Management of Cerebrovascular Disorders

A Comprehensive, Multidisciplinary Approach

Alejandro M. Spiotta
Raymond D. Turner
M. Imran Chaudry
Aquilla S. Turk
Editors

Springer

Management of Cerebrovascular Disorders

Alejandro M. Spiotta
Raymond D. Turner
M. Imran Chaudry • Aquilla S. Turk
Editors

Management of Cerebrovascular Disorders

A Comprehensive, Multidisciplinary Approach

Springer

Editors

Alejandro M. Spiotta, MD
Department of Neurosurgery
Medical University of South Carolina
Charleston, SC, USA

Raymond D. Turner, MD
Department of Neurosurgery
Medical University of South Carolina
Charleston, SC, USA

M. Imran Chaudry, MD
Department of Neurosurgery
Medical University of South Carolina
Charleston, SC, USA

Aquilla S. Turk, DO
Department of Neurosurgery
Medical University of South Carolina
Charleston, SC, USA

ISBN 978-3-319-99015-6 ISBN 978-3-319-99016-3 (eBook)
https://doi.org/10.1007/978-3-319-99016-3

Library of Congress Control Number: 2018965921

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my mentors, past and present, for inspiring me to become an academic neurosurgeon. Thank you, Vicki, for your endless support and understanding. To Lucia, Daniela, Victor, and Robert – dream big and go for it!

Alejandro M. Spiotta

To the people of the great state of South Carolina.

Raymond D. Turner

Foreword

Dans les champs de l'observation le hazard ne favorise que les espirits prepares
Translation: Chance favors the prepared mind.
Attribution: Louis Pasteur, Lecture at University of Lille, December 7, 1985

Chance favors the prepared mind. I was reminded of this aphorism during my endovascular fellowship at UCSF. Strategy can make the difference between success and failure in neurointerventional procedures. The concept holds true at many levels of the human experience, certainly in medicine and its procedural disciplines. Major advances in computer-aided imaging and microcatheter engineering now permit endovascular procedures to treat a wide variety of cerebral vascular diseases. The point of impact is often 150 centimeters away from the site of access in the femoral artery. As endovascular specialists, we manipulate devices with limited degrees of freedom: we can push, pull, and rotate clockwise or counterclockwise. We rely on representations of physiology and anatomy, mostly using catheter angiography and fluoroscopic "roadmap" imaging. The devices are small in size; cerebral stents, for example, are measured in 250 micrometer increments. Precision and accuracy in size and placement are fundamental to procedural success. Technical skill requires acquisition of knowledge and intuition about device behavior under specific anatomical circumstances. For mechanical thrombectomy in acute ischemic stroke, technical success is also measured by speed of revascularization. Clinical outcome is the ultimate performance measure, and there is a growing body of scientific evidence to support the importance of endovascular techniques in the treatment of many neurological diseases with vascular etiologies. Moreover, the list of conditions we treat continues to grow through iterative and paradigm-shifting advancements.

In *Management of Cerebrovascular Disorders*, Drs. Spiotta, Turk, Turner, and Chaudry have brought together a panel of thought leaders in our specialty, known for their insights into the development and application of minimally invasive surgical and endovascular techniques to treat cerebral vascular diseases. Each chapter provides a succinct and comprehensive review of a specific category of disease seen through the lens of a recognized expert. Relying on the authors' combined experience and a detailed review of the medical evidence, this text is an excellent

compendium of our most current knowledge, using state-of-the-art procedures; and it is written in a manner that is accessible to students and experienced practitioners alike. Because open surgical and endovascular techniques are complementary, the editors have supplemented when appropriate with chapters on the nexus of endovascular and conventional "open" cerebrovascular surgery, including patient assessment, and practice in a hybrid operating environment utilizing the best methods to achieve optimal outcomes. Strategy is predicated on the concept of causality, the principle that events have causes and consequences. Success should not be left to chance. The knowledge and perspective about neurovascular diseases in this text will help the reader battle chance head-on.

Philip M. Meyers, MD, FACR, FSNIS, FSIR, FAHA
Radiology and Neurological Surgery
Columbia University, College
of Physicians and Surgeons
New York, NY, USA

Neuroendovascular Services,
New York-Presbyterian Hospitals – Columbia Doctors,
Neurological Institute of New York
New York, NY, USA

Preface

This volume attempts the daunting task of bringing the reader (student, resident, fellow, or specialized attending) "up to speed" in both foundational and cutting-edge concepts in the medical and surgical/endovascular management of patients with cerebrovascular diseases. Every author was handpicked for their particular expertise in the topic to be covered in a concise fashion. For the efforts and participation of our contributing authors, the editors are forever indebted.

The management of patients suffering from cerebrovascular disorders can be exhilarating, challenging, rewarding, and humbling. The care of the cerebrovascular patient brings together a melting pot of physicians including neurosurgeons, neurologists, neuroradiologists, and neurointensivists, among many others. Those of us who have the opportunity to take care of these patients should consider ourselves very fortunate, as our generation has been part of some major advances that have greatly helped us impact the lives of those afflicted with cerebrovascular disorders. The introduction of the detachable coil and the rapid advances that followed in the field of neuroendovascular surgery have revolutionized our approaches to the treatment of aneurysms, now proven to be a tried-and-true approach with data from randomized trials. Trials involving carotid and intracranial atherosclerosis, and most recently, the landmark positive thrombectomy trials, have drastically and forever altered the landscape in ischemic stroke treatment. The development and maturation of neurocritical care, a field driven forward by a group of intensivists from diverse backgrounds with a singular focus to provide specialized, intensive care to the neurologically injured patient, has immensely improved the outcomes of our patients. Currently, three randomized controlled trials are underway employing novel minimally invasive methods of evacuating deep spontaneous intracerebral hematomas, with the promise that these techniques may confer benefit over medical management.

Each of these advances has proven to be remarkable. To have all these advances arise in such a short period of time is truly monumental and reflects the incredible passion and dedication of those taking care of the patients. "Take care of the patient, the rest will follow" (Edward C. Benzel). It also reflects the contributions of our

predecessors, to which we are eternally grateful – *we stand on the shoulders of you, giants*. Thank you.

As we all strive to take care of our patients as best we can, our quest for novel therapeutic approaches, cost effectiveness, and outcomes research catapults the field forward in leaps and bounds. I eagerly await what lies ahead for our patients.

Charleston, SC, USA

Alejandro M. Spiotta, MD
Raymond D. Turner, MD
M. Imran Chaudry, MD
Aquilla S. Turk, DO

Contents

Contributors

Amin Aghaebrahim, MD Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA

Pedro Aguilar-Salinas, MD Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA

Department of Surgery – Division of Neurosurgery, University of Arizona, Tucson, AZ, USA

Syed Uzair Ahmed, MD Division of Neurosurgery, Department of Surgery, University of Saskatchewan, Saskatoon, SK, Canada

Ali Alawieh, MD Medical Scientist Training Program, Medical University of South Carolina, Charleston, SC, USA

Andrei V. Alexandrov, MD Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Anne W. Alexandrov, PhD, AGACNP-BC, ANVP-BC, FAAN Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

College of Nursing, University of Tennessee Health Science Center, Memphis, TN, USA

Marjan Alimi, MD Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA

Mohammed Alshareef, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Charles Andrews, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Rocco Armonda, MD Department of Neuroendovascular Surgery, MedStar Washington Hospital Center, MedStar Georgetown University Hospital, Washington, DC, USA

Adam Arthur, MD, MPH Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Semmes-Murphy Neurologic and Spine Clinic, Memphis, TN, USA

Benjamin Atchie, DO Department of Neuro-Interventional Surgery, RIA Neurovascular, Englewood, CO, USA

Mark D. Bain, MD Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA

Chirantan Banerjee, MD, MPH Department of Neurology, Stroke Division, Medical University of South Carolina, Charleston, SC, USA

Daniel L. Barrow, MD Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Mustafa K. Baskaya, MD Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Donnie L. Bell, MD Department of Radiology and Neurology, Kings County Hospital Center/SUNY Downstate Medical Center, Brooklyn, NY, USA

Randy Bell, MD Department of Neurosurgery, Walter Reed National Military Medical Center, Bethesda, MD, USA

Leonardo B. C. Brasiliense, MD Department of Surgery – Division of Neurosurgery, University of Arizona, Tucson, AZ, USA

Patrick Britell, MD Department of Anesthesia and Perioperative Medicine, Medical University of South Carolina, Charleston, SC, USA

Julio A. Chalela, MD Department of Neurology and Neurosurgery, Neurosciences Intensive Care Unit, Medical University of South Carolina, Charleston, SC, USA

Ronil V. Chandra, MBBS, MMed, FRANZCR Interventional Neuroradiology, Department of Imaging, Monash Health and Monash University, Melbourne, VIC, Australia

M. Imran Chaudry, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Guang-Hong Chen, PhD Departments of Medical Physics and Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Marc I. Chimowitz, MBChB Department of Neurology, Stroke Division, Medical University of South Carolina, Charleston, SC, USA

Ulas Cikla, MD Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Alexander Coon, MD Departments of Neurosurgery, Neurology, and Radiology, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA

R. Webster Crowley, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Katyucia De Macedo Rodrigues, MD Department of Neuroradiology, University of Massachusetts Medical School, Worcester, MA, USA

Robert Dempsey, MD Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Gary Duckwiler, MD Department of Radiological Sciences, UCLA Health, Los Angeles, CA, USA

Trevor M. Dudley, BA Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA

Amgad El Mekabaty, MD Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, Baltimore, MD, USA

Department of Radiology and Radiological Sciences, University Hospital of Basel, Basel, Switzerland

Jason A. Ellis, MD Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA

Northwell Health, New York, NY, USA

Kyle M. Fargen, MD, MPH Department of Neurological Surgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

Daniel Felbaum, MD Department of Neurosurgery, MedStar Georgetown University Hospital, Washington, DC, USA

Wuwei Feng, MD, MS Department of Neurology, Medical University of South Carolina, Charleston, SC, USA

Vernard S. Fennell, MD, MSc Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

Gates Vascular Institute at Kaleida Health, Buffalo, NY, USA

David Fiorella, MD, PhD Cerebro vascular Center, Department of Neurological Surgery, Stony Brook University Medical Center, Stony Brook, NY, USA

Don Frei, MD Department of Neuro-Interventional Surgery, RIA Neurovascular, Englewood, CO, USA

Dheeraj Gandhi, MBBS Departments of Diagnostic Radiology and Nuclear Medicine, Neurology and Neurosurgery, Center of Metabolic Imaging and Therapeutics and Executive Committee Member for the Comprehensive Stroke Center, Johns Hopkins Hospital, Baltimore, MD, USA

Tarun Girotra, MD Department of Neurology, University of New Mexico, Albuquerque, NM, USA

Nitin Goyal, MD Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Ricardo A. Hanel, MD, PhD Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA

Gillian Harrison, MD Department of Neurosurgery, New York University Medical Center, New York, NY, USA

Don Heck, MD Novant Health Forsyth Medical Center, Winston-Salem, NC, USA

Joshua A. Hirsch, MD Department of Radiology, Massachusetts General Hospital/ Harvard Medical School, Boston, MA, USA

Ferdinand K. Hui, MD Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD, USA

Carey School of Business, Johns Hopkins University, Baltimore, MD, USA

Department of Interventional Stroke, Johns Hopkins National Capital Region, Baltimore, MD, USA

Muhammad Shazam Hussain, MD, FRCP(C) Cerebrovascular Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Seby John, MD Neurology and Neurointerventional Surgery, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

Julie Kanter, MD Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

Niren Kapoor, MBBS, PhD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Michael E. Kelly, MD, PhD Division of Neurosurgery, Department of Surgery, University of Saskatchewan, Saskatoon, SK, Canada

Anna L. Kuhn, MD Department of Radiology, Umass Medical School, Worcester, MA, USA

Anthony D. Kuner, MD Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Min Lang, MD, MS Cerebrovascular Center, Cleveland Clinic Foundation, Cleveland, OH, USA

David J. Langer, MD Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA

Jonathan Lena, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Thabele M. Leslie-Mazwi, MD Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

Jussie Lima, MD Department of Neurology, Hartford Hospital/University of Connecticut, Farmington, CT, USA

Demetrius K. Lopes, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Stephen R. Lowe, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Casey Madura, MD, MPH Pediatric Neurosurgery, Helen DeVos Children's Hospital – Spectrum Health, Grand Rapids, MI, USA

Jaime L. Martinez, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Sarah McCormick, RT(R)(CT) Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Maurice M. Miller, MD Department of Interventional Neuroradiology, West Virginia University, Morgantown, WV, USA

Amrendra S. Miranpuri, MD Department of Neurosurgery, Carle Foundation Hospital, Urbana, Illinois, USA

J. Mocco, MD Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Nina Z. Moore, MD, MSE Cerebrovascular Center, Cleveland Clinic Foundation, Cleveland, OH, USA

Kyle Mueller, MD Department of Neurosurgery, MedStar Georgetown University Hospital, Washington, DC, USA

Stephan A. Munich, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Sabareesh K. Natarajan, MD, MSc Department of Neurosurgery, University at Buffalo, State University of New York, Buffalo, NY, USA

Peter Kim Nelson, MD Bernard and Irene Schwartz Interventional Neuroradiology Section, Departments of Neurology, Neurosurgery and Radiology, New York University Langone Medical Center, New York, NY, USA

Ron Neyens, PharmD, BCPS Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC, USA

May Nour, MD, PhD Department of Interventional Neuroradiology, UCLA Health, Los Angeles, CA, USA

Abhi Pandhi, MD Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Sunil J. Patel, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Lissa Peeling, MD Division of Neurosurgery, Department of Surgery, University of Saskatchewan, Saskatoon, SK, Canada

Charles J. Prestigiacomo, MD, FAANS, FACS Department of Neurological Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

G. Lee Pride Jr., MD Departments of Radiology and Neurosurgery, UT Southwestern Medical Center, Dallas, TX, USA

Ajit S. Puri, MD, DM Department of Diagnostic Radiology and Neuroradiology, UMass Memorial Health Care, Worcester, MA, USA

Rabia Qaiser, MD Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA

Ralph Rahme, MD Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA

Division of Neurosurgery, SBH Health System, Bronx, NY, USA

Ansaar T. Rai, MD Department of Interventional Neuroradiology, West Virginia University, Morgantown, WV, USA

Peter A. Rasmussen, MD Cerebrovascular Center, Cleveland Clinic Foundation, Cleveland, OH, USA

Eytan Raz, MD, PhD Departments of Neurointerventional Radiology and Neuroradiology, NYU Langone Health, New York, NY, USA

Howard A. Riina, MD Department of Neurosurgery, New York University Medical Center, New York, NY, USA

Christina Roels, PharmD, CPP, BCPS Department of Pharmacy, Novant Health Forsyth Medical Center, Winston-Salem, NC, USA

Peter Rozman, MD Department of Neurosurgery, New York University Medical Center, New York, NY, USA

Howard A. Rowley, MD Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Eric Sauvageau, MD Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA

James Scozzafava, MD Department of Adult Critical Care Medicine, Saskatoon Health Region, Saskatoon, Saskatchewan, Canada

Division of Stroke Neurology, Neurosciences Program, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Hakan Seckin, MD Department of Neurosurgery, Lokman Hekim Hospital, Istanbul, Turkey

Maksim Shapiro, MD Departments of Neurointerventional Radiology and Neurology, NYU Langone Health, New York, NY, USA

Hazem Shoirah, MD Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Adnan H. Siddiqui, MD, PhD Departments of Neurosurgery and Radiology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

Jasmeet Singh, MD Department of Radiology and Neurosurgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

Bowman Gray Center, Winston-Salem, NC, USA

Alejandro M. Spiotta, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Gary K. Steinberg, MD, PhD Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA

Charles M. Strother, MD, PhD Department of Radiology, UW School of Medicine and Public Health, Madison, WI, USA

Omar Tanweer, MD Department of Neurosurgery, New York University Medical Center, New York, NY, USA

Abdul R. Tarabishy, MD Department of Radiology, West Virginia University, Morgantown, WV, USA

Philipp Taussky, MD Department of Neurosurgery, University of Utah School of Medicine, Salt Lake City, UT, USA

Gabor Toth, MD Cerebrovascular Center, Cleveland Clinic Lerner College of Medicine, Mayfield Heights, OH, USA

James Towner, MD Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA

Robert K. Townsend, MD Department of Neurological Surgery, Wake Forest University, Winston-Salem, NC, USA

Aquilla S. Turk, DO Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Raymond D. Turner, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Alexander Vandergrift, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Jan Vargas, MD Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

Ajay K. Wakhloo, MD, PhD Department of Radiology, University of Massachusetts Medical School, Worcester, MA, USA

Zhikui Wei, MD, PhD Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Babu G. Welch, MD Departments of Neurological Surgery and Radiology, UT Southwestern Medical Center, Dallas, TX, USA

John A. Wilson, MD Department of Neurological Surgery, Wake Forest University, Bowman Gray Center, Winston-Salem, NC, USA

Alex M. Witek, MD Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA

Stacey Q. Wolfe, MD Department of Neurological Surgery, Wake Forest University, Bowman Gray Center, Winston-Salem, NC, USA

Henry H. Woo, MD Department of Neurosurgery, North Shore University Hospital, Manhasset, NY, USA

Part I
Introduction

Chapter 1
The History of Vascular Neurosurgery: A Journey of Evolution and Revolution

Charles J. Prestigiacomo

The history of vascular neurosurgery is as rich and complex as any other field in medicine. Its birth and development emerged from the necessity, creativity, and technology needed to care for patients with potentially life-threatening lesions. Its growth and technological changes have influenced many other subdisciplines of our field. As a matter of fact, of the numerous evolutionary and revolutionary advances in the practice of neurological surgery, most have arisen from this need to treat and cure vascular disease of the brain and spinal cord. From anatomy to pathophysiology, from preoperative imaging to intraoperative optics, from creative microsurgical approaches to innovative endovascular techniques, vascular neurosurgery has brought a plethora of challenges to the practitioners of this art and science, and throughout its history, the neurosurgeon and the many collaborators and scientists have responded.

The historical review of this subject can take many forms. Developments in anatomy, imaging, technology, and techniques influenced the unique histories of each of the vascular diseases that neurological surgeons treat. Though each is deserving of extensive analysis, a brief historical survey of the many technological advances that influenced the growth of vascular neurosurgery will be presented prior to discussing the historical development and growth of the subdisciplines within vascular neurosurgery.

C. J. Prestigiacomo (✉)
Department of Neurological Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: presticj@uc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_1

The Rise of Vascular Anatomy

Galen first introduced the concept that a circulation of arteries and veins (centered on the heart) existed [1, 2]. Though not well conceived, Galen stated that vital spirits were produced in the left ventricle of the heart and traveled to the brain. The concept was further developed by numerous anatomists until the cohesive and correct concept of circulation was introduced by Harvey and elegantly described in the intracranial circulation by Thomas Willis in 1664 (Fig. 1.1) [3, 4].

Unlike the revolutionary change in the understanding of the cerebrovasculature as presented by Willis, there have been many incremental and evolutionary advances in developing a greater understanding of cerebrovascular anatomy. Authors, anatomists, and surgeons such as Krayenbuhl, Seeger, Lasjunias, Berenstein, Yaşargil, and Rhoton provided guidance and insight to every neurosurgeon and endovascular therapist in gaining the intricate fundamental knowledge of the anatomy of the arteries and veins of the brain and spinal cord. However, these authors brought a more important perspective. In addition to providing the detailed anatomy, these authors contributed to our understanding of the surgical anatomy of the surrounding structures. The intricate descriptions of Yaşargil and Rhoton in describing the subarachnoid cisterns and the numerous skull base corridors of approach brought a new understanding of how vascular lesions of the brain could be treated. Lasjunias,

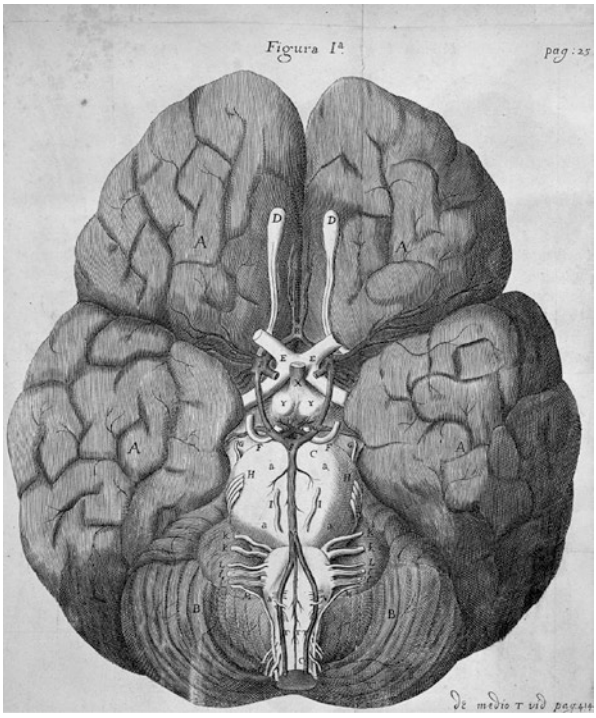


Fig. 1.1 Illustration by Christopher Wren of the basal view of the brain demonstrating the vascular arterial ring to be later named the circle of Willis (Willis, 1664, public domain)

Berenstein, and terBrugge introduced the need to understand the embryology of the cerebrovasculature such that it would become critical in understanding and thus treating some of the most complex vascular lesions. These critical elements have now become the fundamentals for all cerebrovascular and endovascular therapists.

Technological Growth

The History of Cerebrovascular Imaging

Dedicated imaging for the cerebral vasculature was developed long after the first attempts to treat vascular disease. The development of angiography was essentially an extension of the search to better diagnose intracranial lesions. Plain cranial X-rays, pneumoencephalography, and myelography were the basic methods of imaging the central nervous system before 1927 [5–7].

The first images of the human vasculature were obtained by Haschek and Lindenthal in 1896 (Fig. 1.2) [8]. By injecting a mixture of petroleum, quicklime (calcium oxide), and mercuric sulfide, they were able to visualize the vasculature of the hand of a cadaver with X-ray. Antonio Caetano de Abreu Freire Egas Moniz, a Portuguese neurologist, had an interest in developing a technique to image tumors of the brain [9, 10]. Recognizing the sedating effects and imaging qualities of bromine, Moniz hypothesized that injecting bromine compounds would travel to the brain (hence its sedating effects) and thus allow the brain to be imaged with X-ray. Further inspired by Sicard's work on the use of iodized oil myelography, Moniz set out to develop a technique that would improve the diagnosis of intracranial tumors [7]. On June 28, 1927, after several frustrating attempts on cadaver heads and dogs, Moniz and his colleague Almeida Lima successfully demonstrated the displacement of the anterior and middle cerebral arteries in a 20-year-old man with a pituitary adenoma after a direct surgical exposure of the carotid artery [11]. By 1931, Moniz

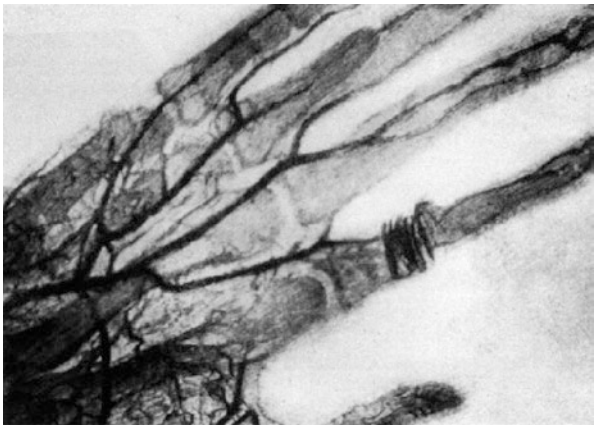


Fig. 1.2 First roentenogram of human vasculature in a postmortem hand by Haschek and Lindenthal 1 year after the discovery of X-ray (1896). The authors used Teichman's mixture injected into the amputated hand (public domain)

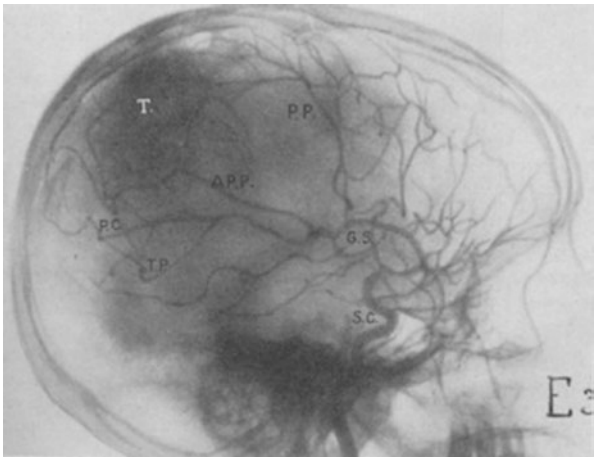


Fig. 1.3 First cerebral angiogram. Egas Moniz performed the first cerebral angiogram demonstrating a lateral view of the intracranial vessels for the first time in a living person (From Moniz [10], with permission)

was able to perform a complete angiogram which included arterial and venous phases (Fig. 1.3) [9, 11]. Angiography's preeminence as a diagnostic tool came in 1936 with Loman and Myerson's percutaneous carotid puncture technique [12]. Interestingly, the *Lancet* foreshadowed the potential of angiographic techniques as early as 1931, when it commented that not only might it be able to diagnose aneurysms but also that "its possibilities as an avenue for therapeutics should not be lost sight of in the future" [13, 14].

This technique became the standard for diagnosing intracranial lesions of all kinds, most significantly vascular lesions for the next 40 years. With better capabilities than standard skull X-ray and while being safer and having better direct imaging capacity than pneumoencephalography, cerebral angiography was used in creative ways that took great advantage of anatomical knowledge. Epidural and subdural hematomas were diagnosed by the notable absence of a capillary blush along the inner table; tumors of various lobes were defined by a notable shift of the Sylvian triangle or the Sylvian point; hydrocephalus was diagnosed by detecting a shift in the true venous angle [15, 16]. These skills became the standard in the image-based diagnosis of all intracranial pathology – until the early 1970s.

Up until 1971, intracranial imaging was limited to the *direct* imaging of the vasculature and ventricles and the *indirect* assessment of the brain parenchyma and its surrounding structures. Diagnosis of parenchymal lesions was by interpretation of surrogate evidence. Sir Godfrey Hounsfield revolutionized this field of imaging. An electrical engineer by training, Hounsfield was given the opportunity to perform independent research funded by EMI and develop the algorithms that would allow him to identify objects by obtaining X-ray images at different angles. This concept rapidly expanded to include the application to medical imaging. Initial studies were performed on a preserved human brain and subsequently on a fresh cow brain. By late 1971, Hounsfield's scanner was able to identify a cerebral cyst in a patient at Atkinson Morley Hospital [17, 18].

The technology and its application exploded. With the development of spiral and later multi-detector CT, higher resolution and greater tissue definition became a reality. The consequent reduction in scan time was a necessary by-product of the technology which created the ideal environment to develop CT angiography. By the late 1990s, the multi-row CT scanner, with thinner slice acquisition and reduced scanning time, now allowed clinicians to obtain long segment scans while injecting intravenous contrast. CT angiography was born [19–21].

In the ensuing 20 years, continued improvements in CT technology and the birth and rise of magnetic resonance imaging have changed the way vascular lesions are diagnosed. Cerebral angiography, initially used to provide clinicians a diagnosis via direct and indirect imaging evidence, has been displaced as a screening tool in favor of these less invasive techniques. As was once predicted, catheter-based angiography has blossomed into a versatile, effective, and safe therapeutic tool that has given birth to numerous new treatment paradigms.

History of the Microscope and Intraoperative Imaging

Neurological surgery in general and vascular neurosurgery in particular have benefited from the technological advances in illumination and magnification. Given that most neurosurgical procedures require dissection of the tissue to depths beyond 3 cm from the surface, proper illumination became the initial priority. Though this was achieved, in part by the use of external light sources with ever-improving efficiency and power beyond natural lighting entering the windows of the operative theater, the ability to provide illumination to the deeper portions of the surgical field remained elusive. The introduction of scopes with lenses to bring light directly to the surgical field began. Contemporaneous to this, there came an understanding and desire to magnify the operative field so as to ease identification of structures and thus render surgery safer [22].

Magnification in the form of operating loupes entered the surgical theater in the mid-nineteenth century [23]. Though initially used as corrective lenses, single-lens spectacles were designed with magnifying properties to be used for surgery. It wasn't until 1876 that Saemisch, a German ophthalmologist, wore the first true binocular compound magnifying loupes in the surgical theater [23]. Though this solved the initial problems with magnification, it failed to address other important issues for proper visualization during surgery: illumination, the depth of field, and the field of view. For the neurosurgeon, the use of loupes has been of great benefit in the initial stages of most cranial operations and for some spinal surgeries to this day.

By the early 1900s, microscopes had become well-entrenched in the realm of experimental and animal research. In 1921, research on live animals describing the flow of endolymph in pigeons was reported [24]. Taking note of this, Carl Nylen, a Swedish otolaryngologist, subsequently developed and constructed an operating monocular microscope to treat a case of chronic otitis media (Fig. 1.4) [24, 25].

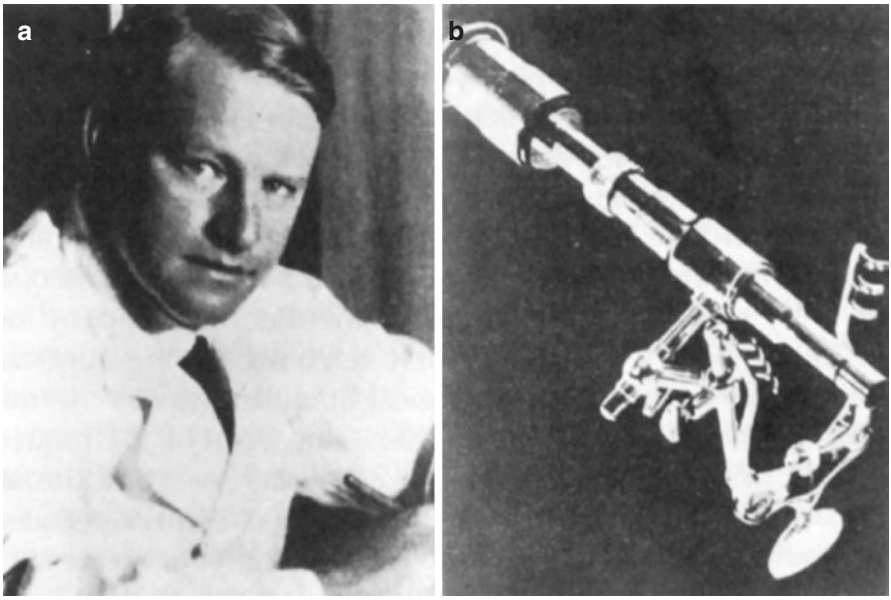


Fig. 1.4 Carl Nylen and the first monocular operating microscope (From Kriss and Kriss [25], with permission)

The field of otolaryngology through the work of Nylen's chairman, Gunnar Holmgren, and others provided the environment upon which further developments to the microscope could be made. By the 1950s, the field of otolaryngology (specifically otology) enjoyed the early rewards of technological improvements in lens crafting, fiber optics, and illumination.

Theodore Kurze was the first neurosurgeon to bring the operating microscope to the neurosurgical theater [25]. Having watched a film depicting surgery of the stapes as performed by William House, Kurze spent a year with House practicing microsurgery in the laboratory. In August 1957, Kurze was the first neurosurgeon to resect a neurilemoma from the facial nerve of a 5-year-old patient [25]. In the ensuing years, Kurze trained Drs. Pool, Rand, and Drake in the use of the surgical microscope, each of whom introduced the technology and techniques at their own institutions.

The surgical microscope provided much that was necessary to succeed in vascular and skull base surgery. The ability to provide excellent illumination, controlled magnification, and an excellent depth of field within an adequate field of view made the surgical microscope indispensible in the realm of neurovascular surgery. Adjunctive devices such as neuronavigation, fluorescence-enhanced microscopy, ultrasound, and intraoperative angiography have thus created an impressive armamentarium of techniques by which the neurosurgeon can ensure a safe, successful operation with a minimum risk of complications.

Endovascular Origins

Being able to visualize neurovascular pathology, both from the diagnostic perspective as rendered by cerebral angiography and noninvasive imaging and from the therapeutic perspective in the form of the surgical microscope and all its adjunctive devices, is certainly mission-critical in effecting success. Within vascular neurosurgery, each of these technologies was incorporated in unique and sometimes subtle ways that helped surgeons expand their skills and treat progressively more complex lesions with better outcomes.

The concept of endovascular treatment grew from attempts to treat aneurysms endovascularly since the nineteenth century [13]. Careful observations and subsequent experiments in animals by Velpeau suggested that metallic objects, such as needles, could result in local thrombosis sufficient to occlude an artery [26]. Independently, Phillips demonstrated that the use of a needle with an applied electric current also resulted in thrombosis within a vessel. These concepts were first studied in humans for the treatment of aortic aneurysms. It wasn't until approximately a century later that the technique was attempted for intracranial lesions [27, 28].

As previously discussed, neuroendovascular therapy has an extensive history. Although there were many approaches at endosaccular occlusion of aneurysms, true catheter-based endovascular approaches to vascular diseases of the central nervous system did not take place until 1960 [29].

Prior to Luessenhop, the direct intravascular approach to treatment of vascular pathology preceded Gardner's resourceful, yet inadvertent, "intravascular" approach to intracranial vascular pathology. Brooks has been incorrectly credited with the first such attempt when he placed a piece of muscle intravascularly to obliterate a traumatic carotid fistula in 1930 [30, 31]. When reviewing his commentary to Noland and Taylor, Brooks appropriately (and perhaps for the first time) points out the rationale for failure of Hunterian ligation in the treatment of carotid-cavernous fistulae, pointing out that the fistulous site must be obliterated for success. He reports having placed the muscle into the carotid artery to attempt to obliterate a fistula in a patient but never reported the free flow of such a piece of muscle to the distal circulation to do so [32]. Arutiunov and Burlutsky expanded upon this concept in the ensuing years and presented their important findings in 1964 [33].

Catheter technology had developed sufficiently by 1960, such that Luessenhop and Spence were able to intraoperatively cannulate the internal carotid artery [34]. They were the first to successfully deposit silastic spheres into the internal carotid circulation to treat an arteriovenous malformation in the operating room. Two years later, Rothenberg et al. introduced the concept of using balloons in the treatment of intracranial aneurysms when he developed the angiotactic balloon [35]. A polyester sleeve wrapped around a neoprene balloon was attached to a 4-French delivery system. This sleeve could then be deployed in situ, with inflation of the balloon, as was demonstrated in their animal model, substantiating that the intravascular use of balloons might be helpful in the treatment of intracranial vascular disease – a concept that would become important in endovascular therapy.

The remainder of the history of neuroendovascular therapy as well as vascular neurosurgery remains entwined with the history of the treatment of specific vascular diseases. Each lesion presents unique challenges and hence unique solutions developed by creative, evolutionary steps and at times revolutionary leaps. What is evident throughout this rich, colorful history is the overriding passion and drive that was demonstrated by the pioneers and the courage of the patients. Additionally, it is intriguing to note that in most cases, the concepts and logic on how to approach the clinical issues were clear and at times obvious. It was the need for technology to "catch up" with the ideas that at times delayed the progress.

History of Aneurysm Therapy

Intracranial aneurysms were first thought to be a cause of subarachnoid hemorrhage (SAH) in the seventeenth century [36]. Morgagni likewise emphasized the concept that intracranial aneurysms could be the cause of hemorrhage [37]. He was also the first to report the presence of incidental "dilatations" of both posterior cerebral arteries in 1725, possibly making this the first description of an intracranial aneurysm. The first documented account of an unruptured intracranial aneurysm did not occur until 1765 by Francesco Biumi in Milan [38]. In 1814, the first verified account of an aneurysmal rupture was reported by Blackall [39].

Despite recognizing these lesions during the mid-eighteenth century, there is no mention of any treatment being offered. Indeed, the reports at this time were based on postmortem findings. Treatment of vascular lesions of the head and neck did not begin until the late nineteenth century, several years after Hunter's description of proximal femoral artery ligation for popliteal aneurysms as an alternative to leg amputation [40, 41].

Building upon the success of Hunterian ligation in the peripheral circulation, the concept of carotid artery ligation for intracranial vascular pathology began to take form. The first successful carotid sacrifice for an indication other than hemorrhage was by Cooper in 1808 for an aneurysm of the left cervical internal carotid artery (Cooper's first carotid ligation in 1805 was unsuccessful) [42]. Cooper, interestingly, surmised at the time that the partial resolution in pulsations was attributed to retrograde filling from distal collateral circulation. Benjamin Travers first reported successful treatment of an intracranial lesion (carotid-cavernous fistula) in 1809 [43].

The years that followed were filled with clinical reports of carotid ligation for numerous nontraumatic indications. A full century after Hunterian ligation was first described; carotid occlusion for an intracranial aneurysm was performed. During surgery for resection of a middle fossa tumor in a 48-year-old woman, Victor Horsley identified a pulsating tumor, most likely an aneurysm. Horsley subsequently ligated her right common carotid artery. She was reported to be doing well 5 years later [44].

The following years were then devoted to developing more sophisticated methods of carotid occlusion progressing from various types of suture to mechanical

clamps that would allow for progressive, controlled narrowing of the artery to the point of occlusion in an attempt to encourage collateral flow and allow for aborting the procedure in case of new neurological deficits [13].

Reports demonstrated mortality rates generally below 20% [45–48]. Unfortunately, successful obliteration of the aneurysm was low, with success usually occurring for aneurysms of the internal carotid artery (ICA) itself. Winn's report evaluating the rehemorrhage rate in 34 patients with posterior communicating artery aneurysms essentially found no difference between those treated with carotid occlusion and the conservatively managed nonoperative group [49].

Because of the difficulties noted and because of significant concerns regarding delayed thrombotic/embolic events from cervical carotid occlusion, the methods of cervical carotid occlusion were superseded by intracranial methods. The first successful intracranial carotid occlusion was described by Hamby and Gardner in 1932 [50]. Zeller was the first to attempt this procedure in 1911, but his patient died from hemorrhage after an assistant accidentally avulsed the ligated artery by pulling the ligature [51]. In 1935, Dandy introduced the use of the Cushing silver clip (developed in 1911) to achieve proximal supraclinoid ICA occlusion for the treatment of intracranial aneurysms [52].

Direct Approaches to Aneurysm Therapy

By the early 1900s, it was clear that, although a significant amount of knowledge had been gained on the pathology of aneurysms and some technical advances toward the treatment of these lesions had taken place, the overall outcomes were still dismal. Indeed, Harvey Cushing thought that the aneurysm was "a lesion having such remote surgical bearings, whether there are surgical indications further experience alone can tell" [53]. Ayer later echoed these sentiments by stating that subarachnoid hemorrhage "has little interest from a standpoint of active surgical procedure" [54].

Because of the many difficulties encountered with the indirect approaches of cervical carotid ligation, more direct approaches were sought. Although there were real concerns with a direct attack on the neck of an aneurysm, there were significant benefits. The technology in the 1930s made securing an aneurysm at the neck rather dangerous, as ligatures and silver clips were the only devices developed at the time. Thus, risks of exsanguination secondary to avulsion of the aneurysm at the neck were quite real. However, preservation of the parent vessel and a higher chance of cure for aneurysms beyond the carotid terminus were sufficient reason to embolden surgeons in their quest for new techniques.

Norman McComish Dott, a pupil of Cushing and one of the several men to help establish neurosurgery in Great Britain, was the first surgeon to be credited with the first direct attack on an intracranial aneurysm [13, 55]. On April 22, 1932, in treating a middle-aged man who had sustained three subarachnoid hemorrhages secondary to an aneurysm of the ICA terminus at the origin of the proximal middle cerebral artery, Dott encountered "formidable" bleeding during the exposure. He harvested

the muscle from the patient's thigh and placed it on the exposed aneurysm dome. He reported that hemorrhage stopped after approximately 12 min. He applied further muscle pledgets in the region and surrounding the parent artery. The patient was reported to have made an excellent recovery with no further hemorrhagic events. Additional reports by Tonnis, Dandy, and Jefferson added to the early literature of wrapping [46, 56, 57].

The next advance in aneurysm treatment was aneurysm trapping, which was initially described by Walter Dandy in 1936 [45]. He performed cervical internal carotid ligation and clipping of the supraclinoid carotid artery for a cavernous aneurysm. Logue clipped the A1 segment to trap an anterior communicating artery aneurysm in 1956, and Tindall et al. added contralateral common carotid artery narrowing to assist in thrombosis [58, 59].

The Aneurysm Clip

On March 23, 1937, a new era in cerebrovascular surgery began. Walter Dandy reported exposing an aneurysm of the posterior communicating artery via his hypophyseal approach in a 43-year-old man presenting with a third nerve palsy. Having identified the neck of the aneurysm, he placed a silver clip across its neck and cauterized its dome. By 1944, he had amassed sufficient cases that he published his observations and results in the first monograph of aneurysm surgery, *Intracranial Arterial Aneurysms* [46].

This first clip used by Dandy was a malleable Cushing- or Mackenzie-type silver clip. Simple, yet important, modifications to the concept followed with the development of a U-shaped clip to allow the tips of the clip to approximate first and essentially trap the aneurysm neck within the clip, thus obliterating the aneurysm.

Further modifications to the clip came quickly [13]. Developments such as adjustable clips, cross-action "alpha" clips, and Drake's fenestrated clips for basilar tip aneurysms have enabled surgeons to treat aneurysms that were previously deemed unclippable [60]. Sundt's encircling clip-graft was another significant innovation in aneurysm clip technology that allowed for repair of vessel tears or small irregularities that are untreatable by ordinary clipping methods [61].

Currently, modifications to the aneurysm clip are based on metallurgy and different design configurations. Concurrent with the development of the aneurysm clip came many other developments in techniques and parallel technologies that helped improve the surgical treatment of patients with cerebral aneurysms [62]. As discussed, the introduction of the surgical microscope revolutionized the approach to treating aneurysms. The elegant microsurgical techniques of Yaşargil and Fox helped to redefine the surgical approaches to aneurysms, emphasizing the importance of understanding cisternal anatomy and microvascular anatomy in maximizing patient results [63]. During this period, others, such as Drake, set the standards for surgery of posterior circulation aneurysms, along with the development and use of the first fenestrated aneurysm clip [60].

Endosaccular Alternatives to Clipping

As aneurysm clip technology continued to develop, surgeons continued to reflect on alternative techniques for the management of aneurysms. The concept that aneurysms could be treated endoluminally was serendipitous. In 1936, Gardner opened a giant ICA aneurysm, thinking it to be a large tumor. He subsequently packed it with five cotton sponges [64]. The patient did well until 2 years later when the sponges were removed because of infection.

Thereafter, endosaccular attempts to thrombose aneurysms included the use of silk suture, electrothrombosis with copper wire, magnetically guided iron filings, and horse or hog hair through a transfundal approach [13]. Except for a few select procedures, the aforementioned techniques all involved transcranial approaches to the aneurysm. The technology for safe navigation intravascularly was not far behind. By 1962, Rothenberg et al. developed an intravascular catheter that could release an expandable sleeve and occlude an aneurysm in an experimental animal model [35]. Two years later, modern endovascular therapy for aneurysms was born.

Endovascular Therapy for Aneurysms

Though revolutionary in appearance, technique, and devices, the historical record suggests that perhaps endovascular therapy for aneurysms was an inevitable evolution. Luessenhop continued to build on his work with Spence. In 1964, Luessenhop and Velasquez demonstrated that balloons could be safely introduced into the internal carotid artery and actually demonstrated temporary exclusion of an aneurysm from the circulation during balloon inflation [29].

Though additional trials with magnetically guided iron filings via an intravascular route were attempted, subsequent years of research focused on the use of intravascular balloons to endovascularly occlude aneurysms [13]. During this period, a tremendous amount of research in the field of materials science enabled biomedical engineers to bond soft shapeable tubing of different compositions in such a way as to provide proximal catheter support with distal catheter flexibility and softness, resulting in a vast improvement in the navigation properties of the catheter. With the birth of the microcatheter, endovascular surgery's explosive growth paralleled that which was seen with the advent of the aneurysm clip.

Unlikely to have been greatly influenced by work in the Western Hemisphere, Serbinenko began searching for the endovascular treatment of intracranial vascular disease as a young neurosurgeon training at the N. N. Burdenko Institute in the mid-1950s. By 1969, Khilko and Zubkov demonstrated that stable thrombus could be formed within an aneurysm by saturation with coagulants and reduction of flow to the aneurysm by temporary parent vessel constriction [65].

Serbinenko began to research and develop skills and techniques for the use of balloons in earnest [66]. By 1974, Serbinenko reported the use of selective catheterization

to deliver and deploy detachable balloons filled with a hardening agent (liquid silicone) for the treatment of a variety of vascular lesions in 300 patients at the Burdenko Institute. He began in 1963 with balloon exploration of the intracranial circulation and first occluded the internal carotid artery with a balloon via an approach through the external carotid artery in 1964. Most important to this historical review, he reported the successful detachment of balloons within a basilar tip aneurysm and supraclinoid carotid aneurysm.

Encouraged by this, Debrun et al. made minor modifications to Serbinenko's concept by introducing contrast into the balloon and an elastic band at its neck, which tightened to prevent leakage of contrast upon detachment [67]. DiTullio et al. developed the one-way valve for balloons, whereby contrast injection opened the valve, and the internal hydrostatic balloon pressure, once inflated, would prevent outflow of contrast [68].

In 1982, Romodanov and Shcheglov reported their results in the treatment of 119 patients with detachable, silicone-filled latex balloons [69]. They reported 108 occlusions with 93 parent vessel preservations and 4 deaths. Higashida et al. and Moret et al. used hydroxyethyl methacrylate as the filling solution for the balloon, further refining this technique [70–72]. Although initially promising, significant complications were reported with this technique, which included intraoperative and delayed rupture, as well as recanalization.

The use of coils for endovascular vessel occlusion began in earnest almost a century after its initial use for aortic aneurysms, with the introduction of the Gianturco coil [73]. In 1985, Braun et al. reported the first intracranial aneurysm treated with coil embolization [74]. Interestingly, the use of coils in this setting was the result of an unsuccessful balloon occlusion for a giant internal carotid artery aneurysm. The introduction of platinum coils with Dacron (E.I. duPont de Nemours and Co., Wilmington, DE) fiber to induce thrombosis for the treatment of vascular malformations and aneurysms was reported by Hilal et al. in 1988 [75]. Although some successes were reported, the inability to precisely control these pushable coils resulted in a significant incidence of parent vessel occlusion and distal embolization. A controllable delivery system with the ability to retrieve, reposition, and redeploy the coil to a satisfactory configuration prior to detachment was necessary to increase the safety of the procedure.

Intrigued by Mullan's work on electrothrombosis and Serbinenko's endovascular techniques, Guido Guglielmi began developing techniques that would combine these concepts. Guglielmi first constructed a microwire with a small magnet that would be introduced endovascularly within an aneurysm. He then developed a technique whereby a suspension of iron microspheres would be injected into the circulation and be attracted to the small magnet within the aneurysm, thus inducing thrombosis. The magnet would then be electrolytically detached from the microwire and left in situ [13].

Approximately 1 year later, Guglielmi began working with Ivan Sepetka of Target Therapeutics and developed the first-generation electrolytically detachable coil [76]. In 1990, the first coil was introduced in a patient for a traumatic

carotid-cavernous fistula who failed balloon occlusion [77]. One month later, the first aneurysm was treated with this electrolytically detachable coil [78]. Interestingly, the initial reports suggested that aneurysmal thrombosis was a consequence of the thrombogenic properties of the coils in conjunction with electrothrombosis during detachment. This was later found not to be the case.

Since that time, the tremendous explosion in endovascular technology and techniques has challenged the role of microsurgery in the treatment of aneurysms. Early endovascular studies revealed that, although small aneurysms with small necks and a 2 to 1 dome-to-neck ratio had excellent long-term results, outcomes for large aneurysms or those with broad necks (>4 mm) had a significant recanalization rate [79]. To address this, Moret et al. [72] introduced the balloon remodeling technique. By placing a balloon across the neck of the aneurysm during coil deployment from a second microcatheter, better packing was achieved with less risk of coil protrusion into the parent artery.

Because of the limitations of coil embolization for aneurysm treatment, additional advances have been made in an attempt to reduce the recurrence rate of endovascular aneurysm therapy. Numerous studies have been published, evaluating the role of endovascular aneurysm therapy [80].

Similar to the explosion in the various kinds of aneurysm clips in the 1960s and 1970s, this past decade has seen the development of several different generations of the original coil along with variations in basic coil morphology [81]. The addition of bioactive coatings on or within the coil has resulted in a new direction of aneurysm treatment [82]. Such technology may increase the healing at the aneurysm neck, thereby reducing aneurysm recurrence.

Endovascular Hunterian ligation, aneurysm trapping, and parent vessel occlusion have all been reevaluated since being introduced in the early twentieth century [83]. Similar to its surgical predecessors, endovascular Hunterian ligation has a limited role in the current armamentarium of aneurysm therapy.

As with open surgical techniques, these concepts of "indirect" aneurysm therapy have been reintroduced with greater sophistication. Whereas at first the indirect approaches to aneurysm therapy involved flow reversal and trapping of aneurysms, now the indirect approach involves the use of stents for diversion of flow away from the aneurysm inflow zones [84]. First used as adjuncts for broad-necked aneurysms, stents are now being evaluated for their ability to alter flow along the aneurysm neck and, thus, influence recanalization.

History of Vascular Malformation Therapy

The history of resecting the various types of vascular malformations truly resides in the progress of anatomical and physiological knowledge, coupled with the rise of technical expertise and technology. Vascular malformations, specifically arteriovenous malformations, were recognized since the days of the Egyptians (Amenhotep I

during the sixteenth century BC), who specifically cautioned physicians to not attempt to treat these lesions when they occurred anywhere in the body [85–87]. Intracranial vascular lesions were first reported by Virchow and Luschka in the late nineteenth century [88]. Subsequently, attempts to resect these lesions in the late nineteenth century to the early twentieth century were clearly fraught with danger given that hemostasis as a technique for the central nervous system had yet to be perfected.

Though first exposed by Giordano in 1897, his surgical procedure focused on ligating a parietal feeding artery with no sign of cure [89]. The literature does suggest that the first successful resection of an AVM was performed in same year by Jules-Emile Pean [90]. Subsequent case reports of AVM surgery by pioneers such as Bailey, Dandy, and Cushing demonstrated very poor outcomes. Indeed, Cushing and Bailey were more adamant against the neurosurgeons' role in treating AVMs than Cushing was with regard to aneurysms. Most interestingly, it was Cushing himself who observed the positive effects of radiation therapy on AVMs as early as 1928, a finding that was first reported by Vilhelm Magnus in 1914 [91, 92].

The second successful resection of an AVM was reported by Olivecrona [93]. Unique to this report was Olivecrona's systematic approach to the lesion, describing the careful ligation of superficial feeding arteries with circumferential dissection of the nidus. Of note, he echoed the concept of ligating the venous outflow vessels as the last, critical portion of the surgery.

It is interesting to note that the first angiographic diagnosis of the AVM was in 1936, several years *after* the numerous and some successful surgical resections [94–96]. This, in addition to the eventual addition of microscopic surgery, enhanced knowledge in anatomy and physiology, and McCormack's careful stratification of vascular lesions during the 1950s and 1960s brought a greater understanding to vascular malformations of the brain [97].

With the advent of the better methods of illumination, the microscope, and the microsurgical techniques as introduced by Donaghy, Krayenbuhl, and Yaşargil, the systematic approach to AVM resection blossomed. This was the stage of mastery. With Yaşargil's case series of ten patients, AVM surgery became safe and efficacious far beyond the initial attempts to successfully treat these lesions [90, 98]. As the technical microsurgical expertise was maturing, the simultaneous birth of radiosurgery toward the end of the 1960s and the growth of endovascular during the same period brought a new era to AVM therapy [99]. The year 1968 saw the development of the gamma knife by Lars Leksell as a natural outgrowth from recognizing radiation's effects on AVMs [92]. As noted, the very first endovascular procedure in the modern era was in fact to treat a fistula of the carotid artery by Luessenhop [29]. Furthermore, microcatheter technology developed primarily as a means of gaining access distally, and the calibrated leak balloon catheter was developed to gain access to pedicle feeders of AVMs. The historical aspects of radiosurgery and endovascular therapy for these lesions are too rich to describe in this brief overview and are described elsewhere.

Ischemic Therapy and Revascularization

The history of ischemic therapy is the history of our struggle with control. Recognized since the days before Hippocrates, the term apoplexy was used to describe what we today refer to as a stroke [100]. Derived from the ancient Greek to mean "to be stricken from," the term suggests man's helplessness in providing any form of therapy for this disease. It was believed that the hand of the gods was at play, punishing an individual for some bad behavior, and thus humans were helpless to provide any treatment that would interfere with the will of the gods.

Though there was some observational insight as to the function of the carotid artery – Rufus attributed the term "carotid" to mean "fall into a deep sleep" – the true link between the carotid's role in supplying blood to the brain was centuries away [101].

Wepfer, several centuries later, was the first to link the ischemic and hemorrhagic intracranial pathology to the signs and symptoms of stroke [102]. As correlative pathology leads to a greater understanding of the pathophysiology of stroke, clinicians were emboldened to attempt to prevent strokes.

Surgery of the Carotid Artery

Paré was recorded as being the first to treat a traumatic injury of the carotid artery in 1552 [103]. The first to be reported in the English literature occurred several hundred years later, in 1804. Abernethy successfully treated an injury to the carotid artery when he saved the life of a man who was gored in the neck by a cow in 1798 (but was reported in 1804) [104]. Unfortunately the patient died several days later. Petit, however, was the first to suggest that someone could survive in the setting of an occluded carotid, bringing forward the concept that elective surgery of the carotid was feasible [105]. It was thus that a few years later, Hebenstreit electively and successfully occluded a carotid artery [40]. This led the way for the first elective occlusion of a carotid artery to treat an aneurysm (in the form of Hunterian ligation).

As a reconstructive operation for a carotid arteriovenous aneurysm, von Parczewski performed the first end-to-end anastomosis in 1916 [106]. Thereafter, surgery for the carotid, including resection and reconstruction, was developed by oncological surgeons operating for neck cancer. By 1914, Ramsey Hunt reported the clear association of cervical carotid disease with hemiplegia and stroke and urged clinicians to examine the cervical vessels for diminution of pulsations in the setting of neurovascular symptoms [107].

The birth of angiography and the recognition that atherosclerosis of the carotid artery could in fact be the cause of stroke served as the critical elements in genesis of endarterectomy. Dr. DeBakey's landmark carotid endarterectomy for atherosclerotic

disease was thus performed by in 1953 [108–110]. Interestingly, DeBakey was also the first to treat carotid disease "endovascularly" in 1967 when he performed a carotid angioplasty for fibromuscular dysplasia, though he performed it through a carotid cutdown procedure [111]. A decade later, percutaneous carotid angioplasty was performed by Mattias with good success [112, 113]. In 1994, Marks and his group introduced the concept of placing a stent across a spontaneous carotid dissection refractory to medical management in two patients with good outcomes [114]. What followed was the explosive growth of carotid angioplasty and the many excellent trials that enhanced our understanding of the benefits and limitations for endarterectomy and angioplasty and stenting in the setting of atherosclerotic disease of the carotid arteries.

Thrombolysis

Though prevention of stroke became an important tactic in treating ischemic disease, there was still the need to better understand and perhaps abort a stroke in evolution. With the NINDS ivTPA trial, a new era in stroke management was born [115]. No longer was there a sense of helplessness among clinicians. It was clear that in the right circumstances, a stroke and its sequelae could be reversed or indeed aborted. Intra-arterial chemical thrombolysis was first used in 1999 which was the result of numerous clinical case series that suggested excellent outcomes with minimal risk. The PROACT II trial confirmed a modest benefit to intra-arterial thrombolysis with urokinase [116]. However, when urokinase was removed from the market, the procedure suffered. Clinicians searched for a different technology to treat acute stroke. Surgical embolectomy first performed in 1963 by Chou, though technically feasible, did not demonstrate significantly good clinical outcomes [117]. However, in performing chemical thrombolysis, occasional mechanical disruption of the clot yielded some anecdotal success. It was thus that a drive to develop dedicated mechanical clot retrieval devices was born. The Merci retriever became the first FDA-approved device for the endovascular treatment of acute ischemic stroke. Subsequent to that, devices such as the Penumbra neurovascular system designed around aspiration of the clot was successfully developed. Finally, the development of stent-retriever devices continues the technological march to treating embolic stroke [118–120].

Hemorrhagic Strokes

The treatment of intracerebral hemorrhage (ICH) would seem to be straightforward: Identify the hematoma and evacuate the hematoma through a minimally directed surgery, leaving the smallest "footprint" possible in order to ensure the best possible outcome. Despite this straightforward directive, and despite the seeming simplicity

in the approach to this rather common disease entity, excellent results have eluded the neuroscience community.

Though Piorry is initially credited with discussing trepanation as a means of evacuating an intracerebral hematoma in 1834, the first successful craniotomy for the evacuation of an intracerebral hematoma was performed in 1888 by MacEwen [121, 122]. In the years that followed, there was rather slow progress in understanding how best to maximize outcomes. Though detailed techniques were published, outcomes were inconsistent. In 1961 McKissock et al. published the first randomized trial for the treatment of intracerebral hematomas [123, 124]. This prospective trial failed to identify any significant differences in outcome between those patients treated with maximal medical management compared to those treated by surgery. By the 1980s, it was determined that patients undergoing surgical evacuation of lobar hemorrhages had better outcomes than patients treated for deep, central hemorrhages [125, 126]. Thus, the last 20 years of surgical research in ICH have focused on approaching deep-seated clots through minimally invasive means. Neuroendoscopy, stereotactic aspiration, focal thrombolysis, and aggressive medical management techniques continue to undergo development and evaluation as we struggle to achieve improved outcomes [127, 128].

The Bypass

Attempts to enhance or supplement the intracranial circulation overlap with the history of arterial reconstruction of the carotids. Nonetheless, the first attempts at intracranial revascularization were born from the transposition of the temporalis over the convexity of stroke patients in 1943 [129]. The concept of the indirect bypass blossomed. Creative approaches were undertaken with the use of omental flaps, dural leaflets, burr holes, and the transposition of the superficial temporal artery upon the surface of the brain, termed encephaloduroarteriosynangiosis (EDAS), most commonly used for symptomatic moyamoya disease [130, 131].

The direct approach to revascularization gained a firm foothold in 1960 with the first microsurgical saphenous vein bypass from the cervical carotid artery to the supraclinoid carotid artery by Jacobsen and Suarez [132]. Seven years later, Donaghy and Yaşargil simultaneously completed the first successful superficial temporal artery to middle cerebral artery bypass in Vermont and Zurich [133]. With acceptance of the microscope into the neurosurgical theater, the development and adoption of microsurgical instruments form other specialties, the rise of oncological and skull base neurosurgery and the growth in the passion to advance surgical anatomy; the 1970s and the 1980s became a period of novel approaches to effect extracranial to intracranial bypasses. Though of benefit in the setting of oncological resection and giant aneurysms, the benefits in the setting of cerebral ischemia were not well known. In order to determine its efficacy in this setting, Barnett et al. initiated the Extracranial-Intracranial (EC-IC) Bypass Trial in 1977, the results of which were reported 12 years later [134]. Unfortunately, the results of this prospective,

randomized multicenter trial failed to demonstrate any clinical benefit in preventing cerebral ischemia in any group of patients, much to the shock of the neurosurgical community. However, later analysis revealed some substantial flaws in the methodologies. Unfortunately since that time, additional surgical (COSS Trial) and endovascular (SAMMPRIS) trials have not demonstrated significant benefits, though subgroup analysis suggests some benefits in certain populations [135, 136]. Though it would be simple to conclude that such interventions are not of any benefit in preventing cerebral ischemia, additional studies may be required to understand if there are some smaller populations that might show benefit.

Summary

The treatment of cerebrovascular disease has changed dramatically. The historical record reveals tremendous growth and creativity spurred by the seeming hopelessness of the disease process. Striking without warning, killing a large proportion of individuals at some of their most productive times of their lives, affecting families in ways never conceived, clinicians felt compelled to "make things better." The ideas, at times straightforward, lacked the necessary technology to properly implement or execute the treatment. Sometimes, what was truly lacking was the understanding of the disease process itself. Yesterday as today, the vision of curing AVMs and aneurysms drives us forward. We have become bolder over the centuries: We now dare to abort strokes in progress. We now dare to use the body's natural highway (its circulation) to guide us to the site of pathology and treat it through the smallest of footprints. The greatest lessons of this rich history, however, lie with the intrepid individuals and their patients who dared to push the field of anatomy and surgery to gain knowledge. Tomorrow, as today, the field will continue to move forward through the careful evolution of current practices and the eventual revolution in therapy that will follow. One thing is certain: Whether gene therapy, robotics, or computer-brain interface technology expands, its applications in the treatment of cerebrovascular disease are assured.

References

1. Hankinson RJ. The Cambridge companion to Galen. Cambridge/New York: Cambridge University Press; 2008.
2. Nutton V. Ancient medicine. London/New York: Routledge; 2004.
3. Harvey W. Exercitatio Anatomica de Mortu Cordis et Sanguinis in Animalibus. London; 1628.
4. Willis T. Cerebri Anatome: cui accessit nervorum descriptio et usus. London; 1664.
5. Schuller A. Rontgendiagnostick der Erkrankungen des Kopfes. Vienna/Liepzig: Holder; 1912.

6. Dandy WE. Ventriculography following the injection of air into cerebral ventricles. Abb Surg. 1918;68:5.
7. Sicard JA, Forestier J. Methode radiographique d'exploration de la cavite epidurale par le lipiodol. Rev Neurol (Paris). 1921;28:1264.
8. Haschek E, Lindenthal OT. Ein Beitrag zur praktischen Verwerthung der Photographie nach Röntgen. Wien Klin Wschr. 1896;9:63–4.
9. Moniz E. L'encephalographie arterielle, son importance dans la localization des temeurs cerebrales [in French]. Rev Neurol. 1927;2:72–90.
10. Moniz E. Cerebral angiography: its application in clinical practice and physiology. Lancet. 1933;225:1144–7.
11. Antunes JL. Egaz Moniz and cerebral angiography. J Neurosurg. 1974;40:427–32.
12. Loman J, Myerson A. Visualization of the cerebral vessels by the direct intracrotid injection of thorium dioxide (Thorotrast). AJR Am J Roentgenol. 1936;35:188–93.
13. Prestigiacomo CJ. Historical perspectives: the microsurgical and endovascular treatment of aneurysm. Neurosurgery. 2006;59(S5):39–47.
14. Sprigge SS. Annotation: arterial encephalography. Lancet 1931;221:863.
15. Mokrohisky JF, Paul RE, Lin PM, et al. The diagnostic importance of normal variants in deep cerebral phlebography, with special emphasis on the true and false venous angles of the brain and evaluation of venous angle measurements. Radiology. 1956;67:34–47.
16. Schlesinger B. The insulo-opercular arteries of the brain, with special reference to angiography of striothalamic tumours. Amer J Roentgenol. 1953;70:555.
17. Ambrose J. Computerized transverse axial scanning (tomography). 2. Clinical application. Br J Radiol. 1973;46:1023–47.
18. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. Br J Radiol. 1973;46:1016.
19. Napel S, Marks MP, Rubin GD, et al. CT angiography with spiral CT and maximum intensity projection. Radiology. 1992;185(2):607–10.
20. Schwartz RB, Jones KM, Chernoff DM, et al. Common carotid artery bifurcation: evaluation with spiral CT. Work Prog Radiol. 1992;185(2):513–9. PubMed: 1410365.
21. Vieco PT, Shuman WP, Alsofrom GF, Gross CE. Detection of circle of Willis aneurysms in patients with acute sub-arachnoid hemorrhage: a comparison of CT angiography and digital subtraction angiography. AJR Am J Roentgenol. 1995;165(2):425–30.
22. Uluc K, Kuioth GC, Baskava MK. Operating microscopes: past, present, and future. Neurosurg Focus. 2009;27(3):E4.
23. Shanelec D. Opticals principals of loupes. Calif Dental Assoc J. 1992;20(11):25–32.
24. Dohlman GF. Carl Nylen and the birth of the otomicroscope and microsurgery. Arch Otolaryngol. 1969;190:161–5.
25. Kriss TC, Kriss VM. History of the operating microscope: from magnifying glass to microneurosurgery. Neurosurgery. 1998;42:899–908.
26. Velpeau A. Memoire sur la piqureou l'acupuncturedes arteres dans les traitement des aneurismes [in French]. Gaz Med Paris. 1831;2:1–4.
27. Phillips BA. A series of experiments performed for the purpose of showing that arteries may be obliterated without ligature, compression or knife. London: Longman; 1834.
28. Werner SC, Blakemore AH, King BG. Aneurysm of the internal carotid artery within the skull: wiring and electrothermic coagulation. JAMA. 1941;116:578–82.
29. Luessenhop AJ, Spence W. Artificial embolization of cerebral arteries: report of use in a case of arteriovenous malformation. JAMA. 1960;172:1153–5.
30. Brooks B. Discussion of Noland L, Taylor AS. Pulsating exophthalmus, the result of injury. Trans South Surg Assoc. 1930;43:176–7.
31. Vitek JJ, Smith MJ. The myth of the Brooks method of embolization: a brief history of the endovascular treatment of carotid-cavernous sinus fistula. J Neurointerv Surg. 2009;1:108–11.
32. Brooks B. The treatment of traumatic arteriovenous fistula. South Med J. 1930;23:100–6.

33. Arutiunov AI, Burlutsky AP. New modification of Brooks operation. Presented at Materiali k ob'edinenoy conferencii neurochirurgov, Leningrad; 1964.
34. Luessenhop AJ, Velasquez AC. Observation on the tolerance of the intracranial arteries to catheterization. J Neurosurg. 1964;21:85–91.
35. Rothenberg SF, Penka EJ, Conway LW. Angiotactic surgery: preliminary studies. J Neurol Neurosurg Psychiatry. 1962;19:877–83.
36. Bonet T. Sepulchretum sive Anatomia practica ex Cadaveribus Morbo Denatis. Geneva; 1679.
37. Morgagni JB. De Sedibus et Causis Morborum per Anatomen Indagatis, Book 1, Letters 3 and 4; 1769.
38. Biumi F. Observationes anatomicae, scholiis illustrati. Observatio V. In: Sandifort E, editor. Thesaurus Diessertationem. Milan: S & J Luchtmans; 1765. p. 373.
39. Blackall J. Observations on the Nature and Cure of Dropsies. London: Longman, Hurst, Rees, Orne, and Brown; 1814.
40. Hamby WB. Intracranial Aneurysms. Springfield: Charles C. Thomas; 1952.
41. Hunter J. Works. London: Jas F. Palmer; 1835.
42. Cooper A. A case of aneurysm of the carotid artery. Tr Med Chir Soc Edinburgh. 1809;1:1.
43. Travers B. A case of aneurism by anastomosis in the orbit, cured by ligation of the common carotid artery. Med Chir Tr. 1811;2:1.
44. Keen WW. Intracranial lesions. Med News NY. 1890;57:443.
45. Dandy WE. The treatment of carotid-cavernous arteriovenous aneurysms. Ann Surg. 1935;102:916–26.
46. Dandy WE. Intracranial Aneurysms. Ithaca: Comstock; 1944.
47. Poppen JL. Specific treatment of intracranial aneurysms. Experiences with 143 surgically treated patients. J Neurosurg. 1951;8:75–102.
48. Schorstein J. Carotid ligation in saccular intracranial aneurysms. Brit J Surg. 1940;28:50–70.
49. Winn HR, Richardson AE, Jane JA. Late morbidity and mortality of common carotid ligation for posterior communicating aneurysms. A comparison to conservative management. J Neurosurg. 1977;47:727–36.
50. Hamby WB, Gardner WJ. Treatment of pulsating exophthalmos with report of 2 cases. Arch Surg. 1933;27:676–85.
51. Zeller O. Die chirurgische behandlung der durch aneurysma arterio-venosumder carotis int. *im sin. cavernosus hervorgerufenen pulsierenden exophthalmos [in German]*. Schweiz Med Wehnschr. 1911;79:1266–8.
52. Dandy WE. Results following ligation of the internal carotid artery. Arch Surg. 1942;45:521–33.
53. Cushing H. Contributions to study of intracranial aneurysms. Guys Hosp Rep. 1923;73:159–63.
54. Ayer WD. So-called spontaneous subarachnoid hemorrhage. Am J Surg. 1934;26:143–51.
55. Dott NM. Intracranial aneurysms: cerebral arterio-radiography. Edinburgh Med J. 1933;40:219–40.
56. Tonnis W. Zur behandlung intrakranieller aneurysmen [in German]. Arch F Klin Chir. 1936;189:474–6.
57. Jefferson G. Compression of the chiasm, optic nerves, and optic tracts by intracranial aneurysms. Brain. 1937;60:444–97.
58. Logue V. Surgery in spontaneous subarachnoid hemorrhage: operative treatment of aneurysms on the anterior cerebral and anterior communicating arteries. Br Med J. 1956;1:473–9.
59. Tindall G, Kapp J, Odom G, Robinson SC. A combined technique for treating certain aneurysms of the anterior communicating arteries. J Neurosurg. 1970;33:41–7.
60. Del Maestro RF. Origin of the Drake fenestrated aneurysm clip. J Neurosurg. 2000;92:1056–64.
61. Sundt TM Jr, Murphy F. Clip-grafts for aneurysm and small vessel surgery. *Part 3. Clinical experience in intracranial internal carotid artery aneurysm*. J Neurosurg. 1969;31:59–71.
62. Bottrell 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.

63. Yaşargil GM, Fox JL. The microsurgical approach to intracranial aneurysms. Surg Neurol. 1975;3:7–14.
64. Gardner WJ. Cerebral angiomas and aneurysms. Surg Clin North Am. 1936;16:1019–30.
65. Khilko VA, Zubkov YN. Intravascular surgery in pathological states vascularized by the external carotid artery, and stenotic and occlusive processes of cerebral arteries. In: Endovascular neurosurgery. Leningrad: Medicina; 1975. p. 75.
66. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125–45.
67. Debrun G, Lacour P, Caron JP. Experimental approach to the treatment of carotid cavernous fistula with an inflatable and isolated balloon. Neuroradiology. 1975;9:9–12.
68. DiTullio MV Jr, Rand R, Frisch E. Development of a detachable vascular balloon catheter: a preliminary report. Bull Los Angel Neurol Soc. 1976;41:2–5.
69. Romodanov AP, Shcheglov IV. Intravascular occlusion of saccular aneurysms of the cerebral arteries by means of a detachable balloon catheter. In: Krayenbühl H, editor. Advances in technical standards in neurosurgery. New York: Springer-Verlag; 1982. p. 25–48.
70. Higashida RT, Halbach VV, Barnwell SL, Dowd C, Dormandy B, Bell J, Hieshima GB. Treatment of intracranial aneurysms with preservation of the parent vessel: result of percutaneous balloon embolization in 84 patients. AJNR Am J Neuroradiol. 1990;11:633–40.
71. Higashida RT, Halbach VV, Hieshima GB, Weinstein PR, Hoyt WF. Treatment of a giant carotid ophthalmic artery aneurysm by intravascular balloon embolization therapy. Surg Neurol. 1988;30:382–6.
72. Moret J, Cognard C, Weill A, Castaings L, Rey A. Reconstruction technique in the treatment of wide-neck intracranial aneurysms: long-term angiographic and clinical results – report of 56 cases [in French]. J Neuroradiol. 1997;24:30–44.
73. Gianturco C, Anderson JH, Wallace S. Mechanical devices for arterial occlusion. Am J Roentgenol Radium Ther Nucl Med. 1975;124:428–35.
74. Braun IF, Hoffman JC Jr, Casarella WJ, Davis PC. Use of coils for transcatheter carotid occlusion. AJNR Am J Neuroradiol. 1985;6:953–6.
75. Hilal SK. Catheter with a magnetic tip for cerebral angiography. Med Tribune. 1969;2:1.
76. Guglielmi G. Endovascular treatment of intracranial aneurysms. Neuroimaging Clin N Am. 1992;2:269–78.
77. Therapeutics T. Target therapeutics: history of the GDC. Fremont: Target Therapeutics; 1995.
78. Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. *Part 2: Clinical experience*. J Neurosurg. 1991;75:8–14.
79. Viñuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. J Neurosurg. 1997;86:475–82.
80. Molyneux AJ, LeRoux PD. Surgical or endovascular treatment of intracranial aneurysms: a comparison of techniques. In: LeRoux PD, Winn HR, Newell DW, editors. Management of cerebral aneurysms. Saunders: Philadelphia; 2003. p. 983–95.
81. Pierot L, Flandroy P, Turjman F, Berge J, Vallee JN, Bonafe A, Bracard S. Selective endovascular treatment of intracranial aneurysms using micrus microcoils: preliminary results in a series of 78 patients. J Neuroradiol. 2002;29:114–21.
82. Murayama Y, Viñuela F, Tateshima S, Song JK, Gonzalez NR, Wallace MP. Bioabsorbable polymeric material coils for embolization of intracranial aneurysms: a preliminary experimental study. J Neurosurg. 2001;94:454–63.
83. Berenstein A, Ransohoff J, Kupersmith M, Flamm E, Graeb D. Transvascular treatment of giant aneurysms of the cavernous carotid and vertebral arteries. Surg Neurol. 1984;21:3–12.
84. Wakhloo AK, Lanzino G, Lieber BB, Hopkins LN. Stents for intracranial aneurysms: the beginning of a new endovascular era? Neurosurgery. 1998;43:377–9.
85. Krayenbuhl H, Yasargil MG. Dae Hiraneurysma. Basel: Geigy; 1958. p. 66.
86. Fein JM. Historical introduction. In: Fein JM, Flamm ES, editors. Cerebrovascular surgery, vol. 1. Berlin: Springer Verlag; 1985. p. 1–10.

87. Osler W. Remarks on arterio-venous aneurysm. Lancet. 1915;185:949–55.
88. Pool JL. Treatment of arteriovenous malformations of the cerebral hemispheres. J Neurosurg. 1962;19:136–41.
89. Giordano. Compendio di chirurgia operatoria italiana 1897;2:100.
90. Yasargil MG. Pathologic considerations. In: Yasargil MG, editor. Microneurosurgery, ACM of the brain: history, embryology, pathologic considerations, hemodynamics, diagnosis studies, microsurgical anatomy, vol. 3A. New York: Thieme; 1987. p. 3–22.
91. Colby GP, Coon AL, Huang J, Tamargo RJ. Historical perspective of treatments of cranial arteriovenous malformations and dural arteriovenous fistulas. Neurosurg Clin N Am. 2012;23:15–25.
92. Cushing H, Bailey P. Tumors arising from blood vessels of the brain: angiomatous malformations and haemangioblastomas. Springfield: Bailliere, Tindall and Cox; 1928.
93. Olivecrona H, Riives J. Arteriovenous aneurysms of the brain: their diagnosis and treatment. Arch Neurol Psychiatr. 1948;59:567–602.
94. French LA. Surgical treatment of arteriovenous malformations: a history. Clin Neurosurg. 1977;24:22–33.
95. Bergstrand H, Olivecrona H, Tonnis W. Gefa Bimibdildungen und gefa bgeschwultse des gehirna. Leipzig: Thieme; 1936.
96. Wyburn-Mason MR. Arteriovenous aneurysm of midbrain and retinae facial nevi and mental changes. Brain. 1943;66:163.
97. McCormick WF. Classification, pathology, and natural history of angiomas of the central nervous system. Wkly Update Neurol Neurosurg. 1978;14:2–7.
98. Krause F. Krankenvorstellungen aus der Hirnchirurgie, Bericht u¨ber die Verhandlungen der Deutschen Gesellschaft fu¨r Chirurgie. Zbl Chir. 1908;35:61–7.
99. Niranjan A, Lunsford LD. A brief history of arteriovenous malformation radiosurgery. In: Niranjan A, Kano H, Lunsford LD, editors. Gamma knife radiosurgery for brain arteriovenous malformations. Basel: Karger Publishers; 2014.
100. Hippocrates. Trans. Jones J. Loeb. London: Classic Library; 1957.
101. Pare A. The works of that famous chirurgion Ambrose Parey, Translated out of Latin and compared with the French by Thomas Johnson: From the first English edition, London, 1634. New York: Milford House; 1968.
102. Wepfer J. Observatio Anatomica. Zurich; 1704.
103. Pare A. In: Key G, editor. The apologie and treatise of ambroise pare conraining the voyages made in the divers places and many writings upon surgery. London: Falcon Education Books; 1957.
104. Abernethy J. The surgical works of John Abernethy. London; 1814.
105. Petit JL. Chirug Mem de l'Academy des Sciences. Paris: Royal Academy of Science; 1765.
106. Gurdjian E, Webster J. Thrombosis of the internal carotid artery in the neck and in the cranial cavity: symptoms and signs, diagnosis and treatment. Trans Am Neurol. 1951;241:242–54.
107. Hunt JR. The role of the carotid arteries in the causation of vascular lesions of the brain with remarkson certain special features of the symptomatoogy. Am J Med Sci. 1914;704:713.
108. Friedman SG. The first carotid endarterectomy. J Vasc Surg. 2014;60:1703–8.
109. DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. JAMA. 1975;233:1083–5.
110. Strully KJ, Hurwitt ES, Blankenburg HW. Thromboendarterectomy for thrombosis of the carotid artery in the neck. J Neurosurg. 1953;10:474–82.
111. Morris GC Jr, Lechter A, DeBakey ME. Surgical treatment of fibromuscular disease of the carotid artery. Arch Surg. 1968;96:636.
112. Robishek F, Rousch TS, Cook JW, Reemes MK. From Hippocrates to Palm-Schatz, the history of carotid surgery. Eur J Vasc Endovasc Surg. 2004;27:389.
113. Mathias K, Jager H, Hennigs S, Gissler HM. Endoluminal treatment of internal carotid artery stenosis. World J Surg. 2001;25:328–36.
114. Marks M, Dake M, Steinberg G, Norbash A, Lane B. Stent placement for arterial and venous cerebrovascular disease: preliminary experience. Radiology. 1994;91:441–6.

115. NINDS Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
116. Furlan A, Higashida R, Wechsler L. Intra-arterial Prourokinase for Acute Ischemic Stroke The PROACT II study: a randomized controlled trial. JAMA. 1999;282:2003–11.
117. Chou SN. Embolectomy of the middle cerebral artery: a report of a case. J Neurosurg. 1963;20:161–3.
118. Gobin YP, Starkman S, Duckwiler GR, Grobelny T, Kidwell CS, Jahan R, Pile-Spellman J, Segal A, Vinuela F, Saver JL. MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke. 2004;35:2848–54.
119. 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;40:2761–8.
120. Castaño C, Dorado L, Guerrero C, Millán M, Gomis M, Perez de la Ossa N, Castellanos M, García MR, Domenech S, Dávalos A. Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study. Stroke. 2010;41:1836–40.
121. Fazio C. Clinical pathology of hypertensive intracerebral hemorrhage: historical aspects. In: Mizukami M, Kogure K, Kanaya H, et al., editors. Hypertensive intracerebral hemorrhage. New York: Raven Press; 1983. p. 105–13.
122. MacEwan W. An address on the surgery of the brain and spinal cord. Br Med J. 1888;2:302–11.
123. Penfield W. The operatie treatment of spontaneous intracerebral hemorrhage. Can Med Assoc J. 1933;28:369–74.
124. McKissock W, Richardson A, Taylor J. Primary intracerebral hemorrhage: a controlled trial of surgical and conservative treatment in 180 unselected cases. Lancet. 1961;2:221–32.
125. Deogaoknkar M, Carter LP. Historical considerations. In: Winn HR, editor. Youmans neurological surgery. 5th ed; 2003. p. 1461–6.
126. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97.
127. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. J Neurosurg. 1989;70(4):530–5.
128. Niizuma H, Suzuki J. Stereotactic aspiration of Putaminal hemorrhage using a double track aspiration technique. Neurosurgery. 1988;22:432–6.
129. Kredel FE. Collateral cerebral circulation by muscle graft. South Surg. 1942;11:235–44.
130. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H. Cerebral revascularization using omental transplantation for childhood moyamoya disease. J Neurosurg. 1993;79:192–6.
131. Karasawa J, Kikuchi H, Furuse S. A surgical treatment of moyamoya disease. Encephalomyo-synangiosis. Neurol Med Chir (Tokyo). 1977;17:29–37.
132. Jacobsen JH, Suarez EL. Microsurgery in anastomosis of small vessels. Surg Forum. 1960;11:243–5.
133. Donaghy RPM, Yasargil MG. Extra-intracranial blood flow diversion. AANS Abstract 52, Chicago; 1968.
134. EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. New England Journal of Medicine. 1985;313:1191–200.
135. Grubb RL, Powers WJ, Clarke WR, et al. Surgical results of the carotid occlusion surgery study. J Neurosurg. 2013;118(1):25–33.
136. Chimowitz M, Lynn M, Derdeyn C, Turan T, Fiorella D, Lane B, Janis L, Lutsep H, Barnwell S, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993–1003.

Chapter 2
Evolution of Endovascular Technique

May Nour and Gary Duckwiler

From the advent of digital subtraction angiography and diagnostic angiography to early device development, the field of neurointervention has made great strides in neurovascular disease diagnosis and treatment. We will detail some of the most prominent advances in the field, which have shaped the current state of practice as they relate to vascular lesions including vascular malformations, aneurysms, vascular tumors, and ischemic stroke-related large vessel occlusions.

Introduction of Digital Subtraction Angiography and Early Diagnostic Angiography

The first attempt at angiography in 1896 followed the invention of X-ray in 1895. Using an amputated cadaver hand, Hascheck and Lindenthal first described the visualization of the vascular network using a mixture of mercuric sulfide, petroleum, and quicklime as a contrast agent [1]. Years later, in 1927, Moniz is known for performing the first cerebral angiogram using iodinated contrast composed of 25% sodium iodide solution. Angiography during his initial attempt was performed with percutaneous access and direct injection into the carotid artery in the context of transient carotid ligation/occlusion [2]. Cerebral venography followed by Moniz in 1931 who by that time became proficient at performing cerebral angiography in patients with a wide range of neurological disease. The idea of separating

M. Nour (✉)
Department of Interventional Neuroradiology, UCLA Health, Los Angeles, CA, USA
e-mail: MNour@mednet.ucla.edu

G. Duckwiler
Department of Radiological Sciences, UCLA Health, Los Angeles, CA, USA
e-mail: gduckwiler@mednet.ucla.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_2

confounding anatomical background from angiographic signal was first introduced in 1934 by Ziedses des Plantes as an initial concept termed film subtraction angiography [3]. Hand in hand with the development of radiographic technology, enhancing signal obtained from the vessels continued to be investigated including the possibility of intravenous rather than intra-arterial iodinated contrast injection; however, given the dilution in contrast and subsequently signal, arterial injection became a more favorable choice [4]. Until the 1950s, percutaneous access of the carotid artery and brachial artery for opacification of the vertebral artery had been the method used for cerebral vessel catheterization [5]. This of course later evolved with the evolution of catheter technology. Another pivotal development in angiography was the construction of a real-time digital fluoroscopic image processor at the University of Wisconsin which was described by Kruger et al. in 1977 [6]. This processor yielded 30 subtraction images per second and permitted the elimination of bony structures and soft tissues for the first time, in an interactive manner [6]. The evolution of digital subtraction angiography continued over the course of the years to include further refinement in resolution and has been further enhanced by the development and current use of three-dimensional, rotational angiography. The precise visualization yielded by the advancement in cerebral vascular imaging has served as a founding platform for the understanding and subsequent targeted therapeutic treatment across a wide range of neurovascular disease.

Advancing Access to the Cerebral Circulation

Surgically inoperable lesions including challenging arteriovenous malformations, fistulas, and aneurysms served as the driving factor in the development of more advanced catheters and microcatheters with the ability to reach the target lesion.

Gaining Precise Access and Targeted Treatment of Intracranial Vascular Lesions

Catheters and Microcatheters

The navigation of catheters endovascularly, particularly in the tortuous and small caliber of the cerebral circulation, poses unique challenges. Early efforts of Luessenhop and Velasquez in 1964 demonstrated the first successful cerebral catheterization [7]. Silastic tubing was inserted into the internal carotid artery by way of a glass chamber which was surgically connected to the external carotid artery. In 1966, the microcatheter described by the name of para-operational device (POD) was engineered as a combination of polyethylene proximally and silicone rubber distally forming a soft 7 cm tip of 1.3 mm in outer diameter [8]. Additionally, the distal tip of the microcatheter included a 1 mm micro-magnet which allowed for

pull and vibration achieved by the application and manipulation of an external magnetic field. Another technical strategy introduced by these early scholars was use of a guide catheter which Frei and colleagues termed by the name of plastic T [8]. This concept continued to propagate in 1968 where Yodh et al. [9] developed six iterations of a microcatheter with an implanted 1.3 mm magnet in the silastic microcatheter tip, some of which were designed to detach. These detachable constructs contained 0.5 mm cooper wire wrapped in ten turns and attached by paraffin wax which was intended to melt upon the introduction of heat via electric current. One year later, in 1969, the first report of middle cerebral artery catheterization was published describing access using the POD catheter through percutaneous carotid puncture [10].

Iterations of the POD catheters continued to evolve and included the POD with incorporated detachable balloon [11]. Later in the 1970s, detachable balloons were described by Serbinenko [12] and Debrun [13] for the endovascular treatment of carotid-cavernous fistulas. To better understand the technique, Debrun et al. described the methodology of detachable balloon synthesis using latex sleeves created using stainless steel molds, steam-treated in two different iterations, Type I and Type II, which differ in the balloon catheter construction [13]. The former did not involve firm attachment of the balloon to the catheter nor does it need a second catheter for detachment, while the latter involved the balloon being tied to the catheter by a latex thread, was self-sealing, and required a coaxial catheter for detachment. Although their results were favorable for carotid-cavernous and vertebra-vertebral fistulas, less favorable results were seen with aneurysm treatment with a risk of morbidity, mortality, and recanalization of the aneurysms that was seen in a subset of their patients [13]. Calibrated-leak balloon catheters and flow-directed microcatheters were also described for the treatment of arteriovenous malformations using bucrylate, hydroxyethylmethacrylate, or isobutyl 2-cyanoacrylate [13–17].

The next significant turning point in microcatheter evolution occurred in the 1980s with the development of the Tracker microcatheter which occurred as a modification to an existing Target Therapeutics product by one of its biomechanical engineers by the name of Erik Engelson [18]. This new microcatheter distinguished itself by a property of variable stiffness owing to varying consistency of polyethylene. He continued to advance the use of existing microcatheters by also developing shapeable tip microwires which were more navigable as well as adding a radiopaque marker in the distal portion of the microcatheter to allow for visualization. This essentially marked the beginning of the so-called “over-the-wire” catheterization.

Microcatheter technology continued to improve and expand to include flow-directed microcatheters. The Balt Magic (Montmorency, France) provided a more flexible alternative to the Tracker catheter owing to its polyurethane and silicone composition [19]. The Balt Magic, along with the Marathon (EV3, Irvine, California) microcatheter, has been particularly useful in tortuous distal vessel access. In addition to the flow-directed microcatheters, further modifications have been made to aid in the safe delivery of embolic agents whereby the Apollo (EV3, Irvine, California) and Sonic (Balt, Montmorency, France) microcatheters also include a

detachable tip, which can be safely retained after embolization and catheter withdrawal. A valuable addition to the current microcatheters which is particularly helpful in the treatment of high flow lesions is the Scepter balloon (Microvention, Tustin, California). This dual lumen microcatheter which has a balloon at the catheter tip, which allows for concurrent inflation of the balloon for flow arrest and injection of embolic material through its inner lumen.

Embolic Agents

The evolution of endovascular embolization with polyvinyl alcohol (PVA) particles (Boston Scientific/Target Therapeutics, Cordis J&J Endovascular, Miami, FL, USA) began with use of sponge material for embolization in 1974 [20, 21]. In the late 1970s, Irv Kricheff described flow-directed bead embolization to reduce vascular flow to arteriovenous malformations [22, 23]. Also useful in the preoperative embolization of richly vascularized head and neck tumors, the ability of these particles to decrease tumor blush angiographically often translates into a surgical benefit during excision [24–28]. Typically made of foam sheet which is vacuum dried and ground, particles are subsequently sieved and are manufactured in sizes as small as 100 uM and as large as 1100 uM; their irregularity in shape promotes their aggregation when reconstituted in suspension [29]. The mechanism by which they contribute to vascular embolization includes lodging into small vessels correlating with their selected size and adherence to vessel wall which both contribute to flow stagnation and therefore embolization of the vessels targeted [30]. Nontarget embolization must be avoided as the PVA particles are known to accumulate in the catheter hub [31].

Isobutyl 2-Cyanoacrylate (IBCA) and N-Butyl-2-Cyanoacrylate (NBCA) Glue

Early on, IBCA was used as an embolic agent in cerebral vascular lesion embolization; however due to its handling characteristics, it was later replaced with NBCA glue [32]. In the year 2000, the FDA approved NBCA glue (TruFill, Cordis, Miami Lakes, Fl) as a synthetic agent for arteriovenous malformation (AVM) embolization. The embolization agent mix is composed of NBCA, which polymerizes when exposed to an anionic environment [33]; ethiodized oil (Savage Laboratories, Melville, NY, USA), a vehicle for retardation of polymerization and opacification; and tantalum powder which also allows for radiographic visualization. Pretreatment of the catheter with dextrose 5% in water (D5W) is essential to avoid premature polymerization due to contact with anionic material. Following NBCA glue injection, the catheter tip is swiftly withdrawn to avoid catheter adherence to the vessel being treated. The glue material creates a permanent cast within the vasculature and, in generating inflammation in the vessel wall, leads to fibrosis to achieve embolization [33].

Ethylene Vinyl Alcohol Copolymer (Onyx)

Soon following FDA approval of NBCA for cerebral AVM embolization in 2004, in 2005, the FDA approved ethylene vinyl alcohol copolymer (EVOH) (Onyx, Micro Therapeutics, Inc., Irvine, CA), although first introduced in 1990 [34]. The agent precipitates in aqueous solutions and thus is prepared with dimethyl sulfoxide (DMSO), which acts as its solvent. Once the DMSO rapidly disperses, the EVOH mixture precipitates. Akin to NBCA preparation, tantalum powder is used for radiographic visualization. The Onyx preparations differ in viscosity with the commonly used Onyx-18 and Onyx-34 with lower concentration correlating with lower viscosity. Catheter pretreatment is accomplished by the use of DMSO flush. Catheter dead space is then filled with Onyx, and endovascular delivery is performed under fluoroscopy, which forms a visible vascular cast. Longer injection times can be performed as compared to NBCA glue, and the risk of catheter tip adhesion in the event of reflux is considerably less, although catheter tip entrapment is still possible, and thus the advantage of using detachable tip microcatheters. Given suspension in DMSO, initial injection rate is <0.3 ml over greater than 40 seconds to avoid the risk of DMSO-related vasospasm and necrosis.

Absolute Alcohol

Ethanol embolization may also be utilized particularly in the case of venous and venolymphatic malformations. The alcohol serves to induce thrombosis and fibrosis and has been described in use for neck and oral/facial slow flow malformations [35–37]. Given its ability to widely diffuse, it has the risk of damage to the surrounding tissue, including possible skin necrosis when used percutaneously, and as such should be used with precaution.

Evolution of Endovascular Aneurysm Treatment

Early attempts at endovascular aneurysm embolization with balloon occlusion occurred as early 1974 as described by Serbinenko [38]. Four years later, Debrun reported the use of silicone-filled latex balloons in aneurysm embolization, and even later, silicone detachable balloons were developed by Hieshima and Interventional Therapeutics (ITC). However, radiographic recanalization of balloon-treated aneurysms was seen in a significant number of cases [13]. In the 1980s, a study reporting results of balloon occlusion in over 100 aneurysms addressed the inability to effectively treat wide-necked aneurysms, small aneurysms, and in ruptured aneurysms as well as in cases of vasospasm [39]. Aneurysm rupture and its associated morbidity/mortality also became a concern as the relatively non-compliant balloons filled with hydroxyethylmethacrylate preserved their

own shape rather than adapting to the shape of the fragile aneurysms. As such, the endovascular community searched for the next technical advance in aneurysm treatment.

First introduced in 1988, the idea of pushable coils for use in embolization of cerebral aneurysms was a desirable one that was unfortunately limited by the stiffness and irretrievable nature of these early coils [40, 41]. As such, the development of soft platinum coils by Guglielmi in 1989 dramatically changed the course of endovascular aneurysm embolization. The naissance of the GDC system occurred as a research continuum from bench side to the AngioSuite at the University of California, Los Angeles (UCLA). Several integral members of the development team along with Guglielmi included neurointerventionalist Vinuela and Target Therapeutic engineer Ivan Sepetka [42–44]. The structure of these coils consisted of a soft, platinum detachable material ranging in length from 2 to 30 cm, connected to a stainless steel pusher wire. The technique involves the over wire navigation of the microcatheter to the aneurysm, followed by delivery of these platinum coils and their subsequent electrolytic detachment. The first human use of GDC coil occurred at UCLA in 1990 [45], and now, coil embolization of aneurysm is a standard for endovascular aneurysm embolization. Detachment methods for the currently utilized coils include both electrolytic and mechanical means. Decades later, the trend for increase in endovascular treatment of aneurysms has grown as the leading method of treatment when anatomically feasible and continues to grow with less adjusted morbidity as compared with surgical clipping [46, 47]. The need for effective treatment of wide-necked aneurysms which are not amenable to primary coil embolization further advanced the field to include stent-assistive devices beginning with open-cell, Neuroform (Stryker, Kalamazoo, MI, USA) stent which received FDA approval under Humanitarian Device Exemption (HDE) in 2002. In 2007, the first closed-cell stent approved by the FDA for the adjunctive treatment of intracranial aneurysms in the United States was the Enterprise (Cordis Neurovascular, Miami, FL) stent. Many groups have described their embolization experience in the treatment of wide-necked aneurysms with each of these stents [48–50]. Other stents described as aneurysm stent-assistive devices in Europe have included the Leo (Balt, Montmorency, France) and detachable Solitaire (Covidien, Irvine, California) stent, among others [51, 52].

However, even with aneurysm stent-assistive devices, wide-necked aneurysms continue to be a challenge, as persistent flow can continue to impact the coil construct and remodel the coil mass or even lead to aneurysm growth. To address these issues, lower porosity stents and flow-diverting devices have been developed. To accommodate for smaller vessel calibers and with a degree of decreased stent porosity than its predecessors, Microvention's (Tustin, CA, USA) Low-profile Visualized Intraluminal Support device, LVIS Jr., along with its larger version LVIS, was approved for use under HDE in 2014. Intra-saccular flow-diverting devices, which have yet to gain FDA approval, include the WEB device produced by Sequent Medical, which consists of a microbraided structure intended for delivery within the aneurysm and functions to stagnate flow in a similar fashion to a dense coil mesh.

Compared to the purely intra-saccular treatment of aneurysm, the introduction of flow-diverting stents including the Pipeline embolization device (EV3, Covidien, CA, USA) and Surpass flow diverter (Stryker, Kalamazoo, MI, USA) relies on low porosity (30–35% metal surface area coverage versus 6.5–9.5% in stents used for Neuroform/Enterprise, 18–22% LVIS/LVIS Jr.) [53, 54]. The flow diversion is thought to change the parent vessel hemodynamics and decrease blood flow into the aneurysm leading to thrombosis. This is particularly useful in lesions where the anatomical pathology is complex or the disease involves portions of the parent vessel extending outside of the aneurysm sac [55–61].

Evolution of Endovascular Stroke Treatment

The endovascular treatment of acute stroke has considerably evolved since its inception beginning with intra-arterial urokinase infusion in the late 1980s/early 1990s [62, 63]. Investigators continued to assess the efficacy of IA thrombolysis with pro-urokinase/urokinase [64–66] and tissue plasminogen activator (tPA) [67, 68]. The use of IA thrombolytic therapy was aimed at delivering a more concentrated dose of these agents in direct proximity to the clot in an effort to achieve more effective recanalization, thereby reducing systemic exposure. In spite of the effective recanalization demonstrated by thrombolysis in acute myocardial infarction (TIMI) score in the intra-arterial treatment group, clinical improvement defined as a modified Rankin Scale (mRS) of 0–1 in PROACT and 2 or less in PROACT II was not significantly different from placebo in spite of a trend toward improvement in morbidity [64]. Combined thrombolysis using intravenous (IV) tPA in conjunction with IA tPA was further investigated in multiple trials including Emergency Management of Stroke (EMS) [69] and Interventional Management of Stroke (IMS) [68].

With a lack of positive clinical results, the technical advances in the field continued to evolve to meet the clinical need. Endovascular treatment of stroke next addressed mechanical thrombectomy in combination with thrombolysis. Clouded by a small sample population and possible selection bias, the RECANALISE trial assessed 53 patients, a subset of whom were treated with mechanical thrombectomy if IA tPA was unable to achieve a desirable TIMI [2, 3] recanalization [70]. No significant difference in 90-day Rankin scores was identified in the patient study group [70].

From a technical perspective, mechanical thrombectomy efforts began with the development of both aspiration and retriever devices which have continued to be refined since inception. In 2004, the first mechanical thrombectomy device FDA approved for stroke was the Mechanical Embolus Removal in Cerebral Ischemia (MERCI, Concentric Medical, California, USA) device [71].

The major initial randomized control trials addressing the possible benefit of endovascular intervention for large vessel acute ischemic stroke including IMS-III [72], SYNTHESIS [73], and MR RESCUE [74] did not demonstrate a statistically significant clinical benefit of endovascular therapy. Several confounding factors which likely contributed to the lack of benefit noted include less refined imaging

inclusion/exclusion criteria, the use of IA thrombolysis and first-generation thrombectomy devices, as well as significant time delays in endovascular treatment with time of up to 381 minutes of mean time to groin puncture in the MR RESCUE trial [75].

The biggest shift in paradigm occurred beginning in 2014 with the validation of endovascular thrombectomy as the standard of care in ischemic stroke caused by large vessel occlusion, presenting within 6 h of symptom onset. After the results of the MR CLEAN trial were announced at the World Stroke Conference in 2014 [76], a number of trials followed suit confirming the clinical benefit [76–80]. Patients had a more advanced imaging selection criteria in some of the trials including perfusion data, received standard doses of IV TPA when eligible, and confirmed proximal large vessel occlusions prior to enrollment. The positive results were also owed in part to the development of more effective second-generation stent retrievers including the Solitaire FR (EV3/Medtronic, California, USA) and TREVO (Concentric Medical/Stryker, California, USA) devices [81, 82]. Achieving more effective recanalization from the first-generation devices [81, 83, 84], small construction differences are seen with an open-ended basket of the Solitaire FR stent retriever and a closed-ended and stent wire radiopaque nature of the TREVO. Others in the market which are also constructed of nitinol memory wire include CATCH (Balt Extrusion, Montmorency, France) and REVIVE (Codman & Shurtleff Inc., Massachusetts, USA). In terms of aspiration, the penumbra (Penumbra Inc., California, USA) system initially developed as a multicomponent system with a reperfusion catheter, separator, and thrombus removing ring [85]. While aspiration is currently used in clinical practice alone or in conjunction with stent retriever devices, no evidence of clinical efficacy for aspiration has been demonstrated in a randomized trial. The THERAPY trial designed for addressing the question of aspiration benefit was halted after the positive endovascular study results were published in 2014 and 2015. As such, the 108 patients enrolled in the THERAPY trial underpowered the study for an ability to show significance in their primary endpoint of 90-day mRS 0–2, correlating to functional independence [86]. Additional efforts at reducing distal emboli and improving clot thrombectomy have shown the clinical benefit of proximal balloon guide use during clot retrieval [87]. More recently, a number of reperfusion catheters have been in use adjunctively in the clinical setting with second-generation stent retrievers, although no data currently exists for their efficacy. Studies aimed at investigating efficacy of thrombectomy in acute ischemic stroke have mostly focused on anterior circulation occlusions. Given the small percentage of posterior circulation occlusions, no dedicated study has evaluated the efficacy of any of the specific thrombectomy or aspiration devices exclusively in the vertebrobasilar or posterior cerebral artery infarcts. The improvement and evolution of endovascular thrombectomy devices over the past years since MERCI was approved in 2004 has positively affected treatment outcomes and has allowed endovascular thrombectomy to become the standard of care, at this interval in patients presenting within 6 h of symptom onset. Further trials evaluating late presentation past the current 6-h time point are ongoing, which include DAWN and POSITIVE.

Summary

Since the 1960s with the first reported endovascular catheterization, the diagnostic and therapeutic horizon of neurointervention has continued to expand. This is in part due to the conception, development, and rapid evolution of catheter, device, and embolic materials. Endovascular treatment of fistulas, arteriovenous malformations, aneurysms, and acute ischemic stroke due to large vessel occlusion has become more refined and increasingly widespread. The persistent refinement of these tools will serve to challenge the field in seeking further continued improvement in patient outcomes.

References

1. Hascheck ELT. Ein beitrag zur praktische verwerthung der photographie nach roentgen. Wien Klin Wochenschr. 1896;9:63–4.
2. E M. Radiografia das arterias cerebrais. J Soc Cienc Med Lisb. 1927;XCL:8.
3. BG Z des P. Planirafie en Subtractie. The Netherlands, University of Utrecht. 1934.
4. Robb GPSI. Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man. AJR Am J Roentgenol. 1939;41:1–17.
5. Gould PL, LA Peyton WTF. Vertebral angiography by retrograde injection of the brachial artery. J Neurosurg. 1955;12:369–74.
6. Kruger RA, Mistretta CA, Crummy AB, et al. Digital k-edge subtraction radiography. Radiology. 1977;125:234–5.
7. Luessenhop AJVA. Observations on the tolerance of the intracranial arteries to catheterizations. J Neurosurg. 1964;21:85–91.
8. Frei EH, Driller JNH. The POD and its applications. Med Res Engin. 1966;5:11–8.
9. Yodh SB, Pierce NTWR. A new magnet system for intravascular navigation. Med Biol Eng. 1968;6:143–7.
10. Driller J, Hilal SKMW. Development and use of the POD catheter in the cerebral vascular system. Med Res Engin. 1969;8:11–6.
11. Montgomery DB, Hale JRPN. A magnetically guided catheter system for intracranial use in man. IEEE Trans Magn. 1970;6:374–5.
12. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125–45.
13. Debrun G, Lacour P, Caron JP, Hurth M, Comoy J, Keravel Y. Detachable balloon and calibrated-leak balloon techniques in the treatment of cerebral vascular lesions. J Neurosurg. 1978;49(5):635–49.
14. Kerber CW, Bank WO, Cromwell LD. Calibrated leak balloon microcatheter: a device for arterial exploration and occlusive therapy. Am J Roentgenol. 1979;132(2):207–12.
15. Debrun GM, Vinuela FV, Fox AJ, Kan S. Two different calibrated-leak balloons: experimental work and application in humans. Am J Neuroradiol. 1982;3(4):407–14.
16. Iwata H, Hata Y, Matsuda T, Taki W, Yonekawa Y, Ikada Y. Solidifying liquid with novel initiation system for detachable balloon catheters. Biomaterials. 1992;13(13):891–6.
17. Taki W, Handa H, Yamagata S, Ishikawa M, Iwata H, Ikada Y. Radiopaque solidifying liquids for releasable balloon technique: a technical note. Surg Neurol. 1980;13(2):140–2.
18. Kikuchi Y, Strother CMBM. A new catheter for endovascular interventional procedures. Radiology. 1987;165:870–1.
19. Kurata A, Irikura K, Miyasaka Y, Yada KKS. Experience with BALT magic catheter (PURSIL catheter); especially investigation about advantage, disadvantage and the applications. No Shinkei Geka. 1992;20(8):849–56.

20. Tadavarthy SM, Knight L, Ovitt TW, Snyder C, Amplatz K. Therapeutic transcatheter arterial embolization. Radiology. 1974;112(1):13–6.
21. Tadavarthy SM, Moller JH, Amplatz K. Polyvinyl alcohol (IVALON)—a new embolic material. Am J Roentgenol. 1975;125(3):609–16.
22. Kricheff II. Therapeutic vascular occlusion. J Dermatol Surg Oncol. 1978;4(11):874–80.
23. Kricheff II, Berenstein A. Simplified solid-particle embolization with a new introducer. Radiology. 1979;131(3):794–5.
24. Gemmete JJ, Ansari SA, McHugh J, Gandhi D. Embolization of vascular tumors of the head and neck. Neuroimaging Clin N Am. 2009;19:181–98.
25. Lazzaro MA, Badruddin A, Zaidat OO, Darkhabani Z, Pandya DJ, Lynch JR. Endovascular embolization of head and neck tumors. Front Neurol. 2011;2:64.
26. Duffis EJ, Gandhi CD, Prestigiacomo CJ, Abruzzo T, Albuquerque F, Bulsara KR, et al. Head, neck, and brain tumor embolization guidelines. J Neurointerv Surg. 2012;4(4):251–5.
27. Cho AA, Annen M. Endovascular embolization of complex hypervascular skull base tumors. Oper Tech Otolaryngol Head Neck Surg. 2014;25(1):133–42.
28. Rzewnicki I, Kordecki K, Lukasiewicz A, Janica J, Pulawska-Stalmach M, Kordecki JK, et al. Palliative embolization of hemorrhages in extensive head and neck tumors. Polish J Radiol. 2012;77:17–21.
29. Derdeyn CP, Moran CJ, Cross DT, Dietrich HH, Dacey RG. Polyvinyl alcohol particle size and suspension characteristics. Am J Neuroradiol. 1995;16(6):1335–43.
30. Quisling RG, Mickle JP, Ballinger WB, Carver CC, Kaplan B. Histopathologic analysis of intraarterial polyvinyl alcohol microemboli in rat cerebral cortex. Am J Neuroradiol. 1984;5(1):101–4.
31. Derdeyn CP, Graves VB, Salamat MS, Rappe A. Collagen-coated acrylic microspheres for embolotherapy: in vivo and in vitro characteristics. Am J Neuroradiol. 1997;18(4):647–53.
32. Brothers MF, Kaufmann JCE, Fox AJ, Deveikis JP. N-butyl 2-cyanoacrylate – substitute for IBCA in interventional neuroradiology: histopathologic and polymerization time studies. Am J Neuroradiol. 1989;10(4):777–86.
33. Pollak JS, White RI. The use of cyanoacrylate adhesives in peripheral embolization. J Vasc Interv Radiol. 2001;12(8):907–13.
34. Taki W, Yonekawa Y, Iwata H, Uno A, Yamashita K, Amemiya H. A new liquid material for embolization of arteriovenous malformations. Am J Neuroradiol. 1990;11(1):163–8.
35. Talens FA, Ferrer MS, González-Cruz SA, Martínez SV, Poveda RR, Sanchis BJM, et al. Alcohol sclerotherapy to treat vascular malformations in the oral cavity. Radiologia. 2014;55(6):514–22.
36. Górriz-Gómez E, Vicente-Barrero M, Loras-Caballero ML, Bocanegra-Pérez S, Castellano-Navarro JM, Pérez-Plasencia D, et al. Sclerotherapy of face and oral cavity low flow vascular malformations: our experience. Br J Oral Maxillofac Surg. 2014;52(1):43–7.
37. Blum L, Gallas S, Cottier JP, Sonier Vinikoff CB, Lorette G, Herbreteau D. Percutaneous sclerotherapy for the treatment of soft-tissue venous malformations: a retrospective study of 68 patients. J Radiol. 2004;85:107–16.
38. FA S. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125–45.
39. Romodanov APSV. Intravascular occlusion of saccular aneurysms of the cerebral arteries by means of a detachable balloon catheter. In: Advances and technical standards in neurosurgery. Berlin Heidelberg: Springer; 1982. p. 25–48.
40. Hilal SK, Khandji AG. Synthetic fibre-coated platinum coils successfully used for endovascular treatment of arteriovenous malformations, aneurysms and direct arteriovenous fistulas of CNS. Am J Neuroradiol. 1988;9:1030.
41. Hilal SK, Khandji ASR. Obliteration of intracranial aneurysms with pre-shaped highly thrombogenic coils. Radiology. 1989;173:250–7.
42. Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. J Neurosurg. 1991;75:8–14.

43. Guglielmi G, Viñuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: electrochemical basis, technique, and experimental results. J Neurosurg. 1991;75:1–7.
44. Guglielmi G. History of endovascular endosaccular occlusion of brain aneurysms: 1965–1990. Interv Neuroradiol. 2007;13:217–24.
45. Guglielmi G, Vinuela F, Briganti F, Duckwiler G. Carotid-cavernous fistula caused by a ruptured intracavernous aneurysm: endovascular treatment by electrothrombosis with detachable coils. Neurosurgery. 1992;31(3):591–7.
46. Qureshi AI, Vazquez G, Tariq N, Suri MF, Lakshminarayan K, Lanzino G. Impact of international subarachnoid aneurysm trial results on treatment of ruptured intracranial aneurysms in the United States. Clinical article. J Neurosurg. 2011;114(3):834–41.
47. McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ. Comparative effectiveness of unruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. Stroke. 2013;44(4):988–94.
48. Kadkhodayan Y, Rhodes N, Blackburn S, Derdeyn CP, Cross DT, Moran CJ. Comparison of enterprise with neuroform stent-assisted coiling of intracranial aneurysms. Am J Roentgenol. 2013;200(4):872–8.
49. King B, Vaziri S, Singla A, Fargen KM, Mocco J. Clinical and angiographic outcomes after stent-assisted coiling of cerebral aneurysms with Enterprise and Neuroform stents: a comparative analysis of the literature. J Neurointerv Surg. 2014;7(12):1–5.
50. Durst CR, Khan P, Gaughen J, Patrie J, Starke RM, Conant P, et al. Direct comparison of Neuroform and Enterprise stents in the treatment of wide-necked intracranial aneurysms. Clin Radiol. 2014;69(12):e471–6.
51. Lubicz B, Collignon L, Raphaeli G, Bandeira A, Bruneau M, De Witte O. Solitaire stent for endovascular treatment of intracranial aneurysms: immediate and mid-term results in 15 patients with 17 aneurysms. J Neuroradiol. 2010;37(2):83–8.
52. Zhang J, Wang D, Li X. Solitaire AB stent-assisted coiling embolization for the treatment of ruptured very small intracranial aneurysms. Exp Ther Med. 2015;10(6):2239–44.
53. Xiang J, Damiano RJ, Lin N, Snyder KV, Siddiqui AH, Levy EI, et al. High-fidelity virtual stenting: modeling of flow diverter deployment for hemodynamic characterization of complex intracranial aneurysms. J Neurosurg. 2015;123(4):832–40.
54. Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. Neurosurgery. 2009;64(4):632–42.
55. Fiorella D, Woo HH, Albuquerque FC, Nelson PK. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. Neurosurgery. 2008;62(5):1115–20.
56. Fischer S, Vajda Z, Perez MA, Schmid E, Hopf N, Bäzner H, et al. Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. Neuroradiology. 2012;54(4):369–82.
57. Fiorella D, Kelly ME, Albuquerque FC, Nelson PK. Curative reconstruction of a giant midbasilar trunk aneurysm with the pipeline embolization device. Neurosurgery. 2009;64(2):212–7.
58. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. Am J Neuroradiol. 2011;32(1):34–40.
59. Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. Am J Neuroradiol. 2010;31(6):1139–47.
60. Chalouhi N, Zanaty M, Tjoumakaris S, Gonzalez LF, Hasan D, Kung D, et al. Treatment of blister-like aneurysms with the pipeline embolization device. Neurosurgery. 2014;74(5):527–32.
61. Yeung TW, Lai V, Lau HY, Poon WL, Tan CB, Wong YC. Long-term outcome of endovascular reconstruction with the pipeline embolization device in the management of unruptured dissecting aneurysms of the intracranial vertebral artery. J Neurosurg. 2012;116(4):882–7.

62. Poeck K. Intraarterial thrombolytic therapy in acute stroke. Acta Neurol Belg. 1988;88(1):35–45.
63. Casto L, Moschini L, Camerlingo M, Gazzaniga G, Partziguain T, Belloni G, et al. Local intraarterial thrombolysis for acute stroke in the carotid artery territories. Acta Neurol Scand. 1992;86(3):308–11.
64. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999;282(21):2003–11.
65. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery. Stroke. 1998;29(1):4–11.
66. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. Stroke. 2007;38(10):2633–9.
67. Broderick J. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the interventional management of stroke study. Stroke. 2004;35(4):904–11.
68. Broderick JP. The Interventional Management of Stroke (IMS) II study. Stroke. 2007;38(7):2127–35.
69. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) bridging trial. Stroke. 1999;30(12):2598–605.
70. Mazighi M, Serfaty J-M, Labreuche J, Laissy J-P, Meseguer E, Lavallée PC, et al. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. Lancet Neurol. 2009;8(9):802–9.
71. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. Stroke. 2008;39(4):1205–12.
72. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368(10):893–903.
73. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med. 2013;368(10):904–13.
74. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke – study protocol. N Engl J Med. 2013;368(10):914–23.
75. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. Ann Neurol. 2000 Apr;47(4):462–9.
76. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2014;372(1):141217070022009.
77. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):150211090353006.
78. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
79. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):150211090353006.
80. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):1–11.
81. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. 2012;380(9849):1241–9.

82. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. 2012;380(9849):1231–40.
83. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. 2012 Oct 6;380(9849):1231–40.
84. Rohde S, Haehnel S, Herweh C, Pham M, Stampfl S, Ringleb PA, et al. Mechanical thrombectomy in acute embolic stroke: preliminary results with the revive device. Stroke. 2011;42(10):2954–6.
85. Bose A, Henkes H, Alfke K, Reith W, Mayer TE, Berlis A, et al. The penumbra system: a mechanical device for the treatment of acute stroke due to thromboembolism. Am J Neuroradiol. 2008;29(7):1409–13.
86. Mocco J, Zaidat O, Von Kummer R, Yoo A, Gupta R, Lopes D, et al. Results of the THERAPY trial: a prospective, randomized trial to define the role of mechanical thrombectomy as adjunctive treatment to IV rtPA in acute ischemic stroke. Int J Stroke. 2015;10:10.
87. Nguyen TN, Malisch T, Castonguay AC, Gupta R, Sun CHJ, Martin CO, et al. Balloon guide catheter improves revascularization and clinical outcomes with the solitaire device: analysis of the North American solitaire acute stroke registry. Stroke. 2014;45(1):141–5.

Chapter 3
Importance of a Comprehensive Approach

Raymond D. Turner

Stroke is the second leading cause of death worldwide and the foremost cause of disability [1]. For over a decade and a half, the Brain Attack Coalition (BAC) has been developing recommendations for the treatment of stroke, and the Joint Commission has been certifying centers based on these recommendations [2]. These guidelines are designed to improve access and triage decision making for patients in efforts to obtain the best possible population-based clinical outcomes. The current highest level of Joint Commission certification is Comprehensive Stroke Center (CSC).

Defining Comprehensive Stroke Center

In general, a certified CSC has the necessary facilities, personnel, processes, and expertise to manage stroke patients, with the goal of optimizing population-based patient outcomes. Part of this certification requires that the approved centers have the ability to track data, identify positive and negative trends, and modify the processes in the patient care pathway in order to optimize standardized outcomes. While centers are approved for 2 years, it is important to note that there is an interim analysis at 1 year. The Joint Commission is regularly reviewing and updating the requirements based on patient outcome data and expert recommendation. The most current detailed CSC requirements can be found at https://www.jointcommission.org/certification/advanced_certification_comprehensive_stroke_centers.aspx.

In order to track quality metrics, the AHA/ASA put out a scientific statement detailing 26 metrics that should be used across all CSCs [3]. They are divided into

R. D. Turner (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: turnerrd@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_3

three disease categories: ischemic stroke, aneurysms (ruptured and unruptured), and non-trauma-related hemorrhagic stroke and AVMs (ruptured and unruptured). The metrics address all phases of the care pathway, from triage and initial management to critical care through rehab, as well as the participation in clinical research studies. Due to a lack of data, currently there are little-to-no benchmarks established for quality metrics that centers need to achieve, particularly in regard to complication rates. However, there are goals that are set related to timing of triage and treatment.

The effectiveness of the certification in reducing mortality and morbidity has yet to be elucidated. Most recently in the USA, the impact of stroke mortality improved from the third to fourth leading cause of death. The AHA/ASA attributed this improvement to a multitude of factors, such as changes in interventions, improvement in stroke prevention, and risk factor modifications, particularly hypertension. However, it is important to note that the CSC program certification is relatively new, and while there are approximately 100 joint commission CSCs, there are other centers functioning like a CSC that are in the queue for certification site visit. Therefore, it is likely premature to see any measured effect in a large population analysis [4].

Disease-Specific Considerations: AIS

There are several core measures that have been identified with best practices for triage and management of acute ischemic stroke. The initial triage of all suspected stroke patients should begin with the NIHSS. Utilization of this scale standardizes the examination of the patient and is a predictor of stroke outcomes. All suspected strokes should also obtain a non-contrast CT scan of the brain. Based on clinical imaging and laboratory data, patients who qualify for intravenous thrombolysis with tPA should receive this without delay. The standardized goal is to administer this drug within 60 min upon arrival to the hospital. All suspected large vessel occlusions (LVO) should be referred to neuro-endovascular surgeons for evaluation for mechanical thrombectomy.

Triage: Primary Versus Comprehensive

There is currently a debate regarding the triage of patients at the EMS level. Should a patient be transported directly to a CSC or to a PSC? Obviously, if the CSC is a shorter transport, patients should triage to the CSC. This argument likely holds true for when they are equidistant. However, it is unknown at this point if there is a time cutoff that would dictate improved value by accepting a slightly longer transport time in order to reach a CSC over a PSC. In some cases, particularly those patients with low likelihood of harboring LVO, either PSC or CSC, may be appropriate. However, this discussion has ramifications in patients with LVO. There are several endeavors

underway at the EMS triage level that will try to correlate a noninvasive "in the field" exam or study that will predict patients who have LVO from those who do not.

IV tPA + EVT Versus EVT Alone

There have been several retrospective studies published looking at the outcomes of suspected LVO patients, those treated with IV tPA and endovascular therapy (EVT) vs ETV alone. The Catalan Stroke Code and Reperfusion Consortium reported in stroke that their observational study of >1100 patients demonstrated no difference in good outcomes (mRS 0–2) at 3 months [5]. A meta-analysis of six randomized control trials also demonstrated the observation that IV tPA did not impact the rate of good outcome in mechanical thrombectomy patients with large vessel occlusion [6]. A third group published their experience with 90 consecutive patients demonstrated so significant difference in good outcomes; however the cost of treatment favored ETV alone vs IV tPA + ETV ($33,810 vs $40,743; $p = 0.02$) [7].

While these studies are of interest and trigger good academic debate, it is important to note their primary limitation is that these are really two different treatment groups. While these studies generally had similar demographics, stroke severity, etc., in all studies, patients presenting within the IV tPA-recommended guidelines received that therapy. Therefore, the ETV-only groups are patients with AIS presenting later by comparison to the tPA group, or were disqualified for other reasons; yet their imaging suggested that they may receive benefit if they revascularized the patient with ETV. Therefore, the ETV group may have a propensity for better outcomes due to a number of factors, such as good collateral flow. Nevertheless, this fuels the academic fire to consider a head-to-head RCT of EVT with or without tPA, especially if similar good outcomes and avoidance of bad outcomes can be obtained for lower socioeconomic costs.

Disease-Specific Considerations: Aneurysms

It has been shown that large volume centers that treat aneurysms are able to obtain better outcomes compared to low volume centers. The analysis of the California hospitals demonstrated that in-hospital mortality was lower at the higher volume centers; however length of stay and charges were higher [8]. Barker et al. reported that high volume centers were more likely to discharge patients to home after elective aneurysm surgery, there was a trend toward lower mortality, and length of stay was not significantly different [9]. Analysis of ruptured and unruptured aneurysms in New York state demonstrated lower morbidity and mortality in high volume centers [10]. Hoh et al. demonstrated that high volume endovascular centers had lower morbidity and mortality rates compared to low volume centers [11].

One key issue with these studies and others is the lack of standardized definition of high volume vs low volume. Furthermore, the data of these studies were largely obtained in the late 1990s and early 2000s, well prior to the formation of CSC designations. This is confounded by the issue that some of these studies set the benchmark for a high volume center as low as eight procedures per year for a hospital or three procedures per year for a surgeon. The CSC requirement (currently) for approved centers is 15 aneurysm procedures per year. These case minimums have changed over the years, but in essence acknowledge that there is practical experience required to have optimized population-based outcomes [12]. Grigoryan et al. looked at the implications of case minimum requirements, which determined that very few centers (at that time) qualify for CSC certification, making the argument that cerebrovascular disease should be treated in regionalized centers [13].

Another consideration for the treatment of cerebral aneurysms, among other diseases (AVMs), is the specific members of the team caring for the patient. MUSC delineated the experience of developing a comprehensive approach to cerebral aneurysm care from the traditional independent approach [14]. Creating a single team of open and endovascular-trained neurosurgeons, interventional neuroradiology, and neuro-critical care specialists, the group saw an increase in patient volume, increase in case mix index (a measure of severity of the patient's comorbidities), lower length of stay, and lower mortality rates with a comprehensive team approach.

Disease-Specific Considerations: ICH

Intracranial hemorrhage is a complex disease that is typically secondary to poor management of chronic physiological conditions, such as hypertension and diabetes. However, in some cases, underlying vascular etiologies such as vascular malformations or aneurysms may be present. Approximately 30% of patients will have an increase in ICH following the ictal bleed [15]. Patient's medical conditions may also be complicated by the use of anticoagulation. For example, reversal of vitamin K antagonists has historically been limited to combinations of vitamin K and fresh frozen plasma; however recent evidence suggests that four-factor prothrombin complex concentrate may be superior [16]. Stopping and reversing these medications for the benefit of the patient in terms of ICH management must be balanced with the risk of why they are on those medications prior to the hemorrhage. For example, stopping the prophylactic aspirin in a patient with ICH is a relatively easy risk/benefit analysis; however managing the anticoagulation in a patient with a left ventricular assist device (LVAD) and ICH is a more challenging scenario.

While management of ICH guidelines assists with the decision analysis of these patients, their complexity may require additional experience and expertise [17]. Aggressive intracranial pressure monitoring, surgery, and seizure treatment are not uncommon in the acute care of these patients whose mortality and morbidity are significant. Given the complex and diverse decision analysis required to treat these

patients, a comprehensive team approach of neuro-critical care, neurosurgery, and vascular neurology is required to optimize the components of treatment.

Beyond CSC: Comprehensive *Systems* of Care

While the current state of stroke designation is focused on hospital-based accreditation, population-based approaches need to be considered in the ability to deliver optimal care across a geographical area. These systems of care will differ across the USA, as the geographical constraints and opportunities to access healthcare differ in the various environments (urban, rural, etc.). The other consideration is the cerebrovascular disease that requires treatment. Acute ischemic stroke is extremely time sensitive; however a small ICH may not be as critical.

The FAST-MAG study looked at routing suspected acute ischemic stroke patients to the nearest primary stroke center vs the nearest adult ER in the Los Angeles County area. They found that volume increased at the PSCs without sacrificing prehospital care time. However, this is in a confined geographical area where there were 29 PSCs by the end of the study enrollment. This is a very different scenario if you live in Wyoming, where there is only one PSC at the time of this writing.

This is important because while the number of endovascular patients with aneurysms and AVMs have remained stable, there has been an increase in endovascular treatment of AIS since the trials demonstrated superior outcomes to IV tPA alone at the end of 2014 and early 2015. From an access to care standpoint, this is now critical to consider as the patients who need the most urgent care are the largest growing treatment eligible population in cerebrovascular disease. However, training new physicians takes time, and if there is a large increase in the large number of endovascular surgeons to treat AIS, it will inevitably dilute the volumes each physician treats of the other cerebrovascular disease. While correlating high volume to better outcomes has not been established for AIS, it has been demonstrated for diseases such as aneurysms. It is possible that without novel access and care delivery platforms, we could be sacrificing the outcomes of one disease (aneurysms) to meet the need of another (AIS).

There are several models being implemented currently to address these issues. Stroke mobiles are currently in service in Cleveland, Houston, Memphis, and Chicago and are used to assist in triage and CT imaging in the field rather than at a hospital, moving the decision point from in-hospital to the point of first contact. The MUSC group in Charleston is creating a single physician team, including triage and treatment processes across multiple healthcare systems, concentrating expertise within a finite group of doctors, rather than a single hospital. Others, such as in Charlotte, are creating multiple teams of experts at each hospital. While no one solution will prevail, innovation solutions will eventually help model out the best approaches given the needs and resources of a particular area. This is an extremely dynamic time in the treatment of cerebrovascular disease, and the only certainty is how we optimize workflow will like continue to evolve.

References

1. The top 10 causes of death. World Health Organization. http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 18 Apr 2017.
2. Alberts MJ, Hademenos G, Latchaw RE. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA. 2000;283(23):3102–9.
3. Leifer D, Bravata DM, Connors JJ. Metrics for measuring quality of care in comprehensive stroke centers: detailed follow-up to Brain Attack Coalition comprehensive stroke center recommendations: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(3):849–77.
4. Lackland DT, Roccella EJ, Deutsch AF. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014;45(1):315–53.
5. Abilleira S, Ribera A, Cardona P. Outcomes After Direct Thrombectomy or Combined Intravenous and Endovascular Treatment Are Not Different. Stroke. 2017;48(2):375–8.
6. Tsivgoulis G, Katsanos AH, Mavridis D, Magoufis G, Arthur A, Alexandrov AV. Mechanical Thrombectomy Improves Functional Outcomes Independent of Pretreatment With Intravenous Thrombolysis. Stroke. 2016;47(6):1661–4.
7. Rai AT, Boo S, Buseman C. Intravenous thrombolysis before endovascular therapy for large vessel strokes can lead to significantly higher hospital costs without improving outcomes. J Neurointerv Surg. 2017;10(1):17–21.
8. Bardach NS, Zhao S, Gress DR, Lawton MT, Johnston SC. Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke. 2002;33(7):1851–6.
9. Barker FG, Amin-Hanjani S, Butler WE, Ogilvy CS, Carter BS. In-hospital mortality and morbidity after surgical treatment of unruptured intracranial aneurysms in the United States, 1996–2000: the effect of hospital and surgeon volume. Neurosurgery. 2003;52(5):995–1007. discussion 1007-9
10. Berman MF, Solomon RA, Mayer SA, Johnston SC, Yung PP. Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. Stroke. 2003;34(9):2200–7.
11. Hoh BL, Rabinov JD, Pryor JC, Carter BS, Barker FG. In-hospital morbidity and mortality after endovascular treatment of unruptured intracranial aneurysms in the United States, 1996–2000: effect of hospital and physician volume. AJNR. 2003;24(7):1409–20.
12. TJC. Update: Comprehensive Stroke Center Case Volume Requirements. Jt Comm Perspect. 2014;34(7):10. https://www.jointcommission.org/assets/1/18/S10_CSC_Case_Volume.pdf
13. Grigoryan M, Chaudhry SA, Hassan AE, Suri FK, Qureshi AI. Neurointerventional procedural volume per hospital in United States: implications for comprehensive stroke center designation. Stroke. 2012;43(5):1309–14.
14. Krishna V, Walsh K, Turner RD, Chalela J, Turk A, Patel SJ. Impact of integrated cerebrovascular program on outcomes in patients with intracranial aneurysms. J Neurointerv Surg. 2013;5(3):264–8.
15. Brott T, Broderick J, Kothari R. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28(1):1–5.
16. Steiner T, Poli S, Griebe M. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. The Lancet Neurology. 2016;15(6):566–73.
17. Hemphill JC, Greenberg SM, Anderson CS. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032–60.

Chapter 4
The Hybrid Operating Room

Kyle Mueller, Daniel Felbaum, Randy Bell, and Rocco Armonda

Advancements in neuroendovascular surgery have created a new era in the treatment of neurovascular diseases. The meteoric increase in technology coupled with device improvement has continued to propel our ability to treat a variety of cerebrovascular pathology via endovascular routes. At the same time, many complex cases are often managed best with the utilization of both open and endovascular techniques rather than as distinct therapeutic interventions [1, 2]. This has benefited patients by providing surgeons more avenues to safely intervene in neurovascular disease. Importantly, each individual can receive a tailored treatment plan that combines both open and endovascular tools. This marriage of open and endovascular surgery allows the surgeon the opportunity to combine the full array of capabilities in both specialties and unite them into a hybrid operating room [3]. This can result in specific challenges of patient selection, room layout, table adaptability, and anesthesia coordination which can be controlled in a single environment. Overall, as the discipline advances toward a combined effort in treating neurovascular disease, the evolution of the space in which we operate should also likely adapt. This will allow us a more efficient coordination and concentrated focus on the patient. This chapter will explore the challenges, layout, and patient selection of merging both worlds into one space: establishing a hybrid neurointerventional operating suite.

K. Mueller · D. Felbaum
Department of Neurosurgery, MedStar Georgetown University Hospital, Washington, DC, USA

R. Bell
Department of Neurosurgery, Walter Reed National Military Medical Center, Bethesda, MD, USA

R. Armonda (✉)
Department of Neuroendovascular Surgery, MedStar Washington Hospital Center, MedStar Georgetown University Hospital, Washington, DC, USA

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_4

Background

Cerebrovascular pathology can present with a wide variety of acuity of illness. Patients may present with an incidental finding or with life-threatening emergencies. The optimal care of these patients requires the need for various hospital resources such as intensive care units (ICU), operating rooms (OR), and radiology and endovascular suites. The current neurointerventional suite of today has evolved from traditional imaging suites. In the past, the major focus of these spaces was on diagnostic cerebral angiograms. Now these spaces serve as complex neuroendovascular operating rooms in which diseases such as complex intracranial aneurysms and large vessel occlusions can be methodically and comprehensively treated [3–5]. Treating and utilizing these rooms as similar to operating rooms require a change in mindset and culture. This poses many challenges for institutions. Traditionally, at most US hospitals, the operating room and endovascular suite are isolated and may geographically be distant. This can be fraught with medical issues when dealing with fragile and critically ill patients, particularly when resources such as anesthesia and/or ICU services are in a separate portion of the hospital. These logistical issues can place critical patients in situations that require multiple dangerous road trips. Not infrequently, many neurovascular patients require specialized airway equipment, emergency ventriculostomy kits, and surgical support that are not immediately available.

The current healthcare environment is also plagued with rising costs and limited resources. The continuation of this trend will force hospital administrators to operate with increased scrutiny on how resources are utilized as well as the associated cost. This will force us to be creative and smart in how we better utilize the resources and infrastructure we have. Into these challenges comes the hybrid operating room with combined full open and endovascular capabilities.

Obstacles to Establishment: Cost, Room Layout, and Specialized Equipment

Cost is usually the greatest limiting step in the procurement of a hybrid neurointerventional operating room. As the number of open microsurgical cases diminishes throughout the country, health economist and hospital administrators are hesitant to invest in a room that may not pay for itself. The increased cost for this room combined with the increased size creates a double challenge for the administration. The hospital administrators will be looking at what added revenues and incentives that embarking on such an endeavor would have. Recent clinical trials using endovascular thrombectomy have revolutionized the treatment of stroke from large vessel occlusion [6–10]. The development of comprehensive stroke centers will hopefully allow more patients to be funneled to high-volume centers which will bring in more revenue for the hospital to help offset costs elsewhere.

Operating room space has always been a premium. Combined space and personnel limit the number of ORs a hospital can staff. The hybrid rooms are typically larger than most operating rooms. In addition, many hospitals are limited by an established infrastructure with limited ability to expand. Strategies to overcome this include shared space with vascular and cardiothoracic surgery services, ability to use the space for diagnostic purposes, and room planning to allow the movement of imaging arms to allow versatility of room usage [4]. A significant investment and startup costs for renovations will be needed in order to bring about the change to have a more comprehensive, efficient system of the future. As hospitals struggle to stay economically balanced, this becomes a challenge.

The blueprint for a hybrid suite must consider both the inner room design as well as its position within the functional hospital system. Figures 4.1a, b are taken from within our hybrid operating room and shows several features important to its design. The unique space requires considerations for placing imaging equipment that is least intrusive and most adaptable. Ceiling-mounted equipment can be moved with more versatility and may best serve patients in such a constrained space as opposed to floor mounted that may be difficult to adapt to a variety of patient positions and pathologies. The mobility, in and out, of imaging equipment is a critical component in room design is shown nicely in Fig. 4.2. The surgical table must be dynamic in that it can be fixed during open cases and floating for endovascular procedures. Figure 4.3 demonstrates the radiolucent headholder, a necessary component, which allows 3D rotational angiograms to be performed after open microsurgical procedures. Dual rooms that are connected will achieve a better conservation of space in an ergonomic manner in addition to adapting to the unpredictable nature of emergent cases. The ability to have the table centered and avoid movement is typically preferred rather than rotating it into imaging mode. This is because of the access lines, anesthesia, and the endotracheal tube remaining free of manipulation by a centered fixed position. This allows for efficient flow during the case. Specifically, there is less risk to the patient and easier utilization of the 3D rotational angiography function. The control room is usually placed outside of the operating space to allow for image reconstructions and clinical decision-making away from the surgical space. These rooms should be placed in proximity to imaging and the ICU to further optimize care and provide a more efficient synchrony while limiting complications.

Patient Selection

The use of the hybrid room is ideal for the complex neurovascular patients, many of which require the application of combined endovascular and microsurgical procedures. The versatility of these rooms allows them to be expanded to other areas such as spine and skull base surgery. Neurovascular surgery technology has dramatically increased over the years, yet open microsurgery still maintains advantages in certain clinical circumstances. Many lesions are often best treated with a combined approach.

Fig. 4.1 (**a**, **b**) Intraoperative pictures demonstrating a typical setup for a hybrid OR for the bed, equipment, and anesthesia

Fig. 4.2 The dynamic nature of the hybrid OR must allow efficient transfer of equipment between open and endovascular cases

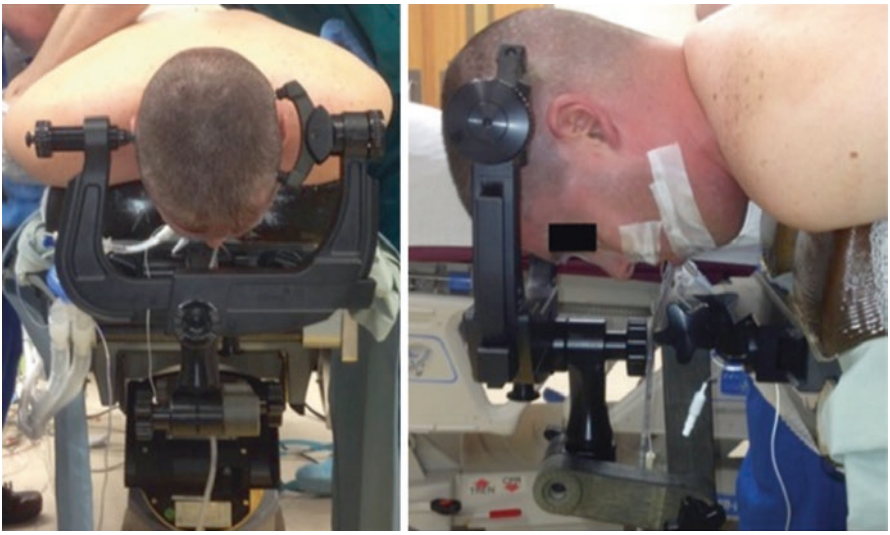


Fig. 4.3 The optimal radiolucent headholder fixated to a patient that will allow for a 3D rotational intraoperative angiogram

Several case examples of patients that would be optimally treated in a hybrid operating room are described. An evolving indication includes the treatment of an intracranial hemorrhage as depicted in Fig. 4.4. This patient was treated in the operating room with image-guided, endoscopic, minimally invasive removal of the hematoma as compared to traditional open craniotomy. Utilization of a hybrid room for this condition is both safe and can be more effective [5, 11]. Another common condition, ruptured intracranial aneurysms, will optimally be treated in hybrid OR's due to increased endovascular techniques in conjunction with open microsurgery if needed. Figure 4.5 demonstrates a patient that presented with a subarachnoid hemorrhage from a ruptured anterior communicating artery aneurysm. During endovascular coil embolization, there was intraprocedural rupture leading to

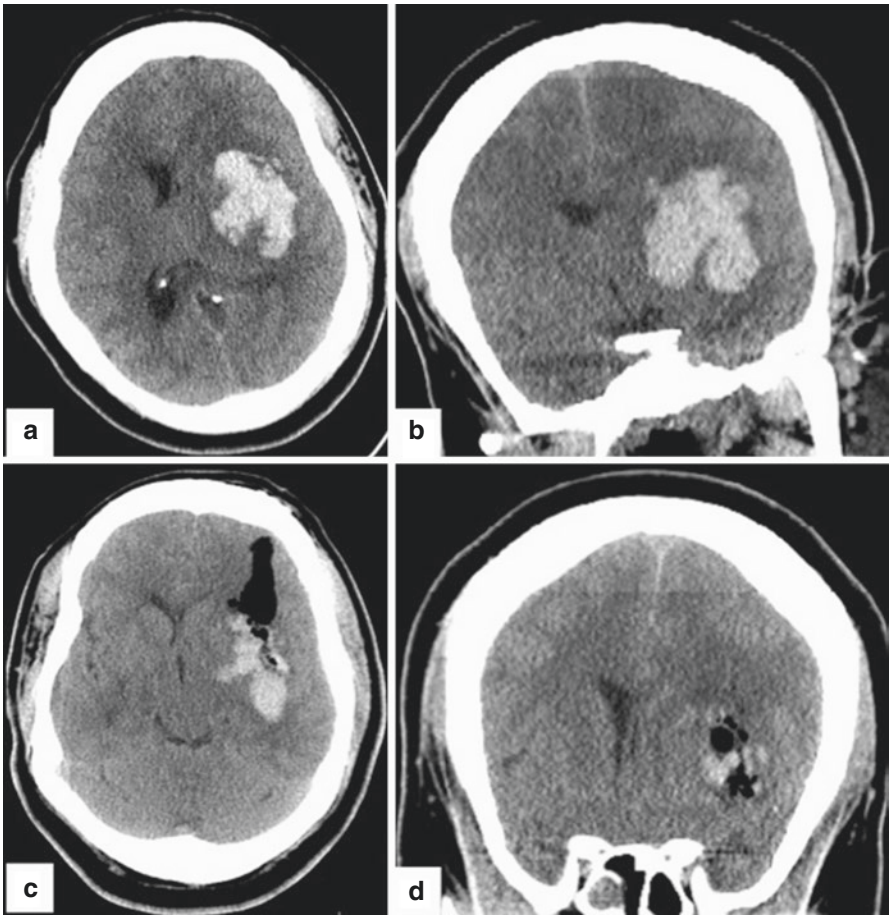


Fig. 4.4 A 45-year-old African American female presented with sudden onset aphasia and right hemiparesis. (**a**, **b**) Axial and coronal CT scans demonstrating a large basal ganglia hemorrhage. (**c**, **d**) Vascular lesion was ruled out, and patient was taken to the OR for image-guided minimally invasive endoscopic evacuation of hematoma

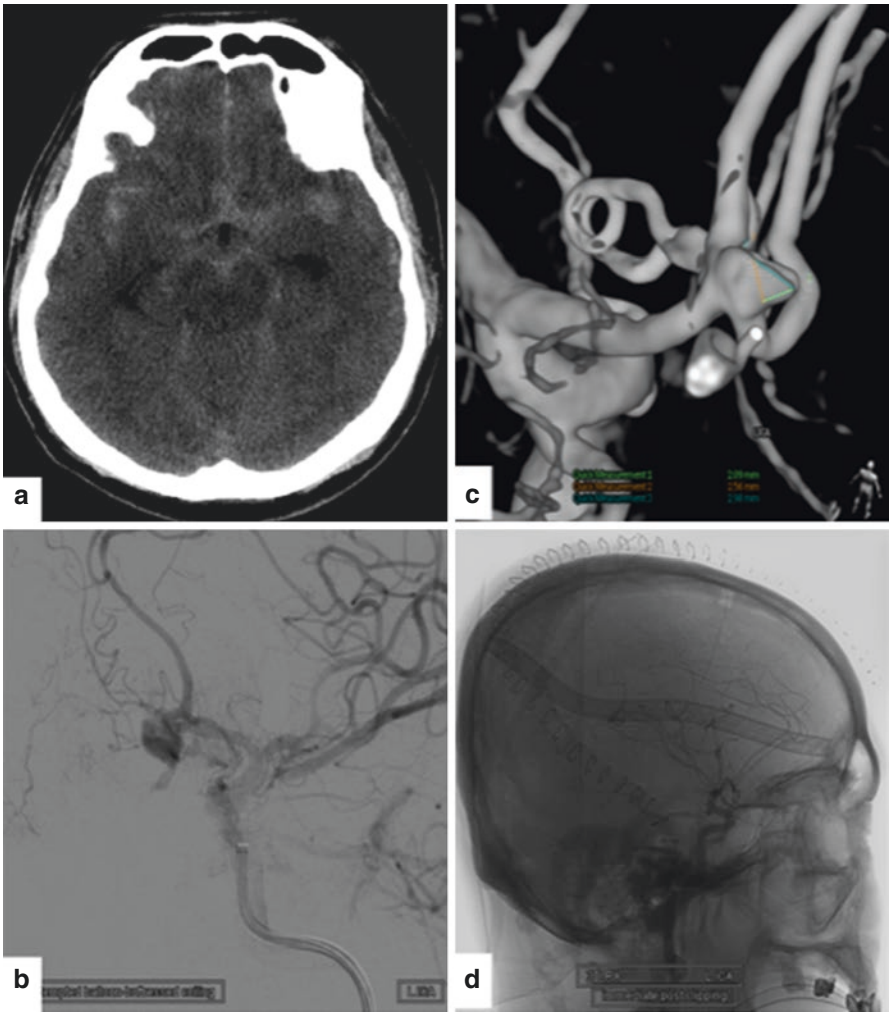


Fig. 4.5 A 55-year-old Korean gentleman presented with sudden onset headache and diffuse subarachnoid hemorrhage from a ruptured anterior communicating artery aneurysm. (**a**) Initial head CT showing diffuse subarachnoid hemorrhage. (**b**) Cerebral angiogram demonstrated ruptured anterior communicating artery aneurysm. Intraprocedural rupture occurred during attempted coil embolization requiring emergent transfer to the OR for microsurgical clipping. (**c**) 12-month follow-up angiogram showing enlarged triangular remnant requiring (**d**) repeat microsurgical clipping resulting in aneurysm obliteration

emergent open microsurgical clipping. A remnant remained that was present on follow-up angiogram that required subsequent clipping. Ruptured aneurysms that are associated with large hematomas are ideal for endovascular treatment as well as open decompression [12]. These types of cases are ideally suited for a hybrid operating room.

Other applications include the use of the 3D rotational angiogram post-microsurgical clipping to insure the aneurysm is ideally occluded and parent arteries are preserved. Figure 4.6 shows a patient with a ruptured anterior communicating artery aneurysm that underwent microsurgical clipping. Postoperative angiogram demonstrated residual filling of the aneurysm not appreciated on indocyanine green (ICG) angiography necessitating a return to the operating room. Hybrid OR's help to prevent a delay in detection, correction, or treatment of underlying vascular conditions.

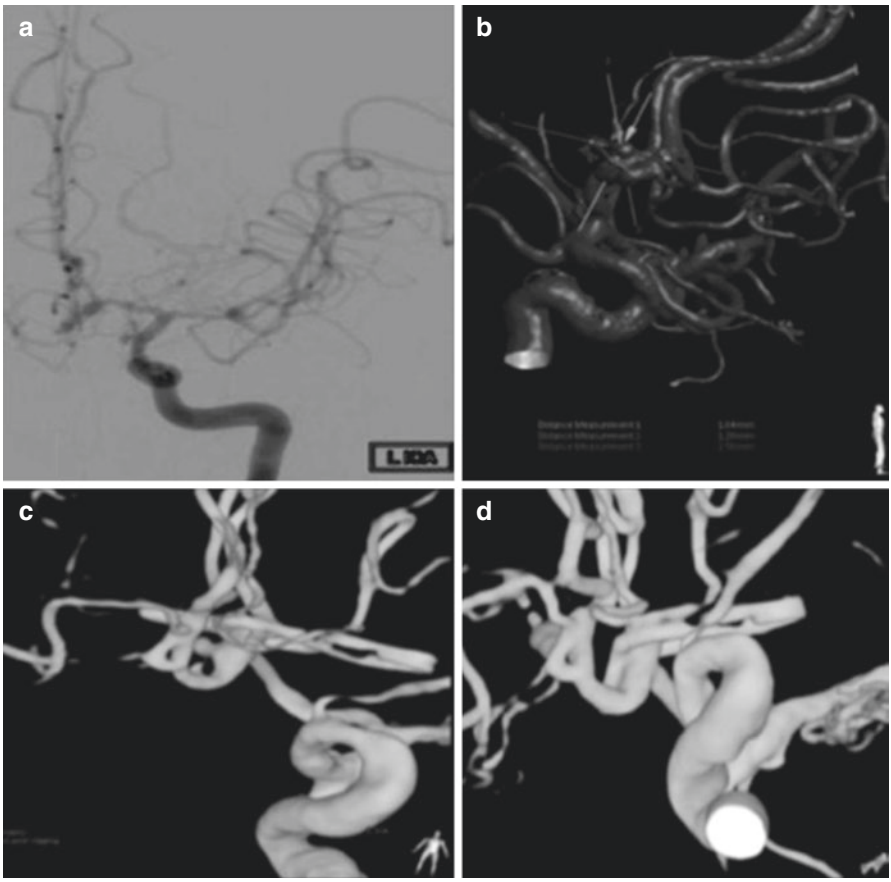


Fig. 4.6 (**a**, **b**, **c**) A 51-year-old Hispanic female presented with a Hunt and Hess 4, Fisher grade 3 subarachnoid hemorrhage from a wide-based anterior communicating artery aneurysm that underwent microsurgical clipping. Of note, the patient also had a chronic left supraclinoid ICA occlusion with collateral filling from the posterior circulation. (**d**) Postoperative angiogram demonstrated residual filling of the aneurysm necessitating return to the OR for repeat clipping

Other applications include the combined use of embolization and hematoma removal in a ruptured AVM or tumor embolization followed by microsurgical resection. Additional complex approaches to dural AVMs, bypass/trapping giant aneurysms, and in cases of penetrating trauma to insure underlying neurovascular injuries are not present as a decompressive craniectomy is emergently needed [13].

In the area of spine and skull base surgery, the use of combined percutaneous embolization, vertebroplasty, and open surgical decompression can be performed in one space [9]. Such combinations may limit blood loss, time of surgery, and physiologic stress to compromised patients [14]. This reflects the versatility that these rooms can have with applications to treat multiple types of pathology.

Conclusion

The future management of complex neurovascular disease should utilize a hybrid operating room. Figure 4.7 summaries the overall benefit of a hybrid operating room, specifically showing the ability to minimize patient transports and maximize therapeutic interventions. With increasing technology and improved techniques, employing both endovascular and open microsurgery to treat complex cerebrovascular disease will help improve patient outcomes. Many logistical obstacles including cost, infrastructure, and resources all will need to be evaluated before undertaking such a task. Solutions to these challenges must be overcome to better treat complex cerebrovascular disease and improve outcomes for our patients.

