictor of anesthetic risk and the need for postoperative ventilatory support. While it would be easy to suggest that regional anesthesia is preferable to general in such high-risk patients, it has not been established that this is true.[29] Although cases have been successfully conducted using both regional and general anesthesia, significant respiratory involvement may predispose patients with ALS to perioperative respiratory failure. Accordingly, it may be necessary to support ventilation in the ALS patient both during and in the immediate postoperative period regardless of anesthetic technique.[30,31]

The primary concern about bulbar dysfunction is dysphagia and the risk of recurrent pulmonary aspiration.[22] For this reason, aspiration prophylaxis should be considered but there is no evidence that this reduces the perioperative risk of aspiration pneumonitis in the ALS patient. Moreover, because of the inability to swallow properly, many ALS patients will require placement of a feeding tube. This can typically be accomplished under regional anesthesia, but may require the use of noninvasive ventilation both during and after the procedure.[31]

Lastly, there has been concern about the possibility that regional anesthesia may facilitate progression of neurodegenerative diseases such as ALS. Evidence for this is entirely anecdotal, however, and there are several case reports of uneventful neurologic recovery following epidural anesthesia and peripheral nerve blocks in ALS patients.[32–36] Perhaps the most one can say is that regardless of the type of anesthesia, the proximate cause of neurologic deterioration is difficult to establish in a relentlessly progressive neurologic disorder.

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disease (after Alzheimer's disease). Classically considered a movement disorder, secondary to degeneration of dopaminergic neurons in the basal ganglia and nigrostriatal system, it is now recognized that PD is a multisystem neurodegenerative process. It afflicts about 1 million Americans, or approximately 1% of patients over age 60, and its prevalence is projected to double in the next 15–20 years.[37] Fifteen years after diagnosis, 40% of PD patients are living in long-term care facilities and mortality is almost twice the expected rate. Most cases of Parkinson"s disease are idiopathic, but environmental factors, including exposure to volatile anesthetics, [38,39] and genetic predisposition have been implicated; a recent meta-analysis indicated that for those with a first-degree relative with PD the relative risk of developing PD is 2.9.[40] The common feature of the disease is neuronal loss and gliosis of the substantia nigra, pars compacta. By the time motor symptoms develop, 70% of the dopamine producing cells in the striatum have degenerated, leading to a relative imbalance between the inhibitory properties of dopamine and the excitatory properties of acetylcholine within the striatum.[41] However, pathology extends beyond the striatum and dopamine. The pathologic hallmark of PD is the Lewy body, an intracellular aggregate of abnormal proteins including α synuclein, which is present in nearly all forms of PD.[42] This α synuclein pathology and concomitant neurodegeneration are seen in numerous areas of the central and peripheral nervous system including noradrenergic, serotonergic, and cholinergic neurons of the brainstem and in the amygdala, cingulate gyrus, and neocortex. Moreover, changes in these regions may actually precede the striatal degeneration. Therefore, it is overly simplistic to see PD only as a movement disorder.

Cardinal clinical features of Parkinson's disease include a resting rhythmic tremor, muscular rigidity, and bradykinesia. These are often associated with a lack of spontaneous movement, masked facies, cogwheel rigidity, a monotonous voice, stooped posture, and a shuffling gait leading to postural

instability and impaired locomotion.[43,44] Not surprisingly, given the widespread neurodegeneration, non-motor features of the disease represent important sources of disability and, in long-standing PD, are often the predominant problem. Autonomic dysfunction (postural hypotension), daytime sleepiness, depression, anxiety, hallucinations, and psychosis are common; dementia is almost universal in patients with long-standing PD,[44] and can be as high as 90% in patients 90 years old or greater.[45]

There is no cure for Parkinson's disease. Therapy has focused almost exclusively on the motor aspects of the disease, and only recently have the cognitive and non-motor symptoms received attention. Given that the main deficit in PD is inadequate dopamine in the basal ganglia, pharmacologic therapy aims to increase the activity of dopamine relative to acetylcholine in this region. This is typically accomplished with dopamine receptor agonists, such as bromocriptine and pergolide or with levodopa (L-DOPA), a prodrug that undergoes decarboxylation in both the periphery and central nervous system to produce dopamine. Peripheral conversion of L-DOPA to dopamine produces side effects such as nausea, vomiting, and hemodynamic instability, so combined treatment with carbidopa, a decarboxylase inhibitor that does not cross the blood–brain barrier, is common. L-DOPA is the most potent, best-tolerated symptomatic therapy and may even slow disease progression, but dopamine agonists are often first-line therapy because L-DOPA is associated with a higher incidence of dyskinesias.[44] Dopamine agonists have their own problems, however, including leg edema, hallucinations, somnolence, and development of impulse control disorders, such as binge eating or compulsive gambling. A variety of other drugs used to treat Parkinson's disease also act by altering the dopamine/acetylcholine balance in the brain. Usually used as initial therapy of mild Parkinson's disease or as an adjunct to levodopa therapy in patients with dose-related fluctuations, benztropine and other anticholinergic agents block cholinergic transmission and amantadine, an antiviral agent, alters the uptake and release of dopamine at presynaptic sites.[44] Because monoamine oxidase (MAO) is the major enzyme involved in oxidative metabolism of dopamine in the striatum, type-B MAO inhibitors such as selegiline are often employed. Early concerns that the combination of L-DOPA and selegiline may lead to increased mortality have not been substantiated and selegiline has become a first-line treatment choice for many clinicians.[46,47]

When motor complications become disabling and medical therapy fails, deep brain stimulation (DBS) is recommended.[48] DBS involves surgical placement of electrodes in the subthalamic nucleus and other brain regions, and stimulation at high frequencies. In this case stimulation leads to effects similar to lesioning of the same region, possibly by jamming or desynchronizing the region being stimulated.[49] In a 4-year, multicenter trial of patients with bilateral DBS showed an improvement in activities of daily living and PD symptoms.[50] Given the success of DBS in managing medically refractory PD, other surgical approaches for the control of PD, such as thallamotomy and pallidotomy have become increasingly less common as they involve destructive brain lessioning.[46]

Transplantation of fetal midbrain or stem cells into human PD patients is another exciting alternative. The cells function and survive for up to 14 years, but begin to develop Lewy bodies and fail after about 10 years.[51,52] Indeed, some argue that pharmacologic and surgical treatments are inherently limited because they only address a late, specific event—loss of striatal dopamine neurons—in what is likely to be a widespread disease.

Perioperative management of the patient with Parkinson's disease is challenging. Attention should be directed toward maintenance of perioperative drug therapy, potential adverse drug interactions, and the physiologic perturbations associated with the disease. It is also important to recognize that emotional stress, which is unavoidable and difficult to address in the perioperative period, can also exacerbate PD. One major problem is that the half-life of levodopa is short (about 60–90 min).[44] Therefore, even brief interruptions in drug therapy are undesirable and can result in an acute exacerbation of the symptoms of Parkinson's disease or the development of neuroleptic malignant syndrome, a potentially fatal disorder that presents as hyperthermia, akinesia, altered consciousness, muscle rigidity, and autonomic dysfunction.[44,53–55] Consequently, interruption of anti-Parkinson's drug therapy should be as brief as possible. However, maintenance of therapy is difficult when the patient is unable to take medications *per os* for lengthy periods. Intravenous levodopa has been used successfully in the perioperative period but, without coadministration of a decarboxylase inhibitor (not yet available in intravenous form), cardiovascular side effects such as hypertension, hypotension, and arrhythmias can be anticipated. Levodopa and carbidopa are absorbed in the small intestine and thus must first traverse the stomach, making administration of tablets through a gastric tube suboptimal or ineffective because patients with Parkinson's disease often have delayed gastric emptying.[56,57] One recent report involving six patients noted success in administering intravenous amantadine in the perioperative period without the adverse effects of amantadine administration or perioperative complications and this may, therefore, represent a viable alternative.[58]

In addition, Parkinson's disease takes a toll on body systems that are vitally important during and after surgery. Respiratory dysfunction is especially prominent.[59,60] Parkinson's disease can produce restrictive lung disease secondary to chest-wall rigidity, but pulmonary function tests often reveal a obstructive pattern with a characteristic "sawtooth" pattern on flow volume loops, which are improved, but not normalized, with levodopa.[60,61] Upper airway abnormalities also occur. Involuntary movements of the glottis and supraglottic structures cause intermittent airway obstruction, a condition that can be exacerbated by levodopa withdrawl.[60,62] Upper airway obstruction, laryngospasm, and respiratory arrest are documented complications of Parkinson's disease and may occur outside the setting of anesthesia and surgery.[60,63–65] Perhaps not surprisingly, therefore, laryngospasm has been reported postoperatively in awake patients hours after surgery.[66] Direct visualization of the larynx during such episodes reveals complete apposition of the vocal cords requiring succinylcholine for relief.[65] While some of these cases occurred despite maintenance of anti-Parkinson's drug therapy, most followed withdrawal or pharmacologic antagonism of Parkinson's medication.[64,66] Indeed, not only should interruption of drug therapy be minimized, but also the dosage may need to be increased if airway problems persist despite otherwise adequate therapy.

Parkinson's patients are predisposed to aspiration because they often have severe, but asymptomatic, dysphagia and dysmotility which, combined with upper airway abnormalities, presents an especially troublesome situation.[67,68] In fact, pulmonary aspiration is a frequent cause of death among patients with Parkinson's disease. As such, administration of antacids and pro-kinetic agents should be considered, but whether anesthesia actually increases the risk of aspiration in these patients is unknown. Metoclopramide must be avoided, however,

because it is a dopamine receptor antagonist and could acutely exacerbate the disease. In contrast, prokinetic agents, such as cisapride or domperidone, have no effect on central dopaminergic balance and are reasonable alternatives.[69]

Nervous system dysfunction is also common. Autonomic insufficiency affects the ability of Parkinson's patients to respond to the hypovolemia and vasodilation sometimes associated with anesthesia and surgery.[70,71] Orthostatic hypotension and/or thermoregulatory or genitourinary dysfunction suggests preexisting autonomic insufficiency and should heighten awareness of the potential for perioperative hemodynamic instability and altered responses to vasopressors such as norepinephrine (noradrenaline).[72] At the level of the central nervous system, psychiatric complications such as anxiety, confusion, and even frank psychosis occur more frequently in patients with Parkinson's disease than the general population, and can be especially problematic in the perioperative period.[44] Often related to or exacerbated by fluctuations in anti-Parkinson's drugs, the first line of treatment is to look for and remedy reversible causes as one would in any patient with delirium.[73,74] Pharmacologic treatment is difficult, however, because the usual remedies (e.g., benzodiazepines for anxiety and antipsychotics for psychosis) can produce severe side effects, such as oversedation or acute exacerbation of motor symptoms in elderly patients with PD.[73,75] In the event such treatment becomes necessary, consultation with a specialist is recommended.

Anesthetics and a number of other agents used perioperatively may affect the disease process. Volatile anesthetics can alter dopaminergic balance in the brain but whether they exacerbate Parkinson's disease is unknown.[76,77] In fact, provided the intraoperative electrophysiological approach is based on multi-unit recording, deep brain stimulation surgery has been performed successfully under general anesthesia with a volatile agent, suggesting activity in dopaminergic circuits are reasonably well maintained.[78] Propofol produces both dyskinesias and ablation of resting tremor, suggesting that it has both excitatory and inhibitory effects in this patient population, but it also has been used successfully to sedate Parkinson's patients during DBS surgery.[79,80] Dexmedetomidine also appears to be safe and, when used for deep brain lead implantation and stimulation, has the advantage of not interfering with motor symptoms.[81] Ketamine should be used cautiously, if at all, because of potential interactions between levodopa and its sympathomimetic properties. However, in a single case report, ketamine temporarily stopped the motor symptoms of the disease.[82] Butyrophenones (e.g., droperidol) and phenothiazines, which block dopamine receptors and exacerbate Parkinson's disease and so should be avoided.[83] In at least one case, droperidol may have induced parkinsonism in a normal patient.[84] Ondansetron, a 5HT-3 serotonin receptor antagonist, appears to be a safe treatment or prevention of emesis in these patients and has been used successfully to treat the psychosis of chronic levodopa therapy.[85] Although opioids are more likely to produce muscular rigidity in a patient with Parkinson's disease, acute dystonia has been observed only rarely and enhancement of opioid neurotransmission during disease progression may be a compensatory mechanism that prevents motor complications.[86,87] Meperidine should be avoided in a patient taking an MAO inhibitor, however, because of the potential for the development of stupor, rigidity, agitation and hyperthermia.[88] Responses to depolarizing as well as nondepolarizing muscle relaxants are thought to be normal in Parkinson's disease, despite a single case report of succinylcholine-induced hyperkalemia.[89–91]

Finally, with the advent and increasing popularity of DBS, issues arise about the safety of MRI or intraoperative electrocautery in PD patients with stimulator leads in place.[92,93] In theory, extraneous current can heat the electrode tip, causing brain tissue damage, but there is limited experience with this circumstance clinically. To reduce the risk of injury, the bipolar mode should be used if electrocautery is needed and the leads and generator should not be located between the surgical site and ground plate. In the case of an MRI, the neurostimulator should be switched off.

ALZHEIMER'S TYPE DEMENTIA

Dementia is a chronic and progressive decline in intellectual function. As such, it is distinct from normal age-related memory impairment or the acute confusion of delirium. The differential diagnosis of dementia is extensive, but Alzheimer's disease (AD) is the most common type.[94,95] This section will, therefore, focus on AD because it is the most prevalent type of dementia and because there is little evidence that the form of dementia alters perioperative considerations.

Alzheimer's-type dementia is a chronic neurodegenerative disease that afflicts nearly 5 million Americans, making it the fourth leading cause of death in the US and a major public health problem.[94–96] AD rarely presents before age 65, but increases in incidence two-fold every 5 years thereafter until, by age 90, up to 50% of people are affected.[94–96] The clinical diagnosis of AD is difficult because, at least early on, symptoms are often subtle, nonspecific and not easily distinguished from other dementias. Therefore, the definitive diagnosis is made post mortem with demonstration of gross atrophy of the cerebral cortex in conjunction with the neuropathological hallmarks of the disease, namely, neurofibrillary tangles consisting of phosphorylated tau protein and neuritic plaques composed of amyloid β (Aβ). Recent advances in neuroimaging for amyloid plaques and biomarker discovery, particularly for Aβ and tau in plasma and cerebrospinal fluid, promise to enhance the ability to diagnose AD early,[97] but there is enough overlap in the distribution and levels of these markers between demented and nondemented persons that at present none are a foolproof surrogate for a clinical or histopathological diagnosis. AD is insidious, relentless, and devastating. There is a transitional phase, called mild cognitive impairment (MCI), between normal aging and AD, that is defined by a decrease in cognition in any domain, most commonly episodic memory, without impairment of activities of daily living.[98,99] The criteria used to define it vary but, in general, about 10–20% of community-dwelling elders have MCI.[100] A large percentage will ultimately convert to AD, which suggests MCI is an early phase of AD in many people.[99] Full blown AD affects much more than memory; namely, language, visuospatial skills, judgment, reasoning, decision-making, and the ability to manage complex tasks deteriorate. Also common are behavioral and psychiatric abnormalities, such as depression, hallucinations, delusions, anxiety, aggression, and agitation. Ultimately, the patient becomes incapacitated to the point of being unable to perform basic activities of daily living.[101] There is currently no cure and death usually occurs within 2–16 years of onset.

AD is probably the end result of a number of biologic and environmental factors.[95] There is a genetic component to the disease as demonstrated by linkage studies revealing rare mutations in the amyloid precursor protein and presenilin genes and increased susceptibility to AD among carriers of the apolipoprotein gene E4 allele.[102] Most of these genetic alterations

are neither necessary nor sufficient to cause AD, however, indicating genetic susceptibility works in combination with other factors. Low education level, prior history of head trauma, thyroid disease, and exposure to general anesthesia have been investigated as possible risk factors, with mixed results.[103] Because depression is prevalent in patients with dementia, there is also debate about whether depression is a risk factor for dementia or, conversely, whether subclinical dementia leads to depression.

The pathological hallmarks of AD are extracellular plaques and intracellular neurofibrillary tangles composed of Aβ and tau protein, respectively. This pathology develops long before symptoms develop; indeed, deposition of Aβ in brain parenchyma is believed to be an early critical event in the development of AD.[95] Note, however, that a person can have a high burden of Aβ and be cognitively intact initially. How Aβ and tau produce neurodegeneration and functional impairment is not definitively known, but free radical-mediated oxidative damage, CNS inflammation, energy depletion, calcium-mediated neurotoxicity, and abnormal metal homeostasis are a few of the many theories.[95,104,105] If the exact mechanism of injury is uncertain, the result is clear. Patients with AD have profound and accelerated cortical atrophy, synapse loss, reactive gliosis, cerebral hypometabolism, and breakdown in cerebral network activity.[106] All major neurotransmitter systems are damaged, particularly in areas associated with memory and cognition such as the hippocampus, basal forebrain, and cerebral cortex, and cerebral proinflammatory cascades are activated, leading to a state of chronic neuroinflammation.

Therapeutic approaches to AD reflect this understanding of the disease pathogenesis, but none have proven effective at stopping or reversing disease progression. Given deficiencies in central cholinergic activity, a mainstay of medical therapy for AD is the administration of anticholineasterases, such as donepezil and rivastigmine.[107] Widely used, these drugs have favorable but mild effects on neuropsychiatric and functional outcomes, mostly in early to moderate stage disease.[108a] They also have a variety of side effects including reversible hepatotoxicity, gastrointestinal symptoms (nausea, vomiting, diarrhea, dyspepsia, abdominal pain), and dermatitis, and the potential for interactions with hepatically metabolized drugs such as cimetidine and warfarin also exists.[106] Memantine, a mild, partial NMDA glutamate receptor antagonist, is also widely used but, like donepezil, it produces marginal improvement in cognition early on in the disease, but does not change disease trajectory.[108a] Numerous other agents, such as estrogen, antioxidants (e.g., vitamin E), statins, and anti-inflammatory agents, have also been tried.[106] Some show promise but the data are not conclusive and, at times, are conflicting.[108b,109a] Anti-inflammatory agents have been studied fairly extensively but with conflicting results.[109b,110] Some of the confusion may relate to the age of the study cohort, duration of treatment, and the fact that some NSAIDs have cyclooxygenase-independent effects on Aβ processing, whereas others do not.[111] In fact, any benefit of NSAIDs may be unrelated to their anti-inflammatory actions.[111]

Given the hypothesis that Aβ plays a prominent role in AD pathogenesis, many preventative/treatment efforts are focused on reducing the Aβ burden. Unfortunately, most of these trials have been disappointing. A phase 3 trial of the semagacestat, a γ secretase inhibitor that blocks conversion of the large amyloid precursor protein (APP) to Aβ, was terminated early due to lack of improvement in cognition and adverse side effects.[112] Likewise, two recent trials of monoclonal antibodies intended to capture and clear peripheral and central Aβ proved ineffective.[113,114] Moreover, an early clinical trial testing a vaccine to Aβ was aborted due to development of encephalitis, but the results were encouraging enough that newer, less immunogenic vaccines are being tested.[115] Whether these more sophisticated and targeted molecular approaches to AD are successful remains to be seen.[116] Indeed, these failures have led some to question as to the underlying assumption that Aβ is the cause of AD,[117] but there is hope that earlier intervention, when plaques and tangles are present, but the neural damage has not yet occurred, will prove more effective.[118]

Perioperative care of the patient with Alzheimer's disease is challenging. First, the anticholinesterases used to treat AD may interfere with metabolism of drugs such as succinylcholine and remifentanil that are degraded by plasma anticholinesterases.[119] Second, because pre-existing cognitive impairment predisposes to delirium, the AD patient is at high risk for postoperative confusion.[73,120,121] There is, however, no reason to think that the precipitating causes of delirium in the demented patient differ from those in the normal patient, although their threshold for developing a cognitive disturbance is presumably lower. Thus, one should assiduously avoid precipitators of delirium, such as cerebral hypoxia and hypoperfusion, endocrine or ionic imbalances, postoperative pain, sepsis, bowel or bladder distension, and use of medications prone to trigger delirium, such as high-dose steroids, neuroleptics, benzodiazepines, ketamine, tertiary anticholinergics, opioids, H-2 blockers, and droperidol.[73] Somewhat counterintuitively, the type of anesthesia (regional vs. general) does not seem to matter as far as complications or mortality after hip fracture repair are concerned, but the rate of ICU admission is higher when this procedure is done under general anesthesia.[122] Excessively deep anesthesia may be a risk, however, as the AD patient with amnesia and severe cortical atrophy and synaptic loss might be exquisitely sensitive to the central nervous system depressant effects of general anesthetic agents. Some literature challenges this assumption,[123,124] but one should be cautious about excessively deep anesthesia in the demented patient with a clearly abnormal brain, if for no other reason than both preexisting cognitive impairment and deeper anesthesia as judged by processed EEG are associated with a higher incidence of postoperative delirium.[125,126]

Whether general anesthesia worsens preexisting dementia is not clear. Studies that demonstrate persistent postoperative cognitive dysfunction (POCD) in elderly surgical patients, including specific deficits in memory and executive function, have typically excluded patients with MCI or AD.[127,128] Thus, while it is reasonable to infer that a demented patient might be at greater risk for additional cognitive decline perioperatively than a cognitively intact person, this is unproven. Moreover, because poor baseline cognitive performance makes further decline difficult to detect with standard testing, it may be unprovable.[129] More provocative is the question of whether surgery and general anesthesia can cause dementia.[130] Evidence from animals indicates that some commonly used general anesthetic agents and surgery itself enhance the molecular events associated with AD, including producing an increase in cerebral levels of Aβ and phosphorylated tau protein.[131–134] Epidemiological studies on the topic are retrospective and inconclusive, with some finding no association between surgery/anesthesia and subsequent dementia, and others suggesting that there is one.[103,135–137] The slow development and progression of dementia makes this a difficult problem to study, but well-controlled, prospective studies are clearly necessary.

DEMYELINATING DISEASES

Guillain–Barré, Multiple Sclerosis, and Nitrous Oxide Neuropathy

Guillain–Barré (Acute Idiopathic Polyneuritis)

Guillain–Barré is the most common demyelinating paralytic disease in Western countries, with an incidence of 1.1 per 100,000 person years and occurs more frequently in men.[138] Prevailing theories define it as a postinfectious autoimmune disease; it usually develops after a prodromal bacterial or viral illness (*Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, or mycoplasma).[138] The pathogenesis results from antibody mediated segmental demyelination of peripheral nerves and varying degrees of secondary axonal degeneration, in addition to direct helper T cell reactivity to Schwann cells and myelin, leading to the recruitment of macrophages.

The clinical course of Guillain–Barré is characterized by an acute (days) or subacute (weeks) progressive, ascending, symmetrical paralysis usually beginning in the lower limbs and progressing to the upper limbs, trunk, and cranial nerves.[139] There is significant variability in the clinical course of the disease. Typically, the disease progresses for 2–4 weeks, plateaus for several weeks, and then slowly recedes. Dysautonomia, paresthesias, numbness, and pain without objective sensory loss are common findings.[138] All brainstem functions including pupillary responses, corneal reflexes and vestibulo-ocular reflexes may be lost such that the condition mimics brainstem death.[140,141] Outcome is variable; 70% of patients have complete functional recovery at 1 year, but up to 20% are left with severe motor sequelae.[138] Even most patients with complete functional recovery have persistent weakness or numbness not affecting daily life. The 1-year mortality rate is 3–7%.[138] Risk factors for an unfavorable outcome include advanced age, rapid onset and progression of the disease, comorbidities, cardiac and pulmonary complications, a requirement for ventilatory support, and systemic infection.[138] The diagnosis is usually made on clinical grounds and verified by nerve conduction studies and CSF analysis.[139]

A number of therapies have been used to alter the course of this disease, but none are curative. Based on the assumption that Guillain–Barré is an immune-mediated disease, high-dose steroids have been employed, but efficacy is not substantiated by controlled studies. Based on the same theory, plasma exchange and high-dose intravenous immunoglobulins have been evaluated. In prospective randomized studies, they are equally effective in producing functional improvement and are often used early in the disease to both shorten the duration and decrease the risk of respiratory failure.[142] Because such therapies are not curative, symptomatic and supportive care is often required. Mechanical ventilation and hemodynamic support may be necessary due to respiratory failure and autonomic insufficiency, respectively.[138] Severe pain is common in Guillain-Barré and may present prior to onset of weakness. Unfortunately pain associated with Guillain-Barré is often difficult to control and resistant to narcotics, nonsteroidal and steroidal anti-inflammatory agents.[143,144] Both carbamazepine and gabapentin decrease fentanyl consumption during the acute phase in patients admitted to the ICU, however, and pain scores are lower among patients treated with gabapentin.[145] Chronic pain is also common and often managed with tricyclic antidepressants, tramadol, gabapentin, carbamazepine, or mexilitene.[143]

Anesthetizing the patient with Guillain-Barré presents challenges related to abnormal responses to muscle relaxants, dysautonomia, pulmonary insufficiency, and cranial nerve dysfunction. First, since muscle denervation is prominent, patients recovering from Guillain–Barré are at risk for a hyperkalemic response to succinylcholine.[146,147] The response to nondepolarizing muscle relaxants is also variable. Resistance to block may appear early, whereas sensitivity to blockade occurs later and has persisted for up to 4 years following the initial illness.[148]

Autonomic dysfunction occurs in two-thirds of patients with Guillain–Barré and affects both the sympathetic and parasympathetic nervous systems.[149] This dysautonomia is due to both under- and overactivity of the sympathetic and parasympathetic nervous systems; indeed, some patients are hypertensive and have elevated plasma catecholamine levels, especially during the acute phases of the disease. This dysfunction can lead to a range of autonomic abnormalities including sweating, gastrointestinal dysfunction, hypotension, hypertension, abnormal hemodynamic responses to drugs, abnormal thermoregulation, arrhythmias, and even death.[149] Hence, the ability of the patient to compensate for the vasodilatory effects of regional or general anesthesia may be compromised, potentially leading to severe hemodynamic instability and even circulatory collapse. There may also be exaggerated responses to vasoactive agents and vasodilators should be used with extreme caution. Similarly, antiarrhythmics should be used with caution as the heart is relatively denervated in patients with Guillain–Barré and may have unexpected proarrhythmic effects.[149]

Ventilatory impairment is a principal characteristic of the disease with 25% of patients requiring artificial ventilation.[138] Diaphragmatic, intercostal, and accessory muscle weakness produces a restrictive pulmonary defect and respiratory failure manifests initially as weakness of forced exhalation and an impaired cough.[143] Rapid shallow breathing pattern, asymmetric movement of the chest and abdomen during inspiration, and use of accessory muscles suggest impending respiratory failure. Decreased minute ventilation and hypercarbia lead to rapidly progressive ventilatory failure despite intact carbon dioxide responsiveness and ventilatory drive.[143] Vital capacity is a good predictor of the need for mechanical ventilation.[143] When the vital capacity decreases below 15 mL/kg, mechanical ventilation is often required because further deterioration is likely as the disease progresses. However, these criteria may be altered in the anesthetized patient. To the extent that volatile anesthetics have intrinsic muscle relaxant properties and high spinal or epidural anesthesia impairs intercostal muscle function, preoperative status may not predict postoperative respiratory function. Thus, Guillain–Barré patients with adequate ventilatory function preoperatively may need ventilatory support postoperatively regardless of the type of anesthetic administered.

Finally, cranial nerve dysfunction results in an inability to handle secretions and a predisposition to aspiration pneumonitis and positional airway obstruction.[143] Accordingly, aspiration prophylaxis should be considered perioperatively but it is unlikely to mitigate aspiration risk in these patients. In fact, one indication for early tracheostomy is that bulbar muscle weakness, and aspiration risk, may persist long after ventilatory function returns to normal.

Multiple Sclerosis

Multiple sclerosis (MS) is an acquired disease of the central nervous system characterized by demyelinating plaques within the brain and spinal cord.[150] The precise etiology is unknown but autoimmune, viral, and inflammatory mechanisms, combined

with genetic susceptibility, have been implicated.[150,151] The incidence varies by geographic latitude, being lowest near the equator (1:100,000) and increasing as one moves toward the poles.[152] In the US and Canada, the incidence varies between 6 and 80 per 100,000, with urban dwellers and members of higher socioeconomic groups at greatest risk.

Symptoms generally develop between the ages of 20 and 40 with clinical manifestations reflecting the site of central nervous system demyelination.[153] A predilection for periventricular white matter, optic nerves, pons, medulla and spinal cord lead to the common clinical manifestations. These include optic neuritis, decreased visual acuity, diplopia, nystagmus, weakness, impotence, paresthesias, spasticity, ataxia, bladder dysfunction and autonomic insufficiency. This disease is marked by periods of unpredictable exacerbation and remission. Typically, symptoms develop over a few days, remain stable for a few weeks, and then improve. Improvements are most likely due to a correction in nerve conduction physiology and not remyelination. Ultimately, therefore, remission is incomplete and severe disability can result. There are no specific diagnostic tests for MS so the diagnosis is based on clinical findings supported by laboratory and radiologic tests. Evidence for the diagnosis includes neurologic abnormalities that are separated both in time and place, plaques on head or spinal cord MRI or CT scan, delayed conduction on visual, somatosensory, or auditory evoked potentials, and elevations of CSF IgG and myelin basic protein.[153] Death is usually the result of respiratory muscle paralysis and infection.[154]

There is no definitive therapy for MS.[153] Treatment is directed toward amelioration of acute exacerbations, prevention of relapses, and relief of symptoms. Disease modifying therapies (DMT) for MS have traditionally required administration of injectable drugs including interferon-beta, glatiramer acetate, natalizumab and mitoxantrone. While these drugs are effective in enhancing recovery from acute episodes, reducing the number of relapses, and deterring progression of the disease, they have also been fraught with problems associated with drug administration via injection.[153,155] Recently three orally administered drugs have been approved for the treatment of MS including fingolimod, teriflunomide and dimethyl fumarate, all of which are associated with decreased CNS lesions, suppressed relapse rates, and have reasonable safety profiles.[155]

Perioperative issues generally relate to disease severity and progression, associated disorders, preoperative drug therapy, and complications of therapeutic regimens. Because of the waxing and waning clinical course of the disease and the fact that perioperative exacerbation can occur, it is important to document the location and severity of neurologic deficits preoperatively. Autonomic insufficiency, as indicated by a history of impotence, bladder and bowel dysfunction, sweating and cardiovascular disturbances, is also important because of the possibility of perioperative hemodynamic instability and an inability to compensate for the vasodilatory effects of general, spinal, or epidural anesthesia.[149] Interestingly, catecholamine levels may be either elevated (chronic progressive MS) or reduced (relapsing–remitting MS). Whether sensitivity to vasopressors is altered remains unknown, but because 20–50% of patients with MS have evidence of autonomic insufficiency the potential for altered responses should be anticipated.[149,156] Spasticity, contractures, and limitation of movement become a problem as the disease progresses. These make surgical positioning difficult and occasionally complicate airway management. Cranial nerve involvement and respiratory muscle weakness are also common in MS. In particular, patients should be questioned about a history of upper airway incompetence, inability to clear secretions, and aspiration. Clinical assessment is usually adequate for evaluating the severity of respiratory muscle weakness in patients, but PFTs may be indicated in some cases.[157]

One important consideration in the operating room or ICU is that MS patients are exquisitely sensitive to hyperthermia.[158,159] Small increases in body temperature can cause profound deterioration in neurologic function and make subclinical lesions clinically apparent. As such, active warming devices should be used cautiously during the perioperative period and even mild hyperthermia treated aggressively. A controversial and poorly investigated allegation is that surgery, anesthesia, or particular anesthetic agents can exacerbate MS.[160] The greatest controversy concerns a traditional reluctance to use spinal or epidural anesthesia in a patient with MS.[161,162] This reluctance is based, in part, on potentially increased permeability of the blood–brain barrier to local anesthetics and a demyelination-induced predisposition of the spinal cord to local anesthetic toxicity.[163] One speculation is that epidural is more appropriate than spinal anesthesia because the former produces a lower CSF concentration of local anesthetic.[164] There are, however, no large, controlled studies to resolve the issue and case reports of both neurologic complications and uncomplicated use of spinal and epidural anesthesia exist.[164–166] Moreover, while MS is considered to target the central nervous system, a recent case report suggests that peripheral nerve blocks may contribute to peripheral nerve injury in patients with MS.[167]

There are also some minor issues related to drug effects to consider. Responses to muscle relaxants may be altered. Succinylcholine-induced hyperkalemia is a risk in the patient with severe neurologic disability and muscle atrophy but succinylcholine has been used safely in patients in remission or with mild neurologic symptoms. Data concerning the response to nondepolarizing muscle relaxants are limited. Proliferation of extrajunctional cholinergic receptors and resistance to atracurium are reported in MS but, because MS can be associated with myasthenia gravis, increased sensitivity can also occur.[168,169]

Nitrous Oxide Induced Myeloneuropathy

In addition to its analgesic/anesthetic properties, nitrous oxide inactivates vitamin B12 (cobalamin) and methionine synthase.[170–172] Consequently, use of this drug can lead to the development of subacute combined degeneration, a myeloneuropathy originally described in patients with vitamin B12 deficiency. Vitamin B12 and the enzyme methionine synthase are essential for the production of methionine, an amino acid precursor required for maintenance of the myelin sheath. Nitrous oxide inactivates vitamin B12 by oxidizing the cobalt in cobalamin, thereby inhibiting the activity of methionine synthase.[170–172]

Subacute combined degeneration (SCD) after inhalation of nitrous oxide continues to be described in healthy chronic abusers of the drug, but it has also been documented following a single, otherwise uncomplicated anesthetic in patients with vitamin B12 deficiency.[173–175] In this context, the condition is sometimes termed "anesthesia paresthetica" but remains pathophysiologically identical to SCD.[176] Vitamin B12 deficiency is common in elders and patients with pernicious anemia, tropical sprue, malnutrition, chronic gastritis, HIV infection, gastrectomy, or surgical resection of the terminal ileum.[177] Both serum vitamin B12 concentration and brain methionine synthase activity typically decrease significantly

following a single exposure to nitrous oxide, but recover within 48–72 hours.[178] The presumption is that repeated, frequent administration of nitrous oxide, or even a single administration to a patient with a vitamin B12 deficiency because of a coexisting disease state, is required for the subsequent development of nitrous oxide-induced SCD.[173]

The patient who develops subacute combined neurodegeneration after receiving nitrous oxide is usually normal upon emergence from anesthesia and in the immediate perioperative period but develops symptoms of the illness weeks to months later.[173,175] Symptoms include paresthesias (pins and needles sensations in the hands and legs), impotence, bladder and bowel dysfunction, weakness and spasticity leading to paraplegia, ataxia, personality changes, and progressive intellectual impairment.[173,179] Lhermitte's sign, a characteristic electric shock sensation down the back and into the legs upon flexion of the neck, may also be present.[173,179] Decreased proprioceptive, vibratory, and touch sensation in a stocking-glove distribution, muscle weakness, decreased deep tendon reflexes, and abnormalities on electrophysiologic testing are frequently identified.[175,179,180] These neurologic findings are the result of progressive demyelination in the posterior columns of the spinal cord; variable degeneration of the lateral and anterior columns of the spinal cord, brain, optic, and peripheral nerves may also occur. Demyelination, which typically begins in the lower cervical or upper thoracic cord, is detectable by MRI and, as demonstrated by enhancement after gadolinium, is associated with breakdown of the blood–brain barrier.[173,181,182]

The most effective treatment is prevention through preoperative recognition of B12 deficiency in at-risk patients.[183] If the disease develops, however, the key is early recognition because treatment is straightforward and simple: vitamin B12 or cyanocobalamin injections stop progression of the disease. Provided treatment is begun promptly, complete resolution of symptoms can be expected.[173] Thus, nitrous oxide-induced subacute combined neurodegeneration is unique among the neurologic diseases in this chapter in that it is caused by an anesthetic agent and can be treated effectively.

REFERENCES

1. Ross CA, Tabirizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2010;10:83–98.
2. Bjorkqvist M, Wild EJ, Thiele J, et al. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *J Exp Med*. 2008;205:1869–1877.
3. van der Burg JM, Björkqvist M, Brundin P. Beyond the brain: Widespread pathology in Huntington's disease. *Lancet Neurol*. 2009;8:765–774.
4. Zielonka D, Piotrowska I, Marcinkowski JT, Mielcarek M. Skeletal muscle pathology in Huntington's disease. *Front Physiol*. 2014;5:380.
5. Walker FO. Huntington's disease. *Lancet*. 2007;369:218–228.
6. Kivela JE, Sprung J, Southorn PA, Watson JC, Weingarten TN. Anesthetic management of patients with Huntington disease. *Anesth Analg*. 2010;110:515–523.
7. Rodrigo MRC. Huntington's chorea: Midazolam, a suitable induction agent? *Br J Anaesth*. 1987;59:388–389.
8. MacPherson P, Harper I, MacDonald I. Propofol and remifentanil total intravenous anesthesia for a patient with Huntington disease. *J Clin Anesth*. 2004;16:537–538.
9. Esen A, Karaaslan P, Can Akgun R, Arslan G. Successful spinal anesthesia in a patient with Huntington's chorea. *Anesth Analg*. 2006;103:512–513.
10. Whittaker M. Plasma cholinesterase variants and the anaesthetist. *Anaesthesia*. 1980;35:174–197.
11. Gualandi W, Bonfanti G. A case of prolonged apnea in Huntington's chorea. *Acta Anaesthesiol*. 1968;19(Suppl 6):235–238.
12. Costarino A, Gross JB. Patients with Huntington's chorea may respond normally to succinylcholine. *Anesthesiology*. 1985;63:570.
13. Nagele P, Hammerle AF. Sevoflurane and mivacurium in a patient with Huntington's chorea. *Br J Anaesth*. 2000;85:320–321.
14. Kulemeka G, Mendonca C. Huntington's chorea: Use of rocuronium. *Anaesthesia*. 2001;56:1019.
15. Farina J, Rauscher LA. Anaesthesia and Huntington's chorea. A report of two cases. *Br J Anaesth*. 1977;49:1167–1168.
16. Kaufman MA, Erb T. Propofol for patients with Huntington's chorea? *Anaesthesia*. 1990;45:889–890.
17. Sriganesh K, Saini J. Exacerbation of involuntary movements after propofol anesthesia in a patient with Huntington disease. *J Neurosurg Anesthesiol*. 2013;25:212–214.
18. Fernandez IG, Sanchez MP, Ugalde AJ, Hernandez CM. Spinal anaesthesia in a patient with Huntington's chorea. *Anaesthesia*. 1997;52:391.
19. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. *Orphanet J Rare Dis*. 2009;4:3.
20. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population: Validation of a scoring system and a model for survival prediction. *Brain*. 1995;118:707–719.
21. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet*. 2007;369:2031–2041.
22. Radunović A, Mitsumoto H, Leigh PN. Clinical care of patients with amyotrophic lateral sclerosis. *Lancet Neurol*. 2007;6:913–925.
23. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med*. 1994;330:585–591.
24. Turner MR, Parton MJ, Leigh PN. Clinical trials in ALS: An overview. *Semin Neurol*. 2001;21:167–175.
25. Prabhakar A, Owen CP, Kaye AD. Anesthetic management of the patient with amyotrophic lateral sclerosis. *J Anesth*. 2013;27:909–918.
26. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. *JAMA*. 1970;213:1867–1871.
27. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: A review. *Anesthesiology*. 1984;61:173–187.
28. Kelsaka E, Karakaya D, Zengin EC. Use of sugammadex in a patient with amyotrophic lateral sclerosis. *Med Princ Pract*. 2013;22:304–306.
29. Jackson CE, Bryan WW. Amyotrophic lateral sclerosis. *Semin Neurol*. 1998;18:27–39.
30. Moser B, Lirk P, Lechner M, Gottardis M. General anaesthesia in a patient with motor neuron disease. *Eur J Anaesthesiol*. 2004;21:921–923.
31. Boitano LJ, Jordan T, Benditt JO. Noninvasive ventilation allows gastrostomy tube placement in patients with advanced ALS. *Neurology*. 2001;56:413–414.
32. Hara K, Sakura S, Saito Y, Maeda M, Kosaka Y. Epidural anesthesia and pulmonary function in a patient with amyotrophic lateral sclerosis. *Anesth Analg*. 1996;83:878–879.
33. Kochi T, Oka T, Mizuguchi T. Epidural anesthesia for patients with amyotrophic lateral sclerosis. *Anesth Analg*. 1989;68:410–412.
34. Jacka MJ, Sanderson F. Amyotrophic lateral sclerosis presenting during pregnancy. *Anesth Analg*. 1998;86:542–543.
35. Hebl JR, Horlocker TT, Schroeder DR. Neuraxial anesthesia and analgesia in patients with preexisting central nervous system disorders. *Anesth Analg*. 2006;103:223–228.
36. Sertöz N, Karaman S. Peripheral nerve block in a patient with amyotrophic lateral sclerosis. *J Anesth*. 2011;26:314–315.
37. Marras C, Lang A. Invited article: Changing concepts in Parkinson disease: Moving beyond the decade of the brain. *Neurology*. 2008;70:1996–2003.
38. Peretz C, Alexander BH, Nagahama SI, Domino KB, Checkoway H. Parkinson's disease mortality among male anesthesiologists and internists. *Mov Disord*. 2005;20:1614–1617.
39. Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R. Familial and environmental risk factors in Parkinson's disease: A case-control study in north-east Italy. *Acta Neurol Scand*. 2002;105:77–82.
40. Thacker EL, Ascherio A. Familial aggregation of Parkinson's disease: A meta-analysis. *Mov Disord*. 2008;23:1174–1183.
41. Galvan A, Wichmann T. Pathophysiology of Parkinsonism. *Clin Neurophysiol*. 2008;119:1459–1474.
42. Jellinger KA. Formation and development of Lewy pathology: A critical update. *J Neurol*. 2009;256:270–279.
43. Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. *N Engl J Med*. 2005;353:1021–1027.
44. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology*. 2009;72:S1–S136.
45. Buter TC, van den Hout A, Matthews FE, et al. Dementia and survival in Parkinson disease: A 12-year population study. *Neurology*. 2008;70:1017–1022.
46. Olanow CW, Myllylä VV, Sotaniemi KA, et al. Effect of selegiline on mortality in patients with Parkinson's disease: A meta-analysis. *Neurology*. 1998;51:825–830.
47. Goetz CG, Pal G. Initial management of Parkinson's disease. *BMJ*. 2014;349:g6258.
48. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease. *Arch Neurol*. 2011;68:165.
49. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol*. 2009;8:67–81.

50. Rodriguez-Oroz MC. Bilateral deep brain stimulation in Parkinson's disease: A multicentre study with 4 years follow-up. *Brain*. 2005; 128:2240–2249.
51. McKay R, Kittappa R. Will stem cell biology generate new therapies for Parkinson's disease? *Neuron*. 2008;58:659–661.
52. Mendez I, Viñuela A, Astradsson A, et al. Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years. *Nat Med*. 2008;14:507–509.
53. Stotz M. Fulminant neuroleptic malignant syndrome after perioperative withdrawal of antiParkinsonian medication. *Br J Anaesth*. 2004;93:868–871.
54. Young CC, Kaufman BS. Neuroleptic malignant syndrome postoperative onset due to levodopa withdrawal. *J Clin Anesth*. 1995;7:652–656.
55. Stagg P, Grice T. Nasogastric medication for perioperative Parkinson's rigidity during anaesthesia emergence. *Anaesth Intensive Care*. 2011;39:1128–1130.
56. Nyholm D, Lewander T, Johansson A, et al. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: Long-term exposure. *Clin Neuropharmacol*. 2008;31:63–73.
57. Nyholm D, Lennernas H. Irregular gastrointestinal drug absorption in Parkinson's disease. *Expert Opin Drug Metab Toxicol*. 2008;4:193–203.
58. Raz A, Lev N, Orbach-Zinger S, Djaldetti R. Safety of perioperative treatment with intravenous amantadine in patients with Parkinson disease. *Clin Neuropharmacol*. 2013;36:166–169.
59. Pal PK, Sathyaprabha TN, Tuhina P, Thennarasu K. Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord*. 2007;22:420–424.
60. Vincken WG, et al. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med*. 1984;311:438–442.
61. De Letter M, Santens P, De Bodt M, et al. The effect of levodopa on respiration and word intelligibility in people with advanced Parkinson's disease. *Clin Neurol Neurosurg*. 2007;109:495–500.
62. Vincken WG, Darauay CM, Cosio MG. Reversibility of upper airway obstruction after levodopa therapy in Parkinson's disease. *Chest*. 1989;96:210–212.
63. Easdown LJ, Tessler MJ, Minuk J. Upper airway involvement in Parkinson's disease resulting in postoperative respiratory failure. *Can J Anaesth*. 1995;42:344–347.
64. Gdynia H-J, Kassubek J, Sperfeld A-D. Laryngospasm in neurological diseases. *Neurocrit Care*. 2006;4:163–167.
65. Backus WW, Ward RR, Vitkun SA, Fitzgerald D, Askanazi J. Postextubation laryngeal spasm in an unanesthetized patient with Parkinson's disease. *J Clin Anesth*. 1991;3:314–316.
66. Liu EH, Choy J, Dhara SS. Persistent perioperative laryngospasm in a patient with Parkinson's disease. *Can J Anaesth*. 1998;45:495.
67. Sapir S, Ramig L, Fox C. Speech and swallowing disorders in Parkinson disease. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16:205–210.
68. Miller N, Noble E, Jones D, Burn D. Hard to swallow: Dysphagia in Parkinson's disease. *Age Ageing*. 2006;35:614–618.
69. Jost WH. Gastrointestinal motility problems in patients with Parkinson's disease. Effects of antiparkinsonian treatment and guidelines for management. *Drugs Aging*. 1997;10:249–258.
70. Walter BL. Cardiovascular autonomic dysfunction in patients with movement disorders. *Cleve Clin J Med*. 2008;75(Suppl 2):S54–S58.
71. Fereshtehnejad S-M, Lökk J. Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. *Parkinson's Disease*. 2014;2014:1–10.
72. Senard JM, et al. Adrenergic supersensitivity in parkinsonians with orthostatic hypotension. *Eur J Clin Invest*. 1990;20:613–619.
73. Rudolph JL, Marcantonio ER. Postoperative delirium. *Anesth Analg*. 2011;112:1202–1211.
74. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354:1157–1165.
75. Poewe W, Gauthier S, Aarsland D, et al. Diagnosis and management of Parkinson's disease dementia. *Int J Clin Pract*. 2008;62:1581–1587.
76. Salord F, Keita H, Lecharny JB, et al. Halothane and isoflurane differentially affect the regulation of dopamine and gamma-aminobutyric acid release mediated by presynaptic acetylcholine receptors in the rat striatum. *Anesthesiology*. 1997;86:632–641.
77. Mantz J, Varlet C, Lecharny JB, et al. Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. *Anesthesiology*. 1994;80:352–363.
78. Lefaucheur J-P, Gurruchaga JM, Pollin B, et al. Outcome of bilateral subthalamic nucleus stimulation in the treatment of Parkinson's disease: Correlation with intra-operative multi-unit recordings but not with the type of anaesthesia. *Eur Neurol*. 2008;60:186–199.
79. Deogaonkar A, Deogaonkar M, Lee JYK, Ebrahim Z, Schubert A. Propofol-induced dyskinesias controlled with dexmedetomidine during deep brain stimulation surgery. *Anesthesiology*. 2006;104:1337–1339.
80. Khatib R, Ebrahim Z, Rezai A, et al. Perioperative events during deep brain stimulation: the experience at Cleveland Clinic. *J Neurosurg Anesthesiol*. 2008;20:36–40.
81. Rozet I, Muangman S, Vavilala MS, et al. Clinical experience with dexmedetomidine for implantation of deep brain stimulators in Parkinson's disease. *Anesth Analg*. 2006;103:1224–1228.
82. Hetherington A, Rosenblatt RM. Ketamine and paralysis agitans. *Anesthesiology*. 1980;52:527.
83. Wiklund RA, Ngai SH. Rigidity and pulmonary edema after Innovar in a patient on levodopa therapy: Report of a case. *Anesthesiology*. 1971;35:545–547.
84. Rivera VM, Keichian AH, Oliver RE. Persistent parkinsonism following neuroleptanalgesia. *Anesthesiology*. 1975;42:635–637.
85. Zoldan J, Friedberg G, Livneh M, Melamed E. Psychosis in advanced Parkinson's disease: Treatment with ondansetron, a 5-HT3 receptor antagonist. *Neurology*. 1995;45:1305–1308.
86. Mets B. Acute dystonia after alfentanil in untreated Parkinson's disease. *Anesth Analg*. 1991;72:557–558.
87. Samadi P, Bedard PJ, Rouillard C. Opioids and motor complications in Parkinson's disease. *Trends Pharmacol Sci*. 2006;27:512–517.
88. Zornberg GL, Bodkin JA, Cohen BM. Severe adverse interaction between pethidine and selegiline. *Lancet*. 1991;337:246.
89. Gravlee GP. Succinylcholine-induced hyperkalemia in a patient with Parkinson's disease. *Anesth Analg*. 1980;59:444–446.
90. Black S, Muzzi DA, Nishimura RA, Cucchiara RF. Preoperative and intraoperative echocardiography to detect right-to-left shunt in patients undergoing neurosurgical procedures in the sitting position. *Anesthesiology*. 1990;72:436–438.
91. Muzzi DA, Black S, Cucchiara RF. The lack of effect of succinylcholine on serum potassium in patients with Parkinson's disease. *Anesthesiology*. 1989;71:322.
92. Davies RG. Deep brain stimulators and anaesthesia. *Br J Anaesth*. 2005;95:424.
93. Minville V, Chassery C, Benhaoua A, et al. Nerve stimulator-guided brachial plexus block in a patient with severe Parkinson's disease and bilateral deep brain stimulators. *Anesth Analg*. 2006;102:1296.
94. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*. 2013;80:1778–1783.
95. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell*. 2012;148:1204–1222.
96. Mayeux R. Clinical practice. Early Alzheimer's disease. *N Engl J Med*. 2010;362:2194–2201.
97. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263–269.
98. Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270–279.
99. Petersen RC, Caracciolo B, Brayne C, et al. Mild cognitive impairment: A concept in evolution. *J Intern Med*. 2014;275:214–228.
100. Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: A clinical perspective. *Mayo Clin Proc*. 2014;89:1452–1459.
101. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263–269.
102. Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: The implications of systematic meta-analyses. *Nat Rev Neurosci*. 2008;9:768–778.
103. Bohnen NI, Warner MA, Kokmen E, Beard CM, Kurland LT. Alzheimer's disease and cumulative exposure to anesthesia: A case-control study. *J Am Geriatr Soc*. 1994;42:198–201.
104. Mucke L, Selkoe DJ. Neurotoxicity of amyloid-protein: Synaptic and network dysfunction. *Cold Spring Harbor Perspectives in Medicine*. 2012;2:a006338.
105. Pithadia AS, Lim MH. Metal-associated amyloid-beta species in Alzheimer's disease. *Curr Opin Chem Biol*. 2012;16:67–73.
106. Cummings JL. Alzheimer's disease. *N Engl J Med*. 2004;351:56–67.
107. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: Clinical trials and drug development. *Lancet Neurol*. 2010;9:702–716.
108a. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366:893–903.
108b. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: A systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clin Proc*. 2013;88:1213–1221.

109a. Dysken MW, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. *JAMA*. 2014;311:33–44.

109b. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology*. 2008;70:1672–1677.

110. ADAPT Research Group, Martin BK, Szekely C, Brandt J, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): Results of a randomized, controlled trial of naproxen and celecoxib. *Arch Neurol*. 2008;65:896–905.

111. Scharf JM, Daffner KR. NSAIDs in the prevention of dementia: A Cache-22? *Neurology*. 2007;69:235–236.

112. Doody RS, Raman R, Farlow M, et al. A Phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369:341–350.

113. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370:311–321.

114. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370:322–333.

115. Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, Costa-Jussa F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. *Brain Pathol*. 2004;14:11–20.

116. Lemere CA, Masliah E. Can Alzheimer disease be prevented by amyloid-β immunotherapy? *Nature Publishing Group*. 2010;6:108–119.

117. Karran E, Hardy J. Antiamyloid therapy for Alzheimer's disease--are we on the right road? *N Engl J Med*. 2014;370:377–378.

118. Sperling RA, et al. The A4 study: Stopping AD before symptoms begin? *Sci Transl Med*. 2014;6:228fs13.

119. Crowe S, Collins L. Suxamethonium and donepezil: A cause of prolonged paralysis. *Anesthesiology*. 2003;98:574–575.

120. Rudolph JL, Jones RN, Rasmussen LS, et al. Independent vascular and cognitive risk factors for postoperative delirium. *Am J Med*. 2007;120:807–813.

121. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia*. 2008;63:941–947.

122. Seitz DP, Gill SS, Bell CM, et al. Postoperative medical complications associated with anesthesia in older adults with dementia. *J Am Geriatr Soc*. 2014;62:2102–2109.

123. Perez-Protto S, Geube M, Ontaneda D, et al. Sensibilité aux anesthésiques volatils chez des patients atteints de démence: Une analyse cas-témoin. *Can J Anaesth*. 2014;61:611–618.

124. Mashour GA, Avidan MS. Dementia and sensitivity to anesthetics. *Can J Anaesth*. 2014;61:599–604.

125. Chan MTV, Cheng BCP, Lee TMC, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25:33–42.

126. Radtke FM, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth*. 2013;110:i98–i105.

127. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008;108:18–30.

128. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet*. 1998;351:857–861.

129. Silverstein JH, Steinmetz J, Reichenberg A, Harvey PD, Rasmussen LS. Postoperative cognitive dysfunction in patients with preoperative cognitive impairment: Which domains are most vulnerable? *Anesthesiology*. 2007;106:431–435.

130. Kuehn BM. Anesthesia-Alzheimer disease link probed. *JAMA*. 2007;297:1760.

131. Xie Z, Moir RD, Romano DM, et al. Hypocapnia induces caspase-3 activation and increases Abeta production. *Neurodegener Dis*. 2004;1:29–37.

132. Xie Z, Dong Y, Maeda U, et al. The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. *Anesthesiology*. 2006;104:988–994.

133. Planel E, Richter KE, Nolan CE, et al. Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. *J Neurosci*. 2007;27:3090–3097.

134. Culley DJ, Xie Z, Crosby G. General anesthetic-induced neurotoxicity: An emerging problem for the young and old? *Curr Opin Anaesthesiol*. 2007;20:408–413.

135. Gasparini M, Vanacore N, Schiaffini C, et al. A case-control study on Alzheimer's disease and exposure to anesthesia. *Neurol Sci*. 2002;23:11–14.

136. Lee TA, Wolozin B, Weiss KB, Bednar MM. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. *J Alzheimers Dis*. 2005;7:319–324.

137. Chen P-L, Yang CW, Tseng YK, et al. Risk of dementia after anaesthesia and surgery. *Br J Psychiatry*. 2014;204:188–193.

138. van den Berg B, Walgaard C, Drenthen J, et al. Guillain-Barre syndrome: Pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol*. 2014;10:469–482.

139. Vucic S, Kiernan MC, Cornblath DR. Guillain-Barré syndrome: An update. *J Clin Neurosci*. 2009;16:733–741.

140. Stojkovic T, Verdin M, Hurtevent JF, et al. Guillain-Barre syndrome resembling brainstem death in a patient with brain injury. *J Neurol*. 2001;248:430–432.

141. Coad NR, Byrne AJ. Guillain-Barre syndrome mimicking brainstem death. *Anaesthesia*. 1990;45:456–457.

142. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev*. 2014;9.

143. Hughes RAC, Wijdicks EF, Benson E, et al. Supportive care for patients with Guillain-Barre syndrome. *Arch Neurol*. 2005;62:1194–1198.

144. Ruts L, van Koningsveld R, Jacobs BC, van Doorn PA. Determination of pain and response to methylprednisolone in Guillain-Barre syndrome. *J Neurol*. 2007;254:1318–1322.

145. Pandey CK, Raza M, Tripathi M, et al. The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barre syndrome patients in the intensive care unit. *Anesth Analg*. 2005;101:220–225. table of contents.

146. Reilly M, Hutchinson M. Suxamethonium is contraindicated in the Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry*. 1991;54:1018–1019.

147. Feldman JM. Cardiac arrest after succinylcholine administration in a pregnant patient recovered from Guillain-Barre syndrome. *Anesthesiology*. 1990;72:942–944.

148. Fiacchino F, Gemma M, Bricchi M, Giudici D, Ciano C. Hypo- and hypersensitivity to vecuronium in a patient with Guillain-Barre syndrome. *Anesth Analg*. 1994;78:187–189.

149. Flachenecker P. Autonomic dysfunction in Guillain-Barre syndrome and multiple sclerosis. *J Neurol*. 2007;254(Suppl 2):II96–II101.

150. Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med*. 2006;354:942–955.

151. Olsson T, Hillert J. The genetics of multiple sclerosis and its experimental models. *Curr Opin Neurol*. 2008;21:255–260.

152. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: A systematic review. *Neurology*. 2008;71:129–135.

153. Myhr K-M. Diagnosis and treatment of multiple sclerosis. *Acta Neurol Scand Suppl*. 2008;188:12–21.

154. Hirst C, Swingler R, Compston DAS, Ben-Shlomo Y, Robertson NP. Survival and cause of death in multiple sclerosis: A prospective population-based study. *J Neurol Neurosurg Psychiatry*. 2008;79:1016–1021.

155. Kim W, Zandona ME, Kim S-H, Kim HJ. Oral disease-modifying therapies for multiple sclerosis. *J Clin Neurol*. 2015;11:9–19.

156. Labuz-Roszak B, Pierzchala K. Difficulties in the diagnosis of autonomic dysfunction in multiple sclerosis. *Clin Auton Res*. 2007;17:375–377.

157. Smeltzer SC, Skurnick JH, Troiano R, et al. Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function. *Chest*. 1992;101:479–484.

158. Guthrie TC, Nelson DA. Influence of temperature changes on multiple sclerosis: Critical review of mechanisms and research potential. *J Neurol Sci*. 1995;129:1–8.

159. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000;343:938–952.

160. Watt JW. Anaesthesia for chronic spinal cord lesions and multiple sclerosis. *Anaesthesia*. 1998;53:825–826.

161. Perlas A, Chan VWS. Neuraxial anesthesia and multiple sclerosis. *Can J Anaesth*. 2005;52:454–458.

162. Vercauteren M, Heytens L. Anaesthetic considerations for patients with a pre-existing neurological deficit: Are neuraxial techniques safe? *Acta Anaesthesiol Scand*. 2007;51:831–838.

163. McFarland HF. The lesion in multiple sclerosis: Clinical, pathological, and magnetic resonance imaging considerations. *J Neurol Neurosurg Psychiatry*. 1998;64(Suppl 1):S26–S30.

164. Bader AM, Hunt CO, Datta S, Naulty JS, Ostheimer GW. Anesthesia for the obstetric patient with multiple sclerosis. *J Clin Anesth*. 1988;1:21–24.

165. Bamford C, Sibley W, Laguna J. Anesthesia in multiple sclerosis. *Can J Neurol Sci*. 1978;5:41–44.

166. Crawford JS. Epidural analgesia for patients with chronic neurological disease. *Anesth Analg*. 1983;62:621–622.

167. Koff MD, Cohen JA, McIntyre JJ, Carr CF, Sites BD. Severe brachial plexopathy after an ultrasound-guided single-injection nerve block for total shoulder arthroplasty in a patient with multiple sclerosis. *Anesthesiology*. 2008;108:325–328.

168. Brett RS, Schmidt JH, Gage JS, Schartel SA, Poppers PJ. Measurement of acetylcholine receptor concentration in skeletal muscle from a patient with multiple sclerosis and resistance to atracurium. *Anesthesiology*. 1987;66:837–839.
169. Somer H, Muller K, Kinnunen E. Myasthenia gravis associated with multiple sclerosis. Epidemiological survey and immunological findings. *J Neurol Sci*. 1989;89:37–48.
170. Drummond JT, Matthews RG. Nitrous oxide degradation by cobalamin-dependent methionine synthase: Characterization of the reactants and products in the inactivation reaction. *Biochemistry*. 1994;33:3732–3741.
171. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. *Br J Anaesth*. 1987;59:3–13.
172. Chanarin I. The effects of nitrous oxide on cobalamins, folates, and on related events. *Crit Rev Toxicol*. 1982;10:179–213.
173. Singer MA, Lazaridis C, Nations SP, Wolfe GI. Reversible nitrous oxide-induced myeloneuropathy with pernicious anemia: Case report and literature review. *Muscle Nerve*. 2008;37:125–129.
174. Cheng HM, Park JH, Hernstadt D. Subacute combined degeneration of the spinal cord following recreational nitrous oxide use. *BMJ Case Rep*. 2013;2013.
175. Gursoy AE, Kolukisa M, Babacan-Yildiz G, Celebi A. Subacute combined degeneration of the spinal cord due to different etiologies and improvement of MRI findings. *Case Rep Neurol Med*. 2013;2013(159649).
176. Kinsella LJ, Green R. 'Anesthesia paresthetica': Nitrous oxide-induced cobalamin deficiency. *Neurology*. 1995;45:1608–1610.
177. Nilsson-Ehle H. Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy. *Drugs Aging*. 1998;12:277–292.
178. Culley DJ, Raghavan SV, Waly M, et al. Nitrous oxide decreases cortical methionine synthase transiently but produces lasting memory impairment in aged rats. *Anesth Analg*. 2007;105:83–88.
179. Heyer EJ, Simpson DM, Bodis-Wollner I, Diamond SP. Nitrous oxide: Clinical and electrophysiologic investigation of neurologic complications. *Neurology*. 1986;36:1618–1622.
180. Lin C-Y, Guo WY, Chen SP, et al. Neurotoxicity of nitrous oxide: Multimodal evoked potentials in an abuser. *Clin Toxicol (Phila)*. 2007;45:67–71.
181. Ilniczky S, Jelencsik I, Kenez J, Szirmai I. MR findings in subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia--two cases. *Eur J Neurol*. 2002;9:101–104.
182. Beltramello A, Puppini G, Cerini R, et al. Subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia: Role of magnetic resonance imaging. *J Neurol Neurosurg Psychiatry*. 1998;64:563–564.
183. Holloway KL, Alberico AM. Postoperative myeloneuropathy: A preventable complication in patients with B12 deficiency. *J Neurosurg*. 1990;72:732–736.

Postoperative and Intensive Care Including Head Injury and Multisystem Sequelae

23

S.H. Worah • A. Minokadeh

Critical care, including postoperative care, of the neurologically ill patient involves application of the general critical care principles of management with an added focus on prevention and treatment of secondary brain injury. Systemic and neurologic monitoring is typically required and the knowledge and implementation of emergent, timely intervention is paramount. Neurologic injuries, including traumatic brain injuries (TBI), may incur complications or *sequelae*, which result from the *primary* (initial) injury or a *secondary* (subsequent) injury. The lesion sustained at the time of impact, described as the *primary injury,* results from the high-energy acceleration or deceleration of the brain within the cranial vault. The *secondary injury* manifests as a result of a more complex process induced by alterations in cerebral blood flow (CBF), inflammation, hypermetabolism, and tissue necrosis. Sequelae of head injury often correlate with the severity of head injury. The Glasgow Coma Scale (GCS) is a commonly used tool for quantifying the severity of head injury. The GCS score ranges from 3 to 15. Scores of 9 through 15 indicate mild-to-moderate head injury, and a score of 8 or less indicates severe injury. Multisystem sequelae of severe head injury include airway obstruction, respiratory dysfunction, cardiovascular dysfunction, fat embolism syndrome, hematologic abnormalities, neuromuscular dysfunction, metabolic abnormalities, electrolyte imbalances, gastrointestinal abnormalities, immunologic abnormalities, endocrine abnormalities, infectious complications, secondary brain injury, and cerebral hyperperfusion syndrome (CHS). Independent predictors of poor outcome include hypotension, hypoxia, hypoglycemia, hyperthermia, hypocapnia, and intracranial hypertension.

RESPIRATORY COMPLICATIONS

Alteration in Ventilatory Control

Spontaneous respirations are controlled by neural centers in the pons (pontine respiratory group [PRG]) and medulla oblongata (dorsal respiratory group [DRG] and ventral respiratory group [VRG]). These centers send impulses down the spinal cord to the motor neurons supplying the respiratory muscles. Efferent impulses from the DRG travel primarily to the inspiratory muscles whereas those from the VRG travel mainly to the expiratory muscles, some inspiratory muscles, as well as muscles of the tongue, pharynx, and larynx. On either side of the medulla between the nucleus ambiguus and the lateral reticular nucleus lie a group of synaptically coupled neurons, which form a complex called the pre-Botzinger complex (pre-BOTC). This pre-BOTC is responsible for the initiation of the rhythmic respirations and is, therefore, also known as the pacemaker of respirations. Chemoreceptors in the medulla respond primarily to changes in pCO_2 and, to a lesser extent, to changes in pH and pO_2 by altering respiratory patterns to compensate for imbalances.[1] These compensatory responses are affected in brain injury leading to hypoxia, hypercapnia, or both. In patients with mild-to-moderate brain injury, the primary response is that of hyperventilation and hypocapnia, which in turn reduces cerebral blood flow causing a relative decrease in the ICP. In contrast, patients with severe brain injury are prone to develop significant hypopnea or even apnea causing a sudden, severe increase in pCO_2 levels. Hypercarbia can cause cerebral vasodilatation, which in turn leads to an increase in the ICP.

Alterations in respiratory patterns are common in patients with brain injury. These include the following:

Cheyne–Stokes pattern: Cheyne–Stokes is a common pattern of cyclical breathing seen in patients with neurologic injuries. It is characterized by repeated crescendo-decrescendo patterns of breathing and includes a period of apnea at the end of each cycle. The level of consciousness also follows this pattern where the patient becomes increasingly alert to nearly awake during the crescendo phase and possibly vocalizing at the peak of this phase. A gradual slowing of respirations follows a waning of consciousness until the patient is completely apneic and unarousable. This pattern of breathing is associated with deep cerebral hemispheric lesions (stroke, TBI, brain tumor), severe metabolic derangements and central chemosensitivity to changes in CO_2 and O_2 tensions. High pCO_2 leads to excessive compensatory hyperventilation, in turn causing decreased pCO_2, which causes apnea, restarting the cycle.

Biot's (ataxic) pattern: Ataxic breathing refers to an irregular pattern of both rate and rhythm of breathing. It occurs with lesions in the dorsomedial medulla and may be accompanied by hypersensitivity to respiratory depressants and is considered to be a preterminal event.

Apneustic pattern: Pontine injury can result in a long, gasping inspiration followed by an insufficient length of expiration.

Cluster pattern: Cluster breathing is associated with an irregular frequency and amplitude followed by apneic episodes of varying duration. It can occur due to upper medullary and lower pontine lesions, anoxic encephalopathy, Shy–Drager syndrome as well as subarachnoid, cerebellar and brainstem hemorrhagic lesions.

Central hyperventilation pattern: Patients during early periods of brainstem herniation may cause an increase in the rate and depth of respirations resulting in respiratory alkalosis. This must be differentiated from Kussmaul's respiration, which is described below.

Kussmaul's pattern: Initially, acidosis prompts rapid, shallow breathing. As acidosis worsens, Kussmaul's breathing develops, characterized by deep, labored, and gasping breaths. This compensatory overbreathing can result in reduced carbon dioxide tension and reduced cerebral blood flow (Fig. 23.1).