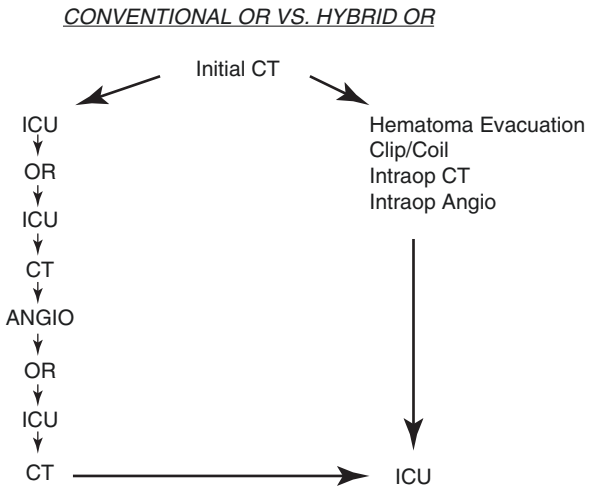


Fig. 4.7 A flowchart that details the advantages of a hybrid operating room by limiting patient transfers and increasing possible interventions

References

1. Murayama Y, Arakawa H, Ishibashi T, Kawamura D, Ebara M, Irie K, Takao H, Ikeuchi S, Ogawa T, Kato M, Kajiwara I, Nishimura S, Abe T. Combined surgical and endovascular treatment of complex cerebrovascular disease in the hybrid operating room. J NeuroInterv Surg. 2013;5:489–93.
2. Fandino J, Taussky P, Marbacher S, Muroi C, Diepers M, Fathi AR, et al. The concept of a hybrid operating room: applications in cerebrovascular surgery. Acta Neurochir Suppl. 2013;115:113–7.
3. Iihara K, Satow T, Matsushige T, Kataoka H, Nakajima N, Fukuda K, et al. Hybrid operating room for the treatment of complex neurovascular and brachiocephalic lesions. J Stroke Cerebrovasc Dis. 2012;22:e277–85.
4. Murayama Y, Saguchi T, Ishibashi T, Ebara M, Takao H, Irie K, Ikeuchi S, Onoue H, Ogawa T, Abe T. Endovascular operating suite: future directions for treating neurovascular disease. J Neurosurg. 2006;104(6):925–30.
5. Jolesz FA. Intraoperative imaging in neurosurgery: where will the future take us? Acta Neurochir Suppl. 2011;109:21–5.
6. Berkhemer OA, Fransen PS, Beumer D, et al. MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11–20.
7. Goyal M, Demchuk AM, Menon BK, et al. ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.
8. Saver JL, Goyal M, Bonafe A, et al. SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285–95.
9. Campbell BC, Mitchell PJ, Kleinig TJ, et al. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
10. Jovin TG, Chamorro A, Cobo E, et al. REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
11. Chalouhi N, Theofanis T, Jabbour P, Dumont AS, Fernando Gonzalez L, Starke RM, et al. Safety and efficacy of intraoperative angiography in craniotomies for cerebral aneurysms and arteriovenous malformations: a review of 1093 consecutive cases. Neurosurgery. 2012;71:1162–9.
12. Goren O, Monteith SJ, Hadani M, Bakon M, Harnof S. Modern intraoperative imaging modalities for the vascular neurosurgeon treating intracerebral hemorrhage. Neurosurg Focus. 2013;34(5):1–7.
13. Mori R, Yuki I, Kajiwara I, Nonaka Y, Ishibashi T, Karagiozov K, Dahmani C, Murayama Y. Hybrid operating room for combined neuroendovascular and endoscopic treatment of ruptured cerebral aneurysms with intraventricular hemorrhage. World Neurosurg. 2016;89:727e9–e12.
14. Fathi AR, Nevzati E, Marbacher S, Gugliotta M, Remonda L, Fandino J. Validation and accuracy of intraoperative CT scan using the Philips Allura Xper FD20 angiography suite for assessment of free-hand pedicle screw placement. J Neurol Surg A Cent Eur Neurosurg. 2012;73:741–6.

Part II
Hemorrhagic

Chapter 5
Diagnosis, Medical Management, and Complications of Aneurysmal Subarachnoid Hemorrhage

Patrick Britell, Charles Andrews, Niren Kapoor, and Julio A. Chalela

Initial Presentation

Aneurysmal subarachnoid hemorrhage (aSAH) carries significant morbidity and mortality. Although major differences in the incidence of the disease exist, the incidence of aSAH ranges from 2 to 16 per 100,000 people [1]. Despite advancements in the treatment of patients with aSAH, 12–15% of patients will still die prior to hospital admission [2, 3]. The incidence of aSAH increases with age, with median age of onset >50 years of age, and is more common in women than in men [4–7]. The clinical hallmark of aSAH, in an awake patient, is the complaint of the sudden onset of the "worst headache of life" [8]. In 10–40% of patients, this thunderclap headache is preceded 7–30 days by a warning or sentinel headache [9–11]. This sentinel headache signifies a slow bleed from the aneurysmal site and carries with it a tenfold increased risk of rebleeding. Additional signs and symptoms of aSAH include nausea with or without vomiting, stiff neck, photophobia, cranial nerve palsies and other focal neurological deficits, and seizures, up to and including the loss of consciousness. Individual variation in the signs and symptoms is common leading to high incidence of misdiagnosis or delayed diagnosis. This can occur in up to

P. Britell
Department of Anesthesia and Perioperative Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: britell@musc.edu

C. Andrews · N. Kapoor
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: andrewscm@musc.edu; kapoorn@musc.edu

J. A. Chalela (✉)
Department of Neurology and Neurosurgery, Neurosciences Intensive Care Unit, Medical University of South Carolina, Charleston, SC, USA
e-mail: chalela@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_5

12% of patients [12, 13]. Patients misdiagnosed at initial presentation have a four times greater likelihood of death or significant disability at 1 year [12].

Diagnosis of Aneurysmal Subarachnoid Hemorrhage

A non-contrast head CT scan is highly sensitive for subarachnoid hemorrhage, reaching close to 100% sensitivity in the initial 3–5 days after aSAH [14]. In patients with a negative head CT but high suspicion for aSAH, lumbar puncture should be performed to look for xanthochromia. Brain magnetic resonance imaging (MRI) sequences, specifically fluid-attenuated inversion recovery (FLAIR), diffusion-weighted images (DWI), and gradient echo (GRE) sequences, are also shown to have high sensitivity for subarachnoid hemorrhage and can replace the role of lumbar puncture when CT scan is negative [15, 16]. Patients with aneurysmal subarachnoid hemorrhage should be admitted and treated in a neurointensive care unit with availability of a neurointensivist, a neurosurgeon, and an endovascular team. Multiple studies have shown that treatment in high-volume centers are associated with better outcomes in patients with aSAH, and it is recommended that such patients be transferred from low-volume centers to high-volume tertiary care centers as early as possible [17, 18].

Digital subtraction angiography (DSA) is widely used for characterization and investigation of ruptured cerebral aneurysms. This will be discussed later in this chapter. Recent advances in CT angiography (CTA) have allowed initial aneurysm detection using CTA. This can be followed by catheter angiography if endovascular therapy of the aneurysm is considered. However, aneurysms less than 3 mm in size are hard to visualize on CTA, and DSA should be considered in the CTA-negative aSAH patient if there is a diffuse aneurysmal pattern of bleeding, especially when accompanied with loss of consciousness [19–22]. CTA is considered sufficient if the aneurysm will be treated with surgical clipping.

Grading of Aneurysmal Subarachnoid Hemorrhage

Grading of aSAH can be based on several scales. The Hunt and Hess scale (HHS) and World Federation of Neurological Surgeons (WFNS) scale are the two most common and validated scales used to grade the clinical severity of aSAH (Table 5.1). It is important to determine the initial clinical severity as this has important implications for prognosis following aSAH.

In contrast to the Hunt and Hess scale, the Fisher scale (FS) and modified Fisher scale (mFS) are best known scales to assess the amount of blood seen on CT scan following aSAH and are useful in predicting the occurrence and frequency of vasospasm and should be assessed upon initial encounter.

Table 5.1 Hunt and Hess scale and World Federation of Neurological Surgeons scale

Grade	Hunt and Hess	WFNS
1	Asymptomatic or minimal headache. Slight nuchal rigidity	GCS 15, no motor deficit
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	GCS 13–14, no motor deficit
3	Drowsy, confusion, or mild focal neurological deficit	GCS 13–14, with motor deficit
4	Stupor, moderate to severe hemiparesis. Early decerebrate rigidity and vegetative disturbances	GCS 7–12, with or without motor deficit
5	Deep coma, decerebrate rigidity, moribund appearance	GCS 3–6, with or without motor deficit

Cerebral Vasospasm, Delayed Cerebral Ischemia, and Delayed Ischemic Neurologic Deficits

Vasospasm is the most severe and disabling complication of aSAH, and therefore special attention must be given to it. Defined as a temporary focal or diffuse narrowing of the cerebral blood vessels due to contraction of arterial smooth muscle, it is the leading cause of disability in aSAH [23]. The occurrence of vasospasm after aSAH has been recognized for over a century [24]. Vasospasm affects up to 70% of patients but only results in delayed ischemic neurologic deficit (DIND) in 25–30% of patients [23, 25]. Vasospasm usually ensues on post bleed day 3, peaks around day 6–8, and subsides by day 12 [23, 25, 26]. Risk factors for vasospasm include female gender, history of hypertension, smoking, cocaine use, poor aSAH grade, the amount of aSAH (based on the modified Fisher score), and the presence of intraventricular hemorrhage [23, 26, 27].

Vasospasm is largely a result of local microvascular dysfunction from multiple molecular factors leading to overwhelming vasoconstrictive effects [28]. It should be noted that delayed cerebral ischemia (DCI) or delayed ischemic neurologic deficits (DIND) are often the result of vasospasm and largely determine morbidity and mortality in subarachnoid hemorrhage. Surveillance for vasospasm has the opportunity to detect early microvascular and macrovascular changes and potentially avoid cerebral ischemia and worse outcomes. There are a multitude of ways to detect vasospasm each with their own strengths and weaknesses.

Transcranial Doppler

Transcranial Doppler (TCD) is the most widely used surveillance tool for the diagnosis of cerebral vasospasm as it is economical, noninvasive, and portable and can be repeated frequently. The basic principle for TCD is that as the arteries narrow, blood flow velocity within the examined vessel increases. It is suited mainly for examination of the proximal intracranial vessels (middle cerebral artery). In general

very low velocities (<120 cm/sec) or very high velocities (>200 cm/sec) tend to be better predictors of the absence or presence of vasospasm compared to intermediate values [23, 29]. The Lindegaard ratio, a relation between extracranial internal carotid velocity and ipsilateral middle cerebral artery velocity, helps distinguish between hyperemia (ratio ≤ 3) and vasospasm (ratio > 3). Limitations of TCD include that it is operator-dependent, requires adequate acoustic windows, and does not examine the distal portions of the cerebral arteries [23].

Digital Subtraction Angiography

The gold standard for detecting vasospasm remains digital subtraction angiography (DSA). This allows direct visualization of vessel caliber and typical comparison with preexisting images if the patient's aneurysm was coiled. This method, though is highly invasive, requires transfer of the patient out of the ICU and includes risks inherent with catheterization of cerebral vessels. It does, on the other hand, have the possibility of direct treatment once vasospasm is detected. Typically, this is done with angioplasty and/or intra-arterial vasodilators, but this will be further discussed later. This procedure may be done as routine screening, but given the risks of this procedure, it mostly commonly is done when there is a high suspicion of vasospasm [29].

Perfusion Imaging

As opposed to TCD which detects cerebral blood flow velocity, CT angiography (CTA) directly images the intracranial vessels. The addition of computed tomography perfusion (CTP) provides quantitative perfusion parameters of cerebral blood flow in milliliters per 100 g/min, cerebral blood volume, and mean transit time [30, 31]. Low cerebral blood flow, prolonged mean transit time, and prolonged mean transit time signal irreversible ischemia (Fig. 5.1). Cerebral ischemia can be detected based on side-to-side comparisons or using absolute quantitative thresholds [30]. Penumbral tissue, i.e., reversible ischemia (preserved cerebral blood volume with low cerebral blood flow), can be detected with CTP. The limitations of CTA/CTP include the need to transport the patient to the radiology department, artifact resulting from coils or clips, and the use of iodinated, potentially nephrotoxic contrast materials. Magnetic resonance imaging can be used in an analogous manner to CTA/CTP and may detect ischemia very early on even before frank vasospasm occurs [31, 32]. Unfortunately, many patients with aSAH are unstable and cannot undergo magnetic resonance imaging or have devices that are incompatible with it.

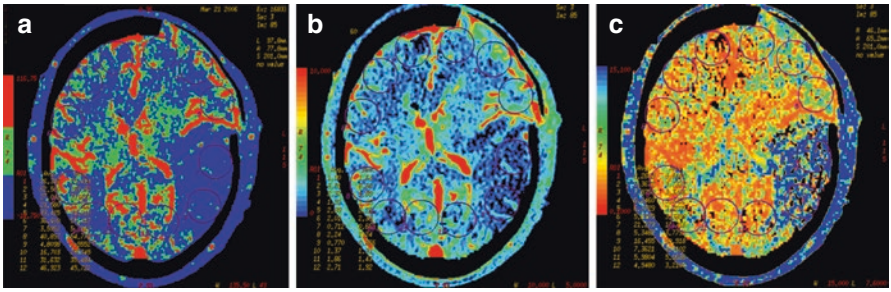


Fig. 5.1 CT perfusion showing decreased cerebral blood flow (**a**) and cerebral blood volume (**b**) as well as prolonged mean transit time (**c**) in a patient with vasospasm in the left middle cerebral artery territory. The patient suffered an infarct in that location

Continuous Electroencephalogram

Continuous electroencephalogram (cEEG) provides a unique means to monitor patients with subarachnoid hemorrhage. While it may primarily be useful in determination of seizures, especially in patients with poor neurologic exams, it also appears highly sensitive at detecting cerebral ischemia. As CBF continues to decrease in regional brain tissue, EEG demonstrates an increase in slower frequencies at these locations and loss of alpha activity. Vespa et al. demonstrated that EEG could detect vasospasm on average almost 3 days prior to TCDs or angiogram [33]. While "raw" EEG interpretation does demonstrate and correlate with cerebral ischemia, it remains intensely time-consuming and is not continuously feasible with most institutions. Quantitative EEG (qEEG), on the other hand, can also determine ischemia and thus vasospasm without the clinical intensity of "raw" EEG. qEEG can determine power of different frequencies and ratios of these frequencies as well. These ratios or percentages of frequencies can also be time compressed and shown in color-mapped digital or spectral arrays, creating easy-to-view, large amounts of data on a single screen [34]. EEG also allows continuous evaluation and monitoring for vasospasm, which few other surveillance methods permit.

Brain Tissue Oxygen Monitoring and Microdialysis

Invasive tissue monitoring can allow us to obtain information regarding microcirculatory changes and regional blood flow. The two most common techniques to monitor the microenvironment are cerebral microdialysis and brain tissue oxygen monitoring (PbO_2). Microdialysis requires placement of a cerebral microcatheter in a region of interest and is capable of monitoring local metabolic markers (mainly glutamate, lactate, and glucose). Microdialysis is capable of determining changes in

these makers suggestive of ischemia before patients become symptomatic with vasospasm. Staub et al. demonstrated that elevated levels of nitrate, lactate, and taurine are all suggestive of poor outcomes in patients with subarachnoid hemorrhage [35]. Placement of the catheter, the extensive labor of microdialysis itself, and its inability for global cerebral monitoring have limited its use [32]. PbO_2 monitoring similarly monitors the microenvironment and has a strong correlation with vasospasm prediction but suffers many of the same limitations as microdialysis.

Jugular Bulb Oximetry

Jugular bulb oximetry can provide continuous monitoring of a global view of CBF. This requires an invasive catheter or bulb to be placed in the jugular vein, in retrograde fashion. The venous oxygen saturation can then be compared with the arterial saturation to yield the oxygen extraction, which can be observed over time [32]. This approach however is not widely used for surveillance given its invasive demands and inconclusive results.

Prevention of Vasospasm

The only approved drug for prevention of vasospasm is oral nimodipine. Nimodipine has been shown to have a statistically significant impact on outcome, albeit the benefit is modest [36]. Nimodipine blocks L-type of calcium channels and prevents calcium influx into the cells. The exact mechanism on how it is neuroprotective is not clear, but it involves more than preventing vasospasm. Nimodipine administration is cited as class IA evidence by the American Stroke Association SAH guidelines [37]. The main side effect of nimodipine is hypotension. This can be avoided by reducing the usual dose of 60 mg q 4 h to 30 mg q 2 h. Other agents tested for the prevention of vasospasm include statins, magnesium, endothelin antagonists, milrinone, and cisternal injections of vasoactive agents. Although promising in animal studies and early clinical studies, they have not been proven to impact functional outcome in humans [23, 25, 29]. Statins are widely used, but the STASH trial failed to show the benefit of simvastatin use [38].

Meticulous critical care management with particular attention to volume status is crucial in preventing vasospasm [37]. Patients should be kept euvolemic to slightly hypervolemic, and sodium levels should be kept within normal range. Cerebral salt-wasting syndrome due to excessive release of brain natriuretic peptide may develop and lead to hyponatremia and hypovolemia. Volume and sodium should be replaced using crystalloids and/or oral sodium tablets, and excessive natriuresis may be ameliorated by administration of oral fludrocortisone. Hyponatremia appears to have at least a temporal association with vasospasm. There is no role for prophylactic

elevation of the blood pressure using pressors or inotropes, but hypotension is best avoided. Hypoxia, hypocarbia, hyperglycemia, fever, infections, seizures, and elevated intracranial pressure should be treated aggressively as they can increase cerebral oxygen consumption and confound the clinical picture [29]. Anemia is common, and although presumably very low hemoglobin may be deleterious in the setting of vasospasm, the ideal transfusion threshold for SAH has not been established [38].

Treatment of Vasospasm

Promptly normalizing cerebral blood flow and restoring neurologic function are the treatment goals in vasospasm. Treatment should be symptom specific, but in poor-grade patients or sedated patients, that may be challenging. An arterial line and a central venous line allow continuous blood pressure monitoring and catecholamine infusion. A blood pressure goal above the baseline blood pressure is set (typically mean arterial pressure 90–110 mm Hg), and the patient is monitored for symptom improvement upon achievement of the desired goal. In recent years this therapy, known in the past as triple-H (hypertensive, hypervolemic, hemodilution), has shifted toward euvolemia with induced hypertension. Invasive hemodynamic monitoring with a transpulmonary thermodilution monitoring catheter (PiCCO Plus, Pulsion Medical Systems SE, Feldkirchen, Germany) and titration of vasopressors and crystalloids based on physiologic variables appear to influence outcome [39]. Cardiac and pulmonary complications (ischemia, pulmonary edema) occur frequently especially in elderly patients. Failure to respond to medical therapy within 2 h should lead to consideration of endovascular therapies [40].

Digital subtraction angiography allows the endovascular surgeon to confirm the presence of vasospasm, grade its severity, and direct treatment to the affected vessels. Endovascular options include administration of vasodilators, use of balloon angioplasty, or a combination of both strategies. The use of papaverine has been abandoned due to its short action and side effect profile and replaced by intra-arterial nicardipine and verapamil, agents that appear to be safe and effective. In general, balloon angioplasty is used for proximal large vessels, and vasodilators are used for distal vessels. Compared to vasodilator infusion, balloon angioplasty has better angiographic results, longer-lasting benefit, and, more importantly, a more robust clinical response [41]. Combination therapy using angioplasty and vasodilator infusion appears to be the best strategy [42]. Figure 5.2 illustrates the dramatic angiographic improvement seen with balloon angioplasty when used with vasodilators. Complications associated with endovascular therapy include hypotension (related to vasodilator use), vessel perforation, distal occlusion, hemorrhagic infarction, arterial dissection, and rupture of unsecured aneurysms [42]. The angiographic success rate is close to 100%, but the clinical response is slightly lower highlighting the multifactorial etiology of delayed ischemic deficit.

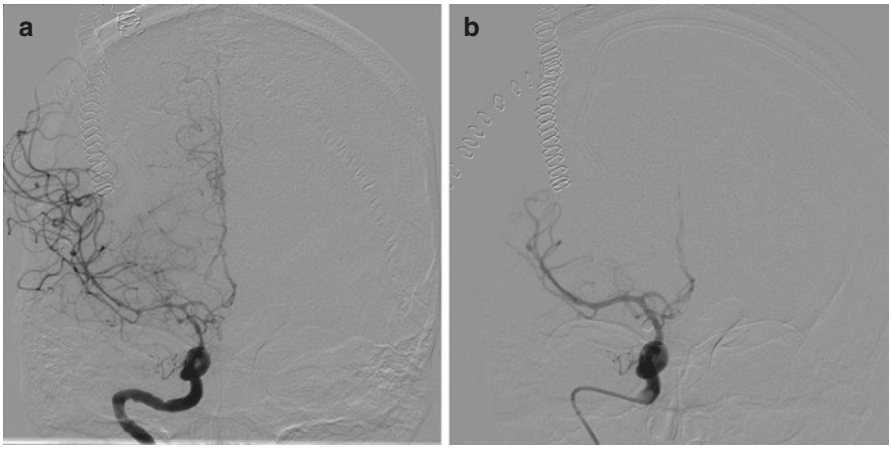


Fig. 5.2 Cerebral angiogram showing severe vasospasm in the distal carotid artery as well as in the middle cerebral artery and anterior cerebral artery (**a**). Following balloon angioplasty and verapamil infusion, there is restoration of vessel diameter to baseline level (**b**)

Other Neurologic Complications of aSAH

Rebleeding in patients with aSAH is associated with a high mortality and poor prognosis. The first 2–12 h after the rupture of aSAH is associated with maximal risk of rebleeding [43–47]. It is estimated that between 4% and 13% of patients will rebleed within 24 h.

Factors leading to an increased incidence of rebleeding include longer time to aneurysm treatment, high Hess and Hunt or WFNS grades, occurrence of sentinel headache, larger aneurysm size, and systolic blood pressure > 160 mmHg [46]. Due to the high risk of rebleeding associated with delayed treatment, every effort should be made to obtain definitive treatment of the aneurysm as early as possible.

Antifibrinolytic agents such as aminocaproic acid and tranexamic acid are often times used to reduce the incidence of aneurysm rebleeding when there is delay in securing the aneurysm [48]. These agents should only be used for a short term (<72 h), as they are known to increase the risk of myocardial infarction, DVT, and pulmonary embolism.

Acute Hydrocephalus

Acute hydrocephalus is a common complication in aSAH occurring in 15–90% of patients. Acute hydrocephalus associated with aSAH is treated with external ventricular drainage (EVD). Often, neurological improvement can be seen immediately in patients after the insertion of EVD. There is a small risk of aneurysm rebleeding after EVD insertion due to removal of the tamponade effect from hydrocephalus [49].

Seizures

Patients with aSAH have a high incidence of seizure or seizure-like episodes. Up to 26% of patients can present these episodes, although it is controversial if they are epileptic in nature [50, 51]. Delayed-onset seizures are seen in a smaller subset (3–7%) of patients [52]. Risk factors for the development of seizures in aSAH include rupture of middle cerebral artery, rupture of an anterior communicating artery aneurysm, high-grade Fisher or modified Fisher scale, intraparenchymal hematoma, prior history of seizures, rebleeding, or a history of hypertension [53–55]. The type of aneurysmal treatment also seems to influence the rate of periprocedural seizure development. Endovascular treatment carries a lower risk of seizure development compared to surgical clipping [56].

Nonconvulsive status epilepticus was found to have a strong correlation with poor outcome in two large single-institute retrospective studies [57, 58]. Routine long-term use of anticonvulsants in aSAH patients is not recommended unless there is definitive evidence of epileptic activity seen on EEG monitoring, but short-term (usually 7 days) prophylactic therapy is commonly used in many high-volume centers, especially in patients with high-grade aSAH. The prophylactic use is based on the presumption that seizures in an acutely ill patient with high-grade aSAH can either cause additional injury or higher chance of rebleeding.

Medical Complications Following Subarachnoid Hemorrhage

Cardiac Dysfunction

Cardiac dysfunction can occur in 20–30% of aSAH patients. Generally, cardiac dysfunction following aSAH can be classified as either neurogenic stunned myocardium (NSM) or stress-induced cardiomyopathy (also called Takotsubo cardiomyopathy) [59]. Despite the fact that traditionally in neurogenic stunned myocardium ballooning occurs at the base of the heart, while in stress-induced cardiomyopathy ballooning occurs apically, their etiology is similar in that they are caused by excess catecholamines at the level of the cardiac myocyte [60]. This catecholamine excess is mediated by complex pathways related to increased intracranial pressure and the activation of neuroendocrine pathways.

Manifestations can include arrhythmia, wall motion abnormalities, and troponin I elevations. Coronary angiography is rarely indicated as the majority of these changes are not related to coronary artery disease.

Treatment for cardiac dysfunction related to subarachnoid hemorrhage is largely supportive. Initially, in the setting of catecholamine excess, hypertension will predominate. Controlling the blood pressure is paramount in preventing re-rupture until the aneurysm has been secured. While variation occurs between centers, it is generally accepted to maintain systolic blood pressure less than 160 mmHg.

Easily titratable intravenous vasodilators such as nicardipine and clevidipine are ideal for this task.

However, as the natural course progresses, hypotension ensues secondary to unopposed vasodilation and cardiac dysfunction. As discussed previously, in cerebral vasospasm it may be necessary to augment systolic blood pressure with vasopressors or inotropes due to cardiac dysfunction. Small unruptured aneurysms should not be a contraindication vasopressor-induced hypertension in the setting of vasospasm [61].

Pulmonary Dysfunction

Mechanical ventilation in a SAH is generally necessitated by the need for airway protection or hypoxia. Pulmonary dysfunction affects a significant proportion of subarachnoid patients with up to 27% incidence of acute lung injury (PaO_2 to FiO_2 ratio of less than 300) [62]. These patients should be managed with low tidal volume ventilation (6 ml/kg) based on predicted body weight according to ARDSNET protocol [63]. Plateau pressures should be kept less than 30 cm H_2O. Permissive hypercapnia while generally tolerated in the ARDS population is a matter of controversy in the neurocritically ill. Hypercapnia will increase cerebral vasodilation and can increase ICP. However, a small study by Westermaier et al. found that therapeutic hypercapnia up to 60 mmHg resulted in a reproducible increase of CBF and tissue oxygenation [64]. However, the effect of hypercapnia on clinical outcome remains unclear. Even in the setting of pulmonary edema, diuresis should be used with extreme caution to avoid hypovolemia in the aSAH patient as this can exacerbate vasospasm.

Hyponatremia

Fifty percent of patients admitted with subarachnoid hemorrhage will develop hyponatremia [65]. Previously, it was thought that most hyponatremia in the setting of aSAH was related to cerebral salt wasting (CSW). While similar to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in that patients will have a low plasma osmolality (<280mOSM/Kg), inappropriate urinary concentration (>100mOSM), and elevated urine sodium (>40 mmol/L), in cerebral salt wasting the patient will be also be hypovolemic. It was initially postulated that a rise in atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) following aSAH mediates the loss of sodium in these patients. However, it is becoming more apparent that a large segment of patients who were initially thought to be in CSW are actually either in a combination of CSW and SIADH or are experiencing acute ACTH deficiency [65].

The treatment of hyponatremia should be directed at its etiology, i.e., determining serum osmolality, urine osmolality, and urine sodium concentration. However, based on the consensus guidelines from the Neurocritical Care Society, fluid restriction should not be used in SIADH in the setting of aSAH [66]. However, free water can be limited through enteral routes as mild hypertonic solutions are used to correct hyponatremia. Caution should be used not to correct hyponatremia too abruptly. Vasopressin receptor antagonists can be used with "extreme caution to avoid hyponatremia" per the NCS guidelines [66]. Additionally, hydrocortisone or fludrocortisone can be used to limit natriuresis.

Hyperglycemia

Admission of hyperglycemia has been associated with poor-grade aSAH. Elevated serum glucose has also been associated with an increase in incidence of vasospasm. Liberal glucose management >220 mg/dL has been associated with increased risk of infection, while tighter glucose control 80–110 mg/dL has been associated with more episodes of hypoglycemia. These episodes of hypoglycemia were also associated with an increased incidence of vasospasm and poorer 3-month outcomes [67]. It appears that extremes of range should be avoided. Blood glucose should be kept less than 200 mg/dL to avoid the increase in infectious complications and more than 80 mg/dL to avoid incidences of hypoglycemia [68].

Infection and Pyrexia

Fevers occur frequently in the SAH patient and are independently associated with poor outcome. Although in aSAH fevers are more likely associated with a systemic inflammatory reaction than an infectious etiology, it is still important to clinically assess and treat infectious etiologies accordingly [68]. Procalcitonin and C-reactive protein can be useful in delineating an infectious from a noninfectious etiology and guiding antibiotic therapy [69].

Regardless of etiology, fevers need to be controlled. First-line treatment using intermittent dosing of acetaminophen or NSAIDs can help to control fever. However, when this is ineffective, surface cooling with fans, cooling blankets, or ice packs can be employed. But the most effective way to reduce the temperature of a febrile aSAH patient remains the utilization of noninvasive targeted temperature management systems such as the Arctic Sun (Bard Medical). The main drawback of these systems is the cost and increased incidence of shivering.

Shivering can increase basal metabolic up to fivefold leading to a decrease in brain tissue oxygenation and therefore must be controlled [70]. Methods of control

include intravenous magnesium, skin surface counter warming, propofol infusion, and buspirone. Other medications such as meperidine are effective but have a more undesirable side effect profile. In extreme situations, neuromuscular blockade can be employed.

Deep Venous Thrombosis

aSAH is a prothrombotic state, and the incidence of deep venous thrombosis can be up to 18%. There is little dispute that sequential compression devices should be used in all subarachnoid hemorrhage patients. Based on consensus recommendations, unfractionated heparin can be started 24 h. Screening lower extremity ultrasound can be effective in early detection and should be considered in patients at high risk of developing DVT [71].

The Role of Neurocritical Care

Neurocritical care is a relatively new specialty (compared to many fields of training) but one that was born out of necessity over the past several decades. Formal training did not begin until the 1980s and the Society of Neurocritical Care was not formed until 2002. Still in this short time of existence, the specialty has made its mark on both neurological and neurosurgical care.

The rise and specialization of neurocritical care have greatly affected the outcomes of the aSAH patient. Josephson et al. demonstrated that a neurointensivist decreased the length of stay for aneurysmal subarachnoid hemorrhage patients and also reduced the number of patients requiring ventriculoperitoneal shunt placement [72]. Additionally, an increased percentage of patients were sent home or to rehab [73]. A decreased length of stay has been shown in multiple studies [18, 74]. Lerch et al. published on the fact that despite more severe-grade patients in their historical analysis, they experienced improved outcomes with a standardized neurocritical care treatment. They highlighted the importance of neuro-resuscitation (prior to aneurysm securement), treatment of brain edema, elevated ICP, detection and treatment of cerebral vasospasm, and treatment of medical complications as the keys to better outcomes [75]. It has been demonstrated that medical complications have a large impact on patient outcomes and that critical care strategies to prevent these may lead to improvements in patient outcomes [76]. Neurocritical care, thus, appears to reduce length of stay, improve patient outcomes, and result in reduced costs to a large proportion of patients in these units.

The impact of specialized neurocritical care is attributable to much more than the physicians and mere creation of the specialty. Like other specialty ICUs, the staff, nurses, respiratory therapists, and pharmacists deserve as much recognition for their expertise and advancement of care of the aSAH patient.

References

1. Feigin VL, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
2. Schievink WI, et al. Sudden death from aneurysmal subarachnoid hemorrhage. Neurology. 1995;45(5):871–4.
3. Truelsen T, et al. Changes in subarachnoid hemorrhage mortality, incidence, and case fatality in New Zealand between 1981–1983 and 1991–1993. Stroke. 1998;29(11):2298–303.
4. Ingall T, et al. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000;31(5):1054–61.
5. Mahindu A, et al. Similarities and differences in aneurysmal subarachnoid haemorrhage between eastern Finland and northern Sydney. J Clin Neurosci. 2008;15(6):617–21.
6. Shea AM, et al. Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003. Neurosurgery. 2007;61(6):1131–7. discussion 1137-8.
7. Vadikolias K, et al. Incidence and case fatality of subarachnoid haemorrhage in Northern Greece: the Evros Registry of Subarachnoid Haemorrhage. Int J Stroke. 2009;4(5):322–7.
8. Bassi P, et al. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand. 1991;84(4):277–81.
9. de Falco FA. Sentinel headache. Neurol Sci. 2004;25(Suppl 3):S215–7.
10. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23(10):935–41.
11. Jakobsson KE, et al. Warning leak and management outcome in aneurysmal subarachnoid hemorrhage. J Neurosurg. 1996;85(6):995–9.
12. Kowalski RG, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. JAMA. 2004;291(7):866–9.
13. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306–18.
14. Cortnum S, Sorensen P, Jorgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. Neurosurgery. 2010;66(5):900–2. discussion 903.
15. Fiebach JB, et al. MRI in acute subarachnoid haemorrhage; findings with a standardised stroke protocol. Neuroradiology. 2004;46(1):44–8.
16. Shimoda M, et al. Problems with diagnosis by fluid-attenuated inversion recovery magnetic resonance imaging in patients with acute aneurysmal subarachnoid hemorrhage. Neurol Med Chir (Tokyo). 2010;50(7):530–7.
17. Bardach NS, et al. Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke. 2002;33(7):1851–6.
18. Varelas PN, et al. The impact of a neuro-intensivist on patients with stroke admitted to a neurosciences intensive care unit. Neurocrit Care. 2008;9(3):293–9.
19. Donmez H, et al. Comparison of 16-row multislice CT angiography with conventional angiography for detection and evaluation of intracranial aneurysms. Eur J Radiol. 2011;80(2):455–61.
20. McCormack RF, Hutson A. Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? Acad Emerg Med. 2010;17(4):444–51.
21. McKinney AM, et al. Detection of aneurysms by 64-section multidetector CT angiography in patients acutely suspected of having an intracranial aneurysm and comparison with digital subtraction and 3D rotational angiography. AJNR Am J Neuroradiol. 2008;29(3):594–602.
22. Dupont SA, et al. The use of clinical and routine imaging data to differentiate between aneurysmal and nonaneurysmal subarachnoid hemorrhage prior to angiography. Clinical article. J Neurosurg. 2010;113(4):790–4.
23. Baggott CD, Aagaard-Kienitz B. Cerebral vasospasm. Neurosurg Clin N Am. 2014;25:497–528.
24. Gull SW. Cases of aneurysm of the cerebral vessels. Guys Hospital Reports. 1859;5:281–304.
25. Umamaheswara Rao GS, Muthuchellappan R. Cerebral vasospasm: current understanding. Curr Opin Anesthesiol. 2015;29:554–1.

26. Stein SC, Levine JM, Nagpal S, et al. Vasospasm as the sole cause of cerebral ischemia: how strong is the evidence? Neurosurg Focus. 2006;21(3):E2.
27. Machdonald RL, Rosengart A, Huo D, et al. Factors associated with vasospasm after planned surgical treatment of subarachnoid hemorrhage. J Neurosurg. 2003;99:644–52.
28. Janjua N, Mayer SA. Cerebral vasospasm after subarachnoid hemorrhage. Curr Opin Crit Care. 2003;9(2):113–9.
29. Findlay JM, Nisar J, Darsaut T. Cerebral vasospasm: a review. Can J Neurol Sci. 2016;43:15–32.
30. Rordorf G, Koroshetz WJ, Copen WA, Gonzalez G, Yamada K, Schaefer PW, et al. Diffusion- and perfusion-weighted imaging in vasospasm after subarachnoid hemorrhage. Stroke. 1999;30:599–605.
31. Frontera JA, Ahmed A, Zach V, et al. Acute ischaemia after subarachnoid haemorrhage, relationship with early brain injury and impact on outcome: a prospective quantitative MRI study. J Neurol Neurosurg Psychiatry. 2015;86:71–8.
32. Kistka H, Dewan MC, Mocco J. Evidence-based cerebral vasospasm surveillance. Neurol Res Int. 2013;2013:256713.
33. Vespa PM, et al. Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. Electroencephalogr Clin Neurophysiol. 1997;103(6):607–15.
34. Foreman B, Claassen J. Quantitative EEG for the detection of brain ischemia. Crit Care. 2012;16(2):216.
35. Staub F, et al. Multiple interstitial substances measured by microdialysis in patients with subarachnoid hemorrhage. Neurosurgery. 2000;47(5):1106–15.
36. Dorhout Mees SM, Rinkel GJE, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid hemorrhage. Stroke. 2009;39:514–5.
37. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage – a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:1711–37.
38. Kirkpatrick PJ, Turner CL, Smith C, et al. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014;13:666–75.
39. Yoneda H, Nakamura T, Shirao S, et al. Multicenter prospective cohort study on volume management after subarachnoid hemorrhage. Hemodynamic changes according to severity of subarachnoid hemorrhage and cerebral vasospasm. Stroke. 2013;44:2155–61.
40. Rosenwasser RH, Armonda RA, Thomas JE, et al. Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options. Neurosurgery. 1999;44:975–9.
41. Kerz T, Boor S, Ulrich A, et al. Endovascular therapy for vasospasm after aneurysmatic subarachnoid hemorrhage. British J Neurosurg. 2016;30(5):549–53.
42. Brisman JL, Eskridge JM, Newell DW. Neurointerventional treatment of vasospasm. Neurol Res. 2006;28:769–76.
43. Hillman J, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg. 2002;97(4):771–8.
44. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the cooperative aneurysm study. Neurosurgery. 1983;13(5):479–81.
45. Naidech AM, et al. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch Neurol. 2005;62(3):410–6.
46. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke. 2001;32(5):1176–80.
47. Tanno Y, et al. Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan. A cooperative study. J Neurol Sci. 2007;258(1–2):11–6.
48. Starke RM, et al. Endothelial nitric oxide synthase gene single-nucleotide polymorphism predicts cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2008;28(6):1204–11.

49. Hellingman CA, et al. Risk of rebleeding after treatment of acute hydrocephalus in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2007;38(1):96–9.
50. Gilmore E, et al. Seizures and CNS hemorrhage: spontaneous intracerebral and aneurysmal subarachnoid hemorrhage. Neurologist. 2010;16(3):165–75.
51. Hart RG, et al. Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms. Neurosurgery. 1981;8(4):417–21.
52. Rhoney DH, et al. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology. 2000;55(2):258–65.
53. Ukkola V, Heikkinen ER. Epilepsy after operative treatment of ruptured cerebral aneurysms. Acta Neurochir. 1990;106(3–4):115–8.
54. Choi KS, et al. Seizures and epilepsy following aneurysmal subarachnoid hemorrhage: incidence and risk factors. J Korean Neurosurg Soc. 2009;46(2):93–8.
55. Lin CL, et al. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2003;99(6):978–85.
56. Byrne JV, et al. Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization. Neurosurgery. 2003;52(3):545–52. discussion 550-2.
57. Dennis LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery. 2002;51(5):1136–43. discussion 1144.
58. Little AS, et al. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. J Neurosurg. 2007;106(5):805–11.
59. Krishnamoorthy V, et al. Cardiac Dysfunction after neurologic injury. What do we know and where are we going. Chest. 2016;149(5):1325–31.
60. Wittstein IS, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
61. Reynolds MR, et al. The safety of vasopressor-induced hypertension in subarachnoid hemorrhage patients with coexisting unruptured, unprotected intracranial aneurysms. J Neurosurg. 2015;123:862–71.
62. Kahn JM, et al. Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors and outcome. Crit Care Med. 2006;34(1):196–202.
63. 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;342:1301–8.
64. Westermaier T, et al. Controlled hypercapnia enhances cerebral blood flow and brain tissue oxygenation after aneurysmal subarachnoid Hemorhage; results of a phase 1 study. Neurocrit Care. 2016;25:205–14.
65. Hannon MJ, Thompson CJ. Neurosurgical hyponatremia. J Clin Med. 2014;3:1084–104.
66. Diringer MN, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care society's multidiciplinary consensus conference. Neurocrit Care. 2011;15:211–40.
67. Naidech AM, et al. Moderate hypoglycemia is associated with vasospasm, cerebral infarction and 3 month disability after subarachnoid hemorrhage. Neuro Crit care. 2010;12:181–7.
68. Oliveria-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology. 2011;56:1299–304.
69. Limper M, de Kruif MD, Druits AJ, et al. The diagnostic role of procalcitonin and other biomarkers in descriminating infectious from noninfections fever. J Infect. 2010;60(6):409–16.
70. Badjatia N, Strongolis E, Gordon E, et al. Metabolic impact of shivering during theraputic temperature modulation: the bedside shivering assessment scale. Stroke. 2008;39:3242–7.
71. Mack WJ, Ducruet AF, Hickman ZL, et al. Doppler ultrasonography screening of poor-grade subarachnoid patients increases the diagnosis of deep venous thrombosis. Neurol Res. 2008;30:889–92.

72. Josephson SA, et al. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management. J Neurosurg. 2010;112(3):626–30.
73. Samuels O, et al. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;14(3):334–40.
74. Knopf L, et al. Impact of a neurointensivist on outcomes in critically ill stroke patients. Neurocrit Care. 2012;16(1):63–71.
75. Lerch C, et al. Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2006;5(2):85–92.
76. Wartenberg KE, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Crit Care Med. 2006;34(3):617–23. quiz 624.

Chapter 6
Clip Versus Coil Debate

Donnie L. Bell, Ronil V. Chandra, Thabele M. Leslie-Mazwi, and Joshua A. Hirsch

Intracranial aneurysms were first described in the late eighteenth century by Giovanni Morgagni and Biumi of Milan. Initial attempts at treatment of these lesions were cervical artery ligation, wrapping, thrombosis induction (utilizing hairs, electrical current, iron fillings), and ligatures in the early twentieth century. Later in 1937, Walter Dandy pioneered surgical clipping for the treatment of intracranial aneurysms. Since that time, surgical clipping remained the standard treatment for saccular aneurysms, until 1974, when Serbinenko et al. ushered in endovascular treatment with detachable balloon occlusion of these lesions. Later in 1991, the introduction of the Guglielmi detachable coil for the treatment of saccular aneurysms in high-risk surgical candidates offered an endovascular alternative with improved deployment precision and durability [1, 2]. Endovascular techniques for treating both saccular and fusiform aneurysms have steadily evolved, and the number and complexity of intracranial aneurysms amenable to endovascular coiling have grown. As such, several attempts have been made to compare the efficacy and outcomes of microsurgical clipping and endovascular coiling of ruptured as well as unruptured intracranial aneurysms. In this chapter, we will review the literature comparing the two techniques and examine current trends in treatment at tertiary care centers. Finally, we will explore newer endovascular devices and microsurgical

D. L. Bell (✉)
Department of Radiology and Neurology, Kings County Hospital Center/SUNY Downstate Medical Center, Brooklyn, NY, USA

R. V. Chandra
Interventional Neuroradiology, Department of Imaging, Monash Health and Monash University, Melbourne, VIC, Australia
e-mail: ronil.chandra@monash.edu

T. M. Leslie-Mazwi · J. A. Hirsch
Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA
e-mail: tleslie-mazwi@mgh.harvard.edu; jahirsch@partners.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_6

approaches for treating intracranial aneurysms. The long-standing microsurgical clipping versus endovascular coiling debate has now expanded with the advent of these novel devices and approaches.

Evidence for Microsurgical Clipping Versus Endovascular Coiling

The majority of the evidence for treatment efficacy and outcomes for ruptured intracranial aneurysms arises from three major randomized controlled trials including Vanninen et al., the international subarachnoid aneurysm trial (ISAT), and the Barrow ruptured aneurysm trial (BRAT) as well as the continued follow-up of these trials; it should be noted that to date, a randomized controlled trial comparing endovascular coiling and microsurgical clipping in unruptured intracranial aneurysms has not been completed and unruptured lesions will be discussed separately. Although the randomized controlled trials for ruptured lesions are not without limitations taken together, they have formed the basis for patient selection, treatment decision-making, and prognostication for ruptured intracranial aneurysms, excluding more recent advances and including the introduction and adoption of balloon- and stent-assisted coiling, flow diversion, and other novel approaches that will be discussed later. Notably, these trials utilized first-generation bare platinum coils; although second-generation coated coils have been since introduced, a meta-analysis of their use does not suggest improved occlusion rates [3]. Additionally, numerous observational studies have contributed to our understanding of the treatment of ruptured intracranial aneurysms.

The first randomized trial comparing microsurgical clipping and endovascular coiling was by Vanninen et al. in 1999. This was a single-center trial of ruptured intracranial aneurysms presenting <72 h from ictus where 52 aneurysms were coiled and 57 clipped. In the trial, no significant differences in clinical or neurophysiologic outcomes at 3 months and 1 year were found [4, 5]. The second randomized trial, ISAT, completed in 2002, now with 10 years of follow-up, demonstrated both short-term improved dependency and death with coiling yet a significantly higher rebleeding rate from the target aneurysm of roughly 2% with coiling [6]. ISAT also demonstrated a robust neuropsychiatric benefit of coiling as compared to clipping with an odds ratio of 0.58, $p < 0.01$ [7]. The findings of ISAT have been critiqued however due to concerns regarding the level of expertise of the neurosurgeons involved in the study, inclusion of primarily low-grade patients with anterior circulation aneurysms, lack of consistent intraoperative and follow-up angiography, and concerns regarding statistical methodology [8]. Currently, ISAT II is underway to compare the two treatment modalities in a greater variety of clinical grades, aneurysm locations, and lesion complexity [9]. The most recent randomized trial, BRAT, completed in 2007, now with 6 years of follow-up, revealed improved outcomes with coiling in posterior circulation aneurysms with 70% of coiling versus 40% of clipping patients having a favorable outcome, lower complete obliteration rates with

coiling (48%) versus clipping (96%) yet no rebleeding within the trial follow-up period, and higher retreatment rates for coiling (16.4%) versus clipping (4.6%). Additionally, BRAT demonstrated no differences in shunt-dependent hydrocephalus between microsurgical clipping and endovascular coiling [10]. One of the main limitations of BRAT was the 38% crossover rate of patients initially assigned to coiling and clipping, due to enrollment of patients regardless of whether their aneurysms were amenable to both treatment modalities, yet the study still demonstrated an advantage for coiling [11].

A recent meta-analysis of these randomized trials demonstrated improved outcomes with coiling with an absolute risk reduction of poor outcome by 7.8% [12]. Further, a recent comparative effectiveness study that included 5229 patients with ruptured aneurysms, 1228 clipped, and 4001 coiled demonstrated a decreased frequency of clipping from 27% to 21% between 2006 and 2011 and improved outcomes and complication rates with coiling [13]. However, these investigations and trends only partially aid in the decision-making process for patient selection and treatment modality in an individual patient, where age, aneurysm location and morphology, other comorbidities, and newer treatment modalities influence treatment choice. The American Heart Association (AHA) and European Stroke Organisation guidelines for management of aneurysmal subarachnoid hemorrhage recommend that older patients, poor clinical grade following rupture, those with comorbidities precluding surgery, small aneurysm neck, and posterior circulation aneurysms are better candidates for coiling; alternatively, readily accessible anterior circulation aneurysms, younger patients, or aneurysms associated with large intraparenchymal hematomas are better candidates for microsurgical clipping [14, 15]. Other factors that have traditionally favored specific treatment modalities in both the ruptured and unruptured setting include aneurysm-associated oculomotor cranial nerve palsy and arteries arising from the aneurysm dome favoring microsurgical clipping, while aneurysmal wall calcification favors endovascular coiling [16, 17]. Additionally, in the Cerebral Aneurysm Rerupture After Treatment (CARAT) study, intraprocedural rupture was more common in the microsurgical clipping group occurring in 19% of patients as opposed to 5% with endovascular coiling; however, rerupture-associated morbidity/mortality was doubled with coiling 63% versus 31% with clipping [18].

To date, no randomized controlled clinical trial has been completed to evaluate microsurgical clipping versus endovascular coiling for unruptured intracranial aneurysms. Due to the results of the international study of unruptured intracranial aneurysms (ISUIA) trial originally published in 2003 and reanalyzed in 2014 demonstrating improved outcomes at 1 year in older patients (>50 years) and posterior circulation aneurysms, advances in endovascular treatment, and large prospective and retrospective clinical trials, endovascular coiling of unruptured intracranial aneurysms has become the preferred treatment option. Between 2001 and 2008, coiling outpaced clipping with 34,054–29, 866 cases, respectively [19]. A recent large retrospective study comparing microsurgical clipping and endovascular coiling of unruptured intracranial aneurysms between 2006 and 2011 totaling 4899 patients demonstrated similar mortality yet increased morbidity (discharge to long-term care facilities; ischemic, hemorrhagic, and neurologic complications; and

ventriculostomy) with microsurgical clipping [20]. The AHA 2015 guidelines for the management of unruptured intracranial aneurysms regarding microsurgical clipping versus endovascular coiling suggest both treatments are effective yet with endovascular coiling resulting in improved outcomes albeit with a higher risk of aneurysm recurrence. Further, the guidelines recommended that patients be counseled concerning the risks and benefits of microsurgical clipping and endovascular coiling [21].

Given the increased scrutiny on healthcare affordability, it is also worth considering the cost-effectiveness of microsurgical clipping and endovascular coiling. Although endovascular coiling appears to be more cost-effective than microsurgical clipping at the time of treatment due to decreased periprocedural complications and shorter length of stay, over time the costs are thought to equilibrate due to increased follow-up and retreatment associated with coiling [22].

Treatment Approaches at Tertiary Care Centers

Tertiary care centers are distinguished by their specialization, higher procedural volumes, and greater case complexity, and as such, they are often referral centers. In these settings, the most advanced treatment modalities are available, both prior to regulatory approval in the setting of institutional review board (IRB)-approved clinical trials and following approval of the newest devices.

At these centers, the clip versus coil debate is expanding for both ruptured and unruptured intracranial aneurysms. With the advent of stent- and balloon-assisted coiling, flow diversion, and hybrid approaches appropriating coils and flow diversion as well as other novel devices, the number and complexity of intracranial aneurysms amenable to endovascular treatment, namely, wide-necked, small, giant, partially thrombosed, and fusiform, have significantly increased. Notably, the majority of these devices were approved or widely used after completion of the three randomized controlled trials comparing microsurgical clipping and endovascular coiling for ruptured intracranial aneurysms and observational studies for unruptured aneurysms.

Of these new technologies, flow diversion is the most mature. Flow diverters are low-porosity braided endoluminal stent devices that reduce aneurysmal flow thereby promoting progressive aneurysm thrombosis, neck neoendothelialization, and in some instances involution of the aneurysm while maintaining patency of the parent and branch vessels. There are no randomized controlled trials given the recent regulatory approval of flow diverters in April of 2011 in the United States. The literature for these devices is therefore observational and suggests high-occlusion rates for intracranial internal carotid artery aneurysms (>90%), however, with increased complications in large (>10 mm) and posterior circulation aneurysms [23, 24]. The 3-year follow-up results of one of the original trials, the Pipeline for Uncoilable or Failed Aneurysms Trial (PUFS), have further demonstrated the efficacy and long-term durability of flow diversion with an aneurysm occlusion rate of 93% and

no recanalizations [25]. A meta-analysis of 29 studies utilizing flow diverters that included ruptured and unruptured, fusiform and complex, and posterior circulation lesions revealed a 76% complete occlusion rate and morbidity and mortality of 5% and 4%, respectively [26]. Complications due to flow diverter deployment include ischemic stroke (6%), delayed intraparenchymal hemorrhage (3%), endoleak and aneurysm growth, device shortening and/or migration, and delayed aneurysm rupture (3%). Of these, delayed aneurysm rupture and intraparenchymal hemorrhage are the most feared, with a morbidity/mortality rate of ~70–80% [27]. Risk factors include posterior circulation aneurysms, nontherapeutic dual antiplatelet regimens, and large or giant aneurysm size [26, 28]. A recent matched comparison study between endovascular coils and flow diversion for the treatment of saccular intracranial aneurysms that excluded fusiform and anterior communicating artery aneurysms demonstrated improved occlusion rates with flow diversion (86%) versus endovascular coiling (41%) with similar morbidity and mortality and a 34% decrease in retreatment with flow diversion [29]. The EVIDENCE trial, a randomized controlled trial comparing endovascular coiling to flow diversion, is planned [30].

The surgical alternative for the treatment of complex aneurysms including blister aneurysms, fusiform aneurysms, and otherwise unclippable aneurysms includes deconstructive techniques such as parent vessel occlusion with or without bypass and constructive techniques such as clip wrapping. Clip wrapping of complex aneurysms can confer protection against aneurysmal growth and subarachnoid hemorrhage with low morbidity and mortality [31]. However, wrapping may induce foreign body reaction with resultant granuloma formation and neurologic deficits [32]. To limit this, more recently inert wrapping materials such as Gore-Tex (W. L. Gore and Associates Flagstaff, AZ, USA) and collagen-impregnated Dacron (Boston Scientific, Oakland, NJ, USA) have been utilized [33, 34].

Wide-Necked Aneurysms

Prior to the development of balloon- and stent-assisted coiling and flow diversion/disruption, wide-necked aneurysms were not ideal for coiling, and microsurgical clipping was preferred. Balloon- and then stent-assisted coiling were introduced in 1997 and 2002, respectively, enabling endovascular treatment of these lesions [35, 36]. Particularly, in the ruptured setting, balloon-assisted coiling gained favor as it does not require dual antiplatelet therapy. However, a recent case series of 97 patients with ruptured wide-necked aneurysms comparing balloon- and stent-assisted coil embolization with 65 patients treated with the stent-assisted technique demonstrated no statistical difference in periprocedural complications, immediate occlusion rates, or favorable outcomes at discharge and follow-up [37]. More recently, these lesions are being treated with flow diversion. These devices represent a significant improvement over coiling with higher long-term occlusion rates, shorter procedural times with resultant lower radiation doses, and low complication rates.

Small Aneurysms

Historically, small saccular aneurysms (≤10mm), particularly in the ruptured setting and ≤3 mm, are thought to pose a higher risk of intraprocedural rupture during endovascular treatment, and microsurgical clipping (including clip wrapping) has been regarded as a safer alternative (Fig. 6.1). Recently, several centers have treated these lesions with flow diverters. Although flow diverters do not induce immediate thrombosis like coils and require dual antiplatelet therapy, their deployment does not require entry into the aneurysm with the attendant risk of perforation. The largest series of small aneurysms (≤7 mm) treated with flow diversion that included 149 lesions demonstrated complete occlusion rate of 87%, good clinical outcome in 96%, and symptomatic complications and mortality of 6% and 1%, respectively [38]. Additional observational studies of small unruptured and ruptured blister aneurysms treated with flow diversion suggest flow diversion as a promising solution for these challenging lesions as well as with occlusion rates of 80% versus 70% for stent-assisted coiling in one study [39–41].

Fusiform Aneurysms

As they incorporate the vessel circumferentially, fusiform aneurysms have always posed treatment challenges, for both microsurgical and endovascular approaches.

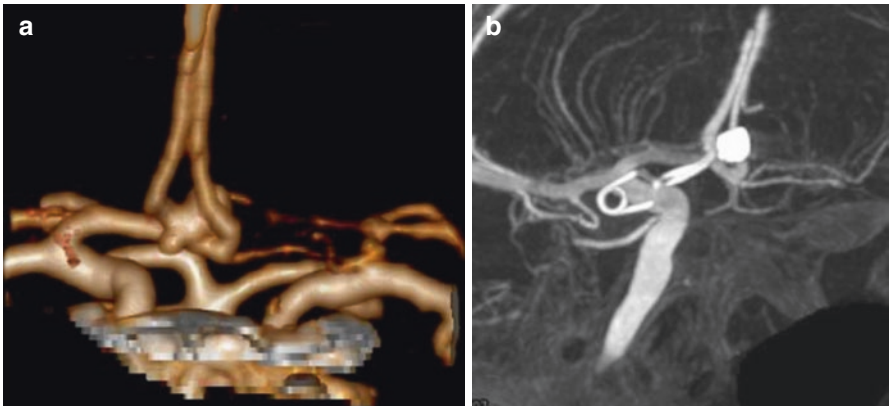


Fig. 6.1 59F Fisher Grade 2 subarachnoid hemorrhage (not shown) secondary to ruptured anterior communicating artery (ACOM) aneurysm. (**a**) 3D CT angiogram (CTA) demonstrating two anterior ACOM aneurysms, one pointing superior and posterior measuring 6 mm and another pointing inferior and anterior measuring 3 mm. (**b**) A 6-month follow-up MR angiogram (MRA) following coiling of the larger aneurysm and clipping smaller aneurysm (could not be coiled due to difficult angles) demonstrates complete occlusion of the lesions

In cases where parent vessel sacrifice is possible (including endovascular and surgical trapping with or without bypass), this deconstructive approach is definitive. However, some lesions are not amenable to parent vessel sacrifice and require reconstructive approaches. This is a setting again where flow diversion has led to a shift in treatment strategies. In tertiary care centers, these lesions are increasingly treated with flow diverters that lead to progressive aneurysm thrombosis and vascular remodeling as opposed to clip wrapping [42–44].

Giant and Partially Thrombosed Aneurysms

In giant aneurysms (≥25mm) that are often associated with intra-aneurysmal thrombus formation, traditional microsurgical clipping and endovascular coiling techniques become more challenging. Microsurgical clipping of giant lesions can be difficult due to the requirement for larger exposures and clips and is associated with high procedural morbidity; endovascular coiling is more hazardous due to greater coil requirement, coil compaction into thrombus in partially thrombosed lesions, persistent mass effect that may lead to clinical symptoms, and high recurrence rates. In this setting, parent vessel sacrifice is also a consideration; however, again, flow diverters offer a solution that may achieve aneurysm occlusion and parent vessel reconstruction while preserving vital arterial perforators and tributary branches. In one case series, 83% of large or giant aneurysms (>20 mm) treated with flow diversion resulted in aneurysm involution, with improvement in cranial neuropathies (75%) and headache (100%) [45]. Yet, hemorrhagic complications have been seen more frequently in giant aneurysms treated with flow diversion, accounting for ~80% of delayed aneurysm ruptures and ~20% of delayed intraparenchymal hemorrhages [27]. Proposed mechanisms for delayed aneurysm rupture include inflow jet modification resulting in increased intra-aneurysmal pressures, other hemodynamic alterations including fluctuations in wall shear stress, and/or exuberant aneurysm thrombus formation with autolysis of the aneurysm wall [46]. Delayed intraparenchymal hemorrhage is postulated to result from hemorrhagic transformation of ischemic events in the setting of dual antiplatelet therapy, altered hemodynamics resulting in diminished Windkessel effect and increased distal arterial pressures, and/or catheter-related foreign body emboli [47, 48]. Some authors suggest that combined coiling and flow diversion for giant aneurysms may help prevent flow diversion-associated delayed aneurysmal rupture by stabilizing thrombus formation (Fig. 6.2) [49, 50]. A retrospective study demonstrated that only 20% of giant aneurysms treated with flow diversion with concomitant or prior adjunctive coiling suffered delayed rupture [27]. Lastly, some evidence suggests that maintenance of P2Y12 platelet inhibition within therapeutic ranges may limit delayed intraparenchymal hemorrhages [28].

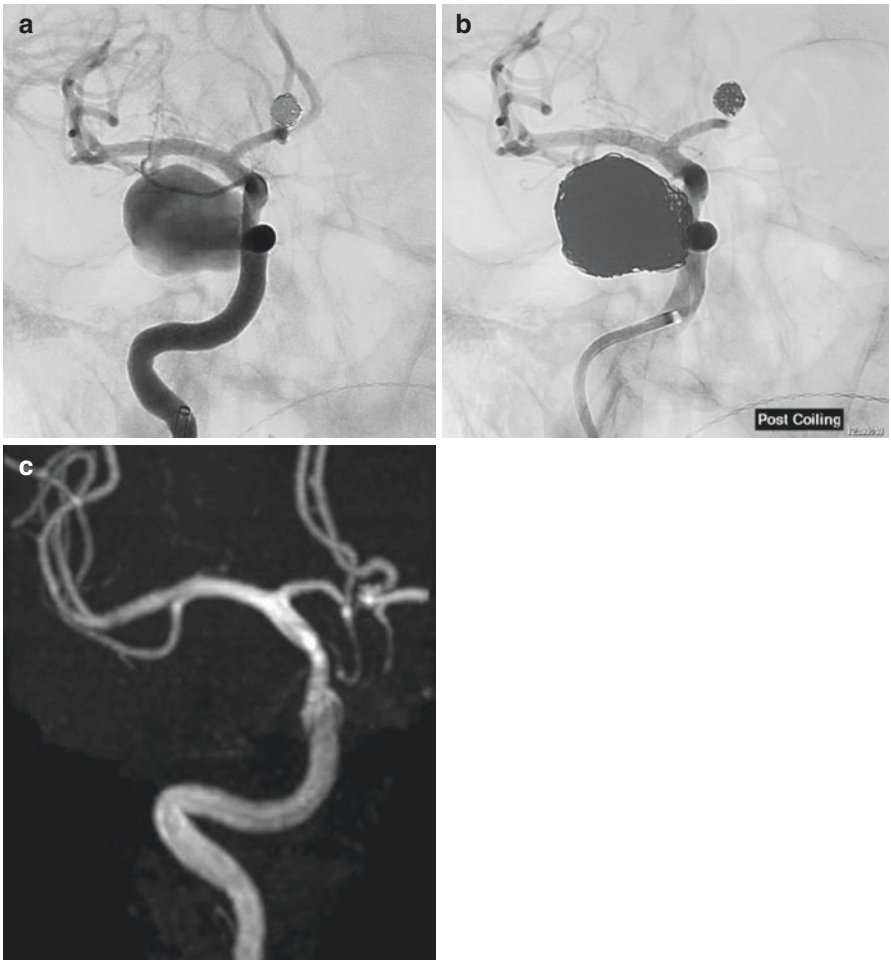


Fig. 6.2 51F progressive right retro-orbital headache and intermittent sixth nerve palsy. (**a**) Digital subtraction angiogram (DSA) demonstrating a right 28-mm giant cavernous internal carotid artery (ICA). (**b**) Non-subtracted radiograph depicts coils and a SILK flow diverter used to treat the lesion. A previously coiled ACOM aneurysm is also noted. The patient experienced complete resolution of the right cranial nerve palsy post-procedure. (**c**) A 6-month follow-up MRA demonstrates complete occlusion of the lesion

Other Novel Endovascular Devices

Recently, several novel endovascular devices to treat intracranial aneurysms growing on the experience with coils and flow diverters have been developed. General categories of these devices include intra-saccular flow disruptors, vascular remodeling devices, and hybrid devices. Instead of residing in the vascular lumen-like flow diverters, intra-saccular flow disrupters are mesh devices deployed within aneurysms

over the neck aimed at reducing aneurysmal blood flow with resultant progressive thrombosis and neck neoendothelialization. A significant advantage of intra-saccular flow disruptors is the lack of necessity for periprocedural dual antiplatelet therapy. Vascular remodeling devices are stents with specialized configurations to aid in endovascular coiling of challenging aneurysm configurations such as wide-necked and bifurcation aneurysms. Examples include the Reverse Barrel™ vascular reconstruction device (Medtronic, Minneapolis, MN, USA), pCONus Bifurcation Aneurysm Implant (Phenox, Bochum, Germany), and PulseRider® (Pulsar Vascular, San Jose, CA, USA). An example of a hybrid device is the Endovascular Clip System (Evasc, Vancouver, BC, CA) that is an endoluminal device composed of an anchor and a nonporous leaf that is placed over the neck of the aneurysm to prevent intra-aneurysmal flow and promote progressive thrombosis and neck neoendothelialization [51]. Another hybrid device, the Comaneci device (Rapid Medical, Israel), a retrievable stent, enables assisted coiling similar to balloon and stent assistance without the parent vessel occlusion with balloon inflation or permanence of stent placement [52].

Novel Surgical Techniques

Although new clip mechanisms and configurations are continuously being developed, the most notable recent advances of microsurgical clipping are the application of intracranial-intracranial bypass (in situ, reimplantation, reanastamosis, and intracranial grafts) and the adoption of minimally invasive approaches [53–55]. Recently, the use of a modified pterional keyhole approach to successfully treat 14 anterior circulation aneurysms in carefully selected patients was reported [56]. Additionally, several case reports, a case series of ten patients harboring 11 aneurysms, and a cadaveric study have been published describing the successful utilization of the endoscopic endonasal approach for the treatment of select anterior and posterior circulation aneurysms [57–61]. Other minimally invasive approaches include lateral supraorbital and orbital-pterional craniotomies [55].

Management of Surgical and Endovascular Residuals and Recurrence

The recurrence rates following endovascular coiling range from 5% for small aneurysms (<10 mm) to as high as 87% for giant aneurysms, with an overall recurrence rate of ~20% and retreatment rate of ~10% [62]. In the CARAT study, the overall risk of rerupture from a residual or recurrence was 2.2% in the first year, 0.2% in the second, and 0% in the third year following endovascular coiling with greater risk with decreasing degrees of angiographic occlusion ranging from 1% with complete occlusion to 18% with <70% occlusion [63]. These results were analogous to ISAT

where the rerupture rate was 2.5% the first year and then 0.2% annually thereafter [64]. Mechanisms for aneurysm recurrence following endovascular coiling include device migration, coil compaction (without or with extrusion), and aneurysm regrowth. Alternatively, recurrence rates following complete microsurgical clipping are low, approximately 0.25–0.5% annually, yet these recurrences may carry a rupture risk of up to 50% [65]. Although many recurrences may be managed via the initial treatment modality, there are some instances where microsurgical and endovascular techniques can be complimentary. For endovascular coiling recurrences due to aneurysm regrowth, microsurgical clipping (without or with dome transection and coil extraction), wrapping, or bypass when feasible has been suggested for more recently flow diverter placement in an attempt to reconstruct the parent vessel [24, 66, 67]. Repeat surgery for aneurysms can be formidable, particularly following long time intervals from the original treatment due to peri-aneurysmal scar tissue and adhesions that may increase the risk of intraoperative rupture, cerebrospinal fluid (CSF) leaks, and obscuration of the aneurysm site due to prior clip placement. In this setting, endovascular techniques, both with traditional endovascular coiling and flow diversion, have been shown to be safe and effective in several case series [68, 69].

Summary

Microsurgical clipping and endovascular coiling are effective treatment modalities for the treatment of unruptured and ruptured intracranial aneurysms. The decision between the two techniques for an individual patient is highly influenced by the aneurysm characteristics and clinical presentation. Due to the introduction of a number of novel devices to the endovascular armamentarium, with flow diverters being the most mature as well as minimally invasive microsurgical approaches, the microsurgical clipping versus endovascular coiling debate has expanded to include new endovascular devices, hybrid treatments, and minimally invasive microsurgical approaches.

References

1. Smith RR, Zubkov YN, Tarassoli Y. The history of aneurysm surgery. In: Cerebral aneurysms: microvascular and endovascular management. New York: Springer US; 1994. p. 1–9.
2. Guglielmi G, Viñuela F, Duckwiler G, et al. Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils. J Neurosurg. 1992;77(4):515–24.
3. Rezek I, Mousan G, Wang Z, Murad MH, Kallmes DF. Coil type does not affect angiographic follow-up outcomes of cerebral aneurysm coiling: a systematic review and meta-analysis. Am J Neuroradiol. 2013;34(9):1769–73.

4. Vanninen R, Koivisto T, Saari T, Hernesniemi J, Vapalahti M. Ruptured intracranial aneurysms: acute endovascular treatment with electrolytically detachable coils--a prospective randomized study. Radiology. 1999;211:325–36.
5. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. Stroke. 2000;31(10):2369–77.
6. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RSC. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet. 2015;385(9969):691–7.
7. Scott RB, Eccles F, Molyneux AJ, Kerr RSC, Rothwell PM, Carpenter K. Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the international subarachnoid aneurysm trial (ISAT). Stroke. 2010;41(8):1743–7.
8. Ogilvy CS. Neurosurgical clipping versus endovascular coiling of patients with ruptured intracranial aneurysms. Stroke. 2003;34(10):2540–2.
9. Darsaut TE, Jack AS, Kerr RS, Raymond J. International subarachnoid aneurysm trial – ISAT part II: study protocol for a randomized controlled trial. Trials. 2013;14(1):156.
10. Zaidi HA, Montoure A, Elhadi A, et al. Long-term functional outcomes and predictors of shunt-dependent hydrocephalus after treatment of ruptured intracranial aneurysms in the BRAT trial: revisiting the clip vs coil debate. Neurosurgery. 2015;76(5):608–15.
11. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P. The barrow ruptured aneurysm trial. J Neurosurg. 2015;123(September):609–17.
12. Lanzino G, Murad MH, D'Urso PI, Rabinstein AA. Coil embolization versus clipping for ruptured intracranial aneurysms: a meta-analysis of prospective controlled published studies. AJNR Am J Neuroradiol. 2013;34(9):1764–8.
13. McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ. Comparative effectiveness of ruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. Am J Neuroradiol. 2014;35(1):164–9.
14. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711–37.
15. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35(2):93–112.
16. McCracken DJ, Lovasik BP, McCracken CE, et al. Resolution of oculomotor nerve palsy secondary to posterior communicating artery aneurysms: comparison of clipping and coiling. Neurosurgery. 2015;77(6):931–9.
17. Bhatia S, Sekula RF, Quigley MR, Williams R, Ku A. Role of calcification in the outcomes of treated, unruptured, intracerebral aneurysms. Acta Neurochir. 2011;153(4):905–11.
18. Elijovich L, Higashida RT, Lawton MT, Duckwiler G, Giannotta S, Johnston SC. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: the CARAT study. Stroke. 2008;39(5):1501–6.
19. Mahaney KB, Brown RD, Meissner I, et al. Age-related differences in unruptured intracranial aneurysms: 1-year outcomes. J Neurosurg. 2014;121(5):1024–38.
20. McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ. Comparative effectiveness of unruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. Stroke. 2013;44(4):988–94.
21. Thompson BG, Brown RD, Amin-Hanjani S, et al. Guidelines for the management of patients with unruptured intracranial aneurysms, Stroke. 2015;46(8):2368–400.
22. Lad SP, Babu R, Rhee MS, et al. Long-term economic impact of coiling vs clipping for unruptured intracranial aneurysms. Neurosurgery. 2013;72(6):1000–11.

23. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. AJNR Am J Neuroradiol. 2011;32(1):34–40.
24. Becske T, Kallmes DF, Saatci I, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858–68.
25. Becske T, Potts M, Shapiro M, Kallmes D, Nelson PK. Pipeline for uncoilable or failed aneurysms: 3-year follow-up results. J Neurosurg. 2016;14:1–8.
26. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44(2):442–7.
27. Rouchaud A, Brinjikji W, Lanzino G, Cloft HJ, Kadirvel R, Kallmes DF. Delayed hemorrhagic complications after flow diversion for intracranial aneurysms: a literature overview. Neuroradiology. 2016;58(2):171–7.
28. Delgado Almandoz JE, Crandall BM, Scholz JM, et al. Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. Am J Neuroradiol. 2014;35:128–35.
29. Chalouhi N, Tjoumakaris S, Starke RM, et al. Comparison of flow diversion and coiling in large unruptured intracranial saccular aneurysms. Stroke. 2013;44(8):2150–4.
30. Turjman F, Levrier O, Combaz X, et al. EVIDENCE trial: design of a phase 2, randomized, controlled, multicenter study comparing flow diversion and traditional endovascular strategy in unruptured saccular wide-necked intracranial aneurysms. Neuroradiology. 2014;57(1):49–54.
31. Deshmukh VR, Kakarla UK, Figueiredo EG, Zabramski JM, Spetzler RF. Long-term clinical and angiographic follow-up of unclippable wrapped intracranial aneurysms. Neurosurgery. 2006;58(3):434–41.
32. Yoon MA, Kim E, Kwon B-J, et al. Muslinoma and muslin-induced foreign body inflammatory reactions after surgical clipping and wrapping for intracranial aneurysms: imaging findings and clinical features. J Neurosurg. 2010;112(3):640–7.
33. Safavi-Abbasi S, Moron F, Sun H, et al. Techniques and outcomes of gore-Tex clip-wrapping of ruptured and Unruptured cerebral aneurysms. World Neurosurg. 2016;90:281–90.
34. Di Santo M, Vaz G, Doquier MA, Raftopoulos C. Evaluation of a clip-reinforced wrapping technique with collagen-impregnated Dacron for intracranial aneurysms inaccessible to other treatment. Clin Neurol Neurosurg. 2015;138(2015):151–6.
35. Alaraj A, Wallace A, Dashti R, Patel P, Aletich V. Balloons in endovascular neurosurgery: history and current applications. Neurosurgery. 2014;74(2 SUPPL):163–90.
36. Fiorella D, Albuquerque FC, Masaryk TJ, Rasmussen PA, McDougall CG. Balloon-in-stent technique for the constructive endovascular treatment of “ultra-wide necked” circumferential aneurysms. Neurosurgery. 2005;57(6):1218-27-27. http://www.ncbi.nlm.nih.gov/pubmed/16331170. Accessed 10 July 2014.
37. Cai K, Zhang Y, Shen L, Ni Y, Ji Q. Comparison of stent-assisted coiling and balloon-assisted coiling in the treatment of ruptured wide-necked intracranial aneurysms in the acute period. World Neurosurg. 2016;8750(16):30855.
38. Griessenauer CJ, Ogilvy CS, Foreman PM, et al. Pipeline embolization device for small intracranial aneurysms: evaluation of safety and efficacy in a multicenter cohort. Neurosurgery. 2017;80(4):579–87.
39. Linfante I, Mayich M, Sonig A, Fujimoto J, Siddiqui A, Dabus G. Flow diversion with Pipeline Embolic Device as treatment of subarachnoid hemorrhage secondary to blister aneurysms: dual-center experience and review of the literature. J Neurointerv Surg. 2016:neurintsurg-2016-012287.
40. Kallmes DF, Brinjikji W, Boccardi E, et al. Aneurysm study of pipeline in an observational registry (ASPIRe). Interv Neurol. 2016;5(1–2):89–99.
41. Chalouhi N, Starke RM, Yang S, et al. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. Stroke. 2014;45(1):54–8.

42. Monteith SJ, Tsimpas A, Dumont AS, et al. Endovascular treatment of fusiform cerebral aneurysms with the Pipeline Embolization Device. J Neurosurg. 2014;120(4):945–54.
43. Delgado Almandoz JE, Crandall BM, Fease JL, et al. Successful endovascular treatment of three fusiform cerebral aneurysms with the pipeline embolization device in a patient with dilating HIV vasculopathy. J Neurointerv Surg. 2014;6(2):e12.
44. Szikora I, Tura E. Evolution of flow-diverter Endothelialization and Thrombus Organization in Giant Fusiform Aneurysms after flow diversion: a histopathologic study. AJNR Am J Neuroradiol. 2015;36(9):1716–20.
45. John S, Bain MD, Hussain MS, Bauer AM, Toth G. Long-term effect of flow diversion on large and giant aneurysms: MRI-DSA clinical correlation study. World Neurosurg. 2016;93:60–6.
46. Saatci I, Yavuz K, Ozer C, Geyik S, Cekirge HS. Treatment of intracranial aneurysms using the pipeline flow-diverter embolization device: a single-center experience with long-term follow-up results. Am J Neuroradiol. 2012;33(8):1436–46.
47. Kulcsár Z, Houdart E, Bonafé A, et al. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. Am J Neuroradiol. 2011;32(1):20–5.
48. Fox B, Humphries WE, Doss VT, Hoit D, Elijovich L, Arthur AS. Rupture of giant vertebrobasilar aneurysm following flow diversion: mechanical stretch as a potential mechanism for early aneurysm rupture. Case Reports. 2014;2014(oct29 1):bcr2014011325-bcr2014011325.
49. Nossek E, Chalif DJ, Chakraborty S, Lombardo K, Black KS, Setton A. Concurrent use of the pipeline embolization device and coils for intracranial aneurysms: technique, safety, and efficacy. J Neurosurg. 2015;122(April):904–11.
50. Siddiqui AH, Kan P, Abla AA, Hopkins LN, Levy EI. Complications after treatment with pipeline embolization for giant distal intracranial aneurysms with or without coil embolization. Neurosurgery. 2012;71(2):509–13.
51. Sorenson T, Brinjikji W, Lanzino G. Newer endovascular tools: a review of experimental and clinical aspects. J Neurosurg Sci. 2016;60(1):116–125. http://www.ncbi.nlm.nih.gov/pubmed/26373669.
52. Fischer S, Weber A, Carolus A, Drescher F, Götz F, Weber W. Coiling of wide-necked carotid artery aneurysms assisted by a temporary bridging device (Comaneci): preliminary experience. J Neurointerv Surg. 2016;neurintsurg-2016-012664.
53. Segawa H, Kohno M, Nakatomi H, Sano K, Saito I, Shiokwa Y. New aneurysm clip and applier for narrow spaces: technical note. Neurosurgery. 1999;45(4):939–43.
54. Krammer MJ, Lumenta CB. The new aneurysm clip system for particularly complex aneurysm surgery: technical note. Neurosurgery. 2010;66(6):336–8. https://doi.org/10.1227/01.NEU.0000369644.26132.56.
55. Davies JM, Lawton MT. Advances in open microsurgery for cerebral aneurysms. Neurosurgery. 2014;74(2 SUPPL):7–16.
56. Mocco J, Komotar RJ, Raper DMS, Kellner CP, Connolly ES, Solomon RA. The modified pterional keyhole craniotomy for open cerebrovascular surgery: a new workhorse? J Neurol Surgery, Part A Cent Eur Neurosurg. 2013;74(6):400–4.
57. Yildirim AE, Divanlioglu D, Karaoglu D, Cetinalp NE, Belen AD. Pure endoscopic Endonasal clipping of an incidental anterior communicating artery aneurysm. J Craniofac Surg. 2015;26(4):1378–81.
58. Eloy JA, Carai A. Case report combined endoscope-assisted transclival clipping and endovascular stenting of a basilar trunk aneurysm: case report. Neurosurgery. 2008;62(March):142–3. https://doi.org/10.1227/01.NEU.0000297101.34508.43.
59. Kassam AB, Mintz AH, Gardner PA, Horowitz MB, Carrau RL, Snyderman CH. The expanded endonasal approach for an endoscopic transnasal clipping and aneurysmorrhaphy of a large vertebral artery aneurysm: Technical case report. Neurosurgery. 2006;59(1 SUPPL. 1):162–5. https://doi.org/10.1227/01.NEU.0000220047.25001.F8.
60. Gardner PA, Vaz-Guimaraes F, Jankowitz B, et al. Endoscopic endonasal clipping of intracranial aneurysms: surgical technique and results. World Neurosurg. 2015;84(5):1380–93.

61. Szentirmai O, Hong Y, Mascarenhas L, et al. Endoscopic endonasal clip ligation of cerebral aneurysms: an anatomical feasibility study and future directions. J Neurosurg. 2015;124(February):1–6.
62. Crobeddu E, Lanzino G, Kallmes DF, Cloft HJ. Review of 2 decades of aneurysm-recurrence literature, part 1: reducing recurrence after endovascular coiling. AJNR Am J Neuroradiol. 2013;34(2):266–70.
63. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: The Cerebral Aneurysm Rerupture After Treatment (CARAT) study. Stroke. 2008;39(1):120–5.
64. 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 (London, England). 2002;360(9342):1267–74.
65. Owen CM, Montemurro N, Lawton MT. Microsurgical management of residual and recurrent aneurysms after coiling and clipping: an experience with 97 patients. Neurosurgery. 2015;62(1):92–102.
66. Islak C. The retreatment: indications, technique and results. Eur J Radiol. 2013;82(10):1659–64.
67. Waldron JS, Halbach VV, Lawton MT. Microsurgical management of incompletely coiled and recurrent aneurysms: trends, techniques, and observations on coil extrusion. Neurosurgery. 2009;64(SUPPL. 5):301–15. https://doi.org/10.1227/01.NEU.0000335178.15274.B4.
68. Li K, Cho YD, Kang HS, Kim JE, Han MH, Lee YM. Endovascular management for retreatment of postsurgical intracranial aneurysms. Neuroradiology. 2013;55(11):1345–53.
69. Adeeb N, Griessenauer CJ, Moore J, et al. Pipeline embolization device for recurrent cerebral aneurysms after microsurgical clipping. World Neurosurg. 2016;93:341–5.

Chapter 7
Microsurgical Clipping of Unruptured Aneurysms: The Basics

James Towner, Amrendra S. Miranpuri, Ulas Cikla, and Mustafa K. Baskaya

Technical Considerations

In the case of elective clipping of unruptured aneurysms, the surgeon has the luxuries of time and careful planning, which he or she should leverage fully to ensure a fully optimized case. Prior to entering the operating theater, it is important to reassess the patient's history, specifically reviewing their history for any prior subarachnoid hemorrhage (SAH) or cranial trauma, cranial surgery, endovascular therapy – both neurosurgical and otherwise – and medications, including antiplatelets, anticoagulation, and antiepileptics. Next, review all imaging modalities obtained in the workup of their lesion, including catheter-based angiogram, computed tomography angiography, and magnetic resonance angiography. These images should be reviewed with careful attention paid to any vascular variants or anomalies, aneurysm dome projection and configuration, distance from the Sylvian fissure to the aneurysm when applicable, presence of multiple aneurysms, estimating the skull thickness, anterior clinoid process (ACP) anatomy, frontal sinus size and configuration, and cortical veins. Finally, the patient should be asked for any changes in their medical history since their last office visit, and a brief physical examination should be performed.

The operating room staff should, ideally, be part of a specialized operative team comfortable with nuances, tools, and terminology associated with aneurysm man-

J. Towner
Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA
e-mail: james_towner@urmc.rochester.edu

A. S. Miranpuri (✉)
Department of Neurosurgery, Carle Foundation Hospital, Urbana, Illinois, USA
e-mail: amrendra.miranpuri@carle.com

U. Cikla · M. K. Baskaya
Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: cikla@neurosurgery.wisc.edu; m.baskaya@neurosurgery.wisc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_7

agement consisting of the surgeon, surgical assistance, neuro-anesthesiologist, and scrub and circulating nurses. When operating in a hybrid operating theater with biplane endovascular capabilities, two radiologic technicians should also be present [1]. An anesthesia plan should be briefly reviewed, including alerting the neuro-anesthesiologist of the need for burst suppression during temporary clip placement and determining which agents to use, such as propofol, etomidate, or pentobarbital [2]. The operating table should be appropriate for the planned procedure and any possible additional procedures (i.e., radiolucent for endovascular use if necessary) but at a minimum should allow position changing throughout the case, such as head-of-bed alterations, Trendelenburg, reverse Trendelenburg, and bed tilting. An arterial line and Foley catheter should be placed after induction of anesthesia. Both groin regions should be shaved, prepped, and draped, if the operating room has endovascular capabilities. If an intraoperative angiogram is anticipated, a femoral arterial sheath can be placed at this time. If indocyanine green is to be used, a microscope with near-infrared indocyanine green video angiography must be available [3]. If intraoperative monitoring, such as continuous electroencephalography and motor or somatosensory evoked potentials, is to be used, it can be placed at this time. The operative microscope should be inspected and balanced, the interpupillary distance of the eye pieces adjusted for the surgeon, and a beam splitter set to the assistant's eye piece. The surgeon should decide if he plans to operate in a standing position or sitting position. If sitting, the operating stool height and armrests should be adjusted by the surgeon. The surgeon should inspect and review the microsurgical tools with the scrub nurse prior to beginning the case. Standard instruments include retractors, microinstruments, and aneurysm clips [4]. The microinstruments should include microdissectors and probes, straight and curved microscissors, and sharp dissectors, including an arachnoid knife, diamond knife, and beaver blade. An irrigating bipolar cautery avoids the need for continuous irrigation during surgical dissection and minimizes tissue adherence to the bipolar tips. Microsuction tips should be smooth and have pressure-regulating holes to provide low-pressure suction when dissecting around arteries and veins. A high-speed drill with a perforator bit and craniotome for fashioning the craniotomy, as well as a matchstick or diamond burr for sphenoid wing, ACP, or other skull base drilling, should be available. A micro-Doppler can be invaluable for assessing patency of arteries adjacent to the clip construct.

Once the patient is deeply anesthetized, the patient's head should be secured in a rigid head holder such as a Mayfield-Keys or Sugita, which should be radiolucent if endovascular procedures might be performed. Pin sites should not obstruct the planned surgical incision or possible extensions of the incision. The pins should be placed in a "headband" distribution, above the temporalis muscle to minimize risk of hematoma formation or pin slippage. If neuronavigation is to be used, as is often considered in cases of pericallosal or distal MCA segment aneurysms, it should be set up and the patient's preoperative scan registered to the patient. If the self-retaining retractor system attaches to the head holder, adequate positioning of the bar and space for attaching the system should be ensured.

A strategy for brain relaxation should be considered and discussed with the neuro-anesthesiologist at this time. Mannitol is often suitable for elective operations.

If the patient has central venous access, 3% normal saline can also be considered. A pCO2 goal should be discussed with the anesthesiologist, as well as any anticipated adjustments to the goal (i.e., when opening the dura). A lumbar drain or external ventricular drain can be placed preoperatively, while the patient is under general anesthesia. A ventriculostomy can also be performed intraoperatively via Paine's point, or alternatively a subarachnoid cistern (i.e., carotid cistern or lamina terminalis) can be opened early in the operation for rapid CSF drainage [5]. Additional bony removal, such as further drilling of the sphenoid wing or an orbitozygomatic (OZ) osteotomy, should be considered prior to extensive retraction of the brain. Two units of typed and crossed blood should be in the room or on call and immediately available at the start on the case.

An appropriate incision should be planned, with every attempt made to limit the incision to behind the hairline for cosmesis. Hair should be clipped, rather than shaved. The patient's eyes should be protected with watertight protective closure using an adhesive barrier such as a small Tegaderm (3 M, St Paul, Minn) dressing. The patient's external auditory meatus should be protected from blood or preoperative skin preparation agents with a small plug of petroleum gauze.

During the case, the surgeon should be positioned at the patient's head with their assistant to the left and the scrub nurse to the right. Adjustments should be made to the position based on the location of the lesion, patient positioning, and intraoperative adjustments of the bed.

Craniotomy for Anterior and Posterior Circulation Aneurysm

Pterional Craniotomy

The work horse for anterior circulation aneurysms is the pterional craniotomy with or without an OZ osteotomy. A pterional craniotomy will provide access to the internal carotid artery (ICA), anterior cerebral artery (ACA), middle cerebral artery (MCA), and distal basilar artery (BA).

Positioning

Patient is placed supine on the operating table. An ipsilateral shoulder cushion or bolster is placed to aid in neck positioning in patients with unfavorable body habitus. The head is placed with 20° extension and rotated 15°–30° contralateral to the lesion. These maneuvers will result in the malar eminence being elevated to the highest point in the surgical field and allow gravity to assist in frontal and temporal lobe retraction. The surgical field from a top-down viewpoint will provide an unobstructed view of the sphenoid wing and ACP.

Skin Incision and Scalp Dissection

The incision should begin 0.5–1 centimeter (cm) anterior to the tragus and curve anteriorly ending in the midline behind the hairline. An incision 1 cm anterior to the tragus avoids the main trunk of the superficial temporal artery and facial nerve twigs. There are several techniques for dissecting the temporalis muscle, including interfascial dissection and submuscular dissection [6]. The goal of all techniques is ultimately to protect the facial nerve and optimize exposure. The fastest and safest method is to incise the temporalis muscle at the zygomatic arch and continue along the same path as the skin incision, ending 1 cm below the superior temporal line. The dissection is then continued anteriorly, leaving a small cuff of muscle and fascia to allow for reattachment of the temporalis at the end of the case. Fishhook retractors are used to retract the scalp and muscle inferiorly in order to clearly expose the pterion.

Craniotomy

The craniotomy can be completed with a minimum of two burr holes, but as many as three or more burr holes can be used, depending on how easily the dura is stripped from the inner table of the skull. The first burr hole is placed very low on the temporal squama immediately above the zygoma and the second at the "keyhole" or pterion. Optional additional burr holes may be created at the superoanterior and superoposterior limits of the craniotomy. After the dura is stripped, the craniotome is used to fashion a bone flap by proceeding from the posterior margin of the temporal squama burr hole superiorly along the temporalis incision, curving anteromedially to the supraorbital notch. Then craniotome is taken laterally along the floor of the anterior cranial fossa to the pterional burr hole. Care must be taken when stripping the dura along the anterior aspect of the craniotomy, as the dura thins and risk of inadvertent durotomy is highest here. The craniotome is then used to carry a cut from the temporal squama burr hole superoanteriorly, until resistance is encountered at the sphenoid ridge. A cut is then made inferiorly from the pterional burr hole, again until resistance from the sphenoid ridge is met. The skull flap can then be removed by fracturing it at the sphenoid ridge. The next step is to drill down the lesser wing of the sphenoid medially until encountering the superior orbital fissure. If the frontal sinus is opened during the craniotomy, a vascularized flap of pericranium can be laid over the opening. The squamosal portion of the temporal bone is then drilled down to the floor of the middle cranial fossa.

Durotomy

The middle meningeal artery should be coagulated with bipolar cautery, and any bleeding from the bone can be controlled with bone wax. The dura should then be opened in a C shape, extending from the floor of the middle cranial fossa to the

floor of the anterior cranial fossa. The dura should be retracted inferiorly with tacking sutures.

Orbitozygomatic Osteotomy

The OZ osteotomy can be added to a standard pterional craniotomy in order to improve access. An OZ osteotomy should be considered when approaching basilar apex aneurysms or any challenging anterior circulation aneurysms.

The positioning, skin incision, and durotomy are the same as the standard pterional craniotomy described above.

Osteotomy

Following the craniotomy and durotomy described for the pterional craniotomy above, the OZ osteotomy may be undertaken. A malleable ribbon retractor can be used to protect the frontal lobe and orbital contents during the osteotomy. A reciprocating saw should be used to make the cuts. The first cut is made lateral to the supraorbital notch in a posterior direction for approximately 2.5 cm and then turned laterally across the orbital roof, ending toward the inferior orbital fissure. The next cut is made through the root of the zygoma, anterior to the temporomandibular joint. The temporalis muscle is then dissected free from the bone, and it is removed in one piece. Steps of muscle dissection and osteotomy cuts of the OZ in details can be reviewed in a previously published paper [7].

Far-Lateral Craniotomy

A far-lateral suboccipital-transcondylar craniotomy offers a versatile approach to the vertebral artery (VA) and proximal posterior inferior cerebellar artery (PICA) segments.

Positioning

The patient is placed in three-quarter prone position with the side ipsilateral to the aneurysm placed up. The head should be flexed with a fingerbreadth left between the chin and the chest, in order to maintain patency of venous drainage from the skull. The head is rotated 45 degrees contralaterally and then flexed 30 degrees contralaterally toward the opposite shoulder. When completed, the ipsilateral mastoid process will be elevated to the highest point of the surgical field. The goal of these maneuvers is to place the clivus vertical to the ground. The ipsilateral shoulder

is then gently taped inferiorly in order to increase space between the neck and shoulder for surgeon maneuverability.

Incision

A hockey stick incision is made, beginning at the mastoid tip and curving to the inion at the midline and then inferior to the spinous process at C4. The midline dissection is carried down along the avascular, midline nuchal ligament to the C2 spinous process. It is then carried laterally 1 cm below the superior nuchal line, leaving a muscular-facial cuff for reattaching the muscle at the end of the case. The muscle flap is then retracted inferolaterally. The VA is identified and protected as it travels medially from the C1 transverse foramen to the sulcus arteriosus of the posterior arch of C1.

Craniotomy

A curette is used to strip the dura from the posterior margin of the foramen magnum, and the craniotome is used to fashion a craniotomy. The bone cut begins at the foramen magnum and is taken superiorly to the transverse sinus. It is then curved laterally to the sigmoid sinus and finally taken inferiorly, ending at the foramen magnum. If the patient has adherent dura and a burr hole is required, it can be placed at the asterion, junction of the transverse and sigmoid sinus, in the superolateral aspect of the craniotomy. The posterior arch of C1 is then removed with the craniotome. Two cuts are required, with the first cut medial to the sulcus arteriosus and the second cut in the midline of the posterior arch. Next, the lateral foramen magnum and posterior one-third to half of the occipital condyle are removed with a diamond bit in a high-speed drill. Significant venous bleeding from the condylar emissary vein is encountered as the condyle is drilled down, but it is easily controlled with bone wax and should not preclude further drilling of the condyle if less than the desired amount has yet to be removed. Care must be taken to avoid removing greater than two-thirds of the condyle, as this may compromise stability of the occipital cervical junction requiring operative fixation [8].

Durotomy

A dural incision is made beginning from the inferior midline portion of the C1 laminectomy in a superior direction across the circular sinus. Cuts are then made from the superior and inferior extents of the vertical dural incision, toward the lateral extent of the craniotomy. Dural tacking sutures are then used to retract the dural flap laterally.

Unique Considerations for Aneurysms of the Anterior Communicating Artery Complex

The anterior communicating artery (AcoA) is the connection between the right and left anterior hemisphere circulations, constituting the anterior-most segment of the circle of Willis. It bridges the two A1 segments of the ACA, is superior to the optic chiasm, and lies approximately 12.7 mm medial to the bifurcation of the internal cerebral artery [9]. The AcoA is, on average, between 2 and 3 mm in length [9]. There are many named arterial branches surrounding the AcoA complex, which warrant strong consideration when planning and executing a surgical strategy. These include the bilateral A1 segments, A2 segments, recurrent artery of Heubner, AcoA perforators, orbitofrontal branches, and frontopolar segments. In addition, there are on average 6.4 branches arising from the superior surface of the A1 segment, which project into the anterior perforated substance [10]. Surgical team should be aware of the presence of the median artery of callosum, which is a large single trunk of AcoA perforator, or so-called A2.

When evaluating AcoA aneurysms, careful assessment of the adjacent vasculature is important. Asymmetry of the A1 segment is an anatomic variant that contributes to the formation of aneurysms [9, 11]. While found in 10% of the general population, this phenotype is seen in approximately 80% of patients with AcoA aneurysms [11, 12]. Angiographically occult A1 segments are often encountered, but true aplasia of an A1 segment is very rare; in patients with suspected A1 segment aplasia, an A1 segment is often identified intraoperatively [13, 14]. AcoA complex aneurysms typically lend themselves to a standard pterional craniotomy, but in the case of large or giant aneurysms, an OZ osteotomy or bifrontal craniotomy may be required. In cases of symmetric A1 segments, a right-sided craniotomy is preferred to avoid retraction of the language-dominant hemisphere. However, in cases of hypoplastic A1 segments, an approach ipsilateral to the dominant A1 is preferred to allow for proximal arterial control, early visualization of the aneurysm neck, and aneurysm dome avoidance.

AcoA aneurysms typically arise from two sections of the anterior communicating artery complex: the junction of the A1 and A2 sections or the anterior communicating artery proper.

The projection of the aneurysm dome can vary in three-dimensional space and for simplification can be divided into predominantly superior-, inferior-, anterior-, and posterior-projecting. Each projection carries important operative considerations. Superior-projecting aneurysms are the most commonly encountered and are associated with asymmetric A1 segments [11]. These aneurysms will project into the interhemispheric fissure, blocking visualization of the contralateral A2 segment. Inferior-projecting aneurysms hinder visualization of the contralateral A1 segment. Anterior-projecting aneurysms block the A1–A2 junction and obscure visualization of the contralateral optic nerve. Posterior-projecting aneurysms can block visualization of the contralateral A2 segment, and the aneurysm neck is closely associated with

AcoA perforators. Head rotation can be used to optimize approach to aneurysms projecting in various planes. Superior- and anterior-projecting aneurysms are optimally visualized with 30 degrees of head rotation, while posterior-projecting aneurysms are best seen with 15 degrees and inferior-projecting aneurysms with 45 degrees of head rotation [15] (*Case 1*, Fig. 7.1; *Case 2*, Fig. 7.2).

Unique Considerations for Posterior Communicating Aneurysms

The posterior communicating artery (PcoA) is the connection between the anterior and posterior intracranial circulation. It arises from the posteromedial communicating segment of the ICA within the carotid cistern. The origin of the PcoA is immediately proximal to the anterior choroidal artery (AChorA), which must be carefully

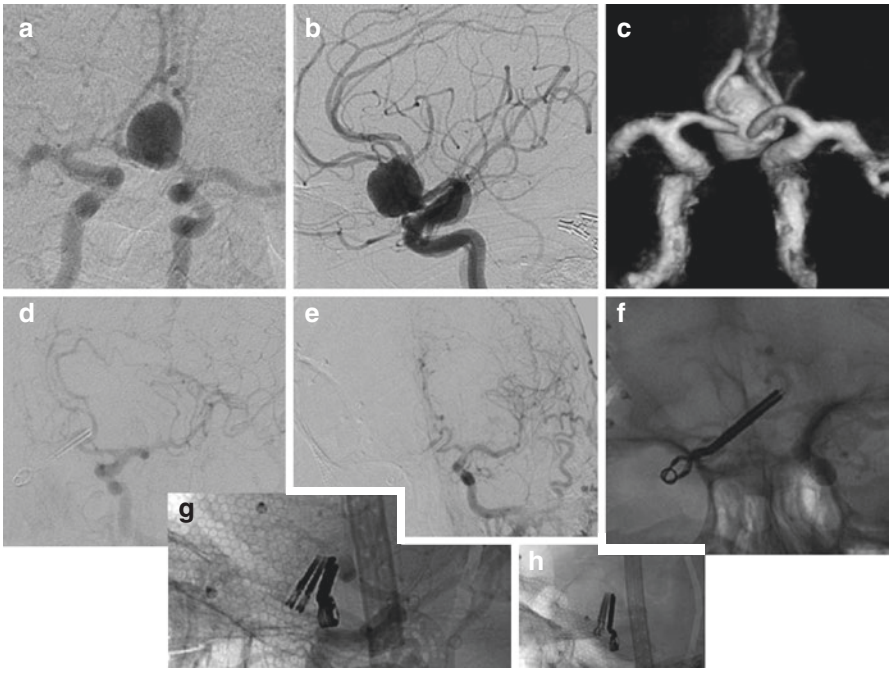


Fig. 7.1 *Case 1.* A 76-year-old right-handed man with a history of multiple sclerosis was found to have a large anterior communicating artery (AcoA) aneurysm on head MRI done for evaluation of multiple sclerosis status. After uncomplicated microsurgical clipping, the patient was discharged home without any neurological deficit. (**a**–**c**) Preoperative, anteroposterior (AP) (**a**), lateral (**b**), and 3D reconstruction angiograms (**c**) show a complex large AcoA aneurysm with superior projection. (**d**–**e**) Postoperative lateral (**d**) and AP (**e**) angiograms confirm total obliteration of the aneurysm and preservation of the parent arteries. (**f**–**h**) Postoperative AP (**f**) and oblique (**g**, **h**) non-subtracted bone-window angiograms demonstrate the positions of a long straight and two small Sugita clips

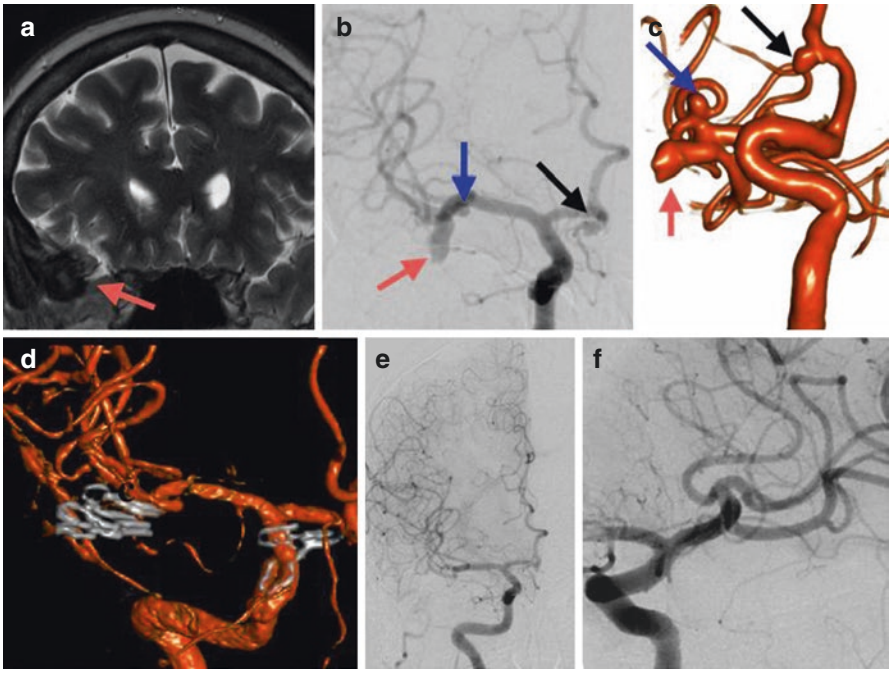


Fig. 7.2 *Case 2.* A 65-year-old woman with a new onset of seizure was found to have three cerebral aneurysms during workup. After uncomplicated microsurgical clipping, the patient was discharged home without any neurological deficit. (**a**) Preoperative coronal brain MRI shows partially thrombosed giant middle cerebral artery (MCA) bifurcation aneurysm (red arrow). (**b**) Preoperative oblique angiogram demonstrates an AcoA aneurysm (black arrow), the giant partially thrombosed right MCA bifurcation aneurysm (red arrow), and a right M2 aneurysm (blue arrow). (**c**) Preoperative 3D reconstruction angiogram of the AcoA aneurysm (black arrow), the right giant MCA (red arrow), and the right M2 bifurcation aneurysms (blue arrow). (**d**) Postoperative 3D reconstruction (**d**), postoperative AP (**e**), and oblique (**f**) angiograms show complete obliteration of aneurysms with multiple clips

protected during operative interventions. The PcoA courses posteromedially over the oculomotor nerve to connect with the second segment of the posterior cerebral artery (PCA), within the interpeduncular cistern. During embryologic development, the PcoA initially supplies blood to the PCA, but in the majority of people, the basilar artery eventually supplants the PcoA in this role. When this fails to occur, as is the case in approximately 8–20% of the population, fetal posterior circulation is retained, resulting in a PcoA that courses posterolaterally, either dorsal or lateral to the oculomotor nerve [13, 16, 17].

There are a variable number – approximately eight – of anterior thalamo-perforating arteries arising from the superior surface of the PcoA; these supply the thalamus, hypothalamus, subthalamus, and internal capsule. The perforators variably supply, in decreasing frequency, the anterior floor of the third ventricle, posterior perforated substance, optic tract, pituitary stalk, and optic chiasm [14]. The premammillary, or thalamotuberal, branch is the largest, often arising in the middle of

the PcoA. This branch courses anteriorly to the mammillary bodies to enter the floor of the third ventricle, supplying the posterior hypothalamus, ventral thalamus, and posterior limb of the internal capsule [14, 18].

Caution must be taken when evaluating the PcoA, because its caliber is highly variable and does not correlate to the number or size of essential anterior thalamoperforators arising from it [19]. To further complicate matters, evaluation of anterior thalamoperforators is often difficult during catheter angiograms, as the MCA candelabra often obscures their opacification. The anterior thalamoperforators arise within the anterior half of the PcoA in 50%, the posterior half of the PcoA in 20%, and equally the anterior and posterior halves in 25% of the population [14]. If the PcoA should be sacrificed during surgery, it is imperative to sacrifice it as closely as possible to the junction with the second segment of the PCA artery. Additionally, the anterior thalamoperforators should be excluded from the clip construct.

PcoA aneurysms represent approximately 26% of all ICA aneurysms [20]. The clinical presentation of these aneurysms is most commonly either SAH or, unique to PcoA aneurysms, a pupil-involved oculomotor palsy (ONP). Approximately 20% of PcoA aneurysms present with ONP. Conversely, 80% of patients with pupil-involving third nerve palsies will have a PcoA aneurysm. As such, an isolated pupil-involving third nerve palsy should be considered secondary to a PcoA until proven otherwise. A third nerve palsy, whether in the context of a ruptured or unruptured aneurysm, is often seen with posterior- and inferior-projecting aneurysms. Aneurysms presenting with third nerve palsies often improve following occlusion of the aneurysm, with chance of recovery likely related to time from onset. The choice to clip or coil PcoA aneurysms presenting with third nerve palsies can present a conundrum for treating physicians. Several meta-analyses indicate significant, superior recovery of oculomotor nerve palsies in patients with ruptured PcoA aneurysm treated with surgical clip ligation of the aneurysm. However, recovery rates of oculomotor palsies associated with unruptured aneurysms treated with clip ligation versus endovascular coiling are not significantly different [21, 22].

The approach of PcoA aneurysm projections presents unique intraoperative challenges. When infratentorial and projecting posterolaterally, these aneurysms increase the risk for ONP or adherence to the oculomotor nerve. Dissecting the aneurysm from the oculomotor nerve is unnecessary, as traction may result in a permanent deficit and the decrease in pulsations from a treated aneurysm likely is the major contributor to resolution of ONP seen in treated, unruptured aneurysms. These aneurysms may also be supratentorial and project superolaterally. In this case, they may become adherent to the temporal lobe. In the setting of a rupture, this could result in a temporal lobe intracerebral hemorrhage or temporal horn intraventricular hemorrhage. Alternatively, the aneurysm may adhere to the tentorial dura, in which case patients may present with a subdural hematoma in the event of rupture [14]. When projecting anterolaterally, the aneurysm may obscure the origin of the PcoA during operative dissection.

The majority of PcoA aneurysms should be accessible through a pterional craniotomy. In some giant or large PcoA aneurysms or in the presence of very short and lateral course of supraclinoid ICA, ACP removal is indicated. We prefer extradural drilling of the ACP in such cases (*Case 3*, Fig. 7.3a–e). The origins of the PcoA, the

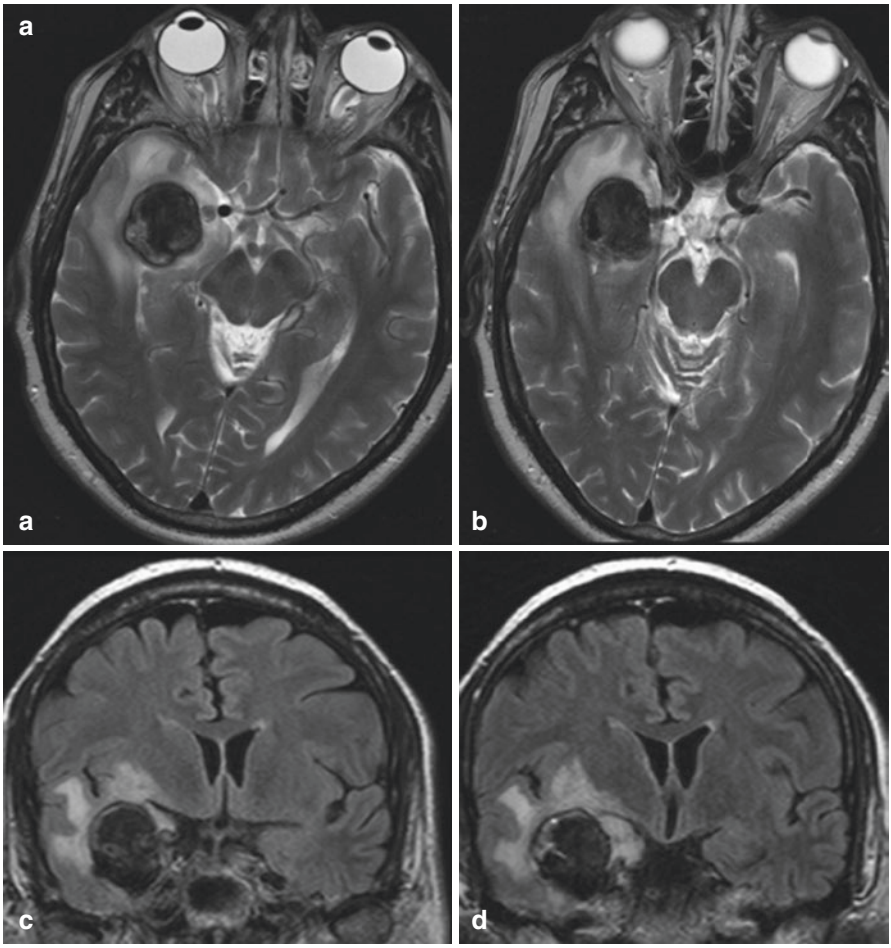


Fig. 7.3 *Case 3*. (**a**) A 64-year-old male presented with seizures. Brain MRI shows a giant thrombosed aneurysm of the fetal PcoA. Axial T2 (a, b) and coronal T1 (c, d) MR images demonstrate the detailed location of the aneurysm and the mass effect to the temporal and frontal lobes of the brain. (**b**) Preoperative DSA (a, b, c, d) revealed multilobulated PcoA aneurysm. (**c**) Intraoperative pictures via right cranio-orbital approach show PcoA (yellow arrow) and the aneurysm (blue A) (a, b). After temporary clipping (c), further dissection was achieved, and thrombosed part of the aneurysm was started to be cut (**d**). A combination of sharp (d) and blunt dissection was done under temporary clipping to reveal the detailed anatomy of the aneurysm, the surrounding brain, and the cerebral vasculature. (**d**) Intraoperative image shows the primer incision (yellow arrow) to the thrombosed part of the aneurysm (a). The thrombus inside the aneurysm was dissected out for the elimination of the mass effect (b). After removal of the thrombosed portion, the vascular anatomy around the aneurysm was able to be seen better (c). The intraoperative picture shows the final view after total removal of the thrombus and aneurysm wall around it (d). (**e**) Intraoperative picture shows preservation of the PcoA (yellow arrow) after clipping (a). The flow of the PcoA was confirmed with a micro-Doppler ultrasound (b). Postoperative DSA images show total obliteration of the aneurysm with preservation of the cerebral vasculature (c, d)

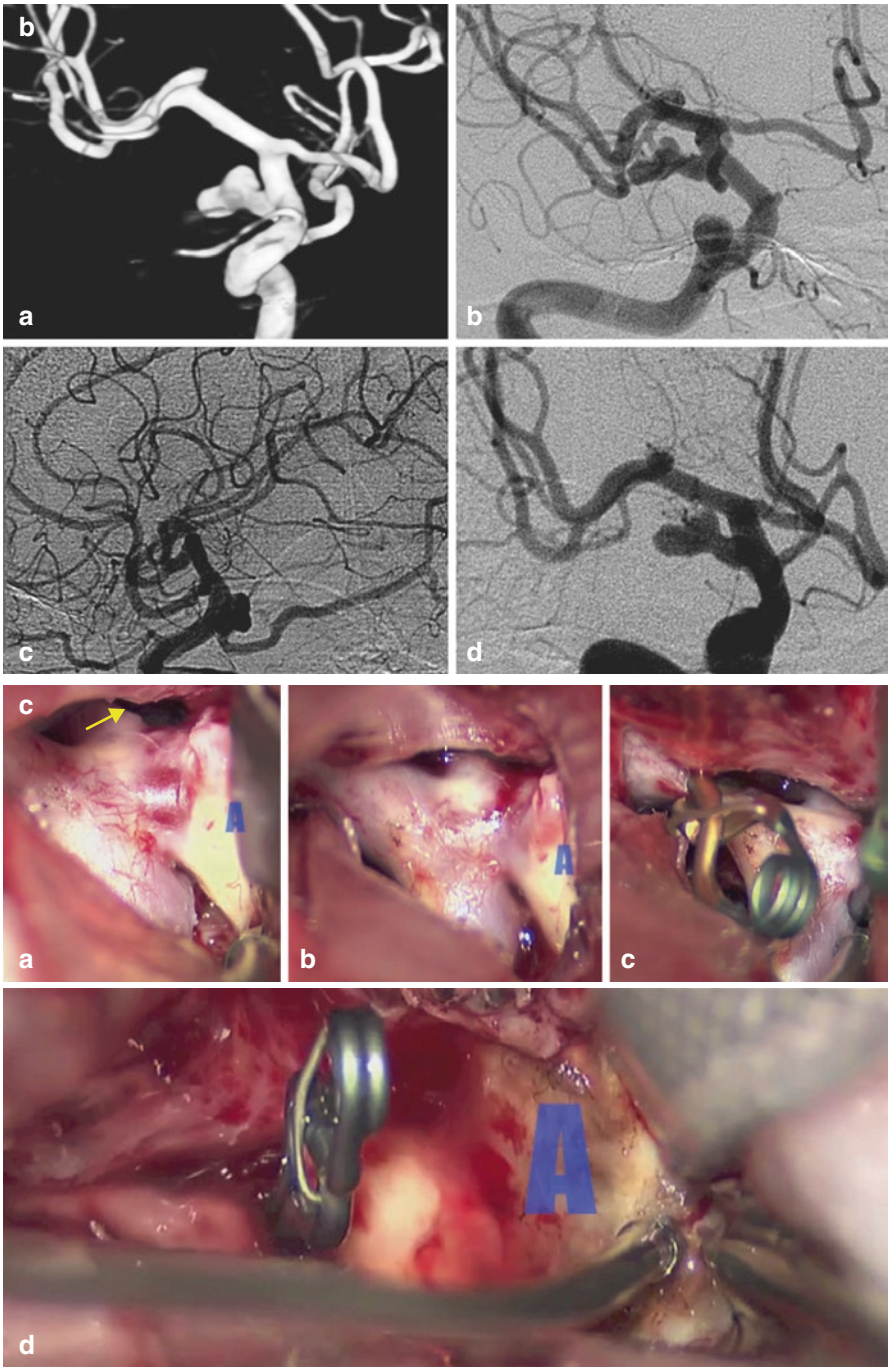


Fig. 7.3 (continued)

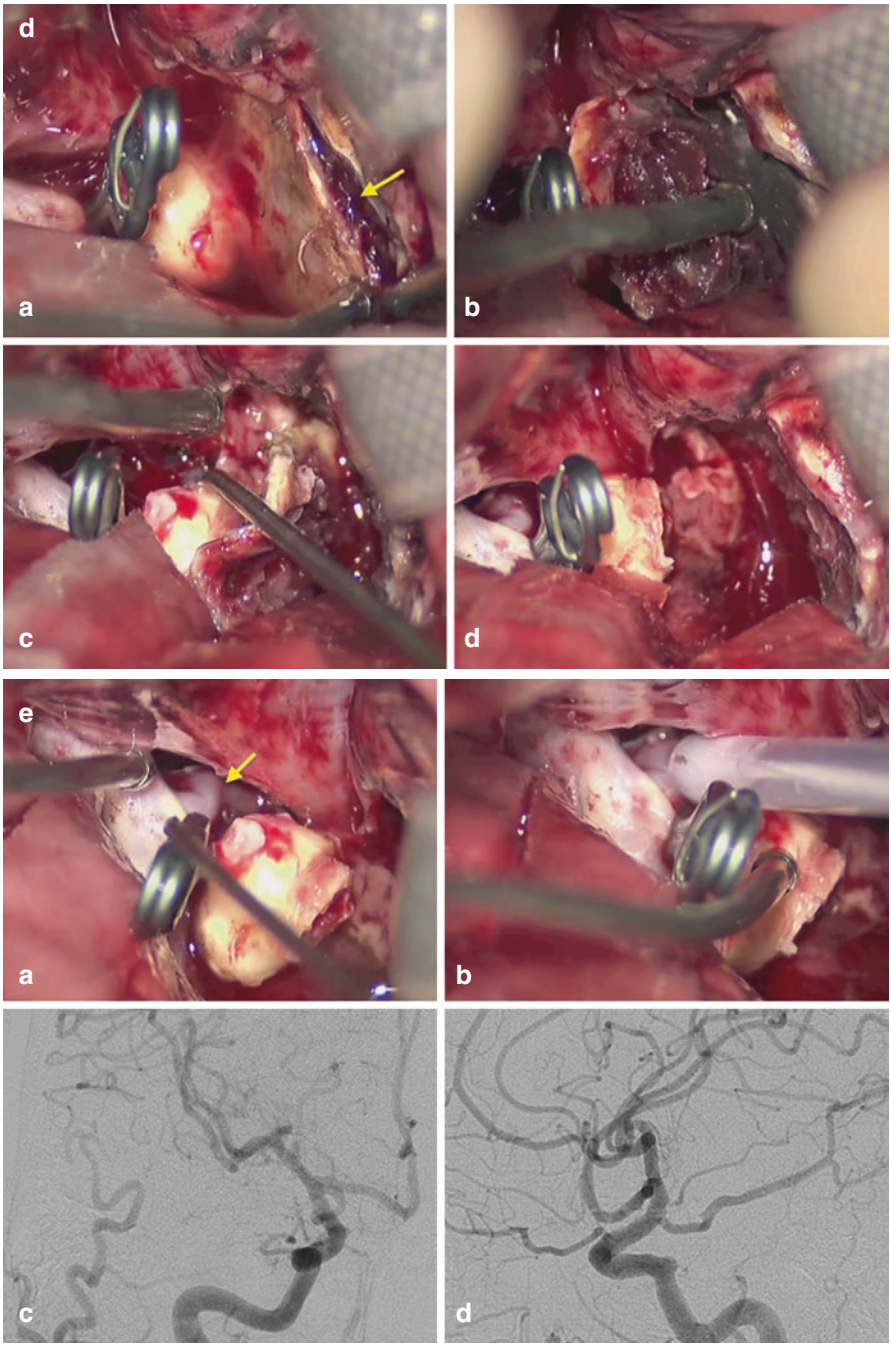


Fig. 7.3 (continued)

anterior thalamoperforators, and the AChorA should be identified, with the latter two often displaced medially by large PcoA aneurysms. If the aneurysm is adherent to the temporal lobe, care should be taken during dissection to ensure the dome is not avulsed. A simple straight or gently curved clip is generally sufficient for occluding these aneurysms.

Unique Considerations for Anterior Choroidal Artery Aneurysms

The AChorA arises from the communicating segment of the ICA 2–5 mm distal to the origin of the posterior communicating artery [11, 23, 24]. The AChorA is a small vessel ranging from 0.5 to 2 mm in diameter [11, 24, 25]. The majority of AChorA arise as a single trunk [11, 24]. The two segments of the AChorA are the cisternal segment, which encompasses the origin to the choroidal fissure, and the plexal segment, which encompasses the branches passing through the choroidal fissure to supply the choroid plexus of the temporal horn [11, 24, 25]. The cisternal segment of the AChorA projects posterolaterally from the ICA, coursing through the carotid cistern before turning posteromedially into the crural cistern. From there, it continues to the ambient cistern prior to entering the choroidal fissure. Between 2 and 18 perforators arise along the course of the cisternal segment of the AChorA, including at the origin of the AChorA [26]. These perforators variably supply many structures, leading to a spectrum of presentations of infarcts, ranging from asymptomatic to severely disabling strokes. The most consistent deficit is contralateral hemiplegia secondary to infarction of the pyramidal tract in the posterior limb of the internal capsule [27]. Other possible sequelae of infarcts include contralateral hemisensory loss (due to involvement of the ventral posterolateral nucleus of the thalamus or thalamocortical sensory fibers) or homonymous hemianopia (from a lateral geniculate body or geniculocalcarine tract infarction) [27].

Aneurysms of the AChorA are infrequent, occurring as 2–5% of all intracranial aneurysms [26]. AChorA aneurysms arise at the posterolateral wall of the communicating segment of the internal carotid artery and project laterally along the course of the AChorA. Lehecka et al. described four possible variations of AChorA aneurysms in relation to the parent vessel [26]. The first is the aneurysm arising anterolateral to the AChorA; the second is the aneurysm arising superolateral to the AChorA; the third is the aneurysm arising posterolateral to the AChorA; and the fourth is the aneurysm arising between a duplicated AChorA [26]. Given the small size of the AChorA and the many important perforators arising from it, there is little room for error in clipping, with rates of permanent AChorA syndrome ranging from 5.3% to 15.7% in surgical series [28, 29].

A standard pterional craniotomy is often adequate for approaching these aneurysms. The head should be turned contralaterally, approximately 20°, tilted laterally, and kept neutral in an anterior-posterior direction [26, 30]. The goal of these maneuvers is to position the Sylvian fissure vertically in order to facilitate exposure of the distal ICA. One must avoid turning the head too far contralaterally, which would cause the temporal lobe to block visualization of the aneurysm. As these aneurysms are often intimately involved with the medial temporal lobe, it is important to avoid undue traction on the lobe given the risk of aneurysm rupture in cases where the aneurysm is adherent to the medial temporal lobe. A wide Sylvian dissection from the limen insula to the ICA bifurcation and entire length of the supraclinoid ICA is crucial to have full control of the proximal and distal neck of the aneurysm. Once the final clip has been placed, it is essential to confirm patency of the AChorA with either microvascular Doppler, noninvasive indocyanine green angiography, or catheter angiography.

Unique Considerations for Ophthalmic Artery Aneurysms

The ophthalmic segment of the ICA extends from the cavernous sinus roof to the origin of the PcoA. The dura originating from the superomedial ACP forms the distal dural ring, the site at which the ICA enters the subarachnoid space. This ring of dura, which is thick laterally and thins medially, acts as an anchor between the ICA and adjacent structures. The ophthalmic artery projects medially from the superomedial surface of the ophthalmic segment of the ICA immediately distal to the distal dural ring. In approximately 8% of the population, the ophthalmic artery will arise from the intracavernous carotid artery [13]. The artery projects medially beneath the optic nerve; it enters the optic canal inferolateral to the optic nerve. Distal to the origin of the ophthalmic artery, the superior hypophyseal artery (SHA) arises posteromedially and is the only other named branch arising from the ophthalmic segment of the ICA. The SHA ranges from a single branch to as many as five small branches [14]. No perforators from this segment supply the brain parenchyma, but some may supply the optic nerve or chiasm. Ophthalmic artery aneurysms most often arise just distal to the origin of the ophthalmic artery and project superiorly or superomedially. Aneurysms originating further along the ophthalmic ICA segment, incorporating the SHA or perforating branches, are considered SHA aneurysms. Ophthalmic artery aneurysms have a profound female predominance, with females representing more than 80% of patients with this particular aneurysm [31]. In addition, they have a tendency toward multiplicity, with 45% of patients harboring multiple aneurysms [31].

Surgery of ophthalmic artery aneurysms, as well as other supraclinoid ICA aneurysms, necessitates a thorough anatomic understanding of the ACP. The ACP is the posterior continuation of the lesser wing of the sphenoid bone, forming the roof of

the superior orbital fissure and the lateral wall of the optic canal. The falciform ligament is the dura from the ACP to the planum sphenoidale and can form a sharp edge, which may compress the optic nerve. The ACP often blocks intraoperative visualization of the ophthalmic artery origin and should be removed to provide adequate exposure of the proximal ICA for adequate proximal control.

Understanding the relationship of the ophthalmic artery to the optic nerve is important for understanding clinical presentations and surgical approaches to these aneurysms. The ophthalmic artery often runs inferolaterally to the optic nerve in the optic canal. As such, ophthalmic artery aneurysms are associated with visual symptoms in approximately 30% of patients. With aneurysms of 1 cm or more, this is often manifested as an ipsilateral, monocular nasal visual field deficit [31, 32]. Initially, an aneurysm may compress the inferolateral optic nerve and cause a superior nasal quadrantanopia. With larger aneurysms, the superolateral optic nerve is displaced superomedially into the falciform ligament, causing an inferior nasal quadrantanopia. Surgical series report variable degrees of vision improvement following surgical clip ligation of ophthalmic artery aneurysms [18].

An ipsilateral pterional craniotomy with unroofing of the optic canal and removal of the ACP is the most appropriate approach for the majority of these aneurysms. When bilateral, it is possible to address contralateral ophthalmic ICA segment aneurysms from a single approach. With bilateral ophthalmic segment aneurysms, it is advised to approach the symptomatic or larger aneurysm from an ipsilateral craniotomy. When positioning for ophthalmic artery aneurysms, the anterior cranial fossa should be vertically oriented to optimize the operative view of the clinoidal triangle. When the ACP is likely to be drilled or aneurysms are large and/or complex, it is prudent to have the neck prepped for access to the cervical ICA for proximal control. After the initial pterional craniotomy is completed, the posterior orbital roof and the superior and medial surfaces of the superior orbital fissure are removed extradurally. This is followed by removal of the ACP. For unruptured aneurysms, either an intradural or extradural resection can be chosen. However, in ruptured aneurysms an intradural removal of the ACP might be chosen to provide early visualization and access to the aneurysm in the case of an intraoperative rupture. After removing the ACP, cavernous sinus bleeding is often encountered from the cavernous cave (the space between the proximal and distal dural rings housing the clinoidal segment of the ICA), which can be controlled with packing with a hemostatic agent or injecting fibrin glue. Often the optic nerve must be manipulated during aneurysm dissection, but it is important to section the falciform ligament prior to mobilizing the optic nerve, as compression against the falciform ligament may cause or exacerbate visual field deficits. A straight or side-angled clip is often appropriate for clipping ophthalmic artery aneurysms, but a fenestrated, angled clip is typically necessary for SHA aneurysms, given ICA perforators' intimate involvement with these aneurysms (*Case 4*, Fig. 7.4).

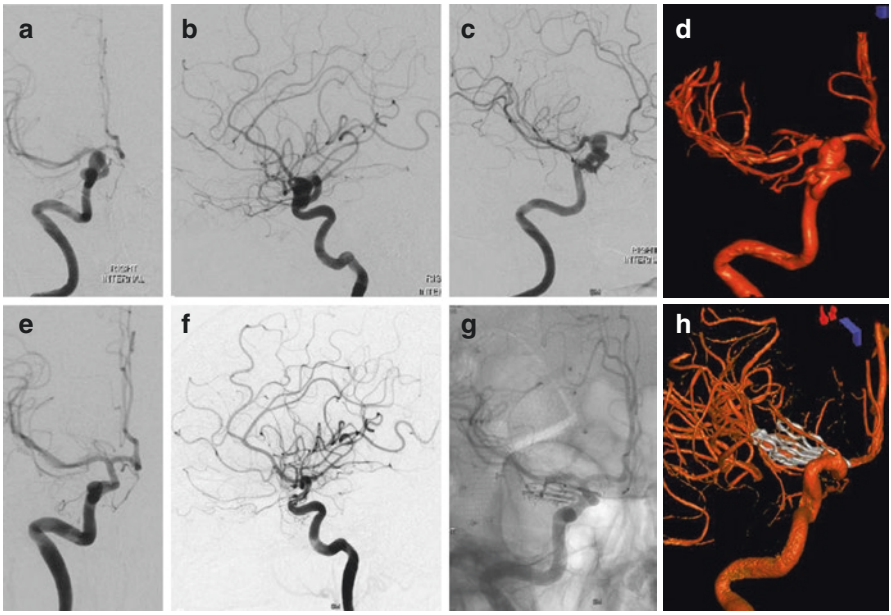


Fig. 7.4 *Case 4.* A 49-year-old female, with a complaint of continuous headache after a major car accident, was found to have an ophthalmic artery aneurysm on her workup. After uncomplicated microsurgical clipping performed via pterional craniotomy with extradural drilling of the ACP and optic roof, and sectioning the entire distal dural ring, the patient was discharged home without any neurological deficit. (**a**–**d**) Preoperative, anteroposterior (AP) (**a**), lateral (**b**), oblique (**c**), and 3D reconstruction angiograms (**d**) show a right complex ophthalmic bilobed aneurysm with involving clinoidal extradural ICA. (**e**, **f**) Postoperative AP (**e**) and lateral (**f**) angiograms reveal total obliteration of the aneurysm and preservation of the parent arteries. (**g**, **h**) Postoperative AP bone-window DSA (**g**) and 3D reconstruction angiogram (**h**) reveal successful clipping of the aneurysm and the positions of the multiple aneurysm clips

Unique Considerations for MCA Aneurysms

The MCA is the larger terminal branch of the ICA. It projects laterally, consisting of four segments. These are the M1 (sphenoidal), the M2 (insular), the M3 (opercular), and the M4 (cortical) segments [33]. The sphenoidal segment extends laterally from the bifurcation of the ICA, parallel to the sphenoid ridge, to the first genu of the MCA at the limen insula. This segment often contains the initial division of the MCA. The insular segment extends from the limen insula to the turn of the branches at the circular sulcus. The opercular segment extends from the circular sulcus through the operculum until reaching the convexity. The cortical segment is composed of the branches on the hemispheric surface. Lenticulostriate arteries arise from the posterior aspect of the M1 and M2 segments and enter the anterior perforated substance to supply the internal capsule and parts of the corpus striatum [14].

In more than 80% of patients with MCA aneurysms, the lesion arises at the initial division of the MCA trunk. However, in 12% of patients, they will arise from the more proximal portion of the M1 segment [14]. Mycotic and traumatic aneurysms are more commonly located along the most distal MCA segments. MCA bifurcation aneurysms project laterally in 45%, inferiorly in 38%, superiorly in 15%, and medially in 2% [34].

MCA aneurysms presented with rupture in 90% of patients in one case series, but as with other aneurysms, they can present with focal neurologic deficits due to mass effect when they are large or giant in size [34].

MCA bifurcation aneurysms are best approached through a pterional craniotomy. When positioning for these aneurysms, the head should be elevated above the heart to aid in venous drainage, in slight extension for gravity-assisted frontal lobe retraction, and turned 20°–30° to the contralateral side. Rotation beyond 30 degrees risks shortening the angle between the operative view and the M1 course, causing it to appear shorter and causing the aneurysm dome to obscure the aneurysmal neck [14]. Modifications to the craniotomy for MCA bifurcation aneurysms include the following: ensuring the bone flap is flush with the anterior cranial fossa and medial enough to allow a subfrontal view of the M1 segment of the MCA, as well as removing the lateral sphenoid wing until entrance of the meningo-orbital artery. When bony removal is flush with the anterior cranial fossa, less frontal lobe retraction is necessary for viewing the MCA bifurcation. Following the craniotomy and dural opening, the Sylvian fissure must be separated for access to the proximal MCA segments. The Sylvian fissure may be opened in a medial to lateral or lateral to medial direction. A medial to lateral opening of the Sylvian fissure allows visualization of the terminal ICA and proximal M1 segment distal to the aneurysm, affording access to vessels for proximal control prior to encountering the aneurysm. A medial transsylvian approach is the safest approach to the majority of lateral- and superior-projecting MCA aneurysms. A lateral to medial opening of the Sylvian fissure is often faster, requiring less dissection. However, the aneurysm dome is encountered before the aneurysm neck is seen and access to vasculature for proximal control is not possible prior to exposing the aneurysm. A lateral transsylvian approach is quite useful for anterior-projecting aneurysms, which can obscure the proximal MCA exposure and may have domes adherent to the sphenoid ridge. A lateral transsylvian approach can also be used for inferior-projecting aneurysms, as the dome will be encountered following exposure of the aneurysm neck and proximal MCA segment. When dividing the Sylvian fissure, the arachnoid should be sharply dissected along the frontal aspect of the Sylvian fissure in order to preserve the inferior draining connections from the Sylvian veins to the sphenoparietal sinus. Veins bridging the frontal lobe and Sylvian fissure can be safely divided, but the superficial and middle cerebral veins must be preserved. If brain relaxation measures have caused the Sylvian fissure to become difficult to identify, the cortical MCA segments can be traced medially to where they emerge from the fissure. A straight or gently curved clip placed parallel to the MCA divisions can be used in MCA bifurcation aneurysms (*Case 2*, Fig. 7.2).

Unique Considerations for PICA Aneurysms

The PICA originates from the VA. Many muscular and segmental arterial branches arise from the VA, but the two largest branches are PICA and the anterior spinal artery, which arises distal to PICA. The origin of PICA arises from the posterior or lateral wall of the VA, approximately 13–16 mm proximal to the origin of the BA [35]. In 57% of patients, PICA appears above the level of the foramen magnum [35, 36]. In 18% of patients, PICA originates below the level of the foramen magnum, and the remainder of patients' PICA arises at the level of the foramen magnum [35, 36]. PICA is absent or hypoplastic in up to 20% of patients. PICA is often described as having five segments [35, 37–39]. The segments are the anterior medullary, lateral medullary, tonsillomedullary, telovelotonsillar, and cortical. The anterior medullary segment begins at the origin and extends along the anterior face of the medulla to the inferior olivary prominence. The lateral medullary segment extends from the inferior olivary prominence to the descending half of the caudal loop, corresponding to the origins of cranial nerves (CN) IX, X, and XI. The tonsillomedullary segment begins as the ascending half of the caudal loop and extends to the superior surface of the cerebellar tonsils. The telovelotonsillar segment forms the cranial loop of PICA, with a choroidal branch arising at the apex. Medullary perforators from PICA most often arise from the first three segments of PICA.

In patients with saccular PICA aneurysms, the defect arises from the PICA origin in nearly two-thirds of patients and from the distal PICA segments in one-third of patients [39]. Aneurysms arising from the PICA origin most often project superiorly, and those arising from more distal segments often occur at vessel bends along the caudal or cranial loops and project in the direction of blood flow. PICA aneurysms can also be fusiform in nature, arising along any portion of the vessel.

The most common presentation of PICA aneurysms is SAH, seen in two-thirds of patients. Focal deficits, while rare, have been described, related to mass effect from large aneurysms.

Aneurysms arising from the proximal segments of PICA can be addressed most often from a far-lateral-transcondylar approach, which provides excellent access to the VA for proximal control. Aneurysms arising from the cortical segment of PICA can often be addressed from a midline suboccipital craniotomy. A straight clip placed perpendicular to the VA can be used for these aneurysms if the origin of PICA can be clearly visualized and excluded from the clip blades. Often it is necessary to utilize a tandem clip strategy when the PICA origin is at the base of a superior-projecting aneurysm. In the case of tandem clip construct, a fenestrated straight clip is placed along the base of the aneurysm with the fenestration encircling the PICA followed by a straight clip above the portion of the aneurysm excluded by the fenestration [13]. In cases of PICA aneurysms arising from the fourth or fifth segments, the vessel may be sacrificed if necessary with only minor consequences, as the brainstem perforators arise proximally, from the first three segments (*Case 5*, Fig. 7.5).

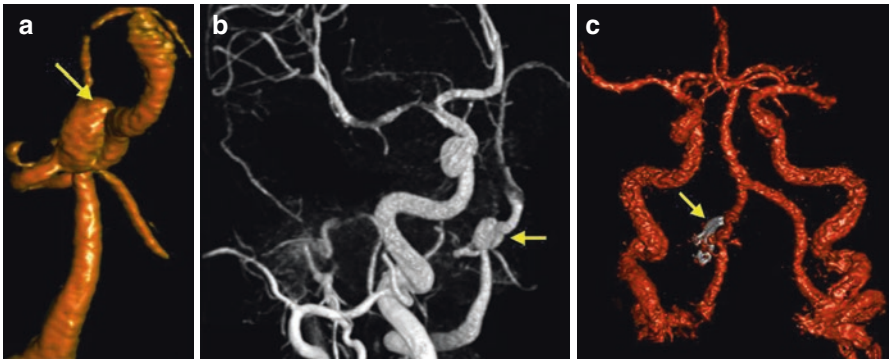


Fig. 7.5 *Case 5.* A 61-year-old female with a known right-sided 2 cm vestibular schwannoma was found to have a 7 mm right posterior cerebellar artery (PICA) aneurysm. After uncomplicated microsurgical clipping, the patient was discharged home without any neurological deficit. (**a**, **b**) Preoperative 3D reconstruction angiogram shows a fusiform aneurysm of the proximal right PICA (arrow). (**c**) Postoperative intravenous digital subtraction angiogram (DSA) reveals total obliteration of the aneurysm and preservation of the parent arteries after successful microsurgical clipping

Unique Considerations for Basilar Aneurysms

The BA is formed from the union of the two vertebral arteries at the pontomedullary sulcus. It travels through the prepontine cistern in a straight configuration in 25–50% of patients and an S shape in the remainder [40]. The average length of the BA is 32 mm [41]. Fenestrations of the BA are seen in 1–5% of patients and are frequently associated with aneurysms [42]. The anterior inferior cerebellar arteries arise from the BA in the proximal portion of the BA. Along its course, the BA gives rise to an average of three paired sets of brainstem perforators: the paramedian, short circumflex, and long circumflex. It terminates in the interpeduncular cistern, bifurcating into the PCAs immediately above the origin of the paired superior cerebellar arteries. The BA terminates at the level of the posterior clinoid process in approximately 50%, above the process in 30%, and below it in 20% [35]. Surrounding the basilar bifurcation laterally are the third nerve and uncus on both sides, anteriorly the dorsum sella and upper clivus, posteriorly the mesencephalon, and superiorly the floor of the third ventricle.

The basilar bifurcation is the most common location for basilar aneurysms. Basilar bifurcation aneurysms have been associated with higher rupture risks in several series, a finding which argues for treatment of these aneurysms [43–45]. Around 80% of basilar bifurcation aneurysms present with hemorrhage, but when large, they may present uniquely with oculomotor nerve palsies, focal deficits from brainstem compression, or even hydrocephalus from compression of the third ventricle and cerebral aqueduct.

Many surgical approaches can be considered with basilar bifurcation aneurysms, depending on the aneurysm size, projection, and location relative to the clivus and

posterior clinoid process. A right-sided approach is most often chosen to avoid retraction of the dominant hemisphere. However, in cases of established deficits, the side corresponding to the deficit should be used for the approach. Aneurysms less than 1 cm from the top of the posterior clinoid, which represent the majority of these lesions, can be approached with a pterional craniotomy combined with an OZ osteotomy. Aneurysms greater than 1 cm below the posterior clinoid are often obscured by the posterior clinoid. They may be more easily accessed via a subtemporal craniotomy, though this approach is not without shortcomings, as it requires significant retraction of the temporal lobe and does not provide reliable visualization of the contralateral P1 segment of the PCA. It is essential to preserve all brainstem perforators throughout the dissection, as disruption of even a small perforator may leave the patient with profound deficits. Recently, a transcavernous approach has gained wide acceptance for access to basilar bifurcation aneurysms. This consists of extradural drilling of the ACP and skeletonizing the oculomotor nerve. This is the approach of choice in our practice for almost all of the basilar bifurcation aneurysms. In cases with a low basilar bifurcation, posterior clinoid drilling is necessary for proximal control. A straight or gently curved clip applied parallel to the PCA is often acceptable for clipping basilar bifurcation aneurysms.

References

1. Murayama Y, Saguchi T, Ishibashi T, et al. Endovascular operating suite: future directions for treating neurovascular disease. J Neurosurg. 2006;104:925–30.
2. Randell T, Niemela M, Kytta J, et al. Principles of neuroanesthesia in aneurysmal subarachnoid hemorrhage: the Helsinki experience. Surg Neurol. 2006;66:382–8. discussion 8.
3. Roessler K, Krawagna M, Dorfler A, Buchfelder M, Ganslandt O. Essentials in intraoperative indocyanine green videoangiography assessment for intracranial aneurysm surgery: conclusions from 295 consecutively clipped aneurysms and review of the literature. Neurosurg Focus. 2014;36:E7.
4. Hernesniemi J, Niemela M, Karatas A, et al. Some collected principles of microneurosurgery: simple and fast, while preserving normal anatomy: a review. Surg Neurol. 2005;64:195–200.
5. Paine JT, Batjer HH, Samson D. Intraoperative ventricular puncture. Neurosurgery. 1988;22:1107–9.
6. Poblete T, Jiang X, Komune N, Matsushima K, Rhoton AL Jr. Preservation of the nerves to the frontalis muscle during pterional craniotomy. J Neurosurg. 2015;122:1274–82.
7. Seckin H, Avci E, Uluc K, Niemann D, Baskaya MK. The work horse of skull base surgery: orbitozygomatic approach. Technique, modifications, and applications. Neurosurg Focus. 2008;25:E4.
8. Rhoton AL Jr. The far-lateral approach and its transcondylar, supracondylar, and paracondylar extensions. Neurosurgery. 2000;47:S195–209.
9. Perlmutter D, Rhoton AL Jr. Microsurgical anatomy of the anterior cerebral-anterior communicating-recurrent artery complex. J Neurosurg. 1976;45:259–72.
10. Rosner SS, Rhoton AL Jr, Ono M, Barry M. Microsurgical anatomy of the anterior perforating arteries. J Neurosurg. 1984;61:468–85.
11. Yaşargil MG. Microneurosurgery. Stuttgart/New York: Georg Thieme Verlag/Thieme Medical Publishers; 1987.

12. Kirgis HD, Fisher WL, Llewellyn RC, Peebles EM. Aneurysms of the anterior communicating artery and gross anomalies of the circle of Willis. J Neurosurg. 1966;25:73–8.
13. Lawton MT. Seven aneurysms: tenets and techniques for clipping. New York: Thieme; 2011.
14. Le Roux PD, Winn HR, Newell DW. Management of cerebral aneurysms. Philadelphia: Saunders; 2004.
15. Ozdemir M, Comert A, Ugur HC, Kahilogullari G, Tubbs RS, Egemen N. Anterior communicating artery aneurysm surgery: which is the most appropriate head position? J Craniofac Surg. 2014;25:2205–8.
16. Ture U, Yasargil MG, Al-Mefty O, Yasargil DC. Arteries of the insula. J Neurosurg. 2000;92:676–87.
17. Gibo H, Lenkey C, Rhoton AL Jr. Microsurgical anatomy of the supraclinoid portion of the internal carotid artery. J Neurosurg. 1981;55:560–74.
18. Spetzler RF, Kalani Y, Nakaji P. Neurovascular surgery. New York: Theime; 2015.
19. Vincentelli F, Caruso G, Grisoli F, Rabehanta P, Andriamamonjy C, Gouaze A. Microsurgical anatomy of the cisternal course of the perforating branches of the posterior communicating artery. Neurosurgery. 1990;26:824–31.
20. Sahs AL, Perret G, Locksley HB, Nishioka H, Skultety FM. Preliminary remarks on subarachnoid hemorrhage. J Neurosurg. 1966;24:782–8.
21. Zheng F, Dong Y, Xia P, et al. Is clipping better than coiling in the treatment of patients with oculomotor nerve palsies induced by posterior communicating artery aneurysms? A systematic review and meta-analysis. Clin Neurol Neurosurg. 2017;153:20–6.
22. Gaberel T, Borha A, di Palma C, Emery E. Clipping versus coiling in the management of posterior communicating artery aneurysms with third nerve palsy: a systematic review and meta-analysis. World Neurosurg. 2016;87:498–506. e4
23. Fujii K, Lenkey C, Rhoton AL Jr. Microsurgical anatomy of the choroidal arteries: lateral and third ventricles. J Neurosurg. 1980;52:165–88.
24. Rhoton AL Jr, Fujii K, Fradd B. Microsurgical anatomy of the anterior choroidal artery. Surg Neurol. 1979;12:171–87.
25. Erdem A, Yasargil G, Roth P. Microsurgical anatomy of the hippocampal arteries. J Neurosurg. 1993;79:256–65.
26. Lehecka M, Dashti R, Laakso A, et al. Microneurosurgical management of anterior choroid artery aneurysms. World Neurosurg. 2010;73:486–99.
27. Leys D, Mounier-Vehier F, Lavenu I, Rondepierre P, Pruvo JP. Anterior choroidal artery territory infarcts. Study of presumed mechanisms. Stroke. 1994;25:837–42.
28. Lee YS, Park J. Anterior choroidal artery aneurysm surgery: ischemic complications and clinical outcomes revisited. J Korean Neurosurg Soc. 2013;54:86–92.
29. Bohnstedt BN, Kemp WJ 3rd, Li Y, et al. Surgical treatment of 127 anterior choroidal artery aneurysms: a cohort study of resultant ischemic complications. Neurosurgery. 2013;73:933–9. discussion 9-40.
30. Heros RC. Microneurosurgical management of anterior choroidal artery aneurysms. World Neurosurg. 2010;73:459–60.
31. Day AL. Aneurysms of the ophthalmic segment. A clinical and anatomical analysis. J Neurosurg. 1990;72:677–91.
32. Date I, Asari S, Ohmoto T. Cerebral aneurysms causing visual symptoms: their features and surgical outcome. Clin Neurol Neurosurg. 1998;100:259–67.
33. Gibo H, Carver CC, Rhoton AL Jr, Lenkey C, Mitchell RJ. Microsurgical anatomy of the middle cerebral artery. J Neurosurg. 1981;54:151–69.
34. Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome. Neurosurgery. 1996;38:2–11.
35. Huber P, Bosse G. Cerebral angiography. New York: Thieme-Stratton; 1982.
36. Bambakidis NC, Dickman CA, Spetzler RF, Sonntag VKH. Surgery of the craniovertebral junction [DVD included]. New York/Stuttgart: Thieme; 2013.

37. Lister JR, Rhoton AL Jr, Matsushima T, Peace DA. Microsurgical anatomy of the posterior inferior cerebellar artery. Neurosurgery. 1982;10:170–99.
38. Rhoton AL Jr. Anatomy of saccular aneurysms. Surg Neurol. 1980;14:59–66.
39. Hudgins RJ, Day AL, Quisling RG, Rhoton AL Jr, Sypert GW, Garcia-Bengochea F. Aneurysms of the posterior inferior cerebellar artery. A clinical and anatomical analysis. J Neurosurg. 1983;58:381–7.
40. Lang J. Skull base and related structures: atlas of clinical anatomy. Stuttgart: Schattauer; 2001.
41. Saeki N, Rhoton AL Jr. Microsurgical anatomy of the upper basilar artery and the posterior circle of Willis. J Neurosurg. 1977;46:563–78.
42. Campos J, Fox AJ, Vinuela F, et al. Saccular aneurysms in basilar artery fenestration. AJNR Am J Neuroradiol. 1987;8:233–6.
43. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. N Engl J Med. 1998;339:1725–33.
44. Ishibashi T, Murayama Y, Urashima M, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke. 2009;40:313–6.
45. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38:1404–10.

Chapter 8
Complex Intracranial Aneurysms: Strategies for Surgical Trapping and Cerebral Revascularization

Ralph Rahme, Marjan Alimi, and David J. Langer

Background: The "Complex" Aneurysm

The majority of intracranial aneurysms can be successfully treated using standard reconstructive microsurgical or endovascular techniques, such as simple clip ligation or coil embolization. For ruptured aneurysms, early treatment is essential to eliminate the risk of rebleeding and allow aggressive medical and/or endovascular management of delayed cerebral ischemia (DCI), which typically occurs in the first 2 weeks after subarachnoid hemorrhage (SAH). However, there is a subset of "complex" aneurysms that do not lend themselves to simple reconstructive procedures and require more technically elaborate management strategies. Non-saccular lesions, including dissecting/blister, mycotic, and fusiform/serpentine aneurysms, have no clearly identifiable neck and are thus inherently classified as "complex." Likewise, saccular aneurysms may present certain morphological and angio-anatomic characteristics that make their treatment more challenging. Such characteristics include large (>10 mm) or giant (>24 mm) size, wide neck (>4 mm) or low dome/neck ratio (<2), presence of intraluminal thrombus, calcified or atherosclerotic neck, arterial branches or perforators originating from the aneurysmal dome or neck, and recurrent aneurysms after clipping or coiling [1–3]. While some of these complex aneurysms may still be amenable to reconstructive procedures, such as

R. Rahme (✉)
Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA

Division of Neurosurgery, SBH Health System, Bronx, NY, USA
e-mail: rrahme@northwell.edu

M. Alimi · D. J. Langer
Department of Neurosurgery, Lenox Hill Hospital, Hofstra Northwell School of Medicine, New York, NY, USA
e-mail: dlanger@northwell.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_8

clipping or clip-wrapping for blister aneurysms, stent- or balloon-assisted embolization for large and wide-necked aneurysms, and flow diverter embolization for non-saccular lesions, many ultimately require a deconstructive procedure, i.e., occlusion of the parent artery or its branches along with the aneurysm. While this can be achieved either microsurgically or endovascularly, it typically mandates microsurgical cerebral revascularization, i.e., bypass surgery, to replace flow in the occluded vascular territory, particularly in the setting of SAH. In this chapter, we will focus on deconstructive microsurgical techniques and bypass surgery for complex intracranial aneurysms.

How Often Are Aneurysm Trapping and Bypass Required in the Real World?

In large microsurgical series, the proportion of intracranial aneurysms that are deemed complex, requiring microsurgical deconstruction and bypass, varies considerably according to the location of the aneurysm. For instance, while anterior cerebral artery (ACA) aneurysms only rarely require bypass surgery (<1%), the rate of bypass may reach 3–4% for middle cerebral artery (MCA) aneurysms and can be as high as 25–30% for posterior inferior cerebellar artery (PICA) aneurysms [1, 3–6]. This high variability is related to major differences in aneurysm morphology and arterial branch anatomy among various aneurysm locations. The rate of bypass surgery for ruptured blister or dissecting aneurysms also appears to be higher than for saccular aneurysms, ranging from 18% to as high as 95%, likely related to the absence of a clippable healthy wall in the aneurysm-bearing portion of the parent artery [7–9].