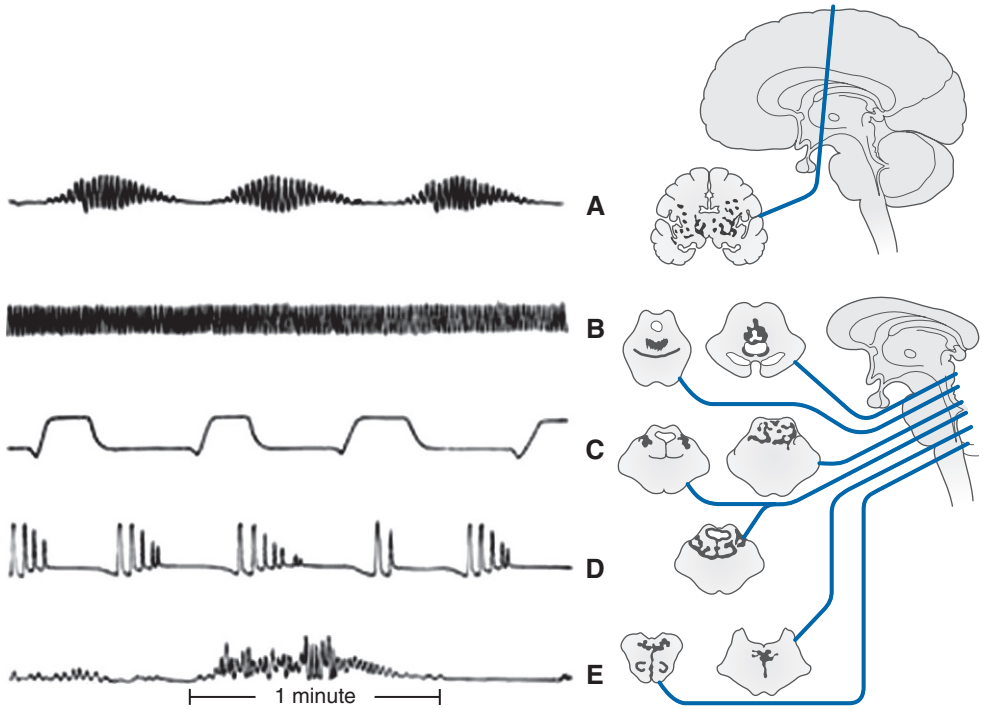


Fig. 23.1 Abnormal respiratory patterns associated with pathologic brain lesions. **A,** Cheyne–Stokes respiration. **B,** Central neurogenic hyperventilation. **C,** Apneustic breathing. **D,** Cluster breathing. **E,** Ataxic breathing. *(Adapted from Plum F, Posner JB: Diagnosis of Stupor and Coma, 3rd ed. New York, Oxford University Press, 1980.)*

Anatomic Considerations

Respiratory complications can be separated into upper respiratory and lower respiratory tract complications.

Upper respiratory tract (airway) complications are a leading cause of morbidity and mortality in brain-injured patients. In addition, traumatic injuries may cause significant bone injuries such as fractures and displacements that can subsequently lead to bone fragments being embedded in the soft tissues of the airway. Airway dysfunction and edema are relatively common especially following TBI. The patients may lose sensorimotor functional integrity of the airway leading to an increased incidence of aspiration pneumonia. Cranial nerve injuries may further render the patient susceptible to pulmonary aspiration syndrome.[2–4] Airway protection is ideally managed with endotracheal intubation in patients with extensive brain injury. Injuries involving the cervical spine and/or facial structures may require emergent control of airway via a cricothyrotomy or tracheostomy.[5] Airway edema, secondary to direct trauma or in the postoperative setting, is assessed by performing the "leak test". The lack of detection of the characteristic audible leak upon deflation of the endotracheal tube cuff signifies the presence of significant tracheal edema. Airway edema is a major problem in the pediatric age group due to the inherent narrowing of the subglottic portion of the airway along with smaller diameter of the airways. Nonetheless, it is always prudent to maintain a secure airway in suspected or documented cases involving edema of the airway until one can establish resolution of this edema. Therapeutic modalities include parenteral steroids, inhaled racemic epinephrine and upright positioning. A helium/oxygen mixture can be used to treat dyspnea due to airway edema following extubation.[6] This mixture generates less resistance than atmospheric air when passing through the narrow airways of the lungs, and thus requires less effort by a patient to breathe in and out of the lungs (Fig. 23.2).

Lower respiratory complications may occur as a result of pulmonary edema, pneumonia, acute lung injury or acute respiratory distress syndrome, or due to physical trauma. Pulmonary edema secondary to neurologic injury and pulmonary thromboembolism causes respiratory dysfunction and cardiovascular compromise (discussed later).

Pneumonia

It is known that up to 24% of TBI patients on mechanical ventilation develop ventilator-associated pneumonia (VAP).[7] In TBI, the risk of developing pneumonia increases by 7% per day of mechanical ventilation.[8] Nosocomial pneumonia in mechanically ventilated patients increases ICU and hospital length of stay, days on mechanical ventilation, morbidity, and mortality.[9] Treatment involves initiation of empiric antibiotic therapy to cover Gram-positive organisms, including MRSA, and Gram-negative bacteria, including pseudomonas. The antibiotic therapy can be modified once results of cultures sent prior to initiation of antibiotics are available. VAP management should include modification of risk factors such as daily awakening trials, head of bed elevation greater than 30 degrees, deep tracheal suctioning, early extubation, early initiation of enteral nutrition, and restriction of gastric acid suppressants. Antibiotics must be continued until resolution of the infectious process is reached, which may take anywhere between 8 and 21 days. Radiologic resolution of the process may take from weeks to months and, therefor,e therapy is not dependent upon X-ray.[10]

Acute Lung Injury or Acute Respiratory Distress Syndrome

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) may occur as a result of secondary brain injury, direct trauma, infection or blood product transfusion.[11–13] The pathophysiology involved in both of these conditions is similar and, in fact, may progress from ALI to ARDS. ALI/ARDS are both forms of noncardiogenic pulmonary edema, which lead to respiratory failure and hypoxemia. Abnormalities in gas exchange can be exacerbated by simultaneous injury to the respiratory control centers in the brainstem. In patients with severe TBI, the combination of lung pathology and

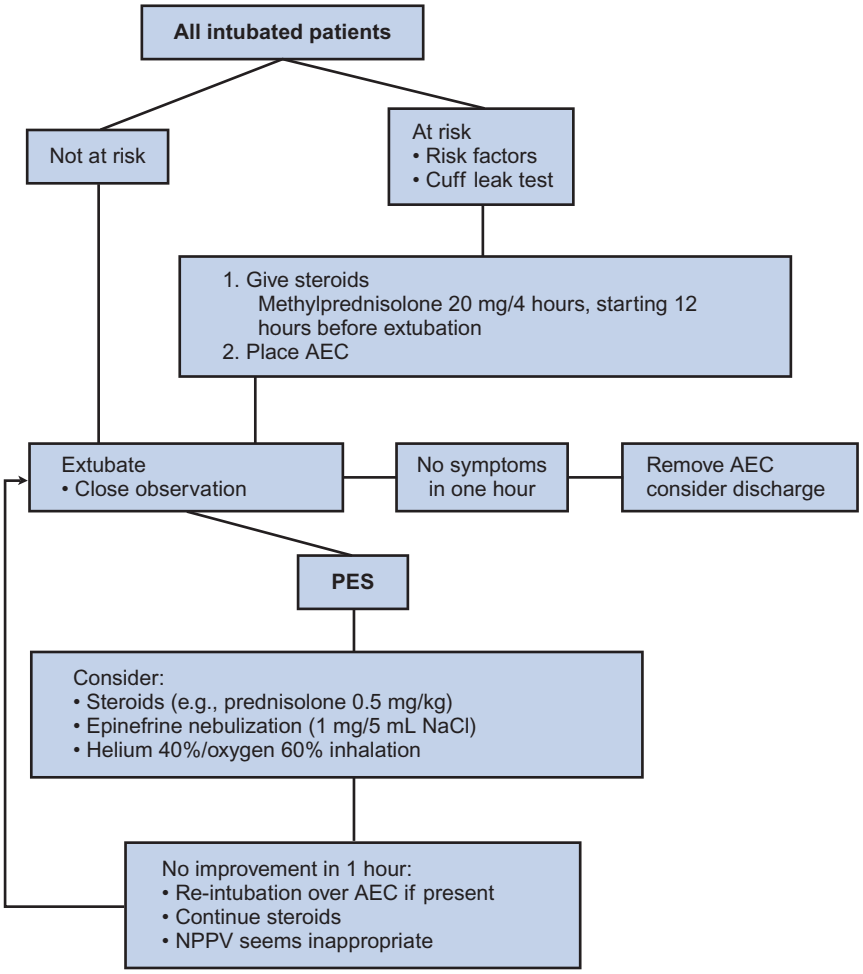


Fig. 23.2 Post-extubation laryngeal edema therapy flow chart. AEC, airway exchange catheter; NaCl, 0.9% saline; NPPV, non-invasive positive pressure ventilation; PES, post-extubation stridor. *(Adapted from Post-extubation laryngeal edema and extubation failure in critically ill adult patients; Bastiaan HJ Wittekamp, Walther NKA van Mook, Dave HT Tjan, Jan Harm Zwaveling, Dennis CJJ Bergmans: Critical Care 2009, 13:233)*

dysfunctional respiratory drive and mechanics can lead to significant hypoxemia and hypercarbia. Mechanical ventilation of the lungs, which is necessary for maintenance of adequate gas exchange, has been shown to decrease further tissue damage.[14]

Some common ventilatory modes utilized to ventilate and oxygenate these patients include volume-cycled assist control ventilation/continuous mandatory ventilation (ACV or CMV), which involves delivery of similar volumes of breath per cycle. This is usually the default mode for most patients receiving mechanical ventilation. Alternatively, pressure control ventilation (PCV) is the mode of choice in cases involving poor lung compliance, such as ARDS, where the high peak inspiratory pressures in volume cycled ventilation result in lower delivered tidal volumes.[15] The parameters of ventilation must be adjusted to achieve adequate oxygenation and carbon dioxide elimination.[16] Synchronized intermittent mandatory ventilation mode (SIMV) enables ventilator–patient synchrony, that is, coordination of patient and machine initiated breaths. Pressure support ventilation (PSV) is usually utilized along with SIMV to permit better support of the patient initiated breaths. Both these modes are used in conjunction to assist in weaning patients from mechanical ventilation.

Advanced modes, if available, may also be used to assist patients who are on mechanical ventilation. These include airway pressure release ventilation (APRV), pressure regulated volume control (PRVC), volume assured pressure support (VAPS), neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV), adaptive support ventilation, volume support ventilation, high frequency oscillatory ventilation (HFOV), and high frequency jet ventilation (HFJV). The common theme amongst these modes of ventilation is the aim of ensuring adequate oxygenation and ventilation, preventing further additional lung injury, minimizing patient ventilator dyssynchrony, and enabling faster weaning from mechanical ventilation.

Positive end expiratory pressure (PEEP) is a therapeutic modality that is used concomitantly with the abovementioned modes of ventilation. It refers to the pressure in the airways at the end of passive expiration. PEEP is used commonly to improve oxygenation by recruiting and stabilizing lung units that participate in gas exchange. There is conflicting evidence in the literature regarding use of PEEP in patients with brain injury. It has been postulated that application of PEEP may lead to an increase in the intracranial pressure as a result of increased venous pressure and decreasing cerebral venous return, thereby causing a decrease in the cerebral perfusion pressure.[17] However, the jugular veins are Starling resistors, and in the head elevated position, there is a limited correlation between intrathoracic and intracranial pressure.[18] In any event, the benefits of the administration of low-to-moderate amounts of PEEP, by improving oxygenation, outweigh the potential risks.

Chest Trauma

Direct trauma to the chest may lead to fracture(s) of the rib cage causing a flail chest, pulmonary contusions, pneumothorax, hemothorax, chylothorax or a combination of any of these conditions. In addition, it may also cause cardiovascular injuries, which have a very high mortality rate. Management of these conditions is usually surgical in nature and involves operative repair, thoracocentesis and/or thoracostomy, oxygen supplementation with or without mechanical ventilation.

Neurogenic Pulmonary Edema

NPE is an acute and life-threatening complication that may occur secondary to CNS injury, e.g., trauma, hemorrhage, infection, inflammation, space occupying lesions, ischemic events, or post neurosurgical states. NPE can develop in patients with autoimmune neurologic conditions, such as multiple sclerosis and Guillain–Barré syndrome. The incidence of NPE in patients with traumatic brain injuries can be as high as 20%.[19]

Pathophysiology

It has been postulated that sudden, rapid and intense elevation of ICP leads to an activation of the sympathetic nervous system causing a catecholamine surge. The exact sources of this surge, labeled "NPE trigger zones," have been identified in the hypothalamus and the medulla.[20] This surge in catecholamines leads to an arterial vasoconstriction and increased systemic vascular resistance (SVR), as well as venoconstriction resulting in increased preload and cardiac output. The influx of large volumes of blood into the pulmonary arterial circulation, in combination with pulmonary venous constriction, results in increased pulmonary capillary pressure, swelling and subsequent destruction of the capillary and alveolar walls, and leakage of fluid and cells into the interstitium and intra-alveolar space (Fig. 23.3).[21]

Diagnosis and Management

Respiratory distress or failure in a patient with acute and severe CNS injury is common. NPE is a diagnosis of exclusion where one must rule out all other causes of noncardiogenic edema, especially aspiration pneumonia, and volume overload. Two types of NPE have been described. The first and more common one is the *early* form where symptoms develop within minutes to hours following the neurologic injury. The second type of NPE, also known as the *delayed* form, is not as common and develops 12–24 hours following the injury.[22] In either of these cases, the patient becomes acutely dyspneic and hypoxemic within a span of minutes and exhibits clinical signs of pulmonary edema, such as pink, frothy sputum, and bilateral rales. Radiographic imaging revealing bilateral fluffy pulmonary infiltrates corroborates the clinical suspicion of pulmonary edema.

Management of NPE involves treatment of the primary neurologic condition in order to minimize sympathetic discharges causing the lung injury.[23] The following diagnostic criteria have been suggested by Davison et al.[24] to establish a diagnosis of NPE in the group of patients who may benefit from sympathetic blockade: (1) bilateral infiltrates; (2) PaO_2:FiO_2 < 200; (3) no evidence of left atrial hypertension; (4) presence of severe CNS injury, which could lead to an increased ICP; and (5) absence of other causes of respiratory distress or ARDS (e.g., aspiration, massive blood transfusion, sepsis). Mechanical ventilation is usually required in cases involving NPE and involves utilization of moderate levels of PEEP (up to 15 cm H_2O) to improve oxygenation.[25,26]

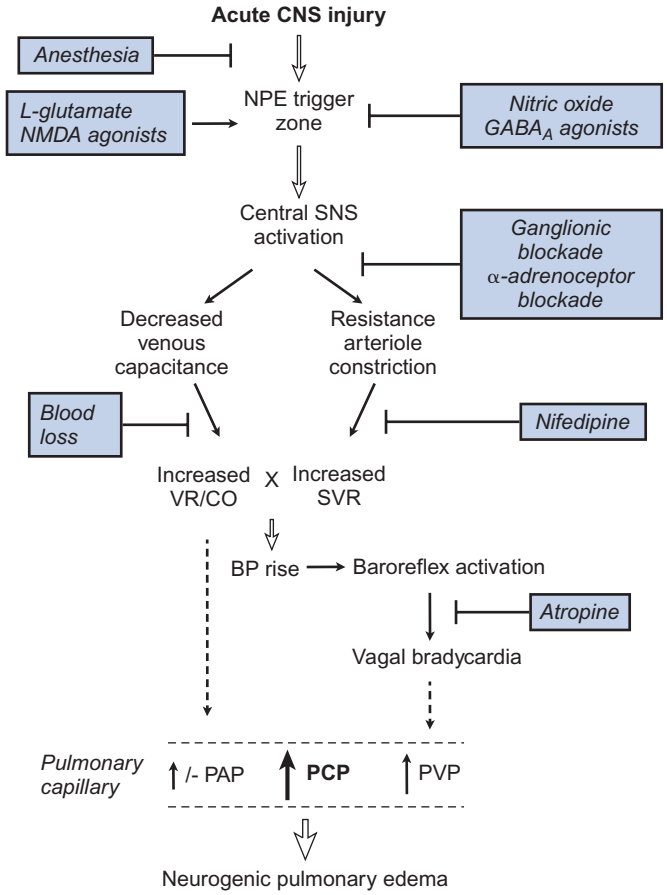


Fig. 23.3 Hemodynamic events leading to NPE. Rectangles with horizontal bars: sites of experimental interventions that may lead to NPE. CNS, central nervous system; NMDA, N-methyl-D-aspartate; NPE, neurogenic pulmonary edema; GABA, gamma-aminobutyric acid; SNS, sympathetic nervous system; VR, venous return; CO, cardiac output; SVR, systemic vascular resistance; BP, blood pressure; PAP, pulmonary arterial pressure; PCP, pulmonary capillary pressure; PVP, pulmonary venous pressure. *(Adapted from Šedý J, Kuneš J, Zicha J. Pathogenetic Mechanisms of Neurogenic Pulmonary Edema. J Neurotrauma. 2015 Aug 1;32(15):1135-1145.*

Deep Vein Thrombosis and Pulmonary Embolism

Patients with neurologic injuries including spinal cord injuries have a high risk of pulmonary embolism and deep vein thrombosis. This is especially true in patients with associated multiple trauma and fractures. Management of these injuries involves immobilization of the affected areas, which poses a significant risk for development of deep vein thrombosis and subsequent pulmonary embolism. Therefore, use of sequential compression devices (SCD) is highly recommended, particularly when the risk of developing an intracranial bleed following the initial injury precludes the utilization of pharmacologic prophylaxis for prevention of these conditions.

CARDIOVASCULAR COMPLICATIONS

Most neurologic injuries, with the exception of the mild variety, are associated with autonomic dysfunction. Initial responses to neurologic injuries include an increase in heart rate, blood pressure and cardiac output as a compensatory phenomenon. However, these compensatory mechanisms become exhausted once the duration of injury becomes more prolonged or if

there are associated severe secondary injuries. This leads to a significant alteration in the systemic hemodynamics that in turn triggers the release of greater amounts of catecholamines into the circulation. There is evidence to show that the extent of catecholamines is directly proportional to the severity of the brain injury and to patient outcomes.[27] Excessive catecholamine release, mainly from the hypothalamus,[28] is the likely cause of myocardial damage seen on autopsy in patients with severe TBIs. However, it has been argued that the levels of circulating catecholamines in the blood may be less important than intracardiac noradrenergic neuronal activity in myocardial damage and necrosis. Troponin I levels correlate with the extent of left ventricular dysfunction and severity of neurologic injury.[29–33]

Conduction Abnormalities

Cardiac dysrhythmias are a significant complication of neurologic injuries. Autonomic dysregulation (dysautonomia), electrolyte imbalances and hypoxemia are some risk factors that may precipitate these dysrhythmias. Dysautonomia uncouples the relationship between heart rate and sympathetic nervous system regulation. It may last up to 3 months following injury and is directly proportional to the severity of neurologic injury.[34,35] Arrhythmias are frequent following TBI with tachyarrhythmias being the most common and up to 95% of patients who suffer brain injuries (traumatic and atraumatic hemorrhagic) manifest electrocardiographic changes within the first 48 hours. Sinus and supraventricular tachycardias, prolonged qT_c intervals (>440 msec), increased P wave amplitude, shortened P–R intervals, nonspecific ST segment and T wave alterations are some of the common presentations of such arrhythmias[36,37] and are associated with an increased mortality in patients particularly when they persist for a prolonged period of time. The supraventricular and nodal arrhythmias, though associated with a 50% mortality rate, are postulated to be the result of terminal events than being the cause of high mortality. However, there is no significant correlation between the type of neurologic injury and specific ECG changes.[38] In the pediatric population with TBI, there is ample evidence to suggest a high incidence of electrolyte abnormalities, especially hypokalemia, which has been linked to the high incidence of cardiac conduction abnormalities.[39–42] This is associated with an increased incidence of longer qT_c intervals and greater qT_c dispersion, but there is no evidence that links these findings to a higher mortality rate in children.[43]

Hypertension

Systemic hypertension is a common complication following brain injury and is associated with an increased mortality.[44] Hypertension leads to cerebral hyperperfusion and subsequent intracranial hypertension, which is a known risk factor for poor outcomes in TBI patients.[45–48] TBI, particularly involving the brainstem, is associated with an increased release of catecholamines causing hypertension. TBI impairs cerebral autoregulation and disrupts the capillary endothelium, which worsens the effects of hypertension. Dysfunctional arterioles in the cerebral vasculature lose their ability to vasoconstrict in response to hypertension causing an increase in the cerebral blood flow (CBF), volume (CBV), and pressure (CPP), which leads to a higher risk of development of cerebral edema. Similarly, systemic hypotension leads to a reduction in CBF and CPP as a result of the failure of the cerebral arterioles to vasodilate. It should be noted that patients with chronic hypertension are at an increased risk of cerebral hypoperfusion as a result of the rightward shift of their autoregulation curve.

The brain trauma foundation has recommended that CPP be maintained between 50 and 70 mmHg.[49] In patients with TBI, hypertension is generally treated when the SBP increases above 200 mmHg. Beta blockers are usually the first line of antihypertensive agents as they help with the management of hypertension as well as complications arising from the release of excess catecholamines such as tachyarrhythmias, myocardial ischemia and immune suppression.[50,51] Esmolol and labetalol are commonly used in the management of hypertension in patients with brain injuries as they do not increase ICP significantly. In patients who develop myocardial ischemia or infarction, metoprolol is a better choice as it improves morbidity and is associated with higher survival rates. A recent systematic review has suggested that patients who are exposed to beta blockers either prior to or immediately after severe TBI show a reduction in in-hospital mortality of 65%.[52] The American Heart Association guidelines recommend use of labetalol or nicardipine in the management of acute hypertension in the setting of ICH or ischemic stroke.[53] In a recent pilot study, clevidipine, a new and short-acting calcium channel antagonist, is shown to be safe and effective in the rapid reduction of blood pressure in a group of patients with intracranial hemorrhage.[54] Vasodilating agents such as hydralazine, nitroglycerine and nitroprusside are usually avoided as they may cause increased cerebrovascular dilation leading to an increase in CBF, ICP and cerebral edema.[55]

Hypotension

Hypotensive episodes play a major part in determining outcomes in patients with severe TBI. It has been shown that even a single episode of hypotension (SBP < 90 mmHg) doubles the rate of mortality in severely head injured patients.[56] Hypotension following head injury is generally attributed to hypovolemia and/or hypovolemic shock and is treated with isotonic crystalloids. Although in a recent trial of ICU patients with hypovolemic shock who received crystalloids vs. colloids no difference in the 28-day overall mortality rate was demonstrated, the 90-day mortality rate was improved in the colloid group.[57] The SAFE trial, on the other hand, found higher mortality rates in patients with TBI who were resuscitated with 4% albumin compared to the ones that received crystalloids.[58] If hypotension persists despite adequate fluid replacement, then vasopressors or a combination of vasopressors and inotropes is used to raise the CPP to more than 50 mmHg. Phenylephrine (0.5–2 µg/kg/min) and vasopressin (0.04 units/min) are α-adrenergic agonists with pure vasopressor effect. Norepinephrine (0.1–1 µg/kg/min) is predominantly an α-agonist with vasopressor effects, but it also has some inotropic effects. Epinephrine (adrenaline) (0.1–1 µg/kg/min) with a combined α and β-adrenergic agonistic activity has more inotropic than vasopressor effects. Although dopamine has mainly dopaminergic (splanchnic vasodilation) effects at doses of 2–3 µg/kg/min, it has β-adrenergic (inotropic) effects at doses of 5–10 µg/kg/min and mainly α-adrenergic (vasopressor) effects at doses of 10–15 µg/kg/min, with significant overlap and individual variations.

Fat Embolism Syndrome

This consists of a triad of cerebral dysfunction, fever, and hypoxemia in the setting of injury to a marrow-containing bone. During such injury, bone intramedullary pressure rises higher than the venous pressure, and fat globules gain access to the veins and then to the vasculature. The fat globules then embolize to the lung vasculature.[59] Fat, platelet, and fibrin collections plug cerebral arterioles, leading to ischemia and distal

hemorrhage. Similar lesions may exist in the liver, kidney, heart, and lung. Additional lesions may occur and manifest as pneumonitis, pulmonary edema, and disseminated intravascular coagulation (DIC). Symptoms appear 24–48 hours after the initiating injury. Changes in mental status are most commonly seen, with symptoms progressing from restlessness to confusion and then coma. Respiratory failure generally occurs after mental status changes. Chest radiograph reveals diffuse bilateral infiltrates compatible with ARDS. Another finding is petechiae over the neck, chest, and axillae. When FES occurs perioperatively, patients may fail to regain consciousness after general anesthesia. Management consists of respiratory and cardiovascular support in the form of supplemental oxygen, mechanical ventilation, and vasopressors.

HEMATOLOGIC COMPLICATIONS

Anemia

Anemia may be present in patients with TBI as a result of cerebral or extracerebral hemorrhage, either of which may be compounded by preexisting disease. Anemia decreases the oxygen-carrying capacity of the blood because hemoglobin (Hb) carries more than 90% of the oxygen in the blood, which is evident from the blood oxygen content (CaO_2) equation, as follows:

$$CaO_2 = 1.34 \times Hb \times SaO_2 + 0.0031 \times PaO_2 \quad (23.1)$$

Decreased oxygen content in the blood (CaO_2) decreases oxygen delivery (DO_2), which is the product of oxygen content in the blood plus cardiac output. Organs with high oxygen requirements, such as the brain and the heart, are most sensitive to the effects of anemia. The heart may be most affected because of a combination of high oxygen requirements (myocardial O_2 consumption [MVO_2] is greater than 7.6 mL/min/100 g compared to average total body O_2 consumption of approximately 3.5 mL/min/100 g) and high oxygen extraction ratio (OER, 65%), in comparison with the total body average (25%).

Treatment of acute anemia consists of replacement of red blood cells (RBCs) plus supportive therapy in the form of intravenous fluids, vasopressor therapy, supplemental oxygen, ventilatory support, and sedation. The threshold, as well as the target of transfusion of RBCs, is not well defined from clinical evidence. The Transfusion Requirements in Critical Care (TRICC) trial showed that a restrictive transfusion strategy (transfusing when the Hb is less than 7 g/dL to keep Hb between 7 and 9 g/dL) is at least as effective as, and possibly superior to, a liberal transfusion strategy (transfusing when the Hb is less than 10 g/dL to keep Hb between 10 and 12 g/dL).[60] Furthermore, when intravascular volume and other supportive therapies are provided, Hb levels of 5 g/dL seem to be well tolerated. More recent studies in TBI patients with acute anemia have shown conflicting results with one showing a mean 7 day Hb concentration of less than 9 g/dL to be associated with an increased mortality,[61] whereas another study identifying a transfusion threshold of 10 g/dL was associated with a higher incidence of adverse events.[62] The use of $PbtO_2$ or $SjvO_2$ monitoring may aid in determining the adequacy of oxygen delivery to the brain to meet metabolic requirements.[63] Transfusion of RBCs may be associated with multiple complications, such as hemolytic transfusion reaction, allergic and anaphylactic reactions, transfusion-related acute lung injury, post-transfusion purpura, transfusion-associated graft-versus-host disease, transfusion-related immune modulation (suppression), fever, infection, and hyperbilirubinemia. Prospective trials are needed to better determine the optimal transfusion trigger in TBI and neurologically injured patients.

Disseminated Intravascular Coagulation

Many patients with head injury have clotting abnormalities, including disseminated intravascular coagulation (DIC). Low-grade DIC is seen in 8.4% of patients with primary ICH and is associated with increased morbidity and mortality.[64] The brain is rich in tissue thromboplastin, which is a main activator of DIC. The excessive coagulation that causes DIC may be triggered through different pathways. It can be triggered by endothelial cell injury, which activates the intrinsic pathway; by tissue injury, which activates the extrinsic pathway; or by RBC and platelet injury, which causes the release of procoagulant phospholipids.[65] With excessive coagulation, the anticoagulant and fibrinolytic systems are overwhelmed, leading to diffuse microvascular thrombi, which leads to decreased blood supply to various organs. The risk of bleeding is greater because both coagulation factors and platelets are consumed in thrombosis.

Diagnosis of DIC is based on the presence of a disorder known to be associated with DIC and abnormal results of global coagulation tests, including low platelet count, elevations of fibrin-related markers (e.g., FDPs), increased prothrombin time (PT), and decreased fibrinogen level.[66] Treatment consists of treating the underlying disorder and correcting the resulting coagulopathy and anemia. Coagulopathy is treated with the replacement of consumed coagulation products in the form of fresh frozen plasma (FFP), platelets, and cryoprecipitate to achieve a fibrinogen level above 100 mg/dL, a platelet count of more than 50,000/mm^3, and an activated partial thromboplastin time close to normal values.

Anemia is treated with transfusion of packed RBCs. Administration of heparin for DIC is controversial, and evidence supporting its use is limited. The use of heparin is based on the finding of clinical evidence of excessive thrombosis. However, it is given at doses lower than those used to treat thrombosis (5–10 units/kg/h with or without a loading dose). Antifibrinolytics such as tranexamic acid (TXA), ε-aminocaproic acid (EACA) and aprotinin have also been used to treat TBI patients with bleeding, with the most promising results being seen in TXA.[67] Recently, newer formulations of individual factor concentrates, such as recombinant factor VIIa (rFVIIa), as well as pooled factor concentrates, such as prothrombin complex concentrate (PCC), have been used in patients with TBI with one study demonstrating a significant decrease in mortality rates with use of PCC as compared to rFVIIa. A secondary outcome showed a fivefold decrease in mean cost of therapy with PCC as compared to rFVIIa.[68]

NEUROMUSCULAR COMPLICATIONS

Diaphragmatic paralysis following head trauma has been reported, although it is more commonly seen in patients with stroke (contralateral phrenic nerve paralysis). CNS injuries may lead to damage of the respiratory pacemaker (pre-BOTC) resulting in diaphragmatic paralysis. Causes include upper cervical cord injuries, brainstem ischemia and hemorrhage, encephalitis, and neurosurgical complications. About 40% of patients with complete tetraplegia require lifetime mechanical ventilation.[69] Diaphragmatic paralysis may cause difficulty in weaning patients from the ventilator because of poor inspiratory effort and decreased cough reflex. Neuromuscular electrophysiologic studies may help predict respiratory recovery.

The long-term survival rates for ventilator dependent quadriplegic patients have been shown to range from 90% in the first year to 33% at 5 years following injury with intensive medical support.[70]

ELECTROLYTE IMBALANCES

Fluid and electrolyte imbalance is the most common complication of TBI. The mechanisms of this imbalance include brain injury, diuretics (mannitol), hypovolemia, myoglobinuria, and renal failure.

Hyponatremia

Hyponatremia is common and is mainly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or the cerebral salt-wasting syndrome (CSWS). The posterior pituitary antidiuretic hormone (ADH) regulates water balance and osmolality in the body. Hypothalamic baroreceptors are sensitive to minor (1%) increases in serum osmolarity and respond by increasing the release of ADH. At serum osmolality levels greater than 280 mOsm/L, ADH is secreted linearly to increase free water absorption with increases in osmolarity.[71] SIADH occurs when there is continued release of ADH despite low serum sodium levels and hypervolemia. Laboratory findings in SIADH include a serum osmolality level of less than 280 mOsm/L, a serum sodium value of less than 135 mEq/L, high urine osmolality, and a urinary sodium concentration of less than 25 mEq/L.

CSWS causes profound natriuresis that is stimulated by increased levels of atrial natriuretic factor (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These peptides suppress aldosterone synthesis and lead to natriuresis, diuresis, and vasodilatation. Hyponatremia in CSWS results from increased renal excretion of sodium (150–200 mEq/L/day), which is followed by excretion of water, with resultant hypovolemia. The main risk that hyponatremia and hypo-osmolality pose to the brain is that of cerebral edema, which leads to life-threatening intracranial hypertension when the increase in intracranial volume exceeds 10%.[72]

Hypernatremia

Hypernatremia may occur in TBI as a result of an inadequate intake of water, high-calorie enteral feeding leading to diarrhea, diabetes insipidus (DI), mannitol, phenytoin, correction of hyperglycemia, and increased total body sodium content resulting from prolonged volume depletion that stimulates aldosterone secretion and causes renal retention of sodium. Chronic hypernatremia is better tolerated than acute hypernatremia. Acute hypernatremia may cause water shift from cerebral tissues and cellular dehydration. Symptoms include lethargy, muscle tremor, rigidity, hyperreflexia, seizures and coma.

DI may be neurogenic (decreased ADH release from the pituitary) or nephrogenic (decreased sensitivity of renal collecting tubules to ADH). Neurogenic DI, which is more common with basilar skull fractures and increased ICP, may indicate impending brain death. Clinical manifestations of DI include increased urinary output (200–300 mL/h), decreased urinary specific gravity (<1.005), decreased urine osmolality to less than serum osmolality, hypernatremia, and dehydration.

Hypomagnesemia, Hypokalemia, and Hypocalcaemia

Patients with severe head injury are at high risk for development of hypomagnesemia, hypokalemia, and hypocalcemia. These electrolyte abnormalities have been linked to cardiac arrhythmias associated with prolongation of the QT interval. Treatment consists of replacing the electrolyte deficits and correcting the underlying cause. Hypokalemia is most often caused by a extracellular shift of potassium due to alkalosis that results from spontaneous or mechanical hyperventilation. In addition, actual potassium loss may occur through the use of corticosteroids or diuretics.

GASTROINTESTINAL ABNORMALITIES AND NUTRITION

Stress Ulcer

Patients with TBI are at increased risk for stress gastritis and ulceration, the risk factors for which include TBI itself, critical illness, mechanical ventilation, coagulopathy, and steroid use. Prophylaxis against stress gastritis and ulceration in the form of proton pump inhibitors (PPIs), such as esomeprazole (40 mg IV daily), or H_2-antagonists, such as famotidine (40 mg IV daily), is recommended for all critically ill patients with TBI.

Nutrition

Nutrition is an important aspect of the care of the critically ill patient with TBI. TBI is associated with hypermetabolism, hypercatabolism, hyperglycemia, and nitrogen wasting. Patients with TBI are at risk for malnutrition, immunocompromise, and poor healing if their nutritional, specifically protein, requirements are not met. Nutrition should be provided to patients with TBI as soon as the acute issues of stabilization and treatment are addressed. Appropriate nutritional support has been shown to improve patient outcomes.[73] Recommendations based on level II evidence suggest that patients should be fed to attain full caloric replacement by day 7 after injury.[74]

Enteral nutrition (EN) is the preferred route of nutrition because it is associated with less risk of hyperglycemia and septic complications than total parenteral nutrition (TPN).[75] TBI is associated with decreased gastric emptying and increased reflux.[76] Increased ICP and low GCS scores at admission are associated with higher rates of gastric atony, ileus, and stress-related gastritis. Early (<36 h from TBI) enteral nutrition is associated with shorter ICU stays and fewer infectious complications as compared to late (>36 h from TBI) EN.[77] Tighter control of serum glucose levels without reduction of nutritional support may improve the prognosis in TBI. Aspiration of enteral feeds occurs in up to 45% of patients with TBI and is not reduced by jejunal placement of feeding tubes. Precautions include checking gastric residual content after 4 hours of stopping feeding, elevating the head of the bed to at least 30 degrees, and detection of abdominal distention. Metoclopramide (10 mg IV every 8 h) may improve gastric motility and decreases reflux. Jejunal placement of feeding tubes may overcome the problem of gastric atony and ileus, but does not necessarily decrease the risk of aspiration.[75]

TPN is initiated if EN is not tolerated or not feasible. Benefits of TPN include a lesser degree of negative nitrogen balance, which may improve survival by avoiding protein malnutrition and the associated immunosuppression. Complications of TPN include fluid overload, cerebral edema, hyperglycemia, electrolyte imbalance, and catheter-related complications such as sepsis. About 75% of the total caloric requirements are provided in the form of glucose or dextrose to avoid the use of amino acids as a source of energy.

Total calories are calculated on the basis that fat provides 9 kcal/g, and glucose and protein provide 4 kcal/g each. However, protein is provided mainly to meet nitrogen

requirements and not as a calorie source. Because of the increased protein catabolism in TBI, the goal of achieving a positive nitrogen balance may not be attained until several days after TBI, and patients may require twice as much protein (2 g/kg/day) as in a standard diet (0.8 g/kg/day). One study demonstrated that a positive nitrogen balance could be obtained earlier with the use of insulin-like growth factor-1 (IGF-1) and growth hormone therapy.[71] Patients with moderate-to-severe TBI were treated with IGF-1 infusion and subcutaneous growth hormone within 72 hours of injury. Within the treatment group, a positive nitrogen balance was achieved within the first 24 hours following therapy.[71] Prealbumin, a serum protein with a half-life of 2 to 3 days, and urine urea nitrogen (UUN) levels are measured to assess nitrogen balance and guide protein supplementation.

ENDOCRINE ABNORMALITIES

Hyperglycemia and Hypoglycemia

Maintaining euglycemia is vital after TBI and neurosurgery. Both hyperglycemia and hypoglycemia can exacerbate neurologic injury. Hyperglycemia during neuronal injury, such as ischemic stroke, cerebral hemorrhage, or cerebral trauma, is associated with increased morbidity and mortality.[78,79] During severe TBI, hyperglycemia (serum glucose greater than 170 mg/dL or 9.4 mmol/L) is associated with a lower rate of survival.[80] Hyperglycemia and the infusion of glucose-containing fluids have been shown to worsen neurologic outcome of cerebral ischemia and stroke mainly because during focal ischemia, glucose is converted to lactate, which exacerbates secondary neuronal injury.[81–83] Intensive insulin therapy in patients with TBI and in patients with non-neurologic critical illnesses is associated with decreases in the occurrence of polyneuropathy in critical illness, in days of ventilator dependency, in ICP, and in incidence of seizures, as well as better long-term rehabilitation.[84] In addition to providing strict glucose control, insulin may have neuroprotective effects because it shares significant homology with nerve growth factor (NGF), which facilitates neuronal repair.

On the other hand, hypoglycemia is associated with worse outcome during SAH, ICH, TBI, and cerebral infarction. The brain may suffer an "energy crisis" when brain glucose levels are less than 12.6 mg/dL (0.7 mmol/L) or the lactate-to-pyruvate ratio is less than 40. In one study, the risk of brain energy crisis was 23% more likely with each 1 mmol/L decrease in systemic glucose concentration and 10% more likely with each 1 unit/L increase in insulin infusion, despite adjustment for ICP and GCS score. Among patients receiving neurointensive care, episodes of low brain glucose levels and high levels of metabolic distress markers are associated with greater mortality and poorer outcome among survivors. A reasonable balanced goal of glycemic control among patients with TBI may be to maintain serum glucose between 100 and 150 mg/dL (5.5 and 8.25 mmol/L).

Syndrome of Inappropriate Antidiuretic Hormone Secretion

As previously described, increased ADH secretion following TBI may result in SIADH, which causes water retention with continued sodium excretion, leading to hyponatremia.[85] Symptoms of hyponatremia include nausea, vomiting, headache, mood lability, confusion, seizures, and coma. SIADH is also seen in patients with SAH, brain tumor, brain abscess, meningitis, and encephalitis. Treatment of SIADH involves free water restriction to achieve a negative water balance, loop diuretics, and the infusion of hypertonic saline. In mild cases, water restriction alone may be adequate. However, a high urine osmolarity may not allow adequate water excretion. Therefore, in moderate cases, loop diuretics are used to decrease urine osmolarity, because they impair renal concentrating ability. In more severe cases (serum sodium levels <120 mEq/L), hypertonic saline is used as a slow infusion (25–100 mL/h), which compensates for the diuretic-induced natriuresis. Serum sodium, urine osmolality, and urine specific gravity should be measured at regular intervals (4–6 h) to guide therapy.

It is important to distinguish between SIADH and CSWS because their respective therapies vary greatly. In contrast to SIADH management, the treatment for CSWS consists of sodium and volume repletion. Fluid restriction and diuresis in a patient with CSWS can be fatal because of the possibility of severe hypovolemia and cerebral infarction. Indications for the use of hypertonic (3%) NaCl in the treatment of hyponatremia include clinically relevant hyponatremia with serum sodium less than 120 mEq/L, seizures, and cerebral edema. Hypertonic (3%) NaCl is given slowly (25–100 mL/h), with frequent monitoring of serum sodium levels to avoid correction at rates above 0.5 mEq/L/h or greater than 12 mEq/day. Rapid correction of hyponatremia has been associated with central pontine myelinolysis (CPM). The risk of CPM is increased with chronic (longer than 48 h) hyponatremia.

Hypopituitarism

Hypopituitarism secondary to TBI may be partial or complete and immediate or delayed.[86] Within 1–2 years of TBI, 28–57% of patients have one or more anterior pituitary hormone deficiencies. Isolated growth hormone deficiency is the most common (20%),[87] followed by adrenocorticotropic hormone (ACTH) deficiency (10%).[88] TBI-induced hypopituitarism may be due to infarction, which could be caused by compression from increased ICP, hypoxia, or skull fracture. During the early period of TBI, ACTH release leads to increased levels of serum cortisol, with some correlation with the severity of injury.[89,90] However, within 1 week to 2 months of injury, adrenal failure may be encountered in cases of moderate-to-severe TBI, resulting in a significant decrease in cortisol levels.[91]

Therefore, all patients in whom secondary hypoadrenalism due to decreased ACTH is suspected should receive corticosteroid coverage until testing indicates an intact pituitary–adrenal axis. An occult ACTH and cortisol deficiency may become acutely apparent during acute stress and may manifest as hyponatremia and hypovolemic shock. Less acute deficiency may manifest as mild-to-moderate hypotension, fatigue, lethargy, weight loss, abdominal pain, hypoglycemia, frequent hunger, headaches, and light-headedness. During acute TBI, about 50% of patients have low triiodothyronine (T_3) syndrome (euthyroid sick syndrome [ESS]), which consists of a low level of free T_3 with normal levels of free thyroxine (T_4) and thyroid-stimulating hormone. At 12 months after injury, about 6% of patients have TSH deficiency.[92,93] Thyroid hormone replacement therapy is not administered to treat low T_3 syndrome, which occurs because of impairment of conversion of T_4 to T_3 due to inhibition of type I deiodinase, which is inhibited during stress or illness.

As mentioned previously, decreased secretion of pituitary ADH leads hypernatremia from DI. Treatment of DI consists of treatment of the underlying cause (trauma, elevated ICP), correction of hypovolemia, hypernatremia, and hormonal deficiency. Hypovolemia is corrected with IV fluids at a rate that achieves a 1:1 ratio with urine output. Hypernatremia is corrected with enteral water or parenteral (5% dextrose in water

[D_5W]) solution. The use of D_5W is avoided in the neurosurgical patient in order to avoid hyperglycemia, which may worsen the neurologic outcome of ischemic brain injury. Total body water deficit is calculated according to the following formula:

$$H_2O\,\text{deficit} = \frac{\text{serum}\,Na^+ - 140}{140 \times 0.6 \times \text{body wt}\,(\text{kg})} \qquad (23.2)$$

The goal of free water replacement is to correct serum sodium by a rate no faster than 0.5 mEq/L/h or 12 mEq/L/24 h with the target being a reduction in serum sodium to less than 160 mEq/L and serum osmolarity to less than 320 mEq/L.

Serum electrolyte levels should be monitored every 4 to 6 hours until hypernatremia is resolved. Blood glucose should be monitored frequently and treated with IV insulin, because hyperglycemia may cause additional osmotic diuresis.

Hormonal replacement is reserved for cases of severe DI or to avoid administering large volumes of free water. Desmopressin is a synthetic analogue of vasopressin (ADH) that lacks pressor activity and causes free water absorption at the distal tubules and collecting system of the kidneys. It can be administered IV or subcutaneously at 0.3 µg/kg/day, divided and given twice daily. The oral dose is 0.05–1.2 mg/day divided and given twice or three times daily. The intranasal dose is 10–40 µg one or two times a day; its effects last 8 to 20 hours. This dose is repeated when urine output increases again to 200 mL/h. Excessive doses of desmopressin can cause oliguria, hyponatremia, and water intoxication.

Vasopressin is the pituitary hormone that possesses both vasopressor and antidiuretic properties. It is mainly used clinically as a vasopressor infusion (0.04 unit/min, IV). However, it can be used for the treatment of DI associated with hypotension.

Hypopituitarism is associated with a twofold increase in mortality due to cardiovascular, respiratory, or cerebrovascular disease.[94] Affected patients are advised to remain under the care of an endocrinologist and to have their cardiovascular risks assessed regularly.

INFECTIOUS COMPLICATIONS

Sepsis is the most common cause of late mortality in TBI. Risk factors include prolonged ventilatory support, massive transfusion, and nutritional insufficiency. Urinary tract infections (UTIs) are the most common nosocomial infections, followed by pneumonia. Risk factors for UTI include indwelling urinary catheters, prolonged antibiotic use, urinary stasis, unsealed collection ports, and elevated serum creatinine concentration. Treatment consists of appropriate selective antibiotic therapy and removal of the infected catheters.

Respiratory tract infections are generally separated into early- and late-onset infections. Early-onset infections tend to be caused by antibiotic-sensitive organisms, whereas late-onset infections are often caused by antibiotic/antimicrobial resistant organisms. These resistant organisms are either selected through previous antibiotic treatment or are hospital-acquired species. Regardless of the etiology, nosocomial infections are associated with increased mortality.[95]

Intravenous catheter-related infections are the cause of bacteremia in less than 1% of ICU patients.[96] The incidence of meningitis in TBI is about 13%. Risk factors include dural tears with CSF leakage, CSF rhinorrhea or otorrhea, ICP monitoring for longer than 72 hours, ICP catheter manipulation, and antibiotic flushes of ICP catheters. The use of prophylactic antibiotics and antibiotic coated external ventricular drains suggest a beneficial effect on the incidence of ventriculostomy-related infections.[97] Penetrating brain injuries increase the risk of brain abscess and empyema, particularly subdural empyemas, which are most common in frontal and compressed skull fractures (up to 66% mortality rate).

Fever seems to be an independent predictor of poor outcome in TBI.[98] Systemic temperatures higher than 38.5 °C should be treated, but lower temperature treatment thresholds should be used in patients with increased ICP.

SECONDARY BRAIN INJURY

Prevention of secondary brain injury is continued in the postoperative period. Studies have shown that patients who sustain secondary brain injury have less favorable outcomes.[99,100] Hypotension, hypoxia, hyperthermia, hyperglycemia, hypoglycemia, increased ICP, and any aggravating factors, such as pain, nausea, vomiting, seizures, hypertension, hypercarbia, and impaired cerebral venous drainage, should all be prevented and treated. Conscious, mechanically ventilated patients are sedated with a short-acting agent, such as propofol or dexmedetomidine, to allow intermittent neurologic assessment. Pain due to the operative procedure or the primary or associated injury is relieved with opioids and non-narcotic analgesics. Nausea and vomiting are treated with stomach suctioning, provided that no basilar skull fractures are present, and with pharmacologic agents such as ondansetron. The risk-to-benefit ratio for seizure prophylaxis after head trauma is somewhat controversial. Phenytoin or other antiepileptic drugs (AED) may be given for 2 weeks or longer after head injury if there is seizure activity.

Sedation and Analgesia

Sedation and analgesia in post-TBI and postoperative patients presents a unique challenge. Sedation and analgesia are necessary because both pain and agitation increase ICP. In addition, inadequate analgesia may lead to agitation, hypertension, and vomiting, which may raise the risk of intracranial bleeding or other neurologic complications. On the other hand, narcotic analgesics may cause respiratory depression and hypercapnia, leading to cerebral vasodilation and increased ICP. Similarly, oversedation may mask neurologic deficits and interfere with proper neurologic examination. There is evidence that pain after neurosurgical procedures is more severe than expected, which may result in undertreatment by the perioperative team.[101] Pain experienced by patients after craniotomy seems to be of somatic origin, most likely involving the scalp, pericranial muscles, and soft tissue, and from manipulation of the dura mater.[102] Although pain may often be treated as a secondary concern, uncontrolled pain has systemic effects that may directly affect patient outcome (Box 23.1).

In general, short-acting agents are preferred because they allow interruption for neurologic examination. To avoid peaks and troughs with the use of short-acting agents, administration by continuous intravenous infusion is preferred. Commonly used drugs include propofol, midazolam, fentanyl, remifentanil, and dexmedetomidine. Dexmedetomidine is a highly selective α_2-adrenergic agonist that allows patients to be comfortably sedated yet easily arousable for serial neurologic examinations. It is also used intraoperatively for awake craniotomy and preoperatively for sedation of patients with aneurysmal SAH. The administration of dexmedetomidine toward the end of major inpatient surgical procedures has been associated with opioid-sparing effects, reducing morphine requirements by as much as 60%.[103]

BOX 23.1 Systemic Organ Responses to Pain

Respiratory	Increased skeletal muscle tension
	Decreased total lung compliance
Endocrine	Increases in adrenocorticotropic hormone, cortisol, glucagon, epinephrine, aldosterone, antidiuretic hormone, catecholamines, and angiotensin II
	Decreases in insulin and testosterone
Cardiovascular	Increased myocardial work (mediated by catecholamines, angiotensin II)
Immunologic	Lymphopenia
	Depression of reticuloendothelial system
	Leukocytosis
	Reduced killer T-cell cytotoxicity
Hematologic	Increased platelet adhesiveness
	Diminished fibrinolysis
	Activation of coagulation cascade
Gastrointestinal	Increased sphincter tone
	Decreased smooth muscle tone
Genitourinary	Increased sphincter tone
	Decreased smooth muscle tone

Adapted from: Ortiz-Cardona J, Bendo AA: Perioperative pain management in the neurosurgical patient. Anesthesiol Clin 2007;25:655–674.

Opioids are commonly used for postoperative analgesia. Patient-controlled analgesia (PCA) has been used to control pain effectively in patients who have undergone craniotomy. Morphine is the most commonly used opioid. Side effects of opioid use include nausea, vomiting, decreased gastrointestinal motility, constipation, pruritus, and respiratory depression. These side effects may lengthen both recovery time and length of hospital stay.

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are excellent alternatives to opioids in providing analgesia for most postoperative patients. However, NSAIDs are associated with platelet dysfunction and may increase the bleeding time. This can lead to a higher risk of postoperative bleeding, particularly after hematoma evacuation, aneurysm repair, and resection of arterial venous malformations (AVM). The use of *N*-methyl-D-aspartate receptor antagonists such as ketamine in patients who have undergone craniotomy should be avoided, given the resulting increase in ICP seen with their use in both human and animal studies.[104,105] Ketamine also causes increases in both CBF and cerebral metabolic rate. Scalp blocks have been used successfully to provide transitional analgesia, similar to that of intravenous morphine, in the immediate postoperative period after remifentanil-based anesthesia.[106] Scalp blocks decrease pain and pain medication requests and increase the time between the end of the procedure and the first request for postoperative analgesics.[107] Although commonly practiced, infiltration of the wound incision site has not been shown to be effective in improving post-craniotomy pain scores.

Normothermia

Fever in the brain-injured patient is associated with increased morbidity and mortality. In a meta-analysis conducted by Greer and colleagues including more than 14,000 patients, fever alone was a significant and independent predictor of morbidity and mortality across such different disease entities as ischemic stroke, hemorrhagic stroke, and TBI.[108] Induced normothermia via intravascular cooling catheter is effective in reducing fever burden and may offer a means to attenuate secondary injury, as evidenced by a reduction in the intracranial hypertension burden.[109] Surface cooling has also been shown to be superior to conventional measures in effectively controlling fever.[110]

Control of Intracranial Pressure

The brain, blood, and CSF contents within the cranium constitute a nearly incompressible system, with some capacitance afforded by blood vessels and vertebral spaces. Once capacitance has been maximized, ICP rises dramatically with small increases in intracranial volume. Normally ICP is 10 mmHg or less, and changes in ICP are generally tolerated over a CPP range of 50–150 mmHg. But as CPP is reduced, vasodilatation and increased ICP occur at a logarithmic rate.[111] Increased ICP leads to decreased CBF, which leads to a compensatory increase in MAP and a compensatory decrease in cerebrovascular resistance, which is maximal at CPP values of about 50 mmHg. Although an increase in cerebral vasodilation is a compensatory mechanism to increase CBF, it does reduce CBV, which may further raise ICP, perpetuating a vicious circle of increased ICP and decreased perfusion. Therefore, it is essential to break this circle by treating any increase in ICP once the compensatory mechanisms have been maximized.

In TBI, increased ICP may be caused by an increase in volume of any one of the components of the cranial compartment: intravascular blood, brain, or CSF. In addition, extravascular blood, depressed skull fractures, and foreign bodies may further raise ICP. Decreased cerebral venous drainage may cause diastolic decreases in CPP or interrupted perfusion leading to anaerobic metabolism and lactate production, which leads to cerebral edema and to further increases in ICP. The utility of ICP monitoring and ICP-guided intensive care of TBI has come under question.[112] One study showed that ICP monitoring was associated with increased risk of prolonged mechanical ventilation and other complications and that it limited the benefits from therapeutic interventions, including medications, hyperventilation, and keeping CPP above 70 mmHg.

ICP monitoring should be performed according to the guidelines for surgical and neurointensive therapy published by the Brain Trauma Foundation and other professional organizations. These guidelines recommend ICP monitoring for patients with severe TBI and some patients with moderate TBI according to coexisting conditions. An ICP reading higher than 20 mmHg is considered an indication for ICP-reducing therapy and for maintaining an MAP of 80 to 100 mmHg. In general, intraparenchymal and intraventricular ICP monitoring devices are considered more accurate and preferable to subdural, subarachnoid, or epidural monitors. Imaging signs of increased ICP include cerebral edema (particularly progressive), midline shift, and cisternal compression. These signs may exist without confirmation by an ICP monitor. Patients with imaging signs of increased ICP should be monitored and treated aggressively in an ICU setting until resolution of neurologic symptoms and clinically relevant imaging abnormalities.

The aim of treating increased ICP is to ensure adequate CPP, because CPP = MAP – ICP. The definitive treatment of increased ICP is to eliminate or minimize the primary cause of increased ICP. In addition, measures aimed at reducing the volume of one of the three normal components of the cranium (blood, CSF, and cellular water) are performed. Intravascular cerebral blood volume may be reduced by reducing CBV, improving venous drainage, or both. Acute

reductions in CBF and CBV can be achieved almost immediately with hyperventilation, which decreases $PaCO_2$ causing vasoconstriction. The risks associated with this systemic vasoconstriction include cerebral and myocardial ischemia. Thus, hyperventilation should be used only for short periods for necessary, immediate control of ICP. The efficacy of a hyperventilation-induced decrease in ICP is most prominent during the first 12 to 24 hours of hyperventilation.[113]

Reducing the cerebral metabolic rate may be a safer way of achieving a "coupled" decrease in CBF and CBV. Decreases in cerebral metabolic rate may be achieved with physiologic or pharmacologic measures. Drugs that have been shown to decrease cerebral metabolic rate include barbiturates, benzodiazepines, etomidate, propofol, opioids, and lidocaine. Reports of seizure activity and worsening of ischemic and TBI in animals exposed to high doses of opioids have not been substantiated in humans.[114,115] Instead opioid-induced analgesia has been shown to prevent pain- and catecholamine-induced spikes in ICP, and opioid analgesics are used for analgesia and enhancement of sedation in patients with TBI. Osmotic diuretics such as mannitol are used to reduce ICP by shifting water from the intracellular and interstitial spaces into the intravascular space and then into the renal excretory system. This osmotic shift of intracellular water is induced through the presence of an intact semipermeable vascular membrane, also known as the blood–brain barrier (BBB). With a damaged BBB, hyperosmolar agents may shift water from the vascular space into the cellular and interstitial compartments, thus increasing ICP. A rebound increase in cerebral edema and ICP may occur once mannitol has been discontinued, owing to the formation and accumulation of idiogenic osmoles in the brain. Idiogenic osmoles consist mainly of taurine and other amino acids and are formed in the brain secondary to long-standing hyperosmolality. Once formed, osmoles are removed at a rate that could be slower than the rate of normalizing extracellular osmolality, possibly leading to an osmotic intracellular shift of water. Maintaining intravascular osmolality or hyperosmolality is essential in avoiding this complication.

Hypertonic saline (HS) achieves shifting of water into the intravascular space as mannitol does, but without the associated diuresis. Also like mannitol, HS requires the presence of a semipermeable membrane to exert its water-shifting effect. With an intact BBB, HS can achieve a rapid (maximum effect at 20 min) and significant (40%) decrease in ICP.[116] The efficacy of HS in reducing ICP has been shown in ischemic stroke, ICH, SAH, TBI, and postoperative cerebral edema.[117] Sodium chloride, with a reflection coefficient of 1.0, is better excluded from brain with an intact BBB than mannitol (reflection coefficient of 0.9). Because of its lack of diuretic effect, HS may increase CBF while decreasing ICP, which may be an advantage in cases of hypotension or decreased CBF.[118] In the presence of an intact BBB, HS has been shown to be more effective than mannitol in controlling ICP[119,120] and to be effective when other medical therapies had failed.[121,122]

CSF drainage may decrease ICP by decreasing CSF volume. This is usually achieved by placement of a cerebral ventricular catheter, which can be used both to monitor ICP as well as drain CSF. The rate and volume of CSF drainage are controlled to avoid bleeding, ventricular collapse, and brain herniation due to rapid or excessive SCF drain. Surgical intervention may provide the most definitive therapy of increased ICP by removing blood clots or other mass-forming tissues. Acute change in neurologic status or level of consciousness may warrant surgical intervention in addition to other therapeutic measures aimed at decreasing ICP and improving CPP. Evacuation of acute epidural or cerebellar hematoma has been shown to improve outcome in TBI with raised ICP, but no such improvement has been shown consistently in ICH or subdural hematoma.[123]

Acute change in neurologic status or level of consciousness may warrant surgical intervention in addition to other therapeutic measures aimed at decreasing ICP and improving CPP. In cases of increased ICP that is refractory to medical treatment and is not associated with mass lesion, decompressive craniectomy may prevent transtentorial herniation, break the self-propagating cycle of increasing ICH and cerebral edema, and improve overall CPP. Hemicraniectomy may be performed when there is unilateral focal injury or as a bifrontal craniectomy when there is frontal injury or diffuse injury. Decompressive craniectomy has been shown to decrease mortality and increase functional neurologic recovery in patients with malignant MCA infarction (>50% MCA territory) and decreased level of consciousness.[124–128] Currently, there is no prospective, randomized trial to support decompressive craniectomy in TBI over maximal medical therapy.[129]

Brain Physiologic Monitoring

New monitoring techniques are available to provide crucial information on brain physiology and metabolism. Brain physiologic monitoring has been used to guide management of ICP, MAP, and FiO_2. Systemic hypoxemia ($PaO_2 < 50–60$ mmHg) is associated with systemic, including cerebral, vasodilation, which is a compensatory mechanism to increase oxygen delivery (DO_2) to body tissues, including the brain. On the other hand, high FiO_2 (>0.6) may lead to the generation of free radicals, which may cause cellular and mitochondrial injury, leading to decreased neuronal recovery.[130] These monitoring tools include cerebral oxygen monitoring, intracerebral microdialysis and continuous electroencephalography. These monitoring modalities are described in detail in Chapter 5.

Cerebral physiologic monitoring has the promise to provide brain-specific endpoints in contrast to more global indices commonly used in the resuscitation of neurocritical care patients. While none of the above techniques have been found to be sufficiently effective to become "standard of care", multimodal monitoring has the potential for guiding management of the critically ill neurologically injured patient. Large, prospective trials are needed to validate their use in guiding management of the neurologically injured patient.

REFERENCES

1. Barrett KE, Boitano S, Barman SM, Brooks HL. Chapter 36. Regulation of respiration. In: Barrett KE, Boitano S, Barman SM, Brooks HL, eds. *Ganong's Review of Medical Physiology*. New York, NY: McGraw-Hill; 2012:24e.
2. Harrison-Felix C, Kreider SE, Arango-Lasprilla JC, et al. Life expectancy following rehabilitation: A NIDRR Traumatic Brain Injury Model Systems study. *J Head Trauma Rehabil*. 2012;27:E69–E80.
3. Greenwald Brian D, Hammond Flora M, Cynthia Harrison-Felix, Risa Nakase-Richardson, Howe Laura LS, Scott Kreider. Mortality following traumatic brain injury among individuals unable to follow commands at the time of rehabilitation admission: A National Institute on Disability and Rehabilitation Research traumatic brain injury model systems study. *J Neurotrauma*. 2015;32:1883–1892.
4. Harrison-Felix Cynthia C, Pretz Christopher, Hammond Flora M, et al. Life expectancy after inpatient rehabilitation for traumatic brain injury in the United States. *J Neurotrauma*. 2015;32:1893–1901.
5. American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support Program for Doctors*. 8th ed. Chicago: American College of Surgeons; 2008.
6. Wittekamp Bastiaan HJ, Walther NKA van Mook, Tjan Dave HT, Zwaveling Jan Harm, Bergmans Dennis CJJ. Clinical review: Post-extubation laryngeal edema and extubation failure in critically ill adult patients. *Crit Care*. 2009;13:233.

7. Straube B, Blum JD. The policy on paying for treating hospital-acquired conditions: CMS officials respond. *Health Aff (Project Hope)*. 2009;28:1494.
8. Spicer RS, Miller TR, Hendrie D, Blincoe LJ. Quality-adjusted life years lost to road crash injury: Updating the injury impairment index. *Ann Adv Automot Med*. 2011;55:365.
9. Hui Xuan, Haider Adil H, Hashmi Zain G, et al. Increased risk of pneumonia among ventilated patients with traumatic brain injury: Every day counts! *J Surg Res*. September 2013;Volume 184(Issue 1):438–443.
10. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;Vol. 171(No. 4):388–416. http://dx.doi.org/10.1164/rccm.200405-644ST.
11. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest*. 2007;131(5):1308–1314.
12. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: Prospective nested case-control study. *Am J Respir Crit Care Med*. 2007;176(9):886–891.
13. Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. *Crit Care Med*. 2005;33(6):1191–1198.
14. Xiaoming J, Malhotra A, Saeed M, Mark RG, Talmor D. Risk factors for acute respiratory distress syndrome in patients mechanically ventilated for greater than 48 hours. *Chest*. 2008;133(4):853–861.
15. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med*. 1990;16(6):372–377.
16. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308.
17. Shapiro HM, Marshall LF. Intracranial pressure responses to PEEP in head injured patients. *J Trauma*. 1978;18:254–256.
18. Huynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. *J Trauma*. 2002 Sep;53(3):488–492.
19. Bratton SL, Davis RL. Acute lung injury in isolated traumatic brain injury. *Neurosurgery*. 1997;40:707–712.
20. Simon RP. Neurogenic pulmonary edema. *Neurol Clin*. 1993;11:309–323.
21. Šedý J, Kuneš J, Zicha J. Pathogenetic mechanisms of neurogenic pulmonary edema. *J Neurotrauma*. 2015;32:1135–1145.
22. Colice GL. Neurogenic pulmonary edema. *Clin Chest Med*. 1985;6(3):473–489. PubMed PMID: 3907948.
23. Davison DL, Terek M, Chawla LS. Neurogenic pulmonary edema. *Crit Care*. 2012;16(2):212. http://dx.doi.org/10.1186/cc11226. PubMed PMID:22429697;PubMed Central PMCID:PMC3681357.
24. Fontes RB, Aguiar PH, Zanetti MV, Andrade F, Mandel M, Teixeira MJ. Acute neurogenic pulmonary edema: Case reports and literature review. *J Neurosurg Anesthesiol*. 2003;15(2):144–150. PubMed PMID:12658001.
25. McGuire G, Crossley D, Richards J, Wong D. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med*. 1997;25(6):1059–1062. PubMed PMID:9201061.
26. Coles JP, Fryer TD, Coleman MR, et al. Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism. *Crit Care Med*. 2007;35(2):568–578. http://dx.doi.org/10.1097/01.CCM.0000254066.37187.88. PubMed PMID:17205016.
27. Rios-Romenets S, Castano-Monsalve B, Bernabeu-Guitart M. Pharmacotherapy of the cognitive sequelae secondary to traumatic brain injury. *Rev Neurol*. 2007;45(9):563–570. PubMed PMID:17979087.
28. Neil-Dwyer G, Cruickshank JM, Doshi R. The stress response in subarachnoid haemorrhage and head injury. *Acta Neurochir Suppl (Wien)*. 1990;47:102–110. PubMed PMID:2407054.
29. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation*. 2008;118(4):397–409. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.677625. PubMed PMID:18645066.
30. Nguyen H, Zaroff JG. Neurogenic stunned myocardium. *Curr Neurol Neurosci Rep*. 2009;9(6):486–491. PubMed PMID:19818236.
31. Gregory T, Smith M. Cardiovascular complications of brain injury. *Contin Educ Anaesth Crit Care Pain*; December 22, 2011.http://dx.doi.org/10.1093/bjaceaccp/mkr058.
32. Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B, O'Gorman P. Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage. *Br Med J*. 1978;2(6143):990–992. PubMed PMID:361155;PubMed Central PMCID:PMC1607890.
33. McMahon CG, Kenny R, Bennett K, Kirkman E. Modification of acute cardiovascular homeostatic responses to hemorrhage following mild to moderate traumatic brain injury. *Crit Care Med*. 2008;36(1):216–224. http://dx.doi.org/10.1097/01.CCM.0000295425.41831.85. PubMed PMID:18090349.
34. Baguley IJ, Heriseanu RE, Felmingham KL, Cameron ID. Dysautonomia and heart rate variability following severe traumatic brain injury. *Brain Inj*. 2006;20(4):437–444. http://dx.doi.org/10.1080/02699050600664715. PubMed PMID:16716989.
35. Keren O, Yupatov S, Radai MM, et al. Heart rate variability (HRV) of patients with traumatic brain injury (TBI) during the post-insult sub-acute period. *Brain Inj*. 2005;19(8):605–611. PubMed PMID:16175814.
36. McLeod AA, Neil-Dwyer G, Meyer CH, Richardson PL, Cruickshank J, Bartlett J. Cardiac sequelae of acute head injury. *Br Heart J*. 1982;47(3):221–226. PubMed PMID:7059399;PubMed Central PMCID:PMC481125.
37. Oppenheimer SM, Cechetto DF, Hachinski VC. Cerebrogenic cardiac arrhythmias. Cerebral electrocardiographic influences and their role in sudden death. *Arch Neurol*. 1990;47(5):513–519. PubMed PMID:2185720.
38. Singla SL. Jagdish, Garg P, Mehta RK. Electrocardiographic changes in craniocerebral trauma--could they serve as prognostic indicators? *J Indian Med Assoc*. 2002;100(3):188–190. PubMed PMID:12408282.
39. Polderman KH, Bloemers FW, Peerdeman SM, Girbes AR. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med*. 2000;28(6):2022–2025. PubMed PMID:10890658.
40. Lazar L, Erez I, Gutermacher M, Katz S. Brain concussion produces transient hypokalemia in children. *J Pediatr Surg*. 1997;32(1):88–90. PubMed PMID:9021578.
41. Pomeranz S, Constantini S, Rappaport ZH. Hypokalaemia in severe head trauma. *Acta Neurochir (Wien)*. 1989;97(1-2):62–66. PubMed PMID:2718795.
42. Trouwborst A, Kooijman J. The alterations of plasma potassium in patients with severe acute head injury. *Injury*. 1984;15(5):293–295. PubMed PMID:6706386.
43. Ozdemir D, Ozdemir N, Unal N, Tektas S. QTc dispersion in children with severe head trauma. *Pediatr Emerg Care*. 2005;21(10):658–661. PubMed PMID:16215468.
44. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: Results from the IMPACT study. *J Neurotrauma*. 2007;24(2):294–302. http://dx.doi.org/10.1089/neu.2006.0032. PubMed PMID:17375994.
45. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34(2):216–222. PubMed PMID:8459458.
46. Cortbus F, Jones PA, Miller JD, Piper IR, Tocher JL. Cause, distribution and significance of episodes of reduced cerebral perfusion pressure following head injury. *Acta Neurochir (Wien)*. 1994;130(1-4):117–124. PubMed PMID:7725934.
47. Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. *J Neurosurg*. 1981;54(3):289–299. http://dx.doi.org/10.3171/jns.1981.54.3.0289. PubMed PMID:7463128.
48. Narayan RK, Greenberg RP, Miller JD, et al. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. *J Neurosurg*. 1981;54(6):751–762. http://dx.doi.org/10.3171/jns.1981.54.6.0751. PubMed PMID:7241184.
49. Brain Trauma F, American Association of Neurological S, Congress of Neurological S, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma*. 2007;24(Suppl 1):S59–64. http://dx.doi.org/10.1089/neu.2007.9987. PubMed PMID: 17511547.
50. Schroeppel TJ, Fischer PE, Zarzaur BL, et al. Beta-adrenergic blockade and traumatic brain injury: protective? *J Trauma*. 2010;69(4):776–782. http://dx.doi.org/10.1097/TA.0b013e3181e981b8. PubMed PMID:20938265.
51. Arbabi S, Campion EM, Hemmila MR, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. *J Trauma*. 2007;62(1):56–61. http://dx.doi.org/10.1097/TA.0b013e31802d972b discussion -2. PubMed PMID: 17215733.
52. Alali AS, McCredie VA, Golan E, Shah PS, Nathens AB. Beta blockers for acute traumatic brain injury: A systematic review and meta-analysis. *Neurocrit Care*. 2014;20(3):514–523. http://dx.doi.org/10.1007/s12028-013-9903-5. PubMed PMID:24062229.
53. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke*. 2007;38(6):2001–2023. http://dx.doi.org/10.1161/STROKEAHA.107.183689. PubMed PMID:17478736.
54. Graffagnino C, Bergese S, Love J, et al. Clevidipine rapidly and safely reduces blood pressure in acute intracerebral hemorrhage: The ACCELERATE trial.