Deconstructive Microsurgery: Complete Versus Partial Trapping

When feasible, complete aneurysm trapping, i.e., occlusion of both its proximal inflow and distal outflow, usually with clips, is the most definitive treatment for unclippable complex aneurysms. Thus, it is the preferred treatment modality whenever it can be safely achieved. However, this requires that both its inflow (parent vessel) and outflow (distal portion of parent vessel or proximal portion of branches) are surgically accessible for clip placement. Likewise, the absence of vital perforators arising from the aneurysmal portion of the vessel is an absolute prerequisite for complete aneurysm trapping. In some cases, aneurysm trapping can allow aneurysm excision and in situ microsurgical reconstruction of the parent artery. For instance, if the aneurysm is excised from a non-branching linear segment of artery, end-to-end anastomosis of the cut vessel edges can be performed to restore flow. Alternatively, if the aneurysm is excised from an arterial bifurcation, direct branch reimplantation onto the parent artery can be performed via end-to-side anastomosis, end-to-end

anastomosis, or a combination thereof. In situ microsurgical reconstruction of the parent artery may be the most physiological flow replacement technique when a deconstructive procedure is indicated, since it precludes the need for additional bypass procedures. Moreover, both parent artery reanastomosis and branch reimplantation require only a single end-to-end or end-to-side anastomosis and are therefore relatively quick. However, a tension-free anastomosis is essential to avoid suture pullout or breakage. Therefore, some degree of tortuosity or redundancy of the parent artery and extensive dissection prior to vessel reconstruction are mandatory to provide long enough and freely mobilizable vessel segments. It is also imperative for aneurysm excision to be complete, with no pathological arterial wall remaining in the transected ends. Unfortunately, this is not always possible, particularly in perforator-rich zones, where the ability to mobilize vessels can be extremely limited. Likewise, excision of aneurysms involving long arterial segments can result in large gaps that are impossible to repair primarily. In such cases, consideration may be given for an interposition venous or arterial graft. Ideally, the latter should be harvested and ready to implant before aneurysm excision to minimize ischemia time. Likewise, if needed, an extracranial-intracranial (EC-IC) bypass should also be ideally performed, for the same reason, before aneurysm excision. Therefore, before committing to a strategy of aneurysm excision and in situ microsurgical reconstruction, careful preoperative angiographic assessment is mandatory to ensure a high likelihood of technical success and minimize the risk of ischemic complications [3].

Unfortunately, complete trapping may not be always safe or feasible. Occasionally, surgical access to either the afferent or efferent vessel can be technically challenging or risky, thus precluding complete aneurysm trapping. Likewise, the presence of vital perforators arising from the aneurysm itself constitutes a contraindication to complete trapping. In such cases, consideration should be given to partial trapping, i.e., intraaneurysmal flow reduction and/or reversal by either proximal or distal parent vessel occlusion. By reducing and/or reversing flow through the aneurysmal portion of the vessel, partial trapping can lead to gradual intraaneurysmal thrombosis with concomitant vascular remodeling. Perforator patency is usually preserved as a result of continuous flow demand. Unfortunately, however, this is not always the case, since rapid complete intraaneurysmal thrombosis may unpredictably occur, leading to occlusion of perforators and cerebral infarction. Another infrequent but unpredictable potential hazard with this treatment strategy, particularly in the setting of SAH, is aneurysm rupture precipitated by intraaneurysmal thrombosis. To ensure adequate flow in the distal cerebral vasculature, an EC-IC or intracranial-intracranial (IC-IC) bypass is often performed prior to partial aneurysm trapping. The decision to add a distal bypass depends on the size of the vessel being occluded and its vascular territory, as well as the status of circle of Willis (CoW) and leptomeningeal collaterals. Given its preservation of a physiological anterograde flow into the trapped perforators, distal outflow occlusion may be particularly advantageous for aneurysms arising from perforator-rich vessels, such as the proximal MCA and PICA. In fact, good clinical outcomes after distal occlusion, with fairly low rates (0–12.5%) of aneurysm rupture and perforator infarct, have been well documented by a handful of small microsurgical series [2, 10, 11].

To Bypass or Not to Bypass?

Whenever complete or partial aneurysm trapping is being contemplated, a decision whether or not to replace flow in the distal vascular territory, with either an EC-IC or IC-IC bypass, should be made preoperatively. For unruptured aneurysms, this decision largely relies on the size of the vessel being sacrificed, the extent of its vascular territory, and whether sufficient CoW and leptomeningeal collaterals exist to maintain distal flow after aneurysm trapping. For this reason, the importance of a careful preoperative review of angiographic studies and a balloon test occlusion (BTO) of the parent artery cannot be overemphasized in this setting. In our practice, we also routinely assess the intracranial flow map in each patient preoperatively, using the technique of quantitative magnetic resonance imaging via noninvasive optimal vessel analysis (NOVA qMRA®, VasSol Inc., River Forest, IL, USA). Understanding baseline intracranial flow dynamics is essential, as it allows us to tailor a bypass strategy individually for each patient [12–14]. Patient age is another factor many surgeons take into consideration when making the decision to bypass. In fact, occlusion of a major cerebral artery has been associated with an increased risk of de novo aneurysm formation, likely resulting from increased hemodynamic stress in the collateral circulation [15–18]. Given a longer remaining life expectancy, younger patients would theoretically be at greater risk for de novo aneurysm formation. For this reason, many surgeons advocate routine flow replacement bypass for young patients, irrespective of the extent of angiographic collateral flow and results of BTO. However, a flow replacement bypass performed in the setting of little or no flow demand in the cerebral vasculature is at risk of failure, irrespective of the surgeon's level of technical proficiency. Thus, in our practice, we do not endorse the policy of universal flow replacement bypass for young patients but rather rely in our decision-making on objective anatomic and physiologic data provided by preoperative angiographic studies, BTO, and qMRA.

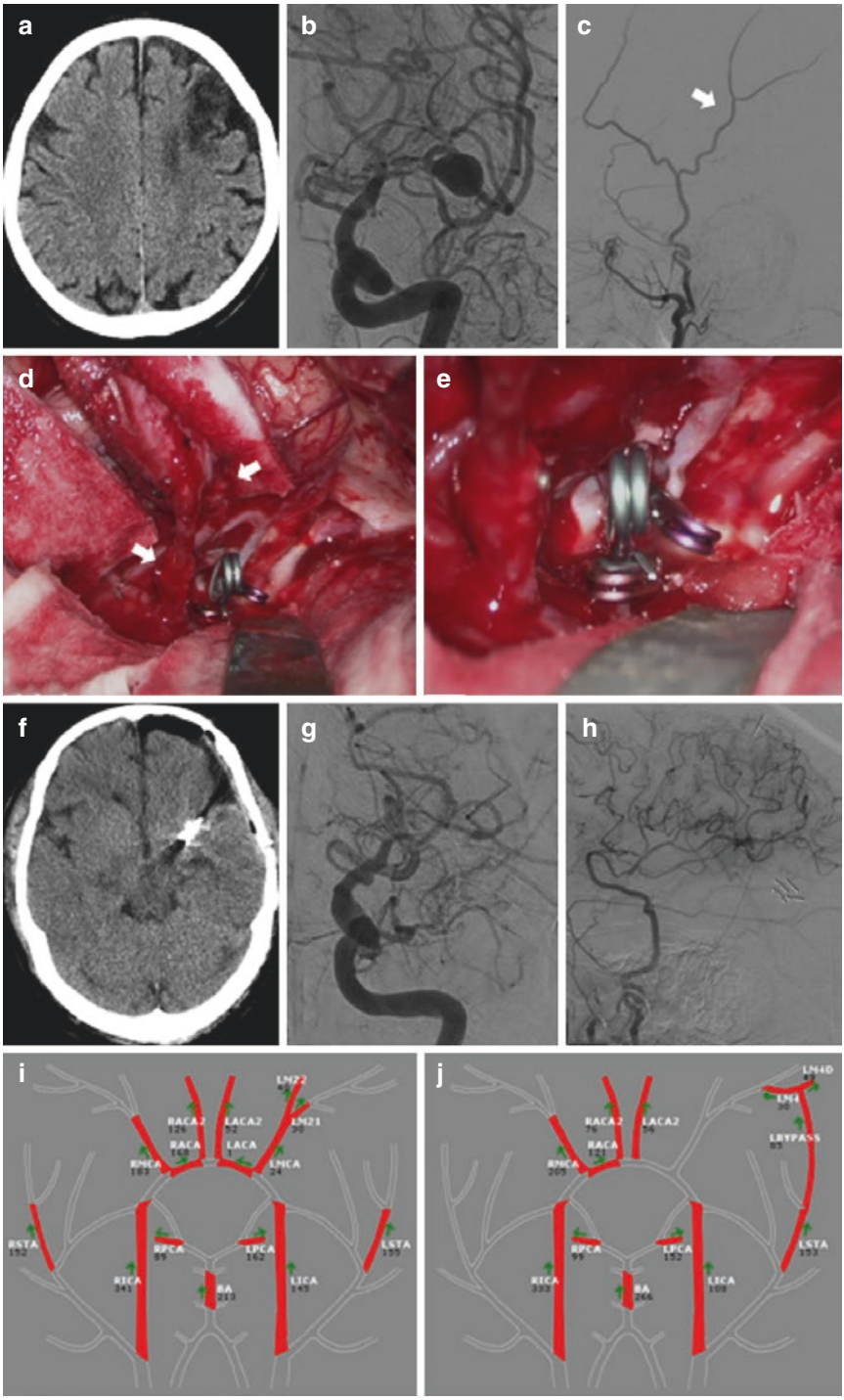
In the setting of SAH, the decision process described above becomes less relevant given the high risk of DCI. In our practice, flow replacement bypass is typically performed whenever trapping of a ruptured aneurysm is expected to occlude a major cerebral artery, apart from a nondominant vertebral artery (VA), irrespective of the preoperative angiographic findings and extent of collateral circulation. Likewise, although preoperative BTO can help assess the quality of collateral flow and cerebrovascular reserve, its results seldom impact our decision to perform a bypass in this setting. The only exception to this rule is in patients who present late, beyond the time window for DCI, i.e., after the second week post-SAH. Early therapeutic ICA sacrifice in the setting of SAH has been associated with very high rates of cerebral ischemia and mortality, both acutely and in a delayed fashion, as a result of DCI [19]. In contrast, the outcomes after aneurysm trapping and bypass have been generally shown to be favorable, essentially paralleling those observed in patients after simple aneurysm clipping [1, 3, 5, 7, 8, 11, 20]. In fact, flow replacement bypass surgery has been shown to preserve cerebral blood flow (CBF) during the second week after SAH, at a time when the risk of DCI is maximal [20]. Moreover, when cerebral

vasospasm occurs, it tends to spare the bypass graft, which allows the latter to be used as an endovascular conduit to treat DCI [20]. In experienced hands, the technical bypass success rates are very high, ranging from 80% to 100% [1, 3, 5–8, 11, 20].

Timing of Bypass: Before or After Attacking the Aneurysm?

There is no doubt that a thoroughly planned bypass strategy ahead of the actual surgical procedure allows the surgeon and operating room personnel to be well prepared in advance, which in turn helps optimize intraoperative efficiency and minimize complications. The determination as to whether an aneurysm is safely clippable can often be made preoperatively, after careful review of angiographic studies (Fig. 8.1). For instance, angiographically large or giant-sized aneurysms that incorporate branching arteries are often associated with a greater difficulty at direct clipping. In cases where simple clip reconstruction is unlikely to succeed, an EC-IC or IC-IC bypass should be given consideration prior to attacking the aneurysm, thus providing the surgeon with more options in terms of parent artery occlusion and aneurysm trapping should the need arise. This extra degree of freedom becomes particularly important when tackling lesions with a notoriously high risk of intraoperative rupture, such as dissecting and blister aneurysms. However, in many cases, the determination that an aneurysm is unclippable can only be made after the parent artery and aneurysm neck have been fully dissected and the local microvascular anatomy has been directly assessed. For instance, dense calcifications or atheroma in the aneurysm neck, which are not always obvious on preoperative angiographic studies, may impede the ability of clip blades to fully close onto the aneurysm neck. In such cases, aneurysm manipulation should be halted and the bypass procedure performed prior to permanently securing the aneurysm. For this reason, it is always advisable to assume the worst-case scenario when surgically approaching complex intracranial aneurysms and prepare for a potential bypass procedure, even when the latter is unlikely to be required. In other words, the potential donor and recipient vessels should be dissected out and prepared for a possible bypass before the aneurysm is approached. Specifically, the superficial temporal artery (STA) should always be preserved when it is of suitable size in the event that it may serve as a donor vessel, even when the use of a high-flow transplanted conduit had been planned. Having a multitude of options intraoperatively is paramount when tackling these challenging lesions and increases the likelihood of a good outcome.

In contrast to the scenario of planned revascularization described above, a rescue bypass procedure may be occasionally required after an unsuccessful clipping attempt. When permanent clip application leads to partial or complete occlusion of the parent artery or a major branch of it, clip repositioning should be performed to deobstruct the normal vessels while keeping the aneurysm neck occluded. However, clip repositioning may not be always possible, particularly when intraoperative aneurysm rupture has occurred within or close to its neck. Any attempts to reposition


a
b
c
d
e
f
g
h
i
LM22
RACA2
LACA2
LM21
RACA
LACA
RMCA
LMCA
RSTA
RPCA
LPCA
LSTA
RICA
BA
LICA
j
LM4D
LM1
LBYPASS
RACA2
LACA2
RACA
RMCA
RPCA
LPCA
LSTA
RICA
BA
LICA

the clip in that setting would lead to profuse intraoperative bleeding from the rupture site. In such instances, a rescue EC-IC or IC-IC bypass becomes indicated to supplement or replace flow in the distal territory of the occluded vessel. Needless to say, a rescue bypass needs to be performed rapidly and efficiently to minimize ischemia time, especially in the setting of marginal CoW and leptomeningeal collaterals.

EC-IC Versus IC-IC Bypass: Which Is Better?

When feasible, an IC-IC bypass constitutes an elegant alternative to EC-IC bypass for several reasons. First, it obviates the need for donor vessel harvesting, additional neck incisions, or cervical carotid artery manipulation. Second, it requires no graft or a short graft, which may translate into a higher long-term patency rate. Third, the bypass graft is less vulnerable to accidental injury, kinking, or compression, given its exclusively intracranial location [21]. However, IC-IC bypasses are generally technically challenging considering the smaller vessel size and the often deep and narrow surgical corridors. More importantly, they require dissection and temporary occlusion of an uninvolved intracranial donor artery, which leads to an additional risk of arterial injury and/or cerebral ischemia, particularly in the setting of SAH [3].

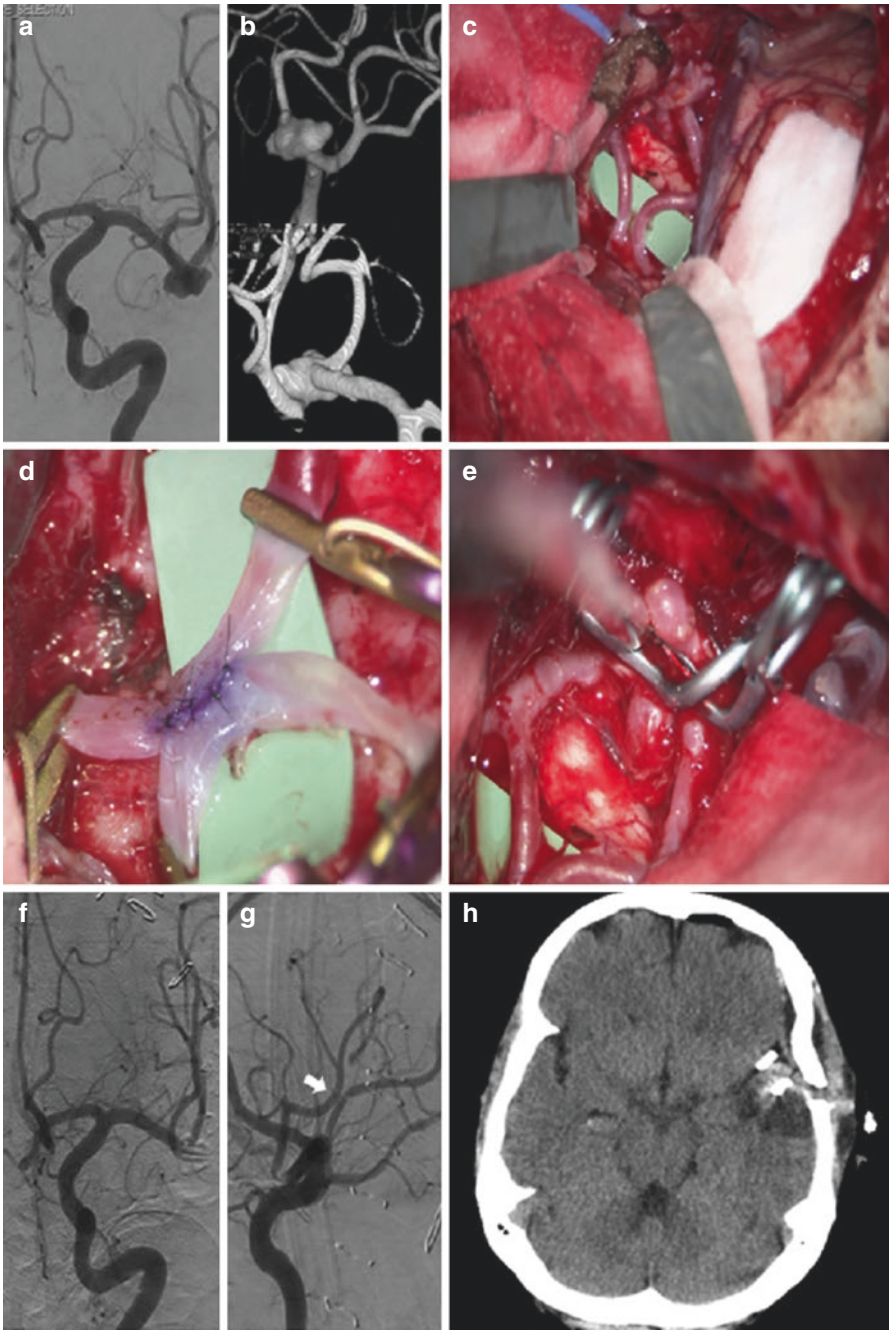
Compared with either IC-IC bypass or aneurysm excision with local reconstruction, EC-IC bypass does not often require interruption of flow in a major cerebral artery, which translates into a lower risk of cerebral infarction. This is especially true when the external carotid artery (ECA) or one of its branches is used as donor vessel and a distal cerebral artery as recipient vessel, as in the case of the very commonly performed STA-MCA bypass. Likewise, the excimer laser-assisted

Fig. 8.1 A 71-year-old diabetic and hypertensive man presented with mild aphasia secondary to a recent left MCA territory stroke. (**a**) Head CT shows a small left frontal infarct. (**b**) Left ICA angiogram reveals an 8-mm saccular aneurysm of the left MCA bifurcation with a 2-mm neck. There is an associated high-grade, flow-limiting stenosis of the M1 segment, which makes endovascular access particularly challenging and risky. Although the aneurysm's narrow neck makes it potentially clippable, the presence of significant atherosclerotic disease in the MCA puts the patient at imminent risk of perioperative stroke. We elected to proceed with surgical revascularization of the left MCA territory followed by clip deconstruction of the MCA bifurcation and aneurysm. (**c**) Left ECA angiogram demonstrates a well-sized parietal branch of the STA, which divides into two equally sizeable branches (white arrow). A "Y" bypass making use of these two donor vessels was thus planned. (**d**, **e**) Intraoperative microphotographs show a successful "Y" bypass to both M2 trunks (**d**, white arrows), followed by complete clip deconstruction of the MCA bifurcation and aneurysm (**e**). (**f**) Postoperative head CT. (**g**) Postoperative left ICA angiogram reveals successful occlusion of the MCA bifurcation and aneurysm, with preservation of the lenticulostriate arteries along the M1 segment. (**h**) Postoperative left ECA angiogram demonstrates a patent "Y" bypass supplied solely by the parietal branch of the STA, with robust opacification of the distal left MCA territory. (**i**) Preoperative NOVA qMRA shows markedly reduced flow (20–40 mL/min) in the left MCA territory. (**j**) Postoperative NOVA qMRA demonstrates high flow (85 mL/min) in the bypass graft

non-occlusive anastomosis (ELANA) technique can be employed to obviate the need for intracranial flow interruption when a high-flow bypass to a large intracranial artery, such as the ICA or proximal MCA, is required [22, 23].

In light of these considerations, we generally favor EC-IC bypass in most cases, except when a side-to-side in situ IC-IC bypass constitutes a more straightforward alternative. This is usually the case when the distal portion of the occluded vessel travels close and parallel to its contralateral counterpart in the midline or to a similarly sized artery, as is the case with distal PICA-PICA, ACA-ACA, and MCA-MCA bypasses [5, 6, 21]. Our general policy is to favor a side-to-side strategy for PICA preservation whenever the local anatomy is deemed appropriate. While equally feasible, an occipital artery (OA) to PICA bypass can be problematic, given that the OA is typically tortuous, which makes it difficult to dissect and makes the graft length somewhat unpredictable until all of the dissection has been carried out. For this reason, we reserve the OA-PICA bypass solely for cases where the PICA-PICA option is deemed unsuitable and where the OA is angiographically robust. Likewise, we find the MCA-MCA bypass, either M2-M2 or M3-M3, to be extremely valuable in managing complex MCA bifurcation aneurysms (Figs. 8.2 and 8.3). By practically converting the MCA bifurcation into a single M2 vessel, MCA-MCA bypass tremendously simplifies clip reconstruction at the MCA bifurcation, allowing to safely deconstruct any of the two M2 branches along with the aneurysm. Moreover, in cases where a complete takedown of the MCA bifurcation is necessary, a side-to-side M2-M2 or M3-M3 bypass allows a single EC-IC bypass graft to perfuse the entire MCA territory. However, if an MCA-MCA bypass is not feasible, consideration may be given, for unruptured aneurysms, to partial trapping via proximal parent vessel occlusion. By preserving patency of the MCA bifurcation, this relatively simple option allows both M2 vessels to be perfused via a single distal EC-IC bypass graft. Alternatively, complete aneurysm trapping requiring takedown of the MCA bifurcation with two distal EC-IC bypass procedures, one for each M2 vessel, may become necessary, particularly in the setting of a ruptured aneurysm.

Fig. 8.2 A 65-year-old woman presented with an incidental left MCA aneurysm. (**a**, **b**) Left ICA angiogram reveals a 10-mm, wide-necked saccular aneurysm of the MCA bifurcation, which incorporates one of the two M2 branches. Note the proximity of the two M2 trunks on 3D angiography (**b**), making them suitable for a side-to-side anastomosis. (**c**–**e**) Intraoperative microphotographs demonstrate a global view of the MCA bifurcation, aneurysm, and M2 trunks (**c**). An in situ M2-M2 bypass was successfully performed (**d**), followed by clip deconstruction of the aneurysm and the incorporated M2 branch (**e**). (**f**, **g**) Postoperative left ICA angiogram shows complete aneurysm obliteration with robust opacification of the entire MCA territory via the widely patent in situ M2-M2 bypass (**g**, white arrow). Following surgery, the patient developed expressive aphasia, which resolved spontaneously over a period of 1 week. (**h**) Postoperative head CT reveals a small infarct in the vicinity of the aneurysm clips, likely secondary to inadvertent occlusion of a cortical MCA branch


a
b
c
d
e
f
g
h

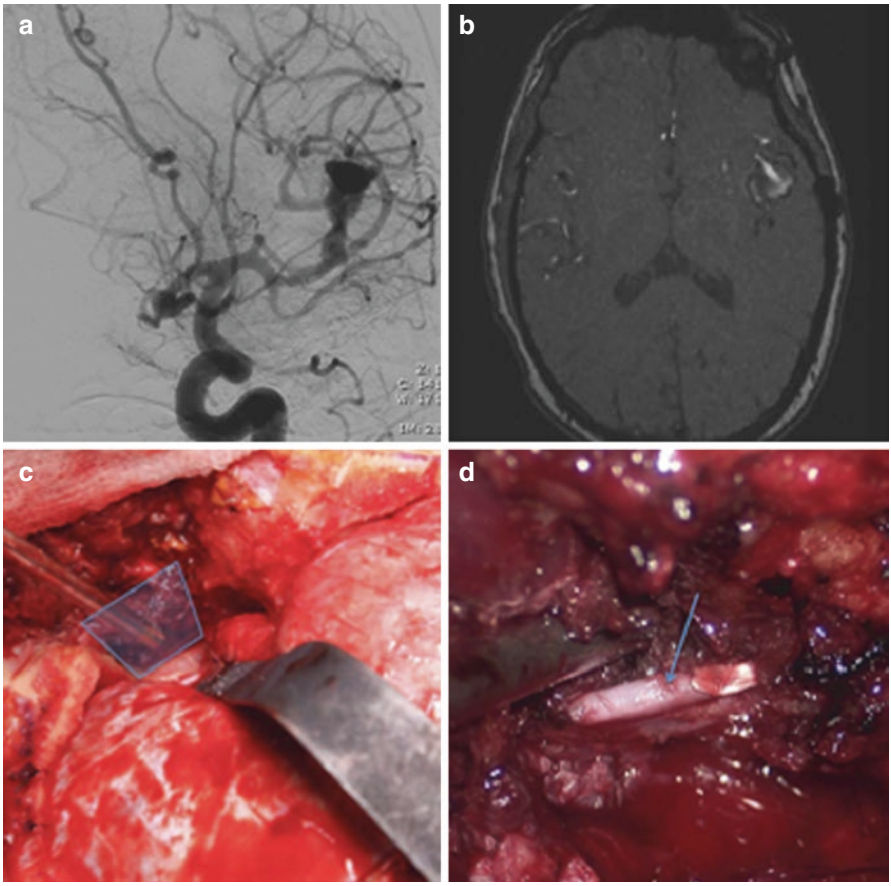


Fig. 8.3 A 36-year-old man presented with a gradually enlarging, dysplastic aneurysm of the left MCA. (**a**) Left ICA angiogram shows a complex fusiform aneurysm of the bifurcation of the superior M2 division of the left MCA (M2-M3 junction). (**b**) Brain MRA demonstrates the presence of an intraaneurysmal thrombus. We elected to proceed with surgical revascularization of the superior M2 trunk followed by aneurysm deconstruction. The patient had a prior history of left craniotomy for meningioma resection, during which the left STA was sacrificed. The left IMax was thus selected as an alternative donor vessel. (**c**–**e**) Intraoperative microphotographs illustrate the surgical approach: extradural subtemporal drilling of the floor of the middle cranial fossa (**c**, shaded blue area), dissection of the IMax in the infratemporal fossa (**d**, blue arrow), and use of a SVG (**e**, blue arrow) connected proximally to the IMax via an end-to-end anastomosis in the infratemporal fossa (**e**, black arrow) and distally to an M3 vessel via an end-to-side anastomosis in the distal Sylvian fissure (**e**, green arrow). (**f**) Postoperative head CTA reveals the SVG course (black arrow) from infratemporal fossa to intracranial space. Following the bypass procedure, the patient was taken immediately to the angiography suite, where proximal coil deconstruction of the aneurysm and parent vessel was performed. A small portion of the aneurysmal dome was intentionally left open to preserve patency of the bifurcation. (**g**) Postoperative left ICA angiogram demonstrates complete obliteration of the aneurysm and parent artery. (**h**) Left ECA angiogram at 2 years shows a patent and mature IMax-SVG-M3 bypass graft, providing robust opacification of the distal MCA territory. Note the persistently open M2 bifurcation, which allows perfusion of both M3 branches via a single distal bypass graft (Parts from Nossek et al. [30], with permission)

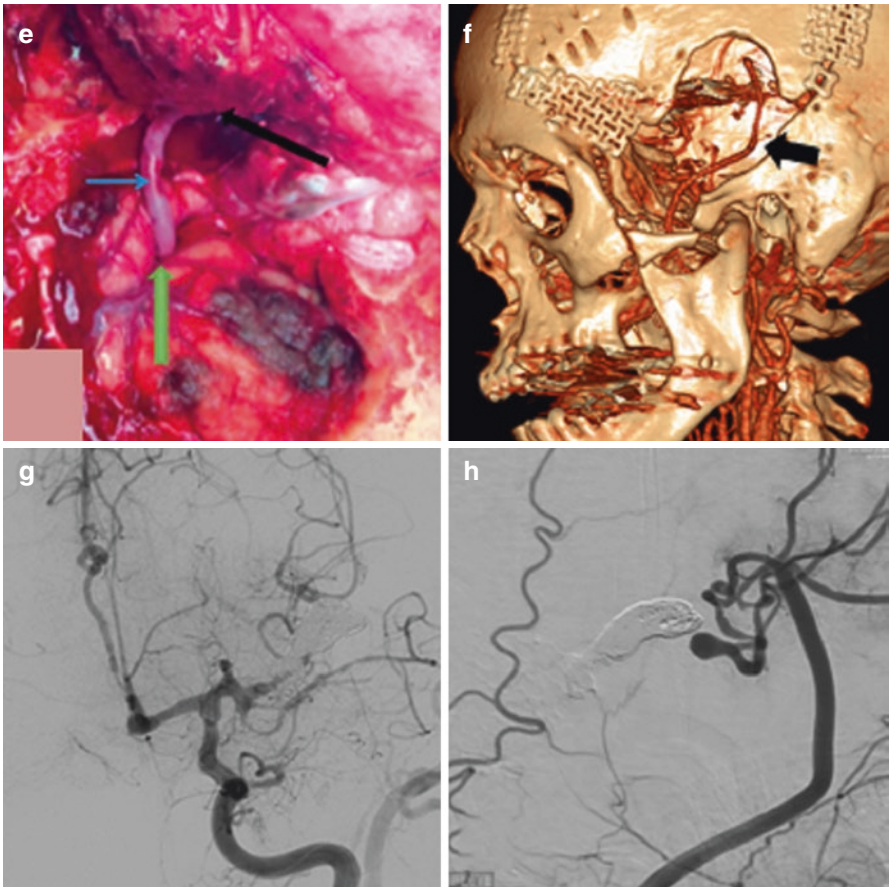


Fig. 8.3 (continued)

Planning the EC-IC Bypass: Donor, Recipient, and Graft Vessels

When planning an EC-IC bypass, it is first essential to determine the amount of blood flow that needs to be replaced, since this will often dictate the type of bypass needed and the choice of donor, recipient, and graft vessels. Depending on the blood flow provided, EC-IC bypass can be grossly classified into low-flow (20–30 mL/min), intermediate-flow (40–60 mL/min), and high-flow (70–140 mL/min). Amin-Hanjani and Charbel [24, 25] advocate the use of flow-assisted surgical technique (FAST), i.e., measuring the flow in the vessel to be replaced and choosing a suitable donor vessel accordingly. Cut-flow measurements of the STA using a micro-flow probe (Intracranial Charbel Micro-Flow Probe®, Transonic Systems Inc., Ithaca, NY, USA) can be extremely useful when planning a flow replacement bypass, particularly in the MCA territory.

A standard STA-MCA bypass typically provides 20–30 mL/min via the M3 or M4 segment of the MCA [26–28] and is best indicated when either the superior or inferior division of the MCA is sacrificed. STA grafts can, however, provide flows in the intermediate- or even high-flow range. This is especially true as the graft gradually matures over time to match flow demand in a chronically ischemic MCA territory [29]. Other types of low-flow bypass can also be performed using either the STA or occipital artery (OA) as donor vessel, to provide flow to the distal portion of a cerebral or cerebellar artery, such as the posterior cerebral artery (PCA), superior cerebellar artery (SCA), and PICA. Such bypasses only require donor vessel dissection and preparation, followed by a single end-to-side intracranial anastomosis. There is no need for additional graft harvesting or neck incisions. They are generally less technically challenging and quicker to perform than other types of EC-IC bypass. Moreover, in contrast to transplanted conduit high-flow bypass, they do not require wide Sylvian fissure dissection or a deep microsurgical field, which can be problematic in patients with high-grade SAH and substantial cerebral edema. Finally, in experienced hands, excellent long-term patency rates in the range of 95–100% are the norm.

When occlusion of the proximal MCA, basilar artery (BA), or a largely dominant VA is being contemplated, either an intermediate- or a high-flow bypass becomes indicated, depending on the extent and quality of CoW and leptomeningeal collaterals. A double-barrel STA-MCA bypass makes use of both the parietal and frontal branches of the STA to replace flow in both the superior and inferior divisions of the MCA, thus providing 50 mL/min or more blood flow in the MCA territory [28]. Another technique of intermediate-flow bypass using the main trunk of the STA as donor vessel, the MCA as recipient, and a short interposition saphenous vein graft (SVG) was recently shown to provide blood flow in the range of 20–100 mL/min [29]. However, we feel that extreme caution should be exercised when selecting an appropriate donor vessel for flow replacement in the MCA and that the STA, given its variable size and flow-carrying capacity, may not be the best option for this purpose. In our practice, we favor the use of a modified technique of intermediate-flow EC-IC bypass, which we term subcranial-intracranial (SC-IC) bypass, using the internal maxillary (IMax) trunk as donor vessel, the M2 or M3 segment of the MCA as recipient, and a short cephalic vein graft (CVG). This SC-IC bypass requires only 8–10 cm of graft length and has been shown to provide blood flow in the range of 30–60 mL/min [30, 31]. The CVG has a diameter ranging from 1.5 to 2 mm, which is very well matched with the size of the MCA. It has little to no valves and very few branches, which makes harvesting easier than that of the SVG. Finally, in contrast to the radial artery graft (RAG), the use of the CVG is not associated with any risk of ischemic complications in the upper extremity. For these reasons, we favor the use of a CVG whenever a short interposition graft is indicated [31]. We generally consider the STA-MCA bypass as a second-line option after either an IMax-MCA or a standard EC-IC bypass using a transplanted arterial or venous graft. An advantage of intermediate-flow bypass techniques that make use of the STA and IMax is that they usually involve a single cranial incision, thus obviating the need for

additional neck incisions, cervical carotid artery manipulation, or long EC-IC bypass grafts [29–32].

Therapeutic occlusion of the ICA generally requires a high-flow bypass for adequate flow replacement. However, it should be noted that, in the current era of endovascular flow diversion, ICA sacrifice and flow replacement are seldom required in the management of complex ICA aneurysms. In those rare cases, an EC-IC bypass with a transplanted conduit is indicated if the patient fails BTO preoperatively. For this purpose, the cervical carotid system is used as donor vessel and the M2 or M3 segment of the MCA as recipient, with either an arterial or venous interposition graft in between. We generally favor the use of the ECA as donor vessel over the common carotid artery (CCA) or internal carotid artery (ICA), since this would avoid any reduction of CBF as result of temporary clipping during the proximal anastomosis. Preservation of CBF throughout the procedure is particularly important in patients with SAH. In regard to the interposition graft, a minimum length of 18–20 cm is usually required to connect the cervical carotid system with the proximal MCA. For this reason, either a SVG or a radial artery graft (RAG) is usually preferred. The main advantage of a SVG is that very high flows can be achieved in the bypass, over 200 mL/min in some cases. However, this may lead to a potentially increased risk of hyperperfusion syndrome [20, 29]. Moreover, there is an abundance of unidirectional valves in the lumen of the SVG and frequent discrepancy between its size and that of the MCA, which could lead to excessive turbulence at the distal anastomosis site and an increased risk of delayed graft thrombosis [30]. Despite a somewhat lower flow-carrying capacity, the RAG tends to be well matched in caliber to the proximal MCA and has the advantage of being a normal physiological conduit for arterial blood, which could translate into a higher long-term patency rate. However, the RAG has an inherent risk of spasm and is not an option for patients with bilaterally poorly developed palmar arches [30]. For this reason, in our practice, we still consider the SVG as a first-line option for long EC-IC bypass grafts.

The Bypass Is In: Now What?

"The operation begins when the bypass is in" is a statement that summarizes our general philosophy and reflects the importance of assessing the entire case once again with the new graft in place. Following bypass construction and before any deconstructive procedure, we usually start by confirming patency and assessing flow in the bypass graft, using a combination of different modalities. While the micro-Doppler probe can provide a quick subjective assessment of graft patency, we generally rely on the Charbel micro-flow probe to quantitatively measure flows in the bypass construct. Indocyanine green (ICG) video-angiography is also frequently obtained to demonstrate anatomic patency of the bypass. Finally, an intraoperative angiogram is always performed prior to any deconstructive procedure, not only to confirm patency and study flow in the newly created bypass graft but also to reveal

what cannot be readily seen with the microscope, specifically the status of CoW and leptomeningeal collaterals with the graft in place. At that point, the decision must be made on how best to deconstruct the aneurysm and parent artery. When readily achievable, complete or partial microsurgical trapping remains the preferred approach. However, we will often defer direct microsurgical attack on the aneurysm where the deconstruction puts perforators at risk, involves cranial nerve dissection, or requires significant brain retraction or manipulation, particularly in the setting of SAH. In such cases, to entertain flow demand and maintain graft patency, we typically occlude the parent artery using a permanent aneurysm clip placed on a surgically accessible, perforator-free portion of the vessel. We then transfer the patient directly to the angiography suite, where a high-quality angiogram is obtained to fully understand intracranial flow dynamics with the graft in place. Then, the aneurysm and parent artery can often be directly deconstructed using endovascular techniques. In fact, modern hybrid angiography suites should make the decision-making process much more streamlined and allow direct endovascular treatment when microsurgical deconstruction is deemed unsafe.

Principles of Postoperative Care

When a deconstructive procedure and bypass are being contemplated, patients are typically started on full-dose aspirin (e.g., 325 mg daily) preoperatively, which is continued for a minimum of 6 months after surgery. Postoperatively, patients are closely monitored in the neurointensive care unit (NICU) and are kept euvolemic and normotensive. Hypovolemia and hypotension should be avoided at all costs to prevent bypass graft thrombosis and, in the setting of SAH, minimize the risk of DCI. If the latter occurs, aggressive triple H therapy (hypertension-hypervolemia-hemodilution) should be instituted. As mentioned above, cerebral vasospasm generally spares the bypass graft, which allows the latter to be used as access route should endovascular treatment for DCI become indicated. Patients undergo head CT and cerebral catheter angiography on the first postoperative day to rule out ischemic complications and confirm bypass patency. NOVA qMRA is also routinely obtained postoperatively to assess flow through the graft, which helps us better understand flow demand and the relationship between conduit selection and flow. We believe this type of feedback is essential, as it helps surgeons match their preoperative bypass plans with desired postoperative results, based on objective quantitative data. For patients with unruptured aneurysms, the typical length of stay in the NICU is 48 h, following which they are gradually mobilized and transferred to the floor. They are typically discharged home on the fourth or fifth postoperative day. In contrast, patients with unruptured aneurysms undergo standard SAH management, including DCI watch which requires a longer stay in the NICU.

Conclusion

Complex intracranial aneurysms often require surgical or endovascular deconstruction to achieve complete obliteration and eliminate the risk of hemorrhage. A microsurgical bypass to replace flow in the parent artery may thus become necessary to prevent cerebral ischemia and, in the setting of aneurysmal SAH, DCI-related morbidity and mortality. Complete aneurysm trapping is always desirable if it can be achieved safely. Otherwise, partial trapping, either proximal or distal, can help prevent aneurysm rupture by reducing or reversing intraaneurysmal flow. The bypass procedure is best performed before exploring the aneurysm, hence the importance of meticulous preoperative planning. The vascular neurosurgeon has a variety of bypass options, donor and recipient vessels, and interposition grafts to choose from. While personal preference certainly matters, the specific type of bypass is often dictated by the aneurysm location, local microvascular anatomy, parent artery caliber, and quality of collateral flow. In experienced hands, microsurgical trapping and bypass have high technical success rates, with clinical outcomes essentially similar to those observed after simple clipping.

References

1. Kivipelto L, Niemelä M, Meling T, Lehecka M, Lehto H, Hernesniemi J. Bypass surgery for complex middle cerebral artery aneurysms: impact of the exact location in the MCA tree. J Neurosurg. 2014;120(2):398–408.
2. Esposito G, Fierstra J, Regli L. Distal outflow occlusion with bypass revascularization: last resort measure in managing complex MCA and PICA aneurysms. Acta Neurochir. 2016;158(8):1523–31.
3. Tayebi Meybodi A, Huang W, Benet A, Kola O, Lawton MT. Bypass surgery for complex middle cerebral artery aneurysms: an algorithmic approach to revascularization. J Neurosurg. 2017;127(3):463–79.
4. Rodríguez-Hernández A, Sughrue ME, Akhavan S, Habdank-Kolaczkowski J, Lawton MT. Current management of middle cerebral artery aneurysms: surgical results with a "clip first" policy. Neurosurgery. 2013;72(3):415–27.
5. Abla AA, Lawton MT. Anterior cerebral artery bypass for complex aneurysms: an experience with intracranial-intracranial reconstruction and review of bypass options. J Neurosurg. 2014;120(6):1364–77.
6. Abla AA, McDougall CM, Breshears JD, Lawton MT. Intracranial-to-intracranial bypass for posterior inferior cerebellar artery aneurysms: options, technical challenges, and results in 35 patients. J Neurosurg. 2016;124(5):1275–86.
7. Shimizu H, Matsumoto Y, Tominaga T. Non-saccular aneurysms of the supraclinoid internal carotid artery trunk causing subarachnoid hemorrhage: acute surgical treatments and review of literatures. Neurosurg Rev. 2010;33(2):205–16.
8. Kazumata K, Nakayama N, Nakamura T, Kamiyama H, Terasaka S, Houkin K. Changing treatment strategy from clipping to radial artery graft bypass and parent artery sacrifice in patients with ruptured blister-like internal carotid artery aneurysms. Neurosurgery. 2014;10(Suppl 1):66–73.

9. Owen CM, Montemurro N, Lawton MT. Blister aneurysms of the internal carotid artery: microsurgical results and management strategy. Neurosurgery. 2017;80(2):235–47.
10. Nussbaum ES. Surgical distal outflow occlusion for the treatment of complex intracranial aneurysms: experience with 18 cases. Neurosurgery. 2015;11(Suppl 2):8–16.
11. Hara T, Arai S, Goto Y, Takizawa T, Uchida T. Bypass surgeries in the treatment of cerebral aneurysms. Acta Neurochir Suppl. 2016;123:57–64.
12. Langer DJ, Lefton DR, Ostergren L, Brockington CD, Song J, Niimi Y, Bhargava P, Berenstein A. Hemispheric revascularization in the setting of carotid occlusion and subclavian steal: a diagnostic and management role for quantitative magnetic resonance angiography? Neurosurgery. 2006;58(3):528–33.
13. Amin-Hanjani S, Shin JH, Zhao M, Du X, Charbel FT. Evaluation of extracranial-intracranial bypass using quantitative magnetic resonance angiography. J Neurosurg. 2007;106(2):291–8.
14. Starke RM, Chwajol M, Lefton D, Sen C, Berenstein A, Langer DJ. Occipital artery-to-posterior inferior cerebellar artery bypass for treatment of bilateral vertebral artery occlusion: the role of quantitative magnetic resonance angiography noninvasive optimal vessel analysis: technical case report. Neurosurgery. 2009;64(4):E779–81.
15. Fujiwara S, Fujii K, Fukui M. De novo aneurysm formation and aneurysm growth following therapeutic carotid occlusion for intracranial internal carotid artery (ICA) aneurysms. Acta Neurochir (Wien). 1993;120(1–2):20–5.
16. Inui Y, Oiwa Y, Terada T, Nakakita K, Kamei I, Hayashi S. De novo vertebral artery dissecting aneurysm after contralateral vertebral artery occlusion – two case reports. Neurol Med Chir (Tokyo). 2006;46(1):32–6.
17. Arambepola PK, McEvoy SD, Bulsara KR. De novo aneurysm formation after carotid artery occlusion for cerebral aneurysms. Skull Base. 2010;20(6):405–8.
18. Tutino VM, Mandelbaum M, Choi H, Pope LC, Siddiqui A, Kolega J, Meng H. Aneurysmal remodeling in the circle of Willis after carotid occlusion in an experimental model. J Cereb Blood Flow Metab. 2014;34(3):415–24.
19. Meling TR, Sorteberg A, Bakke SJ, Slettebø H, Hernesniemi J, Sorteberg W. Blood blister-like aneurysms of the internal carotid artery trunk causing subarachnoid hemorrhage: treatment and outcome. J Neurosurg. 2008;108(4):662–71.
20. Endo H, Fujimura M, Shimizu H, Inoue T, Sato K, Niizuma K, Tominaga T. Cerebral blood flow after acute bypass with parent artery trapping in patients with ruptured Supraclinoid internal carotid artery aneurysms. J Stroke Cerebrovasc Dis. 2015;24(10):2358–68.
21. Korja M, Sen C, Langer D. Operative nuances of side-to-side in situ posterior inferior cerebellar artery-posterior inferior cerebellar artery bypass procedure. Neurosurgery. 2010;67(2 Suppl Operative):471–7.
22. Langer DJ, Van Der Zwan A, Vajkoczy P, Kivipelto L, Van Doormaal TP, Tulleken CA. Excimer laser-assisted nonocclusive anastomosis. An emerging technology for use in the creation of intracranial-intracranial and extracranial-intracranial cerebral bypass. Neurosurg Focus. 2008;24(2):E6.
23. Burkhardt JK, Esposito G, Fierstra J, Bozinov O, Regli L. Emergency non-occlusive high capacity bypass surgery for ruptured Giant internal carotid artery aneurysms. Acta Neurochir Suppl. 2016;123:77–81.
24. Amin-Hanjani S, Du X, Mlinarevich N, Meglio G, Zhao M, Charbel FT. The cut flow index: an intraoperative predictor of the success of extracranial-intracranial bypass for occlusive cerebrovascular disease. Neurosurgery. 2005;56(1 Suppl):75–85.
25. Amin-Hanjani S, Charbel FT. Flow-assisted surgical technique in cerebrovascular surgery. Surg Neurol. 2007;68(Suppl 1):S4–11.
26. Baaj AA, Agazzi S, van Loveren H. Graft selection in cerebral revascularization. Neurosurg Focus. 2009;26(5):E18.
27. Lee M, Guzman R, Bell-Stephens T, Steinberg GK. Intraoperative blood flow analysis of direct revascularization procedures in patients with moyamoya disease. J Cereb Blood Flow Metab. 2011;31(1):262–74.

28. Duckworth EA, Rao VY, Patel AJ. Double-barrel bypass for cerebral ischemia: technique, rationale, and preliminary experience with 10 consecutive cases. Neurosurgery. 2013;73(1 Suppl Operative):ons30–8.
29. Kaku Y, Takei H, Miyai M, Yamashita K, Kokuzawa J. Surgical treatment of complex cerebral aneurysms using interposition short vein graft. Acta Neurochir Suppl. 2016;123:65–71.
30. Nossek E, Costantino PD, Eisenberg M, Dehdashti AR, Setton A, Chalif DJ, Ortiz RA, Langer DJ. Internal maxillary artery-middle cerebral artery bypass: infratemporal approach for subcranial-intracranial (SC-IC) bypass. Neurosurgery. 2014;75:87–95.
31. Nossek E, Costantino PD, Chalif DJ, Ortiz RA, Dehdashti AR, Langer DJ. Forearm cephalic vein graft for short, "middle"-flow, internal maxillary artery to middle cerebral artery bypass. Operative Neurosurgery. 2016;12:99–105.
32. Yağmurlu K, Kalani MYS, Martirosyan NL, Safavi-Abbasi S, Belykh E, Laarakker AS, Nakaji P, Zabramski JM, Preul MC, Spetzler RF. Maxillary artery to middle cerebral artery bypass: a novel technique for exposure of the maxillary artery. World Neurosurg. 2017;100:540–50.

Chapter 9
Microsurgical Treatment of Complex Intracranial Aneurysms

Zhikui Wei, Ulas Cikla, Hakan Seckin, and Mustafa K. Baskaya

Complex intracranial aneurysms (CIA) are rare cerebrovascular lesions that pose significant neurosurgical challenges [1]. CIAs are aneurysms with one or more of the following features: (1) giant size, (2) difficult access, (3) complicated aneurysmal wall structure, and (4) involvement with arterial trunks or branches [2]. Their presentations can vary as to the shape, size, location, orientation, thrombosis, neck calcification, and the relationships with the parent arteries and perforators, all of which play critical roles in clinical decision-making.

Complex clip reconstructions are microsurgical interventions that employ multiple clips, including straight, fenestrated, and complex-shaped clips to achieve the goal of aneurysmal obliteration and vascular flow preservation. They are versatile and efficient microsurgical tools for selected patients with complex intracranial aneurysms. In this chapter, recent developments in complex clip reconstruction are discussed focusing on the complex aneurysms in the anterior and posterior cerebral circulation. In addition, two cases are included to demonstrate the utility of complex clip reconstruction in the treatment of CIAs.

Z. Wei · U. Cikla · M. K. Baskaya (✉)
Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: zwei@uwhealth.org; cikla@neurosurgery.wisc.edu; m.baskaya@neurosurgery.wisc.edu

H. Seckin
Department of Neurosurgery, Lokman Hekim Hospital, Istanbul, Turkey

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_9

Clip Reconstructions for Middle Cerebral Artery (MCA) and Internal Carotid Artery (ICA) Aneurysms

Middle cerebral artery (MCA) aneurysms represent 33% of all intracranial aneurysms [3]. MCA aneurysms can present as CIA with large size, involvement of neural and vascular structures, and complex wall structures. These aneurysms are difficult to clip precisely by a single clip without compromise or kinking of the parent or perforator vessels. To overcome this problem, Babbu et al. reported a "multi-clip" method to achieve a precise and complete clipping [4]. In this multi-clip method, the first clip is placed in the distal part of the aneurysm sac using a standard clip. Then a second miniclip or a fenestrated clip is positioned to "jump" the blades of the first clip for accurate and precise clipping of the aneurysmal sac remnant [4]. In an aneurysm that has a perforator branch at the neck of an aneurysm, Drake's tandem clipping technique can be utilized. In this technique, a first clip is placed slightly away from the perforator, and the second clip is applied over the first to catch the remnant of the sac in a tandem fashion [4].

MCA aneurysms often have wide necks that splay the bifurcation. Clatterbuck et al. [5] reported an orthogonal interlocking tandem clipping technique to completely obliterate an aneurysm and simultaneously "reconstruct" the MCA bifurcation. In a case with a bilobed aneurysm at the MCA bifurcation [5], the authors placed the first clip, which was a long curved clip, across the fundus along the long axis of the M1 segment. Subsequently, a fenestrated straight clip was set at a right angle to the first clip, incorporating it into the fenestration [5]. In another case of a giant aneurysm at the MCA bifurcation, the aneurysm was clipped first with several long straight clips placed across the fundus along the long axis of the M1 segment, followed by two fenestrated clips placed at right angles to the first clip to complete the clip reconstruction [5]. Postoperative angiogram confirmed the complete obliteration of the aneurysms [5].

Occasionally, MCA aneurysms can present as fusiform aneurysms. In a recent report, a new fenestrated Yasargil T-bar clip was used to treat the fusiform M1 aneurysm [6]. These clips have T-shaped blades as opposed to traditional straight edges. They also have fenestrations with variable sizes and blade angles [6]. In a case of fusiform aneurysm of the M1 segment, the fenestration of the clip was placed around the M1 segment, while the blades were placed along the lateral wall of the M1 segment to reconstruct the vessel wall [6]. This method reconstructed posteromedial wall and preserved the origin of the lenticulostriate arteries. The obliteration of aneurysm was confirmed using postoperative angiogram [6]. This new clip allowed successful reconstruction of the M1 segment with a single clip application.

Non-branching segment of internal carotid artery (ICA) can sometimes give rise to complex aneurysm such as blister-like aneurysms. These are rare but dangerous vascular lesions, representing 1% of all intracranial aneurysms [7]. Blister-like aneurysms represent great challenges for clinical management. Surgical treatments

of these aneurysms included direct clipping, direct micro-suturing, and wrapping or endovascular treatment [7, 8]. Kantelhardt et al. recently reported a combined method of suture and clipping for the reconstruction of a ruptured blister-like aneurysm [8]. In this method, the aneurysm is first trapped by temporary clips. Then the vessel wall is adapted by microsutures. Clips are then applied over the sutures, which now serve to prevent dislocation of the clips. This clip and microsuture combination technique is faster than watertight microsutures. More importantly, it also facilitates precise approximation of the edges of the vascular defect and allows consecutive safe clip placement for aneurysm obliteration and vascular reconstruction [8]. Indeed, although various surgical techniques have been described to treat blister-like aneurysms of the supraclinoid ICA, in our experience, excluding the diseased segment of the artery with trapping and bypass is superior and safer than direct clipping or clip-wrapping technique [9].

Clip Reconstruction of Anterior Communicating Artery (ACOMA) and Anterior Cerebral Artery (ACA) Aneurysms

AcomA aneurysms often present in a complex manner. They may have broad A1–A2 junction and are located near the origins of the recurrent artery of Heubner and AcomA perforators. These aneurysms are difficult to reconstruct with a single clip due to the complex wall structure of the aneurysms and potential compromise of the branch arteries and perforators [10].

Straight fenestrated clips can be placed in a successive array to create tunnels that reconstruct origins of branching vessels at the neck of complex aneurysms [11]. This technique has been used to treat AcomA or other anterior circulation aneurysms. In a report by Yang and Lawton, three variations of fenestrated tubes were conceived, namely, the antegrade fenestration tubes, the retrograde fenestration tubes, and the aneurysm dome fenestration tubes [11]. In an illustrative case, the antegrade fenestration tube, built with stacked straight fenestrated clips with an open fenestration tube, was used to clip an AcomA aneurysm with a broad A1–A2 junction where an antegrade fenestration tube was created to transmit the ipsilateral A2, the recurrent artery of Heubner, and the perforators [11]. In retrograde fenestration tubes, a closed fenestration tube was built with stacked straight fenestrated clips and a non-fenestrated clip at the end and was used to reverse the direction of blood flow into the efferent artery exiting from the base of the tube. This technique was used to treat an ICA bifurcation aneurysm that had efferent ACA and MCA originating from the base of an aneurysm [11]. In the dome fenestration tube, the stacked straight fenestrated clips are placed perpendicular to the aneurysm neck rather than parallel to the neck [11]. The dome fenestrated tube was used successfully to reconstruct a supraclinoid ICA aneurysm where the fenestration tube was used to encircle the thickened aneurysm sac [11].

Similar to complex AcomA aneurysms, giant distal anterior cerebral artery (ACA) aneurysms are also rare anterior circulating aneurysms that represent great challenges for neurovascular surgeons. They may have complex arterial branches at the aneurysmal neck and deep location in the skull base. Various techniques have been used to treat these aneurysms, including endovascular interventions, surgical trapping, clip reconstruction, and bypass techniques. In a recent report, a direct clip reconstruction of a 5 cm giant partially thrombosed aneurysm of the distal ACA was described [12]. In this report, microdissection was carried out after thromboendarterectomy to expose the ipsilateral and contralateral A1 and A2 and the aneurysm. The neck of the aneurysm was reconstructed using temporary clips under pentobarbital burst suppression. A postoperative angiography revealed obliteration of the aneurysm and filling of the entire pericallosal artery. The patient experienced a short hospital stay and made an excellent recovery [12].

Clip Reconstruction for Paraclinoid Aneurysms

Paraclinoid aneurysms are thought to be among the most difficult aneurysms to be treated by microsurgery due to the complexity of their vascular anatomy, frequently large and irregular size, proximity to obstructing parts of the medial sphenoid wing, and direct proximity to the optical apparatus [13]. However, some progress has been made in the microsurgical treatment of these aneurysms. In a recent report, Seifert et al. reported their experience with exclusive intradural exposure and clip reconstruction in complex paraclinoid aneurysms [14]. Their reconstruction approach was used in treating a paraclinoid aneurysm where the aneurysmal dome was below the carotid artery. This anatomy allowed microsurgical approach using fenestrated clips under temporary occlusion of the extracranial carotid artery and application of the suction decompression technique [14]. The principles of the clipping techniques essentially follow the Sugita tandem clipping method where fenestrated and angled clips are placed one after the other, locking themselves in place [14]. In an operative video atlas manuscript, Liu reported a similar approach where a large complex ventral paraclinoid carotid artery aneurysm was first decompressed with an initial trapping and direct suction decompression strategy followed by various fenestrated clip reconstructions of the internal carotid artery (ICA) via a modified orbitozygomatic approach [15]. In a case series by Xu et al., microsurgical treatment of large and giant paraclinoid aneurysms were performed using a combination of endovascular and open microsurgical approaches [16]. In direct microsurgical treatment, tandem right-angled fenestrated clips were placed across the carotid artery, and one or two additional long angled or curved clips were added to reinforce the aneurysm neck occlusion [16].

Clip Reconstruction of Posterior Circulation Aneurysms

Posterior circulation aneurysms, representing only 10–15% of all intracranial aneurysms, are ambitious targets for microsurgical interventions [17]. The contributing factors include deep location of the aneurysms, obstructing bony prominences, and the presence of nearby critical structures, such as brain stem perforators and lower cranial nerves. Although most posterior circulation aneurysms are treated with endovascular approaches, open surgical approaches have been utilized to treat selected aneurysms that are not suitable for endovascular treatment [17].

Recent literature has provided ideas that make open microsurgical treatment an option for selected posterior circulation aneurysms. In a recent Neurosurgical Focus video, microsurgical clipping with hypothermic circulatory arrest has been used to a treat a giant vertebrobasilar junction aneurysm after initially failed coil occlusion of the right vertebral artery [18]. This method has been rarely used and provided insights into developing new strategies for microsurgical treatment of posterior circulation aneurysm.

Modifications of existing surgical approaches have also been developed to improve the microsurgical treatment of posterior circulation aneurysms. Gross et al. have discussed the application of petrosal approaches to posterior circulation aneurysms, especially basilar aneurysms [19]. In the anterior petrosal approach, low-lying basilar apex and upper basilar trunk aneurysms are exposed via a subtemporal-transtentorial approach with added traction on the temporal lobe. In addition, an extradural petrous apicectomy was included to provide an additional 1–1.5 cm exposure of the basilar artery [19]. In the posterior petrosal approach, a presigmoid retrolabyrinthine exposure was employed in addition to a temporooccipital craniotomy and mobilization of a skeletonized sigmoid sinus after dividing the superior petrosal sinus and tentorium [19]. This approach, however, has been associated with a relatively high rate of CSK leak [19]. In a report by McLaughlin and Martin, a modified technique for tentorial incision and reflection that optimizes the exposure of the aneurysm was introduced. The key steps for this approach include the critical dissection of the trochlear nerve from its dural canal up to the entrance in the cavernous sinus and extension of the tentorial incision up to the Meckel cave. This technique results in a significantly increased visibility and maneuverability for basilar aneurysms by increasing the rostrocaudal and anterolateral exposure [17].

Exposure to posterior inferior cerebellar artery (PICA) aneurysms is usually opened between vagus, accessory, and hypoglossal nerves for safe clipping [20]. In a recent report, three anatomical triangles and their relationships with PICA aneurysms are defined [20], namely, the vagoaccesory triangle, suprahypoglossal triangle, and infrahypoglossal triangle. The vagoaccesory triangle is defined by CN X superiorly, CN XI laterally, and medulla medially. It can be further divided by CN

XII into the suprahypoglossal triangle and infrahypoglossal triangle. These triangles provided anatomical framework to improve the access and exposure of the PICA aneurysms. For example, PICA aneurysms originating distally on the VA near the vertebrobasilar junction can be accessed via the suprahypoglossal triangle, whereas PICA aneurysms originate distally on the VA can be found within the vagoaccessory triangle [20].

Case Presentations

Case 1: Giant Left MCA Aneurysm

A right-handed 71-year-old female with a history of DM and HTN presents with two episodes of roughly 1 min of the inability to speak. Imaging studies, including head CT, MRI, and diagnostic angiogram, were performed and demonstrated a giant left MCA bifurcation aneurysm measuring 3.2 × 2.0 × 1.4 cm with a large thrombus and a dysplastic neck (Fig. 9.1). The patient elected to have surgery to treat her aneurysm. A left pterional craniotomy was performed to access the giant MCA aneurysm for this case. Immediately after opening the dura, the aneurysm was evident, and the Sylvian fissure was dissected free. After careful dissection circumferentially around the aneurysm, the M1 segment in the ICA was identified to obtain proximal control with temporary clips. A thromboendarterectomy was then performed during which there was brisk bleeding at the center of the aneurysm, and it was controlled with temporary clips. Most of the dome of the aneurysm was removed. Further dissection and aneurysm wall resection were performed to make this giant base easier for clipping. In the end, two clips were placed across the neck of the aneurysm, including a large straight clip and a large fenestrated clip perpendicular to the other clip. This combination was sufficient to prevent the aneurysm from filling. There was a small residual base left on purpose to ensure flow from the M1 and to all of the distal MCA branches. Two additional fenestrated clips were placed below the large stray clip to eliminate a little bit more of the residual neck, and the transected portion of the aneurysm dome was oversewn in a simple running fashion to enforce the clipping. An ICG video angiography confirmed that there was a good flow. An intraoperative angiography confirmed the obliteration of the aneurysm (Fig. 9.2). The postoperative course was uneventful. The patient recovered well from her surgery and experienced no neurological symptoms at 3-year follow-up.

Case 2: Large Left ICA Aneurysm

A 62-year-old man reports word-finding difficulty, confusion, seizure, and subsequent aphasia for a couple of months. A CT scan was performed and illustrated a large frontotemporal mass measuring approximately 8 cm in the greatest

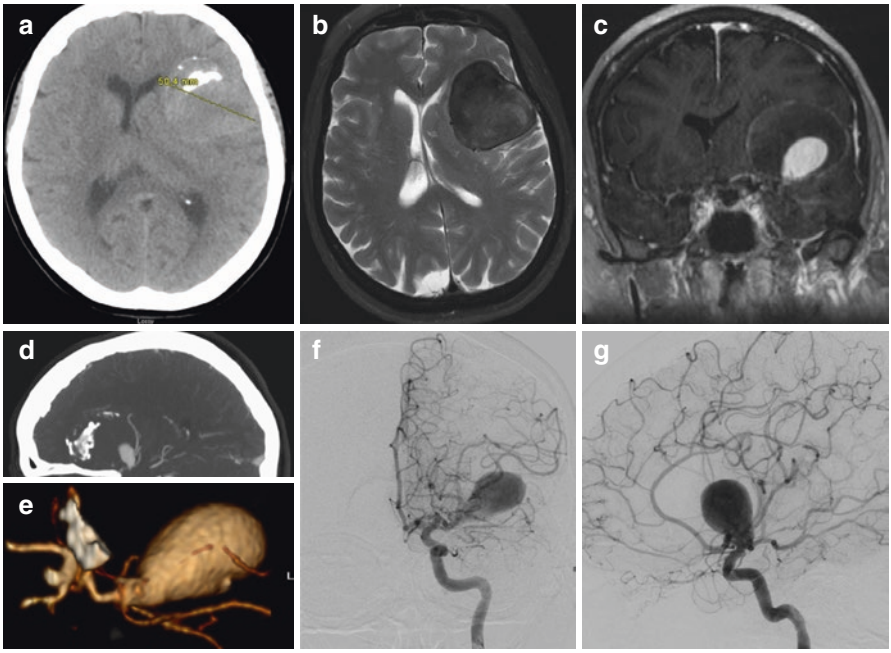


Fig. 9.1 Preoperative imaging studies for a giant left MAC aneurysm in case 1. (**a**) Non-contrast axial-view computerized tomography (CT) of the head demonstrating a well-circumscribed, partially calcified mass in the frontoparietal area of the brain causing a 7 mm midline shift. (**b**) T2-weighted axial-view magnetic resonance imaging (MRI) of the head revealing a well-circumscribed hypointense heterogeneous mass in the left frontoparietal area of the brain. (**c**) T1-weighted, post-contrast, coronal-view MRI demonstrating a central hyperintense, contrast-filling mass representing the living part of the aneurysm. (**d**) CT angiogram demonstrating a giant, partially thrombosed, left M1/M2 bifurcation aneurysm in sagittal view. (**e**) 3D CT angiogram reveals a giant MCA bifurcation aneurysm. (**f**) Digital subtraction angiogram (DSA) of the left internal carotid artery (ICA) with AP projection demonstrating a giant, left M1/M2 bifurcation aneurysm. (**g**) Lateral projection of DSA demonstrating a giant, left M1/M2 bifurcation aneurysm

dimension. This was followed with an MRI scan and an angiogram, which showed a large left ICA bifurcation aneurysm that had a significant amount of thrombosis with filling (Fig. 9.3). The patient elected to undergo surgical treatment. A left-sided orbitozygomatic skull base approach was performed for this case. Upon opening the dura, the aneurysmal mass was apparent on the aperture of the Sylvian fissure. After careful dissection, a small segment of the supraclinoid ICA was isolated for proximal control. The aneurysmal thromboendarterectomy was performed, and the aneurysm was mobilized. It was noted that the MCA bifurcation, the M1 segment, the anterior choroidal artery, and the lenticulostriate arteries were adherent to the aneurysmal wall, which were dissected free subsequently and protected. Before temporary clips were placed on the A1, M1, and supraclinoid ICA, fresh arterial bleeding was experienced and was controlled with suction. Under temporary clipping, thrombectomy was continued with thromboendarterectomy and incision of a redundant

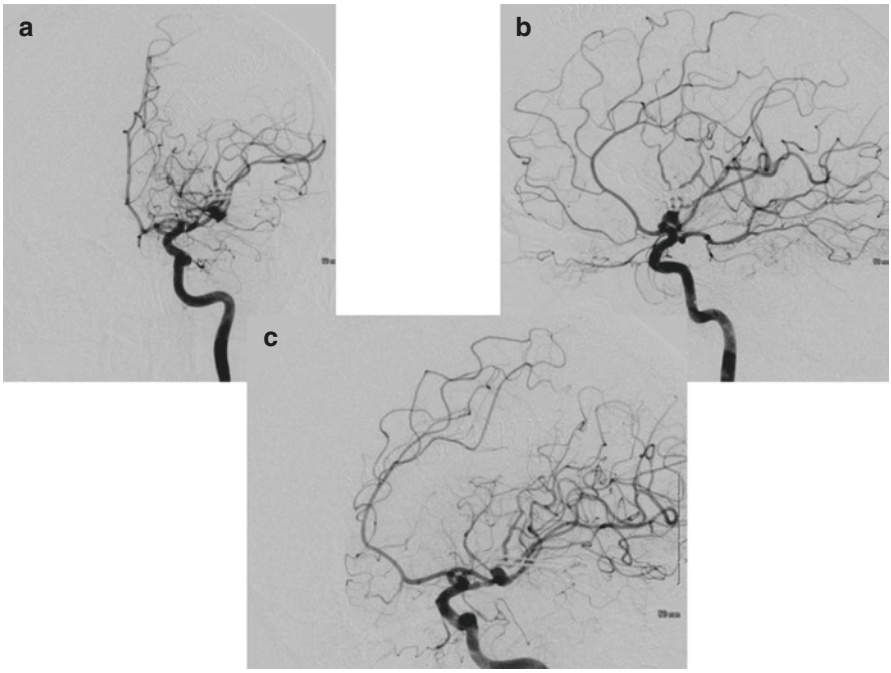


Fig. 9.2 Postoperative imaging studies for a giant left MCA aneurysm in case 1. (**a**) Postoperative AP projection of DSA with left carotid injection, demonstrating no residual filling. (**b**) Postoperative lateral DSA revealing no residual filling. (**c**) Postoperative oblique DSA demonstrating the patent cerebral vasculature with no aneurysmal filling

aneurysmal wall. Ten aneurysm clips, including straight and bayonet clips, were stacked to reconstruct the aneurysm (Fig. 9.4). Indocyanine green video angiography confirmed the patency of all cerebral vessels. Postoperative angiogram confirmed the obliteration of the aneurysm (Fig. 9.4). The patient did well postoperatively and had no neurological symptoms at 1-year follow-up after the surgery [18].

Summary

Complex aneurysms are those with a wide neck, unusual branches, and efferent arteries that sometimes require sophisticated clipping techniques to achieve the goal of aneurysmal obliteration and parent and branch artery preservation. Complex clip reconstruction has proven to be useful in the microsurgical intervention for these aneurysms with careful preoperative surgical planning and clip construction. Whereas anterior cerebral circulation aneurysms have better defined surgical approaches and clipping techniques, posterior circulation aneurysms require modification of existing approaches to achieve proper exposure of aneurysms for surgical

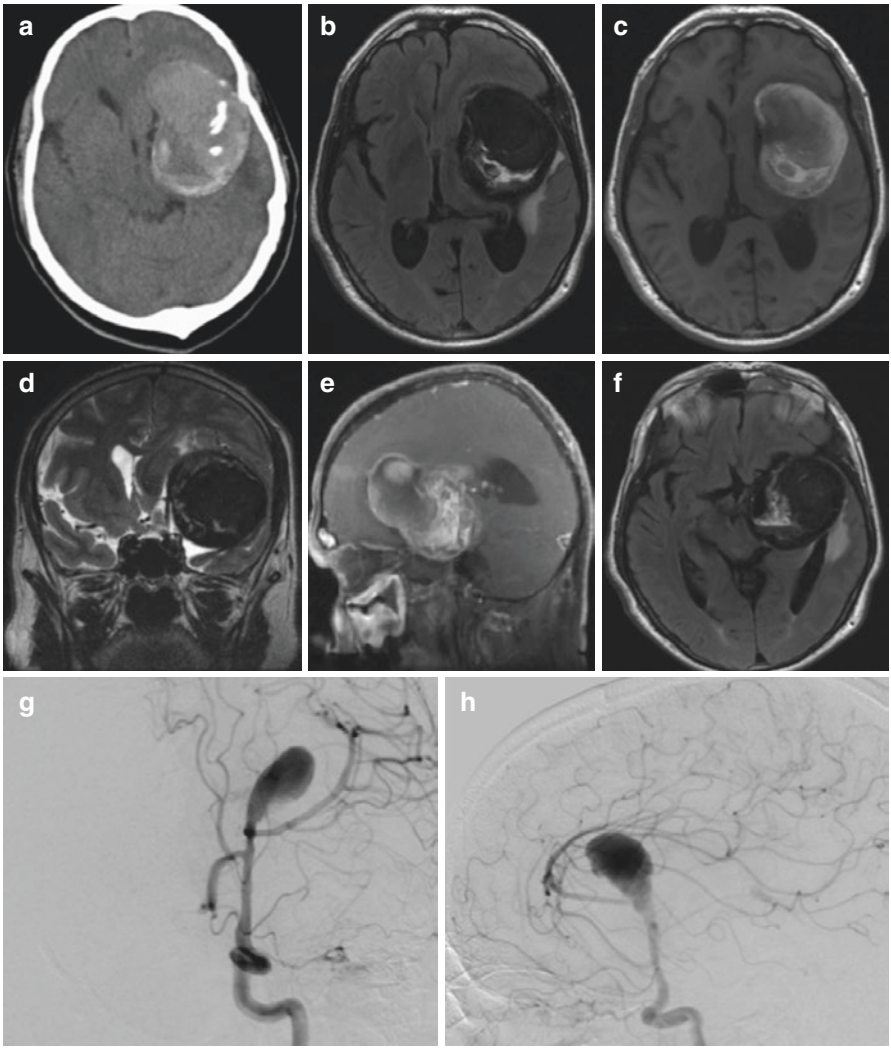


Fig. 9.3 Preoperative imaging studies for a large left ICA aneurysm in case 2 (Cikla et al. [18]). (**a**) Non-contrast, axial CT of the head revealing a left frontotemporal, well-circumscribed heterogeneous, 8 cm mass causing 6 mm midline shift. The lesion harbors some centrolateral, strongly hyperdense areas representing calcification. (**b**) FLAIR MRI revealing perilesional edema, mass effect to the thalamus, and anterior limb of the internal capsule. (**c**) Non-contrast, T1-weighted axial magnetic resonance images revealing a round, well-circumscribed left frontotemporal lesion which is hyperintense to the brain parenchyma with posterior heterogeneity. The lesion is 8 cm in maximal diameter with 6 mm of midline shift from left to right. (**d**) T2-weighted coronal magnetic resonance images of the head revealing a left frontotemporal, hypointense mass lesion with peripheral hyperintensities causing approximately 6 mm midline shift due to mass affect. (**e**) T1-weighted, post-contrast, sagittal magnetic resonance images revealing an 8 × 8 cm, hyperintense mass lesion harboring heterogenous areas. (**f**) FLAIR MRI reveals perilesional edema with mass effect to the brain stem. (**g**) Preoperative oblique DSA with left ICA injection demonstrates a giant carotid bifurcation aneurysm. (**h**) Preoperative lateral DSA of the left ICA demonstrates the carotid bifurcation aneurysm

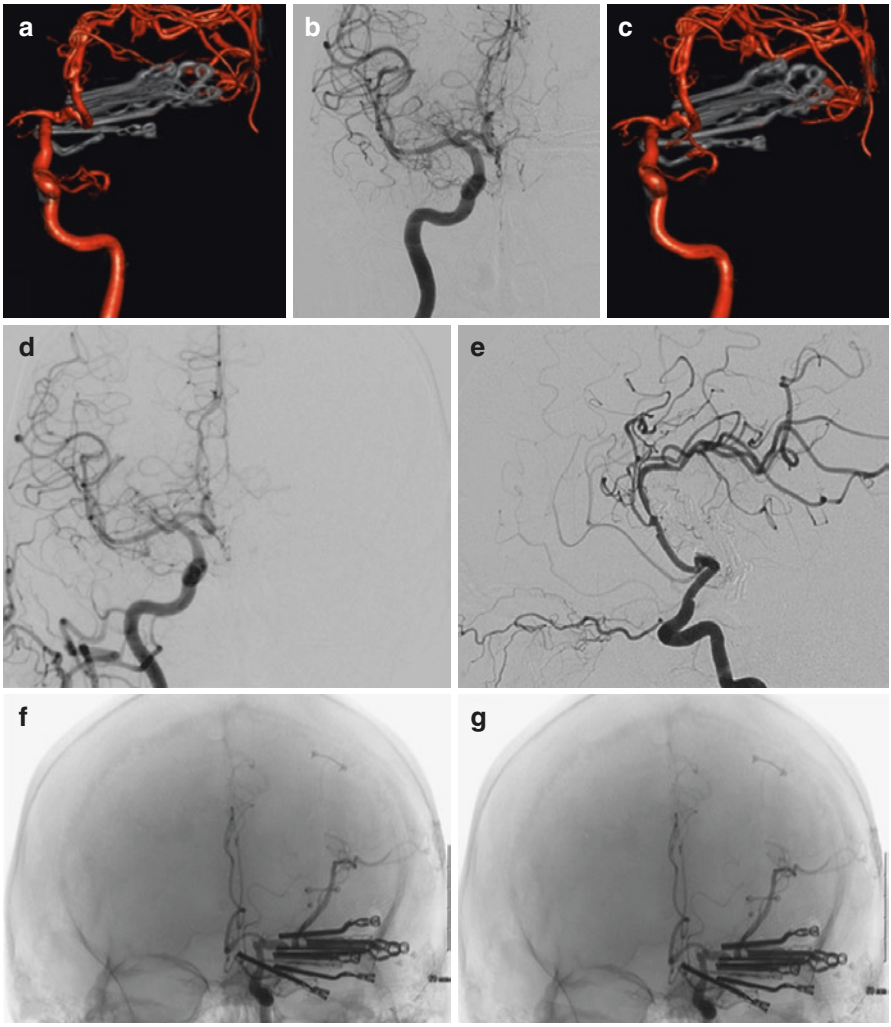


Fig. 9.4 Postoperative imaging studies for a large left ICA aneurysm in case 2 (Cikla et al. [18]). (**a** and **c**) Postoperative, 3D CTA reveals successful clipping of the aneurysm without any residual filling. (**b** and **d**) Postoperative, AP-DSA confirms total obliteration of the aneurysm. (**e**) Postoperative, DSA with lateral projection reveals no residual filling. (**f** and **g**) Postoperative AP-DSAs confirm the patency of cerebral blood flow after multiple clipping

clipping. Application of microsurgical techniques combined with novel clip construct and new surgical approaches have increased the versatility and success of microsurgical treatment for complex intracranial aneurysms.

References

1. Cantore G, Santoro A, Guidetti G, Delfinis CP, Colonnese C, Passacantilli E. Surgical treatment of giant intracranial aneurysms: current viewpoint. Neurosurgery. 2008;63(279–89):289–90.
2. Andaluz N, Zuccarello M. Treatment strategies for complex intracranial aneurysms: review of a 12-year experience at the University of Cincinnati. Skull Base. 2011;21:233–42.
3. Diaz FG, Guthikonda M, Guyot L, Velardo B, Gordon V. Surgical management of complex middle cerebral artery aneurysms. Neurol Med Chir. 1998;38:50–7.
4. Babbu D, Sano H, Kato Y, Arabi O, Karagiozov K, Yoneda M, Imizu S, Watanabe S, Oda J, Kanno T. The "multi clip" method in unruptured complex middle cerebral artery aneurysms-a case series. Minim Invasive Neurosurg. 2006;49:331–4.
5. Clatterbuck RE, Galler RM, Tamargo RJ, Chalif DJ. Orthogonal interlocking tandem clipping technique for the reconstruction of complex middle cerebral artery aneurysms. Neurosurgery. 2006;59:ONS347–51; 351–2.
6. Baskaya MK, Uluc K. Application of a new fenestrated clip (Yasargil T-bar clip) for the treatment of fusiform M1 aneurysm: case illustration and technical report. Neurosurgery. 2012;70:339–42.
7. Ishikawa T, Nakamura N, Houkin K, Nomura M. Pathological consideration of a "blister-like" aneurysm at the superior wall of the internal carotid artery: case report. Neurosurgery. 1997;40:403–6.
8. Kantelhardt SR, Archavlis E, Giese A. Combined suture and clipping for the reconstruction of a ruptured blister-like aneurysm. Acta Neurochir. 2016;158:1907–11.
9. Cıkla U, Baggott C, Başkaya MK. How I do it: treatment of blood blister-like aneurysms of the supraclinoid internal carotid artery by extracranial-to-intracranial bypass and trapping. Acta Neurochir. 2014;156:2071–7.
10. Solomon RA. Anterior communicating artery aneurysms. Neurosurgery. 2001;48:119–23.
11. Yang I, Lawton MT. Clipping of complex aneurysms with fenestration tubes: application and assessment of three types of clip techniques. Neurosurgery. 2008;62(371–8):378–9.
12. Cikla U, Yilmaz T, Li Y, Baskaya MK. Clip reconstruction of giant distal anterior cerebral artery aneurysm: 3-dimensional operative video. Neurosurgery. 2015;11(Suppl 3):463.
13. Heros RC, Nelson PB, Ojemann RG, Crowell RM, DeBrun G. Large and giant paraclinoid aneurysms: surgical techniques, complications, and results. Neurosurgery. 1983;12:153–63.
14. Seifert V, Güresir E, Vatter H. Exclusively intradural exposure and clip reconstruction in complex paraclinoid aneurysms. Acta Neurochir. 2011;153:2103–9.
15. Liu JK. Direct suction decompression and fenestrated clip reconstruction of complex paraclinoid carotid artery aneurysm: operative video and nuances of skull base technique. Neurosurg Focus. 2015;39(Video Suppl 1):V4.
16. Xu B, Sun Z, Romani R, Jiang J, Wu C, Zhou D, Yu X, Hernesniemi J, Li B. Microsurgical management of large and giant paraclinoid aneurysms. World Neurosurg. 2010;73:137–46.
17. McLaughlin N, Martin NA. Extended subtemporal transtentorial approach to the anterior incisural space and upper clival region: experience with posterior circulation aneurysms. Neurosurgery. 2014;10(Suppl 1):15–23. discussion 23–4
18. Cikla U, Uluc K, Baskaya MK. Microsurgical clipping of a giant vertebrobasilar junction aneurysm under hypothermic circulatory arrest. Neurosurg Focus. 2015;39(Video Suppl 1):V13.
19. Gross BA, Tavanaiepour D, Du R, Al-Mefty O, Dunn IF. Petrosal approaches to posterior circulation aneurysms. Neurosurg Focus. 2012;33:E9.
20. Rodríguez-Hernández A, Lawton MT. Anatomical triangles defining surgical routes to posterior inferior cerebellar artery aneurysms: clinical article. J Neurosurg. 2011;114:1088–94.

Chapter 10
Unassisted Aneurysm Coil Embolization

Kyle M. Fargen, Jasmeet Singh, John A. Wilson, and Stacey Q. Wolfe

The invention of the detachable coils by Guglielmi and colleagues in the late 1980s [1, 2] and the period of rapid endovascular technological innovation that followed have revolutionized the way that cerebral aneurysms are being treated. The development of new coil technologies with a wide variety of shapes, sizes, and materials, as well as enhanced detachment mechanisms, more navigable catheters, and refinement of procedural techniques, has further widened the applicability of endovascular coil embolization to a spectrum of aneurysms that traditionally would have been treated only with surgical clipping. Coil-assisted devices, such as self-expanding implantable stents and balloon microcatheters, have allowed neurointerventionists to improve angiographic occlusion and reduce recurrence rates for wide-necked aneurysms or those with challenging morphology. The latest additions to the endovascular armamentarium, flow-diverting stents and intrasaccular devices, provide further options for treating challenging fusiform dissecting aneurysms or challenging bifurcation aneurysms. The success of minimally invasive endovascular techniques has led many centers to now preferentially treat the majority of cerebral aneurysms via endovascular approaches.

Although there is a large assortment of endovascular devices and techniques to choose from, there is a subset of patients where primary coiling remains the

K. M. Fargen (✉)
Department of Neurological Surgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

J. Singh
Department of Radiology and Neurosurgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

Bowman Gray Center, Winston-Salem, NC, USA
e-mail: jsingh@wakehealth.edu

J. A. Wilson · S. Q. Wolfe
Department of Neurological Surgery, Wake Forest University, Bowman Gray Center, Winston-Salem, NC, USA
e-mail: jawilson@wakehealth.edu; sqwolfe@wakehealth.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_10

preferred treatment option. In many instances, aneurysms have straightforward anatomy and can be treated easily and safely with unassisted coiling. In a recent survey of US physicians that treat brain aneurysms, over 50% of respondents reported that they recommended treatment of most unruptured posterior communicating artery, anterior communicating artery, and vertebral-posterior inferior cerebellar artery aneurysms with primary coiling as opposed to other open or endovascular approaches (unpublished data). This chapter will describe the indications and contraindications to unassisted coiling, basic techniques, coil selection strategies, and outcomes associated with this technique.

Indications for Unassisted Coil Embolization

The decision to pursue endovascular treatment of an aneurysm is based on patient factors, aneurysm location and morphology, and physician preference. Once endovascular management has been decided, the primary factor determining candidacy for unassisted coiling is aneurysm morphology. Cerebral aneurysms are classically divided into two main subtypes based on broad morphology: saccular (berry) and fusiform. Saccular aneurysms are true aneurysms that are outpouchings of arteries, usually at branching points, into the subarachnoid space. Anatomically, a saccular aneurysm is differentiated from the normal parent vessel by the aneurysm neck, which is the segment of the aneurysm separating the dome (or main compartment of the aneurysm) from the underlying parent vessel. The aneurysm neck may be long and clearly delineated or may be very short and wide. In most cases, the aneurysm neck has a relatively well-defined anatomic location that can be drawn as a line separating normal parent vessel from aneurysm. Histologically, the aneurysm dome is composed of thickened intima and muscularis without an internal elastic lamina. The normal muscularis layer and internal elastic lamina of the parent artery stop abruptly at the aneurysm neck. Failure to obliterate the histologically diseased neck during treatment may allow for progressive regrowth and recurrence with continued hemodynamic stresses. Successful coil embolization is therefore dependent upon obliteration of the aneurysm dome, to prevent future hemorrhage; occlusion of the aneurysm-parent vessel interface (the “neck”), to prevent aneurysm recurrence; and sparing of the parent vessel to prevent thromboembolic complications. As such, the aneurysm neck represents an important histologic, anatomic, and angiographic landmark that must be respected when selecting treatment strategies.

Saccular aneurysms come in a variety of shapes and sizes that may differ based on the location of the parent vessels and size and orientation of the bifurcating branches. Aside from standard measurements of aneurysm maximum dome diameter, width, height, and neck size, one very useful means of quantifying aneurysm morphology is by calculating the dome/neck ratio. This ratio is calculated by dividing the maximum width (or length) of the dome by the maximum length of the neck. Most aneurysms have a dome/neck ratio that falls somewhere between 0.5 and 5. A high dome/neck ratio indicates a larger aneurysm dome with a comparatively

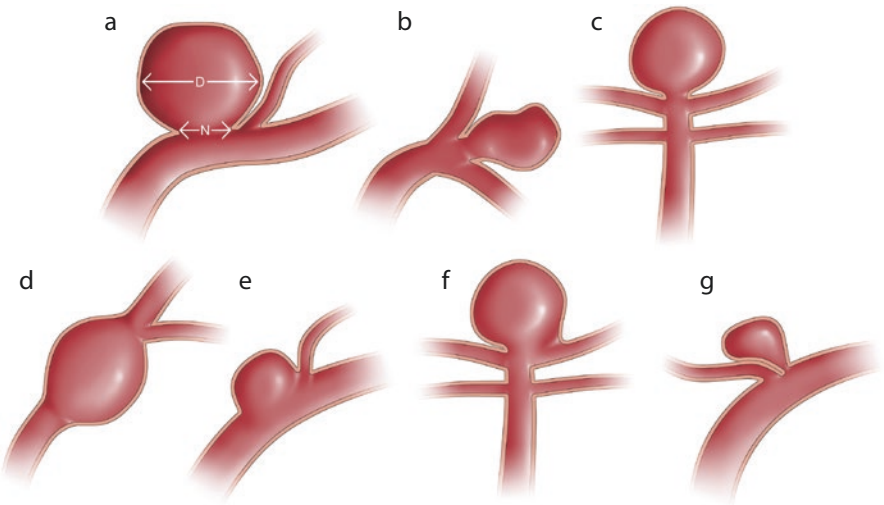


Fig. 10.1 Favorable and unfavorable aneurysm morphologies for unassisted coiling. The dome/neck ratio (upper left) is helpful in determining candidacy

narrower neck, while a low dome/neck ratio indicates a smaller aneurysm dome with a wider neck.

A high dome/neck ratio is favorable for coil embolization, while a low dome/neck ratio makes endovascular treatment more challenging (Fig. 10.1). Coil technologies are characterized by differing loop sizes, length, and shape, but most coil loops are round in conformation. Larger coil diameters have larger loops, which are less likely to prolapse through a considerably narrower neck into the parent vessel. The larger the disparity between dome width and neck size, the greater the packing density that can be obtained as the larger framing coils are less likely to be forced through the neck during coiling. On the other hand, aneurysms with low dome/neck ratios may be challenging to treat with primary coiling. Coil loops that are smaller than the neck width may very easily prolapse down into the parent vessel, as there is no inferior wall to buttress them into position within the dome. Consequently, satisfactory packing density may not be obtainable as further packing with coils could force loops of coil downward into the parent vessel, increasing the risk of potential thromboembolic complication. In situations where the dome/neck ratio is low, coil-assisted techniques using an adjunctive balloon catheter or self-expanding stent should be considered up front to aid in obtaining adequate packing density and protecting the parent vessel from coil prolapse. While aneurysm morphology is highly variable and the anatomical considerations should be considered on a case-by-case basis, a neck width of more than 4 mm or a dome/neck ratio of less than 2 is considered by many to represent the threshold for a “wide-necked” aneurysm. In cases meeting these criteria, consideration of alternative endovascular strategies or surgical clipping is encouraged, although many wide-necked aneurysms with dome/neck ratios of 1–2 may be treated safely and effectively with primary coiling.

Table 10.1 Relative contraindications to unassisted coil embolization

Relative contraindications
Neck width > 4 mm
Poor dome/neck ratio (<2)
Fusiform shape
Incorporation of bifurcating branch into the neck
Large or giant aneurysm
Challenging access or aneurysm catheterization
Treatment of aneurysm recurrence

Those aneurysms with dome/neck ratios of less than 1 are probably poor candidates for unassisted coiling (Table 10.1). Consequently, fusiform cerebral aneurysms, which have no defined neck and therefore no way to keep coils from intruding upon flow through the parent vessel, should not be treated with unassisted coiling.

Large and giant aneurysms (those with maximum diameters of 15 mm or greater) have historically high recurrence rates with endovascular techniques [3, 4]. Progressive recanalization has been reported in as high as 43–69% of large or giant aneurysms treated with unassisted coiling in some series [5]. Poor angiographic outcomes with primary coiling are largely secondary to progressive coil compaction that occurs in the months that follow coil embolization. With stent-assisted coiling or adjunctive flow diversion, considerably improved success rates are now being achieved. Improved outcomes associated with the use of stents are likely secondary to not only a flow-diverting effect but also enhanced endothelialization across the aneurysm neck from the stent lattice. Similarly, the use of a stent or balloon may improve packing density during coiling, which may help to prevent recurrence. When able, physicians should consider using coil-assisted techniques when treating large or giant aneurysms.

Other important anatomical factors should be considered in determining candidacy for treatment. Bifurcation aneurysms, such as those at the middle cerebral artery (MCA) or basilar apex, may incorporate bifurcating branches into the aneurysm neck. For instance, basilar apex aneurysms often have one or both posterior cerebral artery P1 segments incorporated into a wide neck. Even minor encroachment of coil mass into these bifurcating branches may place the patient at high risk for thromboembolic complication. In these situations, protection of the bifurcating branches with balloon or stent assistance may be preferred. New intrasaccular devices may also be preferred in challenging bifurcation aneurysms. Additionally, MCA aneurysms treated with coiling have historically inferior complete occlusion rates compared to surgical clipping. Therefore physicians should consider adjunctive treatments at the MCA bifurcation if endovascular treatment is chosen.

Finally, there are other important considerations when electing an endovascular strategy. Unassisted coil embolization is often the technique of choice when treating simple aneurysms after acute rupture as it does not require the use of dual antiplatelet agents, which is particularly important if external ventricular drainage or other procedures are necessary. Oftentimes challenging or complex aneurysms may be treated in a staged fashion, with an intentional subtotal unassisted coiling or balloon-assisted coiling procedure to secure the aneurysm but leaving a neck

residual, followed by a definitive flow diverter or stent-assisted coiling procedure once dual antiplatelet agents can be safely used [6]. While re-treating aneurysms that have previously been treated with unassisted coiling and have recurred is an option, those that require retreatment should probably be treated definitively with an adjunctive assist technique or with flow diversion, if possible, to promote thrombosis. Lastly, aneurysms that are difficult to catheterize or are prone to catheter prolapse, such as ophthalmic aneurysms with an acute angle between the internal carotid artery and an anterosuperiorly directed dome, can often be successfully treated with flow diversion, which does not require aneurysm catheterization.

Basic Techniques

Preparation and Access

Prior to obtaining vascular access, the interventionalist should develop a procedural plan and evaluate for potential pitfalls. First, patients with severe tortuosity, advanced age, severe peripheral vascular disease, and posterior circulation aneurysms may be good candidates for transradial or transbrachial arterial access, as opposed to transfemoral. Direct carotid puncture is also an option for patients with challenging anterior circulation access as it usually provides robust and stable access for carotid circulation aneurysms but has an inherent risk of carotid dissection. Appropriate guide catheters, sheaths, or intermediate catheters should be selected that provide the proximal support necessary to catheterize the aneurysm. Second, interventionalists should develop a backup plan should unassisted coiling be insufficient or should complication occur. For instance, using a 6-French guide catheter allows for placement of a second microcatheter for balloon or stent assistance or for dual microcatheter technique yet still allows for angiographic runs to be performed through the guide catheter. During the treatment of ruptured aneurysms, it is wise to have a balloon microcatheter preselected and available should aneurysm perforation occur. Alternatively, should coil loops prolapse into the parent vessel, having a backup plan for either balloon-assisted or stent-assisted coiling is wise.

Once access has been obtained, a 6-French guiding catheter is positioned in the origin of the vessel through which coiling of the aneurysm will be performed. Intra-arterial verapamil may then be administered to prevent or relieve vasospasm. Using road map guidance, the guide catheter is placed as distal as safely possible. The closer the guide catheter is to the aneurysm, the better control the operator will have over the microcatheter. This is particularly important when there are a number of vessel loops between the guide catheter and the aneurysm, such as in anterior communicating artery aneurysms, where the microcatheter must navigate through the carotid siphon and then into the A1 segment. Placing the guiding catheter into the petrous carotid segment may be preferable in such cases. Stability of the guide catheter is necessary for successful microcatheter navigation. If stable purchase cannot be obtained, consideration of a coaxial system or alternate access site is

encouraged. Following placement of the guide catheter, administration of intravenous heparin should be considered (if not already administered), depending on the patient's circumstances. The guide catheter is usually connected to a continuous heparinized saline flush during the entirety of the coiling procedure to prevent stagnation of blood in the catheter, which could result in thromboembolism.

Working Views

Baseline anteroposterior and lateral cerebral angiography should be performed to develop a pretreatment understanding of the patient's anatomy. This will be helpful when reviewing posttreatment angiography as a comparator when detecting potential procedural complications, such as thromboembolism. Next, angiographic working views should be obtained. These fluoroscopic positions are extremely important for successful aneurysm treatment because they provide visualization of the necessary anatomy and are often the only views used throughout the entirety of the embolization procedure. Failure to obtain adequate working views may result in inadvertent coil placement into the parent or bifurcating vessel, aneurysm perforation, or failure to obtain satisfactory aneurysm occlusion. The most important factors to consider when selecting working views are shown in Table 10.2.

Table 10.2 Important factors in selecting working views. If the minimum necessary cannot be met, consideration of an alternative set of views or treatment strategy is encouraged

Factor	Ideal	Minimum necessary
Aneurysm anatomy	Clearly delineated parent vessel, the neck, and aneurysm dome on both views	Clear delineation of the neck on 1 view
Bifurcating branches	Clear visualization of bifurcating branch origin(s) on both views	Clear visualization of bifurcating branch origin(s) on 1 view
Daughter sacs/lobes	Clear visualization of daughter sac or lobules on at least 1 view	Appreciation of double density representing daughter sac or lobules on 1 view
Load assessment	Visualization of the guide catheter tip and entire length of exposed microcatheter on both views	Visualization of the guide catheter tip and entire length of exposed microcatheter on 1 view, *or* 1 view of proximal microcatheter if high degree of confidence of stable guide support
Navigation to aneurysm	Amenable visualization of pathway in proximal vessels allowing for ease of microcatheter navigation to aneurysm on both views	Visualization of pathway in proximal vessels allowing for microcatheter navigation to aneurysm on at least 1 view
Visualization	Use of maximum magnification on both views	Maximum allowable magnification on 1 view that delineates the neck from parent vessel
Complication recognition	Visualization of distal, downstream vessels on at least 1 view allowing for early detection of thromboembolic complications	

Three-dimensional angiography may be performed to assist with understanding aneurysm morphology and selection of an appropriate view. Most importantly, working views should clearly show (1) the relationship between the aneurysm neck, parent vessel, and any bifurcating branch origins and (2) the guide catheter tip and exposed microcatheter on at least one view. The inability to meet the minimum necessary criteria with a given set of working views should prompt consideration of obtaining new views (with three-dimensional angiography assistance) or consideration of alternate treatment strategies, such as flow diversion or the use of balloon or stent assistance. As these views are integral to providing satisfactory aneurysm treatment and avoiding complications, the importance of adequate working views cannot be understated.

Aneurysm Catheterization

Once satisfactory working views have been obtained, a microcatheter and microwire are selected for aneurysm catheterization. The selection of wire and microcatheter is often based on physician preference. Often, a 10, 14, or 17 catheter (inner diameter of 0.014 or 0.017 inches, all capable of housing a 0.014 inch microwire and most coil technologies) is used. Additionally, pre-shaped microcatheters (curved, 45° and 90°) are available that may assist with aneurysm catheterization or coiling based on aneurysm anatomy, though most aneurysms can be accessed with a straight microcatheter. Steam-shaping of straight microcatheter tips may also be performed based on physician preference. Microwire selection is often based on preference, but certain qualities should be strongly considered. Microwires should be steerable (torque applied to the wire reliably results in rotation of the wire in the patient), have an atraumatic tip, and provide adequate support to allow the microcatheter to climb over the wire when advanced without the wire losing its position. Shaping of the microwire is necessary to allow for steering into branches or the aneurysm ostium.

There are multiple techniques for microcatheter and microwire navigation. The technique used is often based on training style but also the number of surgeons present. Single individual procedural techniques include the underhand and overhand techniques, while if two surgeons are present, a dual-surgeon technique can be used. In both single-surgeon techniques, the left hand is placed on the microcatheter just proximal to the guide catheter and is used to advance or withdraw the microcatheter. Synchronously, the right hand is used to spin, advance, or withdraw the microwire either with the palm up (underhand) or palm facing down (overhand). In the dual-surgeon technique, the microcatheter is controlled by one surgeon, while the microwire is controlled by the second.

A major principle of microcatheter and microwire navigation involves the concept of “load” (or “tension”) within the system. In a perfect system, advancement of the microcatheter into the guide catheter by a distance of 1 mm will result in 1 mm of forward motion of the microcatheter on fluoroscopy. This concept is often referred to as “one-to-one movement,” because for every unit of distance, the

microcatheter is advanced outside the patient and an equal distance is traveled by the microcatheter tip within the patient. The presence of one-to-one movement is highly favorable for catheter navigation because the operator has complete control over catheter movement. The presence of one-to-one movement also indicates a little forward load or tension within the system. However, in most cases, vascular looping or tortuosity results in a loss of one-to-one movement as the microcatheter interacts with the vessel walls and builds up load within the loops. For instance, as the microcatheter and wire are advanced through the carotid siphon, increased forward load is required to move the catheter distally. This load is reflected in external displacement of the microcatheter between the lesser (short) curve of the vessel to the greater (long) curve and proximal displacement of the guide catheter tip (Fig. 10.2). Excessive load within the system results in a loss of fine control of the microcatheter and wire steering but can also result in sudden release of that potential energy into the catheter tip, resulting in "jumping" of the microcatheter and wire forward. Therefore, failure to recognize the buildup of load in the system when

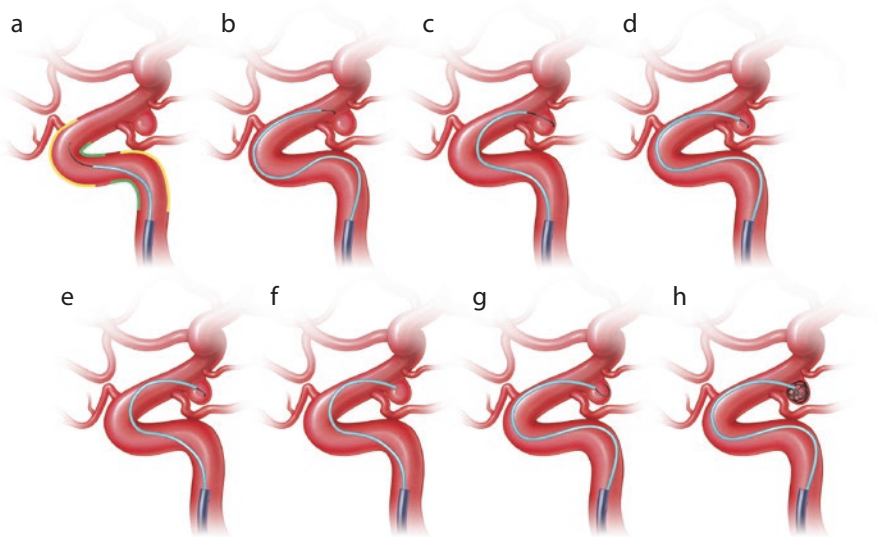


Fig. 10.2 Catheterization of the aneurysm. The short (lesser) and long (greater) curves are shown in green and yellow, respectively (**a**). The microwire and microcatheter are advanced proximal to the aneurysm. Doing so introduces load into the system, reflected by the microcatheter pushed externally to the greater vessel curves and descent of the guide catheter (**b**). Load is removed from the system by gently withdrawing the microcatheter, resulting in the guide catheter returning to its previous position and the microcatheter shifting to the lesser curves. The microwire is then advanced into the aneurysm (**c**). The wire is pinned, and the mirocatheter is advanced over the wire into the aneurysm, just beyond the neck. Note that load is again introduced into the system with this maneuver (**d**). With the catheter in the desired position, a small amount of load is once again removed (**e**). Note that the microcatheter tip position does not change but instead the shape of the exposed microcatheter. The wire is then gently removed from the microcatheter (**f**). A framing coil is then deployed into the aneurysm (**g**). Oftentimes this may require forward load on the microcatheter if the coil pushes the microcatheter proximally. Coiling is then completed (**h**)

attempting to catheterize the aneurysm can lead to sudden aneurysm perforation by the wire and catheter launching forward unexpectedly. Alternatively, excessive load may cause proximal displacement of the guide catheter, resulting in the system prolapsing into the aorta, or looping of the microcatheter proximally. Load can be removed from the system by withdrawing the microcatheter slowly, which results first in the shifting of the exposed catheter from the greater curves to the lesser curves of the proximal vessels and then second in proximal movement of the catheter tip. Therefore, understanding the load in the system comes not only from appreciating the loss of one-to-one movement but also by constant appreciation of the guide catheter tip and the movement of the exposed microcatheter within the greater and lesser curves of the vessels proximal to the aneurysm. This fact underlies the importance of having the guide catheter tip and microcatheter length viewable on at least one working view and further supports the concept of placing the guide catheter as distally as safely possible.

Under road map guidance using the working view, the microcatheter and microwire are then carefully and slowly navigated to the aneurysm (Fig. 10.2). This is performed by leading with the microwire and gently spinning the wire so that it steers in the direction of interest. Control of the wire is enhanced by having proximal support from the microcatheter, so after the wire is advanced a reasonable distance without the catheter, it is helpful to "pin" the wire by holding it in place and then advancing the microcatheter to a point near the wire tip. The wire is then slowly steered and advanced forward. This process is repeated until the microcatheter and wire are near the aneurysm neck. Attention should be paid toward inadvertent advancement of the wire into tiny perforating branches so that this can be immediately recognized and/or avoided.

Catheterization of the aneurysm is then performed by slowly and carefully advancing the microwire into the aneurysm. Contact with the aneurysm dome wall by the microwire is not necessary or recommended. Next, with appreciation of the load within the system, the microcatheter is slowly advanced over the microwire while pinning the microwire. Often, even with the microwire pinned, the microwire will continue to demonstrate subtle movements while the microcatheter is being advanced. This may necessitate slight withdrawal or advancement of the wire to hold a stable position. This "push and pull" is important for keeping a steady wire position, particularly when the system is under load. If one-to-one movement is absent with microcatheter advancement, extreme care is necessary when supplying forward force on the microcatheter. Often times removing load from the system before delicate microcatheter work will improve control. The microcatheter should then be advanced into the aneurysm over the wire, away from the aneurysm wall. If the catheter is too deep in the aneurysm and in contact with or near the aneurysm dome wall, there is a risk of perforation from the leading segment of the coil when it is deployed. In most cases, position of the microcatheter at, or just beyond, the neck is usually preferred. Once a satisfactory position is reached, the microcatheter is pulled back slightly to remove excess load from the system, which will subtly straighten the microcatheter in the proximal loops but not affect catheter tip position. Care must be taken with this step because if too much load is removed, the

microcatheter tip may lose its position and fall into the parent vessel. The microwire is then removed under initial fluoroscopic visualization to ensure the catheter tip does not shift.

Aneurysmography

In complex aneurysms or those with unclear angioarchitecture, aneurysmography is a useful option. This angiographic technique involves the gentle injection of contrast dye through the microcatheter into the aneurysm using a 1 ml syringe. While the volume and force of injection is substantially less than that provided through the guide catheter, aneurysmography may be helpful in visualizing the relationship of the aneurysm neck, parent vessel, bifurcating branches, and dome anatomy. Further, because the injection is distal and localized, aneurysmograms usually provide an unobscured view without overlap from nonrelevant branches. Because of these factors, an aneurysmogram often serves as a superior road map for coiling.

Coil Selection

Since the first use of the Guglielmi detachable coil, coil technology has rapidly evolved with an ever-increasing number of new products from a variety of companies in the market. Most experienced neurointerventionists have their "go-to" coils for their cases which they use based on personal experience. Many physicians have thus developed an algorithm in coil selection that has developed over the years depending on operator experience, availability, cost, and ease of use. There are however practical considerations that can aid the proceduralist in objectively choosing the most appropriate coil for a case.

Basic Coil Design

One of the most important factors in coil design is compatibility with the host. A biocompatible coil should be composed of inert material that allows an effective treatment without the concern for an adverse systemic host response. Metal strength is determined experimentally and is referred to as the shear modulus. The shear modulus is the coefficient of elasticity for a shearing force, defined as the ratio of the shear stress to the shear strain.

A platinum (92%)/tungsten (8%) alloy has become the mainstay material for most current coil designs [7]. This alloy has been shown to be a safe and inert alloy for deployment inside the cerebral vasculature [8]. There are some vendors who offer lines of coils with coating to cause increased fibrosis in aneurysms, such as

hydrogel-coated coils. These bioactive coils may promote aneurysm occlusion but have also been associated with hydrocephalus [9].

The intravascular behavior of a coil is the result of an interaction between the primary material, resistance to deformity (stiffness, secondary and tertiary structures), and the mechanism of detachment. All coils start off as a basic platinum alloy wire. The diameter of this wire, which can be highly variable, is thought to be the most impactful factor in determining a coil's stiffness. Usually, the larger the diameter of the stock wire (D1), the stiffer the coil. This straight stock wire is then wound around a mandrel, a straight metal rod in the case of coils, to give it the "slinky-like" structure. This is referred to as the coil's primary wind (D2) or secondary structure. The mandrel can also be of variable sizes such that coils can be wound to produce highly variable secondary structure sizes.

$$k = \frac{D_1^4 G}{8 D_2^3 n} = \text{Stiffness } \alpha \frac{D_1 G}{D_2 n}$$

This equation describes the relative contributions of the diameter of the stock wire ($D1$) and the primary wind ($D2$) to the spring constant or stiffness of the coil. G = shear modulus, n = number of turns per unit distance.

Usually, coils are described as a "10" or an "18" coil, with "10" coil referring to a secondary diameter thickness of 0.010 inch and "18" coil wound to 0.015 inch thickness. The 10 and 18 terminology is based on the old original Tracker 10 and 18 microcatheters. Many of the currently available coils have variable secondary diameters ranging from 0.010 to 0.015 inches. Once a secondary structure is established, a number of tertiary shapes and configurations are available to provide the advertised properties of being three-dimensional, spherical, complex, or helical (Fig. 10.3). The size of the tertiary shape is what the coil manufacturers advertise as the "size" or diameter of the coil. For example, a 5 mm coil will have a majority of coil loops that are 5 mm in diameter, irrespective of the tertiary shape [10].

The coil is attached to a rigid pusher wire that allows for advancement through the microcatheter. The attachment site (interface between coil and pusher) is the location of the detachment zone. A variety of detachment mechanisms are available for different coils including electrolytic, hydraulic, and mechanical. While the original electrolytic detachment system used by the Guglielmi coil notoriously took minutes to detach the coil, nearly all current detachment systems take mere seconds. There is currently no clear clinical advantage of any one system over another.

Coil Shapes

There are various shapes advertised for a plethora of coils with fancy names. There are however three main types of coils: framing coils, filling coils, and finishing coils.

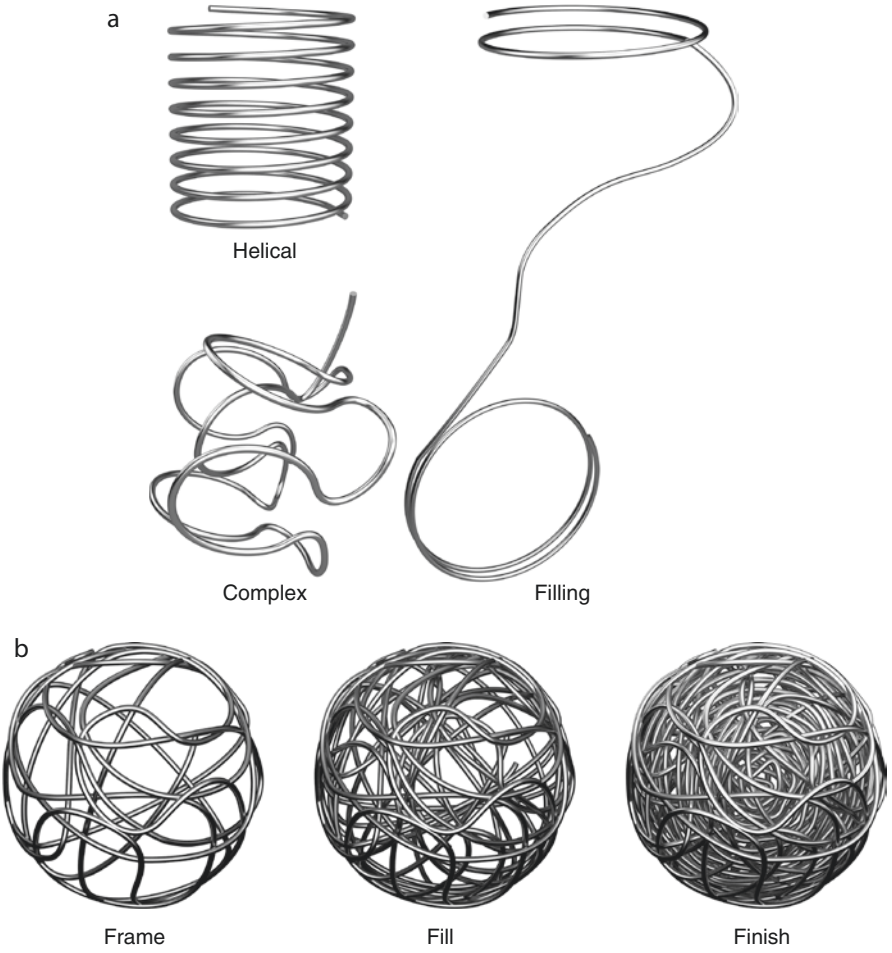


Fig. 10.3 (**a**, **b**) General coil shapes and coiling strategy. Helical coils have a predictable shape, while complex coils acquire unique conformations. Filling coils are designed to seek unfilled spaces within the aneurysm. In general, successful coiling is initiated with large framing coils, followed by smaller coils used to fill the spaces within the framing coils, and then finally very small finishing coils

Framing Coils Framing coils are usually three-dimensional coils (3D), which are designed to form a stiff, peripheral basket (or "frame") under the aneurysm wall as they exit the microcatheter tip. Therefore these ovalize or form a spherical shape. Usually one or two framing coils are used. Target 3D (Stryker Neurovascular, Fremont, California), Micrusphere 18, and Presidio 10 (Codman Neurovascular, Ratham, Massachusetts, USA) are some examples of commonly used framing coils. The coils are designed so that at least some of the coil loops extend across the aneurysm neck. They are stiff and offer slight centrifugal radial force to allow filling of

the inner space of the basket with smaller size 3D coils in a Russian doll technique (onion skinning of progressively decreasing diameters of coils). Alternatively, the scaffold provided by the framing coil can be used to use filling or finishing coil to pack the aneurysm. As framing coils establish an important foundational coil mass boundary within the aneurysm that dictates the success of further coiling, the position of the framing coil when deployed should be an important consideration. Importantly, choosing an appropriately sized framing coil has a significant impact on the long-term outcomes, namely, recanalization and retreatment rates [11]. Therefore it is advisable to withdraw and then redeploy framing coils that fail to acquire the desired frame shape or to select alternate sizes or technologies if the frame that is created is undesirable.

Filling Coils These coils are designed to occupy space within the frame created by the framing coil. These may be helical and have two-dimensional (2D) or random shapes. The 2D coils were originally designed to be framing coils with the first helical loop smaller than the rest, with the hope that the smaller loops would tumble within the aneurysm without finding the outflow to the parent vessel. These tend be softer coils and are used to pack the aneurysm.

Finishing Coils When the aneurysm is at the final stages of embolization, these extremely soft coils can find places within the coil mesh and neck of the aneurysm to improve packing density. These are usually very small in diameter and very short in length. Importantly, due to their small size and length, there may be a higher risk of dislodgement from the aneurysm with prolapse into the parent artery.

General Coil Selection Strategy

In general for an unruptured saccular aneurysm, start with a framing 3D coil matched to the size of the diameter of the dome of the aneurysm. Some operators may oversize the coil by 1 mm to ovalize the aneurysm to theoretically narrow the neck and improve the dome/neck ratio. Most operators will match the aneurysm dome diameter to the coil diameter in a ruptured aneurysm. For an irregular nonspherical ruptured aneurysm, a mean measurement of the maximum dimensions may be the best indicator of an appropriate initial coil. Initial coil does not have to be a stiff 3D coil; soft filling coils may sometimes be used in very irregular-shaped ruptured aneurysm as framer or initial coils. Some coil designs have smaller initial loops that confine the first loop(s) to within the aneurysm, have extremely soft loops that can fill very irregularly shaped aneurysms, or simply have no tertiary shape at all, allowing progressive folding and/or filling irrespective of the size or shape of the aneurysm. In general, volume packing density between 25% and 33% usually provides adequate occlusion of the aneurysm with low recanalization rates [12, 13]. As a rule, the first and last coils are the most important to frame and occlude the aneurysm without complication. The first coil should be placed with limited

repositioning to minimize the risk of disrupting intra-aneurysmal thrombus, and the final coil should occlude the neck without prolapsing coil into the parent vessel, to prevent a thrombogenic surface that could result in thromboembolism.

Dual Microcatheter Technique

The double or dual microcatheter technique to treat wide-necked intracranial aneurysms was originally described by Baxter et al. in 1998 [14]. In this technique, two microcatheters are navigated one after the other into the aneurysm such that they lie side by side within the neck or dome. A framing coil is initially deployed through one microcatheter but is not detached. Sequential placement of coils is then performed within the lattice of the initially deployed but not detached coil through the second microcatheter. This is performed until satisfactory occlusion of the aneurysm is seen. The initial coil is then detached. This technique is very useful in wide-necked aneurysms with incorporation of branch vessel origins in the aneurysm base. A common example would be a wide-necked basilar tip aneurysm with incorporation of bilateral posterior cerebral arteries. This technique results in stabilization of the tumbling of the initial coil with narrowing of the neck, preventing any coil prolapse into the parent artery, and can be very useful to prevent the need for stent assistance in the case of a ruptured aneurysm. The technique also theoretically would reduce thromboembolic events that can be associated with using a balloon remodeling technique.

Outcomes

Outcomes of coil embolization can be divided into four areas: clinical outcomes, rates of occlusion, durability, and rebleeding. There are caveats when looking at the literature, however. With inherent differences between ruptured and unruptured aneurysms, clinical outcomes and durability can differ between these groups. Additionally, with the technologic advancements in coils, balloon remodeling, and stent-assisted coiling, current outcomes of modern primary coiling alone are difficult to isolate; however, the following provides a synopsis of the historical and current literature.

Clinical outcome should be the cornerstone of the decision-making process, and outcomes are often compared to microsurgical clipping. To date, there have been three randomized, prospective studies comparing clipping and coiling of ruptured aneurysms [15–18]. The International Subarachnoid Aneurysm Trial (ISAT) demonstrated clinical superiority of coiling over clipping in 2143 patients (1594 available for a 12-month follow-up) who had aneurysms demonstrating clinical equipoise, namely, small- and medium-sized saccular Acom and Pcom aneurysms, with 23.7% (coiling) vs 30.6% (clipping) dead or dependent at 1 year [15]. This was

again demonstrated in the Barrow Ruptured Aneurysm Trial (BRAT), which randomized all ruptured aneurysms and allowed for 38% crossover for optimal treatment, resulting in a 23.2% (coiling) vs 33.7% (clipping) rate of death or dependence at 1 year [16]. At 3 and 6 years, there was no benefit except in posterior circulation aneurysms [17]. In the Finnish randomized trial, MRI showed equal number of ischemic deficits in both groups at 1 year [18].

Outcomes in unruptured aneurysms have been less rigorously studied, but in a recent meta-analysis, database registry studies of unruptured aneurysms favored coiling over clipping with regard to independent outcome and lower mortality (OR = 0.34, CI 0.29–0.41, and OR = 1.74, CI 1.52–1.98, respectively) [19]. In the Matrix and Platinum Science (MAPS) trial, at 1 year 95.8% of patients with unruptured aneurysms ($N = 398$) and 90.4% ($N = 228$) of those with ruptured aneurysms were independent (mRS ≤ 2), though this included stent-assisted coiling in addition to primary coiling [20].

Safety is certainly paramount to any surgical technique. Reported rates of complications occurring during Guglielmi detachable coil embolization vary widely, with estimates ranging from 2.5% to 28% [21]. Murayama et al. reviewed 916 aneurysms undergoing coil embolization, with only 49 utilizing balloon assistance [22]. While the coil technology has since improved, this likely gives us the best assessment of pure risk of primary coil embolization. Patients were divided into an early (1990–1995) and late (1995–2002) cohort, due to improved experience and technology. Technical complications occurred in 69 patients (8.4%) [22]. Thromboembolic complications occurred in 4.4% of patients, including distal emboli and parent artery occlusion, of which 1% developed a permanent neurologic deficit with 0.6% mortality. Aneurysm perforation occurred in 2.3% with 1.4% neurologic morbidity and 0.7% mortality. Less frequent complications included arterial dissection (0.7%), coil migration (0.5%), coil rupture (0.4%), and new mass effect (0.1%). The later cohort (1995–2002) had an overall lower rate of intraprocedural complications (7.3 vs 11.3%) [22]. While advances in technology have created softer and more stable coils that may mitigate some of these complications, increasing case complexity, such as stent assistance and the concomitant use of dual antiplatelet agents, increases the risk for intraprocedural complications and new diffusion abnormalities on MRI [23].

Aneurysm occlusion is classically graded by the Raymond-Roy Occlusion Classification, where Class I indicates complete occlusion, Class II indicates residual neck, and Class III residual aneurysm filling [24]. In ruptured aneurysms, ISAT demonstrated a complete occlusion rate of 66%, as compared to 82% in clipped aneurysms [15]. BRAT showed an even lower occlusion rate with 48% Raymond-Roy Class I occlusion vs 96% complete obliteration with clipping [16]. Similarly, the MAPS, Cerecyte, and HELPS trials showed complete occlusion rates of 42–76%, including aneurysms treated with adjuvant balloon or stent remodeling [20, 25, 26]. Murayama et al. demonstrated a complete occlusion rate of 57% in the latter group of aneurysms undergoing primary coiling [22].

While the occlusion rate is significantly lower in coiled aneurysms than those clipped, it is the rate of rehemorrhage and retreatment that is clinically most important. Prevention of hemorrhage, or rebleeding, is the overarching benchmark of

successful treatment. Raymond et al. demonstrated that recurrent aneurysms have a low incidence of rebleeding [27]. In 501 aneurysms, they showed a recurrence rate of 33.6% at 1 year, but a hemorrhage rate of only 0.8% over a mean clinical follow-up period of almost 3 years. ISAT had a relatively high rehemorrhage rate of 4.1% during the first year (3.6% in the clipping group), which then approached 0% in the 10 years of follow-up [15]. BRAT [16] and HELPS [26] demonstrated a 0% rehemorrhage rate, with CARAT [28], MAPS (1.3%) [20], and Cerecyte (0.2%) [25] also demonstrating very low rebleeding rates.

Durability includes the rates of recanalization as well as the rates of retreatment, perhaps and more clinically a relevant benchmark. As previously stated, volume packing density between 25% and 33% usually provides adequate occlusion of the aneurysm with low recanalization rates [12, 13]. Initial angiographic occlusion class is a predictor of aneurysm recurrence and rehemorrhage [27, 28]. Mascitelli et al. found that among Raymond-Roy Class III aneurysms, the subgroup with residual contrast opacification within the coil interstices (Class IIIa) was likely to improve to Class I or II on follow-up angiography, compared to aneurysms with contrast opacification along the aneurysm wall, outside of the coil mass (83.3 vs 15%, $p < 0.01$) [29]. Similar to the 33.6% recanalization rate in Raymond's study [28], Murayama et al. demonstrated a 21% recanalization rate of aneurysms undergoing primary coiling [22]. Though recanalization rates have decreased with adjuvant treatment such as neck remodeling (BRAT showed a 10% recanalization rate over 6 years) [17], rates of retreatment are not insignificant. ISAT showed a 15% retreatment rate in the coil embolization group as compared to 4.1% in the clipping group [15]. BRAT showed a similar rate (16.4% (coil) vs 4.6% (clip)) [17].

In summary, when discussing treatment options with our patients, we counsel that the literature demonstrates that clinical outcome after coil embolization, especially within a year in those with ruptured aneurysms, is superior to microsurgical clipping. However, there is a significant chance of residual aneurysm and recanalization, resulting in a retreatment rate around 15%, but with good angiographic follow-up, the risk of rehemorrhage is exceedingly low.

Conclusions

Unassisted coiling is a safe and effective treatment strategy for both ruptured and unruptured aneurysms with favorable anatomy. Those aneurysms best suited for unassisted coiling have straightforward microcatheter access, are small or medium sized, and have a narrow neck and a high dome/neck ratio. Aneurysms with wide necks or incorporate bifurcating branches are less favorable due to the possibility of coil prolapse and thromboembolic complication. A wide selection of different microcatheter shapes and coil conformations is available to tailor the treatment to unique aneurysm anatomy. Operators should prepare for the potential need for additional microcatheters by using an appropriately sized guide catheter (usually 6 French),

should dual microcatheter technique or balloon or stent assistance be required. Overall, outcomes with unassisted coiling of appropriate aneurysms are excellent, with retreatment rates approximating 15%.

References

1. Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: electrochemical basis, technique, and experimental results. J Neurosurg. 1991;75(1):1–7.
2. Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. J Neurosurg. 1991;75(1):8–14.
3. Gruber A, Killer M, Bavinzski G, Richling B. Clinical and angiographic results of endosaccular coiling treatment of giant and very large intracranial aneurysms: a 7-year, single-center experience. Neurosurgery. 1999;45(4):793–803. discussion 803-794
4. van Rooij WJ, Sluzewski M. Coiling of very large and giant basilar tip aneurysms: midterm clinical and angiographic results. AJNR Am J Neuroradiol. 2007;28(7):1405–8.
5. Sluzewski M, Menovsky T, van Rooij WJ, Wijnalda D. Coiling of very large or giant cerebral aneurysms: long-term clinical and serial angiographic results. AJNR Am J Neuroradiol. 2003;24(2):257–62.
6. Brinjikji W, Piano M, Fang S, et al. Treatment of ruptured complex and large/giant ruptured cerebral aneurysms by acute coiling followed by staged flow diversion. J Neurosurg. 2016;125(1):120–7.
7. White JB, Ken CG, Cloft HJ, Kallmes DF. Coils in a nutshell: a review of coil physical properties. AJNR Am J Neuroradiol. 2008;29(7):1242–6.
8. Marks MP, Tsai C, Chee H. In vitro evaluation of coils for endovascular therapy. AJNR Am J Neuroradiol. 1996;17(1):29–34.
9. Meyers PM, Lavine SD, Fitzsimmons BF, et al. Chemical meningitis after cerebral aneurysm treatment using two second-generation aneurysm coils: report of two cases. Neurosurgery. 2004;55(5):1222.
10. Eddleman CS, Welch BG, Vance AZ, et al. Endovascular coils: properties, technical complications and salvage techniques. J Neurointerv Surg. 2013;5(2):104–9.
11. Ishida W, Sato M, Amano T, Matsumaru Y. The significant impact of framing coils on long-term outcomes in endovascular coiling for intracranial aneurysms: how to select an appropriate framing coil. J Neurosurg. 2016;125(3):705–12.
12. Sluzewski M, van Rooij WJ, Slob MJ, Bescos JO, Slump CH, Wijnalda D. Relation between aneurysm volume, packing, and compaction in 145 cerebral aneurysms treated with coils. Radiology. 2004;231(3):653–8.
13. Uchiyama N, Kida S, Nomura M, et al. Significance of volume embolization ratio as a predictor of recanalization on endovascular treatment of cerebral aneurysms with guglielmi detachable coils. Interv Neuroradiol. 2000;6(Suppl 1):59–63.
14. Baxter BW, Rosso D, Lownie SP. Double microcatheter technique for detachable coil treatment of large, wide-necked intracranial aneurysms. AJNR Am J Neuroradiol. 1998;19(6):1176–8.
15. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P, International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. 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(9488):809–17.
16. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Russin JJ, Partovi S, Nakaji P, Wallace RC. The barrow ruptured aneurysm trial: 6-year results. J Neurosurg. 2015;123(3):609–17.

17. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, Albuquerque FC. The barrow ruptured aneurysm trial. J Neurosurg. 2012;116(1):135–44.
18. Koivisto T, Vanninen E, Vanninen R, Kuikka J, Hernesniemi J, Vapalahti M. Cerebral perfusion before and after endovascular or surgical treatment of acutely ruptured cerebral aneurysms: a 1-year prospective follow-up study. Neurosurgery. 2002;51:312–25.
19. Delgado FA, Andersson T, Delgado FA. Clinical outcome after surgical clipping or endovascular coiling for cerebral aneurysms: a pragmatic meta-analysis of randomized and non-randomized trials with short- and long-term follow-up. J Neurointerv Surg. 2016;6
20. McDougall CG, Johnston SC, Gholkar A, Barnwell SL, Vazquez Suarez JC, Massó Romero J, Chaloupka JC, Bonafe A, Wakhloo AK, Tampieri D, Dowd CF, Fox AJ, Imm SJ, Carroll K, Turk AS, MAPS Investigators. Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial. AJNR Am J Neuroradiol. 2014;35(5):935–42.
21. Koebbe CJ, Veznedaroglu E, Jabbour P, Rosenwasser RH. Endovascular management of intracranial aneurysms: current experience and future advances. Neurosurgery. 2006;59(5 Suppl 3):S93–102.
22. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, Martin N, Vinuela F. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg. 2003;98:959–66.
23. Takigawa T, Suzuki K, Sugiura Y, Suzuki R, Takano I, Shimizu N, Tanaka Y, Hyodo A. Thromboembolic events associated with single balloon-, double balloon-, and stent-assisted coil embolization of asymptomatic unruptured cerebral aneurysms: evaluation with diffusion-weighted MR imaging. Neuroradiology. 2014;56(12):1079–86.
24. Raymond J, Roy D. Safety and efficacy of endovascular treatment of acutely ruptured aneurysms. Neurosurgery. 1997;41:1235–46.
25. Molyneux AJ, Clarke A, Sneade M, Mehta Z, Coley S, Roy D, Kallmes DF, Fox AJ. Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. Stroke. 2012;43(10):2544–50.
26. White PM, Lewis SC, Gholkar A, Sellar RJ, Nahser H, Cognard C, Forrester L, Wardlaw JM, HELPS trial collaborators. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. Lancet. 2011;377(9778):1655–62.
27. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke. 2003;34:1398–403.
28. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR, CARAT Investigators. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the cerebral aneurysm Rerupture after treatment (CARAT) study. Stroke. 2008;39(1):120–5.
29. Mascitelli JR, Moyle H, Oermann EK, Polykarpou MF, Patel AA, Doshi AH, Gologorsky Y, Bederson JB, Patel AB. An update to the Raymond-Roy Occlusion Classification of intracranial aneurysms treated with coil embolization. J Neurointerv Surg. 2015;7(7):496–502.

Chapter 11
Balloon-Assisted Treatment of Intracranial Aneurysms: The Conglomerate Coil Mass Technique

David Fiorella and Henry H. Woo

Endovascular techniques for the treatment of intracranial aneurysms have rapidly evolved over the past 20 years since the introduction and subsequent US Food and Drug administration approval of the Guglielmi detachable coil (GDC). During this interval, a number of different coil designs and adjunctive devices have been developed to facilitate the treatment of more complex and challenging cerebral aneurysms. One such adjunctive device, the hypercompliant occlusion balloon, can be temporarily inflated during the delivery of embolization coils to prevent their prolapse into the parent vessel. This technique, known as balloon-assisted treatment (BAT), remains somewhat controversial as many operators do not incorporate this approach into their practice favoring stent-supported techniques instead. Moreover, those operators who do practice BAT use a variety of different approaches. In this review, we discuss the theoretical concepts underlying BAT, the potential advantages and disadvantages of this approach, and finally the technical evolution of BAT in our endovascular practice.

Adapted and updated from Fiorella D, Woo HH, Balloon assisted treatment of intracranial aneurysms: the conglomerate coil mass technique. J Neurointervent Surg 2009 Dec;1 (2):121–31, with permission.

D. Fiorella (✉)
Cerebro vascular Center, Department of Neurological Surgery, Stony Brook University Medical Center, Stony Brook, NY, USA
e-mail: dfiorella@notes.cc.sunysb.edu

H. H. Woo
Department of Neurosurgery, North Shore University Hospital, Manhasset, NY, USA

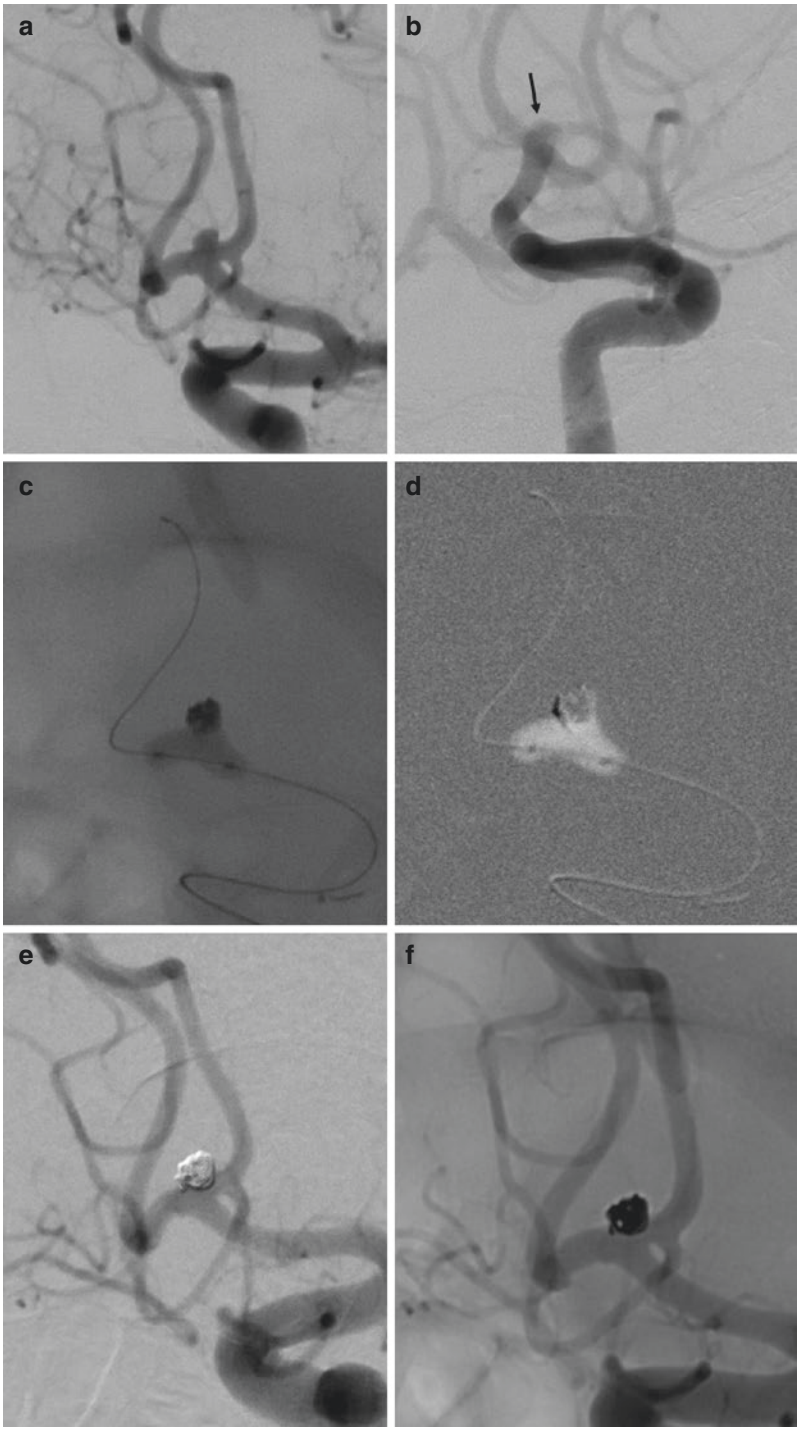
A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_11

What Are the Major Anatomical Limitations of Endovascular Aneurysm Treatment?

In general, the primary anatomical limitations faced during the coil embolization of cerebral aneurysms are those which make it difficult to densely fill the aneurysm with coils without having those same coils prolapse into the parent artery. The aneurysms which most often present these challenges fall into several (related) anatomical categories:

1. *Wide neck*: The definition of a "wide-necked" aneurysm varies considerably but has been described in absolute terms as having a neck measuring more than 4 mm in any dimension or, more accurately, in relative terms as having a dome/neck ratio of <1.5 [1]. The geometry of these aneurysms is such that the neck is often insufficient to stably retain a spherically shaped three-dimensional coil within the aneurysm fundus (Fig. 11.1). Moreover, once detached, an apparently "stable" coil can subsequently prolapse out of the aneurysm into the parent artery and on occasion even embolize into the distal cerebrovasculature.
2. *Complex anatomy at the parent artery-aneurysm interface*: On occasion the morphology of the aneurysm fundus is such that it wraps around or otherwise obscures the parent artery and precludes visualization of the parent vessel-aneurysm neck interface on one or both of the standard angiographic views. As the aneurysm fundus is densely packed with embolization coils, the parent artery becomes increasingly more difficult to visualize, and it becomes progressively more difficult to determine whether the embolization coils are being retained within the aneurysm or are extending into the parent artery. In this scenario, the inflated balloon(s) can often be used to assist in defining an optimized view of the parent artery (Fig. 11.2).

Fig. 11.1 Patient with subarachnoid hemorrhage attributed to a ruptured anterior communicating artery aneurysm (ACOMM). Conventional angiography in the working angles for coil embolization (**a**, **b** (arrow)) demonstrates a 2.5 mm broad-based aneurysm arising from a 2.5 mm neck. The height of the aneurysm measured perpendicular to the ACOMM complex is less than 2 mm. The aneurysm is so shallow that it is difficult to perceive on the lateral projection (**b**, arrow). The dome: neck ratio is approximately 1.0, and given the configuration of the aneurysm, in particular the shallow nature of the dome, it seems highly unlikely that coils would be retained within the aneurysm sac. A 4 × 7 mm "ball-shaped" balloon was manipulated across the aneurysm neck and the aneurysm was catheterized with a standard 0.017" ID microcatheter. A native image in the frontal working projection (**c**) shows the balloon inflated after the completion of coil embolization. A blank fluoroscopic roadmap obtained after balloon deflation (**d**) in the frontal working angle shows a "negative defect" corresponding to the volume filled by the previously inflated balloon. The coil mass remains almost perfectly subtracted on the blank map, indicating that no coils have prolapsed and the conglomerate mass within the aneurysm fundus is stable. Subtracted (**e**) and native (**f**) images from the completion angiography performed in the working angles for coil embolization show complete embolization of the aneurysm with the exception of a tiny defect within the medial aspect of the aneurysm coil mass corresponding to the location of the microcatheter tip


a
b
c
d
e
f

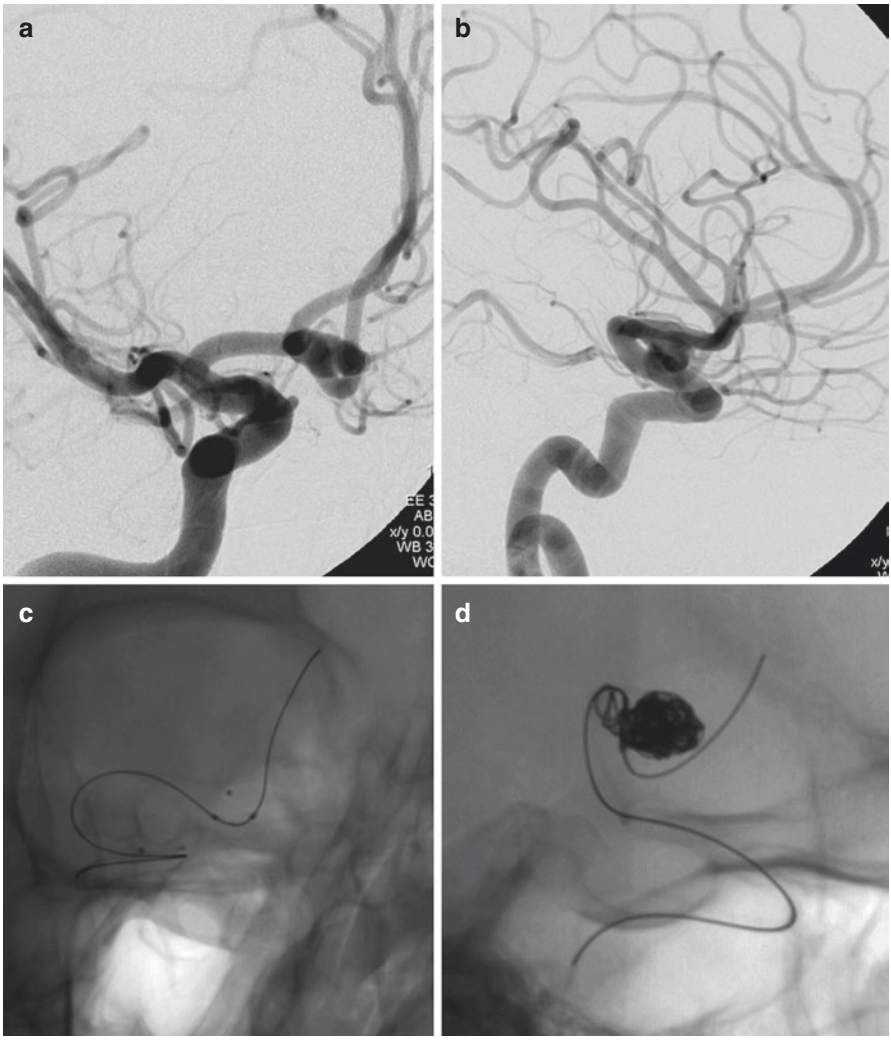


Fig. 11.2 Patient with a ruptured ACOMM aneurysm and an aplastic left A1 segment of the anterior cerebral artery. Right internal carotid (ICA) angiography in a frontal (**a**) and lateral (**b**) projection demonstrates the aneurysm to be complex and wide necked, nearly circumferentially incorporating a segment of the anterior communicating artery. The demarcation between the aneurysm neck and parent artery was difficult to ascertain from the working projections and three-dimensional angiogram. Native image (**c**) demonstrates a balloon in position across the anterior communicating artery, extending from the right A1 into the left A2. After the first round of balloon inflation and coil placement, rotation of the imaging intensifier showed the ACOMM (demarcated by the uninflated balloon catheter) to be free of embolization coils which wrapped around the proximal aspect of the ACOMM complex inferiorly (**d**). The image intensifier was reoriented to demonstrate the proximal ACOMM in an approximately "down-the-barrel" projection, and coil embolization was completed. Subtracted (**e**) and native (**f**) images from the treatment angiogram demonstrate complete occlusion which remained stable at 6-month angiographic follow-up (**g**, **h**)

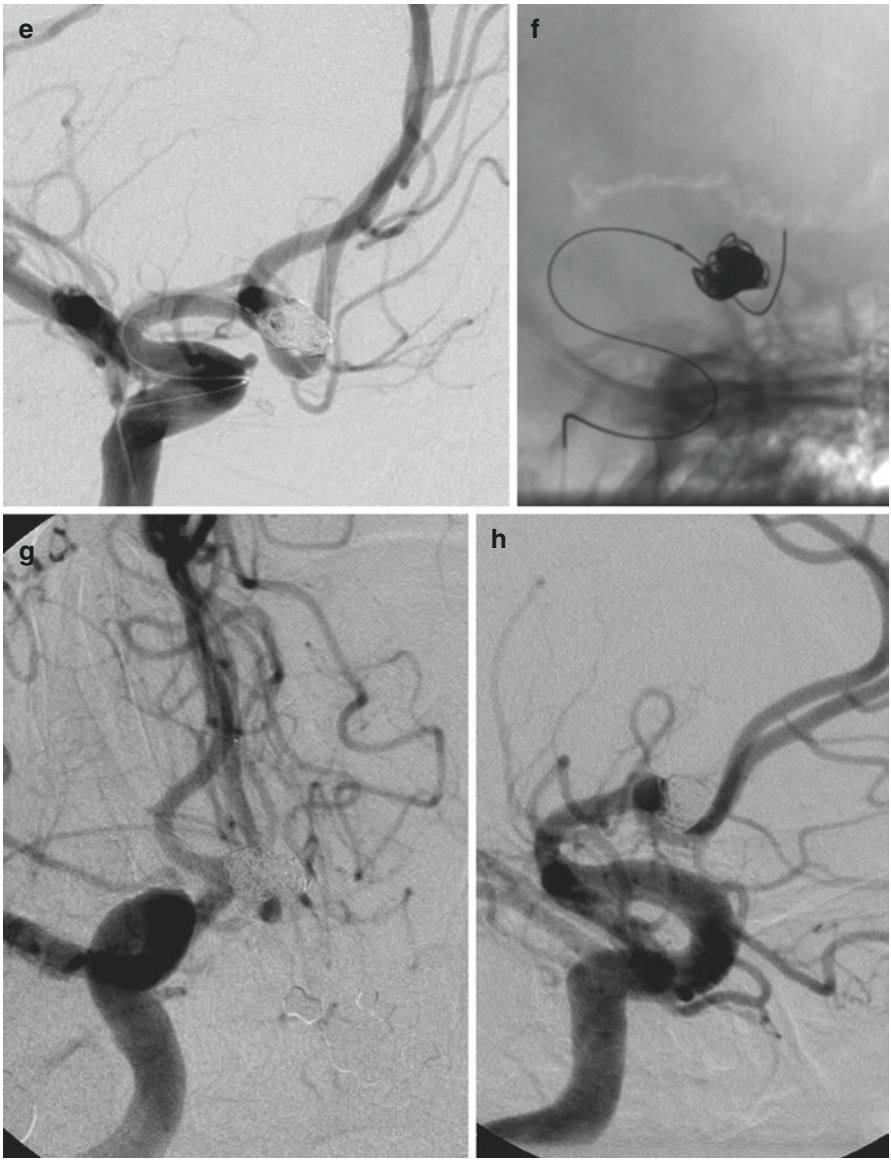


Fig. 11.2 (continued)

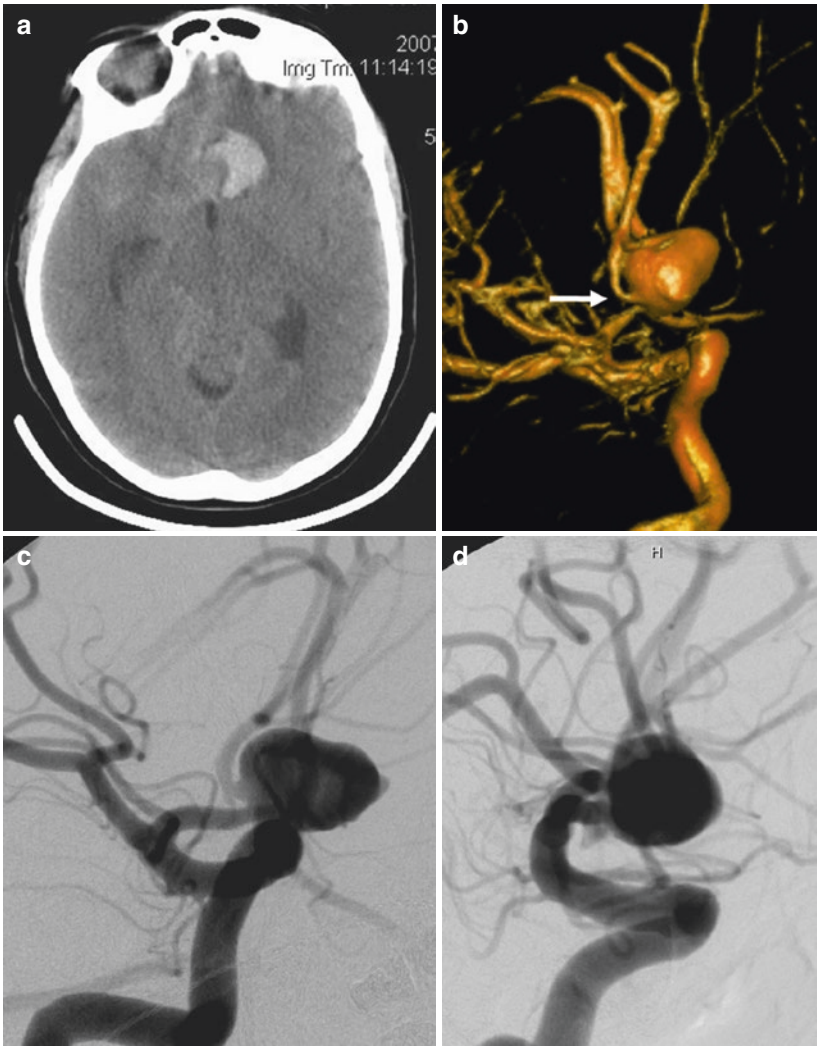
3. *Branch arteries are incorporated into the proximal aneurysm fundus*: Very wide-necked aneurysms (often those occurring at bifurcations) may actually incorporate the origins of important branch arteries which arise several millimeters into the aneurysm fundus. In these cases, it is exceedingly challenging to densely fill the aneurysm fundus with embolization coils without occluding the branch vessel arising from sac [2] (Fig. 11.3).

What Is Balloon-Assisted Treatment of Cerebral Aneurysms?