Cerebrovasc Dis. 2013;36(3):173–180. http://dx.doi.org/10.1159/000351149. PubMed PMID:24135526.
55. Mayer SA, Kurtz P, Wyman A, et al. Clinical practices, complications, and mortality in neurological patients with acute severe hypertension: The Studying the Treatment of Acute hyperTension registry. *Crit Care Med*. 2011;39(10):2330–2336. http://dx.doi.org/10.1097/CCM.0b013e3182227238. PubMed PMID:21666448.
56. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34:216–222.
57. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. *JAMA*. 2013;310(17):1809–1817. http://dx.doi.org/10.1001/jama.2013.280502.
58. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
59. Kao SJ, Yeh DY, Chen HI. Clinical and pathological features of fat embolism with acute respiratory distress syndrome. *Clin Sci (Lond)*. 2007;113(6):279–285. http://dx.doi.org/10.1042/CS20070011. PubMed PMID:17428199.
60. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409–417. http://dx.doi.org/10.1056/NEJM199902113400601. PubMed PMID:9971864.
61. Sekhon MS, McLean N, Henderson WR, Chittock DR, Griesdale DE. Association of hemoglobin concentration and mortality in critically ill patients with severe traumatic brain injury. *Crit Care*. 2012;16(4):R128. http://dx.doi.org/10.1186/cc11431. PubMed PMID:22817913;PubMed Central PMCID:PMC3580711.
62. Robertson CS, Hannay HJ, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. *JAMA*. 2014;312(1):36–47. http://dx.doi.org/10.1001/jama.2014.6490. PubMed PMID:25058216;PubMed Central PMCID:PMC4113910.
63. Oddo M, Bosel J. Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Monitoring of brain and systemic oxygenation in neurocritical care patients. *Neurocrit Care*. 2014;21(Suppl 2):S103–S120. http://dx.doi.org/10.1007/s12028-014-0024-6. PubMed PMID: 25208670.
64. Rajajee V, Brown DM, Tuhrim S. Coagulation abnormalities following primary intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2004;13(2):47–51. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2004.01.002. PubMed PMID:17903949.
65. Levi M. Disseminated intravascular coagulation. *Crit Care Med*. 2007;35(9):2191–2195. PubMed PMID:17855836.
66. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: Comparing current criteria. *Crit Care Med*. 2006;34(3):625–631. PubMed PMID:16521260.
67. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev*. 2015;5:CD004896http://dx.doi.org/10.1002/14651858.CD004896.pub4. PubMed PMID: 25956410.
68. Joseph B, Hadjizacharia P, Aziz H, et al. Prothrombin complex concentrate: An effective therapy in reversing the coagulopathy of traumatic brain injury. *J Trauma Acute Care Surg*. 2013;74(1):248–253. http://dx.doi.org/10.1097/TA.0b013e3182788a40. PubMed PMID:23271101.
69. DeVivo MJ, Go BK, Jackson AB. Overview of the national spinal cord injury statistical center database. *J Spinal Cord Med*. 2002;25(4):335–338. PubMed PMID:12482178.
70. Wicks AB, Menter RR. Long-term outlook in quadriplegic patients with initial ventilator dependency. *Chest*. 1986;90(3):406–410. PubMed PMID:3743155.
71. Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. *Kidney Int*. 1976;10:25–37.
72. Laureno R, Illowsky K. Myelinolysis after correction of hyponatremia. *Ann Int Med*. 1997;126(1):57–62.
73. Hatton J, Kryscio R, Ryan M, et al. Systemic metabolic effects of combined insulin-like growth factor-I and growth hormone therapy in patients who have sustained acute traumatic brain injury. *J Neurosurg*. 2006;6:843–852.
74. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons et al. Guidelines for the management of severe traumatic brain injury: XII: Nutrition. *J Neurotrauma*. 2007;24(Suppl 1):S77–S82.
75. Heyland DK, Dhaliwal R, et al. Canadian Critical Care Clinical Practice Guidelines Committee: Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27:355–373.
76. Jackson MD, Davidoff G. Gastroparesis following traumatic brain injury and response to metoclopramide therapy. *Arch Phys Med Rehabil*. 1989;70:535–553.
77. Grahm TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery*. 1989;25:729–735.
78. Bhalla A, Tilling K, Kolominsky-Rabas P, et al. Variation in the management of acute physiological parameters after ischaemic stroke: A European perspective. *Eur J Neurol*. 2003;10:25–33.
79. Walia S, Sutcliffe AJ. The relationship between blood glucose, mean arterial pressure and outcome after severe head injury: An observational study. *Injury*. 2002;33:339–344.
80. Jeremitsky E, Omert LA, Dunham CM, et al. The impact of hyperglycemia on patients with severe brain injury. *J Trauma*. 2005;58:47–50.
81. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
82. Bruno A, Levine SR, Frankel MR, et al. NINDS rt-PA Stroke Study Group: Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59:669–674.
83. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery*. 2000;46:335–342.
84. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449–461.
85. Mattson DL. Importance of the renal medullary circulation in the control of sodium excretion and blood pressure. *J Physiol Regul Integr Comp Physiol*. 2003;284:R13–R27.
86. Leal-Cerro A, Flores JM, Rincon M, et al. Prevalence of hypopituitarism and growth hormone defciency in adults long-term after severe traumatic brain injury. *Clin Endocrinol (Oxf)*. 2005;62:525–532.
87. Tanriverdi F, Senyurek H, Unluhizarci K, et al. High risk of hypopituitarism after traumatic brain injury: A prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. *J Clin Endocrinol Metab*. 2006;91:2105–2111.
88. Agha A, Rogers B, Sherlock M, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab*. 2004;89:4929–4936.
89. Barton RN, Stoner HB, Watson SM. Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. *J Trauma*. 1987;27:384–892.
90. Feibel J, Kelly M, Lee L, Woolf P. Loss of adrenocortical suppression after acute brain injury: Role of increased intracranial pressure and brain stem function. *J Clin Endocrinol Metab*. 1983;57:1245–1250.
91. Dimopoulou I, Tsagarakis S, Douka E, et al. The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: Incidence of hypo-responsiveness and relationship to outcome. *Intensive Care Med*. 2004;30:1216–1219.
92. Tsagarakis S, Tzanela M, Dimopoulou I. Diabetes insipidus, secondary hypoadrenalism and hypothyroidism after traumatic brain injury: Clinical implications. *Pituitary*. 2005;8:251–254.
93. Novitzky D, Matthews N, Shawley D. Triiodothyronine replacement on the recovery of stunned myocardium in dogs. *Ann Thorac Surg*. 1991;51:10–17.
94. Toogood AA, Stewart PM. Hypopituitarism: Clinical features, diagnosis, and management. *Endocrinol Metab Clin N Am*. 2008;37:235–261.
95. Girou E, Brun-Buisson C, Taillé S, et al. Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA*. 2003;290:2985–2991.
96. Hugonnet S, Sax H, Eggimann P, Chevrolet JC, Pittet D. Nosocomial bloodstream infection and clinical sepsis. *Emerg Infect Dis*. 2004 Jan;10(1):76–81.
97. Sonabend AM, Korenfeld Y, Crisman C. Prevention of ventriculostomy-related infections with prophylactic antibiotics and antibiotic-coated ventricular drains: A systematic review. *Neurosurgery*. 2011;68(4):996–1005.
98. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol*. 1994;6:4–14.
99. Pietropaoli JA, Rogers FB, Shackford SR, et al. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. *J Trauma*. 1992;33:403–407.
100. Sarrafzadeh AS, Peltonen EE, Kaisers U, et al. Secondary insults in severe head injury—do multiply injured patients do worse? *Crit Care Med*. 2001;29:1116–1123.
101. Rahimi SY, Vender JR, Macomson SD, et al. Postoperative pain management after craniotomy: Evaluation and cost analysis. *Neurosurgery*. 2006;59:852–857.

102. De Benedittis G, Lorenzetti A, Migliore M, et al. Postoperative pain in neurosurgery: A pilot study in brain surgery. *Neurosurgery*. 1996;38:466–469.
103. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg*. 2004;98:153–158.
104. Belopavlovic M, Buchthal A. Modification of ketamine-induced intracranial hypertension in neurosurgical patients by pretreatment with midazolam. *Acta Anaesthesiol Scand*. 1982;26:458–462.
105. Crosby G, Crane AM, Sokoloff L. Local changes in cerebral glucose utilization during ketamine anesthesia. *Anesthesiology*. 1982;56:437–443.
106. Ayoub C, Girard F, Boudreault D, et al. A comparison between scalp nerve block and morphine for transitional analgesia after remifent-anil-based anesthesia in neurosurgery. *Anesth Analg*. 2006;103:1237–1240.
107. Bala I, Gupta B, Bhardwaj N, et al. Effect of scalp block on postoperative pain relief in craniotomy patients. *Anaesth Intensive Care*. 2006;34:224–227.
108. Greer DM, Funk SE, Reaven NL, et al. Impact of fever on outcome in patients with stroke and neurologic injury: A comprehensive meta-analysis. *Stroke*. 2008;39:3029–3035.
109. Puccio AM, Fischer MR, Jankowitz BT, et al. Induced normothermia attenuates intracranial hypertension and reduces fever burden after severe traumatic brain injury. *Neurocrit Care*. 2009;11(1):82–87.
110. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. *Crit Care Med*. 2004;32(12):2508–2515.
111. Kofke WA, Stiefel M. Monitoring and intraoperative management of elevated intracranial pressure and decompressive craniectomy. *Anesthesiol Clin*. 2007;25:579–603.
112. Cremer OL, van Dijk GW, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Crit Care Med*. 2005;33(10):2207–2213 Oct.
113. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg*. 1991;75:731–739.
114. Kofke WA, Attaallah AF, Kuwabara H, et al. The neuropathologic effects in rats and neurometabolic effects in humans of large-dose remifentanil. *Anesth Analg*. 2002;94:1229–1236.
115. Kofke WA, Garman RH, Garman R, Rose ME. Opioid neurotoxicity: Fentanyl-induced exacerbation of cerebral ischemia in rats. *Brain Res*. 1999;818:326–334.
116. Lescot T, Degos V, Zouaoui A, et al. Opposed effects of hypertonic saline on contusions and noncontused brain tissue in patients with severe traumatic brain injury. *Crit Care Med*. 2006;34:3029–3033.
117. Qureshi AI, Suarez JI, Bhardwaj A, et al. Use of hypertonic (3%) saline/ acetate infusion in the treatment of cerebral edema: Effect on intra-cranial pressure and lateral displacement of the brain. *Crit Care Med*. 1998;26:440–446.
118. Tseng MY, Al-Rawi PG, Pickard JD, et al. Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. *Stroke*. 2003;34:1389–1396.
119. Schwarz S, Schwab S, Bertram M, et al. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. *Stroke*. 1998;29:1550–1555.
120. Vialet R, Albanèse J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med*. 2003;31:1683–1687.
121. Horn P, Münch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res*. 1999;21:758–764.
122. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26:1118–1122.
123. Manno EM, Atkinson JL, Fulgham JR, Wijdicks EF. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. *Mayo Clin Proc*. 2005;80:420–433.
124. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: A pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215.
125. Vahedi K, Vicaut E, Mateo J, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke*. 2007;38:2506.
126. Jüttler E, Schwab S, Schmiedek P, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): A randomized, controlled trial. *Stroke*. 2007;38:2518.
127. Hofmeijer J, Kappelle LJ, Algra A, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): A multicentre, open, randomised trial. *Lancet Neurol*. 2009;8:326.
128. Jüttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *NEJM*. 2014;370:1091.
129. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *NEJM*. 2011;364:1493–1502.
130. Fiskum G, Rosenthal RE, Vereczki V, et al. Protection against ischemic brain injury by inhibition of mitochondrial oxidative stress. *J Bioenerg Biomembr*. 2004;36:347–352.

Chronic Pain Management

24

J.E. Pope • T.R. Deer

INTRODUCTION

The successful treatment of pain in the preoperative patient is important with all surgical specialties, but in many instances it is more critical in the patient undergoing neurosurgical or spinal based surgeries. Attention to the hemodynamic swings associated[1–4] with pain in the immediate postoperative period, with mindful management, sets the patient up for an expedited and uncomplicated recovery. Acute pain can commonly increase sympathetic tone, leading to hypertension, tachycardia, and increased intracranial pressure.

In a comprehensive, retrospective review of postoperative pain, comparing those undergoing intracranial surgery to those with select extracranial procedures, the intracranial group did have significantly less pain than the comparison group ($p < 0.05$).[5] A subset of intracranial patients did, however, have significantly more pain than others in the group: those requiring frontal craniotomies required more opioids and had elevated heart rates, blood pressure, and intracranial pressure (ICP). The analysis was inconclusive regarding those undergoing intracranial procedures. Notwithstanding, some studies suggest that a large volume local anesthetic block in the cranium prior to incision may lower the overall opioid requirements in the postoperative period.[6] This has not been substantiated in a prospective fashion. It is well substantiated that spinal neurosurgery is more painful than after craniotomy.

There are many inherent factors managing pain in the neurosurgical group; these include the desire to limit postoperative sedation, as it is clinically imperative to reliably obtain an accurate neurologic exam to guide treatment, as the surrogate monitors are secondary measures of neurologic function, and have inherent flaws. This gold-standard monitor of a cogent and uncompromised neurologic assessment can be affected adversely if the patient is sedated or obtunded. Employing medications with pharmacokinetically short half-lives can help remedy the paradox by keeping patients sedated when needed and awake when an exam is warranted. This strategy, however, is not without consequence and can result in cumulative effects of the infusion.[7] This conflict of treatment goals can lead to the withholding of pain medication and pain management techniques, which also creates a poor patient outcome. In some instances, this has created an interest in the use of mixed agonist/antagonist or partial agonist opioids. The assertion that these are innately safer, however, is a misconception, and the respiratory depression created with these agents is hard to reverse with opioid antagonists and may lower the ceiling of pain control through opioid agonism. Opioids used inappropriately can, with their known side-effect profiles of cough, nausea, vomiting, and respiratory depression, increase patient morbidity and mortality, as one may suspect that this could raise intracranial pressure.[7–10]

Fairly regularly, waking the patient up in the operating room to demonstrate retained (or improved) motor and cognitive function is commonplace, despite intraoperative use of sensory and motor system monitors (SSEPS, MEPS). The use of rapidly acting intraoperative intravenous or inhalational anesthetics has led to the potential paradigm of an awake patient with poor analgesia. Two points deserve a mention: (1) the anesthetic plan needs to be clearly defined to the patient, setting expectations; and (2) the need for an awake patient does not mean that they cannot have pain control. The anesthesia plan should include both intraoperative and postoperative planning to ensure adequate analgesia, despite a reliable neurologic assessment; one does not preclude the other.

Pain care in the postoperative period needs to be based on pain treatment as the primary goal. Although the hemodynamic consequences of pain, including heart rate and blood pressure, can be treated with sympatholytics (β-blockers, etc.), this obviously provides inappropriate analgesia. Studies have shown that pain in the postoperative period can adversely influence patient outcome independent of hemodynamic or intracranial endpoints.[10–14] Proper pain control may stabilize hemodynamics, reduce blood pressure, and lower $CMRO_2$ (cerebral metabolic oxygen consumption), as well as lower the ICP. In addition to the pain issues, the perioperative period in the intracranial patient is complex, and needs to be considered systemically, as the question becomes: how far reduced is the intracranial compliance? The surgical stress response causes elevations in body oxygen consumption and serum catecholamine concentrations. Systemic hypertension is often present after neurosurgical procedures and has been linked to intracranial hemorrhage. Bleeding in the postoperative period can lead to increased mortality, morbidity, and hospitalization. The cerebral consequences of the recovery period can lead to cerebral hyperemia and increased ICP. Prevention or control of pain is one of the major factors in limiting these adverse systemic effects.

Over the last decade or so, developments in intravenous opioids, new regional techniques, and local anesthetics have greatly enhanced our abilities to treat this patient group. Preemptive analgesia may lead to the improved stability of the patient throughout the surgical experience. To minimize pain and decrease the stress response and hemodynamic changes, the surgeon and anesthesiologist must function together to provide optimal care.

Philosophically, the presence of pain and the body's reaction to it can be altered by many strategies. The opportunity for interruption of the pain pathway can be divided into four components: transduction, transmission, modulation, and perception. Transduction occurs when one type of energy (temperature, mechanical) is converted to electrical energy via ionic charge separation, that is, action potentials. Secondly, transmission is the transfer of pain impulse through the nervous system by the first order, second order, and third order neurons via the C and A delta fibers through the spinothalamic tracts to the thalamus and cortex. Pain modulation describes the alteration of the pain signal (either augmentative or diminish) as it travels. Perception is the subjective and emotional

interpretation of pain, occurring in the somatosensory cortex and limbic system. The patient's genetic, social, and cultural backgrounds influence this interpretation. The remaining sections of this chapter focus on key points to enhance outcomes, patient satisfaction, and patient safety.

ACUTE PAIN MANAGEMENT ASSESSMENT

Anesthesia management begins with appropriate preoperative planning. Several factors need to be assessed: the importance of reducing anxiety, the pain treatment history, and an evaluation of any comorbidities that may influence the response to, or management of the planned pain care.

Chronic long-term opioid use for chronic pain makes determining the baseline dose for opioids in the management of chronic pain patients somewhat difficult. Predictably, physical tolerance and dependence occurs. The analgesic tolerance to opioid medication can influence dosing in both the intraoperative anesthetic and postoperative pain course. It is important to realize that the use of chronic medications is for a stable pain condition and it will be necessary to supplement this baseline dose with additional medication. It is well established that patients with chronic opioid use become tolerant to the opioid effects of nausea, vomiting, sedation, euphoria, and respiratory depression, where there is minimal tolerance to papillary constriction and constipation. Regional anesthesia is very helpful in mitigating the need for a largely weighted opioid pain care regimen. This includes intracranial field blocks to help reduce the opioid requirement postoperatively.

Patient controlled analgesic regimens are also helpful, reducing the lag time between the patient requesting and obtaining an analgesic dose of medicine. Studies suggest the overall dose is lower and pain control is improved when employing these therapies, either the PCIA (patient controlled intravenous analgesia), the PCEA (patient controlled epidural analgesia) or the PCRA (patient controlled regional analgesia). With the aid of ultrasound guidance, regional analgesia has become a major player in the acute and subacute pain management phase of recovery, providing dense pain coverage while reducing the risk of neuraxial bleeding or infection. When employing neuraxial regional analgesia, it is important to acknowledge and consider the bleeding risks, as outlined in the most recent version of the American Society of Regional Analgesia Recommendations on anticoagulant management for regional analgesia.

Consideration for organ system-specific influences on the anesthetic plan is essential. A patient with renal disease is prone to complications from drugs with metabolites removed by the kidneys. Meperidine, for example, breaks down to normeperidine, which has the potential to reduce the seizure threshold. Some opioids have active metabolites that should be considered. Morphine and hydromorphine are metabolized to M3G/M6G and H3G/M6G, respectively, and are renally excreted. The 6-glucoronide metabolite is pharmacologically active at the mu receptor, while the 3G metabolite has been implicated in lowering the seizure threshold and reducing unwanted side effects.

Opioids predictively can contribute to the slowing of the gastrointestinal system through a mu-mediated mechanism, while regional or local analgesia can cause increased peristalsis and surgical neuroaxial anesthesia can exacerbate ileus. In these cases, it is important to implement a bowel support regimen as a standard part of the program when using intravenous or oral opioids or epidural infusions. Further, a history of urinary retention may cause concern for regional neuroaxial analgesia as neuroaxially administered opioids and local anesthetics can cause urinary retention.

SYSTEMIC MEDICATIONS FOR ACUTE PAIN MANAGEMENT

In very rare situations general anesthesia with volatile anesthetics plays a role in the postoperative or acute pain management plan. Resting the brain after injury or surgery is sometimes required and typically involves an intravenous anesthetic route; however, an appreciation for the difference in hemodynamics and $CMRO_2$ consumption may make it advantageous in certain cases. The use of these drugs in limiting the stress response is restricted because of the effects that higher concentrations can have on CBF, cerebral blood volume, and ICP.

Etomidate

When given by the intravenous route, etomidate may have some ability to blunt the adrenocortical system's response to stress. This effect is seen in the blunting of the rise in cortisol expected with similar tissue trauma. Etomidate is thought to accomplish this by blocking enzymes in the cortisol synthesis pathway. The clinical benefit of this drug has not been proved in prospective randomized trials. Its long recovery time may also limit its use as a neuroanesthetic agent. Long-term administration can cause an Addisonian presentation and should be avoided.

Ketamine

Ketamine can raise the $CMRO_2$ at anesthetic doses, but may be helpful as an adjuvant at very low doses to a refractory pain patient. Caution needs to be exercised when employing this medication in the pain care regimen of the neurosurgical patient.

Opioids

Recent years have shown a dramatic increase in the utilization of high-potency short-acting opioids. Half-lives, distribution properties, and side effects play a role in the decision to use opioids in the management of the postoperative patient. The choice depends on the need for a neurologic examination, the comorbidities of the patient, and the anticipated length of infusion.

Propofol

Propofol has been used to try to limit the wake-up time from general anesthesia and to blunt the initial stress and pain responses. Long-term administration needs caution, as propofol infusion syndrome can occur in doses of 4–5 mg/kg/h for as little as 48 hours, heralded by metabolic acidosis, rhabdomyolysis, acute renal failure, and cardiac failure. The treatment is supportive and includes cessation of propofol.

Alpha2-Adrenergic Agonists

Dexmedetomidine is a highly selective alpha2 agonist (1620:1), as compared to clonidine (220:1) alpha2 to alpha1. Both clonidine and dexmedetomidine attenuate the response to laryngoscopy and reduce the MAC, but both can cause hypotension, which needs to be mitigated in low compliant, pressure-dependent cerebral blood flow clinical scenarios. Dexmedetomidine provides sedation, anxiolysis, potent analgesia, and spontaneous breathing. Clonidine has been used in patients with brain trauma and after extensive neurologic

surgery to blunt the stress response. The drug has also been shown to blunt the possibilities of vasogenic edema. The use of spinal or epidural alpha-adrenergic blockade has also been shown to reduce the stress response. It is unclear whether the reduction in adrenergic response with epidural or intrathecal clonidine is a direct effect of the alpha-adrenergic blockade or a response to the clonidine-induced analgesia. The use of systemic beta-adrenergic and alpha-adrenergic agents has been shown to stabilize the hemodynamic response and the cerebral circulation.

Nonsteroidal Anti-Inflammatory Drugs

The perioperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) may enhance the ability of other techniques such as regional analgesia and anesthesia in blocking the stress response. The enhancement of regional analgesia and anesthesia is related to the NSAIDs' action at peripheral receptors involved in the tissue trauma cascade, along with central mechanisms, including prostaglandin reduction. Caution needs to be exercised in treating patients with known renal, cardiovascular, or gastrointestinal comorbidities. NSAIDs can interfere with platelet aggregation. Furthermore, NSAIDS may affect bone healing and have been implicated in failed lumbar fusions, although retrospective reviews failed to demonstrate significance. Cyclooxygenase-2 (COX-2) inhibitors have been implicated with increasing cardiac morbidity when taken long-term; however, acute perioperative administration data are lacking.

Neuropathic Pain Agents

Anticonvulsants are often used after intracranial surgery to prevent seizures. These drugs may also offer some improvement in neuropathic pain syndromes and reduce the opioid requirements. The classic drugs used for neuropathic pain, of the anticonvulsant class, include gabapentin, pregabalin, carbamazepine, oxycarbazepine, lamictal, and topiramate. Baclofen, a GABA-B agonist, has been used to treat spinal-induced spasticity and has been reported in some patients to improve pain of neuropathic origin. Antidepressant neuropathic pain agents include duloxetine, amitriptyline, nortriptyline, venlafaxine, to name a few. These function not as ion channel blockers, but mostly as neurotransmitter reuptake inhibitors. Caution should be exercised, as they can interfere with platelet aggregation and have the potential to contribute to bleeding.

REGIONAL ANALGESIC OPTIONS

Neuroaxial Epidural Infusion Therapy

The use of epidural infusion therapy has increased in recent years as a primary method of acute pain control in patients undergoing surgical procedures involving peripheral nerves. The proper use of an epidural infusion requires a working knowledge of dermatomal anatomy, drug pharmacokinetics, drug synergies, and postoperative follow-up requirements. Several factors promote the need for success: it is essential to place the catheter congruent with the patient's site of pain. Pharmacokinetically, the potency is greater when medications are delivered epidurally versus intravenously. Redistribution occurs creating untoward, unwanted side effects. The physiochemical properties of the epidural agent chosen can influence the drug's distribution. A lipophilic drug such as fentanyl requires placement of the catheter at a level near the nerve innervation of the surgical site. With morphine, which is much less lipid soluble, the catheter placement is less critical because the drug may cover several interspaces prior to being absorbed. Hydromorphone has intermediate properties. Further, for more than a decade, data have demonstrated an antinociceptive synergy between intrathecal morphine and local anesthetics during visceral and somatic nociception at dosages that do not impair motor function. The combination of local anesthetics and opioids offers a synergistic effect that leads to better analgesia than either drug infused alone. Local anesthetic infusion therapy has been shown to be the most effective method of blunting the stress response to tissue trauma. The addition of opioids helps eliminate the problem of tachyphylaxis that may develop with local anesthetics alone.

Peripheral Nerve Blockade

Peripheral nerve infusions of local anesthetic can be beneficial in the intraoperative period as well as for postoperative pain control. Common sites for continuous infusion include the brachial plexus and the femoral nerve. A nerve stimulator or ultrasound is helpful in guiding the proper placement of the catheter. In general, a blunt-tipped needle is preferable to a sharp bevelled needle to reduce the risk of nerve injury.

COMPLICATIONS OF NEUROANESTHESIA PAIN MANAGEMENT

Mental Status Changes

Serial neurologic checks are often an essential part of the postoperative course. If pain treatment interferes with this assessment, the overall benefit of the pain treatment may be lost. Establishing a team approach with the surgical team and the nursing team to balance the risks and benefits of pain therapies is crucial.

Elevation of Arterial Carbon Dioxide

The importance of ICP varies in the neurosurgical population. In patients in whom this is an important factor, it is crucial to have some method of monitoring postsurgical carbon dioxide (CO_2). Despite the benefits of improved hemodynamics in ensuring the stability of the patient with elevated ICP, the risk of excessive sedation and hypercarbia could be a problem, and the patient must be watched closely. Arterial CO_2 and pH are ways to monitor for possible complications and may be early indicators of impending problems.

Reduction of Arterial Oxygen

Hypoxemia may create multiple problems in the patient with neuronal tissue trauma. Anaerobic metabolism occurs when neurons do not have enough oxygen substrate, which can result in a reduction of adenosine triphosphate and subsequent cell death. The use of supplemental oxygen and oxygen saturation, as well as serial arterial blood gas monitoring, is essential in patients receiving systemic opioids.

Hypotension

In the patient with possible spinal cord trauma, the use of regional anesthesia can be helpful in controlling the stress response and subsequent systemic changes. The resultant decrease in mean arterial pressure can decrease perfusion to the neurologic tissue and create ischemia. Careful attention to blood pressure is crucial when using local anesthetics postoperatively.

Cerebrospinal Fluid Leak

The chance of subarachnoid puncture when placing an epidural catheter must be weighed against the benefit of the catheter. The risks of brain herniation must also be discussed

with the surgeon if there is any intracranial disease process. Placing the catheter intraoperatively may be helpful in certain situations.

Nerve Injury

When using regional techniques in those with coexisting neurologic disease, a risk of nerve injury exists if the patient has abnormal nociception in the area of the proposed procedure. This risk also exists for the patient under general anesthesia or heavy sedation who may be unable to respond to inadvertent intraneural injection.

Infection

In the sedated patient, aspiration precautions should be ordered. This should be accompanied by frequent neurologic checks. If aspiration is a risk, sedating medications should be used with caution. It goes without saying, however, that regional anesthesia should be avoided in the patient with local infection at the site of the proposed regional procedure or systemic infection. Vigilance once the catheter is placed is also essential, reducing the chance of it becoming a nidus for infection.

CREATING A CASE-SPECIFIC PAIN MANAGEMENT PLAN

Intracranial Surgery

Intracranial procedures present some of the most difficult problems in pain management. The use of regional anesthesia is not an option. Oversedating the patient can lead to hypercarbia and hypoxemia, reducing intracranial compliance. Cognitive function might be impaired because of the surgical area involved. Despite these limitations, controlling pain in this group is crucial because of the increased morbidity and mortality associated with an uncontrolled hemodynamic response to pain and surgery. Pain treatment in this patient population must consider multiple factors.

Extremity Surgery

The patient requiring surgery of the extremities gives the anesthesiologist many options. A discussion should occur regarding the patient's postoperative neurologic function and the need for serial functional checks. If the issue of sensory loss is minimal, the use of regional anesthesia is optimal because of the blunting of both pain and the stress responses. Other techniques are also acceptable in this population. Care must be taken when regional anesthesia is employed, as vigilance is required for early indication of compartment syndrome.

Neuraxial Surgery

When neurologic surgery is performed on the structures of the neuroaxis, regional anesthesia may result in an improved outcome with an effect on both postoperative pain and blood loss. These surgeries have no effect on cognitive response and are appropriate for postoperative PCA.

CHRONIC PAIN MANAGEMENT

Pain care has evolved rapidly over the last decade.[15–18] The ideology of monotherapy using opioids for chronic pain has fallen by the wayside, as mounting evidence suggests that opioid therapy is not benign, not sustainable, and contributes to the epidemic of prescription drug misuse in the US.[19–22] Innovative therapies and implantable technologies are now being used earlier in the pain care algorithm, away from salvage therapy.[23–25] Further, despite the introduction of the gate control theory by Melzak and Wall, along with spinal cord stimulation work by Norman Shealy, the mechanisms of neuromodulation still remain uncertain.[26,27] As new innovative therapies enter into the market, the placement within the spectrum of pain will continue to evolve. We explore chronic pain, the pathways of nociception, and strategies to manage it sustainably and safely, utilizing an evidence-based approach.

DEFINITION AND TAXONOMY OF PAIN

Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of damage.[28] Importantly, this implies that pain is an experience that may or may not have objective evidence and avoids causality associated with a stimulus. Typically, for chronic pain it is helpful to classify the pain in terms of nociceptive, neuropathic, or mixed. Neuropathic pain is pain that results in dysfunction of the central or peripheral nervous system. Nociceptive pain is pain that results from normal transmission of pain via activation of nociceptors. Mixed, conceptually, is a combination of both. Pain becomes chronic when the duration lasts more than 6 months, and as can be described by studies focused on the dorsal root ganglion (DRG),[19] the firing threshold to transmit a painful signal is less in the chronic pain state. This notion of reinforcing pain transmission can be attributed to central sensitization, which describes the "wind-up" that occurs through membrane channel deregulation. Further, it is helpful to classify the pain as viscerally or somatically mediated, for, as we will see, the transmission of these drastically differ.

The architecture of the spinal cord is topographically arranged. Different tracts deliver and transmit different perceptions to and from the periphery. The most common is through the nociceptive pathways, which include the spinothalamic tract (STT) and the postsynaptic dorsal column (PSDC). Myellinated A delta and unmyelinated C are engaged in nociception, with the first order neuron located in the DRG and terminating in the dorsal horn, the second order neuron crossing traveling to the thalamus, and the third order from the thalamus to the cortex. The dorsal horn is histologically and topographically characterized by Rexed laminae. The nerve may then ascend or descend a few levels ipsilaterally with terminations within the dorsal horn, before crossing the midline via the anterior white commissure and ascending in the STT and to the thalamus (ventral posterolateral nucleus) and to the somatosensory cortex, where somatotopic encoding provides for specific localization. C-fibers terminate in Rexed lamina I and II, where cutaneous A-delta nociceptors terminate in the ipsilateral Rexed laminae I and V of the dorsal horn.

As can be expected, the visceral nociceptive afferents again have first order neurons located in the dorsal root ganglia; however, they may extend to adjacent vertebral body levels before terminating in the ipsilateral dorsal horn. Visceral nociception then travels in the ipsilateral postsynaptic dorsal column (PSDC) pathway and STT bilaterally. The visceral nociceptors are largely distributed in Rexed laminae I, II, V, X ipsilaterally and laminae III and X contralaterally.

Notwithstanding, the face is innervated uniquely. The sensory nucleus of the trigeminal nerve, the trigeminal nucleus caudalis transmits painful sensations from the face. It has a large sensory nucelus that extends to the upper portion of the cervical spine, to the C2 or C3 level.[30] The primary nociceptive

afferent has its cell body in the trigeminal ganglion, which synapses in the ipsilateral trigeminal nucleus caudalis, then crosses and ascends in the STT to terminate in the VPM (ventral posteromedial nucleus) of the thalamus.

As can be appreciated, modulating the ascending nociceptive experience is a vital, inherent tool that we all possess, utilizing the bulbospinal tracts. These tracts are characterized as the periaqueductal gray (PAG), nucleus raphe magnus (NRM), rostroventral medulla (RVM), and the anterior pretectal nucleus.[31]

Modulation of these systems is vital in delivery of sustained pain care strategies. Spinal cord stimulation, DRG spinal stimulation, and HF10 (high frequency stimulation 10), and burst stimulation have been developed to utilize the above, with different targets and mechanism of action, grounded by science and evidence.

EVOLUTION OF THE ALGORITHM

Philosophically, pain care has changed. The idea of opioid dose escalation without a ceiling to help define failure is an antiquated approach. The immunologic, endocrinopathic, and sleep disturbance challenges with long-term opioid use are well defined.[32] Data suggest that diversion and misuse of prescription opioids leads to nearly 16,000 deaths annually (Fig. 24.1).[21] Research suggests that the risk of overdose or death is up to ninefold higher if the patient is maintained on more than 120 morphine equivalents per day.[19] And with the predictable opioid physical dependence and tolerance that occur with chronic use, some US states are holding physicians liable, most notably in West Virginia.[33]

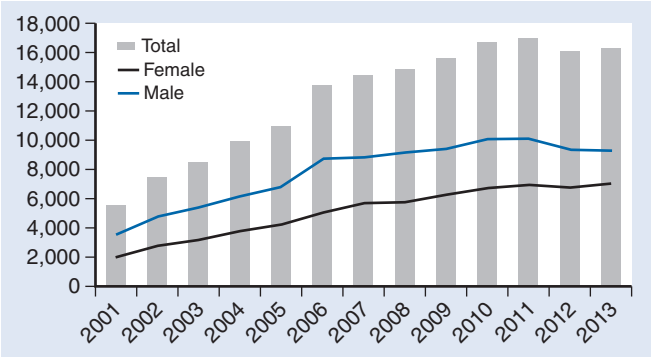


Fig. 24.1 Number of deaths from prescription opioids.[34,35]

Similarly, the stepwise approach of defining when to intervene based on a previous more conservative failure, is changing somewhat, as pain care therapies are entering an age of dramatically reduced number needed to treat (NNT). SAFE principles often help guide proper[24] safety, appropriateness, fiscal neutrality, and efficacy. In the place of monotherapy using opioid treatment for chronic pain comes a more multifaceted approach. This more patient-centric model focuses on using a combination of therapies, guided by science and evidence, to provide the best chance of sustained management. We propose an algorithmic approach to pain care, centered on patient safety and efficacy (Fig. 24.2).

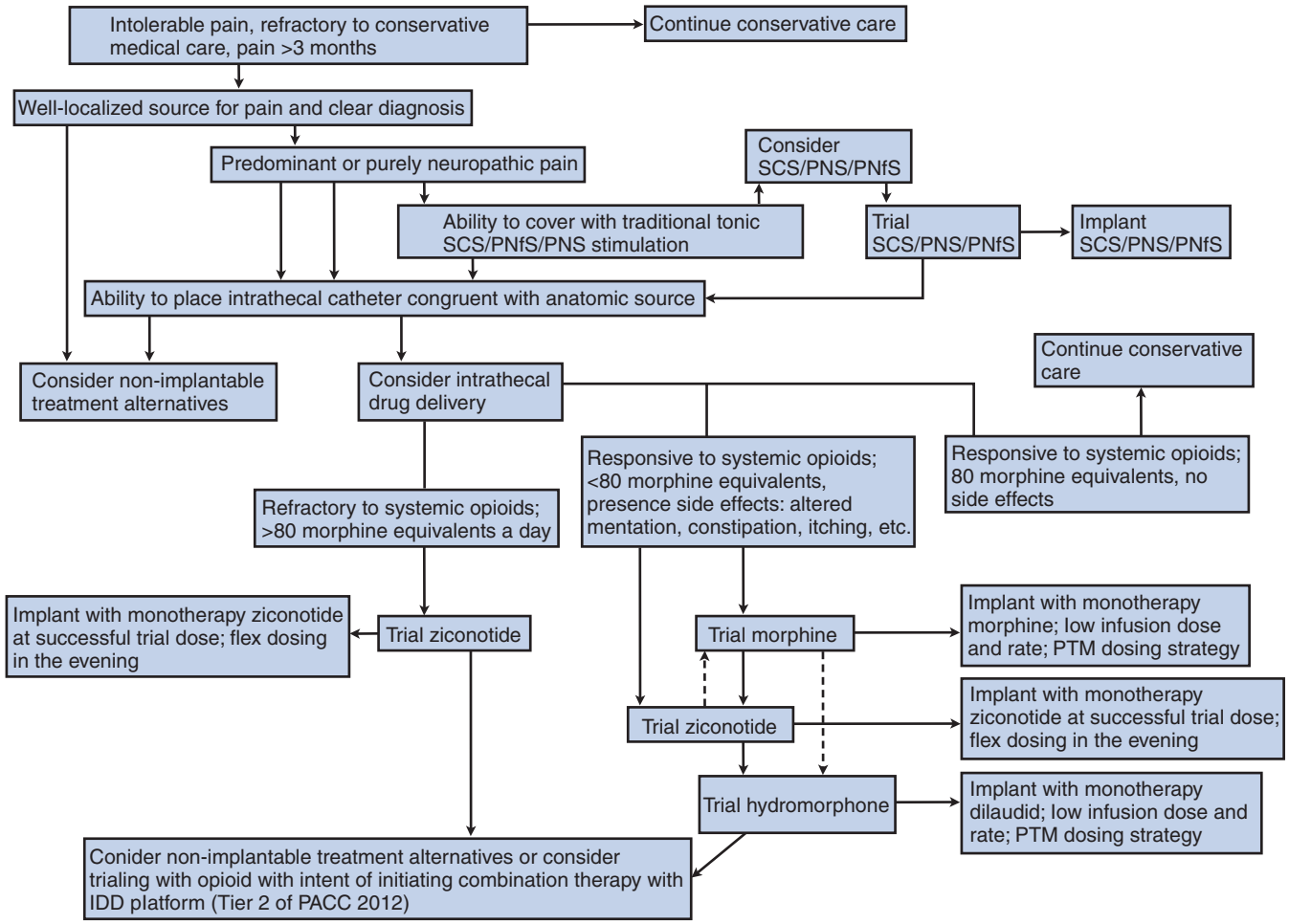


Fig. 24.2 Algorithm for implantable therapies.[36] SCS, spinal cord stimulation; PNS, peripheral nerve stimulation; PNfS, peripheral nerve field stimulation.

ABLATIVE VS. AUGMENTATIVE THERAPIES

Interventions in chronic pain management are centered on augmentative and ablative therapies to prolong the desired effect from injection, when needed. The destructive treatment strategy includes radiofrequency ablation or surgical resection or destruction, where the augmentative includes neuromodulation, by either chemical or electrical means. We will discuss these in turn.

The neuroablative therapies include treatments for arthropathy of the spine and peripheral joints. There are good prospective observational and randomized data for facet denervation by medial branch neurotomy.[37] This philosophy has been extended into the periphery with genicular nerve radiofrequency for the knee, suprascapular radiofrequency for the shoulder, trigeminal radiofrequency for the face, occipital radiofrequency for headache and plantar radiofrequency for the foot.[38–40] Importantly, creating a histologic lesion can only be performed on sensory nerves. Mixed nerves lend themselves to pulsed radiofrequency, which does not produce a histologic lesion and is considered more of a neuromodulation strategy, as compared to an ablative one.

Augmentative therapies focus on neuromodulating the nervous system, with targets in the periphery or centrally. Central targets include spinal cord stimulation, dorsal root spinal stimulation, high frequency stimulation 10,000 Hz (HF10), burst stimulation, to name a few. These therapies require a trial to determine success with improvement in pain and function before the permanent therapy is placed. The placement of the therapy can be performed employing cylindrical leads introduced through needles placed within the epidural space, or through a laminectomy or laminotomy for placement of a paddle. Both lead systems require placement of an internal pulse generator (IPG) to power the system, which can last for up to 7–10 years. The IPG can be a primary device or a rechargeable system, with both advantages and disadvantages.

Peripheral targets have also been sought after, with the traditional usage of modifying equipment for the central axis to be sued in the periphery. Novel equipment has been developed, with implantation of a lead system with an eternal battery source placed as a patch. This solves many of the problems associated with the former approach, as leads can be placed distally without the confounder of tunneling them around or near peripheral joints.

SELECTED INTERVENTIONS

When employing devices to manage pain, it is essential to obtain psychological clearance and to select the device based on evidence. The pain community now has level one evidence for spinal cord stimulation, peripheral nerve stimulation, and intrathecal therapy. More studies are ongoing; fostering a new age of evidence-based pain care.

Intrathecal Therapy

Intrathecal therapy (IT) is the delivery of mediation to the spinal space by chronic infusion. Although seemingly simple, it is vastly complex. Balancing placement of the catheter, medication selected, estimating pharmacokinetic profiles, while appreciating pharmacodynamics, makes it a satisfying therapy when employed mindfully.

The historical adage that IT should be positioned as salvage therapy has changed.[29] The potency increase in delivery of medication into the intrathecal space, the reduction of systemic side effects, and the additional ability to offer adjuvant medications has led IT to be a necessary and essential modality. As one can appreciate, many factors need to be considered when selecting the medication to consider for IT therapy.[41] It is the authors' opinion that the trial is an essential component to the therapy, although admittedly the literature does not clearly define one methodology as being superior to another.[42,43] Trialing strategies range between no trial, trial with epidural medication placement, intrathecal placement, bolus delivery as a single shot, and catheter placement with short-term infusion.[42,43] Pharmacokinetic modeling suggests anatomic, congruent placement with the patient's site of pain for optimal outcomes.

The authors typically perform dual diagnostic fluoroscopically guided trials, with a selected medication, as a single bolus and 23 hour admittance, with direct observation of improvement in pain and function, prior to proceeding with placement of the device. The polyanalgesic consensus conference of 2012 describes algorithms for medication selection based on the type of pain, whether it is neuropathic or nociceptive.[44]

Once the device is implanted, continued vigilance with management is crucial.[45] Most reported morbidity and mortality associated with IT therapy was associated with iatrogenic origins.[45]

The implanted reservoir delivers medication by programmed modes and the refill interval is dependent on the dosage and concentration of the medication chosen. the consequence of concentration and dose escalation can be a granuloma, a noninfectious collection of cells around the catheter tip that can lead to failure of the therapy or compressive symptoms. Interestingly, a new pump, the Prometra II, has less than anticipated granuloma formation, likely related to its valvegated mechanism of delivery.[46]

Spinal Cord Stimulation

Spinal cord stimulation (SCS) has undergone a renaissance recently, although it was first introduced in 1967. The evolution went from intrathecal placement to epidural placement, from focus on hardware and lead arrays to software and waveform advancements, to novel targets. We will explore these therapies, appreciating the uniqueness of each.

Tonic Spinal Cord Stimulation

Tonic spinal cord stimulation relies on placement of an overlying perceived therapeutic paresthesia on the typical region of pain. Barolat helped define this paradigm that governs the placement of leads and electrodes within the epidural space.[47] Disease indications include neuropathic pain of the trunk and limb, with the most common clinical diagnoses of failed back surgery syndrome, refractory radiculopathy, or complex regional pain syndrome.[15]

Once disease indications and patient selection criteria are met, the patient undergoes a trial; in the US this typically lasts 4–7 days. Data suggest that trials greater than 4.9 days show no improved conversion of the trial to the permanent therapy. The trial is typically performed under local anesthetic or mild conscious sedation, keeping the patient cogent throughout the procedure. Once the needles are placed within the epidural space, most commonly ipsilateral and left paramedian at the T12–L1 interspace using fluoroscopic guidance, the leads are advanced within the posterior epidural space to the target location. After the patient describes coverage overlying their typical painful area, the trial procedure is over and the patient is discharged home for up to a week, with return visits for dressing checks and optimization on postoperative days 1, 3 or 4, and then 6 or 7. Postoperative antibiotics are commonly given through the duration of the trial, along with continued cessation of anticoagulants (with authorization from the prescribing

provider). This cadence allows for optimization of the trial experience via programing and vigilance with the dressing. New innovations have recently been described, further minimizing the hardware associated with the trial by using an invisible trial, blue tooth technology, allowing the patient to focus more on the therapy.[48]

Once the trial is deemed successful, the leads are removed. Anticoagulants can be re-initiated 24 hours after lead removal. Lab work is suggested prior to the permanent therapy, as are other mitigating strategies for surgical site infections.[49] The implant procedure is performed under local anesthesia, conscious sedation, or if paddle placement is desired and monitoring is performed,[50] general anesthesia can be employed. The type of lead array (percutaneous versus paddle) is chosen based on many factors; however, complex pain patterns are becoming less of a reason. The patient typically has the IPG placed in the left flank or buttock, avoiding osteal landmarks, and allowing or reprogramming as needed.

New waveforms and targets have been created, requiring nomenclature development. The previously described spinal cord stimulation paradigm is now called "tonic stimulation." New waveforms now include high-frequency stimulation 10,000 (HF10), burst stimulation.

High-Frequency Stimulation 10,000 Hz

High-frequency stimulation is any stimulation frequency modality above that which traditional stimulation employs (>40–100 Hz) and, therefore, it is a moving target. HF10, as the name suggests, functions at 10,000 Hz and appears to have a different mechanism of action compared to traditional tonic stimulation,[51] where wide dynamic range neurons play a central role, although the exact mechanism remains unknown. The novel feature is that the placement of leads divorces the need for discrete therapeutic paresthesia. Leads are placed anatomically without the need for intraoperative testing. Most importantly, this modality creates a paresthesia-free treatment strategy. Data have been presented for up to 18 months demonstrating significant improvement in back and leg pain (with or without previous spinal surgery).[52] The energy requirement requires daily charging, which eliminates the possibility of a primary cell as a power source with current battery technology (Fig. 24.3).

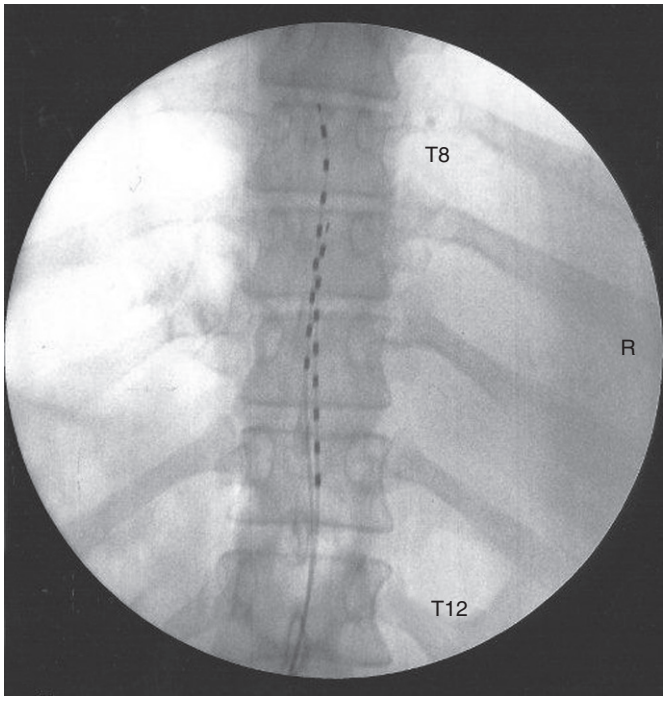


Fig. 24.3 High frequency 10 spinal cord stimulation lead placement.

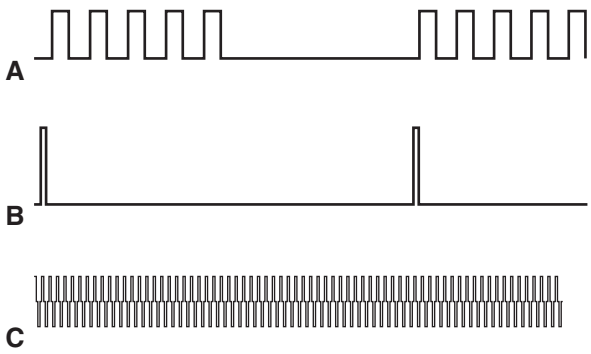


Fig. 24.4 Burst stimulation **(A)**, as compared to tonic **(B)** or high frequency stimulation **(C)**.

Burst Stimulation

Burst stimulation mimics the natural overriding nature of burst nerve transmission and serves as a conduit for neuromodulation. Fostered by Dr. DeRidder, burst stimulation delivers 40 Hz bursts with five spikes at 500 Hz per burst.[16] This waveform offers an additional unique mechanism of action. Leads are placed based on Barolat mapping, similar to tonic SCS, but the mechanism of action is additionally different. It also stimulates a medial pathway, uniquely influencing the affective component of pain and reducing global pain perception.[53] This unique waveform is currently under investigation and is limited to investigational use, requiring an IDE (investigational device exemption). The other unique feature of burst stimulation is that it is also paresthesia free, but because of the traditional placement strategy within the epidural space, patients can switch between tonic and burst stimulation. The energy requirement is similar to tonic SCS, with recharging intervals every week and the ability to employ a primary cell. The waveform differences are illustrated, clearly defining the difference (Fig. 24.4).

Dorsal Root Ganglion Spinal Stimulation

The DRG, serving as the primary afferent cell body, has long been a therapeutic target for many years for pain management.[54] The dorsal root ganglion is a paired structure that rests underneath the pedicle and has very little cerebrospinal fluid bathing it. There is extensive evidence of its role in neuropathic pain.[54] This target has been exploited recently in the realm of neuromodulation by placement of a novel device and lead system, designed specifically for DRG stimulation (Fig. 24.5). A large prospective, randomized study is concluding with evidence suggesting superiority to traditional spinal cord stimulation for the treatment of CRPS of the lower extremity.

Peripheral Nerve Stimulation

Peripheral nerve stimulation strategies have traditionally been relegated to the modification of central accessing equipment for use in the periphery. Innately, this created challenges, including migration, erosion, cost, and tunneling around major joints, with minimal expansion to the distal periphery. A new novel peripheral nerve stimulation strategy has been developed that involves the placement of an implantable wire under the skin with communication with an EPG (external pulse generator) (Fig. 24.6).[55,56] The EPG can be removed as needed and is held in place by a patch. This modality was rigorously tested in a multicenter, prospective, randomized study, providing level one evidence of its use for mononeuritis treatment.

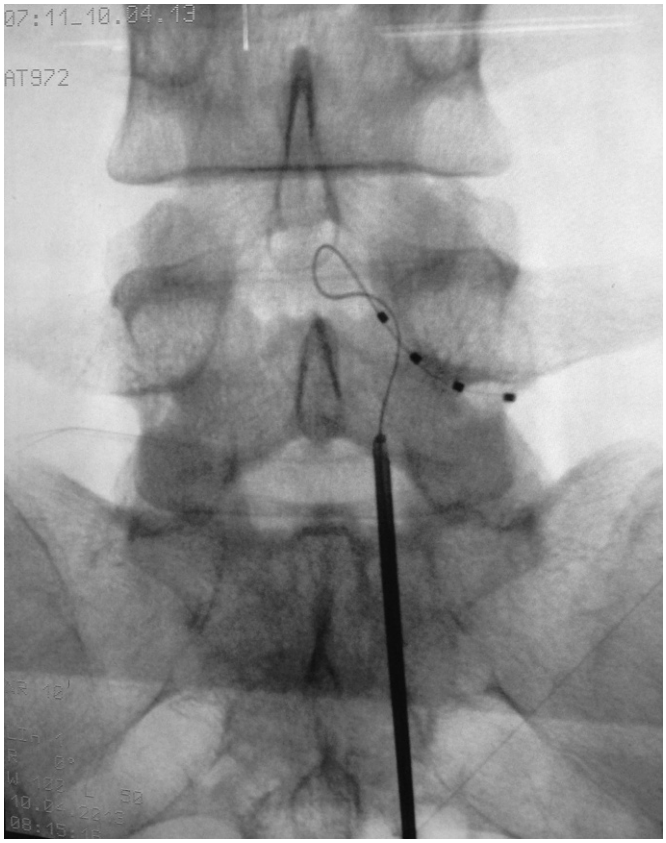


Fig. 24.5 Placement of the DRG stimulation lead at L5.

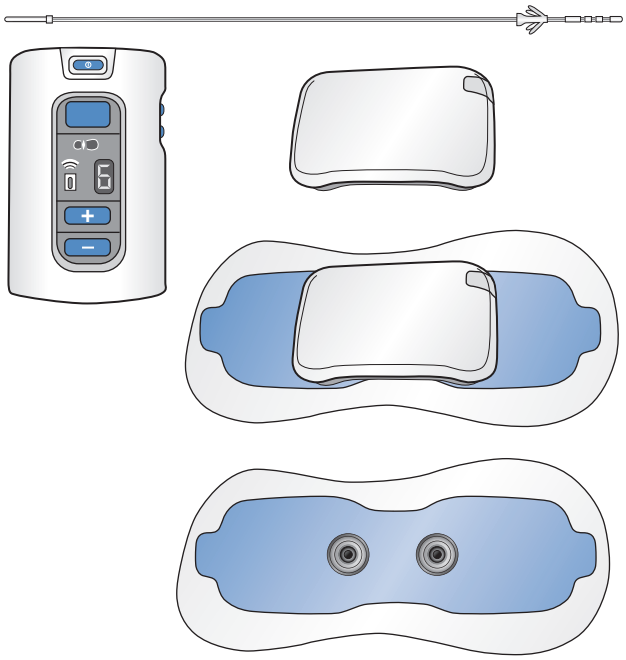


Fig. 24.6 The novel StimRouter lead system.

FUTURE DIRECTIONS

Chronic pain care is changing. The days of reliance on subjective data are over. Level one evidence is being generated describing disease-specific indications for certain disease specific modalities and treatment strategies. DRG stimulation has a number needed to treat of near one if the permanent therapy is placed. HF10 data are very compelling for the ongoing treatment of low back and leg pain at 18 months with significant pain improvement. Tonic–SCS is an invaluable tool for the treatment of many refractory disease states. Clearly, the future of the therapy is defined by moving toward minimally invasive techniques and disease-specific indications, while offering a patient-centric hardware platform that supports many therapeutic options. The contention that pain care is a luxury is also becoming antiquated. Data suggest inactivity fosters increased morbidity and mortality. It is vital to work towards placement of therapy in the algorithm to give the patient the best chance to succeed.

REFERENCES

1. Beilin B, Shavit Y, Trabekin E, et al. The effects of postoperative pain management on immune response to surgery. *Anesth Analg*. 2003;97(3):822–827.
2. Bellieni CV, Burroni A, Perrone S, et al. Intracranial pressure during procedural pain. *Biol Neonat*. 2003;84:202–205.
3. Bruder N, Ravussin P. Cerebral and systemic haemodynamic changes during neurosurgical recovery. *Ann Fr Anesth Reanim*. 2004;23:410–416.
4. Chiaretti A, Genovese O, Antonelli A, et al. Patient-controlled analgesia with fentanyl and midazolam in children with post-operative neurosurgical pain. *Childs Nerv Syst*. 2008 Jan;24(1):119–124.
5. Dunbar PJ, Visco E, Lam AM. Craniotomy procedures are associated with less analgesic requirements than other surgical procedures. *Anesth Analg*. 1999;88:335–340.
6. Grossman R, Ram Z, Perel A, Yusim Y, Saslansky R, Berkenstadt H. Control of posoperative pain after awake craniotomy with local intradermal analgesia and metamizol. *IMAJ*. 2007;9:380–382.
7. Fodale V, La Monaca E. Propofol infusion syndrome: An overview of a perplexing disease. *Drug Saf*. 2008;31(4):293–303.
8. Leith B. Pharmacological management of pain after intracranial surgery. *J Neurosci Nurs*. 1998;30:220–224.
9. Leslie K, Troedel S, Irwin K, et al. Quality of recovery from anesthesia in neurosurgical patients. *Anesthesiology*. 2003;99:1158–1165.
10. Leslie K, Williamns DL. Post-operative pain, nausea, and vomiting in neurosurgical patients. *Curr Opin Anesthesiol*. 2005;18:461–465.
11. Klimek M, Ubben JF, Ammann J, Borner U, Klein J, Verbrugge SJ. Pain in neurosurgically treated oatients: A prospective observational study. *J Neurosurg*. 2006;104:350–359.
12. Maxy R, Glassman S. The effect of nonsteroidal antiinflamatory drugs on osteogenesis and spinal fusion. *Regional Anesthesia Pain Med*. 2001;26:156–158.
13. Mordhorst C, Latz B, Kerz T, et al. Prospective assessment of postoperative pain after craniotomy. *J Neurosurg Anesthesiol*. 2010;22(3):202–206.
14. Oritz-Cardona J, Bendo A. Perioperative pain management in the neurosurgical patient. *Anesthesiol Clin*. 2007;25(3):655–674.
15. Pope JE, Falowski S, Deer TR. Advanced waveforms and frequency with spinal cord stimulation: Burst and high frequency energy delivery. *Expert Rev Med Devices*. 2015;12:431–437.
16. De Ridder D, Vanneste S, Plaizer M, van der Loo E, Menovsky T. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. *Neurosurgery*. 2010; May;66(5):986–990.
17. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High frequency spinal cord stimulation fo the treatment of chronic back pain patients: Results of a prospective multicenter European Clinical Study. *Neuromodulation*. 2013 Jan-Feb;16(1):59–65.
18. Liem L, Russo M, Huygen FJ, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root gangion neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16:471–482.
19. Dunn KM, Saunders KW, Rutter CM. Overdose and prescribed opioids. Associations among chronic noncancer pain patients. *Ann Intern Med*. 2010;152(2):85–92.
20. Fitzgibbon DR, Rathmell JP, Michna E, et al. Malpractice claims associated with medication management for chronic pain. *Anesthesiology*. 2010;112:948–956.
21. Centers for Disease Control and Prevention. National Vital Statistics System mortality data. http://www.cdc.gov/nchs/deaths.htm. Accessed 30.04.15.
22. Chou R, Turner JA, Devine EB. The effectiveness and risks of long-term opiod therapy for chronic pain: A systemic review for a National Institutes of Health Pathways to Prevention workshop. *Ann Intern Med*. 2015;162:276–286.
23. Deer T, Caraway D, Wallace M. A definition of refractory pain to help determine suitability for device implantation. *Neuromodulation*. 2014 Dec;17(8):711–715. http://dx.doi.org/10.1111/ner.12263. No abstract available. PMID:25521165.

24. Porree L, Krames E, Pope J, et al. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. *Neuromodulation*. 2013;16:125–141.
25. Pope JE, Deer TR, McRoberts WP. Intrathecal therapy: The burden of being positioned as a salvage therapy. *Pain Med*. 2015;16:2036–2038.
26. Melzack R, Wall PD. Pain mechanisms: A new theory. *Science*. 1965;150:971–979.
27. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulaton of the dorsal columns: Preliminary clinical report. *Anesth Analg*. 1967;46(4):489–491.
28. "Part III: Pain Terms, A Current List with Definitions and Notes on Usage" (pp 209-214) Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy, edited by H. Merskey and N. Bogduk, IASP Press, Seattle, ©1994.
29. Pope JE, Deer TR, Kramer J. A systematic review: Current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Medicine*. 2013;14:30–1496.
30. Goadsby PJ, Hoskin KL. The distribution of trigeminovascular afferents in the nonhuman primate brain Macaca nemestrina: A c-fos immunocytochemical study. *J Anat*. 1997 Apr;190(Pt 3):367–375.
31. Boonpirak N, Apinhasmit W. Length and caudal level of termination of the spinal cord in Thai adults. *Acta Anatominca*. 1994;149:74–78.
32. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among outpatients on opioid therapy in a large US health-care system. *Addiction*. 2010;105:1776–1782. http://dx.doi.org/10.1111/j.1360-0443.2010.03052.x. PMID:20712819.
33. https://www.pharmacist.com/west-virginia-supreme-court-rules-addicts-can-sue-pharmacies-doctors.
34. Centers for Disease Control and Prevention. National Vital Statistics System mortality data. *Available from URL*. http://www.cdc.gov/nchs/deaths.htm; 2015.
35. http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates.
36. Pope JE, Deer TR. Intrathecal drug delivery for pain: A clinical guide and future directions. *Pain Manag*. 2015;5(3):175–183. http://dx.doi.org/10.2217/pmt.15.12.
37. Cohen SP, Huang JHY, Brummet C. Facet joint pain-advances in patient selection and treatment. *Nature Reviews Rheumatology*. 2013;9:38–116.
38. Choi WJ, Hwang SJ, Song JG, et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: A double-blind randomized controlled trial. *Pain*. 2011;152(3):481–487. http://dx.doi.org/10.1016/j.pain.2010.09.029. Epub 2010 Nov 4.
39. Anthony M. Headache and the greater occiptial nerve. *Clin Neurol Neurosurg*. 1992;94(4):297–301.
40. Goske S1, Erdemir A, Petre M. Reduction of plantar heel pressures: Insole design using finite element analysis. *J Biomech*. 2006;39(13):2363–2370. Epub 2005 Sep 28.
41. Deer TR, Pope JE. Factors to consider in the choice of intrathecal drug in the treatment of neuropathic pain. *Expert Rev Clin Pharmacol*. 2015 Sep;8(5):507–510.
42. Pope JE, Deer TR. Intrathecal pharmacology update: Novel dosing strategy for intrathecal therapy and monotherapy ziconotide. *Neuromodulation*. 2015 Jul;18(5):414–420. http://dx.doi.org/10.1111/ner.12274. Epub 2015 Feb 24.
43. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: Recommendations on trialing for intrathecal (intraspinal) drug delivery: Report of an interdisciplinary expert panel. *Neuromodulation*. 2012;15:420–435.
44. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: Report of an interdisciplinary expert panel. *Neuromodulation*. 2012;15:436–466.
45. Coffey RJ, Owens ML, Broste SK, et al. Medical practice perspective: Identification and mitigation of risk factors for mortality associated with intrathecal opioids for non-cancer pain. *Pain Med*. 2010 Jul;11(7):1001–1009.
46. Pope JE. *Intrathecal Drug Delivery*. Montreal, Canada: International Neuromodulatoin Society Proceedings; June 13, 2015.
47. Barolat G, Oakley J, Law J. Epidural spinal cord stimulation with multiple electrode paddle lead is effective in treating low back pain. *Neuromodulation*. 2001;2:59–66.
48. http://investors.sjm.com/investors/financial-news/news-release-details/2015/St-Jude-Medical-Receives-FDA-Approval-for-the-Industrys-First-Spinal-Cord-Stimulation-Trial-System-to-Incorporate-Bluetooth-Wireless-Technology-and-Apple-Digital-Devices/default.aspx.
49. Deer TR, Provenzano DA. Recommendations for reducing infection in the practice of implanting spinal cord stimulation and intrathecal drug delivery devices: A physician's playbook. *Pain Physician*. 2013 May-Jun; 16(3):E125–E128.
50. Falowski SM, Celii A, Sestokas AK. Awake vs. asleep placement of spinal cord stimulators: A cohort analysis of complications associated with placement. *Neuromodulation*. 2011 Mar-Apr;14(2):130–134. http://dx.doi.org/10.1111/j.1525-1403.2010.00319.x. discussion 134–5. Epub 2010 Dec 13.
51. Pope JE, Deer TR, Amirdelfan K, Kapural L, Verrills P. New concepts for waveform and current delivery for spinal cord stimulation: Burst and high frequency. Minimally Invasive Surgery for Pain. 2015.
52. Kapural L, Yu C, Doust MW, et al. 188 Randomized controlled clinical trial evaluating the safety and effectiveness of 10 kHz high-frequency and traditional low-frequency stimulation for the treatment of chronic back and leg pain: 18-Month results. *Neurosurgery*. 2015 Aug;62(Suppl 1):228–229. http://dx.doi.org/10.1227/01.neu.0000467152.83171.84.
53. Courtney P, Espinet A, Mitchell B. Improved pain relief with burst spinal cord stimulation for two weeks in patients using tonic stimulation: Results from a small clinical study. *Neuromodulation*. 2015 Jul;18(5):361–366. http://dx.doi.org/10.1111/ner.12294. Epub 2015 Apr 16.
54. Koopmeiners AS, Mueller S, Kramer J. Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation*. 2013 Jul-Aug;16(4):304–311. http://dx.doi.org/10.1111/ner.12028. discussion 310–1. Epub 2013 Feb 19.
55. Deer TR, Levy RM, Rosenfeld EL. Prospective clinical study of a new implantable peripheral nerve stimulation device to treat chronic pain. *Clin J Pain*. 2010 Jun;26(5):359–372.
56. Deer TR, Pope JE, Kaplan M. A novel method of neurostimulation of the peripheral nervous system: The StimRouter implantable device. *Pain Management*. April 2012;16(2):113–117.

Anesthesia for Neurosurgery in the Pregnant Patient

25

D.J. Wlody • D.R. Gambling • T.L. Griffiths

INTRODUCTION

Neurologic disorders requiring surgical intervention during pregnancy are not uncommon, and many anesthesiologists eventually encounter a pregnant woman in need of a neurosurgical procedure. The anesthetic management of such patients can be complicated by the physiologic changes that occur during pregnancy. These changes might require adjustments in anesthetic management that would be inappropriate for a nonpregnant patient with the same neurosurgical condition.

Maternal well-being must remain a primary concern, but it is important to recognize that interventions which benefit the mother might have the potential to harm the fetus. Thus, the major challenge in providing anesthesia for neurosurgery performed during pregnancy is to provide an appropriate balance between competing, and sometimes contradictory, clinical goals.[1]

MATERNAL PHYSIOLOGIC CHANGES DURING PREGNANCY

The pregnant woman undergoes a number of physiological adaptations to pregnancy. The earliest of these changes are hormonally driven, while changes that occur later in pregnancy are associated with the mechanical effects of the enlarging uterus, increased metabolic demands of the fetus, and a low resistance placental circulation.

Nervous System

Inhalation Anesthetic Requirements

Anesthetic requirements for volatile anesthetics during pregnancy, as measured by minimum alveolar concentration (MAC), are decreased by 30% from the nonpregnant state.[2,3] Higher levels of plasma endorphins[4] and progesterone[5] are said to account for this change. Hence, inspired anesthetic concentrations that would be appropriate in the nonpregnant patient could have exaggerated effects during pregnancy. However, the relationship between pregnancy and MAC is complicated by the findings from one study that showed no differences in electroencephalographic measures during sevoflurane anesthesia between pregnant and nonpregnant women.[6] The authors of that study suggested that a decrease in MAC during pregnancy does not correlate with an enhanced hypnotic effect of sevoflurane on the brain. They believe that pregnant women should receive the same dose of volatile agent as a nonpregnant woman in order to prevent intraoperative awareness, and we should reconsider MAC as an indicator of the efficacy of volatile anesthetics.