Balloon-assisted aneurysm treatment (BAT; i.e., balloon remodeling, balloon protection), first described concurrently by Dr. Peter Kim Nelson (in the USA) and Pr. Jacques Moret (in Europe), is a technique in which a temporary occlusion balloon is positioned within the parent artery across the aneurysm neck and inflated, while coils are introduced into the aneurysm fundus through a second parallel catheter [3, 4]. The inflated balloon prevents the coil loops from herniating into the parent artery

Fig. 11.3 Patient with a large ruptured ACOMM aneurysm. An image from the presenting head CT shows subarachnoid hemorrhage surrounding a large ACOMM aneurysm (**a**). A selected reconstructed three-dimensional projection from rotational angiographic source data shows the aneurysm to be extremely wide necked incorporating the right aspect of the ACOMM complex and right A2 (**b**). While the contralateral left A2 arose from the left aspect of the ACOMM complex and was essentially free of the aneurysm neck, the right A2 segment arose from the proximal aspect of the aneurysm fundus (arrow, **b**). The working angles for coil embolization (**c**, **d**) confirm the complex anatomy at the aneurysm neck. The subtracted frontal (**c**) working angle shows the ipsilateral A2 arising from the aneurysm fundus several millimeters away from the ipsilateral A1. The lateral working angle (**d**) was chosen to display a "down-the-barrel" view of the ACOMM and proximal A2 segment; however, this anatomy is almost impossible to perceive due to vascular superimposition. After diagramming the "volume at risk," it was determined that the most efficient means by which the right A2 and ACOMM complex could be protected was to place a single balloon catheter from the contralateral A1 into the ipsilateral A2. Given the very large interface between the planned coil mass and the "volume at risk" to be protected, we felt that it was essential to introduce multiple coils without losing microcatheter access to the aneurysm and thereby construct the most stable "conglomerate mass" possible. For this reason, two microcatheters were manipulated into the aneurysm via the right internal carotid artery guiding catheter. A subtracted image in the working projection (**e**) schematically demonstrates the microcatheter positioning. The solid lines indicate the position of the two microcatheters placed into the aneurysm for embolization. The dotted line depicts the trajectory of the 4 × 7 mm balloon catheter which was placed via the left A1 to lie across the right aspect of the ACOMM and extend into the proximal right A2. A total of 14 embolization coils (40 cm of Presidio-18, 151 cm of Cashmere-14 (Micrus Endovascular, San Jose, CA), and 36 cm of Hydrocoil-10 (Microvention/Terumo, Alisa Viejo, CA)) were placed during three balloon inflations. The blanked roadmap in the lateral working projection (**f**) demonstrates the "negative defect" of the deflated balloon demarcating the "down-the-barrel" projection of the proximal A2 and ACOMM complex. The coils surrounds nearly 180 degrees of the ACOMM complex and right A2 segment and remains nearly perfectly subtracted after balloon deflation indicating stability of the conglomerate mass. Frontal (**g**, subtracted; **h**, native) and lateral (**i**, subtracted; **j**, native) projections in the working angles following coil embolization show adequate occlusion of the aneurysm with a small amount of residual filling at the right A1–A2 junction. The residual area of filling corresponds to the intra-aneurysmal volume which was protected by the balloon to allow continued patency of the right A2 segment as it arose from the proximal aneurysm fundus. Although there is essentially no anatomical "neck" to prevent the prolapse of coils into the orifice of the right A2, the stability of the conglomerate mass allowed the coil reconstruction of the A1–A2 junction around the outside of the balloon. The lateral working angle (**i**, **j**) depicts the patent proximal right A2 and ACOMM (white circle) in the "down-the-barrel projection." The ACOMM anatomy is now better appreciated with the aneurysm fundus being filled with embolization coils

during delivery into the aneurysm. During the delivery of the framing coil, the balloon technique essentially "forces" the coil to achieve its complex or spherical configuration within the confines of aneurysm fundus. During the placement of the subsequent filling coils, the balloon again prevents prolapse of the new coil during deployment, but also prevents the displacement of the other previously detached coils by the new coil. Thus, the balloon essentially "forces" these filling coils to "nest" somewhere within the structure of the preexisting intra-aneurysmal coil mass. After a coil has been placed completely within the aneurysm, the balloon can then



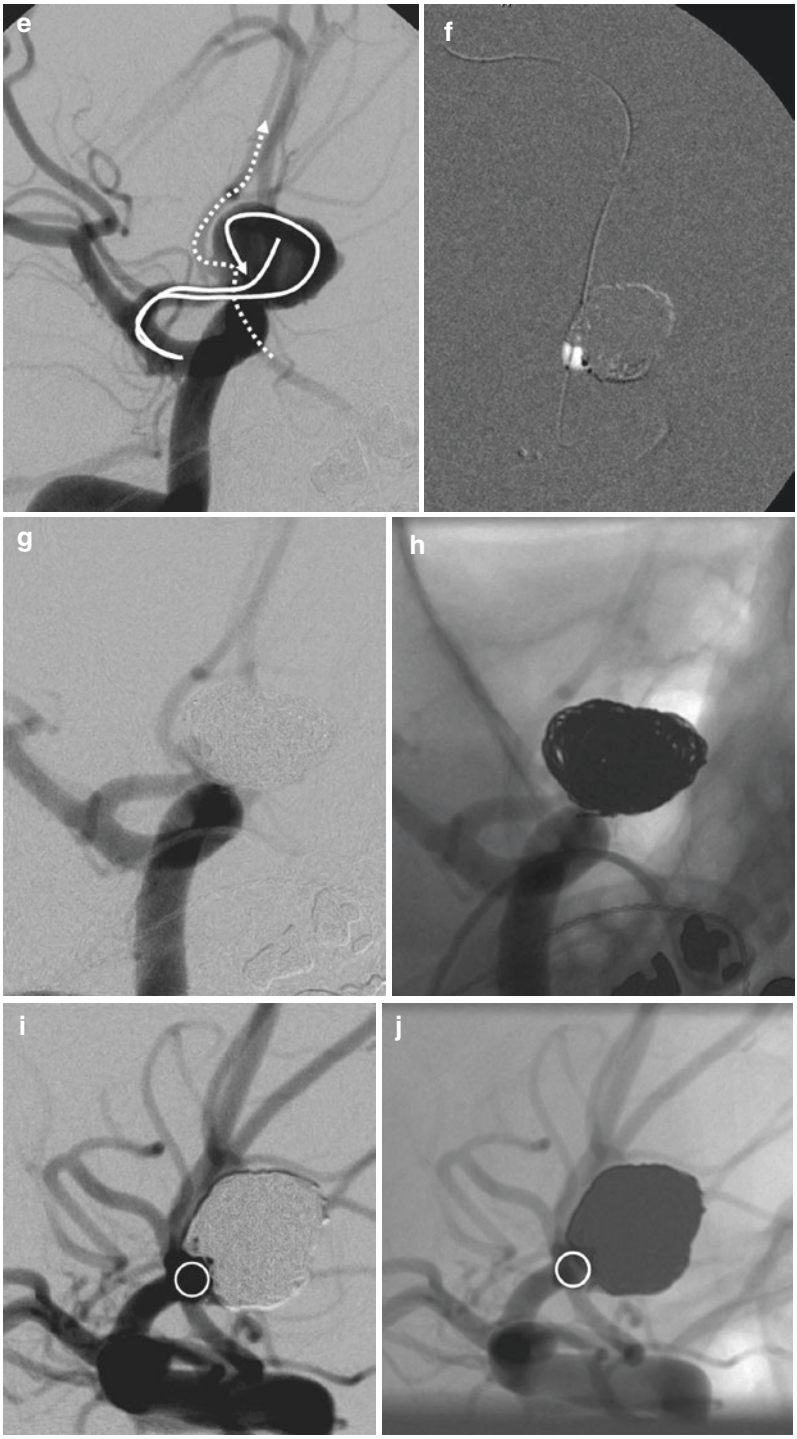


Fig. 11.3 (continued)

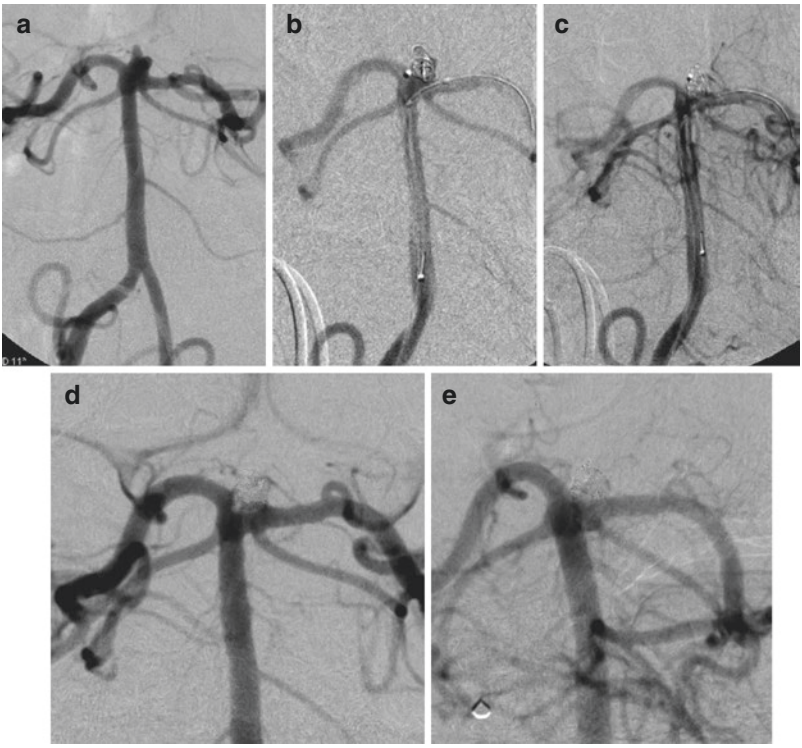


Fig. 11.4 Young female with subarachnoid hemorrhage. The initial angiographic image (**a**) in the frontal working angle for coil embolization shows a small, very wide-necked basilar artery apex aneurysm with a dome/neck ratio ~1.0. It is difficult to envision creating a stable coil mass within the aneurysm without an adjunctive device. Given that the aneurysm was ruptured, treatment was performed using a traditional balloon-assisted technique (BAT). A number of attempts were required to achieve a stable configuration of the framing coil within the aneurysm. During each of the preceding attempts, the introduced coil would prolapse out of the aneurysm with deflation of the balloon. Finally, after multiple cycles of balloon inflation and deflation with coil introduction and removal, a stable configuration of the framing coil was finally achieved (**b**). Then, additional coils were introduced into the aneurysm under balloon protection (**c**). The aneurysm was effectively coiled to complete occlusion (**d**) which was demonstrated to be durable (**e**) at 1-year angiographic follow-up. While this technique was ultimately successful, it was very time-consuming; it involved extensive manipulation of a framing coil within a small ruptured aneurysm and required a number of inflation-deflation cycles of the occlusion balloon

be deflated to "test" the coil for stability. If stable, the coil can be detached. If the coil begins to prolapse after the balloon is deflated, it can be removed and repositioned. Not uncommonly, several balloon inflations and attempted deliveries are required to achieve a stable configuration of a given coil within the aneurysm (Fig. 11.4). Thus, during traditional BAT these serial inflation-deflation cycles are repeated (occasionally multiple times) for each coil until the embolization is completed.

What Are the Arguments in Favor of BAT?

The balloon is in many aspects an optimal adjunctive device for aneurysm coil embolization for the following reasons:

1. *Reliable parent artery protection*: While inflated, the balloon provides a much more reliable and robust parent artery protection than do the available Nitinol, self-expanding, intracranial microstents (Neuroform, Boston Scientific, Fremont, CA; Enterprise, Codman Neurovascular, Warren, NJ). First, the contrast-inflated balloon can be unambiguously visualized to demonstrate the location of the parent artery. The self-expanding stents are radiolucent, and as such, the exact anatomy of the interface between the parent artery and aneurysm fundus sometimes remains unclear. As such, during the embolization of aneurysms with complex anatomy, it is sometimes difficult to confidently ascertain whether coils are completely free of the parent artery. Second, the interstices of the self-expanding stents are large enough (2 French) to accommodate the unimpeded passage of a microcatheter into the aneurysm. These interstices may become even larger when the stent is deployed across an aneurysm which arises from a curved segment of the cerebrovasculature [5]. The area of these interstices is sometimes sufficient to allow the prolapse of coils through the stent and into the parent artery (Fig. 11.5).

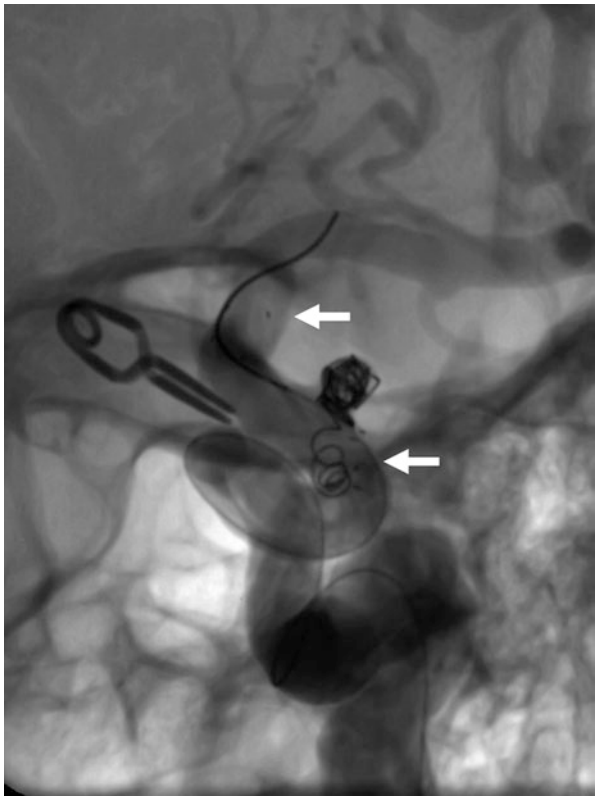


Fig. 11.5 Coil prolapse through an intracranial self-expanding stent. Native image from a trans-stent coiling of a small carotid-ophthalmic segment aneurysm depicts a stent in position across the aneurysm neck (arrows demarcate the stent end markers). The intra-aneurysmal coil mass shows a vivid stent effect with a flat edge at the aneurysm-parent vessel interface. However, an immediately following detachment, a coil herniated through the interstices of the stent. A second stent was subsequently deployed across the aneurysm to secure the coil and prevent further prolapse or distal embolization

In contrast to the stent, the balloon provides a completely continuous, radio-opaque barrier along the aneurysm neck. As such, unless the coiling microcatheter gets pushed out of the aneurysm or coils prolapse around the outside of the balloon (which typically indicates that the balloon is underinflated or improperly sized/shaped), there is no way that coils can come into the parent artery while the balloon is inflated.

2. *Unambiguous parent artery visualization*: Once positioned across the neck of the aneurysm, the balloon can often times provide invaluable assistance with respect to pre- (or more appropriately stated intra-) treatment planning. With the balloon inflated, the framing coil can be placed within the aneurysm but not detached. If optimally sized, the framing coil then provides a radio-opaque demarcation of the boundaries of the aneurysm. At this point, with the balloon inflated and the framing coil in place, the image intensifiers/detectors can be manipulated under fluoroscopic visualization to best depict the parent artery (demarcated by the contrast filled balloon) free of the aneurysm fundus (demarcated by the framing coil). This technique is very useful to determine the most optimal working angles for coil embolization. This is particularly useful in achieving a perfect "down-the-barrel" projection of the parent artery in the region of the aneurysm neck. This "down-the-barrel" projection is usually the most reliable demonstration of the parent artery boundaries during complex cases (Fig. 11.6).
3. *Rupture protection*: Intra-procedural aneurysm rupture is a potentially catastrophic complication which can often be managed and considerably mitigated using with a balloon-assisted technique. In the absence of an occlusion balloon, procedural aneurysm perforation usually results in immediate extravasation which can be controlled only by reversing heparinization, lowering blood pressure, and quickly placing additional embolization coils. Aneurysm perforation is particularly difficult to manage in the setting of stent-assisted coiling since these procedures are usually performed with the patient on dual antiplatelet therapy in addition to full procedural heparinization.

   During BAT, an occlusion balloon is inflated across the aneurysm neck, and the lesion is essentially isolated from the cerebral circulation. Correspondingly, the inflated balloon actively prevents or minimizes any extravasation from the aneurysm should it re-rupture during the introduction of coils. If there is evidence of aneurysm rupture during coiling (e.g., the coil passes outside of the confines of the aneurysm roadmap), the balloon can be left inflated, while the heparinization is reversed, and additional coils are introduced into the aneurysm fundus. In this way the amount of extravasation which occurs after rupture can be minimized or eliminated altogether. The occlusion balloon in this scenario functions similarly to the temporary surgical clips used to control intraoperative aneurysm rupture during surgery.
4. *Temporary device*: The absolute requirement for dual antiplatelet medications represents one significant potential drawback of the application of intracranial stents for aneurysm treatment. This is particularly an issue in the setting of acute subarachnoid hemorrhage in which platelet inhibition represents a significant hazard during subsequent intensive care management [6]. In contrast to stenting, BAT can be performed with heparinization alone in patients with subarachnoid

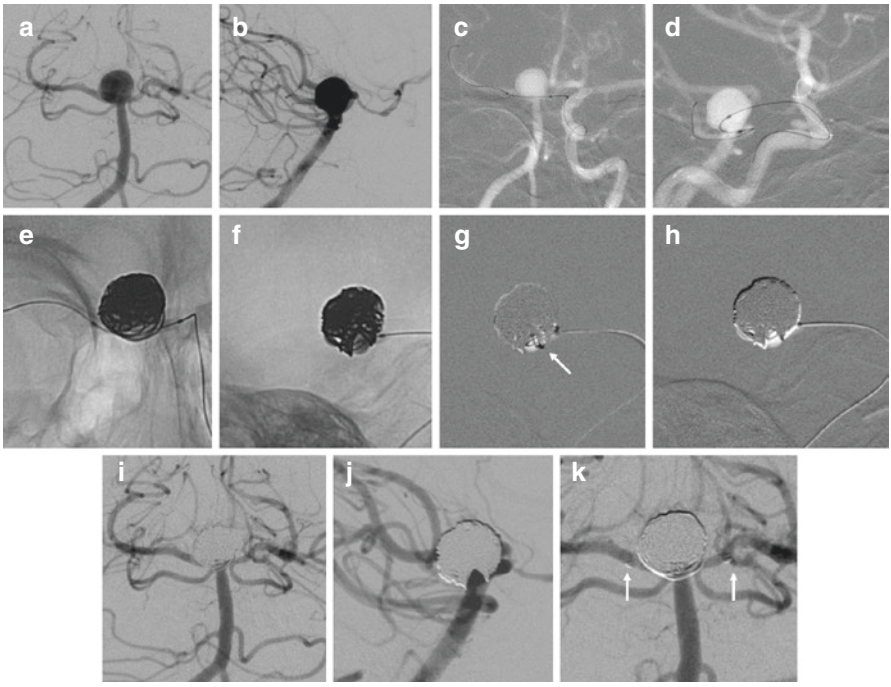


Fig. 11.6 Patient with an incidental basilar apex aneurysm. Initial frontal (**a**) and lateral (**b**) working angles show a very wide-necked aneurysm wrapping around the anterior and posterior aspects of the basilar apex and incorporating both proximal P1 segments into the neck. On the frontal working angle (**a**), it is difficult to visualize the origins of either P1 as they are obscured by the aneurysm. On the lateral view (**b**), the anatomy is difficult to assess due to superimposition of many branch vessels and the aneurysm. Fluoroscopic roadmap images in the frontal (**c**) and lateral (**d**) projections show a 4 × 15 cylindrical balloon in position across the basilar apex via the left PCOMM. This balloon position allows the protection of the entire "volume at risk" with a single balloon catheter. Once coils have been placed in the aneurysm, the detectors were manipulated to optimize the working angles. While the frontal (**e**) angle cannot show the parent artery due to superimposition, the lateral (**f**) angle has been manipulated into an exact "down-the-barrel" projection, viewing the balloon and its central microwire on axis. The lateral blank roadmap (**g**) following balloon deflation after the first round of coiling demonstrates some coil prolapse along the anterior aspect of the basilar apex (arrow). At this point, this compartment of the aneurysm lacked a sufficient number of coils to create a stable conglomerate mass. Fortunately, reinflation of the balloon displaced these coils back into the aneurysm. The microcatheter was reoriented into this anterior compartment, the balloon was reinflated, and a number of additional coils were placed. During the second balloon deflation, the blank roadmap in the lateral working projection (**h**) shows that the prolapsed coils which were displaced into the fundus by the balloon became enmeshed with the new coils introduced during the second round of coiling. Now, after the second balloon deflation, the basilar (demarcated by the "negative defect" of the deflated balloon) remains free of coils, indicating that conglomerate mass is now completely stable. Completion angiography in the frontal (**i**) and lateral (**j**) working angle shows complete aneurysm occlusion. The lateral working angle (**j**) demonstrates the coil reconstructed basilar apex, with 270° of its circumference surrounded by embolization coils. At the conclusion of coiling, the balloon catheter was exchanged for a stent delivery system and a self-expanding microstent was placed from the right to the left P1. A magnified frontal (**k**) view at the end of the procedure shows the coil mass within the basilar apex and the stent end markers (arrows) in the left and right P1's

hemorrhage. In some elective BAT cases, we do pretreat patients with aspirin or sometimes both aspirin and clopidogrel. These antiplatelet medications provide prophylaxis against procedural thromboembolic complications and to allow the accommodation of a stent if one is ultimately deemed necessary at some point during the procedure. However, if an elective patient is pretreated with both antiplatelet agents and no intracranial stent is used, we typically discontinue clopidogrel immediately after the procedure and stop aspirin after 2–4 weeks.

5. *Improved microcatheter access (stability and reaccess)*: The temporary occlusion balloon can often function to stabilize the microcatheter at the aneurysm neck, preventing excessive kickback during coiling. This augmentation of microcatheter stability can facilitate dense aneurysm packing with coils. If the microcatheter should get pushed out of the aneurysm during coiling, the balloon can be deflated, and it presents no barrier to aneurysm reaccess. In contrast, an in situ stent frequently impairs microcatheter access into the aneurysm and also provides no additional support for the stability of the microcatheter once it is navigated into the aneurysm.
6. *Packing density*: The improved access to the aneurysm as well as the more robust nature of the parent artery protection offered by the balloon may contribute to a more aggressive coiling of the aneurysm and a higher packing density in some cases.
7. *Dynamic parent artery protection*: Initially, the balloon is sometimes inflated to the point that it herniates slightly into the aneurysm neck during coil placement. As the coiling is completed, the balloon can be inflated less aggressively to allow the coil mass to form an interface with the parent artery that exactly approximates the aneurysm neck (Fig. 11.7).

What Are the Potential Disadvantages of BAT?

1. *Temporary protection may be unreliable*: The overriding belief which discourages some operators from using a balloon remodeling technique is the absence of a permanently implanted device to secure the coil mass in place. This raises the concern that the entire coil mass could spontaneously begin to prolapse into the parent artery at some point during the case. Once the operator gains sufficient experience with the technique, particularly when applied using the "conglomerate mass" approach, it becomes evident that this is not a common or unmanageable problem. In some cases, when a very wide-necked aneurysm has been densely packed down to the parent artery, the operator may elect to place a stent at the conclusion of coiling to definitively stabilize the coil mass. With this approach, one gains all of the above advantages of BAT while alleviating any concerns that the coil mass could begin to prolapse after the procedure is complete (Fig. 11.6). Similarly, if any coil prolapse is noted during the procedure, the operator retains the ability to exchange the balloon catheter for a stent delivery system.
2. *Time*: When applied using a traditional approach (i.e., an inflation-deflation cycle with each coil introduction), the BAT approach can consume a considerable

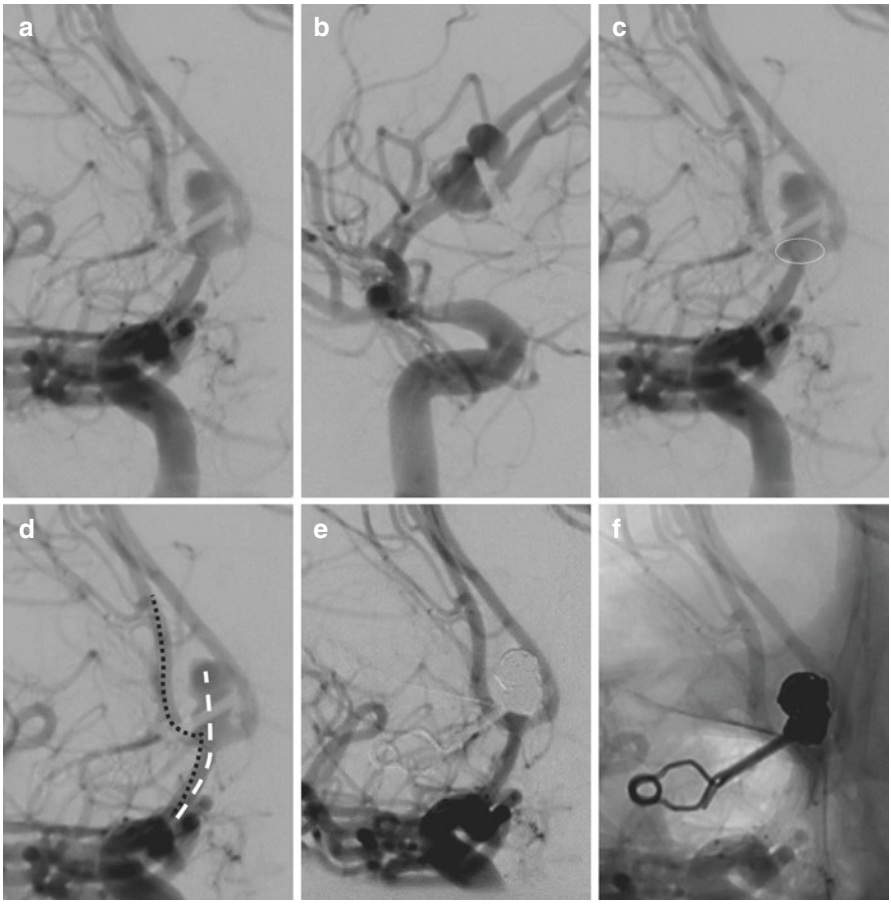


Fig. 11.7 Patient with wide-necked ruptured ACOMM aneurysm originally clip-wrapped at an outside institution after direct clipping was unsuccessful. The left A1 segment was aplastic, with both A2 segments filling from the right anterior circulation. Angiography in the frontal (**a**) and lateral (**b**) working projections demonstrates a wide-necked ACOMM aneurysm incorporating the entire ACOMM complex and proximal right A2 segment. The "volume at risk" (dotted line) is depicted schematically on the frontal (**c**) working projection. The more difficult branch to protect and catheterize is clearly the ipsilateral (right) A2. As such, a 4 × 7 mm balloon was manipulated into position within the ACOMM and proximal right A2. The position of the microcatheters is diagrammatically depicted on the subtracted frontal working projection (**d**). The balloon catheter position is marked by a black dotted line, while the microcatheter position is demarcated by a white dashed line. Eleven coils were introduced during two 5-min balloon inflations (38 cm of Cashmere-14, 20 cm of Ultipaq-10 (Micrus Endovascular) and 4 cm of Hydrosoft-10 (Microvention/Terumo)). Subtracted (**e**) and native (**f**) images following coil embolization demonstrate complete, dense occlusion of the aneurysm with the coil mass forming a homogeneous flat interface with the ACOMM complex. Both A2 segments remain widely patent

amount of time and require extensive manipulation of the coiling microcatheter and embolization coils. The deflation times for the balloons can last up to 15–30 s in some cases, adding a significant amount of additional time to each coil placement and detachment cycle.

3. *Brain ischemia*: While the balloon is inflated, the parent artery is completely occluded, resulting in reduced blood flow (and depending on the status of the collateral circulation) and potentially ischemia of the region of brain supplied by that vessel. For this reason, it is useful to assess very closely the patterns of collateral circulation which are in place during balloon inflation. For aneurysms of the carotid artery, the balloon should be positioned specifically to avoid inducing unnecessary ischemia by occluding these collaterals. Specifically, one should avoid when possible having the balloon extend into the ICA terminus if the ACOMM provides collateral flow or occluding the PCOMM when that vessel could otherwise provide perfusion to the hemisphere. The repetitive inflation and deflation of the balloon with each coil introduction may also raise the risk of thromboembolic events by repeatedly agitating the forming coil mass and also potentially resulting in small amounts of blood being aspirated into the balloon and ultimately embolized during the procedure.
4. *Durability of coil embolization*: While BAT may allow the embolization of very wide-necked aneurysms, the results may not be durable, given the propensity of these lesions to recur [7]. Some operators have suggested that the application of a stent may in fact improve the durability of coil embolization by providing some degree of flow redirection and neoendothelial/overgrowth at the aneurysm-parent artery interface [8]. However, there are several arguments which can be made against using a stent primarily. First, the BAT likely allows a more meticulous and complete packing of the aneurysm which might lessen the risk of recanalization. Second, following BAT, if the operator believes that either the coil mass is unstable or otherwise requires a stent, one can be placed at that time. The balloon catheter can be exchanged over a 0.010″ 300 cm exchange microwire (e.g., Xcelerator-10, eV3, Irvine, CA) for a microcatheter, then a 0.014″ exchange wire, and ultimately a stent delivery system.

Balloon-Assisted Coiling in Our Practice: The Conglomerate Coil Mass Technique

What Is the "Conglomerate Coil Mass Technique" of BAT?

Having recognized that the potential and practical limitations of balloon-assisted coiling are primarily related to the repetitive cycles of inflation and deflation associated with the introduction of each coil, we began to place multiple embolization coils (3–7 coils) during each balloon inflation (typically lasting 5–10 min).

Several observations led to the evolution of this technique. First, we noticed that during traditional BAT occasionally a newly introduced coil would lead to the prolapse of a formerly placed and previously detached coil. Often times, we would continue embolization with the idea that a stent would be required at the conclusion of the coiling to secure the prolapsed coil. However, we often found that if the prolapsed loop(s) were pushed back into the aneurysm during subsequent balloon inflations and additional coils were introduced and detached, the prolapsed loops actually enmeshed within the newly introduced coils, ultimately forming a stable intra-aneurysmal "conglomerate mass" and obviating the need for a stent (Fig. 11.6).

Second, in some very wide-necked aneurysms, we found that the original framing coil was unstable despite multiple attempts at repositioning. Moreover, even when stable within the aneurysm, the coil would frequently shift during balloon deflation. In contrast, when multiple coils were introduced and detached during the initial balloon inflation, they formed a stable intra-aneurysmal "conglomerate mass" which did not appreciably shift or prolapse when the balloon(s) were ultimately deflated.

Third, continuous occlusion times of between 5 min and 10 min with intermittent perfusion seemed very well tolerated in most patients. In the setting of adequate direct collateral circulation (e.g., robust ACOMM collateral which remains patent during BAT), much longer occlusion times are acceptable. The duration of acceptable occlusion times during endovascular procedures can be extrapolated from the literature describing the application of temporary aneurysm clips during surgery. During aneurysm surgery, temporary clip occlusion times of between 10 min and 20 min are routinely necessary and typically well tolerated by most patients [11–13]. As opposed to the placement of temporary aneurysm clips, the application of an occlusion balloon as an endovascular "temporary clip" is performed with full heparinization (often times with adjunctive antiplatelet medications in patients with unruptured aneurysms), does not require manipulation of the parent artery or regional perforator vessels, and is not performed in conjunction with brain retraction. For these reasons, it would seem that endovascular balloon occlusion would be at least as well tolerated as temporary clip application when applied over similar time intervals.

Fourth, during the occasional procedural rupture using traditional BAT, the conglomerate technique was used by default in an attempt to achieve complete aneurysm occlusion and halt any further hemorrhage. In these cases, it became evident that very dense packing could be achieved quite quickly using this technique.

Arguments in Favor of the "Conglomerate Mass" Technique Versus a Traditional Approach to BAT

We find in our practice that this BAT technique provides several potential advantages over the traditional approach.

1. The conglomerate mass created with the introduction of multiple coils was more stable than individually placed coils and allowed the coil embolization of very wide-necked aneurysms without the use of an adjunctive stent (Fig. 11.1).

2. This approach allowed the dense packing of small, soft, finishing coils at the level of the aneurysm neck, facilitating very high packing densities and more homogeneous coil reconstructions of segmental neck defects (Fig. 11.7).
3. The rapid placement and detachment of multiple coils in succession shortened the overall procedural time for aneurysm coiling in comparison to the standard BAT approach (Fig. 11.8).
4. Placing multiple coils during a single balloon inflation allowed for fewer overall balloon inflations and less coil manipulation/repositioning. This technique likely results in shorter cumulative total balloon occlusion times in many cases.
5. Unexpected procedural aneurysm perforation becomes more manageable, as many coils are introduced quickly and the aneurysm is typically very well occluded at the time of the initial balloon deflation (i.e., the time when procedural perforation becomes evident).

The Conglomerate Coil Mass Technique: Technical Points, Equipment, and Procedural Details

Key Technical Points

Anticoagulation/Antiplatelet Regimen: Full Anticoagulation Is Required for BAT Using the Conglomerate Coil Mass Technique

For these cases, it is required that patients, regardless of their rupture status, are completely heparinized (activated clotting time of 250–300 s) prior to balloon inflation. The application of complete heparinization can be deferred until the microcatheters are in appropriate position for the initiation of coiling. Patients with unruptured wide-necked aneurysms undergoing elective embolization with BAT are pretreated with aspirin (81–325 mg per day given the morning of the procedure) and sometimes clopidogrel (75 mg per day for 5–7 days or 600 mg the day prior to the procedure with 75 mg the morning of the procedure) particularly if stent use is anticipated. If stenting is not performed, in most cases, the clopidogrel can be discontinued immediately after the procedure and the aspirin stopped at 2–4 weeks.

Balloon Selection, Positioning, and Navigation

Strategies for balloon selection and positioning are based upon a thorough understanding of the anatomy of the aneurysm, the parent artery, and the relevant adjacent branch vessels. Two general factors govern these decisions.

First, the operator must define the exact volume of the parent artery and regional branch vessels (i.e., the parent artery-aneurysm complex) which is at risk for coil prolapse and therefore must be protected with the balloon(s) – the “volume at risk.” Sometimes it is helpful to actually trace this volume out on the image or on a sheet of paper. This volume will then determine which balloon(s) should be selected and

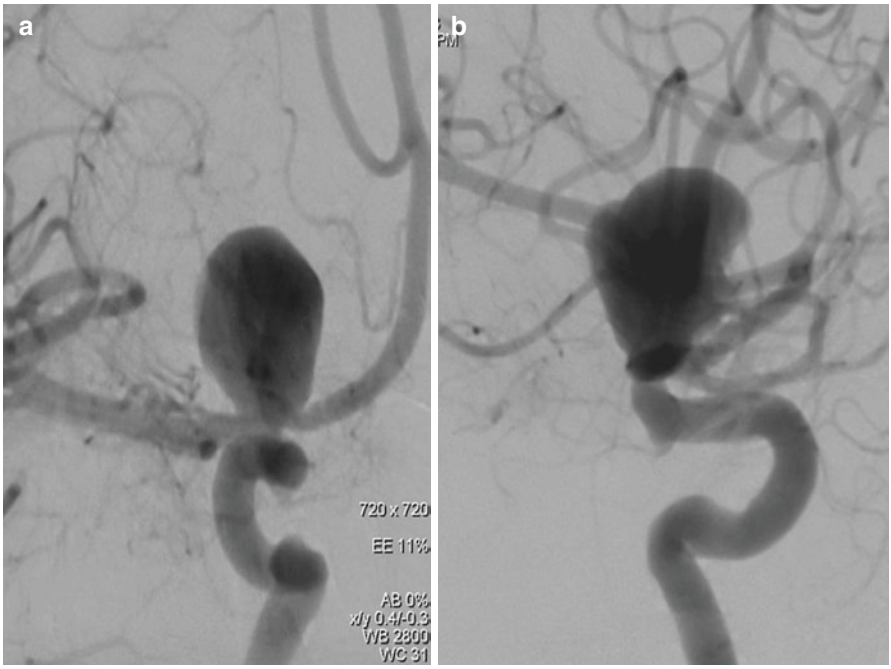


Fig. 11.8 Very large ruptured ICA terminus aneurysm presenting with subarachnoid and a right frontal parenchymal hemorrhage. Angiography in the initial frontal (**a**) and lateral (**b**) working projections demonstrates a large, wide-necked ICA terminus aneurysm incorporating a short segment of the proximal right M1. The right A1 essentially arises from the aneurysm fundus. While there were two patent and equally sizes A1s, the ACOMM complex was tiny. As such, it was decided that patency of the right A1 had to be maintained during treatment. Coronal (**c**) and surface-shaded three-dimensional (**d**) reconstructions of computed tomographic angiography (CTA) source images show the right A1 arising at an acute angle just distal to the neck of the aneurysm. The planned microcatheter positions are schematically superimposed upon the frontal working projection (**e**) with the dash-dotted line representing a 4 × 15 mm balloon extending from the ICA into the right M1, a dotted line representing a 4 × 7 mm balloon extending from the ICA terminus into the right A1, and a solid line representing a microcatheter wrapped around the dome of the aneurysm with the tip positioned near the A1 outflow zone. A native (**f**) image in the frontal working projection demonstrates the simultaneously inflated balloons with the microcatheter in position wrapping around the dome of the aneurysm. During 3 balloon inflations lasting 12, 8, and 8 min, respectively, a total of 25 coils were introduced. Subtracted (**g**) and native (**h**) images in the frontal working projection for coil embolization demonstrate a dense coil mass within the aneurysm forming a flat interface with the parent arteries. A tiny defect at the medial aspect of the coil mass corresponds to the intra-aneurysmal portion of the ACOMM-proximal right A2 segment junction, the patency of which was preserved by the 4 × 7 mm balloon to allow continued filling of the right A2. A tiny focus of thrombus at the lateral aspect of the coil mass, seen as a tiny lucent defect within the right M1, was prophylactically treated with several milligrams of IA abciximab and post-procedural aspirin

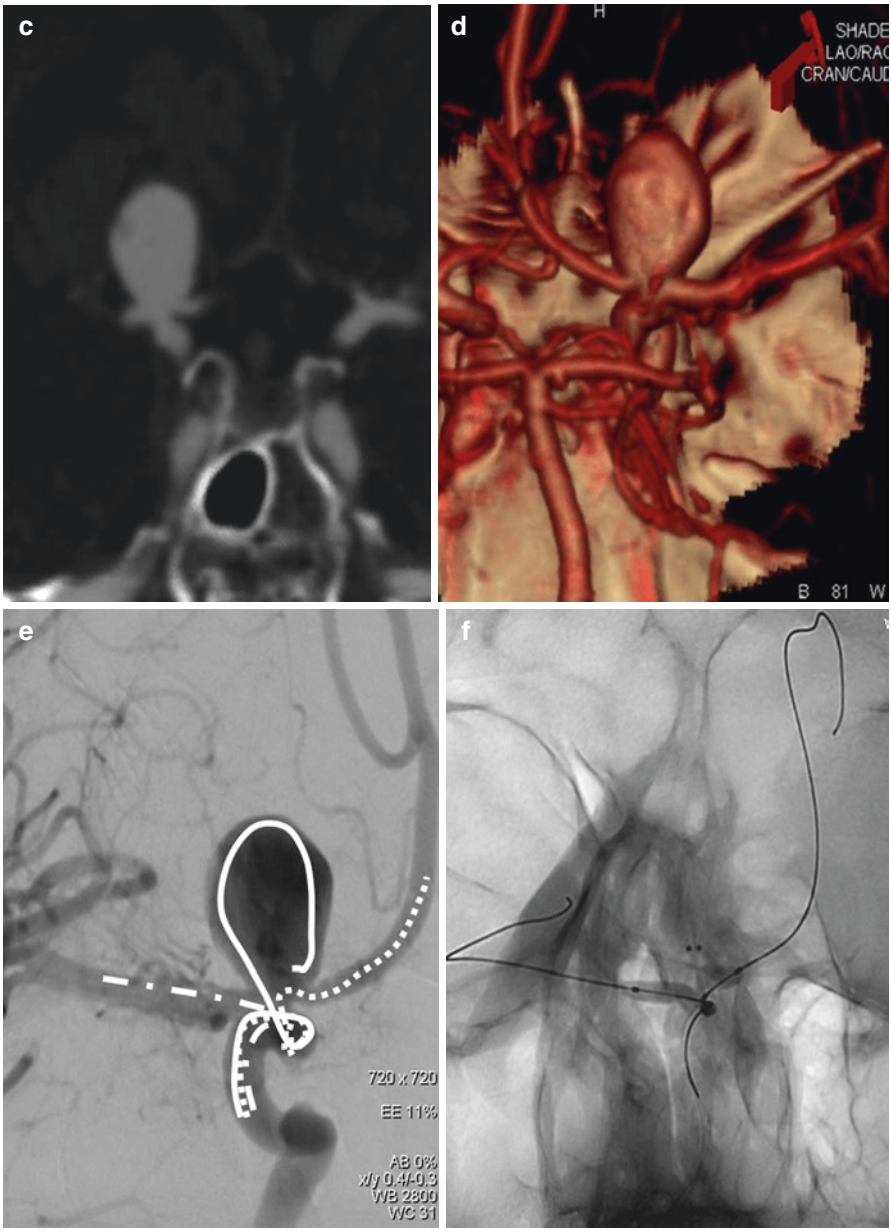


Fig. 11.8 (continued)

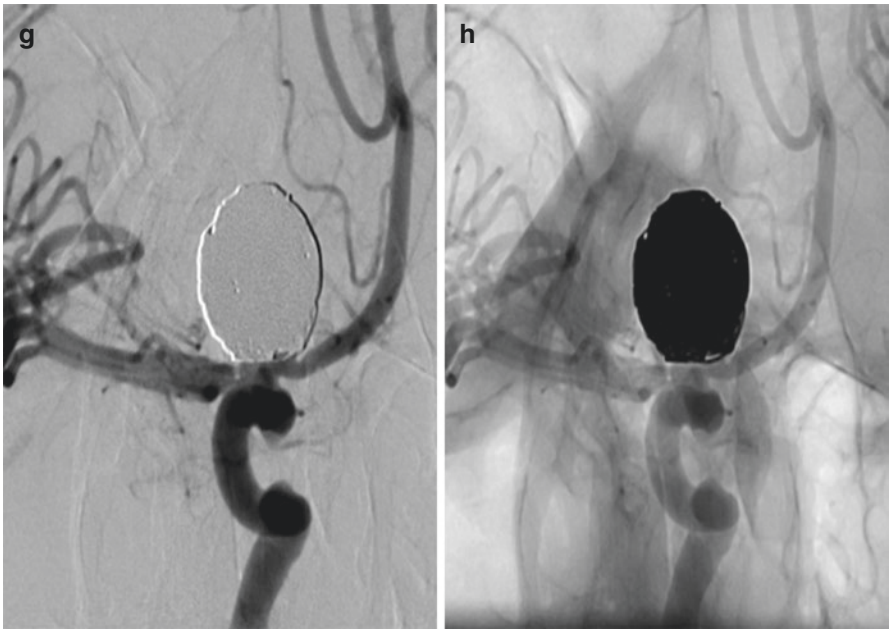


Fig. 11.8 (continued)

where it/they should be positioned such that the required space can be completely filled during the inflations (Figs. 11.3, 11.6, and 11.7).

Second, for bifurcation aneurysms, the operator must determine which branch(es) is(are) most likely to be occluded by the prolapse of an individual coil or the forming coil mass. This can often be done by visualizing the aneurysm completely filled by a symmetric spherical or elliptical coil mass, since the favored configuration of implanted coils typically conforms to this shape. The branch vessel most likely to be occluded by the coil mass is the one which will require not only balloon protection but control via catheterization with the balloon microwire. This microwire control allows the operator to seamlessly exchange the balloon catheter for a stent delivery system in the case that coils prolapse into the orifice of the vessel during or after treatment.

The available single lumen, hypercompliant temporary occlusion balloons accommodate only a 0.010″ microwire. Given the limited torque response of the smaller 0.010″ microwires, the negotiation of complex cerebrovascular anatomy with the balloon catheter can be very challenging. In addition, the balloon catheters are larger and more rigid than the standard 0.017″ ID microcatheters and as such have a tendency to "override" the relatively soft 0.010″ microwire in the absence of excellent distal wire purchase. For this reason, we prospectively navigate predictably difficult anatomy with a standard microcatheter and 0.014″ microwire to achieve distal access within the targeted anatomy (foregoing any attempt at primary catheterization with the balloon). We then exchange the microcatheter for the

occlusion balloon of choice over a 300 cm, 0.010″ exchange length microwire (Xcelerator-10, eV3, Irvine, CA). After this exchange, we maintain the 300 cm microwire in place through the balloon catheter for the entire case, allowing for a seamless exchange to a stent delivery system should this be necessary at some point during the case.

Microcatheter Positioning

As the stability of the conglomerate mass is predicated upon the introduction of multiple coils during a single balloon inflation, it is important that the microcatheter does not get rejected from the aneurysm after only one or two coils are placed. For this reason, a stable and deep access into the aneurysm is preferable. In larger aneurysms, we have achieved this with a microcatheter position which courses around the aneurysm dome and/or through the introduction of a second microcatheter into the aneurysm for coiling (Figs. 11.8). Coils can then be introduced into the aneurysm until the microcatheter(s) is/are rejected.

Coils with Rapid Detachment

The rapid delivery and detachment of multiple coils requires a rapid detachment mechanism. The standard electrolytic detachment, which can require between 15 s and 45 s per coil, is not compatible with the conglomerate coil mass technique.

Soft Coils of Long Length

Softer coils work best with this technique as they do not reject the microcatheter from the aneurysm during their introduction. They also tend to fill the interstices within the developing coil mass, and in the region of the aneurysm neck, they "mold" around the outside of the balloon to form a more continuous interface at the parent artery-aneurysm neck interface (Fig. 11.8). The longer coils provide more length available to insinuate and enmesh within the forming coil mass. They also provide a greater volume of filling per coil, reducing the total number of coils introduced and thereby reducing the collective amount of time for coil preparation, loading, and delivery.

Efficient Coil Preparation and Delivery

The entire team must be fully engaged with the procedure while the balloon(s) is(are) inflated. The expected sequence of coils should be preselected and readily available from the technologist. During the introduction of one coil, the operator should be asking for the next coil which should be immediately ready for

introduction as soon as the preceding coil is detached and removed. The assistants to the primary operator must be familiar with the process of coil preparation and microcatheter loading so that this can be performed as efficiently as possible. These considerations are critical to limiting time required to prepare and introduce each coil. If the time allotted to place each coil can be reduced, more coils can be successfully introduced into the aneurysm during a given inflation, the overall number of inflations required can be reduced as can the overall collective procedural time.

Equipment

Balloon Catheters

The original temporary occlusion balloons (Endeavor, Boston Scientific, Fremont, CA) relied on flow direction and were subsequently limited in terms of navigability. A new generation of hypercompliant, wire-guided, temporary occlusion balloon catheters have been developed for use in the cerebrovasculature. These devices are now widely used for temporary vessel occlusion, angioplasty of cerebral vasospasm, mechanical disruption of thrombus in the setting of acute ischemic stroke, and balloon-assisted treatment of cerebral aneurysms.

In the USA, the Hyperglide and Hyperform (eV3, Irvine, CA) balloons are most frequently used for BAT. These balloons accommodate a 0.010″ microwire which occludes the distal end hole of the catheter when passed out the microcatheter tip. When a mixture of contrast-saline is injected into the proximal hub around the microwire through a rotating hemostatic valve, the injectate is directed into the balloon chamber resulting in balloon inflation. The hypercompliance of the balloon material allows for multiple inflations without a significant change in the profile of the distal catheter when the balloon is deflated (i.e., the material collapses around the distal catheter and does not form "wings" as would a semicompliant or noncompliant "wrapped" angioplasty balloon). Also, the hypercompliant inflation profile makes for a very soft, atraumatic, and "moldable" balloon which can be inflated such that it insinuates into adjacent vessels or the aneurysm neck.

The available balloons come in two general shapes, a conformable ball-shaped (e.g., Hyperform 4 × 7 mm and 7 × 7 mm) which is typically used for bifurcation and terminal aneurysms and a more cylindrically shaped tubular balloon (e.g., Hyperglide 4 × 10, 15, 20, 30 mm) which is most often used for side wall aneurysms. These two different shaped balloons can sometimes be used in combination to achieve more extensive and complex remodeling.

Microcatheters

Any standard 0.017″ internal diameter (ID) microcatheter (SL-10, Boston Scientific, Fremont, CA; Echelon-10, eV3, Irvine, CA; Prowler-10, Codman Neurovascular, Warren, NJ) can be used in conjunction with the available hypercompliant balloon

catheters through a standard 6F, 0.070″ ID guiding catheter system with the exception of the 7 × 7 mm Hyperform balloon. The 7 × 7 mm Hyperform balloon requires a larger guiding catheter (7F) to accommodate a parallel microcatheter.

Rotating Hemostatic Valve (RHVs)

There are a number of different options for managing the proximal aspect of the guiding catheter. The two microcatheters can be placed side by side through a single RHV port. We do not prefer this technique, as this setup makes the independent positioning of the two catheters more challenging. Two RHVs can be coupled together to provide two ports for microcatheter access; however, the additional RHV adds considerably to the dead space of the guiding catheter system. Finally, a W-shaped adapter (e.g., The Sequel, Cook Medical, Indianapolis, IN) with two valve ports and a one side arm integrated into a single RHV, in our opinion, represents an optimal solution by minimizing dead space and providing an independent access for both microcatheters.

Procedural Details

Diagnostic angiography is first performed to approximate the working angles for coil embolization and to obtain accurate measurements of the aneurysm fundus for coil selection. The framing coils and the anticipated filling/finishing coils are then removed from the stock and placed in an accessible position such that they may be opened and provided to the operators efficiently. The volume distribution which must be protected with the balloon(s) is determined at this point, and the appropriate balloon(s) are opened and prepared. Regardless of rupture status, full heparinization (ACT of approximately 250–300 s) is usually instituted at the time that the balloons are being inflated.

Once the balloons are in position and the aneurysm is catheterized, it is sometimes useful to inflate the balloons and partially deploy the framing coil into the aneurysm. The coil outlines the confines of the aneurysm, while the contrast opacified balloon(s) demarcate the parent artery. Then under live native fluoroscopy, the image detectors can be manipulated to demonstrate the parent arteries (demarcated by the contrast-inflated balloon(s)) to best advantage as separate from the aneurysm fundus (demarcated by the aneurysm coil). This technique can be used to optimize the working angles for embolization.

At this point, the coil can be removed and the balloons deflated and to allow cerebral reperfusion. A new angiographic run is performed in these optimized working angles and if possible displayed as a reference image which can be viewed throughout the case. The balloons can then be reinflated and coils delivered into the aneurysm. During the initial inflation, typically between three and seven coils can be deployed over 5–10 min depending on the aneurysm size. Following placement of these coils, a blank roadmap image can be created with the balloon(s) inflated.

Then the balloon(s) can be deflated with fluoroscopic visualization on a blank roadmap. The balloons deflate to form a negative defect in the region of the parent artery (Figs. 11.1, 11.3, and 11.6). On the blank map, even the most subtle shift of the coil mass or an individual coil loop will be evident. An angiographic run is performed at this time to confirm the patency of the parent arteries and branches. Additional rounds of balloon inflation and embolization are then performed as needed. Usually the endpoint of the case is indicated when the microcatheter has been rejected from the aneurysm during the introduction of small diameter, short finishing coils (e.g., 2 mm Ultipaq or DeltaPlush (Micrus Endovascular, San Jose, CA); 2 mm Hydrosoft or Hypersoft (Microvention/Terumo, Alisa Viejo, CA)). For smaller aneurysms (<7 mm), it is not uncommon that the entire embolization can be completed during a single balloon inflation.

Limitations

The occlusion times accepted using this technique are longer than those traditionally used during balloon-assisted coil embolization. However, certain subsets of patients may not tolerate these lengths of occlusion, and caution should be exercised in these cases. The literature describing occlusion times with temporary surgical clips have indicated that older patients and those with subarachnoid hemorrhage may be at a higher risk of ischemia with temporary occlusion [9–15]. Further work with procedural neuromonitoring and anesthetic optimization may make this approach safer and more effective in the future.

The technique described in the present manuscript has been derived *solely* from our collective clinical experience. To date, beyond our empirical observations from individual cases, there are no studies which support the conglomerate coil mass technique as a general approach to aneurysm coil embolization.

Summary

The balloon-assisted treatment (BAT) of aneurysms offers several theoretical and practical advantages over unassisted or stent-supported coil embolization. By introducing a number of coils during a single balloon inflation, the procedures may be completed more quickly with fewer balloon inflations. In addition, our clinical experience suggests that when a number of coils are placed during a single balloon inflation they form a “conglomerate mass” which is more stable than any individually placed aneurysm coil. Using this “conglomerate mass” technique, we have (in some cases) been able to achieve a very dense packing of wide-necked and complex aneurysms without adjunctive stents.

References

1. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg. 2003;98(5):959–66.
2. Kelly ME, Gonugunta V, Woo HH, Turner R, Fiorella D. Double-balloon trapping technique for embolization of a large wide-necked superior cerebellar artery aneurysm: case report. Neurosurgery. 2008;63(4 Suppl 2):291–2. discussion 2.
3. Baldi S, Mounayer C, Piotin M, Spelle L, Moret J. Balloon-assisted coil placement in wide-neck bifurcation aneurysms by use of a new, compliant balloon microcatheter. AJNR Am J Neuroradiol. 2003;24(6):1222–5.
4. Nelson PK, Levy DI. Balloon-assisted coil embolization of wide-necked aneurysms of the internal carotid artery: medium-term angiographic and clinical follow-up in 22 patients. AJNR Am J Neuroradiol. 2001;22(1):19–26.
5. Ebrahimi N, Claus B, Lee CY, Biondi A, Benndorf G. Stent conformity in curved vascular models with simulated aneurysm necks using flat-panel CT: an in vitro study. AJNR Am J Neuroradiol. 2007;28(5):823–9.
6. Tumialan LM, Zhang YJ, Cawley CM, Dion JE, Tong FC, Barrow DL. Intracranial hemorrhage associated with stent-assisted coil embolization of cerebral aneurysms: a cautionary report. J Neurosurg. 2008;108(6):1122–9.
7. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke. 2003;34(6):1398–403.
8. Fiorella D, Albuquerque FC, Deshmukh VR, McDougall CG. Usefulness of the Neuroform stent for the treatment of cerebral aneurysms: results at initial (3-6-mo) follow-up. Neurosurgery. 2005;56(6):1191–201. discussion 201-2
9. Ferch R, Pasqualin A, Pinna G, Chioffi F, Bricolo A. Temporary arterial occlusion in the repair of ruptured intracranial aneurysms: an analysis of risk factors for stroke. J Neurosurg. 2002;97(4):836–42.
10. Samson D, Batjer HH, Bowman G, Mootz L, Krippner WJ Jr, Meyer YJ, et al. A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery. 1994;34(1):22–8. discussion 8-9.
11. 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(6):817–24.
12. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell RM. 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(5):785–91.
13. Mizoi K, Yoshimoto T. Permissible temporary occlusion time in aneurysm surgery as evaluated by evoked potential monitoring. Neurosurgery. 1993;33(3):434–40. discussion 40.
14. Mizoi K. Temporary arterial occlusion in aneurysm surgery. No Shinkei Geka. 1998;26(6):477–89.
15. 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. Neurosurg Focus. 1997;2(6):e4.

Chapter 12
Stent-Assisted Coil Embolization

Stephan A. Munich, Demetrius K. Lopes, and R. Webster Crowley

The endovascular treatment of cerebral aneurysms has become progressively more frequent over the last decade. While endovascular techniques were traditionally reserved for narrow-necked, saccular aneurysms, improvements in endovascular techniques and devices have enabled neuroendovascular surgeons to consider treatment for more complex lesions. Perhaps, no development has had as much impact on the ability to treat an increasing number of aneurysms as the intracranial stent. Wide-necked aneurysms that were once deemed amenable only to surgical clipping now may warrant serious endovascular consideration, due in large part to the advent and refinement of intracranial stents that allow for coil embolization while protecting parent artery patency. In this chapter we will review the indications, techniques, perioperative management, and results of this stent-assisted coil embolization.

Brief Historical Overview

Catheterization of the intracranial vessels was first described in 1964 by Luessenhop and Velasquez [1]. Ten years later, Serbinenko reported the endovascular treatment of over 300 patients using both detachable and nondetachable balloons to treat direct carotid-cavernous fistulae and cerebral aneurysms [2]. Unfortunately, the first generation of balloons lacked compliance and frequently deflated over time.

Given the failure and morbidity associated with these early balloons, Guglielmi introduced soft, controllable, retrievable, and detachable platinum coils for as means

S. A. Munich · D. K. Lopes · R. W. Crowley (✉)
Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA
e-mail: webster_crowley@rush.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_12

of endosaccular obliteration of cerebral aneurysms [3, 4]. While detachable coils became increasingly used for aneurysm treatment, the primary treatment method for wide-necked and irregularly shaped aneurysms remained microsurgical clipping. Attempts to treat these aneurysms with coiling alone frequently resulted in either incomplete coiling or coil migration or prolapse.

The first report of stent-assisted coil embolization was described by Higashida in 1997 for the treatment of a ruptured vertebral artery aneurysm [5]. In this case, a balloon-expandable coronary stent was deployed, and coiling was performed via catheterization of the aneurysm through the stent tines. Since that time, with the development of intracranial stents, stent-assisted coiling has become an integral part of the armamentarium of the neurointerventionalist. Improvements in catheters, microcatheters, coils, and stents have improved the safety and efficacy of stent-assisted coil embolization and paved the way for their routine use.

Indications and Contraindications

Clearly not every intracranial aneurysm requires stent-assisted coiling for treatment. Many aneurysms can be treated effectively with primary coiling alone. Aneurysms that are considered for stent-assisted coil embolization are typically wide-necked aneurysms or those that incorporate branch arteries into the aneurysm neck. A number of aneurysms that may not be ideal for primary coiling, and would generally be candidates for stent assistance, may also be reasonable candidates for other adjuvant strategies such as balloon remodeling or dual catheter embolization. It is therefore important to consider all of these techniques when devising a treatment plan.

Traditional definitions of wide aneurysm neck include a neck diameter of larger than 4 mm and a dome-to-neck ratio of less than 2. In these situations, coiling alone is associated with an increased risk of coil migration and compromise of parent vessel patency. Stent assistance provides a permanent buttress for the coil mass, thereby preventing herniation into the parent artery. Stent assistance may also permit increased packing density, which has been associated with higher rates of aneurysm occlusion [6, 7].

A significant consideration for utilizing stent-assisted coiling techniques is the requirement for dual antiplatelet therapy. Patients with histories of significant gastrointestinal hemorrhage, bleeding diatheses, or significant coagulation disorders may be at increased risk of hemorrhagic complications related to dual antiplatelet therapy. Similarly, assessment of patient compliance with dual antiplatelet therapy is critical. Patients with medical, social, and/or psychiatric conditions that may preclude compliance with dual antiplatelet therapy may be better suited with other techniques.

The use of stent-assisted coiling in the acute period following aneurysm rupture remains a controversial topic primarily due to the need for dual antiplatelet therapy. While there is increasing data supporting its use, particular consideration should be given to avoiding stent placement in patients who may be at increased risk for developing hydrocephalus and, therefore, require CSF diversion procedures. The

risk associated with performing these procedures in a patient with platelet inhibition must be considered.

Preoperative Preparation/Evaluation

Preparation for stent-assisted coiling begins well before the patient is in the angiography suite. Critical evaluation of noninvasive imaging (e.g., CTA, MRA) should suggest the possibility of the need for stent assistance. It can also warn the surgeon of potential obstacles that may be encountered during the procedure (e.g., tortuous anatomy necessitating the need for an intermediate support catheter, the need for "Y" or "X" stenting techniques, etc.).

The importance of a preoperative, baseline neurologic exam prior to endovascular aneurysm treatment cannot be understated. This is particularly important with stent-assisted techniques in which in-stent stenosis or compromise of small branch vessels may result in subtle postoperative deficits. For these reasons, frequent and precise postoperative neurologic assessments are of equal importance.

When the situation allows, such as in planned, elective cases, preoperative antiplatelet therapy is recommended. Traditional dosing schemes include aspirin 325 mg daily and clopidogrel 75 mg daily for at least 5 days prior to the scheduled procedure. Alternatively, loading doses of aspirin 325–650 mg and clopidogrel 300–600 mg can be administered the evening before the scheduled procedure. We prefer a loading dose of aspirin 325 mg and clopidogrel 600 mg. Confirmation of adequate platelet inhibition with point-of-care testing has become standard in many centers. Adequate platelet inhibition has been shown to be associated with a decreased risk of thromboembolic complications; conversely, insufficient platelet inhibition has been shown to be associated with increased frequency of complications in some studies [8–10].

Resistance to aspirin is relatively rare, occurring in 2–5% [11, 12]. However, resistance to clopidogrel has been reported in up to 50% [13]. Given the high incidence of clopidogrel resistance, alternative antiplatelet agents are sometimes utilized. Identifying resistance to either agent with point-of-care testing allows surgeons to adjust antiplatelet therapy, theoretically ensuring platelet inhibition and decreasing thromboembolic complications. Their increased reliability is due primarily to their administration in the active form.

Review of Equipment

The critical decision involved in stent-assisted coiling is which stent to use. Until recently, the only stents designed for intracranial use were the Neuroform (Stryker, Fremont, CA) and the Enterprise (Codman Neuro, Raynham, MA). Within the last several years, however, a number of variations of the low-profile visualized

Table 12.1 Overview of stents commonly used in stent-assisted coiling techniques

	Neuroform®	Enterprise™	LVIS™	LVIS Jr™
Cell geometry	Open	Closed	Closed	Closed
Stent material	Nitinol	Nitinol	Nitinol	Nitinol
Available lengths	15–30 mm	14–37 mm	24–55 mm	23–46 mm
Available diameters	2.5–4.5 mm	4.5 mm	3.5–5.5 mm	2.5–3.5 mm
Retrievable	No	Yes	Yes	Yes
Recommended microcatheter inner diameter	ID 0.027 in	ID 0.021 in	ID 0.021 in	ID 0.017 in
Metal coverage	11%	10%	20%	20%

intraluminal support device (LVIS) (Microvention, Tustin, CA) have become available. A summary of the available intracranial stents used in stent-assisted coiling is provided in Table 12.1. Each of the stents has unique features that differentiate them and therefore may allow neuroendovascular surgeons the opportunity to more individually tailor treatment.

The Neuroform stent is an open-cell intracranial stent used in stent-assisted coil embolization. This design makes the stent easily conformable to both the vessel wall and the aneurysm neck. This may provide wider neck coverage for bifurcation aneurysms and excellent wall apposition, which may decrease the risk of stent-related thromboemboli. Another benefit of the open-cell design is that it makes it easier for a coiling microcatheter to pass through the stent into the aneurysm. Of course there are potential downsides to the stent. Most notably, it requires a 0.027″ microcatheter, which may limit the ability to place the stent in smaller vessels or in branch vessels that are particularly tortuous or arise at acute angles. In addition, the open-cell design is theoretically more penetrable to coils. Just as the stent allows for easier passage of coiling microcatheters, the coils themselves are more likely to find their way through an open cell into the parent vessel. This should be taken into consideration when coiling an aneurysm following placement of a Neuroform stent. In other words, one should not coil indiscriminately, but rather careful attention should be paid to ensuring parent artery patency. While much of the Neuroform experience in the United States is with the classic device, at the time of this publication the Neuroform Atlas (Stryker, Fremont, CA) was just recently approved by the FDA. This is essentially a smaller Neuroform that is delivered through an 0.017″ microcatheter.

The Enterprise stent is a closed-cell intracranial stent used for stent-assisted coil embolization. The closed-cell design provides a more reliable buttress to subsequent coils but is less conformable to the parent artery, particularly at curves or angles, such as those seen with bifurcation aneurysms. Criticism of the Enterprise includes its propensity to ovalize in such curves, something that has reportedly been improved upon in the second generation Enterprise 2. The stent is deliverable through a 0.021″ microcatheter, which has often led to it being the stent of choice as the second stent in a Y- or X-stent construct when compared to the 0.027″ catheter needed for the original Neuroform, as the smaller catheter is more likely to pass through a cell of an existing stent.

The LVIS stents are also now available for use in the stent-assisted coil embolization. The LVIS is deliverable through a 0.021″ microcatheter, with available sizes up to 5.5 mm. LVIS Blue is the newest modification of the original LVIS design. The angle of the braid is smaller, resulting in better wall apposition and increased flow diversion, although this change came with an associated increase in difficulty passing a coiling catheter through the cells of the stent. While a microcatheter can be passed through its cells with significant effort, the difficulty in achieving this suggests that it should be used almost exclusively with the jailing technique, discussed below. The LVIS Jr. stent was the first stent available in the USA that can be delivered through a 0.017″ microcatheter, a significant advance in the treatment of intracranial aneurysms. This is significant not only for the improved ability to access smaller, more tortuous vessels, but it also allows for the deployment of the stent through dual-lumen balloon catheters such as the Scepter (Microvention, Tustin, CA) or the Eclipse (Balt, Montmorency, France). This enables the neuroendovascular surgeon to first attempt treatment without a stent using balloon remodeling, and if this technique fails, a stent can be placed through the balloon catheter.

In addition to the widely available stents, a number of devices exist that are currently in clinical trials or are available out of the USA. The LEO Baby (Balt, Montmorency, France) stent is a low-profile braided stent that is also deliverable through a 0.017″ microcatheter. It is not yet available in the USA, but there is a considerable international experience with it, and many people who have access to it prefer it for small vessel aneurysms. Other devices that are designed for stent assistance of bifurcation devices include the Barrel device (ev3/Covidien), which is a stent with an enlarged mid-segment, and the pCONus bifurcation aneurysm implant (Phenox, Bochum, Germany), which aims to produce the waffle-cone effect described below and is not currently available in the USA. Lastly, the PulseRider (Codman Neuro, Raynham, MA) is an FDA-approved device that is not technically a stent but is a luminal device designed to support coil placement by maintaining luminal patency.

Stent-assisted coiling can be performed using a variety of coils. A review of coil characteristics is beyond the scope of this chapter but can be found in a review by White et al. [14]. It is advisable that the surgeon uses the type of coils with which he/she is most comfortable.

Stenting Techniques

"Traditional" Stent-Assisted Coiling

Stent-assisted coiling traditionally was considered aneurysm coiling via a microcatheter that was navigated into the aneurysm through the struts of a stent that had been completely deployed across the aneurysm neck (Figs. 12.1 and 12.2). The inherent difficulty in this technique lies in having to catheterize through the very narrow stent struts, which is made even more difficult when a closed-cell stent is

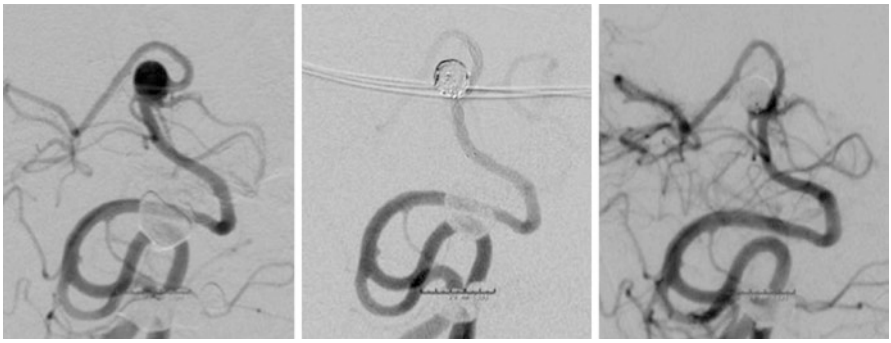


Fig. 12.1 Basilar apex aneurysm in which both posterior cerebral arteries (PCA) arise from the left side of the aneurysm. It was treated with a single LVIS Jr. stent and subsequent coil embolization. The coiling microcatheter was advanced into the aneurysm after placement of the stent. The unusual configuration of the aneurysm allowed a single-stent to cover both PCAs and the left superior cerebellar artery by placing the stent from the right PCA to the basilar artery. The second and third images demonstrate that the stent caused mild straightening of the right PCA

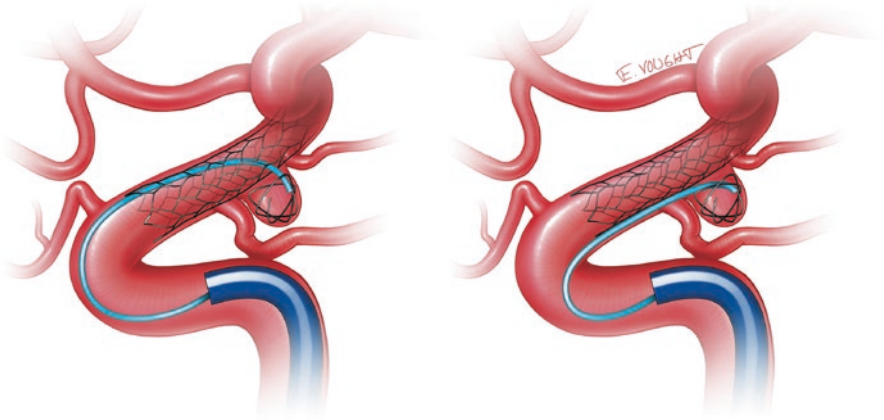


Fig. 12.2 Illustration depicting techniques for stent-assisted coil embolization. The left image shows traditional stent-assisted coil embolization, where the coiling microcatheter is passed into the aneurysm through a cell of the already-placed stent. The right image shows the jailing technique, in which the coiling microcatheter is passed into the aneurysm prior to stent deployment. This results in the coiling catheter being located outside of the stent in a parallel fashion

used. When this technique is used, maintaining microcatheter access within the aneurysm is particularly important, since reaccess through stent struts is even more challenging when a coil mass is present within the aneurysm. Although this technique may be used to treat an aneurysm that has not been previously treated with a stent, it is obviously the only option for the re-treatment of recurrent or residual aneurysms where a stent has already been placed.

Jailing Technique

In this technique, the microcatheter is navigated into the aneurysm before deployment of the stent. Once the microcatheter is within the aneurysm, the stent is deployed through a second parallel microcatheter, "jailing" the coiling microcatheter between the stent and the parent vessel wall, while the microcatheter tip remains in the aneurysm (Fig. 12.2). The aneurysm is then coiled and the microcatheter removed. While the presence of the coiling microcatheter outside of the stent may initially prevent complete wall apposition of the stent, the radial force of the stent typically results in adequate opening once the microcatheter is removed. However, if wall apposition remains insufficient, balloon angioplasty can be performed to further expand the stent.

This technique may be considered technically easier since it does not require passing a microcatheter through the stent struts. Jailing the microcatheter gives it stability and may make it less susceptible to kickback. However, this can also be a shortcoming of this technique, as the stent limits the ability of the microcatheter to move back and forth with coil deployment. This movement can be useful, as it may enable the microcatheter to move to pockets of decreased resistance, filling portions of the aneurysm that otherwise may not have filled. Perhaps more importantly, kickback of the microcatheter can prevent undue forward pressure that can cause intraoperative aneurysmal rupture. It is therefore critical to be mindful of this lack of catheter feedback that normally exists during coil embolization.

Y-Stenting

Stent-assisted coil embolization of bifurcation aneurysms presents a unique challenge since there are potentially three parent arteries (the main trunk and the two branches of the bifurcation) that require protection by a stent. For the Y-stenting technique, a stent is deployed from one of the branch vessels into the main trunk. A microcatheter is then navigated through the struts of the stent into the other branch vessel, and a second stent is deployed from there into the main trunk. This results in single-stent coverage in each branch vessel and overlapping, double-stent coverage in the main trunk, forming a "Y." A coiling microcatheter is then passed through the stents into the aneurysm, and the aneurysm is coiled, with the stents providing protection to both of the branch vessels and the main trunk (Fig. 12.3). As is the case with single-stent placement, jailing the coiling catheter is also an option. A variation of the standard Y-stent technique is the double-barrel technique, in which the two stents are deployed alongside each other without having one pass through the other. This, however, results in a stent-stent interface within the center of the artery lumen, rather than along the arterial wall, and therefore is not generally the preferred Y-stent technique.

Other variations are the X-stent configuration, or the H-stent configuration, which are occasionally needed at the anterior communicating artery complex.

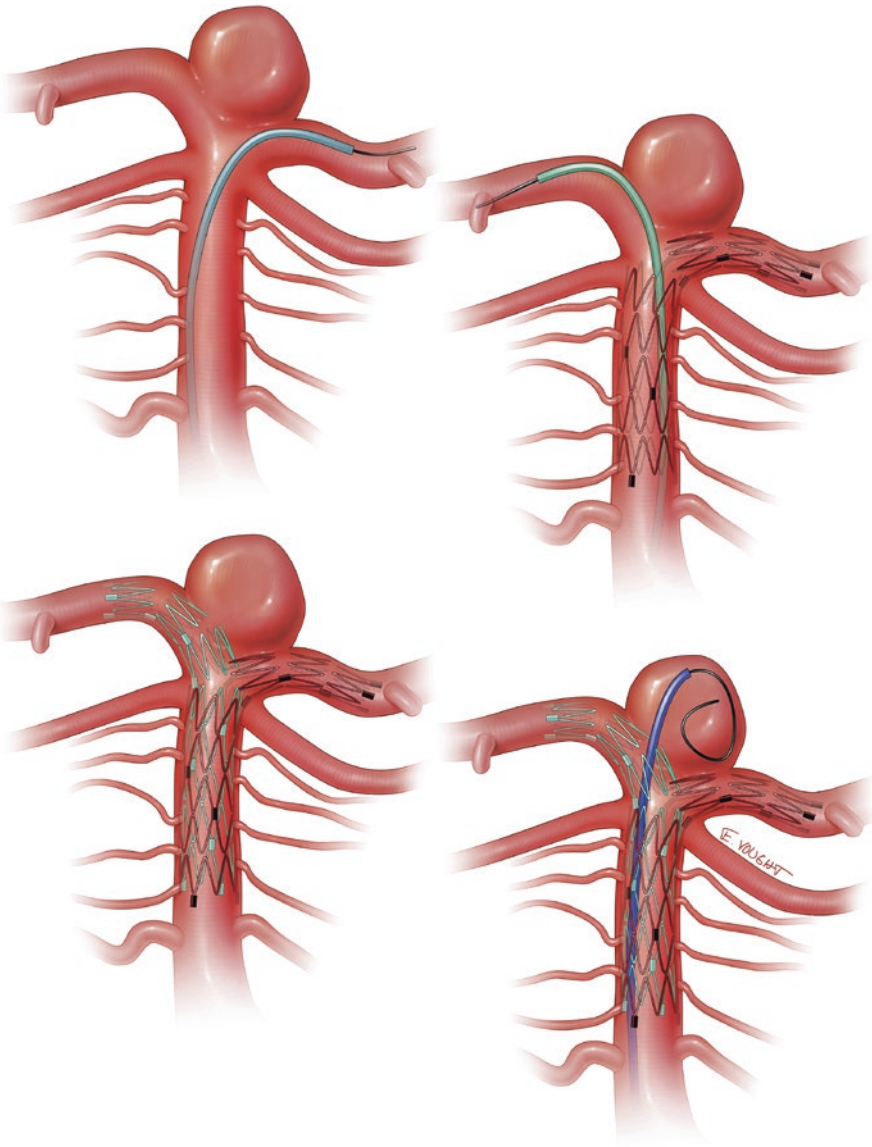


Fig. 12.3 Illustrative schematic depicting Y-stent-assisted coil embolization of a basilar apex aneurysm. The first microcatheter is placed in the left PCA, followed by stent deployment centered over the aneurysm neck. Next, a second microcatheter is advanced through the first stent into the right PCA, and again a stent is placed from that point into the basilar artery. Following deployment of both stents, a coiling microcatheter is advanced through the stents into the aneurysm, and coiling performed

Unlike basilar or middle cerebral artery bifurcation aneurysms, these aneurysms usually have two main trunks and two branch vessels that require protection from the stents. For the X-stent technique, one stent is placed from an A1 segment across the anterior communicating artery to the contralateral A2, before the second stent is placed from the other A1 segment, through the existing stent, to the last remaining A2 segment. The H-stent entails deploying the two stents from each A1 to A2 without crossing over the AComm, a maneuver that generally sacrifices the anterior communicating artery.

Though various stent constructs have been successfully used for Y- or X-stent configurations, there is no consensus on the type of stents to use. Many advocate for an open-cell stent as the first stent that is deployed. The argument is that this permits easier catheterization through the stent struts into the second branch vessels, a phenomenon that is becoming less of a concern with the development of stents that are deliverable through 0.017″ microcatheters. Another argument favoring placement of an open-cell stent first is that it reduces the constraint placed on the second stent that is seen when a closed-cell stent is placed through another closed-cell stent, although some argue that this constraint can be a good thing, as it may result in mild flow-diverting effect away from the aneurysm.

One additional possible variation that treating physicians should consider is the timing of the treatment steps of a Y-stent-assisted coil embolization. While it may seem optimal to place both stents and coil the aneurysm in one setting, in some situations it may be beneficial to stage the treatments. First, a newly placed stent is more likely to be displaced with manipulation (Fig. 12.4), particularly if reasonable force is required to pass the second microcatheter through a cell for placement of the second stent. Again, this may be less of a concern with stents that are deliverable through 0.017″ microcatheters; however, if the first stent is in a tenuous position, for instance, if there is not a reasonable amount of length of stent proximal to the aneurysm neck, staging the first and second stents should be strongly considered. The other reason to consider staging is to reduce the amount of radiation in one procedure. This may not be an issue for straightforward cases; however, for cases that require substantial time and effort to catheterize one or both of the branch vessels, procedural times can be excessive, and again staging should be considered.

Finally, it is important to recognize that some aneurysms that are felt to require treatment with a Y-stent may, in fact, receive sufficient parent artery protection with the placement of a single stent in an L-shaped or half T configuration (Fig. 12.5). This can generally be achieved by pushing the stent out of the microcatheter while crossing the aneurysm neck rather than unsheathing the stent by retracting the microcatheter. While this does not provide the complete parent artery protection you would expect from the Y-stent, it may in essence turn the wide-necked aneurysm into a narrow-necked one. This result is essentially what the Barrel device is designed to achieve. The obvious benefit of eliminating the need for a second stent is that it limits the amount of metal placed within the artery. This may decrease the

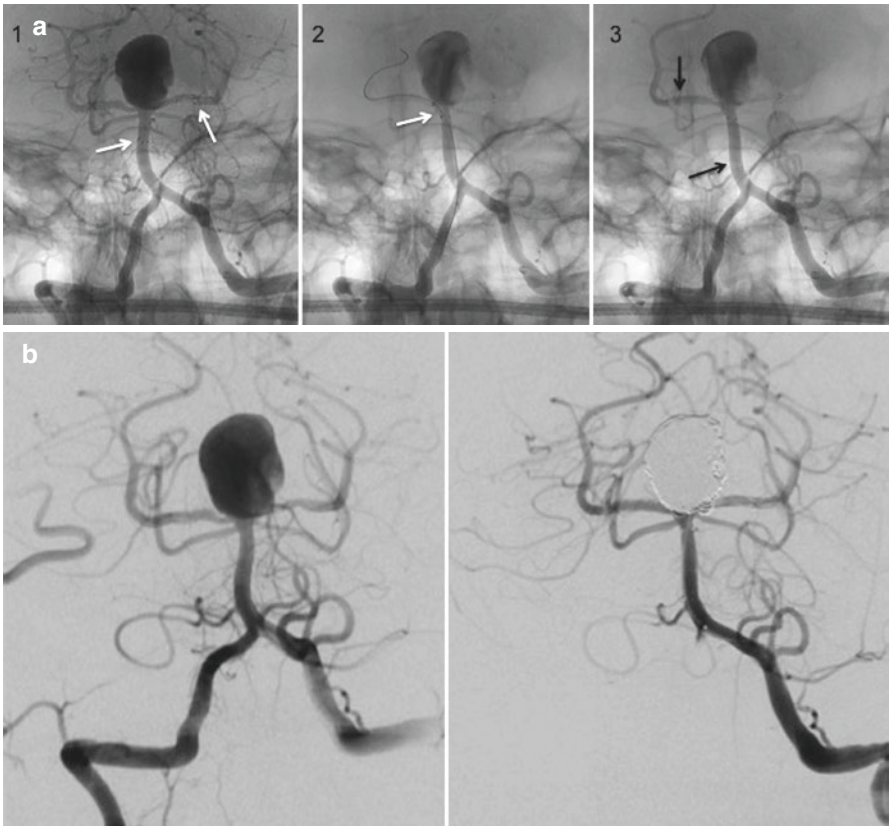


Fig. 12.4 (**a**, **b**) Large basilar apex aneurysm treated with Y-stent-assisted coil embolization. (**a**) Unsubtracted images are shown demonstrating placement of the stents. Panel 1 shows placement of the initial Neuroform stent from the left PCA to the basilar artery, with white arrows indicating the proximal and distal tines of the stent. Panel 2 shows that the proximal tines of the Neuroform, indicated by the white arrow, have migrated distally with passage of a 0.021″ microcatheter through the stent cells into the right PCA. The second stent, an Enterprise stent, was then placed from the right PCA into the basilar. The black arrows indicate the proximal and distal tines of the Enterprise stent. Following successful deployment of both stents, coil embolization was performed after passing the coiling microcatheter through the stents into the aneurysm. (**b**) Pre- and posttreatment images are shown

risk of thrombus formation or perforator occlusion, which clearly can have devastating results in the basilar artery or the M1 segment of the middle cerebral artery.

Waffle-Cone Technique

The waffle-cone technique, named for the appearance of the stent and coil mass after treatment, is a technique in which the distal aspect of a stent is deployed within the aneurysm fundus and extends into the parent artery. The flared distal stent tines

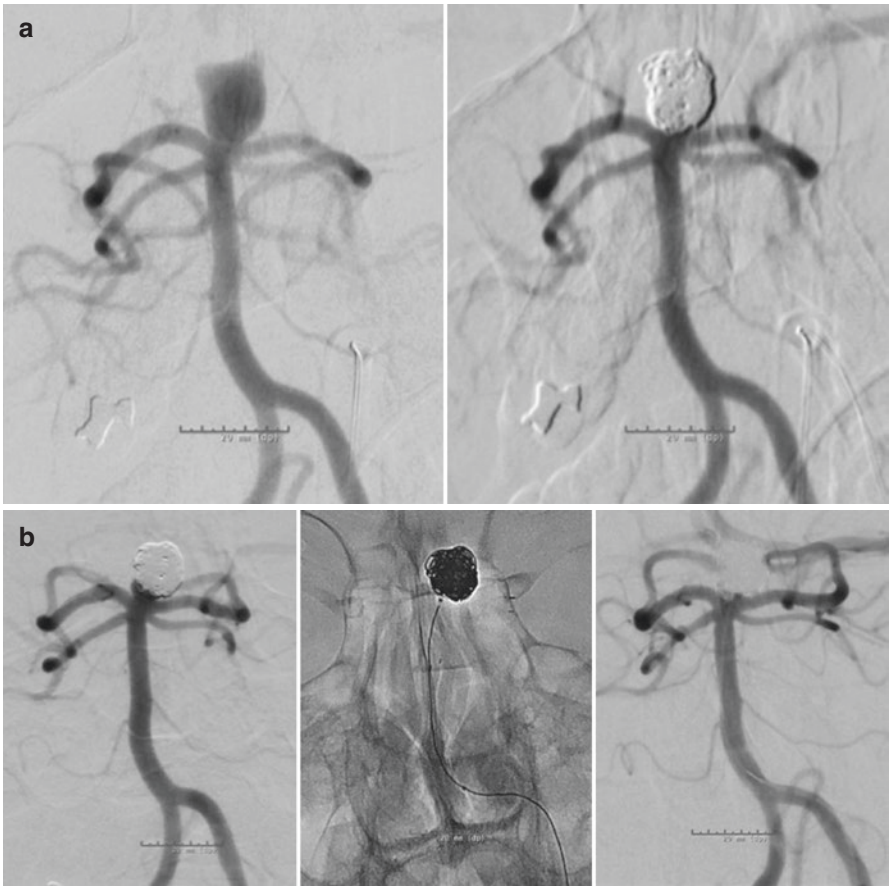


Fig. 12.5 (**a**, **b**) Large basilar apex aneurysm in a patient who presented with subarachnoid hemorrhage. Initial treatment was performed with single-catheter coil embolization, with pre- and posttreatment images shown (**a**). Several months later, a substantial recurrence was noted (**b**). Stent-assisted coil embolization was performed using an Atlas stent in an L configuration, which obviated the need for a second stent. Coil embolization was then performed after passing the coiling catheter through the stent into the aneurysm

help maintain stent position, reconstruct the neck, and support the coil mass within the aneurysm. The microcatheter then passes into the aneurysm along the axis of the stent (rather than through the stent struts as in Y-stenting), and coiling is completed in the usual fashion.

This technique theoretically offers some advantages over Y-stenting [15]. First, it is arguably technically easier, as there is no need to pass a microcatheter through a cell of the existing stent for placement of a second stent or aneurysm coils. It also does not require catheterizing the branch vessels, which may come off the aneurysm neck at very acute angles. Secondly, because only one stent is utilized, there is less metal surface area within the vessel, possibly reducing the risk of thromboembolic

complications. One downside of this technique is that while it does theoretically provide excellent protection of the branch vessels arising from the neck of the aneurysm, it may provide very little protection of the parent artery that the stent comes from. Therefore, coiling cannot be performed without careful attention paid to coil prolapse into the parent artery. It also is obviously not advisable with stents that have a distal tip, as the tip would need to be within the aneurysm sac. One additional limitation is that the neck of the aneurysm needs to be smaller than the diameter of the stent, which is generally no bigger than 4.5 mm.

Of note, the pCONus is designed to act in this fashion; however, unlike the standard intracranial stents that have been described for the technique, it also incorporates a nylon net at the distal aspect. This theoretically keeps coils in the aneurysm and prevents herniation into the parent vessel. The PulseRider also allows for a similar effect when its leaflets are deployed within the aneurysm dome rather than in the associated branch vessels.

Rescue Stenting

While most stent-assisted coil embolizations are planned ahead of time, the technique is quite versatile and may be used as a rescue strategy when other techniques fail. For example, if treatment with single-catheter or balloon-assisted techniques results in coil loop herniation into, or impingement of, the parent vessel, a stent may be required to preserve parent vessel patency. This is a particular advantage of dual-lumen balloons such as the Scepter, which allow for balloon-assisted coil embolization and then stent placement through the inner lumen if coil prolapse is seen once the balloon is deflated. When a dual-lumen balloon is not already in place, a new microcatheter must be advanced past the prolapsed coil mass in order to place the stent. In these instances, special attention should be paid to ensure that the catheter does not disturb or go through the coil mass, which could result in coil migration or incomplete opening of the stent. It is also occasionally necessary to place additional overlapping stents for rare instances when a coil tail or loop herniates through an existing stent.

Of course, a major consideration for stent placement is the antiplatelet therapy. In preparation for the possibility of rescue or unanticipated stent placement, some centers initiate dual antiplatelet therapy prior to elective aneurysm treatment, even if a stent is not planned. However, this is probably not the norm at most centers, and therefore patients will often require intraoperative administration of antiplatelet medications once a stent is deemed necessary.

Clearly, oral administration of aspirin or clopidogrel will take time to act before adequate antiplatelet activity is present. Therefore, an intravenous antiplatelet medication is often administered intraoperatively. Abciximab, a GPIIb/IIIa inhibitor with a time of onset of 10 min, is probably the most commonly described medication for this indication. A bolus of 0.125–0.25 mg/kg is administered, which allows for antiplatelet coverage until traditional antiplatelet agents are administered orally or rectally. If, for some reason, it is anticipated that long-acting antiplatelet agents will not

be able to be given for a particularly long time, abciximab can be given as an infusion, typically for an additional 12 h. While intraoperative administration of abciximab may give some neuroendovascular surgeons a pause, evidence suggests that there is no difference in complications associated with stenting intracranial aneurysms when pretreated with antiplatelets or if given abciximab intraoperatively [16].

Results and Literature Review

Coil embolization remains the workhorse of endovascular cerebral aneurysm treatment. For "routine" aneurysms with favorable anatomic characteristics, long-term occlusion rates are good, with an excellent procedural safety profile. However, additional techniques are often necessary for the treatment of wide-necked aneurysms. The addition of a stent to standard endovascular coiling results in better occlusion rates. However, it does require antiplatelet medication, and therefore it is important to consider more than just aneurysmal configuration when deciding whether to employ stent-assisted coil embolization.

Two meta-analyses published in 2016 compared stent-assisted coiling and primary coiling alone [17, 18]. Both studies demonstrated no statistically significant difference in immediate occlusion rates. However, progressive thrombosis was significantly more likely in aneurysms that underwent stent-assisted coiling (range 29.9–40.9% vs. 17.5–22.7%). Additionally, the rate of recurrence was found to be lower in aneurysms treated with stent assistance (range 12.7–13.3% vs. 27.9–29.1%). These studies found no difference in the periprocedural morbidity, which ranged from 11.8% to 12.2% in the stent-assisted coiling group and 8.0–12.0% in the coiling-only group. In one of these meta-analyses, the rate of ischemic/thrombotic complications was found to be the same [18]; however, in the other study, perioperative ischemic strokes occurred more frequently in the stent-assisted coiling group (4.7% vs. 2.0%) [17].

Long-term results of stent-assisted coiling have been encouraging. Johnson et al. found an annual recurrence rate of 0.89% in 262 aneurysms with a mean follow-up of 3.63 years [19]. Most aneurysm recurrences (9.7%) were diagnosed at the 6-month follow-up, with only 1.7% being diagnosed subsequently. They found large (10–25 mm) and giant aneurysms required re-treatment more frequently. Overlapping or Y-configurations were also found to require re-treatment at a higher rate, though a higher proportion of large/giant aneurysms were treated using these configurations.

In contrast to primary coiling, the success of stent-assisted coiling depends not only on coil embolization but also on stent deployment. In an analysis of 1510 aneurysms treated in 1457 patients, Shapiro et al. found the technical stent-related failure rate to be 9% [20], with stent migration or premature/misplaced deployment occurred in 5% and the inability to deploy the stent in 4%. The rates of overall stent problems and delivery failure were found to significantly decrease with physician experience.

The two most studied stents used in stent-assisted coiling are Neuroform and Enterprise. A comparative analysis including 47 studies and 2111 aneurysms treated with Neuroform stent and 2127 treated with Enterprise demonstrated no difference in initial occlusion rates (52.7% in Neuroform group vs. 52.8% in the Enterprise group) [21]. However, there was a statistically significant difference in the rate of complete occlusion at the last follow-up, which occurred in 61.1% of patients treated with Neuroform and in 74.7% of patients treated with Enterprise. Similarly, the rates of recanalization were significantly more in patients treated with Neuroform (13.9% vs. 10.6%). There was no difference in the rates of permanent morbidity and mortality.

More recently, the low-profile visualized intraluminal support (LVIS) device has been introduced. A systematic review of 384 patients with 390 aneurysms treated with the LVIS for stent-assisted coiling found the device to be safe and effective [22]. The overall technical success rate was 96.8%. Raymond class I or II occlusion was observed in 87.2% on immediate control angiogram and progressed to 93.1% at follow-up (mean 6 months). Aneurysm recanalization occurred in 2.5%. The overall procedure-related complication rate was 6.5%, with symptomatic thromboembolic events occurring in 2.4%. These data compare favorably with those of the Neuroform and Enterprise stents and demonstrated the LVIS device's safety and efficacy for stent-assisted coiling of cerebral aneurysms.

Small Aneurysms

Stent-assisted coiling may be a particularly useful strategy for the endovascular treatment of small aneurysms. Though the decision whether or not to treat small aneurysms remains controversial, some argue that they cause more extensive subarachnoid hemorrhage when they rupture [23]. Due to their small dome size, these aneurysms usually have a much lower dome-to-neck ratio and therefore may be less likely to support coils alone without a stent. The use of a stent in the treatment of these aneurysms provides support to the coil mass but also to the microcatheter used for coiling.

Small case series have been reported supporting the safety and efficacy of stent-assisted coiling in the treatment of small aneurysms [24–26]. In these series, the rate of periprocedural complications was between 0% and 12%. Complete occlusion was reported to occur between 77% and 100%.

Y- and X-Configured Stent-Assisted Coiling

The use of multiple stents in Y- or X-configurations introduces a layer of complexity to the procedure that necessitates an experienced operator. The Y-stenting procedure has many potential variations consisting of many constructs: open-cell stent + closed-cell stent, two open-cell stents, two closed-cell stents, overlapping limb, and

kissing stents. While it is predominantly employed at the basilar apex, it is applicable for wide-necked bifurcation aneurysms at other locations [27].

A multicenter study of cerebral aneurysms undergoing Y-stent-assisted coiling demonstrated the safety and efficacy of this technique [27]. Acceptable initial aneurysm occlusion (Raymond class I or II) occurred in 84%, which progressed to 93% at follow-up (mean 9.8 months). In aneurysms that initially were Raymond III, 83% progressed to better occlusion grades at follow-up. Technical complications related to stent deployment occurred in 6.7%, and intraoperative rupture was observed in 4.4%.

Given the relatively small number of indications for Y-stenting, comparison of the various aforementioned stent constructs is difficult. In one study evaluating the use of two closed-cell stents, there were no deployment failures [28]. Perioperative morbidity was 12% and due to thromboembolic complications. Initial complete occlusion occurred in 36%, with an additional 36% progressing from incomplete occlusion to complete occlusion at follow-up (mean 16 months). Y-stenting with two open-cell stents has been equally achievable, with one group demonstrating no deployment failures and 5% perioperative morbidity [29]. Initial complete occlusion was observed in 85%, with an additional 5% progressing from incomplete occlusion to complete occlusion at follow-up. Comparison of various stent constructs across multiple centers revealed no difference in initial aneurysm occlusion, occlusion at follow-up, need for re-treatment, in-stent stenosis, or clinical outcome [27].

Regarding the X-stent configuration, although reports of large cohorts for this technique are lacking in the literature, small series have demonstrated safety and efficacy of X-stent-assisted coiling when performed by experienced practitioners [30–32].

Waffle-Cone Technique

Several small series utilizing the waffle-cone technique are reported in the literature [33–36]. These studies report high rates (>95%) of technical success, with perioperative morbidity occurring in 0–10%. Raymond class I or II occlusion also occurred in >90% of cases. These data suggest that the waffle-cone technique may be an acceptable alternative to Y-stenting for wide-necked, bifurcation aneurysms.

More recently, the pCONus bifurcation aneurysm implant (Phenox, Bochum, Germany) was designed for use in a waffle-cone-like fashion for bifurcation aneurysms. Early experience with this device has demonstrated acceptable clinical and radiographic outcomes, with perioperative morbidity ranging from 5% to 12% and Raymond class I or II occlusion occurring in 75–82% [37–40].

Stent-Assisted Coiling in the Acute Rupture Period

Stent-assisted coiling in the setting of acute subarachnoid hemorrhage is highly controversial, largely due to the necessity for antiplatelet therapy. This can be very problematic in patients with recent bleeds, particularly those with ventriculostomies

or at high risk for one. Therefore, balloon-assisted coiling is almost certainly preferable in the setting of subarachnoid hemorrhage for the practitioner who is experienced with this technique. However, stent-assisted coiling may be a safe, reasonable option, with several studies demonstrating its efficacy and safety. A comparison of stent-assisted coiling and balloon-assisted coiling for ruptured wide-necked aneurysms demonstrated no statistically significant difference in periprocedural complications (coil protrusion, symptomatic ischemic events, and hemorrhage related to antiplatelet medication) or clinical outcome [41]. Favorable clinical outcome (modified Rankin Scale score 0–2) occurred in 91.8% of patients treated with stent-assisted coiling and in 90.6% of those undergoing balloon-assisted coiling. Adequate aneurysm occlusion (Raymond class 1 or 2) occurred in 84.4% of patients undergoing stent-assisted coiling and in 83.3% of patients undergoing balloon-assisted coiling.

A systematic review of 17 studies including 339 patients similarly demonstrated safety and efficacy of stent-assisted coiling in acutely ruptured cerebral aneurysms [42]. Raymond class 1 or 2 occlusion was achieved in 82% of patients. In 96% of the cases reviewed, dual antiplatelet therapy was administered only after the procedure (i.e., no preoperative loading doses). The rate of thromboembolic complications was 5.6%, while hemorrhagic complications occurred in 8%. Of note, the rate of EVD-related hemorrhagic complications was 10%; however, approximately half of these occurred at one center.

Another endovascular option for neuroendovascular surgeons who are looking to avoid stent placement for wide-necked acutely ruptured aneurysms is to postpone stent placement until at least several days after the ictus. For some patients it may be feasible to partially coil the aneurysm dome in the acute phase, and return for more definitive stent-assisted coiling once a ventriculostomy tube is removed, a shunt placed, or when the concern for hydrocephalus has lessened. However, one recent series suggests that stent-assisted coiling at any time during the acute rupture period may be safe [43]. Thromboembolic events occurred in 5.7% of patients treated between post-bleed days 0 and 3 and in 5.4% of those treated between post-bleed days 4 and 10. Similarly, hemorrhagic complications occurred in 2.9% of patients in the early cohort and in 5.4% of those in the late cohort. Comparable results were reported in a series of 59 patients treated with stent-assisted (with Enterprise) coiling within 48 h of aneurysm rupture [44]. Procedure-related complications in this series occurred in 6.8% of patients.

Conclusion

Stent-assisted coil embolization is undoubtedly a valuable tool for the treatment of cerebral aneurysms. While it is clearly not a technique that should be applied to every aneurysm, the continued development and refinement of intracranial stents have allowed for safe and effective endovascular treatment of an increasing number of aneurysms. It is important to be cognizant that, as is the case with many surgical

techniques, one approach does not fit all. Just as some aneurysms may be better suited for balloon-assisted or single-catheter coil embolization, the same stent-assisted technique is not useful across all aneurysms that are deemed to warrant stent assistance. It therefore behooves the treating physician to be familiar with all of these techniques, including single-stent placement with or without jailing of the microcatheter, X- or Y-stenting, waffle-cone stenting, and rescue-stent placement including the placement of overlapping stents. By gaining familiarity with these variations and technical nuances, treatment can be tailored to find the optimal option for each individual aneurysm.

References

1. Luessenhop AJ, Velasquez AC. Observations on the tolerance of the intracranial arteries to catheterization. J Neurosurg. 1964;21:85–91.
2. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125–45.
3. Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. J Neurosurg. 1991;75:8–14.
4. Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: electrochemical basis, technique, and experimental results. J Neurosurg. 1991;75:1–7.
5. Higashida RT, Smith W, Gress D, Urwin R, Dowd CF, Balousek PA, et al. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery. Case report and review of the literature. J Neurosurg. 1997;87:944–9.
6. Linzey JR, Griauzde J, Guan Z, Bentley N, Gemmete JJ, Chaudhary N, et al. Stent-assisted coiling of cerebrovascular aneurysms: experience at a large tertiary care center with a focus on predictors of recurrence. J Neurointerv Surg. 2017;9(11):1081–5.
7. Sadato A, Adachi K, Hayakawa M, Kato Y, Hirose Y. Effects of anatomic characteristics of aneurysms on packing density in endovascular coil embolization: analysis of a single center's experience. Neurosurg Rev. 2016;39:109–14. discussion 114
8. Delgado Almandoz JE, Crandall BM, Scholz JM, Fease JL, Anderson RE, Kadkhodayan Y, et al. Last-recorded p2y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. AJNR Am J Neuroradiol. 2014;35:128–35.
9. Heller RS, Dandamudi V, Lanfranchi M, Malek AM. Effect of antiplatelet therapy on thromboembolism after flow diversion with the pipeline embolization device. J Neurosurg. 2013;119:1603–10.
10. Tan LA, Keigher KM, Munich SA, Moftakhar R, Lopes DK. Thromboembolic complications with pipeline embolization device placement: impact of procedure time, number of stents and pre-procedure p2y12 reaction unit (pru) value. J Neurointerv Surg. 2015;7:217–21.
11. Harrison P, Segal H, Blasbery K, Furtado C, Silver L, Rothwell PM. Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry. Stroke. 2005;36:1001–5.
12. Mansour K, Taher AT, Musallam KM, Alam S. Aspirin resistance. Adv Hematol. 2009;2009:937352.
13. Mallouk N, Labruyere C, Reny JL, Chapelle C, Piot M, Fontana P, et al. Prevalence of poor biological response to clopidogrel: a systematic review. Thromb Haemost. 2012;107:494–506.

14. White JB, Ken CG, Cloft HJ, Kallmes DF. Coils in a nutshell: a review of coil physical properties. AJNR Am J Neuroradiol. 2008;29:1242–6.
15. Horowitz M, Levy E, Sauvageau E, Genevro J, Guterman LR, Hanel R, et al. Intra/extra-aneurysmal stent placement for management of complex and wide-necked- bifurcation aneurysms: eight cases using the waffle cone technique. Neurosurgery. 2006;58:ONS-258–262; discussion ONS-262.
16. Levitt MR, Moon K, Albuquerque FC, Mulholland CB, Kalani MY, McDougall CG. Intraprocedural abciximab bolus versus pretreatment oral dual antiplatelet medication for endovascular stenting of unruptured intracranial aneurysms. J Neurointerv Surg. 2016;8:909–12.
17. Feng M, Wen W, Feng Z, Fang Y, Liu J, Huang Q. Endovascular embolization of intracranial aneurysms: to use stent(s) or not? Systematic review and meta-analysis. World Neurosurg. 2016;93:271–8.
18. Phan K, Huo YR, Jia F, Phan S, Rao PJ, Mobbs RJ, Mortimer AM. Meta-analysis of stent-assisted coiling versus coiling-only for the treatment of intracanial aneurysms. J Clin Neurosci. 2016;31:15–22.
19. Lopes DK, Johnson AK, Kellogg RG, Heiferman DM, Keigher KM. Long-term radiographic results of stent-assisted embolization of cerebral aneurysms. Neurosurgery. 2014;74:286–91.
20. Shapiro M, Becske T, Sahlein D, Babb J, Nelson PK. Stent-supported aneurysm coiling: a literature survey of treatment and follow-up. AJNR Am J Neuroradiol. 2012;33:159–63.
21. King B, Vaziri S, Singla A, Fargen KM, Mocco J. Clinical and angiographic outcomes after stent-assisted coiling of cerebral aneurysms with enterprise and neuroform stents: a comparative analysis of the literature. J Neurointerv Surg. 2015;7:905–9.
22. Zhang X, Zhong J, Gao H, Xu F, Bambakidis NC. Endovascular treatment of intracranial aneurysms with the lvis device: a systematic review. J Neurointerv Surg. 2017;9(6):553–7.
23. Russell SM, Lin K, Hahn SA, Jafar JJ. Smaller cerebral aneurysms producing more extensive subarachnoid hemorrhage following rupture: a radiological investigation and discussion of theoretical determinants. J Neurosurg. 2003;99:248–53.
24. Fang CLM, Zhang PL, Wang W, Tan HQ, Xu HW, Zhou B. Endovascular treatment for very small supraclinoid aneurysms with stent-assisted coiling. Long-term follow-up in six cases. Interv Neuroradiol. 2009;15:37–44.
25. Li CH, Su XH, Zhang B, Han YF, Zhang EW, Yang L, et al. The stent-assisted coil-jailing technique facilitates efficient embolization of tiny cerebral aneurysms. Korean J Radiol. 2014;15:850–7.
26. Zhao R, Shen J, Huang QH, Nie JH, Xu Y, Hong B, et al. Endovascular treatment of ruptured tiny, wide-necked posterior communicating artery aneurysms using a modified stent-assisted coiling technique. J Clin Neurosci. 2013;20:1377–81.
27. Fargen KM, Mocco J, Neal D, Dewan MC, Reavey-Cantwell J, Woo HH, et al. A multicenter study of stent-assisted coiling of cerebral aneurysms with a y configuration. Neurosurgery. 2013;73:466–72.
28. Jeon P, Kim BM, Kim DJ, Kim DI, Park KY. Y-configuration double-stent-assisted coiling using two closed-cell stents for wide-neck basilar tip aneurysms. Acta Neurochir (Wien). 2014;156:1677–86.
29. Ko JK, Han IH, Cho WH, Choi BK, Cha SH, Choi CH, et al. Crossing y-stent technique with dual open-cell stents for coiling of wide-necked bifurcation aneurysms. Clin Neurol Neurosurg. 2015;132:54–60.
30. Saatci I, Geyik S, Yavuz K, Cekirge S. X-configured stent-assisted coiling in the endovascular treatment of complex anterior communicating artery aneurysms: a novel reconstructive technique. AJNR Am J Neuroradiol. 2011;32:E113–7.
31. Cohen JE, Melamed I, Itshayek E. X-microstenting and transmesh coiling in the management of wide-necked tent-like anterior communicating artery aneurysms. J Clin Neurosci. 2014;21:664–7.

32. Bartolini B, Blanc R, Pistocchi S, Redjem H, Piotin M. “Y” and “x” stent-assisted coiling of complex and wide-neck intracranial bifurcation aneurysms. AJNR Am J Neuroradiol. 2014;35:2153–8.
33. Lee SM, Kim YJ, Ho KJ. The effectiveness of the waffle-cone technique in treating complex intracranial aneurysms. Interv Neuroradiol. 2015;21:470–8.
34. Padalino DJ, Singla A, Jacobsen W, Deshaies EM. Enterprise stent for waffle-cone stent-assisted coil embolization of large wide-necked arterial bifurcation aneurysms. Surg Neurol Int. 2013;4:9.
35. Liu W, Kung DK, Policeni B, Rossen JD, Jabbour PM, Hasan DM. Stent-assisted coil embolization of complex wide-necked bifurcation cerebral aneurysms using the “waffle cone” technique. A review of ten consecutive cases. Interv Neuroradiol. 2012;18:20–8.
36. Xu F, Qin X, Tian Y, Gu Y, Leng B, Song D. Endovascular treatment of complex intracranial aneurysms using intra/extra-aneurysmal stent. Acta Neurochir. 2011;153:923–30.
37. Lubicz B, Morais R, Alghamdi F, Mine B, Collignon L, Eker OF. The pconus device for the endovascular treatment of wide neck bifurcation aneurysms. J Neurointerv Surg. 2016;8:940–4.
38. Perez MA, Bhogal P, Moreno RM, Wendl C, Bazner H, Ganslandt O, et al. Use of the pCONus as an adjunct to coil embolization of acutely ruptured aneurysms. J Neurointerv Surg. 2017;9(1):39–44.
39. Ulfert C, Pfaff J, Schonenberger S, Bosel J, Herweh C, Pham M, et al. The pCONus device in treatment of wide-necked aneurysms: technical and midterm clinical and angiographic results. Clin Neuroradiol. 2018;28(1):47–54.
40. Fischer S, Weber A, Titschert A, Brenke C, Kowoll A, Weber W. Single-center experience in the endovascular treatment of wide-necked intracranial aneurysms with a bridging intra−/extra-aneurysm implant (pconus). J Neurointerv Surg. 2016;8:1186–91.
41. Cai K, Zhang Y, Shen L, Ni Y, Ji Q. Comparison of stent-assisted coiling and balloon-assisted coiling in the treatment of ruptured wide-necked intracranial aneurysms in the acute period. World Neurosurg. 2016;96:316–21.
42. Bodily KD, Cloft HJ, Lanzino G, Fiorella DJ, White PM, Kallmes DF. Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature. AJNR Am J Neuroradiol. 2011;32:1232–6.
43. Qian Z, Feng X, Kang H, Wen X, Xu W, Zhao F, et al. Ruptured wide-necked aneurysms: is stent-assisted coiling during post-hemorrhage days 4–10 safe and efficient? World Neurosurg. 2017;101:137–43.
44. Liu A, Peng T, Qian Z, Li Y, Jiang C, Wu Z, et al. Enterprise stent-assisted coiling for wide-necked intracranial aneurysms during ultra-early (48hours) subarachnoid hemorrhage: a single-center experience in 59 consecutive patients. J Neuroradiol. 2015;42:298–303.

Chapter 13
Complex Stent Reconstruction for the Treatment of Intracranial Aneurysms

Pedro Aguilar-Salinas, Leonardo B. C. Brasiliense, Jussie Lima, Amin Aghaebrahim, Eric Sauvageau, and Ricardo A. Hanel

The natural history of unruptured intracranial aneurysms (IA) has been described in multiple international studies, but some controversy remains regarding instances in which these lesions should be treated. In 1998, the International Study of Unruptured Intracranial Aneurysms (ISUIA) estimated the risks of rupture based on a retrospective cohort of 722 patients with a history of subarachnoid hemorrhage (SAH). A rupture rate of 0.5% per year was found for IAs less than 10 mm in diameter and 0.7% per year in IAs larger than 10 mm [1]. A prospective study published in 2003, the ISUIA-2, included a total of 4060 patients [2]. The observational arm consisted of 1692 subjects with a mean follow-up of 4.1 years. Outcomes showed that the risk of rupture was dependent on size and location. The highest risk of rupture was reported in the posterior circulation (including aneurysms located in the posterior communicating artery) and for large (13–24 mm) and giant (≥25 mm) aneurysms. Subsequent cohorts have reported other predictors of aneurysm rupture, which include older age, hypertension,

P. Aguilar-Salinas
Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA

Department of Surgery – Division of Neurosurgery, University of Arizona, Tucson, AZ, USA

A. Aghaebrahim · E. Sauvageau · R. A. Hanel (✉)
Lyerly Neurosurgery – Baptist Health System, Baptist Neurological Institute, Jacksonville, FL, USA
e-mail: Amin.Aghaebrahim@bmcjax.com; Eric.Sauvageau@bmcjax.com; rhanel@lyerlyneuro.com

L. B. C. Brasiliense
Department of Surgery – Division of Neurosurgery, University of Arizona, Tucson, AZ, USA
e-mail: lbrasiliense@email.arizona.edu

J. Lima
Department of Neurology, Hartford Hospital/University of Connecticut, Farmington, CT, USA
e-mail: lima@uchc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_13

the presence of a daughter sac, smoking, and family history of SAH [3–7]. Endovascular management has emerged as a feasible, safe, and effective modality for the treatment for IAs. In the setting of unruptured IAs, the results of ISUIA-1 and ISUIA-2 reported lower rates of morbidity and mortality in comparison to surgical clipping.

Regarding ruptured aneurysms, the International Subarachnoid Aneurysm Trial (ISAT) included 2143 patients with SAH in the UK [8]. The study was a randomized multicenter clinical trial designed to assess the safety and efficacy of coiling embolization versus surgical clipping. Results favored endovascular coiling over surgical clipping at 1-year follow-up with percentage dead or disabled (23.5% vs. 30.9%; $p < 0.05$). Recently, a longer follow-up of the ISAT cohort was published. Patients in the endovascular treatment group were more likely to be alive and independent (modified Rankin Scale 0–2) at 10 years than patients in the surgical clipping group (OR 1.34, 95%CI 1.07–1.67) [9]. A similar study performed in the USA, the Barrow Ruptured Aneurysm Trial (BRAT), evaluated the safety and efficacy of surgical clipping versus coiling embolization in acutely ruptured IAs and compared functional outcomes based on clinical and angiographic data [10]. The 1-year results favored endovascular management over surgical clipping (*mRS* > 2 was reported in 23.2% in the endovascular group and 33.7% in the surgical clipping arm; $p < 0.05$). The 3-year follow-up of the BRAT cohort reported a favorable 5.8% absolute difference in the endovascular arm compared with the outcomes in the surgical clipping arm, but the difference did not obtain statistical significance ($p = 0.25$). In addition, subjects in the surgical clipping arm had a significantly higher degree of aneurysm occlusion and a lower rate of recurrence and retreatment. Interestingly, younger patients and patients with lesions located in the anterior communicating complex had better outcomes with clipping at the 3-year analysis [11]. However, the limitations of single-coil embolization have become evident over time. More recently, the 6-year follow-up of the BRAT cohort was published, and the results showed that complete aneurysm occlusion was achieved in 96% (111/116) of the subjects in the surgical clipping group and in 48% (23/48) of the subjects in the endovascular group ($p < 0.01$) [12]. The overall retreatment rate for clipping was 4.6% (13/280) and for coiling was 16.4% (21/128). In addition, they found no significant difference in poor clinical outcomes (mRS > 2, $p = 0.24$) between the two treatment groups.

Primary coil embolization (with or without balloon remodeling) is particularly challenging in the treatment of large- or wide-necked aneurysms due to the risk of coil protrusion into the parent vessel and a higher rate of aneurysm recanalization. The introduction of self-expanding intracranial stents has increased the options for the treatment of this subset of aneurysms. These stents have facilitated endosaccular embolization by providing support to coils, increased packing density, and providing a scaffold for endothelialization over time. Despite the advances in endovascular technology, wide-necked aneurysms arising at vascular bifurcations remain technically difficult to treat. A wide-necked aneurysm is usually defined as a lesion with a neck size ≥4 mm or a dome-to-neck ratio <2. The apex of a bifurcation is the site of highest hemodynamic wall shear stress and wall tension in the vascular network [13, 14]. This subset of aneurysms may require complex endovascular approaches to embolize the aneurysm sac and preserve blood flow

through branching vessels at the bifurcation. A single stent may be insufficient to cover the aneurysm neck, and frequently, multiple-stent reconstructions are required to achieve a complete initial occlusion. Recently a meta-analysis reviewed 38 articles that included 2446 patients with 2556 wide-necked aneurysms treated with single coiling or stent-assisted coiling; the study demonstrated the safety of these techniques, but long-term occlusion rates were found to be suboptimal [15]. Among all aneurysms, 496 were located at bifurcations. Specifically, for wide-necked bifurcation aneurysms, the authors found a long-term (>6 months) complete or near-complete occlusion rate of 71.9% (95% CI, 52.6–91.1) and recanalization and retreatment rates of 9.8% (95% CI, 7.1–12.5) and 5.2% (95% CI, 1.9–8.4), respectively.

Self-Expanding Intracranial Stents

The basic structure of a vascular stent consists of a mesh composed of thin metal struts, which results in free spaces known as cells. Stents can be classified based on their cell design construction. A closed-cell design refers to a cell that is surrounded by the strut configuration, whereas in an open-cell design, a cell is partially surrounded, and several bridging membranes interconnect struts along the device structure. Based on design and arrangements, stents have several features that should be taken into consideration when choosing the device. For instance, open-cell stents have more flexibility and better conformability for tortuous vessel anatomy, but protrusion of struts into the aneurysm, when present in an outer curve, may be more frequent, whereas closed-cell stents have a larger radial force in straight vessels, but kinking and flattening of the device may occur in sharp curves [16, 17]. Table 13.1 summarizes stent features.

The introduction of self-expanding intracranial stents in the endovascular armamentarium has allowed neurointerventionalists to treat IAs that are not amenable for simple coiling embolization. Currently, there are four intracranial stents available in the USA: the Neuroform stent (Stryker Neurovascular, Fremont, CA, USA), the Enterprise stent (Codman, Miami Lakes, FL, USA), and more recently two iterations of the low-profile visualized intraluminal support device (LVIS and LVIS Jr.,

Table 13.1 Definitions of stent features and terms

Concept	Definition
Conformability	Bending stiffness. Stent's ability to adapt to tortuous vessel anatomy
Gator backing	Protrusion of struts into the aneurysm sac
Kinking	Narrowing of stent struts into the vessel lumen
Metal coverage	Metal-covered area divided by total stent area
Ovalization	Narrowing/flattening of the stent lumen
Radial force	Outward force. Force that stents apply to the vessel wall and allows to support coils or stent resistance to be compressed
Wall apposition	Stent's ability to be in contact with adjacent vessel wall

Microvention, Tustin, CA, USA). Stents have different features and come in various sizes and diameters. Because there is no ideal stent for all cases, knowledge of stent characteristics is required to choose the appropriate device on a case-by-case basis and overcome anatomical limitations such as parent vessel size, tortuous anatomy, or sharply angled vessels. Table 13.2 summarizes the characteristics of different intracranial stents.

Dual-antiplatelet therapy is a crucial component to the successful placement of intravascular devices, and its efficacy relies on the ability to prevent platelet aggregation and reduce the risk of device thrombosis or thromboembolic complications [18]. While a number of different antiplatelet agents are currently available, the indication for each drug is often individualized and based on several factors including efficacy, cost, personal experience, and availability. Aspirin and clopidogrel remain the most widely accepted agents and first-line therapy in most neurovascular centers. Aspirin irreversibly inactivates platelet cyclooxygenase-1, thus ultimately blocking the production of thromboxane. It has a fast onset of action with a maximum effect at 30–60 min. Clopidogrel is a thienopyridine derivative that prevents platelet aggregation by irreversible blockage of the P2Y12-ADP receptor. It requires hepatic metabolism to produce an active metabolite. Some platelet inhibition can be seen after a single dose of 75 mg, but a steady state is seen within 7 days of continued administration. When necessary, a loading dose of 300–600 mg may achieve levels of inhibition between 40% and 50% within 5 h [19, 20]. Patient response to clopidogrel is measured using assays that analyze the level of inhibition of the P2Y12 receptor. The most widely used test is the Accumetric's VerifyNow (San Diego, CA), which reports platelet reactivity in percent inhibition and P2Y12 Reaction Units (PRU). In general, the goal is to achieve a percent inhibition $\geq$30% or <210 PRU to demonstrate an adequate response [21, 22]. However, clopidogrel resistance has been estimated to occur in nearly one third of patients undergoing endovascular procedures, but mechanisms remain poorly understood with some evidence of a multifactorial component and increased resistance in individuals with genetic polymorphisms in the alleles CYP2C19 and CYP3As [23–26]. Consequently, newer P2Y12 receptor inhibitors have been developed such as ticagrelor, prasugrel, and cangrelor. Contrary to clopidogrel, ticagrelor does not require hepatic activation, and it reversibly binds with the P2Y12-ADP receptors. It has faster onset and offset compared to clopidogrel without increase in major or minor bleeding events; in fact, it has been demonstrated that a loading dose of ticagrelor (180 mg) results within 30 min approximately in the same level of platelet inhibition achieved after 8 h of a loading dose of clopidogrel (600 mg) [27, 28]. Also, it is mainly metabolized via the CYP34A enzyme that could make it advantageous in the setting of mutations in CYP2C19 and has been demonstrated to be an effective and safe alternative to patients with poor response to clopidogrel in neuroendovascular procedures [29]. Prasugrel irreversibly inhibits the P2Y12-ADP receptor, and compared to clopidogrel, it has a more potent antiplatelet effect and a lower variability in platelet response. However, rates of hemorrhagic complications have been reported in neuroendo-

Table 13.2 Summary of intracranial stents

	Neuroform[b]	Neuroform Atlas[c]	Enterprise	Enterprise 2	LVIS	LVIS Jr	LEO +	LEO+ Baby	ACCLINO flex stent
FDA approval[a]	2002	No	2007	2015	2014	2014	No	No	No
Overall design	Laser-cut nitinol stent with interconnections at certain intervals	Laser-cut nitinol stent. Open-cell distal end and closed-cell proximal end	Laser-cut nitinol stent with flared ends	Laser-cut nitinol stent with flared ends	Laser-cut nitinol stent with two radiopaque helical strands within the body device	Laser-cut nitinol stent with three radiopaque helical strands within the body device	Braided stent with nitinol wires and two longitudinal radio-opaque platinum wires	Braided stent with nitinol wires and two longitudinal radio-opaque platinum wires	Laser-cut nitinol with a middle marker on the transport wire
Cell design	Open	Hybrid	Closed	Closed	Closed	Closed	Closed	Closed	Closed
Metal surface coverage	6–9%	6–9%	10%	10%	12–22%	12–22%	12–17%	12–17%	6–9%
Markers	4 on both ends	3 on both ends	4 on both ends	4 on both ends	4 on both ends	3 on both ends	No	No	3 on both ends
Diameters (mm)	2.5, 3, 3.5, 4, 4.5	3.0, 4.0, 4.5	4.5	4.0	3.5, 4.5, 5.5	2.5, 3.5	3.5, 4.5, 5.5	2.0, 2.5	3.5, 4.5
Lengths (mm)	10, 15, 20, 30	15, 21, 24, 30	14, 22, 28, 37	16, 23, 30, 39	17, 18, 22, 23, 30, 32, 33	13, 17, 18, 23, 28, 33, 34	12, 18, 25, 30, 35, 40, 50, 60, 75	12, 18, 25	15, 20, 25, 30, 35
Parent vessel diameter (range, mm)	2.0–4.5	2.0–4.5	2.5–4.0	2.5–4.0	2.5–4.5	2.0–3.0	3.1–6.5	1.5–3.1	2.0–4.0
Retrievable	No	No	Partially (up to 75% of its length deployed)	Partially (up to 75% of its length deployed)	Partially (up to 75% of its length deployed)	Partially (up to 80% of its length deployed)	Partially (up to 90% of its length deployed)	Partially (up to 90% of its length deployed)	Partially (up to 90% of its length deployed)
Microcatheter	0.027 in	0.0165 in/0.017 in	0.021 in	0.021 in	0.021 in	0.017 in	Vasco+21/ Vascro+25/ Vasco+28	Vasco+10	0.0165 in/0.017 in

LVIS low-profile visualized intraluminal support. The LEO +, LEO Baby, and ACCLINO flex stent are not available in the USA

[a]Under Humanitarian Device Exemption

[b]The last generation available is the Neuroform EZ

[c]Ongoing clinical trail

vascular procedures when using aspirin and prasugrel as dual-antiplatelet strategy [30]. Cangrelor is a novel intravenous P2Y12 inhibitor, which provides an immediate effect and that also can be rapidly reversed. This drug has been exclusively tested in percutaneous coronary interventions with a substantial reduction in ischemic events and no increased in severe bleeding compared with clopidogrel [31–33]. Although this drug has not been tested in neuroendovascular procedures, it seems a promising alternative in the setting of emergency cases or in which clopidogrel resistance is demonstrated.

In general, stent-assisted embolization requires placing patients on dual-antiplatelet therapy with aspirin (325 mg/day) and a thienopyridine derivative, typically clopidogrel (75 mg daily) for at least 7 days before the procedure. A bolus of clopidogrel (300–600 mg) can be used if a faster intervention is required and usually adequate platelet inhibition is obtained within 2–6 h post-loading dose [34, 35]. In our practice, we routinely check preoperative PRUs, and in the setting of poor response to clopidogrel, we switch to ticagrelor (180 mg initial dose, followed by 90 mg every 12 h with 81 mg of aspirin) [29]. The intervention is performed under conscious sedation or general anesthesia. Intravenous heparin is infused to maintain an activated clotting time greater than 200 s. Accurate vessel measurements are obtained from working angle angiograms and 3-D reconstructions. Stents are deployed under fluoroscopy, and a final angiogram is performed to evaluate immediate aneurysm embolization and parent vessel patency. Dual-antiplatelet therapy is usually maintained for 3 months followed by aspirin alone continued indefinitely.

Y-Stenting Configuration

The Y-stenting technique is a feasible reconstruction for bifurcation aneurysms. It consists of deploying the stents inside the bifurcation vessels to create an artificial aneurysm neck, which enables safe embolization by protecting the branching vessels from coil herniation [14, 36, 37]. This technique was first described for basilar apex aneurysms, but it is also feasible for aneurysms located in the anterior communicating artery (ACoA), internal carotid artery (ICA) terminus, and middle cerebral artery (MCA) bifurcation. Stent placement can be performed either through the interstices of the first device, more commonly used, or in a “kissing” fashion (parallel deployment) [38]. Chow et al. described the technique in 2004 for the treatment of a basilar apex aneurysm using two Neuroform stents and demonstrated encouraging results [39]. After this first experience, other authors have contributed to the literature reporting their case series in different aneurysm locations with overall good technical and clinical outcomes. Table 13.3 summarizes studies with at least ten cases reported using the Y-stenting technique in different bifurcation locations.

With the basic principle that the rate of thromboembolic complications is likely related to the amount of intravascular metal, our preference is to maximize the use of a single stent very often mitigating the need of a second device with the assistance of balloon remodeling to protect the non-stented branch.

Table 13.3 Summary of studies of endovascular treatment of wide-necked bifurcation aneurysms with Y-stenting configuration

Study (year)	Aneurysms	Type of stents used	Rate of periprocedural complications (%)	Complete aneurysm occlusion at last follow-up (%)	Rate of retreatment (%)
Spiotta et al. [42]	ACoA = 1 BA = 18	Neuroform	31.6	63.2	21
Chalouhi et al. [51]	BA = 16	Enterprise/ Neuroform	6.2	81.2	0
Zhao et al. [15]	ACoA = 2 PComm = 3 MCA = 3 BA = 3	Enterprise/ Neuroform	9	81.8	9
Lee et al. [4]	MCA = 3 BA = 9	Neuroform	0	100	0
Fargen et al. [45]	ACoA = 3 Pericallosal = 1 MCA = 2 BA = 39	Enterprise/ Neuroform	11	60	10
Yavuz et al. [44][a]	ICA-T = 16 ACoA = 42 MCA = 113 BA = 22	Enterprise/ Neuroform/ Solitaire	2.7	97.8	Not reported
Straus et al. [61]	ICA-T = 2 ACoA = 2 MCA = 10	Enterprise/ Neuroform	0	93	Not reported
Bartolini et al. [70][b]	ICA-T = 1 ACoA = 30 MCA = 57 BA = 17	Enterprise/ Neuroform/ Solitaire AB/ LVIS/LVIS Jr/ Baby LEO	10	85.8	2.3
Heller et al. [50]	ICA-T = 4 MCA = 2 BA = 14	Enterprise/ Neuroform	0	80	15
Jeon et al. [48]	BA = 25	Enterprise	12	80.9	Not reported
Ko et al. [53][c]	ACoA = 8 Distal ACA = 2 MCA = 1 BA = 9	Neuroform	45	93.3	0
Limbucci et al. [47]	ICA-T = 2 ACoA = 14 MCA = 20 BA = 11 Vertebrobasilar junction = 1	Enterprise	4.2	93.6	4.1

ACA anterior cerebral artery, *ACoA* anterior communicating artery, *BA* basilar apex, *ICA-T* internal carotid artery terminus, *MCA* middle cerebral artery, *LVIS* low-profile visualized intraluminal support

[a]Five ACoA aneurysms were treated with X-stent reconstruction

[b]Seven ACoA aneurysms were treated with X-stent reconstruction

[c]Regarding rate of periprocedural complications, authors include technical and neurological and non-neurological events

Endovascular Experience per Aneurysm Location

Basilar Apex Aneurysms

The basilar apex is the most common location of aneurysms in the posterior circulation [40, 41]. The catheterization of the basilar artery (BA) is technically easy due to the straight angle of its anatomy; however, it is a rich area of perforators that has to be taken into consideration when selecting an endovascular strategy. The Y-stent configuration has been broadly reported in retrospective case series and mostly used to treat basilar apex aneurysms. Although initial case series showed high rates of periprocedural complications with this technique [42, 43], larger series have demonstrated its safety and effectiveness [44].

When considering Y-stent reconstruction for the treatment of basilar apex aneurysms, accurate measurements should be obtained from both P1 segments and proximal landing zones in the basilar trunk in order to determine the device size. Initially, open-cell stents were favored for this technique due to their inherent strut configuration, but successful reconstructions have been reported using exclusively closed-cell stents [45–48]. The vascular anatomy is paramount for the success of this technique. It is not uncommon to find that one of the posterior cerebral arteries (PCA) originates at a more acute angle in relation to the basilar trunk, which may increase the difficulty of stent deployment. Therefore, we suggest that this P1 segment should be stented first (stenting the harder branch first should be the principle).

The technique for Y-stenting consists in advancing a 6-F guide catheter into the distal segment of one of the vertebral arteries (VA) under roadmap guidance. Subsequently, a microcatheter is advanced over a 0.014-in guidewire to the most difficult P1-segment configuration. The guidewire is removed, and the stent system is brought to the PCA. The first stent is deployed from the P1 segment into the upper segment of the basilar artery. Very often, we placed a microcatheter into the aneurysm and attempt coiling with a single stent in place, with or without balloon remodeling into the so far not-stented branch (see Fig. 13.1). Very often, we can obtain successful aneurysm treatment without using a second stent.

If a second stent is needed to perform a Y reconstruction, a microcatheter is carefully navigated through the first stent's cells, and a second device is deployed with half of the stent in the contralateral P1 segment and the other half extending down within the lumen of the previously placed stent. Although coiling through the struts of both stents is a feasible option, the high metal coverage of crossing devices at the aneurysm neck can create technical difficulties. Therefore, we prefer to place a coiling microcatheter into the aneurysm sac before placing the second device. Our preference with the current commercially available devices (Neuroform, Enterprise and LVIS) is to either combine two braided devices (LVIS or LVIS Jr. more frequently) or an open-cell stent followed by a closed-cell device (Neuroform as first stent and Enterprise as second). Especially when using braided devices, we recommend to perform a cone-beam CT with reconstruction (Xpert CT by Phillips) to evaluate the stent wall apposition. Immediate angiographic occlusion has been

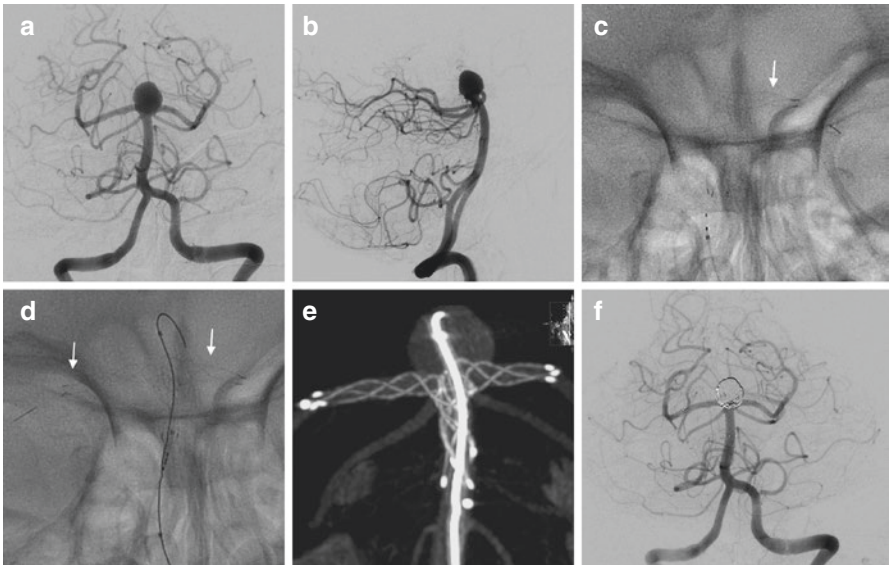


Fig. 13.1 Case illustration. A 70-year-old female with an incidentally found basilar apex aneurysm was decided to be treated with a Y-stent reconstruction. Cerebral angiogram with anteroposterior (**a**) and lateral (**b**) views demonstrated a wide-necked aneurysm. After determining accurate vessel measurements, decision was made to use low-profile stents (LVIS Jr). (**c**) Anteroposterior fluoroscopy view demonstrating the placement of the first stent from the left P1 (*white arrow*) across the aneurysm neck into the basilar artery. (**d**) Anteroposterior fluoroscopy view depicting the Y-stent reconstruction with both stents (*white arrows*) placed in the posterior cerebral arteries and a coiling microcatheter placed in the aneurysm sac. (**e**) Cone-beam CT (Xpert CT by Phillips) reconstruction demonstrating the wall apposition of the devices in the vessels. (**f**) Final digital subtracted angiogram demonstrating the patency of both posterior cerebral arteries and a near-complete aneurysm occlusion

reported as the highest predictor of long-term aneurysm occlusion [49]. One should keep in mind that when a balloon is used, as described above (typically Scepter, Microvention Terumo), a low-profile stent such as LVIS Jr. can be deployed through the lumen of the balloon.

The rate of periprocedural complications has been reported to range between 0% and 45% and derive mainly from thromboembolic events and technical events such as stent migration, stent prolapse, and coil herniation which have been reported to range from 1% to 3% [42–45, 48–53]. Spiotta et al. reported a rate of periprocedural complications of 31.6% including stent migration, artery dissection, and transient ischemic events [42]. Contrary to those results, Chalouhi et al. reported a lower rate of complications of 6.2% in the treatment of 16 basilar apex aneurysms. These authors did not find significant differences when comparing this technique with single stenting or coil embolization without stent assistance [51]. Fargen et al. reported the first multicenter experience in the treatment of 45 aneurysms, and among all lesions, 39 were located in the basilar apex [45]. The authors compared

clinical and angiographic results based on the cell design stent and found no statistical difference. To date, the largest case series published using the Y-stenting technique included 188 patients with 193 bifurcation aneurysms with a low rate of procedural complication of 2.7%, mortality rate of 0.5%, and a high rate (97.8%) of complete aneurysm occlusion at 6 months [44]. Among all lesions, 22 were located at the basilar apex. Overall, the rates of aneurysm occlusion at the last follow-up range between 63% and 100% with retreatment in approximately 10% of the cases [42, 45, 48, 50, 51].

ICA Terminus Aneurysms

The ICA terminus is a unique point in the cerebral vasculature where, similar to other bifurcation locations, there is high wall shear stress. Between 2% and 9% of all intracranial aneurysms are located at the ICA terminus, and they most commonly arise at the junction of the ICA and the M1 segment [54–57]. These aneurysms typically project longitudinally following the blood flow direction. Successful surgical clipping has been reported but requires advanced surgical skills and experience since the exposure is challenging due to a large number of perforators surrounding the base or dome of the aneurysm [58]. When the dome-to-neck ratio is favorable, single-coil embolization and balloon-assisted embolization are valid strategies with overall good results [59, 60]. However, wide-necked aneurysms at the ICA bifurcation remain challenging to treat. Y-stenting reconstruction is a feasible technique, and although it has been poorly reported in this subset of aneurysms, a safe technical profile has been demonstrated [47].

The technique for stent deployment should follow the general rule of deploying the first device in the branch with the sharpest angle. A similar technique with a single stent or balloon usage on the other branch, as described for basilar apex lesions, also applies for ICA terminus aneurysms. Accurate proximal measurements of the A1 and the M1 segments should be obtained to choose the device size. In the article published by Yavuz et al., 16 aneurysms were treated using open- and closed-cell stents. Although authors did not breakdown the rate of complications per aneurysm location, their overall results demonstrated safety and efficacy of the technique at 6-month follow-up [44]. Strauss et al. treated 14 aneurysms in the anterior circulation with the Y-stenting configuration, and among all lesions, 2 were located at the ICA terminus with no technical difficulties. One of the patients was successfully treated and achieved complete aneurysm occlusion at 6 months, but the second patient died 24 h post-intervention, which was attributed to her poor preoperative status [61]. A more recent publication reported 4 aneurysms out of 20 located in the ICA terminus. The authors reported no periprocedural complications and overall good rates of aneurysm occlusion [50]. Similar results were reported by Limbucci et al. in the treatment of two aneurysms located in the ICA bifurcation [47].

Anterior Communicating Artery (ACoA) Aneurysms

Aneurysms located in the ACoA account for the most common location based on historical cohorts with rates ranging between 23% and 39% [2, 62]. Surgical clipping has demonstrated to be an effective strategy but requires surgical expertise to dissect the lesion due to the unique position of the arterial segment and arterial branches which can be difficult to find and easily injured [63, 64]. When a favorable dome-to-neck ratio is present, coiling with or without device assistance has shown satisfactory outcomes [65–68]. Occasionally, a single device is not enough to reconstruct the parent vessel, and dual-stent reconstruction is warranted such as X- or Y-configurations.

When considering Y-stenting configuration, it is paramount to identify both A1 and A2 segments since it is not uncommon to find asymmetry among vessels. As a general rule, the patient should have a "good-sized" A1 artery since the proximal edges of both stents will be placed in this segment and distal edges will be located in both of the proximal A2 segments. The ipsilateral ICA should be catheterized extending into the dominant A1. Subsequently, coils are deployed into the aneurysm sac with the goal of achieving an initial complete occlusion. Rohde et al. described the first experience using Y-stent reconstruction for the treatment of a recurrent ACoA aneurysm using two closed-cell stents (Enterprise) and proof of aneurysm occlusion at 6-month follow-up [69]. Further small case series have demonstrated technical feasibility and overall good outcomes [45, 49]. In a Turkish study, the authors treated 42 aneurysms in the ACoA with dual-stent reconstructions exclusively with closed-cell stents (Enterprise and Solitaire). For 5 out of 42 ACoA aneurysms, they opted for stenting in X configuration. Although angiographic occlusion rates were not separated per aneurysm location, the overall rate for the total sample was 97.8% [44]. In a European study, the authors analyzed dual-stent reconstructions with X- and Y-configuration for the treatment of 105 aneurysms, and among all lesions, they treated 30 located in the ACoA. Interestingly, in nine patients, the attempt to place the stent failed, and three of them had their aneurysm located in the ACoA [70]. Their results were not reported per aneurysm location, but the overall rate of aneurysm occlusion at the last available imaging follow-up (a mean of 17 months) was 85.8% with only two re-treatments during the study period.

MCA Bifurcation Aneurysms

In general, aneurysms located in the MCA represent approximately 20% of all intracranial aneurysms, and among these, the MCA bifurcation is the most common location – approximately 75% of cases [2, 71, 72]. Surgical clipping remains the gold standard to treat this type of aneurysm due to straightforward access through the Sylvian fissure. However, endovascular alternatives have been explored, and Y-stent configuration has demonstrated good clinical outcomes. The first successful case was reported in 2005 with a dual-stent reconstruction using Neuroform stents [73].

It is recommended that the distal edge of the first stent be placed in the proximal segment of the larger M2 branch and subsequently a second device be deployed from the proximal segment of the other M2 branch to the M1 segment so that the proximal ends of both stents align. The coil embolization should be performed after both stents are placed either with the jailing technique or through the stent struts. Several case series have shown overall good outcomes. Straus et al. treated ten MCA bifurcation aneurysms with no complications, and imaging follow-up was available for six lesions demonstrating complete occlusion [61]. Yavuz et al. reported the largest series of treatments for this subset of aneurysms [44]. The authors successfully intervened in 113 lesions that accounted for 58.5% of the total sample, and most of them (87.6%) were treated with closed-cell stents. Bartolini et al. reported the treatment of 105 aneurysms, of which 57 lesions were located at the MCA bifurcation. As previously mentioned, the authors reported dual-stenting failure in nine cases, and the most common locations were the MCA bifurcation in four cases and the ACoA in three [70]. More recently, Limbucci et al. reported a case series that included 20 MCA aneurysms, and similar to the Turkish study, they performed all interventions with closed-cell stents in this subset of aneurysms [47]. Although the authors did not show outcomes per aneurysm location, their study demonstrated the safety and efficacy in the total sample with two procedural complications and complete aneurysm occlusion in 93.6% at the last follow-up.

X-Stenting Configuration

The X-stenting technique is a valid alternative for the treatment of wide-necked aneurysms located in the ACoA. The clinical experience is limited to case reports or small case series with overall good outcomes [74–76]. The technique consists of deploying one of the stents from one of the A2 segments to the contralateral A1 and subsequently to navigate the stent system from the opposite ICA and deploy the second device in the same fashion through the interstices of the first stent placed. We prefer to coil after both devices are placed. The target is to maintain the patency of both branches while the X configuration supports the coil mass and decreases the jet flow entering the aneurysm sac (Fig. 13.2). This hemodynamic phenomenon is believed to be enhanced with closed-cell stents. Although this technique is feasible, the major limitation is the vessel size where the stent may be deployed, and we agree with Saatci et al. that a good-sized A1 segment is paramount for the success of this technique [76]. Otherwise, a Y-configuration reconstruction through the larger vessel is an alternative option, especially for patients with A1 hypoplasia on one side. Bartolini et al. reported their experience with dual-stent reconstructions and treated seven aneurysms with X-stenting configuration [70]. Although the authors did not perform any conclusive analysis per technique, they described difficulties in dual-stent reconstructions mostly for aneurysms located in the ACoA and MCA bifurcation. Undoubtedly, larger studies are required to evaluate the safety and effectiveness of this type of configuration, but outcomes to date are encouraging.

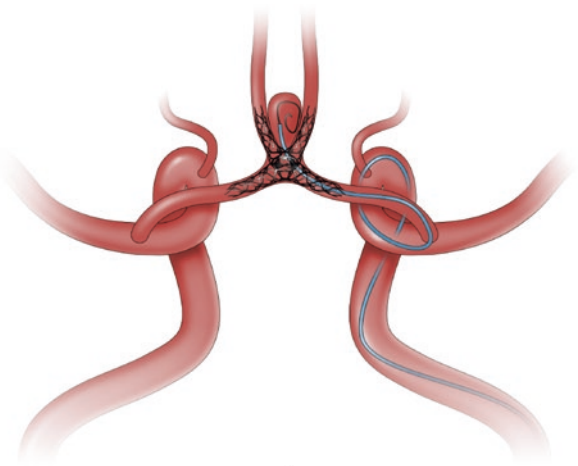


Fig. 13.2 X-stent reconstruction for the treatment of a wide-necked aneurysm located in the anterior communicating artery

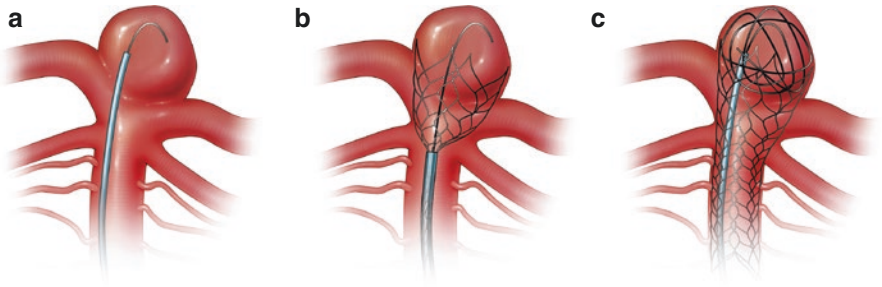


Fig. 13.3 Waffle-cone technique for the treatment of an aneurysm located at the basilar apex. A microcatheter is navigated over a microwire into the aneurysm sac. (**a**) Once in place, an intracranial stent is deployed within the aneurysm, (**b**) and finally coils are deployed resulting in a cone-shaped configuration that preserves both branches (**c**)

Waffle-Cone Technique

The waffle-cone technique is an uncommon alternative to the Y-stenting technique (Fig. 13.3). This procedure was first described by Horowitz et al. in 2006 and was described as the "waffle-cone" technique because of the appearance of the stent-coil combination after treatment [77]. The procedure consists of placing the distal edge of a stent in the base of the aneurysm neck and coiling through the implant resulting in a cone-shaped configuration that preserves both branches. This stent configuration is recommended when the acute angulation of branch arteries at the location of a wide-necked aneurysm make it difficult to navigate any stent system. Additional benefits include a reduction in the amount of metal and a technically easier strategy than dual-stent reconstructions. The waffle-cone technique has been used to treat aneurysms located in the basilar apex, ACoA, and MCA bifurcation. Initially, open-cell stents were used for this reconstruction, but successful cases with closed-cell stents have also been reported [78].

Endovascular Experience per Aneurysm Location

Basilar Apex Aneurysms

Although the clinical experience with the waffle-cone technique is limited, it is a valid alternative for the treatment of wide-necked bifurcation aneurysms. In the treatment of lesions located at the basilar apex, accurate measurements should be obtained of the size of the aneurysm neck and the diameter of the BA in order to determine the diameter of the stents. The procedure is technically easier than other reconstructions since only one device is used. The stent system is brought within the aneurysm sac and carefully deployed to anchor the distal edge of the device inside the lesion. Once the stent is placed, a rotational cone-beam CT angiogram is recommended to evaluate stent wall apposition. After successful stenting, a microcatheter is navigated to the aneurysm dome over a microwire through the lumen reconstruction. Enough coils should be deployed to obtain a near or complete aneurysm embolization. Horowitz et al. described this technique using open-cell stents with favorable results in four wide-necked bifurcation aneurysms located at the BA with no complications and immediate near-to-complete aneurysm occlusion [77]. A similar successful case was reported by Yang et al. using a Neuroform stent. In theory, open-cell stents facilitate blood flow from the parent artery through the stent reconstruction into the branching arteries where it covers them at their origins. However, a few cases have been reported with closed-cell stents resulting in overall good outcomes [78, 79]. Compared to the Y-stenting configuration, the waffle technique involves a shorter total length of stented vessel and no stents overlapping, which may reduce the risk of stent thrombosis. The rate of periprocedural complications has been reported up to 2%, mainly thromboembolic events. Regarding aneurysm occlusion, the rates have ranged between 60% and 100% at the last follow-up available [77, 78, 80].

ACoA and MCA Aneurysms

Experience with the waffle technique in other locations other than the basilar apex is very limited in part due to the vascular anatomy which precludes this technique in certain locations. Only a few cases have been reported; Horowitz et al. successfully treated one aneurysm located at the ACoA and two at the MCA with no complications and satisfactory immediate results [77]. Similar results have been described in the treatment of three ACoA aneurysms and one MCA aneurysm [81]. In the largest series reported, to our knowledge, in these locations using the waffle technique, Liu et al. reported 6 ACoA aneurysms and 3 MCA aneurysms with encouraging results and long-term aneurysm occlusion [80]. Although the technique itself is feasible, there is no current evidence to support its recommendation for the treatment of these lesions, and other alternatives should be considered before using waffle technique for ACoA or MCA aneurysms.

T-Stent Configuration

The T-stent reconstruction is also known as the nonoverlapping Y-configuration and was first described by Cho et al. in 2012 for the treatment of six basilar apex aneurysms [82]. Their results showed a safe and feasible alternative to other traditional stent reconstructions. From a technical point of view, this is a modified Y-stent reconstruction, and the general rule of stenting the hardest branch should be followed. The first stent is navigated into the P1 segment of the PCA, and a microcatheter for coil delivery should be placed in the aneurysm sac. The first stent is deployed from the P1 segment to the basilar trunk. Later, a second stent is navigated and deployed into the contralateral PCA without overlapping the initial device. Finally, coils are deployed as compactly as possible under devices protection. This reconstruction may be performed on a staged fashion, or both stents can be placed in the same procedure. This technique shows clear advantages over the traditional Y-configuration: (1) no stent deployment through the struts of one of the devices, (2) less amount of metal inside the basilar trunk, and (3) proper apposition of the stents into the arterial wall. However, the alignment of the second stent without overlapping may be challenging, or otherwise, the stent may be placed far distal resulting in sufficient aneurysm neck coverage to protect against coil protrusion. Therefore, accurate vessel measurement should be obtained.

Publication on this technique is scant, and long-term outcomes are unknown. To date, Aydin et al. have published the largest case series [83]. They intervened 24 patients with 24 aneurysms located in the anterior circulation. T-stent reconstruction was performed using low-profile stents (Leo + Baby; Balt). The technical success rate was 95.8%, and an immediate total occlusion rate of 79.2% was achieved. The rate of periprocedural complications was 16.7% with no mortality and a permanent morbidity of 4.2%. At the last imaging follow-up, the rate of aneurysm occlusion was achieved in 81.2% of the cases.

Cross-Court Approach for Aneurysm Stenting

When dealing with complex aneurysms, contralateral approaches or posterior to anterior/posterior strategies are feasible options for stenting (Fig. 13.4). Some examples of these maneuvers include as follows: ipsilateral A1 to contralateral A1 for ACoA lesions, P1 into the posterior communicating artery (PComm) and distal ICA (reverse PComm stenting), contralateral vertebral access to posterior inferior cerebellar artery (PICA) aneurysms, contralateral carotid to A1-M1 stenting for carotid terminus lesions, contralateral carotid to distal ICA into the PComm, ICA-PComm approach for P1-P1 stenting for basilar tip aneurysms, and ICA-PComm approach for basilar and superior cerebellar artery aneurysms. Taking advantage of these anatomical connections should be taken into consideration before considering more complex stent reconstructions.

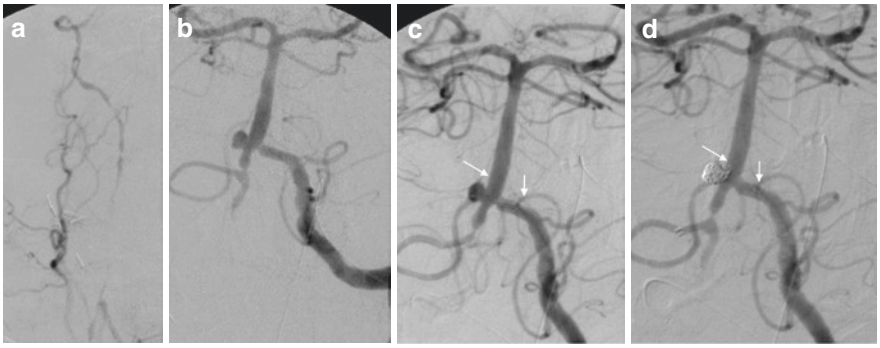


Fig. 13.4 Case illustration. A 73-year-old male presented to the hospital with a subarachnoid hemorrhage, Hunter and Hess grade 4. A cerebral angiogram was performed, which revealed a right vertebral artery (VA) dissection (**a**) and a pseudoaneurysm (**b**) arising from the origin of the right posterior inferior cerebellar artery (PICA). Decision was made to secure the lesion and due to inaccessibility through the right VA, a contralateral approach was performed. A microcatheter was navigated through the left VA, and a coiling microcatheter was placed into the pseudoaneurysm sac. (**c**) An intracranial stent was deployed from the proximal basilar artery into the left vertebral artery (*white arrows*). (**d**) Final digital subtracted angiogram demonstrating complete occlusion of the lesion and patency of the right PICA, basilar artery, and left VA

Here, we will illustrate the utilization of the contralateral vertebral approach to PICA aneurysms (Fig. 13.5). Aneurysms located in the PICA are extremely rare with an estimated prevalence that ranges between 0.5% and 3% [62]. For lesions involving the VA/PICA origin, the goal of any therapy should be aneurysm occlusion with preservation of the PICA. With the advance of technology and the development of smaller intracranial stents, endovascular approaches may be feasible and safe. In fact, current microcatheters may easily be navigated into any of the vertebral arteries (VAs) and, subsequently, into the PICA. In some instances, due to the variability in the anatomy of the VAs and the sharp angle of the PICA origin, a straightforward access may be difficult, and a contralateral approach to the aneurysm should be performed. The technique consists as follows: a 6-F guide catheter is positioned in both VAs; then a microcatheter is navigated to the PICA, distal to the aneurysm, through the contralateral VA; and it is positioned across the aneurysm neck. Then, a microcatheter is navigated to the PICA aneurysm through the contralateral VA, and it is positioned across the aneurysm neck. Finally, the stent is slowly deployed. Once the stent is placed, a microcatheter for coiling is navigated into the guide placed in the VA ipsilateral to the lesion and navigated through the struts of the stent [84]. Recently, we published a dual-center study for the treatment of PICA aneurysms with the LVIS Jr. stent [85]. This device is an excellent alternative for the treatment of these lesions since it can be delivered through a 0.017-in microcatheter, which also allows for coiling. In our series, two patients were treated through a contralateral approach

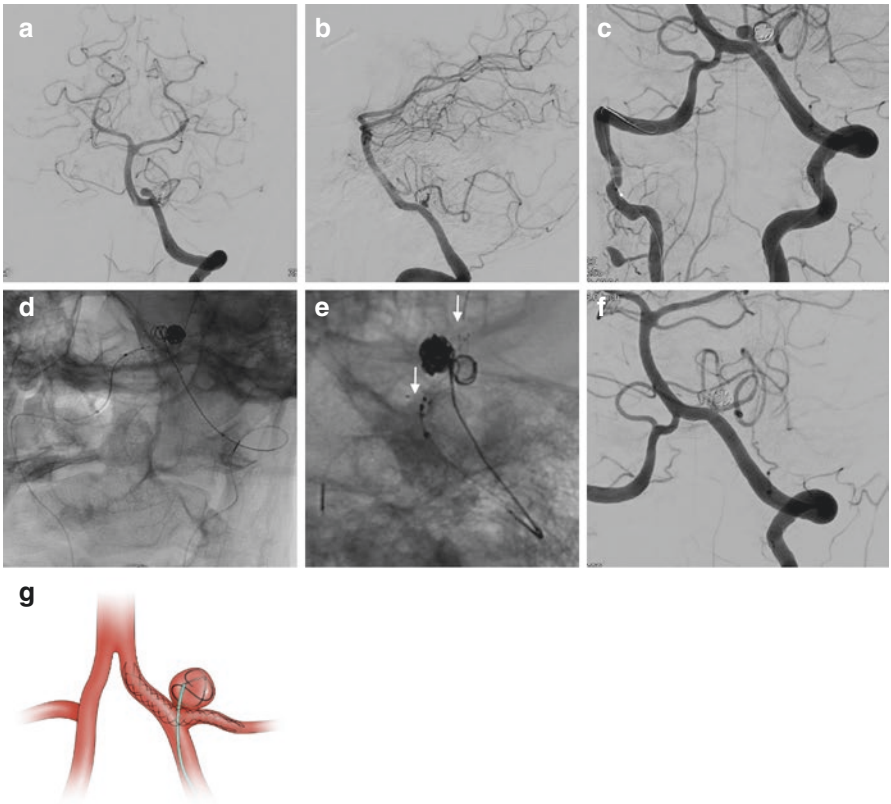


Fig. 13.5 Case illustration. A 52-year-old female with history of a left-sided posterior cerebellar inferior artery (PICA) aneurysm that was previously coiled presented with recurrence of the lesion. Cerebral angiogram with anteroposterior (**a**) and lateral (**b**) views demonstrated a daughter sac coming from the PICA origin aneurysm. Catheterization of the PICA from the ipsilateral vertebral artery was unsuccessful, and decision was made to navigate a second microcatheter through the right vertebral artery and ultimately to catheterize the left PICA (**c**). A microcatheter was navigated into the aneurysm sac through the ipsilateral vertebral artery, and the second microcatheter was positioned across the aneurysm neck; once in place, coils were deployed (**d**), and an LVIS Jr (*white arrows*) was slowly deployed spanning the aneurysm (**e**). A final angiogram demonstrated patency of the PICA and near-complete aneurysm occlusion (**f**). Another valid strategy is to deploy the stent first and eventually coil the aneurysm through the struts of the device (**g**)

with no technical complications. Other case series using older stents have reported technical difficulties and limitations for the treatment of this type of aneurysms, especially when lesions are located in distal segments of the PICA [86–88]. Current data are scant to provide enough evidence to support either surgery or endovascular treatment, but a multidisciplinary team should address treatment choice for PICA aneurysms.

Current and Future Endovascular Alternatives for Wide-Necked Bifurcation Aneurysms

Despite the advance in neuroendovascular technology, there is no current standard of treatment for bifurcation aneurysms, and other stent-like devices have been used with encouraging results. The pCONus (Phenox, Bochum, Germany) is a self-expanding device with four distal petals and a nylon cross in the distal end of the shaft to support coils inside the aneurysm. The device is designed to optimize the waffle-stenting technique. The experience with this new technology is limited to small case series, but results have demonstrated its safety and overall good rates of aneurysm occlusion at midterm follow-up [89–92].

The PulseRider (Pulsar Vascular, San Jose, CA, USA) is a novel device with lesser metal content than intracranial stents, and it supports the aneurysm neck while maintaining coil mass inside the sac. Its deployment does not require branch vessel catheterization, and unlike y-stenting configuration, one device is sufficient. However, literature offers limited data, and larger prospective studies are needed to evaluate the safety and efficacy of this technology [93–95].

Recently, flow diverters have revolutionized the treatment of large side-wall aneurysms demonstrating safety and long-term efficacy in multicenter cohorts [96, 97]. However, their usage on bifurcation aneurysms remains controversial, especially because the aneurysm neck may not be completely covered by the flow diverter and aneurysm thrombosis over time is uncertain. A few case series have been published with the emphasis on bifurcation aneurysms, and the rate of periprocedural complications has been reported in up to 9.4% with rates of aneurysm occlusion ranging from 33.3% to 97.7% [98–100].

Based on flow diversion technology, a new concept in intrasaccular flow disruption has been developed. The Woven EndoBridge device (WEB, Sequent Medical, Palo Alto, CA, USA) is a self-expanding ovoid mesh that is placed inside the aneurysm sac, modifying the blood flow and inducing lesion thrombosis; additionally, its placement does not require dual-antiplatelet therapy, and it can be used in acutely ruptured aneurysms. Several studies have demonstrated its safety, but complete aneurysm occlusion is far from definitive with rates ranging from 53.1% to 69% [101–104].

Other devices are currently under evaluation, and preclinical studies have shown promising results. The Artisse device (formerly known as the Luna Parent Vessel Occlusion device, LUNA, Medtronic, Minneapolis, MN, USA) is a self-expanding ovoid mesh of nitinol wires. Its design intends to disrupt the flow inside the aneurysm, and a study in rabbits showed a rate of 88% complete aneurysm occlusion at 3 months; additionally, microscopic examinations demonstrated neointimal overgrowth in all cases [105]. A preliminary experience has been reported in France in the treatment of 64 aneurysms with an excellent technical profile but suboptimal rates of aneurysms occlusion: 40% at 6-month follow-up [106]. A clinical trial evaluating this device is planned to be started in the USA in July 2017.

The Reverse Barrel Vascular Reconstruction Device (VRD, Medtronic, Minneapolis, MN, USA) is a resheathable stent-like device with a cone shape in the middle of the implant that prevents coil herniation into the parent vessel. A study in canine models demonstrated excellent technical outcomes in the treatment of 32 aneurysms, and histological examinations showed neointimal formation onto the device [107]. An ongoing French registry has reported preliminary results in seven patients treated with this new technology, and initial results showed immediate complete occlusion in 71% of the cases and no technical complications [108].

The Endovascular Clip Systems (eCLIPs, Evasc Medical Systems, Vancouver, BC, USA) is a hybrid leaf-shaped device that works as a flow diverter and as an intrasaccular flow disrupter. A preclinical study in eight porcine models has shown a good technical profile and complete aneurysm occlusion at 30-day angiography in all cases with neo-endothelialization at microscopic examinations [109]. The fast evolution of new endovascular technology should be taken with cautious optimism, and pros and cons of each technology should be considered when deciding treatment management for bifurcation aneurysms.

Conclusions

The decision-making process to treat wide-necked bifurcation aneurysms relies on a thorough knowledge of the patient's vascular anatomy as well as the neurosurgical armamentarium available. The goal of treatment should be to obtain a long-term aneurysm occlusion with patent bifurcation branches. This chapter summarized complex stent reconstructions that should be considered in the decision process based on appropriate patient selection and the neurointerventionalist experience. Certainly, the Y-stenting configuration has demonstrated reproducibility, safety, and effectiveness for aneurysms in multiple cohorts, but other reconstructions, although feasible, still lack strong evidence to use in comparison to other approaches. In addition, future devices should be designed to overcome current difficulties in covering the aneurysm neck, conformability on sharply curved vessels, and complete aneurysm obliteration.

References

1. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. N Engl J Med. 1998;339(24):1725–33.
2. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms I. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103–10.

3. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg. 2000;93(3):379–87.
4. Lee EJ, Lee HJ, Hyun MK, Choi JE, Kim JH, Lee NR, Hwang JS, Kwon JW. Rupture rate for patients with untreated unruptured intracranial aneurysms in South Korea during 2006–2009. J Neurosurg. 2012;117(1):53–9.
5. Investigators UJ, Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med. 2012;366(26):2474–82.
6. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. Stroke. 2013;44(9):2414–21.
7. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke. 2010;41(9):1969–77.
8. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R; International Subarachnoid Aneurysm Trial Collaborative G. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. J Stroke Cerebrovasc Dis. 2002;11(6):304–14.
9. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet. 2015;385(9969):691–7.
10. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, Albuquerque FC. The barrow ruptured aneurysm trial. J Neurosurg. 2012;116(1):135–44.
11. Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, Nakaji P, Wallace RC. The barrow ruptured aneurysm trial: 3-year results. J Neurosurg. 2013;119(1):146–57.
12. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Russin JJ, Partovi S, Nakaji P, Wallace RC. The barrow ruptured aneurysm trial: 6-year results. J Neurosurg. 2015;123(3):609–17.
13. Munarriz PM, Gomez PA, Paredes I, Castano-Leon AM, Cepeda S, Lagares A. Basic principles of hemodynamics and cerebral aneurysms. World Neurosurg. 2016;88:311–9.
14. Gao B, Baharoglu MI, Cohen AD, Malek AM. Y-stent coiling of basilar bifurcation aneurysms induces a dynamic angular vascular remodeling with alteration of the apical wall shear stress pattern. Neurosurgery. 2013;72(4):617–29. discussion 628–619
15. Zhao B, Yin R, Lanzino G, Kallmes DF, Cloft HJ, Brinjikji W. Endovascular coiling of wide-neck and wide-neck bifurcation aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2016;37(9):1700–5.
16. Krischek O, Miloslavski E, Fischer S, Shrivastava S, Henkes H. A comparison of functional and physical properties of self-expanding intracranial stents [Neuroform3, Wingspan, Solitaire, Leo+, Enterprise]. Minim Invasive Neurosurg. 2011;54(1):21–8.
17. Nam HG, Yoo CM, Baek SM, Kim HK, Shin JH, Hwang MH, Jo GE, Kim KS, Cho JH, Lee SH, Kim HC, Lim CH, Choi H, Sun K. Enhancement of mechanical properties and testing of nitinol stents in cerebral aneurysm simulation models. Artif Organs. 2015;39(12): E213–26.
18. Heer T, Juenger C, Gitt AK, Bauer T, Towae F, Zahn R, Senges J, Zeymer U; Acute Coronary Syndromes Registry I. Efficacy and safety of optimized antithrombotic therapy with aspirin, clopidogrel and enoxaparin in patients with non-ST segment elevation acute coronary syndromes in clinical practice. J Thromb Thrombolysis. 2009;28(3):325–32.
19. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost. 1999;25(Suppl 2):15–9.
20. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003;107(23):2908–13.
21. Gasparyan AY. Aspirin and clopidogrel resistance: methodological challenges and opportunities. Vasc Health Risk Manag. 2010;6:109–12.

22. Prabhakaran S, Wells KR, Lee VH, Flaherty CA, Lopes DK. Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting. AJNR Am J Neuroradiol. 2008;29(2):281–5.
23. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. Circulation. 2004;109(25):3064–7.
24. Comin J, Kallmes DF. Platelet-function testing in patients undergoing neurovascular procedures: caught between a rock and a hard place. AJNR Am J Neuroradiol. 2013;34(4):730–4.
25. Fifi JT, Brockington C, Narang J, Leesch W, Ewing SL, Bennet H, Berenstein A, Chong J. Clopidogrel resistance is associated with thromboembolic complications in patients undergoing neurovascular stenting. AJNR Am J Neuroradiol. 2013;34(4):716–20.
26. Goh C, Churilov L, Mitchell P, Dowling R, Yan B. Clopidogrel hyper-response and bleeding risk in neurointerventional procedures. AJNR Am J Neuroradiol. 2013;34(4):721–6.
27. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–57.
28. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120(25):2577–85.
29. Hanel RA, Taussky P, Dixon T, Miller DA, Sapin M, Nordeen JD, Tawk RG, Navarro R, Johns G, Freeman WD. Safety and efficacy of ticagrelor for neuroendovascular procedures. A single center initial experience. J Neurointerv Surg. 2014;6(4):320–2.
30. Akbari SH, Reynolds MR, Kadkhodayan Y, Cross DT 3rd, Moran CJ. Hemorrhagic complications after prasugrel (Effient) therapy for vascular neurointerventional procedures. J Neurointerv Surg. 2013;5(4):337–43.
31. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV Jr, Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med. 2009;361(24):2318–29.
32. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimsky P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Genereux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA, Investigators CP. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med. 2013;368(14):1303–13.
33. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS, Goodman SG, White HD, Mahaffey KW, Pollack CV Jr, Manoukian SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Harrington RA, Investigators CP. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med. 2009;361(24):2330–41.
34. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, Bestehorn HP, Buttner HJ, Neumann FJ. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. Circulation. 2005;111(20):2560–4.
35. Nordeen JD, Patel AV, Darracott RM, Johns GS, Taussky P, Tawk RG, Miller DA, Freeman WD, Hanel RA. Clopidogrel resistance by P2Y12 platelet function testing in patients undergoing neuroendovascular procedures: incidence of ischemic and hemorrhagic complications. J Vasc Interv Neurol. 2013;6(1):26–34.
36. Cekirge HS, Yavuz K, Geyik S, Saatci I. A novel "Y" stent flow diversion technique for the endovascular treatment of bifurcation aneurysms without endosaccular coiling. AJNR Am J Neuroradiol. 2011;32(7):1262–8.
37. Saglam M, Kizilkilic O, Anagnostakou V, Yildiz B, Kocer N, Islak C. Geometrical characteristics after Y-stenting of the basilar bifurcation. Diagn Interv Radiol. 2015;21(6):483–7.

38. Melber K, Meila D, Draheim P, Grieb D, Greling B, Schlunz-Hendann M, Brassel F. Vascular angular remodeling by kissing-Y stenting in wide necked intracranial bifurcation aneurysms. J Neurointerv Surg. 2016; https://doi.org/10.1136/neurintsurg-2016-012858.
39. Chow MM, Woo HH, Masaryk TJ, Rasmussen PA. A novel endovascular treatment of a wide-necked basilar apex aneurysm by using a Y-configuration, double-stent technique. AJNR Am J Neuroradiol. 2004;25(3):509–12.
40. Ogilvy CS, Crowell RM, Heros RC. Basilar and posterior cerebral artery aneurysms. In: Ojemann RG, Ogilvy CS, Crowell RM, Heros RC, editors. Surgical management of neurovascular disease. 3rd ed. Baltimore: Williams and Wilkins; 1995. p. 269–90.
41. Henkes H, Fischer S, Mariushi W, Weber W, Liebig T, Miloslavski E, Brew S, Kuhne D. Angiographic and clinical results in 316 coil-treated basilar artery bifurcation aneurysms. J Neurosurg. 2005;103(6):990–9.
42. Spiotta AM, Gupta R, Fiorella D, Gonugunta V, Lobo B, Rasmussen PA, Moskowitz SI. Mid-term results of endovascular coiling of wide-necked aneurysms using double stents in a Y configuration. Neurosurgery. 2011;69(2):421–9.
43. Thorell WE, Chow MM, Woo HH, Masaryk TJ, Rasmussen PA. Y-configured dual intracranial stent-assisted coil embolization for the treatment of wide-necked basilar tip aneurysms. Neurosurgery. 2005;56(5):1035–40; discussion 1035–1040.
44. Yavuz K, Geyik S, Cekirge S, Saatci I. Double stent-assisted coil embolization treatment for bifurcation aneurysms: immediate treatment results and long-term angiographic outcome. AJNR Am J Neuroradiol. 2013;34(9):1778–84.
45. Fargen KM, Mocco J, Neal D, Dewan MC, Reavey-Cantwell J, Woo HH, Fiorella DJ, Mokin M, Siddiqui AH, Turk AS, Turner RD, Chaudry I, Kalani MY, Albuquerque F, Hoh BL. A multicenter study of stent-assisted coiling of cerebral aneurysms with a Y configuration. Neurosurgery. 2013;73(3):466–72.
46. Conrad MD, Brasiliense LB, Richie AN, Hanel RA. Y stenting assisted coiling using a new low profile visible intraluminal support device for wide necked basilar tip aneurysms: a technical report. J Neurointerv Surg. 2014;6(4):296–300.
47. Limbucci N, Renieri L, Nappini S, Consoli A, Rosi A, Mangiafico S. Y-stent assisted coiling of bifurcation aneurysms with Enterprise stent: long-term follow-up. J Neurointerv Surg. 2016;8(2):158–62.
48. Jeon P, Kim BM, Kim DJ, Kim DI, Park KY. Y-configuration double-stent-assisted coiling using two closed-cell stents for wide-neck basilar tip aneurysms. Acta Neurochir. 2014;156(9):1677–86.
49. Zhao KJ, Yang PF, Huang QH, Li Q, Zhao WY, Liu JM, Hong B. Y-configuration stent placement (crossing and kissing) for endovascular treatment of wide-neck cerebral aneurysms located at 4 different bifurcation sites. AJNR Am J Neuroradiol. 2012;33(7):1310–6.
50. Heller RS, Rahal JP, Malek AM. Y-stent embolization technique for intracranial bifurcation aneurysms. J Clin Neurosci. 2014;21(8):1368–72.
51. Chalouhi N, Jabbour P, Gonzalez LF, Dumont AS, Rosenwasser R, Starke RM, Gordon D, Hann S, Tjoumakaris S. Safety and efficacy of endovascular treatment of basilar tip aneurysms by coiling with and without stent assistance: a review of 235 cases. Neurosurgery. 2012;71(4):785–94.
52. Lee WJ, Cho CS. Y-stenting endovascular treatment for ruptured intracranial aneurysms: a single-institution experience in Korea. J Korean Neurosurg Soc. 2012;52(3):187–92.
53. Ko JK, Han IH, Cho WH, Choi BK, Cha SH, Choi CH, Lee SW, Lee TH. Crossing Y-stent technique with dual open-cell stents for coiling of wide-necked bifurcation aneurysms. Clin Neurol Neurosurg. 2015;132:54–60.
54. Kyoshima K, Kobayashi S, Nitta J, Osawa M, Shigeta H, Nakagawa F. Clinical analysis of internal carotid artery aneurysms with reference to classification and clipping techniques. Acta Neurochir. 1998;140(9):933–42.
55. Miyazawa N, Nukui H, Horikoshi T, Yagishita T, Sugita M, Kanemaru K. Surgical management of aneurysms of the bifurcation of the internal carotid artery. Clin Neurol Neurosurg. 2002;104(2):103–14.

56. Sakamoto S, Ohba S, Shibukawa M, Kiura Y, Okazaki T, Arita K, Kurisu K. Characteristics of aneurysms of the internal carotid artery bifurcation. Acta Neurochir. 2006;148(2):139–43. discussion 143
57. Gupta SK, Khosla VK, Chhabra R, Mohindra S, Bapuraj JR, Khandelwal N, Mukherjee KK, Tewari MK, Pathak A, Mathuriya SN. Internal carotid artery bifurcation aneurysms: surgical experience. Neurol Med Chir (Tokyo). 2007;47(4):153–7; discussion 157–158.
58. Lehecka M, Dashti R, Romani R, Celik O, Navratil O, Kivipelto L, Kivisaari R, Shen H, Ishii K, Karatas A, Lehto H, Kokuzawa J, Niemela M, Rinne J, Ronkainen A, Koivisto T, Jaaskelainen JE, Hernesniemi J. Microneurosurgical management of internal carotid artery bifurcation aneurysms. Surg Neurol. 2009;71(6):649–67.
59. van Rooij WJ, Sluzewski M, Beute GN. Internal carotid bifurcation aneurysms: frequency, angiographic anatomy and results of coiling in 50 aneurysms. Neuroradiology. 2008;50(7):583–7.
60. Oishi H, Yamamoto M, Nonaka S, Arai H. Endovascular therapy of internal carotid artery bifurcation aneurysms. J Neurointerv Surg. 2013;5(5):400–4. https://doi.org/10.1136/neurintsurg-2012-010414.
61. Straus D, Johnson AK, Lopes DK. Overlapping stents in "Y" configuration for anterior circulation aneurysms. EJMINT Original Article. 2013:1304000095.
62. Locksley HB. Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Based on 6368 cases in the cooperative study. J Neurosurg. 1966;25(2):219–39.
63. Sekhar LN, Natarajan SK, Britz GW, Ghodke B. Microsurgical management of anterior communicating artery aneurysms. Neurosurgery. 2007;61(5 Suppl 2):273–90; discussion 290-272.
64. Hernesniemi J, Dashti R, Lehecka M, Niemela M, Rinne J, Lehto H, Ronkainen A, Koivisto T, Jaaskelainen JE. Microneurosurgical management of anterior communicating artery aneurysms. Surg Neurol. 2008;70(1):8–28; discussion 29.
65. Proust F, Debono B, Hannequin D, Gerardin E, Clavier E, Langlois O, Freger P. Treatment of anterior communicating artery aneurysms: complementary aspects of microsurgical and endovascular procedures. J Neurosurg. 2003;99(1):3–14.
66. Elias T, Ogungbo B, Connolly D, Gregson B, Mendelow AD, Gholkar A. Endovascular treatment of anterior communicating artery aneurysms: results of clinical and radiological outcome in Newcastle. Br J Neurosurg. 2003;17(3):278–86.
67. Raslan AM, Oztaskin M, Thompson EM, Dogan A, Petersen B, Nesbit G, Lee DS, Barnwell SL. Neuroform stent-assisted embolization of incidental anterior communicating artery aneurysms: long-term clinical and angiographic follow-up. Neurosurgery. 2011;69(1):27–37; discussion 37.
68. Brasiliense LB, Yoon JW, Orina JN, Miller DA, Tawk RG, Hanel RA. A reappraisal of anterior communicating artery aneurysms: a case for stent-assisted embolization. Neurosurgery. 2016;78(2):200–7.
69. Rohde S, Bendszus M, Hartmann M, Hahnel S. Treatment of a wide-necked aneurysm of the anterior cerebral artery using two Enterprise stents in "Y"-configuration stenting technique and coil embolization: a technical note. Neuroradiology. 2010;52(3):231–5.
70. Bartolini B, Blanc R, Pistocchi S, Redjem H, Piotin M. "Y" and "X" stent-assisted coiling of complex and wide-neck intracranial bifurcation aneurysms. AJNR Am J Neuroradiol. 2014;35(11):2153–8.
71. Dashti R, Hernesniemi J, Niemela M, Rinne J, Porras M, Lehecka M, Shen H, Albayrak BS, Lehto H, Koroknay-Pal P, de Oliveira RS, Perra G, Ronkainen A, Koivisto T, Jaaskelainen JE. Microneurosurgical management of middle cerebral artery bifurcation aneurysms. Surg Neurol. 2007;67(5):441–56.
72. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; International Subarachnoid Aneurysm Trial Collaborative G. 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(9488):809–17.

73. Sani S, Lopes DK. Treatment of a middle cerebral artery bifurcation aneurysm using a double neuroform stent "Y" configuration and coil embolization: technical case report. Neurosurgery. 2005;57(1 Suppl):E209; discussion E209.
74. Lazzaro MA, Zaidat OO. X-configuration intersecting Enterprise stents for vascular remodeling and assisted coil embolization of a wide neck anterior communicating artery aneurysm. J Neurointerv Surg. 2011;3(4):348–51.
75. Zelenak K, Zelenakova J, DeRiggo J, Kurca E, Boudny J, Polacek H. Flow changes after endovascular treatment of a wide-neck anterior communicating artery aneurysm by using X-configured kissing stents (cross-kissing stents) technique. Cardiovasc Intervent Radiol. 2011;34(6):1308–11.
76. Saatci I, Geyik S, Yavuz K, Cekirge S. X-configured stent-assisted coiling in the endovascular treatment of complex anterior communicating artery aneurysms: a novel reconstructive technique. AJNR Am J Neuroradiol. 2011;32(6):E113–7.
77. Horowitz M, Levy E, Sauvageau E, Genevro J, Guterman LR, Hanel R, Wehman C, Gupta R, Jovin T. Intra/extra-aneurysmal stent placement for management of complex and wide-necked- bifurcation aneurysms: eight cases using the waffle cone technique. Neurosurgery. 2006;58(4 Suppl 2):ONS-258–262; discussion ONS-262.
78. Sychra V, Klisch J, Werner M, Dettenborn C, Petrovitch A, Strasilla C, Gerlach R, Rosahl S, Holtmannspotter M. Waffle-cone technique with Solitaire AB remodeling device: endovascular treatment of highly selected complex cerebral aneurysms. Neuroradiology. 2011;53(12):961–72.
79. Padalino DJ, Singla A, Jacobsen W, Deshaies EM. Enterprise stent for waffle-cone stent-assisted coil embolization of large wide-necked arterial bifurcation aneurysms. Surg Neurol Int. 2013;4:9.
80. Liu W, Kung DK, Policeni B, Rossen JD, Jabbour PM, Hasan DM. Stent-assisted coil embolization of complex wide-necked bifurcation cerebral aneurysms using the "waffle cone" technique. A review of ten consecutive cases. Interv Neuroradiol. 2012;18(1):20–8.
81. Guo X, Chen Z, Wang Z, Guan S. Preliminary experiences of "waffle cone" technique for the treatment of intracranial aneurysm. Zhonghua Yi Xue Za Zhi. 2014;94(17):1346–8.
82. Cho YD, Park SW, Lee JY, Seo JH, Kang HS, Kim JE, Han MH. Nonoverlapping Y-configuration stenting technique with dual closed-cell stents in wide-neck basilar tip aneurysms. Neurosurgery. 2012;70(2 Suppl Operative):244–9.
83. Aydin K, Sencer S, Barburoglu M, Berdikhojayev M, Aras Y, Sencer A, Izgi N. Midterm results of T-stent-assisted coiling of wide-necked and complex intracranial bifurcation aneurysms using low-profile stents. J Neurosurg. 2017;127(6):1288–96. https://doi.org/10.3171/2016.9.JNS161909.
84. Zaidat OO, Szeder V, Alexander MJ. Transbrachial stent-assisted coil embolization of right posterior inferior cerebellar artery aneurysm: technical case report. J Neuroimaging. 2007;17(4):344–7.
85. Samaniego EA, Abdo G, Hanel RA, Lima A, Ortega-Gutierrez S, Dabus G. Endovascular treatment of PICA aneurysms with a Low-profile Visualized Intraluminal Support (LVIS Jr) device. J Neurointerv Surg. 2016;8(10):1030–3.
86. Chalouhi N, Jabbour P, Starke RM, Tjoumakaris SI, Gonzalez LF, Witte S, Rosenwasser RH, Dumont AS. Endovascular treatment of proximal and distal posterior inferior cerebellar artery aneurysms. J Neurosurg. 2013;118(5):991–9.
87. Mericle RA, Reig AS, Burry MV, Eskioglu E, Firment CS, Santra S. Endovascular surgery for proximal posterior inferior cerebellar artery aneurysms: an analysis of Glasgow Outcome Score by Hunt-Hess grades. Neurosurgery. 2006;58(4):619–25. discussion 619–625
88. Peluso JP, van Rooij WJ, Sluzewski M, Beute GN, Majoie CB. Posterior inferior cerebellar artery aneurysms: incidence, clinical presentation, and outcome of endovascular treatment. AJNR Am J Neuroradiol. 2008;29(1):86–90.
89. Aguilar-Perez M, Kurre W, Fischer S, Bazner H, Henkes H. Coil occlusion of wide-neck bifurcation aneurysms assisted by a novel intra- to extra-aneurysmatic neck-bridging device (pCONus): initial experience. AJNR Am J Neuroradiol. 2014;35(5):965–71.

90. Gory B, Aguilar-Perez M, Pomero E, Turjman F, Weber W, Fischer S, Henkes H, Biondi A. pCONus device for the endovascular treatment of wide-neck middle cerebral artery aneurysms. AJNR Am J Neuroradiol. 2015;36(9):1735–40.
91. Lubicz B, Morais R, Alghamdi F, Mine B, Collignon L, Eker OF. The pCONus device for the endovascular treatment of wide neck bifurcation aneurysms. J Neurointerv Surg. 2016;8(9):940–4.
92. Ulfert C, Pfaff J, Schonenberger S, Bosel J, Herweh C, Pham M, Bendszus M, Mohlenbruch M. The pCONus Device in Treatment of Wide-necked Aneurysms : Technical and Midterm Clinical and Angiographic Results. Clin Neuroradiol. 2018;28(1):47–54. https://doi.org/10.1007/s00062-016-0542-z.
93. Gory B, Spiotta AM, Mangiafico S, Consoli A, Biondi A, Pomero E, Killer-Oberpfalzer M, Weber W, Riva R, Labeyrie PE, Turjman F. PulseRider stent-assisted coiling of wide-neck bifurcation aneurysms: periprocedural results in an international series. AJNR Am J Neuroradiol. 2016;37(1):130–5.
94. Mukherjee S, Chandran A, Gopinathan A, Putharan M, Goddard T, Eldridge PR, Patankar T, Nahser HC. PulseRider-assisted treatment of wide-necked intracranial bifurcation aneurysms: safety and feasibility study. J Neurosurg. 2017;127(1):61–8. https://doi.org/10.3171/2016.2.JNS152334.
95. Spiotta AM, Chaudry MI, Turk AS, Turner RD. Initial experience with the PulseRider for the treatment of bifurcation aneurysms: report of first three cases in the USA. J Neurointerv Surg. 2016;8(2):186–9.
96. Kallmes DF, Hanel R, Lopes D, Boccardi E, Bonafe A, Cekirge S, Fiorella D, Jabbour P, Levy E, McDougall C, Siddiqui A, Szikora I, Woo H, Albuquerque F, Bozorgchami H, Dashti SR, Delgado Almandoz JE, Kelly ME, Turner R, Woodward BK, Brinjikji W, Lanzino G, Lylyk P. International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. AJNR Am J Neuroradiol. 2015;36(1):108–15.
97. Kallmes DF, Brinjikji W, Boccardi E, Ciceri E, Diaz O, Tawk R, Woo H, Jabbour P, Albuquerque F, Chapot R, Bonafe A, Dashti SR, Delgado Almandoz JE, Given C 2nd, Kelly ME, Cross DT 3rd, Duckwiler G, Razack N, Powers CJ, Fischer S, Lopes D, Harrigan MR, Huddle D, Turner R, Zaidat OO, Defreyne L, Pereira VM, Cekirge S, Fiorella D, Hanel RA, Lylyk P, McDougall C, Siddiqui A, Szikora I, Levy E. Aneurysm study of pipeline in an observational registry (ASPIRe). Interv Neurol. 2016;5(1–2):89–99.
98. Saleme S, Iosif C, Ponomarjova S, Mendes G, Camilleri Y, Caire F, Boncoeur MP, Mounayer C. Flow-diverting stents for intracranial bifurcation aneurysm treatment. Neurosurgery. 2014;75(6):623–31. quiz 631
99. Gawlitza M, Januel AC, Tall P, Bonneville F, Cognard C. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: a single-center series with special emphasis on covered cortical branches and perforating arteries. J Neurointerv Surg. 2016;8(5):481–7.
100. Dabus G, Grossberg JA, Cawley CM, Dion JE, Puri AS, Wakhloo AK, Gonsales D, Aguilar-Salinas P, Sauvageau E, Linfante I, Hanel RA. Treatment of complex anterior cerebral artery aneurysms with Pipeline flow diversion: mid-term results. J Neurointerv Surg. 2017;9(2):147–51. https://doi.org/10.1136/neurintsurg-2016-012519.
101. Muskens IS, Senders JT, Dasenbrock HH, Smith TR, Broekman ML. The Woven Endobridge (WEB) device for treatment of intracranial aneurysms: a systematic review. World Neurosurg. 2016; https://doi.org/10.1016/j.wneu.2016.11.020.
102. Pierot L, Costalat V, Moret J, Szikora I, Klisch J, Herbreteau D, Holtmannspotter M, Weber W, Januel AC, Liebig T, Sychra V, Strasilla C, Cognard C, Bonafe A, Molyneux A, Byrne JV, Spelle L. Safety and efficacy of aneurysm treatment with WEB: results of the WEBCAST study. J Neurosurg. 2016;124(5):1250–6.
103. Pierot L, Moret J, Turjman F, Herbreteau D, Raoult H, Barreau X, Velasco S, Desal H, Januel AC, Courtheoux P, Gauvrit JY, Cognard C, Molyneux A, Byrne J, Spelle L. WEB treatment of intracranial aneurysms: clinical and anatomic results in the French observatory. AJNR Am J Neuroradiol. 2016;37(4):655–9.

104. Pierot L, Spelle L, Molyneux A, Byrne J, Webcast, French Observatory I. Clinical and anatomical follow-up in patients with aneurysms treated with the WEB device: 1-year follow-up report in the cumulated population of 2 prospective, multicenter series (WEBCAST and French observatory). Neurosurgery. 2016;78(1):133–41.
105. Kwon SC, Ding YH, Dai D, Kadirvel R, Lewis DA, Kallmes DF. Preliminary results of the luna aneurysm embolization system in a rabbit model: a new intrasaccular aneurysm occlusion device. AJNR Am J Neuroradiol. 2011;32(3):602–6.
106. Piotin M, Biondi A, Sourour N, Blanc R. O–036 treatment of intracranial aneurysms with the LUNA AES: midterm clinical and angiographic follow-up. J Neurointerv Surg. 2014;6(Suppl 1):A19–20.
107. Tateshima S, Niemann D, Moskowitz S, Baxter B, Frei D. O–017 preliminary experience with a new barrel shaped bifurcation aneurysm bridging device. J Neurointerv Surg. 2013;5(Suppl 2):A10.
108. Piotin M, Blanc R, Berge J, Turjman F. O–030 preliminary French registry clinical experience with the barrel bifurcation vascular reconstruction device. J Neurointerv Surg. 2014;6(Suppl 1):A15–6.
109. Marotta TR, Gunnarsson T, Penn I, Ricci DR, McDougall I, Marko A, Bourne G, Da Costa L. A novel endovascular clip system for the treatment of intracranial aneurysms: technology, concept, and initial experimental results. Laboratory investigation. J Neurosurg. 2008;108(6):1230–40.

Chapter 14
Flow Diversion

Maksim Shapiro, Eytan Raz, and Peter Kim Nelson

Until recently, at-risk patients with intracranial aneurysms were treated either with microsurgical reconstruction of the parent artery by aneurysm clipping or by endovascular approach, principally through deployment of detachable coils within the aneurysm sac (coil-endosaccular), a method more widely adopted following publication of results from the International Subarachnoid Aneurysm Trial [1, 2]. Although continuous innovation in coil design and coatings has broadened the initial complement of bare-platinum coils aimed at improved aneurysm packing and healing, the seemingly inescapable problem of aneurysm recurrence, and the undefined clinical implications of this phenomenon, as pertains to progressive aneurysm growth and rupture, has limited embrace of endosaccular approaches in providing definitive cure—particularly for complex cerebral aneurysms [2–4]—even when supported by other technical advances, such as adjunctive balloon assistance, to improve coil treatment of the aneurysm neck. Since 2007, an alternative endovascular approach, utilizing minimally porous endoluminal devices (MPEDs) or flow diverters (FDs) (targeting primary reconstruction of the affected parent vessel segment), has become increasingly pre-eminent in the repair of unruptured cerebral aneurysms.

M. Shapiro
Departments of Neurointerventional Radiology and Neurology, NYU Langone Health, New York, NY, USA

E. Raz
Departments of Neurointerventional Radiology and Neuroradiology, NYU Langone Health, New York, NY, USA

P. K. Nelson (✉)
Bernard and Irene Schwartz Interventional Neuroradiology Section, Departments of Neurology, Neurosurgery and Radiology, New York University Langone Medical Center, New York, NY, USA
e-mail: nelsop01@med.nyu.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_14

Emergence of Endoluminal Reconstructive Methods: Adjunctive Stent-Supported Coil Embolization

The feasibility of combined stent-supported aneurysm coiling was first established in an experimental aneurysm model [5] and subsequently confirmed by several case reports [6, 7] and small clinical series [8, 9]—documenting results initially with balloon-expandable stents and, following the introduction of Neuroform (Boston Scientific), Leo (Balt), and Enterprise (Codman), with self-expanding microstents.

Stent-Supported Coiling: Clinical Results

While early experience with *stent-supported coil-endosaccular* treatment of wide neck aneurysms was promising [8, 9], long-term angiographic evaluation of the synergy expected from such combined endovascular therapy has been less than altogether encouraging [9]. In a literature review of 39 articles reporting results from 1517 cases of stent-supported coiling, Shapiro et al. [10] found 45% of aneurysms to be completely occluded on initial posttreatment angiography and only 61% occluded on follow-up (Fig. 14.1). Ironically, although intended to support the

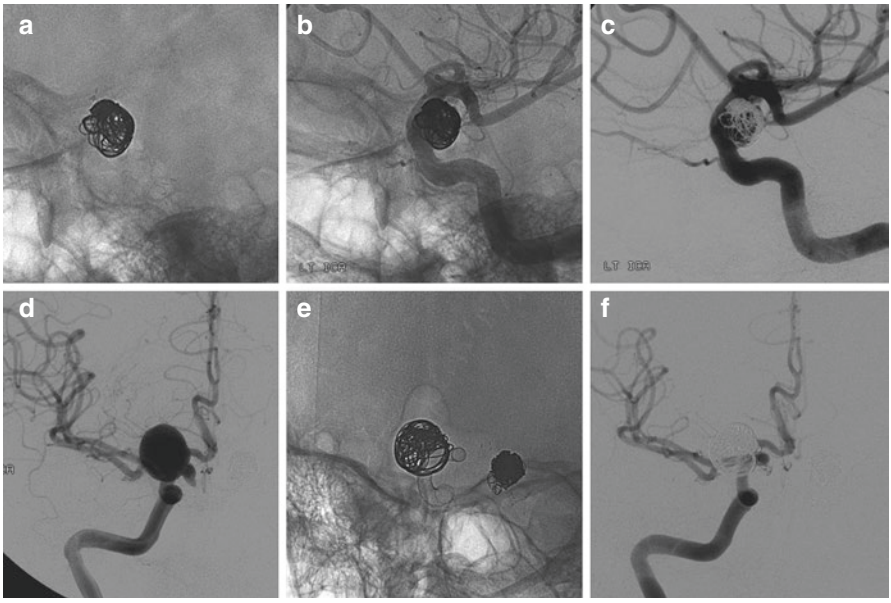


Fig. 14.1 Status post stent-assisted coiling of ruptured left paraophthalmic segment aneurysm with short-term recurrence 6 months post initial treatment (**a–c**). Mirror image right paraophthalmic aneurysm treated with Pipeline and coils, demonstrating complete occlusion 9 months later (**d–f**)

treatment of large and complex-neck aneurysms, small aneurysms account for the majority of aneurysms treated with adjunctive stenting [10]—suggesting tacit recognition for the utility of endoluminal devices at improving occlusion outcomes with coils in the general case.

Primary Endoluminal Technique

Insight into the potential for endoluminal directed aneurysm therapy soon followed commercialization of Neuroform, Enterprise, and Leo. In certain settings, it was observed that aneurysms treated exclusively by stenting alone, without coil placement (typically in the setting of a planned staged treatment or where overlapping stents were used to increase the metallic coverage of the aneurysm neck), occasionally underwent spontaneous thrombosis [11–13], presumably due to alterations in the intra-aneurysmal circulation imposed by the stent construct. With time dedicated minimally porous (higher coverage) endoluminal devices (MPEDs were developed to effect primary parent artery reconstruction without the necessity of aneurysm coils or other embolic materials.

Types of Endoluminal Devices

As of 2017, the Pipeline embolization device (Medtronic, Dublin, Ireland) remains the only endoluminal device cleared by the FDA for use in the United States. Other similar devices, such as the Silk (Balt Extrusion, Montmorency, France), Derivo (Acandis GmbH, Pforzheim, Germany), Flow Re-Direction Endoluminal Device (FRED) (MicroVention, Tustin, California), p64 Flow Modulation Device (Phenox, Bochum, Germany), and Surpass Intracranial Aneurysm Embolization System (Stryker Neurovascular Fremont, California), are approved for human use in Europe, parts of Asia, and Oceana. Since, to this point in time, the published literature predominantly describes the experience with Pipeline, the description below pertains to this device. Two alternative MPEDs, the Surpass Flow Diverter and the MicroVention Flow Redirect Intraluminal Device (FRED), are being evaluated in prospective trials in the United States as of 2017.

The PED is a self-expanding, cylindrically shaped, endovascular construct composed of 48 braided wire strands of cobalt-chromium and platinum-tungsten filaments, with every fourth strand woven into the construct composed of Pt-W to impart greater radio-opacity. The individual strands measure between 28 and 33 microns in diameter with no reported size difference between Co-Cr and Pt-W strands. The available device diameters range from 2.5 to 5.0 mm in 0.25 mm increments, with lengths ranging from 10 to 35 mm. All devices are designed to open approximately 0.25 mm beyond their nominal diameter when unopposed, such that the largest functional diameter would be around 5.25 mm. While a single PED

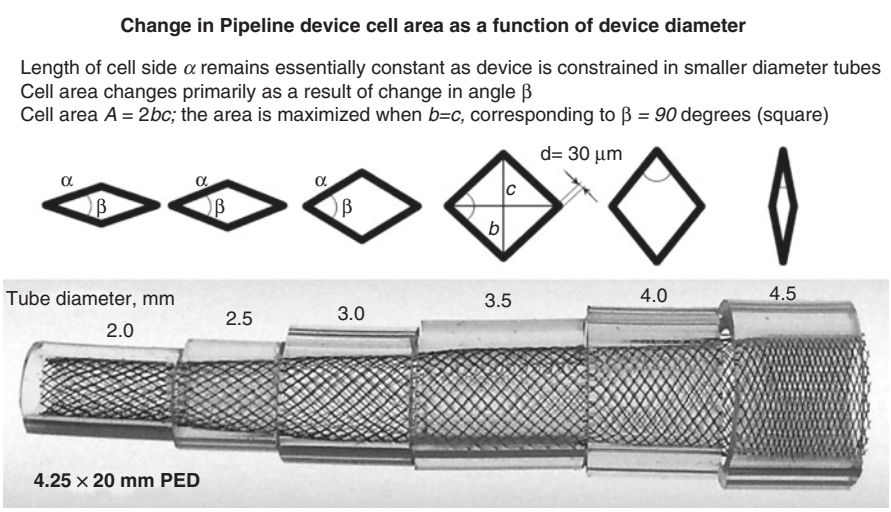


Fig. 14.2 Pipeline embolization device within transparent plastic tubes of predefined diameters. The arrangement demonstrates variation in porosity of the device depending on the diameter of the "vessel" within which it is implanted

provides 30–35% metal surface area coverage at nominal deployment in a straight conduit [12, 14, 15], multiple devices can be strategically telescoped within each other, overlapping devices to create a composite endovascular construct—either to increase the overall length of the construct or to selectively augment the degree of metal surface coverage over the aneurysm neck [12, 14, 15] (Fig. 14.2).

Various iterations of the device delivery system have been utilized, with the partially re-sheathable Pipeline Flex system currently in use throughout the world. As commercially available, the PED is mounted on a delivery microwire and constrained within a removable sheath. It is loaded into and delivered through a standard 0.027″ ID microcatheter (Fig. 14.3). Most anatomical locations accessible with a 0.027″ ID microcatheter can be reconstructed with the PED. A surface-modified device, utilizing a covalently bound phosphorylcholine surface treatment designed to reduce inherent implant thrombogenicity (the Pipeline Flex Embolization Device with Shield Technology), has been available in Europe and Australia since 2016. Both Pipeline Flex and Pipeline Shield are extremely flexible and conform to the native vascular anatomy with very little anatomical distortion regardless of regional tortuosity.

The incorporation of platinum strands allows the PED to be visible throughout its length when implanted in situ. This radio-opacity represents a significant working advantage when compared to previously available self-expanding intracranial stents, which are typically provided with more limited radio-opaque markings restricted to the device ends (Fig. 14.4). At the same time, PED constructs do not produce notable CT artifact, and CT angiography can be used as an effective noninvasive method to evaluate aneurysm treatment in follow-up. While fully MR compatible to 3.0 T, PED constructs (particularly those with overlapping devices) create enough local magnetic susceptibility to reduce signal generated by time-of-

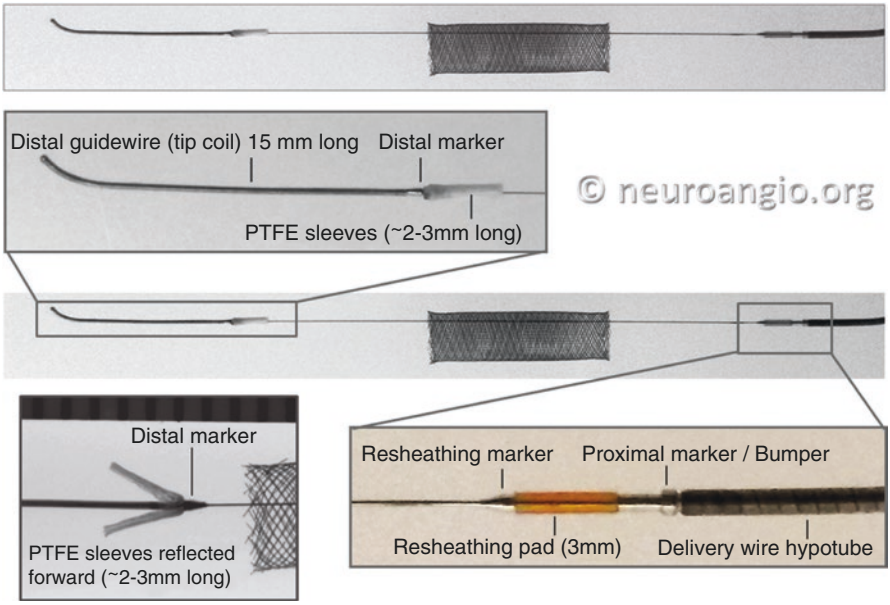


Fig. 14.3 Pipeline Flex embolization device and its delivery system components. (©neuroangio.org used with permission)

flight MR angiography techniques, thus giving the false impression of segmentally absent flow through the construct (Fig. 14.5). Contrast-based MRA sequences, while less sensitive to local susceptibility, nevertheless remain suboptimal for evaluation of the lumen within the implant.

Theoretical Basis of Parent Artery Reconstruction with Endoluminal Stent-Like Devices

As opposed to endosaccular directed therapies, reconstructive endoluminal techniques, like microsurgical clipping, target the arterial deficiency at the aneurysm neck and function to repair the abnormal, aneurysmal segment of the parent artery. This is achieved by implanting a metal scaffolding of sufficiently low porosity (small cell size) across the aneurysm neck to enable (1) thrombosis of the aneurysm and (2) neointimal overgrowth (repaving) of the vascular wall deficiency and any adjacent vessel dysplasia—recreating a structurally sound vascular segment while at the same time permitting uninterrupted perfusion of the parent artery and, ideally, any branch vessels arising adjacent to the lesion (that may be incidentally covered by the bridging devices).

Reconstruction of the deficient vascular segment is multifaceted, evolving over a period of weeks to months, and begins with the *uncoupling of momentum exchange*

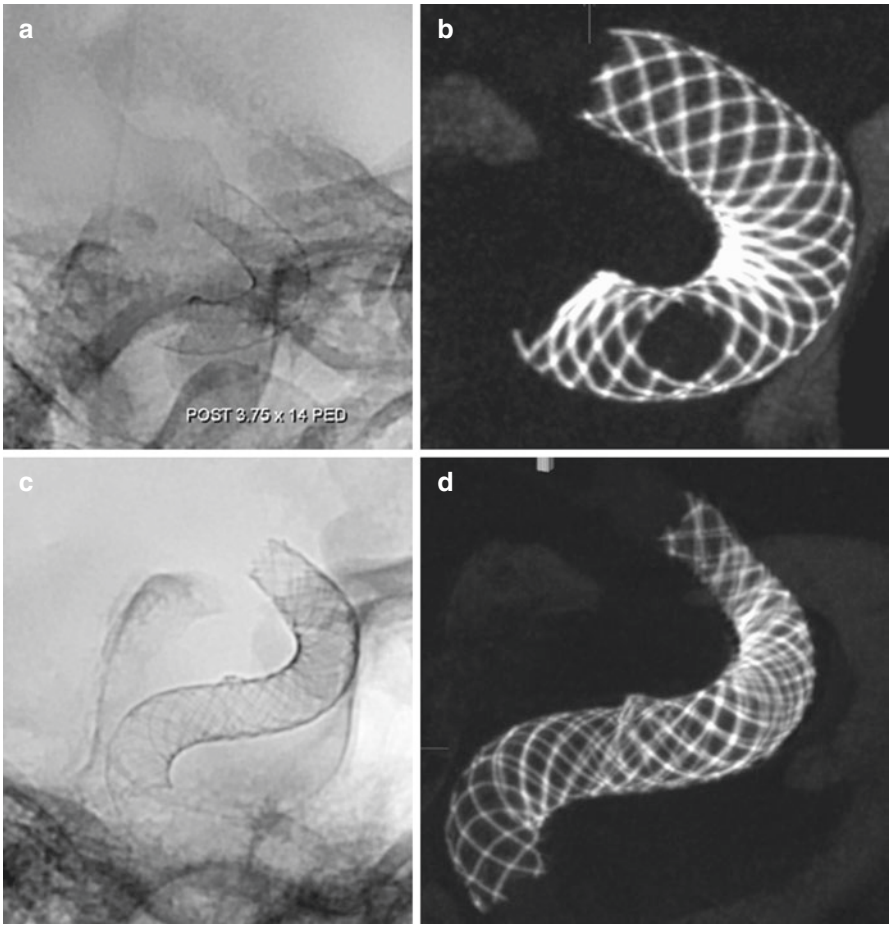


Fig. 14.4 Unsubtracted angiographic and Dyna-CT images of a single Pipeline device in situ (**a**, **b**), demonstrating excellent ability to visualize the construct, including its Pt-W braid with modern equipment. The same patient, following implantation of additional two devices, demonstrating substantial increase in metal coverage over the target anterior genu area (**c**, **d**)

between the parent artery and aneurysm [16–20]. This reduces intra-aneurysmal circulation (prolonging the intra-fundal circulation time)—thereby, contributing to conditions in which thrombosis of the aneurysm is favored. The reparative process is completed upon *neointimal overgrowth of the construct with subintimal incorporation of the stent into the parent vessel wall.* Where intra-aneurysmal flow is sufficiently reduced, gradual aneurysm thrombosis is facilitated, occluding the aneurysm fundus, leading ultimately to curative anatomical vascular repair (neointimal overgrowth of the aneurysm neck). The stages of these transitions [12] can be

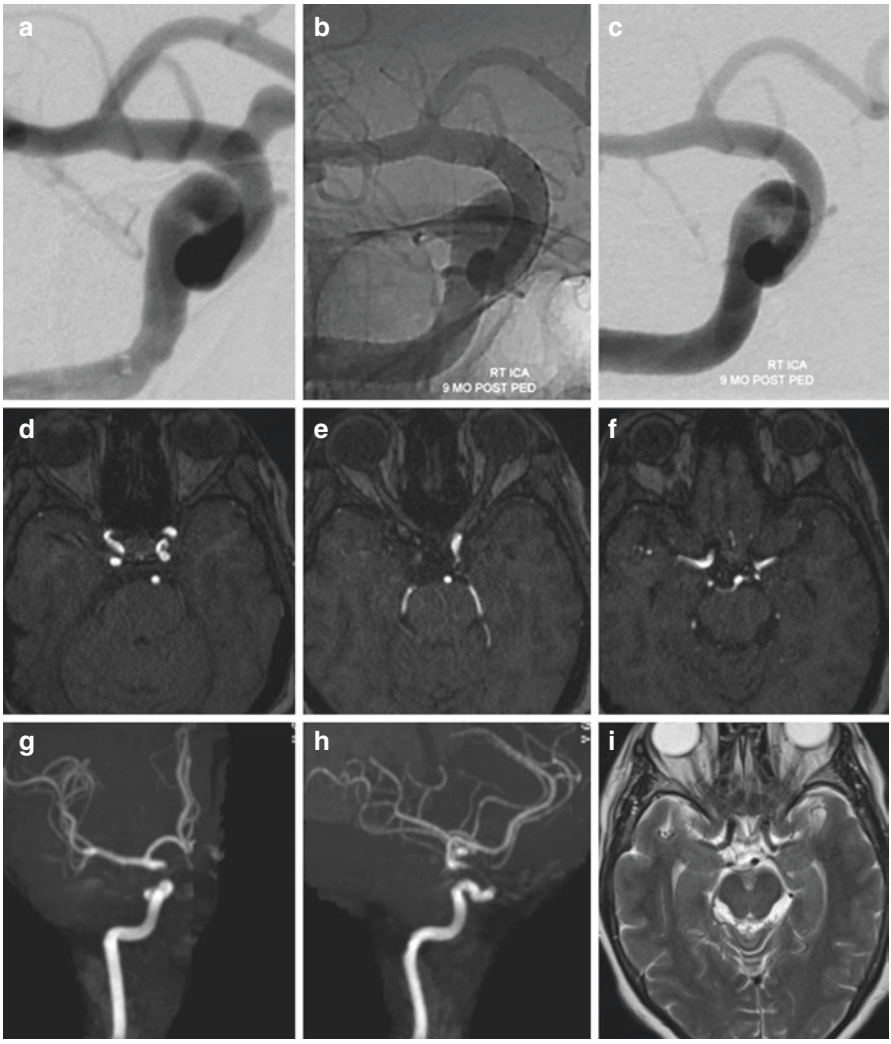


Fig. 14.5 (**a–i**): Right paraophthalmic aneurysm fully occluded following PED treatment. MRA shows typical intra-construct signal loss due to effects of magnetic shielding (**e**). While patency of the parent vessel can be inferred from presence of flow-related enhancement immediately proximal (**d**) and distal (**f**) to the device, as well as from presence of normal T2 flow void (**i**), the possibility of construct-related stenosis cannot be evaluated by TOF MRA methods

characterized as follows: (1) aneurysmal flow disruption, (2) intra-aneurysmal thrombosis, (3) neointimal overgrowth and endothelialization of the construct, and (4) resorption of intra-aneurysmal contents by scavenger cell-mediated processes—with resolution of aneurysmal mass effect.

The Issue of Perforator Branches

When deployed across an aneurysm neck, MPEDs act to reduce the convective component of exchange across the aneurysm neck—diminishing vortical circulation within the aneurysm and leading to intra-aneurysmal stasis and thrombosis. Flow into adjacent branch arteries, however, is governed by the regional cerebrovascular resistance and the arterial to venous pressure gradient across the vascular territory supplied by the index branch. Outside of complicating exigencies (such as parent or branch vessel vasospasm or the construct becoming acutely thrombosed), flow is maintained as long as the impedance across the construct remains significantly below the local cerebrovascular resistance of the jailed vascular territory. Under typical conditions, flow through the microvasculature is determined by various physiological parameters (the mean pressure gradient, cerebrovascular resistance, autoregulatory capacity of the irrigated territory, and intracranial pressure), and, from hemodynamic calculations, greater than 50% surface area coverage of the branch vessel orifice can be tolerated before the covering device begins to contribute significantly to runoff resistance and branch flow starts to diminish [21, 22]. This concept has been validated angiographically in humans, by examining the fate of ophthalmic arteries covered during the treatment of paraophthalmic segment aneurysms [23]. Moreover, histological evaluation of Pipeline 6 months after implantation into the rabbit aorta demonstrates an overgrowth of endothelium uniformly covering the construct [15], except at the orifices of covered branch vessels which present as rounded, funnel-like perforations of the neointimal covering [15, 24]. Thus, the constant flow through the branch vessel appears to inhibit neointimal overgrowth of the construct at branch vessel openings. Parenthetically, however, in vascular territories well supported by collateral pathways, subtle changes in resistance at the branch vessel orifice can lead to recruitment of collateral inflow—allowing arrest of anterograde flow into the index branch and altering the ultimate supply to a jailed vascular territory. Examples are seen frequently where MPEDs are used across the ophthalmic [23] and posterior communicating arteries, the A1 segment, and even anterior choroidal [25] or perforator branches, resulting in asymptomatic occlusion of the covered branches (Fig. 14.6).

Analyses of patients treated with the PED for large and giant ICA aneurysms with coverage of the ophthalmic artery have demonstrated predominance of excellent neuro-ophthalmological outcomes 6 months after the procedure, with very few new deficits, suggesting the possibility for deliberate cerebrovascular remodeling as a separate strategy (delayed mixed-deconstructive) for aneurysm treatment with MPEDs.

Benchmark Studies

Device Geometry

Although nominal metal coverage (reverse of porosity) of the device is listed as 30–35%, in practice, the porosity changes substantially depending on the configuration of the device (curvatures) and its diameter relative to the artery into which it is

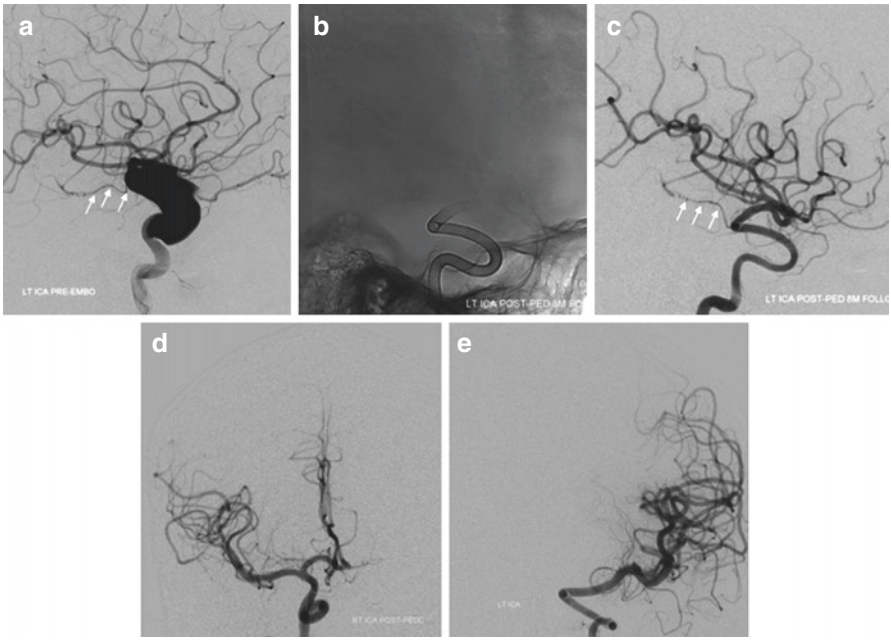


Fig. 14.6 (**a**–**e**): Giant intracranial left ICA aneurysm (**a**) successfully treated by multiple PEDs which required coverage of the left A1 segment, the anterior choroidal (hypoplastic), posterior communicating, and ophthalmic arteries. Eight months posttreatment, the aneurysm is closed. Both ophthalmic artery and A1 segment are no longer visualized, having undergone asymptomatic rearrangement of their supply from the external carotid system and the contralateral A1/ACOM, respectively. The anterior choroidal artery (white arrows), with lesser potential for collateral reconstitution, remains patent

placed. The porosity of any given device is determined by the area of the individual cell (pore) relative to that of its constituent braids (Fig. 14.1) and exhibits a parabolic relationship to the diameter of the device [26] (Fig. 14.7).

In keeping with its parabolic relationship to diameter, the degree of metal coverage falls quickly when the device is oversized relative to the parent artery, with minimized coverage values for all PED implants encountered with as little as 1 mm of oversizing (e.g., implantation of a 4 mm PED into a 3 mm vessel). Thus, in practice, coverage values of 30% are almost never achieved with a single implant—unless compression of the cell structure can be exerted across a very broad-necked aneurysm where the device is not constrained by the diameter of the parent vessel. In most cases, and particularly in large and giant aneurysms for which device was approved, multidevice coverage may be required to achieve the coverage necessary to reproduce the efficacy expected from the PUFS trial (median three devices/aneurysm) [27, 28]. Other reasons to use multiple devices include the overall construct stability imparted by overlapping devices in treating large fusiform aneurysms with long constructs and strategic considerations related to achieving differential coverage of adjacent branch vessels and the aneurysm neck and benefits derived from the use of shorter devices across complex aneurysms in tortuous anatomy where longer individual devices are susceptible to torsion (Fig. 14.8).When creating such constructs, it is advisable to overlap

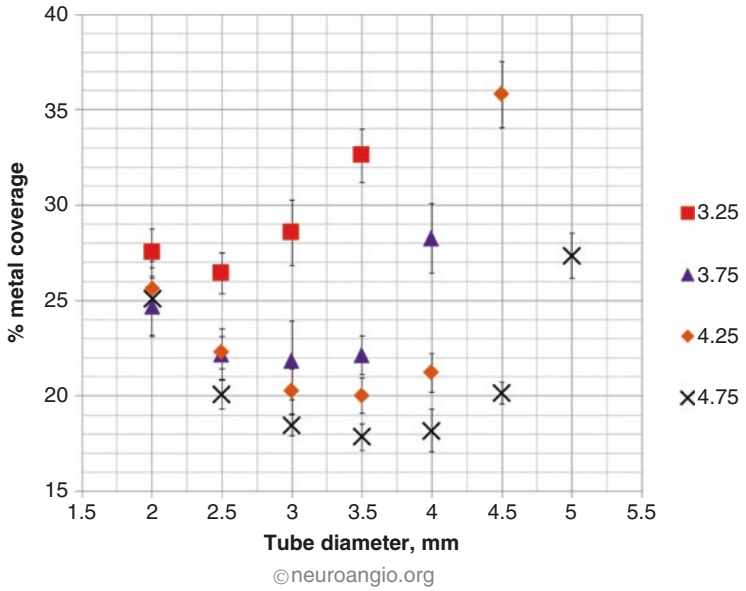


Fig. 14.7 Reverse parabolic relationship between % metal coverage and diameter of target vessel for PEDs of different nominal sizes. The degree of metal coverage steeply declines when any Pipeline device is implanted in a vessel of smaller caliber compared with its nominal size, reaching near-minimum values for as little as 1 mm of oversizing (e.g., implanting a 4 mm device in a 3 mm vessel). Extreme oversizing will eventually produce an increase in metal coverage. For all scenarios, nominally smaller diameter devices have relatively larger metal coverage values than larger diameter ones. For example, a single 4.75 mm device will likely have coverage values in the 20% or below range, while a 3.25 mm device, even when implanted in a 2.5 mm vessel, will still produce >25% coverage. (©neuroangio.org used with permission)

devices of progressively larger diameters in order to achieve a more uniform construct coverage, thereby avoiding extremes of near-perfect braid overlap which produce no effective increase in coverage. Thus, multicoverage does not simply produce a new coverage number—rather, it yields a range of coverage values. This range is widest when identical diameter devices are chosen and becomes progressively tighter when devices of increasingly different diameters are selected (Table 14.1).

Experience with the Pipeline Embolization Device

To date, the PED has been used to treat aneurysms in tens of thousands of patients. Robust evidence of its enduring effectiveness and safety has been provided by the recently concluded PUFS trial [27–29], extending observations available from several earlier single-center series [13, 30] and the PITA trial [31].

PUFS [27] was a single-arm trial of Pipeline for large (>10 mm), wide-necked (>4 mm) aneurysms, involving specifically defined segments of the internal carotid artery (petrous through hypophyseal segments) felt by the US FDA to be appropriate

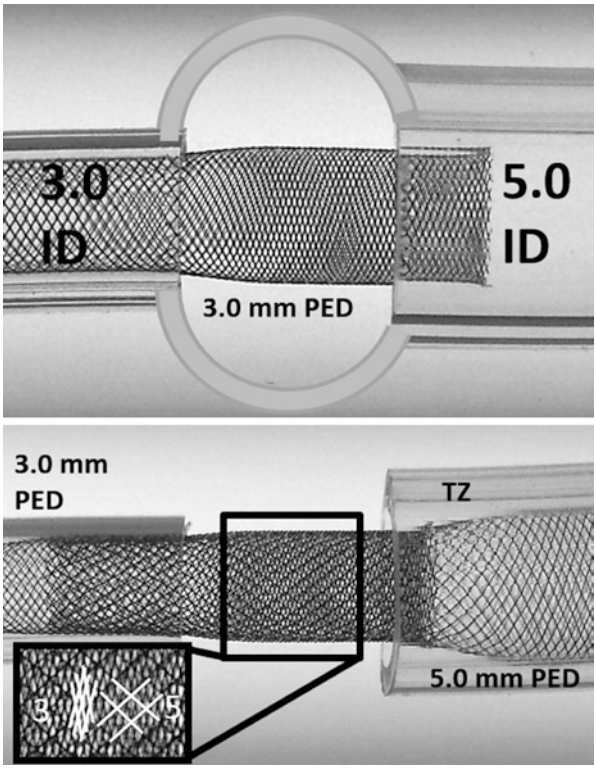


Fig. 14.8 A straightforward strategy for addressing landing zone mismatch using two devices, each appropriately sized to the parent artery. In (A), a 3.0 mm device is deployed from the 3.0 mm landing zone across the entire fusiform aneurysm. A 5.0 mm device is then telescoped into the 3.0 mm device, such that the transition zone TZ is shifted outside of the aneurysm, while the fusiform section is now double-covered. A third 5.0 mm device may be potentially placed across the transition zone TZ to increase coverage in this region

Table 14.1 Table of % metal coverage range achieved by using two overlapping PEDs in various diameter vessels

3 mm vessel	3.25	3.75	4.25	4.75
3.25	30–47%	30–40%	31–37%	34–37%
3.75		20–37%	30–37%	30–35%
4.25			21–35%	31–34%
4.75				20–36%
3.5 mm vessel	3.75	4.25	4.75	
3.75	24–41%	36–37%	33–34%	
4.25		22–36%	31–32%	
4.75			18–31%	
4 mm vessel	3.75	4.25	4.75	
3.75	38–46%	37–39%	36–37%	
4.25		21–35%	29–33%	
4.75			22–32%	
4.5 mm vessel	4.25	4.75		
4.25	36–57%	40–44%		
4.75		25–34%		

Employing devices of different diameter produces the most optimal narrow range of coverage values, minimizing the possibility of focal coverage deficiency

for the initial evaluation of the device. It incorporated a combined safety and efficacy endpoint, with efficacy defined as complete angiographic occlusion of the target aneurysm 180 days after treatment (without evidence of significant device-related stenosis or the use of adjunctive aneurysm implantables—such as coils and other stents). The use of a binary angiographic endpoint (occluded or not occluded) differentiates the PUFS from assorted trials of other endovascular aneurysm treatment devices, which traditionally have incorporated a gradient of occlusion in scoring treatment outcome. Enrollment in the PUFS trial was completed in August 2009 following treatment of 108 patients. Mean aneurysm size was 18.2 mm [22 aneurysms (20.4%) were giant (>25 mm)]. Mean neck size was 8.8 mm. The primary effectiveness endpoint of complete aneurysm occlusion (without device-related stenosis or adjunctive devices) at 6 months was achieved in 73.6% aneurysm, while 5.6% of patients experienced a major ipsilateral stroke or neurologic death. By 1 year, complete aneurysm occlusion was observed in 86.8% of aneurysms. Among the 76 aneurysms evaluated at 3 years angiographic follow-up, 93.4% were completely occluded [28]. At the 5-year conclusion of the PUFS trial [27], 95% of all aneurysms enrolled in the trial were completely occluded by follow-up angiography. There was no instance of aneurysm recanalization throughout the 5-year follow-up interval. The prevalence of major ipsilateral stroke or neurologic death was 5.6%, all occurring within 6 months. No additional adverse neurologic events were reported between 3 and 5 years posttreatment. These results have been supported by various single-center studies and meta-analyses reporting occlusion rates between 70% and 93% over intervals of 6–12 months.

Although impressive, considering the typical morphologies of aneurysms treated in these early studies, analysis of PED treatment failures [32] identified several independent predictors of incomplete aneurysm occlusion: fusiform morphology, decreasing dome to neck ratio, and the presence of previously implanted high-porosity stents in the aneurysmal segment. On an individual case basis, treatment failure tends to involve one of several common mechanisms: device mal-apposition, inadequate coverage, and the incorporation of a branch vessel(s) into the aneurysm fundus. Two of these features (device mal-apposition and inadequate coverage) potentially can be remedied by the operator at the time of treatment—mal-apposition by mechanical correction of an inadequately implanted device (angioplasty or J-wire modification) and, to address inadequate coverage of the aneurysm neck, the deployment of additional devices, either during the initial setting or at a later time (staged treatment). Moreover, various strategies (coil-assisted endoluminal treatment, staged occlusion of the aneurysm, and branch vessel run-off) may be employed to circumvent the effect of a fundal branch on treatment efficacy but require forethought in terms of therapeutic planning. The “Prospective study on Embolization of Intracranial Aneurysms with Pipeline” trial [33], sponsored by Medtronic to expand the US indications for the device, demonstrated 83.5% aneurysm occlusion at 12 months posttreatment, with a corresponding 2% morbidity/mortality rate, in unruptured wide-necked intracranial aneurysms

measuring ≤12 mm, located either in the ICA (up to the terminus) or in the vertebral artery proximal to and including the posterior inferior cerebellar artery (presented at the International Stroke Conference in 2017). In keeping with the overall smaller size of target aneurysms, fewer devices per aneurysm were required in PREMIER for 12-month occlusion rates comparable to PUFS (where a median of three devices/cases were used due to aneurysm complexity). Although conjecture, the substantially lower rate of complications in PREMIER, compared with PUFS and IntrePED [34], is likely due to evolving operator experience, the treatment of less complex target aneurysms, and the overall improvement in antiplatelet management.

Complications

In the initial PUFS communication, Becske et al. reported the primary safety endpoints of major ipsilateral stroke or neurologic death were encountered by 5.6% of patients enrolled. Subsequent meta-analyses, examining composite safety data from various trials and single-center series of flow diverter therapy (FDT), have reported morbidity and mortality rates ranging between 3–8% and 1.3–4%, respectively. Neurologically significant adverse events after PED therapy can be divided broadly into ischemic and hemorrhagic complications.

Ischemic Complications

Ischemic events reportedly complicate 2–3% of PED cases and may be attributed to in situ parent vessel (construct) thrombosis, emboli, or delayed ischemia resulting from device-related stenosis. Since publication of the PUFS trial and IntrePED registry [34], the rate of ischemic events appear to be falling [33], likely due to improved antiplatelet management (which at many centers includes some form of antiplatelet testing), increased operator experience, treatment of less complex aneurysms, and technical refinements facilitating safe, efficient device delivery (reducing the time of the procedure). Moreover, outside of the United States, availability of the surface-modified Pipeline Shield may contribute to fewer ischemic complications by lowering the intrinsic thrombogenicity of the phosphorylcholine-coated device. Beyond the acute stage, symptomatic device-related stenosis reportedly affects <1% of patients treated [27]. However, instances of asymptomatic delayed occlusion (beyond 1 year) may be observed in up to 5% of patients (particularly in those with giant fusiform aneurysms treated with long PED constructs), suggesting the necessity of continued surveillance and prolonged antiplatelet coverage for a subset of complex aneurysms (Fig. 14.9).

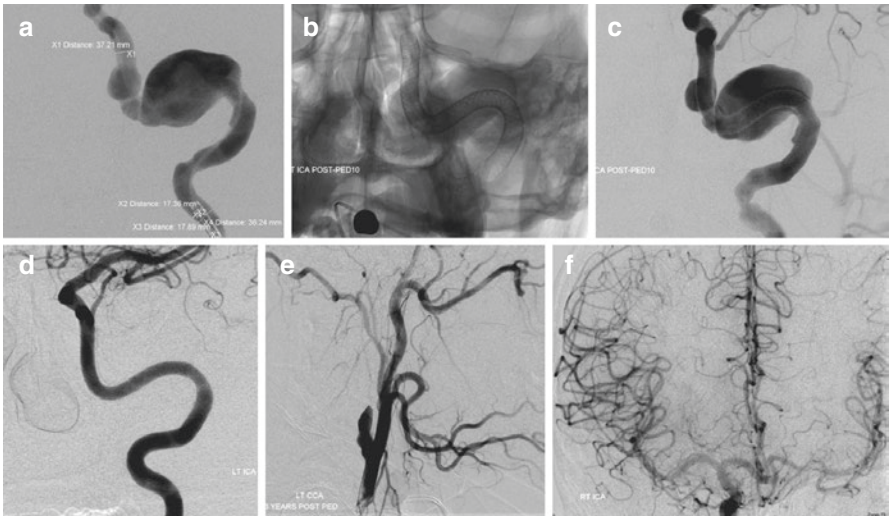


Fig. 14.9 Delayed occlusion of apparently successfully treated giant petrous/proximal cavernous segment aneurysm. Pre- (**a**) and immediate posttreatment (**b**, **c**) angiographic views. A 12-month posttreatment angiogram (**d**) shows apparent complete occlusion with no construct-related stenosis. A 3-year angiogram (**e**, **f**) shows parent vessel occlusion with asymptomatic collateral reconstitution of the left hemisphere

Hemorrhagic Complications

Hemorrhagic complications are observed in 2–3% of cases [27, 34] and include iatrogenic or spontaneous intraparenchymal bleeds and subarachnoid hemorrhage due to acute or delayed aneurysmal rupture.

Parenchymal hemorrhage after flow diversion is a rare but frequently devastating event, occurring with a frequency of 1–2% in most studies. Various mechanisms have been proposed, including subacute hemodynamic changes within the parent artery induced by implantation of the device across the aneurysm neck (reduction in Windkessel effect) and hemorrhagic conversion of ischemic lesions produced by periprocedural emboli (gas, thrombotic or related to foreign bodies). The association of emboli composed of hydrophilic coatings—originating from catheters used in the procedure—has been confirmed by autopsy of patients with fatal hemorrhages [35] and demonstrated by imaging to produce delayed inflammatory reactions (foreign body granulomas) in others [36] (Fig. 14.10). Typical parenchymal hemorrhages occur within 60 days of treatment and, given the ongoing use of dual antiplatelet regimens, are frequently massive and may be fatal. Management requires expertise in neurocritical care and vigilant antiplatelet monitoring to limit hemorrhage expansion while seeking to maintain device (and parent vessel) patency. Full antiplatelet reversal may be feasible when sufficient collaterals are present to permit asymptomatic occlusion of the parent artery with PED thrombosis.

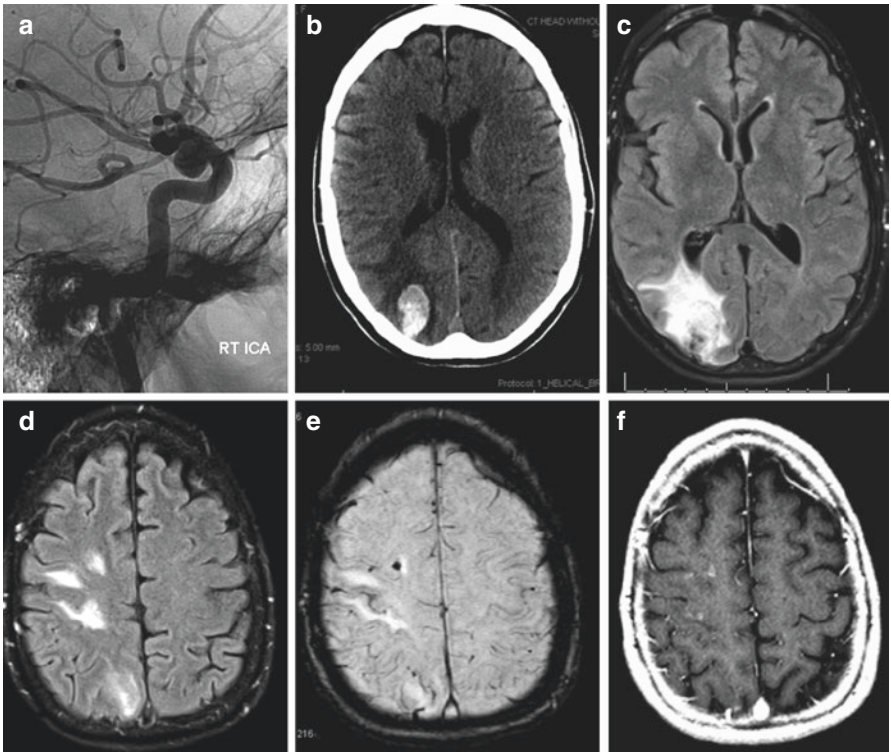


Fig. 14.10 (**a**–**f**) Right paraophthalmic aneurysm treated with PED. Two months post-procedure, the patient developed acute headache and quadrantanopia with a corresponding right occipital hemorrhage (**b**). MRI demonstrates extensive surrounding T2/FLAIR edema, as well as several other foci of edema (**d**), susceptibility (**e**), and enhancement (**f**) in the same hemisphere, characteristic of multiple foreign body emboli (hydrophilic catheter coating)

Delayed Aneurysm Rupture

The prevalence of delayed aneurysm rupture after FDT is estimated to be approximately 1% of cases (Fig. 14.11). While little is known about the etiology of such ruptures, several empirical observations are noteworthy. In a retrospective analysis, Kulcsar et al. [37] found 14 cases of delayed rupture among 1421 aneurysms treated by flow diversion therapy. The mean time to rupture was 60 days, with a median time of 9 days posttreatment. All ruptures occurred in aneurysms >10 mm diameter, with 13 of the 14 aneurysms characterized by diameters >19 mm. 12 of the 14 patients were newly symptomatic. Nine aneurysms were treated with a single device, four with two devices, and one with three devices. Of the 13 patients experiencing subarachnoid hemorrhage (one rupture resulted in a carotid-cavernous sinus fistula), 10 died, 2 remained in a vegetative state, and 1 clinically recovered.

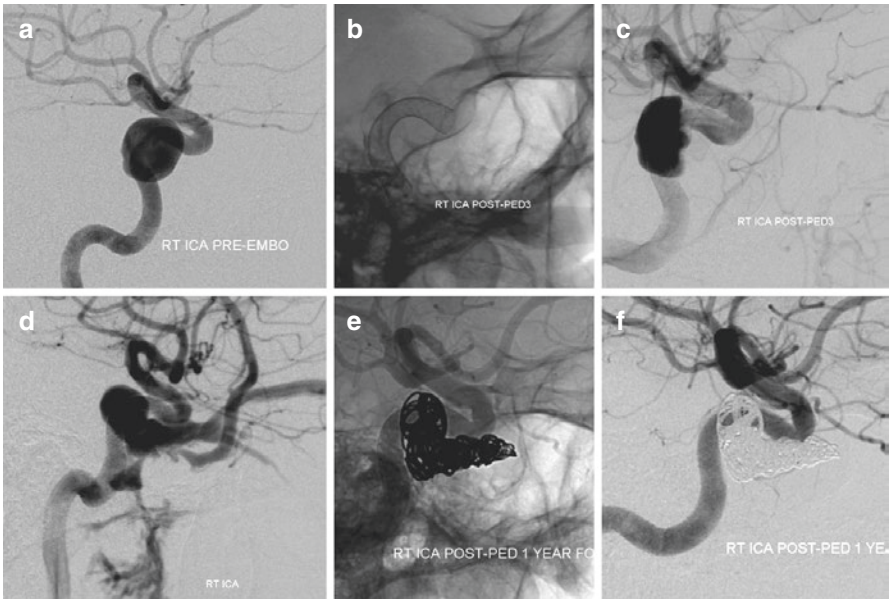


Fig. 14.11 Right cavernous aneurysm before (**a**) and after (**b**, **c**) PED treatment. A 6-month follow-up angiogram (**d**) shows aneurysm rupture with secondary direct carotid-cavernous fistula formation. The fistula was closed by transvenous coil embolization (**e**, **f**)

Parenthetically, although delayed aneurysmal rupture is a concern in FDT of large aneurysms and deservedly garnishes significant attention, delayed ruptures also have been observed after treatment of complex aneurysms by other means. In their report of the results with deconstructive treatment of giant and large internal carotid artery aneurysms with the excimer laser-assisted bypass technique, van Doormsal et al. [38] observed 1 fatal and 2 nonfatal postoperative aneurysm bleeds among 33 patients treated. Additionally, Heran et al. [39] reported 2 deaths from delayed aneurysm rupture (one at 1 month and the other at 5 months posttreatment) among 16 patients with large ophthalmic segment aneurysms undergoing coil-endosaccular embolization (with mostly incomplete angiographic occlusion). Collectively, these diverse instances of delayed rupture (all involving large aneurysms) suggest the presence of a fragile subset of complex aneurysms which are at near-term risk of hemorrhage—either spontaneously (accounting for the natural history risk of large aneurysm rupture) or after treatment by an immediately non-definitive intervention—which itself may independently contribute to the rupture risk. Recall that FDT and forms of deconstructive aneurysms treatment, where the lesion is not completely isolated proximally and distally from the circulation, are initially incomplete and require time to evolve into definitive cure.

Treatment Limitations

The advantages of FDT in providing durable, anatomically correct occlusion of large and giant cerebral aneurysms demonstrated in PUFS had led to much interest in the expanded use of these devices for the treatment of aneurysms beyond the ICA for which there currently are not acceptable treatment options.

Experience in the Posterior Fossa

Initial enthusiasm following the successful use of MPEDs to treat highly complex fusiform basilar aneurysms [40, 41] has been dampened by the high incidence of major ischemic and hemorrhagic complications when applied to a certain holobasilar, fusiform subset (Fig. 14.12) [42]. Increasingly, experience with posterior fossa

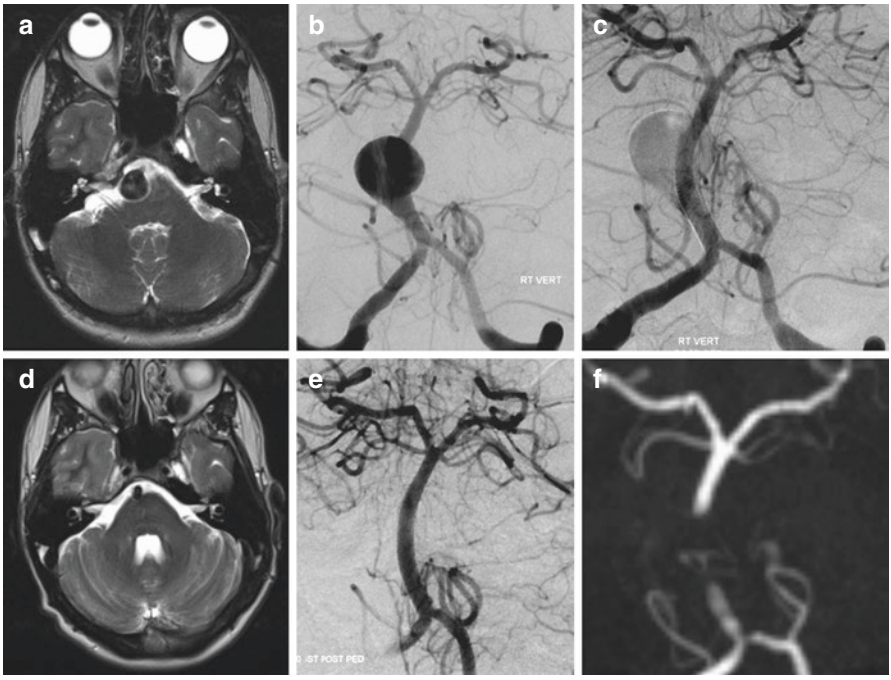


Fig. 14.12 Mid-basilar aneurysm presenting with a CNVI palsy, pre- (**a**, **b**) and immediately posttreatment (**c**) with overlapping PEDs. Delayed posttreatment MR (**d**), angiogram (**e**), and time-of-flight noncontrast MRA (**f**) demonstrating complete aneurysm occlusion with reduction in mass effect. The concurrent MRA shows typical effects of magnetic shielding within the pipeline construct, with robust flow-related enhancement immediately proximally and distally, thereby implying vessel patency

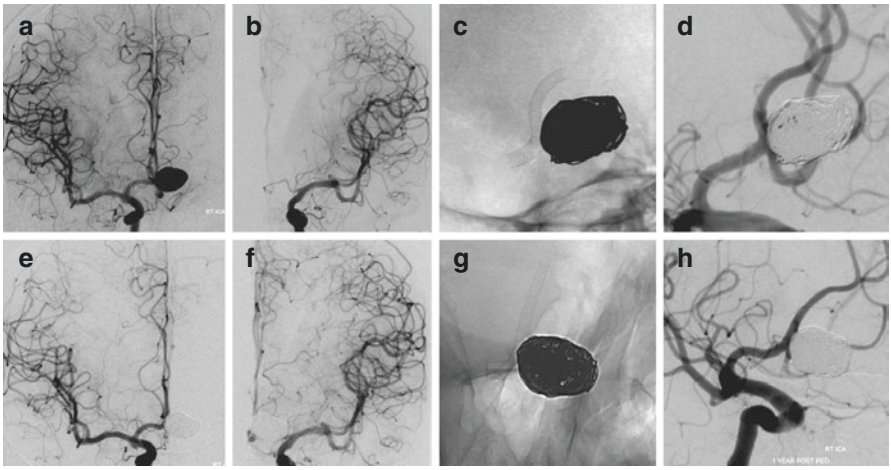


Fig. 14.13 (**a**–**h**): Large anterior communicating aneurysm with a dominant right A1 segment, treated by right A2 to A1 PED placement and coiling. Immediate posttreatment angiogram continues to demonstrate right A1 dominance (**d**). One year later, the aneurysm remains fully occluded. There has been interval hemodynamic rearrangement with right A1 role now limited to ipsilateral anterior cerebral artery support (**e**), while the left A1 has undergone compensatory enlargement and now supplies the entire distal left anterior cerebral artery territory (**f**)

aneurysms is leading to recognition of the heterogeneity of these lesions and providing insight into prognostic features indicating the likelihood of treatment success [43–45].

While recent results from the PREMIER trial [33] as well as the experience outside the United States support the use of MPEDs in the management of smaller, unruptured aneurysms, the application of these devices in the management of bifurcation aneurysms remains investigational (Fig. 14.13). Moreover, due to the time course of aneurysm occlusion after FDT and requirements for antiplatelet medications, their use in the setting of subarachnoid hemorrhage is likely to remain somewhat limited [46, 47]. Nevertheless, even in this setting, the adjunctive use of MPEDs—coupled with other embolic agents, either concomitantly or as part of a staged procedure—may find utility in aneurysmal SAH. For complex ruptured aneurysms, a strategy may involve coiling the aneurysm as completely as possible, with or without balloon assistance, in the acute setting—followed by staged MPED placement 2–4 weeks later—to reduce the likelihood of recanalization, once clinical issues related to the management of SAH (placement of an intraventricular drain for the treatment of hydrocephalus or subsequent angioplasty for treatment of SAH-associated vasospasm) have resolved and antiplatelet drugs may be more safely administered. Furthermore, MPEDs (coupled with acute induction of antiplatelet coverage) increasingly are assuming a primary role in the management of SAH resulting from rupture of blister aneurysms—particularly in settings where the parent vessel cannot be safely sacrificed due to poor collateral support (Fig. 14.14).

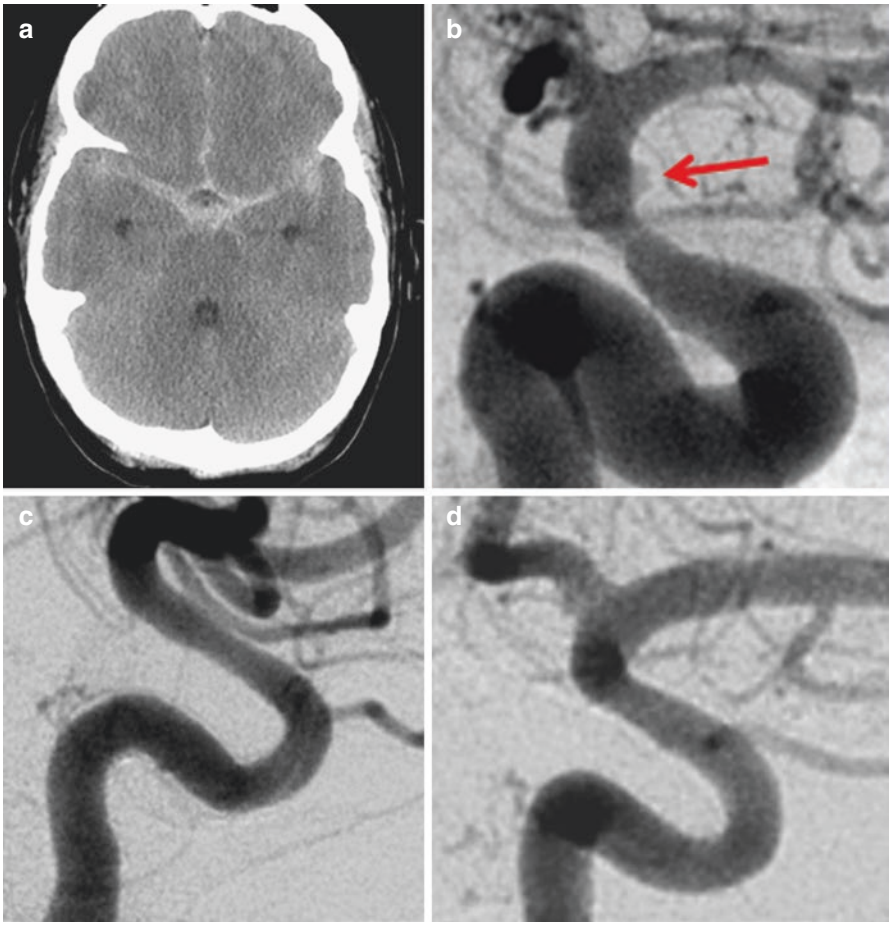


Fig. 14.14 (**a**–**d**): Dorsal wall blister aneurysm before (**b**) and 3 months following (**c**, **d**) Pipeline embolization. Three telescoped devices were used

Conclusions

As documented by the PUFS trial and various single and multi-institutional registries, FDT, in contrast to the often limited results of coil-endosaccular, offers high rates of complete and durable occlusion of large, complex-neck aneurysms, with comparatively lower rates of treatment-associated major morbidity and mortality [48–50], with the added benefit of relief from mass effect. Experience from the PREMIER trial and outside the Unites States suggests these benefits may be generalized to a larger population of cerebral aneurysms, and, thus, in the future will likely play an ever larger role in aneurysm treatment [46]. Nevertheless, several issues regarding their use will require additional experience and further evaluation:

the ideal number of devices (degree of coverage, critical porosity) necessary for definitive aneurysm occlusion, the necessity and duration of antiplatelet coverage, the role of antiplatelet testing, indications for adjunctive coiling, and the spectrum of aneurysm morphologies and locations preferentially addressed by FDT.

References

1. Molyneux A, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. J Stroke Cerebrovasc Dis. 2002;11(6):304–14.
2. Molyneux AJ, et al. Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial: results of a prospective observational study in 20 European centers. AJNR Am J Neuroradiol. 2004;25(1):39–51.
3. White PM, et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. Lancet. 2011;377(9778):1655–62.
4. Aguilar Perez M, et al. The Medina Embolic Device: early clinical experience from a single center. J Neurointerv Surg. 2017;9(1):77–87.
5. Szikora I, et al. Combined use of stents and coils to treat experimental wide-necked carotid aneurysms: preliminary results. AJNR Am J Neuroradiol. 1994;15(6):1091–102.
6. Mericle RA, et al. Temporary balloon protection as an adjunct to endosaccular coiling of wide-necked cerebral aneurysms: technical note. Neurosurgery. 1997;41(4):975–8.
7. Wanke I, et al. Treatment of wide-necked intracranial aneurysms with a self-expanding stent system: initial clinical experience. AJNR Am J Neuroradiol. 2003;24(6):1192–9.
8. Benitez RP, et al. Endovascular occlusion of wide-necked aneurysms with a new intracranial microstent (Neuroform) and detachable coils. Neurosurgery. 2004;54(6):1359–67. discussion 1368.
9. Fiorella D, et al. Usefulness of the Neuroform stent for the treatment of cerebral aneurysms: results at initial (3-6-mo) follow-up. Neurosurgery. 2005;56(6):1191–201. discussion 1201–2.
10. Shapiro M, et al. Stent-supported aneurysm coiling: a literature survey of treatment and follow-up. AJNR Am J Neuroradiol. 2012;33(1):159–63.
11. Ansari SA, et al. *Thrombosis of a fusiform intracranial aneurysm induced by overlapping neuroform stents: case report*. Neurosurgery. 2007;**60**(5):E950–1. discussion E950–1.
12. Fiorella D, et al. Endovascular reconstruction with the Neuroform stent as monotherapy for the treatment of uncoilable intradural pseudoaneurysms. Neurosurgery. 2006;59(2):291–300. discussion 291–300.
13. Lylyk P, et al. Buenos Aires experience with the Neuroform self-expanding stent for the treatment of intracranial aneurysms. J Neurosurg. 2005;102(2):235–41.
14. Fiorella D, Albuquerque FC, McDougall CG. Durability of aneurysm embolization with matrix detachable coils. Neurosurgery. 2006;58(1):51–9. discussion 51–9.
15. Kallmes DF, et al. A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. Stroke. 2007;38(8):2346–52.
16. Barath K, et al. Anatomically shaped internal carotid artery aneurysm in vitro model for flow analysis to evaluate stent effect. AJNR Am J Neuroradiol. 2004;25(10):1750–9.
17. Canton G, et al. Flow changes caused by the sequential placement of stents across the neck of sidewall cerebral aneurysms. J Neurosurg. 2005;103(5):891–902.
18. Lieber BB, Gounis MJ. The physics of endoluminal stenting in the treatment of cerebrovascular aneurysms. Neurol Res. 2002;24(Suppl 1):S33–42.
19. Lieber BB, et al. Particle image velocimetry assessment of stent design influence on intraaneurysmal flow. Ann Biomed Eng. 2002;30(6):768–77.

20. Rudin S, et al. Measurement of flow modification in phantom aneurysm model: comparison of coils and a longitudinally and axially asymmetric stent—initial findings. Radiology. 2004;231(1):272–6.
21. Lopes DK, et al. Fate of branch arteries after intracranial stenting. Neurosurgery. 2003;52(6):1275–8. discussion 1278–9.
22. Wakhloo AK, et al. Self-expanding nitinol stents in canine vertebral arteries: hemodynamics and tissue response. AJNR Am J Neuroradiol. 1995;16(5):1043–51.
23. Puffer RC, et al. Patency of the ophthalmic artery after flow diversion treatment of paraclinoid aneurysms. J Neurosurg. 2012;116(4):892–6.
24. Lieber BB, Sadasivan C. Endoluminal scaffolds for vascular reconstruction and exclusion of aneurysms from the cerebral circulation. Stroke. 2010;41(10 Suppl):S21–5.
25. Raz E, et al. Anterior choroidal artery patency and clinical follow-up after coverage with the pipeline embolization device. AJNR Am J Neuroradiol. 2015 May;36(5):937–42.
26. Shapiro M, et al. Variable porosity of the pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy. AJNR Am J Neuroradiol. 2014;35(4):727–33.
27. Becske T, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858–68.
28. Becske T, et al. Pipeline for uncoilable or failed aneurysms: 3-year follow-up results. J Neurosurg. 2017;127(1):81–8.
29. Becske T, et al. Long-term clinical and angiographic outcomes following pipeline embolization device treatment of complex internal carotid artery aneurysms: five-year results of the pipeline for uncoilable or failed aneurysms trial. Neurosurgery. 2017;80(1):40–8.
30. Szikora I, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR Am J Neuroradiol. 2010;31(6):1139–47.
31. Nelson PK, et al. The pipeline embolization device for the intracranial treatment of aneurysms trial. AJNR Am J Neuroradiol. 2011;32(1):34–40.
32. Shapiro M, Becske T, Nelson PK. Learning from failure: persistence of aneurysms following pipeline embolization. J Neurosurg. 2017;126(2):578–85.
33. Hanel R. Prospective, multi-center study of flow diversion for small and medium-sized aneurysms: results of the Premier trial, in International Stroke Conference (ISC) 2017. Houston; 2017.
34. Brinjikji W, et al. Risk factors for ischemic complications following pipeline embolization device treatment of intracranial aneurysms: results from the IntrePED study. AJNR Am J Neuroradiol. 2016;37(9):1673–8.
35. Hu YC, et al. Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the pipeline embolization device. J Neurosurg. 2014;120(2):365–74.
36. Shapiro M, et al. Foreign body emboli following cerebrovascular interventions: clinical, radiographic, and histopathologic features. AJNR Am J Neuroradiol. 2015;36(11):2121–6.
37. Kulcsar Z, Szikora I. The ESMINT retrospective analysis of delayed aneurysm ruptures after flow diversion (RADAR) study. EJMINT. 2012. http://www.ejmint.org/original-article/1244000088.
38. van Doormaal TP, et al. Giant aneurysm clipping under protection of an excimer laser-assisted non-occlusive anastomosis bypass. Neurosurgery. 2010;66(3):439–47. discussion 447.
39. Heran NS, et al. Large ophthalmic segment aneurysms with anterior optic pathway compression: assessment of anatomical and visual outcomes after endosaccular coil therapy. J Neurosurg. 2007;106(6):968–75.
40. Fiorella D, et al. Curative reconstruction of a giant midbasilar trunk aneurysm with the pipeline embolization device. Neurosurgery. 2009;64(2):212–7. discussion 217.
41. McAuliffe W, Wenderoth JD. Immediate and midterm results following treatment of recently ruptured intracranial aneurysms with the pipeline embolization device. AJNR Am J Neuroradiol. 2012;33(3):487–93.

42. Siddiqui AH, et al. Panacea or problem: flow diverters in the treatment of symptomatic large or giant fusiform vertebrobasilar aneurysms. J Neurosurg. 2012;116(6):1258–66.
43. Chalouhi N, et al. Treatment of posterior circulation aneurysms with the pipeline embolization device. Neurosurgery. 2013;72(6):883–9.
44. Albuquerque FC, et al. A reappraisal of the pipeline embolization device for the treatment of posterior circulation aneurysms. J Neurointerv Surg. 2015;7(9):641–5.
45. Phillips TJ, et al. Safety of the pipeline embolization device in treatment of posterior circulation aneurysms. AJNR Am J Neuroradiol. 2012;33(7):1225–31.
46. Tumialan LM, et al. Intracranial hemorrhage associated with stent-assisted coil embolization of cerebral aneurysms: a cautionary report. J Neurosurg. 2008;108(6):1122–9.
47. Rouchaud A, et al. Delayed hemorrhagic complications after flow diversion for intracranial aneurysms: a literature overview. Neuroradiology. 2016;58(2):171–7.
48. Pelz DM, Lownie SP, Fox AJ. Thromboembolic events associated with the treatment of cerebral aneurysms with Guglielmi detachable coils. AJNR Am J Neuroradiol. 1998;19(8):1541–7.
49. Qureshi AI. Editorial comment—thromboembolic events during neuroendovascular procedures. Stroke. 2003;34(7):1728–9.
50. Soeda A, et al. Thromboembolic events associated with Guglielmi detachable coil embolization of asymptomatic cerebral aneurysms: evaluation of 66 consecutive cases with use of diffusion-weighted MR imaging. AJNR Am J Neuroradiol. 2003;24(1):127–32.

Chapter 15
Dissecting Pseudoaneurysms and Blister Aneurysms

Amgad El Mekabaty, Gabor Toth, Dheeraj Gandhi, Alexander Coon, and Ferdinand K. Hui

A. El Mekabaty
Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, Baltimore, MD, USA

Department of Radiology and Radiological Sciences, University Hospital of Basel, Basel, Switzerland

G. Toth
Cerebrovascular Center, Cleveland Clinic Lerner College of Medicine, Mayfield Heights, OH, USA
e-mail: tothg@ccf.org

D. Gandhi
Departments of Diagnostic Radiology and Nuclear Medicine, Neurology and Neurosurgery, Center of Metabolic Imaging and Therapeutics and Executive Committee Member for the Comprehensive Stroke Center, Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: dgandhi@jhmi.edu

A. Coon
Departments of Neurosurgery, Neurology, and Radiology, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: acoon@jhmi.edu

F. K. Hui (✉)
Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD, USA

Carey School of Business, Johns Hopkins University, Baltimore, MD, USA

Department of Interventional Stroke, Johns Hopkins National Capital Region, Baltimore, MD, USA

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_15

Introduction and Pathophysiology of Dissecting Pseudoaneurysm

In normal cerebral arteries, the strongest layer of the arterial wall is the internal elastic lamina (IEL), which consists mainly of elastic fibers [1]. However, once the IEL is disrupted, these fibers may never reconnect [2, 3]. Therefore, the injured arterial wall is repaired with other matrix components in a biological reaction. Disruptions of the IEL do not always develop into detectable arterial dissections and many disruptions may be repaired without clinical manifestation [4]. The underlying etiology of intracranial artery dissection remains uncertain, but two mechanisms have been proposed: (1) an actual tear in the intima, which allows blood from the lumen into the vessel wall, or (2) rupture of the vasa vasorum in the arterial wall itself, which leads to an intramural hematoma, leading to an accumulation of blood and a separation of arterial layers within the vessel. Both mechanisms can occur simultaneously.

The vessel injury may result in (1) stenosis (where thrombus in the false lumen partially compresses flow within the true lumen), (2) complete occlusion (if thrombus in the false lumen completely obstructs flow within the true lumen), (3) false aneurysm formation (where accumulation of blood is subadventitial) with subsequent hemodynamic and embolic infarctions, or lastly (4) rupture with subsequent subarachnoid hemorrhage (SAH) [5–7]. Of the above, spontaneous dissecting pseudoaneurysms, or pseudoaneurysms occurring after trivial trauma, are by far the most commonly encountered scenario. In a recently published systematic review [8] of medically managed pseudoaneurysms in patients with ICA dissection, there were 40 pseudoaneurysms (24%) following a traumatic ICA dissection, while 126 (76%) were classified as having occurred following "spontaneous" ICA dissection. Connective tissue diseases such as Ehlers Danlos or fibromuscular dysplasia "FMD" may be other predisposing factors.

Radiological Findings and Histopathological Correlation

In contrast to aortic dissecting aneurysms extending toward the carotid arteries, opacification of both the false and true lumen occurs very rarely [9]. Mitzutani et al. [10], proposed a classification system for non-atherosclerotic intracranial aneurysms (fusiform and dissecting aneurysms), based on data of treated 85 aneurysms as well as on the pathological patterns of IEL and the state of the intima (Table 15.1):

1. *Type 1, classic dissecting aneurysms*: The most typical angiographic feature ($n = 65$) was a fusiform aneurysm with an irregular wall. Many of the aneurysms had an irregular stenotic portion near the proximal or distal end. The commonly observed pathological features were widespread disruption of the IEL without intimal thickening and the presence of a pseudolumen.

Table 15.1 Angiographic types of dissecting aneurysms and clinical/pathologic features

Type	Name	Clinical symptoms	Pathological features
Type 1	Classical dissecting aneurysm	Rupture Ischemia	Widespread disruption of IEL without intimal thickening
Type 2	Segment ectasia	Asymptomatic	Stretched/fragmented IEL with intimal thickening No luminal thrombus
Type 3	Dolichoectatic dissecting aneurysm	Symptomatic; progressive course	Fragmented IEL and multiple dissections of thickened intima Luminal thrombus
Type 4	Saccular aneurysm, arising from arterial trunk	Rupture	Minimal disruption of IEL without intimal thickening

IEL internal elastic lamina

2. *Type 2, segmental ectasia:* Angiographic findings (n = 8) showed a fusiform aneurysm with a smooth contour, usually larger in size than the Type 1 aneurysms. There was no evidence of luminal thrombus. Clinical and radiological follow-up showed no significant progression. Postmortem pathological examination revealed a stretched or fragmented IEL and a moderately thickened intima.
3. *Type 3, dolichoectatic dissecting aneurysms:* All of the aneurysms were located on the basilar artery and were conservatively followed up for 1–5 years. The most typical angiographic feature (n = 8) was torturous fusiform appearance with irregular contrast caused by organized laminar thrombus. Fragmentation of the IEL combined with multiple dissection of thickened intima, suggesting a chronic response to hemodynamic stress.
4. *Type 4, saccular aneurysms:* All cases (n = 4) manifested with SAH. On postmortem examination, one aneurysm lacked IEL in its dome.

Clinical Impact of Dissecting Pseudoaneurysm

The natural history of dissecting pseudoaneurysms is different from the more common "saccular" or "berry" aneurysms. The most important secondary feature of a dissecting pseudoaneurysm is its rupture status. While dissecting pseudoaneurysms without SAH tend to follow a benign course, cases presenting with SAH carry a high risk of rebleed. Some authors report a high rebleeding risk (between 24% and 57.1%) in the acute phase within 1 week after the initial SAH associated with a high mortality rate [11, 12]. Clinical data suggest that the rate of rebleeding of ruptured dissecting aneurysms decreases 1 week after SAH [2, 13]. Mitzutani et al., reported though nearly a 10% rebleeding rate after 1 month [12]. While the rupture of a dissecting aneurysm is occasionally the presenting event, formation of "pseudoaneurysm" or "dissecting aneurysm" is more commonly a delayed manifestation. Distal ischemic

strokes may also occur with pseudoaneurysms, and imaging studies suggest that more than 90% of infarcts due to dissection are thromboembolic rather than hemodynamic in origin [14, 15]. Other symptoms include headache, neck pain, or loss of consciousness, especially in the posterior circulation (17, 34). In a recent systematic review on the natural history of (mostly distal) ICA dissecting pseudoaneurysms [8], only 3% (5/166) of the pseudoaneurysms increased in size during follow-up, 52% (86/166) remained unchanged in size, 21% (35/166) decreased in size, while 19% (32/166) resolved completely. Only 2% of cases (4 patients) with a conservatively managed pseudoaneurysm after ICA dissection developed new neurological symptoms during follow-up. All four followed traumatic ICA dissection. No pseudoaneurysms that arose after spontaneous ICA dissection developed symptoms.

General Treatment Paradigms for Dissecting Pseudoaneurysms

Conservative and medical treatment is the most common initial management for asymptomatic and unruptured dissecting pseudoaneurysms. In a recent large series of 120 cases of ICA/vertebral artery (VA) dissecting pseudoaneurysms [16], all patients were placed on a regimen of antithrombotic treatment. Antiplatelet treatment was used in 59% of patients (Aspirin and/or Plavix), heparin and warfarin in 26.8%, and combined antiplatelet and anticoagulation agents in 14.3% of patients. Antithrombotic treatment strategies were distributed similarly among patients with or without history of trauma, extracranial or intracranial pseudoaneurysms, and carotid or vertebral artery (VA) involvement. Yet, antithrombotic therapy to prevent further ischemic events is contraindicated in some instances, and there is considerable uncertainty regarding the optimal management of asymptomatic pseudoaneurysms, particularly if they do not increase in size. Indications for endovascular or surgical management include ruptured, symptomatic, or large-size (>10 mm) pseudoaneurysm [17]. Approaches to endovascular treatment of dissecting aneurysms of the intracranial vessels can be divided into deconstructive (involving occlusion or sacrifice of the parent artery) and reconstructive (preserving blood flow through the parent vessel). Deconstructive endovascular techniques include proximal occlusion of the parent artery with detachable coils and/or balloons and occlusion of the dissected segment of the vessel with coils and/or balloons. Such procedures alone can be sufficient if important branch vessels are not originating from the vessel to be occluded, and collateral blood flow to the remainder of the peripheral circulation is adequate.

In contrast, reconstructive techniques (including stenting, coiling, flow diversion, or a combination) preserve the parent vessel. Surgical options include vessel ligation, clipping (Sundt clip and wrapping), reconstruction with interposition graft, and distal bypass. It should be noted that bland coiling of pseudoaneurysms may have a much higher post coiling growth and recurrence rate, as the aneurysmal sac may consist of adventitia only.

Specific Disease States

Intracranial Dissecting Pseudoaneurysms

Posterior Circulation Dissecting Aneurysms

Dissecting aneurysms have been reported in up to 28% of aneurysms of the intracranial VA, including the PICA [11, 18]. Most of the incidentally detected lesions occurred silently or with minor headache. Flemming et al. [19] reported that the annual prospective risk of hemorrhage from a vertebrobasilar artery non-saccular intracranial aneurysm is 0.9% and that an aneurysm diameter of at least 10 mm is strongly indicative of future rupture. In another series [20], aneurysms of <10 mm had a favorable clinical outcome, but aneurysms of >10 mm with symptoms due to mass effect had a risk of clinical deterioration and enlargement. Therefore, observation with serial radiologic examinations may be the management strategy of choice on patients with asymptomatic unruptured dissecting vertebrobasilar aneurysms (Fig. 15.1).

Medical management of patients with dissecting vertebrobasilar aneurysms who are asymptomatic or present only with pain remains controversial and is not well established. In one series [20], none of the patients (0/56) who presented with pain only at diagnosis had a hemorrhagic or ischemic stroke during observation (no antiplatelet or anticoagulation therapy were used), raising doubt about the necessity for anticoagulation or antiplatelet therapy for patients presenting with pain only. Kim et al. [21] reported a series of unruptured intracranial vertebrobasilar artery dissections (191 patients), including ischemic (n = 110) and nonischemic symptoms (n = 81), where 24.1% received endovascular treatment and 75.9% received medical therapy, with anticoagulation (n = 49), antiplatelet therapy (n = 48), or analgesics (n = 48). Of the medically treated group, 83 patients had aneurysmal dilatation that spontaneously resolved with normal luminal caliber in 9.6% (8/83), stable shape and size of aneurysm in 84.3% (70/83), and progressive enlargement of the dissecting pseudoaneurysm was noted in 6.1% (5 cases). Of these five patients, four were asymptomatic and one patient had brainstem compression symptoms from enlarging basilar dissecting aneurysm.

Proximal artery occlusion entails coil embolization of the non-diseased VA segment proximal to the dissection, which induces distal flow reversal and potentially promotes thrombosis of the aneurysm (Fig. 15.2). However, this technique does not immediately secure the aneurysm. Reports on 196 dissecting VA aneurysms treated with endovascular trapping or sacrifice have shown a re-hemorrhage rate of 3.1% [21–23]. The primary disadvantage of endovascular trapping though is the risk of ischemic stroke when the aneurysm involves a dominant VA [24]. In one report, incidence of ischemic stroke after endovascular trapping of dissecting VA aneurysms was reported at 8% overall and 38% when the aneurysm involved the PICA origin [22].

Recently, flow diversion devices have emerged as an alternative endovascular treatment of ruptured VA dissecting aneurysms [25–28]. Flow diverters preserve flow through the parent VA and branches, but evidence at this point for the efficacy of this

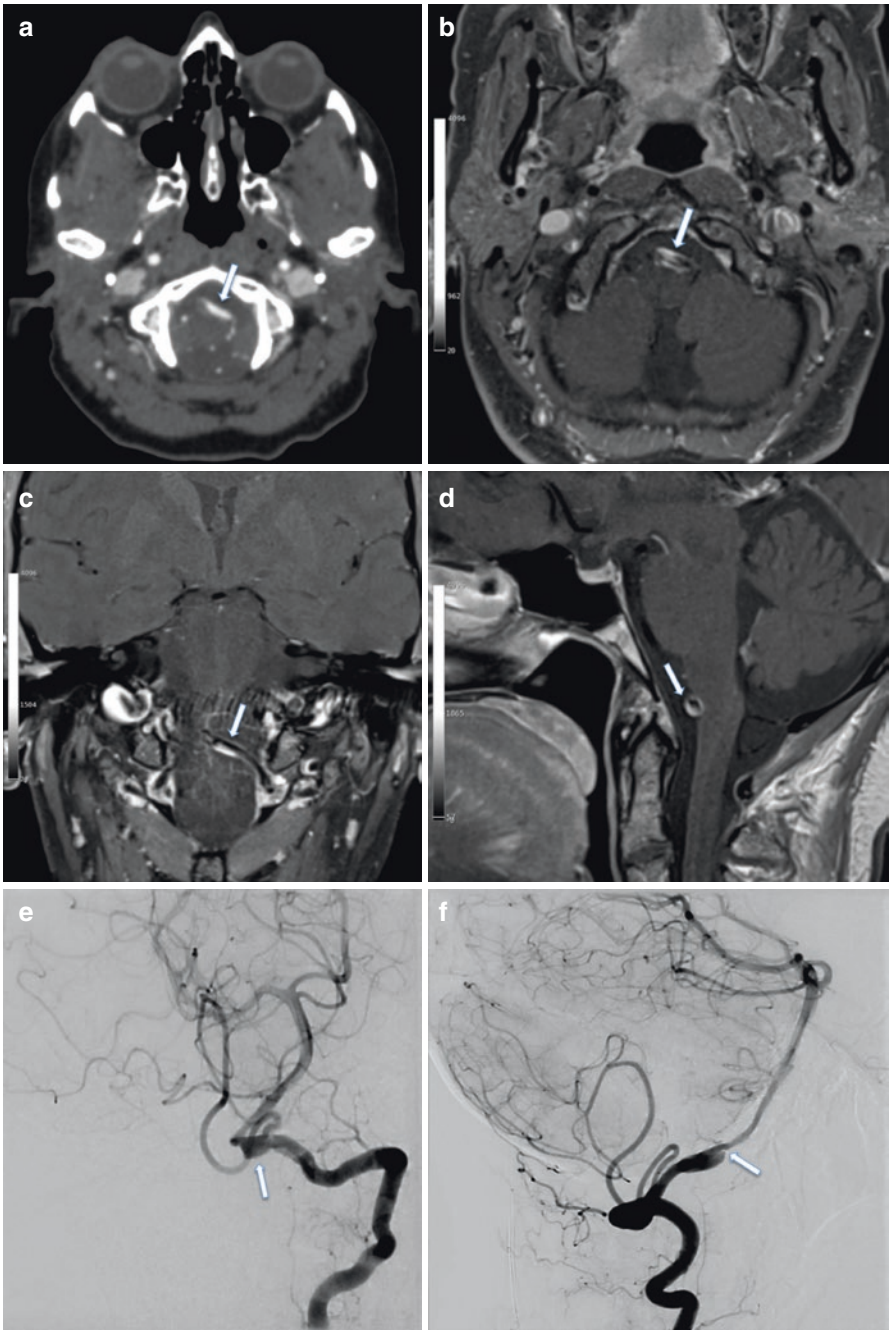


Fig. 15.1 A patient with an incidental left V4 segment fusiform dissecting aneurysm (arrow in **a**). On post-contrast T1-weighted sequence, the mural hematoma (arrow in **b**–**d**) can be appreciated. The digital subtraction angiography (DSA) with a left vertebral artery injection shows clearly the vessel dilatation (arrow in **e**) and the dissection flap (arrow in **f**). A decision was made treat conservatively

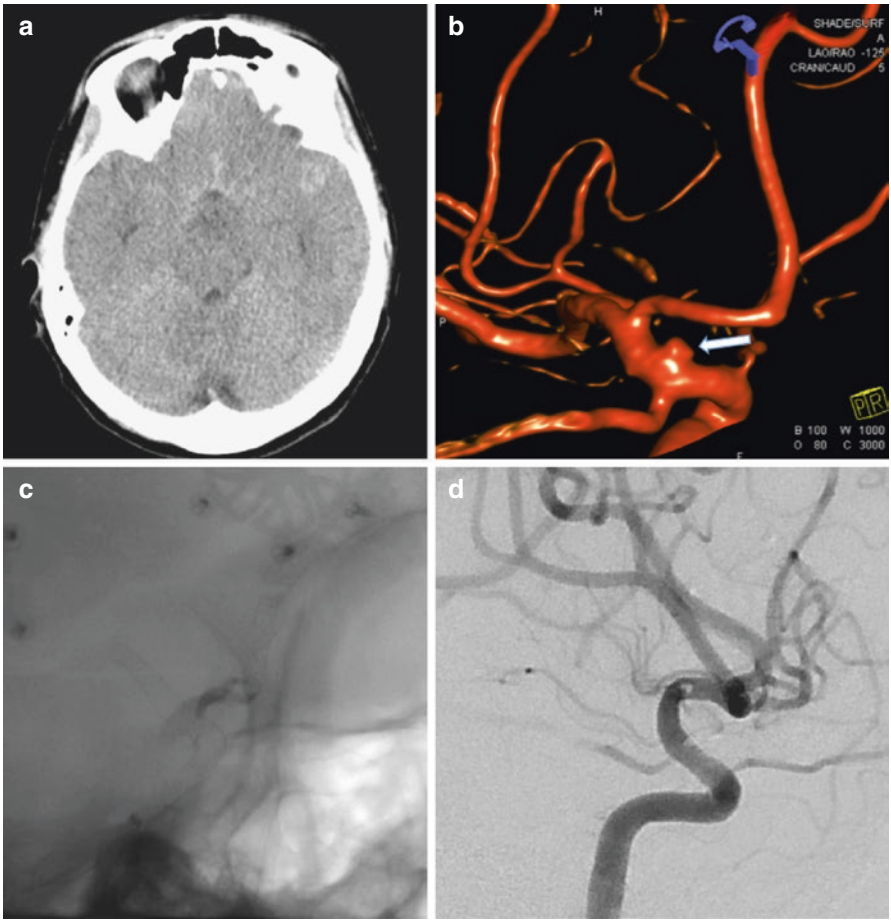


Fig. 15.2 A 56-year-old female with subarachnoid hemorrhage on non-contrast CT (**a**) due to ruptured blister-like aneurysm of the left ICA as seen on the 3D reconstruction of the rotational angiography (arrow in **b**). Clipping was attempted but was unsuccessful in occluding the aneurysm. Pipeline embolization device (PED) was placed in left ICA (**c**, notice the surgical clip). Eight-week follow-up demonstrates complete aneurysm occlusion (**d**)

device in preventing re-hemorrhage is limited to case reports [25, 26]. Flow diversion in basilar dissection is recommended in fetal PCA over sacrifice of parent vessel due to lack of filling through posterior communicating artery (PCOM) to pons. The optimal number of flow diverters necessary to treat such a dissection is unknown. Although overlapping flow diverters have incremental effect on flow diversion, there is an increased risk of perforator occlusion, especially in the perforator rich basilar artery. A relatively new MRI technique, vessel wall imaging [29], might play a role in assessing the vessel wall, especially in giant aneurysms before and after flow-diverter treatment.

Possible complications of flow diversion include device migration, immediate posttreatment aneurysm rupture due to mechanical stretch [30], and hemorrhagic

conversion of ischemic stroke. In patients presenting with SAH, hemorrhagic complications are exacerbated by post-procedural dual antiplatelet therapy.

Surgical treatment options include proximal clipping, trapping, wrapping, or resection with end-to-end anastomosis or bypass (e.g., PICA-to-occipital artery anastomosis or PICA reimplantation to the VA). A recent meta-analysis comparing the clinical outcome of patients with VA dissecting aneurysms treated with proximal occlusion and endovascular trapping found that proximal occlusion was associated with a larger proportion of poor outcomes and mortality ($p = 0.0403$) [31]. There are few case reports in literature about the use of Sundt clip and encircling aneurysm clips in dissecting aneurysm, but these methods are viewed as a last resort in exceptional cases where endovascular treatment is not available [32, 33].

Anterior Circulation Dissecting Pseudoaneurysms

Dissecting aneurysms involving the anterior cerebral artery (ACA) may be classified into three types [34–36]: type I, an extension of the ICA dissection to ACA (occur mostly in young adults and usually present with cerebral infarction); type II, dissection at the A1 segment (usually occurs in young women and often causes SAH); and type III, dissection from the A2 to A4 segment (predominantly in middle-age patients and mostly causes infarctions). Dissecting pseudoaneurysms of the middle cerebral artery (MCA) can also be classified into three types [36]: *type A*, originates from the M1 segment, which poses a treatment challenge in order to preserve the lenticulostriate perforators; *type B*, originates from the M2 segment or MCA bifurcation; and *type C*, originates from the M3 or distal segments. Ischemia has been proposed as the most common symptom in anterior circulation dissections [37], though some studies have observed a comparable occurrence of ischemia and SAH in the case of ACA dissecting pseudoaneurysms [35]. Some authors have suggested that the closer the occlusion is to the end organ, the more likely that ischemia will develop [38].

Dissecting aneurysms revealed by subarachnoid hemorrhage have been effectively treated conservatively with a good outcome and a low rate of rebleeding [39]. Earlier series [40, 41] have reported treatment with stents (single or multiple), presupposing that stents effectively tack down the torn vessel, resulting in aneurysm occlusion and preventing regrowth. This method, which can preserve the parent artery, may be an alternative to parent artery occlusion, especially for patients with high risks of complications after parent artery occlusion. However, there are some limitations, notably the high porosity of the standard stent, which may result in incomplete obliteration of the pseudoaneurysm. Treatment of anterior circulation dissecting pseudoaneurysms with a combination of stents and coils has recently been described in a small number of patients [42–44]. Byoun HS et al. [45] reported a small series of intracranial ICA dissecting pseudoaneurysms ($n = 6$) treated with stent-assisted coiling. There was only one intraoperative aneurysm rupture. Five patients had complete occlusion on follow-up, and good clinical outcome (mRS score 0–1) was achieved in all patients. While preservation of the cervical arteries to

the brain is the ideal goal to reach, there will still be a significant number of cases in which endovascular trapping of the carotid is considered the safest treatment option.

Surgical management is recommended if there is a high risk of rebleeding (rebleeding under conservative treatment, growing aneurysm, giant aneurysm, or uncontrolled hypertension). In a recent meta-analysis [8] of distal ICA dissecting aneurysm, only 9 out of 166 cases (5%) required surgical treatment; 5 underwent resection and interposition bypass, 3 were treated by carotid ligation, and 1 patient underwent extracranial to intracranial bypass.

Extracranial Dissections and Pseudoaneurysms

The estimated annual incidence of cervical artery dissection is 2.6 to 5 per 100,000 [46]; however this is probably an underestimation, as dissections may be asymptomatic. Approximately 1–2% of all ischemic strokes are attributed to cervical artery dissections but are responsible of up to 25% of strokes in young patients [46, 47]. The reported rate of pseudoaneurysm development following carotid and VA dissection varies widely between 5% and 40% [48, 49]. A large number of these pseudoaneurysms are detected at a later time point after the dissection, emphasizing the importance of follow-up imaging in dissection. After imaging documentation of extracranial dissecting pseudoaneurysm, the majority of these cases are reported to either remain stable or decrease in size [48–50], while others have reported an increase in pseudoaneurysm size on follow-up [16]. Rupture of these pseudoaneurysms occurs rarely, and the rate of ischemic complications of dissecting ICA pseudoaneurysms is low [16, 50]. In a large series of extra- and intracranial artery dissection (370 patients), 30.3% developed a dissecting pseudoaneurysm, 81.7% of which were extracranial (53.4%were located at C1; cervical division, 20.8% C2; petrous division, 10.8% at V2 segment and 6.7% at V3 segment and 5.8% at V4 segment) [16].

The most commonly utilized treatment in these cases is medical therapy. The 2014 American Heart Association/American Stroke Association Guidelines recommend an initially conservative treatment strategy in patients with ICA dissection [51], but there is no specific recommendation for ICA dissection pseudoaneurysms. Indication for either endovascular or surgical treatment would include enlargement on follow-up, thromboembolic ischemia and compressive symptoms from large aneurysms. In a recent report [52] on endovascular management of cervical dissections in 116 patients (93 had ICA and 23 had VA dissection), stent placement was used in 90% (n = 104) and coil occlusion (Fig. 15.3) of parent artery in 9.2% (n = 11). Stroke rate was 0.9% and mortality 3.4%, indicating that endovascular treatment is an effective treatment in specific indications. Surgical treatment is reserved for the management of symptomatic patients with lesions in accessible locations and often traumatic dissections (either blunt or penetrating); however, surgical artery preserving techniques are time-consuming compared to endovascular treatment [53].

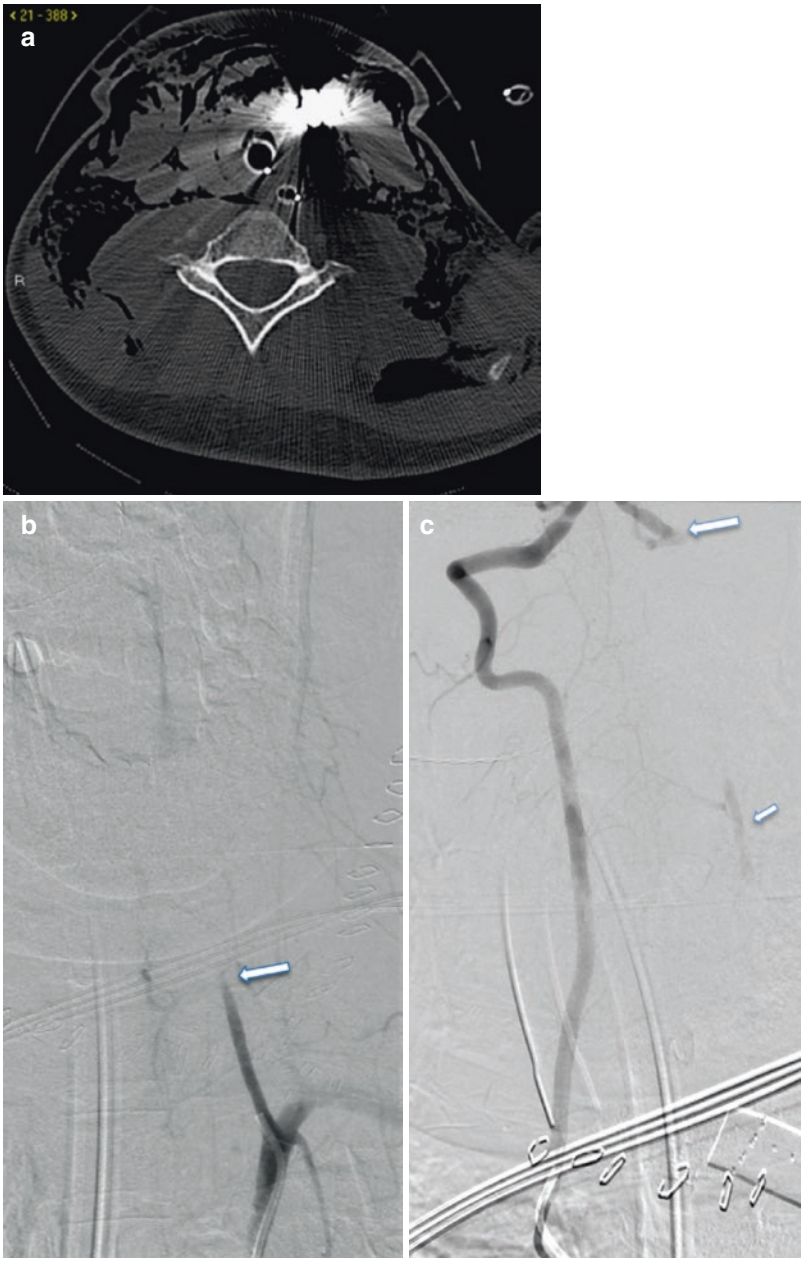


Fig. 15.3 A 23-year-old female with status post gunshot wound to the neck (**a**) presents with surgically uncontrollable bleeding from a left vertebral artery (VA) injury. On digital subtraction angiography (DSA), a selective left (**b**) and right (**c**) VA injection shows a tapered occlusion of left V1–V3 segments (long arrow in **b**–**c**) with partial reconstitution of V2 segment (short arrow in **c**) through the right VA. First coil trapping of the left V1 segment was performed (**d**), followed by coiling of the left V4 segment through catheterization of the right VA and basilar arteries (**e**–**f**). Successful control of bleeding was reached

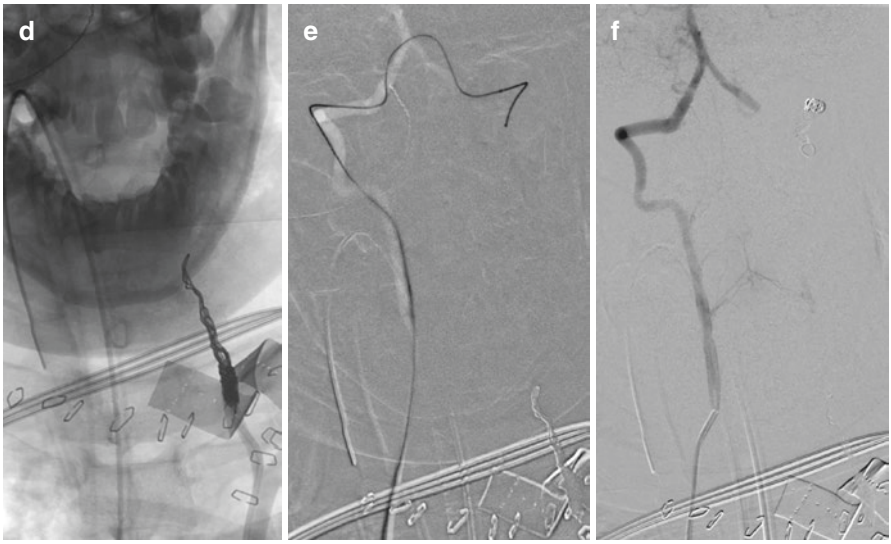


Fig. 15.3 (continued)

Blister Aneurysms

Blister "aneurysms" are rare, fragile, thin-walled, and often broad necked, arising at non-branching sites, typically discovered after rupture, and it is believed they represent a subadventitial dissection with a focal vessel wall defect due to disrupted internal elastic lamina and tunica media, with a thin residual wall consisting only of adventitia and fibrous tissue, and thus not a "true" aneurysm.

Blister "aneurysms" are usually found in the anterior circulation, along the dorsal aspect of the ICA in either the paraophthalmic or paraclinoid [54, 55] regions. Although blister-like aneurysms represents only 0.3–1% of all intracranial aneurysms, they account for about 0.9–6.5% of aneurysmal subarachnoid hemorrhage. Ruptured blister pseudoaneurysms are associated with a high mortality rate and spontaneous or treatment-related rebleed regardless of the treatment type [56–59].

Endovascular treatment of blister-like aneurysms involves stenting, coiling, trapping, and more recently flow diversion (Figs. 15.4 and 15.5). A recent meta-analysis [59] of endovascular treatment of ruptured blister-like aneurysms (265 procedures and mean dome size 2.4 mm) showed that the most common treatment option reported was stent-assisted coiling (44.2%), followed by flow diversion (25.8%) and stenting alone (18.8%). Other less frequently employed endovascular treatment options were deconstructive treatment (9.4%), coiling, with or without balloon assistance (6.3%), combined treatment (3.8%), and Onyx plus stenting (1.3%). As expected, endovascular deconstructive treatment carries a higher chance of immediate complete occlusion of the aneurysm than reconstructive treatment (77.3% vs.

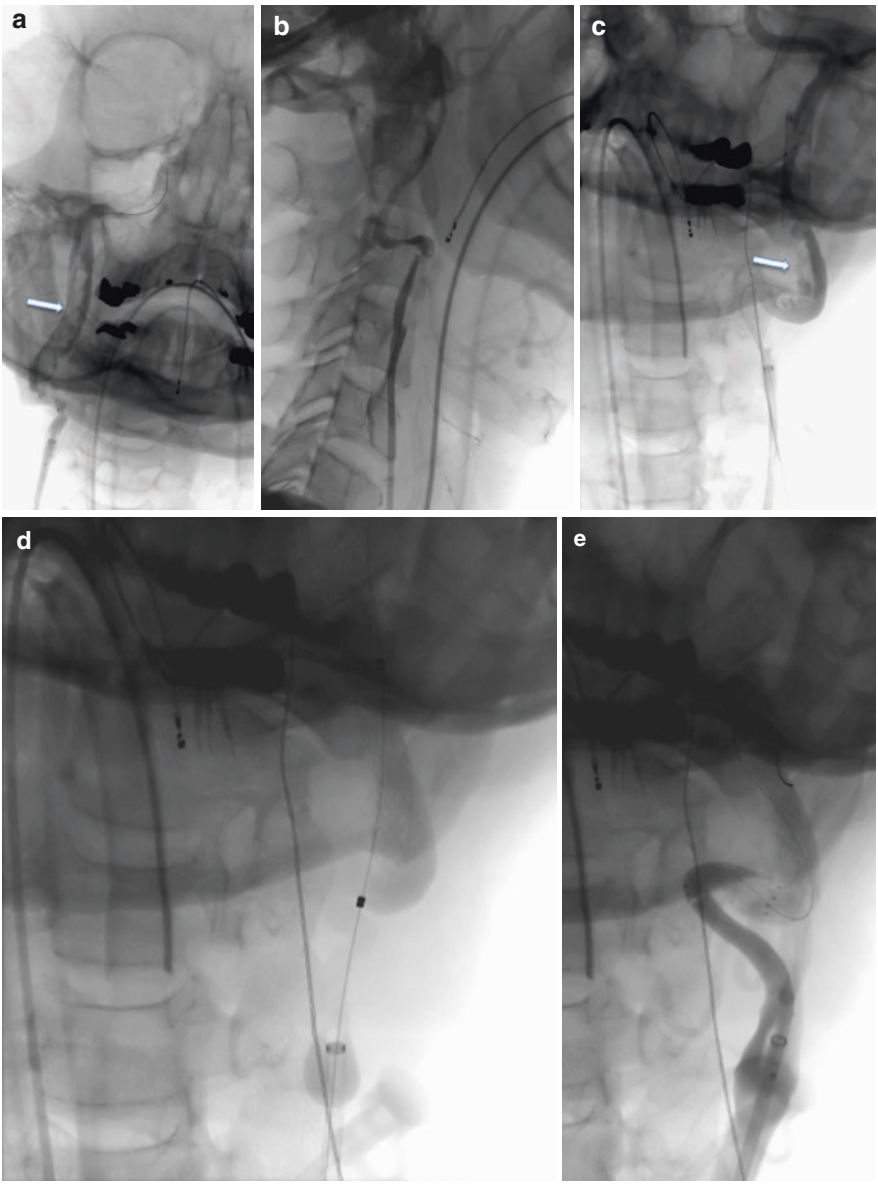


Fig. 15.4 A patient with symptomatic cervical internal carotid artery (ICA) fusiform dissecting aneurysms (right anteroposterior; AP in **a** and left lateral; **b** and AP; **c**) with irregular filling defect on digital subtraction angiography (DSA) representing clot formation (arrow in **a**, **c**). A double stent construct was used to oppose the clot and restore the lumen diameter of the left cervical ICA (**d**–**e**). The right cervical ICA dissecting aneurysm was managed conservatively

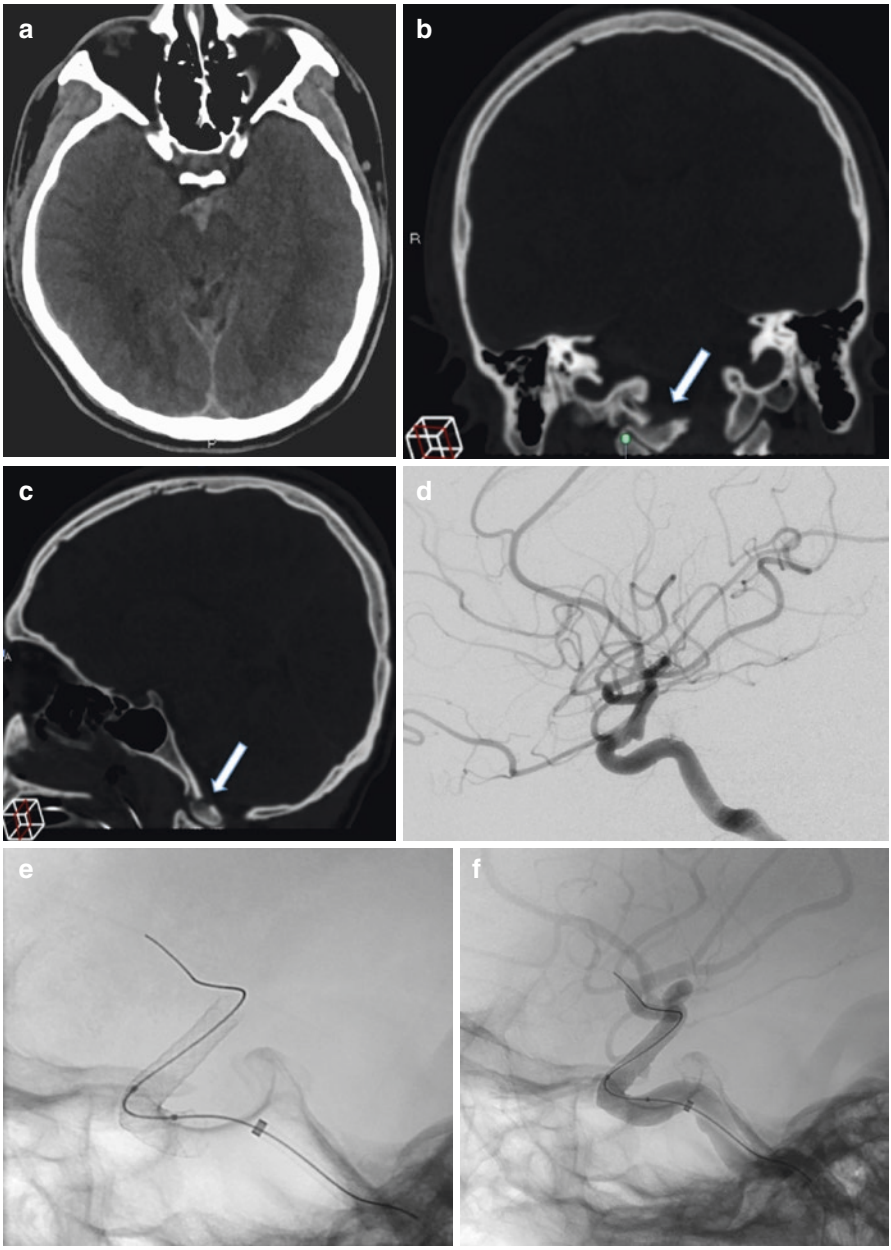


Fig. 15.5 A 21-year-old patient with motor vehicle accident and severe head trauma. (**a**) Non-contrast head CT showing subarachnoid hemorrhage, especially perimesencephalic and along the tentorium. (**b–c**) Head CT in bone window, reveling a dislocated right occipital condyle fracture extending into the clivus (arrow). (**d**) Diagnostic cerebral angiography shows a traumatic blister aneurysm of the communicating segment of the right ICA. (**e–f**) A week later, second angiography verified the persistence of the aneurysm with no dissection flap visible. After deployment of two flow diversion devices across the blister aneurysm (**e**), flow reduction into the aneurysm can be observed (**f**)

33%, $p = 0.0003$), yet it was associated with higher perioperative stroke (29.1% vs. 5%, $p = 0.04$). At follow-up there was no statistical difference in mid- to long-term aneurysm occlusion and retreatment or good neurological outcome. Stenting with or without coiling has a reportedly good outcome (usually mRS score 0–2) between 66% and 100% with mortality rate of 0–30%, while the rate of rebleed and retreatment ranged between 8% and 50% [59].

Recently, flow diversion has been described as a treatment option for blister "aneurysms," as it decreases the manipulation of the fragile wall of the blister-like aneurysm and preserves the parent vessel, reducing the rate of iatrogenic aneurysm rupture and strokes, respectively. In their meta-analysis, Rouchaud et al. [59] reported that treatment with flow diversion (mostly pipeline embolization device; Covidien) was associated a higher rate of mid- to long-term occlusion comparing to other endovascular reconstructive methods (90.8% vs. 69.7%, $p = 0.005$) and consequently lower retreatment rate. There was no statistically significant difference in regard to perioperative strokes, ICH, initial occlusion, or good clinical outcome. Disadvantages of flow diversion include obligatory dual antiplatelet therapy, possible perforator compromise, delayed aneurysm rupture (due to persistent flow into the aneurysm), in-stent thrombosis, and delayed parenchymal hemorrhage [54, 55, 59]. In regard to endovascular deconstructive treatment, it offers a higher initial occlusion rates in comparison with endovascular reconstructive methods, yet with associated higher rate of perioperative stroke [59]. Surgical treatment options for blister pseudoaneurysms include direct clipping, clip reinforced wrapping, and trapping, with or without bypass. It should be noted that because the blister is essentially adventitia only, clipping typically requires approximation of vessel that still contain media and intima and may result in some degree of luminal compromise. Recent reports on surgical treatment options had a range of good clinical outcome (mRS score 0–2) between 59% and 100% and an intraoperative rupture of 0–41% [60–62].

Conclusion

- Pseudoaneurysms differ from "true" aneurysms in that they do not contain the full complement of mural layers.
- Management of intracranial hemorrhagic pseudoaneurysms requires more aggressive management due to high re-rupture and aneurysm growth risk.
- Extracranial, asymptomatic pseudoaneurysms may be managed conservatively with medical therapy consisting of antiplatelet or anticoagulative therapies.
- Unruptured intracranial dissections, such as in the V4 segment, are often managed conservatively with antiplatelet agents.
- Long-term follow-up of dissections is needed to recognize the usually delayed development of dissecting pseudoaneurysms.
- Endovascular or open surgical treatment options include reconstructive and deconstructive methods and should be selected with attention to preserving adequate perfusion to the end organ while reducing risk of rupture, by reducing or

eliminating flow stress on the lesion. Treatment approach must then be carefully tailored based on individual patient vascular anatomy.
– Blister "pseudoaneurysms" are rare, fragile high-risk lesions. Endovascular options, especially flow diversion therapy, may offer higher occlusion and lower retreatment rate.

References

1. E. GL. Medial defects in the circle of willis and their relation to aneurysm formation. J Pathol Bacteriol. 1940;51(2):169–316.
2. Mitchell GM, McCann JJ, Rogers IW, Hickey MJ, Morrison WA, O'Brien BM. A morphological study of the long-term repair process in experimentally stretched but unruptured arteries and veins. Br J Plast Surg. 1996;49(1):34–40.
3. W.E. S. Pathology of the Cerebral Blood Vessels. St. Louis: C.V. Mosby; 1972.
4. Mizutani T, Kojima H, Asamoto S. Healing process for cerebral dissecting aneurysms presenting with subarachnoid hemorrhage. Neurosurgery. 2004;54(2):342–7. discussion 347–348.
5. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med. 2001;344(12):898–906.
6. Fusco MR, Harrigan MR. Cerebrovascular dissections – a review part I: spontaneous dissections. Neurosurgery. 2011;68(1):242–57. discussion 257.
7. Fusco MR, Harrigan MR. Cerebrovascular dissections: a review. Part II: blunt cerebrovascular injury. Neurosurgery. 2011;68(2):517–30. discussion 530.
8. Paraskevas KI, Batchelder AJ, Naylor AR. Fate of distal false aneurysms complicating internal carotid artery dissection: a systematic review. Eur J Vasc Endovasc Surg. 2016;52(3):281–6.
9. Lasjaunias P, Ter Brugge KG, Berenstein A. Surgical neuroangiography, vol. 2.1/2.2. Switzerland: Springer; 2004.
10. Mizutani T, Miki Y, Kojima H, Suzuki H. Proposed classification of nonatherosclerotic cerebral fusiform and dissecting aneurysms. Neurosurgery. 1999;45(2):253–9. discussion 259–260.
11. Yamaura I, Tani E, Yokota M, Nakano A, Fukami M, Kaba K, Matsumoto T. Endovascular treatment of ruptured dissecting aneurysms aimed at occlusion of the dissected site by using Guglielmi detachable coils. J Neurosurg. 1999;90(5):853–6.
12. Mizutani T, Aruga T, Kirino T, Miki Y, Saito I, Tsuchida T. Recurrent subarachnoid hemorrhage from untreated ruptured vertebrobasilar dissecting aneurysms. Neurosurgery. 1995;36(5):905–11. discussion 912-903.
13. Poole JC, Cromwell SB, Benditt EP. Behavior of smooth muscle cells and formation of extracellular structures in the reaction of arterial walls to injury. Am J Pathol. 1971;62(3):391–414.
14. Droste DW, Junker K, Stögbauer F, Lowens S, Besselmann M, Braun B, Ringelstein EB. Clinically silent circulating microemboli in 20 patients with carotid or vertebral artery dissection. Cerebrovasc Dis. 2001;12(3):181–5.
15. Srinivasan J, Newell DW, Sturzenegger M, Mayberg MR, Winn HR. Transcranial Doppler in the evaluation of internal carotid artery dissection. Stroke. 1996;27(7):1226–30.
16. Daou B, Hammer C, Chalouhi N, Starke RM, Jabbour P, Rosenwasser RH, Tjoumakaris S. Dissecting pseudoaneurysms: predictors of symptom occurrence, enlargement, clinical outcome, and treatment. J Neurosurg. 2016;125(4):936–42.
17. Mokri B, Piepgras DG, Houser OW. Traumatic dissections of the extracranial internal carotid artery. J Neurosurg. 1988;68(2):189–97.
18. Yamaura A. Diagnosis and treatment of vertebral aneurysms. J Neurosurg. 1988;69(3):345–9.
19. Flemming KD, Wiebers DO, Brown RD, Link MJ, Nakatomi H, Huston J, McClelland R, Christianson TJ. Prospective risk of hemorrhage in patients with vertebrobasilar nonsaccular intracranial aneurysm. J Neurosurg. 2004;101(1):82–7.