Local Anesthetic Requirements

Local anesthetic requirements for neuraxial anesthesia are decreased by 30–40% during pregnancy. This reduction is in part due to the decreased volume of cerebrospinal fluid (CSF) in the lumbar subarachnoid space secondary to engorgement of the epidural veins.[7] The decrease in local anesthetic requirements precedes the onset of significant epidural venous engorgement, however. In vitro preparations of vagus nerves obtained from pregnant rabbits show increased sensitivity to local anesthetic-induced blockade of nerve conduction.[8] When nerves obtained from nonpregnant rabbits are bathed in a progesterone-containing solution, however, this greater sensitivity is not seen.[9] It is, therefore, suggested that long-term but not short-term exposure to progesterone leads to changes in the neuronal membrane Na^+ channel that increase its sensitivity to local anesthetics.

In summary, parturients may have decreased anesthetic requirements but despite a 30% reduction in MAC, recent research indicates that it might be prudent to use the same dose of volatile agent as in a nonpregnant woman in order to avoid awareness. However, parturients appear to need reduced doses of neuraxial local anesthetics.

Respiratory System

Upper Airway Mucosal Edema

The accumulation of extracellular fluid produces soft tissue edema during pregnancy, particularly in the upper airway where marked mucosal friability can develop. Nasotracheal intubation and the insertion of nasogastric tubes should be avoided unless absolutely necessary because of the risk of significant epistaxis. Laryngeal edema can also reduce the size of the glottic aperture, leading to difficult intubation. Mallampati scores can increase during labor making endotracheal intubation more difficult, and this problem is likely to be worsened in preeclamptic patients. A smaller (6.0–7.0-mm) endotracheal tube is appropriate for most pregnant patients.

Functional Residual Capacity

By the end of the third trimester, functional residual capacity (FRC) decreases 20% from prepregnant values, whereas closing capacity remains unchanged.[10] The FRC drops further in the supine position, a situation in which closing capacity commonly exceeds FRC. This decrease leads to closure of small airways, increased shunt fraction, and a greater potential for arterial oxygen desaturation. Additionally, because FRC represents the store of oxygen available during a period of apnea, decreases in FRC will lead to the rapid development of hypoxemia when the pregnant patient becomes apneic, as occurs during the induction of general anesthesia. Because oxygen consumption rises by as much as 60% during pregnancy,[11] significant desaturation can occur even when intubation is performed expeditiously. This process was demonstrated in a computer model of pregnancy in which apnea was simulated after 99% denitrogenation. Desaturation to 90% occurred in approximately 5 minutes in the pregnant model, versus 7.5 minutes in the nonpregnant model.[12] Thus, at least 2 minutes of preoxygenation and denitrogenation with a tightly

fitting face mask is mandatory before the induction of general anesthesia during pregnancy.[13]

Ventilation

Significant increases in minute ventilation occur as early as the end of the first trimester. At term, minute ventilation increases by 45%, owing to an increase in tidal volume; respiratory rate is essentially unchanged. This most likely results from a progesterone-induced increase in the ventilatory response to carbon dioxide (CO_2); there also appears to be an effect due to pregnancy-induced changes in wakefulness.[14] Because the increase in ventilation exceeds the increase in CO_2 production, the normal arterial partial pressure of CO_2 ($PaCO_2$) diminishes to approximately 32 mmHg. The greater excretion of renal bicarbonate partially compensates for the hypocarbia, so that pH rises only slightly, to approximately 7.42 to 7.44.

Cardiovascular System

Blood Volume

Blood volume increases by 45% during pregnancy, with the majority of this increase occurring by the end of the second trimester. Because plasma volume increases to a greater extent than red blood cell mass, a dilutional anemia commonly occurs. Normal hematocrit at term ranges from 30% to 35% and is often lower in women not receiving supplemental dietary iron.

Cardiac Output

Significant increases in cardiac output (CO) occur as early as the first trimester. Capeless and Clapp[15] demonstrated a 22% rise in CO by 8 weeks' gestation, which represents 57% of the total change seen at 24 weeks.[15] Cardiac output rises steadily throughout the second trimester. Maximum increases in CO occur between 28 and 32 weeks' gestation. At term, cardiac output is approximately 50% above prepregnancy baseline.[16]

Cardiac output can increase by an additional 60% during labor.[17] Part of this increase is caused by the pain and apprehension associated with contractions, an increase that can be blunted with the provision of adequate analgesia. There is a further rise in CO, unaffected by analgesia, from the autotransfusion of 300–500 mL of blood from the uterus into the central circulation with each contraction. Finally, CO increases further in the immediate postpartum period, by as much as 80% above pre-labor values, because of autotransfusion from the rapidly involuting uterus as well as the augmentation of preload after relieving aortocaval compression.

Aortocaval Compression

In the supine position after 20 weeks' gestation, the enlarged uterus can compress the inferior vena cava against the vertebral column. Collateral flow through the epidural venous plexus and paravertebral vessels can partially compensate for decreased caval blood flow, but the net return of blood to the heart can be significantly decreased, leading to reduced CO. This can decrease uterine blood flow (UBF) and impair uteroplacental oxygen delivery. Supine positioning can also produce aortic compression. If this occurs, upper extremity blood pressure might be normal but distal aortic pressure and thus uterine artery perfusion pressure could decrease. The effects of aortocaval compression are magnified in the anesthetized patient when venous return is reduced from sympathetic blockade. Therefore, the supine position must be avoided in pregnant patients undergoing anesthesia after the mid-second trimester. One study evaluated the degree of tilt necessary to minimize aortocaval compression in term, nonlaboring patients prior to cesarean delivery. CO and pulse pressure were highest at 15 degrees of left tilt, equal to full 90 degrees left lateral position.[18]

Gastrointestinal System

Gastric Acid Production

Ectopic gastrin is produced by the placenta. However, plasma gastrin levels appear to be unchanged during pregnancy, and there appears to be no significant difference in either the volume or the acidity of gastric secretions in pregnancy.[19]

Gastric Emptying

Contrary to common belief, gastric emptying is not significantly altered during pregnancy.[20] Gastric emptying is slowed, however, in the presence of painful contractions, and systemic opioids administered to relieve labor pain will further slow gastric emptying.

Gastroesophageal Sphincter

The enlarging uterus causes elevation and rotation of the stomach, which interfere with the pinchcock mechanism of the gastroesophageal sphincter. This change increases the likelihood of gastroesophageal reflux, especially in the morbidly obese parturient.

Pregnancy and Aspiration Pneumonia

The changes described make it more likely that a pregnant patient will regurgitate and aspirate during anesthesia. The time frame for the development of these changes is unclear, but most anesthesiologists begin to use "full stomach" precautions after 16–18 weeks' gestation, by which time uterine growth is such that alterations of gastroesophageal structure and function are likely to occur. Pregnant patients should, therefore, receive aspiration prophylaxis with a nonparticulate antacid and/or a combination of a histamine H_2 blocking drug and metoclopramide. Anesthetic induction is influenced by the presence of a full stomach but, as described later, techniques designed to minimize the risk of aspiration might not be ideal for the patient who has an intracranial lesion.

Renal and Hepatic Systems

Aldosterone levels rise during pregnancy, with concomitant increases in total body sodium and water.[21] These changes can increase edema in an intracranial neoplasm and lead either to worsening signs and symptoms, or to the onset of symptoms from a previously unrecognized mass lesion. Renal blood flow and glomerular filtration rate increase by approximately 60% at term, paralleling the increase in CO. Thus, blood urea nitrogen (BUN) and serum creatinine values are usually one-half to two-thirds those seen in nonpregnant women. What would be considered normal or only mildly elevated BUN and creatinine values in nonpregnant women should be a cause for concern during pregnancy.

Slight increases in serum levels of alanine aminotransferase (ALT), aspartate transaminase (AST), and lactate dehydrogenase (LDH) are not uncommon during normal pregnancy.[22] Plasma cholinesterase levels are decreased, but prolonged neuromuscular blockade does not occur in normal parturients receiving succinylcholine.[23]

Epidural Vascular Changes

Epidural Venous Pressure

A generalized increase in intra-abdominal pressure as well as direct compression of the inferior vena cava leads to a rise in epidural venous pressure. This rise leads to the diversion of a portion of the venous return from the legs and pelvis into the

vertebral venous system, causing engorgement of the epidural veins. It has been suggested that elevated epidural venous pressure, in association with the hemodynamic changes of pregnancy, may predispose to rupture of a preexisting pathologic region of the venous wall. Epidural veins contain no valves; therefore, abrupt pressure changes, such as produced by coughing, sneezing, or a forceful Valsalva maneuver during the second stage of labor, could be transmitted directly to the epidural veins, causing rupture.[24]

Epidural Arterial Vessels

The epidural arterial vessels may undergo degenerative changes during pregnancy secondary to elevations of progesterone and estrogen.[25] The arterial vessels of pregnant women have been shown to demonstrate numerous histologic changes, including fragmentation of the reticulin fibers, diminished acid mucopolysaccharide concentration, and hypertrophy and hyperplasia of smooth muscle cells.[24] These structural changes, in combination with the hemodynamic changes of pregnancy, may predispose to rupture of an epidural artery and subsequent hematoma formation.

EFFECTS OF ANESTHETIC INTERVENTIONS ON UTERINE BLOOD FLOW

At term, normal UBF increases to 700–900 mL/min, which is approximately 10% of the total maternal blood flow.[26] This compares to a nonpregnant UBF of 70 mL/min. The magnitude of UBF is determined by the following equation:

$$\text{UBF} = (\text{UAP} - \text{UVP}) / \text{UVR} \qquad (25.1)$$

where *UAP* is uterine arterial pressure, *UVP* is the uterine venous pressure, and *UVR* is the uterine vascular resistance. Alterations in any of these parameters influence UBF and, therefore, the delivery of oxygen and nutrients to the fetus.

Factors that *decrease uterine arterial pressure* include hypovolemia, sympathetic blockade due to neuraxial anesthesia, aortocaval compression, anesthetic overdose, vasodilators, and excessive positive pressure ventilation. Factors that *increase uterine venous pressure* include vena caval compression, uterine contractions, uterine hypertonus, oxytocin overstimulation, and α-adrenergic stimulation, through adrenergically mediated increases in uterine tone. Factors that *increase uterine vascular resistance* include endogenous catecholamines, untreated pain or noxious stimulation (laryngoscopy and intubation, skin incision), preeclampsia, chronic hypertension, and exogenous vasoconstrictors.

Ephedrine has been considered the drug of choice for treating maternal hypotension, largely on the basis of animal studies showing decreases in UBF despite increased maternal blood pressure after the administration of high doses of pure α-adrenergic agonists. This finding has been interpreted to indicate that uterine vascular resistance is increased to a greater extent than maternal blood pressure when these agents are used. However, later studies using low doses of phenylephrine (50–100 μg) show no evidence of any deleterious effect on fetal well-being. Furthermore, there is a growing body of evidence that fetal well-being is in fact *improved* when phenylephrine is used to treat maternal hypotension.[27,28] The reasons for this improvement are unclear, but it has been proposed that transplacental passage of ephedrine leads to increases in fetal metabolism, resulting in a perhaps clinically insignificant, but nevertheless measurable fetal metabolic acidosis when compared to phenylephrine.

UTEROPLACENTAL DRUG TRANSFER AND TERATOGENESIS

A detailed consideration of the various mechanisms (active transport, facilitated diffusion, pinocytosis) by which substances are transported across the placenta is beyond the scope of this chapter.[29] This discussion concentrates on *passive diffusion,* the mechanism by which most anesthetic drugs administered to the mother reach the fetus. This process does not require the expenditure of energy. Transfer can occur either directly through the lipid membrane or through protein channels that traverse the lipid bilayer.

Determinants of Passive Diffusion

Concentration gradient is the primary determinant of the rate of transfer of drugs across the placenta. As an example, the initial rate of transfer of an inhalation anesthetic is quite rapid. As the partial pressure of the drug increases in the fetus, the rate of transfer decreases. Substances that have a low molecular weight cross the placenta more readily than those that have a higher molecular weight. Drugs with high lipid solubility readily traverse the placenta. Ionization limits placental transfer. Membrane thickness can be increased in certain pathologic states, including chronic hypertension and diabetes. The effects of these conditions on drug transfer are of less concern than the resultant limitation of the transport of oxygen and nutrients, which can lead to intrauterine growth restriction or, in severe cases, fetal demise.

Specific Drugs

Inhalation anesthetics cross the placenta freely owing to their low molecular weight and high lipid solubility. The longer the period of fetal exposure to the drug (induction-to-delivery interval), the more likely the newborn is to be depressed.

The induction drugs thiopental, etomidate, and propofol are highly lipophilic and un-ionized at physiologic pH. Placental transfer is quite rapid. Because most of the blood returning to the fetus from the umbilical vein passes through the fetal liver, extensive first-pass metabolism occurs and neonatal depression after an induction dose of these drugs is uncommon. Both depolarizing and nondepolarizing muscle relaxants are highly ionized at physiologic pH; thus, placental transfer is minimal.

Opioid drugs freely traverse the placenta because of their high lipid solubility and low molecular weight.

The muscle relaxant reversal drugs neostigmine and edrophonium are highly ionized and demonstrate minimal placental transfer.

The anticholinergic drugs atropine and scopolamine freely pass the placenta. Glycopyrrolate is highly ionized and thus crosses the placenta to a minimal degree.

The commonly used anticoagulants heparin and warfarin have remarkably different placental transfer characteristics. Heparin, a highly ionized polysaccharide molecule, does not reach the fetus. Warfarin, which is uncharged and has a molecular weight of only 330, readily passes across the placenta. Because warfarin can cause birth defects, its use is contraindicated during the period of organogenesis (see later).

Of the antihypertensive drugs, all of the β-blocking drugs that have been studied cross the placenta. Labetalol, which is both effective for the mother and safe for the fetus, is the drug of choice for treatment of maternal hypertension.[30] High-dose

infusions of esmolol have been reported to cause persistent fetal bradycardia lasting up to 30 minutes after the termination of the infusion.[31] The effect of a single dose is not known, but there are numerous case reports of its safe use as a bolus during anesthetic induction. Sodium nitroprusside (SNP) freely passes the placenta, a characteristic that has implications for fetal toxicity (see later).

Anesthesia during Pregnancy and the Risk of Birth Defects

Principles of Teratology

It is an established principle that any substance, if administered in large enough quantities for a prolonged period of time during critical periods of gestation, can produce fetal injury ranging from growth restriction to major structural anomalies to death. Thus, it should be a goal of anesthesiologists caring for pregnant women to minimize the fetal exposure to potentially toxic substances. Nevertheless, fears regarding the potential for injury should be tempered by the following considerations:

- Most anesthetics are administered for such a brief period that the potential for toxicity is minimal.
- There is no convincing *human* evidence that any commonly used anesthetic is dangerous to the fetus.
- Maternal hypotension and hypoxemia pose a much greater risk to the fetus than any of the anesthetic drugs.
- Maternal well-being must be a paramount concern. If avoiding a potentially teratogenic drug leads to poor maternal outcome or maternal death, fetal outcome will be equally compromised.
- Anesthetic neurotoxicity to the developing brain is of concern and the focus of ongoing research.[32]

Evaluation of Teratogenic Potential

There are ethical and logistical difficulties inherent in large-scale prospective studies of the teratogenic effects of anesthetics in humans. Hence, there is more reliance on indirect evidence to evaluate the teratogenic potential of these drugs. The principal investigative tools used are small animal studies, retrospective studies of the offspring of women who received anesthesia during pregnancy, and, in the case of inhalation anesthetics, studies of operating room personnel who were exposed to low-level waste anesthetic gases during pregnancy. In the discussion of specific drugs that follows, reference is made to the studies supporting or opposing their teratogenic potential.

Specific Anesthetic Drugs

Animal studies of inhalation anesthetics have demonstrated conflicting results.[33,34] Their reproductive effects appear to be dose-related. These effects are more likely to come from the physiologic disturbances (hypothermia, hypoventilation, poor feeding) produced by the anesthetic state rather than the anesthetic drug itself. When animals are exposed to inspired concentrations of inhalational anesthetics that do not impair feeding behavior or level of consciousness, reproductive effects are minimal.[35]

Nitrous oxide has clearly been shown to increase the incidence of structural abnormalities and fetal loss in rats; the timing of exposure appears to determine the extent of the effect.[36] This effect was initially thought to be the result of inhibition of the enzyme methionine synthetase and subsequent decreases in the levels of methionine and tetrahydrofolate.[37] The mechanism has been called into question, however, because maximal inhibition of methionine synthetase activity occurs at levels of anesthetic exposure that do not have teratogenic effects. Later evidence suggests that the fetal effects of nitrous oxide are from α-adrenergic stimulation and subsequent decreases in UBF.[38] These effects can be reversed by the simultaneous administration of a potent inhalation drug. Studies of operating room personnel exposed to trace levels of nitrous oxide and of women receiving nitrous oxide anesthesia have not shown any teratogenic effect. The reader is referred to the detailed reviews by Burm[39] and Weimann[40] of the reproductive toxicology of nitrous oxide.

Muscle relaxants do not have any teratogenic effect at clinically appropriate doses. Opioids have not been shown to be teratogenic in either human or animal studies.

Several retrospective human studies have suggested that long-term benzodiazepine therapy during pregnancy increases the incidence of cleft lip and cleft palate. These studies have been faulted for failure to control for concomitant exposure to other potentially teratogenic substances. There is little evidence to suggest that a single dose of a benzodiazepine during pregnancy poses any risk to the fetus.[41–43]

There is no human evidence suggesting that clinically useful local anesthetics are teratogenic. Chronic cocaine abuse has been linked to birth defects; this is likely to be secondary to its effects on uteroplacental perfusion.

Warfarin therapy during pregnancy has been correlated with ophthalmologic, skeletal, and central nervous system abnormalities, presumably from microhemorrhages during organogenesis. Because heparin does not cross the placenta, it is the drug of choice in women requiring anticoagulation during pregnancy.

In summary no anesthetic agents are documented teratogens in humans, including nitrous oxide and the benzodiazepines, but anesthetic neurotoxicity to the developing brain is of concern and the focus of ongoing research.

INTRACRANIAL DISEASE

Subarachnoid Hemorrhage: Aneurysm and Arteriovenous Malformation

Subarachnoid hemorrhage (SAH) is most often caused by rupture of an intracranial aneurysm or arteriovenous malformation (AVM). Other, less common causes include hypertensive intracerebral hemorrhage, vasculitis, and bacterial endocarditis. The overall incidence of SAH during pregnancy is approximately 1 in 10,000,[44] which is similar to the incidence in the general population. In the 2011 *Confidential Enquiries into Maternal Deaths in the United Kingdom*,[45] eleven women died of intracranial hemorrhage, 0.48 per 100,000 maternities. Six had SAH and five had intracerebral bleeds. SAH accounted for about 7% of indirect maternal deaths. None of the bleeds were associated with labor and only two women died undelivered. Six of the women presented with sudden collapse or severe headache with rapid deterioration and subsequent death. Four women had no previous symptoms to alert health care providers that they were at risk of an intracranial bleed. In the US, cerebrovascular accidents accounted for 5.4% of all pregnancy-related deaths.[46]

In 1990, Dias and Sekhar[47] published a review of 154 published cases of SAH during pregnancy. The ratio of aneurysms to AVMs was approximately 3:1. However, in a recent report from Japan the ratio of AVM to ruptured aneurysm that produced intracranial hemorrhage during pregnancy was 2:1.[48] For both AVMs and aneurysms, there is a rising incidence of hemorrhage with advancing gestational age, which may be due

to increases in cardiac output or, possibly, from hormonal influences on vascular integrity. Few women bleed during labor and delivery, a finding consistent with the observation that more than 90% of all hemorrhages in nonpregnant patients occur at rest. Thirty-four percent of the patients whose rupture occurs during labor and delivery have hypertension, proteinuria, or both, suggesting that the differentiation between SAH and preeclampsia may be difficult.[47,49]

As the prognosis of SAH remains poor, prompt diagnosis and appropriate treatment are essential, because early treatment may improve outcome. It is, therefore, important to rule out SAH as soon as possible in all patients complaining of sudden onset of severe headache lasting for longer than an hour with no alternative explanation. The three main predictors of mortality and disability are impaired level of consciousness on admission, advanced age, and a large volume of blood on initial cranial computed tomography. The major complications of SAH include re-bleeding, cerebral vasospasm leading to immediate and delayed cerebral ischemia, hydrocephalus, cardiopulmonary dysfunction, and electrolyte disturbances. Prophylaxis and therapy of cerebral vasospasm include maintenance of cerebral perfusion pressure (CPP) and normovolaemia, administration of intravenous nimodipine, moderate hypertension, balloon angioplasty, and intra-arterial nimodipine or papaverine. Occlusion of the aneurysm after SAH is usually attempted surgically ("clipping") or endovascularly by detachable coils ("coiling"). The need for an adequate CPP (for the prevention of cerebral ischaemia and cerebral vasospasm) must be balanced against the need for a low transmural pressure gradient of the aneurysm (for the prevention of rupture of the aneurysm). Effective measures to prevent or attenuate increases in intracranial pressure, brain swelling, and cerebral vasospasm throughout all phases of anaesthesia are necessary for optimal outcome.

Neoplastic Lesions

The incidence of intracranial neoplasms does not appear to be appreciably different in pregnant and nonpregnant women. However, some tumors appear to grow more rapidly or become symptomatic during pregnancy. The reason may be an increase either in peritumoral edema secondary to increased sodium and water retention, or increased blood volume in vascular tumors such as meningiomas.

There is considerable evidence that hormonal influences affect the growth of brain tumors, particularly meningiomas. Meningioma represents the most common primary intracranial tumor, and it has long been recognized that the growth of these lesions frequently accelerates during pregnancy. As early as 1958, a relationship among the menstrual cycle, pregnancy, and symptomatology of meningioma was identified. The incidence of meningioma is higher in women than in men but decreases significantly after menopause, particularly when surgically induced by oophorectomy.[50] Progesterone receptors have been identified in meningiomas; [51] in vitro growth of human astrocytoma cell lines is enhanced by progesterone.[52] Therefore, accelerated tumor growth during pregnancy is likely due, at least in part, to hormonal stimulation.

Gliomas are rare in pregnancy but pose a risk to maternal and fetal life. They have been treated with cesarean delivery followed by craniotomy under the same general anesthetic after 34 weeks' gestation. This is followed by radiotherapy and chemotherapy. However, all cases must be individualized and treatment tailored accordingly.[53]

Poor perinatal outcome and maternal death can be associated with unplanned pregnancies where a brain tumor is diagnosed during pregnancy.[54] Delayed intervention often results in maternal deterioration requiring urgent intervention. Pregnancy should not be considered a major contraindication to performing a neurosurgical procedure, which should be considered early rather than late in most women.[55] A multidisciplinary approach and individualized care play a crucial role in the successful preoperative management of pregnant women requiring neurosurgical procedures.[56]

MANAGEMENT OF ANESTHESIA FOR CRANIOTOMY DURING PREGNANCY

Timing of Surgery in Relation to Delivery

General Concerns

The decision to perform surgery is based on neurosurgical considerations, not obstetric ones.[57] The indication for surgery will be based on the location of the lesion, its pathological features, and the neurological assessment of the patient. When neurosurgery is considered essential but the patient is neurologically stable, then the surgery can be deferred in order to allow fetal maturation. This is accompanied by close monitoring of both the mother and the fetus. Elective surgery should be postponed until the postpartum period.

Whenever craniotomy during pregnancy is contemplated, the physicians caring for the pregnant woman must decide whether the pregnancy will be allowed to proceed to term or whether simultaneous operative delivery will occur. The choice is determined by the gestational age of the fetus, with 32 weeks commonly used as the cutoff. Before this time, pregnancy is allowed to continue; after 32 weeks, cesarean delivery is performed and is followed by immediate craniotomy. This is not because viability begins at 32 weeks, but rather because at this time the risks of preterm delivery are believed to become less than the risks to the fetus from maternal therapies such as controlled hypotension, osmotic diuresis, and mechanical hyperventilation.

Aneurysm Clipping

Dias and Sekhar[47] demonstrated a significantly higher rate of survival for both mother and fetus when aneurysm clipping was performed after SAH in comparison with nonsurgical management.[47] Therefore, in patients with good clinical grade after SAH, aneurysm clipping should be performed as soon as possible to prevent rebleeding. Clipping of unruptured contralateral aneurysms can be delayed until the postpartum period.

Arteriovenous Malformation Resection

The risk of AVM rupture is greatly increased if a patient has come to clinical attention with a hemorrhagic event.[58,59] Resection of unruptured AVMs can be delayed until after delivery with no apparent increase in maternal mortality, especially for patients at lowest risk of spontaneous rupture.[60] Conversely, resection of ruptured AVMs is more controversial. Improved maternal outcome with early operation has been demonstrated, but this difference did not reach statistical significance.[47] The question of early operation for ruptured AVM during pregnancy remains unanswered at this time. The risk of rupture is probably determined primarily by the underlying risk of the lesion, not the pregnancy. An informed decision must weigh the risk of exposing the mother to neurosurgical intervention against the natural history risk of rupture due to characteristics of the lesion or its presentation.

Neoplasm Resection

Resection of a histologically benign neoplasm such as a meningioma can be delayed until after delivery, but only if frequent follow-up and careful monitoring for neurologic deterioration can be ensured.[61]

Surgery for presumed malignant tumors and for those masses producing worsening neurologic deficits—for example, pituitary adenoma with worsening visual field defect—should be performed regardless of gestational age. Gliomas during pregnancy are rare but pose a risk to maternal and fetal life. One case report describes early cesarean delivery followed by craniotomy at 34 weeks' gestation as an effective option in such cases.[53]

Anesthetic Management

Sedative *premedication* may be appropriate in extremely anxious patients, but the risk of hypoventilation, hypercarbia, and subsequent increases in intracranial pressure (ICP) should be considered and guarded against. It might be more appropriate to defer the administration of sedative medications until the patient arrives in the preoperative holding area, where careful observation can be maintained. Because pregnant patients must be considered to be at increased risk of regurgitation and aspiration of gastric contents, medications to decrease the acidity and the volume of the gastric contents should be administered. These include a nonparticulate antacid such as Bicitra 30 mL, metoclopramide 10 mg, and an H_2 receptor antagonist such as famotidine 20 mg iv.

Anesthetic *induction* in the pregnant patient who has an intracranial lesion provides the clearest example of the need to reconcile competing or even contradictory clinical goals. A rapid-sequence induction designed to prevent aspiration does little to prevent the hemodynamic response to intubation that can be catastrophic for the patient who has an intracranial aneurysm or increased ICP. At the same time, a slow "neuroinduction" with propofol, an opioid, a nondepolarizing muscle relaxant, and mask ventilation does little to reduce the risk of aspiration. This technique can also be expected to lead to neonatal depression if cesarean delivery is performed as part of a combined procedure. The decision to proceed with or modify a standard rapid-sequence induction without ventilation must weigh the risk of aspiration against the patient's level of increased intracranial pressure and ability to tolerate a period of hypercarbia.

One acceptable technique for anesthetic induction is described in Box 25.1; other approaches that accomplish the stated goals are equally acceptable.[62] As described previously, aspiration prophylaxis and avoidance of aortocaval compression is mandatory. Cricoid pressure should be maintained from the point at which consciousness is lost until intubation is confirmed by capnography. If cesarean delivery is performed as part of a combined procedure, the physician caring for the newborn should be made aware of the likelihood of neonatal depression and the need to provide ventilatory support.

BOX 25.1 Anesthetic Induction for Craniotomy in a Pregnant Patient

Aspiration prophylaxis with nonparticulate antacid, metoclopramide 10 mg IV and famotodine 20 mg IV
Left uterine displacement to avoid aortocaval compression
Preoxygenation for 3–4 minutes
Propofol 1–2.5 mg/kg
Fentanyl 3–5 µg/kg
Lidocaine 75 mg
Rocuronium 0.9–1.2 mg/kg
Mask ventilation with cricoid pressure, 100% O_2

BOX 25.2 Anesthetic Maintenance for Craniotomy in a Pregnant Patient

Fentanyl 1–2 µg/kg/h
Isoflurane 0.5–1% +/- nitrous oxide
Nondepolarizing muscle relaxant
Propofol 40–200 µg/kg/h for "tight brain"

The use of fetal heart rate (FHR) monitoring during nonobstetric surgery remains controversial. A 2011 Committee Opinion of the American College of Obstetricians and Gynecologists (ACOG) stated that intraoperative fetal monitoring may be appropriate when the following conditions are met: (1) the fetus is viable, (2) it is physically possible to perform monitoring, (3) a health care provider who can perform a cesarean section is present, (4) the woman has given informed consent to emergency cesarean section, and (5) the nature of the surgery will allow its interruption to provide access to perform emergency surgery.[63] The opinion goes on to say that monitoring a previable fetus may be appropriate to facilitate positioning or interventions to optimize oxygenation. Finally, the opinion states that the decision to perform intraoperative monitoring should be individualized based on gestational age, type of surgery, and available facilities.

Monitoring is further complicated by the fact that decreases in short- and long-term FHR variability, as well as a decreased baseline FHR, are commonly seen even in the healthy, uncompromised fetus whose mother is receiving general anesthesia. Because the evidence base in support of fetal monitoring is primarily anecdotal,[64] the decision to use such monitoring should be individualized. It is probably unrealistic to expect that an emergency cesarean delivery could be performed expeditiously during craniotomy because of an ominous FHR value; rather, FHR monitoring may be useful because significant changes should lead to a rapid search for potentially reversible causes of decreased uteroplacental perfusion, such as hypotension and hypoxemia.

Anesthetic *maintenance* is not appreciably different in pregnant and nonpregnant women undergoing craniotomy (Box 25.2). As is the case during induction of anesthesia, every effort should be made to maintain hemodynamic stability as well as to avoid increases in cerebral blood volume that could interfere with surgical exposure.

Adjuvants to Surgery

Osmotic diuresis with mannitol is commonly used to decrease brain bulk and facilitate exposure during craniotomy. Because mannitol has been demonstrated in both animal and human studies to produce fetal dehydration, some have advised against its use during pregnancy. However, the doses given in these early studies were considerably higher than those currently in clinical use. There is no evidence that mannitol 0.25–0.5 g/kg has any significant adverse effect on fetal fluid balance.[65] Furosemide may be an alternative to mannitol.[66]

Maternal hyperventilation can facilitate surgical exposure by decreasing cerebral blood volume. Severe hypocarbia may impair fetal oxygen delivery, however, by shifting the maternal oxygen–hemoglobin dissociation curve to the left. Hyperventilation can also decrease maternal cardiac output by raising intrathoracic pressure. Modest hyperventilation to a $PaCO_2$ value of 25–30 mmHg should provide adequate surgical conditions without significantly compromising the fetus.[66]

There are a number of specific anesthetic concerns during surgery for aneurysm clipping. Controlled hypotension during clipping has been largely supplanted by the use of temporary clip occlusion of proximal vessels. Controlled hypotension has become less commonly used due to concerns that use of controlled hypotension may increase the risk of early and delayed neurological deficits. There may be situations, however, in which this technique becomes necessary. Because UBF varies directly with perfusion pressure, severe hypotension can lead to fetal asphyxia. Blood pressure should, therefore, be lowered only to that level deemed necessary for maternal well-being, and for as brief a period as possible. FHR monitoring might alert the anesthesiologist to the development of fetal hypoxia and lead to the restoration of blood pressure if the need for hypotension is not critical at that time.

There is an additional concern when sodium nitroprusside is used as the hypotensive agent. Because of the limited ability of the fetal liver to metabolize cyanide, it is possible for fetal intoxication to occur in the absence of any signs of maternal toxicity.[67] Although there are several case reports of the safe use of sodium nitroprusside during pregnancy,[68,69] the duration of administration should be limited to a period deemed essential to maternal well-being. The total dose of sodium nitroprusside can also be limited through the administration of adjuvants such as β-blocking drugs and inhalation anesthetics.

Although intraoperative hypothermia to 33°C has not been shown to improve neurologic outcome after craniotomy for SAH,[70] mild permissive hypothermia (35°C) is still used by a number of practitioners. This level of hypothermia has no significant fetal effects. More profound levels of hypothermia, however, can cause fetal arrhythmias and should be avoided.

Avoidance of intraoperative hyperglycemia (>130 mg/dL) will reduce the risk of neurologic injury after transient focal ischemia during aneurysm clipping. Various pharmacological agents have been used to promote cerebral protection during aneurysm surgery, but none has been clearly shown to improve outcome. The benefits of temporary clipping and concomitant use of induced hypertension, deep hypothermia with circulatory arrest and cardiopulmonary bypass, and transient cardiac pause using adenosine to control aneurysmal bleeding, is beyond the scope of this chapter and is covered elsewhere.

Emergence from Anesthesia

Before the removal of the endotracheal tube, the pregnant patient should be fully awake and her airway reflexes intact to minimize the risk of aspiration. Bringing the patient to alertness will also facilitate early neurologic evaluation and eliminate the need for emergency radiologic evaluation of the persistently obtunded patient. At the same time, however, every effort should be made to prevent coughing and straining on the endotracheal tube, which may cause catastrophic intracranial hemorrhage. Prevention may be facilitated through the administration of lidocaine 75–100 mg and fentanyl 25–50 μg at the end of the operation. Another option is to titrate intravenous dexmedetomidine to produce the desired effect of a hemodynamically stable patient who is cooperative and able to tolerate an indwelling endotracheal tube prior to extubation. Because placement of the head dressing is associated with movement that produces airway stimulation and "bucking" of the patient on the endotracheal tube, it is appropriate to maintain neuromuscular blockade until the dressing has been secured. These guidelines do not apply to patients who were obtunded preoperatively or who had a significantly complicated intraoperative course with bleeding, brain swelling, or ischemia. Such patients should remain intubated until their neurologic status can be evaluated.

NEURAXIAL ANESTHESIA IN PARTURIENTS WITH INTRACRANIAL PATHOLOGY

Parturients with intracranial lesions are often thought to have increased intracranial pressure, even if there are no clinical or radiographic signs. Consequently, the risk of brainstem herniation after inadvertent dural puncture is often cited as a contraindication to neuraxial anesthesia. In order to decide if such patients can undergo spinal or epidural analgesia or anesthesia we must understand factors that contribute to brain herniation, such as raised ICP, cerebral edema and hydrocephalus.[71] In the absence of other contraindications to neuraxial anesthesia, pregnant women with space-occupying lesions (SOL) are unlikely to be at increased risk of herniation if there is no mass effect, no clinical or imaging finding of increased ICP and no hydrocephalus. Patients at high risk from herniation following a dural puncture are those where the brain lesion compresses normal brain tissue and causes a midline shift or a downward shift, with or without obstruction to CSF flow (Fig. 25.1). Neuraxial anesthesia has the advantage of avoiding intubation associated valsalva and hypertension, minimizes fetal exposure to anesthetics and allows maternal participation in the birth process. If incremental epidural dosing is used in patients with a SOL but at low risk of herniation, it is best to use no more than 5 mL solution every 5 minutes in order to limit acute increases in ICP.

SPONTANEOUS SPINAL EPIDURAL HEMATOMA

Spontaneous spinal epidural hematoma (SSEH) is a rare cause of spinal cord compression. The lesions are usually associated with congenital or acquired bleeding disorders, hemorrhagic tumors, spinal AVMs, or increased intrathoracic pressure. In a review published in 2003, Kreppel and associates[72] identified 613 cases reported in the literature since 1682. As of 2005, there were six reported cases during pregnancy.[73] In these six cases, the women had profound neurologic deficits, were managed surgically, and exhibited significant neurologic improvement after surgery. Pregnancy was carried to term in three cases, and emergency cesarean delivery was performed before evacuation of the spinal epidural hematoma in three cases.

When an SSEH occurs in the thoracic or lumbar region, the initial presentation consists of lower extremity radicular pain as well as bladder and bowel dysfunction. Motor and sensory deficits are usually progressive within hours of presentation. The definitive diagnosis is made radiologically, with magnetic resonance imaging appearing to be the preferred modality during pregnancy. For patients who have profound and progressive neurologic deficits, the treatment of choice is immediate surgical evacuation of the hematoma. Lawton and coworkers[74] concluded that neurologic outcome was significantly improved in patients who underwent decompression within 12 hours of the onset of symptoms. Although Duffill and colleagues reported the successful nonoperative management of SSEH,[75] there are no case reports of pregnant patients who were managed conservatively.

Cywinski and associates[24] address the possibility of conservative management of the pregnant patient with SSEH. They suggest that the hemodynamic changes seen during vaginal delivery might precipitate expansion of the hematoma. Further, they suggest that cesarean delivery during conservative management of SSEH would be inappropriate, because of the inability to monitor the patient's neurologic status.[24]

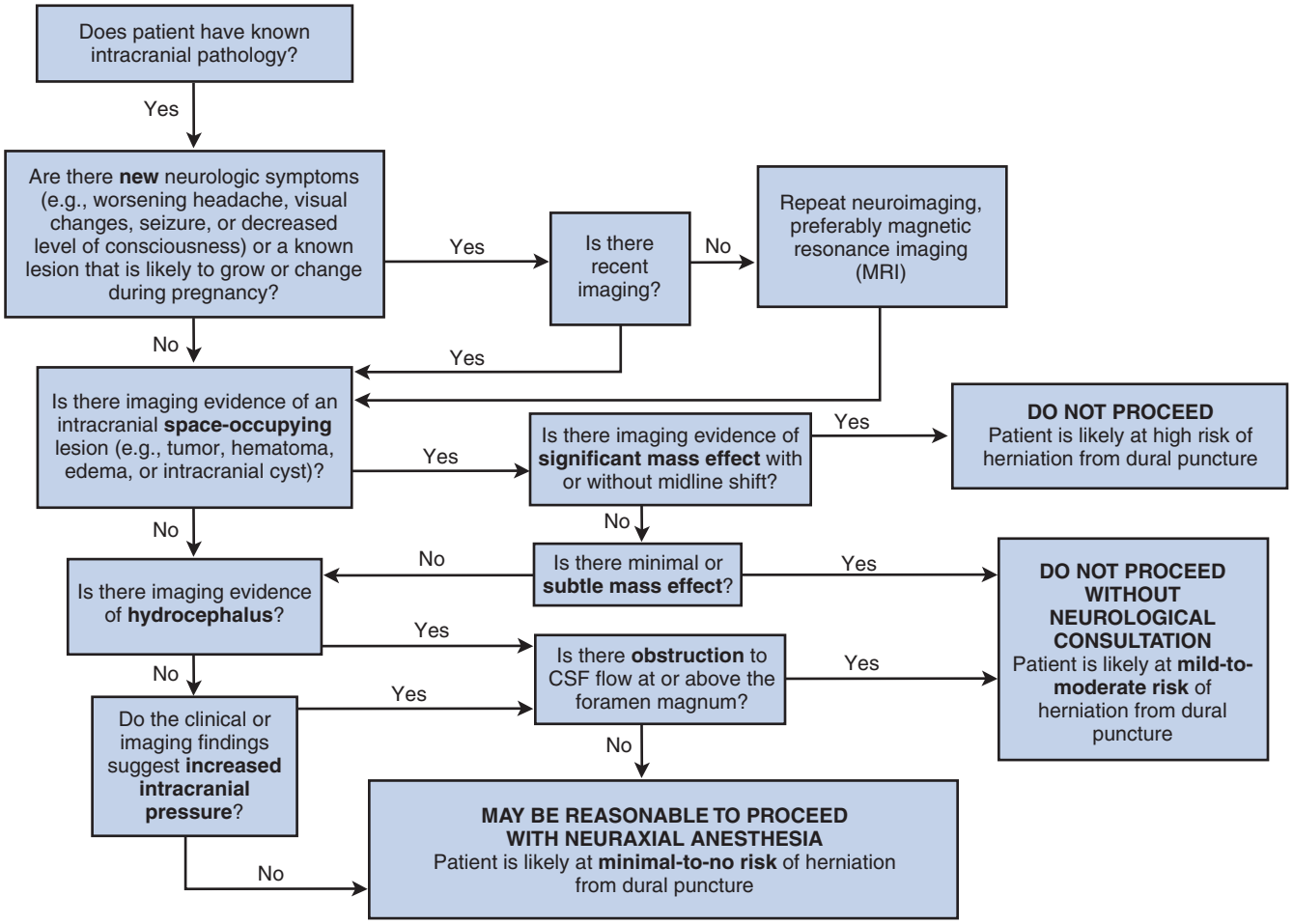


Fig. 25.1 Anesthetic management of the pregnant patient undergoing craniotomy.

Timing of delivery in relation to SSEH surgery depends on gestational age. It has been recommended, in patients with a viable fetus, that cesarean delivery be performed immediately prior to surgical decompression. Vaginal delivery is not recommended, due to the unpredictable duration of labor, and the possibility of more extreme hemodynamic changes, particularly during the second stage of labor.[24]

Anesthetic Management of Surgical Evacuation

The concerns and techniques outlined for anesthetic management of intracranial lesions should be followed for evacuation of SSEH with or without cesarean delivery, including the recommendations for sedative premedication, anesthetic induction and maintenance, FHR monitoring, and emergence.

Anesthetic maintenance is not appreciably different from that for patients undergoing operation for intracranial lesions, except for the need to maintain the mean arterial blood pressure in the high normal range (70–85 mmHg in normotensive patients) to ensure adequate perfusion of the spinal cord.

Positioning considerations are extremely important in the pregnant patient before thoracic or lumbar laminectomy for hematoma evacuation. Aortocaval compression must be avoided to prevent significant reductions in maternal cardiac output, systemic blood pressure, and uteroplacental perfusion in patients for whom prior cesarean delivery is not performed. Physiologic studies reveal better relief of uterine compression of the large maternal vessels in the prone position than in the sitting or lateral position, with the lateral position actually being associated with a higher incidence of aortocaval compression.[76,77]

Jea and colleagues[73] described the use of the four-post Wilson frame for surgery in a patient with SSEH; two posts were placed just below the clavicles on the chest and the other posts centered on the anterosuperior iliac spines to support the pelvis.[73] In this position, the abdomen hung free of compression between the four posts, preventing compression of the abdominal aorta and vena cava. Positioning the patient on a Jackson table would similarly reduce aortocaval compression.

Emergence is managed as for pregnant patients undergoing surgery for intracranial lesions. Additional precautions must be taken to assess the patient's readiness for extubation after being in the prone position for surgery because of possible airway edema. A leak test should be performed when the patient is fully awake before the endotracheal tube is removed.

In summary, surgical management of intracranial and spinal lesions in pregnant women is usually well tolerated by both mother and fetus. Preoperative delivery by cesarean of term or near-term babies is often advised. Attempts to manage by conservative therapy alone may lead to clinical deterioration requiring urgent surgical intervention.[78]

INTERVENTIONAL NEURORADIOLOGY IN PREGNANCY

The neurointerventional radiology suite is one of a growing number "out of OR" sites where anesthesia is often provided to critically ill patients. With improvements in techniques and equipment, coiling of both ruptured and unruptured intracranial aneurysms increasingly provides an alternative to surgical

clipping.[79] Compared to surgery, coiling has a reduced incidence of vasospasm and procedural complications, and a similar incidence of obstructive hydrocephalus, albeit a smaller rate of successful aneurysmal obliteration.[80] While aneurysm coiling may appear to be minimally invasive, there remains a real risk of significant morbidity. Fastidious anesthetic care is, therefore, essential.

Fetal radiation exposure during a neurointerventional procedure is an understandable source of anxiety for pregnant patients. Before the health effects of fetal irradiation can be discussed, one must take into account the expected radiation dose, as well as the gestational age of the fetus. Fetal risk from radiation exposure in the neuroradiology suite depends on the study being performed (e.g., head CT vs. abdominopelvic studies), gestational age, and dose of radiation. Many radiologists believe that radiation exposure is minimal for head CT during pregnancy, but most will still shield the fetus with a lead apron and use the lowest dose of radiation possible. Exposure to radiation is quantitated by the radiation absorbed dose, or rad. One gray, another commonly used measure of radiation exposure, is the equivalent of 100 rad. Adverse effects on the fetus are uncommon below 5 rad (0.05 Gy). If risk–benefit analysis favors using CT, then a radiologist must not delay or withhold imaging but must minimize radiation exposure.[81] The risk of increasing radiation exposure at different stages of gestation has been well described (Table 25.1).[82] Anesthesiologists should have an understanding of the radiation risks to mother and fetus, the ways that these risks can be minimized, and the ability to provide accurate information regarding those risks to an often apprehensive pregnant mother.

CT imaging of the head delivers minimal radiation to the fetus.[81] While fluoroscopy can expose the fetus to greater amounts of radiation, appropriate protective measures can significantly reduce radiation dose.

Lead aprons and thyroid shields are routinely used by radiology personnel. These measures have been shown to reduce total body exposure to radiation in patients undergoing fluoroscopy, and, therefore, one could conclude reduce fetal radiation exposure as well.[83] Ultimately the estimation of radiation dose is best estimated by the physician who performs such procedures on a regular basis so that a realistic risk–benefit discussion can be undertaken.

Anxiety surrounding radiation exposure has been well described, even amongst physicians and health care personnel who operate in the interventional suites. It is clearly understandable that even with the most detailed of explanations, parturients may need significant reassurance.[84]

Besides radiation exposure, there are many technical difficulties presented by an interventional radiology suite. The airway changes of pregnancy are made more challenging due to the inability of most interventional suite operating tables to assist with proper positioning for airway management. During a neurointerventional procedure, the C-arm will typically be in close proximity to the head, making access to the airway difficult. The movements of both the C-arm and the operating table are controlled by the interventional radiologist, greatly increasing the risk of unintentional extubation. The standard positioning of the anesthesia machine to the anesthesiologist's right side is often absent in interventional suites. All of these factors can lead to significant problems in patient management in the event of airway emergency or hemodynamic instability. It is not surprising that anesthesia closed claim trials analysis found that out of OR airway claims occurred twice as frequently as in OR claims.[85]

Many personnel working in neurointerventional suites are unfamiliar with the provision of anesthesia. This unfamiliarity with anesthetic management is only magnified when dealing with a pregnant patient in such an environment, and issues such as aortocaval compression are poorly understood and easily overlooked.

While aneurysm coiling is occasionally performed under moderate sedation administered by the interventional radiologist, the complex issues surrounding the management of the pregnant patient require the presence of an anesthesiologist.

The anesthetic principles that apply to open surgical treatment of ruptured cerebral aneurysms also apply to endovascular treatment. The choice of anesthetic technique varies depending on the institution, with the most common techniques being conscious sedation and general anesthesia. There have been no studies comparing these two techniques. One of the main goals of the anesthetic technique is keeping the patient motionless to optimize the quality of the images used to perform the endovascular procedure; hence, general anesthesia with endotracheal intubation is often preferred for these procedures.[86]

Aneurysm rupture is a major concern during endovascular treatment. There may be an acute, massive rise in blood pressure (with or without bradycardia) secondary to elevated ICP. Hyperventilation and osmotic diuresis are used to control

Table 25.1 Health Effects of Prenatal Radiation Exposure—created from information provided by the International Commission on Radiological Protection

	Blastogenesis 0–2 weeks	Organogenesis (2–8 weeks)	Fetogenesis (8–15 weeks)	Fetogenesis (16–25 weeks)	Fetogenesis (26–38 weeks)
<0.05 Gy	No malignancy-related health issues				
0.05–0.50 Gy	Incidence of implantation failure increases Surviving embryos unaffected	Growth retardation possible Incidence of major malformations increases slightly	Growth retardation possible Reduced IQ (up to15 points) Incidence of severe learning difficulties up to 20%	No malignancy-related health issues	
>0.50 Gy	Incidence of implantation failure increase further (1 Gy will kill 50% of embryos)	Incidence of miscarriage increases Growth retardation likely Substantial risk of major malformations—motor and neurologic	Incidence of miscarriage increases Decreased IQ by >15 points Incidence of learning difficulties > 20%	Incidence of miscarriage increases Decreased IQ by >15 points Incidence of learning difficulties > 20%	Incidence of miscarriage and neonatal death will probably increase

intracranial hypertension. Aggressive treatment of malignant hypertension may induce ischemia; therefore, antihypertensive therapy should be used with caution.

Anticoagulation with heparin is often used for endovascular procedures during the embolization of aneurysms. Patients who have undergone anticoagulation require rapid reversal with protamine if aneurysm rupture occurs during the procedure. However, with the increasing use of intravascular stents, administration of antiplatelet agents (aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists) during these procedures has become more common. In case of aneurysm rupture in this setting, rapid reversal of antiplatelet activity is achieved with platelet transfusion.

Finally, although emergency cesarean section in response to a nonreassuring FHR value is unlikely to be an option in most neuroradiology suites that are distant from the operating room, FHR monitoring may provide some guidance regarding the range of blood pressure that provides adequate uteroplacental perfusion and oxygen delivery.

As an example of current practice, within the University of California, San Diego, parturients undergoing aneurysmal coiling typically will have arterial catheters placed prior to induction of anesthesia. Because of the risks of rapid alterations in the patient's level of consciousness should procedural complications occur, general anesthesia with endotracheal intubation is routinely used. Fetal heart rate monitoring is also utilized as requests for lower blood pressure have to be balanced against the risk of decreased uteroplacental perfusion. Although unruptured aneurysms and AVMs are not typically associated with raised intracranial pressure, it is common for a propofol-based total intravenous anesthetic to be utilized to optimize cerebral metabolic oxygen balance. The additional antiemetic properties of propofol and its ability to facilitate smooth emergence also make propofol a popular choice.

REFERENCES

1. Subramanian R, Sardar A, Mohanaselvi S, Khanna P, Baidya DK. Neurosurgery and pregnancy. *J Neuroanaesth Crit Care*. 2014;1:166–172.
2. Chan MT, Mainland P, Gin T. Minimum alveolar concentration of halothane and enflurane are decreased in early pregnancy. *Anesthesiology*. 1996;85:782–786.
3. Gin T, Chan MT. Decreased minimum alveolar concentration of isoflurane in pregnant humans. *Anesthesiology*. 1994;81:829–832.
4. Gintzler AR, Liu NJ. The maternal spinal cord: Biochemical and physiological correlates of steroid-activated antinociceptive processes. *Prog Brain Res*. 2001;133:83–97.
5. Lee J, Lee J, Ko S. The relationship between serum progesterone concentration and anesthetic and analgesic requirements: A prospective observational study of parturients undergoing cesarean delivery. *Anesth Analg*. 2014;119:901–905.
6. Ueyama H, Hagihira S, Takashina M, et al. Pregnancy does not enhance volatile anesthetic sensitivity on the brain: An electroencephalographic analysis study. *Anesthesiology*. 2010;113:577–584.
7. Igarashi T, Hirabayashi Y, Shimuzu R, et al. The fiberscopic findings of the epidural space in pregnant women. *Anesthesiology*. 2000;92:1631–1636.
8. Flanagan HL, Datta S, Lambert DH, et al. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1987;66:123–126.
9. Bader AM, Datta S, Moller RA, Covino BG. Acute progesterone treatment has no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1990;71:545–548.
10. McAuliffe F, Kametas N, Costello J, et al. Respiratory function in singleton and twin pregnancy. *BJOG*. 2002;109:765–769.
11. Spätling L, Fallenstein F, Huch A, et al. The variability of cardiopulmonary adaptation to pregnancy at rest and during exercise. *Br J Obstet Gynaecol*. 1992;99(Suppl 8):1–40.
12. McClelland SH, Bogod DG, Hardman JG. Apnoea in pregnancy: An investigation using physiological modeling. *Anaesthesia*. 2008;63:264–269.
13. McClelland SH, Bogod DG, Hardman JG. Pre-oxygenation in pregnancy: An investigation using physiological modeling. *Anaesthesia*. 2008;63:259–263.
14. Jensen D, Duffn J. Lam Y- M: Physiological mechanisms of hyperventilation during pregnancy. *Respir Physiol Neurobiol*. 2008;161:76–86.
15. Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. *Am J Obstet Gynecol*. 1989;161:1449–1453.
16. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol*. 1989;161:1439–1442.
17. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labor. *Br Med J*. 1987;295:1169–1172 [Clin Res Ed].
18. Lee SW, Khaw KS, Ngan Kee WD, et al. Haemodynamic effects from aortocaval compression at different angles of lateral tilt in non-labouring term pregnant women. *Br J Anaesth*. 2012;109:950–956.
19. O'Sullivan GM, Bullingham RE. The assessment of gastric acidity and antacid effect in pregnant women by a non-invasive radiotelemetry technique. *Br J Obstet Gynaecol*. 1984;91:973–978.
20. Wong CA, McCarthy RJ, Fitzgerald PC, et al. Gastric emptying of water in obese pregnant women at term. *Anesth Analg*. 2007;105:751–755.
21. Escher G, Mohaupt M. Role of aldosterone availability in preeclampsia. *Mol Aspects Med*. 2007;28:245–254.
22. Bacq Y, Zarka O, Bréchot JF, et al. Liver function tests in normal pregnancy: A prospective study of 103 pregnant women and 103 matched controls. *Hepatology*. 1996;23:1030–1034.
23. Leighton BL, Cheek TG, Gross JB, et al. Succinylcholine pharmacodynamics in peripartum patients. *Anesthesiology*. 1986;64:202–205.
24. Cywinski JB, Parker BM, Lozada LJ. Spontaneous spinal epidural hematoma in a pregnant patient. *J Clin Anesth*. 2003;16:371–375.
25. Nolte JE, Rutherford RB, Nawaz S, et al. Arterial dissections associated with pregnancy. *J Vasc Surg*. 1995;21:515–520.
26. Ngan Kee WD. Uteroplacental blood flow. In: Chestnut DH, ed. *Obstetric Anesthesia, Principles and Practice*. 5th ed. Philadelphia: Elsevier Saunders; 2014:39–54.
27. Ngan Kee WD, Khaw KS. Vasopressors in obstetrics: What should we be using? *Curr Opin Anaesthesiol*. 2006;19:238–243.
28. Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg*. 2002;94:920–926.
29. Zakowski MI, Geller A. The placenta: Anatomy, physiology, and transfer of drugs. In: Chestnut DH, ed. *Obstetric Anesthesia, Principles and Practice*. 5th ed. Philadelphia: Elsevier Saunders; 2014:55–74.
30. Ghanem FA, Movahed A. Use of antihypertensive drugs during pregnancy and lactation. *Cardiovasc Ther*. 2008;26:38–49.
31. Eisenach JC, Castro MI. Maternally administered esmolol produces fetal beta-adrenergic blockade and hypoxemia in sheep. *Anesthesiology*. 1989;71:718–722.
32. Jevtovic-Todorovic V, Absalom AR, Blomgren K, et al. Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth*. 2013;111:143–151.
33. Mazze RI. Fertility, reproduction, and postnatal survival in mice chronically exposed to isoflurane. *Anesthesiology*. 1985;63:663–667.
34. Mazze RI, Wilson AI, Rice SA, et al. Fetal development in mice exposed to isoflurane. *Teratology*. 1985;32:339–345.
35. Mazze RI, Fujinaga M, Rice SA, et al. Reproductive and teratogenic effects of nitrous oxide, halothane, isoflurane, and enflurane in Sprague-Dawley rats. *Anesthesiology*. 1986;64:339–344.
36. Mazze RI, Wilson AI, Rice SA, Baden JM. Reproduction and fetal development in rats exposed to nitrous oxide. *Teratology*. 1984;30:259–265.
37. Fujinaga M, Baden JM. Methionine prevents nitrous oxide-induced teratogenicity in rat embryos grown in culture. *Anesthesiology*. 1994;81:184–189.
38. Fujinaga M. Teratogenicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol*. 2001;15:363–375.
39. Burm AG. Occupational hazards of inhalational anesthetics. *Best Pract Res Clin Anaesthesiol*. 2003;17:147–161.
40. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol*. 2003;17:47–61.
41. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol*. 1994;8:461–475.
42. Rosenberg L, Mitchell AA, Parsells JL, et al. Lack of relation of oral clefts to diazepam use during pregnancy. *N Engl J Med*. 1983;309:1282–1285.
43. Ornoy A, Arnon J, Shectman S, et al. Is benzodiazepine use during pregnancy really teratogenic? *Reprod Toxicol*. 1998;12:511–515.
44. Selo-Ojeme DO, Marshman LAG, Ikomi A. Aneurysmal subarachnoid hemorrhage in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2004;116:131–143.
45. Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *Br J Obstet Gynaecol*. 2011;118(Suppl 1):1–203.
46. Creanga AA, Berg CJ, Syverson C, et al. Pregnancy-related mortality in the United States, 2006-2010. *Obstet Gynecol*. 2015;125:5–12.

47. Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. *Neurosurgery*. 1990;27:855–865.
48. Takahashi JC, Iihara K, Ishii A, et al. Pregnancy-associated intracranial hemorrhage: Results of a survey of neurosurgical units across Japan. *J Stroke Cerebrovasc Dis*. 2014;23:e65–e71.
49. Connolly Jr. ES, Rabinstein AA, Carhuapoma JR, et al., on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737.
50. Schlehofer B, Blettner M, Becker N, et al. Association between brain tumors and menopausal status. *J Natl Cancer Inst*. 1992;84:1346–1349.
51. Cahill DW, Bashirelahi N, Solomon LW, et al. Estrogen and progesterone receptors in meningiomas. *J Neurosurg*. 1984;60:983–985.
52. Gonzalez-Aguero G, Gutierrez AA, Gonzalez-Espinosa D, et al. Progesterone effects on cell growth of U373 and D54 human astrocytoma cell lines. *Endocrine*. 2007;32:129–135.
53. Wu J, Ma YH, Wang TL. Glioma in the third trimester of pregnancy: Two cases and a review of the literature. *Oncol Lett*. 2013;5:943–946.
54. Girault A, Dommergues M, Nizard J. Impact of maternal brain tumours on perinatal and maternal management and outcome: A single referal center retrospective study. *Eur J Obstet Gynecol Reprod Biol*. 2014;183:132–136.
55. Nossek E, Ekstein M, Rimon E, et al. Neurosurgery and pregnancy. *Acta Neurochir (Wien)*. 2011;153:1727–1735.
56. Chowdhury T, Chowdhury M, Schaller B, et al. Perioperative considerations for neurosurgical procedures in the gravid patient: Continuing Professional Development. *Can J Anaesth*. 2013;60:1139–1155.
57. Khan M, Wasay M. Hemorrhagic strokes in pregnancy and puerperium. *Int J Stroke*. 2013;8:265–272.
58. Kim H, Sidney S, McCulloch CE, et al. Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. *Stroke*. 2007;38:2430–2437.
59. Mast H, Young WL, Koennecke H-C, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. *Lancet*. 1997;350:1065–1068.
60. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformations. *Neurology*. 2006;66:1350–1355.
61. Elwatidy S, Jamjoom Z, Elgamai E, Abdelwahab A. Management strategies for acute brain lesions presenting during pregnancy: A case series. *Br J Neurosurg*. 2011;25:478–487.
62. Ravussin P, Tempelhoff R, Modica PA, Bayer-Berger MM. Propofol vs. thiopental-isoflurane for neurosurgical anesthesia: Comparison of hemodynamics, CSF pressure, and recovery. *J Neurosurg Anesthesiol*. 1991;3:85–95.
63. ACOG Committee on Obstetric Practice. ACOG Committee Opinion Number 474, February 2011: Nonobstetric surgery in pregnancy. *Obstet Gynecol*. 2011;117:420–421.
64. Macarthur A. Craniotomy for suprasellar meningioma during pregnancy: Role of fetal monitoring. *Can J Anesth*. 2004;51:535–538.
65. Bharti N, Kashyap L, Mohan VK. Anesthetic management of a parturient with cerebellopontine-angle meningioma. *Int J Obstet Anesth*. 2002;11:219–221.
66. Wang LP, Paech MJ. Neuroanesthesia for the pregnant woman. *Anesth Analg*. 2008;107:193–200.
67. Naulty J, Cefalo RC, Lewis PE. Fetal toxicity of nitroprusside in the pregnant ewe. *Am J Obstet Gynecol*. 1981;139:708–711.
68. Willoughby JS. Sodium nitroprusside, pregnancy, and multiple intra-cranial aneurysms. *Anaesth Intensive Care*. 1984;12:351–357.
69. Conklin KA, Herr G, Fung D. Anaesthesia for caesarean section and cerebral aneurysm clipping. *Can Anaesth Soc J*. 1984;31:451–454.
70. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
71. Leffert LR, Schwamm LH. Neuraxial anesthesia in parturients with intracranial pathology: A comprehensive review and reassessment of risk. *Anesthesiology*. 2013;119:703–718.
72. Kreppel D, Antoniadis G, Seeling W. Spinal hematoma: A literature survey with meta-analysis of 613 patients. *Neurosurg Rev*. 2003;26:1–49.
73. Jea A, Moza K, Levi AD, Vanni S. Spontaneous spinal epidural hematoma during pregnancy: Case report and literature review. *Neurosurgery*. 2005;56.
74. Lawton MT, Porter RW, Heiserman JE, et al. Surgical management of spinal epidural hematoma: Relationship between surgical timing and neurological outcome. *J Neurosurg*. 1996;83:1–7.
75. Duffill J, Sparrow OC, Millar J, et al. Can spontaneous spinal epidural hematoma be managed safely without operation: A report of four cases. *J Neurol Neurosurg Psychiatry*. 2000;69:816–819.
76. Andrews PJ, Ackermann WE, Juneja MM. Aortocaval compression in the sitting and lateral decubitus positions during extradural catheter placement in the parturient. *Can J Anaesth*. 1993;40:320–324.
77. Nakai Y, Mine M, Nishio J, et al. Effects of maternal prone position on the umbilical arterial flow. *Acta Obstet Gynecol Scand*. 1998;77:967–969.
78. Cohen-Gadol AA, Friedman JA, Friedman JD, et al. Neurosurgical management of intracranial lesions in the pregnant patient: A 36-year institutional experience and review of the literature. *J Neurosurg*. 2009;111:1150–1157.
79. Meyers PM, Halback VV, Malek AM, et al. Endovascular treatment of cerebral artery aneurysms during pregnancy: Report of three cases. *Am J Neuroradiol*. 2000;21:1306–1311.
80. Taha MM, Nakahara I, Higashi T, et al. Endovascular embolization vs. surgical clipping in treatment of cerebral aneurysms: Morbidity and mortality with short-term outcome. *Surg Neurol*. 2006;66:277–284.
81. Goldberg-Stein SA, Liu B, Hahn PF, Lee SI. Radiation dose management: Part 2, estimating fetal radiation risk from CT during pregnancy. *AJR Am J Roentgenol*. 2012;198:W352–W356.
82. International Commission on Radiological Protection, editors. Annals of the ICRP, Publication 90: Biological Effects After Prenatal Irradiation (embryo and Fetus) 33 (1-2). Tarrytown, New York: Pergamon, Elsevier Science, Inc.; 2003.
83. Mohapatra A, Greeberg RK, Mastracci TM, et al. Radiation exposure to operating room personnel and patients during endovascular procedures. *J Vasc Surg*. 2013;58:702–709.
84. Krueger KJ, Hoffman BJ. Radiation exposure during gastroenterologic fluoroscopy: Risk assessment for pregnant workers. *Am J Gastroenterol*. 1992;87:429–431.
85. Metzner J, Posner KL, Lam MS, Domino KB. Closed claims analysis. *Best Pract Res Clin Anaesthesiol*. 2011;25:263–276.
86. Guercio JR, Nimjee SM, James ML, McDonagh DL. Anesthesia for interventional neuroradiology. *Int Anesthesiol Clin*. 2015;53:87–106.

SUGGESTED READING

Akins PT, Axelrod Y, Silverthorn JW, et al. Management and outcomes of malignant posterior reversible encephalopathy syndrome. *Clin Neurol Neurosurg*. 2014;125:52–57.

Liakos AM, Bradley NK, Magram G, Muszynski C. Hydrocephalus and the reproductive health of women: The medical implications of maternal shunt dependency in 70 women and 138 pregnancies. *Neurol Res*. 2000;22:69–88.

St Louis EK, Jinnur P, McCarter SJ, et al. Chiari 1 malformation presenting as central sleep apnea during pregnancy: A case report, treatment considerations, and review of the literature. *Front Neurol*. 2014;5:195.

Tandon A, Alzate J, LaSala P, Fried MP. Endoscopic endonasal transsphenoidal resection for pituitary apoplexy during the third trimester of pregnancy. *Surg Res Pract*. 2014;397131. Epub 2014 Jan 2.

Ethical Considerations in the Care of Patients with Neurosurgical Disease

26

J.D. Moreno • S.T. DeKosky

Research advances and heightened clinical capabilities have enabled those who care for patients with neurosurgical disease to make great strides toward restoring the health and well-being of such patients and reducing morbidity and mortality. Yet for every new technologic advance and clinical application, new issues have also arisen for caregivers, such as (1) the appropriate selection of patients for application of new technologies and enrollment in clinical trials, (2) the involvement of patients and families in balancing the risks of new treatments against their possible benefits, and (3) how to make decisions for patients who may not be able to participate in the decision-making process yet for whom significant decisions must be made concerning the kind of care to be delivered.

Such questions demand that clinicians look beyond their clinical training and subspecialty expertise when facing the genuine ethical dilemmas that are now an integral part of the clinical setting. Determining the moral status of one's actions can be a troubling and sometimes arduous process for even the most enlightened of clinicians. Because such moral issues permeate clinical practice and because their resolution often requires serious and extended deliberation, clinicians should become familiar with the systems of "clinical ethics" and research ethics that have emerged over the last 35 years. Such familiarity will enable clinicians to deal more effectively with these difficult issues by applying philosophical reasoning and ethical analysis to the problems they encounter in the course of research and clinical practice.

Heightened sensitivity to ethical concerns in the clinical setting has also been accompanied by increased awareness of and concern for the role of the legal system in clinical practice. As medical and surgical care has become ever more sophisticated and developments in the legal process have both educated patients and encouraged them to assert themselves in the provider–patient relationship, physicians have naturally become more sensitive to the legal status of their actions. A clinical ethics framework that incorporates a perspective of legal concerns as it also tries to determine the appropriateness of an action may lie well beyond narrow legal definitions applicable in a particular situation. Although it is incumbent on the clinician to be aware of the legal backdrop for clinical practice, many ethical dilemmas move beyond mere legal technicalities, requiring the clinician to evaluate concurrent and, at times, conflicting duties, rights, and values that are an inevitable part of the provider–patient relationship. In this chapter, we address the ethical issues that confront caregivers of the neurosurgical patient population.

AN INTRODUCTION TO THE HISTORY AND THEORY OF MEDICAL ETHICS

We begin with an overview of the historic development of medical ethics. The account concentrates mainly on the Western secular tradition that begins with followers of Hippocrates and emerges in a fundamentally altered form in the current framework of clinical ethics. We then describe the essential features of the current framework.

Origins of Contemporary Medical Ethics

Western medical ethics is believed to have originated with the Hippocratic cult (about 450 to 300 BC), a group of early physicians who are thought to have been heavily influenced by the Pythagorean thinkers. Rather than ascribing disease to be solely the province of supernatural or deistic causes, this group was responsible for one of the first systemized efforts to impart a naturalistic approach to the study and practice of medicine. In addition to their accomplishments in mathematics, the Pythagoreans developed a moral philosophy that emphasized respect for life. This outlook would account, for example, for the apparent strictures on abortion and euthanasia that are features of a prominent version of the Hippocratic Oath. For different reasons, the oath also prohibits surgery, which was not regarded as a proper part of a physicians' activities. The attitudes held by the Hippocratic physicians apparently were not widely held among other physician cults of the ancient world.[1]

The Hippocratic tradition urges physicians to "do no harm" and to use their skills for the welfare of the individual patient. For many years these principles were thought to justify medical paternalism because they seemed to generate duties that were mainly intended to minimize physical harm and to improve the patient's physical well-being. Given that the physician possessed specialized knowledge of the physical structures and causal processes of the patient's body, the physician and not the patient was considered most qualified to determine a patient's health care goals and the means to achieving them. On the basis of this reading of the Hippocratic Oath, patients were not thought qualified to shape the course of their individual care because of their general lack of scientific insight into the nature and workings of their own physical condition.

The last 40 years or so have witnessed a trenchant and often passionate critique of the idea that a patient's best interests are limited to or exhausted by his or her physical well-being. Because a patient's best interests must be determined in light of his or her values and life goals and because the value a patient places on physical well-being depends on how it fits within this larger framework of values and projects, the competent and well-informed patient is generally recognized as the best judge of appropriate health care goals. Few would deny the accuracy of the Hippocratic conception of medicine as a science whose goal is the health and physical welfare of the patient nor challenge the claim that physicians must always look after the best interests of their patients. However, the fact that a competent patient lacks specialized medical knowledge is generally recognized to be less important than the fact that each patient is the most qualified judge of the relative value of his or her physical well-being in relation to his or her larger life goals and projects. For this reason, patient self-determination,

as well as its culmination in the doctrine of informed consent, represents the bedrock of contemporary clinical ethics.