20. Kobayashi N, Murayama Y, Yuki I, Ishibashi T, Ebara M, Arakawa H, Irie K, Takao H, Kajiwara I, Nishimura K, et al. Natural course of dissecting vertebrobasilar artery aneurysms without stroke. AJNR Am J Neuroradiol. 2014;35(7):1371–5.
21. Kim BM, Kim SH, Kim DI, Shin YS, Suh SH, Kim DJ, Park SI, Park KY, Ahn SS. Outcomes and prognostic factors of intracranial unruptured vertebrobasilar artery dissection. Neurology. 2011;76(20):1735–41.
22. Madaelil TP, Wallace AN, Chatterjee AN, Zipfel GJ, Dacey RG, Cross DT, Moran CJ, Derdeyn CP. Endovascular parent vessel sacrifice in ruptured dissecting vertebral and posterior inferior cerebellar artery aneurysms: clinical outcomes and review of the literature. J Neurointerv Surg. 2016;8(8):796–801.
23. Lv X, Jiang C, Li Y, Wu Z. Clinical outcomes of ruptured and unruptured vertebral artery-posterior inferior cerebellar artery complex dissecting aneurysms after endovascular embolization. AJNR Am J Neuroradiol. 2010;31(7):1232–5.
24. Sugiu K, Tokunaga K, Watanabe K, Sasahara W, Ono S, Tamiya T, Date I. Emergent endovascular treatment of ruptured vertebral artery dissecting aneurysms. Neuroradiology. 2005;47(2):158–64.
25. Ducruet AF, Crowley RW, Albuquerque FC, McDougall CG. Reconstructive endovascular treatment of a ruptured vertebral artery dissecting aneurysm using the Pipeline embolization device. J Neurointerv Surg. 2013;5(4):e20.
26. Narata AP, Yilmaz H, Schaller K, Lovblad KO, Pereira VM. Flow-diverting stent for ruptured intracranial dissecting aneurysm of vertebral artery. Neurosurgery. 2012;70(4):982–8. discussion 988–989.
27. McTaggart RA, Santarelli JG, Marcellus ML, Steinberg GK, Dodd RL, Do HM, Marks MP. Delayed retraction of the pipeline embolization device and corking failure: pitfalls of pipeline embolization device placement in the setting of a ruptured aneurysm. *Neurosurgery*. 2013;**72**(2 Suppl Operative):onsE245–50. discussion onsE250-241.
28. Munich SA, Tan LA, Keigher KM, Chen M, Moftakhar R, Lopes DK. The pipeline embolization device for the treatment of posterior circulation fusiform aneurysms: lessons learned at a single institution. J Neurosurg. 2014;121(5):1077–84.
29. Mandell DM, Mossa-Basha M, Qiao Y, Hess CP, Hui F, Matouk C, Johnson MH, Daemen MJ, Vossough A, Edjlali M, et al. Intracranial vessel wall MRI: Principles and expert consensus recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol. 2017;38(2):218–29. doi:10.3174/ajnr.A4893. Epub 2016 Jul 28.
30. Fox B, Humphries WE, Doss VT, Hoit D, Elijovich L, Arthur AS. Rupture of giant vertebrobasilar aneurysm following flow diversion: mechanical stretch as a potential mechanism for early aneurysm rupture. BMJ Case Rep. 2014;2014
31. Hernández-Durán S, Ogilvy CS. Clinical outcomes of patients with vertebral artery dissection treated endovascularly: a meta-analysis. Neurosurg Rev. 2014;37(4):569–77.
32. Park PJ, Meyer FB. The Sundt clip graft. Neurosurgery. 2010;66(6 Suppl Operative):300–5. discussion 305.
33. Jafar JJ, Kamiryo T, Chiles BW, Nelson PK. A dissecting aneurysm of the posteroinferior cerebellar artery: case report. Neurosurgery. 1998;43(2):353–6.
34. Hirao J, Okamoto H, Watanabe T, Asano S, Teraoka A. Dissecting aneurysms at the A1 segment of the anterior cerebral artery – two case reports. Neurol Med Chir (Tokyo). 2001;41(5):271–8.
35. Ohkuma H, Suzuki S, Kikkawa T, Shimamura N. Neuroradiologic and clinical features of arterial dissection of the anterior cerebral artery. AJNR Am J Neuroradiol. 2003;24(4):691–9.
36. Zhu W, Liu P, Tian Y, Gu Y, Xu B, Chen L, Zhou L, Mao Y. Complex middle cerebral artery aneurysms: a new classification based on the angioarchitecture and surgical strategies. Acta Neurochir. 2013;155(8):1481–91.
37. Hensler J, Jensen-Kondering U, Ulmer S, Jansen O. Spontaneous dissections of the anterior cerebral artery: a meta-analysis of the literature and three recent cases. Neuroradiology. 2016;58:997.
38. Chaves C, Estol C, Esnaola MM, Gorson K, O'Donoghue M, De Witt LD, Caplan LR. Spontaneous intracranial internal carotid artery dissection: report of 10 patients. Arch Neurol. 2002;59(6):977–81.

39. Thines L, Zairi F, Taschner C, Leclerc X, Lucas C, Bourgeois P, Lejeune JP. Subarachnoid hemorrhage from spontaneous dissection of the anterior cerebral artery. Cerebrovasc Dis. 2006;22(5–6):452–6.
40. Mehta B, Burke T, Kole M, Bydon A, Seyfried D, Malik G. Stent-within-a-stent technique for the treatment of dissecting vertebral artery aneurysms. AJNR Am J Neuroradiol. 2003;24(9):1814–8.
41. Ahn JY, Han IB, Kim TG, Yoon PH, Lee YJ, Lee BH, Seo SH, Kim DI, Hong CK, Joo JY. Endovascular treatment of intracranial vertebral artery dissections with stent placement or stent-assisted coiling. AJNR Am J Neuroradiol. 2006;27(7):1514–20.
42. Ahn JY, Chung SS, Lee BH, Kim SH, Yoon PH, Joo JY, Kim JK. Treatment of spontaneous arterial dissections with stent placement for preservation of the parent artery. Acta Neurochir. 2005;147(3):265–73. discussion 273.
43. Lylyk P, Cohen JE, Ceratto R, Ferrario A, Miranda C. Combined endovascular treatment of dissecting vertebral artery aneurysms by using stents and coils. J Neurosurg. 2001;94(3):427–32.
44. Lanzino G, Wakhloo AK, Fessler RD, Hartney ML, Guterman LR, Hopkins LN. Efficacy and current limitations of intravascular stents for intracranial internal carotid, vertebral, and basilar artery aneurysms. J Neurosurg. 1999;91(4):538–46.
45. Byoun HS, Yi HJ, Choi KS, Chun HJ, Ko Y, Bak KH. Comparison of endovascular treatments of ruptured dissecting aneurysms of the intracranial internal carotid artery and vertebral artery with a review of the literature. J Korean Neurosurg Soc. 2016;59(5):449–57.
46. Lee VH, Brown RD, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. Neurology. 2006;67(10):1809–12.
47. Béjot Y, Daubail B, Debette S, Durier J, Giroud M. Incidence and outcome of cerebrovascular events related to cervical artery dissection: the Dijon Stroke Registry. Int J Stroke. 2014;9(7):879–82.
48. Guillon B, Brunereau L, Biousse V, Djouhri H, Lévy C, Bousser MG. Long-term follow-up of aneurysms developed during extracranial internal carotid artery dissection. Neurology. 1999;53(1):117–22.
49. Touzé E, Randoux B, Méary E, Arquizan C, Meder JF, Mas JL. Aneurysmal forms of cervical artery dissection: associated factors and outcome. Stroke. 2001;32(2):418–23.
50. Djouhri H, Guillon B, Brunereau L, Lévy C, Bousson V, Biousse V, Arrivé L, Tubiana JM. MR angiography for the long-term follow-up of dissecting aneurysms of the extracranial internal carotid artery. AJR Am J Roentgenol. 2000;174(4):1137–40.
51. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, Noorollah LD, Panagos PD, Schievink WI, Schwartz NE, et al. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2014;45(10):3155–74.
52. Moon K, Albuquerque F, Cole TS, Gross BA, McDougall CG. 355 endovascular management of cervical carotid and vertebral artery dissection: indications, techniques, and outcomes from a 20-year experience. Neurosurgery. 2016;63(Suppl 1):205.
53. Horowitz MB, Purdy PD. The use of stents in the management of neurovascular disease: a review of historical and present status. Neurosurgery. 2000;46(6):1335–42. discussion 1342–1333.
54. Linfante I, Mayich M, Sonig A, Fujimoto J, Siddiqui A, Dabus G. Flow diversion with pipeline embolic device as treatment of subarachnoid hemorrhage secondary to blister aneurysms: dual-center experience and review of the literature. J Neurointerv Surg. 2017;9(1):29–33.
55. Griessenauer CJ, Ogilvy CS, Foreman PM, Chua MH, Harrigan MR, He L, Fusco MR, Mocco JD, Stapleton CJ, Patel AB, et al. Pipeline embolization device for small intracranial aneurysms: evaluation of safety and efficacy in a multicenter cohort. Neurosurgery. 2017;105:232–7.
56. Ogawa A, Suzuki M, Ogasawara K. Aneurysms at nonbranching sites in the surpaclinoid portion of the internal carotid artery: internal carotid artery trunk aneurysms. Neurosurgery. 2000;47(3):578–83. discussion 583-576.
57. Ahn JY, Cho JH, Jung JY, Lee BH, Yoon PH. Blister-like aneurysms of the supraclinoid internal carotid artery: challenging endovascular treatment with stent-assisted coiling. J Clin Neurosci. 2008;15(9):1058–61.

58. McLaughlin N, Laroche M, Bojanowski MW. Blister-like aneurysms of the internal carotid artery – management considerations. Neurochirurgie. 2012;58(2–3):170–86.
59. Rouchaud A, Brinjikji W, Cloft HJ, Kallmes DF. Endovascular treatment of ruptured blister-like aneurysms: a systematic review and meta-analysis with focus on deconstructive versus reconstructive and flow-diverter treatments. AJNR Am J Neuroradiol. 2015;36(12):2331–9.
60. Yu J, Xu B, Guo Y, Xu K. Direct clipping of a blister-like aneurysm in the supraclinoid segment of the internal carotid artery: a clinical analysis of nine cases. Int J Clin Exp Med. 2015;8(11):21786–95.
61. Owen CM, Montemurro N, Lawton MT. Blister aneurysms of the internal carotid artery: microsurgical results and management strategy. Neurosurgery. 2017;80(2):235–47.
62. Pahl FH, de Oliveira MF, MeQ TG, Capel Cardoso AC, Rotta JM. Blister-like aneurysms: report of successful surgical treatment of consecutive cases and review of the literature. World Neurosurg. 2016;89:376–81.

Chapter 16
Infectious Intracranial Aneurysms: Epidemiology, Pathophysiology, and Management

Ali Alawieh and Alejandro M. Spiotta

Infectious intracranial aneurysms (IIAs) are rare cerebrovascular lesions caused by the spread of microbial infection to the arterial vessel wall leading to weakening and aneurysmal dilatation. IIAs were initially described by Osler in 1885 [1] as aneurysmal complications of infective endocarditis (IE) and were called "mycotic aneurysms" (MA). The term "mycotic" was not used to indicate a fungal etiology since MA are mostly caused by bacterial infections [2, 3]; rather, it described the appearance of these aneurysms that mimic fungal vegetation. Due to the rare nature of the disease, studies on IIAs are limited to case reports [2–10], case series [11–48], and retrospective studies [3, 49–69] that are not sufficient to draw generalizable conclusions on the epidemiology, management, and outcomes of IIAs. However, it is anticipated that IIAs account for 0.5–6.5% of all aneurysms [2, 3] and are associated with high risk of rupture and mortality [2, 4, 6, 69–71]. Treatment of IIAs may range from conservative medical management with antibiotic therapy and close monitoring, to endovascular embolization, to microsurgical clipping or excision of the aneurysms. In this chapter, we review the pathophysiology, epidemiology, and management of IIAs.

A. Alawieh
Medical Scientist Training Program, Medical University of South Carolina, Charleston, SC, USA

A. M. Spiotta (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: spiotta@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_16

Epidemiology

Based on retrospective studies, IIAs represent 0.5–6.5% of all intracranial aneurysms (IAs), do not show a significant gender bias, and span a wide age range from less than 1 year to more than 80 years of age [2, 3, 55, 56, 62, 63, 66, 69, 72–74]. The highest prevalence of IIA is among patients with infective endocarditis (IE), and around 2–10% of IE patients develop IIA, whereas up to 55% of patients may develop cerebral complications [3, 38, 51, 55, 61, 75]. The relatively low prevalence of IIAs is likely an underestimate since these aneurysms may be small, asymptomatic, or recede after antibiotic therapy without being detected [55, 72, 73]. Common predisposing factors for the development of IIAs are summarized in Fig. 16.1 and include conditions that may increase the likelihood of infectious spread to arterial vessels. In 69% of reported cases, the predisposing condition of IIAs is a valvular heart disease that leads to endocarditis. Other main predisposing factors include meningitis, major surgeries or an immunocompromised state, dental infections, and IV drug use (Fig. 16.1). Depending on the underlying predisposing factor, IIAs may develop secondary to septic emboli that are released from the valvular vegetation in IE and lodges in the vessel wall, result from contiguous spread of infection from a nearby cerebral focus (e.g., meningitis), or arise in the absence of an underlying infection (cryptogenic) [22, 49, 69]. The most common etiology for IIAs (around 68%) is septic embolization after acute or subacute infective endocarditis [3, 22]. A contiguous etiology of IIAs has been documented after meningitis, cavernous sinus

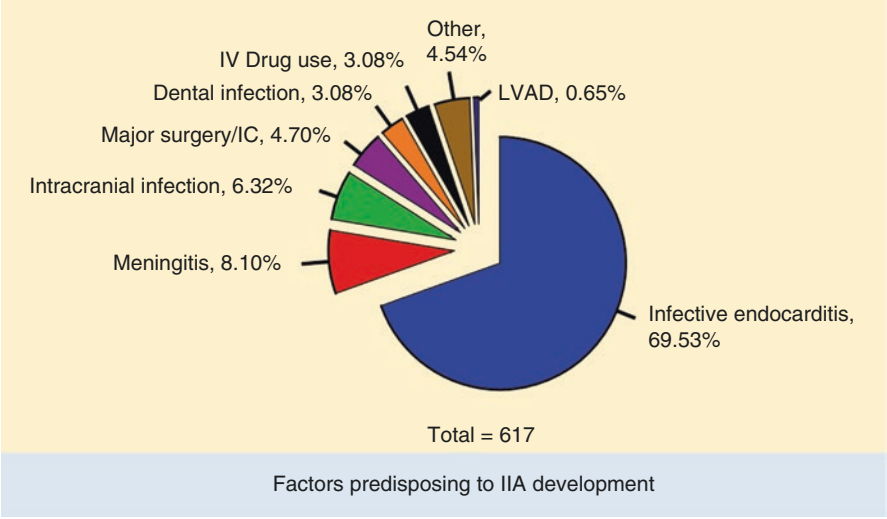


Fig. 16.1 Summary of risk factors predisposing to the development of IIAs in a total of 617 reported cases in the literature and summarized in recent systematic review [71]. IC: immunocompromised. LVAD: left ventricular assist device. Intracranial infections other than meningitis include cavernous sinus thrombophlebitis, orbital cellulitis, or sinusitis. (From Alawieh et al. [71], with permission)

thrombophlebitis, orbital cellulitis, cerebral abscesses, or post-neurosurgical infections [22, 69, 76, 77]. Cases of contiguous spread of infection are more commonly reported in pediatric and immunocompromised (IC) patients [22]. The last subset of IIAs, cryptogenic IIAs, are defined as IIAs that occur in the absence of systemic infection and constitute 10–12.5% of all IIAs [22, 77].

Pathophysiology

In general, IIAs are caused by weakening of the vessel wall due to microbial infection that could be bacterial, fungal, protozoal, or potentially viral in origin [2, 4, 23, 35, 36, 49, 62, 63, 78]. The most common infectious etiology of IIAs is bacterial with *Streptococcus viridans* accounting for the majority of cases followed by *Staphylococcus aureus* [2, 23]. *Streptococcus viridans* and *Staphylococcus aureus* are the most common causes of subacute and acute bacterial endocarditis, respectively, thus explaining their presence in the majority of IIAs [23]. Fungal infections, especially in IC patients [62], may also lead to IIAs with *Aspergillus* being the most common fungal etiology, followed by *Candida spp.* [23]. Few reports have documented IIAs in the setting of viral infections such as herpes zoster or HIV infection [35, 78]. One study has also reported IIA in the context of *Toxoplasma* infection [63]. Negative cultures have been documented in 10–19% of cases with IIAs, a finding that is likely due to the use of empirical antibiotic therapy or because IIAs may still develop in weakened vessel walls after the pathogen has been cleared [56, 62, 79, 80].

Infectious products released from pathogens and inflammatory mediators released by the immune system contribute to the degradation of the vessel wall and subsequent development of IIAs [2]. The pathophysiological mechanism of IIAs has been investigated using animal models and using histological findings from surgical and postmortem samples of human IIAs [3, 37, 81–83]. Using a canine aortic model, Molinari et al. [84] demonstrated that following septic emboli, pathogens escape through the vasa vasorum and infects the adventitial vessel layer first, thus triggering a local inflammatory reaction that propagates to the media and intima [49, 84]. In cerebral vessels that lack vasa vasorum, pathogens are hypothesized to infiltrate the adventitial layer via the Virchow-Robin spaces at the origin of bifurcating vessels [56]. Extravascular spread of intracranial infections after meningitis, cavernous sinus thrombophlebitis, or other sources may follow a similar mechanism infecting the proximal part of large vessels [49]. The alternative hypothesis is that septic emboli block cerebral vessels leading to an initial ischemic insult followed by an inflammatory reaction that propagates from the intima to the media and adventitia [49, 82, 83].

In either cases, inflammatory reaction including neutrophil infiltration to the vessel wall results in the degradation of the adventitia and media, fragmentation of the internal elastic lamina, and proliferation of the intima [2, 49, 56]. Pulsatile pressure against weakened or necrotic vessel walls leads to the development and

growth of IIAs. Since the muscular layer is involved in IIAs, they are often referred to as pseudoaneurysms. Proliferation of the intima and fibrosis of the vessel wall may also lead to thrombosis of the artery and can lead to ischemic sequel [22, 36]. Studies on the dynamics of IIA development by Molinari have shown that following septic emboli, IIAs may develop within 1–3 days in the absence of antibiotic therapy which can be extended to 7 days when antibiotics are administered [84].

Clinical and Radiographic Features

The majority of IIAs are small and asymptomatic and may not be detected except incidentally during the work-up of IE patients [4, 51, 55, 61, 85]. Symptoms develop from enlargement and mass effect, rupture, or downstream thromboembolic infarction. Neurological symptoms in IIA patients are commonly preceded by systemic symptoms such as fever and malaise [86]. Common presenting symptoms for IIAs patients are headache, fever, and focal neurological symptoms such as hemiplegia, hemiparesis, or speech problems [2, 3, 86, 87]. Ruptured IIAs account for around 5% of neurological complications of IE [38, 55, 72]. Ruptured IIAs may result in intracerebral hemorrhage (ICH, most common presentation), subarachnoid hemorrhage (SAH), or subdural hematoma. Due to the lack of prospective studies on IIAs, the rate of rupture is still unknown. Different case series have published a range of 2–75% risk of rupture of IIAs [6, 14, 62, 69]. In a recent systematic review, 75% of patients with IIAs had ruptured or bleeding aneurysms on presentation [71]. The high rate of rupture is attributed to the weakening of the vessel wall after inflammatory-mediated degradation and thinning [2]. There are no validated predictors for rupture of IIAs; yet, enlargement of the aneurysm of serial imaging but not the size alone appears to be a risk factor for subsequent bleed [16]. Slow filling of the aneurysms on angiography have been also suggested as a sign of low rupture risk [42]. Upon rupture, IIAs are associated with a high risk of mortality that may reach up to 80% [6, 14, 49, 69, 70]. This high fatality rate is significantly reduced to around 10–30% mortality in patients with unruptured IIAs [14, 49, 69, 70]. Determinants of outcome after IIAs include the location of aneurysm, the presence of pathogens within the vessel wall, the virulence of bacteria, the host immune defenses, and the efficacy of therapy [55].

Ruptured IIAs account for around 5% of neurological complications of IE [14, 88], and it is expected that the highest risk of rupture occurs within 2 weeks of cardiac surgery due to the maximal antifibrinolytic activity [59]. Pathophysiological and clinical studies have revealed that the time between the onset of IE and neurological symptoms from IIAs ranges between 1 and 30 days with a median of 21 days [37, 38, 56]. In some cases, IIAs may spontaneously occlude and lead to the thrombosis of the parent artery manifesting as an ischemic stroke [62].

Diagnosis

Although IIA are an uncommon complication of IE and other infectious conditions, the fatality of the disease, the high risk of rupture, and the potential avoidance of mortality by early treatment of the aneurysm make timely diagnosis of IIAs both important and necessary [21]. The gold standard for the diagnosis of IIAs is digital subtraction angiography (DSA) especially given the small size of the majority of aneurysm [4, 14, 39, 42, 58, 61, 87]. Due to the invasive nature of DSA, both CTA and MRA are more commonly used for screening of patients with IE and neurological symptoms [4, 14, 39, 42, 58, 61, 87]. However, comparative diagnostic studies have demonstrated that CTA and MRA were able to detect less than 45% and 35% of angiographically detected aneurysms, respectively, with CTA being superior to MRA in multiple studies [39, 51, 86, 89]. Therefore, DSA is indicated in patients with high index of suspicion for the presence of IIAs such as in the event of IE with neurological complaints, even with a normal CTA [2, 4, 61, 89]. The diagnosis of IIAs is more likely in patients with IE presenting with intracranial hemorrhage for which an angiography is used to rule out an IIA [2].

The differential diagnosis for IIAs includes arteritis and noninflammatory or circle of Willis aneurysms [4]. The presence of predisposing factors such as IE or meningitis makes the diagnosis of IIAs more likely [14, 42, 87]. However, specific angiographic features are characteristic of IIAs that include the distal location, the fusiform appearance, the presence of multiple aneurysms, and the change in size or morphology on serial angiography [14, 42, 87]. The presence of angiographic features in the context of IIA predisposing factors has been commonly used to diagnose IIAs [14, 42, 87]. Diagnosis of proximal IIA may be more challenging, and these should be distinguished from noninfectious aneurysms by additional features such as the presence of multiple aneurysms, rapid changes on repeated angiograms, and occlusion of the artery adjacent to the aneurysm [42]. The MCA harbors the highest prevalence of IIAs [3, 12, 49]; however, all cerebral arteries could potentially be a site for IIAs [71]. Rarely, IIAs may occur in the external carotid artery and may rupture leading to airway obstruction and potentially to a stroke [90].

Management

Screening

IIAs are a rare complication of IE, thus screening IE patients for IIAs using CTA or MRA is still debatable [4, 14, 42, 86]. There are currently no guidelines for IIA screening in at-risk patients such as IE [58, 69]. Since CTA and MRA lack the reliable sensitivity to detect IIAs, some reports have proposed an aggressive diagnostic strategy using DSA in all patients with IE [4, 58], but this strategy is not supported by strong evidence [37, 58, 91]. In fact, risk analysis has demonstrated that DSA in

IE patients does not reduce the risk of mortality and should not be indicated [55, 72]. Screening is recommended in patients presenting with neurological symptoms or patients that are at high risk of rupture such as during preoperative work-up for cardiac surgery that will require anticoagulation therapy [4, 21, 32, 57, 58, 72]. Cardiac surgery may increase the risk of rupture of IIAs due to anticoagulation, improved systemic blood pressure, and increased patient mobility after surgery [32]. Unruptured, and undiagnosed, IIAs may bleed within the first 2 weeks after cardiac surgery and lead to devastating outcomes due to anticoagulation therapy [32, 57]. Timely diagnosis of IIAs can be life-saving but requires a high index of suspicion especially in patients presenting with asymptomatic IIAs without signs of hemorrhage and a normal CTA [4, 57, 58].

Treatment

Treatment of IIAs is more challenging compared to circle of Willis aneurysms since IIAs tend to occur in patients with high morbidity in association with a life-threatening diseases such IE, have a fusiform or eccentric shape that challenges conventional treatments, and have a reasonable likelihood to regress during the treatment of the underlying disease [63, 72]. The first challenge in the treatment of IIAs, especially when they are asymptomatic, is to determine whether a neurosurgical procedure or a cardiovascular procedure is to be prioritized [8, 33, 42, 75, 92]. The majority of reported cases of IIAs have prioritized the treatment of IIAs over cardiac surgery using conservative or surgical methods [8, 42, 75, 92]; yet, some reports have suggested that cardiac procedures are the priority to eliminate the underlying condition and prevent future septic emboli [8, 33, 42]. Several instances of IIA rupture within 2 weeks of cardiac surgery have been reported [8, 48, 59]. Therefore, the general recommendation is that patients with IIAs, ruptured or unruptured, should be treated for the aneurysm prior to cardiac surgery unless the aneurysm responds to antibiotic therapy [8, 42, 75, 92]. In the event a cardiac surgery is prioritized, it has been recommended that a biological prosthesis rather than a mechanical prosthesis be used to avoid anticoagulation therapy [42]. The reported delay between presentation and cardiac surgery in patients treated first for IIAs ranges between 9 and 51 days, a number that is continuously decreasing due to the introduction and advancement of neuroendovascular techniques [48].

Treatment options for IIAs can range from conservative medical management to open microsurgery or neuroendovascular approaches. Treatment strategies have significantly evolved over the past decade due to the significant improvement in surgical and endovascular techniques resulting in improved safety and efficacy profiles. In the coming sections, we discuss the different treatment strategies for IIAs and recommend a general management algorithm (Fig. 16.2) with different presentation scenarios (Table 16.1).

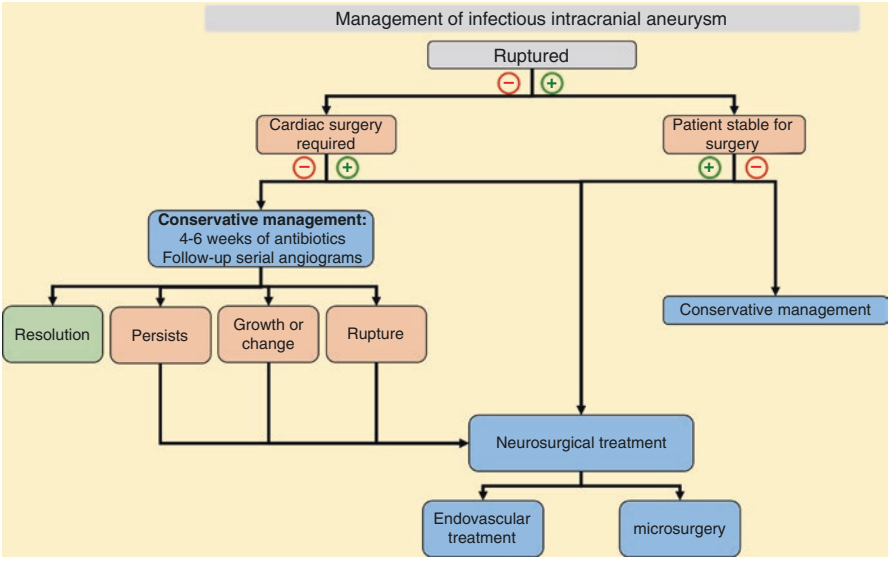


Fig. 16.2 Algorithm for management of IIA patients

Table 16.1 Common case scenarios for IIA patient requiring surgical or endovascular intervention

Response to Ab	Symptoms	Ruptured	Mass effect	Cardiac surgery planned	Eloquent cortex	First-line treatment	Example cases
+	–	–	–	+	–	Endovascular + PVO	
–	+	+	+	–	–	Microsurgical	Figure 5
–	+	–	–	–	–	Endovascular	
–	+	+	–	–	–	Endovascular + PVO	Figure 3,4
–	+	+	–	–	+	Microsurgical + bypass	

Ab antibiotics, *PVO* parent vessel occlusion

Conservative Management

Conservative or medical management of IIAs includes antibiotics and blood pressure control followed by serial imaging using DSA [2, 3, 12, 63, 70]. Treatment with antibiotics targets the underlying cause of the disease (commonly IE) and should be accompanied by careful investigation of the identity of the underlying pathogen as well as its drug susceptibility after empirical treatment [2, 3, 63]. The recommended duration of antibiotic therapy is generally 4–6 weeks, and the average duration between the initiation of therapy and resolution is 37 days [3, 63]. Studies on the medical management of IIAs have demonstrated that, during antibiotic therapy, IIA may resolve with or without thrombosis of the parent vessel, shrink

in size, persist with stable morphology, enlarge, change morphology, or rupture [12, 14, 19–21, 42, 70, 86]. Serial angiography should be performed to monitor the success of antibiotic therapy and detect new aneurysms that may arise, and potentially rupture, during therapy [12, 14, 19–21, 70, 86]. Follow-up angiography has been generally performed within 7–14 days of initial diagnosis [19–21, 86], a duration that reflects data suggesting 7–10 days gap between septic embolization and development of IIAs. Around 10% of IIAs may be missed on initial angiography and detected on repeated imaging [58], and several reports have documented the appearance and rupture of new aneurysms after an initial IIA resolved [19, 58]. Pathophysiological reason behind the development of new IIAs even after medical therapy is that elimination of the pathogen does not reverse the damage afflicted to cerebral vessels. Thus, weakened vessels may still develop aneurysms even in the context of negative cultures and antibiotic therapy [56].

Results of conservative therapy may be variable, with response rates ranging from 10 to 50% as assessed by a decrease in aneurysm size [70]. Medical management is generally justified in cases of unruptured IIAs [3, 13, 63], but if IIAs rupture or fail to respond to treatment on first follow-up angiogram, surgical or endovascular interventions should be considered [3, 13, 24]. On the other hand, medical management should be pursued in patients who are not stable for surgery or for whom surgical or endovascular interventions are associated with high risk of morbidity [3, 21]. Compared to surgical interventions, medical management of IIAs is associated with higher mortality that ranges from 1.3 to 3.1-folds of mortality after surgical and endovascular interventions [42, 54, 71]. In addition, aneurysms that tend to resolve medically are often asymptomatic and are significantly smaller in size compared to those requiring surgical intervention [3].

Surgical Management

Several microsurgical strategies have been used to treat IIAs including resection, clipping, trapping, or wrapping with or without bypass surgery to restore flow to the parent vessel [16, 43, 59, 63, 64, 66, 68]. Early case series by Roach and Drake reported a high morbidity and mortality after microsurgery for IIAs [25]; however, advancement in microsurgical techniques and patient management has significantly reduced the risk associated with surgery, and a lower mortality rate (12–20%) has been reported after surgical compared to medical management (25–27%) of IIA patients [42, 69, 71]. Surgery is indicated for patients with ICH due to ruptured IIAs, those with a mass effect, or those who fail endovascular therapy [12, 49, 50, 63]. A significant proportion of patients with ruptured IIAs die from the fatality of ICH prior to undergoing surgically treatment [93]. In the event of unruptured aneurysms, surgery or endovascular intervention is indicated if the IIAs do not respond to conservative antibiotic therapy [3, 69]. The lack of response to antibiotics is determined on follow-up angiography as the lack of resolution or decrease in aneurysms size (Fig. 16.2). A major advantage of surgical intervention is that the parent artery may be preserved after clipping of the aneurysm or by arterial bypass which is most crucial when the

aneurysm is located proximally or near eloquent cortex [18, 31, 79, 94]. Small aneurysms may be resected followed by end-to-end anastomosis to maintain flow to the parent artery [63, 79, 86]. For larger aneurysms that may require trapping, arterial bypass using the superficial temporal or Sylvian arteries is performed to avoid ischemic complications [18, 79, 86, 94]. However, in proximal aneurysms that carry high risk of mortality associated with parent vessel occlusion, saphenous vein graft may be used to perform bypass after trapping or resection of the aneurysm [18, 31, 79, 86, 94]. Studies have suggested delaying microsurgery for unruptured IIAs until the end of antibiotic therapy since the vessel walls are friable during active inflammation which may present a challenge during clipping or bypass surgeries and increase post-procedural morbidity [33, 42, 59, 95]. Therefore, fibrosis of the vessel wall after antibiotic therapy and clearance of the pathogen may allow for a better outcome after surgery and reduce the risk of parent vessel thrombosis [59].

Although microsurgery may provide better outcomes compared to conservative measures, several limitations challenge the use of microsurgery to treat IIA patients, especially the unstable patient in poor medical condition from sepsis and/or heart failure. IIAs are small, can be multiple, and typically occur in distal locations lacking anatomical landmarks which render precise localization for surgical treatment more challenging [42, 63, 69, 86]. Stereotactic neuronavigation has been used to avoid these limitations and improve localization of IIAs without extensive manipulation of eloquent cortex [41, 42, 96–98]; however, neuroendovascular techniques are currently accepted as the primary treatment option. Exceptions include the patient with an acute herniation syndrome from ICH and mass effect [2], in which surgical evacuation of the hematoma is required as a life-saving measure (refer to Fig. 16.3 for representative case).

Neuroendovascular Management

Neuroendovascular therapy (EVT) has been increasingly used as a first-line treatment for IIAs in multiple centers illustrated by the finding that the majority of IIA cases reported after 1997 were treated with neuroendovascular interventions. Compared to microsurgery, EVT may not require general anesthesia, has lower procedure-associated morbidity, and allows for a rapid reinstatement of anticoagulation therapy to minimize the delay in cardiac surgery [2, 45, 50, 69, 70]. In addition, EVT provides a better tool to simultaneously treat multiple aneurysms that may occur bilaterally, and improvements in microcatheter technology and embolization material have made distally located aneurysms accessible to EVT [3, 50, 63, 67, 69, 70]. In a large set of hospital data for IIA patients, there was no significant difference in outcome between surgical and endovascular approaches [69], and there is yet no prospective studies that compare the two strategies.

Two major neuroendovascular approaches have been commonly used, namely, coil embolization and liquid embolization [2, 3, 40, 45, 69, 70] (example in Figs. 16.4 and 16.5). Liquid embolization may be preferred in case of fragility of the vessel wall that increases the risk of perforation with coils [42, 47, 67].

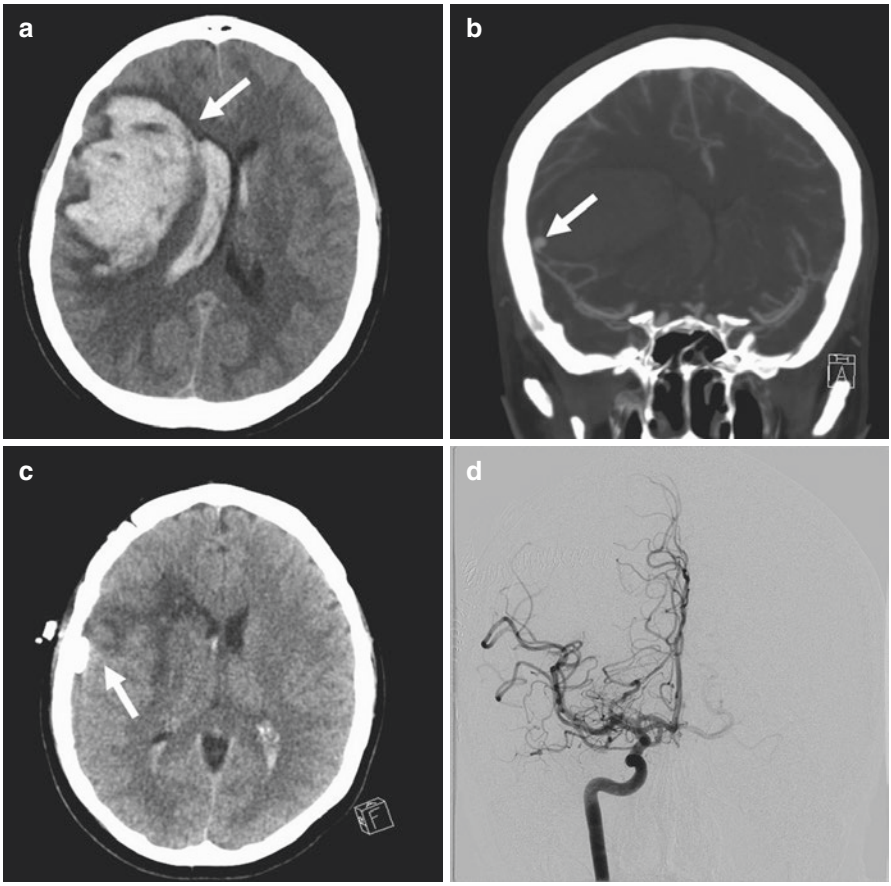


Fig. 16.3 Representative case of ICH secondary to IIA presenting with a mass effect that requires immediate microsurgery. CT scan of the head (**a**) and subsequent CTA (**b**) at presentation demonstrating large ICH secondary to a distal right MCA aneurysm. (**c**, **d**) Postoperative CT (**c**) and (**d**) right internal carotid angiogram revealed resolution of the aneurysm

In contrast to surgery, EVT involves occlusion of the parent artery in the majority of cases (refer to Figs. 16.4 and 16.5 for representative case) and may have a higher risk of ischemic complications [2, 3]. However, radiological infarcts after parent vessel occlusion may be asymptomatic in the majority of cases since distal arterial segments may receive retrograde flow across pial collaterals [17, 49]. It is anticipated that neurological complications may occur in up to 12.5% of patients with EVT involving parent vessel occlusion [63]. Ischemic complications of EVT are significantly different in proximal compared to distal IIAs. In distal IIAs, the risk of ischemic complications is very low since the parent artery may have already been occluded by the septic embolus and

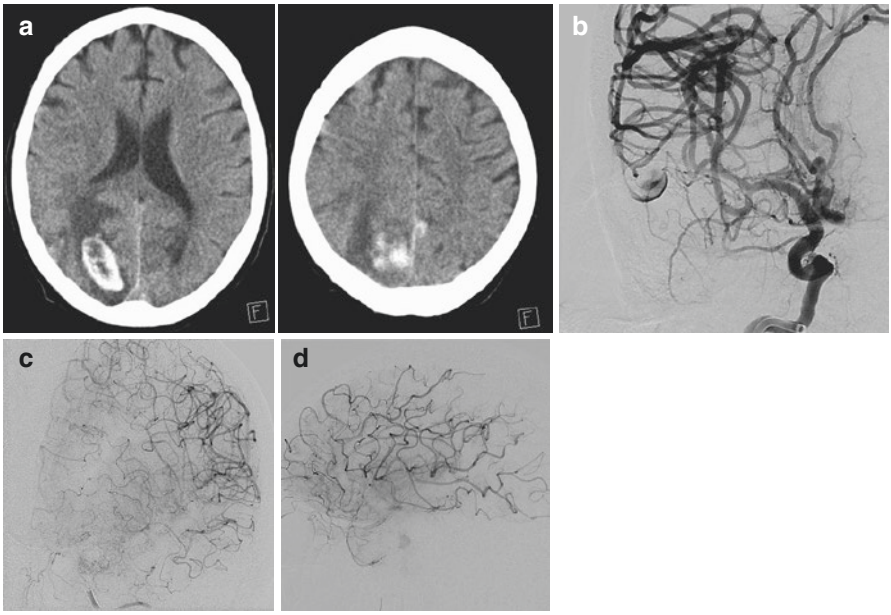


Fig. 16.4 A case of intracerebral hemorrhage secondary to multiple IIAs that differentially resolved by medical therapy or endovascular glue embolization. (**a**) CT scan of the head demonstrating hemorrhage at presentation. The patient had IIAs in the right M1, right M4, left M4, left P4, right occipital, and left occipital aneurysms. Glue embolization with parent artery sacrifice was used to treat the MCA and PCA aneurysms. Occipital aneurysms resolved with medical management. (**b**) Angiogram of the right internal carotid artery demonstrating the MCA aneurysm at presentation. (**c**) Left internal carotid angiogram demonstrating left-sided MCA and PCA aneurysms prior to glue embolization. (**d**) Follow-up angiogram showing complete resolution of all aneurysms

neurological deficits are already present or absent depending on the adequacy of collaterals [65, 67]. However, proximal aneurysms that involve arteries with larger territories, occlusion of the parent artery is associated with a significant risk of ischemic complications [67].

To avoid ischemic complications, super-selective WADA using sodium amobarbital injection to the target artery can be performed to determine the eloquence of the territory before occlusion of the parent artery [16, 40, 62, 63, 73]. This can also be performed by transiently blocking the target artery using a balloon catheter to assess for neurological deficits prior to permanent occlusion [45]. Therefore, an additional advantage of EVT is the reversibility of the procedure until the point of liquid or coil embolization [16, 40, 62, 63, 73].

Finally, we propose a treatment algorithm for the management of IIA patients depending on the initial presentation, patient characteristics, and response to antibiotic therapy (Fig. 16.2), and we describe common case scenarios based on our experience (Table 16.1**,** Figs. 16.3, 16.4, and 16.5).

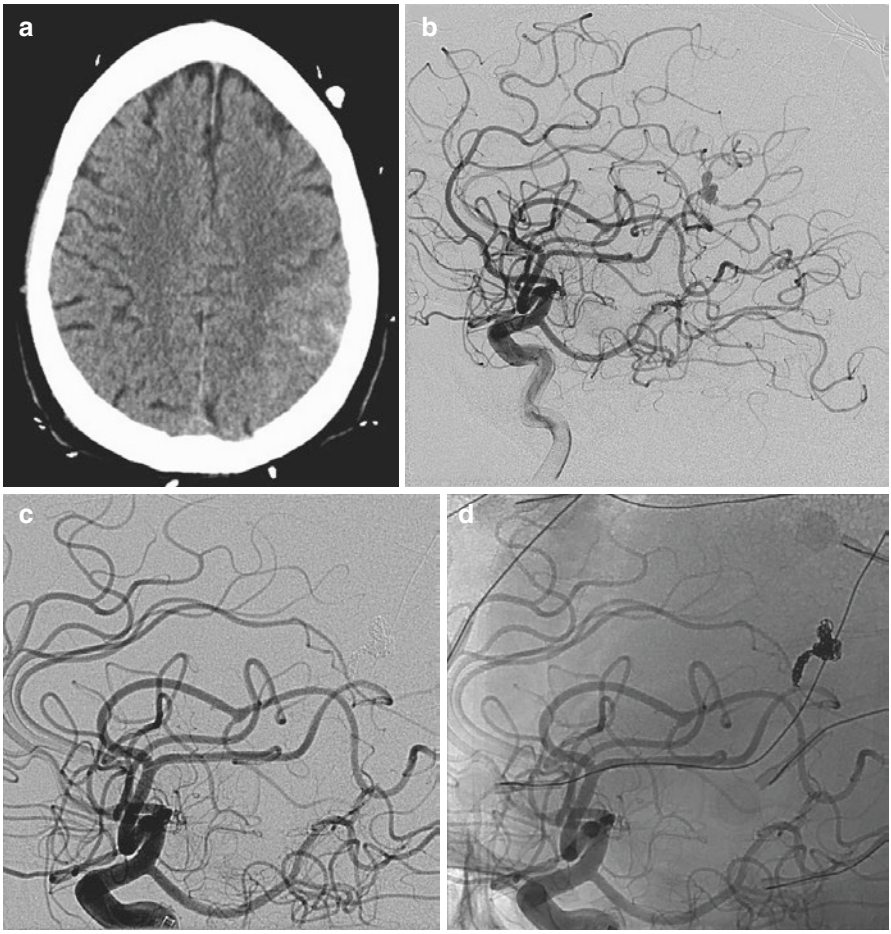


Fig. 16.5 Illustrative example of successful coil embolization of patient with an IIA. (**a**) CT scan of the head demonstrating left-sided subarachnoid hemorrhage. (**b**) Pre-procedural angiogram showing an IIA in the posterior parietal branch of the left MCA that was treated with coil embolization. (**c**, **d**) Post-procedural angiogram demonstrating successful embolization of the aneurysm

Acknowledgments Authors acknowledge support from the American Heart Association to A.A. (15PRE25250009).

References

1. Osler W. The Gulstonian lectures, on malignant endocarditis. Br Med J. 1885;1(1264):577–9.
2. Wang JL, Hinduja AP, Powers CJ. Successful coil embolization of a ruptured mycotic aneurysm that developed three days after septic embolic infarction: case report and review of the literature. J Clin Neurosci. 2017;39:95–8.
3. Jiad E, Gill SK, Krutikov M, Turner D, Parkinson MH, Curtis C, et al. When the heart rules the head: ischaemic stroke and intracerebral haemorrhage complicating infective endocarditis. Pract Neurol. 2017;17(1):28–34.

4. Zhong X, Li X, Shao S, Yang X, Fan X. A case of infectious intracranial dissecting aneurysm. Neurol India. 2017;65(2):405–7.
5. Remirez JM, Sabet Y, Baca M, Maud A, Cruz-Flores S, Rodriguez GJ, et al. Mycotic intracranial aneurysm secondary to left ventricular assist device infection. J Vasc Interv Neurol. 2017;9(3):23–5.
6. Piccirilli M, Prizio E, Cannizzaro D, Tropeano MP, Guidetti G, Santoro A. The only case of mycotic aneurysm of the PICA: clinical-radiological remarks and review of literature. J Clin Neurosci. 2017;38:62–6.
7. Palacios A, Llorente AM, Ordonez O, Martinez de Aragon A. Intracranial mycotic aneurysm in a 5 month-old infant with pneumococcal meningitis. Enferm Infecc Microbiol Clin. 2017;35(4):267–9.
8. Lin CT, Tranmer B, Durham S, Johnson D, Hamlin M, Bolman RM 3rd. Ruptured mycotic aneurysm and cerebral vasospasm in the setting of endocarditis and heart failure requiring cardiothoracic surgery: case report and literature review. World Neurosurg. 2017;100:711 e13–8.
9. Champeaux C, Walker N, Derwin J, Grivas A. Successful delayed coiling of a ruptured growing distal posterior cerebral artery mycotic aneurysm. Neuro-Chirurgie. 2017;63(1):17–20.
10. Schneider MA, Pomidor MA. Cerebral mycotic aneurysm and infective endocarditis: a case study. J Neurosci Nurs. 2016;48(2):100–4.
11. Rhodes HM, Hirigoyen D, Shabnam L, Williams DN, Hansen GT. Infective endocarditis due to Abiotrophia defectiva and Granulicatella spp. complicated by infectious intracranial cerebral aneurysms: a report of three cases and review of the literature. J Med Microbiol. 2016;65(6):493–9.
12. Nonaka S, Oishi H, Tsutsumi S, Teranishi K, Tanoue S, Yasumoto Y, et al. Endovascular therapy for infectious intracranial aneurysm: a report of four cases. J Stroke Cerebrovasc Dis. 2016;25(3):e33–7.
13. Lv N, Zhou Y, Yang P, Li Q, Zhao R, Fang Y, et al. Endovascular treatment of distal middle cerebral artery aneurysms: report of eight cases and literature review. Interv Neuroradiol. 2016;22(1):12–7.
14. John S, Walsh KM, Hui FK, Sundararajan S, Silverman S, Bain M. Dynamic angiographic nature of cerebral mycotic aneurysms in patients with infective endocarditis. Stroke. 2016;47(1):e8–e10.
15. Hamisch CA, Mpotsaris A, Timmer M, Reiner M, Stavrinou P, Brinker G, et al. Interdisciplinary treatment of intracranial infectious aneurysms. Cerebrovasc Dis. 2016;42(5–6):493–505.
16. Fusco MR, Stapleton CJ, Griessenauer CJ, Thomas AJ, Ogilvy CS. Endovascular treatment of intracranial infectious aneurysms in eloquent cortex with super-selective provocative testing: case series and literature review. Interv Neuroradiol. 2016;22(2):148–52.
17. Grandhi R, Zwagerman NT, Linares G, Monaco EA 3rd, Jovin T, Horowitz M, et al. Onyx embolization of infectious intracranial aneurysms. J Neurointerv Surg. 2014;6(5):353–6.
18. Ota T, Yoshino M, Horiba A, Yokoya S, Mizutani T. Ruptured infectious aneurysms of the distal MCA treated with trapping and STA-MCA bypass surgery. Br J Neurosurg. 2012;26(5):767–9.
19. Hourihane JB. Ruptured mycotic intracranial aneurysm. A report of three cases. Vasc Surg. 1970;4(1):21–9.
20. Cantu RC, LeMay M, Wilkinson HA. The importance of repeated angiography in the treatment of mycotic-embolic intracranial aneurysms. J Neurosurg. 1966;25(2):189–93.
21. Ziment I, Johnson BL Jr. Angiography in the management of intracranial mycotic aneurysms. Arch Intern Med. 1968;122(4):349–52.
22. Suwanwela C, Suwanwela N, Charuchinda S, Hongsaprabhas C. Intracranial mycotic aneurysms of extravascular origin. J Neurosurg. 1972;36(5):552–9.
23. Horten BC, Abbott GF, Porro RS. Fungal aneurysms of intracranial vessels. Arch Neurol. 1976;33(8):577–9.
24. Bingham WF. Treatment of mycotic intracranial aneurysms. J Neurosurg. 1977;46(4):428–37.
25. Roach MR, Drake C. Ruptured cerebral aneurysms caused by micro-organisms. N Eng J Med. 1965;273(5):240–4.
26. McNeel D, Evans RA, Ory EM. Angiography of cerebral mycotic aneurysms. Acta Radiol Diagn (Stockh). 1969;9:407–12.

27. Gilroy J, Andaya L, Thomas VJ. Intracranial mycotic aneurysms and subacute bacterial endocarditis in heroin addiction. Neurology. 1973;23(11):1193–8.
28. Ishikawa M, Waga S, Moritake K, Handa H. Cerebral bacterial aneurysms: report of three cases. Surg Neurol. 1974;2(4):257–61.
29. Moskowitz MA, Rosenbaum AE, Tyler HR. Angiographically monitored resolution of cerebral mycotic aneurysms. Neurology. 1974;24(12):1103–8.
30. Bullock R, van Dellen JR, van den Heever CM. Intracranial mycotic aneurysms. A review of 9 cases. S Afr Med J = Suid-Afrikaanse tydskrif vir geneeskunde. 1981;60(25):970–3.
31. Day AL. Extracranial-intracranial bypass grafting in the surgical treatment of bacterial aneurysms: report of two cases. Neurosurgery. 1981;9(5):583–8.
32. Bullock R, Van Dellen JR. Rupture of bacterial intracranial aneurysms following replacement of cardiac valves. Surg Neurol. 1982;17(1):9–11.
33. Morawetz RB, Karp RB. Evolution and resolution of intracranial bacterial (mycotic) aneurysms. Neurosurgery. 1984;15(1):43–9.
34. Dean RH, Waterhouse G, Meacham PW, Weaver FA, O'Neil JA Jr. Mycotic embolism and embolomycotic aneurysms. Neglected lessons of the past. Ann Surg. 1986;204(3):300–7.
35. O'Donohue JM, Enzmann DR. Mycotic aneurysm in angiitis associated with herpes zoster ophthalmicus. AJNR Am J Neuroradiol. 1987;8(4):615–9.
36. Barrow DL, Prats AR. Infectious intracranial aneurysms: comparison of groups with and without endocarditis. Neurosurgery. 1990;27(4):562–72. discussion 72–3.
37. Kanter MC, Hart RG. Cerebral mycotic aneurysms are rare in infective endocarditis. Ann Neurol. 1990;28(4):590–1.
38. Masuda J, Yutani C, Waki R, Ogata J, Kuriyama Y, Yamaguchi T. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. Stroke. 1992;23(6):843–50.
39. Ahmadi J, Tung H, Giannotta SL, Destian S. Monitoring of infectious intracranial aneurysms by sequential computed tomographic/magnetic resonance imaging studies. Neurosurgery. 1993;32(1):45–9. discussion 9–50.
40. Khayata MH, Aymard A, Casasco A, Herbreteau D, Woimant F, Merland JJ. Selective endovascular techniques in the treatment of cerebral mycotic aneurysms. Report of three cases. J Neurosurg. 1993;78(4):661–5.
41. Cunha e Sa M, Sisti M, Solomon R. Stereotactic angiographic localization as an adjunct to surgery of cerebral mycotic aneurysms: case report and review of the literature. Acta Neurochir. 1997;139(7):625–8.
42. Chapot R, Houdart E, Saint-Maurice JP, Aymard A, Mounayer C, Lot G, et al. Endovascular treatment of cerebral mycotic aneurysms. Radiology. 2002;222(2):389–96.
43. Nakahara I, Taha MM, Higashi T, Iwamuro Y, Iwaasa M, Watanabe Y, et al. Different modalities of treatment of intracranial mycotic aneurysms: report of 4 cases. Surg Neurol. 2006;66(4):405–9. discussion 9–10
44. Sundaram C, Goel D, Uppin SG, Seethajayalakshmi S, Borgohain R. Intracranial mycotic aneurysm due to Aspergillus species. J Clin Neurosci. 2007;14(9):882–6.
45. Eddleman CS, Surdell D, DiPatri A Jr, Tomita T, Shaibani A. Infectious intracranial aneurysms in the pediatric population: endovascular treatment with Onyx. Childs Nerv Syst. 2008;24(8):909–15.
46. Bhattacharyya A, Mittal S, Yadav RR, Jain K, Gupta B, Parihar A, et al. Endovascular management of infective intracranial aneurysms with acrylic glue. A report of two cases. Interv Neuroradiol. 2009;15(4):443–7.
47. La Barge DV 3rd, Ng PP, Stevens EA, Friedline NK, Kestle JR, Schmidt RH. Extended intracranial applications for ethylene vinyl alcohol copolymer (Onyx): mycotic and dissecting aneurysms. Technical note. J Neurosurg. 2009;111(1):114–8.
48. Fukuda W, Daitoku K, Minakawa M, Fukui K, Suzuki Y, Fukuda I. Infective endocarditis with cerebrovascular complications: timing of surgical intervention. Interact Cardiovasc Thorac Surg. 2012;14(1):26–30.

49. Esenkaya A, Duzgun F, Cinar C, Bozkaya H, Eraslan C, Ozgiray E, et al. Endovascular treatment of intracranial infectious aneurysms. Neuroradiology. 2016;58(3):277–84.
50. Matsubara N, Miyachi S, Izumi T, Yamanouchi T, Asai T, Ota K, et al. Results and current trends of multimodality treatment for infectious intracranial aneurysms. Neurol Med Chir. 2015;55(2):155–62.
51. Hui FK, Bain M, Obuchowski NA, Gordon S, Spiotta AM, Moskowitz S, et al. Mycotic aneurysm detection rates with cerebral angiography in patients with infective endocarditis. J Neurointerv Surg. 2015;7(6):449–52.
52. Monteleone PP, Shrestha NK, Jacob J, Gordon SM, Fraser TG, Rehm SJ, et al. Clinical utility of cerebral angiography in the preoperative assessment of endocarditis. Vasc Med (London, England). 2014;19(6):500–6.
53. Jadhav AP, Pryor JC, Nogueira RG. Onyx embolization for the endovascular treatment of infectious and traumatic aneurysms involving the cranial and cerebral vasculature. J Neurointerv Surg. 2013;5(6):562–5.
54. Allen LM, Fowler AM, Walker C, Derdeyn CP, Nguyen BV, Hasso AN, et al. Retrospective review of cerebral mycotic aneurysms in 26 patients: focus on treatment in strongly immunocompromised patients with a brief literature review. AJNR Am J Neuroradiol. 2013;34(4):823–7.
55. Pruitt AA, Rubin RH, Karchmer AW, Duncan GW. Neurologic complications of bacterial endocarditis. Medicine. 1978;57(4):329–43.
56. Frazee JG, Cahan LD, Winter J. Bacterial intracranial aneurysms. J Neurosurg. 1980;53(5):633–41.
57. Monsuez JJ, Vittecoq D, Rosenbaum A, Goujon C, Wolff M, Witchitz S, et al. Prognosis of ruptured intracranial mycotic aneurysms: a review of 12 cases. Eur Heart J. 1989;10(9):821–5.
58. Brust JC, Dickinson PC, Hughes JE, Holtzman RN. The diagnosis and treatment of cerebral mycotic aneurysms. Ann Neurol. 1990;27(3):238–46.
59. Aspoas AR, de Villiers JC. Bacterial intracranial aneurysms. Br J Neurosurg. 1993;7(4):367–76.
60. Yamada M, Miyasaka Y, Takagi H, Yada K. Cerebral bacterial aneurysm and indications for cerebral angiography in infective endocarditis. Neurol Med Chir. 1994;34(10):697–9.
61. Corr P, Wright M, Handler LC. Endocarditis-related cerebral aneurysms: radiologic changes with treatment. AJNR Am J Neuroradiol. 1995;16(4):745–8.
62. Venkatesh SK, Phadke RV, Kalode RR, Kumar S, Jain VK. Intracranial infective aneurysms presenting with haemorrhage: an analysis of angiographic findings, management and outcome. Clin Radiol. 2000;55(12):946–53.
63. Chun JY, Smith W, Halbach VV, Higashida RT, Wilson CB, Lawton MT. Current multimodality management of infectious intracranial aneurysms. Neurosurgery. 2001;48(6):1203–13. discussion 13–4.
64. Phuong LK, Link M, Wijdicks E. Management of intracranial infectious aneurysms: a series of 16 cases. Neurosurgery. 2002;51(5):1145–51. discussion 51–2.
65. Andreou A, Ioannidis I, Mitsos A. Endovascular treatment of peripheral intracranial aneurysms. AJNR Am J Neuroradiol. 2007;28(2):355–61.
66. Kannoth S, Iyer R, Thomas SV, Furtado SV, Rajesh BJ, Kesavadas C, et al. Intracranial infectious aneurysm: presentation, management and outcome. J Neurol Sci. 2007;256(1–2):3–9.
67. Dhomne S, Rao C, Shrivastava M, Sidhartha W, Limaye U. Endovascular management of ruptured cerebral mycotic aneurysms. Br J Neurosurg. 2008;22(1):46–52.
68. Hetts SW, Narvid J, Sanai N, Lawton MT, Gupta N, Fullerton HJ, et al. Intracranial aneurysms in childhood: 27-year single-institution experience. AJNR Am J Neuroradiol. 2009;30(7):1315–24.
69. Singla A, Fargen K, Blackburn S, Neal D, Martin TD, Hess PJ, et al. National treatment practices in the management of infectious intracranial aneurysms and infective endocarditis. J Neurointerv Surg. 2016;8(7):741–6.
70. Petr O, Brinjikji W, Burrows AM, Cloft H, Kallmes DF, Lanzino G. Safety and efficacy of endovascular treatment for intracranial infectious aneurysms: a systematic review and meta-analysis. J Neuroradiol. 2016;43(5):309–16.

71. Alawieh A, Chaudry MI, Turner RD, Turk AS, Spiotta AM. Infectious intracranial aneurysms: a systematic review of epidemiology, management, and outcomes. J Neurointerv Surg. 2018; Feb 20. pii: neurintsurg-2017-013603.
72. van der Meulen JH, Weststrate W, van Gijn J, Habbema JD. Is cerebral angiography indicated in infective endocarditis? Stroke. 1992;23(11):1662–7.
73. Frizzell RT, Vitek JJ, Hill DL, Fisher WS 3rd. Treatment of a bacterial (mycotic) intracranial aneurysm using an endovascular approach. Neurosurgery. 1993;32(5):852–4.
74. Kannoth S, Thomas SV. Intracranial microbial aneurysm (infectious aneurysm): current options for diagnosis and management. Neurocrit Care. 2009;11(1):120–9.
75. Yoshioka D, Toda K, Sakaguchi T, Okazaki S, Yamauchi T, Miyagawa S, et al. Valve surgery in active endocarditis patients complicated by intracranial haemorrhage: the influence of the timing of surgery on neurological outcomes. Eur J Cardiothorac Surg. 2014;45(6):1082–8.
76. Han MS, Jung SH, Kim TS, Joo SP. Reconstructive endovascular treatment of an intracranial infectious aneurysm in bacterial meningitis: a case report and review of literature. World Neurosurg. 2016;90:700.e1–5.
77. Clare CE, Barrow DL. Infectious intracranial aneurysms. Neurosurg Clin N Am. 1992;3(3):551–66.
78. Modi G, Ranchod K, Modi M, Mochan A. Human immunodeficiency virus associated intracranial aneurysms: report of three adult patients with an overview of the literature. J Neurol Neurosurg Psychiatry. 2008;79(1):44–6.
79. Bohmfalk GL, Story JL, Wissinger JP, Brown WE Jr. Bacterial intracranial aneurysm. J Neurosurg. 1978;48(3):369–82.
80. Kojima Y, Saito A, Kim I. The role of serial angiography in the management of bacterial and fungal intracranial aneurysms – report of two cases and review of the literature. Neurol Med Chir. 1989;29(3):202–16.
81. Hung SC, Tai CT. Infective endocarditis complicated with thalamic infarction and mycotic aneurysm rupture: a case report. Zhonghua Yi Xue Za Zhi (Taipei). 1998;61(1):53–8.
82. Saito A, Kawaguchi T, Hori E, Kanamori M, Nishimura S, Sannohe S, et al. Subarachnoid hemorrhage after an ischemic attack due to a bacterial middle cerebral artery dissecting aneurysm: case report and literature review. Neurol Med Chir. 2014;54(3):196–200.
83. Kanai R, Shinoda J, Irie S, Inoue K, Sato T, Tsutsumi Y. A case of embolic stroke imitating atherothrombotic brain infarction before massive hemorrhage from an infectious aneurysm caused by streptococci. J Stroke Cerebrovasc Dis. 2012;21(8):910.e13–6.
84. Molinari GF, Smith L, Goldstein MN, Satran R. Pathogenesis of cerebral mycotic aneurysms. Neurology. 1973;23(4):325–32.
85. Lotan E, Orion D, Bakon M, Kuperstein R, Greenberg G. Ruptured intracranial mycotic aneurysm in infective endocarditis: radiological and clinical findings. Isr Med Assoc J. 2014;16(5):317–9.
86. Peters PJ, Harrison T, Lennox JL. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. Lancet Infect Dis. 2006;6(11):742–8.
87. Hage ZA, Naidech AM, Bendok BR. Diagnosing intracranial infectious aneurysms with a simple model. J Neurol Neurosurg Psychiatry. 2008;79(8):853.
88. Ducruet AF, Hickman ZL, Zacharia BE, Narula R, Grobelny BT, Gorski J, et al. Intracranial infectious aneurysms: a comprehensive review. Neurosurg Rev. 2010;33(1):37–46.
89. Walkoff L, Brinjikji W, Rouchaud A, Caroff J, Kallmes DF. Comparing magnetic resonance angiography (MRA) and computed tomography angiography (CTA) with conventional angiography in the detection of distal territory cerebral mycotic and oncotic aneurysms. Interv Neuroradiol. 2016;22(5):524–8.
90. Rogers AC, Bourke M, Galbraith AS, Ryan AG, Cross KS, McMonagle MP. Mycotic aneurysm of the extracranial internal carotid artery, resect and ligate or reconstruct? Ann Vasc Surg. 2016;35:203.e5–e10.

91. Utoh J, Miyauchi Y, Goto H, Obayashi H, Hirata T. Endovascular approach for an intracranial mycotic aneurysm associated with infective endocarditis. J Thorac Cardiovasc Surg. 1995;110(2):557–9.
92. Miura T, Eishi K. Current treatment of active infective endocarditis with brain complications. Gen Thorac Cardiovasc Surg. 2013;61(10):551–9.
93. Voiriot P, Dureux JB. Cerebral mycotic aneurysms. Epidemiology, symptomatic aspects and prognosis. Ann Med Interne. 1989;140(2):118–21.
94. Pavic M, Debourdeau P, Teixeira L, Brunot J, Colle B, Flechaire A. Bacterial cerebral aneurysms without infectious endocarditis: analysis of a case and review of the literature. Rev Med Interne. 2001;22(9):867–71.
95. Fukuda W, Daitoku K, Minakawa M, Suzuki Y, Fukuda I. Management of infective endocarditis with neurological complication. Kyobu Geka. 2015;68(11):896–902.
96. Carvalho FG, Godoy BL, Reis M, Gasparetto EL, Wajnberg E, de Souza JM. Frameless stereotactic navigation for intraoperative localization of infectious intracranial aneurysm. Arq Neuropsiquiatr. 2009;67(3B):911–3.
97. Elowiz EH, Johnson WD, Milhorat TH. Computerized tomography (CT) localized stereotactic craniotomy for excision of a bacterial intracranial aneurysm. Surg Neurol. 1995;44(3):265–9.
98. D'Angelo V, Fiumara E, Gorgoglione L, Florio F, Ceddia A. Surgical treatment of a cerebral mycotic aneurysm using the stereo-angiographic localizer. Surg Neurol. 1995;44(3):263–4.

Chapter 17
Arteriovenous Malformations: Surgical Indications and Technique

Omar Tanweer, Gillian Harrison, Peter Rozman, and Howard A. Riina

Arteriovenous malformations (AVMs) comprise one of four main subtypes of vascular malformations that are considered to be congenital rather than acquired. They are characterized by direct arterial-to-venous shunting, usually through a tangle of vessels called a *nidus*, without the normal intervening capillary beds, and are thus considered to be high-pressure, high-flow malformations. The other three subtypes, developmental venous anomalies, capillary telangiectasias, and cavernous malformations, which are beyond the scope of this chapter, are under much lower hemodynamic pressure and low flow. However, all are considered rare lesions and as such remain incompletely understood.

Attempts to define the exact prevalence of AVMs in the general population have been limited by methodology and sampling; the often cited prevalence of 0.14% is likely an underestimate, and more recent analyses have suggested a prevalence of 1–1.3/100,000 person-years [1, 2]. The rarity of these malformations would require an exceedingly large sample size to determine true prevalence in the general population.

While the underlying pathogenesis of AVMs remains a subject of active research, clinicians generally accept that AVMs, unlike many other vascular pathologies, are present from birth. This assumption finds support in the existence of genetic disorders with predispositions for the development of AVMs (hereditary hemorrhagic telangiectasia, or Sturge-Weber disease, for instance). Studies have implicated elevated levels of vascular endothelial growth factor (VEGF), angiopoietins, and fibroblast growth factors (FGFs) in the ultimate instability of the embryological vascular-capillary plexus that gives rise to the early AVM [3]. Over time, AVMs do remodel and can grow, and it is likely that environmental factors also contribute to the ultimate architecture of the mature AVM.

O. Tanweer (✉) · G. Harrison · P. Rozman · H. A. Riina
Department of Neurosurgery, New York University Medical Center, New York, NY, USA
e-mail: omar.tanweer@nyumc.org; Gillian.Harrison@nyumc.org; Peter.Rozman@nyumc.org; howard.riina@nyumc.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_17

The danger of these rare, congenital malformations is, of course, hemorrhage. Other symptoms such as headaches, seizures, and deficits from steal phenomenon are encountered as well. Over the past century, efforts directed at treating these lesions to prevent this consequence have led to four main treatment modalities that clinicians use today: medical management, endovascular embolization, microsurgical resection, radiosurgery, or some combination of the above. The focus of this chapter is mainly on the indications and techniques for surgical resection, but discussion is afforded to the use of other modalities to render previously high-risk or difficult-to-resect AVMs resectable.

Following a brief discussion of the clinical traits of AVMs and AVM ruptures, we will address the surgical classification, patient stratification, and preoperative planning that lead up to the day of surgery. An overview of surgical technique and intraoperative management follows, as well as a description of common complications and expected surgical outcomes.

Natural History and Clinical Presentations

As with most cerebrovascular lesions, screening for AVMs is not routinely performed, and these lesions are most commonly discovered in the setting of hemorrhage. However, the increasing ease and rapidity, as well as decreasing cost, of imaging studies, have led to more and more incidentally discovered AVMs. This shift has led to increasing interest in, and understanding of, the natural history of the unruptured AVM.

The annual risk of hemorrhage for an AVM is approximately 2.8% per year [4–7]. This figure does not stratify by AVM size or location and fails to take into account history of previous hemorrhage or symptomatic presentation. AVM size particularly has been associated with rupture risk, with smaller AVMs found to be at higher risk of rupture. The risk of hemorrhage is of special importance because approximately half of all AVMs will initially present in this way. Over 80% [8] of these hemorrhages are intraparenchymal. The remainder are intraventricular, usually by direct extension, subarachnoid, or even subdural hemorrhages. Spontaneous intracranial hemorrhage in an otherwise healthy or young individual should always raise the concern for an underlying malformation and prompt appropriate follow-up studies. Estimates of rebleeding rates vary greatly, and such analyses are limited by small study populations.

Cumulative (lifetime) risk of AVM rupture may be calculated as [1 – (risk of no hemorrhage)^n], where n is the remaining life expectancy. For an accepted annual risk of 3%, this is estimated as [105 – age]/100.

Of those AVMs that do not present as hemorrhage, approximately half present as seizures [9]. The exact pathophysiology that underlies AVM-associated seizures is not understood, but certain characteristics of the AVM, such as cortical – particularly temporal or parietal – location or large varices, do seem to predispose to this presentation. There is some suggestion that hemorrhagic presentation is more

common in younger (less than 20 years old) or older (greater than 60 years old) populations, while seizures may predominate in the intervening years.

Beyond hemorrhage and seizure, less common presentations of AVMs include headache without rupture (~15% of total) and neurological deficit either as a result of direct parenchymal compression or steal syndrome. Steal syndrome describes a phenomenon in which the arteriovenous shunt provides a lower resistance than the surrounding capillary beds feeding brain parenchyma and thus results in tissue ischemia.

Surgical Grading Systems

As we consider the lifetime risk of AVM rupture as an impetus to treat the disease process, it becomes apparent that this lifetime risk must be weighed against the risks inherent in surgical resection. Yet not all AVMs portend identical surgical risk. Since 1977, surgeons have developed grading systems to stratify AVMs into surgically favorable and unfavorable strata. The most widely utilized and well known of these systems is the Spetzler-Martin grading system, published in 1986 [10]. The system assigns points to the AVM based on three primary characteristics (size, location, and drainage), and these ultimately summate to grades I–V, with grade I being the lowest risk to resect and grade V carrying the highest risk (Table 17.1). Grade VI also exists and is used to denote AVMs deemed too complex to even consider resection.

In terms of size, AVMs are divided into those with a nidus less than 3 cm in diameter, 3–6 cm in diameter, or greater than 6 cm in diameter. In terms of location, a point is assigned those AVMs that occur in eloquent areas. Eloquent areas are defined as areas responsible for sensorimotor, visual, or language processing, as well as the hypothalamus, internal capsule, brainstem, cerebellar peduncles, and deep nuclei. Finally, drainage addresses whether *any* deep venous structures contribute to the AVM's drainage. Supratentorially, these are considered to be internal cerebral veins, basal vein of Rosenthal, and vein of Galen. Infratentorially, any drainage not to the straight or transverse sinus is considered deep.

This system is elegant in its simplicity and ease of use with available vascular imaging and has been validated in several cohorts by analyzing patient outcomes following surgical resection [11]. Spetzler and Ponce [12] even narrowed the final grades down into only three classes: A, comprising grades I/II; B, comprising grade

Table 17.1 The Spetzler-Martin grading system

Size	<3 cm	1 point
	3–6 cm	2 points
	>6 cm	3 points
Location	Eloquent	0 point
	Non-eloquent	1 point
Drainage	Superficial only	0 point
	Deep	1 point

III; and C, comprising grades IV/V. Class A AVMs are generally considered resectable, and class C AVMs are generally considered unresectable without compelling reason (recurrent hemorrhage, severe neurologic deficit, or associated aneurysms, for instance).

The Spetzler-Martin grading system improved upon earlier classification systems that recognized similar traits as important to surgical outcomes. Luessenhop and Gennarelli (1977) developed the first grading system in which they assigned a grade solely based on number of arterial feeders from a single vascular distribution (i.e., MCA, ACA, etc.) [13]. Luessenhop and Rosa (1984) developed a grading system based on size, which carried over into the Spetzler-Martin system [14].

Shi and Chen (1986) developed a complex system taking into account not only size, eloquence/depth, and venous drainage but also arterial supply [15]. While more granular and subtle than the Spetzler-Martin system, it was quickly abandoned, likely as a result of its complexity.

Lawton and his group at UCSF suggest that further considerations are warranted beyond those that comprise the Spetzler-Martin system. In particular, grade III AVMs span a wide range of pathologies. These include small, eloquent, deep-draining AVMs, medium/deep-draining AVMs (III), and medium/eloquent AVMs alike ("III+"). Surely outcomes and surgical risk must differ between these types. They suggest the use of a supplementary scale taking into account age (<20 years, 20–40 years, >40 years), presence of hemorrhage, and diffuseness or to what extent the brain parenchyma intervenes in the tangled vessels of the AVM. They reported an initial 300-patient analysis, and later 1000-patient analysis, that validates the improved outcome prediction with the addition of this system [16, 17].

All of the grading systems currently in use are now dated in their consideration of surgical resection as the sole treatment modality. As radiosurgery and interventional techniques become more available, curative treatment is becoming a possibility for previously unresectable malformations. Patient stratification is not as simple as a five-point, or even ten-point, grading scale, and a host of patient and anatomical considerations must factor into the ultimate treatment plan.

Risk Factors and Patient Selection

Management of patients with cerebral AVMs can be challenging, and recommendations for treatment require careful consideration of individual risk-benefit profiles. A surgeon's and an institution's experience with AVM management is important, particularly as multimodality management becomes more common; experts in each of the modalities should be available to contribute to a discussion of feasibility and associated risk for each patient.

A widely accepted indication for surgical intervention is prior hemorrhage; after an initial hemorrhage, annual rupture rates ranging from 6–15% in the first year [18, 19] to 2–18% in subsequent years [5, 7, 18, 20–24] have been observed, and prior hemorrhage has been a nearly universal predictor of subsequent hemorrhage across most large series [5, 22, 23, 25–27]. Even for patients with high-grade AVMs,

rebleeding rates of 6% per year have been reported with 65% combined risk of permanent disability or death [28], suggesting that intervention may even be indicated for patients with AVMs classically considered high risk.

For management of unruptured AVMs, decision-making is more complex; surgical intervention must present a lower-risk profile than the natural history. In general, surgery is often considered for young patients with Spetzler-Martin grade I–II AVMs; furthermore, an additional supplementary scale incorporating age, prior hemorrhage, and nidus compactness suggests that surgery may carry acceptably low morbidity for a score ≤ 6 [16, 17]. In addition to surgical morbidity, patient and angioarchitectural factors that alter the natural history and are associated with increased risk of hemorrhage must be incorporated into the preoperative patient selection process.

Patient Factors

Patient age is one of the most important factors to consider in patient selection for surgical intervention. As suggested by the modified Spetzler-Martin scale, age is a critical component for assessing surgical morbidity. In addition to having fewer comorbidities and greater ability to tolerate and recover from neurologic injury, younger patients have higher lifetime risk of hemorrhage, justifying more aggressive treatment modalities. Some studies have identified increasing age as an independent risk factor for hemorrhage – either initial hemorrhagic presentation or re-hemorrhage – with one meta-analysis projecting a 30% increase in hemorrhage risk per decade [22, 26]; however, this has not been consistently supported across comparable large reviews [23, 25], and several cohort studies have in fact identified younger age as a risk factor for hemorrhage [5, 19]. Similarly, some cohort studies have identified gender [19, 29], race [30, 31], or history of hypertension [32, 33] as risk factors for hemorrhagic presentation; however, these results have not been widely studied. More recently, investigators have sought to identify genetic polymorphisms, primarily those involved with inflammatory and angiogenic pathways, associated with cerebral AVM diagnosis, hemorrhagic presentation, and outcome after treatment [34]. Finally, patient preference and lifestyle should be taken into account. Given the heterogeneity of data and spectrum of management options, thorough patient counseling is imperative. In addition, the psychosocial impact of the diagnosis should weigh into the patient's decision-making process.

Angioarchitectural Factors

Angiographic features associated with rupture of cerebral AVMs have been widely studied and have important implications for natural history risk. Table 17.2 summarizes the angioarchitectural characteristics found to be independent risk factors for AVM hemorrhage at time of diagnosis or in follow-up in multivariate analyses.

Table 17.2 Angioarchitectural characteristics associated with hemorrhagic presentation or re-hemorrhage of cerebral AVMs in multivariate analyses

Risk factor for hemorrhagic presentation	Risk factor for subsequent hemorrhage
Small size [22, 32, 38, 44, 45, 47]	Large size [5, 36]
Deep location [22, 37]	Deep location [5, 19, 22, 49]
Infratentorial location [22, 37]	Infratentorial location [5]
Non-borderzone location [22]	Diffuse morphology [24]
Perforating feeders [42]	Arterial aneurysms [25, 26]
Arterial aneurysms [22, 37, 44, 45]	Deep venous drainage [20, 22, 27]
Deep venous drainage [22, 32, 38, 42, 44, 45, 47, 48]	Single draining vein [24, 49]
Single draining vein [37, 47]	Presence of venous varices/ectasias [49]
Presence of venous varices/ectasias [37]	

General characteristics include size and location. Small size, typically defined as <3 cm, has been identified as a risk for hemorrhagic presentation [22, 23]; however, this may reflect a tendency for smaller lesions to escape diagnosis until they hemorrhage, compared to larger lesions which may present with other symptoms [35]. In contrast, multiple studies have either failed to find an association between AVM size and hemorrhage [25] or identified larger size [5, 23, 36] or diffuse morphology [24] as risk factors for subsequent hemorrhage. Deep, infratentorial, or "non-borderzone" (single major arterial feeder) locations have all been associated with higher risk of bleeding at presentation or afterward [5, 19, 22, 25, 36, 37].

Hemodynamic factors and specific vascular features of both the arterial and venous macrocirculation may correlate with hemorrhage risk. Several studies have reported higher feeding artery pressures, typically associated with small AVMs, longer feeding artery length [38–41], perforating arterial feeders [42], or intranidal fistulae [43] as potential risk factors for hemorrhage. Arterial aneurysms, either feeding artery, intranidal, or remote, are not uncommon in AVM patients and have all been studied as potential risk factors. In a recent meta-analysis by Gross et al., 18% of patients had an associated arterial aneurysm, half occurring in feeding arteries, and presence of an aneurysm was a risk factor for hemorrhage, with a hazard ratio of 1.8 (95% CI 1.6–2.0) [25]. Other groups have stratified risk by aneurysm type and reported increased risk of hemorrhagic presentation with feeding artery aneurysms [44] and intranidal aneurysms [45]. Deep venous drainage has been consistently implicated as an important angiographic feature of AVMs; however, studies have variably reported exclusively deep drainage versus a component of deep drainage as a risk factor for initial or subsequent hemorrhage [22, 23, 25, 26, 32, 42, 45–48]. The number of draining veins has also been investigated, with authors reporting presence of a single draining vein as associated with rupture [24, 37, 46, 47, 49], as have venous anomalies such as ectasias, stenosis, or occlusion [25, 33, 37, 46, 49]. In an effort to clarify the significance of angioarchitectural characteristics associated with hemorrhage and thus assist with clinical decision-making, Sahlein et al. proposed outflow impedance as a physiologic mechanism for increased risk of rupture. In addition to identifying a single draining vein as predictive of rup-

ture, they showed that patients with multiple draining veins and outflow stenosis had increased risk of rupture, comparable to those with single veins. Furthermore, an agreement analysis looking at other factors that have an unclear physiologic rationale for increasing risk (small size, deep drainage, deep location, absence of pial-to-pial collaterals) supported the hypothesis that the significance of these factors can be explained by association with more physiologically plausible factors that cause outflow impedance [33]. Importantly, such studies emphasize the need to consider how clinical and angioarchitectural characteristics of AVMs may alter a patient's rupture risk.

Preoperative Planning

Once the decision has been made to treat an AVM, comprehensive preoperative planning is critical to ensure safe, successful intervention. In general, surgical resection is an elective procedure. For life-threatening hemorrhage requiring emergency surgery, clot evacuation without attempting AVM resection is typically performed. For ruptured AVMs that are not immediately life-threatening, delayed resection (at least 1–2 weeks) is commonly advocated, as this allows time for the hematoma to liquefy, surrounding inflammatory changes to resolve, and recovery from temporary neurologic deficit, all of which are important for appropriate decision-making. Though acute intervention has been advocated by some [50], this does not allow time for the patient to recover from temporary deficit or to reassess the AVM architecture after hemorrhage, both of which have implications for choice of treatment modality.

In the setting of hemorrhage, especially if urgent surgery is necessary, head CT and CT angiogram may be sufficient preoperative imaging, as they allow for rapid diagnosis and assessment of angioarchitecture; however, elective preoperative planning should also include MRI and digital subtraction angiography (DSA). MRI and MR angiography (MRA) can provide significant insight into the surrounding brain tissue. Particularly for lesions located in the eloquent cortex, evolving techniques using fiber tractography and functional mapping may prove extremely useful for surgical planning [51]. Future innovations in MRI technique, such as radial phase-contrast MRA, may improve noninvasive evaluation of AVM hemodynamics [52].

DSA remains the gold standard for evaluating AVMs and should be performed early after presentation with hemorrhage and again just prior to surgery. In addition to fully defining the feeding arteries and draining veins, it provides information about hemodynamics; furthermore, superselective microcatheterization of individual feeding pedicles can elucidate angioarchitectural characteristics associated with hemorrhage, such as nidal aneurysms or venous stenosis, that may otherwise be undetected [33, 53]. Preoperative embolization has emerged as an important step in the multidisciplinary management of AVMs. In the acute phase after hemorrhage, identification and embolization of the likely source of hemorrhage, such as intra- or perinidal aneurysms, may help reduce risk of early re-hemorrhage [54, 55]. Preoperative embolization has been shown to enhance the safety and efficacy of

surgery by reducing operative time and blood loss, with no significant difference in postoperative complications or long-term neurologic outcome [56]. Some series have additionally shown improved rates of major neurologic deficit, seizure, and death with embolization prior to surgical resection [57]. Embolization can be used to significantly shrink the nidus size and secure deep arterial feeders or associated aneurysms that may be difficult to access surgically, thus facilitating complete resection [58–62]; moreover, this may effectively decrease the Spetzler-Martin grade of the lesion, thus making previously inoperable lesions operable [63]. Though morbidity and mortality secondary to embolization remain low, particularly with modern techniques and materials, the addition of superselective amytal testing can be utilized during the procedure to predict morbidity from vessel occlusion and thus lower complication rate [64–68].

SRS prior to surgical resection has also been described. Steinberg et al. first described a series of patients who underwent surgical resection of incompletely obliterated AVMs after SRS; they found the AVM to be less vascular, partially thrombosed, and more easily resected than patients who had not undergone SRS [69]. This was echoed in a later case report of a large AVM treated with staged SRS followed by resection, with authors describing gliotic brain tissue with an easily developed plane around the lesion [70]. More recent series have described favorable outcomes for surgery following SRS – radiosurgery significantly decreased lesion size and downgraded the Spetzler-Martin grade – thus facilitating resection with lower rates of preoperative embolization, shorter operative time, decreased blood loss and length of stay, and better functional outcome postoperatively [71–74]. Such results suggest that in carefully selected patients, namely, young patients with high-grade AVMs initially considered inoperable, SRS may play a role in a multimodality treatment plan. See Fig. 17.1 for a case presentation of a ruptured AVM with an associated aneurysm.

Surgical Techniques and Considerations

Surgical resection of AVMs remains among the most challenging lesions in the neurosurgical arena. These cases often involve complex anatomy, long spans of extreme attention to detail, meticulous hemostasis, and extreme psychological stress. These factors can be combated with careful study of preoperative films, operative planning, and honest patient counseling.

Techniques

Positioning will vary based on location of lesion. Attention to positioning to allow for good venous return is important. In addition, if the femoral artery is accessible, an intraoperative angiogram should be planned for. In certain cases an immediate postoperative angiogram would be necessary.

Good communication with the anesthesia team, neuro-monitoring, and the scrub technicians is paramount. Neuro-navigation has started to play a bigger role and should also be coordinated beforehand. A large craniotomy is necessary with ade-

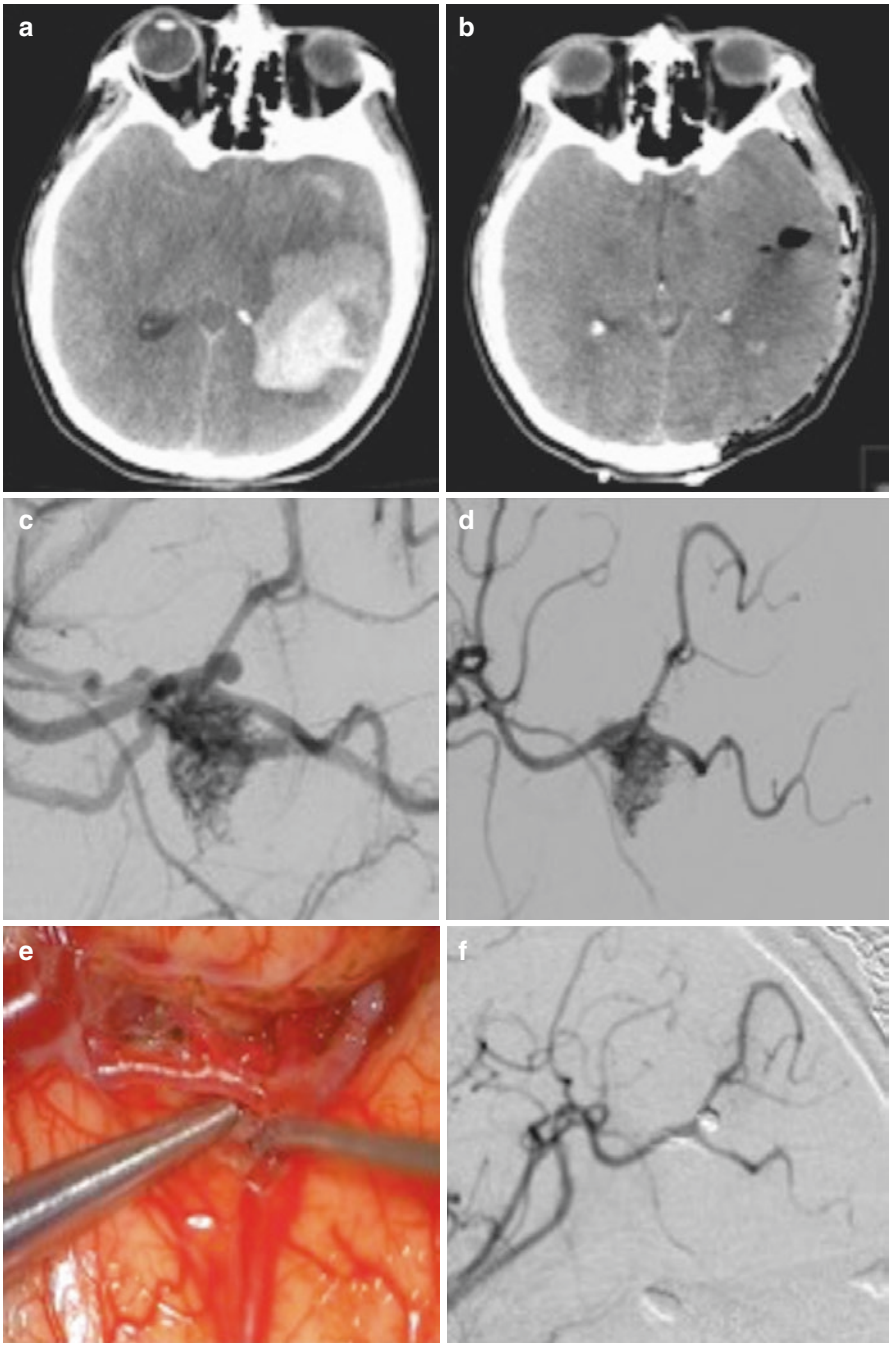


Fig. 17.1 Management of a ruptured left parietal AVM in a 25-year-old male. (**a**) Presentation CT with radiographic and clinical evidence of herniation. (**b**) s/p hemicraniectomy with evacuation of hematoma and no resection of AVM. (**c**) Angiogram showing an aneurysm on the peri-arterial bifurcation. (**d**) Coiling of aneurysm on POD 1. (**e**) Following 10 days of observant management, resection of AVM. (**f**) Intraoperative angiogram showing complete resection of AVM

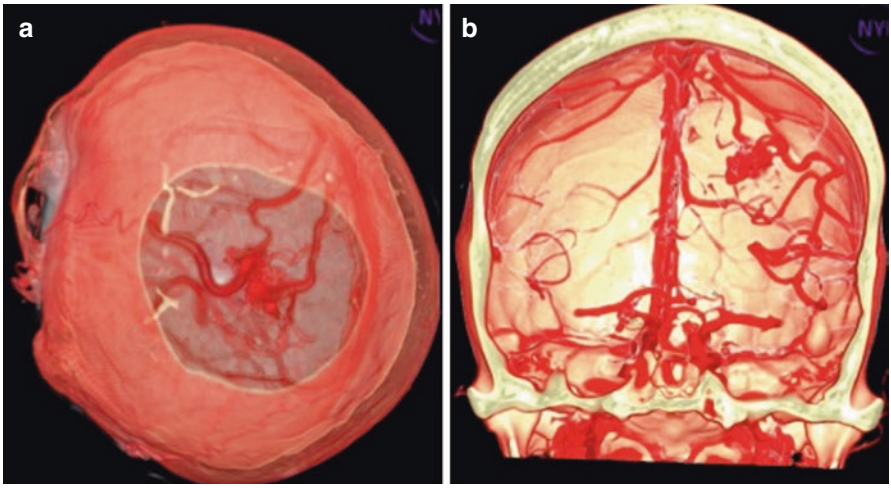


Fig. 17.2 (**a**, **b**) Use of a surgical planning system for visualization of surface vessels, allowing for identification of surface arterial feeders and draining veins

quate exposure of superficial arterial feeders or draining veins that are a distance from the nidus.

Vein preservation is crucial. Often, deciding which vessels are draining veins is among the first decisions to be made, especially in superficially draining AVMs. These draining vessels, due to arterialization, can be confused with arterial pedicles as well as passerby arteries. Careful preoperative examination of films will help prepare you for this decision. In addition, 3-D surgical planning platforms can assist (Fig. 17.2).

Resection of the AVM is usually carried out in a circumferential dissection and in a spiral fashion toward its depth. In cases where there are multiple draining veins, a decision to take a secondary draining vein for the purposes of exposure can be made. AVMs that track down to the ventricle usually have ependymal feeders, and these must be also coagulated, although it is usually the more difficult aspect of the case. As the resection nears completion, the draining vein can be noted to return to a darker color signifying a reduction in arterial shunting. If doubt remains, temporary clipping of the draining vein can be done to see if it is safe to disconnect.

Bipolar electrocautery forceps is one of the most important instruments in this surgery. Minimizing the adherence of the coagulated vessels to the bipolar tips is important for an efficient resection. Irrigating bipolar forceps or bipolars under constant irrigation will reduce that adherence. In addition, newer bipolars with different metallic surfaces allow for a better heat sink capacity and less thermal spread. Constant cleaning of the tips and keeping them in ice water will also allow for efficacious use.

Hemostatic materials are helpful in managing small venous bleeding in the cavity however should not be used for small arterial bleeding. Commonly, these arterial feeders will retract out of sight and can cause adjacent hematomas. These retracted vessels must be followed, even if further white matter dissection has to take place and be coagulated.

Surgical Outcomes and Complications

Surgical outcomes have improved over time with better patient selection and risk stratification, clarification of angioarchitectural risk factors, and refinement of surgical approaches; however, it is essential to critically evaluate treatment outcomes in comparison to the natural history risk. The goal of AVM resection is complete obliteration to mitigate the morbidity and mortality associated with the natural history. To this end, Laakso et al. studied the excess mortality experienced by patients diagnosed with an AVM and found that treatment reduced the excess mortality conferred by an AVM diagnosis [6]. Obliteration rates after surgical resection are extremely high, with reported angiographic cure rates of 94–100% [34, 75, 76].

Outcomes by Spetzler-Martin Grade

Classification of functional outcomes varies by author; however, a common stratification defines outcomes using modified Rankin scale (mRs), with a good outcome defined as ≤ 1 or ≤ 2. Postoperative complications may include hemorrhage, infarct, seizure, infection, need for CSF diversion, or, in extremely rare circumstances, retrograde arterial or venous thrombosis or vasospasm. In their series of 232 patients with Spetzler-Martin grade I or II AVMs who underwent surgical resection, Potts et al. demonstrated a 94% complete obliteration rate with 93% of patients mRS ≤ 2 and 97% of patients unchanged or improved postoperatively; furthermore, surgical mortality rate was only 0.4%, and only 3% of patients were neurologically worse postoperatively. These results were comparable to the summary of surgical series for grades I and II AVMs the authors reported, with mortality rates ranging from 0% to 2.2% (mean 0.3%) and morbidity rates ranging from 0% to 6.6% (mean 2.2%) [76]. Grade III AVMs represent a heterogeneous population, with four combinations of size, venous drainage, and eloquence, and reported surgical outcomes reflect this heterogeneity. Lawton et al. addressed this by analyzing a series of only grade III AVMs and proposing a modification of the Spetzler-Martin scale [75]. They achieved a 97.4% obliteration rate; notably, 25% of patients had undergone some prior treatment, and 75 of 76 patients were embolized preoperatively, with 2 hemorrhages attributed to the endovascular procedure. Postoperatively they reported three hemorrhages and a surgical mortality rate of 3.9%, for an overall surgical risk of 8.0%. Good outcomes (mRS ≤ 2) were achieved in 78.7% of patients, and 3.9% of patients experienced permanent treatment-associated neurological morbidity. The authors further stratified patients by type of grade III AVM, reporting that patients with small AVMs (S1V1E1) did the best, with 97.1% unchanged or improved postoperatively, compared to those with medium/deep AVMs (S2V1E0) or medium/eloquent (S2V0E1), with 92.9% and 85.2% of patients unchanged or improved postoperatively, respectively. Surgical morbidity and mortality for grades IV and V AVMs are high, with rates of up to 26% morbidity and 3.2% mortality described in early series [77–80], prompting many to defer surgical resection for these lesions. More recent series have tended to utilize a multimodality approach more frequently

and have reported complete obliteration rates of 70–97.6%, with morbidity/mortality rates ranging from 10% to 23% [73, 80, 81]. When comparing outcomes after 2000 with the historical cohort prior to 2000, some authors noted a nearly 50% reduction in poor outcomes [82].

Outcomes for Seizures

Persistent seizures or drug-resistant epilepsy are important indications for surgical resection of AVMs, as complete obliteration leads to the best outcomes for seizure control. Some modern series report seizure control rates (Engel class I or II) of 93–100% [83, 84], though outcomes were not analyzed by type of preoperative seizure. In a series of 293 patients with sporadic seizures (41%), chronic seizures (35.9%), or drug-resistant epilepsy (23.3%) who underwent complete surgical resection, seizure control rates were favorable – 85.7% of patients with sporadic seizures, 80.5% with chronic seizures, and 58.3% with drug-resistant epilepsy were seizure-free [85]. Control rates in the drug-resistant subset improved to 80% for patients who underwent extended lesionectomy for seizure control.

Outcomes for ARUBA-Eligible Patients

"A Randomized Trial of Unruptured Brain AVMs" (ARUBA) was a prospective, multicenter, parallel design, nonblinded, randomized controlled trial designed to compare medical management alone to medical management with interventional therapy for prevention of death or stroke in patients with unruptured brain AVMs [86]. The study, which was halted early after interim analysis, concluded that medical management was superior to intervention for prevention of death or stroke in patients with unruptured AVMs followed for 33 months. This surprising result, which is at odds with much of the prior literature, was widely critiqued. Among comments on design, conduct, and result analysis, factors such as selection criteria, lack of standardization of the treatment arm, low enrollment rate, recruitment bias, short follow-up, and inappropriate conclusions were all frequently cited as problematic [87]. Specifically, the low number of randomized patients compared to those who refused or were treated elsewhere, low number of surgically treated patients (18%), and high number of patients treated with radiosurgery (33%) or embolization (32%) followed for a relatively short time period may have contributed to the study's conclusion. In the wake of this study, the importance of solidifying the safety and efficacy of AVM resection was emphasized, and many groups published their experience with surgical intervention for patients who could have been eligible for the ARUBA trial. Authors primarily focused on Spetzler-Martin grades I and II AVMs, as these are the most favorable for surgery and the ones most likely to have been selected for treatment outside the randomization process of ARUBA, and reinforced the low morbidity and mortality associated with intervention [76, 88–92]. A systematic review of this literature included 6 studies with 956 patients; of studies

that included both surgery and radiosurgery with or without embolization, 50–58% of patients underwent surgical resection [93]. Compared to ARUBA, in which 30.7% of patients in the treatment arm reached the primary endpoint of symptomatic stroke or death, these studies reported a mean rate of 8.0% stroke or death, which was similar to the rate for the medical arm (10.1%) of ARUBA. Similarly, the percentage of patients with poor functional outcomes (mRS $\geq$ 2) in the reviewed studies (mean 9.9%) was more comparable to that reported in the medical arm of ARUBA (14%) than the intervention arm (38.6%) [93]. The review summarized that in contrast to the ARUBA results, surgical intervention can effectively treat appropriately selected unruptured AVMs with a safety margin similar to that of medical management [93].

References

1. Berman MF, Sciacca RR, Pile-Spellman J, Stapf C, Connolly ES Jr, Mohr JP, et al. The epidemiology of brain arteriovenous malformations. Neurosurgery. 2000;47(2):389–96; discussion 97.
2. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain J Neurol. 2001;124(Pt 10):1900–26.
3. Moftakhar P, Hauptman JS, Malkasian D, Martin NA. Cerebral arteriovenous malformations. Part 1: cellular and molecular biology. Neurosurg Focus. 2009;26(5):E10.
4. Kondziolka D, McLaughlin MR, Kestle JR. Simple risk predictions for arteriovenous malformation hemorrhage. Neurosurgery. 1995;37(5):851–5.
5. Hernesniemi JA, Dashti R, Juvela S, Vaart K, Niemela M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. Neurosurgery. 2008;63(5):823–9. discussion 9–31.
6. Laakso A, Dashti R, Seppanen J, Juvela S, Vaart K, Niemela M, et al. Long-term excess mortality in 623 patients with brain arteriovenous malformations. Neurosurgery. 2008;63(2):244–53; discussion 53–5.
7. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg. 1990;73(3):387–91.
8. Morgan M, Sekhon L, Rahman Z, Dandie G. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. Stroke. 1998;29(9):2001–2.
9. Brown RD Jr, Wiebers DO, Torner JC, O'Fallon WM. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intracranial vascular malformations in Olmsted country Minnesota. J Neurosurg. 1996;85(1):29–32.
10. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83.
11. Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. Neurosurgery. 1994;34(1):2–6; discussion−7.
12. Han PP, Ponce FA, Spetzler RF. Intention-to-treat analysis of Spetzler-Martin grades IV and V arteriovenous malformations: natural history and treatment paradigm. J Neurosurg. 2003;98(1):3–7.
13. Luessenhop AJ, Gennarelli TA. Anatomical grading of supratentorial arteriovenous malformations for determining operability. Neurosurgery. 1977;1(1):30–5.
14. Luessenhop AJ, Rosa L. Cerebral arteriovenous malformations. Indications for and results of surgery, and the role of intravascular techniques. J Neurosurg. 1984;60(1):14–22.
15. Shi YQ, Chen XC. A proposed scheme for grading intracranial arteriovenous malformations. J Neurosurg. 1986;65(4):484–9.

16. Kim H, Abla AA, Nelson J, McCulloch CE, Bervini D, Morgan MK, et al. Validation of the supplemented Spetzler-Martin grading system for brain arteriovenous malformations in a multicenter cohort of 1009 surgical patients. Neurosurgery. 2015;76(1):25–31; discussion−2; quiz 2–3.
17. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery. 2010;66(4):702–13; discussion 13.
18. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg. 1983;58(3):331–7.
19. Yamada S, Takagi Y, Nozaki K, Kikuta K, Hashimoto N. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. J Neurosurg. 2007;107(5):965–72.
20. Mast H, Young WL, Koennecke HC, Sciacca RR, Osipov A, Pile-Spellman J, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. Lancet. 1997;350(9084):1065–8.
21. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. Stroke. 2004;35(7):1697–702.
22. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology. 2006;66(9):1350–5.
23. Abecassis IJ, Xu DS, Batjer HH, Bendok BR. Natural history of brain arteriovenous malformations: a systematic review. Neurosurg Focus. 2014;37:E7.
24. Pollock B, Flickinger J, Lunsford L, Bissonette D, Kondziolka D. Factors that predict the bleeding risk of cerebral arteriovenous malformations. Stroke. 1996;27:1–6.
25. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. J Neurosurg. 2013;118:437–43.
26. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. Neurology. 2014;83:590–7.
27. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. Stroke. 2009;40(1):100–5.
28. Laakso A, Dashti R, Juvela S, Isarakul P, Niemela M, Hernesniemi J. Risk of hemorrhage in patients with untreated Spetzler-Martin grade IV and V arteriovenous malformations: a long-term follow-up study in 63 patients. Neurosurgery. 2011;68(2):372–7; discussion 8.
29. Tong X, Wu J, Lin F, Cao Y, Zhao Y, Ning B, et al. The effect of age, sex, and lesion location on initial presentation in patients with brain arteriovenous malformations. World Neurosurg. 2016;87:598–606.
30. Yang W, Caplan JM, Ye X, Wang JY, Braileanu M, Rigamonti D, et al. Racial associations with hemorrhagic presentation in cerebral arteriovenous malformations. World Neurosurg. 2015;84(2):461–9.
31. Kim H, Sidney S, McCulloch CE, Poon KY, Singh V, Johnston SC, et al. Racial/Ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. Stroke. 2007;38(9):2430–7.
32. Langer DJ, Lasner TM, Hurst RW, Flamm ES, Zager EL, King JT. Hypertension, small size, and deep venous drainage are associated with risk of hemorrhagic presentation of cerebral arteriovenous malformations. Neurosurgery. 1998;42:481–9.
33. Sahlein DH, Mora P, Becske T, Huang P, Jafar JJ, Connolly ES, et al. Features predictive of brain arteriovenous malformation hemorrhage: extrapolation to a physiologic model. Stroke. 2014;45:1964–70.
34. Spetzler RF, Kondziolka DS, Higashida RT, Kalani MYS. Comprehensive management of arteriovenous malformations of the brain and spine. Cambridge: Cambridge University Press; 2015.
35. Laakso A, Hernesniemi J, Yonekawa Y, Tsukahara T. Surgical management of cerebrovascular disease. Vienna: Springer; 2009.

36. Stefani MA, Porter PJ, terBrugge KG, Montanera W, Willinsky RA, Wallace MC. Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. Stroke. 2002;33(5):1220–4.
37. Lv X, Wu Z, Jiang C, Yang X, Li Y, Sun Y, et al. Angioarchitectural characteristics of brain arteriovenous malformations with and without hemorrhage. World Neurosurg. 2011;76(1–2):95–9.
38. Kader A, Young WL, Pile-Spellman J, Mast H, Sciacca RR, Mohr JP, et al. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. Neurosurgery. 1994;34(5):801–7; discussion 7–8.
39. Miyasaka Y, Yada K, Kurata A, Tokiwa K, Irikura K, Tanaka R, et al. Correlation between intravascular pressure and risk of hemorrhage due to arteriovenous malformations. Surg Neurol. 1993;39(5):370–3.
40. Nornes H, Grip A. Hemodynamic aspects of cerebral arteriovenous malformations. J Neurosurg. 1980;53(4):456–64.
41. Spetzler RF, Hargraves RW, McCormick PW, Zabramski JM, Flom RA, Zimmerman RS. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. J Neurosurg. 1992;76(6):918–23.
42. Pan J, Feng L, Vinuela F, He H, Wu Z, Zhan R. Angioarchitectural characteristics associated with initial hemorrhagic presentation in supratentorial brain arteriovenous malformations. Eur J Radiol. 2013;82:1959–63.
43. Soderman M, Andersson T, Karlsson B, Wallace MC, Edner G. Management of patients with brain arteriovenous malformations. Eur J Radiol. 2003;46(3):195–205.
44. Stapf C, Mohr JP, Pile-Spellman J, Sciacca RR, Hartmann A, Schumacher HC, et al. Concurrent arterial aneurysms in brain arteriovenous malformations with haemorrhagic presentation. J Neurol Neurosurg Psychiatry. 2002;73(3):294–8.
45. Kim EJ, Halim AX, Dowd CF, Lawton MT, Singh V, Bennett J, et al. The relationship of coexisting extranidal aneurysms to intracranial hemorrhage in patients harboring brain arteriovenous malformations. Neurosurgery. 2004;54(6):1349–57; discussion 57–8.
46. Miyasaka Y, Yada K, Ohwada T, Kitahara T, Kurata A, Irikura K. An analysis of the venous drainage system as a factor in hemorrhage from arteriovenous malformations. J Neurosurg. 1992;76(2):239–43.
47. Alexander MD, Cooke DL, Nelson J, Guo DE, Dowd CF, Higashida RT, et al. Association between venous angioarchitectural features of sporadic brain arteriovenous malformations and intracranial hemorrhage. AJNR Am J Neuroradiol. 2015;36:949–52.
48. Duong DH, Young WL, Vang MC, Sciacca RR, Mast H, Koennecke HC, et al. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. Stroke. 1998;29:1167–76.
49. Stefani MA, Porter PJ, TerBrugge KG, Montanera W, Willinsky RA, Wallace MC. Angioarchitectural factors present in brain arteriovenous malformations associated with hemorrhagic presentation. Stroke. 2002;33:920–4.
50. Kuhmonen J, Piippo A, Vaart K, Karatas A, Ishii K, Winkler P, et al. Early surgery for ruptured cerebral arteriovenous malformations. Acta Neurochir Suppl. 2005;94:111–4.
51. Bendok BR, El Tecle NE, El Ahmadieh TY, Koht A, Gallagher TA, Carroll TJ, et al. Advances and innovations in brain arteriovenous malformation surgery. Neurosurgery. 2014;74(Suppl 1):S60–73.
52. Chang W, Loecher MW, Wu Y, Niemann DB, Ciske B, Aagaard-Kienitz B, et al. Hemodynamic changes in patients with arteriovenous malformations assessed using high-resolution 3D radial phase-contrast MR angiography. AJNR Am J Neuroradiol. 2012;33:1565–72.
53. Turjman F, Massoud TF, Vinuela F, Sayre JW, Guglielmi G, Duckwiler G. Correlation of the angioarchitectural features of cerebral arteriovenous malformations with clinical presentation of hemorrhage. Neurosurgery. 1995;37(5):856–60. discussion 60–2.
54. Perata HJ, Tomsick TA, Tew JM Jr. Feeding artery pedicle aneurysms: association with parenchymal hemorrhage and arteriovenous malformation in the brain. J Neurosurg. 1994;80(4):631–4.

55. Mpotsaris A, Loehr C, Harati A, Lohmann F, Puchner M, Weber W. Interdisciplinary clinical management of high grade arteriovenous malformations and ruptured flow-related aneurysms in the posterior fossa. Interv Neuroradiol. 2010;16(4):400–8.
56. Jafar JJ, Davis AJ, Berenstein A, Choi IS, Kupersmith MJ. The effect of embolization with N-butyl cyanoacrylate prior to surgical resection of cerebral arteriovenous malformations. J Neurosurg. 1993;78(1):60–9.
57. Pasqualin A, Scienza R, Cioffi F, Barone G, Benati A, Beltramello A, et al. Treatment of cerebral arteriovenous malformations with a combination of preoperative embolization and surgery. Neurosurgery. 1991;29(3):358–68.
58. Nataraj A, Mohamed MB, Gholkar A, Vivar R, Watkins L, Aspoas R, et al. Multimodality treatment of cerebral arteriovenous malformations. World Neurosurg. 2014;82(1–2):149–59.
59. Natarajan SK, Ghodke B, Britz GW, Born DE, Sekhar LN. Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with onyx: single-center experience and technical nuances. Neurosurgery. 2008;62(6):1213–25. discussion 25–6.
60. Vinuela F, Dion JE, Duckwiler G, Martin NA, Lylyk P, Fox A, et al. Combined endovascular embolization and surgery in the management of cerebral arteriovenous malformations: experience with 101 cases. J Neurosurg. 1991;75(6):856–64.
61. Starke RM, Komotar RJ, Otten ML, Hahn DK, Fischer LE, Hwang BY, et al. Adjuvant embolization with N-butyl cyanoacrylate in the treatment of cerebral arteriovenous malformations: outcomes, complications, and predictors of neurologic deficits. Stroke. 2009;40(8):2783–90.
62. Weber W, Kis B, Siekmann R, Jans P, Laumer R, Kuhne D. Preoperative embolization of intracranial arteriovenous malformations with Onyx. Neurosurgery. 2007;61(2):244–52. discussion 52–4.
63. Spetzler RF, Martin NA, Carter LP, Flom RA, Raudzens PA, Wilkinson E. Surgical management of large AVM's by staged embolization and operative excision. J Neurosurg. 1987;67(1):17–28.
64. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, et al. Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the stroke council, American Stroke Association. Circulation. 2001;103(21):2644–57.
65. Purdy PD, Batjer HH, Samson D, Risser RC, Bowman GW. Intraarterial sodium amytal administration to guide preoperative embolization of cerebral arteriovenous malformations. J Neurosurg Anesthesiol. 1991;3(2):103–6.
66. Rauch RA, Vinuela F, Dion J, Duckwiler G, Amos EC, Jordan SE, et al. Preembolization functional evaluation in brain arteriovenous malformations: the ability of superselective amytal test to predict neurologic dysfunction before embolization. AJNR Am J Neuroradiol. 1992;13(1):309–14.
67. Moo LR, Murphy KJ, Gailloud P, Tesoro M, Hart J. Tailored cognitive testing with provocative amobarbital injection preceding AVM embolization. AJNR Am J Neuroradiol. 2002;23(3):416–21.
68. Tawk RG, Tummala RP, Memon MZ, Siddiqui AH, Hopkins LN, Levy EI. Utility of pharmacologic provocative neurological testing before embolization of occipital lobe arteriovenous malformations. World Neurosurg. 2011;76(3–4):276–81.
69. Steinberg GK, Chang SD, Levy RP, Marks MP, Frankel K, Marcellus M. Surgical resection of large incompletely treated intracranial arteriovenous malformations following stereotactic radiosurgery. J Neurosurg. 1996;84(6):920–8.
70. Firlik AD, Levy EI, Kondziolka D, Yonas H. Staged volume radiosurgery followed by microsurgical resection: a novel treatment for giant cerebral arteriovenous malformations: technical case report. Neurosurgery. 1998;43(5):1223–8.
71. Sanchez-Mejia RO, McDermott MW, Tan J, Kim H, Young WL, Lawton MT. Radiosurgery facilitates resection of brain arteriovenous malformations and reduces surgical morbidity. Neurosurgery. 2009;64(2):231–8; discussion 8–40.

72. Zaidi HA, Abla AA, Nakaji P, Spetzler RF. Prospective evaluation of preoperative stereotactic radiosurgery followed by delayed resection of a high grade arteriovenous malformation. J Clin Neurosci. 2014;21(6):1077–80.
73. Abla AA, Rutledge WC, Seymour ZA, Guo D, Kim H, Gupta N, et al. A treatment paradigm for high-grade brain arteriovenous malformations: volume-staged radiosurgical downgrading followed by microsurgical resection. J Neurosurg. 2014;122:1–14.
74. Tong X, Wu J, Pan J, Lin F, Cao Y, Zhao Y, et al. Microsurgical resection for persistent arteriovenous malformations following gamma knife radiosurgery: a case-control study. World Neurosurg. 2016;88:277–88.
75. Lawton MT, Project UBAMS. Spetzler-Martin grade III arteriovenous malformations: surgical results and a modification of the grading scale. Neurosurgery. 2003;52(4):740–8; discussion 8–9.
76. Potts MB, Lau D, Abla AA, Kim H, Young WL, Lawton MT, et al. Current surgical results with low-grade brain arteriovenous malformations. J Neurosurg. 2015;122:912–20.
77. Heros RC, Korosue K, Diebold PM. Surgical excision of cerebral arteriovenous malformations: late results. Neurosurgery. 1990;26(4):570–7. discussion 7–8.
78. Hartmann A, Stapf C, Hofmeister C, Mohr JP, Sciacca RR, Stein BM, et al. Determinants of neurological outcome after surgery for brain arteriovenous malformation. Stroke. 2000;31(10):2361–4.
79. Nozaki K, Hashimoto N, Miyamoto S, Kikuchi H. Resectability of Spetzler-Martin grade IV and V cerebral arteriovenous malformations. J Clin Neurosci. 2000;7(Suppl 1):78–81.
80. Jizong Z, Shuo W, Jingsheng L, Dali S, Yuanli Z, Yan Z. Combination of intraoperative embolisation with surgical resection for treatment of giant cerebral arteriovenous malformations. J Clin Neurosci. 2000;7(Suppl 1):54–9.
81. Zhao J, Yu T, Wang S, Zhao Y, Yang WY. Surgical treatment of giant intracranial arteriovenous malformations. Neurosurgery. 2010;67(5):1359–70; discussion 70.
82. Reinard KA, Pabaney AH, Basheer A, Phillips SB, Kole MK, Malik GM. Surgical management of giant intracranial arteriovenous malformations: a single center experience over 32 years. World Neurosurg. 2015;84:1765–78.
83. Englot DJ, Young WL, Han SJ, McCulloch CE, Chang EF, Lawton MT. Seizure predictors and control after microsurgical resection of supratentorial arteriovenous malformations in 440 patients. Neurosurgery. 2012;71:572–9.
84. Nagata S, Morioka T, Matsukado K, Natori Y, Sasaki T. Retrospective analysis of the surgically treated temporal lobe arteriovenous malformations with focus on the visual field defects and epilepsy. Surg Neurol. 2006;66:50–5.
85. Von Der Brelie C, Simon M, Esche J, Schramm J, Boström A. Seizure outcomes in patients with surgically treated cerebral arteriovenous malformations. Neurosurgery. 2015;77:762–8.
86. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet. 2014;383:614–21.
87. Magro E, Gentric J-c, Darsaut TE, Ziegler D, Bojanowski MW, Raymond J. Responses to ARUBA: a systematic review and critical analysis for the design of future arteriovenous malformation trials. J Neurosurg. 2016:1–9.
88. Javadpour M, Al-Mahfoudh R, Mitchell PS, Kirollos R. Outcome of microsurgical excision of unruptured brain arteriovenous malformations in ARUBA-eligible patients. Br J Neurosurg. 2016;30:1–4.
89. Moon K, Levitt MR, Almefty RO, Nakaji P, Albuquerque FC, Zabramski JM, et al. Safety and efficacy of surgical resection of unruptured low-grade arteriovenous malformations from the modern decade. Neurosurgery. 2015;77:948–52; discussion 52–3.
90. Lawton MT. The role of AVM microsurgery in the aftermath of a randomized trial of unruptured brain arteriovenous malformations. AJNR Am J Neuroradiol. 2015;36:617–9.

91. Rutledge WC, Abla AA, Nelson J, Halbach VV, Kim H, Lawton MT. Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. Neurosurg Focus. 2014;37:E8.
92. Schramm J, Schaller K, Esche J, Boström A. Microsurgery for cerebral arteriovenous malformations: subgroup outcomes in a consecutive series of 288 cases. J Neurosurg. 2016:1–8.
93. Hong CS, Peterson EC, Ding D, Sur S, Hasan D, Dumont AS, et al. Intervention for a randomized trial of unruptured brain arteriovenous malformations (ARUBA) – eligible patients: an evidence-based review. Clin Neurol Neurosurg. 2016;150:133–8.

Chapter 18
Arteriovenous Malformations: Endovascular Indications and Technique

Katyucia De Macedo Rodrigues, Anna L. Kuhn, Ajay K. Wakhloo, and Ajit S. Puri

Endovascular treatment (EVT) is one of the three main pillars of management of brain arteriovenous malformation (b-AVM). Constant advances in microcatheter technology, embolic agents, and new angiography systems with reduced radiation exposure are likely to continue to expand the role of endovascular therapy in b-AVM treatment. Factors such as natural history, location, size, angioarchitecture, rupture status, and presence of symptoms are considered when determining the role of EVT in the overall patient management. The goal of EVT is defined by these aspects in conjunction with patient medical history and desire of the patient to undergo treatment, as well as local availability of technology and operator experience. Despite the increasing number of case series reporting b-AVM cure after EVT, it is still largely considered a neoadjuvant treatment prior to microsurgery and stereotactic radiosurgery [1]. Nonetheless, it is an important therapeutic option, alongside radiosurgery, for deep-seated lesions.

When performed prior to microsurgical resection, the goal of EVT is to eliminate b-AVM features which are known to increase the risk of rupture ("weak points"), such as nidal and perinidal aneurysms (Fig. 18.1). Also, endovascular

K. De Macedo Rodrigues
Department of Neuroradiology, University of Massachusetts Medical School, Worcester, MA, USA

A. L. Kuhn
Department of Radiology, Umass Medical School, Worcester, MA, USA
e-mail: anna.kuhn@umassmemorial.org

A. K. Wakhloo
Department of Radiology, University of Massachusetts Medical School, Worcester, MA, USA
e-mail: ajay.wahkloo@umassmemorial.org

A. S. Puri (✉)
Department of Diagnostic Radiology and Neuroradiology, UMass Memorial Health Care, Worcester, MA, USA
e-mail: Ajit.Puri@umassmemorial.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_18

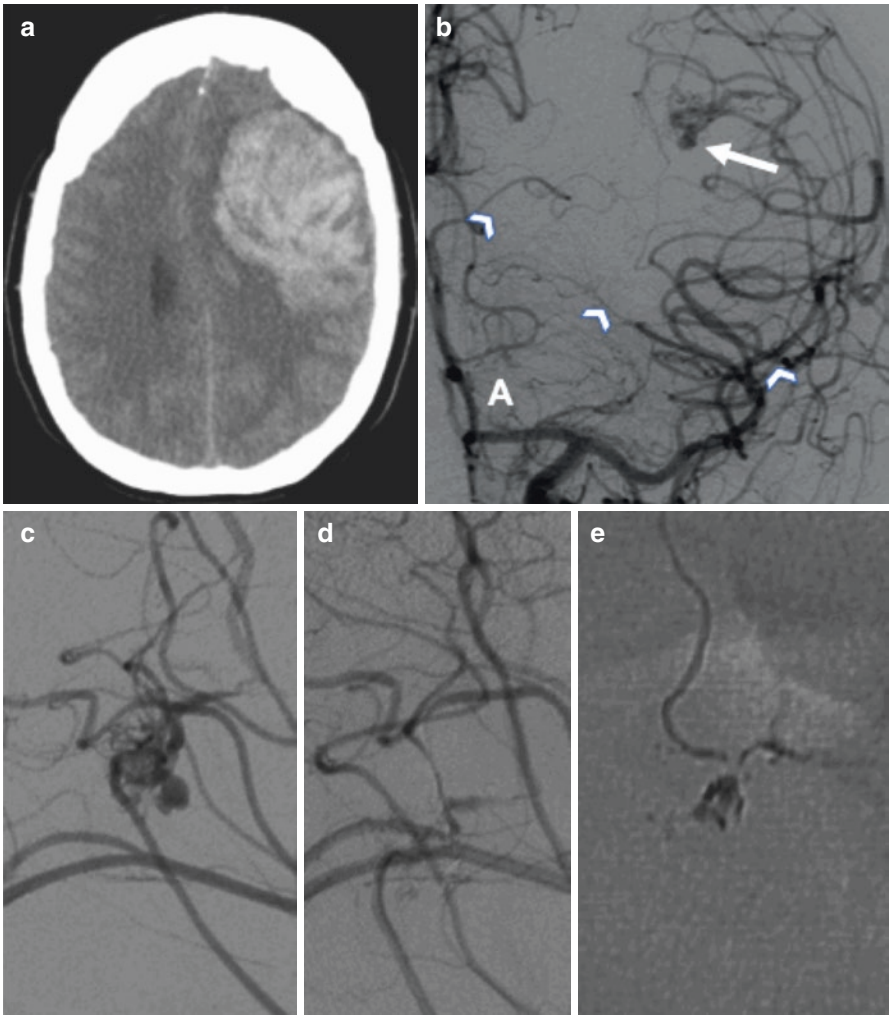


Fig. 18.1 Targeted embolization – a 62-year-old female presenting with right-sided hemiparesis and a head CT showing a large left frontal intraparenchymal hematoma (**a**). (**b**) Left ICA digital subtraction angiography. Arrow points to an aneurysm within the b-AVM nidus. Arrowheads point to displaced vessels/area of decreased initial blush secondary to mass effect from the large frontal hematoma. (**c**) Magnified view of the nidal aneurysm. (**d**) Follow-up angiogram post-embolization with Onyx showing occlusion of the nidal aneurysm and near-complete AVM obliteration. (**e**) Non-subtracted image showing Onyx cast within the nidal aneurysm. Patient later underwent open surgery for hematoma evacuation and b-AVM resection

obliteration of arterial feeders, which are usually difficult to reach intraoperatively, can help control bleeding events early during surgery and improve hemodynamics in order to avoid significant blood loss. In addition, this approach may reduce the overall size of the b-AVM which in turn results in a higher chance of total micro-

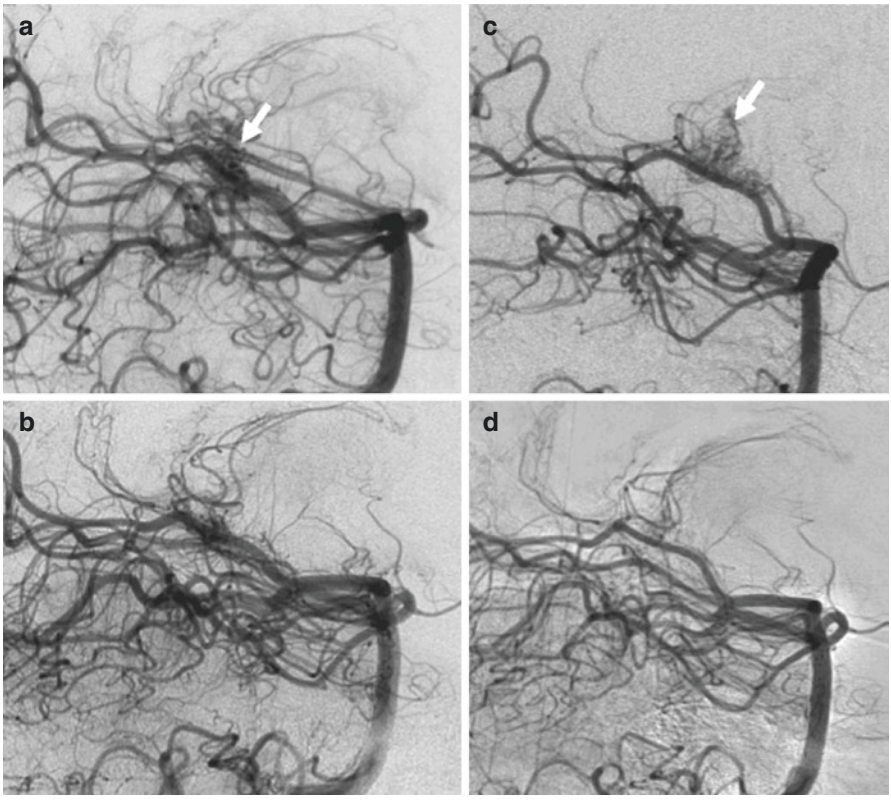


Fig. 18.2 A 35-year-old male who presented with acute intraventricular hemorrhage in the setting of a ruptured choroid plexus b-AVM. He underwent EVT with NBCA with complete obliteration of the b-AVM. (**a**) Pre-embolization angiogram. (**b**) Post-embolization angiogram. Follow-up angiogram performed 2 years after embolization (**c**) showed b-AVM recurrence. Patient then underwent radiation therapy with complete obliteration of the recurrent b-AVM. (**d**) Patient then underwent radiation therapy with complete obliteration of the recurrent b-AVM

surgical resection [2]. Size reduction is desired prior to radiosurgery in order to decrease the target area. Obliteration of AVM weak points is important prior to radiation therapy since it only has a late therapeutic effect. Additionally, preradiosurgical embolization is believed to decrease recanalization and regional remodeling [3] (Fig. 18.2).

As a stand-alone treatment, complete nidal penetration with embolic material is desired to avoid recruitment of new feeders by incompletely packed nidal segments. Small b-AVMs with single arterial feeder and single compartment are favorable for complete occlusion by means of endovascular treatment [4]. In case of palliative treatment, targeting high flow shunts to reduce symptoms/disability secondary to b-AVM flow disturbances related to intracranial steal and venous hypertension is ideal [5].

Timing of Embolization

Despite the findings of the ARUBA trial (A Randomized trial of Unruptured Brain Arteriovenous malformations) suggesting superiority of medical management over intervention, treatment of unruptured b-AVM remains controversial with a standardized management algorithm yet to be established. While many rely on the trial findings to advocate for medical management, criticism on the limited value of trial results when dealing with an individual patient endures. Factors such as the vast heterogeneity of the disease with likely dissimilar lifetime risk of hemorrhage and disability are frequently mentioned limitations. Moreover, length of follow-up likely encompasses most treatment-related complications but is too short to meaningfully display the consequences of a b-AVM rupture. In clinical practice, decision to treat an unruptured b-AVM is made after a detailed discussion with the patient about the natural history of b-AVMs, patient-specific morphologic and hemodynamic characteristics of the AVM which may increase the estimated annual bleeding risk, and the presence of disabling symptoms attributed to the b-AVM. All factors are weighted against the risks associated with treatment. Such a decision may be influenced by evaluation of eloquence of the brain tissue at risk for treatment-related complications performed via amytal test or functional MRI [6, 7].

In the setting of a ruptured b-AVM, initial management should follow general guidelines for acute spontaneous intracerebral hemorrhage with airway assessment, stabilization of blood pressure and intracranial pressure, management of possible concurrent coagulopathy, and minimization of resultant brain injury [8]. A computed tomography angiogram (CTA) has high sensitivity for detection of a b-AVM, although micro-AVMs may be missed and anatomic details may be limited [9]. Evidence of active bleeding on noninvasive imaging such as a spot sign is rarely reported but should prompt immediate endovascular embolization to avoid hematoma expansion or surgical resection if evacuation of the hematoma is required. However, in the setting of a ruptured b-AVM, a focus of increased attenuation adjacent to a hematoma more often represents a nidal or perinidal aneurysm [10] rather than active bleeding. A catheter angiogram performed by an experienced operator will provide details on lesion angioarchitecture and demonstrate the presence of potential culprits for acute bleeding. The use of high frame rates may be beneficial in the hemodynamic evaluation of high flow b-AVMs. Nidal and perinidal aneurysm embolization as well as an attempt to decrease shunt volume in the presence of outflow stenosis is empirically advised and was demonstrated to be safe to perform in the acute phase [11–13]. However, prospective studies demonstrating a measurable decrease in short-term rebleeding rates with treatment in the acute phase are currently lacking. Conversely, some operators advocate for delayed treatment after hematoma resolution, considering the patient's unstable clinical condition post-bleeding event and inability to fully evaluate the AVM due to the presence of the hematoma as well as associated parenchymal edema which may at least partially compress the AVM nidus. Despite the debate related to precise treatment timing, treatment consideration is warranted especially given the significant evidence of substantial increase in rebleeding rates after initial rupture.

Treatment Strategy

A careful evaluation of the b-AVM anatomy and vascular access to the nidus on a cerebral angiogram is of the utmost importance prior to selecting a strategy. After thorough anatomic and hemodynamic b-AVM evaluation is performed and in case of multiple arterial feeders, the chosen access should be the one with higher chances of adequate nidal penetration while maintaining a safety margin from normal branches to avoid nontarget embolization from embolic agent reflux resulting in a stroke. Another significant concern is pattern of venous drainage, particularly in cases of a single draining vein because venous outflow occlusion in the absence of adequate nidal exclusion may lead to increased pressure that may result in b-AVM rupture and hemorrhage [14].

Small low shunting b-AVMs can be safely embolized in a single session (Fig. 18.3). However, there is a concern for normal perfusion breakthrough phenomenon in large and high shunting b-AVMs [15, 16]. In such a case, a staged approach is favored (Fig. 18.4). Other considerations for deliberating staged procedures are radiation dose, iodinated contrast load, and operator fatigue. AVM embolization can have prolonged procedure time with radiation exposure to a narrow field warranting careful attention to patient radiation dose.

When performing staged procedures, addressing modifiable features that are associated with higher incidence of bleeding in the initial sessions is desirable [5]. An increased risk of b-AVM rupture and worse outcome after partial embolization was described by Miyamoto [17]. However, in a later study, Laakso et al. demonstrated no change or decreased bleeding rates after partial embolization [18].

Different techniques can be used when embolization is carried out via arterial access to decrease chances of embolic material reflux into branches supplying normal brain tissue. When compared to arterial feeders that terminate in the b-AVM, it is more challenging when dealing with indirect feeders which supply normal parenchyma but have small branches to the b-AVM ("en passant" feeder). Access to the site of embolization can be performed with a single microcatheter, dual microcatheter which can be within the same or in different feeders (Fig. 18.5), or double-lumen balloon catheter [19]. Flow-directed microcatheters as small as 1.2 French

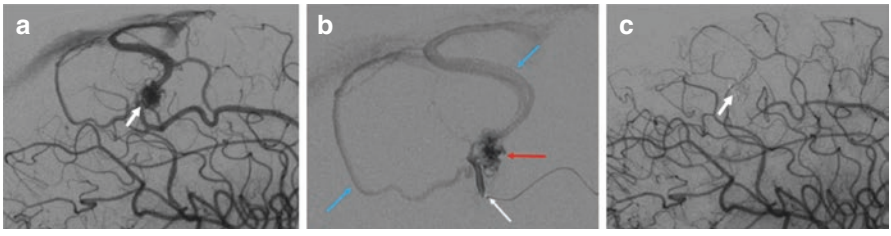


Fig. 18.3 Small b-AVM with single feeding artery. (**a**) Arrow points to b-AVM nidus. (**b**) White arrow shows microcatheter tip wedged in the single feeding pedicle. Red arrow points to b-AVM nidus and blue arrows show draining veins. (**c**) Follow-up angiogram shows complete obliteration of the b-AVM

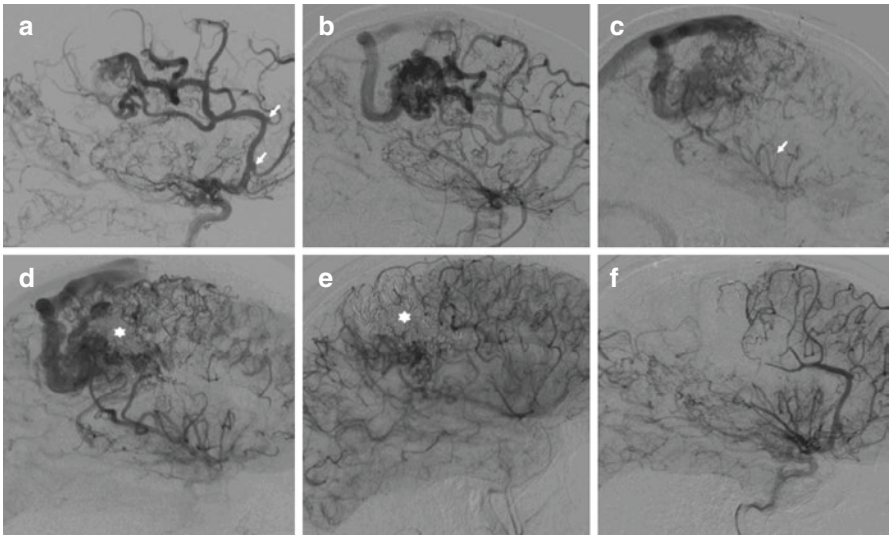


Fig. 18.4 A 49-year-old female with symptomatic right parietal b-AVM with associated occlusion of the proximal right MCA. (**a**) Right ICA angiogram arterial phase shows prominently enlarged right ACA vascular tree without significant opacification of the right MCA vascular tree. Extensive leptomeningeal collateral circulation is noted. Arrows point to flow-related aneurysms in the origin of a frontal polar branch and callosomarginal branch. (**b**) Opacification of the large b-AVM nidus with a single draining vein. (**c**) Delayed phase shows late opacification of small right MCA branches. (**d**) Stage 1 of a three-stage preoperative embolization. Star overlies the Onyx cast. (**e**) Stage 3 embolization shows no evidence of an early draining vein. Star overlies the Onyx cast. (**f**) Postsurgical resection shows resection of the b-AVM/Onyx cast. Note gradual improvement of opacification of the right MCA territory from **d** to **f**

outer diameter are commercially available and facilitate access to very distal and tortuous arteries. Detachable tip catheters are also available [20] and can be helpful in cases where longer injection times with higher risk of catheter retention are anticipated. Another major consideration while choosing the appropriate embolization catheter is compatibility with the embolic material to be used. In order to facilitate the navigation of the microcatheter into the desired position, a supportive guide catheter is critical. In case of difficult access and increased tortuosity, additional distal support can be achieved with the use of an intermediate catheter in a triaxial fashion. As for all neurointerventional procedures, a trade-off between catheter build/stability and flexibility/navigability should be balanced.

Choice of Embolic Material

Historically, many different types of embolic materials have been used for endovascular embolization of b-AVMs, including detachable balloons, hydroxyethyl methacrylate polymerizing solution, Gelfoam, ethanol, microfibrillar collagen material,

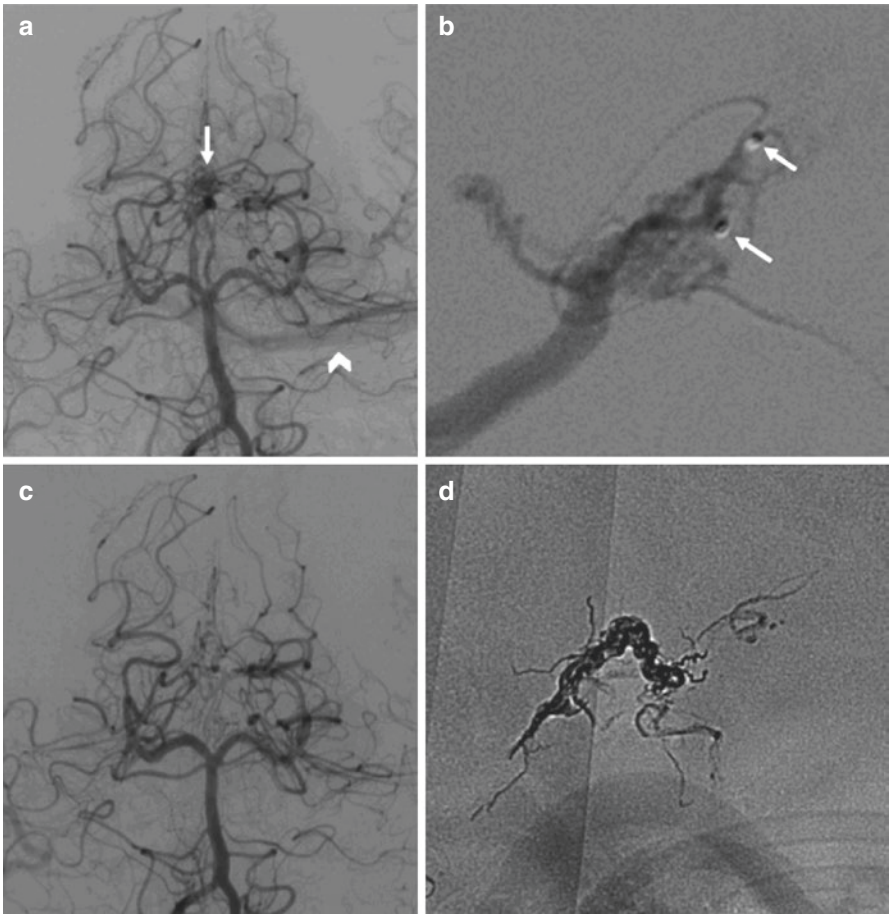


Fig. 18.5 (**a**) Quadrigeminal b-AVM. Arrow shows nidus and arrowhead shows early venous opacification. (**b**) Arrows show microcatheter tips. Two microcatheters in two different feeding pedicles were used to simultaneously inject Onyx into the b-AVM nidus. (**c**) Final angiogram shows complete b-AVM obliteration. (**d**) Non-subtracted lateral view showing the Onyx cast

surgical silk particles, and platinum microcoils. These were used as a single embolic agent or in combination. However, most were shown to produce suboptimal results related to inability to reach the nidus, material reabsorption, and recanalization and have been largely abandoned [21, 22]. In current practice, n-butyl-2-cyanoacrylate (NBCA) and ethylene vinyl alcohol (EVOH) copolymer are the predominantly used embolic agents. Detachable coils are sometimes used in combination with liquid embolic agents. Knowledge of embolic material properties, limitations, and compatibility is fundamental for a successful and safe treatment.

Liquid n-butyl cyanoacrylate (NBCA), generally referred to as glue, is used in combination with ethiodized oil for opacification, which can be enhanced with the addition of tantalum powder. Injection of NBCA results in vessel wall injury and

elicits an inflammatory response with foreign body reaction in and around the treated vessel [2]. Glue polymerizes in contact with ionic substances such as blood and, therefore, should be prepared on a separate table after changing gloves. The catheter must be flushed, and the hub should be coated with dextrose 5% to avoid inadvertent catheter obstruction. The mixture should be prepared immediately before use. An increased ratio of ethiodol to NBCA will result in increased viscosity and indirectly increased polymerization time due to buffering effect between blood and NBCA [23]. Although nidal penetration could be potentially improved with a low viscosity mixture, the short polymerization time may prevent the glue from reaching distant targets and potentially creating suboptimally packed segments of the b-AVM which are no longer accessible for arterial embolization. Small amounts of glacial acetic acid can prolong the polymerization time without interfering with mixture viscosity [24]. Another technique to prolong polymerization time is wedging the catheter in the nidus to promote flow arrest and injecting dextrose 5% to create a nonionic environment, followed by injection of a continuous glue column [25]. However, wedging the catheter is not always possible and may lead to dissection of the feeding artery. Improved nidal penetration can also be achieved with injection of small quantities of glue which are pushed forward through the microcatheter by a bolus of dextrose 5% or continuous injection of dextrose 5% through the guide catheter while injecting glue through the microcatheter [23, 26]. In certain situations, hemodynamic and technical factors such as the presence of fistulous component may call for faster polymerization which may help prevent unintentional venous penetration. Likewise, faster polymerization can be advantageous while performing embolization via venous approach in order to decrease the chance of inadvertent nontarget embolization, particularly to the lungs. While using “fast” glue, caution should be taken to avoid microcatheter retention [27].

Onyx is a liquid embolic agent comprised of ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to convey opacity. To ensure adequate mixing of the tantalum powder, vials need to be placed on a shaker for at least 20 min prior to use and should be aspirated immediately before injection to avoid tantalum settling. The dead space of the microcatheter should be completely filled with DMSO prior to Onyx injection. Onyx is subsequently injected in a slow and steady pace. Onyx is more cohesive than adhesive and is available in the United States in two different concentrations of copolymer with viscosity of Onyx at 6% and 8% (Onyx 18 and 34, respectively). Given lower viscosity, Onyx 18 has greater distal nidal penetration, while use of Onyx 34 may be favored in case of larger shunts [28]. Alternatively, Onyx 34 may be used to create a proximal anti-reflux plug with subsequent use of Onyx 18 for distal penetration. This is feasible due to EVOH precipitation occurring slowly from outside to inside as it contacts blood. This allows the liquid embolic agent to travel through the incompletely polymerized center. Onyx has better penetration into smaller vessels when compared to NBCA. This can be advantageous while attempting complete nidal penetration. Nevertheless, caution must be taken when embolizing arterial feeders that supply cranial nerves to avoid inadvertent injury [29].

Technical Nuances

Embolization can be carried out using a single microcatheter technique when the selected microcatheter should be navigated as close as possible to the b-AVM nidus. Injection of the embolic agent of choice should be performed in a slow and controlled fashion with attention for excessive reflux, venous penetration, and subarachnoid spill, indicative of b-AVM rupture. To avoid reflux into normal branches when using EVOH, initial slow local infusion until a proximal plug is created may be performed followed by continuous distal infusion through the plug.

Other alternatives include the use of a double-lumen balloon catheter to seal the feeding artery while injecting embolic material and the use of the double microcatheter "pressure cooker" technique, when a more proximal catheter is used to create an anti-reflux plug and a distal catheter is used to inject embolic material into the nidus [30]. In the latter, the proximal catheter can be removed after an adequate plug is created. The anti-reflux plug can be attained with the use of liquid embolic material and/or detachable coils (Fig. 18.6) [31]. The use of detachable coils can be particularly beneficial when embolizing via venous access to avoid distal embolization of embolic material while performing embolic material injection against the direction of flow. Placement of two microcatheters in two different arterial feeders for alternate injections to enhance nidal penetration has also been described [19].

In case of high flow b-AVMs, inducing systemic hypotension or even promoting adenosine-induced transient cardiac pause can increase the safety of embolic agent infusion [32]. Careful evaluation between embolic material infusions with follow-up angiogram obtained via guide catheter contrast injection should be performed. In case of venous approach embolization, a diagnostic catheter on the arterial side must not be forgotten to ensure adequate evaluation of the b-AVM.

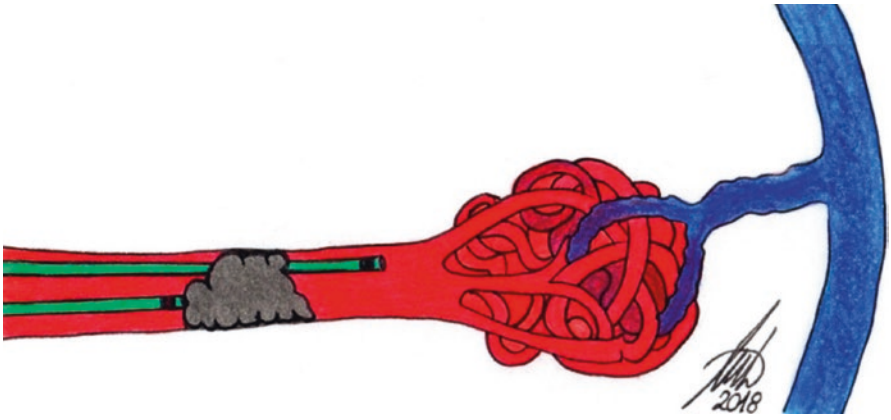


Fig. 18.6 Illustration demonstrating the pressure cooker technique. Embolization catheter is positioned near the b-AVM nidus, while a more proximal catheter creates a safety plug with liquid embolic agent. After the creation of the plug, the proximal catheter may be retrieved

At the end of the embolization session and in order to avoid unintended embolization, the microcatheter must be carefully retrieved under continuous negative pressure which can be created manually using a syringe. Timing of the retrieval will depend on the embolic agent used. Prolonged injection time, vessel tortuosity, and excessive liquid embolic reflux around the microcatheter may lead to microcatheter entrapment [33]. This can be partially mitigated by using microcatheters with a detachable tip. Several other techniques have been described for retrieval of entrapped microcatheter, including "pull-push-pull," "monorail snare," and "over the catheter" [34, 35]. At times, surgical retrieval may be necessary. In these cases, the microcatheter should be cut at the entry point at the femoral artery. Another potential complication is microcatheter breakage with loose fragment. This can be addressed by attempting retrieval of the fragment or securing the fragment against the wall with the use of self-expandable stents [36]. A similar approach can be used in the event of liquid embolic nontarget embolization or coil migration.

References

1. Liu L, Jiang C, He H, Li Y, Wu Z. Periprocedural bleeding complications of brain AVM embolization with Onyx. Interv Neuroradiol. 2010;16(1):47–57.
2. Sadato A, Wakhloo AK, Hopkins LN. Effects of a mixture of a low concentration of n-butylcyanoacrylate and ethiodol on tissue reactions and the permanence of arterial occlusion after embolization. Neurosurgery. 2000;47(5):1197–203. discussion 1204–1195.
3. Miyachi S, Izumi T, Satow T, et al. Effectiveness of preradiosurgical embolization with NBCA for arteriovenous malformations – retrospective outcome analysis in a Japanese registry of 73 patients (J-REAL study). Neurointervention. 2017;12(2):100–9.
4. Radvany MG, Gregg L. Endovascular treatment of cranial arteriovenous malformations and dural arteriovenous fistulas. Neurosurg Clin N Am. 2012;23(1):123–31.
5. Krings T, Hans FJ, Geibprasert S, Terbrugge K. Partial "targeted" embolisation of brain arteriovenous malformations. Eur Radiol. 2010;20(11):2723–31.
6. Purdy PD, Batjer HH, Samson D, Risser RC, Bowman GW. Intraarterial sodium amytal administration to guide preoperative embolization of cerebral arteriovenous malformations. J Neurosurg Anesthesiol. 1991;3(2):103–6.
7. Zhao B, Cao Y, Zhao Y, Wu J, Wang S. Functional MRI-guided microsurgery of intracranial arteriovenous malformations: study protocol for a randomised controlled trial. BMJ Open. 2014;4(10):e006618.
8. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032–60.
9. Gross BA, Frerichs KU, Du R. Sensitivity of CT angiography, T2-weighted MRI, and magnetic resonance angiography in detecting cerebral arteriovenous malformations and associated aneurysms. J Clin Neurosci. 2012;19(8):1093–5.
10. Gazzola S, Aviv RI, Gladstone DJ, et al. Vascular and nonvascular mimics of the CT angiography "spot sign" in patients with secondary intracerebral hemorrhage. Stroke. 2008;39(4):1177–83.
11. Stemer AB, Bank WO, Armonda RA, Liu AH, Herzig DW, Bell RS. Acute embolization of ruptured brain arteriovenous malformations. J Neurointerv Surg. 2013;5(3):196–200.
12. van Rooij WJ, Jacobs S, Sluzewski M, Beute GN, van der Pol B. Endovascular treatment of ruptured brain AVMs in the acute phase of hemorrhage. AJNR Am J Neuroradiol. 2012;33(6):1162–6.

13. Signorelli F, Gory B, Pelissou-Guyotat I, et al. Ruptured brain arteriovenous malformations associated with aneurysms: safety and efficacy of selective embolization in the acute phase of hemorrhage. Neuroradiology. 2014;56(9):763–9.
14. Pan J, He H, Feng L, Vinuela F, Wu Z, Zhan R. Angioarchitectural characteristics associated with complications of embolization in supratentorial brain arteriovenous malformation. AJNR Am J Neuroradiol. 2014;35(2):354–9.
15. Iwama T, Hayashida K, Takahashi JC, Nagata I, Hashimoto N. Cerebral hemodynamics and metabolism in patients with cerebral arteriovenous malformations: an evaluation using positron emission tomography scanning. J Neurosurg. 2002;97(6):1314–21.
16. Rangel-Castilla L, Spetzler RF, Nakaji P. Normal perfusion pressure breakthrough theory: a reappraisal after 35 years. Neurosurg Rev. 2015;38(3):399–404. discussion 404–395
17. Miyamoto S, Hashimoto N, Nagata I, et al. Posttreatment sequelae of palliatively treated cerebral arteriovenous malformations. Neurosurgery. 2000;46(3):589–94. discussion 594–585.
18. Laakso A, Dashti R, Seppanen J, et al. Long-term excess mortality in 623 patients with brain arteriovenous malformations. Neurosurgery. 2008;63(2):244–53. discussion 253–245.
19. Renieri L, Consoli A, Scarpini G, Grazzini G, Nappini S, Mangiafico S. Double arterial catheterization technique for embolization of brain arteriovenous malformations with onyx. Neurosurgery. 2013;72(1):92–8. discussion 98.
20. Herial NA, Khan AA, Sherr GT, Qureshi MH, Suri MF, Qureshi AI. Detachable-tip microcatheters for liquid embolization of brain arteriovenous malformations and fistulas: a United States single-center experience. Neurosurgery. 2015;11(Suppl 3):404–11. discussion 411.
21. Purdy PD, Batjer HH, Risser RC, Samson D. Arteriovenous malformations of the brain: choosing embolic materials to enhance safety and ease of excision. J Neurosurg. 1992;77(2):217–22.
22. Sorimachi T, Koike T, Takeuchi S, et al. Embolization of cerebral arteriovenous malformations achieved with polyvinyl alcohol particles: angiographic reappearance and complications. AJNR Am J Neuroradiol. 1999;20(7):1323–8.
23. Moore C, Murphy K, Gailloud P. Improved distal distribution of n-butyl cyanoacrylate glue by simultaneous injection of dextrose 5% through the guiding catheter: technical note. Neuroradiology. 2006;48(5):327–32.
24. Gounis MJ, Lieber BB, Wakhloo AK, Siekmann R, Hopkins LN. Effect of glacial acetic acid and ethiodized oil concentration on embolization with N-butyl 2-cyanoacrylate: an in vivo investigation. AJNR Am J Neuroradiol. 2002;23(6):938–44.
25. Nelson PK, Russell SM, Woo HH, Alastra AJ, Vidovich DV. Use of a wedged microcatheter for curative transarterial embolization of complex intracranial dural arteriovenous fistulas: indications, endovascular technique, and outcome in 21 patients. J Neurosurg. 2003;98(3):498–506.
26. Rosen RJ, Contractor S. The use of cyanoacrylate adhesives in the management of congenital vascular malformations. Semin Intervent Radiol. 2004;21(1):59–66.
27. Tamatani S, Koike T, Ito Y, Tanaka R. Embolization of arteriovenous malformation with diluted mixture of NBCA. Interv Neuroradiol. 2000;6(Suppl 1):187–90.
28. van Rooij WJ, Sluzewski M, Beute GN. Brain AVM embolization with Onyx. AJNR Am J Neuroradiol. 2007;28(1):172–7. discussion 178.
29. Natarajan SK, Born D, Ghodke B, Britz GW, Sekhar LN. Histopathological changes in brain arteriovenous malformations after embolization using Onyx or N-butyl cyanoacrylate. Laboratory investigation. *J Neurosurg*. 2009;111(1):105–13.
30. Paramasivam S, Niimi Y, Fifi J, Berenstein A. Onyx embolization using dual-lumen balloon catheter: initial experience and technical note. J Neuroradiol. 2013;40(4):294–302.
31. Chapot R, Stracke P, Velasco A, et al. The pressure cooker technique for the treatment of brain AVMs. J Neuroradiol. 2014;41(1):87–91.
32. Pile-Spellman J, Young WL, Joshi S, et al. Adenosine-induced cardiac pause for endovascular embolization of cerebral arteriovenous malformations: technical case report. Neurosurgery. 1999;44(4):881–6. discussion 886–887.
33. Walcott BP, Gerrard JL, Nogueira RG, Nahed BV, Terry AR, Ogilvy CS. Microsurgical retrieval of an endovascular microcatheter trapped during Onyx embolization of a cerebral arteriovenous malformation. J Neurointerv Surg. 2011;3(1):77–9.

34. Vu PD, Grigorian AA. Microcatheter entrapment retrieval from Onyx embolization in brain arteriovenous malformations: a technical note. Interv Neuroradiol. 2015;21(5):620–3.
35. Newman CB, Park MS, Kerber CW, Levy ML, Barr JD, Pakbaz RS. Over-the-catheter retrieval of a retained microcatheter following Onyx embolization: a technical report. J Neurointerv Surg. 2012;4(4):e13.
36. Hu YC, Newman CB, Dashti SR, Albuquerque FC, McDougall CG. Cranial dural arteriovenous fistula: transarterial Onyx embolization experience and technical nuances. J Neurointerv Surg. 2011;3(1):5–13.

Chapter 19
Arteriovenous Malformations: Radiation Therapy

Nina Z. Moore, Min Lang, and Peter A. Rasmussen

Radiation therapy uses energy beams from the high-energy portion of the light spectrum or uses charged electron beams or proton beams to induce damage within a cell to cause the cell to undergo programmed cell death. The light spectrum beams include x-ray or gamma rays. For standard radiation therapy, the sessions are split into fractions to minimize dosing to normal tissue. Radiosurgery, a technique used in the head and neck, focuses on radiation for a one-time treatment session into a selected area. Radiosurgery can use Cobalt-60 (photons), particle beam (proton), or linear accelerator (LINAC)-based systems. Cobalt-60 devices include the machine referred to as Gamma Knife (Elektra Instruments, Stockholm, Sweden). LINAC devices include the machines Novalis Tx (Varian Medical Systems, Inc., Palo Alto, CA) and CyberKnife (Accuray, Sunnyvale, CA) [1].

Radiation Therapy Mechanism for AVM

Through histological evaluation of AVMs after Gamma Knife radiation, Schneider et al. noted endothelial damage post radiation. The endothelial damage then led to proliferation of smooth muscle cells within the AVM arteries and an increase in the extracellular collagen around those cells. Proliferation of cells and collagen deposition caused decreased lumen patency and even obliteration which then shut down the AVM nidus from filling. After the proliferation period, cellular degeneration

N. Z. Moore (✉) · M. Lang · P. A. Rasmussen
Cerebrovascular Center, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: mooren4@ccf.org; langm@ccf.org; rasmusp@ccf.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_19

occurs with hyaline transformation. In their study, the degree of proliferation and cellular degeneration correlated to angiographic and MRI visualization of the AVM disappearing [2]. Kashba et al. confirmed the luminal narrowing due to subependymal wall thickening in their animal model post Gamma Knife [3].

Patient Selection

AVM location can make radiosurgery the best option for treatment in some patients. Radiosurgery is often a good choice for AVMs in locations that involve eloquent areas such as the motor strip, a speech center, the basal ganglia, the thalamus, or the brainstem where surgical resection is deemed to be higher risk leading to new or worsening neurologic deficits. Inoperable AVMs for either their size or deep location can make radiosurgery or staged radiosurgery the safest option as well.

Patients with medical comorbidities that make undergoing general anesthesia more dangerous for surgical resection may be good candidates for radiation therapy which often only requires moderate sedation.

Radiation Therapy

Clinical Outcomes for Radiation Therapy

Though the majority of centers treating AVMs with radiation are now performing radiosurgery, there has been some successful treatment of AVM using conventional radiotherapy. Complete obliteration was only seen in 20% of patients with AVMs undergoing conventional radiotherapy in a study performed by Redekop et al. with an annual risk of hemorrhage being 3.3% per year [4]. The ability to get higher obliteration or eradication rates with radiosurgery and the ability to minimize normal brain exposure to radiation have caused a shift to radiosurgery for the treatment of arteriovenous malformations.

Radiosurgery

LINAC

Clinical Outcomes for LINAC

Table 19.1 demonstrates a 66–89% range of AVM obliteration from LINAC-based radiosurgery for cerebral AVMs. One of these studies found that LINAC radiosurgery yielded obliteration rates based on the volume of the AVM. There were

Table 19.1 Outcomes for LINAC radiosurgery

Author	N	Angiographic obliteration	Permanent deficit	Hemorrhage rate
Friedman et al. [5]	158	69–89%	4.3%	5% (1 yr)
Pollock et al. [6]	315	66%		4.8% (1 yr)
Bostrom et al. [7]	129	71.1%	13.2%	1.7% (2 yr)

obliteration rates of 81%, 89%, and 69% for AVMs between 1 and 4 cc, between 4 and 10 cc, and finally greater than 10 cc in volume, respectively. Obliteration was negatively associated with a history of prior embolization with particulate matter. Doses <1400 cGy did not obtain obliteration [5].

Re-hemorrhage Rates

Re-hemorrhage rates post LINAC therapy have been quoted as 2.7 per person-years for AVMs with volumes less than 14 cc and 7.5% per person-years for AVMS greater or equal to 14 cc [5]. Friedman et al. demonstrated approximately a 5% rate of hemorrhage within the first year after radiosurgery [5]. Re-hemorrhage rates for each LINAC study are seen in Table 19.1.

Complications

As treatment volume increases, the incidence of post-radiosurgical imaging abnormalities and complications increases [5, 8]. For Friedman et al., their patients who had a > 14 cc treatment area receiving 1600 cGy or more radiation had 72% incidence of T2-weighted MRI abnormalities, and 22% had radiation necrosis requiring resection [5]. Bostrom et al. demonstrated a 13.2% permanent deficit with therapy in their population of 129 patient that underwent LINAC radiosurgery (Table 19.1) [7].

Particle Beam

Clinical Outcomes for Particle Beam

At approximately 3 years, Hattangadi-Gluth et al. found in their study of 248 patients with cerebral AVMs, they had an obliteration rate of 64.6% with 5- and 10-year obliteration rates of 70% and 91%, respectively (Table 19.2), with particle beam radiation. Their median time to obliteration was 31 months. Greater obliteration success was seen in smaller volumes, higher prescriptions doses, and higher maximum doses [10].

Table 19.2 Outcomes for particle beam radiosurgery

Author	N	Population	Angiographic obliteration	Permanent deficit	Hemorrhage rate
Steinberg et al. [9]	89		39–94%	9.6%	
Hattangadi-Gluth et al. [10]	248		70% at 5 year 90% at 10 year		7% 5-year cumulative risk
Walcott et al. [11]		Pediatric			

Pediatric patients were treated with proton beam to minimize probability of damage to healthy tissue particularly in the developing brain by a study done by Walcott et al. They found that by giving 15.50+/−1.87 CGE to the 90% isodose line for AVM volumes measuring 4.5 +/−5.0 ml, they could safely treat the high-risk AVMs [11].

Re-hemorrhage Rates

Re-hemorrhage rates have been quoted as a 5-year cumulative incidence of 7% in patients with incompletely obliterated AVMs [10].

Complications

Hattangadi-Gluth et al. found that seizures were the most common complication with 8% occurring acutely and 9.1% long term [10]. Complication risks with proton beam radiosurgery have been directly correlated with treatment dose and volume, patient age, and locations within the thalamus and brainstem [12].

Gamma Knife

Clinical Outcomes for Gamma Knife

Complete obliteration of the cerebral AVM with Gamma Knife is around 80% based on findings from Karlsson et al. with the use of 27 Gy to the periphery of the lesion by 2 years [13] as well as some of the other larger studies of Gamma Knife outcome (Tables 19.3 and 19.4 and Fig. 19.1).

Re-hemorrhage Rates

Karlsson et al. quote a 1.8% annual hemorrhage rate during the latency period post-treatment [13], while Maruyama et al. state there is a 6.3% risk if the patient presented with hemorrhage even after 3 years in their series of 500 patients [24].

Table 19.3 Outcomes for Gamma Knife radiosurgery

Author	N	Average dose/area	Angiographic obliteration	Permanent deficit	Hemorrhage rate
Lunsford et al. [14]	227		58–100%	1.2%	
Yamamoto et al. [15]	121		75%	5%	
Karlsson et al. [13]	272	27Gy to periphery	80%		1.8%/year
Maruyama et al. [16]	500	Median dose 20 Gy	81–91%	1.4%	6.3% risk if presented with hemorrhage even after 3 years

Table 19.4 Outcomes for Gamma Knife radiosurgery based on location or subgroup

Location	Author	N	Angiographic obliteration	Permanent deficit	Hemorrhage rate
Cerebellum	Cohen-Inbar et al. [17]	162	3 years: 38.3% 5 years: 74.2% 7 years: 81.4% 10 years: 86.1%	1.2%	0.96%/year for first 2 years 0.8%/year after 2 years
Brainstem	Maruyama et al. [16]	50	66%	7%	1.7%/year for first 3 years 0% afterward
Thalamus/ basal ganglia	Kano et al. [18]	133	57% at 3 years 72% at 10 years	4.5%	4.7%/year
Corpus callosum	Maruyama et al. [19]	32	64% at 4 years 74% at 6 years	3%	0%
Pediatric	Dinca et al. [20]	363	82.7%		2.2%
	Smyth et al. [21]	40	63% for patients with >18 Gy administered	6%	3.2%/patient/year in first year 4.3/patient/year for years 2–4
	Zeiler et al. [22]	19	81.8% at 3 yrs	0%	
	Nicolato et al. [23]	100	90%	11%	9% during latency period

Complications

Gamma Knife radiosurgery has been found to have about a 1.2–8% risk of permanent neurologic deficits posttreatment, new or worsened seizures in 0.8%, fatal complications in 0.2%, and cranial neuropathy in 1% [6, 14]. The risk of adverse radiation effects increases in the brainstem, thalamus, and larger AVMs as well as with a higher margin dose [25].

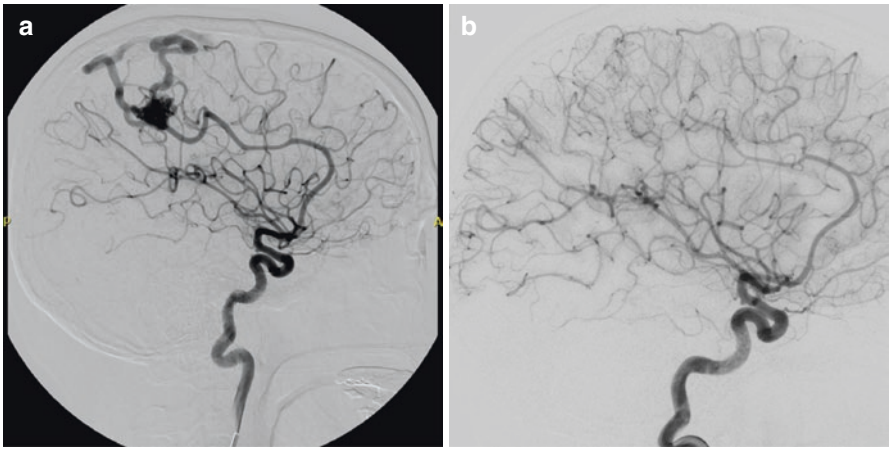


Fig. 19.1 Pre- and post-Gamma Knife treatment. (**a**) Left internal carotid injection of a left parietal AVM. (**b**) Three-year follow-up angiogram demonstrating complete obliteration of the left parietal AVM via a left internal carotid injection

Combined Therapies

Combined Endovascular Embolization and Radiosurgery

The role of endovascular embolization prior to radiosurgery has mixed outcomes in the literature. The benefit of preoperative embolization is that the size of the nidus is reduced to allow for more focused targeting of the AVM and may supply some AVM hemorrhage protection by decreasing the flow into the AVM. The risk of embolization includes the risk of rupture of the AVM due to changes in the fluid flow patterns, later recanalization of the vessels which prevents complete obliteration, or intra-procedural complications. In a case-control study by Lee et al., no statistical difference was seen in the obliteration rates between the patients that underwent preoperative Onyx embolization and those that only had radiosurgery [26]. A few articles site a lower obliteration rate in cerebral AVMs with pre-radiosurgery embolization [5, 27].

Combine Radiosurgery and Microsurgery

From our experience, microsurgery performed after the radiosurgery treatment window of non-obliterated AVMs is made easier by the tissue changes the surrounding brain has undergone. Much like the area of a prior hemorrhage, there is a boundary around the AVM nidus that appears to be avascular and gliotic, making even AVMs

located in eloquent areas less susceptible to new deficits postoperatively, anecdotally. A stable AVM post resection with some residual may also be targeted by radiosurgery particularly if there are no high-risk features or the residual AVM is located in an eloquent area.

Staged Radiosurgery

For large AVMs, the normal prescribed volume does not cover the entire nidus and, if adjusted, doesn't provide enough radiation to obliterate the AVM in many cases. Some centers have started approaching these AVMs, particularly those greater than 10 cc, with intentionally staged Gamma Knife sessions where different portions of the AVM are targeted at each session. Yamamoto et al. reported their 2-year outcomes from staging large AVMs and found that of 20 patients that had undergone staged Gamma Knife and had a follow-up angiogram, 65% had AVM obliteration, while 35% had notable shrinkage of the nidus [28]. At our institution, we perform staged procedures on Spetzler-Martin grades 4 or 5 in quick succession and judge treatment success at the 3-year mark.

Challenging AVM Locations

Brainstem AVMs pose a difficult problem for management decisions. In a study done by Yang et al., 30 patients with brainstem AVMs were divided into conservative and radiosurgery groups with well-matched AVM characteristics and clinical demographics. 43.8% of the radiosurgery group had obliteration over a 4.7 average follow-up period. Recurrent hemorrhage during follow-up was similar in both groups with the radiosurgery group having a statistically significant improvement in modified Rankin Scale scores [29].

Treatment Planning: Gamma Knife

Leksell Stereotactic Frame Placement

Leksell stereotactic frame placement is done at the beginning of the Gamma Knife session. The frame is carefully balanced on the patient's head often using a stack of gauze to appropriately center the frame to avoid post interference in the radiation plan. Local anesthetic is used to numb the location of the posts, and the depth of the anesthetic needle is used to select appropriate pin sizes from the tray. The frame is tightened sequentially with alternation between contralateral

pins to help maintain the patients head within the center of the frame or in a way that prevents shot blockage from the post in lateral lesions. Once the patient is secured within the frame, the pins are checked for complete stability, and the verification helmet is placed over the frame to ensure that the headframe will fit appropriately within the system and have minimal interference with the shots provided by the system.

Cerebral Angiography with Leksell Frame

Preparation for Gamma Knife includes obtaining an angiogram with the Leksell frame in place and secured to the angiography patient table. Radiographic fiducial markers must be visible for appropriate alignment (9 total markers must be visible per image). The magnification of the images must be at 100 and located at 0 degrees. The fluoroscopy detector must be on the left side of the patient for the lateral images. AP and lateral images are selected from the angiographic run and sent to the Gamma Knife center for use within the planning software.

MRI with Contrast with Leksell Frame

Prior to planning, with the Leksell frame in place, the patient undergoes a stereotactic MRI with contrast to help delineate the AVM nidus for planning. With the MRI reference markers, the Gamma Knife software is able to couple the angiographic AP and lateral x-rays with the MRI to help localize the AVM input and output for planning.

Target Selection and Dosing

Using first the cerebral angiogram and then the MRI stereo-localization contrast image, the nidus is targeted (Fig. 19.2). Care is taken to mark any important neurologic structures including the brainstem and optic nerves to calculate dosing to those sensitive structures. Shots are then carefully planned to optimize Gamma Knife efficiency and target coverage while protecting sensitive structures. A dose of 27 Gy divided by the cube root of the volume (cc) is used (Eq. 19.1). This dosing is usually adjusted to ensure safe exposure to adjacent critical structures.

$$\text{Marginal dose} = \frac{27(\text{Gy})}{\sqrt[3]{\text{volume}(\text{cc})}} \tag{19.1}$$

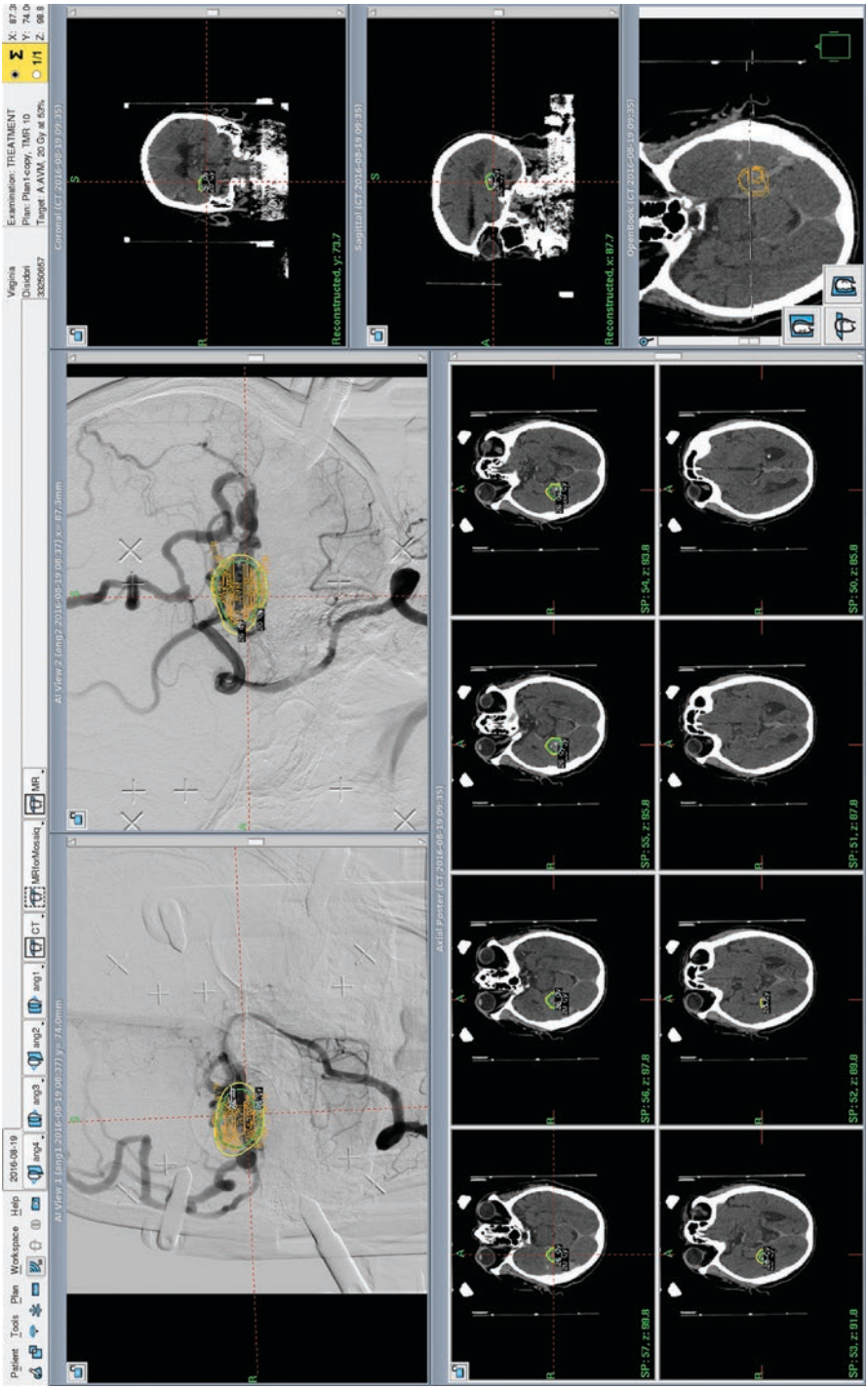


Fig. 19.2 Gamma Knife plan with cerebral angiogram and magnetic resonance stereotactic imaging with contrast

Follow-Up Recommendations

The International Radiosurgery Association recommends that patients be followed with 6-month interval exams and MRI scans up to the 3-year post-treatment mark. At 3 years, an angiogram to determine if AVM obliteration has occurred is recommended. Patients are usually given a dose of steroids at the time of radiosurgery and a short steroid taper. For patients that are experiencing symptoms from increased perilesional edema, additional steroid tapers can be performed. Patients with lobar AVMs are recommended to be placed on an antiepileptic medication due to a slightly increased risk of seizure activity perioperative period particularly in patients with a history of associated seizure [30].

References

1. International Radio Surgery Association. Stereotactic radiosurgery overview. 2016. Available: Irsa.org/radiosurgery.html. 11 Nov 2016.
2. Schneider BF, Eberhard DA, Steiner LE. Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg. 1997;87(3):352–7.
3. Kashba SR, Patel NJ, Grace M, Lee VS, Raoufi-Rad N, Raj JV, Duong TT, Stoodley M. Angiographic, hemodynamic, and histological changes in an animal model of brain arteriovenous malformations treated with gamma knife radiosurgery. J Neurosurg. 2015;123(4):954–60.
4. Redekop GJ, Elisevich KV, Gaspar LE, Wiese KP, Drake CG. Conventional radiation therapy of intracranial arteriovenous malformations: long-term results. J Neurosurg. 1993;78(3):413–22.
5. Friedman WA, Bova FJ, Mendenhall WM. Linear accelerator radiosurgery for arteriovenous malformations: the relationship of size to outcome. J Neurosurg. 1995;82(2):180–9.
6. Pollock BE, Gorman DA, Coffey RJ. Patient outcomes after arteriovenous malformation radiosurgical management: results based on a 5- to 14-year follow-up study. Neurosurgery. 2003;52(6):1291–6. discussion 1296–7.
7. Bostrom JP, Bruckermann R, Pintea B, Bostrom A, Surber G, Hamm K. Treatment of cerebral arteriovenous malformations with radiosurgery or Hypofractionated stereotactic radiotherapy in a consecutive pooled linear accelerator series. World Neurosurg. 2016;94:328–38.
8. Miyawaki L, Dowd C, Wara W, Goldsmith B, Albright N, Gutin P, Halbach V, Hieshima G, Higashida R, Lulu B, Pitts L, Schell M, Smith V, Weaver K, Wilson C, Larson D. Five year results of LINAC radiosurgery for arteriovenous malformations: outcome for large AVMS. Int J Radiat Oncol Biol Phys. 1999;44(5):1089–106.
9. Steinberg GK, Fabrikant JI, Marks MP, Levy RP, Frankel KA, Phillips MH, Shuer LM, Silverberg GD. Stereotactic helium ion Bragg peak radiosurgery for intracranial arteriovenous malformations. Detailed clinical and neuroradiologic outcome. Stereotact Funct Neurosurg. 1991;57(1–2):36–49.
10. Hattangadi-Gluth JA, Chapman PH, Kim D, Niemierko A, Bussiere MR, Stringham A, Daartz J, Ogilvy C, Loeffler JS, Shih HA. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2014;89(2):338–46.
11. Walcott BP, Hattangadi-Gluth JA, Stapleton CJ, Ogilvy CS, Chapman PH, Loeffler JS. Proton beam stereotactic radiosurgery for pediatric cerebral arteriovenous malformations. Neurosurgery. 2014;74(4):367–73. discussion 374.
12. Barker FG 2nd, Butler WE, Lyons S, Cascio E, Ogilvy CS, Loeffler JS, Chapman PH. Dose-volume prediction of radiation-related complications after proton beam radiosurgery for cerebral arteriovenous malformations. J Neurosurg. 2003;99(2):254–63.
13. Karlsson B, Lindquist C, Steiner L. Prediction of obliteration after gamma knife surgery for cerebral arteriovenous malformations. Neurosurgery. 1997;40(3):425–30. discussion 430–1.

14. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette DJ, Jungreis CA, Maitz AH, Horton JA, Coffey RJ. Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg. 1991;75(4):512–24.
15. Yamamoto Y, Coffey RJ, Nichols DA, Shaw EG. Interim report on the radiosurgical treatment of cerebral arteriovenous malformations. The influence of size, dose, time, and technical factors on obliteration rate. J Neurosurg. 1995;83(5):832–7.
16. Maruyama K, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brainstem arteriovenous malformations: factors affecting outcome. J Neurosurg. 2004;100(3):407–13.
17. Cohen-Inbar O, Starke RM, Kano H, Bowden G, Huang P, Rodriguez-Mercado R, Almodovar L, Grills IS, Mathieu D, Silva D, Abbassy M, Missios S, Lee JY, Barnett GH, Kondziolka D, Lunsford LD, Sheehan JP. Stereotactic radiosurgery for cerebellar arteriovenous malformations: an international multicenter study. J Neurosurg. 2017;127(3):512–21.
18. Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Niranjan A, Novotny J Jr, Lunsford LD. Stereotactic radiosurgery for arteriovenous malformations, part 4: management of basal ganglia and thalamus arteriovenous malformations. J Neurosurg. 2012;116(1):33–43.
19. Maruyama K, Shin M, Tago M, Kurita H, Kawamoto S, Morita A, Kirino T. Gamma knife surgery for arteriovenous malformations involving the corpus callosum. J Neurosurg. 2005;102(Suppl):49–52.
20. Dinca EB, de Lacy P, Yianni J, Rowe J, Radatz MW, Preotiuc-Pietro D, Kemeny AA. Gamma knife surgery for pediatric arteriovenous malformations: a 25-year retrospective study. J Neurosurg Pediatr. 2012;10(5):445–50.
21. Smyth MD, Sneed PK, Ciricillo SF, Edwards MS, Wara WM, Larson DA, Lawton MT, Gutin PH, McDermott MW. Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. J Neurosurg. 2002;97(1):48–55.
22. Zeiler FA, Janik MK, McDonald PJ, Kaufmann AM, Fewer D, Butler J, Schroeder G, West M. Gamma Knife Radiosurgery for Pediatric Arteriovenous Malformations: A Canadian Experience. Can J Neurol Sci. Le journal canadien des sciences neurologiques. 2016;43(1):82–6.
23. Nicolato A, Longhi M, Tommasi N, Ricciardi GK, Spinelli R, Foroni RI, Zivelonghi E, Zironi S, Dall'Oglio S, Beltramello A, Meglio M. Leksell Gamma Knife for pediatric and adolescent cerebral arteriovenous malformations: results of 100 cases followed up for at least 36 months. J Neurosurg Pediatr. 2015;16(6):736–47.
24. Maruyama K, Shin M, Tago M, Kurita H, Kawahara N, Morita A, Saito N. Management and outcome of hemorrhage after gamma knife surgery for arteriovenous malformations of the brain. J Neurosurg. 2006;105(Suppl):52–7.
25. Kano H, Flickinger JC, Tonetti D, Hsu A, Yang HC, Flannery TJ, Niranjan A, Lunsford LD. Estimating the risks of adverse radiation effects after gamma knife radiosurgery for arteriovenous malformations. Stroke. 2017;48(1):84–90.
26. Lee CC, Chen CJ, Ball B, Schlesinger D, Xu Z, Yen CP, Sheehan J. Stereotactic radiosurgery for arteriovenous malformations after Onyx embolization: a case-control study. J Neurosurg. 2015;123(1):126–35.
27. Henkes H, Nahser HC, Berg-Dammer E, Weber W, Lange S, Kuhne D. Endovascular therapy of brain AVMs prior to radiosurgery. Neurol Res. 1998;20(6):479–92.
28. Yamamoto M, Akabane A, Matsumaru Y, Higuchi Y, Kasuya H, Urakawa Y. Long-term follow-up results of intentional 2-stage gamma knife surgery with an interval of at least 3 years for arteriovenous malformations larger than 10 cm(3). J Neurosurg. 2012;117(Suppl):126–34.
29. Yang W, Porras JL, Garzon-Muvdi T, Xu R, Caplan JM, Hung AL, Braileanu M, Rong X, Colby GP, Coon AL, Tamargo RJ, Huang J. Management outcome of brainstem arteriovenous malformations: the role of radiosurgery. World Neurosurg. 2016;94:64–72.
30. International RadioSurgery Association Board. Stereotactic radiosurgery for patients with intracranial Arteriovenous Malformations (AVM) radiosurgery practice guideline report, IRSA. 2009. http://irsa.org/AVM%20Guideline.pdf

Chapter 20
Dural Arteriovenous Fistulae: Surgical Indications and Technique

Alex M. Witek, Trevor M. Dudley, and Mark D. Bain

A dural arteriovenous fistula (dAVF) is a focus of abnormal arteriovenous shunting within the layers of the dura. Its feeding arteries are most often branches of the ECA (e.g., occipital artery or MMA) but can also be ICA branches (e.g., ethmoidal branches of the ophthalmic artery or branches of the meningohypophyseal trunk) or meningeal branches of cortical vessels (e.g., PCA or SCA). dAVF can cause numerous symptoms, and a variety of endovascular and open surgical techniques are available to treat them. After providing a brief overview of intracranial dAVF, this chapter will address the indications and techniques for surgical treatment of these complex lesions. Carotid-cavernous fistulae will not be addressed here as they are discussed in a separate chapter.

Presentation

dAVF are rare lesions, comprising only about 7% of all intracranial vascular malformations [1], and they present at a mean age of 59 years [2]. The clinical presentation can range from an incidental finding to devastating hemorrhage or other neurologic deficits. Hemorrhagic presentations can include intracerebral, subarachnoid, or subdural hemorrhage. The most common nonhemorrhagic symptoms include bruit, headache, visual deficit, hemiparesis, aphasia, cranial nerve deficit, seizures, and myelopathy [3–5]. Bruit or pulsatile tinnitus is most common with fistulae of the transverse and sigmoid sinuses and is due to transmission of turbulent flow through the temporal bone. Most of the neurologic symptoms of dAVF can be attributed to venous hypertension, although mass effect from dilated subarachnoid veins can also contribute.

A. M. Witek (✉) · T. M. Dudley · M. D. Bain
Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: witeka@ccf.org; tdudley@neomed.edu; bainm@ccf.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_20

Diagnosis

CT is the first-line modality for diagnosing hemorrhage in patients presenting with neurologic symptoms. CTA or MRI can show prominent cortical vessels or cerebral edema that is often the first indication of vascular pathology, but catheter angiography is the gold standard for diagnosing dAVF. The angiogram should demonstrate the dural-based fistula, its feeding arteries, and the pattern of venous drainage and exclude the presence of an AVM nidus. A thorough angiogram, including bilateral ICA, bilateral ECA, and bilateral vertebral artery injections, is necessary to demonstrate all arterial feeders. Microcatheter injections within feeding arteries can help to clearly define the fistula. In patients presenting with hemorrhage without a clearly identified etiology after initial angiography, clinical suspicion for a vascular malformation should prompt repeat angiography a few weeks later, because the fistulae may not be evident in the setting of acute hemorrhage.

Natural History

The most important factors that determine the risk of hemorrhage or NHND are the presence of previous hemorrhage and the pattern of venous drainage. Several classification systems have been developed to stratify the risk of developing aggressive symptoms, the most common of which are the Borden and Cognard classifications. The Borden classification includes three types. Type I drains directly into dural venous sinuses or dural veins. Type II drains into dural venous sinuses or dural veins but refluxes into cortical veins. Type III drains directly into cortical veins [6]. The Cognard classification includes types I through V. Type I drains into a sinus with normal antegrade flow. Type IIa drains into a sinus with retrograde flow within the sinus. Type IIb drains into a sinus with reflux into cortical veins. Type IIa + b drains into a sinus and demonstrates retrograde flow through both the sinus and cortical veins. Type III drains directly into cortical veins, without venous ectasia. Type IV drains directly into cortical veins which exhibit ectasia (defined as larger than 5 mm and greater than three times the normal vessel diameter). Type V drains directly into cortical veins and demonstrates drainage into spinal perimedullary veins [7].

An aggressive clinical presentation is a strong predictor of future hemorrhage risk. “Aggressive” fistulae are those with symptomatic cortical venous drainage (CVD), which can include hemorrhage, focal neurologic deficits, cognitive dysfunction, myelopathy, intracranial hypertension, and seizures. “Nonaggressive” fistulae can present with no symptoms or with benign symptoms such as a bruit or ophthalmologic findings. For lesions that demonstrate CVD on angiography, those with an aggressive presentation (i.e., symptomatic CVD) have a 7.5% annual hemorrhage risk, compared to 1.5% for those with a nonaggressive presentation (i.e., asymptomatic CVD) [8–10]. For patients without aggressive symptoms on presentation, the pattern of venous drainage (i.e., Borden or Cognard type) can be used to

predict the development of such symptoms. Borden type I lesions follow a benign course, with only 2% developing aggressive symptoms or CVD during follow-up [11]. Lesions with CVD, however, have an unfavorable natural history. For Borden type II and III lesions followed conservatively, one study reported annual rates of new hemorrhage, NHND, and mortality of 8%, 7%, and 10%, respectively [12].

Surgical Indications

Treatment Versus Observation

The decision of whether to treat a dAVF depends on the presence of an aggressive clinical presentation, intolerable symptoms, and CVD. Aggressive lesions should be treated given that they pose a 7.5% annual hemorrhage risk [8]. For nonaggressive lesions, the decision is primarily based on the pattern of venous drainage with treatment indicated for those lesions with CVD (i.e., Borden types II and III; Cognard types IIb and higher). In the absence of CVD, treatment may be indicated for intolerable symptoms such as bruit or headache.

Overview of Treatment Options

Various surgical and endovascular options exist for the treatment of dAVF. Over the past several decades, increasing experience has refined surgical approaches to these lesions. Meanwhile, the advances in endovascular techniques have made many of these lesions treatable with endovascular therapy. Radiosurgery has also been utilized but should be considered a second-line treatment because the obliteration rate for dAVF with CVD is only 56% [13], and the patient is at risk for new hemorrhage or NHND during the latency period. In order for a treatment to be curative, it is necessary to excise the fistula or to completely occlude its arterial input or venous output. It is important to note that ligation or embolization of feeding arteries alone is not likely to be curative because the fistula can derive flow from additional arterial feeders not evident on initial angiography. Occlusion of the venous pouch or the venous drainage is the strategy with the highest likelihood of success. Although angiographic cure is desirable, dAVF are complex lesions that can be technically difficult to treat, so it is necessary to define the goals of therapy on a case-by-case basis. Patients with lesions that are impractical to cure can derive significant benefit from palliative procedures. For example, decreasing flow through the fistula by transarterial embolization can ameliorate symptoms, at least temporarily. Likewise, selective disconnection of retrograde cortical veins from the fistulous segment of sinus has been reported for Borden type II lesions [14].

Endovascular therapy remains the treatment of choice for most dAVF. This can be achieved by transarterial and/or transvenous access and use of coils or liquid embolic agents. Transarterial embolization should generally be limited to ECA branches because embolization of ICA or vertebral artery branches can lead to reflux of embolic material, resulting in neurologic deficits (e.g., monocular blindness from reflux into the ophthalmic artery). This being stated, at times, embolization can be attempted from ICA and vertebral artery feeders. In the current endovascular environment, surgery is indicated for those dAVF that lack sufficient transarterial or transvenous access to the fistula, when the transarterial route poses a risk of neurologic deficits, or if endovascular therapy has failed. Failed embolization can "burn bridges" by limiting endovascular access for future embolization attempts.

Sinus-Type Fistulae

dAVF can be divided into two types based on whether or not they involve a dural venous sinus. Sinus-type fistulae (also referred to as "sinusal" or "indirect" CVD) correspond to Borden types I and II or to Cognard types IIa + b and lower). dAVF involving a venous sinus are generally better approached with endovascular therapy, if possible, because surgery carries a risk of significant blood loss. The fistula is contained within the wall of the sinus and appears angiographically as a diffuse web adjacent to the sinus. For sinus-type fistulae treated with surgery, sacrificing the fistulous segment of the sinus is likely to be most effective. Sinus sacrifice can be accomplished either by surgical ligation or endovascular sacrifice using coils. With this approach, however, there is a risk of adverse events related to disruption of normal venous drainage pathways. In dAVF with cortical venous reflux, however, the venous drainage pathways are already abnormal. If the patient does not already have signs of venous hypertension, then sinus sacrifice should be tolerated. If sinus sacrifice is not possible or desirable, then transarterial embolization and surgical skeletonization are good alternatives.

Non-sinus-Type Fistulae

dAVF that do not involve a sinus (Borden type III or Cognard types III and higher) are more likely to be treated surgically. Transvenous embolization is often not possible for these lesions because such access is difficult to achieve. Transarterial embolization can result in a cure, as long as the embolic material achieves sufficient penetration into the venous pouch, but many of these lesions have non-ECA feeding arteries. For these reasons, ethmoidal and tentorial dAVF, which typically do not involve a sinus, are among the most common locations treated with surgery.

Considerations for Ruptured dAVF

As mentioned previously, treatment is indicated for all dAVF presenting with hemorrhage. These patients may require placement of a ventriculostomy or medical therapy for intracranial hypertension. Rebleeding within the first 2 weeks has been reported in 35% of patients [15]. For patients with a ruptured dAVF, treatment is therefore recommended as soon as reasonably possible, generally within a few days of presentation. If there is a significant intracerebral or subdural hemorrhage, emergent surgery may be indicated to relieve mass effect, and the craniotomy can be planned to allow for evacuation of the hematoma in addition to treatment of the fistula.

Surgical Approaches

Sinus-Type

Although endovascular therapy is generally preferred for fistulae involving a sinus, it is important to be aware of the basic principles of surgical management in the event that a lesion is encountered that is not amenable to embolization. Two basic strategies have been used: sinus ligation/resection, which is the preferred method, and sinus skeletonization, an alternative for patients unable to tolerate sinus sacrifice [16–18]. The decision of which to use depends on whether the patient can tolerate losing the venous drainage pathway provided by the sinus. Both approaches begin with a generous craniotomy that exposes both sides of the sinus. In the case of a transverse/sigmoid dAVF, this involves a craniotomy that extends above and below the transverse sinus or both anterior and posterior to the sigmoid sinus. The surgeon should be prepared for the possibility of significant blood loss [14, 16], because the area around a dAVF can contain enlarged scalp arteries, transosseous channels, and dural arteries that feed the fistula. Bleeding can be controlled with bipolar coagulation on the scalp and dura and wax for bone bleeding. Additional strategies that have been used to mitigate blood loss include cervical exposure of the ECA and preoperative embolization of ECA branches.

Skeletonization involves ligating and dividing all dura adjacent to the sinus, leaving the walls of the sinus itself intact to preserve normal venous flow. The arterial input to a transverse/sigmoid dAVF lies within the dural leaves of the occipital and cerebellar convexity, the tentorium, and the falx. After exposing the sinus with the craniotomy, the dura above and below the sinus is coagulated and opened. The dura is often hypervascular due to the presence of arterial feeders to the fistula, so generous coagulation is performed prior to incising the dura to minimize bleeding from the dural edges. The tentorium adjacent to the sinus (and the falx, if necessary) is likewise coagulated and opened. By coagulating and incising all dural surfaces along a sufficient extent of the sinus, the arterial input to the fistula can be obliterated and the normal venous drainage of the sinus preserved.

Sinus sacrifice begins with the same steps as skeletonization. However, after the transdural arterial input is interrupted, the involved sinus segment is isolated by ligating it at each end. This ligation can be done with a combination of bipolar coagulation, metallic clips, or suture. This diseased portion of the sinus can then be resected. If there is a segment of sinus (e.g., the sigmoid sinus) that cannot be easily accessed for resection or skeletonization, then recurrence of the fistula at that site can be prevented by packing it with materials such as oxidized cellulose, absorbable gelatin sponge, or muscle.

Another approach that has been reported for high-grade fistulae is ligation and division of arterialized veins associated with the diseased segment of the sinus. This turns a high-grade (Borden type II) into a low-grade (Borden type I) fistula. One series utilizing this technique reported similar outcomes and lower complication rates compared to fistula excision, along with tolerable residual symptoms [14]. However, there is limited follow-up data for this method, so these patients warrant close clinical and radiographic follow-up as there is a possibility of progression of the lesion, especially if venous restrictive disease develops.

Non-sinus-Type

In the past, excision of the fistula-containing dura was commonly employed, but it has been shown that simply ligating the draining vein as it exits the dura is sufficient for cure of non-sinus-type fistulae [19–22]. Once the fistula loses it venous outflow, it will thrombose and become obliterated. This is in contrast to pial AVMs, for which ligation of draining veins leads to increased intranidal pressure and rupture. For dAVF involving an isolated segment of a thrombosed sinus, a burr hole or craniectomy placed over the sinus, followed by direct puncture and embolization with microcoils, has also been reported [23, 24]. When planning surgery for a non-sinus-type fistula, it is important to study the angiogram carefully to determine the pattern of venous drainage. The craniotomy should be planned so that it provides access to the draining vein as it emerges from the dura and enters the subarachnoid space.

Cerebral convexity fistulae are best approached by a craniotomy centered over the site where the arterialized vein enters the subarachnoid space, which can be determined by careful study of the preoperative imaging. Stereotactic navigation may be helpful to plan the craniotomy accordingly. Similar to other fistula locations, the dura is generously coagulated before opening it. After opening the dura, the brain and overlying dura are carefully inspected to locate the arterialized draining vein that can be followed back to its dural origin, where it is ligated and divided.

Ethmoidal dAVF are located within the dura of the anterior fossa floor or the anterior-inferior edge of the falx. The arterialized vein typically originates from the anterior fossa dura or from the falx. Exposure of the draining vein can be obtained via a pterional craniotomy, which provides a lateral subfrontal approach, or a low frontal or bifrontal craniotomy, which allows for both a subfrontal and an anterior interhemispheric approach. Pterional craniotomy has the advantage of avoiding the

frontal sinus. A bifrontal craniotomy allows for bilateral exposure, which can be helpful if the laterality of the draining vein is not obvious on the preoperative imaging, although the falx can be opened, if necessary, when using a unilateral approach. A pericranial flap should be harvested if frontal sinus violation is anticipated.

Tentorial dAVF can have significant variability in the location of the fistula and the draining vein, and they have been classified accordingly by Lawton [25]. Careful study of the preoperative angiogram is necessary to identify the point of origin of this vein and whether it drains in a supra- or infratentorial direction, and the craniotomy must be planned accordingly to provide the best access to the vein. If the vein lies posteriorly, near the midline, and drains infratentorially, then it can be accessed with a suboccipital craniectomy and a supracerebellar-infratentorial approach. An infratentorial vein originating more laterally (near the superior petrosal sinus) is best approached by a retrosigmoid approach. If the vein originates from the posterior tentorium and drains supratentorially, an occipital craniotomy and a supratentorial-infraoccipital approach should be used. An anterior vein near the midline (near the vein of Galen) can be approached by a posterior interhemispheric approach. A vein originating from the incisura is best approached by a pterional or subtemporal approach, with possible division of the tentorium.

Example Cases

Ethmoidal dAVF: Lateral Subfrontal Approach

A 65-year-old man presented with headaches, and an MRI showed a tortuous vessel in the left frontobasal region (Fig. 20.1a), concerning for a vascular malformation. An angiogram was obtained and showed an ethmoidal dAVF. The fistula was fed by

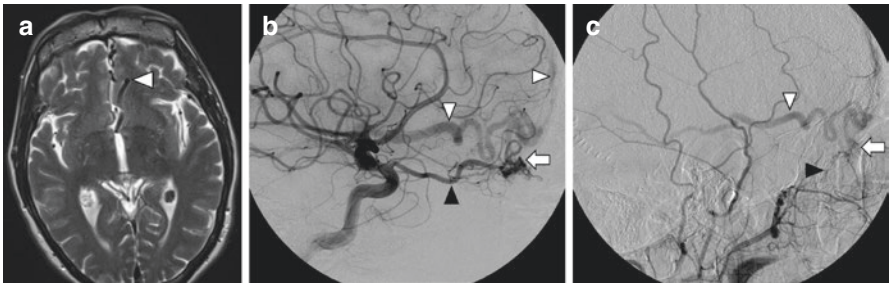


Fig. 20.1 (**a**) MRI (axial T2-weighted) shows a prominent flow void consistent with a large vein. (**b**) DSA (left ICA injection, lateral view) shows an ethmoidal dAVF. There is a fistulous connection along the anterior fossa floor (white arrow), with arterial input from ethmoidal branches of the ophthalmic artery (black arrowhead) and drainage via subarachnoid veins into the basal vein of Rosenthal and superiorly into the superior sagittal sinus (white arrowheads). (**c**) DSA (left ECA injection, lateral view) shows that this ethmoidal dAVF also receives arterial input from branches of the internal maxillary artery (black arrowhead)

bilateral ethmoidal branches of the ophthalmic artery (Fig. 20.1b) and bilateral internal maxillary artery branches (Fig. 20.1c). Venous drainage was via an ectatic vein that traveled posteriorly along the left side of the falx toward the deep venous system, as well as a vein that traveled superiorly to the superior sagittal sinus. Treatment was recommended based on the high-grade angiographic appearance (Borden type III, Cognard type IV). Surgery was deemed safer than embolization given the presence of arterial input from ophthalmic artery branches.

The patient was positioned with the head extended and turned slightly toward the contralateral shoulder. A left pterional craniotomy was performed, and the anterior edge of the craniotomy was carried down to the anterior fossa floor. Using microsurgical dissection, a subfrontal approach was taken so the area of exposure extended from the frontal pole anteriorly to the optic chiasm posteriorly and to the falx medially. An arterialized vein was seen exiting the dura from the floor of the anterior fossa, near the falx. The vein traveled posteriorly between the mesial frontal lobe and the falx, toward the optic chiasm. The falx, which appeared hypervascular, was coagulated and divided along the anterior fossa floor. Inspection of the contralateral anterior fossa floor revealed no abnormalities. The vein was coagulated and divided as close as possible to its site of exit from the anterior fossa dura, and the arterialized vein became smaller and darker.

Tentorial dAVF: Supracerebellar-Infratentorial Approach

A 48-year-old man presented with an 8-month history of headaches, nausea, fatigue, and progressive gait ataxia. MRI of the brain showed edema and enhancement of the right cerebellar hemisphere (Fig. 20.2a). He had previously undergone biopsy of the enhancing region, which showed non-specific findings of thickened, sclerotic vessels. He underwent a cerebral angiogram, during which the vertebral artery injection demonstrated early filling of a cerebellar vein that appeared to originate from the superior aspect of the right cerebellar hemisphere before traveling inferolaterally to drain into the right sigmoid sinus (Borden type III, Cognard type III), with no obvious AVM nidus (Fig. 20.2b). Treatment was indicated due to symptoms attributable to venous hypertension. The lesion was not amenable to embolization due to a lack of sufficient transarterial or transvenous access.

The patient was positioned prone with capital flexion. A right-sided suboccipital craniectomy was performed, exposing the right cerebellar hemisphere and the transverse sinus. Using microsurgical dissection, a supracerebellar-infratentorial plane was developed. This revealed an arterialized vein exiting the inferior surface of the tentorium. The vein bifurcated a short distance from the tentorium, and the medial branch appeared to be thrombosed, while the lateral branch was arterialized and traveled laterally over the superior cerebellar surface (Fig. 20.2c). The arterialized vein was coagulated and divided as close as possible to its exit from the tentorium. After ligation of the vein, the distal portion of the arterialized vein attained a venous appearance.

Tentorial dAVF: Subtemporal Approach

A 56-year-old man presented for an incidental left MCA aneurysm. An angiogram was obtained to further define the aneurysm, and an incidental left tentorial dAVF was encountered. The dAVF was fed by the marginal tentorial artery (i.e., Bernasconi and Cassinari) and the recurrent branch of the inferolateral trunk. The draining vein appeared to exit the anteromedial surface of the tentorium and drain inferiorly via a cerebellar cortical vein toward the transverse sinus (Fig. 20.3). Treatment of this incidental fistula was recommended based on the high-grade angiographic characteristics

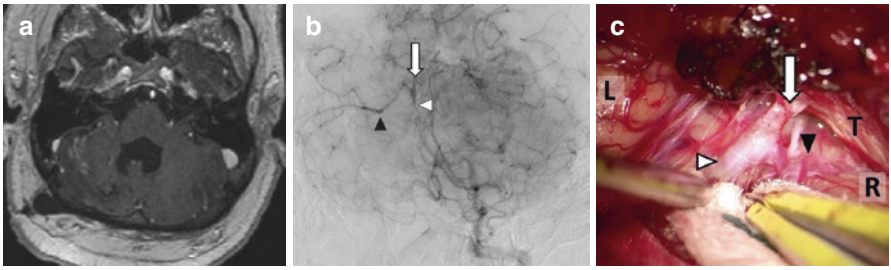


Fig. 20.2 (**a**) MRI (axial MPRAGE with contrast) shows mild enhancement in the right cerebellar hemisphere. (**b**) DSA (left vertebral artery injection, PA view) shows early filling of a vein that originates near the tentorium (arrow) and bifurcates into a medial (white arrowhead) and a lateral branch (black arrowhead). (**c**) Intraoperative photograph following a suboccipital craniectomy and supracerebellar-infratentorial approach. The tentorium (T) and the right (R) and left (L) cerebellar hemispheres are labeled for orientation. The arterialized vein (arrow) is seen exiting the inferior surface of the tentorium before giving off medial and lateral branches. The medial branch (white arrowhead) appears thrombosed, while the lateral branch (black arrowhead) appears arterialized

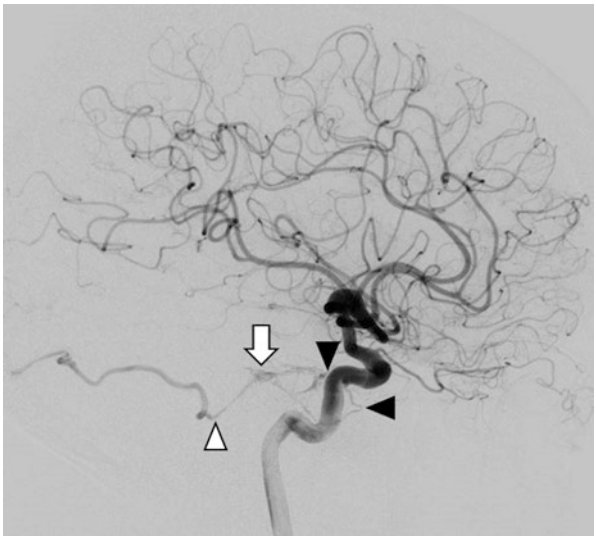


Fig. 20.3 DSA (left ICA injection, lateral view) showing a tentorial dAVF. There is a fistulous connection located along the anteromedial edge of the tentorium (white arrow), with arterial input from the marginal tentorial artery and the inferolateral trunk (black arrowheads), and drainage via a subarachnoid vein (white arrowhead) into the posterior fossa

(Borden type III, Cognard type III). Attempts at transarterial and transvenous access were unsuccessful, so embolization was aborted and a surgical approach was planned.

The patient was positioned supine with the long axis of the cranium parallel to the floor and the vertex tilted slightly downward. A left temporal craniotomy was performed, extending as low as possible to the middle fossa floor. The temporal dura was opened, and the temporal lobe was gently elevated, which was facilitated with the aid of lumbar CSF drainage. The tentorial dura appeared hypervascular. The trochlear nerve was identified entering the edge of the tentorium, and the tentorium was coagulated and divided posterior to the nerve. This revealed an arterialized vein originating from the inferior surface of the tentorium and traveling inferiorly and posteriorly into the posterior fossa. The vein was coagulated and divided at its exit from the tentorium, resulting in its transformation from an arterial to a venous appearance.

Occipital Convexity dAVF: Stereotactic Craniotomy

A 55-year-old female presented with acute onset left-sided hemiparesis, and a CT of the brain showed a hemorrhage involving the right thalamus and perimesencephalic cisterns (Fig. 20.4a). An angiogram showed a dAVF in the right occipital region with arterial input from the right MMA and right PCA and venous drainage via an occipital cortical vein toward the superior sagittal sinus. She underwent transarterial embolization via the posterior MMA branch using Onyx (Covidien, Irvine,

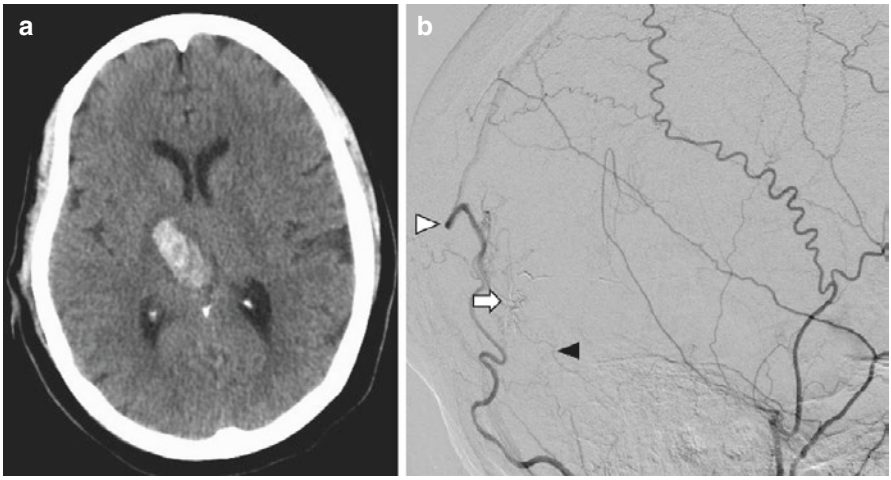


Fig. 20.4 (**a**) CT shows a hemorrhage in the right thalamus. (**b**) DSA (right ECA injection, lateral view) shows recurrent filling of the venous pouch (arrow) that had previously been embolized with Onyx via the MMA. The recurrent dAVF is fed by a branch of the MMA (black arrowhead) and drains via a subarachnoid vein (white arrowhead) into the superior sagittal sinus

CA). She also required ventriculoperitoneal shunt placement for hydrocephalus. A follow-up angiogram 8 months later showed recanalization of the fistula (Fig. 20.4b, Borden type III, Cognard type III). Surgery was indicated due to the presence of CVD and failed endovascular therapy.

The patient was positioned supine with the head turned toward the contralateral shoulder and parallel to the floor. Stereotactic navigation was used to locate the fistulous site, which was easily seen on CT given the Onyx cast, and a right occipital craniotomy was performed. Bipolar coagulation was generously used on the dura prior to dural opening, in order to limit bleeding from the hypervascular dura. An arterialized vein was encountered exiting the dura near the site of previous Onyx embolization and traveling over the occipital convexity toward the superior sagittal sinus. The vein was ligated and divided at it emerged from the dura, after which it no longer appeared arterialized.

Conclusion

Dural arteriovenous fistulae are rare lesions with a wide range of manifestations and clinical courses. Lesions with CVD have a poor natural history and warrant treatment. Endovascular therapy is a good option for many dAVF, while surgery may be indicated for cases with unsuitable transarterial or transvenous access, perceived risk of neurologic deficits from embolization, and persistence of the fistula after previous embolization attempts. The operative strategy is dictated by whether the lesion involves a dural venous sinus or has solely cortical venous drainage, and the surgical approach is chosen to provide the best exposure to the fistula and its venous outflow.

References

1. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke. 2003;34:1163.
2. Signorelli F, Della Pepa GM, Sabatino G, Marchese E, Maira G, Puca A, Albanese A. Diagnosis and management of dural arteriovenous fistulas: a 10 years single-center experience. Clin Neurol Neurosurg. 2015;128:123.
3. Lasjaunias P, Chiu M, ter Brugge K, Tolia A, Hurth M, Bernstein M. Neurological manifestations of intracranial dural arteriovenous malformations. J Neurosurg. 1986;64:724.
4. El Asri AC, El Mostarchid B, Akhaddar A, Naama O, Gazzaz M, Boucetta M. Factors influencing the prognosis in intracranial dural arteriovenous fistulas with perimedullary drainage. World Neurosurg. 2013;79:182.
5. Celik O, Piippo A, Romani R, Navratil O, Laakso A, Lehecka M, Dashti R, Niemelä M, Rinne J, Jääskeläinen JE, Hernesniemi J. Management of dural arteriovenous fistulas – Helsinki and Kuopio experience. Acta Neurochir Suppl. 2010;107:77.

6. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. J Neurosurg. 1995;82:166.
7. Cognard C, Gobin YP, Pierot L, Bailly AL, Houdart E, Casasco A, Chiras J, Merland JJ. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194:671.
8. Zipfel GJ, Shah MN, Refai D, Dacey RG, Derdeyn CP. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. Neurosurg Focus. 2009;26:E14.
9. Söderman M, Pavic L, Edner G, Holmin S, Andersson T. Natural history of dural arteriovenous shunts. Stroke. 2008;39:1735.
10. Strom RG, Botros JA, Refai D, Moran CJ, Dewittet Cross III, Chicoine MR, Grubb RL, Rich KM, Dacey RG, Derdeyn CP, Zipfel GJ. Cranial dural arteriovenous fistulae: asymptomatic cortical venous drainage portends less aggressive clinical course. Neurosurgery. 2009;64:241.
11. Satomi J, van Dijk JM, Terbrugge KG, Willinsky RA, Wallace MC. Benign cranial dural arteriovenous fistulas: outcome of conservative management based on the natural history of the lesion. J Neurosurg. 2002;97:767.
12. Van Dijk JMC, TerBrugge KG, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. Stroke. 2002;33:1233.
13. Chen C-J, Lee C-C, Ding D, Starke RM, Chivukula S, Yen C, Moosa S, Xu Z, Pan DH-C, Sheehan JP. J Neurosurg. 2015;122:353.
14. van Dijk JMC, TerBrugge KG, Willinsky RA, Wallace MC. Stereotactic radiosurgery for intracranial dural arteriovenous fistulas: a systematic review. J. Neurosurg. 2004;101:31.
15. Duffau H, Lopes M, Janosevic V, Sichez JP, Faillot T, Capelle L, Ismaïl M, Bitar A, Arthuis F, Fohanno D. Early rebleeding from intracranial dural arteriovenous fistulas: report of 20 cases and review of the literature. J Neurosurg. 1999;90:78.
16. Sundt TM, Piepgras DG. Early rebleeding from intracranial dural arteriovenous fistulas: report of 20 cases and review of the literature. J Neurosurg. 1983;59:32.
17. Eftekhar B, Morgan MK. Surgical management of dural arteriovenous fistulas of the transverse-sigmoid sinus in 42 patients. J Clin Neurosci. 2013;20:532.
18. Ojemann R, Heros R, Crowell R. *Surgical management of cerebrovascular disease*. 2nd ed. Baltimore: Williams & Wilkins; 1988. p. 415–25.
19. Grisoli F, Vincentelli F, Fuchs S, Baldini M, Raybaud C, Leclercq TA, Vigouroux RP. Surgical treatment of tentorial arteriovenous malformations draining into the subarachnoid space. Report of four cases. J Neurosurg. 1984;60:1059.
20. Thompson BG, Doppman JL, Oldfield EH. Treatment of cranial dural arteriovenous fistulae by interruption of leptomeningeal venous drainage. J Neurosurg. 1994;80:617.
21. Collice M, D'Aliberti G, Talamonti G, Branca V, Boccardi E, Scialfa G, Versari PP. Surgical interruption of leptomeningeal drainage as treatment for intracranial dural arteriovenous fistulas without dural sinus drainage. J Neurosurg. 1996;84:810.
22. Lawton MT, Chun J, Wilson CB, Halbach VV. Ethmoidal dural arteriovenous fistulae: an assessment of surgical and endovascular management. Neurosurgery. 1999;**45**:805.
23. Endo S, Kuwayama N, Takaku A, Nishijima M. Direct packing of the isolated sinus in patients with dural arteriovenous fistulas of the transverse-sigmoid sinus. J Neurosurg. 1998;88:449.
24. Houdart E, Saint-Maurice J-P, Chapot R, Ditchfield A, Blanquet A, Lot G, Merland J-J. Transcranial approach for venous embolization of dural arteriovenous fistulas. J Neurosurg. 2002;97:280.
25. Lawton MT, Sanchez-Mejia RO, Pham D, Tan J, Halbach VV. Tentorial dural arteriovenous fistulae: operative strategies and microsurgical results for six types. Neurosurgery. 2008;62:110.

Chapter 21
Dural Arteriovenous Fistulae: Endovascular Embolization Indications and Techniques

Syed Uzair Ahmed, Lissa Peeling, and Michael E. Kelly

Description and Classification

Cranial dural arteriovenous fistulas (DAVFs) are abnormal dural-based connections between meningeal arteries and venous sinuses, meningeal veins, or cortical veins, without an intermediate capillary network or nidus. They account for 10–15% of aberrant intracranial arteriovenous connections [1, 2]. DAVFs are mostly acquired conditions that occur in middle-aged adults. Lesions in the pediatric population, although rare, are often much more complex and beyond the scope of this chapter.

Exact etiology of adult DAVFs remains unknown. An association with venous sinus thrombosis has been found, and hypercoagulable states have therefore been implicated. Thrombosis has also been reported as a consequence of dural arteriovenous shunting. Other provocative factors have been reported, such as trauma, intracranial surgery, and radiation exposure. However, many DAVFs occur without an identifiable cause.

Two pathophysiological mechanisms for the development of DAVFs have been proposed. One theory holds that these lesions develop in normally occurring vascular channels [3], which open due to venous hypertension secondary to outflow obstruction or venous sinus thrombosis [4]. The second theory proposes that the lesions form due to neovascularization in the dura occurs due to release of angiogenic factors secondary to hypoxia or increased venous pressure in the setting of thrombosis or occlusion. Studies of lesion histology as well as animal models are used to support this hypothesis [5, 6, 7] [1, 8].

Symptoms and clinical course of dural arteriovenous fistulas depend predominantly on the drainage pattern of the lesion, as well as the location, arterial supply, and degree of shunting [1, 9]. A review of 191 reported cases found that lesions

S. U. Ahmed · L. Peeling · M. E. Kelly (✉)
Division of Neurosurgery, Department of Surgery, University of Saskatchewan, Saskatoon, SK, Canada
e-mail: lissa.peeling@usask.ca; m.kelly@usask.ca

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_21

without cortical venous drainage (CVD) typically presented with more benign symptoms related to shunting, such as headache, proptosis, pulsatile tinnitus, and cranial nerve deficits secondary to arterial steal. These lesions can also be asymptomatic and incidental in nature. The natural history of a vast majority of benign DAVFs suggests that they remain stable over the course of many years and thus do not require surgical intervention. Benign DAVFs are a dynamic disease with potential risk of progression of the venous thrombosis, which may reroute the venous drainage. Two scenarios are potentially important: the possible significance of retrograde flow in the sinus and the small, but concerning risk of conversion into an aggressive DAVF. The change of flow in the sinus to retrograde, as outlined by Cognard type IIa, has been associated with papilledema and raised intracranial pressure. Theoretically, retrograde flow in the sinus can preclude cortical veins from draining into the implicated sinus, thereby resulting in increased intracranial pressure. In a Toronto series of 112 conservatively managed patients, 14 (12.5%) patients underwent spontaneous occlusion of their fistulas, and 4 (4.0%) patients converted from having a benign fistula to an aggressive angioarchitecture with new corticovenous reflux [10].

Lesions with CVD often presented with more substantial or aggressive features including neurological sequelae such as hemorrhage, nonhemorrhagic focal neurological deficit (NHND), dementia, or even death [11]. Studies have shown significant variation in the rates of hemorrhage, focal nonhemorrhagic neurological deficit, and mortality in patients with CVD [12, 13, 14]. One study with a mean follow-up of 4.3 years found a 35% rate of hemorrhage, 30% rate of nonhemorrhagic neurological deficit, and 45% rate of mortality in lesions associated with CVD [15]. A meta-analysis of outcomes after intracranial hemorrhage secondary to DAVFs in 326 patients found the rate of mortality after a median follow-up of 12 months to be 4.7% and an overall rate of poor clinical outcome (mRS $\geq$ 3) of 8.3% [16].

Various classification schemes for dural arteriovenous fistulas have been proposed. The most widely utilized classification schemes are those proposed by Borden and Cognard. Both schemata recognize the presence of CVD as a factor predictive of the severity of the lesion. The Borden classification simply stratifies fistulae using their venous drainage and remains the most widely used clinical classification system (Table 21.1) [17]. The more complex Cognard classification accounts for the direction of venous flow, as well as the degree of venous distortion associated with the lesion (Table 21.2). The degree of venous ectasia was used to further stratify the risk of hemorrhage in lesions with CVD. Cognard type V lesions are used to designate lesions with spinal venous drainage [18]. More recently, Zipfel et al. have proposed to modify the Borden and Cognard classification schemes to include the presence of absence of symptoms in aggressive DAVFs [8, 19], as stud-

Table 21.1 Borden classification of dural arteriovenous fistulae

Type 1	Venous drainage into a dural sinus; no CVD
Type 2	Venous drainage into a dural sinus with associated CVD
Type 3	Drainage into cortical veins (CVD)

Table 21.2 Cognard classification of dural arteriovenous fistulae

Type I	Venous drainage into dural sinus with antegrade flow
Type II a	Venous drainage into dural sinus with retrograde flow
Type II b	Venous drainage into dural sinus with antegrade flow and CVD
Type II a + b	Venous drainage into dural sinus with retrograde flow and CVD
Type III	Venous drainage into cortical veins (CVD)
Type IV	CVD with associated venous ectasia(s)
Type V	Venous drainage into spinal perimedullary veins

Table 21.3 Barrow classification of carotid-cavernous fistulas

Type A	Direct shunt from internal carotid artery
Type B	Shunt from meningeal branches of internal carotid artery
Type C	Shunt from meningeal branches of external carotid artery
Type D	Shunt from both internal and external carotid artery branches

ies have indicated a higher annual rate of ICH in symptomatic high-grade DAVFs than in asymptomatic lesions (7.5% vs 1.5%, respectively) [20, 21].

A second category of cranial DAVFs involve the cavernous sinus. Lesions of the cavernous sinus have also been classified using the Barrow classification of carotid-cavernous fistulas (Table 21.3). This anatomical classification divides cavernous sinus shunts into direct and indirect types, with the indirect types of lesions (type B, C, and D) being DAVFs [22]. The indirect fistulas may be from meningeal branches of the ICA (Type B), ECA (Type C), or both (Type D). They present with symptoms that are more insidious and less severe than Type A lesions [23]. Symptoms include red eye, proptosis, increased intraocular pressure, diplopia, pain, and bruit [24]. These fistulas may resolve spontaneously in many cases. Interestingly, high rates of spontaneous resolution following diagnostic angiography have been noted. Symptoms are classically waxing and waning in nature, with worsening symptoms possibly attributable to changing venous drainage patterns.

Common Sites and Feeding Vessels

Dural arteriovenous fistulas are predominantly located around the venous sinuses. These include the cavernous sinus, sigmoid and transverse sinuses, and the superior sagittal sinus. Anterior cranial fossa, occipital sinus, and tentorial lesions have also been described. The sigmoid and transverse sinuses are the most common location, accounting for 30–50% of DAVFs [25, 26]. Multiple DAVFs may occur in 7–10% of cases [25].

Multiple arteries from the extra- and intracranial circulation may supply DAVFs in a given location. All branches of the external carotid artery (ECA) may be implicated, as well as dural arteries of the internal carotid artery (ICA). The vertebral artery (VA) may also supply a lesion through meningeal branches. As well, terminal cerebral branches of the ICA and the VA may supply the lesion directly through pial branches. The diverse routes of arterial supply to the lesion make it imperative that diagnostic angiography of all potential feeders be carried out as part of the diagnostic evaluation of the DAVF. After partial treatment through arterial embolization, the DAVF may recruit new feeding vessels from the contralateral circulation. Possible arterial feeding vessels for common DAVF locations, including carotid-cavernous fistulas, are summarized in Table 21.4 [27].

Treatment of Dural AVFS

Successful treatment of DAVFs requires a complete knowledge and understanding of the complex cerebral anatomy. Surgical ligation of fistulas remains a standard therapy. A multidisciplinary team of cerebrovascular surgeons and interventional

Table 21.4 Major supply to intracranial DAVFs

Location	ECA	ICA	Vertebral
Sigmoid-transverse sinus	Occipital Ascending pharyngeal Posterior auricular Middle meningeal Superficial temporal	Bernasconi-Cassinari meningohypophyseal artery Inferolateral trunk	Posterior meningeal Cerebellar falcine
Cavernous sinus	Middle meningeal Artery of foramen rotundum Ascending pharyngeal Posterior auricular	Meningohypophyseal trunk Inferolateral trunk McConnell's capsular branches	
Tentorial-incisural	Ascending pharyngeal Occipital Middle meningeal Accessory meningeal	Meningohypophyseal trunk	Posterior meningeal Cerebellar falcine Posterior cerebral Superior cerebellar
Superior sagittal sinus	Middle meningeal Superficial temporal Occipital	Anterior falcine Meningohypophyseal trunk	Posterior meningeal
Anterior cranial fossa	Internal maxillary Middle meningeal	ICA Anterior/posterior ethmoidal	

neuroradiologists is required to successfully treat the patients. The goals of treatment vary depending on the presentation. For patients with significant tinnitus but no cortical venous drainage, a less aggressive approach can be undertaken, and in some situations, partial occlusion with reductions of symptoms is adequate. Care must be taken in these patients to ensure that future corticovenous drainage does not develop. This is done with serial imaging follow-up, usually MRI. If a patient presents with a change in their symptomology, such as a reduction or discontinuation of their pulsatile tinnitus, cerebral angiography is suggested, as this may represent a change in the venous outflow.

Lesions presenting with CVD must be angiographically cured. This includes patients presenting with or without hemorrhage. Often a combination of endovascular embolization followed by open surgical ligation is required. Surgery should be considered when (1) a simple fistula exists which is surgically accessible, (2) partial embolization has created a more acceptable lesion for surgery, and (3) the arterial supply to the fistula is by important branches that cannot be embolized without risking cranial nerves or other arterial anastomoses such as the ophthalmic artery. This is the case for most anterior cranial fossa fistulas, as often the feeders arise from ethmoidal branches that cannot be safely embolized with a liquid embolic material due to the proximity of the central retinal artery (Fig. 21.1).

Transarterial Embolization

Transarterial embolization necessitates penetration of the embolic material into the fistulous connection and venous pouch of the fistula. This is required to ensure that the often-multiple feeders to the fistula are interrupted. Standard aneurysm coils are not used but because of their inability to be placed distally are usually reserved for transvenous embolization.

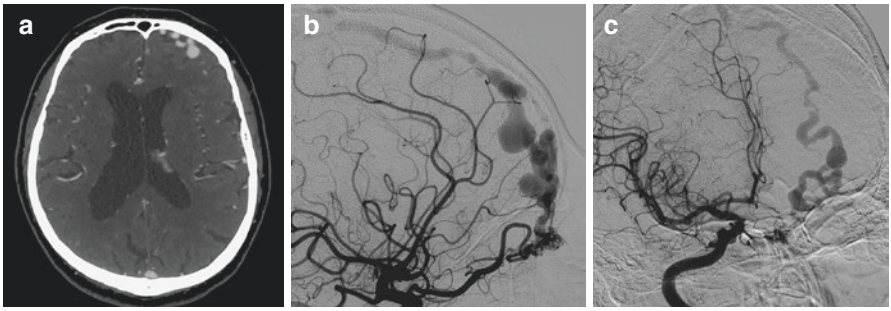


Fig. 21.1 A 79-year-old man presented with an acute left fourth cranial nerve palsy. (**a**) CTA showed the presence of dilated frontal vessels, raising the suspicion of anterior cranial fossa DAVF. (**b**, **c**) Right ICA injections in lateral and AP orientation show supply from the right anterior ethmoidal artery to the left-sided DAVF, with retrograde cortical venous drainage (Borden type 3, Cognard III). Surgical ligation was recommended and successfully performed, leading to total cure of the patient's cranial nerve palsy

Generally, there are two approved embolic materials for embolization of DAVFs: N-butyl cyanoacrylate (NBCA), marketed in the United States as TRUFIL (Cordis Neurovascular, Inc., Miami Lakes, FL, USA), and ethylene vinyl alcohol copolymer or Onyx (Medtronic Neurovascular Inc., Irvine, CA, USA). Onyx is an ethylene vinyl alcohol copolymer that is dissolved in dimethyl sulfoxide. Tantalum powder is dissolved in the material to provide visualization under fluoroscopy. A third material that has become available is PHIL from Microvention. This is available in Europe and is reported to have superior visualization of the liquid embolic, an ability to see the microcatheter tip during injections, minimal streak artifact on imaging, and no tattoo effect from the tantalum powder when treating superficial lesions. It is similar to Onyx in that it is a DMSO-dissolved product, requiring DMSO-compatible delivery catheters, and it is available in three different concentrations/viscosities [28].

The overall principle of using an embolic material is to penetrate and occlude the fistulous connection of the lesion (Fig. 21.2). If this is not successful, then either surgical ligation or transvenous embolization is required. There are multiple techniques available for transarterial embolization. Newer distal access catheters allow for excellent access to the feeding vessel. This reduces the requirement to re-navi-

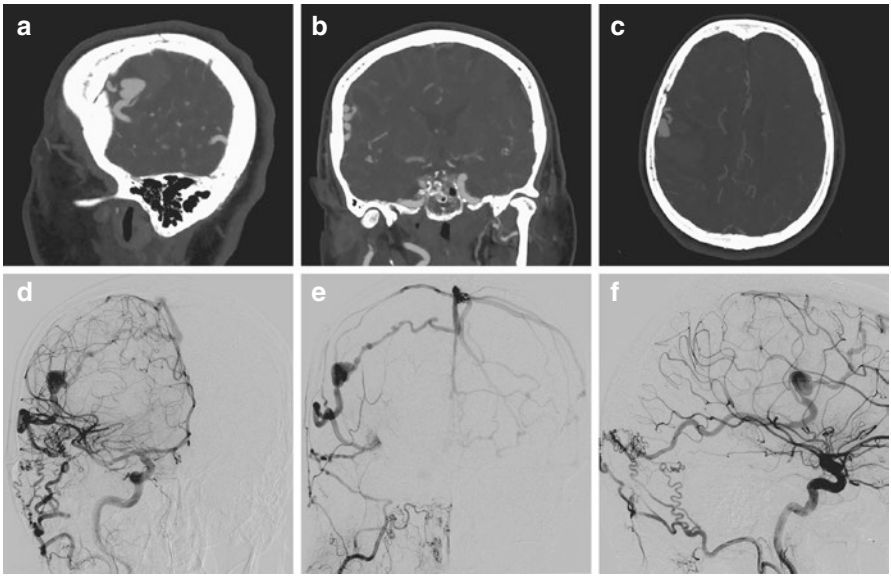


Fig. 21.2 This 69-year-old woman presented with a sudden-onset headache and a right-sided frontoparietal intracerebral hemorrhage; she was diagnosed with a Borden type 2/3 and Cognard IV dural AVF, with occlusion of the superior sagittal sinus. (**a**, **b**, **c**) CTA demonstrated multiple dilated vessels in the region of hemorrhage, raising the suspicion of DAVF. (**d**) Right ICA injection in the AP projection showed takeoff of the occipital artery from the R ICA and multiple occipital artery branches feeding the fistula, with evidence of venous ectasia and occlusion of the superior sagittal sinus. (**e**) Right ECA lateral injection in the AP projection showing supply to the fistula from the posterior division of the middle meningeal artery and cortical venous reflux. (**f**) Lateral view of the right ICA injection showing occipital artery supply to the fistula

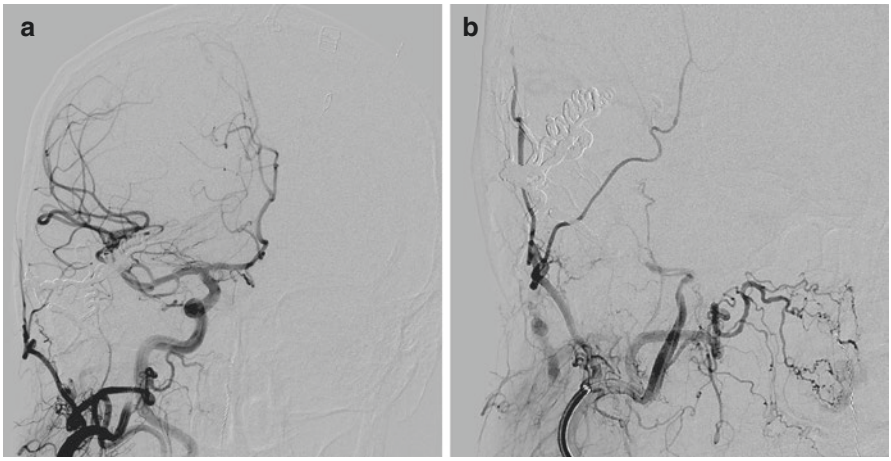


Fig. 21.3 (**a**, **b**) Posttreatment angiogram from the patient in Fig. 21.2, following transarterial Onyx embolization form the middle meningeal artery. AP and lateral views of right CCA injection show complete occlusion of the fistula and venous connection and absence of early venous filling

gate the vessels to get the microcatheters out the various feeding vessels. The distal access catheters also allow for better distal placement of microcatheters to achieve penetration into the fistula (Fig. 21.3). There are multiple microcatheters that are available for embolization with either NBCA or Onyx. Onyx requires the use of catheters that are resistant to the DMSO and will not degrade. A newer technique has been developed called the balloon augmented technique. A Scepter balloon (Microvention Inc. Tustin, CA, USA) can be advanced into the arterial feeder of the fistula. The traditional technique of Onyx embolization required the creation of a plug around the microcatheter. This can require a great deal of time and reflux, and gluing of the microcatheter can result in permanent catheter retention. By inflating the Scepter balloon, this plug is immediately created, and the Onyx can be pushed into the fistula, and reflux is limited. The limitation of the technique is that the balloon catheter is much less navigable into the distal vessel than a flow-directed microcatheter.

Transvenous Embolization

Transvenous embolization should be considered in all cases. The transvenous route allows access to the fistulous connection and venous pouch in many cases. This allows for disconnection of the fistula and angiographic cure. Also, in cases where the sinus is either occluded or there is proximal occlusion, embolization of the residual sinus connection can achieve angiographic cure. Often traditional aneurysm coils can be utilized to occlude the venous pouch via the transvenous approach.

Treatment of Carotid-Cavernous Fistulas

Carotid-cavernous fistulas (CCFs) have variable arterial supply, and this is outlined in Table 21.3. The key to successful management is identification of the supply. For high-flow lesions that occur secondary to a ruptured aneurysm or trauma, transarterial approach can be considered. This usually involved entry into the CCF via the internal carotid artery rent with subsequent coil embolization. Use of liquid embolic material is not recommended because of reflux into the intracranial circulation. Other options include placement of covered stents and vessel sacrifice. However, most lesions can be managed with either a transarterial or transvenous approach to the CCF.

Transvenous approaches remain the mainstay of treatment for indirect CCFs. Access is usually obtained via the inferior petrosal sinus (IPSS) (Fig. 21.4). Even in

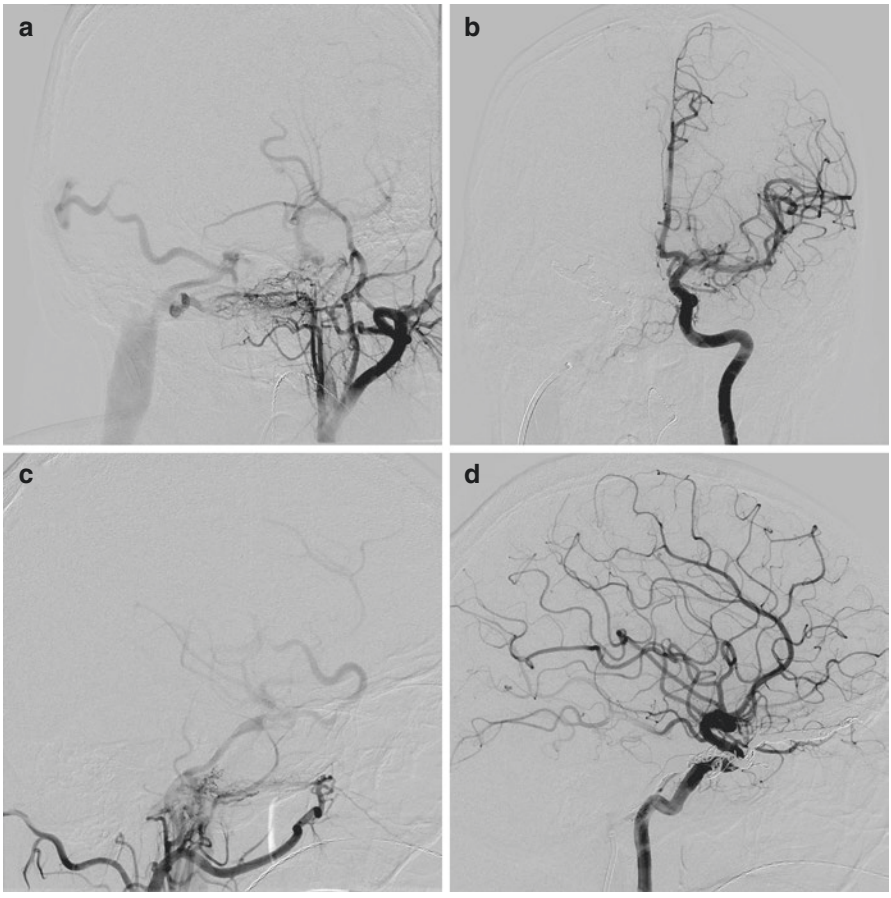


Fig. 21.4 This 42-year-old man presented with right-eye proptosis, chemosis, and diplopia and was found to have a right-sided, indirect CCF with supply from bilateral ICA and ECA branches (Barrow class D). (**a**, **c**) AP and lateral ECA injections showing early filling of the right inferior petrosal sinus and internal jugular vein (IJV). (**b**, **d**) AP and lateral arterial runs show near-complete occlusion of the CCF after transvenous embolization (see Fig. 21.5)

cases where the IPSS is not angiographic visible, we have had success probing the opening and successfully navigating into the cavernous sinus. In cases where access via the IPSS is not viable, other routes must be entertained. This includes direct cutdown or percutaneous access to the superior ophthalmic vein or access via the transfacial vein [29]. In our experience, this is infrequently required. Once the CCF has been entered with the microcatheter, progressive coil embolization is performed. We prefer to get as far into the cavernous sinus as possible and even place coils in the superior ophthalmic vein if allowed (Fig. 21.5). Progressive coiling with serial angiography will show progressive occlusion. Care must be taken during the initial diagnostic angiogram to target the correct side so that unilateral cavernous sinus occlusion will result in angiographic cure. In the occasional cases, bilateral embolization is required to cure the CCF.

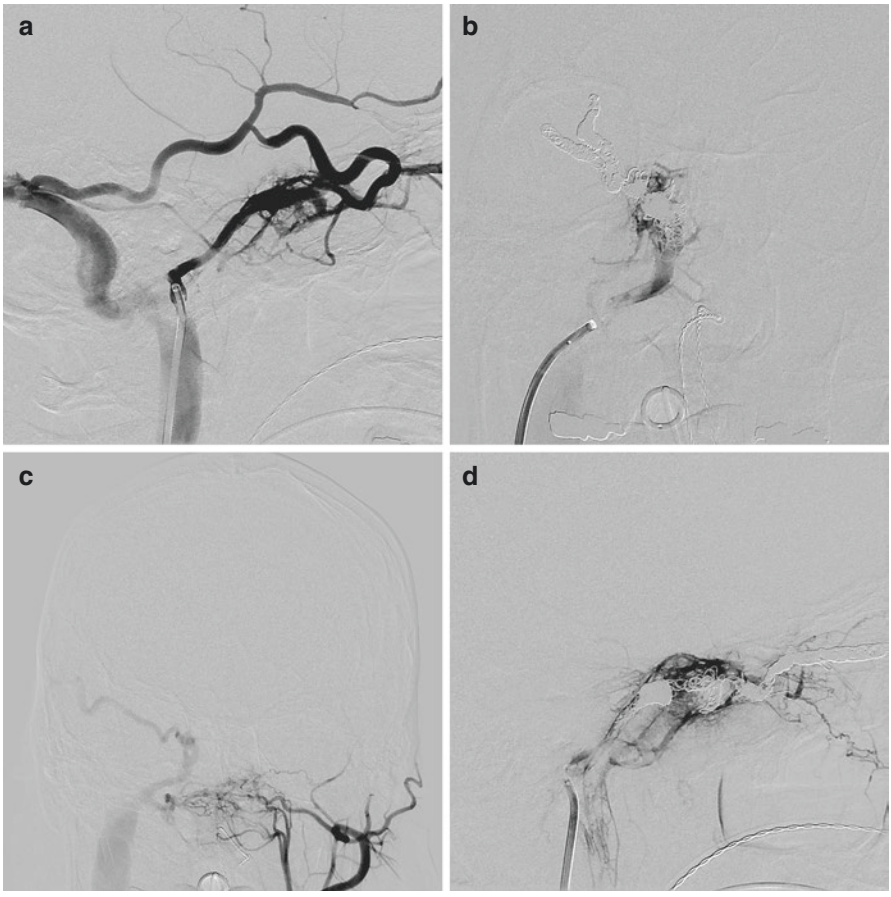


Fig. 21.5 Transvenous embolization of the right-sided CCF with supply from bilateral ICA and ECA meningeal branches: (**a**) Pretreatment venous injection from the inferior petrosal sinus, showing dilated venous anatomy of the cavernous sinus. (**c**) Pretreatment AP view of left ECA injection showing contribution to the right-sided CCF and early filling of the right IJV. (**b**, **d**) Posttreatment AP and lateral views of venous injection showing coils in the right superior ophthalmic vein, cavernous sinus, proximal cortical draining vein, and the inferior petrosal sinus

Complications

Both transarterial and transvenous endovascular treatment of DAVFs have associated complications. The primary concern with endovascular treatment of these lesions revolves around under- and overtreatment of the shunts. Incomplete treatment of DAVFs can lead to recruitment of more arterial feeders and a more difficult-to-treat lesion, while leakage of embolic material into the sinus can lead to pulmonary embolism or venous sinus thrombosis and infarction. Persistent neurological deficits and cranial nerve palsies have also been reported.

Due to the small numbers of cases included in most series, as well as the evolving nature of endovascular therapy for DAVFs, a consistent rate of complications is hard to define. A recent review of 260 cases over 30 years, carried out by Gross et al., places the overall complication rate at 8%. The rate of permanent neurological complications was 3% and included venous infarction, MCA territory infarction, facial nerve palsy, anesthesia dolorosa, and worsened ophthalmoparesis following cavernous DAVFs. The authors found no difference in the rate of complications between DAVFs treated in the pre-Onyx era and after the advent of Onyx [30]. Another review of fewer patients treated solely in the Onyx era found the overall rate of complications to be in the same range, at 10% [31]. A prior study of 40 patients, also treated solely using Onyx, found a slightly higher overall rate of complications, at 23% [32]. Complication avoidance is of paramount importance. This is achieved by a thorough understanding of the anatomy of the lesion. For example, lesions supplied by the neuromeningeal branch of the ascending pharyngeal artery can have higher complication rates during embolization because of the arterial supply to the cranial nerves in the jugular foramen. As well, anastomotic channels between the external carotid artery and intracranial ICA and vertebral artery must be identified and considered to prevent embolic material from entering the intracranial circulation.

References

1. Miller TR, Gandhi D. Intracranial dural arteriovenous fistulae: clinical presentation and management strategies. Stroke. 2015;46(7):2017–25.
2. Newton TH, Cronqvist S. Involvement of dural arteries in intracranial arteriovenous malformations. Radiology. 1969;93(5):1071–8.
3. Kerber CW, Newton TH. The macro and microvasculature of the dura mater. Neuroradiology. 1973;6(4):175–9.
4. Piton J, et al. Fistulae of the lateral sinus. J Neuroradiol. 1984;11(3):143–59.
5. Herman JM, et al. Genesis of a dural arteriovenous malformation in a rat model. J Neurosurg. 1995;83(3):539–45.
6. Rothbart D, et al. Expression of angiogenic factors and structural proteins in central nervous system vascular malformations. Neurosurgery. 1996;38(5):915–24; discussion 924–5.
7. Terada T, et al. Development of acquired arteriovenous fistulas in rats due to venous hypertension. J Neurosurg. 1994;80(5):884–9.

8. Hu YC, et al. Cranial dural arteriovenous fistula: transarterial Onyx embolization experience and technical nuances. J Neurointerv Surg. 2011;3(1):5–13.
9. Kim MS, et al. Clinical characteristics of dural arteriovenous fistula. J Clin Neurosci. 2002;9(2):147–55.
10. Kim DJ, et al. Spontaneous angiographic conversion of intracranial dural arteriovenous shunt: long-term follow-up in nontreated patients. Stroke. 2010;41(7):1489–94.
11. Lasjaunias P, et al. Neurological manifestations of intracranial dural arteriovenous malformations. J Neurosurg. 1986;64(5):724–30.
12. Davies MA, et al. The natural history and management of intracranial dural arteriovenous fistulae. Part 2: aggressive lesions. Interv Neuroradiol. 1997;3(4):303–11.
13. Shin NY, et al. Venous angioarchitectural features of intracranial dural arteriovenous shunt and its relation to the clinical course. Neuroradiology. 2013;55(9):1119–27.
14. Brown RD Jr, Wiebers DO, Nichols DA. Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients. J Neurosurg. 1994;81(4):531–8.
15. van Dijk JM, et al. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. Stroke. 2002;33(5):1233–6.
16. Jolink WM, et al. Outcome after intracranial haemorrhage from dural arteriovenous fistulae; a systematic review and case-series. J Neurol. 2015;262(12):2678–83.
17. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. J Neurosurg. 1995;82(2):166–79.
18. Cognard C, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194(3):671–80.
19. Zipfel GJ, et al. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. Neurosurg Focus. 2009;26(5):E14.
20. Soderman M, et al. Natural history of dural arteriovenous shunts. Stroke. 2008;39(6):1735–9.
21. Strom RG, et al. Cranial dural arteriovenous fistulae: asymptomatic cortical venous drainage portends less aggressive clinical course. Neurosurgery. 2009;64(2):241–7; discussion 247–8.
22. Barrow DL, et al. Classification and treatment of spontaneous carotid-cavernous sinus fistulas. J Neurosurg. 1985;62(2):248–56.
23. Ringer AJ, Salud L, Tomsick TA. Carotid cavernous fistulas: anatomy, classification, and treatment. Neurosurg Clin N Am. 2005;16(2):279–95, viii.
24. Grossman RI, et al. Dural malformations with ophthalmic manifestations: results of particulate embolization in seven patients. AJNR Am J Neuroradiol. 1985;6(5):809–13.
25. Krings T, Geibprasert S, Brugge K. Case-based interventional neuroradiology. Stuttgart: Thieme; 2011.
26. Kirsch M, et al. Endovascular management of dural arteriovenous fistulas of the transverse and sigmoid sinus in 150 patients. Neuroradiology. 2009;51(7):477–83.
27. Dion J. Dural arteriovenous malformations: definition, classification, and diagnostic imaging. In: Awad I, Barrow D, editors. Dural arteriovenous malformations. Park Ridge: AANS; 1993.
28. Leyon JJ, et al. Preliminary experience with the liquid embolic material agent PHIL (precipitating hydrophobic injectable liquid) in treating cranial and spinal dural arteriovenous fistulas: technical note. J Neurointerv Surg. 2016;8(6):596–602.
29. Quinones D, et al. Embolization of dural cavernous fistulas via superior ophthalmic vein approach. AJNR Am J Neuroradiol. 1997;18(5):921–8.
30. Gross BA, et al. Evolution of treatment and a detailed analysis of occlusion, recurrence, and clinical outcomes in an endovascular library of 260 dural arteriovenous fistulas. J Neurosurg. 2016;126:1–10.
31. Rangel-Castilla L, et al. Mid and long term outcomes of dural arteriovenous fistula endovascular management with Onyx. Experience of a single tertiary center. J Neurointerv Surg. 2014;6(8):607–13.
32. Lv X, et al. Complications related to percutaneous transarterial embolization of intracranial dural arteriovenous fistulas in 40 patients. AJNR Am J Neuroradiol. 2009;30(3):462–8.

Chapter 22
Cavernous Malformations

Jason A. Ellis and Daniel L. Barrow

General Description

Cavernous malformations are well-circumscribed, vascular lesions composed of endothelium-lined blood-filled channels situated within the parenchyma of the brain or spinal cord. Also known as cavernomas, these nonneoplastic mass lesions were first described by Plenck in 1776 and later elaborated by Virchow and McCormick [1–3]. They are classically described as having a "mulberry" appearance on gross inspection. A gliotic pseudocapsule of hemosiderin-stained neural tissue with infiltrating inflammatory cells may surround cavernous malformations; however, there is typically no parenchyma within the lesion itself.

Unlike arteriovenous malformations (AVM), cavernous malformations are low pressure, low-flow lesions that may contain or be surrounded by blood at varying stages of degradation. The arterial feeders are generally small with little, if any, hemodynamic influence on the surrounding cerebral blood flow. For this reason, cavernous malformations are angiographically occult and best delineated on MRI. On the other hand, cavernous malformations are often associated with angiographically visible developmental venous anomalies which are critical to the venous drainage of the surrounding parenchyma. The Zabramski cavernous malformation classification is generally helpful for determining the acuity of hemorrhage based

J. A. Ellis (✉)
Hofstra Northwell School of Medicine, Department of Neurosurgery, Lenox Hill Hospital, New York, NY, USA

Northwell Health, New York, NY, USA

Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA
e-mail: jellis2@northwell.edu; https://www.northwell.edu/jason-ellis-md

D. L. Barrow
Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA
e-mail: dbarr01@emory.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_22

on MRI [4]. Type 1 lesions have a hyperintense core on T1 sequences with a hypointense rim on T2 sequences representing subacute hemorrhage. Type 2 lesions have a mixed signal core on both T1 and T2 sequences representing mixed-age hemorrhage. Type 3 lesions are isointense or hypointense on T1 sequences and hypointense on T2 sequences representing chronic hemorrhage. Type 4 lesions are only visible as punctate hypointensities on gradient-echo sequences.

Cavernous malformations may be found throughout the central nervous system with a location frequency in proportion to the amount of neural tissue present. Thus, the majority of cavernous malformations are found in the supratentorial compartment. More specifically, 75% of cavernous malformations are found in a supratentorial location, 20% are in the brainstem, and 5% are in the spinal cord. It has been long known that both familial and spontaneous forms of cavernous malformation exist, while more recent work has identified the specific genetic loci involved in their pathogenesis. Notably, the familial form may be inherited in an autosomal dominant fashion with incomplete penetrance. Patients who harbor multiple cavernous malformations and/or have family members with cavernous malformations should increase suspicion that the familial form may be present. Mutations in one of three genes including KRIT1 (CCM1), MCG4607 (CCM2), or PDCD10 (CCM3) have been associated with most familial cavernous malformations [5].

It is of both heuristic and clinical utility to classify cavernous malformations based on their location within the central nervous system. Although the histopathology and basic pathogenesis are unchanged, the clinical course and therapeutic decision-making for cavernous malformations can vary significantly depending on their location. Indeed, location is the most critical determinant of the natural history for an individual cavernous malformation. The typical anatomic classification scheme identifies supratentorial, posterior fossa, and spinal cord cavernous malformations (Fig. 22.1). The supratentorial variety is further subcategorized as being either superficial or deep. Superficial supratentorial cavernous malformations involve either the cortex or subcortical white matter. Deep supratentorial cavernous malformations involve the basal ganglia or thalamus. The posterior fossa cavernous malformations include those located in the brainstem or in the cerebellum. The clinical management of cavernous malformations in each compartment with special emphasis on the indications and strategy for intervention is addressed in this chapter.

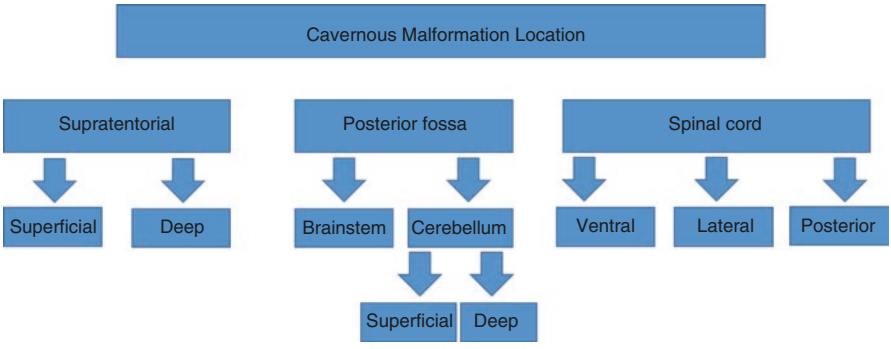


Fig. 22.1 Schematic anatomic classification of cavernous malformations

Overview of Treatment Options

Cavernous malformations may be found incidentally or result in symptoms due to cortical irritation, hemorrhage, or mass effect on surrounding neural structures. Depending on the clinical presentation, one of five strategies may be employed in the management of a particular cavernous malformation including (1) observation, (2) antiepileptic drug therapy, (3) radiosurgery, (4) laser ablation, or (5) microsurgery.

Observation

Observation is the most common approach for managing asymptomatic or minimally symptomatic patients with cavernous malformations. Based on autopsy series, cavernous malformations have an incidence of 0.5% or less in the population [6–8]. Nonetheless, they are being increasingly discovered incidentally during imaging workup for unrelated reasons [9–11]. Conservative follow-up tends to be the mainstay approach to such patients. The appearance on MRI is highly characteristic but not pathognomonic. An associated developmental venous anomaly or a family history will strengthen the certainty of the diagnosis. In our practice, we routinely reimage the patient several months to a year after initial discovery to be sure that the lesion is not changing in some way to suggest that it may be something other than a cavernous malformation. If the lesion is stable and has the typical appearance of a cavernous malformation on follow-up MRI, we generally do not reimage the lesion unless there are associated new onset or progression of neurological symptoms. Small intracapsular hemorrhages are common and generally do not prompt a change in management unless the bleed is associated with a clinical decline.

Incidental cavernous malformations that are located in high-risk areas may present a dilemma for deciding the most appropriate treatment course. Although not without some controversy, high-risk locations have been generally thought to include subependymal or paraventricular areas, the brainstem, and within the spinal cord. Paraventricular cavernous malformations present the theoretical risk of devastating intraventricular hemorrhage resulting in acute hydrocephalus (Fig. 22.2). It is reasoned that this may occur because the paraventricular facet of the cavernous malformation is not protected by the tamponading effect of the parenchyma.

Hemorrhage from brainstem and spinal cord cavernous malformations may also result in devastating acute neurological decline. In many cases, observation may still be favored if the microsurgical approach for resection is associated with the potential for significant morbidity.

Overall, the annual “event rate” or incidence of neurological decline that can be attributed to cavernous malformation seems to be less than 5% [12]. Hemorrhage rates are often quoted at 0.5% per year with the proviso that prior hemorrhage portends a much higher event rate. Additionally, it must be kept in mind that event rates are location specific with deep-seated and eloquent lesions much more likely to result in clinically significant symptoms. Patients with multiple cavernous malformations and/or suspected familial inheritance should be followed more closely for

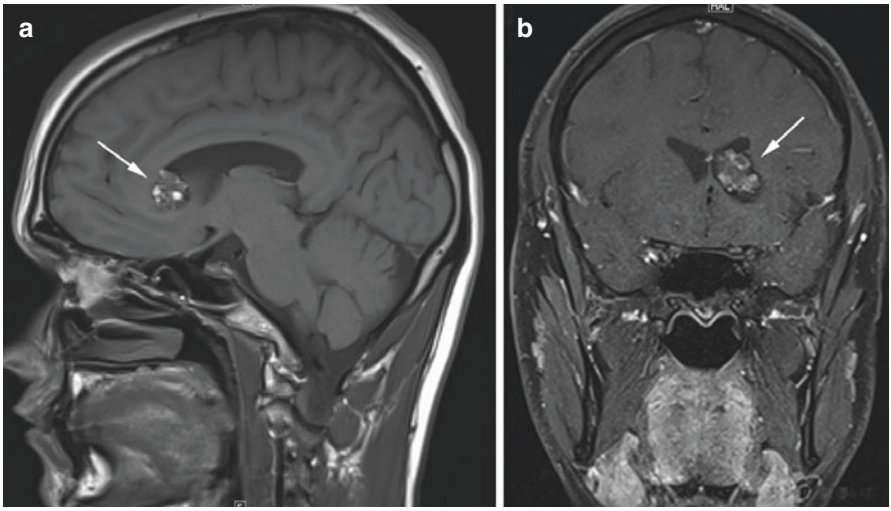


Fig. 22.2 (**a** and **b**) Paraventricular cavernous malformation. Sagittal and coronal T1 MRI demonstrates a caudate head cavernous malformation with exophytic component (arrow) into the left lateral ventricle. The location of this malformation puts the patient at risk for intraventricular hemorrhage

the development of de novo lesions. The decision-making algorithm for managing such patients is complex and is explored in the forthcoming sections.

Antiepileptic Drug Therapy

Seizures are the most common presentation for patients with supratentorial cavernous malformations. Approximately 80% of patients with supratentorial cavernous malformations will have seizures as part of their clinical syndrome [13]. Furthermore, the risk of developing seizures in a patient with a known supratentorial cavernous malformation ranges from 1.5% to 2.5% per year [6, 14]. Seizure onset should be clearly localized at or near the cavernous malformation based on electroencephalographic monitoring to support a diagnosis of lesional epilepsy. It should also be kept in mind that cavernous malformation-related seizures may rapidly secondarily generalize such that focal onset becomes unclear.

Long-term antiepileptic drug therapy is certainly a reasonable approach for patients whose cavernous malformation-related seizures can be eliminated in this manner [15]. However, failure of two adequate trials of antiepileptic drugs to resolve seizures is an indication for an alternative treatment strategy. Additionally, many patients will have both medical and social reasons why long-term antiepileptic drug therapy is undesirable. It has been demonstrated that resection of cavernous malformations associated with epilepsy is more likely to provide seizure freedom and increase the likelihood of antiepileptic drug therapy discontinuation than medical therapy [16].

Radiosurgery

Radiosurgery is a controversial treatment strategy for cavernous malformations. This stems both from the poor results documented in the early literature and from a peculiar aspect of cavernous malformation bleeding known as temporal clustering [17, 18].

The unfavorable radiosurgical results in the early literature have been variably attributed to the use of CT scans for stereotactic planning, lack of experience with dose planning specifically for cavernous malformations, and improper patient selection. It has been suggested that early practitioners did not appreciate the radiosensitizing effects of iron and other blood breakdown products within the surrounding parenchyma leading to overdose and radiation necrosis. As experience has grown, the literature has shown more favorable results wherein patients are generally not harmed. It remains unclear if they are actually helped, however.

Cavernous malformations tend to have a high incidence of repeat hemorrhage within the first 2 years after initial hemorrhage. This natural history phenomenon known as temporal clustering occurs within the same time frame as the proposed latency period before radiosurgery is thought to take effect [19]. Thus, it is very difficult to ascertain whether the decrease in cavernous malformation hemorrhage rates reported several years after radiosurgery is a treatment effect or just a reflection of the lesion's natural history. There is no evidence that radiosurgery actually obliterates cavernous malformations.

Laser Ablation

Laser interstitial thermal therapy is an investigational, "minimally invasive" strategy for treating cerebral cavernous malformations [20]. Like radiosurgery, laser ablation promises a theoretical advantage for addressing deep-seated cavernous malformations without the potential morbidity associated with microsurgical access. The technique involves stereotactically targeting the cavernous malformation with a thin laser fiber probe (Fig. 22.3). Ablations are guided by real-time magnetic resonance thermography which allows thermal energy to be restricted to the zone of interest. While this strategy has a sound theoretical foundation, its safety and long-term effectiveness have yet to be evaluated in large patient cohorts. Additionally, similar to radiosurgery, the therapeutic effects are thought to have a latency which is not yet clearly defined.

Surgery

Microsurgical resection remains the gold standard treatment modality for managing symptomatic cavernous malformations. While it is true that a microsurgical approach can be devised to resect almost any cavernous malformation, one must

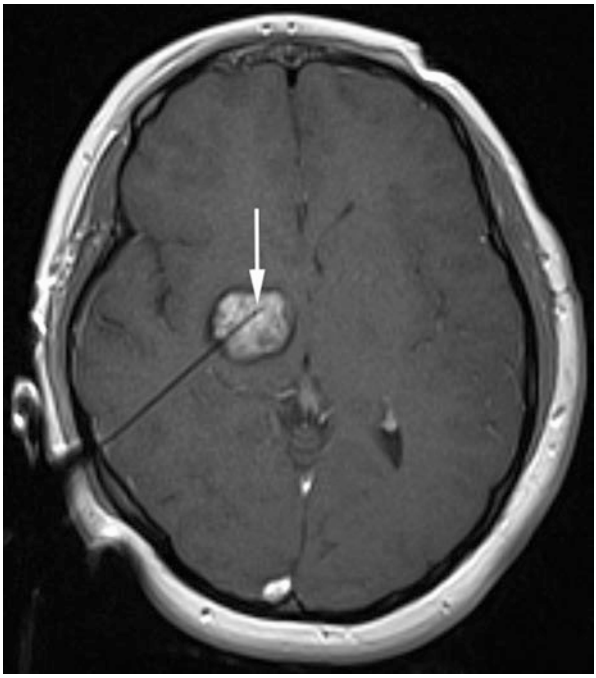


Fig. 22.3 Laser ablation of cavernous malformation. Laser interstitial thermal therapy was used to ablate this right thalamic cavernous malformation. The tip of the laser probe is stereotactically targeted to the center of the cavernous malformation via a right lateral temporal approach

keep in mind the attendant morbidity associated with each approach—especially for lesions that are deep-seated or located in eloquent regions. In some cases, the risks associated with a particular surgical approach will far outweigh the benefits of hemorrhage prevention. In cases where symptoms are clearly due to mass effect, surgery offers the advantage of immediately and permanently removing the offending malformation as well as the associated hemorrhage. In cases where seizures are the main symptom, both the cavernous malformation and surrounding irritative focus of hemosiderin-stained cortex can be resected.

The techniques utilized for the microsurgical removal of cavernous malformations are dependent on the lesion's location. In non-eloquent supratentorial or cerebellar hemispheric regions, it may be quite safe to perform an en bloc resection including a margin encompassing all the hemosiderin-stained neural tissue. In contrast, cavernous malformations in the eloquent cortex, brainstem, deep cerebellar nuclei, or spinal cord may only lend themselves to piecemeal resection.

Supratentorial Cavernous Malformations

Superficial (Cortical and Subcortical)

The vast majority of supratentorial cavernous malformations that are either cortical or subcortical in location will present with seizures or be discovered incidentally. Overt, extracapsular hemorrhage resulting in focal neurological deficits due to mass effect is

also possible. Microsurgical resection is generally straightforward for such symptomatic supratentorial cavernous malformations. The general principles employed include (1) ensuring accurate craniotomy placement with the use of frameless stereotaxy, (2) minimizing transgression of uninvolved cortex, and (3) circumferential isolation and size reduction of the cavernous malformation using bipolar cautery and microscissors to effect an en bloc resection when feasible. Large malformations may warrant piecemeal resection. If the malformation is below the cortical surface, we typically utilize a trans-sulcal approach to expose the lesion. In cases of lesional epilepsy, consideration should be given to resecting the hemosiderin-stained brain tissue as well. However, this must be done with caution or not at all in eloquent regions.

Deep (Thalamus and Basal Ganglia)

Cavernous malformations in the basal ganglia and thalamus are challenging to treat microsurgically. While observation is probably the best strategy for many deep cavernous malformation, progressive neurological decline or hemorrhage may necessitate their surgical removal. The specific operative approach utilized will depend on the exact location of the lesion. One of six unique operative approaches have been suggested based on the region of the thalamus affected [21]. The approaches include (1) orbitozygomatic for anteroinferior thalamus, (2) anterior ipsilateral interhemispheric transcallosal for medial thalamus, (3) anterior contralateral interhemispheric transcallosal for lateral thalamus (Fig. 22.4), (4) posterior interhemispheric transcallosal for posterosuperior thalamus, (5) parieto-occipital transventricular for lateral posteroinferior thalamus, and (6) suboccipital supracerebellar infratentorial for medial posteroinferior thalamus. Tubular retractors and long instruments may be of benefit in some cases of deep cavernous malformation where a transcortical route is taken due to the long working distance.

Posterior Fossa Cavernous Malformations

Brainstem

The indications for resection of cavernous malformations in the brainstem are controversial. In many instances, a conservative approach is adopted unless there is demonstrated progressive neurological decline after multiple hemorrhages. Such an approach is not unreasonable, especially for inexperienced practitioners, given that most patients will experience either temporary or permanent morbidity due to the microsurgical approach itself. Although attempts have been made to define safe zones for entry into the brainstem, transgression of viable parenchyma should generally be avoided [22–24]. Cavernous malformations presenting to a pial surface are most favorable for good operative outcomes (Figs. 22.5 and 22.6).

The two-point method can be used to suggest a variety of operative approaches for individual cavernous malformations [25]. The method involves drawing a line

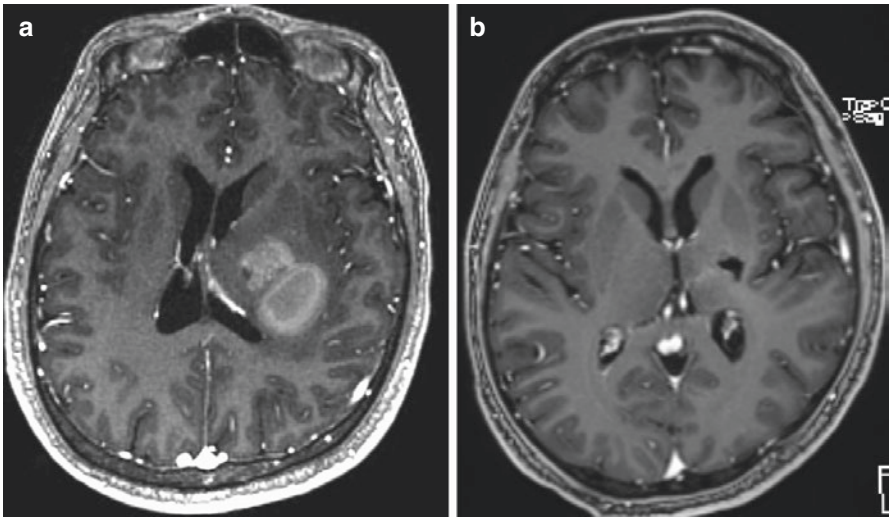


Fig. 22.4 Microsurgical resection of thalamic cavernous malformation. This symptomatic left thalamic cavernous malformation (**a**) was completely resected (**b**) via a right-sided (contralateral) interhemispheric transcallosal approach

on axial imaging from the center of the cavernous malformation to its pial or ependymal presentation and extending the line through the skull to the skin. The point at which the line crosses the skull indicates the bone that needs to be removed, thus suggesting the appropriate skull base approach. Such approaches may include the orbitozygomatic transsylvian, transpetrous, retrosigmoid, far lateral, midline suboccipital, or supracerebellar infratentorial routes. The principles to keep in mind when attempting to resect brainstem cavernous malformations include the following: (1) select an approach that allows direct entry at the site of pial presentation, (2) piecemeal rather than en bloc resection should be favored for large lesions, (3) preserve the associated developmental venous anomaly to avoid brainstem venous infarction, and (4) make no attempt to resect the hemosiderin-stained parenchyma (Fig. 22.7).

Cerebellum

The operative considerations for cavernous malformations in the cerebellum are similar to those already discussed. The best approach is generally one that allows resection with minimal transgression of uninvolved tissue. Cavernous malformations presenting to the petrous face are often best attacked by either a retrosigmoid or, more rarely, a transpetrous approach. Cerebellar hemispheric, vermian, and deep nuclei cavernous malformations can be reached via a midline suboccipital transcortical approach. The telovelar approach may be appropriate for certain cavernous malformations in the cerebellar peduncles.

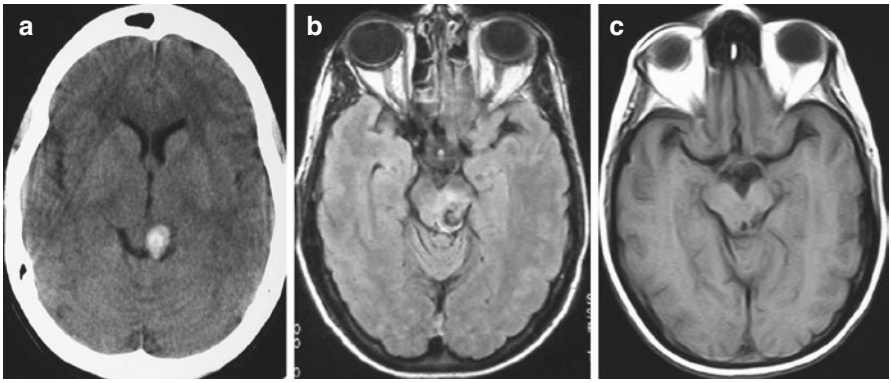


Fig. 22.5 Dorsal midbrain cavernous malformation. CT scan shows an acute hemorrhage in the dorsal midbrain of a patient who presented with diplopia and contralateral sensory loss (**a**). MRI confirmed the lesion to be a tectal cavernous malformation that presents to the posterior lateral surface of the midbrain (**b**). A lateral supracerebellar infratentorial approach allowed for hemorrhage evacuation and complete resection of the cavernous malformation (**c**)

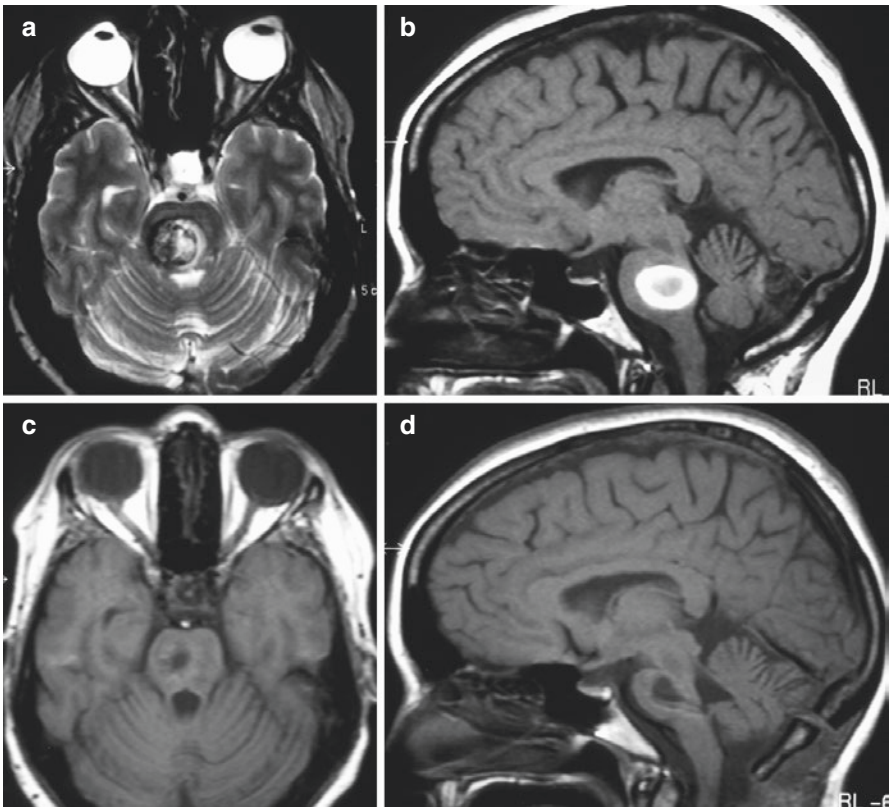


Fig. 22.6 Pontine cavernous malformation. Preoperative MRI (**a**–**b**) shows a large pontine cavernous malformation. The capsule presented to the floor of the fourth ventricle facilitating gross total resection via a telovelar approach (**c**–**d**)

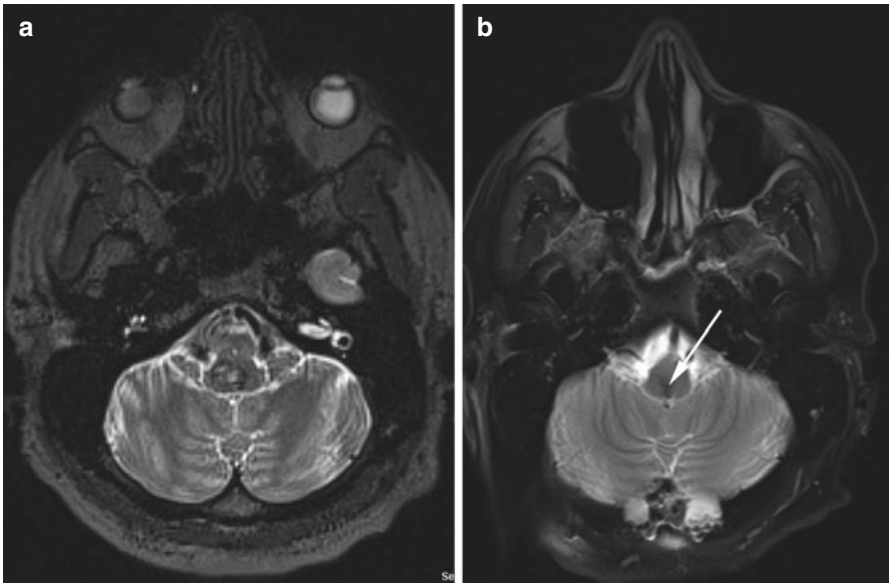


Fig. 22.7 Microsurgical resection of brainstem cavernous malformation. A midline suboccipital craniotomy was used to approach this medullary cavernous malformation (**a**). A complete resection was achieved with only a small rim of hemosiderin-stained medulla (arrow) apparent on postoperative MRI (**b**)

Intramedullary Cavernous Malformations

Spinal cord cavernous malformations present treatment challenges reminiscent of those encountered while treating lesions in other eloquent locations. While sudden, catastrophic extremity paralyses with bowel/bladder dysfunction and/or sensory changes are possible presentations for patients harboring intramedullary spinal cord cavernous malformations, this is decidedly uncommon. Insidious progression of myelopathy and chronic pain are more typical. This more characteristic disease course can be attributed to the recurrent episodes of small hemorrhage events that are typically seen in other locations as well. Asymptomatic or mildly symptomatic patients may be followed conservatively. Surgical removal is indicated for patients with progressive myelopathy attributable to the malformation. More generally, we tend to recommend surgery once the patient with a spinal cord cavernous malformation becomes symptomatic.

Cavernous malformations presenting to the pial surface of the dorsal aspect of the spinal cord are most favorable for resection (Fig. 22.8). Transient—but more often some degree of permanent—posterior column dysfunction is not uncommon after resecting dorsal lesions in the spinal cord. This can also be seen if a posterior myelotomy is necessary to access a deeper cavernous malformation (Figs. 22.9 and 22.10). Ventral and lateral spinal cord lesions may be associated with increased surgical morbidity given the proximity to descending motor fibers. Furthermore, ventral and posterior lateral approaches to the spine often necessitate adjunctive spinal stabilization which can

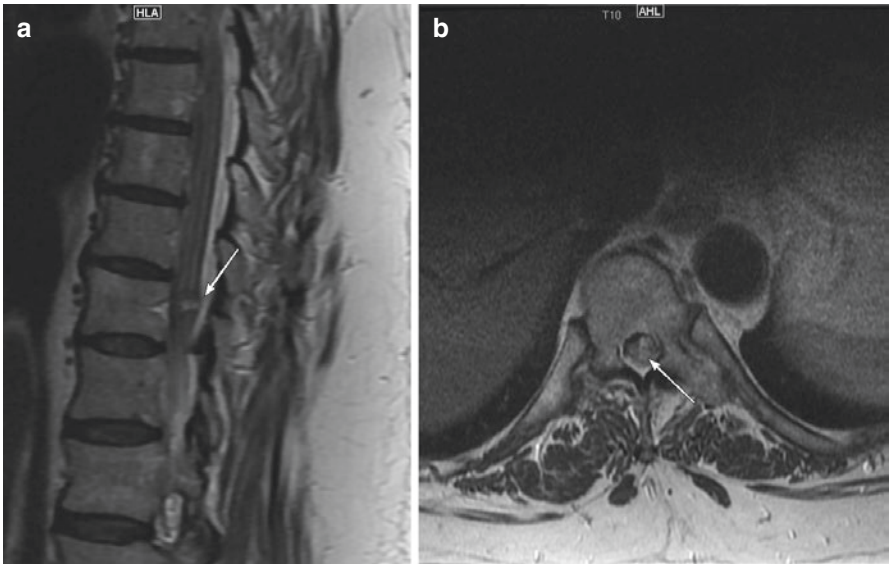


Fig. 22.8 Intramedullary spinal cord cavernous malformation. Axial (**a**) and sagittal (**b**) T2 MRI shows a thoracic intramedullary cavernous malformation that presents to the dorsal pia of the spinal cord (arrow). It was completely resected via midline thoracic laminectomy and dorsal myelotomy

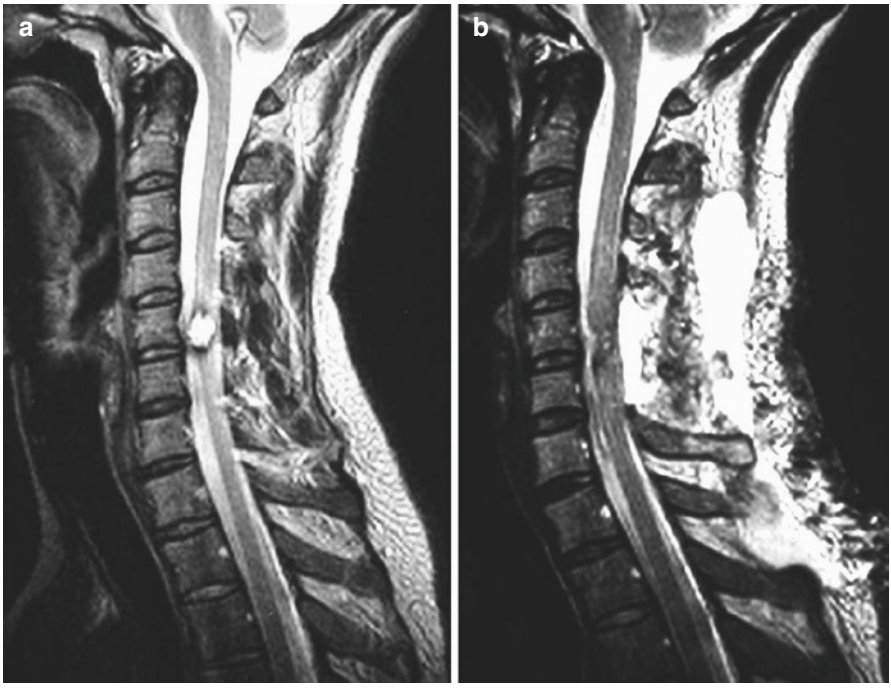


Fig. 22.9 Cervical spinal cord cavernous malformation. A dorsal myelotomy provided an adequate corridor for access to this large and deep cervical cavernous malformation (**a**). Postoperative MRI shows that a complete microsurgical resection was achieved (**b**)

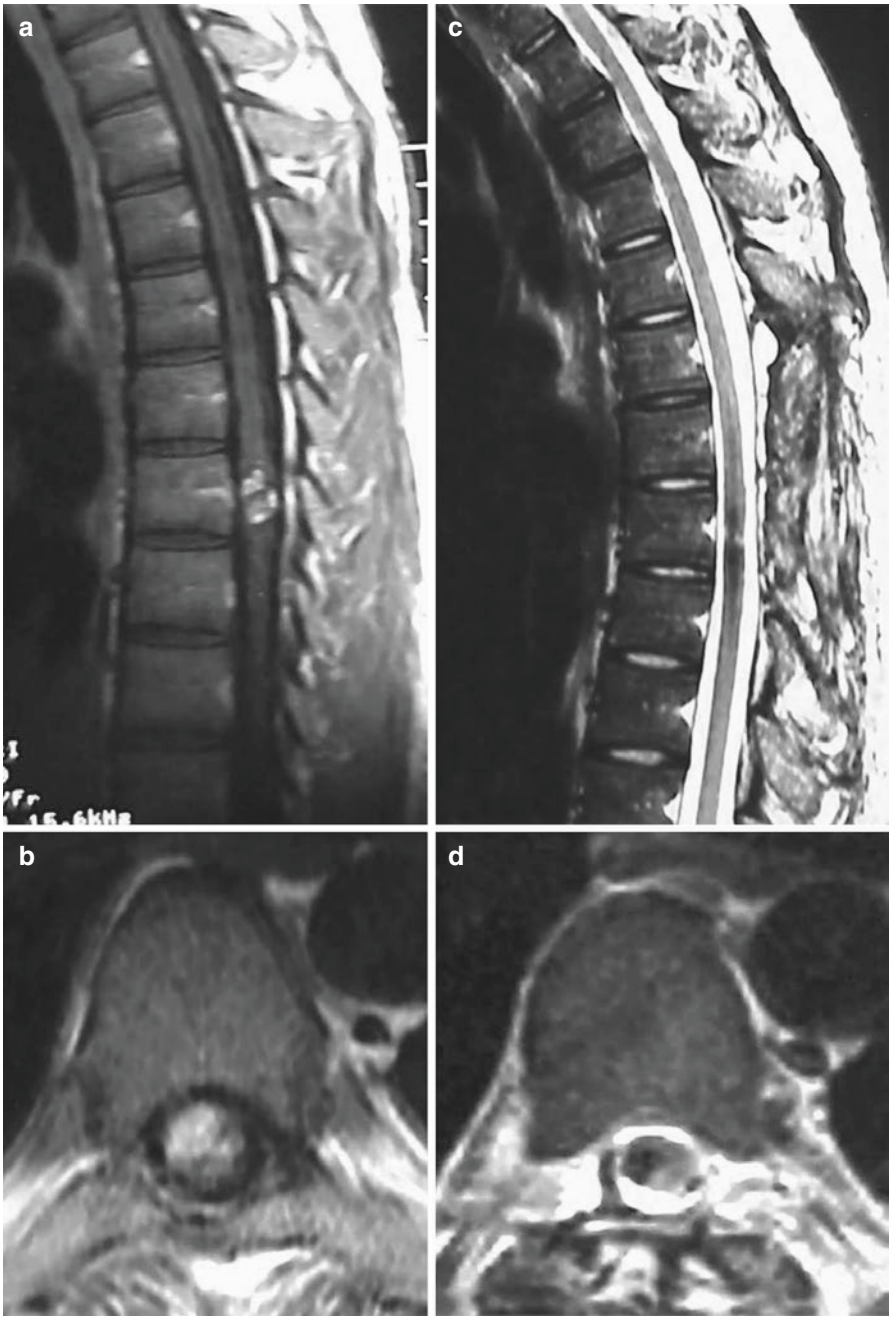


Fig. 22.10 Thoracic spinal cord cavernous malformation. This cavernous malformation has a significant component presenting on the ventral pia of the spinal cord as shown on sagittal and axial MRI (**a**–**b**). However, its eccentric location to the right allowed complete resection via a posterolateral corridor to the spinal canal (**c**–**d**)

increase the surgical morbidity. The general microsurgical techniques employed are similar to those already discussed for brainstem cavernous malformations.

References

1. Heros RC, Morcos JJ. Cerebrovascular surgery: past, present, and future. Neurosurgery. 2000;47(5):1007–33.
2. McCormick WF, Nofzinger JD. "Cryptic" vascular malformations of the central nervous system. J Neurosurg. 1966;24(5):865–75.
3. Virchow R. Die krankhaften Geschwülste: dressig Vorlesungen gehalted während des Wintersemesters 1862–1863 an der Universität zu Berlin. Berlin: August Hirschwald; 1863.
4. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: results of an ongoing study. J Neurosurg. 1994;80(3):422–32.
5. Leblanc GG, Golanov E, Awad IA, Young WL. Biology of vascular malformations of the brain. Stroke. 2009;40(12):e694–702.
6. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. J Neurosurg. 1991;75(5):702–8.
7. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. J Neurosurg. 1991;75(5):709–14.
8. Batra S, Lin D, Recinos PF, Zhang J, Rigamonti D. Cavernous malformations: natural history, diagnosis and treatment. Nat Rev Neurol. 2009;5(12):659–70.
9. Morris Z, Whiteley WN, Longstreth WT Jr, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2009;339:b3016.
10. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med. 2007;357(18):1821–8.
11. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA. 1999;282(1):36–9.
12. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg. 1997;87(2):190–7.
13. Moran NF, Fish DR, Kitchen N, Shorvon S, Kendall BE, Stevens JM. Supratentorial cavernous haemangiomas and epilepsy: a review of the literature and case series. J Neurol Neurosurg Psychiatry. 1999;66(5):561–8.
14. Moriarity JL, Wetzel M, Clatterbuck RE, et al. The natural history of cavernous malformations: a prospective study of 68 patients. Neurosurgery. 1999;44(6):1166–71; discussion 1172–3.
15. Rosenow F, Alonso-Vanegas MA, Baumgartner C, et al. Cavernoma-related epilepsy: review and recommendations for management--report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2013;54(12):2025–35.
16. Noto S, Fujii M, Akimura T, et al. Management of patients with cavernous angiomas presenting epileptic seizures. Surg Neurol. 2005;64(6):495–8; discussion 498–9.
17. Sheehan J, Schlesinger D. Editorial. Radiosurgery and cavernous malformations. J Neurosurg. 2010;113(4):689–90; discussion 690.
18. Barrow DL, Schuette AJ. Cavernous malformations: a paradigm for progress. Clin Neurosurg. 2011;58:27–41.
19. Barker FG 2nd, Amin-Hanjani S, Butler WE, et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. Neurosurgery. 2001;49(1):15–24; discussion 24–5.
20. McCracken DJ, Willie JT, Fernald BA, et al. Magnetic resonance thermometry-guided stereotactic laser ablation of cavernous malformations in drug-resistant epilepsy: imaging and clinical results. Neurosurgery. 2016;12(1):39–48.

21. Rangel-Castilla L, Spetzler RF. The 6 thalamic regions: surgical approaches to thalamic cavernous malformations, operative results, and clinical outcomes. J Neurosurg. 2015;123(3):676–85.
22. Cavalcanti DD, Preul MC, Kalani MY, Spetzler RF. Microsurgical anatomy of safe entry zones to the brainstem. J Neurosurg. 2016;124(5):1359–76.
23. Yagmurlu K, Rhoton AL Jr, Tanriover N, Bennett JA. Three-dimensional microsurgical anatomy and the safe entry zones of the brainstem. Neurosurgery. 2014;10(Suppl 4):602–19; discussion 619–20.
24. Recalde RJ, Figueiredo EG, de Oliveira E. Microsurgical anatomy of the safe entry zones on the anterolateral brainstem related to surgical approaches to cavernous malformations. Neurosurgery. 2008;62(3 Suppl 1):9–15; discussion 15–7.
25. Brown AP, Thompson BG, Spetzler RF. The two-point method: evaluating brain stem lesions. BNI Q. 1996;12:20–4.

Chapter 23
Endovascular Management of Carotid-Cavernous Fistulae

Philipp Taussky and Charles J. Prestigiacomo

The cavernous sinus is a rich and fascinating anatomic structure, serving as a major conduit between the intradural and extradural cranial milieu. Because of the many connections the cavernous sinus has with other structures of the head and neck, diseases of this structure can have a myriad of presentations. Vascular pathology in particular produces a myriad of symptoms and signs that are quite unique. One of the most recognizable of these lesions is the carotid-cavernous fistula (CCF). Dramatic or slowly indolent in its presentation, it can progress to become devastating to vision, cranial nerve function, and potentially cognition. The complexity of lesions in this territory is historically very difficult to treat, carrying significant morbidity and mortality. Though surgical lesions were the initial method by which to effect a cure, advances in endovascular technology have changed the treatment paradigm. This chapter will describe significant historical aspects, the anatomy and presentation of CCF and the endovascular treatment options for these lesions.

Historical Aspects

Though the cavernous sinus was variably recognized as an anatomic entity since the sixteenth century, its association with clinical symptoms did not fully develop until well into the nineteenth century. The description of the parasellar region which we

P. Taussky
Department of Neurosurgery, University of Utah School of Medicine,
Salt Lake City, UT, USA
e-mail: Philipp.Taussky@hsc.utah.edu

C. J. Prestigiacomo (✉)
Department of Neurological Surgery, University of Cincinnati College of Medicine,
Cincinnati, OH, USA
e-mail: presticj@uc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_23

now call the cavernous sinus stems from the days preceding Hippocrates [1]. Interestingly the anatomic understanding of the cavernous sinus was significantly decelerated by the studies of Galen who suggested the presence of a rete mirabile (as demonstrated in many of the mammals studied by Galen) as a means of carrying blood to the brain and other intracranial structures [1]. Vesalius did not directly address this compartment in his original 1538 edition but recognizes his errors after repeated dissections, such that by 1543 Vesalius openly notes that against Galen's dogmatic descriptions, humans do not have a rete [2, 3].

It wasn't until a little over 200 years later when Jacobus Winslow published the only description of the region and coined the term "cavernous sinus" (sinus cavernosi) [4]. Interestingly, his description must be based on a visual inspection of the region, with a heavy influence from Galen's descriptions, since his descriptive term was reflective of the corpora cavernosa of the penis. It would be another two centuries before an in-depth exploration of the cavernous sinus would be undertaken by Parkinson.

Clinical manifestations of diseases of the cavernous sinus, specifically fistulae, were recognized long before the anatomic details were reported. Pulsating exophthalmos was initially recognized by Travers in 1809 who described it as a cirsoid (variceal) "aneurysm by anastomosis," noting that the bruit would disappear during ipsilateral carotid compression [5, 6]. It wasn't until 1838 that the abnormal communication between carotid and cavernous sinus was described by Baron as confirmed by autopsy studies [7].

Travers' observation in 1809 led him to describe carotid ligation as treatment for this disease. Although other techniques such as manual compression were used intermittently, cervical carotid ligation became the treatment of choice for over a century. The nuances and the physiologic rationale for the subsequent surgical modifications of treatment are well described in other sections of this book. Because of the variable success, and as a deeper understanding of the pathophysiology began to develop, clinicians began to target treatment to the inflow and outflow segments of the cavernous carotid artery. Though attempts first focused on extracranial, surgical ligation of various segments of the carotid artery, the mid-twentieth century saw the development of unique approaches to the cavernous sinus to treat CCF. In the 1850s, Brainard described injecting a solution of lactate of iron into dilated orbital veins for a presumed fistula of the cavernous sinus (described as an "erectile tumor") [8]. In subsequent years, Hamby and Gardner began to explore other methods of treatment [9]. Brooks had described a technique (which has often been misquoted in the literature) whereby an attempt to endovascularly occlude the site of the fistula was attempted [10–12]. This approach harkened the birth of endovascular approaches to the treatment of CCF. Parkinson's dedicated work on the anatomy of the cavernous sinus served as a major focal point in developing a surgical treatment paradigm for CCF [13]. However, in developing this better understanding of the cavernous sinus, the endovascular concepts would be matured.

Thus, the first true endovascular attempts to treat CCF were based on open surgical procedures which served as the "approach" to the definitive treatment. However, technology lagged behind the pioneering concepts in therapy for these lesions, thus

limiting the success. As technology improved, dedicated endovascular techniques began to focus on the obliteration of the fistulous site.

The advent of the non-detachable and later the detachable balloon catheter as developed by Serbinenko began the selective endovascular approach to treatment in the early 1970s. Though still only able to occlude the internal carotid near the site of the fistula, by 1974, Serbinenko and his team had successfully treated a fistula with a mounted detachable balloon and preserved flow in the internal carotid artery [14]. Mullan's work in the United States on the electrothrombosis of aneurysms in the 1960s independently influenced him to explore these options in the treatment of CCF [15, 16]. Interestingly, Mullan and his team also began suggesting the concept that transvenous approaches might result in better outcomes and thus advocated for transvenous "packing" of the cavernous sinus along with intraoperative angiography to assess the success of the occlusion.

The modern era of CCF treatment has demonstrated a steady progression of mechanical occlusive agents such as balloons and coils and has evolved to the use of various liquid embolic agents in some instances. With the additional advent of stents and flow diversion techniques, the endovascular management of these lesions continues to evolve. Another interesting aspect to the management of these lesions is the evolution of various arterial and venous approaches that lends a unique perspective in managing these lesions.

Treatment Options of Direct Carotid-Cavernous Fistulas

Prior to endovascular treatment options, carotid-cavernous fistulas posed significant treatment dilemmas, due to its difficult surgical access in the skull base and limited microsurgical treatment options. In the past, management options included cervical arterial ligation, carotid artery banding, placement of muscle plugs into the carotid artery, and direct repair of the fistula under cardiac standstill [17, 18]. Since the 1990s, with the advance of endovascular treatment options, most carotid-cavernous fistulas are nowadays primarily approached using endovascular approaches. These modern endovascular techniques have resulted in a successful occlusion rate of above 90% with a carotid artery patency of above 70–80% [19, 20]. In the following, we will highlight current treatment options and strategies.

Conservative Management

Direct carotid-cavernous fistulas rarely undergo spontaneous resolution on conservative management, and hence conservative management is rarely the treatment of choice [21]. In the absence of treatment, most carotid-cavernous fistulas will cause vision loss due to central retinal vein occlusion or glaucoma (80–90%) [22, 23]. In rare instances, such as severe traumatic brain injuries, an initial conservative approach may be chosen, due to high intracranial pressure of the patient and an inability to lie flat on the angiogram table for the procedure.

Manual Compression

In the absence of other treatment options, due to circumstances such as age, patient preference, or others, an initial course of manual compression of the carotid artery in the mid-cervical region can be performed [24]. External compression is performed on the carotid artery at the mid-cervical region with the contralateral hand with pressure applied until the carotid pulse is stopped. This is performed for 10–15 s about 2–3 times an hour with a 17% occlusion rate at 1-year follow-up [24].

Carotid Artery Sacrifice

Carotid artery sacrifice, or parent artery occlusion, is rarely used as a first treatment option [25]. However, in acute emergencies, carotid sacrifice with or without prior balloon test occlusion may be a lifesaving treatment often in the presence in severe traumatic injuries involving traumatic brain injury, extensive carotid vessel wall damage, or active hemorrhage with an expanding hematoma. Carotid sacrifice can be performed using modern MVP plugs (Medtronic, MN) proximal and distal to the injury, using coil embolization, or using liquid embolics, such as NBCA glue or Onyx. Often, a combination of tools is used in order to minimize the risk of distal embolization o materials. For example, distal to the injury, an MVP plug can be deployed, which functions as a distal door stopper from which coils are deployed from distal to proximally covering the injured segment with Onyx or NBCA used to complete occlude the residual filling of the carotid artery. Again, efforts must be made to avoid either distal embolization or embolization into unwanted territory [25].

Should carotid sacrifice be considered in the absence of the need for an emergency intervention, prior assessment of collateral flow is key to select for patients who can safely undergo carotid artery sacrifice (Philipp Taussky 2011). In general, carotid sacrifice is associated with significant neurological morbidity and mortality [26]. Studies report mortality rates ranging from 0% to 31% and neurological morbidity due to ischemia ranging from 0% to 45% [26–28].

In spite of its shortcomings, ball test occlusion of the parent vessel prior to sacrifice is still considered the gold standard in the evaluation of collateral flow. Typically, either a balloon guide catheter (Flowgate, Stryker or Cello, Medtronic) is used to inflate a balloon in the internal carotid artery inducing flow arrest, or a microcatheter, preferably with dual lumen to allow for flushing during flow arrest, is used (Ascent balloon, Ceronovus or Scepter balloon Microvention). The balloon is typically inflated for a 20–30-min period with neurological exams performed every 2 min or if the patient's general anesthesia SSEPs and MEPs are regularly performed. During this time, another catheter can be introduced from the contralateral groin, and the contralateral circulation can be assessed, particularly the flow across the anterior and posterior communicating artery into the balloon occluded hemisphere. Additionally, stump pressures can be measured, or a hypotensive chal-

lenged can be performed [29, 30]. Stump pressures with a ratio of 60% or greater appear to indicate adequate collateral flow [30]. Despite this, about 5% of patients who pass a balloon test occlusion without a change in their neurological exam will develop neurological deficits in the postoperative period [31]. Overall, carotid sacrifice is associated with a 1.4–1.9% annual risk of new neurological deficits due to ischemia, and as a result, carotid sacrifice is not the primary treatment option [32].

Transarterial Endovascular Embolization

The goal of endovascular treatment of direct carotid-cavernous fistulas is occlusion of the fistulous point between the tears in the carotid artery while preserving parent vessel patency. Oftentimes, when the tear in the cavernous segment of the carotid artery is large enough, the fistula can be directly accessed transarterially through the tear in the vessel using a microcatheter [19, 20]. In our experience, we like a transfemoral route, using a 6F guide catheter and a microcatheter through which coil embolization as well as liquid embolic embolization can be performed. The transarterial route, while often straightforward in its access, can be problematic due to the risk of retrograde herniation of coil material or liquid embolics from the cavernous sinus into the carotid artery through the defect in the cavernous carotid artery [33]. This mishap can, while not completely prevented, at least be minimized by the use of a 5 × 30 HyperForm balloon (Medtronic, MN), which is inflated in the parent vessel during the embolization of the cavernous sinus. Modern stent technology has allowed for additional protection of the parent vessel, such as the deployment of flow diverters across the tear of the parent vessel prior to the application of embolization materials to prevent coil herniation.

Transvenous Endovascular Embolization

In addition to a transarterial approach, direct carotid-cavernous fistulas can be accessed and treated through a transvenous approach via the inferior petrosal sinus or the superior ophthalmic vein to embolize the cavernous sinus [20, 25]. Generally, the transvenous approach may offer a more stable position of the microcatheter used for coil embolization or embolization with liquid embolics [19, 20, 25]. Using an arterial angiogram as a roadmap, the inferior petrosal sinus can be accessed through a transvenous approach. Again, a 5 × 30 Hyperglide may be inflated in the carotid artery during embolization to avoid coil herniation or transarterial embolization of liquid embolic material (Fig. 23.1).

A special technique of transvenous access involves the so-called poke in the eye where the superior ophthalmic vein is directly accessed either surgically or by transcutaneous puncture and the cavernous sinus is then accessed for embolization in a retrograde fashion [34]. In these instances, an 18-gauge needle or angiocatheter on

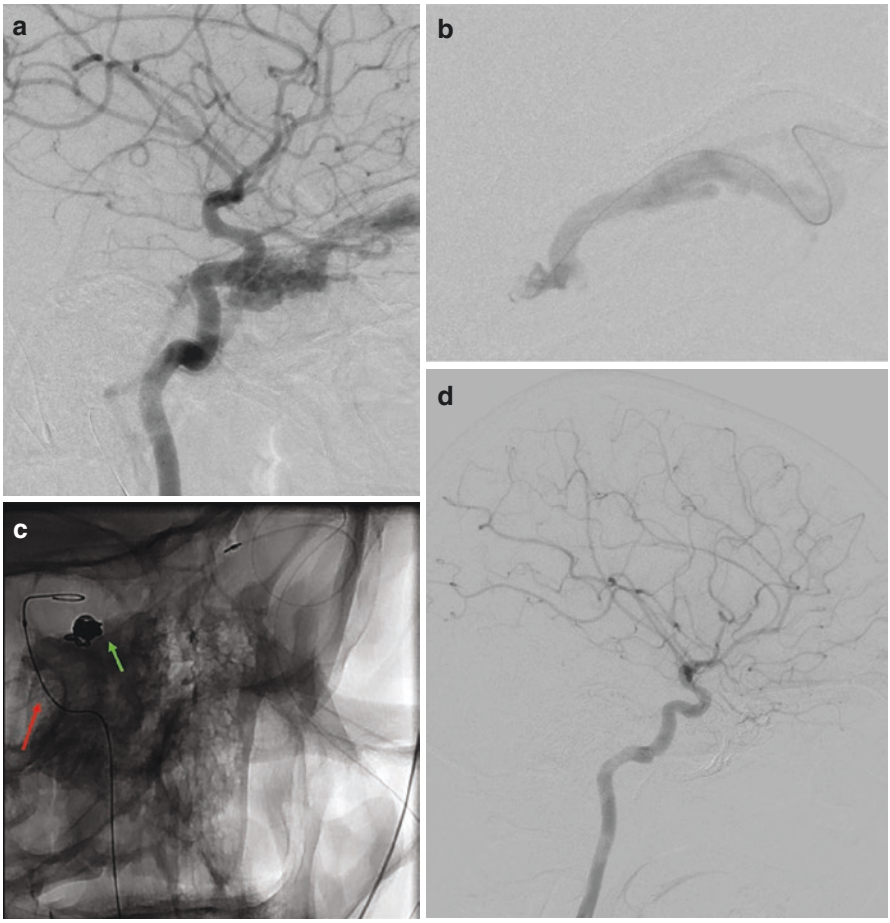


Fig. 23.1 **(a)** A 23-year-old woman with proptosis, diplopia, and pulsatile tinnitus showing a spontaneous left direct carotid-cavernous fistula. **(b)** A transvenous approach was performed accessing the superior ophthalmic vein via the facial vein to the cavernous sinus. **(c)** The typical setup: A 3 × 50-mm hyperglide balloon in the carotid artery to protect from coil herniation (red arrow). Transvenous microcatheter in stable position in the cavernous sinus via the superior ophthalmic vein with coil pack (green arrow). **(d)** Final runs showing complete occlusion of the fistula with patency of the internal carotid artery

a rotatory hemostatic valve is used to access the superior ophthalmic vein, and an Echelon microcatheter (Medtronic, MN) is directly introduced through the superior ophthalmic vein into the cavernous sinus [35]. Either coils or liquid embolics are then used for occlusion of the fistula. While this may be an unfamiliar route for many interventionalists, published reports cite a high success and low complication rate with this method [34, 35].

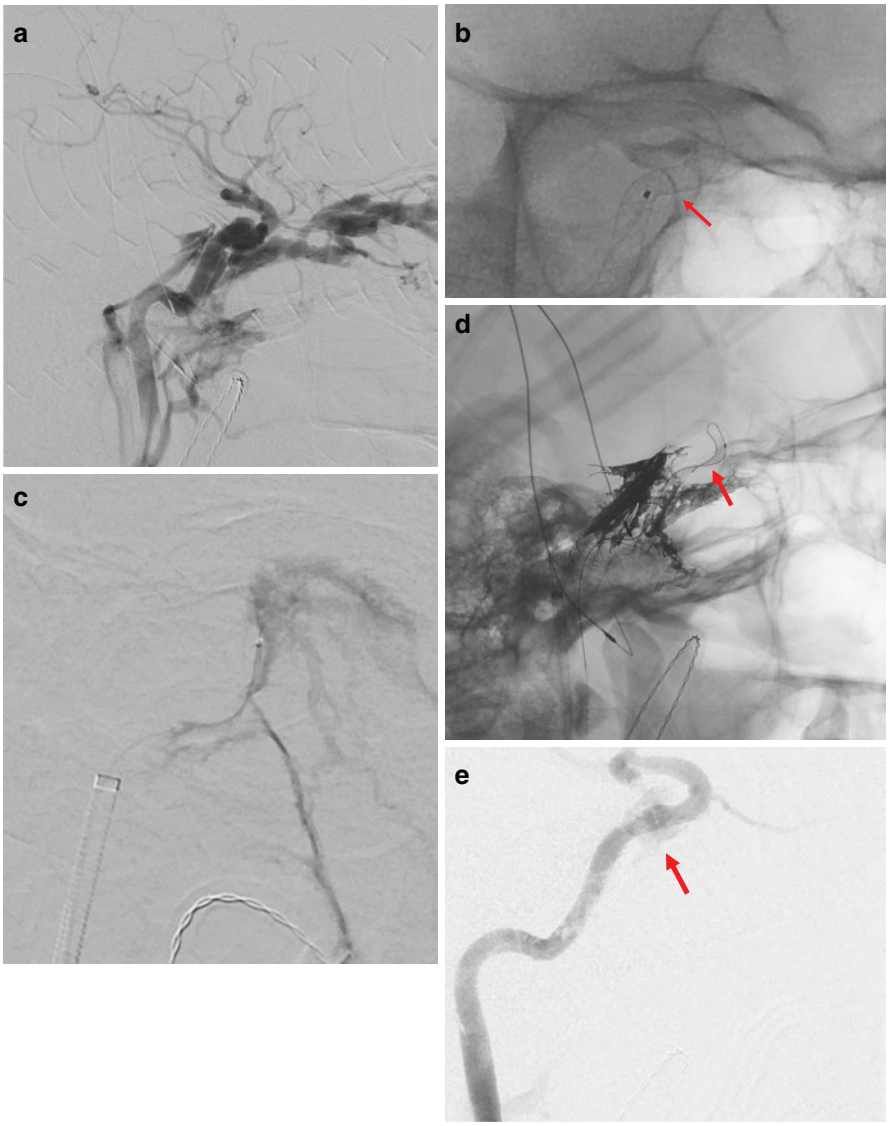


Fig. 23.2 **(a)** A 33-year-old patient presented after a skateboard accident with proptosis, double vision, and severe conjunctival injection. An angiogram showed a direct carotid-cavernous fistula with delayed intracranial filling due to a large tear in the cavernous segment. **(b)** In an initial step, a pipeline flow diverter was placed in the cavernous segment of the carotid artery in an attempt to protect the carotid artery and redirect flow through it (red arrow). **(c)** Transvenous access was then established with a microcatheter in the cavernous sinus. **(d)** Transvenous Onyx embolization was performed with a balloon in the arterial segment to prevent embolic herniation into the carotid artery (red arrow). **(e)** Final runs show minimal contrast leakage across the cavernous segment after Onyx embolization (red arrow). The patient's symptoms recovered completely within days

Transarterial Stent Occlusion

Less commonly, stents can be used in the treatment of direct carotid-cavernous fistulas. Stents, particularly covered stents, facilitate in sealing the tear in the cavernous segment of the carotid artery. While this may be a very intuitive treatment approach, the deployment of a covered stent in the cavernous segment of the carotid artery can be very challenging due to the stiffness of the device [19, 36, 37]. Modern intermediate catheters may help with distal access and deployment of the covered stent; however, navigation and tacking of these stents remain challenging. Moreover, covered stent necessitates the need for dual antiplatelet therapy and, in general, is quite thrombogenic, thus further exposing the patient to risks of distal emboli and strokes.