As medical science has progressed and physicians have developed the ability to alter the course of a person's life with the use of an array of medical technology, patients have taken a greater interest in determining the way their lives should be shaped.[2] The early seeds of patient self-determination and the doctrine of informed consent began developing as early as the latter part of the 19th century. This period and the early part of the 20th century saw many legal cases involving surgical patients whose consent to excision of tissues had not been obtained.[3] Under prevailing legal theories, these actions were at first considered torts, such as battery or "unconsented touching."[4] As medical and judicial systems evolved, they were then gradually brought under a negligence theory.[4] This change strengthened the growing expectation that informing a patient of the reason for the procedure and obtaining consent for it were proper parts of the physician–patient relationship.[5] In theory, at least, obtaining the patient's informed consent became an essential aspect of the developing standard of care. However, honoring this legal requirement in clinical reality awaited the increased attention to ethical issues that emerged in the late 1960s.

Although we focus here on clinical ethics, no survey of the history of medical ethics can omit society's reaction to the abuses of human beings perpetrated by physicians and scientists in the concentration camps of Nazi Germany. The revelations at Nuremberg led to the promulgation in Helsinki and Geneva of international standards for the protection of research subjects.[6] Unfortunately, these efforts did not prevent blatantly unethical practices in the context of subsequent research by American investigators.[7] As a result, strict statutory protections were established to ensure the informed consent of research participants, including protocol review by institutional committees.[8,9] Public recognition of research abuses led to heightened scrutiny of the physician–patient relationship in the clinical setting and greater support for the concept of informed consent.

Technologic advances once again profoundly influenced the direction of medical ethics, beginning in the later 1960s with the arrival of practical artificial respiratory equipment and, in the early 1970s, with the development of materials that facilitated artificial hydration and nutrition. These advances—combined with social and political changes, including the civil rights movement—culminated in the celebrated legal case of Karen Ann Quinlan in 1976.[10] In the Quinlan decision, the New Jersey Supreme Court established that the right to refuse medical treatment was fundamental and could be exercised on behalf of an incompetent patient by informed surrogates who were knowledgeable about the patient's previous values and lifestyle.[10] The family was found to be in the best position to represent the wishes of their close relative.[10]

In summary, the history of Western medical ethics has featured a transition from the "beneficence" orientation (doing good for the patient) of premodern medicine to the view that the patient must ultimately decide what his or her best interests are after going through a process of informed consent. Both morally and legally, patient self-determination has become the gold standard of modern biomedical ethics. In the next section, we review the prevailing philosophical principles and theories that are often used to further assess ethical problems in modern medicine.

Prevailing Theories and Principles

The term medical ethics, as it is used in contemporary society, is somewhat ambiguous. It may refer to those rules of conduct established by the formal bodies of the medical profession in the course of regulating itself, such as the prohibition of the sexual exploitation of one's patients, or it may refer to novel ethical dilemmas that actually confront health care workers and have no obvious solution in terms of traditional values and ethical codes, such as the removal of life-support systems from irreversibly comatose patients.

Two philosophical approaches dominate the literature. Tracing its roots to the German philosopher Immanuel Kant (1724–1804), the Kantian tradition holds that people have a fundamental right to be treated as ends in themselves and not merely as a means to some other end. The basis of the Kantian view is that each person has the capacity to take on projects and to give a distinctive shape to his or her own life. This capacity must be respected in each individual because the value of all other things is derived from the exercise of this capacity. Patient self-determination and informed consent are, therefore, the preeminent Kantian values for clinical ethics, because without them we cannot freely set the ends for ourselves that give all other things their moral worth. As such, they represent the necessary conditions for treating a patient as an end in himself or herself.

Utilitarianism traces its roots back to the English philosophers Jeremy Bentham (1748–1832) and John Stuart Mill (1806–1873).[11] Utilitarianism is a form of consequentialism, which holds that actions or policies are right in proportion to the extent to which they promote the aggregate happiness or well-being. Whereas the Kantian can claim that physicians have special duties to their patients, which derive from the need to respect their patients as ends in themselves, the utilitarian must argue that any duties physicians owe to their patients are rooted in the fact that fulfilling those duties maximizes overall happiness.

Although the principle of autonomy is commonly regarded as the first principle of contemporary medical ethics, those with a more utilitarian slant believe that it is conceptually balanced by the principle of beneficence; the obligation to do good for the patient.[12] Beneficence is closely associated with the traditional Hippocratic obligation to at least not harm the patient, or the principle of nonmaleficence.[12] Arguments that establish the moral basis of beneficence and nonmaleficence are available both to Kantian and utilitarian theories. The main difference between these theories, therefore, lies not in the principles they recognize but in the way they justify those principles and the way they order them in relation to one another.

ISSUES OF CLINICAL DECISION MAKING

The Provider–Patient Relationship

Self-Determination

Strictly speaking, autonomy refers to the potential for the individual to be self-determining. Self-determination is, in this line of thinking, regarded as a good thing in itself and also as a means to an end. It is the expression of an individual's personality. Self-determination is thought to be the best means of identifying an individual's best interest, a determination that involves the incorporation of that person's values into a decision. This concept suggests that each individual is in the best position to assess aspects of decision making in the context of his or her own value system. In the clinical setting, self-determination is exercised through the informed consent process, which allows the patient ultimately to determine the most individually appropriate health care choice on the basis of his or her own values and preferences.[13]

Because self-determination is regarded as good, certain individuals may be obligated to foster another's self-determination, if they have a certain type of relationship with that individual. An example is a parent who has a unique opportunity to help the developing child realize his or her individuality by helping to prepare the child to make his or her own choices. Choices are not thought to be truly the result of self-determination until they are considered judgments that encompass the person's reflective deliberation. It is implicit that these judgments would then also be authentic and reliable representations of that person's character and values.

The promotion of a patient's self-determination is a major responsibility, and many conditions could prevent its realization in the clinical setting.[14] One of these is the sense of vulnerability that can accompany illness. Physicians and other health care providers are in a powerful position, either to exploit this sense of vulnerability or to reduce it and instead promote a feeling that the patient has some measure of control over the situation. Ensuring the patient's control would be a first important step in promoting the patient's self-determination. A second important step would be to help the patient identify his or her own authentic preferences among the diagnostic or treatment options available.

Confidentiality

Confidentiality is one of the pillars of the Hippocratic tradition,[15] and it is a fundamental concept that still forms an essential aspect of the physician–patient relationship.[4] Although its strong theoretical basis is maintained, however, it is a concept under continuous assault in the clinical setting. Computerized databases containing sensitive information, team coverage of patient needs, and the demands of third-party insurers have all converged to threaten this fundamental aspect of the bond between patient and provider.[16]

At its core, the concept of confidentiality means that all information that the patient shares with the provider during the course of being treated should remain private and confidential; it should not be revealed to those outside the patient–provider relationship. The trusting bond and fiduciary nature of the relationship should allow the patient to feel comfortable when revealing to the provider all information necessary to ensure a comprehensive understanding of the patient's circumstances and a correct diagnosis of the patient's condition, thereby fostering an individually appropriate caregiver response. In turn, as a means to encouraging the patient to be forthcoming, the provider ensures that no one else will come to know this highly personal and perhaps embarrassing information. Currently, "intrusions" are permitted into this relationship. Examples are multiple caregivers who learn of the patient's circumstances in acute care settings and the insurance company that learns of the patient's condition to determine whether reimbursement is warranted. Nonetheless, the notion that those who do not need to know these intimate details of the patient's condition will not know is still an essential factor in the bond that ties the patient to the provider.

The costs of not guaranteeing confidentiality or breaching it when previously assured are significant both for the individual patient and for society. Patients who believe they cannot trust their providers and are, therefore, less than candid in their descriptions are likely to suffer the consequences of an incomplete assessment or even a misdiagnosis of their condition. They lose out on what their physicians may have to offer. Also, providers who breach their duty to keep information confidential fail in their ultimate obligation to act beneficently toward their patients and to do them no harm.[17] Moreover, society as a whole is not served well when individuals in need of medical care feel inhibited or are unwilling to seek that care.

Our legal system has recognized the fundamental requirement of confidentiality between doctor and patient.[4] Under most circumstances, information that passes between doctor and patient during the course of care is "privileged," that is, inaccessible in a court of law; a judge or jury will be unable to learn of it.[4] This special exclusion of possibly relevant information further ensures that patients do not feel inhibited when conversing with providers. Despite the essential drive in our court systems to bring out all possibly pertinent information in an individual case, society has nonetheless recognized that our interests as a whole are better served when patients and providers can feel assured that their discussions are private and confidential.

To further safeguard and protect an individual's health information in an era of technologic sophistication, Congress enacted the Health Insurance Portability and Accountability Act (HIPAA) in 2003.[18] The Privacy Rule of HIPAA limits the ability of health plans, hospitals, physicians, and other covered entities to use and share a patient's personal medical information through oral or written communication, computer transmission, and other communication methods. Many have criticized the burden and cost of the implementation of HIPAA and have expressed concern about its impact on research and clinical care,[19] although few would question the challenges to privacy and confidentiality that exist in modern health care environments.

Nonetheless, in certain circumstances, other societal interests are believed to outweigh the interests served by confidentiality. For example, in the midst of certain public health epidemics, in which the obligation to protect the health of society may conflict with the desire to maintain individual confidentiality, a societal consensus is morally and legally justifiable to breach individual confidentiality under certain limited conditions.[4] One example involves laws requiring the reporting of certain diagnoses to health departments[4] and perhaps the tracing of contacts who may have been exposed to an individual's illness. Another example concerns the need to protect the public from harm. Under the state's "police power" (a constitutional concept), physicians have the obligation to report certain medical conditions, such as gunshot wounds.[20] A third example occurs with respect to the state's obligation to protect its most vulnerable members, also known as the state's parens patriae power, which obliges health care providers to routinely breach confidentiality and report instances of known or suspected child abuse.[4] Although the circumstances permitting the breach of confidentiality are limited, they clearly represent instances in which other significant societal interests make such a breach justifiable and even desirable, despite the potential harm that may befall an individual patient.

The Informed Consent Process

As stated earlier, the informed consent process permits the expression of individual self-determination in the clinical setting. From a legal perspective, this means that providers are obligated to disclose to patients all information that will allow them to arrive at an informed decision about their choices, including such information as the patient's diagnosis and prognosis, a description of the proposed intervention and its risks and benefits to the patient, and the existence of alternative interventions, along with their risks and benefits.[21] In some jurisdictions, there is the requirement that information "material" to that individual patient be disclosed.[21–24] This requirement might oblige the provider to disclose certain details that he or she might not normally discuss under routine circumstances. Overall, it is essential that the physician provides information

BOX 26.1 The Elements of Informed Consent*

I. Competence (a threshold requirement)
   1. Information requirements
   2. Information
   3. Understanding
II. Consent requirements
   4. Consent
   5. Authorization

*Our interpretation of these elements as discussed in this chapter may not in all instances be identical with that of Beauchamp and Childress. From Beauchamp T, Childress JF: Principles of Biomedical Ethics, 3rd ed. New York, Oxford University Press, 1989.

to the patient, so that the patient can consider the options and select the choice that promotes the patient's best interests as the patient assesses them.

Philosophically, autonomy and its promotion both undergird the legal doctrine of informed consent and exert greater demands than the doctrine does.[13] Indeed, one seminal philosophical account of the legal doctrine of the informed consent process exhibits a more detailed conceptual scheme than is found in the law (Box 26.1) as we will discuss below.[12]

Competence

The possession of sufficient capacity to either consent to or refuse a proposed intervention is obviously a "threshold" requirement in the informed consent process;[13] that is, only those patients capable of making health care choices reflective of personal values have the ability to give informed consent and to be considered self-determining. Patients whose decisional capacity is impaired or lost are generally considered unable to integrate factual information with personal preferences and are thus viewed as in need of assistance with choices or even protection from harmful choices, through the use of either a surrogate decision maker or some other method of deciding on care.[13] Therefore consideration of how the "capacity to decide" is to be determined in the clinical setting is essential.

Strictly speaking, the word competence denotes a legal concept,[21] meaning that only a court of law can determine whether to suspend the legal presumption of competency, which generally attaches to all who reach the age of 18 years. The legal presumption of competency enables adults to involve themselves in all fundamental activities of citizenship, including the ability to vote, to contract with another, to write a will, and to get married. It is an empowering concept, covering a range of activities in which the individual is presumed capable of participating. A judicial declaration of incompetency is generally intended to apply globally, that is, to formally disempower the individual in most, if not all, major aspects of controlling his or her life.[21]

The routine assessment of competence in the clinical setting usually has little connection with the sort of global assessment that informs a judicial determination. Rather, competence in this setting is generally judged in the context of whether the patient is capable of either consenting to or refusing a particular proposed intervention.[25] The determination is usually made by an attending physician, sometimes with the assistance of a professional from another discipline, such as a psychiatrist.[4]

Competence to decide about medical treatment may call on various abilities, depending on the demands of the task at hand.[25,26] Yet some general abilities are required in the process of becoming involved in treatment decisions. These include the ability to understand or appreciate the nature of various alternatives and their consequences and the ability to communicate a preference.[27] In reaching a personal preference, one must also be capable of reasoning and deliberation, the latter term signaling that this is a process in which the decision maker's own values are gradually brought to bear on the question.[13] Accordingly, the competent decision maker's values will be more or less stable and consistent over time; they will be values that the decision maker recognizes as his or her own.

Information

The patient with decisional authority (or the properly identified surrogate decision maker) is entitled to all the information available about his or her condition that would be relevant to making a decision about treatment. This information includes not only known or estimated risks and benefits of proposed therapies and their alternatives, but also the implications of having no treatment at all.[28] The free flow of information to the patient, however sensitively it may need to be conveyed, is obviously vital for a valid consent process. Likewise, for the provider to suggest an individually appropriate treatment course for that patient, the patient must be encouraged to communicate openly with the provider.[13]

Full information is one of the legal pillars of informed consent, the other being the free and uncoerced consent itself.[13] Exceptions to such disclosure do exist, namely, the "therapeutic privilege," which permits the physician to withhold information from the patient or to seek consent from an appropriate surrogate when provision of such information would be so detrimental that the result would be counter-therapeutic and would bring about harm.[21] Concern is often expressed about doing harm to the patient, particularly by physicians in fields in which terminal illness is common, about the "inhumanity" of telling the patient the unvarnished truth.[29] However, distinguishing between the inherently unwelcome nature of bad medical news and information that might actually induce negative physical consequences in the patient is important. The majority of patients who have been surveyed desire to have information given, even if it foretells their coming demise.[30] In fact, the real need for the therapeutic privilege is rare if it is employed for its actual intent, rather than for the purpose of affording the physician the opportunity to avoid a difficult discussion. Although it is appropriate that information be imparted in a sensitive manner, imparted it should be, nonetheless.

At such times it might be tempting to speak first with, for example, the patient's adult child to enlist his or her support before an encounter with an older patient. For several reasons, this temptation should be avoided. First, certain classes of patients, such as those who are elderly, are too easily stereotyped as unable to manage emotionally powerful information, even though they may be quite functional in other areas of their lives and lacking any psychiatric history relevant to this issue. Second, the information is, after all, confidential information. Because it is of more concern to the patient than to anyone else, he or she has the right to hear it first. Third, the misguided attempt to enlist the adult child's help could backfire in several ways. The grown child may not be prepared for the loss of a parent, may not enjoy the patient's confidence, or may even have a personal agenda that is in conflict with or opposed to the best interests of the patient. There is no barrier to asking the patient whether it would be desirable for the physician to have a conversation with a particular relative, whether privately or with the patient, so that all three can cooperate in planning for the patient's future. In the final analysis, however, the confidentiality of the patient must be respected.

Understanding

A somewhat different objection to the idea of the patient's rendering informed consent is the argument that some medical decisions are so complex that the lay patient cannot be expected to understand their components, thus calling into question the entire foundation of the informed consent concept. Clearly a medical school education should not be a prerequisite for a workable consent process; fortunately, it is not required. Some patients will benefit from a technical presentation of their situation, but such a presentation is not necessarily required for the consent process to be valid. Information should be conveyed to patients so that they clearly understand how the proposed or available options will affect their lives; patients should be able to clearly articulate and understand the risks and benefits of these options as they concretely pertain to their lifestyles and preferences. Such an informing process is inevitably more satisfactory for both patient and provider when the informer knows the patient personally and understands the values that infuse the patient's life.[13] This is a difficult relationship to achieve, particularly for specialists who only briefly come to know the patient in the context of a specific acute situation. Nonetheless, a certain level of intimacy with the patient is essential to truly adhere to the principles that underlie the informed consent process and to help ensure that the patient truly understands the information of critical relevance to his or her personal decision.[21]

Clinically, certain factors are inherent in both the patient's condition and the environment of care that may lessen or even prevent the patient from understanding the information conveyed, no matter how precisely or sensitively it has been imparted. For example, a provider may be unsure whether a patient in an intensive care unit who has been sedated for pain relief can understand sufficiently to engage in informed consent. In addition, the distracting machinery of the environment or the disrupted schedule to which patients must conform also work against full comprehension and understanding on the patient's part. The provider's duty is to do everything possible to lessen or remove impediments that prevent the patient from fully participating in an informed consent process. Such actions might include temporarily moving a patient to more private or serene quarters to carry on a conversation or perhaps lessening a dosage of pain medication so that, although less comfortable, the patient may nonetheless better comprehend and consider the choices that lie before him or her. As well, the physician should be satisfied that there is no metabolic basis (such as a toxic reaction to new medication) to contribute to the patient's lack of understanding.

Consent

Consent refers to the voluntary and uncoerced agreement of the patient. Consent is a more active process than mere assent or dissent. Ideally, it implies deliberation and perhaps also reflection based on one's own values. Obstacles to truly reflective consent in the hospital include such previously cited factors as the physical conditions commonly associated with treatment for acute illness and the disorientation imparted by impersonal hospital routines and protocols. For example, mechanical restraints may be used for legitimate or illegitimate purposes, but they compromise the sense of control and voluntariness that enables a person to make well-considered choices.

Other sorts of constraints on the patient may be more subtle but no less undermining. Examples range from pressures associated with familial dynamics to concern with the financial consequences of one alternative in comparison with another. In extreme circumstances, the physician may be justified in assuming an active role as patient advocate in attempting to determine whether a stated choice is truly what the patient would want for himself or herself or whether it is reflective of certain pressures inflicted on the patient.

Authorization

An action is authorized when the individual with the appropriate authority gives approval. In accordance with the previous discussion, this individual is either the patient or some appropriately appointed representative of the patient. In certain circumstances, such as when an incompetent patient requires emergency care, the requirement for authorization is usually suspended because the immediate needs of the patient are thought to be so critical that time cannot be expended in locating someone other than the patient to provide authorization.[4] In true emergency situations, when a patient's background is unknown (ie, providers are not aware of any previously expressed wish on the patient's part to decline the type of care about to be provided) and care must be provided immediately to avoid irreparable harm to the patient, the requirement for authorization is generally waived.[4] In such cases, the legal presumption is that (1) reasonable persons would consent to such necessary care, (2) there is no reason to believe this patient would refuse the proposed care, and (3) the time needed to locate an appropriate surrogate might otherwise jeopardize the patient's condition. Such a suspension of consent is temporary, however, because if the patient should subsequently regain capacity or an appropriate surrogate later becomes identified, then, of necessity, authorization would have to be obtained for any future interventions.

In a system preoccupied with documentation and record keeping, the signed consent form presumably giving authorization tends to substitute for the consent process itself.[21] Of course, a form that purports to represent an actual event (that of informing the patient), but does not, is neither ethically nor legally valid. Similarly, verbal consent without a form signed by the patient or surrogate may be valid, although documentation of one kind or another is usually advisable (though sometimes not possible).[31] Of overall importance is the dialogue that supports the documentation and that the consent form theoretically reflects.

Decision Making for Incapacitated Patients

The Importance of Prior Discussions

A common remark about the medical profession in the modern world is that some of the physician's traditional "art" has succumbed to a preoccupation with applied science. Patients are often examined more in terms of their discrete diseases requiring investigation and intervention than as suffering individuals who face the dilemmas and perhaps deterioration brought on by medical crises. Whether or not this criticism is fair or historically accurate, many dilemmas arising out of confusing treatment circumstances could be ameliorated if the wishes of the patient were expressed and discussed with the physician before the patient's loss of capacity.[32]

Given that many people in our health care system do not have regular contact with a physician before the onset of serious illness, the opportunity for such ongoing discussions are not available to everyone.[33] In addition, because few physicians are specially trained to undertake such intimate and personal discussions and because such discussions often require a significant amount of (unreimbursed) time, modern conditions for providing care are often not hospitable to fostering this kind of dialogue.[33]

Still, conversations with patients either by primary care physicians or by specialists who have ongoing relationships with

the patient provide excellent occasions for the practice of what is known as "preventive ethics." Properly conducted and documented, such conversations can provide critical guidance even if they do not determine the nature of treatment for a patient who is no longer cogent. The point of such information gathering is not merely to relieve the professional of legal liability. Rather, when physicians discuss preferences in advance, they are acting in a respectful manner that the majority of patients appreciate. These discussions permit the patient to maintain control and to be self-determining, despite any future loss of capacity that may render the patient nonautonomous.[34]

Advance Directives and Proxy Appointments

Because a patient's prospective treatment wishes often involve matters of withholding or withdrawing life-sustaining treatment and because of the potential for legal involvement when such treatment decisions are made, attempts should be made to document these advance discussions. Such documentation is more likely to provide clarity in the midst of uncertainty or memory lapses and may also provide the type of legal evidence that may be necessary before life-sustaining care can be withheld or withdrawn.[32,35]

Making sure that the medical record reflects the details of discussions between providers and patients is wise, and specific mechanisms exist in most communities to highlight the nature of these advance planning discussions. Depending on the legal jurisdiction, patients and physicians have the opportunity to document such preferences via several methods. (Readers should consult their local medical society for the precise arrangements legally available in their own jurisdictions.)

The two most commonly accepted methods for such advance planning documentation are the living will[36] and the durable power of attorney for health care, also known as the health care proxy.[32] Both mechanisms are used only if the patient loses the capacity to participate in the decision-making process. A living will is a document that patients execute before their loss of decisional capacity. The document serves to record for caregivers and loved ones what the patient's preferences are about future treatment options, in terms of either desired treatment or the treatment the patient would wish to be withheld or withdrawn.[28] Both afford the patient and provider ample opportunity to specify particular wishes and preferences, although the benefits of each method differ. Depending on patient circumstance, one method may be preferable to the other. Typically, such documents detail the types of interventions that patients wish to avoid as the ends of their lives approach. Many states have specified the precise form and content that such documents must follow to be legally binding; other states are generally more concerned with the clarity and the substance contained in the document.[28]

In general, when executing a living will, the patient should be as explicit as possible, using precise language that is not susceptible to differing interpretations or misunderstanding. For example, language discussing "heroic" or "extraordinary" care might have different meanings to different interpreters. If a patient is specifically concerned about such potentially intrusive interventions as mechanical ventilation or artificial nutrition and hydration, then the patient should state this concern precisely.[28] Patients are also advised to specify the precise physical circumstances under which they would want to trigger such withholding or withdrawal.[28] For example, they should make clear whether they desire that permanent loss of consciousness or unremitting pain be present before treatment is withheld or withdrawn. The average lay person would of necessity need the input of a medical provider, both in terms of deciphering what future options may face the patient and determining the benefits and burdens of each option.

Even the most precise and specific living will may not cover every possible option that may confront the incapacitated patient; in addition, certain decisions may not be discernible from the contents of the document.[36] Written documents are also helpful only if they are available (as opposed to being locked away in a drawer) and actually enforced. Therefore, many individuals choose to accompany or even replace their living wills with a durable power of attorney for health care or health care proxy.[31] Such a mechanism allows the patient (known as the principal) to legally empower another individual to make whatever treatment decisions the patient would have made had the patient had capacity.[33] Such a mechanism ensures that a healthy advocate will be legally available to assert the patient's prior wishes and also permits flexibility and interpretation should a situation arise that the patient had not previously addressed.[33]

Surrogate Decision Making: Who Decides and on What Basis?

Surrogates or agents specifically appointed by the patient in advance usually have the moral and legal authority to substitute for the patient if the patient becomes incapacitated.[33] Depending on the jurisdiction, legally binding mechanisms can be used before the loss of capacity. In some circumstances, court appointment of a surrogate may be necessary.[4] In some jurisdictions, the fact of biological or spousal connection may be sufficient to both morally and legally empower the surrogate, regardless of a lack of a previously executed document or the lack of court involvement.[4] Once an appropriate surrogate is identified, that person has the responsibility to determine the best course of action for the now incapacitated patient. Just as for the patient, it is essential for the surrogate to go through an "informed consent" process with the patient's providers to ascertain all of the clinically relevant details necessary to understanding the patient's circumstances.[21] However, such decisions clearly extend beyond the realm of medicine and usually involve value judgments that the patient brings to the process.

When a surrogate substitutes for the patient, the ideal method of making a decision is to consider and account for those values that defined the patient while capable, infused that patient's actions, and determined the patient's lifestyle.[33] The ideal requirement is that the surrogate render a "substituted judgment" on the patient's behalf, making the same sort of choice the patient would have made had he or she had the capacity to participate.[33] This is no easy task, although the existence of a well-documented advance directive usually provides the surrogate with the type of information necessary to render such a judgment. In some circumstances, the surrogate may have to interpret or surmise what the patient would have wanted, on the basis of the surrogate's knowledge of the patient as a person and how the patient lived his or her life.[33] In some jurisdictions, such surrogate "interpretations" may not be legally acceptable, depending on the nature of the surrogate appointment and the clarity of the patient's previously expressed wishes.[33]

If such a substituted judgment is not possible, either because the surrogate has insufficient knowledge of the patient as a person or because whatever knowledge is available sheds little light on the current choice at hand, the surrogate would then be morally obligated to make the choice that promotes the patient's "best interests." [12] This judgment is meant to incorporate considerations of a more "objective" nature, such as the patient's prognosis, the patient's pain and suffering,[37] and the patient's present and projected quality of life relative to the life

the patient previously experienced, rather than a derogatory evaluation of personal worth in comparison with other members of society.[28] In most circumstances, particularly those involving decisions to withhold or withdraw life-sustaining treatment, surrogates work with providers to determine the patient's best interests in light of what can be done for the patient's current situation, the patient's underlying health and prognosis, and the burdens the patient may experience as a result of any measurable benefits to be achieved.[27] However, in certain jurisdictions, the legality of such judgments may be challenged, and a concern about bias or prejudice always exists when discussions about "quality of life" emerge.[12]

Particularly when discussion of the patient's best interests focuses on treatments that might be "futile" and in no way beneficial to the patient, there is the potential for tremendous discord because the precise meaning of the concept of "futility" may change, depending on the specific orientation of the decision maker.[38] For example, clinicians may view a course of treatment as "futile" if it does nothing to address the underlying condition that forms the subtext of the patient's current situation.[39] Yet others may regard "futility" as only apparent if no measurable benefit of any sort can be derived from a particular intervention.

Treatment Decisions Requiring Special Attention

"Do Not Resuscitate" Orders

Decisions as to whether to attempt resuscitative measures if a patient experiences a cardiac or pulmonary arrest should, theoretically, be no different from other patient treatment choices. Ideally, a provider would discuss the possible options and their risks and benefits with the patient in advance of any intervention, so that a decision to initiate cardiopulmonary resuscitation (CPR) would reflect the patient's desire that the provider intervene in such circumstances.

However, the reality and mythology that have developed around acute care decisions to resuscitate or to not resuscitate a patient have, for several reasons, brought this particular treatment situation into a different category. Cardiopulmonary resuscitation protocols for the restoration of oxygenation and circulation have been remarkably successful, in terms of both their standardization (by the National Research Council in 1966) and their public acceptance: by 1977, more than 12 million people had been trained in cardiopulmonary resuscitation.[40] Second, because the use of cardiopulmonary resuscitation is often brought on by emergency circumstances, there may be no prior discussion of patient preference upon which to draw and often no knowledge of the patient at all. Third, decisions not to resuscitate require consent not to intervene, which is contradictory to the normal situation of consent to intervene in a particular circumstance. "Do not resuscitate" (DNR) orders require a conscious and, perhaps courageous, effort on the part of a team to recognize before a catastrophic event the inevitability of its occurrence and the likely outcome of intervention. Such forethought must happen in a climate that does little to foster discussion of death and does much to encourage the escalated use of sophisticated acute care technology merely because of its existence, rather than because of its likely benefit.[41]

In one state (New York), legislation exists to actually define the legal parameters of DNR orders,[42] but in most jurisdictions, the use of such orders must, of necessity, become a more familiar and comfortable process for those who often confront patients in the midst of an arrest. As with any other treatment decision, the ethically preferable process for making the DNR decision would be to undergo an informed consent process with the patient or, if the patient is incapacitated, with an appropriate surrogate. In the course of such a discussion, the provider's duty would be to disclose the likelihood and definition of "success" for a person in this particular patient's circumstances and would, as well, require a thorough discussion of all possible aspects of the intervention, including the possibility of connection to a ventilator or injury resulting from the aggressive nature of some resuscitation attempts.[37] Although many patients unexpectedly have an arrest, other patients are likely to fall into a category of arrest "suspects"; their clinical condition would dictate that a discussion of DNR orders, among other possible treatment interventions, would be mandatory as soon as possible in their hospitalization.[36] The goal is to solicit patient input and foster self-determination before the patient loses the capacity to participate in the decision-making process.[43]

Ideally, advance discussions of DNR orders would come in the context of a more general discussion of future treatment options for the particular patient's condition. However, it is possible that permission will be given to place a DNR order in the patient's chart, yet the patient or the surrogate will nonetheless insist on other types of aggressive care that may seem inconsistent with the decision to consent to a DNR order. Such inconsistency may be due to a lack of mutual agreement or understanding about the goals of the treatment process; it may also be the result of a reasoned decision on the part of the patient or surrogate that some interventions are worth certain risk but others are not.[37]

For example, a patient may be willing to undergo the toxic side effects of aggressive, experimental chemotherapy or the bruising recovery that may follow significant surgery yet be unwilling to risk the possibility of winding up dependent on a ventilator as a result of a resuscitation attempt. From the patient's or surrogate's perspective, such choices may not appear inconsistent, although providers would be wise to have the patient or surrogate vocally express reasons for the specific treatment choices made, to ensure full understanding and comprehension by both the patient and the provider.

Of particular concern and difficulty are surgical candidates with preexisting DNR orders in place. Such patients typically have underlying chronic or terminal illnesses that provide the basis for the patient's previous decision to consent to a standing DNR order. However, there may be circumstances in which such patients nonetheless become candidates for surgical intervention, perhaps for palliative purposes or for reasons unconnected to their underlying disease process. In such cases, the decision as to whether the DNR order will remain in place during the surgical intervention should be thoroughly discussed by the patient, surrogate (if involved), surgeon, and anesthesiologist, if possible. It is of critical importance for patients or their surrogates to realize the distinct nature and characteristics of cardiac arrest during the perioperative period. In particular, the facts that cardiac arrest during that period is often directly linked to either the surgical or anesthetic intervention and that resuscitative interventions during such arrests have a very high success rate must be made clear to a patient who seeks surgery for certain, specific objectives. For many providers, the concept of a DNR order during surgery seems incompatible with professional and moral obligations to a patient during the surgical procedure. The often direct link between the caregiver's actions and the patient's arrest creates an inescapable obligation for many providers to intervene in the case of arrest.

An evolving approach to this difficult dilemma involves the protocol of "required reconsideration" whenever a patient with a DNR order in place becomes a candidate for surgery.[44,45]

Such an approach demands active reconsideration of the DNR decision before the surgical intervention. Such discussion must necessarily involve the patient and the patient's surrogate, if appropriate, and should carefully review the distinct quality of perioperative arrest as well as the goals of the patient for the surgical intervention. In most cases, an accommodation can be worked out whereby a temporary suspension of the DNR order is agreed on, with specific parameters set for its reinstitution, either depending on the cause of the perioperative arrest or because of circumstances that arise after the patient's recovery from the surgical intervention. Such a protocol should reflect the patient's values and wishes to the extent possible. If an acceptable agreement cannot be worked out, the involved physicians may either have the option to proceed with the surgery, with a carefully delineated DNR order in place, or choose to decline to intervene, with the obligation to assist the patient in accessing other providers who may be willing to perform the operation despite the constraint of the existing DNR order.

Ultimately, when considering the applicability of a DNR order for a particular patient, one must remember that, although the decision not to resuscitate might logically be accompanied by other choices about reducing the aggressiveness of care, this does not necessarily have to be so. A patient may logically, ethically, and legally desire intensive care intervention, yet be unwilling to be resuscitated should an arrest occur. Each type of intervention should be considered in its own distinct context, and the merits of any particular intervention should be judged; an appropriate surrogate must decide on behalf of the patient, on the basis of an evaluation of what promotes the best interests of the patient.[13]

The "Never" Competent

Decision making for patients who never possessed capacity is similar to the process described for those who congenitally have serious learning difficulties or are severely impaired or for other reasons have never had the opportunity or ability to develop a system of values and preferences that could be used to direct the course of care despite the lack of capacity. Thus "substituted judgment" cannot be rendered on their behalf because they have never possessed the original judgment.[13] Rather, the needs and course of care for those never competent must be based on an objective determination of their specific circumstances. This decision should be based on an examination of the patient's diagnosis and prognosis as well as the benefits and burdens associated with the various care options. The assessment of benefits and burdens includes consideration of pain, suffering, palliation, extension of life, and other determinable measures. In all cases, these considerations are limited to the benefits and burdens imposed on the individual patient. To the extent that this involves an assessment of the patient's "quality of life," this assessment is limited to determining whether the benefits of continued care for the individual patient outweigh the burdens of care experienced by that patient. This does not involve an assessment of the patient's quality of life in comparison to what might be achievable by others.[38]

As surrogates, parents cannot call on their child's background or lifestyle to form a "substituted judgment." The natural course of surrogate decision making is one that relies on an evaluation of the child's best interests, and in such determinations, the parents are generally afforded significant latitude to discern the nature and course of their child's care.[32] When parents' decisions clearly contrast with promoting their child's health and medical well-being, others may be empowered to challenge the choices.[4] For these reasons, should parental conduct appear concretely neglectful—or even abusive—of a child's needs, grounds might be found to disempower the parents and allow others to decide on the child's behalf. Principled choices of parents that they could assert for themselves, such as prioritizing religious faith above risk of death, are considered unacceptable when applied to the children of such individuals.[4] Therefore, parents who subscribe to the Jehovah's Witness faith may refuse lifesaving blood transfusions for themselves, but not on their child's behalf. Parental empowerment does not include the ability to risk death for a child who has not yet attained the capacity to choose such a course for himself or herself.[4]

Children who are on the cusp of capacity (ie, those approaching the murky line that separates adolescence from adulthood) may in certain circumstances be considered to possess sufficient judgment to participate in the decision-making process.[4] Even if their consent is technically not required, from a moral perspective their concerns and desires should warrant serious attention and play a significant, if not determinative, part in the deliberation process.[32]

Critical Care and End-of-Life Decision Making: Special Concerns

The circumstances that surround critical care and end-of-life decision making are often made more controversial and problematic for both patients and providers because of uncertainty about the moral and legal permissibility of certain actions or decisions. This is particularly true when death is a likely or even intended consequence of a choice. In addition, many philosophically based terms are sometimes interjected into discussions without universal clarity or certainty about their intended meanings. For example, comparisons such as ordinary versus extraordinary or withholding versus withdrawing sometimes conjure up misguided notions about what is or is not acceptable in the course of delivering patient care.[46] The unnecessary inclusion of confusing terms often clouds the underlying reasons and justifications for choices made either by or on behalf of a patient.

For patients who possess decisional capacity, the choice of whether to initiate, withhold, or withdraw care is one solely within the orbit of the patient's value system, even if the likely or intended consequence of the patient's choice is significant harm or even death.[46] Despite the discomfort that many providers have with this concept, it is one in accord with the moral and legal frameworks supporting patient autonomy.[47] Thus, a patient can decline the option of life-prolonging surgery, can ask that mechanical ventilation be withheld if respiratory distress occurs, and can even ask for the withdrawal or cessation of such life-prolonging measures as dialysis, artificial nutrition, and hydration (in most jurisdictions), as long as the patient possesses the capacity and information to assess the benefits and burdens of such choices.[38,47] However, in some jurisdictions, such choices may nonetheless require a legal process to carry out the request.[4] This step may stem more from concern about injecting safeguards into such decision processes rather than any move away from fundamental moral or common law support for such patient decisions. Moreover, in most jurisdictions, such patient requests would be accorded respect even if they were transmitted through an appropriately executed living will or appointed surrogate once the patient loses decisional capacity.

Questions of whether there is any moral or legal difference between withholding and withdrawing care, whether the care involved is of an "ordinary" versus "extraordinary" nature, or whether it is acceptable to omit an action that may lead to the

patient's death but not to purposefully act in such a way that may bring about death raise concerns about word origins and their current meaning and significance in the context of care. Many of these terms, although perhaps drawing some useful distinctions in their earlier, theologic origins or perhaps pointing to areas that warrant additional attention, in and of themselves do not determine the morality or legality of the choice carried out.[37] For example, a provider who makes the distinction that "extraordinary" care may be withheld or withdrawn, yet "ordinary" care must be initiated or continued tells us little about the precise nature of the care or its effect on the patient at issue.[28,47]

Although in simpler times distinguishing what was ordinary from what was not perhaps seemed easier, the sophistication of the machinery or commonness of its application in today's sophisticated acute care environment creates situations in which an appropriate intervention for one patient may not be acceptable or even beneficial to another similarly situated patient. In such determinations, the importance is not in what the care is labeled but rather how it affects that patient and fits into the patient's perspective in terms of benefits versus burdens.[37] One patient may believe the receipt of artificial nutrition via a gastrostomy tube is desirable and acceptable, whereas another may view it as extraordinarily burdensome and inconsistent with his or her view of what best suits his or her interests. Such differences between the patients in the meanings that are assigned only underscore how physicians and patients may view choices differently. A provider should not presume that a patient regards a certain course of care in a way similar to the provider.

Similarly, attempts to explain omissions or withholdings as being morally or legally permissible and actions or withdrawals as impermissible only confuse and distort the reasons and justifications that will make such choices either permissible or not. Merely because a provider decides not to initiate a process does not necessarily relieve that provider of responsibility if the outcome was one intended or foreseen.[28] This is particularly so in the context of patient–provider relationships, in which the provider owes duties to the patient and in which a decision not to act may be as influential and responsible for patient's outcome as any concrete activity that the provider undertakes. For example, a decision to withdraw artificial ventilation from a patient, which may or may not bring about the patient's death, is not necessarily any less permissible or unacceptable than the choice to omit or withhold its use in the first place. Some people may believe a distinction exists between an act that is believed to cause the death of the patient and one that merely holds back a possibility from an already dying patient, but from a moral and legal point of view, arguments used to withhold treatment should be equally justifiable and binding as decisions to withdraw or cease.[38] Judicial decisions that have addressed this matter concur that no logical distinction exists.[38]

A decision not to initiate care can be viewed just as "causative" in terms of patient outcome as any act of withdrawing, if the outcome was one that was foreseen and could have been avoided if a different choice was made. In such circumstances the important point is not so much whether one is acting or omitting or withholding or withdrawing, but rather why one is undertaking that course and whether it can be justified in terms of the patient's preference or the best interests of the patient as determined by an appropriate surrogate.[32] Moreover, many commentators have clarified that decisions not to initiate care, because of fear that, once started, a treatment cannot later be stopped, may actually harm certain patient populations.[28] Some patients might benefit from a trial of therapy, even if later on the therapy may no longer serve the patient's interests and should be withdrawn in the name of beneficence, nonmaleficence, or patient autonomy. Not to have tried an intervention for fear of not being able to stop it lacks logic and defies the nature of providing medical care, which often means that certain risks are undertaken for certain potential benefits. One must always remember the provider's duty to relieve pain and suffering and not to cause harm to the patient.[28]

Nonetheless, certain actions on the part of providers and requests on the part of patients trigger additional scrutiny and other societal interests that may take priority over a pure vision of patient autonomy or provider beneficence. For example, societal interests in the sanctity of life and concern for the prevention of suicide are generally used to deny support for patient requests for suicide assistance[38,48] or for provider services to purposefully administer a medication or another intervention for the purpose of causing the patient's death (what is sometimes known as "active euthanasia").[38,48] Although much sympathy is generated for the plight of desperately ill patients seeking relief from their terminal conditions and often grand jury investigations of such matters fail to indict involved parties,[28] most states maintain strict theoretical sanctions and legal prohibitions on provider involvement in such cases.

In two decisions the U.S. Supreme Court reiterated the traditional American condemnation of suicide and upheld the value of the individual human life by unanimously striking down two lower court decisions that had found a constitutional right to die with the aid of a doctor. Although the Court ruled that the constitution does not guarantee Americans such a right, it left the individual states with the power to determine the legality of physician-assisted death.[48,49] In October of 1997, the state of Oregon enacted the Death with Dignity Act into law, becoming the first state to legalize and regulate physician-assisted death. The state's first legal physician-assisted death took place on March 24, 1998. In 2006, the Supreme Court specifically addressed a challenge to this Oregon law in the case of Gonzales v Oregon,[50] ruling that the United States Attorney General could not enforce the Controlled Substances Act against Oregon physicians who prescribed drugs for assisted suicide in the terminally ill, in accord with the Oregon law. The Court affirmed the ability of a state to pass legislation permitting physician-assisted death under defined circumstances.

As these events in Oregon attest, we may be witnessing a shift in societal consensus about how to prioritize values when fundamental questions about the meaning of life and death are the issue. The debate concerns the precise role of the physician and the nature of physician–patient relationship in an era of such sophisticated and often partially successful care that it is sometimes difficult to discern whether, on the whole, an intervention would benefit or burden a patient. Some argue that supporting physician involvement in the intended death of a patient destroys the essential role of the provider as healer and would create an air of uncertainty that would ultimately damage the trust that exists between patient and provider.[27] Others believe that one essential role of the modern physician is relief of suffering, and the possibility of such physician involvement might encourage otherwise desperate patients to try one more round of therapy or intervention, comforted by the knowledge that failure would not lead to unremitting pain or unendurable misery.[27] As the effects of Oregon's Death with Dignity Act become clear and as more states move to enact legislation, the debate over these issues will intensify.

Although the Supreme Court found no constitutional right to physician-assisted death, the Court seemed to recognize the

existence of a legitimate conflict between the needs of some terminally ill individuals and the larger interests of society. In fact, some have argued that, although patients cannot legally ask physicians to end their suffering by invoking a constitutional right to assistance in dying, patients may very well have a constitutional right to palliative care.[51]

However, all judicial decisions that have examined cases of the withholding or withdrawal of patient care have distinguished such circumstances from cases of active euthanasia or other forms of killing or suicide.[28] No physician who has participated in treatment decisions to withhold or withdraw care has ever been found criminally liable and responsible for the patient's death.[28] Cases of assisted suicide and euthanasia have been distinguished on the basis of the nature of the patient's prognosis and clinical circumstances. Patients who refuse care or ask for its withdrawal and who will then die from their underlying conditions are not considered to be committing suicide, nor are the providers who respect such decisions considered to be assisting suicide or killing the patients.[49]

One final distinction deserves examination: the administration of pain relief with the knowledge, though perhaps not the intent, that such medication may ultimately shorten the patient's life or even cause the patient's death. Under the theologic doctrine of "double effect," such action is usually explained and justified by referring to the primary effect and intent of the action, that of relieving pain, while recognizing the possibility or even likelihood that another effect, that of the patient's shortened life or even death, is a possible result of the action.[12] The action is considered permissible because the intent was to relieve suffering, not to cause death.

Theoretically, in current legal climates, the knowledge that an outcome is possible—though not necessarily intended—might still lead to liability on the part of the provider.[46] However, we know of no successful litigation against a provider for administering pain relief to a patient with significant need, even if the outcome of the relief also meant an earlier death for the patient. Justification for such actions are usually, in current climates, based on either the patient's choice to risk death to achieve pain relief (or a similar decision by an authorized surrogate) or on the widely recognized additional role of the provider to relieve pain when possible. Such provider actions are generally distinguished in legal forums from more common examples of "active euthanasia."[36] In fact, many commentators have suggested that it would be unusually cruel and harmful to a patient to respect the patient's wish that care be withdrawn or withheld, yet not provide him or her with pain medication to ease the transition to death.[37]

Artificial Nutrition and Hydration

The use of artificial means to nourish and hydrate patients who are unable to take in food on their own has generated significant debate concerning definitions of "medical care" versus "comfort care."[36] For many caregivers, the question raised is whether there are any limits to patient self-determination or provider obligations in the context of the physician–patient relationship. Many believe that withholding or withdrawing "medical care" in accord with a patient's self-determination is permissible, whereas the provision of artificial nutrition and hydration represents the intrinsic "caring" nature of human interaction and, therefore, must always be provided as a fundamental demonstration of humanity and compassion.[41]

All courts of law that have addressed this question, including the U.S. Supreme Court, have equated the use of artificial nutrition and hydration with the use of other medical technologies and "high-tech" progenies, such as mechanical ventilation and dialysis. They have thus permitted its withholding or withdrawal in accord with the interests of patient self-determination. In the political arena, some legislatures have even made exceptions to their living will or health care proxy legislation to make allowance for such a distinction[4] and, in some circumstances, to refuse to grant permission for patients or surrogates to have such care withheld or withdrawn.[4] Given the sometimes passionate nature of the debate and the pluralistic nature of our society, a compromise has been reached in many instances that recognizes the right of individuals to determine the course of their care, particularly when providers feel unable to abide by such patients' requests. This accommodation usually calls on either individual or institutional providers to disclose to patients and families, before the onset of a relationship, the perspective of the provider about this type of care.[32]

Dilemmas in Team Decision Making: The Role of the Anesthesiologist

Dilemmas in the clinical setting may emerge not only from interaction with patients and families but also in the relationships that are forged under a system of team coverage of patient care needs. Particularly for the neurosurgical patient–whose problems may span the disciplines of neurology, surgery, and anesthesiology, among others–the collection of providers who join to meet the specific needs of an individual patient may generate interdisciplinary disputes, rivalry, or even antagonisms, which may subtly, or perhaps not so subtly, affect patient care. In this regard, the role of the consultant anesthesiologist is briefly examined as just one example.

A cardinal rule of the Hippocratic tradition, which emphasized the appropriateness of calling in consultants, was that physicians were never to disagree with their colleagues in front of the patient.[15] In our own time, the notion of a "united front" before the laity has perhaps a greater command over medicine than in other professions, so that even when physicians are in substantial disagreement over the appropriate course, they rarely present their disagreement to the patient. Considering that the patient whose condition is serious enough to warrant consultation is often in an emotionally vulnerable position, this policy might not seem to be an unwise one.

However, modern legal analysis and case law support the independent authority and responsibility of the anesthesiologist as separate and distinct from other members of the healthcare team. Although the anesthesiologist may have little or no participation in the initial decision to intervene surgically, he or she has separate responsibility to review the patient's condition and to obtain an independent informed consent directly from the patient or the patient's surrogate for the use of anesthetics. In effect, the anesthesiologist must review the feasibility of anesthetic intervention for the particular patient and separately determine whether the surgery should proceed on the basis of this review. The actions or determinations of the anesthesiologist are no longer viewed as subordinate to those of the surgeon. The anesthesiologist has an independent duty to the patient, separate and apart from that of the surgeon or any other member of the health care team. Such duty carries through the entire perioperative period, until such time as the anesthesiologist discharges the patient from his or her care.

Ethical Issues in Innovative Neurosurgery: Role of the Anesthesiologist

The anesthesiologist's specific duties toward the surgical patient, as discussed in the previous paragraph on team decision

making, also extend toward patients undergoing experimental or innovative procedures. Such innovations may occur within or outside of formal clinical studies, as we explain here. Perhaps even more pressing than during standard operations, the anesthesiologist may function as an important consultant to the neurosurgeon (and perhaps, sometimes, as an advocate for the patient) by helping the neurosurgeon appropriately identify those procedures that are, in fact, experimental enough to warrant additional scrutiny and review. The additional review and patient protections required for experimental surgery may not always be apparent to the neurosurgeon, because they traditionally have not always been recognized by the surgical profession in general. Prior research has shown that surgeons generally do not readily identify those innovations that are in fact experimental or that amount to research with human subjects; they do not often submit their innovative procedures to rigorous testing in the form of (controlled) clinical trials nor their innovative surgical techniques to their institutional review boards (IREs) for prior review and monitoring.[52,53]

Every day, US surgeons modify existing operations, attempting to improve their techniques and outcomes. Sometimes this modification occurs on an individual patient basis; sometimes a group of patients undergoes an innovative procedure. Sometimes a group of patients serves as a prospective or historical control. Innovative operations find their way into the professional journals and conferences as case reports, case series, or case-control studies, and a very small percentage as prospective clinical trials. But many, perhaps most of them, have one thing in common: they were performed under the heading of therapy, not of research. Whether they started out as spontaneous technique modifications necessary for a particular patient situation or as informal studies with or without protocols, most of these studies were done without prior IRB review and without specific research consent from patients.[54] In some instances, such review and consent would have been appropriate and necessary, but uncertainties and disagreements exist among surgeons as to what constitutes routine variations on surgical techniques that require no prior approval and what are new or innovative techniques warranting IRB review and patients' specific informed consent for an experimental procedure or a research study.[53,55] This area is where the neurosurgical anesthesiologist can become an important ally of both patients and science, by helping surgeons to correctly identify those innovations that would better be performed under the heading of research. It is, therefore, of paramount importance that anesthesiologists be familiar with the definitions and regulations for human subject research and with the workings of the local IRB.

Necessary knowledge to make judgments about research and innovative practice can be found in documents from both federal agencies and professional societies. The oversight of research, innovation, and standard health care involves multiple jurisdictions: the separate states; federal agencies involved with regulation, funding, or reimbursement; professional societies; and health maintenance organizations (themselves operating under state and/or federal rules) may all be involved. Increasingly, the courts may play a significant role.

At the federal level, there are the regulations of the U.S. Department of Health and Human Services (DHHS) and its Office of Human Research Protections (OHRP; formerly Office for Protection of Research Risks [OPRR]). DHHS has issued a Code of Federal Regulations Title 45 Part 46, on "Protection of Human Subjects."[9] "45 CFR 46," or the Common Rule, so called because it has been adopted by all but 17 state agencies, provides formal definitions of research and the human subject of such research. Subpart A of 45 CFR 46, or the Federal Policy for the Protection of Human Subjects, sets out definitions and general regulations for performing research with human subjects. Research is defined as any systematic investigation designed to develop and contribute to generalizable knowledge. Human subject is defined as a living individual about whom an investigator obtains either (1) data through interaction or intervention (eg, surgery) or (2) identifiable private information. The other subparts of the document specify what additional guidelines are to be followed in case of vulnerable populations.

The Common Rule applies to all research involving humans that is conducted, supported, or otherwise subject to regulation by any federal department or agency. In other words, any institution that receives federal funding falls under and must abide by the Common Rule. This makes the DHHS ultimately responsible over all human subject research that is directly or indirectly funded by federal money. DHHS thus technically has jurisdiction over all surgical clinical research as well, as long as it is conducted in health care institutions that receive federal money. DHHS's definitions of research and human subject are applicable in surgery as much as they are in noninterventional specialties. However, the problem lies in the fact that not all surgical research activities are defined as such and thereby escape the overview of local IRBs and, ultimately, of the Office of Human Research Protections and DHHS. Part of the reason is that surgeons do not always recognize their efforts to improve surgical technique as research (which sometimes is appropriate, sometimes not) and another part is that surgeons are not always adequately aware of the fact that DHHS definitions sometimes do apply to their innovative activities. The lack of awareness is most probably due to inadequate familiarity with the Common Rule and its definitions and regulations.[52,53]

The U.S. Food and Drug Administration (FDA) gained regulatory powers to ensure the safety and effectiveness of new medical devices and medications. The law stipulates that all medical devices manufactured after 1976 are subject to an approval process and then subjected to regulatory controls according to their level of patient risk. However, unless an innovative surgical technique involves such an investigational device or an experimental drug, the FDA has no responsibility or jurisdiction over surgical research.[56]

Local agents under the DHHS Common Rule that do have formal jurisdiction are institutional review boards (IRBs).The IRB, also known as the research ethics committee, has been the local protection mechanism for human research subjects since the latter part of the 20th century. IRBs have the authority and responsibility for approving or disapproving proposals to conduct research involving human subjects.

Voluntary guidelines have been issued by surgical societies such as the American College of Surgeons (ACS). The Committee on Emerging Surgical Technologies (CESTE) of the ACS has issued statements specifically addressing the ethical and responsible implementation of new surgical techniques and innovations.[57]

These self-imposed guidelines for emerging surgical technologies and their application to the care of patients were formulated in 1994 and 1995. In part, they read as follows:

1. The development of a new technology must be accompanied by a scientific assessment of safety, efficacy, and need …
2. Diffusion into clinical practice requires appropriate education of surgeons and evaluation of their use of the new technology …

3. Widespread application of new technologies must be continuously assessed and compared with alternative therapies to ensure appropriateness and cost-effectiveness through outcome studies.

The introduction of new technology to surgeons and the public must be done ethically in accordance with the Statement on Principles of the American College of Surgeons.

These principles require prior and continued IRB (or equivalent) review of the protocol, full description of the procedure, and informed consent of the patient. However, current guidelines remain open to individual interpretation and are not restrictive in character. Other than issuing a reprimand or expelling an unruly surgeon from the Fellowship, the ACS does not have responsibility or legal jurisdiction over the practices of its Fellows, let alone over U.S. surgeons who are not members of the ACS. As such, the Statement on Emerging Surgical Technologies is not legally binding. Other surgical organizations, such as the Society of University Surgeons (SUS), have also attempted to address the challenge of surgical innovations by offering guidance.[58]

Until definitive guidelines or laws regulating innovative and experimental surgery have become established, it is up to individual neurosurgeons, aided by their team, including neuroanesthesiologists, to determine which procedures should be introduced as innovative practice and which should be submitted to more formal scrutiny, such as IRB review and other oversight mechanisms.

Ethics Related to Brain Death

The ancients often regarded the heart as the center of vitality, and for millennia the determination of death was the absence (or cessation) of a heartbeat. In the event of severe brain damage, either traumatic or cerebrovascular, cessation of the respiratory drive resulted in breathing cessation and rapid death by cessation of heartbeat.

In the mid-twentieth century the invention of the positive pressure ventilator led to the technical ability to maintain respiration, and, therefore, cardiac function, in the absence of much of or even all brain function. Further development and wider availability of ventilators and the evolution of intensive care units (ICUs) events led to increasing numbers of cases in which pulmonary and cardiac function were maintained in the face of devastating brain function and no chance of recovery. This led to confusion about what defined death in such cases. The determination of death had multiple ethical, legal, and medical implications, and medicine was unsettled.

In view of these uncertainties the ensuing decades saw new criteria developed to define death as brain death, not cardiac function cessation. Discussions of brain death as the redefinition of death occurred initially in France ("coma dépassé") in the 1950s and 1960s, and the initial formal definition of "irreversible coma" in the US was made by an ad hoc committee at Harvard, which resulted in publication of the Harvard Criteria (1968). Research to determine what constituted brain death continued for years, to assure that a "brain death" definition of death ensured irreversibility of the medical state. Finland was the first nation to pass a law that death would be defined by brain death.

Neuropathological studies of subjects who had been in prolonged coma revealed that the brainstem, locus of the respiratory drive and other brainstem reflexes, was always involved significantly and extensively in cases in which brain injury had resulted in (irreversible) brain death. Thus the formal criteria to determine death evolved with specific procedures and examination requirements to assure that there were no other reasons for unresponsiveness than destruction of brain tissue. The presence of potentially reversible states such as hypothermia, residual anesthesia, or drug overdose had to be ruled out. A careful neurological examination at two time points 24 hours apart, determined by two clinicians with expertise in the examination for determination of brain death, became standards for such determination of death. Procedures that were specified for assessing absence of brainstem reflexes, such as respiratory drive, corneal reflexes, and caloric responsiveness, became standardized.[59] Most hospitals and hospital systems reviewed and approved brain death criteria to be applied whenever the clinical situation presented itself.

Of course, not all cases of protracted coma or unconsciousness will meet criteria for brain death. The term persistent vegetative state has been used to describe cases in which there is destruction of sufficient regions of brain to preclude recovery to full consciousness, but preservation of brainstem function sufficient to enable maintenance of respiration. The public's understanding of the difference between brain death, especially brainstem death, and a chronic vegetative state in which people do not recover consciousness is frequently confused, aided by press or lay spokespeople who are unfamiliar with the differentiation of the two terms and for whom the term "vegetable" carries a striking negative as well as disrespectful connotation. Confusion, religious dicta or opinions, and multiple legal issues have also clouded full understanding. Even the term "brain death" as somehow differentiated from "death" (when we would argue they are inseparable) is a difficult term to explain. Widespread legal cases such as that of Terri Schiavo[60] have also led to misunderstanding and beliefs that people who are neurologically devastated will somehow awaken, given enough time, hope, and prayer. Federal, state, and hospital rules and regulation regarding brain death and criteria for determining the same have aided the clarification in individual cases as families and friends confront these issues suddenly and in a state of emotional upset. Many religious groups have established rules for dealing with the new medicine of brain death, and consultation with the chaplain or the family's religious leader may be helpful in acceptance of facts of a case.

Neurosurgeons and neurologists (who may, along with some anesthesiologists, be part of a hospital brain death consultation team) are familiar with persistent vegetative states (PVS) and the evaluation of the unconscious patient and determining a prognosis in the case of PVS. If the cause of the unconsciousness is trauma, up to 6 months of unconsciousness is necessary to term someone as in a persistent vegetative state. If the cause is vascular (widespread ischemia with or without hemorrhage), a period of 3 months leads to a PVS diagnosis. In the case where a diagnosis of brain death is confirmed, it is legally permissible to remove a person from life support; careful documentation of the strict observance of the brain death protocols is required.

Anesthesiologists play varying but important roles in the diagnosis and care of nonconscious patients with an impending diagnosis of brain death, including ascertainment of the clearance of anesthesia if the patient was under anesthesia, participation in the determination of patient status if the patient was not under their care (brain death protocol execution requires experienced physicians who are not caring for the patient), and aiding in explaining the status of the patient to family and friends. The latter is important especially in the case where naïve, unrealistic, or religious views or suppositions oppose cessation of life support. In such cases, ethical

and humane care for the family and efforts to educate them are the responsibility of the physician as well as the chaplain or clergy, members of the ethics committee, and members of the health care team.

SUMMARY

Full and comprehensive care of the neurosurgical patient requires a thorough understanding of the ethical principles that guide the treatment decision-making process. Caregivers must be sensitive to the right of patients to be self-determining and to participate in the treatment decision-making process to the extent possible. Although decisional incapacity may render a patient unable to participate, the involvement of informed surrogates and the use of advance directives help ensure that treatment decisions are in accord with the patient's wishes and values, even if the patient can no longer participate in those decisions. It is essential to plan proactively for decisional incapacity through the use of advance planning mechanisms.

Particular problems may arise in connection with neurosurgical intervention, such as when DNR orders are in place or with the use of other life-sustaining measures. Clinicians must be cognizant of the autonomous rights of patients, yet patients and surrogates must also be informed of the unique and special characteristics of neurosurgical interventions, which may give rise to a reexamination of the reasons to withhold or withdraw life-sustaining treatments. Providers have a particular obligation to communicate such issues to patients. Anesthesiologists have separate and distinct obligations to the patient, including the obligations to interact directly with the patient, review the patient's readiness for anesthetic intervention, and monitor and oversee the patient's condition during the entire perioperative process in connection with the use of anesthetics. In addition to the reference list for this chapter, readers are encouraged to explore the additional resources in the suggested reading list below.

ACKNOWLEDGMENT

The authors express their gratitude to previous authors of this chapter: Alex John London, Angelique Reitsma, and Connie Zuckerman.

REFERENCES

1. Carrick P. *Medical Ethics in Antiquity*. Dordrecht: D Reidel; 1985.
2. Starr P. *The Social Transformation of American Medicine*. New York: Basic Books; 1982.
3. Schloendorff v Society of New York Hospital, 211 NY 125,105 NE 92 (1914).
4. MacDonald M, Meyer K, Essig B. *Health Care Law*. New York: Matthew Bender; 1991.
5. Salgo v Leland Stanford Jr, University Board of Trustees, 154 Cal App 2d 560,317 P2d 170 (1st Dist.) (1957).
6. Declaration of Geneva. World Med Assoc Bull1:109-110, 1949.
7. Beecher HK. Ethics and clinical research. *N Engl J Med*. 1966;274:1354–1360.
8. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (DREW Publication No {OS] 78-0012, Appendix I, DREW Publication No [OS] 78-0013, Appendix 11, DREW Publication No [OS] 78-0014), Washington, DC, 1978, US Government Printing Office.
9. United States Department of Health and Human Services: Protection of Human Subjects. Title 45, Code of Federal Regulations §46 (revised as of March 8, 1983).
10. In re Quinlan, 70 NJ 10, 355 A.2d 647, rev'd 137 NJ Super. 227, 348 A.2d 801 (1975), cert. denied, 429 US 922(1976).
11. Mill JS. *On Liberty*. London: JW Parker; 1863.
12. Beauchamp T, Childress J. *Principles of Biomedical Ethics*. ed 4. New York: Oxford University Press; 1994.
13. *President's commission for the study of ethical problems in medicine and biomedical and behavioral research: making health care decisions*. Washington: US Government Printing Office; 1982. vol. 1.
14. Katz J. Informed consent: a fairy tale? Law's vision. *U Pitt Law Rev*. 1977;39:137–174.
15. Hippocrates: *Oeuvres Completes d'Hippocrate*. Littre, trans, Paris, 1939-1961, Javal et Bourdeaux.
16. Siegler M. Confidentiality in medicine: a decrepit concept. *N Engl J Med*. 1982;307:1518–1521.
17. US Dept of Health and Human Services: Health Information Privacy. Available at www.hhs.gov/ocr/hipaa.
18. Wilson JF. Health insurance portability and accountability act privacy rule causes ongoing concerns among clinicians and researchers. *Ann Intern Med*. 2006;145:313–316.
19. Brody BA, Englehardt HT. *Bioethics: Readings and Cases*. Englewood Cliffs, NJ: Prentice-Hall; 1987.
20. Whalen v Roe, 429 US 589 (1977).
21. Appelbaum P, Lidz C, Meisel A. *Informed Consent, Legal Theory and Clinical Practice*. New York: Oxford University Press; 1987.
22. Canterbury v Spence, 464 F2d 772 (DC Cir 1972), cert denied, 409 US 1064 (1972).
23. Cobbs v Grant, 8 Cal 3d 229,502 P2d 1, 104 Cal Rptr 505 (1972).
24. Wilkinson v Vesey, I 10 Rl606, 295 A2d 676 (1972).
25. Buchanan A, Brock DW. *Deciding for Others, the Ethics of Surrogate Decision Making*. New York: Cambridge University Press; 1989.
26. Drane J. The many faces of competency. *Hastings Cent Rep*. 1985;15:17–21.
27. Pelligrino E. Doctors must not kill. *J Clin Ethics*. 1992;3:98.
28. Meisel A. *The Right to Die*. New York: John Wiley & Sons; 1989.
29. Novack DH, Plumer R, Smith RL. Changes in physicians' attitudes toward telling the cancer patient. *JAMA*. 1979;241:897.
30. Harris L. Associates: Views of informed consent and decision-making: Parallel surveys of physicians and the public. Vol 2, *President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research*. Washington, DC: US Government Printing Office; 1982. Appendices (Empirical Studies of Informed Consent).
31. Annas G. *The Rights of Patients*. ed 2. Totowa, NJ: Humana Press; 1992.
32. The New York State Task Force on Life and the Law: When Others Must Choose, Deciding for Patients without Capacity, Albany, NY, 1992, The New York State Task Force on Life and the Law.
33. New York State Task Force on Life and the Law: Life-Sustaining Treatment, Making Decisions and Appointing a Health Care Agent, Albany, NY, 1987, The New York State Task Force on Life and the Law.
34. Brody H. The physician/patient relationship. In: Veatch R, ed. *Medical Ethics*. Boston: Jones & Bartlett; 1989:65–91.
35. Cantor N. *Advance Directives and the Pursuit of Death with Dignity*. Bloomington, IN: Indiana University Press; 1993.
36. Dubler NN, Nimmons D. *Ethics on Call*. New York: Harmony Books; 1992.
37. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Deciding to Forgo Life Sustaining Treatment, Washington, DC US, 1983, Government Printing Office.
38. *The Hastings Center: Guidelines on the Termination of Life-Sustaining Treatment and the Care of the Dying*. Bloomington, IN: Indiana University Press; 1987.
39. Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: Its meaning and ethical implications. *Ann Intern Med*. 1990;2:949–954.
40. Donegan JH. New concepts in cardiopulmonary resuscitation. *Anesth Analg*. 1981;60:100.
41. Lynn J, Childress JF. Must patients always be given food and water? *Hastings Cent Rep*. 1983;13:17–21.
42. New York State Public Health Law, Article 29-B (McKinney Suppl 1992).
43. Sulmasy D, Geller G, Faden R, et al. The quality of mercy: Caring for patients with "do not resuscitate" orders. *JAMA*. 1992;267:682–686.
44. Cohen CB, Cohen PJ. Do-not-resuscitate orders in the operating room. *N Engl J Med*. 1991;325:1879–1882.
45. Truog RD, Rockoff MA. DNR in the OR: Further questions. *J Clin Anesth*. 1992;4:177–180.
46. Orentlicher D. Health care reform and the patient-physician relationship. *Health Matrix: J Law-Med*. 1995;5:141–180.
47. Beauchamp TL, Veatch RM. *Ethical Issues in Death and Dying*. ed 2. Upper Saddle River, NJ: Prentice-Hall; 1996.
48. Vacco v Quill, I 17 S.Ct. 2293 (1997).
49. Washington v Glucksberg, 117 SCt 2258 (1997).
50. Gonzales v Oregon, 546 US 243 (2006).
51. Burt RA. The supreme court speaks: not assisted suicide but a constitutional right to palliative care. *N Engl J Med*. 1997;337:1234–1235.
52. Reitsma AM, Moreno JD. Ethical regulations for innovative surgery: The last frontier? *J Am Coll Surg*. 2002;194:792–801.

53. Reitsma AM, Moreno JD. Ethics of innovative surgery: US surgeons' definitions, knowledge, and attitudes. *J Am Coll Surg*. 2005;40:103–110.
54. Margo CE. When is surgery research? Towards an operational definition of human research. *J Med Ethics*. 2001;27:40–43.
55. Angelos P, Lafreniere R, Murphy T, Rose W. Ethical issues in surgical treatment and research. *Curr Probl Surg*. 2003;40:345–448.
56. US Food and Drug Administration. CFR 21, Parts 50 and 56, additional FDA regulations: parts 312 (Investigational New Drug Application), 812 (Investigational Device Exemptions) and 860 (Medical Device Class Procedures). Available at www.fda.gov.
57. American College of Surgeons. Statements on issues to be considered before new surgical technology is applied to the care of patients. *Bull Am Coll Surg*. 1995;80:46–47.
58. American College of Surgeons: Statements on Principles. Available at www.facs.org/fellows-info/statements/stonprin.html.
59. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults. Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. June 8, 2010;74:1911–1918.
60. Haberman Clyde. From private ordeal to national fight: The case of Terri Schiavo. *New York Times*. April 30, 2014.

SUGGESTED READING

Angell M. The case of Helga Wanglie: A new kind of right to die case. *N Engl J Med*. 1991;325:511.
Cruzan v Director, 110 US 2841 (1990).
Gostin L. Life and death choices after Cruzan. *Law Med Health Care*. 1991;19:9–12.
Gostin L, Weir RF. Life and death choices after Cruzan: Case law and standards of professional conduct. *Milbank Q*. 1991;69:143–173.
In re Helga Wanglie, No. PX-91-283, 4th Judicial District Ct, Hennepin County, Minn (July l, 1991).
Jonsen A. Watching the doctor. *N Engl J Med*. 1983;308:1531–1535.
Kant E. *Foundations of the Metaphysics of Morals*. Beck LW, ed. Indianapolis, IN: Bobbs-Merrill; 1959.

The Pituitary Gland and Associated Pathologic States

27

S.C. Daly • H.S. U • J.C. Drummond

The pituitary is often referred to as the "master" hormonal gland because of the innumerable influences it exerts over physiologic homeostasis. It is located in the sella turcica, a bony cavity at the base of the skull in close proximity to the undersurface of the brain. *Pituita*, latin for phlegm, was the source of the name of the pituitary gland, implying early perceptions of its function. Its true function became apparent when acromegaly was linked to the gland by Harvey Cushing in his 1912 treatise, "The pituitary gland and its disorders".[1]

THE ANATOMY AND PHYSIOLOGY OF THE PITUITARY GLAND

Neurodevelopment

The pituitary gland, also known as the hypophysis, is composed of three substructures at maturity, namely, the anterior, intermediate, and posterior lobes. The intermediate lobe is morphologically distinct from the anterior and posterior lobes but its function is uncertain. The anterior and posterior lobes are derived from two distinct embryological structures, Rathke's pouch and the infundibular process respectively. Rathke's pouch is a cephalad evagination of the stomodeal ectoderm, which will later become the pharynx. The infundibular process is a caudad evagination of the floor of the portion of the diencephalon that will eventually form the hypothalamus. These two structures, Rathke's pouch and the infundibular process, begin to come together in approximately the 4th week of gestation. With maturity, Rathke's pouch follows the infundibular process into the intracranial cavity and these two structures merge to give rise to the mature pituitary gland. The mature pituitary gland is anatomically distinct from the brain and is connected to it by the infundibular process (the pituitary stalk). The histology of the two lobes of the mature pituitary gland reflects their embryological origins. The anterior pituitary (adenohypophysis) consists of glandular tissue while the posterior pituitary gland (neurohypophysis) is neural in character. The cells in the anterior pituitary are those that ultimately manufacture and secrete the critical trophic hormones responsible for growth, development and the maintenance of homeostasis. They are, therefore, active early in gestation. Biologically active follicular stimulating hormone (FSH) and luteinizing hormone (LH) has been detected in fetuses at 14 weeks, and biologically active thyroid stimulating hormone (TSH) at 17 weeks.[2]

The Anatomy of the Adult Pituitary Gland

The pituitary gland weighs about 0.5 to 1 g and is approximately 1 cm in horizontal diameter[3] in normal adults. The vertical dimension of the gland varies with age and physiologic status, but is normally less than 8 mm. The gland tends to be the greatest in height between the ages of 10 and 29 years in both sexes and in females there is another increase in height in the fifth decade of life.[4] There is normal physiologic enlargement during the teenage years and pregnancy when it can exceed 10 mm in height.[5]

The anterior pituitary gland makes up 75% of the gland and is the most common site of origin of pituitary adenomas. There is a small intermediate lobe, the function of which is not well established. However, it is often the location of Rathke's pouch cysts and craniopharyngiomas. The posterior pituitary, which includes the pituitary stalk, is an extension of the hypothalamus. Lesions of the posterior pituitary are rare.

The pituitary gland resides in the sella turcica, a saddle-like structure in the superior aspect of the sphenoid bone. Its location in the roof of the sphenoid sinus has made it amenable to surgical approaches through that sinus. Since the sella turcica is a component of the skull, it is lined and enclosed by the dura. Superiorly, a reflection of the dura forms the diaphragma sella, effectively forming a dural sac in which the gland is encased. A small opening in the diaphragma sella accommodates the pituitary stalk, allowing communication between the hypothalamus and the posterior pituitary lobe. The sella is bordered laterally by the cavernous sinuses, which are venous sinuses entirely enclosed by dura. Within these sinuses are the carotid arteries and cranial nerves III, IV, VI, V_1 and V_2 (Fig. 27.1). Communications between the cavernous sinuses are variably found in the dura lining the anterior wall and floor of the sella. Dural communications across the anterior surface of the pituitary sometimes complicate transsphenoidal access to the gland. Beyond the confines of the sella are structures that are essential to the genesis of symptoms from pituitary tumors. These structures must be taken into consideration in the surgical treatment of pituitary diseases. Superiorly, the subarachnoid space sits directly on the diaphragma sella. Within this latter space are the optic nerves and chiasm, which can be impinged upon should a pituitary tumor extend superiorly into the intracranial cavity. In the event that the opening in the diaphragma sella is larger than the diameter of the pituitary stalk, the subarachnoid space will extend to and make direct contact with the superior surface of the pituitary gland or tumors arising from it. In this circumstance, vigorous removal of a pituitary adenoma can lead to tearing of the thin arachnoid membrane and subsequent cerebrospinal fluid leak into the nasal cavity (CSF rhinorrhea). The sella is bordered posteriorly by the basilar sinus and the interpeduncular/prepontine cisterns, in which reside the basilar artery and the brainstem.[6] The venous system of the skull base surrounds the pituitary gland and is important in the surgical approach.

The blood supply to the anterior and posterior pituitary gland is provided by the superior hypophyseal arteries, which branch off of the internal carotid arteries within the cavernous sinus. In addition, a portal circulation system allows for humoral communication between the hypothalamus and the anterior pituitary (Fig. 27.2). This portal system is essential for the multiple feedback loops between the hypothalamus and the anterior pituitary. Sensors reside in the hypothalamus to detect the levels of the end organ hormones (e.g., thyroid

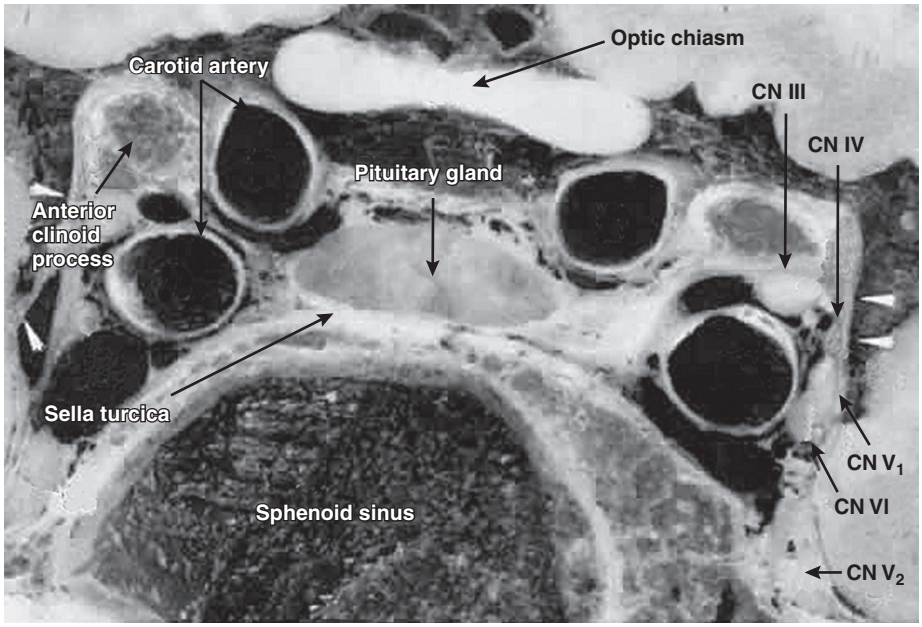


Fig. 27.1 The pituitary gland and adjacent anatomy in the coronal plane as seen in a tissue dissection. The pituitary gland is superior to the sphenoid sinus, within the sella turcica. The optic chiasm lies superior to the pituitary gland. Because of the inferior bony boundary of the sella, an enlarging pituitary lesion will often press upwards toward the optic chiasm. The carotid artery follows a serpiginous path lateral to the pituitary gland. *(From* Anaesthesia for Patients with Endocrine Disease *edited by James (2010) Fig. 2.1, p.16, by permission of Oxford University Press. http://www.oup.com/.)* Cranial nerves III, IV, V_1, VI, and V_2 lie within the cavernous sinus, which surrounds the pituitary gland laterally. CN, cranial nerve.

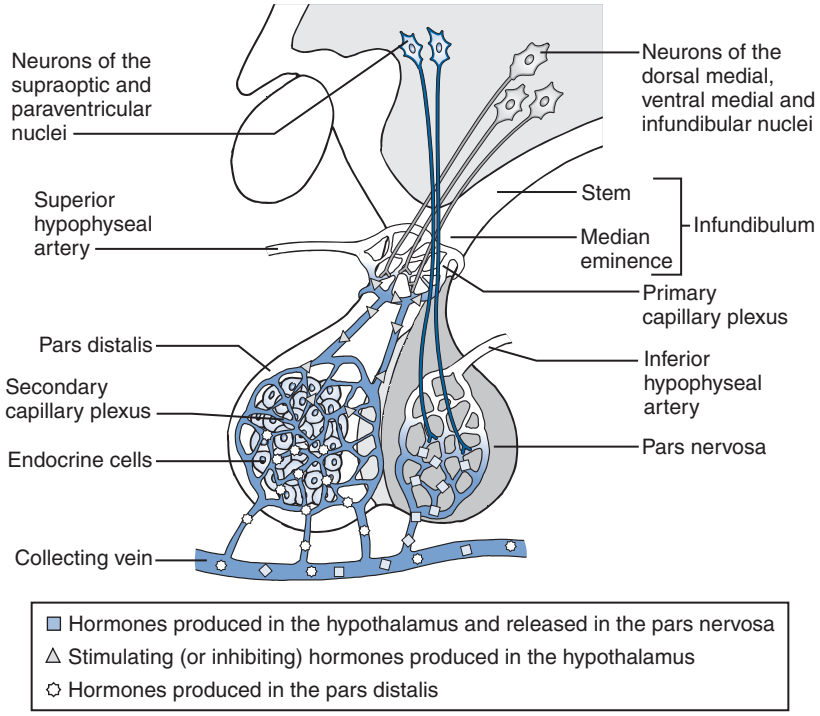


Fig. 27.2 The release of hormones and mediators for the pituitary gland. A branch of the superior hypophyseal artery arborizes to form a capillary bed in the lower hypothalamus and infundibulum (also called the pituitary stalk). Releasing factors produced in the hypothalamus are taken up by these capillaries and transported by the hypothalamic-hypophyseal portal veins (blue) to the anterior pituitary (identified as "pars distalis") where they are released from a secondary capillary plexus. This latter capillary plexus also transports the hormones and stimulating/inhibiting factors subsequently produced in the anterior pituitary to draining veins and on to the systemic circulation.[7] Axons of neurons of the supraoptic and paraventricular nuclei descend through the infundibulum to release hormones directly into the posterior lobe of the pituitary gland (identified as "pars nervosa"). A capillary plexus derived from the inferior hypophyseal artery takes up and carries these hormones, principally ADH and oxytocin, to draining veins and on to the systemic circulation. *(From* Anaesthesia for Patients with Endocrine Disease *edited by James (2010) Fig. 2.2, p. 17 by permission of Oxford University Press. http://www.oup.com/.)*

hormone, cortisol). Depending on whether the end organ hormone is above or below physiologic levels, releasing or inhibitory factors are manufactured and released by specific cells in the hypothalamus. These factors then enter the portal circulation in the hypothalamus and are carried to the anterior pituitary. At the anterior pituitary, these releasing or inhibitory factors in turn act on the respective trophic hormone producing cells to stimulate or inhibit the release of trophic hormones (e.g., TSH, ACTH). These trophic hormones then enter the general circulation to influence the function of the end organs, for example, the thyroid and adrenal glands. The intricate portal vasculature thereby allows minute amounts of factors secreted

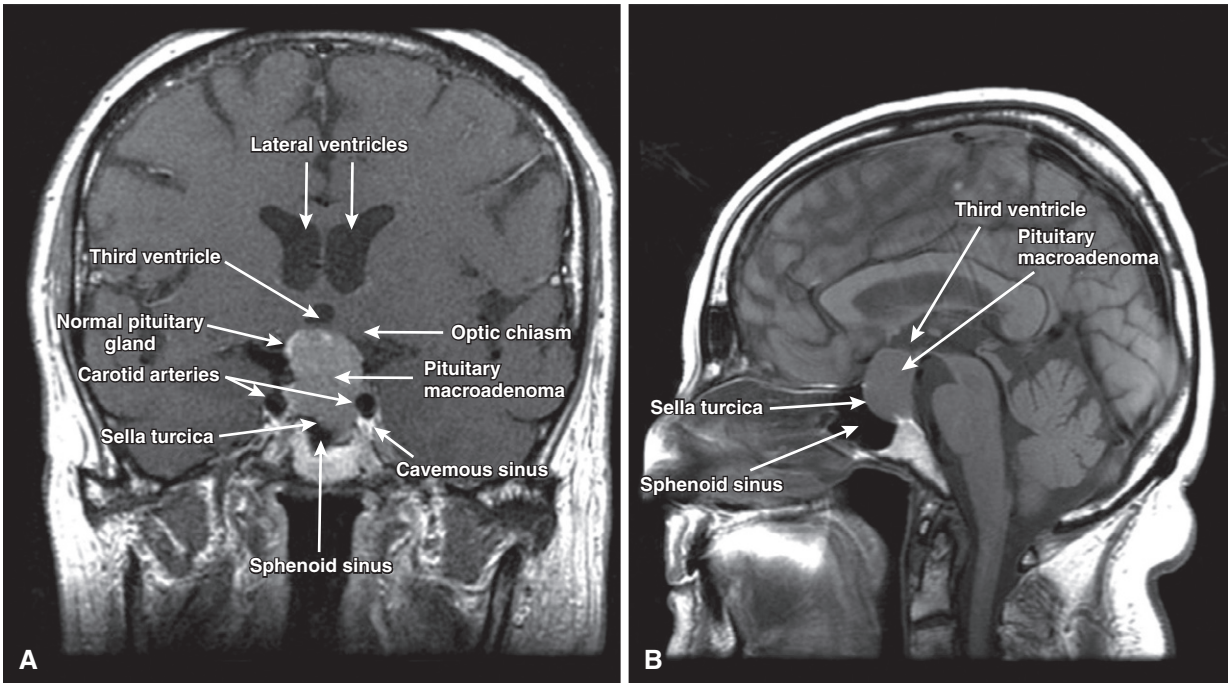


Fig. 27.3 Magnetic resonance images demonstrating a large pituitary adenoma and the anatomy adjacent to the sella turcica. **A,** Coronal plane. Residual normal pituitary tissue is demonstrated being pushed laterally and superiorly by the enlarging pituitary mass. Superiorly, the mass is compressing the optic chiasm, a small portion of which is visible. A thin layer of the bone of the sella turcica can be seen on the inferior border of the mass, with a portion of the sphenoid sinus visible immediately inferior to it. Because of the bony inferior border, the tumor has grown superiorly with resultant compression of the optic chiasm. **B,** Sagittal plane. The third ventricle is superior to the macroadenoma and the prepontine/interpeduncular cistern lies posteriorly. This cistern contains portions of the circle of Willis and its branches. Violation of this cistern can result in significant vascular and neurologic injury. The route to the mass through the nasal cavity and the sphenoid sinus is demonstrated on this image by the trajectory of the arrow through the sphenoid sinus.

by the hypothalamus to achieve precise control of hormone secretion by the target endocrine glands. There is a substantial reserve in the function of the pituitary gland. Ten percent of the gland is normally sufficient for the maintenance of endocrine homeostasis.

Radiologic Examination

The pituitary gland is effectively imaged with magnetic resonance imaging (MRI) with and without gadolinium.[8] The anterior pituitary gland is isointense on T1 weighted imaging and the posterior pituitary is hyperintense. With contrast, the anterior lobe becomes brightly enhanced probably as a result of the lack of a "blood–brain barrier". Evaluation of pituitary adenomas should entail studies with contrast enhancement. Microadenomas are small tumors residing entirely within the substance of the gland. These tumors appear as "punched out lesions" on contrast enhanced MRI scans in which normal gland is brightly enhanced while the tumor appears markedly "underenhanced". In intermediate sized tumors, which often occupy the entire confines of the sella, enhancement of the tumor appears to increase. The normal gland is often visualized as a crescent at the periphery of the tumor (Fig. 27.3B). With large tumors extending into the intracranial cavity, tumor enhancement is increased but is often not homogeneous.

DISEASES OF THE SELLAR AND PARASELLAR REGIONS

Pathologic processes within the sella include various pituitary tumors, craniopharyngiomas, and Rathke's pouch cysts.

Pituitary Tumors

Pituitary tumors are classified functionally into two categories – nonfunctional and functional tumors. The majority of tumors are nonfunctioning (nonsecretory) adenomas. Tumors that oversecrete a specific trophic hormone are considered functional tumors and they lead to distinct hormonal syndromes. Pituitary tumors are also classified according to size as macroadenomas (>1 cm) or microadenomas (<1 cm). The vast majority of pituitary tumors are benign. Pituitary cancers are distinctly rare.

Nonfunctional Pituitary Tumors

Nonfunctional pituitary tumors arise from the growth of transformed cells of the anterior pituitary. These tumors do not secrete any trophic hormones in excessive amounts. Hence, their manifestations are anatomic. As the tumor increases in size, surrounding structures are compressed. Within the sella, the normal gland is compressed and displaced around the tumor mass. This is generally well tolerated until more than 90% of the gland is rendered nonfunctional. In this event, a hypopituitary state ensues. In the female, this is manifested early with abnormalities of menstruation. In the male, a loss of libido occurs.

Growth generally follows the path of lowest structural resistance. Extension superiorly is common since the aperture in the diaphragma sella is frequently incompetent (i.e., it is larger than the diameter of the pituitary stalk). As the tumor extends superiorly above the diaphragma sella, it first occupies the subarachnoid space that separates the diaphragma from the optic nerves/chiasm. With continued growth, the optic structures are elevated and compressed leading to visual

field defects. Bitemporal field cuts are the most common since the majority of optic chiasm resides directly above the sella. Variations of the optic structures do exist. These may lead to the observation of monocular or homonymous field defects from compression of the optic nerve and tract respectively.

Lateral extension of a pituitary tumor into the cavernous sinuses is typically well tolerated and seldom leads to clinical symptoms. Tumor may abut the carotid artery but actual invasion of that vessel is rare. This is presumed to be due to the slow growth and typically nonmalignant nature of these tumors. Inferior extension into the sphenoid sinus also occurs from erosion of the floor of the sella. These are seldom symptomatic as the tumor fills out the sphenoid sinus and is usually discovered before it erodes into the pharynx.

Hypersecretory Pituitary Adenomas

While the majority of tumors are nonfunctional, some secrete specific hormones in excessive amounts leading to specific clinical syndromes. These are classified as hypersecretory pituitary adenomas.[9]

Cushing's Disease

Cushing's disease is a condition of glucocorticoid excess/hypercortisolism (Cushing's syndrome) caused by excessive secretion of adrenocorticotropic hormone (ACTH) from a tumor in the anterior pituitary gland. This leads to diffuse hyperplasia of the adrenal glands. Because of high cortisol levels, endogenous ACTH secretion by nonadenomatous cells is suppressed. ACTH secreting adenomas comprise about 1–2% of all pituitary adenomas[10] and are seen mostly in females (8:1 female to male ratio) with a peak incidence in the third and fourth decades of life.[11] The clinical characteristics include central obesity with moon facies but sparing of the limbs, dorsocervical and supraclavicular fat pad engorgement, red-purple striae, thin fragile skin, hirsutism, easy bruising, acne, proximal myopathy, hypertension, impaired glucose tolerance, insulin resistance, osteopenia, amenorrhea, decreased libido, sexual dysfunction, psychiatric abnormalities ranging from depression and lethargy to paranoia and psychosis, and recurrent superficial fungal skin infections.[12] Other findings may include hypokalemic alkalosis (in about 10–15% of patients), hyperlipidemia, and increased intraocular pressure and/or exophthalmos. The clinical diagnosis is confirmed using one or more of the following tests: late night salivary cortisol levels, low-dose and high dose dexamethasone suppression test, urinary free cortisol, serum ACTH levels and if necessary inferior petrosal sinus sampling to verify the location of ACTH secretion.[13] As the duration of hypercortisolism increases, so does the risk of mortality for the patient;[14] aggressive treatment is therefore indicated. Tumor resection is the first line treatment with success rates ranging from 69% to 98%.[15] Although most adenomas that cause Cushing's disease are noninvasive in nature, the relatively uncommon Crooke's cell tumors are more invasive and often difficult to resect.[16]

Acromegaly

The incidence of acromegaly is 3–4 cases per million per year.[17] This condition results from the overproduction of growth hormone (GH) from an anterior pituitary adenoma. The GH in turn stimulates the overproduction of insulin-like growth factor 1 (ILGF-1) from the liver. This leads to enlargement of acral, that is, the hands and feet, and other parts of the body. In addition, there is enlargement of the heart and vasculature. The clinical characteristics include features such as hypertension, diabetes mellitus, obstructive sleep apnea, mandibular hypertrophy, facial hyperostosis and skin thickening. The diagnosis of acromegaly is based on clinical findings as well as laboratory tests including serum GH, glucose tolerance test, serum ILGF-1, and MRI findings. Laboratory findings indicative of active disease are: random GH $\geq$1 ng/mL; nadir GH after oral glucose tolerance test $\geq$0.4 ng/mL; and elevated ILGF-1 for age.[18] Since acromegaly is associated with increased mortality, aggressive treatment is warranted, usually including surgical excision of the adenoma.

Prolactinomas

Prolactin is produced by the mammotrophs in the anterior pituitary and prolactin release is normally downregulated by dopamine secreted by the hypothalamus. Prolactinoma incidence varies from 10 to 50 per 100,000 and prolactinomas constitute 40% of all pituitary tumors.[19,20] They result in prolactin levels above the normal levels of 3–20 ng/mL in women and 5–15 ng/mL in men.[21] Because women will present with galactorrhea, amenorrhea and infertility, it is usually diagnosed earlier in women than men. Premature osteoporosis may also occur in women. The condition is frequently treated first with dopamine agonists, for example, bromocriptine, carbegoline, terguride, ropinirole, parmipexole, and quinagolide. When medication is ineffective, when intolerance develops, or when significant mass effect occurs, surgical excision of the tumor is undertaken. In making the choice to undertake medical treatment, it must be made clear that the medications are not tumoricidal. Cessation of treatment will, therefore, permit resumption of tumor growth. In addition, medical treatment will to lead to scar formation within the tumor, rendering subsequent surgical treatment complicated and thereby reducing the surgical success rate. The choice of therapy must take these factors into consideration and the patient must be fully educated as to the pros and cons of each therapeutic choice.

Thyrotropin Secreting Hormone Adenomas

Pituitary tumors that release thyrotropin secreting hormone (TSH) are a rare cause of hyperthyroidism. They comprise less than 2% of pituitary tumors. These tumors can co-secrete growth hormone and/or prolactin in addition to TSH. The majority tend to be macroadenomas at the time of diagnosis. In addition, they tend to be locally invasive and difficult to resect. The cure rate is 30–40% with surgery alone and there is a high incidence of hypopituitarism after surgery.[22] These patients will have elevated TSH levels and elevated free thyroid hormone levels with the typical features of hyperthyroidism, which can include a diffuse goiter. Treatment is surgical excision of the adenoma.

Other Conditions Associated with Pituitary Tumors

Pituitary Apoplexy

This condition is one in which a sudden onset of symptoms occurs as a result of either hemorrhage or infarction within the pituitary or a pituitary tumor. It frequently entails the sudden onset of severe headaches that may be associated with compromise of vision, ocular paresis, and vomiting. This presentation is very similar to that of a subarachnoid hemorrhage, which must be ruled out by radiographic studies. Upon identification of an expanding pituitary mass, emergent surgical decompression of the optic apparatus may be necessary. These patients may also present with acute adrenal insufficiency from destruction of the normal gland. This requires high dose intravenous steroid treatment to prevent cardiovascular collapse.[23] Many patients will report a preceding history consistent with either hypo- or hypersecretion of hormones, representing the antecedent presence of a pituitary tumor.

Stalk Effect

The "stalk effect" is the phenomenon of hyperprolactinemia occurring in association with suppression of function of the pituitary stalk. This has traditionally been attributed to mass effect on, or destruction of, the pituitary stalk, somehow resulting in decreased dopamine-mediated inhibition of prolactin secretion from the anterior pituitary. This phenomenon may be more complex than that, with some investigations suggesting that not all cases of hyperprolactinemia entail lack of dopamine suppression but rather the secretion of other factors either from the tumor or the anterior lobe of the pituitary.[24,25] The clinical significance is that hyperprolactinemia does not necessarily represent the presence of a prolactin secreting tumor.

Other Sellar and Parasellar Lesions

Craniopharyngiomas

Craniopharyngiomas are tumors derived from embryonal tissues that occur in parasellar and sellar locations. They are usually identified in pediatric or adolescent patients. The incidence is approximately 0.5–2.0 cases per million persons per year.[26] The tumors are often large at the time of diagnosis and many patients will present with hormone deficiencies and visual field deficits, the latter because these tumors commonly have suprasellar extension.[27] Increased intracranial pressure can also occur as a result of obstructive hydrocephalus. These lesions are often associated with the pituitary stalk and may also present with diabetes insipidus. Treatment is surgical resection by a transsphenoidal, a frontotemporal, or a combined approach.

Rathke's Cleft Cysts

Rathke's cleft cysts are benign lesions in the sellar or suprasellar areas that occur when the Rathke's cleft does not regress fully. These cysts contain mucinous or a gelatinous material and can exert mass effects, causing headaches or endocrine disturbances.[28] They are seldom large enough to cause visual symptoms. For most cases, a transsphenoidal approach is used for resection. These cysts commonly recur and may require multiple interventions.

ANESTHETIC MANAGEMENT OF SURGERY FOR PITUITARY TUMORS

Anesthetic Considerations for Pituitary Surgery

Preoperative Evaluation

The history and physical examination should be reviewed. Neurologic findings, in particular visual field deficits and abnormalities of extraocular movements, should be verified and documented. Signs and symptoms of increased intracranial pressure may be present if there is hydrocephalus from ventricular obstruction, although this is rarely seen. Any increase in intracranial pressure should be addressed in conjunction with the neurosurgical team. The imaging should be reviewed and evaluated for size and location of the tumor and evidence of impingement on the optic chiasm, extension into the cavernous sinuses, or the presence of hydrocephalus.

The endocrine work-up should be reviewed. From among the endocrine abnormalities that can occur, a principal point of emphasis for anesthesiologists is that patients should be euthyroid prior to an elective procedure. In most instances, patients who are clinically hypothyroid or hyperthyroid should be deferred. Serum electrolytes should be reviewed. Severe hyponatremia may occur, usually in association with sellar arachnoid cysts, Rathke's cleft cysts, and pituitary apoplexy.[29] Hyponatremia may represent severe, acute life-threatening adrenal insufficiency warranting immediate steroid therapy. In patients with hypertension, cardiac and renal end-organ effects should be sought. The perioperative administration of steroids should be discussed with the surgical team for all patients. Steroid administration is far from routine. Most patients with pituitary tumors will have sufficient residual normal pituitary tissue to maintain sufficient ACTH release to maintain adequate cortisol levels. These patients will, therefore, not require steroids.

The perioperative management of patients with Cushing's disease is not straightforward. The hypercortisolism is the result of supraphysiologic ACTH secretion from the pituitary tumor. Secretion of ACTH from the normal gland is suppressed. These patients must, therefore, be observed closely after surgery as they are at risk for severe adrenal insufficiency, and the associated cardiovascular compromise, because of the removal of the excessive ACTH source, that is, the tumor. In spite of the residual presence of normal anterior pituitary tissue, the chronically suppressed normal gland will not immediately be able to produce sufficient amounts of ACTH to maintain homeostasis. Therefore, in anticipation of removal of the tumor, the patient may be placed on steroid supplementation intra- and postoperatively. If perioperative steroids are administered, at some stage postoperatively they must be tapered to assess the need for recovery of glandular function. In spite of the possibility of hypocortisolism, some teams may specifically withhold steroids to avoid interference with the postoperative testing that will be performed to verify that pathological ACTH secretion has been eliminated. Observation for adrenal insufficiency must be even more careful in these patients.

In patients with acromegaly, because of the difficult airways and obstructive sleep apnea that can occur in patients with advanced disease (now rare), the airway management plan should be adjusted accordingly.

Intraoperative Considerations

Lesions of the sellar and parasellar regions are approached via both craniotomies and transsphenoidal routes. It is, in particular, for lesions with substantial suprasellar extension that craniotomy may be selected. However, beyond the endocrine considerations, these approaches entail largely the same considerations that apply to other tumor-related frontal and frontotemporal craniotomies. The following discussion will therefore emphasize considerations specific to the transsphenoidal approaches.

Surgical Approach

Broadly, there are two techniques for achieving access to the pituitary gland via the sphenoid sinus; the sublabial, and the transnasal. The choice is determined largely by operator experience and preference. The sublabial approach enters the nasal antrum through an incision below the upper lip and above the teeth. The head is positioned on a "do-nut" foam head rest. Visualization is achieved via an operating microscope, which allows for significant magnification and illumination. C-arm fluoroscopy guidance is sometimes used. Transnasal approaches are accomplished via entry through one nostril. This typically entails some form of neuronavigation guidance, usually with the head secured in pin fixation.

For both approaches, we employ a RAE-type oral endotracheal tube placed in the corner of the mouth opposite the surgeon's dominant hand. A right-handed surgeon will typically stand at the patient's right side. Ergo, the endotracheal tube is placed in the left corner of the patient's mouth.

We believe that preventing coughing and emesis is an important component of anesthetic management. Both have the potential to raise venous and arterial pressure and thereby threaten recent hemostasis. Their prevention is even more important in the event that the arachnoid has been violated and repaired because we think that they have the potential to contribute to the development of a CSF leak. As part of our prevention regiment, we place a pharyngeal pack (a vaginal pack moistened with water) to assure that blood will neither enter the stomach nor collect in the glottis above the cuff of the endotracheal tube. We doubt that omitting the pack and aspirating the blood from the stomach at the end of the procedure nullifies the emetogenic effect of gastric blood. A generous tail is left protruding from the mouth in company with the endotracheal tube. We are aware of the possible adverse effects of pharyngeal packing: sore throat, pharyngeal plexus injury, postoperative stomatitis, tongue swelling, and pack migration.[30–33] These events have not been observed during our long experience, but should be borne in mind.

Prior to placing the pharyngeal pack, we insert an orogastric tube. We withdraw slowly it at the end of the procedure using it to suction the pharynx in the belief that it is less likely to provoke coughing/gagging than the customary Yankauer-type suction. Our practice is to cover all of the anesthesia paraphernalia (endotracheal tube, temperature probe, G-tube) with an adhesive edged plastic drape. The adhesive edge of the drape is placed just under the lower lip for sublabial approaches and just above the upper lip for transnasal procedures. This practice allows the anesthesiologist access to the endotracheal tube without intrusion into the sterile field.

All surgical approaches entail the use of a combination of local anesthetics and vasoconstrictors, usually epinephrine (adrenaline), to decrease mucosal blood loss and to blunt the hemodynamic response to dissection. Substantial increases in blood pressure can occur[34,35] and the anesthesiologist should be in continuous communication with the surgeon. Pauses may be necessary to accomplish the infiltration safely and the anesthesiologist should be prepared with short-acting antihypertensive agents to deal with excessive responses that nonetheless occur. The necessity for prompt recognition of evolving blood pressure responses is one of the reasons that we believe that intra-arterial pressure monitoring is appropriate for these procedures.

Guidance using bitemporal fluoroscopy has been mentioned above. Some surgeons, as a matter of individual preference or training use neuronavigational systems, for example, Brainlab (Brainlab AG, Germany).

Any anesthetic regimen that is consistent with good hemodynamic control and a smooth and timely emergence will be appropriate. At the authors' institution, a balanced anesthetic is used most often with opioids, a volatile agent, and occasionally an infusion of intravenous anesthetics such as propofol or dexmedetomidine.

During the procedure, complete neuromuscular blockade is advisable to ensure absolute immobility of the surgical field. Movement entails a risk of injuries including arterial perforation/hemorrhage, visual damage and cranial nerve injury. The cavernous sinuses, through which the carotid arteries and several cranial nerves pass (see Fig. 27.1), lie lateral to the sella and the distance separating the carotid arteries from the pituitary gland is between 0 and 9 mm.[36] Once within the sphenoid sinus, there is very little or no bone separating surgical instruments from the carotid arteries passing laterally.[37]

There have been reports of asystole or bradycardia, occurring during dissection of the tumor, especially during cavernous sinus exploration. These have been attributed to the trigeminal cardiac reflex. The incidence of this phenomenon, which we have rarely encountered, is reported in retrospective analyses to vary from 0.003% to 10%.[38–41] The events are usually self-limited with cessation of surgical manipulation.

Cerebrospinal fluid (CSF) leakage intraoperatively may occur if the arachnoid is violated during dissection of the lesion. The surgeon typically takes measures to seal the leak in order to prevent a postoperative "CSF leak" and the inherent communication between the nasal cavity and the CSF space. Tissue sealants and packing of the sphenoid sinus (with fascia lata and muscle from the thigh, nasal turbinate mucoperiosteum, or abdominal fat) may be employed. Postoperative CSF diversion by means of a lumbar drain, placed at the end of the procedure, before emergence may also be used as an adjunct to preventing the development of a CSF leak. Anesthesiologists may be called upon to assist with placement.

We facilitate the smooth emergence mentioned above by the introduction of nitrous oxide in the last 15–20 minutes of the procedure (to allow elimination of the volatile agent and intravenous anesthetics) and by administration of lidocaine when the inhaled anesthetic agents are discontinued. Intravenous acetaminophen administered during the last half hour of the procedure combined with residual narcotic is usually sufficient to provide analgesia in the PACU.

It is inevitable that some patients who undergo pituitary surgery will suffer from obstructive sleep apnea and in these patients continuous positive airway pressure (CPAP) devices will appear desirable. However, CPAP has been reported anecdotally to have led to the occurrence pneumocephalus, and, therefore, the opening of a pathway between the nasal cavity and the intracranial space with the inherent meningitis risk. CPAP should generally be avoided.[42] In patients who have a history of obstructive sleep apnea, a nasal trumpet can be placed by the surgeon into one of the nares, in lieu of the standard packing, to help to assure a patent airway in these patients.

Anesthetic Considerations for Specific Disease States

Cushing's Disease

The stigmata and comorbidities associated with Cushing's disease have been described above. In addition, the considerations that argue for and against the administration of steroids have also been mentioned. The decision to give preoperative steroids is one that should be made in conjunction with the surgical team. If steroids are to be withheld, note that because of the half-life of cortisol (~50–75 minutes) and the hypercortisolemic preoperative state of the patient, serum cortisol will not reach levels that are potentially critically low until about 20 hours post-procedure. Observation of the patient for evidence of severe hypoadrenalism should be careful and continuous in the postoperative period.

Table 27.1 Physiologic Changes in Cushing's Disease and Acromegaly and Anesthetic Considerations[66]

	Cushing's Disease	Anesthetic Considerations	Acromegaly	Anesthetic Considerations
Neurologic	Visual field or CN deficits, psychiatric disturbance, anxiety, depression, psychosis Increased ICP (rarely)	Document preexisting deficits	Visual field or CN deficits. Increased ICP (rarely)	Document preexisting deficits. Modify technique to avoid further ICP increase (rarely)
Pulmonary/airway	Aggressive infections, cervical fat pad	Rule out concurrent pulmonary infection	OSA[43], greater incidence of difficult intubation[44,45] (macroglossia, hypertrophy of epiglottis, tonsils, larynx, prognathic jaw)	Use smaller endotracheal tubes. Prepare for difficult airway. Attention to OSA in postoperative period
Cardiovascular	Hypertension, myocardial hypertrophy, CHF, CAD	Evaluate for end stage effects of hypertension	Hypertension, cardiomyopathy[46], valvular disease[47], arrhythmias, CAD[48]	Evaluate for end stage effects of hypertension and ischemic symptoms
Hematologic	Increased thrombotic risk	DVT prevention (SCDs, early ambulation)		
Endocrine	Perioperative adrenal insufficiency, hyperglycemia, hirsutism, amenorrhea	Consider perioperative steroid replacement*; glycemic control	Hyperglycemia, lipolysis, dyslipidemia; possible panhypopituitarism	Glycemic control, verify thyroid function, consider perioperative steroid replacement
	Protein wasting, centripetal fat accumulation, spontaneous tendon rupture, osteoporosis	At risk of pathologic fractures and injury with positioning	Soft tissue, bony overgrowth,[49], vertebral fractures, joint arthropathy	Careful positioning to avoid peripheral nerve injury; document preexisting bone or nerve pathology
Dermatologic	Atrophy of epidermis, easy bruising	Difficult IV placement, risk of skin injury	Thick skin	Difficult IV cannulation
Immunologic	Decreased immunity; mucocutaneous infections	Increased attention to sterility		
Renal	Renal stones, electrolyte abnormalities (hypokalemia, alkalosis)	Assess/correct electrolyte status prior to procedure; evaluate for existing renal injury	High urine output after tumor resection	Assess urine output and electrolytes postoperatively; distinguish DI vs. iatrogenic diuresis
Pediatric considerations	Growth retardation or arrest		Gigantism due to GH excess	

*Refer to discussion on perioperative steroid replacement for Cushing's disease. CN, cranial nerves; ICP, intracranial pressure; OSA, obstructive sleep apnea; CHF, congestive heart failure; CAD, coronary artery disease; DVT, deep venous thrombosis; SCD, sequential compression device.

Prolactinomas

The pathophysiology of prolactinomas does not require anesthetic considerations beyond those related to the mass effects that these tumors may have on adjacent structures and consideration of the possible adverse effects of their pharmacologic treatment. The ergot-derived dopamine agonists can cause cardiac valvular pathology from fibrosis. However, whether or not the low doses of cabergoline used for hyperprolactinemia actually have such side effects is unclear.[50,51] A patient with known hyperprolactinemia and on an ergot-derived dopamine agonist who is found to have a murmur may warrant echocardiographic examination.

Dopamine agonists can also cause decreased blood pressure by central and peripheral mechanisms with decreased sympathetic tone and decreased norepinephrine (noradrenaline) release. In addition, dopamine agonists may cause arrhythmias, including atrial fibrillation. Heart failure has been observed in patients with Parkinson's disease. Again, it is unclear whether the relatively low doses of these medications used for hyperprolactinemia actually have these effects.[52]

Thyrotropin Secreting Hormone Adenomas

The pathophysiology of TSH secreting adenomas may occasionally require medical management of the hyperthyroid state to prepare the patient for surgery. Somatostatin analogs can be used in conjunction with a combination of methimazole, propylthiouracil, and propranolol to return the patient to a euthyroid state prior to pituitary surgery. Somatostatin analogs, for example, octreotide, have been shown to decrease the size of goiters and pituitary tumors themselves in about 40% of patients.[53] Airway management may occasionally be difficult because of their goiter. The systemic effects of hyperthyroidism, including cardiac failure and atrial fibrillation, should be considered, although these are less common than in patients with other forms of hyperthyroidism and the signs and symptoms of hyperthyroidism tend to be mild and may even be overshadowed by other hormones that are cosecreted, for example, growth hormone.[54] There should be attention to the possibility of hypopituitarism and perioperative steroid administration should be considered in the light of the preoperative endocrine evaluation.

Postoperative Management

Pain and nausea and vomiting are the most common complaints in these patients. We administer 1 g of acetaminophen in the last 30 minutes of the procedure. Nausea and vomiting may be detrimental in these patients because of its risks for increasing CSF leakage.[55,56] These complaints are usually not severe and are readily managed with standard pharmacologic therapies.

Surgical complication and mortality rates are low in these cases overall.[57] The mortality rate is approximately 0.5%. Major surgical complications occur in 8-10% of patients. They include CSF leak (~4.7%), meningitis (2%), stroke (1%), vascular injuries (including carotid-cavernous fistula) (0.4%), vision loss (1.8%) and permanent panhypopituitarism.[58] Vision loss and cranial neuropathy that are apparent in the immediate postoperative period warrant immediate imaging to seek evidence of hemorrhage or mass effects, for example, from fat graft packing, that may justify early re-exploration.

Cerebral spinal fluid leakage is suspected in patients with persistent nasal discharge that is salty in taste or is worsened by leaning forward. Patients who have combined approaches and in whom the arachnoid has been violated intraoperatively are at greater risk.[59] CSF leakage is confirmed if the fluid is positive for B_2 transferrin. Treatment for CSF leakage varies with institution, with some choosing early re-exploration and repair and some first employing lumbar drainage and bed rest.

Abnormalities of Salt and Water Homeostasis

Disorders of water and electrolyte homeostasis are sometimes encountered after pituitary surgery. Rates of up to 25% of some form of water imbalance have been reported. However, some surveys have reported incidences of up to 75%.[60,61] This vastly exceeds our experience. There are three types of imbalances that can occur as a result of disturbances in antidiuretic hormone (ADH) secretion: diabetes insipidus (DI); a syndrome of inappropriate ADH secretion (SIADH); and combination of DI-SIADH.

Diabetes Insipidus

The most commonly encountered is DI, usually with onset early in the postoperative period. DI is the result of a lack of sufficient ADH. DI occurs more commonly in association with surgery for macroadenomas, craniopharyngiomas, and Rathke's cleft cysts.[62] The patient will have a large output of dilute urine coupled with polydipsia with a preference for cold water. In the event of insufficient fluid intake, the patient will become hypovolemic, hypernatremic and will have an elevated serum osmolarity. The diagnostic hallmarks are a rising serum sodium (≥145 mmol/L) and osmolarity (>300 mOsm/kg) with a simultaneously dilute (hypo-osmolar) urine (<300 mOsm/kg or urine specific gravity ≤1.005). The large majority of cases of DI are transient. The onset of the DI is usually in the first 24–48 hours and in the majority of patients, it will have resolved by the time of discharge. There are some patients who develop DI in a triphasic fashion with early onset DI in the first postoperative day followed by antidiuresis about 1 week after surgery with subsequent and permanent DI.[63] It is always important to distinguish between a physiologic diuresis, perhaps of an iatrogenic fluid load, and DI. The danger lies in treating a physiologic diuresis with matching fluid replacement. This puts the clinician and the patient in a "chasing your tail" situation that can lead to critical fluid overload. Acromegalic patients deserve special consideration with respect to polyuria because these patients will often exhibit a brisk diuresis of third space fluid after successful tumor resection and diagnostic care will be required to distinguish this physiologic diuresis from DI.[64]

The management of patients with DI must be tailored to the individual. They should remain in a closely monitored setting with daily weights recorded, strict intake and outtake monitoring, and frequent analysis of serum sodium, serum osmolarity, urine osmolarity and subjective thirst rating. With an intact thirst mechanism and fluids available for oral repletion, the majority of these patients will be able to self-regulate In cases in which the patient is unable to keep up with the diuresis and serum sodium exceeds 145 mmol/L, desmopressin (1-deamino-8D-arginine vasopressin; DDAVP) administration should be considered. DDAVP may be given 1 μg subcutaneously or 0.1 mg orally per day. This puts the patient at risk for overcorrection, with attendant hypervolemia and hyponatremia and the patient should continue to be monitored closely.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) with the attendant hyponatremia is occasionally encountered after pituitary surgery. The differential diagnosis should include other potential causes of hyponatremia, including adrenal insufficiency, hypothyroidism, hyperglycemia, and cerebral salt wasting (CSW). The clinical hallmark of SIADH is hyponatremia with serum sodium ≤135 mmol/L in a euvolemic to hypervolemic state. By undefined mechanisms, some loss of the normal control of ADH release occurs resulting in SIADH. This usually occurs later in the postoperative period than DI, with the lowest serum sodium levels occurring 7–9 days postoperatively. The patient may or may not have any symptoms, based on the severity of the hyponatremia. The patient may complain of headache, anorexia, nausea/vomiting, seizures or lethargy. The patient's serum will be hypo-osmolar, the urine will be relatively hyperosmolar, and the patient will be euvolemic or slightly hypervolemic with normal serum blood urea nitrogen (BUN) and creatinine. This is usually treated with fluid restriction with liquids limited to 1000 mL or 700 mL per day, salty foods, and in severe cases with intravenous sodium repletion.[65] If intravenous sodium repletion is necessary, therapy should be aimed at correcting the hyponatremia not more rapidly than 1 mmol/L/h, and if the hyponatremia is deemed to be chronic, no faster than 0.5 mmol/L/h. This slow correction is necessary to avoid central pontine myelinolysis, a rare and catastrophic complication. The patient's serum electrolytes should be closely monitored during this period with severe cases requiring inpatient admission and multiple blood analysis daily and mild cases being treated at home with daily serum analysis. This phenomenon is usually self-limiting and most patients recover by postoperative day 28. If there has been a considerable amount of hemorrhage during the operative course or the recognized presence of subarachnoid blood, cerebral salt wasting, as occurs relatively commonly after subarachnoid hemorrhage associated with aneurysmal rupture, should also be considered as a cause of hyponatremia. Cerebral salt wasting is associated with a hypovolemic state with increased BUN, creatinine, and increased hematocrit indicating a volume contracted state.

SUMMARY

The disorders of the pituitary gland result in a myriad pathologic conditions. In order to care properly for these patients, the anesthesiologist should have an understanding of the potential consequences of both the endocrinopathies and the mass effects caused by these lesions. The preoperative assessment should include: (1) evaluation of the patient's endocrine status and of the physiologic consequences of any abnormalities; (2) review of imaging studies to identify mass effects and adjacent structures at risk; and (3) careful definition of the preoperative neurologic status. A discussion should invariably

be held with the surgical team regarding the hypothalamic–pituitary axis and whether perioperative steroid supplementation is warranted. The overall rates of morbidity and mortality for these procedures are low. However, when complications occur, they can be life threatening. Accordingly, because of the potential for endocrine derangements, the anatomical complexity of the sella turcica and its close proximity to vascular and neural structures, the anesthesiologist should be in close and continuous collaboration with the surgeon in the management of this patient population.

REFERENCES

1. Cushing HW. *The Pituitary Body and its Disorders*. Philadelphia and London: Lippincott; 1912.
2. Pope C, McNeilly JR, Coutts S, Millar M, Anderson RA, McNeilly AS. Gonadotrope and thyrotrope development in the human and mouse anterior pituitary gland. *Dev Biol*. 2006;297:172–181.
3. Guyton AC. *Textbook of Medical Physiology*. Philadelphia: W.B. Saunders Company; 1991:819.
4. Tsunoda A, Okuda O, Sato K. MR height of the pituitary gland as a function of age and sex: Especially physiological hypertrophy in adolescence and in climacterium. *Am J Neuroradiol*. 1997;18:551–554.
5. Elster AD, Chen MY, Williams 3rd DW, et al. Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. *Radiology*. 1990;174:681–685.
6. Rhoton AL. Anatomy of the pituitary gland and sellar region. In: Thapkar K, Kovacs K, Sheithauer B, Lloyd RV, eds. *Diagnosis and Management of Pituitary Tumors*. Totowa: Humana Press; 2001:13–40.
7. Mescher JL. *Junqueira's Basic Histology Text and Atlas*. New York: Mcgraw-Hill Press; 2010.
8. Forbes K, Karis J, White WL. Imaging of the pituitary gland. *Barrow Quarterly*. 2002;18(2).
9. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol*. 2007;156:203–216.
10. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: A community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol*. 2010;72(3):377–382.
11. AbdelMannan D, Selman WR, Arafah BM. Peri-operative management of Cushing's disease. *Rev Endocr Metab Disord*. 2010;11:127–134.
12. Lo JC, Tyrrell JB, Wilson CB. Corticotroph Adenomas. In: Thapar K, Kovacs K, Scheithauer BW, Lloyd RV, eds. *Diagnosis and Management of Pituitary Tumors*. Totowa, New Jersey: Humana Press; 2001:317–319.
13. Stewart PM. Adrenal cortex. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: WB Saunders; 2003:516–519.
14. Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB. Predictors of mortality and long-term outcomes in treated Cushing's disease: A study of 346 patients. *J Clin Endocrinol Metab*. 2013;1022–1030.
15. Kelly DF. Transsphenoidal surgery for Cushing's disease: A review of success rates, remission predictors, management of failed surgery, and Nelson's syndrome. *Neurosurg Forcus*. 2007;23(3):E5.
16. Di leva A, Davidson JM, Syro LV, et al. Crooke's cell tumors of the pituitary. *Neurosurgery*. 2015;76:616–622.
17. Tjörnstrand A, Gunnarsson K, Evert M, et al. The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. *Eur J Endocrinol*. 2014;171:519–526.
18. Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary*. 2013;16:294–302.
19. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: A cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab*. 2006;91:4769–4775.
20. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: A community-based, cross-sectional study in Banbury. *Clin Endocrinol*. 2010;72:377–382.
21. Pasternack JJ. The pituitary gland. In: James MFM, ed. *Anaesthesia for Patient with Endocrine Disease*. New York: Oxford University Press; 2010:26–27.
22. Gatto F, Grasso LF, Nazzari E, et al. Clinical outcome and evidence of high rate post-surgical anterior hypopituitarism in a cohort of TSH-secreting adenoma patients: Might somatostatin analogs have a role as first-line therapy? *Pituitary*. 2015;18:583–591.
23. Russell JS, Miller KK. Pituitary apoplexy. In: Davies TF, ed. *A Case-Based Guide to Clinical Endocrinology*. Totowa, New Jersey: Humana Press; 2008:9–17.
24. Kinoshita Y, Hama S, Tominaga A, et al. Masked hyperprolactinemia: Tumor-derived factors inhibiting prolactin secretion caused by pituitary-stalk damage. *J Clin Neurosci*. 2011;18(12):1651–1655.
25. Skinner DC. Rethinking the Stalk Effect: A new hypothesis explaining suprasellar tumor-induced hyperprolactinemia. *Med Hypotheses*. 2009;72:309–310.
26. Bunin GR, Surawicz TS, Witman PA, et al. The descriptive epidemiology of craniopharyngioma. *J Neurosurg*. 1998;89:547–551.
27. Müller HL. Childhood craniopharyngiomas: Treatment strategies and outcomes. *Expert Rev Neurother*. 2014;14:187–197.
28. Oyesiku NM, Post KD. Rathke cleft cysts. *Neurosurg Focus*. 2011;31(Introduction).
29. Bordo G, Kelly K, McLaughlin N, et al. Sellar masses that present with severe hyponatremia. *Endocr Pract*. 2014;20:1178–1186.
30. Mermer RW, Zwillenberg D, Maron A, et al. Unilateral pharyngeal plexus injury following use of an oropharyngeal pack during third- molar surgery. *J Oral Maxillofac Surg*. 1990;48:1102–1104.
31. Erkalp K, Korkut YA, Meric A, et al. Pharyngeal packing is a predisposing factor for postoperative aphthous stomatitis in nasal surgery. *Otolaryngol Head Neck Surg*. 2010;142:672–676.
32. Kawaguchi M, Sakamoto T, Ohnishi H, et al. Pharyngeal packs can cause massive swelling of the tongue after neurosurgical procedures. *Anesthesiology*. 1995;83:434–435.
33. To EW, Tsang WM, Yiu F, et al. A missing throat pack. *Anaesthesia*. 2001;56:383–384.
34. Chlliah RY, Mannien PH. Hazards of epinephrine in transsphenoidal pituitary surgery. *J Neurosurg Anesthesiol*. 2002;14:43–46.
35. Keegan MT, Atkinson JL, Kasperbauer JL, et al. Exaggerated hemodynamic responses to nasal injection and awakening from anesthesia in a Cushingoind patient having transsphenoidal hypophysectomy. *J Neurosurg Anesthesiol*. 2000;12:225–229.
36. Oskouian RJ, Kelly DF, Laws ER. Vascular injury and transsphenoidal surgery. *Front Horm Res*. 2006;34:256–278.
37. Jufii K, Chambers SM, Rhoton AL. Neurovascular relationships of the sphenoid sinus. *J Neurosurg*. 1979;50:31–39.
38. Chowdry T, Mendelowith D, Golanov E, et al. Trigeminocardiac reflex: The current clinical and physiological knowledge. *J Neurosurg Anesthesiol*. 2015;27:136–147.
39. Cho JM, Min KT, Kim EH, Oh MC, Kim SH. Suden asystole due to trigeminocardiac reflex during transsphenoidal surgery for pituitary tumor. *World Neurosurg*. 2011;477:11–15.
40. Koerbel A, Gharabaghi A, Samii A, et al. Trigeinocardiac reflex during skull base surgery: Mechanism and management. *Acta Neurochir*. 2005;147:727–732.
41. Schaller B. Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas. *Clin Neurol Neurosurg*. 2005;107:468–474.
42. Zlotnik D, Taylor G, Simmoneau A, Viot-Blanc V, Devys JM. Two cases of pneumocephalus following noninvasive continuous positive airway ventilation after transsphenoidal neurosurgery. *Ann Fr Anesth Reanim*. 2014;33:275–278.
43. Davi MV, Dalle Carbonare L, Giustina A, et al. Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. *Eur J Endocrinol*. 2008;159:533–540.
44. Nemergut EC, Zuo Z. Airway management in patients with pituitary disease: A review of 746 patients. *J Neurosurg Anesthesiol*. 2006;18:73–77.
45. Friedel ME, Johnston DR, Singhal S, et al. Airway management and perioperative concerns in acromegaly patients undergoing endoscopic transsphenoidal surgery for pituitary tumors. *Otolaryngology-Head and Neck Surgery*. 2013;149:840–844.
46. Colao A, Marzullo P, Disomma C, Lombardi G. Growth hormone and heart. *Clin Endocrinol*. 2001;54:137–154.
47. Pereira AM, van Theil SW, Lindner JR, et al. Increased prevalence of regurgitant valvular heart disease in acromegaly. *J Clin Endocrinol Metab*. 2004;89:71–75.
48. Lie JT, Grossman SJ. Pathology of the heart in acromegaly: Anatomic findings in 27 autopsied patients. *Am Heart J*. 1980;100:41–52.
49. Jenkins PJ, Sohaib SA, Akker S, et al. The pathology of median neuropathy in acromegaly. *Ann Intern Med*. 2000;133:197–201.
50. De Vecchis R, Esposito C, Ariano C. Cabergoline use and the risk of fibrosis and insufficiency of cardiac valves. Meta-analysis of observational studies. *Herz*. 2013;38:868–880.
51. Samson SL, Ezzat S. AACE/ACE disease state clinical review: Dopamine agonists for hyperprolactinemia and the risk of cardiac valve disease. *Endocr Pract*. 2014;20:608–616.
52. Perez-LLoret S, Rey MV, Crispo J, et al. Risk of heart failure following treatment with dopamine agonists in Parkinson's disease patients. *Expert Opin Drug Saf*. 2014;13:351–360.
53. Socin HV, Chanson P, Delemer B, et al. The changing spectrum of TSH-secreting pituitary adenomas: Diagnosis and management in 43 patients. *Eur J Endocrinol*. 2003;148:433–442.

54. Beck-Peccoz P, Persani L, Mannavola D, Campi I. Pituitary tumours: TSH-secreting adenomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23:596–606.
55. Dunn CJ, Alaani A, Johnson AP. Study on spontaneous cerebrospinal fluid rhinorrhoea: Its aetiology and management. *J Laryngol Otol*. 2005;119:12–15.
56. Snyderman CH, Kassam AB, Carrau R, et al. Endoscopic reconstruction of cranial base defects following endonasal skull base surgery. *Skull Base*. 2007;17:73–78.
57. Kring JG, Kallogjeri D, Wineland A, Nepple KG, Piccirillo JF, Getz AE. Complications following primary and revision transsphenoidal surgeries for pituitary tumors. *Laryngoscope*. 2014; Sep 27; http://dx.doi.org/10.1002/lary.24892.
58. Halvorsen H, Ramm-Peterson J, Josefsen R, et al. Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: A consecutive series of 506 procedures. *Acta Neurochir*. 2014;156:441–449.
59. Ian ME, Iorgulescu JB, El-Sayed I, et al. Risk factors for postoperative cerebrospinal fluid leak and meningitis after expanded endoscopic endonasal surgery. *J Clin Neurosci*. 2015;22:48–54.
60. Kristof RA, Rother M, Neuloh G, Klingmüller D. Incidence, clinical manifestations and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: A prospective observational study. *J Neurosurg*. 2009;111:555–562.
61. Olson BR, Gumowski J, Rubino D, Oldfield EH. Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. *J Neurosurg*. 1997;87:499–507.
62. Schreckinger M, Walker B, Knepper J, et al. Post-operative diabetes insipidus after transsphenoidal surgery. *Pituitary*. 2013;16:445–451.
63. Fisher C, Ingram WR. The effect of interruption of the supraoptico-hypophyseal tracts on the antidiuretic, pressor and oxytocic activity of the posterior lobe of the hypophysis. *Endocrinology*. 1936;20:762–768.
64. Zada G, Sivakumar W, Fishback D, Singer PA, Weiss MH. Significance of postoperative fluid diuresis in patients undergoing transsphenoidal surgery for growth hormone-secreting pituitary adenomas. *J Neurosurg*. 2010;112:744–749.
65. Dumont AS, Nemergut EC, Jane JA, Laws ER. Postoperative care following pituitary surgery. *J Intensive Care Med*. 2005;20:127–140.
66. Newell-Price J, Bertagna X, Grossman AB, Niemann LK. Cushings Syndrome. *Lancet*. 2006;367:1605–1617.

Information Management and Technology

28

P.J. St. Jacques • J.M. Ehrenfeld

INTRODUCTION

Harvey Cushing, an American neurosurgeon, recognized that the perioperative environment required detailed data collection. Working with colleagues in the 1890s, he is credited with bringing the intraoperative anesthetic record into popular use.[1] This early pen and paper example of information technology in the operating room has been in existence for over 100 years and is the primary method of documenting anesthesia care for many practitioners. However, over the last decade, advances in information technology and a national focus on patient safety and the delivery of cost-effective care have led to the investment in and development of sophisticated systems to manage, monitor and document care. Having advanced beyond the pen and paper, we recognize that managing multiple streams of data is of paramount importance.

Other industries, such as manufacturing, transportation, and public utilities, drove the development of information technology to capture and analyze data in order to provide more profitable services or obtain a competitive advantage over others in the same commercial space. However, in medicine the proliferation of health information technology is a development that is relatively recent and continuing to mature. Medicine is a broad discipline. Among the various elements of care, the perioperative environment is complex, esoteric, and hidden behind doors that say "Do Not Enter without Proper Attire." As such, this area has received less informatics-related attention than other areas of the medical enterprise, such as billing, laboratory, and computerized physician order entry. Electronic anesthesia information systems were described as early as 1991.[2] However, implementation rates continued to be low even 25 years later.[3] This low rate has been improving, with new technologies and increased development and research in this critical area.[4]

The legislature has had a significant impact on the development of health information technology (HIT). In 2009 the American Recovery and Reinvestment Act included a significant incentive for organizations to improve HIT implementations. These incentives were designed to encourage the development and implementation of health-related information technology and the development of outcomes measures to gauge the quality and cost efficiency of care.[5,6] The Health Information Technology for Economic and Clinical Health Act (HITECH) provided $26 billion in incentives to improve and implement HIT. HITECH provides for both incentives and penalties to physicians who use or fail to use HIT that meets certain meaningful use (MU) criteria.[7] Coupled with the drive to become more efficient and improve safety, we are finally realizing the benefits to the quality efficiency of care which HIT offers.[8–10]

SCOPE OF HEALTH INFORMATION TECHNOLOGY

Multiple HIT systems are in common use (Table 28.1). These components may be integrated into an enterprise wide system provided by one vendor. Enterprise systems cover several or all the required HIT functions in one installation, but often do not provide the specific tools needed for the most highly technical or low volume services. In contrast, "best of breed" applications have been developed to fulfill these specific niches and are often installed in conjunction with enterprise systems when the enterprise system does not provide adequate functionality in a particular discipline.

A key element for the success of any HIT program is acceptability by clinicians for integration into their preexisting workflow. Barriers to adoption have been studied and include factors such as financial, technical, organizational, and psychological challenges.[11] Properly designed systems will minimize the time required to document and the need to reenter any previously existing data. Toward this aim, the user experience or human factor considerations (the interfacing of systems, the design of the user interface, the actual appearance of the data entry screens, and processes) must be carefully examined when selecting or developing any HIT-related product.

CLINICAL DECISION SUPPORT

Clinical decision support (CDS) is a key function of clinical information systems, including perioperative information management systems (PIMS). CDS can take many forms, ranging from simple data field checks to more complex calculations performed in the background—all designed to help clinicians make better and more timely decisions. Most commercial electronic systems enable end-users and/or system administrators to customize alerts and notifications, which can all be considered part of CDS.[12]

Most CDS within anesthesiology has focused on enabling providers to achieve better compliance with evidence-based process guidelines.[13,14] These include quality measures promulgated by national societies, quality organizations (such as the Surgical Care Improvement Project), and both government and commercial payors.[15] Common implementations of CDS include decision support around prophylactic antibiotic administration (including agent selection, timing, redosing, and appropriate discontinuation), administration of beta blockers in cardiac patients, management of blood glucose levels in diabetic patients, and provision of deep vein thrombosis prophylaxis.[16] Within neurosurgical anesthesia, some CDS systems have focused on appropriate management of antibiotics, intracranial pressure, and ventilation.

Multiple studies have demonstrated that CDS can enable providers to achieve more reliable performance and a handful of studies have even linked CDS to better patient outcomes, including reductions in surgical site infections and postoperative

Table 28.1 Healthcare information technology components

Electronic Medical Record (EMR)	Represents an electronic version of the traditional paper chart. May include physician, nursing and ancillary notes, lab results, radiology results, physician order. May include integrated components of the other modalities
Computerized Physician Order Entry (CPOE)	Application to record physician orders and transmit the orders to the discipline fulfilling the order (eg, pharmacy, radiology, nursing, physical therapy). May include algorithms for error checking, such as drug interactions, allergy information, weight-based calculations. May include additional functionality such as the electronic transmission of prescriptions to outpatient pharmacies
Picture Archiving Communication System (PACS)	Provides storage of and access to images from radiology, ultrasound, and related imaging modalities. Often replaces traditional chemical film imaging with digital radiology capture
Anesthesiology Information Systems (AIMS)	Application designed to record the progress of intraoperative care, including vital signs, medications administration, airway and patient management, documentation of operative times and practitioner comments and attestations of care
Perioperative Information Management System (PIMS)	Series of applications designed to capture and record the documentation of care from multiple disciplines (eg, nursing, anesthesiology, perfusion, respiratory therapy) throughout the perioperative process. Includes preoperative, intraoperative, and postoperative documentation by nursing teams, and AIMS system, OR suite management, supply and equipment tracking, patient status boards and other applications
Specialized Applications	Developed for use in one or two primary areas to cover specific functions. Examples include software to track the flow of patients in the emergency department, applications to record the progress of labor with fetal telemetry, applications to provide integration and remote delivery of data from operative or ICU environments

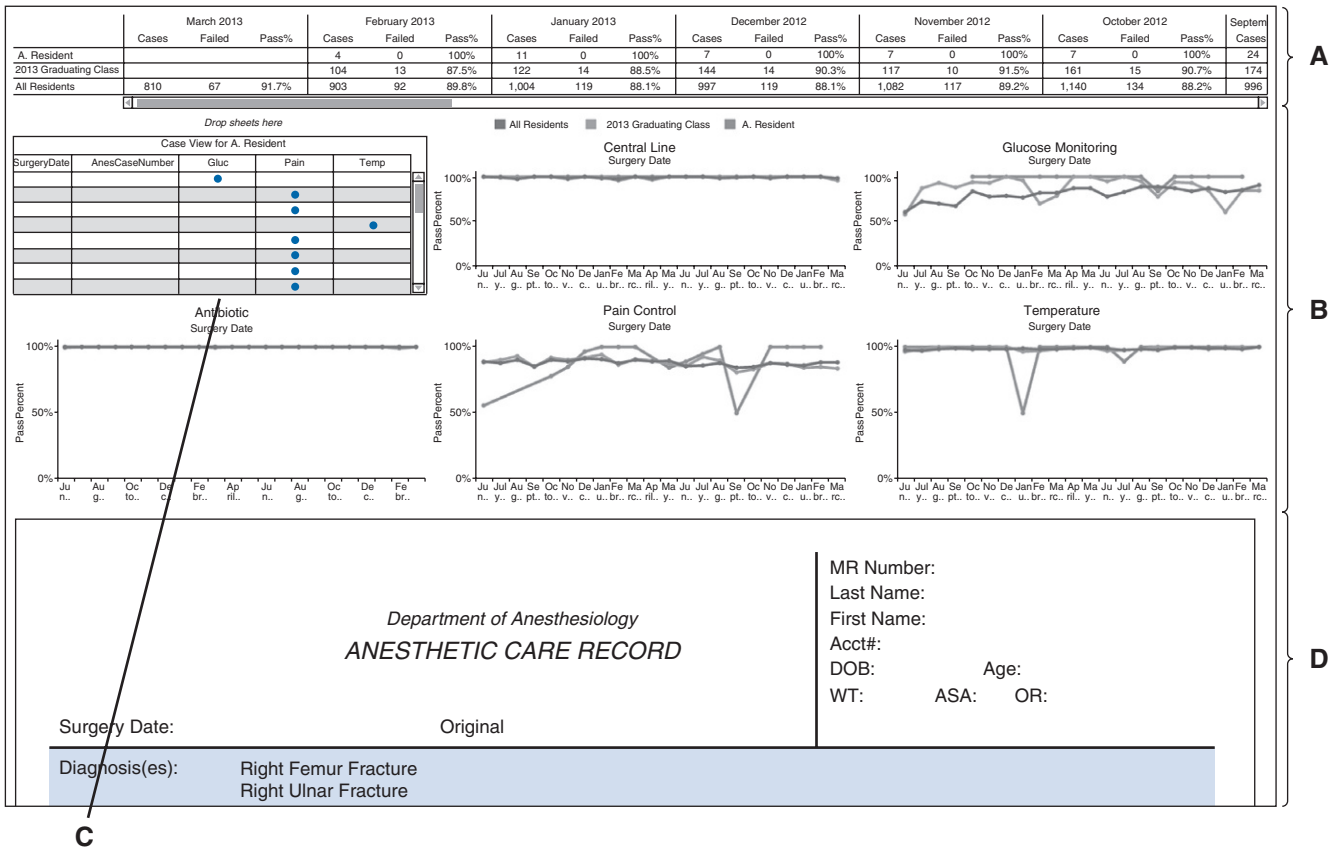


Fig. 28.1 This figure displays a quality dashboard designed for trainees. The panels show: **A,** a tabular view of the performance of a single resident in comparison to CA training level and entire program by month, with "pass/fail" as a binary score taking into account passing on all 5 metrics or not; **B,** a graphical representation of the performance of a single resident in comparison to CA level and entire program by individual metrics by month; **C,** individual case listings showing where performance failures occurred; and **D,** the PDF form of the case record. CA, clinical anesthesia. [Vanderbilt Anesthesia and Perioperative Informatics Research (VAPIR) Division, Vanderbilt University Medical Center, Nashville, TN]

nausea and vomiting.[17,18] There are a multitude of studies that have demonstrated the ability of these systems to improve process reliability, but far fewer that have linked CDS to actual improved surgical or anesthesia outcomes. Other systems have focused on the preoperative setting of care by providing guidance on appropriate testing and patient optimization.[19]

In order to be effective, clinical decision support systems must engage the end-user at the time when the information will be most helpful.[20] If information is not delivered in a timely fashion, delayed, or otherwise out of date, then the impact of the system is likely to be greatly diminished. This requires the information to be delivered in a manner that engages the end-user. This may involve sending an on-screen alert to an end-user on a dedicated workstation, an alphanumeric text page, SMS message, email, or other visual cues.[21–23]

MANAGERIAL FUNCTIONS

Compliance Tracking

In addition to providing CDS, most perioperative information management systems also provide functionality for tracking billing and regulatory compliance. By applying a series of logical business rules across a database of cases, systems can provide concurrency checking to ensure billing times do not overlap, and providers are not signed into an inappropriate number of cases.[24] These compliance checks can take the form of a billing report that coders can use to adjust how payment is requested, or in some cases can provide real-time reminders to clinicians to enable them to adjust their staffing as needed.[25] These systems also commonly can provide checks to detect when data are missing from electronic charts–such as required billing elements or other critical information such as patient drug allergies.[26] At one hospital, software that automatically evaluated the anesthetic records and alerted clinicians to documentation errors led to a decline in the percentage of anesthetic records that could never be billed from 1.31 to 0.04%. The same authors estimated that their system implementation increased departmental revenue by approximately $400,000 per year.[24]

Quality Management

The ability to scan large numbers of cases to evaluate for trends has been a helpful feature for many quality managers. Additionally, the reporting functionality brought by PIMS has enabled departments to use these systems to actively manage quality, participate in incentive programs, and identify problems. At least one center has leveraged their PIMS to develop the capability to automatically scan for downstream events, and then notify the perioperative provider when adverse events have occurred. This is possible through the analysis of postoperative orders, medications, and laboratory values—data which can all be made available electronically for continuous analysis.

A number of systems have also incorporated adverse event reporting. These systems have demonstrated a remarkable ability to identify problems by facilitating data capture, reporting, and analysis.[27,28] Key to the success of adverse event reporting has been integration into the end-users' workflow along with assurance that data will be subject to peer-review protections. Both are possible, but require attention to the detail of implementation. For example, many suggest that peer-review event data be sequestered in a separate database, to ensure adequate legal protection.

Ongoing Professional Performance Evaluation

Since 2008, the Joint Commission has required Ongoing Professional Practice Evaluation (OPPE) as a part of credentialing and privileging providers. These might include periodic chart review, direct observation, monitoring of diagnostic and treatment techniques, or discussions with other individuals involved in the care of the provider's patients. Several institutions have developed processes that leverage data from their automated information systems to facilitate compliance with this requirement. For example, the Massachusetts General Hospital developed an OPPE system that provides automated reports to physicians, listing for a series of metrics the total number of compliant cases and noncompliant cases, and a comparison by percentage to the baseline departmental evaluation. Additionally, a summary statement describes whether a physician's performance was within the group representing 95% of all department physicians and noncompliant cases are listed by medical record number and case date—to enable physicians to review individual cases.[29]

RETURN ON INVESTMENT

It has been difficult to quantify the return on investment of most perioperative information management systems. Although some have estimated the impact of these systems on billing operations,[24] the clinical benefits of a well-implemented system and potential to improve safety, communication, and overall efficiency are difficult to quantify.[30,31] Regardless, adoption of perioperative information management systems has accelerated, and by the end of 2014, 75% of academic centers reported that they were using a perioperative information management systems.[4]

CLINICAL AND OPERATIONS RESEARCH

Information systems have opened the door to a variety of different types of clinical and operations research activities that previously were not possible.[32] The ability to identify cases for analysis,[33] collect data automatically,[34] and, in some cases, even provide on-the-fly patient randomization[35] has led to an explosion in the number of clinical research studies based on data capture in perioperative information management systems.

Many centers have developed large data warehouses to aggregate data from their clinical systems. At Vanderbilt, a Perioperative Data Warehouse (PDW) has been developed which brings together information from the hospital's perioperative information management, laboratory, quality, billing systems, along with additional data from the institution's enterprise wide electronic health record. Containing data on over 1 million patients, more than 3,500 distinct case elements are available, including over 8 billion automatically recorded vital signs readings.

Additionally, several multi-institution national databases have developed, including the Multi-Center Perioperative Outcomes Group (MPOG) database,[36] housed at the University of Michigan, and the National Anesthesia Clinical Outcomes Registry (NACOR) developed by the Anesthesia Quality Institute.[37,38]

CHALLENGES AND FUTURE DEVELOPMENTS

One of the most promising aspects of the adoption of information systems across the perioperative environment is the ability to share, process, and re-purpose clinical and administrative information. The greatest challenges are centered on the lack of system interoperability and the difficulties many centers encounter when trying to integrate a new system into an existing clinical workflow. Clinicians are unlikely to endure processes that require duplicate data entry; although many initial system implementations were based on these types of redundant workflows because of the lack of system integration.

In the future, expect to see more useful information brought by these systems back to clinicians, managers, and even patients, which leverages the power of data that can be harnessed from multiple sources. This paradigm will enable clinicians to learn from past experiences, managers to improve their processes, and patients to better understand their disease processes and how to manage their health.

UNDERSTANDING INFORMATICS HARDWARE

Selecting and installing an information system is a complex process that requires collaboration to evaluate products, identify available resources, create leadership roles, create implementation plans and evaluate results.[39] Most informatics workstations are microcomputer type devices, sometimes with specialized displays for radiology, or whiteboard use. These units are often installed at the bedside, or in nursing stations, operating and procedural locations. Workstations must be installed in all locations where clinicians practice. Installation density should ideally be in high enough volume so that clinicians can complete their tasks without competing for an open workstation. The ergonomics of the workstation are also important, but often not well recognized prior to installation.[40] Clinicians must be able to access these devices in the course of ongoing patient care and do so without suffering work-related injuries. To that end, various mounting devices have been developed to attach the computer workstation to walls of patient rooms, and equipment such as anesthesia machines. Mobile desktop computers mounted to rolling carts known as "workstations on wheels" or "WOWs" which can be brought to any patient care location offer a versatile wireless solution. More recently, the development of handheld smartphone and tablet-based computing power has fostered the development of lightweight applications for information retrieval, data entry and remote monitoring.

Servers store data and process algorithms to modify, warehouse, or synthesize information from existing data. Depending on their use and function, servers may be scaled as single PC-sized devices or massive arrays of high power computers located in a hospital's data center. Data centers also often provide methods for duplicating server functionality so that in the event of a hardware failure of one server, a second server can preserve an intact data set and seamlessly continue whatever work is in progress. Server functionality is often duplicated in more than one physical location so that a local event such as a fire or flood will not destroy existing data or ongoing processing. Advancing these technologies is the development of cloud computing architecture for EMRs.[41] In cloud systems, data are held by a third party in a large, secure, multiple use systems.[42] Each system or user consumes only the total cloud computer resources capacity. This architecture presents advantages in installation, maintenance and expansion, which are particularly beneficial for smaller hospitals and also for hospitals in developing areas.[43]

DATA SECURITY AND CONFIDENTIALITY

Data security has become increasingly important as both the volume of patient data increases and attempts to breach security have become more common. The public has become very familiar with data losses related to the retail and financial industries where millions of pieces of data are potentially exposed. Medical systems have many of the same vulnerabilities and have been placed under strict guidelines regarding the reporting of breaches of security and data loss or theft. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 set forth stringent rules regarding data archiving, transmission, and requirements for reporting breaches and data theft or loss.[44] Significant improvements have been made to secure medical data. In 2013, a review article examined 49 studies related to data security and privacy policies and best practices.[45] However, even with the development of increased security protocols and encryption technologies, data loss has continued to increase.[46]

Compared to a traditional paper medical record, the electronic record offers both improvements and risks to the maintenance of confidentiality. With an electronic record access is greatly facilitated. It is not necessary to physically retrieve a paper chart from the records department. Any record or data can potentially be retrieved from any workstation. This level of easy access is one of the significant benefits of HIT systems, but it also creates risks for confidentiality as employees can potentially just as easily inappropriately review data from individuals who are not their patients as they can view their own patient's data. Inappropriate access to celebrity medical records has been reported in the lay press and several studies have expressed patient's concerns over access and control to the information in their medical records.[47,48] However, through system design these risks can be mitigated through access tracking and auditing. It is also possible to create intelligent auditing algorithms that seek to examine patterns of inappropriate or irregular access for further scrutiny.[49]

PROFESSIONALISM

Issues of professionalism are tightly connected to data security and confidentiality. Professionals must be on guard and prevent crossover of protected patient data to nonprotected data systems. The proliferation and integration of fixed workstations, mobile hand-held applications, email, and social media creates the opportunity for inappropriate use of HIT and the public display of unprofessional behavior.[50,51] In two studies of surgical resident applicants it was found that either 12%[50] or 16%[51] of applicants had frankly unprofessional material such as references to binge drinking, sexually inappropriate material, or HIPAA violations posted on their personal social media profiles. Several incidents have drawn the attention of news media, including posting pictures of, or comments about, patients on social websites. In response to these incidents, guidelines and policies are in development to provide guidance and establish standards.[52]

INFORMATICS RESOURCES AS EDUCATIONAL AND RESEARCH TOOLS

Informatics resources are now available which supplement and in some cases replace traditional textbook, library, and classroom resources. The information age is producing a flood of new information and new knowledge. Fortunately, medical professionals have near universal access to the internet, World Wide Web resources and sophisticated search engines. These tools have simplified finding answers to both broad topics and specific questions using the most up-to-date information available. However, clinicians must carefully formulate their questions and consider the source of the information retrieved. Both peer reviewed and non peer reviewed information may often be found. Additionally, newer resources may offer contrasting or refuting perspectives as older information is not necessarily removed and may be retrieved in preference to newer more accurate information due to the rankings generated by the various search engines in use.

Electronic Textbooks

For centuries textbooks have been the primary source of widely accepted information. While this may still be true, the format of the textbook has changed dramatically over the past

15 years. No longer is it necessary to purchase a physical paper bound book, or travel to a library to review or borrow a book. The majority of major textbooks have their most recent revisions available in an eBook format. In this format, users can pay either a fee or subscription and download a standard format file such as a PDF, or access an online version of the textbook from whatever location they are in, using whatever device (computer, tablet, mobile) they happen to have at the time. Many institutions provide a group subscription to a wide variety of publishers.

Scientific Journals/Medical Literature

Nearly the entire body of published medical literature is available via the World Wide Web. Printed indexes such as the Index Medicus have been replaced by electronic search engines such as Google Scholar, PubMed, and numerous others. These resources allow the user to nearly instantly search decades of published research. Sophisticated algorithms find and present the most relevant results based on the terms and any Boolean logic, which is entered by the user.[53] Because of the volume of information available, a user must effectively formulate the query entered in order to improve the accuracy of the search and narrow the number of items returned.[54] Additionally, many of the search engines include complex features to retrieve full text and graphics-based files, or export lists of references to reference managing software.[55]

Guideline Repositories

Supplementing the scientific literature, guideline repositories provide the clinician with reviewed summaries of established principles. These guidelines serve as an excellent resource to the clinician who is seeking practical advice on a particular clinical topic. The guidelines may either be evidence based, consensus statements, or a combination of both. Guidelines are sometimes established by professional societies such as the American Society of Anesthesiologists (ASA), the Society for Neuroscience in Anesthesiology and Critical Care (SNACC), the Society of Critical Care Medicine (SCCM) and others. Commercial and governmental organizations also publish clinical practice guidelines. Examples include the National Guideline Clearinghouse (US Department of Health and Human Services), the National Institute for Health and Care Excellence (British National Health Services), the Cochrane Library, Up To Date, and others.

Social Media

The last few years have seen an explosion of technologies that promote the interconnected nature of individual users of internet technologies. So-called "social media" enables anyone to participate in a discussion or distribution of their personal knowledge or perspective to a potentially vast audience. Using technologies such as podcasts (audio recordings available via the internet), YouTube (video recordings), blogs ("web logs" of recorded, categorized and searchable text based information) and Wikis (applications allowing group editing of a defined body of content), it is possible to retrieve content on virtually any topic.[56] However, one must use extreme caution with all of these resources as the accuracy, safety and appropriateness of the materials may in some instances be questionable, wrong, or dangerous. As always, the source and peer review process are critically important.

Informatics tools have provided an incredible level of efficiency and sophistication to aid in the accessing of a wide body of medical knowledge. Looking toward the future, this trend will likely continue as search engines and databases become more sophisticated.

CONCLUSION

Though starting at a disadvantage compared to other industries, there have been significant strides in HIT over the past two decades. Government incentives and regulation has coupled with an improved understanding of the safety and economic benefits of electronic medical systems to produce systems that can now capture and process the huge volume of patient information generated on a daily basis. Additionally, HIT systems not only store data, but can also analyze incoming data and provide messages and alerts to clinicians in real time, further improving the safety and reliability of health care. Capturing and refining data into data warehouses and registries is also of significant scientific value as medical operations research investigators seek new knowledge and improvements in health care delivery. The future of medicine is highly dependent on the success of medical informatics systems.

REFERENCES

1. Hirsch NP, Smith GB. Harvey Cushing: His contribution to anesthesia. *Anesth Analg*. 1986 Mar;65(3):288–293. PubMed PMID: 3513665.
2. DeVos CB, Abel MD, Abenstein JP. An evaluation of an automated anesthesia record keeping system. *Biomed Sci Instrum*. 1991;27:219–225. PubMed PMID: 2065158. Epub 1991/01/01. eng.
3. Egger Halbeis CB, Epstein RH, Macario A, Pearl RG, Grunwald Z. Adoption of anesthesia information management systems by academic departments in the United States. *Anesth Analg*. 2008 Oct;107(4):1323–1329. PubMed PMID: 18806048. Epub 2008/09/23. eng.
4. Stol IS, Ehrenfeld JM, Epstein RH. Technology diffusion of anesthesia information management systems into academic anesthesia departments in the United States. *Anesth Analg*. 2014 Mar;118(3):644–650. PubMed PMID: 24557109. Epub 2014/02/22. eng.
5. O'Day B, Kieffer T, Forrestal S, Esposito D. American Recovery and Reinvestment Act investments in data infrastructure. *J Comp Eff Res*. 2014 Nov;3(6):591–600. PubMed PMID: 25494565. Epub 2014/12/17. eng.
6. Selby J, Slutsky J. How a unique provision in the American Recovery and Reinvestment Act set a foundation for the patient-centered outcomes research institute. *J Comp Eff Res*. 2014 Nov;3(6):565–566. PubMed PMID: 25494560. Epub 2014/12/17. eng.
7. Lai M, Kheterpal S. Creating a real return-on-investment for information system implementation: life after HITECH. *Anesthesiol Clin*. 2011 Sep;29(3):413–438. PubMed PMID: 21871403. Epub 2011/08/30. eng.
8. Furukawa MF, Poon E. Meaningful use of health information technology: Evidence suggests benefits and challenges lie ahead. *Am J Manag Care*. 2011 Dec;17. (12 Spec No.):SP76a-SP. PubMed PMID: 22216771. Epub 2012/06/27. eng.
9. Kadry B, Feaster WW, Macario A, Ehrenfeld JM. Anesthesia information management systems: Past, present, and future of anesthesia records. *J Mt Sinai Hosp N Y*. 2012 Jan-Feb;79(1):154–165. PubMed PMID: 22238048. Epub 2012/01/13. eng.
10. Stabile M, Cooper L. Review article: The evolving role of information technology in perioperative patient safety. *Can J Anaesth*. 2013 Feb;60(2):119–126. PubMed PMID: 23224715. Epub 2012/12/12. eng.
11. Boonstra A, Broekhuis M. Barriers to the acceptance of electronic medical records by physicians from systematic review to taxonomy and interventions. *BMC Health Serv Res*. 2010;10:231. PubMed PMID: 20691097. Pubmed Central PMCID: PMC2924334. Epub 2010/08/10. eng.
12. Ehrenfeld JM, Rehman MA. Anesthesia information management systems: A review of functionality and installation considerations. *J Clin Monit Comput*. 2011 Feb;25(1):71–79. PubMed PMID: 20734117. Pubmed Central PMCID: 3387486. Epub 2010/08/25. eng.
13. O'Reilly M, Talsma A, VanRiper S, Kheterpal S, Burney R. An anesthesia information system designed to provide physician-specific feedback improves timely administration of prophylactic antibiotics. *Anesth Analg*. 2006 Oct;103(4):908–912. PubMed PMID: 17000802. Epub 2006/09/27. eng.
14. Ehrenfeld JM, Epstein RH, Bader S, Kheterpal S, Sandberg WS. Automatic notifications mediated by anesthesia information management systems reduce the frequency of prolonged gaps in blood pressure documentation. *Anesth Analg*. 2011 Aug;113(2):356–363. PubMed PMID: 21415437. Pubmed Central PMCID: 3121913. Epub 2011/03/19. eng.

15. Nair BG, Newman SF, Peterson GN, Schwid HA. Smart Anesthesia Manager (SAM)--a real-time decision support system for anesthesia care during surgery. *IEEE Trans Biomed Eng*. 2013 Jan;60(1):207–210. PubMed PMID: 22736635. Epub 2012/06/28. eng.
16. Nair BG, Peterson GN, Newman SF, Wu WY, Kolios-Morris V, Schwid HA. Improving documentation of a beta-blocker quality measure through an anesthesia information management system and real-time notification of documentation errors. *Jt Comm J Qual Patient Saf*. 2012 Jun;38(6):283–288. PubMed PMID: 22737780. Epub 2012/06/29. eng.
17. Nair BG, Horibe M, Newman SF, Wu WY, Peterson GN, Schwid HA. Anesthesia information management system-based near real-time decision support to manage intraoperative hypotension and hypertension. *Anesth Analg*. 2014 Jan;118(1):206–214. PubMed PMID: 24247227. Epub 2013/11/20. eng.
18. Kappen TH, Moons KG, van Wolfswinkel L, Kalkman CJ, Vergouwe Y, van Klei WA. Impact of risk assessments on prophylactic antiemetic prescription and the incidence of postoperative nausea and vomiting: A cluster-randomized trial. *Anesthesiology*. 2014 Feb;120(2):343–354. PubMed PMID: 24105403. Epub 2013/10/10. eng.
19. Hand WR, Bridges KH, Stiegler MP, et al. Effect of a cognitive aid on adherence to perioperative assessment and management guidelines for the cardiac evaluation of noncardiac surgical patients. *Anesthesiology*. 2014 Jun;120(6):1339–1349. PubMed PMID: 24705442. Pubmed Central PMCID: 4108481. Epub 2014/04/08. eng.
20. Epstein RH, Dexter F, Ehrenfeld JM, Sandberg WS. Implications of event entry latency on anesthesia information management decision support systems. *Anesth Analg*. 2009 Mar;108(3):941–947. PubMed PMID: 19224807. Epub 2009/02/20. eng.
21. Rothman BS, Dexter F, Epstein RH. Communication latencies of Apple push notification messages relevant for delivery of time-critical information to anesthesia providers. *Anesth Analg*. 2013 Aug;117(2):398–404. PubMed PMID: 23757478. Epub 2013/06/13. eng.
22. Epstein RH, Dexter F, Rothman B. Communication latencies of wireless devices suitable for time-critical messaging to anesthesia providers. *Anesth Analg*. 2013 Apr;116(4):911–918. PubMed PMID: 23385056. Epub 2013/02/07. eng.
23. Tappan JM, Daniels J, Slavin B, Lim J, Brant R, Ansermino JM. Visual cueing with context relevant information for reducing change blindness. *J Clin Monit Comput*. 2009 Aug;23(4):223–232. PubMed PMID: 19544053. Epub 2009/06/23. eng.
24. Spring SF, Sandberg WS, Anupama S, Walsh JL, Driscoll WD, Raines DE. Automated documentation error detection and notification improves anesthesia billing performance. *Anesthesiology*. 2007 Jan;106(1):157–163. PubMed PMID: 17197858. Epub 2007/01/02. eng:.
25. Freundlich RE, Barnet CS, Mathis MR, Shanks AM, Tremper KK, Kheterpal S. A randomized trial of automated electronic alerts demonstrating improved reimbursable anesthesia time documentation. *J Clin Anesth*. 2013 Mar;25(2):110–114. PubMed PMID: 23333782. Epub 2013/01/22. eng.
26. Sandberg WS, Sandberg EH, Seim AR, et al. Real-time checking of electronic anesthesia records for documentation errors and automatically text messaging clinicians improves quality of documentation. *Anesth Analg*. 2008 Jan;106(1):192–201. table of contents. PubMed PMID: 18165578. Epub 2008/01/01. eng.
27. Vigoda MM, Gencorelli F, Lubarsky DA. Changing medical group behaviors: Increasing the rate of documentation of quality assurance events using an anesthesia information system. *Anesth Analg*. 2006 Aug;103(2):390–395. table of contents. PubMed PMID: 16861422. Epub 2006/07/25. eng.
28. Peterfreund RA, Driscoll WD, Walsh JL, et al. Evaluation of a mandatory quality assurance data capture in anesthesia: A secure electronic system to capture quality assurance information linked to an automated anesthesia record. *Anesth Analg*. 2011 May;112(5):1218–1225. PubMed PMID: 21415434. Epub 2011/03/19. eng.
29. Ehrenfeld JM, Henneman JP, Peterfreund RA, et al. Ongoing professional performance evaluation (OPPE) using automatically captured electronic anesthesia data. *Jt Comm J Qual Patient Saf*. 2012 Feb;38(2):73–80. PubMed PMID: 22372254. Epub 2012/03/01. eng.
30. St Jacques P, Rothman B. Enhancing point of care vigilance using computers. *Anesthesiol Clin*. 2011 Sep;29(3):505–519. PubMed PMID: 21871407. Epub 2011/08/30. eng.
31. Muravchick S, Caldwell JE, Epstein RH, et al. Anesthesia information management system implementation: A practical guide. *Anesth Analg*. 2008 Nov;107(5):1598–1608. PubMed PMID: 18931218. Epub 2008/10/22. eng.
32. Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: Enabling reuse for clinical research. *J Am Med Inform Assoc*. 2013 Jan 1;20(1):144–151. PubMed PMID: 22733976. Pubmed Central PMCID: 3555312. Epub 2012/06/27. eng.
33. Epstein RH, St Jacques P, Stockin M, Rothman B, Ehrenfeld JM, Denny JC. Automated identification of drug and food allergies entered using non-standard terminology. *J Am Med Inform Assoc*. 2013 Sep-Oct;20(5):962–968. PubMed PMID: 23748627. Pubmed Central PMCID: 3756276. Epub 2013/06/12. eng.
34. Mraovic B, Schwenk ES, Epstein RH. Intraoperative accuracy of a point-of-care glucose meter compared with simultaneous central laboratory measurements. *J Diabetes Sci Technol*. 2012 May;6(3):541–546. PubMed PMID: 22768884. Pubmed Central PMCID: 3440046. Epub 2012/07/10. eng.
35. Blum JM, Stentz MJ, Maile MD, et al. Automated alerting and recommendations for the management of patients with preexisting hypoxia and potential acute lung injury: A pilot study. *Anesthesiology*. 2013 Aug;119(2):295–302. PubMed PMID: 23681144. Pubmed Central PMCID: 3813292. Epub 2013/05/18. eng.
36. Bateman BT, Mhyre JM, Ehrenfeld J, et al. The risk and outcomes of epidural hematomas after perioperative and obstetric epidural catheterization: A report from the Multicenter Perioperative Outcomes Group Research Consortium. *Anesth Analg*. 2013 Jun;116(6):1380–1385. PubMed PMID: 22504213. Epub 2012/04/17. eng.
37. Dutton RP. Registries of the anesthesia quality institute. *Int Anesthesiol Clin*. 2014 Winter;52(1):1–14. PubMed PMID: 24370717. Epub 2013/12/29. eng.
38. Dutton RP, Dukatz A. Quality improvement using automated data sources: The Anesthesia Quality Institute. *Anesthesiol Clin*. 2011 Sep;29(3):439–454. PubMed PMID: 21871404. Epub 2011/08/30. eng.
39. Muravchick S, Caldwell JE, Epstein RH, et al. Anesthesia information management system implementation: A practical guide. *Anesth Analg*. 2008 Nov;107(5):1598–1608. PubMed PMID: 18931218. Epub 2008/10/22. eng.
40. Berner K, Jacobs K. The gap between exposure and implementation of computer workstation ergonomics in the workplace. Work: A Journal of Prevention. *Assessment and Rehabilitation*. 2002;19(2):193–199. 01/01/.
41. Zangara G, Corso PP, Cangemi F, Millonzi F, Collova F, Scarlatella A. A cloud based architecture to support Electronic Health Record. *Stud Health Technol Inform*. 2014;207:380–389. PubMed PMID: 25488244. Epub 2014/12/10. eng.
42. Armbrust M, Fox A, Griffith R, et al. A view of cloud computing. *Commun ACM*. 2010;53(4):50–58.
43. Yao Q, Han X, Ma XK, Xue YF, Chen YJ, Li JS. Cloud-based hospital information system as a service for grassroots healthcare institutions. *J Med Syst*. 2014 Sep;38(9):104. PubMed PMID: 25015761. Epub 2014/07/13. eng.
44. Clark LW, Bilimoria NM. How HIPAA final rules affect health information technology vendors. *J Med Pract Manage*. 2013 Jul-Aug;29(1):56–58. PubMed PMID: 24044202. Epub 2013/09/21. eng.
45. Fernandez-Aleman JL, Senor IC, Lozoya PA, Toval A. Security and privacy in electronic health records: A systematic literature review. *J Biomed Inform*. 2013 Jun;46(3):541–562. PubMed PMID: 23305810. Epub 2013/01/12. eng.
46. Miller AR, Tucker CE. Encryption and the loss of patient data. *J Policy Anal Manage*. 2011;30(3):534–556.
47. Caine K, Hanania R. Patients want granular privacy control over health information in electronic medical records. *J Am Med Inform Assoc*. 2013 Jan 1;20(1):7–15. PubMed PMID: 23184192. Pubmed Central PMCID: PMC3555326. Epub 2012/11/28. eng.
48. Dhopeshwarkar RV, Kern LM, O'Donnell HC, Edwards AM, Kaushal R. Health care consumers' preferences around health information exchange. *Ann Fam Med*. 2012 Sep-Oct;10(5):428–434. PubMed PMID: 22966106. Pubmed Central PMCID: PMC3438210. Epub 2012/09/12. eng.
49. Menon AK, Jiang X, Kim J, Vaidya J, Ohno-Machado L. Detecting inappropriate access to electronic health records using collaborative filtering. *Machine Learning*. 2014 Apr 1;95(1):87–101. PubMed PMID: 24683293. Pubmed Central PMCID: PMC3967851. Epub 2014/04/01. Eng.
50. Langenfeld SJ, Cook G, Sudbeck C, Luers T, Schenarts PJ. An assessment of unprofessional behavior among surgical residents on Facebook: A warning of the dangers of social media. *J Surg Educ*. 2014 Nov-Dec; 71(6):e28–e32. PubMed PMID: 24981657. Epub 2014/07/02. eng.
51. Ponce BA, Determann JR, Boohaker HA, Sheppard E, McGwin Jr G, Theiss S. Social networking profiles and professionalism issues in residency applicants: An original study-cohort study. *J Surg Educ*. 2013 Jul-Aug;70(4):502–507. PubMed PMID: 23725938. Epub 2013/06/04. eng.
52. Farnan JM, Snyder Sulmasy L, Worster BK, Chaudhry HJ, Rhyne JA, Arora VM. Online medical professionalism: Patient and public relationships: Policy statement from the American College of Physicians and the Federation of State Medical Boards. *Ann Intern Med*. 2013 Apr 16;158(8):620–627. PubMed PMID: 23579867. Epub 2013/04/13. eng.
53. Cheng S, Hristidis V, Weiner M. Leveraging user query sessions to improve searching of medical literature. *AMIA Annu Symp Proc*. 2013;2013:214–223. PubMed PMID: 24551332. Pubmed Central PMCID: 3900173.

54. Webster AC, Cross NB, Mitchell R, Craig JC. How to get the most from the medical literature: Searching the medical literature effectively. *Nephrology*. 2010 Feb;15(1):12–19. PubMed PMID: 20377765.
55. Ebbert JO, Dupras DM, Erwin PJ. Searching the medical literature using PubMed: A tutorial. *Mayo Clin Proc*. 2003 Jan;78(1):87–91. PubMed PMID: 12528881.
56. Boulos MN, Maramba I, Wheeler S. Wikis, blogs and podcasts: A new generation of Web-based tools for virtual collaborative clinical practice and education. *BMC Med Educ*. 2006;6:41. PubMed PMID: 16911779. Pubmed Central PMCID: 1564136.

Future Advances in Neuroanesthesia

29

W.A. Kofke • J. Hensley

Numerous clinical situations remain as problematic issues which continue to vex neuroanesthesiologists and neurointensivists as they work to optimize outcomes for their patients. Nascent research ongoing at this time may provide a window to a future approach to these problems. In this chapter we review many of these new research areas and speculate as to how they may eventually translate to clinical care of neurosurgical patients in the operating room and neurointensive care unit. Areas to be reviewed include genomics, stem cells, neuroprotection, ICP management, technology, and pharmacology.

GENOMICS

Each cell has to produce proteins in order to function. The specific protein structure is determined by the sequence of base pairs on the organism's DNA combined with post-translational modifications. One estimate is that there are some 35,000–40,000 genes with about 6,000 proteins active at any given time. However, actual protein composition varies according to the needs (and regulation) of the moment such that as many as 100,000 proteins are thought to be transcribed by a cell.[1] Thus, the actual genetic structure of an individual has an important role in the development of and response to disease and the response to therapy.

The field of genomics is significantly complex.[2] Notably the word "gene" has a multitude of definitions,[3] reflecting the wide variety of approaches to the field. The field includes work with single nucleotide polymorphisms (SNPs), transcript mRNA studies, siRNA epigenetics and copy number variants. SNPs are naturally occurring variation in the specific DNA nucleotides that code for specific proteins resulting in naturally occurring variations in proteins with associated variations in function. After a gene has been transcribed into mRNA then further regulation with potential for variation arises such that there can be heritable changes in gene expression or translation without a change in DNA sequence, so-called epigenetics[2] work. This concept is more recently and specifically described in siRNA (short interfering RNA) epigenetics studies wherein a transcribed mRNA is bound by a complementary siRNA, thus interfering (or regulating) the translation of the DNA nucleotide sequence into a protein. These observations have spawned an area of genetics research examining the possible uses of these interfering RNAs as future research or therapeutic tools.[4]

To date, SNPs are the variant type of choice for association studies in common diseases and complex traits.[5] This has resulted in many case control and association studies that have provided valuable information on age-related macular degeneration, diabetes, obesity, cardiovascular diseases, prostate cancer, and breast cancer.[5] However, SNPs are not the only source of polymorphism of the human genome. Another abundant source of polymorphism, the so-called copy number variants, is one that involves deletions, insertions, duplications and complex rearrangements of genomic regions. Such polymorphisms can result in deletion of specific genes, as occurs with rhesus blood type, or with increased numbers of copies of genes, as has been demonstrated with alpha hemoglobin. Indeed, up to 10% of the variation in the human genome has been attributed to copy number variation (also called copy number polymorphism).[5] Notably, the number of combinations and permutations of these causes of variation seem endless. Thus, biostatistical issues with sample size, repeated measures, sample independence, and association versus causation become essential considerations in experimental design and the ability to draw conclusions from the data. One practical result of these constraints with SNP and other studies is that the most robust conclusions can only be derived from variants which have a high enough frequency to reasonably allow for inferences to be drawn.

These and other current advances in causes of genomic variation foretell a day when an individual patient's genome will be part of his/her history and physical examination. This information will be used to allow the anesthesiologist to optimize or individualize specific anesthetic effects, such as hyperemia or neuroexcitation in specific brain areas, define likely anesthetic tolerance and thus appropriate dosing, foretell susceptibility to ischemic and other types of brain damage, and adapt the application of general medical therapies to a person's specific genomic signature.[6] Moreover, this information will undoubtedly lead to efforts to alter an individual's genotype, genomic regulation, or phenotype either with respect to the diseases anesthesiologists see in the operating room (OR) or with respect to specific responses to anesthetic interventions. A series of annual reviews have underscored these issues.[7–9]

Specific Anesthetic Effects of Genetic Factors

Blood Flow and Metabolism

Probably the first report to detail a neurophysiologic effect of an anesthetic drug based on a single nucleotide polymorphism was published by Kofke et al.[10] They determined the cerebral blood flow (CBF) response to increasing doses of remifentanil in human volunteers, determining an element of limbic system activation. However, subjects with an ApoE4 genotype had a different pattern of limbic system response from those who did not possess this SNP. If similar analogous effects of anesthetics are found with other SNPs we can expect an SNP-based selection of anesthetics based on the likelihood of producing some side effects such as cerebral hyperemia, ictal activation or suppression, and variable neuroprotection.

In a non-neurologic context early studies in rodents indicate that changes in chromosome composition affect cardiovascular responses to propofol.[11] Countless other physiologic responses to anesthetics will also undoubtedly be determined with each patient's genome studied for anticipated interactions between genome and reaction to an anesthetic or other perioperative drug.

MAC, Analgesia, and Other Anesthetic Side Effects

Redheads are known to require more anesthesia than the rest of the population.[12] As such this represents probably the first observation of a heritable condition's effect on MAC, although the specific SNP or set of SNPs or other causes of genetic variation producing red hair and linking this to anesthesia are not known. Early studies in nematodes have isolated specific genes which impact on sensitivity to anesthetics.[13,14] Moreover, specific genetic alterations in mice are reported to affect anesthetic sensitivity to disparate anesthetics pentobarbital, ketamine, and nitrous oxide.[15] A clinical correlate of these observations can be found in Mullholland et al.'s report of the effect of various SNPs on several of the EEG responses to desflurane anesthesia in humans,[16] though one might suggest that this is not that important as future management paradigms will most likely entail individual titration. Nonetheless this type of information will likely also relate to pain tolerance,[17] anticipated needs for postoperative pain control regimens and, possibly, susceptibility to addiction. Such studies in humans have been published describing specific SNPs affecting pain tolerance and need for postoperative analgesia.[18–26] In addition, neuropathic pain and more focused pain therapy is suggested in some preclinical studies evaluating effects of siRNA treatment on pain.[27–29] Moreover, SNPs are now being described in humans regarding genetic predisposition to postoperative nausea and vomiting,[30,31] malignant hyperthermia,[32] and cognitive dysfunction.[33]

Pharmacokinetics

Genetic influences on pharmacokinetics have become reasonably well known for a handful of antihypertensive drugs as they relate to genetic effects on metabolism (e.g., hydralazine)[34] and perioperative drugs.[35–37] Certainly, genetic factors are known for such entities as pseudocholinesterase deficiency,[38] the interaction of thiopental with porphyria,[39] or the genetics of malignant hyperthermia.[32,40] Cytochrome P450 is important in the metabolism of many drugs including anesthetics. These genomic variations in cytochrome P450 have been reported to impact on the metabolism of midazolam[41] and opioids,[35,36] with clinical relevance made manifest in a report of genomic differences with cytochrome contributing to mortality from non-medical fentanyl ingestion.[42] Multiple other effects of genetic variation on anesthetic metabolism and side effects have been reviewed.[43] It is clear that increased information will become available with respect to SNPs, arrays of SNPs, and other causes of genetic variation and their impact on anesthetic metabolism.[40]

Ischemic Tolerance

One group reports that up to 10% or more of genes undergo alteration in expression after brain ischemia.[44,45] In humans, alterations in the expression of genes responsible for the inflammatory response have similarly been reported after stroke.[46,47] Many others report increased risk of stroke associated with different genotypes. Thus, the effect of one's genomic inheritance on one's predisposition to stroke and susceptibility to its sequelae may be an important piece of information. However, the preponderance of such research in humans deals with genomic contribution to risk of stroke and not with direct genomic contribution to tolerance of, or vulnerability to, brain ischemia, factors which, arguably, are of greater interest to the neuroanesthesiologist.

These risk-oriented studies are nonetheless important areas of research. However, they are confounded by the natural heterogeneity of clinical stroke and provide no information on the possible genomic contributors in humans to congenitally determined ischemic tolerance or vulnerability. Three lines of genetic research have introduced the notion of gene-based ischemic tolerance which may be a therapeutic target. In the first, altering the genetic makeup of animals subsequent to cerebral ischemia can alter the animal's ischemic tolerance.[48–51] In the second line of work, researchers have demonstrated that environmental factors introduced in advance of a severe ischemic insult can induce genes to produce proteins that provide tolerance to subsequent ischemia. The prototypical paradigm is one of ischemia or other insult inducing upregulation of heat shock proteins, which are important contributors to subsequent tolerance to a greater ischemic stress.[52] Other genes have also been suggested as contributing to ischemic preconditioning.[53,54] Indeed, some authors are now suggesting induction of ischemic tolerance as the basis for recovery in an ischemic penumbra.[55] And, thirdly, Kofke et al. have observed genomic factors apparently contributing to a greater release of biomarkers of brain damage during cardiac surgery.[56]

Cerebral ischemia clearly has a significant effect on transcription and translation of important genes, perhaps related to organismal survival and evolution.[44,45,57,58] The phenomenon of ischemic tolerance has been known for many years. Although incompletely understood, a basis in altered genetic regulation seems likely[44,45,58] with the most attractive corollary that such information will lead to gene-based therapeutics.[57,58] Gidday et al.[59] observed that the extent of cerebral infarction in a neonatal rat model was substantially attenuated if animals were pretreated with small doses of hypoxia first. This work was further developed and supported with similar observations in other ischemic models. Recent work has suggested convincingly that elaboration of heat shock proteins has an important role in ischemic tolerance.[52] Other candidate contributing genes have also been suggested. HIF-1 (hypoxia inducible factor) is one such alternate inducible protective protein.[53] Also described in this context are erythropoietin,[54] glial cell-line-derived neurotrophic factor,[60] and TGF beta-1.[61] One report provides convincing evidence that a significant component of HIF is, in fact, induced expression of erythropoietin.[62]

The preischemic stress does not necessarily have to be an hypoxic/ischemic stress, as fever and acidosis[63] (among others) also induce subsequent ischemic tolerance mediated by induction of a protective protein. Similarly, ischemic tolerance can be pharmacologically induced by pretreatment with estrogen (Bcl-2),[64] cobalt chloride (HIF-1),[53] desferrioxamine (HIF-1),[53] or isoflurane.[65] In contrast, ischemia, despite the induction of a plethora of putative protective genes, also induces the BRCA-1 associated protein BARD-1 that mediates apoptosis,[66] which is thought to be deleterious. Genetic manipulation of mice has also been used and also demonstrates how genetic factors can alter endogenous vulnerability to an ischemic insult.[49–51,57,67,68] Bernaudin et al. identified several genes that appear to be regulated by hypoxia, leading them to suggest that these could have a role in a genetic predisposition to ischemic tolerance.[69] Genetic makeup and gene expression clearly contribute to one's vulnerability to brain ischemia.

Nonetheless the notion of ischemic preconditioning is an increasingly attractive one. Recent research underscores the complexity of this phenomenon with numerous reports on only some of the factors thought to play a role.[70–79] One important practical consideration in translating these findings to clinical management will be defining whether a given preconditioning therapy has, indeed, introduced increased ischemic tolerance. This consideration underlies work which is endeavoring to identify biomarkers, indicating, before ischemia, that tolerance has been enhanced.[80]

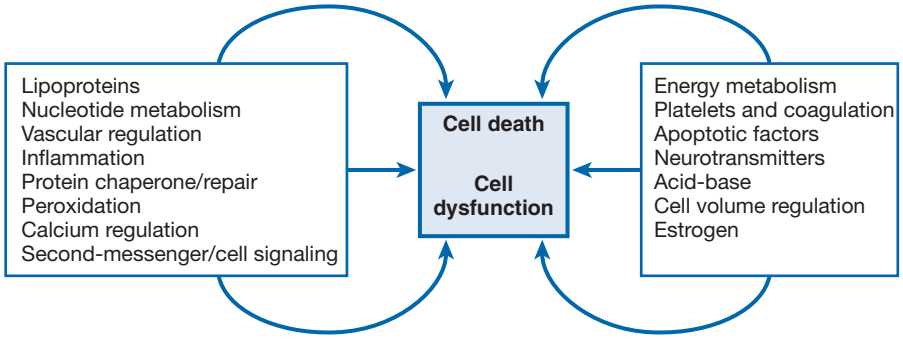


Fig. 29.1 Proposed pathophysiologic axes of cerebral ischemia that can be used as a basis for single nucleotide polymorphism selection in the proposed research.[81]

Hundreds of nucleotide polymorphisms are under active investigation of their contribution to stroke and other cardiovascular diseases. Such studies in humans generally deal with the role of a gene in risk of stroke. Many genes have been suggested, based on animal work such as that described above, to have important roles in determination of tolerance to ischemia. However, of the apparent myriad of potentially important genes only a relative handful of genes have been studied. Nonetheless, one can surmise, based on knowledge about the pathophysiology of cerebral ischemia, that evaluation of pathogenetically grouped genes would be a rational approach to screening for SNPs and other causes of genetic variation with potential therapeutic value. From such an approach one could develop "ischemic axes" with corresponding variant structure and regulation of genes, gene number, transcription, and translation, as depicted in Fig. 29.1. This knowledge could be used to develop new neuroprotective therapies or, if known for an individual patient, be used to tailor optimal neuroprotective therapy. Finding such clinically relevant effects for a given patient's or patient group's genetic variables will then lead to more intense scrutiny of the protein eventually translated that is transcribed by a given gene. Such information will then lead to rational selection of genes for possible gene delivery or perhaps development of drugs which mimic the effect of favorable proteins or inhibit the effects of unfavorable proteins. Examples of the validity of this approach are now appearing.

Several years of work from many investigators has shown the relevance of ApoE polymorphisms to neurologic outcomes. Thus, it should be clear that unlike most gene association studies used to predict a given patient's risk based on his/her genomic profile, knowledge of SNP associations with ischemic tolerance will likely result in new genome-based gene, proteomic, or other categories of neuroprotective therapies. This is simply one example of potential translational outcomes from such genomic association studies. In the case of ApoE, work has followed on the neuroprotective potential of so-called apo-mimetic peptides. Preclinical reports indicate neuroprotective efficacy in hypoxia-ischemia,[82] subarachnoid hemorrhage,[83] peripheral nerve injury,[84] traumatic brain injury,[85] intracerebral hemorrhage,[86] autoimmune encephalitis,[87] and spinal cord injury.[88] It thus seems likely that identified genomic contributors to tolerance or vulnerability to acute brain insults will lead to gene-based therapies and also associated proteomic-based therapies.

Risk of Comorbidities

Gene association studies with stroke are just one example of the role of genomics in defining a given medical risk. Such studies are burgeoning regarding a host of medical conditions. There have been some studies showing statistical associations between specific SNPs and postoperative complications.[89] Specific examples include renal failure,[90,91] post-transplant kidney infection,[92] total hip arthroplasty failure,[93,94] allograft dysfunction,[95] pain intensity and analgesic requirements,[96–102] vasopressor requirements,[103] myocardial infarction,[104] inflammatory response,[105] thromboembolism,[106,107] stroke,[108] and vascular graft patency.[109,110] These studies will undoubtedly contribute to risk assessment in individual patients and lead to new therapeutic strategies designed to minimize perioperative complications.

Application of Therapies to a Specific Genomic Signature

At the time of writing, characterization of the entire genomes of many humans has been accomplished.[111] This, combined with the abovementioned material, indicates a future that will encompass patients arriving for surgery with their entire genomes on record. One expectation is personal genome sequencing in many healthy people who later present for neurosurgery. This will likely also include other personal "omics" profiling. Applied across a population, including neurosurgical patients, this suggests characterization of the genome, epigenome, transcriptome, proteome, cytokine-ome, metabolome, auto antibody-ome, and microbiome (gut, urine, nose, tongue, skin) for possibly billions of individuals. With this we will have a large amount of impressively big data (e.g., a million genes and other -omic information in millions to billions of people). One hoped for consequence of this will be an ability to predict and monitor diseases, resulting in personalized therapies identified from big data analyses that will increase tolerance to various brain insults in individual patients. In addition, -omic profiling may allow us to tailor anesthetics to individuals or at least predict the consequences of anesthesia and surgery. For example, metabolomic profiling using proton magnetic resonance spectroscopy in children under anesthesia has demonstrated that sevoflurane anesthesia results in higher brain lactate and glucose levels in children compared with propofol.[112] Analysis showed a positive correlation between lactate and glucose levels with agitation and delirium.

STEM CELLS

Stem cells seem certain to be an important future therapeutic tool.[113,114] In fact, recent work has shown that transplantation of mesenchymal stem cells into patients following ischemic stroke not only is safe, but also may improve survival and functional outcome.[115] In addition, recent work has shown that injection of mesenchymal stem cells into the intervertebral disc in patients with discogenic back pain may improve pain and function for up to 2 years post-procedure.[116] Larger trials to investigate the utility of this therapy are currently underway.

This will have important implications for neuroanesthesiologists who may encounter patients who are having neural stem cells placed as part of an operative procedure or who have had them placed earlier with a variable extent of post-implantation differentiation. Given the recent data suggesting specific neurotoxicity of some anesthetics in developing brain,[117] it becomes reasonable to suggest that anesthetics used in the context of stem cell placement could significantly affect the success of the graft. Moreover, the physiologic milieu of the implantation may also be important. One well-known example of this is the effect of hyperoxia on immature retinal cells.[118] Blood pressure, pCO2, temperature, and other aspects of anesthetic administration may have a similarly important impact. Future research will be needed to resolve these issues.

NEUROPROTECTION

Neuroprotection has long been and should continue to be a central focus of neuroanesthesia and neurocritical care. At the time of writing, notwithstanding ample promising preclinical work, there are very few neuroprotectant strategies that have sustained scrutiny in clinical trials. There is significant laboratory work which forms much of the basis of neuroanesthesia practice. Much of this is based on the notion that a physiologic or anesthetic decision needs to be made and in the absence of satisfactory human data, the preclinical laboratory data are used to justify a decision.[119] This current situation should eventually be rectified. Some encouraging approaches are currently being evaluated. These probably represent only a small fraction of what will eventually become a part of an evidence-based approach to neuroprotection during neurosurgical procedures.

Hypothermia

Definition of Subsets Suitable for Hypothermia

Hypothermia presently has evidence-based support for its use after global brain ischemia.[120,121] Clifton et al.'s[122] multi-institutional study in TBI indicates that a TBI patient arriving hypothermic should not be rewarmed, although a protective effect of *de novo* induction of hypothermia could not be demonstrated.[123] The authors postulated that earlier induction of hypothermia may improve outcome; however, a second trial did not demonstrate any benefit.[124] Meanwhile, others have shown that induction of long-term (5 days) vs. short-term (2 days) mild hypothermia may be associated with decreased incidence of rebound intracranial hypertension on rewarming and improved functional outcome.[125] The IHAST study[126] in over 1000 patients undergoing aneurysm surgery showed no efficacy from the global practice of inducing moderate hypothermia in all patients undergoing cerebral aneurysm surgery. It still leaves open the question of the potential efficacy for a patient with active severe intraoperative focal temporary brain ischemia, without dealing statistically with all of the patients who did not need the hypothermia. The overwhelming evidence of efficacy in animal studies and humans with deep hypothermic circulatory arrest suggest a need to better focus the clinical studies to better identify the clinical subsets in which it will be found efficacious.[127–130]

New Methods to Induce Hypothermia

As with most neuroprotective therapies, the efficiency and efficacy of induction of hypothermia seems an important factor. Thus some research is ongoing that suggests important advances in the means by which hypothermia will be induced and maintained.

Ice Crystals

Cold fluids have long been used to decrease temperature.[131] This may have problems with the volume of fluid needed to affect the desired endpoints. Reports on using an ice slurry given intravenously[132] may result in an improved method to induce hypothermia quickly, safely, and in a controlled manner. Work is needed to ensure that the infused ice crystals have no sharp edges and thus pose no risk potential for endothelial trauma.

Heat Exchange Techniques

Currently new devices available include surface cooling devices[133] and intravascular cooling devices.[134] Future such devices will certainly have servo control systems that will enable the physicians to program or prescribe the desired central temperature and the device with its software will ensure maintenance of an unchanging level of hypothermia. A current conundrum in temperature reduction therapy is shivering, which can produce adverse systemic effects and prevent achievement of the normo- or hypothermic therapeutic endpoints.[135,136] It is likely that better understanding of this process will yield a reliable and safe pharmacologic approach to prevent shivering.

Hibernation

Hibernating animals routinely tolerate physiologic insults that are known to be deleterious in nonhibernating animals. These animals are able to induce profound decreases in temperature, adjust immune function, and have enhanced antioxidant defenses. They are capable, in a regulated manner, to decrease metabolic rate to as low as 2% of normal.[137] This has led to the notion that whatever neuroprotective mechanisms are operant in hibernating animals may have potential for translation to neuroprotection in humans.[138] A variety of neurally controlled biochemical processes that underlie hibernation have been reported.[137] Neural regulatory mechanisms include hibernation protein complex, and a variety of neurotransmitter systems, hydrogen sulfide[137,139,140] and neural circuits.[137,140] Molecular mechanisms of the organismic tolerance of this condition include a switch to lipid-based biofuel, inactivation of pyruvate dehydrogenase, altered structure and concentration of thyroid hormones, altered neuronal morphology,[140] delta opioids[141,142] and altered pH regulation.[143–145] Moreover, since the heart ordinarily develops lethal arrhythmias at hibernating temperatures a variety of gene-regulated processes have been postulated to allow continued cardiac contraction.[140] Evaluation of the genomes of hibernators is ongoing with the hope that identification of similarities with the human genome will lead to therapies that may activate these otherwise latent genes to better allow humans to tolerate ischemia or hypoxia without neural or other organ injury.[140] These notions form the basis for ongoing research to develop suspended animation methods, with overt intent to copy hibernation biochemistry and physiology [138,139,146,147] translated to attenuate problems in human neuroprotection.

Infrared Light Lasers

Several reports suggest that infrared light can be used to penetrate the skull to improve tissue energetics, notwithstanding an anaerobic condition. Data are very preliminary at this time, but laboratory studies are encouraging. Shining low level infrared light at a specific wavelength improves ATP production in neuronal culture,[148] and improves neurological outcome in animal stroke models.[149–151] Although preliminary studies in humans with stroke appeared promising, further study failed to demonstrate any benefit (NEST-2, NEST-3).[152] However, there may yet be a role for laser therapy in the neurosurgical setting.

Spinal Cord Injury Neuroprotection

Many avenues are being explored with many indications that this injury may be amenable to protection acutely and restoration chronically. Current research suggests the following as approaches likely to be translated eventually to clinical care.

Acute Protection

Promising studies in this area include pharmacological therapies,[153] surgical decompression,[153,154] and hypothermia. Early laboratory studies demonstrated the therapeutic potential of surgically applied hypothermia for several hours in the acute management of spinal cord injury with dramatic attenuation of paraplegia demonstrated by Albin et al.[155–157] In 2007, an NFL football player suffered a complete cervical spine injury and was immediately treated on the field with moderate hypothermia using cold saline IV. This player had a functional outcome that was better than expected and renewed interest in hypothermia as a treatment for SCI.

Maintenance of spinal cord blood flow is likely to be important in the acute management of spinal cord injury. Mesquita et al. are presently developing a near-infrared spectroscopy (NIRS)-based device that could be placed in a manner similar to an epidural catheter to yield continuous real-time spinal cord blood flow information. Preclinical studies in a spinal cord ischemia model are encouraging. This could have a dramatic impact on the management of patients presenting with spinal cord injury or spinal cord ischemia.[158]

Stem Cell Therapy

This is based on the use of embryonic stem cells or progenitor cells from other sources such as bone marrow to promote regeneration of cells and remyelination.[159–162] Animal studies support the feasibility of this approach, showing the capability of embryonic stem cells to develop into glial cells and into neural cells which make synaptic contacts.[159] In addition to these sources the nervous system itself may also be a source of endogenous stem cells.[159]

Genomic Therapy

Preclinical studies suggest a role for siRNAs in potentiating repair after SCI.[163] After spinal cord injury, astrocyte activation promotes glial scar formation. Telomerase reverse transcriptase (TERT) is part of the telomerase enzyme complex that aids in prolonging cell life by protecting the telomere. It is also associated with multiple nontelomere actions including cell activation, proliferation, and apoptosis. Evidence supports the hypothesis that TERT may be involved in astrocyte activation that results in glial scar formation. However, an antisense nucleotide targeting astrocyte TERT mRNA failed to significantly reduce glial scar formation following SCI in rats. Astrocyte activation and glial scar formation is a poorly understood process and the search for other potential molecular targets continues.

Neurotrophin Therapy[153]

A variety of approaches are currently being explored including cytokine blockade,[164] implantation of trophin producing cells,[162,165] viral gene transfer,[166] and implantation of stem cell progenitors of glial cells.[167]

Activity-based Restorative Therapy

Animal studies indicate that the paradigm of Brus-Ramer et al.[168] and others[153,169] offers promising opportunities to restore motor function using activity-dependent processes to strengthen the connectivity between "top-down" and "bottom-up" pathways. This notion has been further elaborated with early studies evaluating nanotechnology to produce focused electrical stimulation while monitoring consequent neurochemical processes deriving from such stimulation.[170] Clinical implementation of this approach is in early stages of study and implementation[159,171] using functional electrical stimulation (FES) has produced encouraging results, indicating the feasibility of this approach, perhaps in combination with stem cell therapy, to promote neural proliferation in areas of the spinal cord adjacent to the injury.[159] Notably, baclofen therapy seems to inhibit such regeneration.[159] A functional translation of this approach is the FES bicycle, used for years to promote return of function.[159] The best known example of this sustained, determined approach to achieve some recovery after a severe spinal cord injury is the case of actor Christopher Reeve who improved by two ASIA grades over 5 to 8 years post injury.[159]

Multimodality Approach to Neuroprotection

Establishing efficacy of new neuroprotective therapies in neurocritical care and stroke has proven to be an exercise in futility.[172] Over 2000 completed clinical trials are listed on the Internet Stroke Trials Registry[173] with few apparent reproducible results of any demonstrable efficacy in the acute context. However, these negative studies belie the supportive basic laboratory studies that justified the time and enormous expense for such attempted translational clinical trials. We provide a rationale to suggest that such results, in retrospect, are altogether predictable and suggest an explanatory model for such reproducible futility in a complex biological system. Many of the points discussed are supported in an editorial by Grotta.[172] It is to be expected that these issues will eventually lead to a commonplace approach to use multimodal therapies for neuroprotection. Donnan,[174] in the 2007 Feinberg lecture, suggests: "We have reached a stage at which research in this area should stop altogether or radical new approaches adopted." The new approaches may include a reevaluation of prospective randomized studies as the only path to new knowledge. A rationale for this approach as advocated by Kofke[81] follows.

Imagine a factory that makes widgets. A number of processes are important for the quality of the final widget as it proceeds: conveyor speed(x_1), presence of raw materials and power(x_2), quality of bolts(x_3), quality of steel(x_4), and type of metal used for circuits(x_5). A weighting factor can be applied to each variable w_i leading to the following general equation describing the widget quality:

$$Q = w_1x_1 + w_2x_2 + w_3x_3 + w_4x_4 \qquad (29.1)$$

Each variable x can be precisely known with very small variation so any change in any of the variables will produce a reproducible and predictable change in the widget quality Q.

In a biological system characterized by severity of a pathophysiologically complex injury, S, a similar equation can be derived with important pathophysiologic factors, x*i*, and weighting factors, w*i*:

$$S = w_1x_1 + w_2x_2 + w_3x_3 + w_4x_4 \qquad (29.2)$$

Notably different from the widget, however, is that there are a large number of disparate and potentially interacting factors known to contribute to with also an unknown number of as yet unknown factors with correspondingly unknown weighting factors and variability, partially represented in Fig. 29.1. Moreover, each pathophysiologic factor x*i* has to be described

over a biologically diverse population such that each factor has an associated central tendency and large normal or non-normal distribution about that mean. Moreover, the weighting factors and pathophysiologic factors also vary as a function of time after the onset of the insult. Thus, the importance of restoring cerebral flow is very high early on but late in the course it becomes a less important contributor to final outcome (e.g., thrombolysis works well if done promptly, but is fruitless if done a day later as the infarction process has completed).

Additionally, in the context of clinical medicine there are also associated system factors, H*i*, such as nursing ratio, nursing experience, availability of drugs and technology, efficiency of rapid response teams, and so on, which are also important to the severity of injury such that the equation can be written as:

$$S = \sum WiXi + \sum WiHi \qquad (29.3)$$

Given the above characterization of the multiple highly variable biological and system factors that enter into a given outcome, it should come as no surprise that clinical studies directed at improving only one of the abovementioned numerous complex factors tend to show no effect, especially if multi-institutional in design (increasing variation in H factors), unless it is truly a breakthrough phenomenon (large W factor such as early thrombolysis in ischemic stroke) or the therapy exerts a multifaceted effect (e.g., hypothermia). This then leads to the notion that the current widely accepted methods of advancing clinical knowledge for complex problems is generally futile, which subsequently produces **innovation paralysis** on the part of institutions, third party payers, clinicians, pharmaceutical companies, and investigators; an alternate method that is based on a multifactorial approach is needed. Rogalewski et al.[175] have recently reviewed and endorsed this concept; however, they fail to suggest a rational means for building the multimodal approach other than trying everything at once. A rational method is needed. Kofke's proposal entails a hybridization of QI methods and standard research techniques to create a novel model of incremental addition of therapies with ongoing evaluation of effects.[81]

INTRACRANIAL PRESSURE MANAGEMENT

Traditional methods of managing intracranial hypertension are primarily phenomenological. That is, the intracranial pressure (ICP) is elevated and therapy is implemented to decrease it. If warranted, investigation may be implemented to identify the etiology of intracranial hypertension (e.g., hydrocephalus or masses). However, vascular factors contributing to intracranial hypertension typically receive scant attention as to their contribution to an ICP problem. These vascular factors include systemic hypertension, cerebral venous hypertension, and hyperemia. Grande and coworkers[176] have emphasized the role of systemic hypertension exacerbating hydrostatic brain edema, leading to venous outflow obstruction, which, in turn, further exacerbates hydrostatic edema in a positive feedback cycle. Piechnik et al.[177] provide a mathematical model underscoring this issue, which, although triggered by systemic hypertension, is propagated by cerebral venous hypertension. Early experimental support is provided by Hayreh[178] and Nemoto.[179]

Another little appreciated factor is the role of normotensive hyperemia in the genesis of hydrostatic edema. Observations after arteriovenous malformation resection and carotid endarterectomy suggest a role for hyperemia contributing to a normal perfusion pressure breakthrough syndrome. Moreover, static observations of multiple patients at different points on the path from normal to hepatic encephalopathy provides strong circumstantial support for the notion that hyperemia precedes brain edema and intracranial hypertension in patients with liver failure.[180,181]

It seems likely that once appropriate monitors have been developed to provide reliable information regarding cerebral venous pressure/volume and cerebral blood flow, manipulation of these physiologic variables will become part of the standard paradigm in the treatment of intracranial hypertension.

TECHNOLOGY

Monitoring

Neuromonitoring has long been an area of active research and clinical contributions in anesthesia. Such a tradition is to be expected into the future. However, this area is full of challenges regarding validation of new monitors as accurately reflecting the desired parameter and, moreover, showing that making such measurements matters in a way that affects outcome. As noted in a quote of Pickering in an editorial on ICP measurement by Crosby and Todd[182]: "Not everything that counts can be counted, and not everything that can be counted, counts."

Continuous regional blood flow and metabolic rate monitoring, long a holy grail of neuromonitoring, should eventually be realized as a clinical reality. Currently attractive noninvasive methods tend to be based on NIRS with other invasive techniques that may also be useful.

Near-Infrared Spectroscopy-based Techniques

Since being first described by Jobsis in 1977 [183] and hailed as the "Monitor of the Future,"[184] NIRS has been developed as a noninvasive monitor of cerebral chromophores, oxyhemoglobin, deoxyhemoglobin, and cytochrome aa3. This is made possible by the property of infrared light being able to penetrate into tissue much deeper than visible light.[185,186] More recently researchers are reporting use of NIRS to facilitate continuous bedside rCBF monitoring. NIRS-based diffuse correlation spectroscopy (DCS), diffuse reflectance spectroscopy (DRS), and NIRS-based ICG blood flow index (BFI) and absolute CBF hold significant promise as bedside monitors of rCBF and metabolic rate ($CMRO_2$). DCS combined with ICG offers the potential for a truly continuous rCBF and $CMRO_2$ monitoring.

Diffuse Correlation Spectroscopy and Diffuse Reflectance Spectroscopy

DCS for continuous evaluation of rCBF[187] and DRS for continuous evaluation of $CMRO_2$ and oxygen extraction fraction (OEF) are recently reported advances using infrared light to provide real-time continuous information on changes in rCBF and $rCMRO_2$, with quantitative information on OEF, with promising studies reported in subprimate animal models and preliminary studies in humans.[188]

Diffuse Correlation Spectroscopy

Near-infrared photons diffuse through thick living tissues.[189] When diffusing photons scatter from moving blood cells, they experience phase shifts that cause the intensity of detected light on the tissue surface to fluctuate in time. These fluctuations are more rapid for faster moving blood cells. Therefore, one can derive information about tissue blood flow far below the tissue surface from measurements of temporal fluctuations impressed on diffusing light. Further details of the DCS method can be found elsewhere.[187,190–193] Changes in DCS CBF were evaluated by Kim et al.[194] in subarachnoid hemorrhage (SAH)

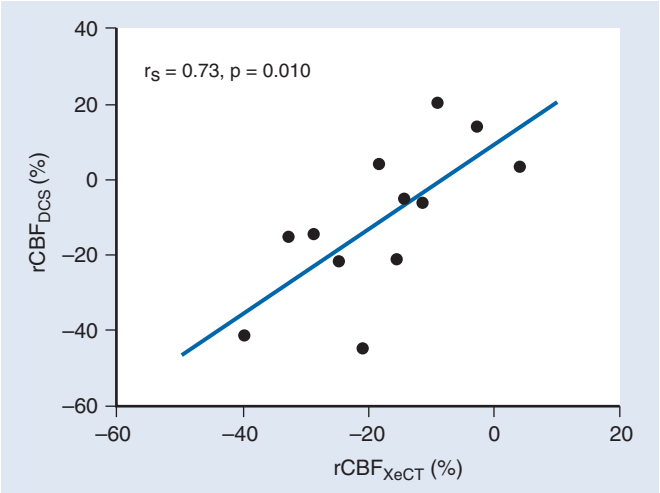


Fig. 29.2 Scatter plot illustrating the correlation between $rCBF_{DCS}$ and $rCBF_{XeCT}$ calculated from ROIs drawn under the optical probes. The fit line has a slope of 1.1 and an offset of 9.3%.[194] *(From Pattinson K, Rogers R, Mayhew S, et al. Remifentanil-Induced Cerebral Blood Flow Effects in Normal Humans: Dose and ApoE Genotype, Anesthesia & Analgesia (2008) 106:1 Wolters Kluwer Health by permission of Oxford University Press (www.oup.com).)*

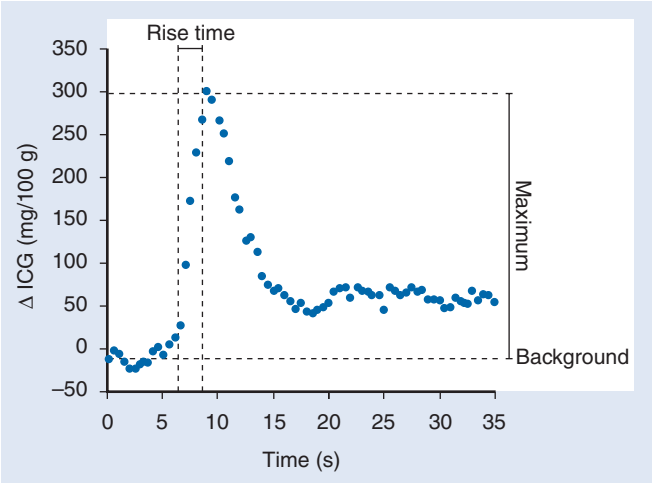


Fig. 29.3 Calculation of blood flow index from indocyanine green kinetics monitored in intact porcine head by near-infrared spectroscopy.[219]

patients undergoing blood pressure manipulation with Xe-CT-CBF assessment. The DCS measure correlated well with the appropriate region of interest in the Xe-CT-CBF (Fig. 29.2).

Diffuse Reflectance Spectroscopy

It is well known that the near-infrared photon fluence rate obeys a diffusion equation in highly scattering media such as tissue. In DRS light measurements employ intensity modulated light sources (i.e., the frequency domain technique). The amplitude of the input source is sinusoidally modulated, producing a diffusive wave within the medium. These disturbances are called *diffuse photon density waves* or simply *diffusive waves*. When everything works, a best estimate of the absorption and scattering coefficients at one or more optical wavelengths is obtained, from which can be derived contributions from different tissue chromophores. Oxy- and deoxyhemoglobin concentrations along with water concentration are the most significant tissue absorbers in the NIR. Their combination gives total hemoglobin concentration, which can be referred to as blood volume and blood oxygen saturation or StO2, both of which are useful physiological parameters. Combined with DCS calculation of CBF these measurements lead to a real time bedside assessment of $CMRO_2$ and OEF.[188,195,196] A detailed theoretical treatment of these concepts can be found at http://www.lrsm.upenn.edu/pmi/non-flash-ver/publicationNF.html.

In early experiments, investigators at the University of Pennsylvania compared DCS measurements of flow variation to other standards. Direct comparisons were made to Doppler ultrasound,[197,198] to laser Doppler flowmetry,[199] to arterial spin labeled MRI,[200–202] and to reports in the literature.[187,199,203–207] Moreover, this group carried out extensive studies in phantoms[187,199,208] wherein the medium's viscosity and the flow speed of scatterers are varied. Overall, these validation studies have shown that DCS measurements of blood flow variations are in good agreement with theoretical expectations and with other measurement techniques. In rodents this method has been demonstrated to detect hyperemia due to hypercapnia [187,206] and ischemia due to middle cerebral artery occlusion[205] and cardiac arrest[206] with appropriate changes in OEF and $CMRO_2$.

Near-Infrared Spectorscopy-based Indocyanine Green, Blood Flow Index and Cerebral Blood Flow

NIRS also allows detection of other IR chromophores such as indocyanine green (**ICG**). ICG has several attributes that make it an ideal tracer to monitor rCBF. ICG has an IR absorption peak at 805 nm[209] and after intravenous injection is limited to the intravascular compartment.[210] These properties then make the use of ICG as a marker of tissue blood flow feasible. It is nontoxic[211] and serious adverse reactions are rare.[211–214] Notably it is rapidly removed from the circulation by the liver through biliary excretion[215] with a circulation half time of 3.3 minutes.[210,216] These kinetic properties make ICG suitable for repetitive measurements, even with short between-study intervals, without accumulation of dye.[216] With a maximal daily dosage of 5 mg/kg[217] and a study dose of 0.1 mg/kg, up to 50 rCBF determinations can be made daily. Thus, although not a true moment-to-moment monitor, being able to evaluate BFI as a proportionate indicator of rCBF every 30 minutes as one manipulates and optimizes physiology or pharmacology at the bedside based on rCBF is, nonetheless, a very attractive notion.

The BFI is based on fluorescein flowmetry for measurement of relative blood flow changes in the intestine using intravital fluorescence microscopy.[218] This method entails use of the ratio of the maximum fluorescence and the rise time of the fluorescence curve. Keubler et al.[219] adapted the mathematical basis for fluorescein flowmetry to the first circulatory passage of an ICG bolus through the brain (Fig. 29.3).

Several approaches to the use of ICG NIRS for rCBF determination or estimation have also been reported. Early studies involved using ICG to determine relative changes in CBF have been described by Roberts et al.,[220] Gora et al.,[221] and Kuebler et al.,[219] with subsequent validation studies reported in animals [219,222,223] and humans.[224,225] Diop et al. report encouraging preclinical studies demonstrating the potential use of ICG combined with DCS to yield continuous absolute CBF, $CMRO_2$, and OEF.[226,227]

Other Near-Infrared Spectroscopy Cerebral Blood Flow Methods

Smith et al.[228] have recently reported an alternate approach, also using NIRS, to measure OEF at bedside. Edwards and Elwell, using the Fick principle, suggested measuring CBF by monitoring changes in oxygenated hemoglobin in response to changes in

FiO2 as a tracer.[229,230] This technique was found to correlate with 133-Xe rCBF measurements in neonates.[231,232] However, subsequent studies in animals and in adults showed an unacceptably high coefficient of variation and it did not correlate with other established methods.[233,234] Moreover, there were concerns that altering FiO2 could be deleterious in brain-injured patients.[230] Acousto-optic techniques are also available which can be used to measure relative changes in CBF. Validation studies are ongoing and the technology is FDA approved[235]

Reliable Measurement of Depth of Hypnosis and Analgesia and Potential for Automated Closed Loop Anesthetic Administration

BIS and patient state index (PSI) monitors have undergone extensive evaluation as monitors of depth of hypnosis with reasonable evidence for a role in some neurosurgical settings.[236] However, this depth of anesthesia monitoring approach provides little insight into adequacy of analgesia. Recent early work[237] in this area suggests that depth of analgesia monitoring will also eventually be developed and validated. Studies have been done on facial EMG, palmar conductance,[238,239] and pupillometry[240] with reasonable results, suggesting that such monitoring should be clinically feasible for future applications. The Analgoscore is another means of monitoring intraoperative pain through the application of an algorithm to blood pressure and heart rate data.[241] This score has been coupled with the closed-loop administration of remifentanil to control intraoperative pain and combined with BIS and neuromuscular blockade monitoring to create a prototype total anesthesia robot,[242,243] which is described in more detail later in this chapter.

The availability of depth of hypnosis, analgesia, and neuromuscular blockade, along with cardiovascular monitoring will then enable the neuroanesthesiologist to precisely titrate the anesthetic drug as a "magic bullet" directed to that element of the anesthetic state most in need of attention.

Continuous Blood Levels of Intravenous Anesthetics

Presently no clinically available technology provides continuous direct measurement of blood levels of anesthetics. One approach has been to use a pharmacodynamic measure such as BIS to derive the blood level that works, even if the exact level is not known, and then titrate anesthetic versus effect rather than a blood level. Pharmacokinetic models combined with target-controlled infusion technology have also been used to predict anesthetic levels and titrate accordingly.

Nonetheless, recent reports indicate that sensitive exhaled gas monitoring can provide end tidal concentrations of propofol. Indications are that such a monitor provides a reliable measure of blood concentration.[244] No comparable technology has been reported for other intravenous anesthetic drugs. One might speculate that a hypnotic, paralytic, or analgesic drug of the future might be designed with a chromophore in its structure that would allow detection and thus continuous monitoring by transcutaneous spectroscopy.

Multimodality Brain Monitoring

Brain tissue pO2 (pbO2), microdialysis, and blood flow methods are receiving significant attention presently. There is ample retrospective evidence to associate a low pbO2, low CBF,[242,243,245–247] and elevated lactate pyruvate ratio with poor outcome[248–251] and certainly it makes physiologic sense. It seems reasonable to expect that these monitors will eventually find a place in titration of the physiologic contributors' secondary processes in brain injury. Multimodality monitoring has recently been evaluated in a consensus statement.[252]

Exhaled Gas Monitoring

Previously the province of nonportable GC-mass spectrometry types of equipment, improved sensor and computing technology has resulted in the capability to place a highly sensitive array of chemical sensors in exhalation tubing of a patient to make significant physiologic inferences.[253] Currently published examples suggest an ability to detect bacterial pneumonia[254] and sinusitis,[255] asthma,[256] aerodigestive tract tumor cells,[257] lung cancer,[258] and tuberculosis.[259] The technology has been reported as being able to detect lipid peroxidation in food.[260] Given that lipid peroxidation[261–264] or perhaps release of other volatile organic compounds occurs with ischemia, it becomes plausible to suggest that this technology will have a place in screening for immediate evidence of ongoing cerebral (or other organ) ischemia in neuroanesthesia and neurocritical care.

Feedback Loops

Anesthesia Robot

Multiple physiologic parameters can be measured with digital output that is amenable to feedback loops. Technology is now available or in development that is demonstrating the feasibility of this concept for parameters that include neuromuscular blockade, depth of hypnosis monitors, facial EMG (analgesia), and blood pressure. Given that the administration of an anesthetic entails provision of hypnosis, analgesia, immobility, and sympathetic reflex control, this then presents the notion of the anesthesiologist explicitly **prescribing an effect** of a drug rather than a dose as the primary goal in the administration of anesthesia. Moreover, for the neuroanesthesiologist, brain oriented parameters such a brain pO2, tissue lactate or glutamate, CBF, or other measures may also be amenable to such an approach. In addition, the notion of providing[265,266] and measuring amnesia is also an attractive possibility, although amnesia monitors at this time remain undescribed (other than after the fact inquiry).

Putting all of these concepts together produces the concept of an anesthesia robot. Researchers at McGill University have described such a system that they have named McSleepy.[242,243] This innovation is both pharmacologic robot and anesthesia information management system. An automated, closed-loop system controls the three variables of general anesthesia: hypnosis, analgesia, and neuromuscular blockade. Bispectral index is used as the control variable for hypnosis, analgoscore for analgesia, and phonomyography for neuromuscular blockade. Based on these data, the computer titrates the appropriate medication (propofol, remifentanil, rocuronium) using three infusion pumps. The system can be used to control induction, maintenance, and emergence from general anesthesia. The system also alerts the anesthesiologist when certain actions should be performed, such as mask ventilation, intubation, and waking the patient. Several safety features have been incorporated into the software. For example, the system will not administer rocuronium until a BIS <60 is reached and maximum and minimum limits can be set for drug administration. In addition, McSleepy can be controlled remotely from any PC, smartphone, or tablet. In fact, researchers used this capability to perform the first transcontinental anesthetic between Montreal, Canada, and Pisa, Italy.[267] Additional features such as voice command and fluid management are on the horizon. A large scale trial is underway to compare the performance of the system to manually controlled anesthesia. This group is also exploring the performance a robotic intubation system called the Kepler Intubation System.[268,269]

Magnetic Resonance in the Operating Room

MR imaging is undergoing evaluation as an aid during neurosurgery. The primary impetus for it is to aid in the provision of more complete tumor resection and to reevaluate stereotactic coordinates intraoperatively as brain anatomy may be altered during the course of a procedure.[270] Another emerging use is for laser tumor ablation under MRI guidance.[271] This introduces a variety of logistical challenges that can substantially increase the time in the operating room[272] or create issues with transport of an anesthetized patient, mid-surgery, to an MR unit. Nonetheless, the introduction of this may translate into a technology providing information of value to both neurosurgeon and anesthesiologist, including biochemical information, such as high energy phosphates, lactate, n-acetylphosphate, and other relevant chemicals. In addition, rCBF and metabolic rate information may also become available during neurosurgical procedures through MRI methodology.[273]

PHARMACOLOGY

Fast on Fast off

Work has been ongoing for decades in an effort to elucidate mechanisms of anesthesia. Implicit in such work has been the assumption that induction of anesthesia and emergence are equal and opposite biological processes. However, Kelz et al. suggest that the neural substrates that underlie induction and emergence are different and present the concept of neural inertia in transitions in levels of consciousness.[274,275] In their work they describe the role of the endogenous orexin system in impacting emergence from, but not entry into the anesthetized state.[276] This then suggests that future pharmacologic work in this area may lead to methods to manipulate the process of emergence from anesthesia such that, rather than awaiting dissipation or antagonizing the induction anesthetic drugs, that specific manipulation of the neural substrates of emergence from anesthesia will lead to faster more reliable emergence from anesthesia after neurosurgical procedures.

Another potential advance is the advent of very-short-acting anesthetic agents. This is best illustrated with remifentanil for analgesia. Work is underway suggesting a future similarly short-acting context insensitive benzodiazepine hypnotic, remimazolam.[277,278] Development of a comparably short-acting neuromuscular blocking drug would then have the stage set for titratable context insensitive anesthesia.

Non-neurotoxic Anesthetics

Postoperative cognitive dysfunction is an object of increasing recent scrutiny, with a fairly robust incidence in elderly patients after noncardiac surgery of about 10–15%.[279–281] Although the precise mechanism of this phenomenon remains to be elucidated there are ample data to suggest that specific neurotoxic effects of anesthetics could be important factors. Eckenhoff et al.[282] reported the amyloidogenic properties of halothane and isoflurane and Bianchi et al.[283] have reported behavioral changes after isoflurane but not sevoflurane anesthesia. Moreover, Wei et al.[284] have reported that intracellular calcium homeostasis may be an important factor. Their work shows that sevoflurane does not increase intracellular calcium and does not cause apoptosis, whereas isoflurane induces release of calcium from intracellular stores with associated apoptosis. In immature brains some anesthetics appear to induce unplanned apoptosis with delayed cognitive deficits.[117] Nitrous oxide has dose-dependent and paradoxical protective and neurotoxic effects.[285] Finally, opioids in moderate to high doses produce hypermetabolism and histologically verifiable brain damage.[286–290] All of these observations and others strongly implicate at least a partial role for many anesthetics in the pathogenesis of POCD. Moreover, a provocative set of studies by Bohnen et al.[291,292] suggest a possible role of cumulative lifetime anesthetic (and surgical) experience in the genesis of Alzheimer's disease with a relevant study by Kofke et al.[10] suggesting a differential pattern of brain blood flow with remifentanil as a function of a subject's ApoE4 status. The apoE4 allele of the ApoE single nucleotide polymorphism relates to one's likelihood of later developing Alzheimer's disease.[293,294] Other genes may also be elucidated as contributing to susceptibility to POCD.

As answers begin to accumulate as to factors that contribute to anesthetic neurotoxicity and POCD, it is to be expected that anesthetic paradigms will be developed that will not have the potential for such deleterious effects.

SUMMARY

This chapter has reviewed some current research in areas relevant to neuroanesthesia and neurocritical care. Some clinical problem areas have been suggested as important subjects of research with a distillation of nascent work, which can be reasonably anticipated to translate to clinical care. If these speculations are borne out, the neuroanesthesia OR of the future will indeed look a good deal different and better than the one of today.

REFERENCES

1. NIAAA. *Concepts and terms in genetic research—a primer*. Bethesda: NIH; 2005. [cited 2008 May 6, 2008]. Available from: http://pubs.niaaa.nih.gov/publications/arh26-3/165-171.htm.
2. NIGMS. *The new genetics*. Bethesda: NIGMS; 2007. [updated June 27, 2007; cited 2008 May 6, 2008]. Available from: http://publications.nigms.nih.gov/thenewgenetics/glossary.html.
3. Chitty M. *Gene definitions & taxonomy for pharmaceuticals*. 2008. [updated March 28, 2008; cited 2008 May 6, 2008]. Available from: http://www.genomicglossaries.com/content/gene_def.asp.
4. Reynolds A, Leake D, Boese Q, et al. Rational siRNA design for RNA interference. *Nat Biotechnol*. 2004;22(3):326–330.
5. Beckmann JS, Estivill X, Antonarakis SE. Copy number variants and genetic traits: Closer to the resolution of phenotypic to genotypic variability. *Nat Rev Genet*. 2007;8(8):639–646.
6. Allen PD. Anesthesia and the human genome project: The quest for accurate prediction of drug responses. *Anesthesiology*. 2005;102(3):494–495.
7. Hegele RA, Dichgans M. Update on the genetics of stroke and cerebrovascular disease 2007. *Stroke*. 2008;39(2):252–254.
8. Dichgans M, Hegele RA. Update on the genetics of stroke and cerebrovascular disease 2006. *Stroke*. 2007;38(2):216–218.
9. Alberts MJ, Tournier-Lasserve E. Update on the genetics of stroke and cerebrovascular disease 2004. *Stroke*. 2005;36(2):179–181.
10. Kofke WA, Blissitt PA, Rao H, Wang J, Addya K, Detre J. Remifentanil-induced cerebral blood flow effects in normal humans: Dose and ApoE genotype. *Anesth Analg*. 2007;105(1):167–175.
11. Stekiel TA, Weber CA, Contney SJ, Bosnjak ZJ. Differences in cardiovascular sensitivity to propofol in a chromosome substitution rat model. *Croat Med J*. 2007;48(3):312–318.
12. Liem EB, Lin CM, Suleman MI, et al. Anesthetic requirement is increased in redheads. *Anesthesiology*. 2004;101(2):279–283.
13. Rajaram S, Sedensky MM, Morgan PG. Unc-1: A stomatin homologue controls sensitivity to volatile anesthetics in Caenorhabditis elegans. *Proc Natl Acad Sci U S A*. 1998;95(15):8761–8766.
14. Kayser EB, Morgan PG, Sedensky MM. GAS-1: A mitochondrial protein controls sensitivity to volatile anesthetics in the nematode Caenorhabditis elegans. *Anesthesiology*. 1999;90(2):545–554.
15. Sato Y, Seo N, Kobayashi E. Genetic background differences between FVB and C57BL/6 mice affect hypnotic susceptibility to pentobarbital, ketamine and nitrous oxide, but not isoflurane. *Acta Anaesthesiol Scand*. 2006;50(5):553–556.

16. Mulholland CV, Somogyi AA, Barratt DT, et al. Association of innate immune single-nucleotide polymorphisms with the electroencephalogram during desflurane general anaesthesia. *J Mol Neurosci*. 2014;52(4):497–506.
17. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology*. 2005;102(3):509–514.
18. Boules ML, Botros SKA, Shaheen IA, Hamed MA. Association of u-opioid receptor gene polymorphism (A118G) with variations in fentanyl analgesia consumption after total abdominal hysterectomy in female Egyptian patients. *Comp Clin Pathol*. 2014;1–6.
19. Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA. Effect of catechol-o-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. *Anesthesiology*. 2013;119(6):1422–1433.
20. Sia AT, Lim Y, Lim ECP, et al. Influence of mu-opioid receptor variant on morphine use and self-rated pain following abdominal hysterectomy. *J Pain*. 2013;14(10):1045–1052.
21. Liao Q, Chen DJ, Zhang F, et al. Effect of CYP3A4*18B polymorphisms and interactions with OPRM1 A118G on postoperative fentanyl requirements in patients undergoing radical gastrectomy. *Mol Med Rep*. 2013;7(3):901–908.
22. Duan G, Xiang G, Zhang X, Yuan R, Zhan H, Qi D. A single-nucleotide polymorphism in SCN9A may decrease postoperative pain sensitivity in the general population. *Anesthesiology*. 2013;118(2):436–442.
23. Storm H, Støen R, Klepstad P, Skorpen F, Qvigstad E, Raeder J. Nociceptive stimuli responses at different levels of general anaesthesia and genetic variability. *Acta Anaesthesiol Scand*. 2013;57(1):89–99.
24. Ochroch EA, Vachani A, Gottschalk A, Kanetsky PA. Natural variation in the mu-opioid gene OPRM1 predicts increased pain on third day after thoracotomy. *Clin J Pain*. 2012;28(9):747–754.
25. Camorcia M, Capogna G, Stirparo S, Berritta C, Blouin JL, Landau R. Effect of u-opioid receptor A118G polymorphism on the ED50 of epidural sufentanil for labor analgesia. *Int J Obstet Anesth*. 2012;21(1):40–44.
26. Zhang W, Yuan JJ, Kan QC, et al. Influence of CYP3A5*3 polymorphism and interaction between CYP3A5*3 and CYP3A4*1G polymorphisms on post-operative fentanyl analgesia in Chinese patients undergoing gynaecological surgery. *Eur J Anaesthesiol*. 2011;28(4):245–250.
27. Hackel D, Krug SM, Sauer RS, et al. Transient opening of the perineurial barrier for analgesic drug delivery. *Proc Natl Acad Sci U S A*. 2012;109(29):E2018–E2027.
28. Yang CH, Huang HW, Chen KH, Chen YS, Sheen-Chen SM, Lin CR. Antinociceptive potentiation and attenuation of tolerance by intrathecal Ĩ²-arrestin 2 small interfering RNA in rats. *Br J Anaesth*. 2011;107(5):774–781.
29. Dray A. Neuropathic pain: Emerging treatments. *Br J Anaesth*. 2008;101(1):48–58.
30. Sugino S, Hayase T, Higuchi M, et al. Association of u-opioid receptor gene (OPRM1) haplotypes with postoperative nausea and vomiting. *Exp Brain Res*. 2014.
31. Ma XX, Chen QX, Wu SJ, Hu Y, Fang XM. Polymorphisms of the HTR3B gene are associated with post-surgery emesis in a Chinese Han population. *J Clin Pharm Ther*. 2013;38(2):150–155.
32. Brandom BW, Bina S, Wong CA, et al. Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population of the United States. *Anesth Analg*. 2013;116(5):1078–1086.
33. Cai Y, Hu H, Liu P, et al. Association between the apolipoprotein E4 and postoperative cognitive dysfunction in elderly patients undergoing intravenous anesthesia and inhalation anesthesia. *Anesthesiology*. 2012;116(1):84–93.
34. Ludden TM, McNay Jr JL, Shepherd AM, et al. Variability of plasma hydralazine concentrations in male hypertensive patients. *Arthritis & Rheum*. 1981;24(8):987–993.
35. Lambert DG. Pharmacogenomics. *Anaesth Intens Care Med*. 2013;14(4):166–168.
36. Cohen M, Sadhasivam S, Vinks AA. Pharmacogenetics in perioperative medicine. *Curr Opin Anaesthesiol*. 2012;25(4):419–427.
37. Fernandez Robles CR, Degnan M, Candiotti KA. Pain and genetics. *Curr Opin Anaesthesiol*. 2012;25(4):444–449.
38. Hanel HK, Viby-Mogensen J, de Muckadell OB. Serum cholinesterase variants in the Danish population. *Acta Anaesthesiol Scand*. 1978;22(5):505–507.
39. Dundee JW, McCleery WN, McLoughlin G. The hazard of thiopental anaesthesia in porphyria. *Anesth Analg*. 1962;41:567–574.
40. Galley HF, Mahdy A, Lowes DA. Pharmacogenetics and anesthesiologists. *Pharmacogenomics*. 2005;6(8):849–856.
41. He P, Court MH, Greenblatt DJ, von Moltke LL. Factors influencing midazolam hydroxylation activity in human liver microsomes. *Drug Metab Dispos*. 2006;34(7):1198–1207.
42. Jin M, Gock SB, Jannetto PJ, Jentzen JM, Wong SH. Pharmacogenomics as molecular autopsy for forensic toxicology: Genotyping cytochrome P450 3A4*1B and 3A5*3 for 25 fentanyl cases. *J Anal Toxicol*. 2005;29(7):590–598.
43. Palmer SN, Giesecke NM, Body SC, Shernan SK, Fox AA, Collard CD. Pharmacogenetics of anesthetic and analgesic agents. *Anesthesiology*. 2005;102(3):663–671.
44. Tang Y, Lu A, Aronow B, Wagner K, Sharp F. Genomic responses of the brain to ischemic stroke, intracerebral hemorrhage, kainate seizures, hypoglycemia, and hypoxia. *Eur J Neurosci*. 2002;15(12):1937–1952.
45. Schwarz D, Barry G, Mackay K, et al. Identification of differentially expressed genes induced by transient ischemic stroke. *Mol Brain Res*. 2002;101(1-2):12–22.
46. Tang Y, Xu H, Du X, et al. Gene expression in blood changes rapidly in neutrophils and monocytes after ischemic stroke in humans: A microarray study. *J Cereb Blood Flow Metab*. 2006;26(8):1089–1102.
47. Sharp FR, Xu H, Lit L, et al. Genomic profiles of stroke in blood. *Stroke*. 2007;38(2 Suppl):691–693.
48. Kitagawa K, Matsumoto M, Kuwabara K, Ohtsuki T, Hori M. Delayed, but marked, expression of apolipoprotein E is involved in tissue clearance after cerebral infarction. *J Cereb Blood Flow Metab*. 2001;21(10):1199–1207.
49. Panahian N, Yoshiura M, Maines M. Overexpression of heme oxygenase-1 is neuroprotective in a model of permanent middle cerebral artery occlusion in transgenic mice. *J Neurochem*. 1999;72(3):1187–1203.
50. Lukkarinen J, Kauppinen R, Grohn O, et al. Neuroprotective role of ornithine decarboxylase activation in transient focal cerebral ischaemia: A study using ornithine decarboxylase-overexpressing transgenic rats. *Eur J Neurosci*. 1998;10(6):2046–2055.
51. Weisbrot-Lefkowitz M, Reuhl K, Perry B, Chan P, Inouye M, Mirochnitchenko O. Overexpression of human glutathione peroxidase protects transgenic mice against focal cerebral ischemia/reperfusion damage. *Mol Brain Res* 53(1-2);333–338.
52. Rajdev S, Hara K, Kokubo Y, et al. Mice overexpressing rat heat shock protein 70 are protected against cerebral infarction. *Ann Neurol*. 2000;47(6):782–791.
53. Sharp F, Bergeron M, Bernaudin M. Hypoxia-inducible factor in brain. *Adv Exp Med Biol*. 2001;502:273–291.
54. Siren A, Ehrenreich H. Erythropoietin—a novel concept for neuroprotection. *Eur Arch Psychiatry Clin Neurosci*. 2001;251(4):179–184.
55. Schaller B, Bahr M, Buchfelder M. Pathophysiology of brain ischemia: Penumbra, gene expression, and future therapeutic options. *Eur Neurol*. 2005;54(4):179–180.
56. Kofke W, Konitzer P, Meng Q, Guo J, Cheung A. Effect of Apolipoprotein E genotype on NSE and S-100 levels after cardiac and vascular surgery. *Anesth Analg*. 2004;99:1323–1325.
57. Yenari M, Dumas T, Sapolsky R, Steinberg G. Gene therapy for treatment of cerebral ischemia using defective herpes simplex viral vectors. *Neuro Res*. 2001;23(5):543–552.
58. Koistinaho JTH. Altered gene expression in brain ischemia. *Neuroreport*. 1997;8(2):i–viii.
59. Gidday J, Fitzgibbons J, Shah A, Park T. Neuroprotection from ischemic brain injury by hypoxic preconditioning in the neonatal rat. *Neurosci Lett*. 1994;168(1-2):221–224.
60. Arvidsson A, Kokaia Z, Airaksinen M, Saarma M, Lindvall O. Stroke induces widespread changes of gene expression for glial cell line-derived neurotrophic factor family receptors in the adult rat brain. *Neuroscience*. 2001;106(1):27–41.
61. Krupinski J, Kumar P, Kumar S, Kaluza J. Increased expression of TGF-beta 1 in brain tissue after ischemic stroke in humans. *Stroke*. 1996;27(5):852–857.
62. Konstantin P, Scharff A, Ruscher K, et al. Hypoxia-induced stroke tolerance in the mouse is mediated by erythropoietin. *Stroke*. 2003;34:1981–1986.
63. Narasimhan P, Swanson R, Sagar S, Sharp F. Astrocyte survival and HSP70 heat shock protein induction following heat shock and acidosis. *Glia*. 1996;17(2):147–159.
64. Alkayed N, Goto S, Sugo N, et al. Estrogen and Bcl-2: Gene induction and effect of transgene in experimental stroke. *J Neurosci*. 2001;21(19):7543–7550.
65. Blanck T, Haile M, Xu F, et al. Isoflurane pretreatment ameliorates postischemic neurologic dysfunction and preserves hippocampal Ca2+/calmodulin-dependent protein kinase in a canine cardiac arrest model. *Anesthesiology*. 2000;93(5):1285–1293.
66. Irminger-Finger I, Leung W, Li J, et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. *Mol Cell*. 2001;8(6):1255–1266.
67. Siushansian R, Bechberger J, Cechetto D, Hachinski V, Naus C. Connexin43 null mutation increases infarct size after stroke. *J Comp Neurol*. 2001;440(4):387–394.

68. Bruce A, Boling W, Kindy M, et al. Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. *Nat Med*. 1996;2(7):788–794.
69. Bernaudin M, Tang Y, Reilly M, et al. Brain genomic response following hypoxia and re-oxygenation in the neonatal rat. Identification of genes that might contribute to hypoxia-induced ischemic tolerance. *J Biol Chem*. 2002;277(42):39728–39738.
70. Tong L, Wu Z, Ran M, et al. The role of sumo-conjugating enzyme Ubc9 in the neuroprotection of isoflurane preconditioning against ischemic neuronal injury. *Mol Neurobiol*. 2015;51:1221–1231.
71. Pinto MC, Simão F, da Costa F, et al. Sarcosine preconditioning induces ischemic tolerance against global cerebral ischemia. *Neuroscience*. 2014;271:160–169.
72. Jiang T, Yu JT, Zhu XC, et al. Ischemic preconditioning provides neuroprotection by induction of AMP-activated protein kinase-dependent autophagy in a rat model of ischemic stroke. *Mol Neurobiol*. 2015;51:220–229.
73. Shah NH, Aizenman E. Voltage-gated potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration. *Transl Stroke Res*. 2014;5(1):38–58.
74. Garcia-Bonilla L, Benakis C, Moore J, Iadecola C, Anrather J. Immune mechanisms in cerebral ischemic tolerance. *Front Neurosci*. 2014;8:44.
75. Gong J, Gong S, Zhang M, et al. Cerebral ischemic preconditioning reduces glutamate excitotoxicity by up-regulating the uptake activity of GLT-1 in rats. *Amino Acids*. 2014;46(6):1537–1545.
76. Lu WC, Li GY, Xie H, Qiu B, Yang RM, Guo ZZ. Erythromycin pretreatment induces tolerance against focal cerebral ischemia through up-regulation of nNOS but not down-regulation of HIF-1Î± in rats. *Neurol Sci*. 2014;35(5):687–693.
77. Li H, Jin M, Lv T, Guan J. Mechanism of focal cerebral ischemic tolerance in rats with ischemic preconditioning involves MyD88- and TRIF-dependent pathways. *Exp Ther Med*. 2014;6(6):1375–1379.
78. Lee YJ, Hallenbeck JM. SUMO and ischemic tolerance. *Neuromolecular Med*. 2013;15(4):771–781.
79. Stetler RA, Leak RK, Gan Y, et al. Preconditioning provides neuroprotection in models of CNS disease: Paradigms and clinical significance. *Prog Neurobiol*. 2014;114:58–83.
80. Koch S, Della-Morte D, Dave KR, Sacco RL, Perez-Pinzon MA. Biomarkers for ischemic preconditioning: Finding the responders. *J Cereb Blood Flow Metab*. 2014;34(6):933–941.
81. Kofke WA. Incrementally applied multifaceted therapeutic bundles in neuroprotection clinical trials…time for change. *Neurocrit Care*. 2010;12(3):438–444.
82. McAdoo JD, Warner DS, Goldberg RN, Vitek MP, Pearlstein R, Laskowitz DT. Intrathecal administration of a novel apoE-derived therapeutic peptide improves outcome following perinatal hypoxic-ischemic injury. *Neurosci Lett*. 2005;381(3):305–308.
83. Gao J, Wang H, Sheng H, et al. A novel apoE-derived therapeutic reduces vasospasm and improves outcome in a murine model of subarachnoid hemorrhage. *Neurocrit Care*. 2006;4(1):25–31.
84. Li FQ, Fowler KA, Neil JE, Colton CA, Vitek MP. An apolipoprotein E-mimetic stimulates axonal regeneration and remyelination after peripheral nerve injury. *J Pharmacol Exp Ther*. 2010;334(1):106–115.
85. Laskowitz DT, Song P, Wang H, et al. Traumatic brain injury exacerbates neurodegenerative pathology: Improvement with an apolipoprotein E-based therapeutic. *J Neurotrauma*. 2010;27(11):1983–1995.
86. Laskowitz DT, Lei B, Dawson HN, et al. The apoE-mimetic peptide, COG1410, improves functional recovery in a murine model of intracerebral hemorrhage. *Neurocrit Care*. 2012;16(2):316–326.
87. Wei J, Zheng M, Liang P, et al. Apolipoprotein E and its mimetic peptide suppress Th1 and Th17 responses in experimental autoimmune encephalomyelitis. *Neurobiol Dis*. 2013;56:59–65.
88. Wang R, Hong J, Lu M, et al. ApoE mimetic ameliorates motor deficit and tissue damage in rat spinal cord injury. *J Neurosci Res*. 2014;92(7):884–892.
89. Ausman JI. Perioperative genomics. *Surg Neurol*. 2006;65(4):422.
90. Isbir SC, Tekeli A, Ergen A, et al. Genetic polymorphisms contribute to acute kidney injury after coronary artery bypass grafting. *Heart Surg Forum*. 2007;10(6):E439–E444.
91. Grigoryev DN, Liu M, Cheadle C, et al. Genomic profiling of kidney ischemia-reperfusion reveals expression of specific alloimmunity-associated genes: Linking "immune" and "nonimmune" injury events. *Transplant Proc*. 2006;38(10):3333–3336.
92. Rodrigo E, Sanchez-Velasco P, Ruiz JC, et al. Cytokine polymorphisms and risk of infection after kidney transplantation. *Transplant Proc*. 2007;39(7):2219–2221.
93. Malik MH, Jury F, Bayat A, et al. Genetic susceptibility to total hip arthroplasty failure: A preliminary study on the influence of matrix metalloproteinase 1, interleukin 6 polymorphisms and vitamin D receptor. *Ann Rheum Dis*. 2007;66(8):1116–1120.
94. Kolundzic R, Orlic D, Trkulja V, et al. Single nucleotide polymorphisms in the interleukin-6 gene promoter, tumor necrosis factor-alpha gene promoter, and transforming growth factor-beta1 gene signal sequence as predictors of time to onset of aseptic loosening after total hip arthroplasty: Preliminary study. *J Orthop Sci*. 2006;11(6):592–600.
95. de Alvarenga MP, Pavarino-Bertelli EC, Abbud-Filho M, et al. Combination of angiotensin-converting enzyme and methylenetetrahydrofolate reductase gene polymorphisms as determinant risk factors for chronic allograft dysfunction. *Transplant Proc*. 2007;39(1):78–80.
96. Sery O, Hrazdilova O, Didden W, et al. The association of monoamine oxidase B functional polymorphism with postoperative pain intensity. *Neuroendocrinol Lett*. 2006;27(3):333–337.
97. Janicki PK, Schuler G, Francis D, et al. A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. *Anesth Analg*. 2006;103(4):1011–1017.
98. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Mol Pain*. 2006;2:24.
99. Chou WY, Yang LC, Lu HF, et al. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand*. 2006;50(7):787–792.
100. Chou WY, Wang CH, Liu PH, et al. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy.[see comment]. *Anesthesiology*. 2006;105(2):334–337.
101. Bessler H, Shavit Y, Mayburd E, et al. Postoperative pain, morphine consumption, and genetic polymorphism of IL-1beta and IL-1 receptor antagonist. *Neurosci Lett*. 2006;404(1-2):154–158.
102. Lee YS, Kim H, Wu TX, et al. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs.[see comment]. *Clin Pharmacol Ther*. 2006;79(5):407–418.
103. Ryan R, Thornton J, Duggan E, et al. Gene polymorphism and requirement for vasopressor infusion after cardiac surgery. *Ann Thorac Surg*. 2006;82(3):895–901.
104. Podgoreanu MV, White WD, Morris RW, et al. Inflammatory gene polymorphisms and risk of postoperative myocardial infarction after cardiac surgery. *Circulation*. 2006;114(1 Suppl):I275–I281.
105. Bittar MN, Carey JA, Barnard JB, et al. Tumor necrosis factor alpha influences the inflammatory response after coronary surgery.[see comment]. *Ann Thorac Surg*. 2006;81(1):132–137.
106. Miriuka SG, Langman LJ, Evrovski J, et al. Thromboembolism in heart transplantation: Role of prothrombin G20210A and factor V Leiden. *Transplantation*. 2005;80(5):590–594.
107. Ozbek N, Atac FB, Yildirim SV, et al. Analysis of prothrombotic mutations and polymorphisms in children who developed thrombosis in the perioperative period of congenital cardiac surgery. *Cardiol Young*. 2005;15(1):19–25.
108. Grocott HP, White WD, Morris RW, et al. Genetic polymorphisms and the risk of stroke after cardiac surgery. *Stroke*. 2005;36(9):1854–1858.
109. Unno N, Nakamura T, Mitsuoka H, et al. Single nucleotide polymorphism (G994→T) in the plasma platelet-activating factor-acetylhydrolase gene is associated with graft patency of femoropopliteal bypass. *Surgery*. 2002;132(1):66–71.
110. Walter DH, Schachinger V, Elsner M, et al. Statin therapy is associated with reduced restenosis rates after coronary stent implantation in carriers of the Pl(A2)allele of the platelet glycoprotein IIIa gene.[see comment]. *Eur Heart J*. 2001;22(7):587–595.
111. Chi KR. The year of sequencing. *Nat Methods*. 2008;5(1):11–14.
112. Jacob Z, Li H, Makaryus R, et al. Metabolomic profiling of children's brains undergoing general anesthesia with sevoflurane and propofol. *Anesthesiology*. 2012;117(5):1062–1071.
113. Csete M. Cellular transplantation. *Anesthesiol Clin North America*. 2004;22(4):887–901.
114. Rosser AE, Zietlow R, Dunnett SB. Stem cell transplantation for neurodegenerative diseases. *Curr Opin Neurol*. 2007;20(6):688–692.
115. Lee JS, Hong JM, Moon GJ, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells*. 2010;28(6):1099–1106.
116. Pang X, Yang H, Peng B. Human umbilical cord mesenchymal stem cell transplantation for the treatment of chronic discogenic low back pain. *Pain Phys*. 2014;17(4):E525–E530.
117. Jevtovic-Todorovic V, Hartman R, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003;23:876–882.
118. Cunningham S, Fleck BW, Elton RA, et al. Transcutaneous oxygen levels in retinopathy of prematurity. *Lancet*. 1995;346(8988):1464–1465.
119. Kofke WA. Making clinical decisions based on animal research data: Pro. *J Neurosurg Anesthesiol*. 1996;8(1):68–72.

120. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549–556.
121. Bernard S, Gray T, Buist M, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557–563.
122. Clifton G, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma*. 1993;10(3):263–271.
123. Clifton G, Choi S, Miller E, et al. Intercenter variance in clinical trials of head trauma—experience of the National Acute Brain Injury Study: Hypothermia. *J Neurosurg*. 2001;95(5):751–755.
124. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): A randomised trial. *Lancet Neurol*. 2011;10(2):131–139.
125. Jiang JY, Xu W, Li WP, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab*. 2006;26(6):771–776.
126. Todd M, Hindman B, Clarke W, Torner J. Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352(2):135–145.
127. Marion D. Moderate hypothermia in severe head injuries: The present and the future. *Curr Opin Crit Care*. 2002;8(2):111–114.
128. Wypij D, Newburger J, Rappaport L, et al. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: The Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg*. 2003;126(5):1397–1403.
129. Augoustides JG, Floyd TF, McGarvey ML, et al. Major clinical outcomes in adults undergoing thoracic aortic surgery requiring deep hypothermic circulatory arrest: Quantification of organ-based perioperative outcome and detection of opportunities for perioperative intervention. *J Cardiothorac Vasc Anesth*. 2005;19(4):446–452.
130. Appoo JJ, Augoustides JG, Pochettino A, et al. Perioperative outcome in adults undergoing elective deep hypothermic circulatory arrest with retrograde cerebral perfusion in proximal aortic arch repair: Evaluation of protocol-based care. *J Cardiothorac Vasc Anesth*. 2006;20(1):3–7.
131. Baumgardner JE, Baranov D, Smith DS, et al. The effectiveness of rapidly infused intravenous fluids for inducing moderate hypothermia in neurosurgical patients. *Anesth Analg*. 1999;89(1):163–169.
132. Vanden Hoek TL, Kasza KE, Beiser DG, et al. Induced hypothermia by central venous infusion: Saline ice slurry versus chilled saline. *Crit Care Med*. 2004;32(9 Suppl):S425–S431.
133. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients.[see comment]. *Crit Care Med*. 2004;32(12):2508–2515.
134. Diringer MN, Neurocritical Care Fever Reduction Trial G. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. *Crit Care Med*. 2004;32(2):559–564.
135. De Witte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. *Anesthesiology*. 2002;96(2):467–484.
136. Mahmood MA, Zweifler RM. Progress in shivering control. *J Neurol Sci*. 2007;261(1-2):47–54.
137. Drew KL, Buck CL, Barnes BM, et al. Central nervous system regulation of mammalian hibernation: Implications for metabolic suppression and ischemia tolerance. *J Neurochem*. 2007;102(6):1713–1726.
138. Bellamy R, Safar P, Tisherman SA, et al. Suspended animation for delayed resuscitation. *Crit Care Med*. 1996;24(2 Suppl):S24–S47.
139. Volpato GP, Searles R, Yu B, et al. Inhaled hydrogen sulfide: A rapidly reversible inhibitor of cardiac and metabolic function in the mouse. *Anesthesiology*. 2008;108(4):659–668.
140. Andrews MT. Advances in molecular biology of hibernation in mammals. *Bioessays*. 2007;29(5):431–440.
141. Borlongan CV, Wang Y, Su T-P. Delta opioid peptide (D-Ala 2, D-Leu 5) enkephalin: Linking hibernation and neuroprotection. *Front Biosci*. 2004;9:3392–3398.
142. Su TP. Delta opioid peptide[D- Ala(2), D-Leu(5)]enkephalin promotes cell survival. *J Biomed Sci*. 2000;7(3):195–199.
143. Swain JA. Hypothermia and blood pH. A review. *AMA Arch Intern Med*. 1988;148(7):1643–1646.
144. Rahn H. Why are pH of 7.4 and PCO2 of 40 normal values for man? *Bull Eur Physiopathol Respir*. 1976;12(1):5–13.
145. Rahn H, Garey WF. Arterial CO2, O2, pH, and HCO3- values of ectotherms living in the Amazon. *Am J Physiol*. 1973;225(3):735–738.
146. Wu X, Drabek T, Kochanek PM, et al. Induction of profound hypothermia for emergency preservation and resuscitation allows intact survival after cardiac arrest resulting from prolonged lethal hemorrhage and trauma in dogs. *Circulation*. 2006;113(16):1974–1982.
147. Tisherman SA. Hypothermia and injury. *Curr Opin Crit Care*. 2004;10(6):512–519.
148. Oron U, Ilic S, De Taboada L, et al. Ga-As (808 nm) laser irradiation enhances ATP production in human neuronal cells in culture. *Photomed Laser Surg*. 2007;25(3):180–182.
149. Oron A, Oron U, Chen J, et al. Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. *Stroke*. 2006;37(10):2620–2624.
150. Detaboada L, Ilic S, Leichliter-Martha S, et al. Transcranial application of low-energy laser irradiation improves neurological deficits in rats following acute stroke. *Lasers Surg Med*. 2006;38(1):70–73.
151. Lapchak PA, Wei J, Zivin JA. Transcranial infrared laser therapy improves clinical rating scores after embolic strokes in rabbits. *Stroke*. 2004;35(8):1985–1988.
152. Lampl Y, Zivin JA, Fisher M, et al. Infrared laser therapy for ischemic stroke: a new treatment strategy: Results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1). *Stroke*. 2007;38(6):1843–1849.
153. Rossignol S, Schwab M, Schwartz M, et al. Spinal cord injury: Time to move? *J Neurosci*. 2007;27(44):11782–11792.
154. Baptiste DC, Fehlings MG. Update on the treatment of spinal cord injury. *Prog Brain Res*. 2007;161:217–233.
155. Albin MS, White RJ, Acosta-Rua G, et al. Study of functional recovery produced by delayed localized cooling after spinal cord injury in primates. *J Neurosurg*. 1968;29(2):113–120.
156. Albin MS, White RJ, Locke GS, et al. Localized spinal cord hypthermia—anesthetic effects and application to spinal cord injury. *Anesth Analg*. 1967;46(1):8–16.
157. Albin MS, White RJ, Locke GE, et al. Spinal cord hypothermia by localized perfusion cooling. *Nature*. 1966;210(5040):1059–1060.
158. Mesquita RC, D'Souza A, Bilfinger TV, et al. Optical monitoring and detection of spinal cord ischemia. *PLoS One*. 2013;8(12):e83370 [Electronic Resource].
159. McDonald JW, McDonald JW. Repairing the damaged spinal cord: From stem cells to activity-based restoration therapies. *Clin Neurosurg*. 2004;51:207–227.
160. McDonald JW, Howard MJ. Repairing the damaged spinal cord: A summary of our early success with embryonic stem cell transplantation and remyelination. *Prog Brain Res*. 2002;137:299–309.
161. Coutts M, Keirstead HS. Stem cells for the treatment of spinal cord injury. *Exp Neurol*. 2008;209(2):368–377.
162. Yoshihara T, Ohta M, Itokazu Y, et al. Neuroprotective effect of bone marrow-derived mononuclear cells promoting functional recovery from spinal cord injury. *J Neurotrauma*. 2007;24(6):1026–1036.
163. Tao X, Ming-Kun Y, Wei-Bin S, Hai-Long G, Rui K, Lai-Yong T. Role of telomerase reverse transcriptase in glial scar formation after spinal cord injury in rats. *Neurochem Res*. 2013;38(9):1914–1920.
164. Genovese T, Mazzon E, Crisafulli C, et al. TNF-alpha blockage in a mouse model of SCI: Evidence for improved outcome. *Shock*. 2008;29(1):32–41.
165. Zhang X, Zeng Y, Zhang W, et al. Co-transplantation of neural stem cells and NT-3-overexpressing Schwann cells in transected spinal cord. *J Neurotrauma*. 2007;24(12):1863–1877.
166. Koda M, Kamada T, Hashimoto M, et al. Adenovirus vector-mediated ex vivo gene transfer of brain-derived neurotrophic factor to bone marrow stromal cells promotes axonal regeneration after transplantation in completely transected adult rat spinal cord. *Eur Spine J*. 2007;16(12):2206–2214.
167. Biernaskie J, Sparling JS, Liu J, et al. Skin-derived precursors generate myelinating Schwann cells that promote remyelination and functional recovery after contusion spinal cord injury. *J Neurosci*. 2007;27(36):9545–9559.
168. Brus-Ramer M, Carmel JB, Chakrabarty S, et al. Electrical stimulation of spared corticospinal axons augments connections with ipsilateral spinal motor circuits after injury. *J Neurosci*. 2007;27(50):13793–13801.
169. Frigon A, Yakovenko S, Gritsenko V, et al. Strengthening corticospinal connections with chronic electrical stimulation after injury.[comment]. *J Neurosci*. 2008;28(13):3262–3263.
170. Andrews RJ. Neuroprotection at the nanolevel—part II: nanodevices for neuromodulation—deep brain stimulation and spinal cord injury. *Ann N Y Acad Sci*. 2007;1122:185–196.
171. McDonald JW, Becker D, Holekamp TF, et al. Repair of the injured spinal cord and the potential of embryonic stem cell transplantation. *J Neurotrauma*. 2004;21(4):383–393.
172. Grotta J. Neuroprotection is unlikely to be effective in humans using current trial designs.[see comment]. *Stroke*. 2002;33(1):306–307.
173. Medicine WUSo, NINDS, Association AS. *Stroke Trials Registry St Louis*; 2008. [updated January 4, 2008January 7, 2008]. Available from: http://www.strokecenter.org/trials/index.aspx.
174. Donnan GA. The 2007 Feinberg lecture: A new road map for neuroprotection. *Stroke*. 2008;39(1):242.
175. Rogalewski A, Schneider A, Ringelstein EB, Schabitz WR. Toward a multimodal neuroprotective treatment of stroke. *Stroke*. 2006;37(4):1129–1136.

176. Grande P, Asgeirsson B, Nordstrom C. Volume-targeted therapy of increased intracranial pressure: The Lund concept unifies surgical and non-surgical treatments. *Acta Anaesth Scand*. 2002;46(8):929–941.
177. Piechnik SK, Czosnyka M, Richards HK, et al. Cerebral venous blood outflow: A theoretical model based on laboratory simulation. *Neurosurgery*. 2001;49(5):1214–1222. discussion 22–3.
178. Hayreh SS, Edwards J. Ophthalmic arterial and venous pressures. Effects of acute intracranial hypertension. *Br J Ophthalmol*. 1971;55(10):649–663.
179. Nemoto EM. Dynamics of cerebral venous and intracranial pressures. [see comment]. *Acta Neurochir Suppl*. 2006;96:435–437.
180. Aggarwal S, Kramer D, Yonas H, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: A retrospective study. *Hepatology*. 1994;19:80.
181. Aggarwal S, Obrist W, Yonas H, et al. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: Relationship to outcome. *Liver Transpl*. 2005;11(11):1353–1360.
182. Crosby G, Todd MM. On neuroanesthesia, intracranial pressure, and a dead horse. *J Neurosurg Anesthesiol*. 1990;2(2):143–144.
183. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*. 1977;198(4323):1264–1267.
184. Fox EJ. The monitor of the future? *Anaesthesia*. 1983;38(5):433.
185. Hongo K, Kobayashi S, Okudera H, Hokama M, Nakagawa F. Noninvasive cerebral optical spectroscopy: Depth-resolved measurements of cerebral haemodynamics using indocyanine green. *Neurol Res*. 1995;17(2):89–93.
186. Experimental study of migration depth for the photons measured at sample surface. In: Cui W, Kumar C, Chance B, eds. *Proceedings of Time-Resolved Spectroscopy and Imaging of Tissues*. Los Angeles, California: The International Society for Optical Engineering; 1991. 1991 January 23-24.
187. Cheung C, Culver JP, Takahashi K, Greenberg JH, Yodh AG. In vivo cerebrovascular measurement combining diffuse near-infrared absorption and correlation spectroscopies. *Phys Med Biol*. 2001;46(8):2053–2065.
188. Chandra M, Balu R, Yodh A, Frangos S, Park S, Kofke W. Continuous non-invasive measurement of cerebral blood flow, metabolic rate for oxygen and oxygen extraction fraction in critically ill brain injured patients. *Neurocrit Care*. 2014;12.
189. Yodh A, Chance B. Spectroscopy and imaging with diffusing light. *Phys Today*. 1995;48(3):34–40.
190. Boas D, Yodh A. Spatially varying dynamical properties of turbid media probed with diffusing temporal light correlation. *J Opt Soc Am*. 1997;14(1):192–215.
191. Boas DA, Campbell LE, Yodh AG. Scattering and imaging with diffusing temporal field correlations. *Phys Rev Lett*. 1995;75(9):1855–1858.
192. Maret G, Wolf P. Multiple light scattering from disordered media, the effect of Brownian motion of scatterers. *Z Phys B: Condens Matter*. 1987;65(1):409–413.
193. Pine DJ, Weitz DA, Chaikin PM, Herbolzheimer E. Diffusing wave spectroscopy. *Phys Rev Lett*. 1988;60(12):1134–1137.
194. Kim MN, Durduran T, Frangos S, et al. Noninvasive measurement of cerebral blood flow and blood oxygenation using near-infrared and diffuse correlation spectroscopies in critically brain-injured adults. *Neurocrit Care*. 2010;12(2):173–180.
195. Corlu A, Durduran T, Choe R, et al. Uniqueness and wavelength optimization in continuous-wave multispectral diffuse optical tomography. *Opt Lett*. 2003;28(23):2339–2341.
196. Corlu A, Choe R, Durduran T, et al. Diffuse optical tomography with spectral constraints and wavelength optimization. *Appl Opt*. 2005;44(11):2082–2093.
197. Yu G, Durduran T, Zhou C, et al. Noninvasive monitoring of murine tumor blood flow during and after photodynamic therapy provides early assessment of therapeutic efficacy. *Clin Cancer Res*. 2005;11(9):3543–3552.
198. Menon C, Polin GM, Prabakaran I, et al. An integrated approach to measuring tumor oxygen status using human melanoma xenografts as a model. *Cancer Res*. 2003;63(21):7232–7240.
199. Durduran T. *Non-invasive Measurements of Tissue Hemodynamics with Hybrid Diffuse Optical Methods*. Philadelphia: University of Pennsylvania; 2004.
200. Durduran T, Yu G, Burnett MG, et al. Diffuse optical measurement of blood flow, blood oxygenation, and metabolism in a human brain during sensorimotor cortex activation. *Opt Lett*. 2004;29(15):1766–1768.
201. *Preoperative Measurement of co2 Reactivity and Cerebral Autoregulation in Neonates with Severe Congenital Heart Defects*. In: Durduran T, Zhou C, Yu G, et al., eds. San Jose, CA: SPIE Photonics West; 2007.
202. Yu G, Floyd T, Durduran T, et al. Validation of diffuse correlation spectroscopy for muscle blood flow with concurrent arterial spin labeled perfusion MRI. *Opt Express*. 2007;15(3):1064–1075.
203. Li J, Dietsche G, Iftime D, et al. Noninvasive detection of functional brain activity with near-infrared diffusing-wave spectroscopy. *J Biomed Opt*. 2005;10(4):44002.
204. Durduran T, Choe R, Yu G, et al. Diffuse optical measurement of blood flow in breast tumors. *Opt Lett*. 2005;30(21):2915–2917.
205. Culver JP, Durduran T, Furuya D, Cheung C, Greenberg JH, Yodh AG. Diffuse optical tomography of cerebral blood flow, oxygenation, and metabolism in rat during focal ischemia. *J Cereb Blood Flow Metab*. 2003;23(8):911–924.
206. Culver JP, Durduran T, Cheung C, Furuya D, Greenberg JH, Yodh AG. Diffuse optical measurement of hemoglobin and cerebral blood flow in rat brain during hypercapnia, hypoxia and cardiac arrest. *Adv Exp Med Biol*. 2003;510:293–297.
207. Jaillon F, Li J, Dietsche G, Elbert T, Gisler T. Activity of the human visual cortex measured noninvasively by diffusing-wave spectroscopy. *Opt Express*. 2007;15(11):6643–6650.
208. Boas D. *Diffuse photon probes of structural and dynamical properties of turbid media: theory and biomedical applications*. Philadelphia: University of Pennsylvania; 1996.
209. Landsman ML, Kwant G, Mook GA, Zijlstra WG. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. *J Appl Physiol*. 1976;40(4):575–583.
210. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: Observations on its physical properties, plasma decay, and hepatic extraction. *J Clin Invest*. 1960;39:592–600.
211. Fox IJ, Wood EH. Indocyanine green: Physical and physiologic properties. *Mayo Clin Proc*. 1960;35:732–744.
212. Garski TR, Staller BJ, Hepner G, Banka VS, Finney Jr RA. Adverse reactions after administration of indocyanine green. *JAMA*. 1978;240(7):635.
213. Speich R, Saesseli B, Hoffmann U, Neftel KA, Reichen J. Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med*. 1988;109(4):345–346.
214. Benya R, Quintana J, Brundage B. Adverse reactions to indocyanine green: A case report and a review of the literature. *Cathet Cardiovasc Diagn*. 1989;17(4):231–233.
215. Wheeler HO, Cranston WI, Meltzer JI. Hepatic uptake and biliary excretion of indocyanine green in the dog. *Proc Soc Exp Biol Med*. 1958;99(1):11–14.
216. Haller M, Akbulut C, Brechtelsbauer H, et al. Determination of plasma volume with indocyanine green in man. *Life Sci*. 1993;53(21):1597–1604.
217. Pulsion Medical Systems. *Product training ICG-PULSION: Pulsion Medical Systems*. 2007. cited 2007 May 1, http://www.pulsion.com/index.php?id=736.
218. Perbeck L, Lund F, Svensson L, Thulin L. Fluorescein flowmetry: A method for measuring relative capillary blood flow in the intestine. *Clin Physiol*. 1985;5(3):281–292.
219. Kuebler WM, Sckell A, Habler O, et al. Noninvasive measurement of regional cerebral blood flow by near-infrared spectroscopy and indocyanine green. *J Cereb Blood Flow Metab*. 1998;18(4):445–456.
220. Roberts I, Fallon P, Kirkham FJ, et al. Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet*. 1993;342(8884):1425.
221. Gora F, Shinde S, Elwell CE, et al. Noninvasive measurement of cerebral blood flow in adults using near-infrared spectroscopy and indocyanine green: A pilot study. *J Neurosurg Anesthesiol*. 2002;14(3):218–222.
222. De Visscher G, Leunens V, Borgers M, Reneman RS, Flameng W, van Rossem K. Nirs mediated CBF assessment: Validating the indocyanine green bolus transit detection by comparison with coloured microsphere flowmetry. *Adv Exp Med Biol*. 2003;540:37–45.
223. Springett R, Sakata Y, Delpy DT. Precise measurement of cerebral blood flow in newborn piglets from the bolus passage of indocyanine green. *Phys Med Biol*. 2001;46(8):2209–2225.
224. Keller E, Nadler A, Alkadhi H, Kollias SS, Yonekawa Y, Niederer P. Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution. *Neuroimage*. 2003;20(2):828–839.
225. Terborg C, Bramer S, Harscher S, Simon M, Witte OW. Bedside assessment of cerebral perfusion reductions in patients with acute ischaemic stroke by near-infrared spectroscopy and indocyanine green. *J Neurol Neurosurg Psychiatry*. 2004;75(1):38–42.
226. Diop M, Elliott JT, Tichauer KM, Lee TY, St. Lawrence K. A broadband continuous-wave multichannel near-infrared system for measuring regional cerebral blood flow and oxygen consumption in newborn piglets. *Rev Sci Instrum*. 2009;80(5).
227. Diop M, Verdecchia K, Lee TY, St Lawrence K. Calibration of diffuse correlation spectroscopy with a time-resolved near-infrared technique to yield absolute cerebral blood flow measurements. *Biomed Opt Express*. 2011;2(7):2068–2082.
228. Smith M, Leung T, Tisdall M, Tachtsidis I, Elwell C. Measurement of cerebral oxygen extraction fraction using near infrared spectroscopy in healthy adult volunteers. *J Neurosurg Anesthesiol*. 2007;19(4):324.
229. Edwards AD, Wyatt JS, Richardson C, Delpy DT, Cope M, Reynolds EO. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet*. 1988;2(8614):770–771.
230. Elwell CE, Cope M, Edwards AD, Wyatt JS, Delpy DT, Reynolds EO. Quantification of adult cerebral hemodynamics by near-infrared spectroscopy. *J Appl Physiol*. 1994;77(6):2753–2760.

231. Bucher HU, Edwards AD, Lipp AE, Duc G. Comparison between near infrared spectroscopy and 133Xenon clearance for estimation of cerebral blood flow in critically ill preterm infants. *Pediatr Res*. 1993;33(1):56–60.
232. Skov L, Pryds O, Greisen G. Estimating cerebral blood flow in newborn infants: Comparison of near infrared spectroscopy and 133Xe clearance. *Pediatr Res*. 1991;30(6):570–573.
233. Elwell CE, Cope M, Edwards AD, Wyatt JS, Reynolds EO, Delpy DT. Measurement of cerebral blood flow in adult humans using near infrared spectroscopy—methodology and possible errors. *Adv Exp Med Biol*. 1992;317:235–245.
234. Newton CR, Wilson DA, Gunnoe E, Wagner B, Cope M, Traystman RJ. Measurement of cerebral blood flow in dogs with near infrared spectroscopy in the reflectance mode is invalid. *J Cereb Blood Flow Metab*. 1997;17(6):695–703.
235. Schytz HW, Guo S, Jensen LT, et al. A new technology for detecting cerebral blood flow: A comparative study of ultrasound tagged NIRS and 133Xe-SPECT. *Neurocrit Care*. 2012;17(1):139–145.
236. Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev*. 2007;4:CD003843.
237. Bennett HL, Patel L, Farida N, Beddell S, Bobbin M. Separation of the hypnotic component of anesthesia and facial EMG responses to surgical stimulation. *Anesthesiology*. 2007;107:A730.
238. Gjerstad AC, Storm H, Hagen R, et al. Comparison of skin conductance with entropy during intubation, tetanic stimulation and emergence from general anaesthesia. *Acta Anaesthesiol Scand*. 2007;51(1):8–15.
239. Storm H, Shafiei M, Myre K, et al. Palmar skin conductance compared to a developed stress score and to noxious and awakening stimuli on patients in anaesthesia. *Acta Anaesthesiol Scand*. 2005;49(6): 798–803.
240. Larson MD, Kurz A, Sessler DI, et al. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. *Anesthesiology*. 1997;87(4):849–855.
241. *The 'Analgoscore': A novel score to monitor intraoperative pain and its use for remifentanil closed-loop application*. In: Hemmerling TM, Salhab E, Aoun G, Charabati S, Mathieu PA, eds. 2007 IEEE International Conference on Systems, Man, and Cybernetics, SMC 2007; 2007 Montreal, QC.
242. Hemmerling TM, Arbeid E, Wehbe M, et al. Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: A randomized controlled trial. *Br J Anaesth*. 2013;110(6):1031–1039.
243. Wehbe M, Arbeid E, Cyr S, et al. A technical description of a novel pharmacological anesthesia robot. *J Clin Monit Comput*. 2014;28(1): 27–34.
244. Takita A, Masui K, Kazama T. On-line monitoring of end-tidal propofol concentration in anesthetized patients. [see comment]. *Anesthesiology*. 2007;106(4):659–664.
245. Firlik KS, Fukui MB, Yonas H. Quantitative cerebral blood flow determinations in acute ischemic stroke: Relationship to computed tomography and angiography. *Stroke*. 1997;28(11):2208–2213.
246. Firlik AD, Rubin G, Yonas H, Wechsler LR. Relation between cerebral blood flow and neurologic deficit resolution in acute ischemic stroke. *Neurology*. 1998;51(1):177–182.
247. Rubin G, Firlik AD, Levy EI, Pindzola RR, Yonas H. Relationship between cerebral blood flow and clinical outcome in acute stroke. *Cerebrovasc Dis*. 2000;10(4):298–306.
248. Stiefel M, Spiotta A, Gracias V, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg*. 2005;103(5):805–811.
249. Bellander B-M, Cantais E, Enblad P, et al. Consensus meeting on microdialysis in neurointensive care. *Intensive Care Med*. 2004;30(12):2166–2169.
250. Sarrafzadeh A, Haux D, Sakowitz O, et al. Acute focal neurological deficits in aneurysmal subarachnoid hemorrhage: Relation of clinical course, CT findings, and metabolite abnormalities monitored with bedside microdialysis. *Stroke*. 2003;34(6):1382–1388.
251. Sarrafzadeh AS, Haux D, Ludemann L, et al. Cerebral ischemia in aneurysmal subarachnoid hemorrhage: A correlative microdialysis-PET study. *Stroke*. 2004;35(3):638–643.
252. Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(9):1189–1209.
253. Thaler ER, Hanson CW. Medical applications of electronic nose technology. *Expert Rev Med Devices*. 2005;2(5):559–566.
254. Hockstein NG, Thaler ER, Lin Y, et al. Correlation of pneumonia score with electronic nose signature: A prospective study. *Ann Otol Rhinol Laryngol*. 2005;114(7):504–508.
255. Thaler ER, Hanson CW. Use of an electronic nose to diagnose bacterial sinusitis. *Am J Rhinol*. 2006;20(2):170–172.
256. Dragonieri S, Schot R, Mertens BJ, et al. An electronic nose in the discrimination of patients with asthma and controls. *J Allergy Clin Immunol*. 2007;120(4):856–862.
257. Gendron KB, Hockstein NG, Thaler ER, et al. In vitro discrimination of tumor cell lines with an electronic nose. *Otolaryngol Head Neck Surg*. 2007;137(2):269–273.
258. Anonymous. Electronic nose shows promise for detecting early-stage lung cancer. *Disease Management Advisor* 11(6):71–72.
259. Fend R, Kolk AH, Bessant C, et al. Prospects for clinical application of electronic-nose technology to early detection of Mycobacterium tuberculosis in culture and sputum. *J Clin Microbiol*. 2006;44(6):2039–2045.
260. Olsen E, Vogt G, Ekeberg D, et al. Analysis of the early stages of lipid oxidation in freeze-stored pork back fat and mechanically recovered poultry meat. *J Agric Food Chem*. 2005;53(2):338–348.
261. Behn C, Araneda OF, Llanos AJ, et al. Hypoxia-related lipid peroxidation: Evidences, implications and approaches. *Respir Physiol Neurobiol*. 2007;158(2-3):143–150.
262. Muralikrishna Adibhatla R, Hatcher JF. Phospholipase A2, reactive oxygen species, and lipid peroxidation in cerebral ischemia. *Free Radic Biol Med*. 2006;40(3):376–387.
263. Warner DS, Sheng H, Batinic-Haberle I. Oxidants, antioxidants and the ischemic brain. *J Exp Biol*. 2004;207(Pt 18):3221–3231.
264. Salvemini D, Cuzzocrea S. Superoxide, superoxide dismutase and ischemic injury. *Curr Opin Investig Drugs*. 2002;3(6):886–895.
265. Sonner JM, Li J, Eger 2nd, EI. Desflurane and the nonimmobilizer 1,2-dichlorohexafluorocyclobutane suppress learning by a mechanism independent of the level of unconditioned stimulation. *Anesth Analg*. 1998;87(1):200–205.
266. Pastalkova E, Serrano P, Pinkhasova D, Wallace E, Fenton AA, Sacktor TC. Storage of spatial information by the maintenance mechanism of LTP. *Science*. 2006;313(5790):1141–1144.
267. Hemmerling TM, Arbeid E, Wehbe M, Cyr S, Giunta F, Zaouter C. Transcontinental anaesthesia: A pilot study. *Br J Anaesth*. 2013;110(5):758–763.
268. Hemmerling TM, Taddei R, Wehbe M, Zaouter C, Cyr S, Morse J. First robotic tracheal intubations in humans using the Kepler intubation system. *Br J Anaesth*. 2012;108(6):1011–1016.
269. Hemmerling TM, Wehbe M, Zaouter C, Taddei R, Morse J. The Kepler intubation system. *Anesth Analg*. 2012;114(3):590–594.
270. Yrjana SK, Tuominen J, Koivukangas J. Intraoperative magnetic resonance imaging in neurosurgery. *Acta Radiol*. 2007;48(5):540–549.
271. Rahmathulla G, Recinos PF, Kamian K, Mohammadi AM, Ahluwalia MS, Barnett GH. MRI-guided laser interstitial thermal therapy in neuro-oncology: A review of its current clinical applications. *Oncology*. 2014;87(2):67–82.
272. Archer DP, McTaggart Cowan RA, Falkenstein RJ, et al. Intraoperative mobile magnetic resonance imaging for craniotomy lengthens the procedure but does not increase morbidity. *Can J Anaesth*. 2002;49(4):420–426.
273. Detre JA, Zhang W, Roberts DA, et al. Tissue specific perfusion imaging using arterial spin labeling. *NMR Biomed*. 1994;7:75–82.
274. Friedman EB, Sun Y, Moore JT, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: Evidence for neural inertia. *PLoS One*. 2010;5(7).
275. Joiner WJ, Friedman EB, Hung HT, et al. Genetic and anatomical basis of the barrier separating wakefulness and anesthetic-induced unresponsiveness. *PLoS Genet*. 2013;9(9).
276. Kelz MB, Sun Y, Chen J, et al. An essential role for orexins in emergence from general anesthesia. *Proc Natl Acad Sci U S A*. 2008;105(4):1309–1314.
277. Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo-and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg*. 2012;115(2):274–283.
278. Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg*. 2013;117(5):1093–1100.
279. Johnson T, Monk T, Rasmussen L, et al. ISPOCD2 Investigators. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology*. 2002;96(6):1351–1357.
280. Moller J, Cluitmans P, Radmussen L, et al. Long-term postoperative cognitive dysfunction in the elderly: I SPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet*. 1998;351:857–861.
281. Abildstrom H, Christiansen M, Siersma V, Rasmussen L. Investigators. I. Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. *Anesthesiology*. 2004;101(4):855–861.
282. Eckenhoff R, Johansson J, Wei H, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology*. 2004;101:703–709.

283. Bianchi SL, Tran T, Liu C, et al. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. *Neurobiol Aging*. 2007.
284. Wei H, Kang B, Wei W, et al. Isoflurane and sevoflurane affect cell survival and BCL-2/BAX ratio differently. *Brain Res*. 2005;1037(1-2):139–147.
285. Jevtovic-Todorovic V, Todorovic S, Mennerick S, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat Med*. 1998;4(4):460–463.
286. Kofke W, Attaallah A, Kuwabara H, et al. Neuropathologic effects in rats and neurometabolic effects in humans of high-dose remifentanil. *Anesth Analg*. 2002;94:1229–1236.
287. Kofke W, Garman R, Janosky J, Rose M. Opioid neurotoxicity: Neuropathologic effects of different fentanyl congeners and effects of hexamethonium-induced normotension. *Anesth Analg*. 1996;83:141–146.
288. Kofke WA, Garman RH, Stiller RL, Rose ME, Garman R. Opioid neurotoxicity: Fentanyl dose response effects in rats. *Anesth Analg*. 1996;83:1298–1306.
289. Kofke W, Garman R, Tom W, Rose M, Hawkins R. Alfentanil-induced hypermetabolism, seizure, and neuropathology in rats. *Anesth Analg*. 1992;75:953–964.
290. Sinz E, Kofke W, Garman R. Phenytoin, midazolam, and naloxone protect against fentanyl-induced brain damage in rats. *Anesth Analg*. 2000;91:1443–1449.
291. Bohnen N, Warner M, Kokmen E, Beard C, Kurland L. Alzheimer's disease and cumulative exposure to anesthesia: A case-control study. *J Am Geriatr Soc*. 1994;42(2):198–201.
292. Bohnen N, Warner M, Kokmen E, Kurland L. Early and midlife exposure to anesthesia and age of onset of Alzheimer's disease. *Int J Neurosci*. 1994;77(3-4):181–185.
293. Corder E, Saunders A, Strittmatter W, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921–923.
294. Roses A, Saunders A. ApoE, Alzheimer's disease, and recovery from brain stress. *Ann NY Acad Sci*. 1997;826:200–212.

Index

Note: Page numbers followed by *b* indicate boxes, *f* indicate figures and *t* indicate tables.

D

E

F

G

H

N

O

Q

R

S

T

U

V

W

X

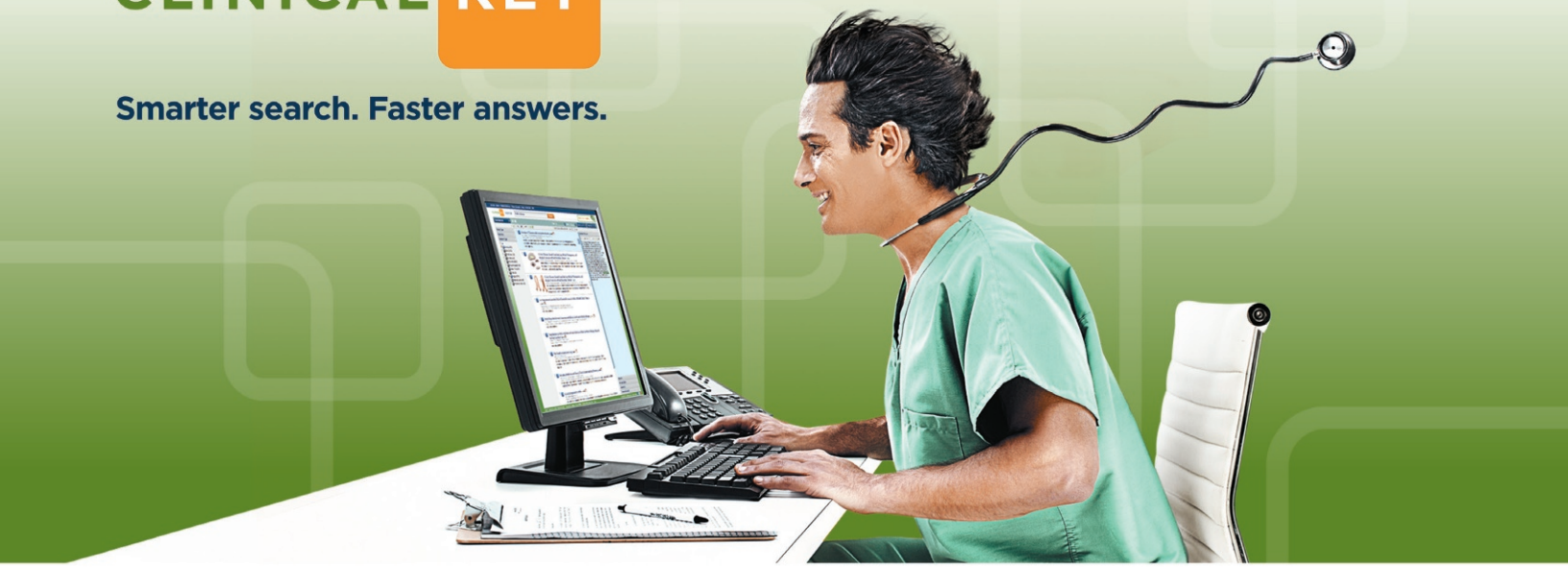
This page intentionally left blank

This page intentionally left blank

This page intentionally left blank

CLINICAL KEY™

Smarter search. Faster answers.



Smarter, Faster Search for Better Patient Care

Unlike a conventional search engine, ClinicalKey is specifically designed to serve doctors by providing three core components:

1 Comprehensive Content

The most current, evidence-based answers available for every medical and surgical specialty.

2 Trusted Answers

Content supplied by Elsevier, the world's leading provider of health and science information.

3 Unrivaled Speed to Answer

Faster, more relevant clinical answers, so you can spend less time searching and more time caring for patients.

Start searching with ClinicalKey today!

Visit ***ClinicalKey.com*** for more information and subscription options.

ELSEVIER