In an off-label use of flow diverters, few case reports exist of obliterating direct carotid-cavernous fistulas with pipeline embolization device (Medtronic, MN) [38] (Fig. 23.2). Clearly, one device is not enough to occlude the fistula; hence, multiple devices were deployed by Nossek and colleagues across the tear in the carotid artery, resulting in complete fistula occlusion [38]. However, multiple pipeline devices will also increase the risk of distal emboli and stent occlusion and, hence, may not be the primary treatment option in most instances. Yoon describes the use of a pipeline embolization device in connection with one coil to occlude a trigemino-carotid fistula; such an approach of pipeline flow diversion with minimal coiling may be preferable to multiple stents [33].

References

1. Parkinson D. Lateral sellar compartment O.T. (cavernous sinus): history, anatomy, terminology. Anat Rec. 1998;251:486–90.
2. Singer C, Vesalius A. Vesalius on the human brain. London: Oxford University Press; 1952.
3. Bataille B, Wager M, Lapierre F, Goujon JM, Buffenoir K, Rigoard P. The significance of the rete mirabile in Vesalius's work: an example of the dangers of inductive inference in medicine. Neurosurgery. 2009;60(4):761–8.
4. Thakur JD, Sonig A, Khan IS, Connor DE Jr, Pait TG, Nanda A. Jacques Benigne Winslow (1669–1760) and the misnomer cavernous sinus. World Neurosurg. 2014;81(1):191–7.
5. Locke CE. Intracranial arteriovenous aneurism or pulsating exophthalmos. Ann Surg. 1924;80:272–85.
6. Travers B. A case of aneurism by anastomosis in the orbit, cured by the ligature of the common carotid artery. Med Chir Trans. 1811;2:1–16.
7. Baron M. Comptu rendu des travaux de la societe anatomique pendant l'anne 1835. Bull Acad Med. 1835;Paris 1:178.
8. Brainard CW. Case of erectile tumour of the orbit, cured by infiltration with the solution of the lactate of iron and puncture with hot needles, after the ligature of the carotid artery had failed: with observations on the effect of that solution in obliterating the bloodvessels. Lancet. 1853;62:162.
9. Hamby WB. Carotid-cavernous fistula. Report of 32 surgically treated cases and suggestions for definitive operation. J Neurosurg. 1964;21:859–66.
10. Brooks B. Discussion of Nolan L and Taylor AS. Trans South Surg Assoc. 1931;43:176–7.

11. Brooks B. The treatment of traumatic arteriovenous fistula. South Medical J. 1930;23: 100–6.
12. Vitek JJ, Smith MJ. The myth of the Brooks method of embolization: a brief history of the endovascular treatment of carotid-cavernous sinus fistula. J Neurointerv Surg. 2009;1(2):108–11.
13. Parkinson D. Carotid cavernous fistula. History and anatomy. In: Dolenc VV, editor. The cavernous sinus: a multidisciplinary approach to vascular and tumorous lesions. Wien: Springer; 1987. p. 3–29.
14. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974;41:125–45.
15. Mullan S, Raimondi AJ, et al. Electrically induced thrombosis of intracranial aneurysms. J Neurosurg. 1965;22:539–47.
16. Mullan S. Treatment of carotid-cavernous fistulas by cavernous sinus occlusion. J Neurosurg. 1979;50:131–44.
17. Parkinson D. Carotid cavernous fistula: direct repair with preservation of the carotid artery. Technical note. J Neurosurg. 1973;38(1):99–106.
18. Fu Y, Ohata K, Tsuyuguchi N, Hara M. Direct surgery for posttraumatic carotid-cavernous fistula as a result of an intradural pseudoaneurysm: case report. Neurosurgery. 2002;51(4):1071–3; discussion 1073–1074
19. Mergeani A, Popescu D, Laza C, Dorobat B, Bajenaru OA, Antochi F. A review on endovascular techniques for treatment of direct post-traumatic carotid-cavernous fistula supported by case presentations. Maedica (Buchar). 2012;7(4):332–8.
20. Chi CT, Nguyen D, Duc VT, Chau HH, Son VT. Direct traumatic carotid cavernous fistula: angiographic classification and treatment strategies. Study of 172 cases. Interv Neuroradiol. 2014;20(4):461–75.
21. Bradac GB, Bender A, Curio G, Debrun G. Report of two cases of spontaneous direct carotid-cavernous fistula. Diagnostic and therapeutic considerations. Neuroradiology. 1985;27(5):436–9.
22. Miller NR. Severe vision loss and neovascular glaucoma complicating superior ophthalmic vein approach to carotid-cavernous sinus fistula. Am J Ophthalmol. 1998;125(6):883–4.
23. Gonzalez Castro LN, Colorado RA, Botelho AA, Freitag SK, Rabinov JD, Silverman SB. Carotid-cavernous fistula: a rare but treatable cause of rapidly progressive vision loss. Stroke. 2016;47(8):e207–9.
24. Higashida RT, Hieshima GB, Halbach VV, Bentson JR, Goto K. Closure of carotid cavernous sinus fistulae by external compression of the carotid artery and jugular vein. Acta Radiol Suppl. 1986;369:580–3.
25. Korkmazer B, Kocak B, Tureci E, Islak C, Kocer N, Kizilkilic O. Endovascular treatment of carotid cavernous sinus fistula: a systematic review. World J Radiol. 2013;5(4):143–55.
26. Philipp Taussky WTC. Decision making strategies for EC-iC bypass in the treatment of Skull Base tumors. In: Abdulrauf SI, editor. Cerebral revascularization: techniques in Extracranial-to-intracranial bypass surgery, vol. 1. Philadelphia: Elsevier; 2011. p. 349–54.
27. Lawton MT, Spetzler RF. Internal carotid artery sacrifice for radical resection of skull base tumors. Skull Base Surg. 1996;6(2):119–23.
28. Feiz-Erfan I, Han PP, Spetzler RF, Lanzino G, Ferreira MA, Gonzalez LF, Porter RW. Salvage of advanced squamous cell carcinomas of the head and neck: internal carotid artery sacrifice and extracranial-intracranial revascularization. Neurosurg Focus. 2003;14(3):e6.
29. Kato K, Tomura N, Takahashi S, Sakuma I, Sasaki K, Kitani H, Watarai J. Balloon occlusion test of the internal carotid artery: correlation with stump pressure and 99mTc-HMPAO SPECT. Acta Radiol. 2006;47(10):1073–8.
30. Wang AY, Chen CC, Lai HY, Lee ST. Balloon test occlusion of the internal carotid artery with stump pressure ratio and venous phase delay technique. J Stroke Cerebrovasc Dis. 2013;22(8):e533–40.
31. Segal DH, Sen C, Bederson JB, Catalano P, Sacher M, Stollman AL, Lorberboym M. Predictive value of balloon test occlusion of the internal carotid artery. Skull Base Surg. 1995;5(2):97–107.

32. Roski RA, Spetzler RF, Nulsen FE. Late complications of carotid ligation in the treatment of intracranial aneurysms. J Neurosurg. 1981;54(5):583–7.
33. Yoon NK, Awad AW, Gee JM, Taussky P. Ruptured persistent trigeminal artery causing direct cavernous sinus fistula treated with pipeline embolization and minimal coiling. World Neurosurg. 2018;109(471–475):e471.
34. Jiang C, Lv X, Li Y, Wu Z, Shi J. Surgical access on the superior ophthalmic vein to the cavernous sinus dural fistula for embolization. J Neurointerv Surg. 2013;5(3):e13.
35. Chalouhi N, Dumont AS, Tjoumakaris S, Gonzalez LF, Bilyk JR, Randazzo C, Hasan D, Dalyai RT, Rosenwasser R, Jabbour P. The superior ophthalmic vein approach for the treatment of carotid-cavernous fistulas: a novel technique using Onyx. Neurosurg Focus. 2012;32(5):E13.
36. Kocer N, Kizilkilic O, Albayram S, Adaletli I, Kantarci F, Islak C. Treatment of iatrogenic internal carotid artery laceration and carotid cavernous fistula with endovascular stent-graft placement. AJNR Am J Neuroradiol. 2002;23(3):442–6.
37. Briganti F, Tortora F, Marseglia M, Napoli M, Cirillo L. Covered stent implantation for the treatment of direct carotid-cavernous fistula and its mid-term follow-up. Interv Neuroradiol. 2009;15(2):185–90.
38. Nossek E, Zumofen D, Nelson E, Raz E, Potts MB, Desousa KG, Tanweer O, Shapiro M, Becske T, Riina HA. Use of pipeline embolization devices for treatment of a direct carotid-cavernous fistula. Acta Neurochir. 2015;157(7):1125–9; discussion 1130.

Chapter 24
Spontaneous Intracerebral Hemorrhage

Jan Vargas, Alejandro M. Spiotta, and Raymond D. Turner

Background and Demographics

Spontaneous intracerebral hemorrhage (ICH) is responsible for 10–15% of strokes, with an annual incidence of 10–30 per 100,000, a 1-year mortality rate of more than 40%, and a 5-year mortality rate of approximately 29.2% [1]. When associated with intraventricular hemorrhage (IVH), the mortality rate increases to 50–80% [2, 3, 4]. Functional independent outcome (defined as mRS of 0–2) is estimated at 16.7–24.6% at 1 year following ICH [1]. Mortality can be estimated by calculating the ICH score (Tables 24.1 and 24.2). The long-term rate of recurrence is estimated to be 1.3–7.4% per year over an average follow-up of 1–7 years.

ICHs can be divided into supratentorial and infratentorial based on location, with considerable controversy concerning outcomes in patients with primary supratentorial ICH compared to infratentorial ICH [5]. Most ICHs are supratentorial, and spontaneous supratentorial ICH can be further subdivided into deep (subcortical) and superficial (lobar). Risk factors for mortality in the setting of ICH are increasing age, decreasing Glasgow Coma Scale score, increasing ICH volume, and presence of intraventricular hemorrhage [1].

J. Vargas · A. M. Spiotta · R. D. Turner (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: turnerrd@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_24

Table 24.1 The ICH score is used to calculate the predicted mortality for patients with ICH

GCS	
3–4	2 pts
5–12	1 pt
13–15	0 pt
ICH volume	
≥30 cm3	1 pt
<30 cm3	0 pt
IVH	
Yes	1 pt
No	0 pt
Location	
Infratentorial	1 pt
Supratentorial	0 pt
Age	
>= 80 years	1 pt
<80 years	0 pt

Table 24.2 With increases in ICH, the predicted mortality of patients increase

ICH score	Mortality (%)
0	No mortality
1	13
2	26
3	72
4	97
5	100
6	100

Pathophysiology

The neurological injury is felt to be not only due to the immediate mechanical disruption caused by the original hemorrhage but also from the accumulation of perihematoma edema (PHE) secondary to an inflammatory reaction incited by hemoglobin breakdown products such as iron and the presence of thrombin. There is evidence that local mass effect limits regional perfusion, causing further secondary ischemic injury. Additionally, if the hematoma is of sufficient size, it may lead to elevated intracranial pressure and a global reduction in the perfusion to the cerebrum. Animal models have demonstrated that early removal of cerebral hematomas can lead to improved late outcomes by improving regional perfusion [6]. This second phase of injury results in the extension of damage to potentially viable tissue [4, 7, 8, 9, 10, 11, 12].

Medical Therapy

With the exception of strict blood pressure control, no medical intervention has been shown to improve outcomes for patients with spontaneous ICH [13]. The recently halted ATACH-2 trial concluded that aggressive blood pressure reduction to a goal of 110–139 mmHg did not reduce the rate of death or disability when compared to blood pressure reduction to a goal of 140–179 mmHg and in fact increased the rate of renal adverse events [14]. There has been evidence in animal models that iron chelators, such as deferoxamine, can mitigate the injury of hematoma breakdown products [10, 11, 12, 15, 16]. The iDEF study is a phase II, multicenter, randomized trial comparing intravenous deferoxamine infusion to saline placebo in the hopes of determining if iron chelation agents can improve functional outcomes in spontaneous ICH [17].

Open Surgical Evacuation

The most recent guidelines for the management of spontaneous ICH published by the American Stroke Association in 2007 recommend immediate surgery for cerebellar hemorrhages greater than 3 cm with evidence of brainstem compression or hydrocephalus and suggest considering a standard craniotomy for patients with supratentorial lobar hemorrhages within 1 cm of the cortical surface, with the goal being to prevent impending mortality [18].

For patients that do not meet these criteria, there is a lack of consensus on appropriate treatment despite the theoretical benefits of early hematoma evacuation and prevention of secondary insults following spontaneous ICH. The Surgical Trial in Intracerebral Hemorrhage (STITCH) trial was a multicenter, randomized investigation that ultimately failed to show any overall benefit to early surgery versus medical management for patients with spontaneous, supratentorial ICH (both lobar and subcortical), with favorable outcomes observed in 26% of the surgical group compared to 24% in the medical group [13]. However, a subgroup analysis of the STITCH I data suggested that favorable outcomes were more likely with surgery performed on hematomas less than 1 cm from the cortical surface [19]. These findings lead to the STITCH II trial which enrolled only lobar hemorrhages. The STITCH II trial also failed to demonstrate an overall benefit for the surgical evacuation of superficial lobar hemorrhages compared to medical management, however a trend toward improvement in those with poorer prognosis from neurological decline and impending herniation [20] (Fig. 24.1). A subsequent meta-analysis of 14 trials of surgery for intracerebral hemorrhage demonstrated improved outcomes with surgery if randomization was performed within 8 h of hemorrhage, if the volume of hematoma was between 20 and 50 mL with a Glasgow Coma Scale of 9–12, or if patient age was

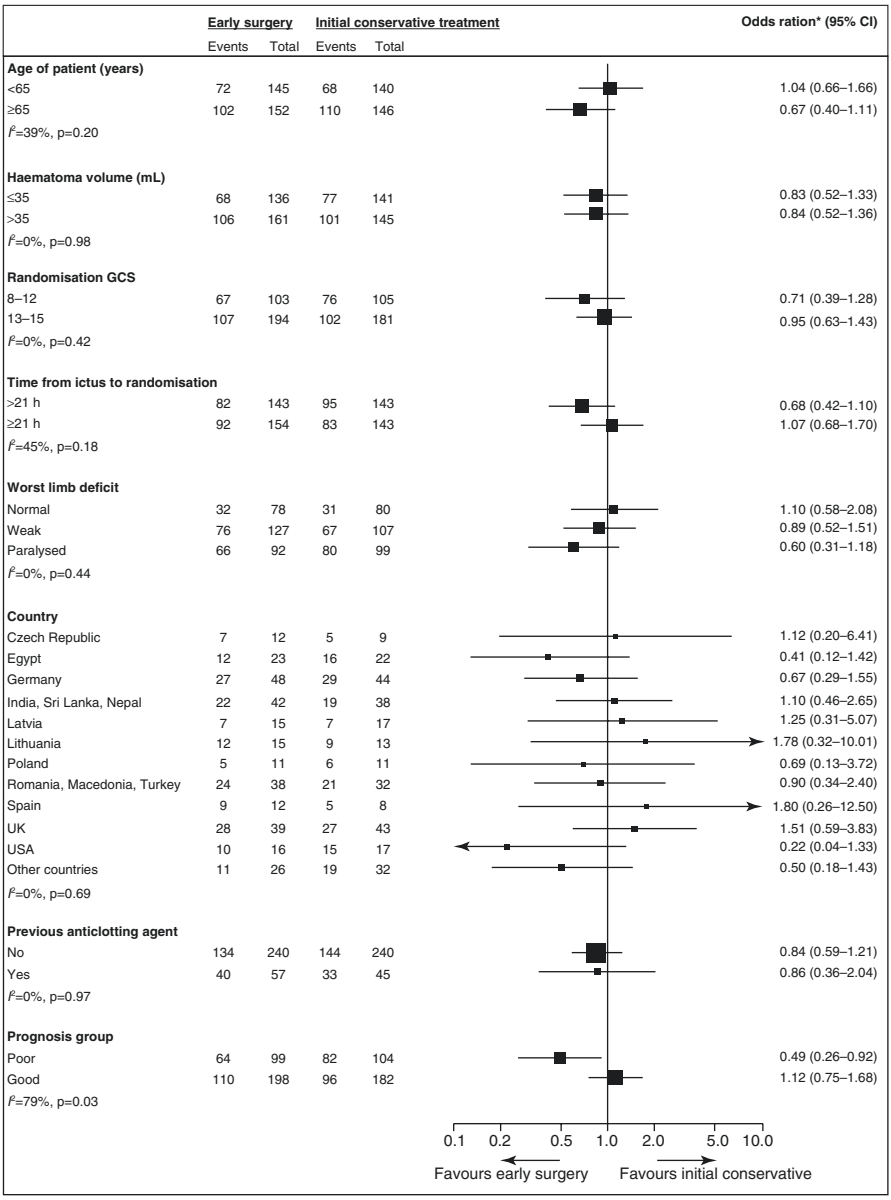


Fig. 24.1 Subgroup analysis of STICH II demonstrated that of all patient factors, poor prognosis was the only factor favoring surgery compared to medical management among patients with exclusively lobar hemorrhages treated with early surgery. (Adapted from Mendelow et al. [20], with permission)

between 50 and 69 years [21]. When the results of STITCH II were pooled with this data, the subgroup of patients with lobar intracranial hemorrhage and no IVH demonstrated a trend toward benefit with surgery, but this trend was not significant [20].

The STITCH trials suggested that while surgery may improve outcomes in some patients with superficial lobar hemorrhages, attempts at targeting deeper lesions may disrupt viable tissue and overcome any benefits yielded by hematoma evacuation. This has led to an interest in developing minimally invasive approaches for accessing and evacuating deep-seated hematomas.

History of Minimally Invasive Surgery Techniques

A minimally invasive approach to the evacuation of intracranial hematomas has been a topic of interest for some time. In 1989, Auer et al. published their experiences in early endoscopic irrigation and aspiration-based evacuation of ICH. This trial demonstrated a significant improvement in 6-month mortality rate when compared to medical management [22].

There are several reports of the use of stereotactic minimally invasive techniques such as direct aspiration or mechanical clot disruption to safely remove deeper hemorrhages [22, 23, 24, 25, 26]. More recently, newer methods for hematoma disruption have been introduced, such as ultrasound or injection of recombinant tissue plasminogen activator directly into the hematoma [27, 28].

Recently, Zhou et al. performed a meta-analysis of 12 trials with a total of 1955 patients, comparing the effectiveness of minimally invasive surgery to other treatments, using death or dependence in activities of daily living as the primary outcome. The authors found that MIS techniques were associated with a 46% relative reduction in the odds ratio of death or dependence and a 47% reduction in the odds ratio of death (Fig. 24.2) [29].

The Clot Lysis Evaluating Accelerated Resolution of IVH Phase II (CLEAR II) trial aimed to investigate the benefit of clearing intraventricular blood in the setting of spontaneous ICH or subarachnoid hemorrhage [30]. IVH has been shown to be an independent risk factor for poor outcome and occurs in about 40–45% of ICH [19, 31, 32]. The patients who received intraventricular rtPA via an external ventricular drain showed a trend toward lower mortality at 30 days (18% vs. 23% in placebo groups); however, this was not statistically significant. There was a significant relationship observed with respect to the rate of clot resolution and clinical improvement at 96 h. In addition, a greater percentage of patients treated with intraventricular tPA demonstrated mRS $\leq$4 (52% vs. 27%) and NIHSS <10 (54% vs. 29%) at 30 days. While the trial was not powered to assess functional outcomes, it demonstrated the safety of a minimally invasive approach to the treatment of IVH and paved the way for the launch of the CLEAR III trial.

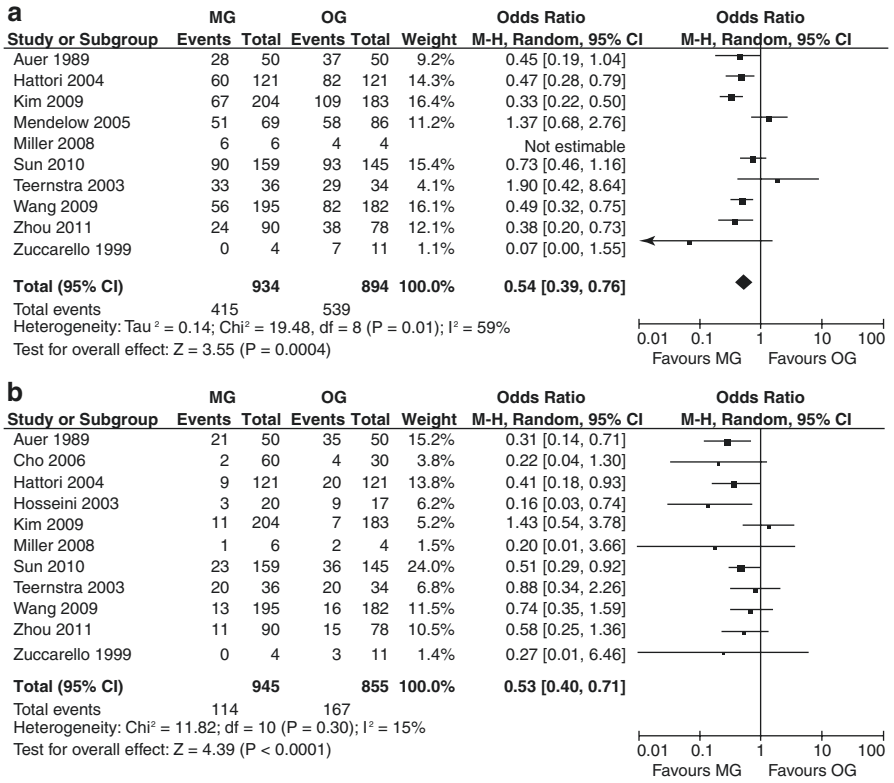


Fig. 24.2 (**a**) Comparison of minimally invasive surgery versus other treatment options for death or dependence (primary outcome). (**b**) Comparison of minimally invasive surgery versus other treatment options for death (secondary outcome). MG, minimally invasive group; OG, other treatment groups. CLEAR trials. (Adapted from Zhou et al. [29], with permission)

MISTIE

The Minimally Invasive Surgery Plus Tissue-Type Plasminogen Activator for ICH Evacuation (MISTIE II) investigation was a controlled, phase II trial which included 123 patients randomized between medical management and minimally invasive surgery followed by catheter drainage with daily rtPA (recombinant tissue plasminogen activator) irrigation. Ventricular drainage catheters were inserted using stereotactic navigation into prespecified targets using standardized trajectories.

MISTIE-II trial showed a strong trend toward clinical benefit in patients with ICH treated with minimally invasive surgery versus those which received medical management. Surgical patients had a significant reduction in perihematoma edema volume, shorter hospital length of stay and reduced hospital costs, and greater gain activities of daily living scores on the Stroke Impact Scale [27]. The international MISTIE-III trial is currently enrolling patients with a projected completion date in 2018.

New Techniques for MIS Evacuations

Apollo (First Generation)

The Penumbra Apollo (Penumbra Inc., Alameda, CA) is an aspiration–irrigation system which allows the removal of hemorrhage via a wand with controlled aspiration. A vibrational element housed within the wand vibrates at high frequency to break down the hemorrhagic products inside of the wand and prevent clogging. The wand can be used in conjunction with commercially available endoscopes and is positioned in the hematoma under stereotactic guidance via a cranial burr hole with a small dural incision (Figs. 24.3, 24.4, and 24.5).

Since its approval, the Apollo system has been used for the evacuation of both intraventricular and intracerebral hemorrhages, including those associated with

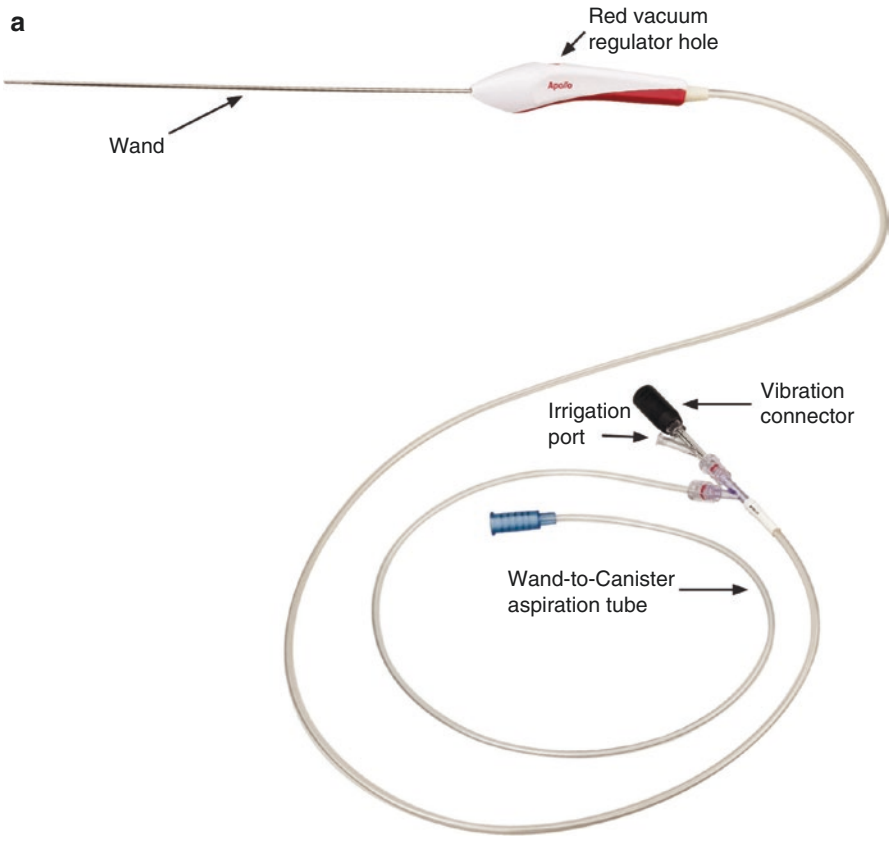


Fig. 24.3 (**a**) Apollo (Penumbra Inc., Alameda, CA) is the first-generation aspiration–irrigation wand approved for minimally invasive ICH evacuation. Picture is the handheld wand, designed to be utilized within a neuroendoscope, an aspiration tubing. (**b**) The aspiration Apollo system. (Courtesy of Penumbra Inc., Alameda CA, USA)

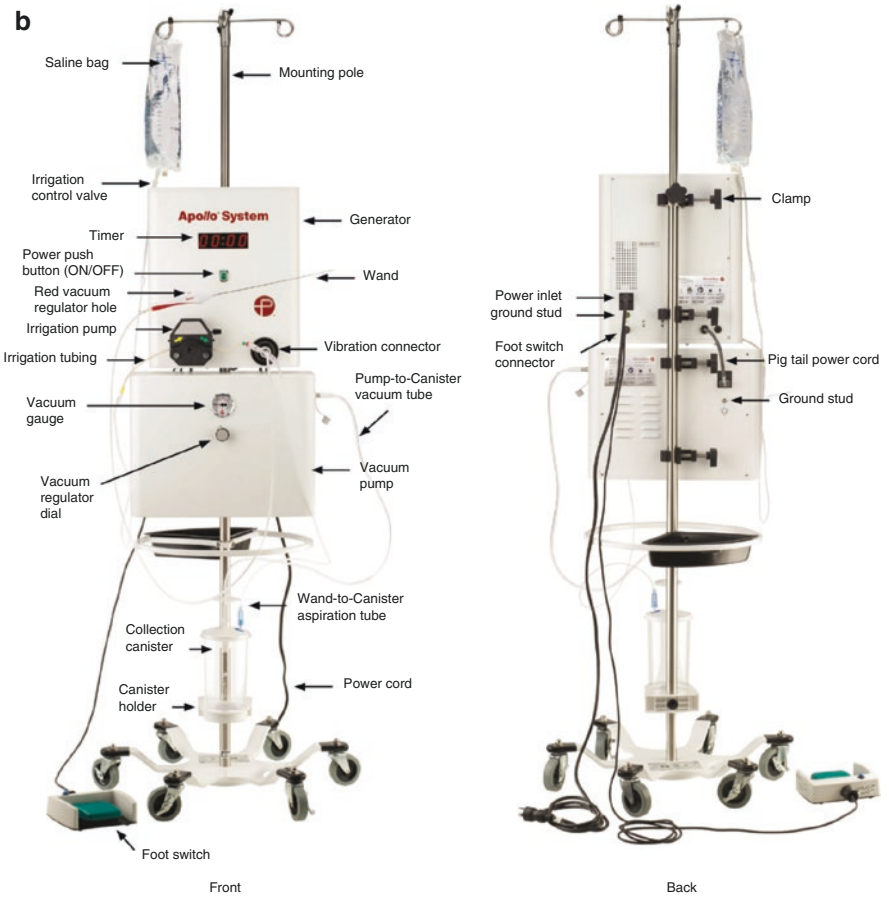


Fig. 24.3 (continued)

ruptured aneurysms [33, 34, 35, 36, 37]. Enrollment has begun for the Minimally Invasive Endoscopic Surgical Treatment With Apollo Versus Medical Management for Supratentorial ICH (INVEST) trial [38], a prospective multicenter US trial designed to enroll 222 patients at up to 30 centers. Patients between the ages of 22 and 80 or <85 in good baseline functional status presenting with a moderate- to large-volume supratentorial ICH (30–80 cm) within 24 h of onset are eligible for enrollment. Qualifying patients will be randomly assigned (1:1) to either minimally invasive surgery (MIS) with Apollo or to best medical management (MM) following a stability scan. The primary end points are mRS 0–3 at 180 days and mortality at 30 days. Secondary end points include Stroke Impact Scale (SIS) mobility, SIS activities of daily living, and length of hospitalization [38].

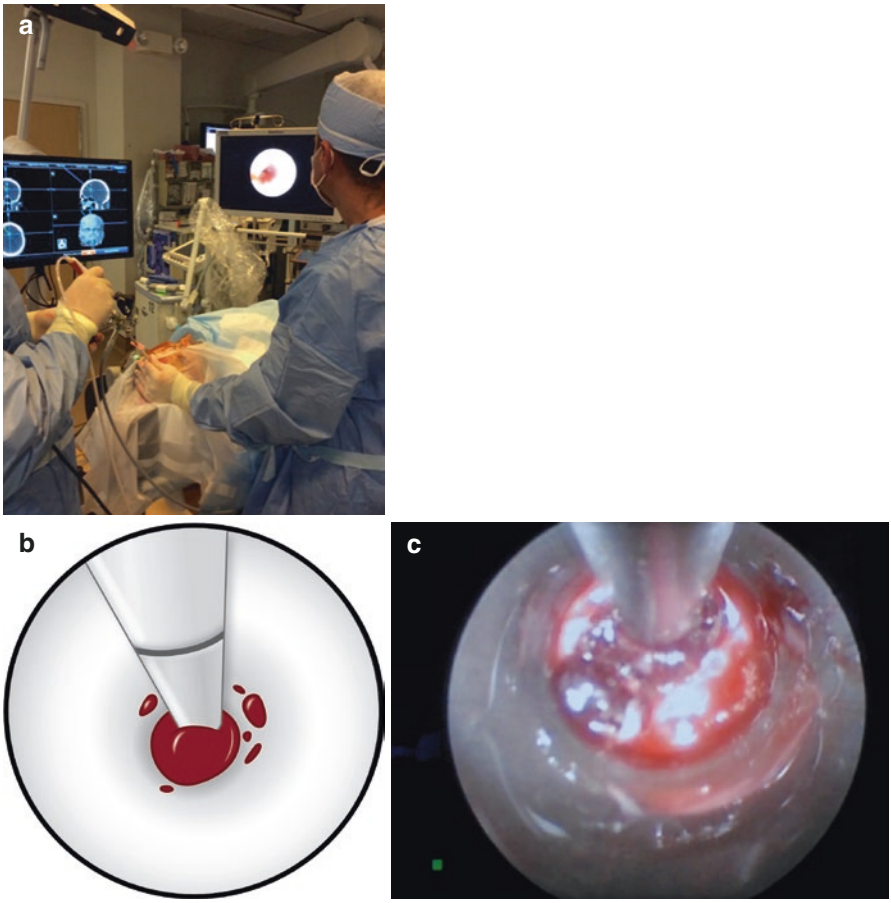


Fig. 24.4 (**a**) Intracerebral hematoma evacuation in the neuroangiography suite with the Apollo system (Penumbra Inc.). A small incision is made, and the neuroendoscope is inserted into the most superficial aspect of the hematoma utilizing neuronavigation (background, left). Evacuation is achieved with the aid of neuronavigation and direct visualization with the endoscope (background, right) (**b** and **c**)

Artemis (Second Generation)

Newly released, the Artemis Neuro Evacuation Device (Penumbra Inc., Alameda, CA) is powered by the Penumbra Pump MAX and a rotating inner shaft with a distal bident tip to break up and remove clot safely within the cannula of the Artemis device. This new-generation device symbolizes how rapidly technology is being released and updated to treat ICH in an MIS fashion. Performed through a 19 F sheath, the Artemis device requires only a 6 mm burr hole. The Artemis device is available in three sizes (OD), 2.8 mm, 2.1 mm, and 1.5 mm, which are compatible with a large variety of commercially available neuroendoscopes. This new iteration

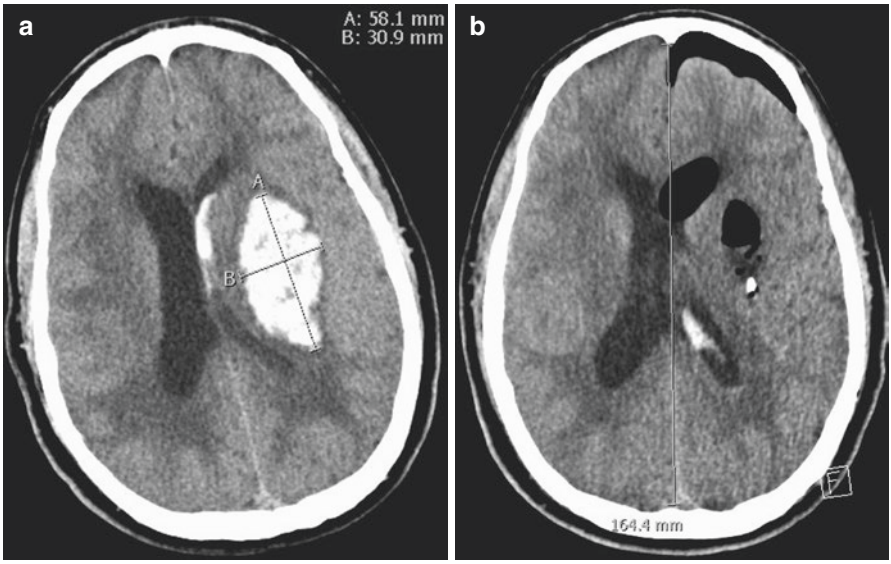


Fig. 24.5 (**a** and **b**) Left-sided basal ganglia intracerebral hematoma pre- (**a**) and post (**b**) evacuation with the Apollo system

offers an increase aspiration efficiency by more than 400% by modifications made to the cannula and a larger lumen aspiration tubing. Use of the Artemis will be allowed in the INVEST trial (Fig. 24.6).

NICO

The NICO BrainPath system consists of a 13.5 mm sheath with an internal obturator that is placed stereotactically through a small craniotomy into intracranial hematomas (Fig. 24.7a–c). The obturator is designed to displace rather than disrupt brain parenchyma during placement, minimizing damage to underlying functional tissue. Once placed, the obturator is removed, allowing access to the hematoma which can be evacuated using conventional suction and bipolar cautery under the operating microscope or an exoscope which is aligned down the length of the BrainPath sheath. The NICO BrainPath sheath has been approved for visualization of the surgical field during brain and spinal surgery.

In addition to its BrainPath sheath, NICO also manufactures the Myriad handpiece, consisting of a wand with a side port equipped with a reciprocating cutting blade. The handpiece has an aspiration mechanism that pulls tissue into the side port. Using a foot petal, the surgeon can control both the strength of aspiration and turn the cutting blade on or off. The Myriad handpiece has been approved for the

Fig. 24.6 Artemis Neuro Evacuation Device. (Courtesy of Penumbra Inc., Alameda, CA, USA)

morcellation and removal of tissue during pelviscopic, laparoscopic, percutaneous, and open surgical procedures whenever access to the surgical site is limited.

The NICO BrainPath has been successfully used for the evacuation of intracerebral hematomas, with reported at least 87% reduction in hematoma volume, although 3 of the 11 patients (27%) suffered postoperative complications including a fatal hemorrhage [37, 38, 39, 40] (Fig. 24.8a, b). The NICO BrainPath system will also be part of a randomized controlled trial, which will include up to ten centers [41].

Summary

ICH is a devastating disease for which traditional surgical management has not been well established. Open surgery has been shown to be of minimal benefit for deep-seated spontaneous ICHs, due to the damage incurred on potentially salvageable tissue during the approach to the lesion. While minimally invasive approaches to hematoma evacuation have been described for several decades, advances in neuronavigation and neuroimaging have allowed for more precise placement and access of deep-seated lesions, thus minimizing the trauma to viable brain parenchyma and improving success rates. Completion of three ongoing trials (MISTIE-III, INVEST, ENRICH) will likely change the management of spontaneous ICH in favor of MIS evacuation.

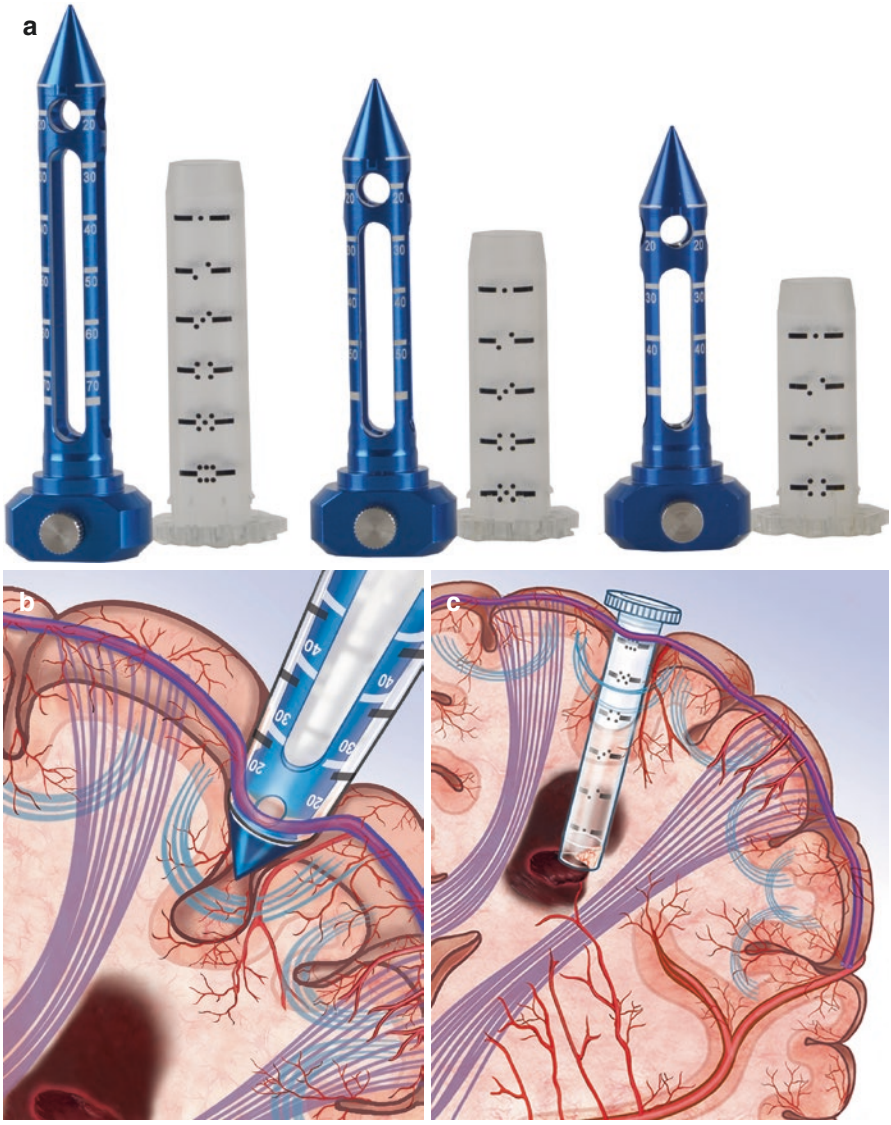


Fig. 24.7 (**a**) The NICO BrainPath access port system (NICO Corporation) is available in different lengths to access hemorrhages at different depths. (**b**) A trans-sulcal approach is taken to access the hematoma, and once reached the inner obturator is removed. (**c**) Illumination is provided by either a microscope or exoscope, and the hematoma is evacuated with standard surgical instruments. (A, courtesy of NICO Corporation, Indianapolis, IN, USA)

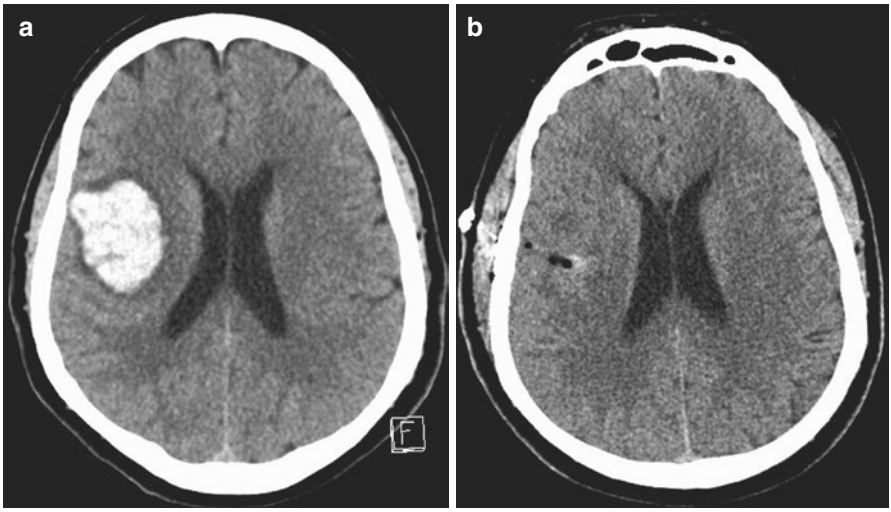


Fig. 24.8 Large right intracerebral hematoma approaching the cortical surface pre- (**a**) and post (**b**) evacuation with the NICO BrainPath system

References

1. Poon MT, Fonville AF, Al-Shahi SR. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85(6):660–7.
2. Dennis MS. Outcome after brain haemorrhage. Cerebrovasc Dis. 2003;16(Suppl 1):9–13.
3. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. Neurology. 2005;65(4):518–22.
4. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009;373(9675):1632–44.
5. Samarasekera N, Fonville A, Lerpiniere C, Farrall AJ, Wardlaw JM, White PM, et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome: population-based study. Stroke. 2015;46(2):361–8.
6. Nehls DG, Mendelow DA, Graham DI, Teasdale GM. Experimental intracerebral hemorrhage: early removal of a spontaneous mass lesion improves late outcome. Neurosurgery. 1990;27(5):674–82. discussion 82
7. Xi G, Wagner KR, Keep RF, Hua Y, de Courten-Myers GM, Broderick JP, et al. Role of blood clot formation on early edema development after experimental intracerebral hemorrhage. Stroke. 1998;29(12):2580–6.
8. Lee KR, Kawai N, Kim S, Sagher O, Hoff JT. Mechanisms of edema formation after intracerebral hemorrhage: effects of thrombin on cerebral blood flow, blood-brain barrier permeability, and cell survival in a rat model. J Neurosurg. 1997;86(2):272–8.
9. Lee KR, Colon GP, Betz AL, Keep RF, Kim S, Hoff JT. Edema from intracerebral hemorrhage: the role of thrombin. J Neurosurg. 1996;84(1):91–6.
10. Wang G, Shao A, Hu W, Xue F, Zhao H, Jin X, et al. Changes of ferrous iron and its transporters after intracerebral hemorrhage in rats. Int J Clin Exp Pathol. 2015;8(9):10671–9.
11. Wang G, Hu W, Tang Q, Wang L, Sun XG, Chen Y, et al. Effect comparison of both iron chelators on outcomes, iron deposit, and iron transporters after intracerebral hemorrhage in rats. Mol Neurobiol. 2016;53(6):3576–85.

12. Qing WG, Dong YQ, Ping TQ, Lai LG, Fang LD, Min HW, et al. Brain edema after intracerebral hemorrhage in rats: the role of iron overload and aquaporin 4. J Neurosurg. 2009;110(3):462–8.
13. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97.
14. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–43.
15. Song S, Hua Y, Keep RF, He Y, Wang J, Wu J, et al. Deferoxamine reduces brain swelling in a rat model of hippocampal intracerebral hemorrhage. Acta Neurochir Suppl. 2008;105:13–8.
16. Okauchi M, Hua Y, Keep RF, Morgenstern LB, Xi G. Effects of deferoxamine on intracerebral hemorrhage-induced brain injury in aged rats. Stroke. 2009;40(5):1858–63.
17. Yeatts SD, Palesch YY, Moy CS, Selim M. High dose deferoxamine in intracerebral hemorrhage (HI-DEF) trial: rationale, design, and methods. Neurocrit Care. 2013;19(2):257–66.
18. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, 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):2001–23.
19. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD, Investigators S. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl. 2006;96:65–8.
20. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet. 2013;382(9890):397–408.
21. Gregson BA, Broderick JP, Auer LM, Batjer H, Chen XC, Juvela S, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. Stroke. 2012;43(6):1496–504.
22. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. J Neurosurg. 1989;70(4):530–5.
23. Backlund EO, von Holst H. Controlled subtotal evacuation of intracerebral haematomas by stereotactic technique. Surg Neurol. 1978;9(2):99–101.
24. Barrett RJ, Hussain R, Coplin WM, Berry S, Keyl PM, Hanley DF, et al. Frameless stereotactic aspiration and thrombolysis of spontaneous intracerebral hemorrhage. Neurocrit Care. 2005;3(3):237–45.
25. Higgins AC, Nashold BS, Cosman E. Stereotactic evacuation of primary intracerebral hematomas: new instrumentation. Appl Neurophysiol. 1982;45(4–5):438–42.
26. Marquardt G, Wolff R, Janzen RW, Seifert V. Basal ganglia haematomas in non-comatose patients: subacute stereotactic aspiration improves long-term outcome in comparison to purely medical treatment. Neurosurg Rev. 2005;28(1):64–9.
27. Mould WA, Carhuapoma JR, Muschelli J, Lane K, Morgan TC, McBee NA, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. Stroke. 2013;44(3):627–34.
28. Newell DW, Shah MM, Wilcox R, Hansmann DR, Melnychuk E, Muschelli J, et al. Minimally invasive evacuation of spontaneous intracerebral hemorrhage using sonothrombolysis. J Neurosurg. 2011;115(3):592–601.
29. Zhou X, Chen J, Li Q, Ren G, Yao G, Liu M, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. Stroke. 2012;43(11):2923–30.

30. Naff N, Williams MA, Keyl PM, Tuhrim S, Bullock MR, Mayer SA, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. Stroke. 2011;42(11):3009–16.
31. Daverat P, Castel JP, Dartigues JF, Orgogozo JM. Death and functional outcome after spontaneous intracerebral hemorrhage. A prospective study of 166 cases using multivariate analysis. Stroke. 1991;22(1):1–6.
32. Hallevi H, Albright KC, Aronowski J, Barreto AD, Martin-Schild S, Khaja AM, et al. Intraventricular hemorrhage: Anatomic relationships and clinical implications. Neurology. 2008;70(11):848–52.
33. Fiorella D, Gutman F, Woo H, Arthur A, Aranguren R, Davis R. Minimally invasive evacuation of parenchymal and ventricular hemorrhage using the Apollo system with simultaneous neuronavigation, neuroendoscopy and active monitoring with cone beam CT. J Neurointerv Surg. 2015;7(10):752–7.
34. Spiotta AM, Fiorella D, Vargas J, Khalessi A, Hoit D, Arthur A, et al. Initial multicenter technical experience with the Apollo device for minimally invasive intracerebral hematoma evacuation. Neurosurgery. 2015;11(Suppl 2):243–51. discussion 51
35. Tan LA, Lopes DK, Munoz LF, Shah Y, Bhabad S, Jhaveri M, et al. Minimally invasive evacuation of intraventricular hemorrhage with the Apollo vibration/suction device. J Clin Neurosci. 2016;27:53–8.
36. Turner RD, Vargas J, Turk AS, Chaudry MI, Spiotta AM. Novel device and technique for minimally invasive intracerebral hematoma evacuation in the same setting of a ruptured intracranial aneurysm: combined treatment in the neurointerventional angiography suite. Neurosurgery. 2015;11(Suppl 2):43–50; discussion−1.
37. Ding D, Przybylowski CJ, Starke RM, Sterling Street R, Tyree AE, Webster Crowley R, et al. A minimally invasive anterior skull base approach for evacuation of a basal ganglia hemorrhage. J Clin Neurosci. 2015;22(11):1816–9.
38. Przybylowski CJ, Ding D, Starke RM, Webster Crowley R, Liu KC. Endoport-assisted surgery for the management of spontaneous intracerebral hemorrhage. J Clin Neurosci. 2015;22(11):1727–32.
39. Labib MA, Shah M, Kassam AB, Young R, Zucker L, Maioriello A, et al. The safety and feasibility of image-guided BrainPath-mediated transsulcul hematoma evacuation: a Multicenter Study. Neurosurgery. 2017;80(4):515–24.
40. Fiorella D, Arthur AS, Mocco JD. 305 The INVEST trial: a randomized, controlled trial to investigate the safety and efficacy of image-guided minimally invasive endoscopic surgery with Apollo vs best medical management for supratentorial intracerebral hemorrhage. Neurosurgery. 2016;63(Suppl 1):187.
41. Bauer AM, Rasmussen PA, Bain MD. Initial single-center technical experience with the BrainPath system for acute intracerebral hemorrhage evacuation. Oper Neurosurg. 2016;0:1–7.

Part III
Ischemic

Chapter 25
Carotid Artery Stenting Versus Endarterectomy for Atherosclerosis: An Evidence-Based Review

Robert K. Townsend, Kyle M. Fargen, Jasmeet Singh, John A. Wilson, and Stacey Q. Wolfe

Background

Stroke is a leading cause of death and disability both worldwide and in the United States. Stroke fell from the fourth most prevalent to the fifth most prevalent cause of death in the United States in 2013 but remains the leading preventable cause of disability. About 795,000 people have a new or recurrent stroke in the United States each year, and approximately 89% of those strokes are ischemic [1]. A significant portion of ischemic strokes are caused by emboli from occlusive atherosclerotic disease of the carotid artery bifurcation, as first described by Chiari in 1905 [2]. In the 1950s Fisher went on to describe the relationship between carotid artery disease, transient ischemic attacks, and stroke in multiple publications, even postulating that removal of the occlusive plaque could potentially prevent stroke [3]. This publication would herald the era of carotid surgery.

Currently, both endarterectomy and angioplasty and stenting are widely performed revascularization procedures for the prevention of future stroke secondary to moderate to severe atherosclerotic carotid artery disease. Both procedures have

R. K. Townsend
Department of Neurological Surgery, Wake Forest University, Winston-Salem, NC, USA

K. M. Fargen (✉)
Department of Neurological Surgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

J. Singh
Department of Radiology and Neurosurgery, Wake Forest University, Wake Forest Baptist Health, Winston-Salem, NC, USA

Bowman Gray Center, Winston-Salem, NC, USA

J. A. Wilson · S. Q. Wolfe
Department of Neurological Surgery, Wake Forest University, Bowman Gray Center, Winston-Salem, NC, USA

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_25

Table 25.1 Summary of trials evaluating the safety and efficacy of CEA and CAS

Study name	Year	Symptomatic, asymptomatic, both	No of patients (total, CEA/CAS)	30-day stroke % (CEA/CAS/*p*)	30-day death % (CEA/CAS/*p*)	30-day MI % (CEA/CAS/*p*)	30-day death, stroke, or MI % (CEA/CAS/*p*)
CAVATAS	2001	Both	504, 253/251	4/4/NS	2/3/NS	1/0/NS	NR
SAPPHIRE	2004	Both	334, 167/167	3.3/3.1/NS	2/0.6/NS	6.6/1.9/*0.04*	9.9/4.4/NS
SPACE	2008	Symptomatic	1214, 601/613	5.5/7.2/NS	1/1/NS	NR	NR
EVA-3S	2008	Symptomatic	527, 262/265	2.7/8.8/*0.004*	1.2/0.8/NS	0.8/0.4/NS	NR
CREST	2010	Both	2502, 1240/1262	2.3/4.1/*0.01*	0.3/0.7/NS	2.3/1.1/*0.03*	4.5/5.2/NS
ICSS	2010	Symptomatic	1649, 821/828	3.3/7/*0.001*	0.5/1.3/NS	0.6/0.3/NS	4/7.4/*0.003*
ACT I	2016	Asymptomatic	1453, 364/1089	1.4/2.8/NS	0.3/0.1/NS	0.9/0.5/NS	2.6/3.3/NS

been the focus of numerous prospective trials that have aimed to explore the safety and efficacy of these techniques. The sections that follow will highlight these individual trials, which are summarized in Table 25.1.

History of Carotid Endarterectomy (CEA)

The first published case of carotid surgery was put forth by Felix Eastcott in 1954, in which a patient with recurrent transient ischemic attacks (TIAs) underwent excision of the carotid bifurcation, ligation of the external carotid artery (ECA), and direct reanastomosis of the common carotid artery (CCA) to the internal carotid artery (ICA) [4]. The first CEA had actually been performed the year before, in 1953, by Michael DeBakey on a 53-year-old bus driver with persistent right arm weakness and difficulty speaking. The patient was followed until his death 19 years later, due to heart disease. At the time of death, it was determined that the carotid artery was patent, and there had been no more strokes [5].

CEA was first shown to reduce incidence of stroke in patients with symptomatic carotid artery stenosis in a randomized multicenter trial in 1969 [6]. As a result of this and several other natural history studies indicating the relationship between carotid artery stenosis and risk of disabling stroke or death [7, 8], the number of CEAs performed increased significantly throughout the 1970s and 1980s, being performed 107,000 times in 1985 in the United States [9]. CEA was not without opponents. A retrospective study of 228 consecutive CEAs in 1977 reported a combined stroke-mortality rate for the series of 21.1% [10]. While the body of knowledge about carotid artery stenosis and evidence both for and against CEA as a treatment were accumulating rapidly, there was not yet data clearly supporting CEA as a treatment over best medical management. This data was materialized from three large randomized controlled studies published in the 1990s: NASCET, ACAS and ECST [11, 12, 13].

North American Symptomatic Carotid Endarterectomy Trial (NASCET)

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was a non-blinded, multicenter randomized controlled trial that began enrolling patients in 1987 and randomized into either best medical management or best medical management and CEA [11]. Inclusion criteria were TIA or stroke within 120 days, in the carotid artery distribution ipsilateral to an angiographically demonstrated carotid artery stenosis of greater than 30%, amenable to CEA. Patients 80 years of age or older, those with life expectancy of less than 5 years, those with potential cardiac source of emboli, or patients who could not withstand surgery were excluded from the study. Patients were stratified by degree of stenosis; those with 30–69% stenosis were identified as "moderate," and patients with 70–99% stenosis were identified as "high grade." The primary endpoint of the study was fatal or nonfatal ipsilateral carotid distribution

stroke. Secondary endpoints were strokes in any territory and death. Randomization of high-grade patients was halted in 1991, after interim analysis of 659 patients with high-grade stenosis revealed an absolute reduction of 17% in the risk of ipsilateral stroke at 18 months ($p < 0.001$), from 26% to 9%, and an absolute reduction of 5% in risk of major or fatal stroke in any territory or death from any cause at 18 months ($p < 0.01$) (NASCET investigators, Stroke 1991). While no more patients with high-grade stenosis were randomized to best medical management alone, the patients who had already been randomized were followed a mean of 8 years, and CEA was found to be a durable treatment in that group. Randomization within the moderate stenosis group continued through 1996. Final analysis revealed the following: 858 patients with stenosis of 50–69% had 5-year ipsilateral stroke rate of 15.7% in CEA group and 22.2% in the medical group ($p = 0.045$), and 1368 patients with less than 50% stenosis had 5-year ipsilateral stroke rate of 14.9% in CEA group and 18.7% in the medical group, which was nonsignificant. The overall conclusions from the NASCET trial were the following: patients with stenosis of 70–99% derive clear, durable benefit from CEA; patients with stenosis of 50–69% stenosis derive modest benefit from CEA, and the benefit exists only if the surgeon performing the CEA has operative risks of disabling stroke or death that are less than 2%; and patients with stenosis of less than 50% do not derive benefit from CEA and should receive best medical management.

European Carotid Surgery Trial (ECST)

The European Carotid Surgery Trial (ECST) was the European counterpart of the NASCET, with enrolled 3024 patients from 1981 to 1994 [13]. The primary endpoint was major stroke or death. The ECST found an 11.6% absolute risk reduction of stroke at 3 years following surgery in patients with greater than 60% stenosis (as calculated by the NASCET; the same stenosis graded by the method in the ECST would be calculated as 80%). In general, the results of the ECST were well corroborated by NASCET.

Asymptomatic Carotid Atherosclerosis Study (ACAS)

The Asymptomatic Carotid Atherosclerosis Study (ACAS) was a prospective, randomized, multicenter trial that enrolled 1662 patients from 1987 to 1993 [12]. Inclusion criteria were 40–79-year-old patients found to have asymptomatic but hemodynamically significant carotid stenosis, as defined by angiography within 60 days of randomization showing 60% stenosis. Patients with symptomatic carotid artery stenosis, who could not take aspirin, were not fit for surgery, or whose life expectancy was less than 5 years were excluded. Patients were randomized into either risk modification plus aspirin 325 mg daily or risk modification plus aspirin 325 mg daily plus carotid endarterectomy. The primary endpoints, initially, were TIA or cerebral infarction occurring in the ipsilateral carotid distribution and any

TIA, stroke, or death occurring in the perioperative period. The primary endpoints were changed in 1993 to include only stroke. Secondary endpoints included recurrent stenosis, rate of progression or regression of carotid atherosclerosis in the medically treated group, and the incidence of TIA, myocardial infarction (MI), and death related to vascular disease during follow-up. The estimated 5-year risk of ipsilateral stroke and any perioperative stroke or death was 11% in the group treated only medically and 5.1% in the group treated with CEA ($p = 0.004$), with reduction in 5-year ipsilateral stroke risk of 53% (95% CI 22–72%) in patients receiving CEA. Overall, the ACAS provided evidence that patients with asymptomatic carotid artery stenosis of 60% or greater can reduce the 5-year risk of stroke ipsilateral to the affected artery but only if the patient is healthy enough to undergo elective surgery and the surgeon can perform CEA with less than 3% perioperative morbidity and mortality. The ACAS also showed that CEA is more protective for men than it is for women; however, the findings were significant in both groups.

These studies provided the evidence for well-defined guidelines for patient selection for CEA. There is significant benefit for CEA in symptomatic patients with carotid stenosis of 70–99%, moderate benefit in patients with symptomatic carotid stenosis of 50–69% given low surgical morbidity, and moderate benefit in patients with asymptomatic carotid stenosis of greater than 60%, again given low surgical morbidity.

History of Carotid Artery Angioplasty and Stenting (CAS)

Despite the efficacy of CEA in treatment of carotid artery stenosis, open surgery and the frequent need for general anesthesia were both disadvantages of this treatment modality. The concomitant progress being made in percutaneous transluminal angioplasty of peripheral arteries led to the hypothesis that the carotid artery could be accessed in a similar fashion. The first carotid artery balloon angioplasty was performed in 1977 by Klaus Mathias [14], though the first balloon-expandable stents were not used in the carotid artery until 1989 [15]. The beginning of carotid artery stenting (CAS) was fraught with difficulty; early stents were highly susceptible to external compression, and iatrogenic arterial dissection and distal embolic events were not uncommon [16]. The introduction of embolic protection devices in 1990 [17] and nitinol carotid stents was the first step toward addressing these concerns; however, CAS continued to be questioned as a viable treatment option when compared to the success of CEA, and investigators quickly began to enroll patients in trials to address this question.

Modern carotid angioplasty and stenting are performed with the aid of monorail balloon and self-expanding stent technology and with the aid of distal embolic protection filters that capture debris that is released during angioplasty, device manipulation, and stent deployment. Currently, reimbursement for carotid artery angioplasty and stenting by the Centers for Medicare and Medicaid Services mandates that at least one qualifying criterion is met (Table 25.2).

Table 25.2 Qualifying criteria for carotid angioplasty and stenting

Centers for medicare and medicaid services criteria qualifying for CAS
Anatomic
Contralateral carotid occlusion
Contralateral laryngeal nerve palsy
Tracheostomy/tracheostoma
Previous radiation therapy/surgery on the neck
Bilateral stenosis
Lesion inaccessible by surgery (i.e., high bifurcation)
Severe intracranial stenosis
Neck immobility
Restenosis after endarterectomy
Carotid artery stenosis of 70% or more
Comorbidities
Congestive heart failure (NYHA III/IV)
Left ventricular ejection fraction <30%
Unstable angina
Renal failure
Chronic obstructive pulmonary disease
Planned coronary artery bypass grafting or valve replacement
Planned peripheral vascular surgery
Age >80 years
Myocardial infarction within 6 weeks of procedure

Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first multicenter prospective randomized controlled trial designed to compare CEA to carotid artery angioplasty (CAA) [18]. Of note, stents were used in only 26% of cases in the endovascular arm, once they were available. CAVATAS enrolled 504 patients in 22 centers in Europe, Australia, and Canada between 1992 and 1997. Patients were included if they were found to have stenosis of the common carotid artery, carotid bifurcation, or ICA that the investigators believed should be treated and was equally suitable for treatment with either modality. The determination of whether stenosis was clinically important was left to individual investigators, and interestingly, there was no age limit, nor was there a stipulation about symptomatic vs asymptomatic status of stenosis. Patients were excluded if they were not suitable for either treatment for any reason. 504 patients were found to meet these criteria; 251 were randomized to the endovascular arm, and 253 were randomized to the CEA arm. There were no significant differences in any major adverse event in the perioperative period between patients with endovascular

intervention and patients with CEA: rate of disabling stroke or death at 30 days was 6.4% for endovascular patients and 5.9% for CEA patients; and rate of any stroke or death was 10% for endovascular patients and 9.9% for CEA patients. There was also no significant difference in rate of ipsilateral stroke at 3 years (14.3% endovascular and 14.2% CEA). The rate of major groin or neck hematoma was lower in endovascular patients than in CEA patients, occurring in 1.2% and 6.7% ($p < 0.0015$), respectively. The rate of cranial nerve palsy was also lower in the endovascular patients than in CEA patients, with no instances and 8.7% ($p < 0.0001$), respectively.

Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE)

With the increasing availability of carotid stents, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial was a prospective, randomized, controlled trial designed to demonstrate non-inferiority of stented angioplasty over CEA in the management of atherosclerotic carotid stenosis and enrolled patients from 2001 to 2006 [19]. Patients were included if they had symptomatic carotid stenosis of greater than 50% as measured by the NASCET protocol and if they were greater than 50 years of age. Patients were excluded if the stenosis was not atherosclerotic, if they could not take aspirin and clopidogrel and had a contrast contraindication, or if the artery was occluded. 1214 patients were found to fit these criteria, with 613 randomized to CAS and 601 randomized to CEA. The primary endpoint was ipsilateral carotid artery distribution stroke or death by any cause within 30 days of treatment; secondary endpoints included fatal or disabling stroke within 30 days of treatment, procedural failure, recurrent stenosis of 70% or greater at any point in follow-up, and carotid artery occlusion within 30 days of treatment. No significant difference was found in the rates of primary endpoint, 6.92% in patients who underwent CAS, and 6.45% in patients who underwent CEA. Nor was any significant difference found in the secondary endpoints other than in the life-table rates of recurrent stenosis, which was found to occur at a rate of 10.7% in CAS patients versus 4.6% in CEA patients ($p = 0.0009$). Subgroup analysis further revealed an age-related increase in the rate of primary outcome events in patients who underwent CAS, but not in patients who underwent CEA. The breakpoint was determined to be 68 years of age; patients younger than that age in the CAS arm experienced a lower rate of primary outcome events than did the CEA patients, and patients older than that age in the CAS arm experienced a higher rate of primary outcome events than did the CEA patients. So while the SPACE trial was unable to demonstrate non-inferiority of CAS over CEA, this was perhaps due to the enrollment of the trial being halted after interim analysis revealed that 2500 patients would be required to appropriately power the study, which was admitted to be a financial impossibility.

Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)

The EVA-3S trial was a concomitant multicenter, prospective, randomized controlled trial designed to assess non-inferiority of CAS versus CEA, which was halted when interim analysis demonstrated significantly elevated 30-day rate of stroke and death in the CAS arm of the study [20]. At that time 527 patients had been enrolled, randomized, and treated. The 30-day incidence of any stroke or death was 3.9% in patients who underwent CEA, compared to 9.6% in patients who underwent CAS. At 6 months, the incidence of any stroke or death was 6.1% in patients who underwent CEA, compared to 11.7% in patients who underwent CAS ($p = 0.02$). It should be noted that embolic protection devices were not required until 2003 in this study, a caveat that was addressed by other trials. Furthermore, critics of the EVA-3S trial claim that the certification criteria for operators in the CAS arm of the study required less in the way of experience than did the certification criteria for operators in the CEA arm of the study. This observation is moderately supported by the fact that the 9.6% overall rate of stroke and death in the CAS arm of the EVA-3S trial is somewhat higher than other comparable randomized trials.

Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)

The SPACE and EVA-3S trials both failed to demonstrate non-inferiority of CAS compared to CEA, and thus CAS failed to assert itself as a treatment option in patients for whom CEA was an acceptable option. However, the NASCET and the ACAS trials were both careful to include only patients who were at low surgical risk. The SAPPHIRE trial was a large multicenter prospective, randomized, controlled trial designed to establish non-inferiority of CAS with embolic protection compared to CEA in patients at high risk for surgery [21]. Patients ($N = 747$) were enrolled from 2000 to 2002 if they had at least one coexistent condition that increased their risk of CEA, symptomatic carotid artery stenosis greater than 50%, or asymptomatic carotid artery stenosis greater than 80%. Surgical high-risk criteria included clinically significant cardiac or pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, prior radical neck dissection or radiation therapy, recurrent stenosis, or age >80 years. Patients meeting those criteria were randomized only if all trial investigators agreed that the patient was a suitable candidate for either CEA or stenting. Patients on whom all investigators did not agree were not randomized but instead were entered into the registry of the appropriate treatment and were still followed up. Of the 747 patients enrolled, 334 met the criteria for randomization, and 167 were randomized to receive CAS or CEA. The primary endpoints were the cumulative incidence of all-cause death, myocardial

infarction (MI), and stroke within 30 days of treatment and the cumulative incidence of ipsilateral stroke occurring between 31 days and 1 year. Different from other studies, MI was included as a component of the primary endpoint due to the fact that the occurrence of either Q wave or non-Q wave MI in the perioperative period increases risk of future complications and death (Kim, Circulation 2002). Secondary endpoints included incidence of target-vessel revascularization at 1 year, cranial nerve palsy, and complications at the surgical site or vascular access site. The rate of stroke, all-cause death, or MI at 30 days after treatment was 4.8% in patients in the CAS arm compared to 9.8% in patients in the CEA arm (nonsignificant). The rate of stroke, all-cause death, or MI at 1 year was 12.2% in patients in the CAS arm compared to 20.1% in patients in the CEA arm, a difference that was significant in non-inferiority analysis ($p = 0.004$), as well as different in superiority analysis in the as-treated cohort ($p = 0.048$), and not significant in the intent to treat cohort ($p = 0.053$). The SAPPHIRE trial firmly established that CAS with embolic protection is non-inferior to CEA in patients at high risk for CEA.

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

CREST is a multicenter randomized controlled trial that enrolled 2502 patients from 2000 to 2008 including only endovascular surgeons who underwent rigorous certification. Both asymptomatic and symptomatic patients were included in the trial, although the trial began with symptomatic stenosis [22]. Patients must have had symptomatic stenosis of 50% or asymptomatic stenosis of 60% and be clinically appropriate for either CEA or CAS. The decision of whether or not to use embolic protection device was left to operator discretion. The primary endpoints were rate of stroke, death, or MI within 30 days of randomization and stroke ipsilateral to treated artery within 4 years of procedure. The rate of primary endpoint at 30 days was 5.2% in patients who underwent CAS and 4.5% in patients who underwent CEA (nonsignificant). However, the rate of minor strokes was higher in patients who underwent CAS (3.2%) than it was in patients who underwent CEA (1.7%) ($p = 0.01$). MI and cranial nerve palsy were both more common after CEA than after CAS (2.3% vs 1.1% $p = 0.03$ and 0.3% vs 4.7% $p < 0.0001$, respectively). Importantly, quality of life analyses among survivors at 1 year revealed that stroke had a stronger negative impact on patients than MI did. While the CREST results provided strong data indicating that CAS and CEA in their current forms are comparable treatments for both symptomatic and asymptomatic carotid artery stenoses, the data are limited in generalizability by two items in study design. First, the highly rigorous credentialing required for endovascular surgeons to participate in the study limit generalizability to all interventionists. Second, the use of only one endovascular system – while optimizing intra-study reliability – limits application of data to that system only.

International Carotid Stenting Study (ICSS)

ICSS is a multicenter randomized controlled trial that enrolled 1713 patients from 2001 to 2008 and only included patients with symptomatic stenosis of greater than 50% by NASCET protocol [23]. Patients that met the inclusion criteria were randomized to CEA or CAS arms of the study, and embolic protection devices were used when safe. The primary endpoint of the trial is the 3-year rate of fatal or disabling stroke in any territory. The analysis of the primary endpoint has not been published yet. The primary analysis of the interim publication was the 120-day rate of stroke, all-cause death, or periprocedural MI. The rate of the primary interim analysis was 8.5% in patients who underwent CAS and 5.2% in patients who underwent CEA ($p = 0.006$). Risks of any stroke and all-cause death were also higher in patients who underwent CAS. The long-term follow-up is still being completed and analyzed.

Asymptomatic Carotid Trial I (ACT I)

ACT I, published in 2016, is the most recently published prospective randomized controlled trial comparing CEA and CAS [24]. Between 2005 and 2013, 1453 patients were enrolled and randomized. The primary aim was to compare the outcomes of CEA versus stenting with embolic protection in patients who were at standard risk for surgical complications. Patients <80 years of age with asymptomatic carotid stenosis ≥70% who were deemed to be standard risk for surgery were eligible for enrollment and were randomized in a 3:1 ratio into stenting or CEA arms of the study. The primary endpoints were the composite rate of death, all stroke, or MI within 30 days of treatment or ipsilateral stroke within 365 days of treatment. Secondary endpoints included the rate of cranial nerve injury; peripheral nerve injury; vascular injury; non-cerebral bleeding; incisional complications; anesthesia-related complications; freedom from ipsilateral revascularization at 6 months, 1 year, and 5 years; freedom from death through 5 years; and freedom from all stroke through 5 years. The investigators found that stenting was non-inferior to endarterectomy with respect to rate of death, all stroke, or MI within 30 days (3.8% and 3.4%, $p = 0.01$ for non-inferiority). In fact, stenting was non-inferior to CEA in every measure in the study; the only measure found to be significantly different in any way was the rate of cranial nerve palsy, which was 1.1% in patients who underwent CEA versus 0.1% in patients who underwent CAS ($p = 0.02$).

Summary and Recommendations

For patients with atherosclerotic carotid stenosis, the options for treatment have significantly evolved since the 1950s. The NASCET and ACAS trials firmly established CEA as superior to best medical management for both symptomatic and

Table 25.3 Indications and relative contraindications for CEA and CAS

	Indications	Relative contraindications
Carotid endarterectomy	Recently symptomatic stenosis of >50% Asymptomatic stenosis of >60%	Baseline dense hemispheric neurologic deficit Life expectancy <5 years Stenosis of <50% High-risk surgical patient Contralateral carotid occlusion Previous neck surgery or radiation Lesion superior to C2 or inferior to the clavicle
	Indications	*Relative contraindications*
Carotid angioplasty and stenting	Symptomatic patient with >50% stenosis who is high risk for CEA	Age >70 years Tortuous aorta or carotid artery Life expectancy of <5 years Echolucent (lipid rich) plaque Lesion >15 mm in length Pre-occlusive highly calcified (circumferential) artery

asymptomatic carotid atherosclerotic diseases in the early 1990s; however, medical management has improved since that time with the evolution of statins and antiplatelet drugs. CREST-2 is currently enrolling patients to answer the question of best treatment for asymptomatic carotid stenosis in the modern era. Endovascular techniques for CAS have evolved significantly since the first carotid angioplasty in 1977 and provide a minimally invasive treatment option for carotid stenosis. However, until the recent publication of ACT I [24], data continued to support CEA as the preferred treatment for stenosis in patients who are at acceptable risk for surgery, regardless of the symptomatic or asymptomatic nature of the stenosis. In light of the current literature, CAS is non-inferior to CEA for patients <80 years of age with asymptomatic stenosis ≥70% (ACT I [24]) and in patients with high-grade stenosis at high risk for CEA (SAPPHIRE [21]), given an experienced endovascular surgeon and use of an embolic protection devices. Table 25.3 summarizes the indications and contraindications for CEA and CAS. Given the slightly higher risk of stroke in CREST and its impact on quality of life [22], CEA may be preferred over CAS in symptomatic patients without surgical high-risk factors.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133(4):447–54.
2. Estol CJ. Dr C. Miller Fisher and the history of carotid artery disease. Stroke. 1996;27(3):559–66.
3. Fisher M. Occlusion of the internal carotid artery. AMA Arch Neurol Psychiatry. 1951;65(3):346–77.
4. Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. Lancet. 1954;267(6846):994–6.

5. DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. JAMA. 1975;233(10):1083–5.
6. Bauer RB, Meyer JS, Fields WS, Remington R, Macdonald MC, Callen P. Joint study of extracranial arterial occlusion. 3. Progress report of controlled study of long-term survival in patients with and without operation. JAMA. 1969;208(3):509–18.
7. Busuttil RW, Baker JD, Davidson RK, Machleder HI. Carotid artery stenosis – hemodynamic significance and clinical course. JAMA. 1981;245(14):1438–41.
8. Kartchner MM, McRae LP. Noninvasive evaluation and management of the asymptomatic carotid bruit. Surgery. 1977;82(6):840–7.
9. Pokras R, Dyken ML. Dramatic changes in the performance of endarterectomy for diseases of the extracranial arteries of the head. Stroke. 1988;19(10):1289–90.
10. Easton JD, Sherman DG. Stroke and mortality rate in carotid endarterectomy: 228 consecutive operations. Stroke. 1977;8(5):565–8.
11. Committee NS. NASCET: North American Symptomatic Carotid Endarterectomy Trial. Stroke. 1991;22(6):711–20.
12. ACAS. Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;273(18):1421–8.
13. Farrell B, Fraser A, Sandercock P, Slattery J, Warlow C. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351:1379–87.
14. Mathias K. A new catheter system for percutaneous transluminal angioplasty (PTA) of carotid artery stenoses. Fortschr Med. 1977;95(15):1007–11.
15. Diethrich EB, Marx P, Wrasper R, Reid DB. Percutaneous techniques for endoluminal carotid interventions. J Endovasc Surg. 1996;3(2):182–202.
16. Jordan WD, Voellinger DC, Fisher WS, Redden D, McDowell HA. A comparison of carotid angioplasty with stenting versus endarterectomy with regional anesthesia. J Vasc Surg. 1998;28(3):397. -402-3
17. Theron J, Courtheoux P, Alachkar F, Bouvard G, Maiza D. New triple coaxial catheter system for carotid angioplasty with cerebral protection. AJNR Am J Neuroradiol. 1990;11(5):869–74; discussion–7.
18. Brown MM, Rogers J, Bland J. Endovascular versus surgical treatment in patients with carotid stenosis in t... Lancet. 2001;357:1729–1737.
19. 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.
20. 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):885–92.
21. 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):1493–501.
22. Clark WM, Brooks W, Mackey A, et al. Stenting verus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11–23.
23. 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(9719):985–97.
24. 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):1011–20.

Chapter 26
Carotid Endarterectomy Technique

Robert Dempsey and Casey Madura

Indications

Carotid endarterectomy (CEA) remains one of the only neurosurgical procedures backed by level 1 evidence. The following is a summary of the major trials which have leaned evidentiary backing to the selection of patients who might benefit from CEA:

1. The Veterans Administration Cooperative Study (VA) [1] investigated the benefit of CEA in asymptomatic male patients with stenosis between 50% and 99%. All patients received aspirin, with half randomized to receive CEA in addition.
2. The Asymptomatic Carotid Surgery Trial (ACAS) [2] evaluated 1662 patients with at least 60% carotid stenosis without symptoms. Randomization was to surgery and aspirin versus aspirin only. Angiographic evaluation of the stenosis was required prior to surgery.
3. The Asymptomatic Carotid Surgery Trial (ACST) [3] evaluated 3210 patients with asymptomatic carotid stenosis of at least 60%. Patients were randomized to receive surgery regardless of symptoms or to delay surgery if/until symptoms developed.
4. The European Carotid Surgery Trial (ECST) [4] randomized 3024 patients with symptomatic carotid stenosis to medical versus surgical treatment, defining

R. Dempsey (✉)
Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: dempsey@neurosurgery.wisc.edu

C. Madura
Pediatric Neurosurgery, Helen DeVos Children's Hospital – Spectrum Health, Grand Rapids, MI, USA
e-mail: Casey.Madura@helendevoschildrens.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_26

symptomatic as experiencing a cerebral ischemic event, with concordant symptoms, within 6 months.

5. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [5] evaluated 2926 patients with symptomatic carotid stenosis, randomizing those to surgical versus medical groups. Symptomatic was defined as a cerebral ischemic event, with concordant symptoms, within 4 months.

Based on these trials, the following conclusions have been reached, assuming a 3% risk of surgical complications:

Asymptomatic carotid stenosis: There is a 29% relative risk reduction (1–3% absolute risk reduction) for asymptomatic patients with 60% or greater carotid stenosis. This assumes a life expectancy of at least 3 years. Long-term analysis [6] has confirmed this result. It is important to keep in mind that this assumed a perioperative stroke risk under 2.3% and that the benefit was only seen in men [7].

Symptomatic carotid stenosis: CEA provides significant benefit (17% absolute risk reduction in the rate of ipsilateral stroke) for symptomatic patients with 70–99% carotid stenosis. Patients with 50–69% stenosis also benefited from CEA, though to a lesser degree. A meta-analysis of the major studies evaluating the role of CEA versus best medical management confirmed these findings [8].

The pooled data from the symptomatic carotid stenosis trials [9] also indicated that men patients under the age of 75 and patients whose presentation was stroke (rather than transient ischemic attack) experienced greater benefit than the opposite for stenosis >50%. The same analysis indicated that surgery within 2 weeks of symptom onset was beneficial (assuming stable symptoms). In fact, national guidelines in the United Kingdom mandates no more than 1 week between presentation with symptomatic carotid stenosis and definitive treatment [10].

It is important to recognize that these studies were performed largely *before* the development of improved medical therapy [11] and the institution of stenting methods. While CEA for symptomatic carotid stenosis remains unquestioned, the benefit of CEA in asymptomatic patients is no longer clear. This is an active area of study, and a new international trial, ECST-2, is underway investigating this very question [7] as well as the relative benefits of CEA vs. stenting. A number of reviews are available summarizing the findings of these trials [7, 11–14].

Preoperative Considerations

Anesthetic Considerations: Local Versus General Anesthesia

CEA may safely be performed under either local or general anesthesia. The General Anesthesia versus Local Anesthesia (GALA) trial [15] represents the largest study to date investigating the differences between CEA performed under the two different anesthetic techniques. Vaniyapong et al. [16] performed a comprehensive review

of all prospective randomized controlled trials (RCTs), 14 in all, investigating the difference between the two techniques. Stoneham et al. [10] published a review of the anesthetic techniques required for effective local anesthesia during CEA.

Overall, there is no conclusive evidence that morbidity and mortality are significantly different under either technique. The common thread among the 14 trials included in the Cochrane review is surgeon and patient comfort. Given that the indications for CEA rest upon an assumption of a baseline level of surgical morbidity and mortality, the only conclusion that can be drawn is to ensure that all parties involved in each CEA are comfortable with the choice of anesthesia. Outcomes such as risk of stroke, death, myocardial infarction, local hemorrhage, and cranial nerve injury were not statistically different [16].

Some factors were different. The rate of shunting was significantly higher in the group of patients undergoing general anesthesia. Additionally, blood pressure management seems to differ between the two types of anesthesia. In the GALA trial, those patients undergoing general anesthesia tended to require upward manipulation of their blood pressure, with the opposite being true for local anesthesia [15]. Although not definitive, review of data from the American College of Surgeons' National Surgical Quality Improvement program suggests a possible benefit of decreased length of hospital stay and lower cost of care in patients undergoing CEA under local anesthesia [10, 17].

Role of Intraoperative Monitoring

The case in favor of cerebrovascular monitoring during CEA has been clear for some time. Babikian and Cantelmo provide a concise summary of the evidence [18]. Despite all the advances in surgical and neuroendovascular technology, cerebral embolism remains one of the most common complications in CEA [19], with some studies citing up to a 5.14% risk of ipsilateral stroke from randomization out to 30 days post-procedure for patients undergoing CEA [20]. The goal of monitoring is to minimize the clinical effect of these events.

Cerebrovascular monitoring can take many forms. The most direct is to keep the patient awake. This allows continuous examination during the procedure. This, of course, requires some form of local or regional anesthesia. As stated above, multiple trials have failed to disclose a significant advantage or disadvantage favoring local, regional, or general anesthesia.

Electroencephalography (EEG) is another common form of cerebrovascular monitoring. It measures the activity of the cerebral cortex, demonstrating a decrease in cerebral function in the face of insufficient blood flow. This can be manifested as slowed, attenuated, and/or ceased activity compared to a preoperative and pre-cross-clamping baseline. Sensitivity and specificity are 70% and 96%, respectively [21], and factors such as depth of anesthesia and patient body temperature can alter the data. Therefore, to be effective, an experienced operating room team is required.

EEG also cannot measure the function of deeper brain structures, so that cerebral injury in these locations will go undetected.

Another available monitoring technique is the transcranial Doppler (TCD). TCDs measure the velocity of cerebral blood flow as a surrogate for cerebral ischemia. Reported sensitivity and specificity for the detection of cerebral ischemia in patients undergoing CEA is 81% and 92%, respectively [21]. TCD's advantage over EEG is the fact that it directly measures blood flow rather than using an indirect marker of cerebral function to detect ischemia. As a result, TCDs are capable of detecting both large and microemboli [19, 22–24]. The main disadvantage of TCDs is the same as for the use of EEG. An experienced, consistent team is required to produce consistent results. Even when this is the case, TCDs may not always be available as a monitoring technique due to anatomical constraints or limited "windows" [25].

Somatosensory evoked potentials (SSEPs) represent a third type of cerebral function monitoring available to surgeons and anesthesiologists. SSEPs measure the cortical response to a stimulus of the sensory pathway, therefore representing an indirect measure of cerebral function. Criteria for a change in SSEPs that is considered clinically significant include an increase in latency of at least 10% and/or a decrease in amplitude of the response by at least 50% [26]. Direct comparison of SSEPs to EEG in detecting clinically significant events have demonstrated a significant increase in sensitivity [25]. SSEPs suffer the same drawbacks of EEG. Specifically, anesthetic agent and depth as well as a host of other factors may alter the results, requiring experienced interpretation. Additionally, as its name implies, SSEPs only test one function of the cortex. Significant events leaving the sensory cortex intact may, therefore, go undetected.

EEG, TCD, and SSEP represent the three best-studied techniques for monitoring cerebral function during CEA under general anesthesia. A host of other techniques are available and are beyond the scope of this chapter. For a full discussion, the reader is referred to the outstanding review by Li et al. [25]

Regardless of the type of monitoring used, the goal is to detect cerebral ischemia as soon as possible. Early detection may allow alterations in the anesthetic or surgical technique to prevent clinically significant neurological morbidity in the postoperative period. In the current era of emphasis on clinical quality, rather than just overall throughput, the extra time taken to implement these techniques may be well worth the time. With strong evidence that ischemic events are likely during and immediately following CEA, it is difficult to justify reasons to forgo the use of some type of monitoring.

The Use of Shunts in CEA

During the cross-clamping phase of CEA, the use of a shunt to ensure adequate blood flow to the ipsilateral cerebral cortex is an option. The data supporting this is well summarized in a Cochrane Review by Chongruksut et al. [27]. In this review,

only six total randomized controlled trials, each of limited value, were included. Primary outcomes included the risk of all stroke (not transient ischemic attacks), all ipsilateral stroke, death from any cause, arterial complications, and other complications such as hemorrhage, infection, and others. Each was evaluated in a 24-h and 30-day window. Unfortunately, the risk of any one of these events was so low in aggregate, that any difference in primary outcome was far from statistically significant.

The authors of this review note a few important details. First, all of these trials were conducted in patients undergoing general anesthesia during CEA. Second, none of the included trials compared selective shunting to no shunting. Third, missing data required testing of both best- and worst-case scenarios resulting in extremely wide confidence intervals.

The use of shunting, therefore, should be based on surgeon preference. A major objection among surgeons who routinely do not shunt or who only selective shunt is the risk of arterial injury during insertion of the shunt. While such injuries are a risk of shunt insertion, shunt insertion can be accomplished safely in the hands of experienced surgeons [28, 29]. At our own institution, some surgeons routinely shunt, while others only selectively shunt.

Preoperative Imaging

Prior to any actual operating, it is critical to study as much information as is available about the patient. Particular attention should be paid to the CT angiogram of the head and neck as well as the ultrasound. The CTA will demonstrate the extent and severity of the plaque as well as the location of the bifurcation, allowing the surgeon to assess the extent of dissection that will be needed in order to fully expose it. Additionally, the CTA will demonstrate the bony anatomy and gives hints as the ability of the surgeon to turn and extend the head of the patient during the operation. Finally, the CTA of the head demonstrates the cerebral circulation, giving the surgeon a hint at the patient's ability to provide collateral flow from the contralateral side during cross-clamping of the carotid artery.

Other imaging is very important. Careful review of the ultrasound will demonstrate any asymmetry of the plaque. This is seen by acknowledging any turbulent flow around the location of the plaque. An MRI of the head will demonstrate other lesions, especially the location of any prior strokes.

This type of preparation is critical as it will minimize the disruptions to an otherwise very straightforward procedure. Preoperative knowledge of a high bifurcation, for example, will allow the surgeon to extend the normal dissection distally along the carotid *before* the vessel is opened. It also means that consideration of the location of the 12th cranial nerve begins *before* it is already injured. For those who selectively shunt, review of the collateral circulation may increase or decrease the suspicion of its need. Assessment of the plaque will also help identify particularly thick or calcified portions that may be difficult to incise initially.

Operative Details and Nuances

As discussed above, CEA may be performed, at the discretion of the surgeon, under local or general anesthesia. The description of the procedure in this chapter assumes the use of general anesthesia. Careful attention should be paid to the team aiding the surgeon during CEA. Anesthesiologists, nurses, and OR techs should be part of a dedicated neuro team as familiarity with the steps of CEA is critical to its success.

The patient is positioned supine on the operating room table. A roll is placed beneath the scapula, allowing for slight extension of the neck. The head is turned 35°. Care must be taken not to over-rotate the head as this will bring the internal jugular and sternocleidomastoid muscle on top of the carotid, adding to the difficulty of the operation. 1-inch tape is used to close the jaw, providing slight superior distraction of the chin. This allows for an additional 1.5 cm of exposure of the internal carotid artery (ICA) in cases of high bifurcations or plaques that would otherwise require dislocation of the jaw.

Prior to any incision, verification of appropriate personnel and equipment is paramount. Assurance of familiarity with the operation among the team allows quick response to any situations that may arise. A functioning operating microscope and headlight are critical for adequate visualization. Monitoring with EEG is standard at our institution, and verification of adequate EEG monitoring is needed prior to initiation of the case.

The target of the operation is the anterior triangle of the neck (Fig. 26.1). External landmarks leading to this area are critical to ensuring safe access to this area. The sternocleidomastoid (SCM) muscle runs longitudinal through the field, and its anterior border marks the location of the vessels within the carotid sheath. The trachea marks the medial-most extent of the operative field, while the mastoid identifies the most distal extent. The mastoid is particularly important in serving as a general landmark for the location of the carotid canal and hypoglossal canal so that in cases of distal dissection, the transmitted structures can be identified at the skull base.

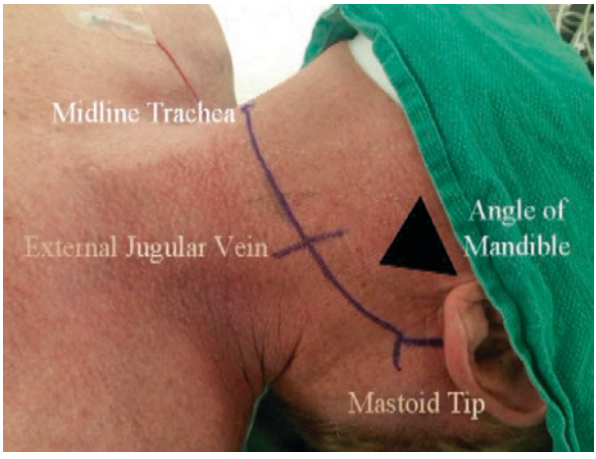


Fig. 26.1 The target of the operation is the anterior triangle of the neck

The external jugular vein serves as a key landmark in multiple ways. First, it sits directly over the SCM. Second, during closure, sutures placed on cut ends of the sectioned vessel allow accurate re-approximation of the wound. Third, when patients are obese, making palpation of underlying structures more difficult, it can serve as a marker for the location of the SCM as it lies directly superficial to it.

Once the incision has been marked based on landmarks, the necessary equipment is noted to be available, the entire operative team feels comfortable, and the field is infiltrated with lidocaine with epinephrine and prepped in standard sterile fashion. Surgeon and assistant face each other across the shoulders with the carotid in the center of the field. Incision in the skin typically will allow quick identification of the platysma muscle. This is the only muscle that requires division during the procedure, contributing to the fact that postoperative pain control is relatively easy after CEA. Careful attention to hemostasis begins immediately and continues throughout the entire procedure as the patient will be heparinized during the procedure.

Dissection begins by sharply dividing the platysma, taking care not to injure the underlying vessels. The external jugular is then identified and doubly ligated. The SCM can be identified at this point, and the platysma is elevated off of it. Identification of the anterior border of the SCM is critical as dissection proceeds both proximally and distally. Electrocautery is used to free the attachments to this portion of the muscle to maximize hemostatic control.

Distal exposure of the SCM is critical, especially in cases of high bifurcations and/or long plaques. Identification of the silvery insertional tendon of the SCM ensures adequate distal dissection in most cases. Further distal dissection can be achieved by detaching the SCM from its cutaneous attachment. This dissection allows any lymph nodes encountered to be retracted laterally and avoids the slow but steady bleeding associated with violation of these structures.

At this point, the internal jugular (IJ) should be visible. Its attachments to the carotid sheath are taken down using a combination of blunt and careful sharp dissection. Its major tributaries should be identified, including the common facial vein. The common facial may be single or multiple and large or small. In any case, suture ligation and sharp sectioning ensure appropriate hemostasis, and the sutures, much like those on the external jugular, serve as markers during closure.

Once freed, the jugular vein may be retracted laterally, exposing the carotid within its sheath (Fig. 26.2). The 10th nerve may also be visible at this time depending on its location. The sheath is divided longitudinally along the carotid, thus avoiding injury to the 10th nerve, especially in cases where it runs an aberrant course.

Following the sheath into the bifurcation will preferentially lead the surgeon to the internal carotid artery (ICA). Exposure along the ICA must continue distal to the plaque to allow for adequate closure. The 12th nerve is frequently encountered as it crosses the vessel and must be sought out and protected. In cases where very distal exposure of the ICA is needed, the 12th nerve may be freed of its attachments and transposed medially and superiorly. Care should be taken to circumferentially dissect around the ICA to allow adequate vascular clipping.

The next step is to circumferentially dissect the common carotid artery (CCA) and the bifurcation. 360° exposure of the common carotid artery is a critical step as it allows complete distal control. The bifurcation is then carefully inspected and

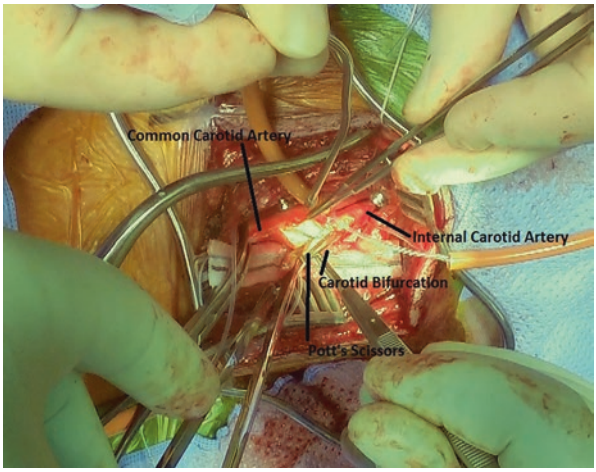


Fig. 26.2 Once freed, the jugular vein may be retracted laterally, exposing the carotid within its sheath

dissected from of its attachments. It is critical to be aware of the presence of external adhesions of the vessel to surrounding tissue that are the result of the inflammatory process associated with plaque formation. These adhesions can be exceedingly difficult to dissect, and efforts to detach them can easily lead to violation of the often extremely thin vessel.

Finally, the external carotid artery (ECA), identified for the fact that it has branches, is dissected. The superior thyroid artery, the first branch of the ECA, is dissected circumferentially to allow temporary clipping during the endarterectomy. This clipping is critical as it prevents rotational distortion of the bifurcation that would otherwise occur if the superior thyroid artery were included in vascular clamping of the ECA. Now, the medial portion of the bifurcation may be freed from any attachments.

At this point in the operation, it is critical for the surgeon to assess his/her exposure. The ICA, ECA, CCA, including the bifurcation, and the superior thyroid artery should be circumferentially freed. Any residual attachments may hinder the surgeon's ability to effectively cross-clamp the vessels. The 9th (at the bifurcation), 10th, and 12th nerves should be visualized as described above. It is not until this point in the operation that the surgeon may conclude that vascular control of the operative field has been achieved.

Preparation for the endarterectomy is now begun. Polyethylene (PE) tubing is looped around the ICA, CCA, and ECA. This tubing is especially effective because of its low profile and its ability to slide along tissue without catching. The tubing is then threaded through a piece of red Robinson catheter and secured with hemostat clips. This setup allows for cinching of the vessel later in the case. Placement around the ICA and CCA is straightforward. Care must be taken to include to the ascending pharyngeal origin distal to the location of the tubing. This is achieved by sweeping a right angle clamp underneath the ECA at its most proximal extent (achievable *only* if the previous dissection is truly circumferential) from proximal to distal.

Time is now taken to set up the surgical field in a sequential order with only necessary instruments on the Mayo table. During this prep, the patient is heparin-

ized, and the superior thyroid artery is clipped with an aneurysm clip. The shunt (if needed) is prepped, and the instruments are arranged on the Mayo table in the order of their use. The preferred sequence of events is reviewed with the scrub tech, and comfort with all phases of the endarterectomy is ensured. The microscope should be prepared at this time. Assurance of adequate intraoperative monitoring (if being used) should be requested. Such preparation allows for a very fast, controlled, and efficient endarterectomy and minimization of cross-clamping times.

Cross-clamping is then initiated. The order is stereotyped beginning with a distal aneurysm clip on the internal carotid, above the level of the plaque. A vascular clamp occludes the common carotid followed by cinching of the PE tubing on the external carotid artery.

The endarterectomy now begins. An 11-blade knife is used to make a stab incision just proximal to the plaque in the CCA. Take care to incise only into the lumen of the vessel in order to avoid injury to the back wall of the vessel. Angled Potts scissors are used to extend the arterial incision, taking care to stay exactly in the midline of CCA, bifurcation, and ICA. This is critical as a calcified plaque will often try to force the scissors off course resulting in an uneven arteriotomy and extremely difficult closure. At this point, a shunt can be placed if desired. The field is irrigated with heparinized saline, and the operative microscope is brought into the field.

Dissection of the plaque begins proximally, allowing normal media and adventitia to remain. This is accomplished with a small blunt instrument such as the Penfield 4 or Crile ganglion knife. Bilateral dissection of the plaque at its proximal extent will identify a transition between normal and abnormal media. After careful 360° dissection, sharp truncation of the plaque is achieved with tenotomy scissors.

Dissection proceeds distally through the bifurcation into the ICA (Fig. 26.3). The plaque within the bifurcation may be extremely adherent requiring efficient but careful dissection. The remaining vessel wall may be extremely thin. There is almost always a discrete ending to the plaque within the ICA. Careful attention to resumption of normal intima will allow the surgeon to carefully cut the plaque with microscissors. Such fine instruments are critical as this allows a smooth transition back to normal vasculature and avoids a loose shelf of intima that otherwise would require a tack-down suture. This leaves only the plaque within the ECA. This portion is dissected as

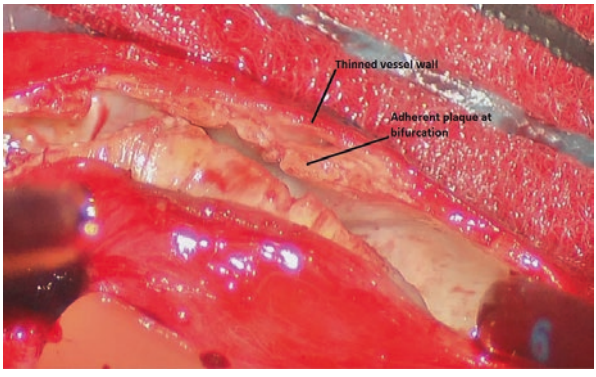


Fig. 26.3 Dissection proceeds distally through the bifurcation into the ICA

much as possible into the ECA until it can be everted out of the vessel and sectioned sharply.

The remaining vessel is now inspected. Any loose pieces of intima are removed, and any shelves of intima along the distal portion are tacked down. Loose debris within the vessel represents a source of thrombosis and/or embolism that may lead to perioperative stroke.

Closure now begins. The shunt, if used, serves as a useful template for closure. 6-0 prolene is our preferred suture for closure. The first sutures are placed distally in the ICA under the visualization provided by the operating microscope. The closure is extended as far as the shunt will allow, or in cases where a shunt is not used, approximately two-thirds of the way along the arteriotomy. This allows the final sutures to be in the larger and more forgiving CCA. The shunt (if used) is removed, and the microscope is taken out of the field. Just prior to complete closure of the arteriotomy, the ICA clip is removed to back bleed any loose debris from the vessel. After the ICA is clamped again, the ECA and then the CCA are unclamped to allow initial flow into the ECA. Then the left is opened. The field is irrigated with heparinized saline, and the closure is inspected.

The arteriotomy is inspected, and hemostasis is ensured. A small drain can be left with the surgical bed, underneath the platysma. The deep tissues are re-approximated over the carotid sheath. This is simply to reduce dead space within the operative bed. The platysma is re-approximated carefully with interrupted sutures, using the sutures on the EJ as a marker. This is a critical step as this muscle represents the strength of the wound closure. The skin is closed with a subcuticular suture to minimize scarring.

Postoperative Considerations

Postoperative care in CEA patients is critical. Monitored evaluation (ICU or step-down unit) overnight is required, with particular attention paid to blood pressure control. Perioperative threats to life include stroke and hemorrhage, each of which may be mitigated by ensuring appropriate hemodynamics. Typical hospital stay is 1 or 2 days assuming the patient recovers back to his/her neurological baseline, the family/caregivers feel comfortable with any postoperative care that is required, and the patient's blood pressure is well-controlled. Pain is typically minimal as muscle interruption is minimized in the procedure.

References

1. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med. 1993;328(4):221–7.
2. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995;273(18):1421–8.

3. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363(9420):1491–502.
4. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351(9113):1379–87.
5. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998;339(20):1415–25.
6. Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet. 2010;376(9746):1074–84.
7. O'Brien M, Chandra A. Carotid revascularization: risks and benefits. Vasc Health Risk Manag. 2014;10:403–16.
8. 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(9352):107–16.
9. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Collaboration CET. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363(9413):915–24.
10. Stoneham MD, Stamou D, Mason J. Regional anaesthesia for carotid endarterectomy. Br J Anaesth. 2015;114(3):372–83.
11. Young KC, Jain A, Jain M, Replogle RE, Benesch CG, Jahromi BS. Evidence-based treatment of carotid artery stenosis. Neurosurg Focus. 2011;30(6):E2.
12. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev. 2005;4:CD001923.
13. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2011;4:CD001081.
14. Meerwaldt R, Hermus L, Reijnen MM, Zeebregts CJ. Carotid endarterectomy: current consensus and controversies. Surg Technol Int. 2010;20:283–91.
15. Lewis SC, Warlow CP, Bodenham AR, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet. 2008;372(9656):2132–42.
16. Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev. 2013;12:CD000126.
17. Erickson KM, Cole DJ. Anesthetic management of carotid endarterectomy. Curr Opin Anaesthesiol. 2013;26(5):523–8.
18. Babikian VL, Cantelmo NL. Cerebrovascular monitoring during carotid endarterectomy. Stroke. 2000;31(8):1799–801.
19. Pennekamp CW, Moll FL, de Borst GJ. The potential benefits and the role of cerebral monitoring in carotid endarterectomy. Curr Opin Anaesthesiol. 2011;24(6):693–7.
20. Ringleb PA, Allenberg J, Brückmann 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):1239–47.
21. 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):266–79.
22. Moppett IK, Mahajan RP. Transcranial Doppler ultrasonography in anaesthesia and intensive care. Br J Anaesth. 2004;93(5):710–24.
23. Jansen C, Ramos LM, van Heesewijk JP, Moll FL, van Gijn J, Ackerstaff RG. Impact of microembolism and hemodynamic changes in the brain during carotid endarterectomy. Stroke. 1994;25(5):992–7.
24. Skjelland M, Krohg-Sørensen K, Tennøe B, Bakke SJ, Brucher R, Russell D. Cerebral microemboli and brain injury during carotid artery endarterectomy and stenting. Stroke. 2009;40(1):230–4.

25. Li J, Shalabi A, Ji F, Meng L. Monitoring cerebral ischemia during carotid endarterectomy and stenting. J Biomed Res. 2016;31:11.
26. Nwachuku EL, Balzer JR, Yabes JG, Habeych ME, Crammond DJ, Thirumala PD. Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: a systematic review and meta-analysis. JAMA Neurol. 2015;72(1):73–80.
27. 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.
28. Hamdan AD, Pomposelli FB, Gibbons GW, Campbell DR, LoGerfo FW. Perioperative strokes after 1001 consecutive carotid endarterectomy procedures without an electroencephalogram: incidence, mechanism, and recovery. Arch Surg. 1999;134(4):412–5.
29. Hertzer NR, O'Hara PJ, Mascha EJ, Krajewski LP, Sullivan TM, Beven EG. Early outcome assessment for 2228 consecutive carotid endarterectomy procedures: the Cleveland Clinic experience from 1989 to 1995. J Vasc Surg. 1997;26(1):1–10.

Chapter 27
Steno-occlusive Carotid Artery Disease: Carotid Artery Stenting Technique

Vernard S. Fennell, Sabareesh K. Natarajan, and Adnan H. Siddiqui

Indications for Case Selection

Ischemic strokes are a major cause of death and major morbidity in the USA [1]. Strokes are the fifth leading cause of death in the USA; and more than 140, 000 individuals die each year from stroke – that equates to 1 American every 4 min [1, 2]. Compelling data suggest that steno-occlusive carotid artery disease may contribute to 15–25% of ischemic strokes [3, 4], the prevalence of which increases steadily with advancing age from 0.5% at 60 years to 10% at 80 years [5]. Carotid revascularization has proven to be an effective means for reducing the risk of stroke in properly selected patients, with much of the early data derived from open surgical carotid endarterectomy (CEA) trials [6–11]. The use of carotid artery stenting (CAS) as an alternative to CEA for revascularization has steadily advanced. The results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial showed noninferiority with respect to CEA as it pertains to high-surgical-risk patients [12]. More recently, the Carotid Revascularization Endarterectomy versus Stenting Trial, I and II (CREST I and II)

V. S. Fennell (✉)
Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

Gates Vascular Institute at Kaleida Health, Buffalo, NY, USA
e-mail: vfennell@ubns.com

S. K. Natarajan
Department of Neurosurgery, University at Buffalo, State University of New York, Buffalo, NY, USA

A. H. Siddiqui
Departments of Neurosurgery and Radiology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA
e-mail: asiddiqui@ubns.com

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_27

revealed initially comparable results with respect to durability (restenosis rates) and, at the 10-year follow-up, found no difference in the combined endpoints of stroke, death, or myocardial infarction [13, 14].

Several studies have examined the utility of CAS [12, 13, 15–23]. A multidisciplinary collection of societies, including the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, endorses CAS as an alternative to CEA for average risk, symptomatic patients when the anticipated perioperative mortality or stroke is <6% in symptomatic patients and 3% in asymptomatic patients [24, 25]. This is with the assumption of at least a 5-year life expectancy with CEA. However, there are differing opinions with respect to how CAS should be implemented and that is reflected in the current regulations. The Food and Drug Administration (FDA) has approved several systems for use in CAS and has categorized them as "safe and effective" alternatives to CEA [26]. The FDA's categorizations are based on studies of more than 8000 patients. The FDA has supported the use of CAS for revascularization in symptomatic patients with >50% stenosis and asymptomatic patients with >80% stenosis who have lesions that are high-surgical risk secondary to anatomical constraints or severe medical comorbidities. However, the Centers for Medicare and Medicaid Services (CMS) has a threshold of "reasonable and necessary," which is at best vague and at worst contradictory to the FDA requirements of "safe and effective" [26, 27]. Currently, the CMS reimburses for CAS in patients deemed high risk for CEA, defined by comorbidities or anatomical high-surgical-risk factors [28]. The CMS criteria for significant comorbidities or high-risk criteria (Table 27.1) are somewhat more Spartan than are the FDA criteria for determining high-risk criteria for CAS (Table 27.2) [27, 28]. CMS reimbursement is also contingent upon the patient meeting the following criteria: (1) symptomatic carotid stenosis >70%, (2) participation in an investigational device clinical trial and >50% symptomatic stenosis or asymptomatic stenosis >80%, or (3) participation in an FDA-approved study at a designated center and treatment within the study parameters and approved device indications. Most US patients require assistance with respect to paying for medical care, especially procedures [29]. As a result, the CMS requirements for CAS play a dominant role in patient selection. Despite clinical equipoise between CAS and CEA, the position of the CMS with respect to not altering the requirements for reimbursement remains steadfast [26]. In time, the 10-year-follow-up results of CREST II may alter patient treatment selection [14].

Intraprocedural Considerations

As with all surgical or interventional procedures, the intraprocedural considerations require planning and an understanding of the critical aspects of the case. The most notable advances with respect to CAS have come with dramatic improvements in devices and techniques for protection against intracranial embolization of plaque debris during the procedure s. Some of the first randomized controlled trials

Table 27.1 Centers for Medicare and Medicaid Services criteria high-surgical-risk significant comorbidities and/or anatomical risk factors

Significant comorbid conditions
Class III or Class IV congestive heart failure
Left ventricular ejection fraction <30%
Unstable angina
Contralateral carotid occlusion
Recent myocardial infarction
Previous carotid endarterectomy with recurrent stenosis
Previous radiation treatment of the neck
Anatomical risk factors
Recurrent stenosis
Previous radical neck dissection
Carotid artery symptoms include
Transient ischemic attack
Focal cerebral ischemia producing a non-disabling stroke
Transient monocular blindness (amaurosis fugax)

Source: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=157&ver=29&NcaName=Carotid+Artery+Stenting+(1st+Recon)&bc=BEAAAAAAEAAA&&fromdb=true

Table 27.2 Food and Drug Administration criteria: high-risk candidates for carotid endarterectomy

Significant medical morbidities
Class III, Class IV heart failure
Left ventricular ejection fraction <30%
Recent myocardial infarction (>24 h, <30 days)
Unstable angina
Concurrent need for coronary revascularization
Abnormal stress test
Severe pulmonary disease
Chronic O_2 therapy
Resting PaO2 <60 mmHg
Baseline hematocrit >50% of normal
FEV1 <50% of normal
Age >80 years
Significant anatomical abnormalities
Contralateral carotid artery occlusion
Contralateral laryngeal palsy
Previous radiation of head or neck
Previous carotid endarterectomy with recurrent stenosis
Surgically difficult to access high cervical lesions or common carotid artery lesions below the clavicle
Severe tandem lesions
Laryngotomy or tracheostomy
Inability to extend the head as a result of arthritis or other conditions

Source: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm542254.htm

comparing CAS without embolic protection to CEA did not show favorable results for CAS [30, 31]. The Wallstent trial was the first multicenter randomized trial to compare CAS and CEA but was stopped early after analysis revealed a 30-day stroke or mortality of 12.1% in the CAS group versus 4.5% in CEA group [32, 33]. Embolic protection was not used and was thought to be a major contributor to the differences in outcomes. Most CAS procedures are now performed with some form of embolic protection. Embolic protection devices can be subdivided into essentially three groups: (1) distal occlusion balloons, (2) distal filters, and (3) proximal occlusion systems.

Distal occlusion balloons, introduced by Theron, were initially used as some of the first proximal protection devices [34]. In this system, the balloon is inflated in the internal carotid artery, between the stenotic lesion and the intracranial circulation. The balloon has the benefit of impeding debris-containing blood flow by way of cessation of flow and by manual aspiration of flow to the external carotid artery (ECA). However, distal balloons cannot allow for intracerebral oxygenation, and the inflation of the balloon can increase the risk of vessel spasm and dissection. Another disadvantage is that stenting devices are unable to be assessed angiographically, while the protection balloon is deployed.

Distal filters act as a windsock and catch debris distal to the lesion and before proceeding intracranially with the stent. Distal filters are able to trap medium to large particles (generally >80 μm) [35]. The filter can be mounted over a guidewire and then retrieved. It can alternatively come mounted on its own delivery and retrieval system as well. A distal filter has the benefit of maintaining intracerebral oxygenation and affords the added benefit of angiographic assessment throughout the entirety of the procedure.

Proximal flow occlusion systems (e.g., Mo.Ma, Medtronic) consist of two compliant balloons. One balloon resides in the ECA and one in the common carotid artery (CCA). This dual balloon occlusion produces complete cessation of flow with flow reversal and restricts emboli from traveling distally and intracranially. These systems also have the advantage of avoiding the need to cross the lesion before establishing protection and placing a stent. However, dual proximal occlusion is obviated in patients with insufficient cerebral collateralization. The balloon can be deflated during portions of the procedure if additional angiographic detail is needed. However, this maneuver may compromise protection. Proximal protection device also requires larger-caliber guide catheters (9-French); as a result, navigating a tortuous arch could prove prohibitive.

Before choosing an embolic protection strategy, we assess the collateral circulation by performing a full diagnostic angiogram. If appropriate, we obtain CT perfusion studies with and without acetazolamide challenge to assess for sufficient flow reserve. If there is not satisfactory collateralization radiographically, we typically use distal filters. We prefer small, low-profile distal filter systems that are steerable through tortuous anatomy. Only low-profile, soft-tipped systems are compatible with crossing a lesion because they are less traumatic and help to avoid complications. In our practice, we often utilize proximal protection with balloon occlusion in symptomatic lesions with angiographically difficult to traverse lesions. If the ECA

is appropriately sized and navigable, we use dual balloon occlusion (e.g., Mo.Ma). If the ECA anatomy is unfavorable, a single CCA balloon may be used.

A key issue is the selection of an appropriate stent. Intraprocedurally, this may become more prominent in challenging anatomy, particularly if the diagnostic angiogram was completed with a more navigable diagnostic catheter. Important considerations are the aortic arch type, carotid artery morphology, and lesion anatomy. Although an exhaustive review of all stents used for CAS is outside the scope of this chapter, several characteristics are crucial. Stent design, material, shape, cell type, and available sizes as well as the type of guide catheter required are all very important considerations. The free cell area (the area of the stent occupied by the stent tines) is the optimal measure for describing the coverage of carotid stents. Large registries contend that stents with smaller free cell areas are more advantageous with respect to containing arterial plaque behind the stent struts and, as a result, are associated with lower event rates than stents having larger free cell areas [36].

Technical Nuances

Most patients at our institution undergo a noninvasive imaging study (i.e., magnetic resonance angiography [MRA] or computed tomographic angiography [CTA]) before the CAS procedure is contemplated. This study allows us to be aware of arch type and tortuosity as well as atherosclerotic burden. Furthermore, it enables us to make decisions on target vessels as well as the embolic protection type. We then prepare the patent for diagnostic angiography (digital subtraction angiography [DSA]). However, multiple noninvasive adjuncts suggesting that a lesion is amenable to CAS can potentially influence additional preparation for stent placement immediately after the angiogram has been performed. For example, if CTA is suggestive of stenosis and carotid Doppler imaging confirms stenosis, we often prepare for DSA along with CAS, provided that the stenosis is also exhibited on DSA.

In anticipation of a possible CAS, patients are pretreated with dual antiplatelet therapy. Our pretreatment regimen consists of 5–7 days of aspirin (325 mg daily) and clopidogrel (75 mg daily). For patients who are symptomatic, either clinically or by discrete magnetic resonance imaging (MRI) findings (i.e., evidence of acute ischemia), a 5–7-day pretreatment regimen is typically not prescribed. In those cases, we administer a loading dose of aspirin (650 mg) and clopidogrel (600 mg), returning to the lower-dose daily regimen after CAS. Prior to CAS, we confirm the therapeutic action of both aspirin and clopidogrel. If patients are not within the therapeutic effectiveness range with clopidogrel, it is our practice to then switch to ticagrelor (180 mg loading dose and 90 mg twice daily).

We perform the stenting procedure in an angiographic suite with biplane digital subtraction angiography. At our institution, we use conscious sedation, while the patient is awake. Conscious sedation allows us the luxury of immediate neurologic assessment throughout the entirety of the procedure.

Case Illustration

A 65-year-old gentleman with a history of hypertension and coronary artery disease for which he had undergone coronary artery bypass grafting presented with symptoms of right-upper extremity numbness and slight weakness. Brain MRI showed areas of restricted diffusion in the left hemisphere. Cervical CTA showed a high-grade stenosis of the left carotid artery. DSA showed >90% stenosis with the lesion located at the C2 vertebral level (Fig. 27.1a). High-grade stenosis (>70%) of the right carotid artery was noted as well.

The patient was taken to the angiography suite. The carotid artery was accessed via a transfemoral approach. An 8-French sheath was inserted transfemorally. An 8-French concentric balloon guide catheter (Concentric Medical/Stryker) was navigated over the aortic arch with a 5-French, 125 cm Vitek catheter (Cook Medical) over an exchange length 0.038-inch wire. Angiographic runs of the carotid artery and the site of the lesion were completed. An Emboshield NAV6 FilterWire (distal embolic protection device, Abbott Vascular) was navigated past the lesion.

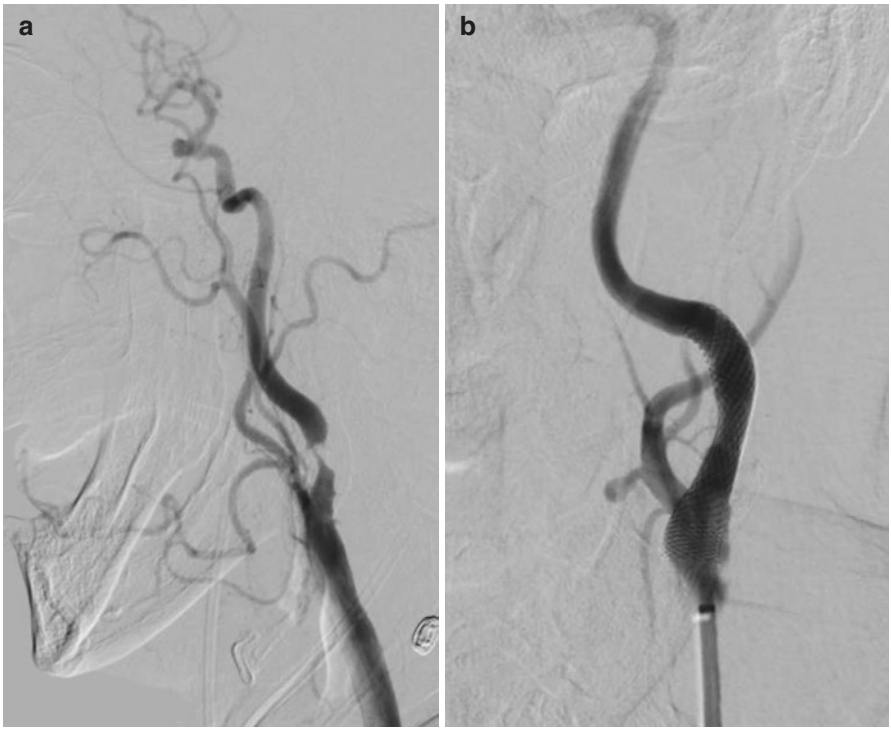


Fig. 27.1 (**a**) Lateral view of angiogram of left carotid artery showing high-grade stenosis. (**b**) Lateral angiogram after carotid stenting shows restored flow

Prestenting angioplasty was performed utilizing a 4-mm × 30-mm Aviator balloon (Cordis/Cardinal Health). An 8 mm × 29 mm Wallstent (Boston Scientific) was deployed. The NAV6 FilterWire was retrieved, and flow was restored (Fig. 27.1b).

Conclusion

Carotid artery stenting (CAS) is a safe, effective, and well-codified therapeutic adjunct in the treatment of steno-occlusive atherosclerotic carotid artery disease.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. On behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133:e38–360.
2. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2015. National Center for Health Statistics Data Brief. No. 267. US Department of Health and Human Services. https://wwwcdcgov/nchs/data/databriefs/db267pdf. Accessed 19 June 2017.
3. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32:2735–40.
4. Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, Biasi G, Norgren L. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg. 2009;37:1–19.
5. Prati P, Vanuzzo D, Casaroli M, Di Chiara A, De Biasi F, Feruglio GA, Touboul PJ. Prevalence and determinants of carotid atherosclerosis in a general population. Stroke. 1992;23:1705–11.
6. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD. For the North American symptomatic carotid endarterectomy trial collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med. 1998;339:1415–25.
7. European Carotid Surgery Trialists' Collaborative Group. MRC European carotid surgery trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet. 1991;337:1235–43.
8. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351:1379–87.
9. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;273:1421–8.
10. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363:1491–502.

11. North American Symptomatic Carotid Endaretectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325:445–53.
12. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351:1493–501.
13. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363:11–23.
14. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, Moore WS, Hill MD, Mantese VA, Clark WM, Timaran CH, Heck D, Leimgruber PP, Sheffet AJ, Howard VJ, Chaturvedi S, Lal BK, Voeks JH, Hobson RW 2nd. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374:1021–31.
15. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet. 2001;357:1729–37.
16. Diethrich E, Fogarty TJ, Zarins CK, Hopkins LN, Roubin GS, Wholey MH, Nimsky S, McKinlay S, Siami FS. CaRESS: carotid revascularization using endarterectomy or stenting systems. Tech Vasc Interv Radiol. 2004;7:194–5.
17. Gahremanpour A, Perin EC, Silva G. Carotid artery stenting versus endarterectomy: a systematic review. Tex Heart Inst J. 2012;39:474–87.
18. Hill MD, Brooks W, Mackey A, Clark WM, Meschia JF, Morrish WF, Mohr JP, Rhodes JD, Popma JJ, Lal BK, Longbottom ME, Voeks JH, Howard G, Brott TG, CREST Investigators. Stroke after carotid stenting and endarterectomy in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Circulation. 2012;126:3054–61.
19. Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG, CREST Investigators. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke. 2010;41:S31–4.
20. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X, EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med. 2006;355:1660–71.
21. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W, SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet. 2006;368:1239–47.
22. Timaran CH, Mantese VA, Malas M, Brown OW, Lal BK, Moore WS, Voeks JH, Brott TG, Investigators C () CREST Investigators. 2013 Differential outcomes of carotid stenting and endarterectomy performed exclusively by vascular surgeons in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). J Vasc Surg 57:303–308.
23. Zarins CK, White RA, Diethrich EB, Shackelton RJ, Siami FS, CaRESS Investigators. Carotid revascularization using endarterectomy or stenting systems (CaRESS): 4-year outcomes. J Endovasc Ther. 2009;16:397–409.
24. Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott T, Caplan LR, Day A, Goldstone J, Hobson RW 2nd, et al. Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the ad hoc committee, American Heart Association. Stroke. 1995;26:188–201.
25. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/

SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary <span class="“subtitle”>A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography 2011;57:1002–1044.

26. White CJ, Jaff MR. Catch-22: carotid stenting is safe and effective (Food and drug administration) but is it reasonable and necessary (Centers for Medicare and Medicaid Services)? J Am Coll Cardiol Intv. 2012;5:694–6.
27. US Food and Drug Administration. Meeting materials of the circulatory system device advisory panel; 2017. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm542254.htm. Accessed 19 June 2017: in Department of Health and Human Services.
28. Centers for Medicare and Medicaid Services. Decision memo for Percutaneous Transluminal Angioplasty (PTA) of the carotid artery concurrent with stenting (CAG-00085R3), p. 1–49. April 30, 2007. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=194&ver=16&NcaName=Percutaneous+Transluminal+Angioplasty+(PTA)+of+the+Carotid+Artery+Concurrent+with+Stenting+(3rd+Recon)&bc=BEAAAAAAEAAA&&fromdb=true. Accessed 19 June 2017: in CMS.gov, Centers for Medicare and Medicaid Services, p. 1–49.
29. Weiner S. “I Can’t afford that!”: dilemmas in the care of the uninsured and underinsured. J Gen Intern Med. 2001;16:412–8.
30. Lin PH, Barshes NR, Annambhotla S, Huynh TT. Prospective randomized trials of carotid artery stenting versus carotid endarterectomy: an appraisal of the current literature. Vasc Endovasc Surg. 2008;42:5–11.
31. Ricotta JJ 2nd, Malgor RD. A review of the trials comparing carotid endarterectomy and carotid angioplasty and stenting. Perspect Vasc Surg Endovasc Ther. 2008;20:299–308.
32. Alberts MJ, Publications Committee of WALLSTENT. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy (abstract 53). Stroke. 2001;32:325.
33. Alberts MJ, McCann R, Smith TP, Stack R, Roubin G, Schneck M, Haumschild D, Iyer S, Schneider Wallstent Endoprosthesis Clinical Investigators. A randomized trial of carotid stenting vs. endarterectomy in patients with symptomatic carotid stenosis: study design. J Neurovasc Dis. 1997;2:228–34.
34. Theron JG, Payelle GG, Coskun O, Huet HF, Guimaraens L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. Radiology. 1996;201:627–36.
35. Reimers B, Corvaja N, Moshiri S, Sacca S, Albiero R, Di Mario C, Pascotto P, Colombo A. Cerebral protection with filter devices during carotid artery stenting. Circulation. 2001;104:12–5.
36. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, Cremonesi A, Setacci C. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg. 2007;33:135–41. discussion 142-133.

Chapter 28
Management of Intracranial Stenosis

Chirantan Banerjee and Marc I. Chimowitz

Management of Intracranial Stenosis

Atherosclerotic stenosis of the major intracranial arteries (middle cerebral, basilar, intracranial internal carotid, and vertebral) is one of the most common causes of stroke worldwide and is associated with a high risk of recurrent stroke [1]. However, there have only been a few randomized clinical trials evaluating different therapeutic approaches for secondary prevention in patients with intracranial arterial stenosis. In this chapter, we will review and discuss the results of these trials and the different approaches to treating intracranial atherosclerotic disease (ICAD).

Antithrombotic Therapy: Anticoagulation Versus Aspirin

The first use of anticoagulation as treatment of ICAD was in 1955 when warfarin was used to treat basilar artery stenosis [2]. The efficacy of warfarin was initially compared with aspirin in a retrospective, multicenter study among patients with symptomatic 50–99% intracranial stenosis between 1985 and 1991 [3]. Fewer major vascular events occurred in the warfarin group as compared to aspirin. However, when the multicenter, double-blind, randomized trial Warfarin-Aspirin Recurrent Stroke Study (WARSS) compared warfarin (target international normalized ratio [INR] 1.4–2.8) to aspirin 325 mg/day in subjects with heterogeneous causes of stroke, there was no difference found in the rate of recurrent ischemic stroke, death, or major hemorrhage. Although more than half of the qualifying strokes in WARSS

C. Banerjee (✉) · M. I. Chimowitz
Department of Neurology, Stroke Division, Medical University of South Carolina, Charleston, SC, USA
e-mail: banerjeec@musc.edu; mchimow@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_28

were lacunar (1237 out of 2206), even in the subgroup of patients with large artery stenosis, there was no difference seen between the two groups [4].

The first randomized clinical trial focused on patients with ICAD was the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial. This was a multicenter, double-blind, randomized trial that compared warfarin (target INR 2–3) versus aspirin (1300 mg/day) in patients with 50–99% intracranial stenosis with TIA or stroke within 90 days of enrollment [5]. The trial was halted after 569 patients were enrolled because the warfarin arm had a significantly higher rate of major systemic hemorrhage and death. The primary endpoint in the trial was a combined endpoint of ischemic stroke, intracranial hemorrhage (ICH), and vascular death. Over a mean follow-up of 1.8 years, both groups had the same rate of the combined primary endpoint (22%). Recurrent ischemic stroke in the territory of the symptomatic vessel was also similar between the two arms. Subgroups of patients that were previously thought to benefit from anticoagulation such as severe (70–99%) stenosis, patients on antithrombotic therapy prior to the qualifying ischemic event, and those with stenosis in the posterior circulation did not benefit from warfarin in the WASID trial [6, 7]. In the warfarin arm, the percentage of time spent within the target INR was 63%, as compared to 94% compliance in the aspirin group [5]. INR <2 significantly increased risk of stroke, whereas INR >3 was associated with increased risk of hemorrhage.

Among Asian subjects with ICAD-related acute stroke (onset <48 h before enrollment) in the randomized, multicenter FISS-tris trial, anticoagulation with low-molecular-weight heparin nadroparin calcium was compared to aspirin 160 mg/day for lowering early recurrent stroke risk [6]. Subjects in both arms had similar outcomes at 10 days [6].

Antithrombotic Therapy: Other Antiplatelet Agents

Several antiplatelet medications have been shown to be effective for secondary stroke prevention in randomized, multicenter clinical trials after index noncardioembolic ischemic stroke or TIA. These include aspirin, clopidogrel, combination aspirin-extended release dipyridamole, cilostazol, and ticagrelor. However, none of them have been compared to each other or placebo in randomized trials specifically in patients with ICAD. There have however been a few studies comparing dual-antiplatelet therapy to monotherapy in patients with ICAD. In a sub-study of the CLopidogrel plus Aspirin for Infarction Reduction (CLAIR) trial [7, 8], ICAD patients with acute stroke (<=7 days prior to enrollment) were randomized to receive aspirin (75–160 mg/day) or clopidogrel (300 mg load on day 1, followed by 75 mg/day) plus aspirin (75–160 mg/day). Microembolic signals on transcranial Doppler examination, which is a known biomarker of high recurrent stroke risk in ICAD, were evaluated on day 2 and day 7 in the two groups. In the dual-antiplatelet therapy group, there was a lower rate of microembolic signals than patients on aspirin alone [7].

Further evidence in support of the combination of aspirin and clopidogrel when compared to aspirin alone for early secondary prevention of stroke comes from the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial that was conducted in China. In this trial, clopidogrel plus aspirin versus aspirin alone was initiated <24 h of symptom onset in high-risk patients with acute minor stroke or TIA [9]. In the dual antiplatelet treatment group, aspirin was stopped after 21 days. The primary endpoint was 90-day risk of any stroke (ischemic or hemorrhagic). CHANCE showed that the 90-day outcome was significantly lower in the dual-antiplatelet therapy arm, and a secondary subgroup analysis suggested that subjects with ICAD may benefit the most from combination therapy [10].

In another multicenter, double-blind study among Korean patients [11], those with acute symptomatic stenosis in the M1 segment of middle cerebral artery or basilar artery measured by TCD and MRA were randomized to dual therapy with cilostazol 200 mg/day and aspirin 100 mg/day or aspirin alone for 6 months. The progression of symptomatic ICAD as evaluated by MRA was significantly lower in the combination therapy group. There was no stroke recurrence in both groups. In a subsequent trial [12], the same entry criteria were used, and patients were randomized to combined aspirin (75–150 mg/day) plus cilostazol (100 mg twice daily) versus aspirin (75–150 mg/day) plus clopidogrel (75 mg/day). At 7 months, there was no significant difference in the progression of symptomatic ICAD evaluated by MRA or new ischemic lesions on MRI [12].

Taken as a whole, these studies comparing dual-antiplatelet therapy with aspirin alone suggest that short-term dual therapy may be more effective than aspirin alone for preventing microemboli, progression of stenosis, and stroke in patients with ICAD, but an adequately powered randomized trial comparing these treatments in subjects with ICAD is needed to provide more definite evidence. When dual antiplatelet treatment is used in this setting, it is typically limited to 90 days because of the increased risk of major hemorrhage with long-term combination aspirin and clopidogrel as seen in the CHARISMA [13] and MATCH [14] trials.

Management of Vascular Risk Factors

Hypertension, hyperlipidemia, smoking, and diabetes mellitus are modifiable risk factors of ICAD. The randomized, multicenter Perindopril PRotection aGainst REcurrent Stroke Study (PROGRESS) demonstrated that blood pressure lowering with perindopril with/without indapamide reduced the risk of stroke during 4 years of follow-up [15]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that low-density lipoprotein (LDL) cholesterol <1·81 mmol/L (70 mg/dL) was associated with an 18% relative reduction in stroke risk compared to a level >2·59 mmol/L (100 mg/dL) over almost 5 years [16]. Both PROGRESS and SPARCL trials however were not specific to patients with ICAD and included other stroke etiologies. We started to gain an understanding of the

prominent role of risk factor modification in secondary prevention with ICAD from sub-analyses of the WASID trial [17, 18]. Prior to WASID, the commonly held anecdotal hypothesis was to maintain a higher than normal blood pressure in patients with intracranial stenosis to maximize cerebral perfusion. This was dispelled when a WASID sub-study found that subjects with a mean systolic blood pressure >=140 mm Hg had a significantly higher rate of stroke, MI or vascular death during the 1.8 year follow-up (31% vs 18%, $p = 0.0005$) as compared to subjects with mean systolic blood pressure <140 mm Hg [18]. In another WASID analysis, when compared to patients with mean cholesterol <200 mg/dL, those with total mean cholesterol >200 mg/dL during follow-up had a higher risk of stroke, MI, or vascular death (26% vs 19%, $p = 0.02$) [19]. Among Chinese patients with asymptomatic MCA stenosis and increased LDL cholesterol (3.00–5.00 mmol/L; 116–193 mg/dL), the randomized, double-blind Regression of Cerebral Artery Stenosis (ROCAS) study found that patients randomized to simvastatin 20 mg/day versus placebo had significantly lower rates of all-cause mortality, any clinical events, subclinical brain infarcts, as well as progression of cerebral white matter lesions [20–22]. With regard to glycemic control in WASID, patients with a mean HbA1c ≥7% during follow-up had a higher rate of stroke, MI, or vascular death compared to those patients with mean HbA1c <7% (31% vs 20%), but this trend was not statistically significant ($p = 0.20$) [19], likely due to lack of a larger sample size and insufficient power.

In the WASID trial, risk factor control was done per usual standard of care at the time. There was only a modest improvement in risk factor profiles such as cholesterol and smoking in the cohort during follow-up [19]. After the above subgroup analyses showed significant reduction in recurrent stroke risk with reduction in blood pressure and cholesterol, aggressive medical management was incorporated in the Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial [17]. This incorporated targets for systolic blood pressure of <140 mm Hg (<130 mm Hg in diabetes patients), LDL <70 mg/dL and the use of a lifestyle modification program. The lifestyle modification program incorporated a treatment plan for physical activity, nutrition, weight management, and tobacco cessation [17].

Medical management and risk factor modification should begin early after the index stroke/TIA. Early initiation of treatments after a minor stroke or TIA in the prospective Early Use of Existing Preventive Strategies for Stroke (EXPRESS) study [23] was associated with an 80% reduction in the 3-month risk of recurrent stroke. Similarly, in the SOS-TIA study, early initiation of antihypertensive, antiplatelet, and statin drugs was associated with an 80% reduction in the 90-day stroke rate as predicted from ABCD2 scores [24]. Both of these studies, however, were not confined to patients with ICAD.

Endovascular Therapies for ICAD

Angioplasty emerged as a potential therapy for secondary stroke prevention in patients with ICAD in the 1980s. Its use was usually limited to patients with severe

>70% intracranial stenosis who had stroke/TIA despite being on antithrombotic therapy. No randomized multicenter clinical trial has evaluated angioplasty to other therapeutic approaches or intensive medical therapy. Most of the data on angioplasty in ICAD comes from retrospective, single-center, nonrandomized studies with heterogeneous entry criteria and a short duration of follow-up. Periprocedural stroke rates in these studies have been variable, ranging anywhere from <5% to as high as 50% [25–35]. Recently symptomatic and clinically unstable patients overall seemed to have higher periprocedural stroke rates. Angioplasty with or without stent placement in ICAD was studied in a Cochrane review [36]. Data from 79 open-label case series with three or more cases were included. Angioplasty showed an overall perioperative rate of stroke of 7.9%, perioperative death rate of 3.4%, and perioperative stroke or death of 9.5%. The Cochrane review concluded that although feasible, angioplasty with or without stenting carries a significant morbidity and mortality risk. More recent single-center series suggest that the periprocedural risk with submaximal angioplasty may be lower than previously reported [37, 38]. The main technical limitations of angioplasty include dissection, immediate elastic recoil of the artery, and residual stenosis following the procedure as well as restenosis in the intermediate to long term.

Around the time that the WASID trial results were published, the self-expanding Wingspan stent (Stryker Neurovascular) was approved under a humanitarian device exemption (HDE) by the Food and Drug Administration for use in patients with atherosclerotic intracranial arterial 50–99% stenosis who were refractory to medical therapy. Refractory to medical therapy was not defined and was largely interpreted in clinical practice to have occurred when a patient with 50–99% ICAD experienced a stroke or TIA while receiving antithrombotic therapy. Guided by findings from the WASID trial and the results of single-arm studies using the Wingspan stent [39–41], the randomized, multicenter NIH-funded SAMMPRIS trial was designed and funded by the National Institutes of Health (NIH). In SAMMPRIS, patients with a non-disabling stroke or TIA within the previous 30 days that was secondary to 70–99% stenosis of a major intracranial artery were randomized to percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan stent plus aggressive medical management versus treatment with aggressive medical management alone [42, 43]. After enrolling 451 of the planned 764 patients (59%) into the trial between November 2008 and April 2011, enrollment in the study was halted by NIH on the recommendation of the Data Safety Monitoring Board because of a significantly higher rate of 30-day stroke or death among subjects in the angioplasty and stenting arm, as compared with those treated with medical therapy alone (14.7% vs 5.8%). A large proportion of the periprocedural strokes that occurred within 30 days in the PTAS group (76%) occurred within 1 day of the procedure, and the rest occurred within 7 days. There were five fatal strokes within 30 days in the stenting arm. Symptomatic intracranial hemorrhage occurred in ten patients in the stenting group within 30 days of the procedure, whereas there were no hemorrhages in the medical management group in that period [42]. The observed rate of periprocedural stroke in the PTAS group was higher than expected from previously published Wingspan registries [39–41]. This was likely due to higher severity of stenosis and earlier window of treatment after an ischemic event (30 days), as well as a more

rigorous outcome adjudication process in SAMMPRIS [42, 43]. Periprocedural ischemic strokes were most often due to occlusion of perforating vessels, primarily noted in the basilar artery territory. Periprocedural hemorrhages were either subarachnoid hemorrhage attributed to wire perforation or delayed intraparenchymal hemorrhage due to reperfusion [44]. In the SAMMPRIS cohort, older age, diabetes, basilar artery stenosis, and nonsmoking status (smoking increases conversion of clopidogrel to its active metabolite [45]) were significantly associated with periprocedural stroke, whereas high degree of stenosis and clopidogrel load with an activated clotting time above the target range were risk factors associated with periprocedural intracranial hemorrhages [46]. A post hoc analysis that evaluated site and operator experience in SAMMPRIS found that the increased periprocedural risk was not due to operator inexperience [47].

The rate of stroke or death at 1 year in the PTAS group was significantly higher when compared to the medical management arm (20% vs 12%). This continued to remain significantly higher for the PTAS group compared with the medical management arm at a mean follow-up of 32 months (23% vs 15%) [43]. Although these long-term differences were primarily driven by the 30-day outcomes, the benefit was sustained over time as the rates of stroke and death beyond 30 days were similar between the two groups. In the SAMMPRIS trial, several patient characteristics were independently associated with a high risk of recurrent stroke despite aggressive medical management. These included an old infarct in the territory of the stenosis on baseline brain imaging, a new stroke presentation, and absence of statin use at enrollment [46].

In January 2015, based on the results of SAMMPRIS, the US FDA modified the Humanitarian Device Exemption approval for use of the Wingspan stent to patients who have had ≥2 strokes (not TIAs) despite aggressive medical management, whose most recent stroke occurred ≥7 days prior to planned PTAS with Wingspan, and who have 70–99% intracranial stenosis.

SAMMPRIS is not the only randomized trial that has shown that stenting is inferior to medical management for symptomatic intracranial stenosis. The industry-funded randomized, multicenter Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial was initiated soon after the start of SAMMPRIS and had similar patient inclusion criteria [48, 49]. VISSIT employed the PHAROS Vitesse balloon-expandable neurovascular stent system (Codman Neurovascular) as opposed to the self-expanding Wingspan stent used in SAMMPRIS. Medical management in the VISSIT trial had similar targets as SAMMPRIS, except the target for LDL cholesterol was <100 mg/dL as opposed to <70 mg/dL in SAMMPRIS. VISSIT trial enrollment was also halted early after 112 patients out of a planned 250 patients were enrolled. The rate of ischemic stroke or TIA at 30 days was 24.1% in the stent group as compared to 9.4% in the medical therapy arm. There were no intracranial hemorrhages in the medical therapy arm at 30 days, but 8.6% in the stent group suffered intracranial hemorrhage in the same period. The benefit of medical therapy persisted at 1 year, with 36.2% in the stenting group having a stroke or TIA, as opposed to 15.1% in the medical group.

Thus, evidence from both the SAMMPRIS and VISSIT trials does not support stenting of patients with ICAD. This holds true even in high-risk subgroups of ICAD patients because patients with the highest risk of stroke on medical therapy were also found to have the highest risk for stroke from stenting [50].

Surgical Therapy

Surgical augmentation of intracranial flow by means of extracranial to intracranial bypass surgery was studied as a therapeutic option for patients with symptomatic ICAD in the 1980s. In patients with extracranial carotid occlusion or intracranial carotid or middle cerebral artery stenosis, the international, randomized, multicenter extracranial to intracranial (EC-IC) bypass trial [51] compared extracranial to intracranial bypass (superficial temporal artery to middle cerebral artery) with medical therapy against medical therapy alone. The results were published in 1985, and over a 55-month follow-up with >1400 patients enrolled, surgery did not lower the rate of stroke and was associated with a worse outcome in patients with middle cerebral artery stenosis as compared to medical therapy [51]. After the trial, extracranial to intracranial bypass surgery no longer remained a therapeutic option for treatment for the secondary prevention of stroke in patients with symptomatic anterior circulation ICAD. A case series of patients who underwent superficial temporal to superior cerebellar artery bypass for vertebrobasilar insufficiency found a high perioperative complication rate [52].

Novel Treatment Approaches

Remote limb ischemic conditioning involves producing repetitive, transient noninjurious ischemia of a limb by inflating a BP cuff to 200 mm Hg for 5 min followed by reperfusion for 5 min and repeated for four to five cycles. This results in release of circulating mediators and neurogenic mechanisms that may increase cerebral blood flow [53, 54]. Two small randomized trials in China suggest that daily ischemic conditioning for 180–300 days lowers the risk of stroke in subjects with ICAD compared with medical management [55, 56].

Indirect revascularization surgery via encephaloduroarteriosynangiosis (EDAS) has also been described recently in symptomatic ICAD, with the rationale that while some patients with ICAD develop adequate leptomeningeal collaterals on their own, other patients who remain symptomatic can potentially benefit from the additional collaterals created as a result of the EDAS procedure. In a single-center study [57, 58], patients with symptomatic ICAD despite optimal medical therapy underwent indirect revascularization by EDAS. The probability of stroke-free survival at 2 years was 94.3%. There were no hemorrhages or stroke-related deaths

during follow-up. Careful patient selection employing additional imaging selection criteria for evidence of hypoperfusion and poor collateral flow may help select the patients most likely to benefit from such a procedure [58].

References

1. Gorelick P, Wong K, Bae H, Pandey D. Large artery intracranial occlusive disease, a large worldwide burden but a relatively neglected frontier. Stroke. 2008;39:2396–9.
2. Millikan CH, Siekert RG, Shick RM. Studies in cerebrovascular disease. III. The use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. Proc Staff Meet Mayo Clin. 1955;30:116–26.
3. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, Pessin MS, Weichel E, Sila CA, Furlan AJ, Kargman DE, Sacco RL, Wityk RJ, Ford G, Fayad PB. The warfarin-aspirin symptomatic intracranial disease study. Neurology. 1995;45:1488–93.
4. Mohr JP, Thompson JLP, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P, Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345:1444–51.
5. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG, Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352:1305–16.
6. Wong KS, Chen C, Ng PW, et al., FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol. 2007;6:407–13.
7. Wang X, Lin WH, Zhao YD, Chen XY, Leung TW, Chen C, Fu J, Markus H, Hao Q, Wong KS, CLAIR Study Investigators. The effectiveness of dual antiplatelet treatment in acute ischemic stroke patients with intracranial arterial stenosis: a subgroup analysis of CLAIR study. Int J Stroke. 2013;8(8):663–8.
8. Wong KSL, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, Han Z, Tan KS, Ratanakorn D, Chollate P, Zhao Y, Koh A, Hao Q, Markus HS, CLAIR study investigators. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9:489–97.
9. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC, CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9.
10. Liu L, Wong KS, Leng X, Pu Y, Wang Y, Jing J, Zou X, Pan Y, Wang A, Meng X, Wang C, Zhao X, Soo Y, Johnston SC, Wang Y, CHANCE Investigators. Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. Neurology. 2015;85(13):1154–62.
11. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke. 2005;36:782–6.
12. Kwon SU, Hong KS, Kang DW, et al. Efficacy and safety of combination antiplatelet therapies in patients with symptomatic intracranial atherosclerotic stenosis. Stroke. 2011;42:2883–90.
13. Bhatt DL, Fox KA, Hacke W, et al., CHARISMA investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706–17.
14. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ, MATCH investigators. Aspirin and clopidogrel compared with clopi-

dogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:331–7.
15. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033–41.
16. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
17. Turan TN, Lynn MJ, Nizam A, et al., SAMMPRIS Investigators. Rationale, design, and implementation of aggressive risk factor management in the Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial. Circ Cardiovasc Qual Outcomes. 2012;5:e51–60.
18. Turan TN, Cotsonis G, Lynn MJ, Chaturvedi S, Chimowitz M, Warfarin- Aspirin Symptomatic Intracranial Disease (WASID) Trial Investigators. Relationship between blood pressure and stroke recurrence in patients with intracranial arterial stenosis. Circulation. 2007;115:2969–75. https://doi.org/10.1161/CIRCULATIONAHA.106.622464.
19. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, Frankel M, Chimowitz MI, WASID Study Group. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology. 2007;69:2063–8. https://doi.org/10.1212/01.wnl.0000279338.18776.26.
20. Mok VC, Lam WW, Fan YH, Wong A, Ng PW, Tsoi TH, Yeung V, Wong KS. Effects of statins on the progression of cerebral white matter lesion: post hoc analysis of the ROCAS (Regression of Cerebral Artery Stenosis) study. J Neurol. 2009;256:750–7.
21. Fu JH, Mok V, Lam W, Wong A, Chu W, Xiong Y, Ng PW, Tsoi TH, Yeung V, Wong KS. Effects of statins on progression of subclinical brain infarct. Cerebrovasc Dis. 2010;30:51–6.
22. Mok VC, Lam WW, Chen XY, Wong A, Ng PW, Tsoi TH, Yeung V, Liu R, Soo Y, Leung TW, Wong KS. Statins for asymptomatic middle cerebral artery stenosis: the Regression of Cerebral Artery Stenosis study. Cerebrovasc Dis. 2009;28(1):18–25.
23. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJ, Bosch S, Alexander FC, Silver LE, Gutnikov SA, Mehta Z, Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population- based sequential comparison. Lancet. 2007;370:1432–42.
24. Lavallée PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6:953–60.
25. Higashida RT, Tsai FY, Halbach VV, Dowd CF, Smith T, Fraser K, Hieshima GB. Transluminal angioplasty for atherosclerotic disease of the vertebral and basilar arteries. J Neurosurg. 1993;78:192–8.
26. Clark WM, Barnwell SL, Nesbit G, O'Neill OR, Wynn ML, Coull BM. Safety and efficacy of percutaneous transluminal angioplasty for intracranial atherosclerotic stenosis. Stroke. 1995;26:1200–4.
27. Takis C, Kwan ES, Pessin MS, Jacobs DH, Caplan LR. Intracranial angioplasty: experience and complications. AJNR Am J Neuroradiol. 1997;18:1661–8.
28. Marks MP, Marcellus M, Norbash AM, Steinberg GK, Tong D, Albers GW. Outcome of angioplasty for atherosclerotic intracranial stenosis. Stroke. 1999;30:1065–9.
29. Connors JJ 3rd, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. J Neurosurg. 1999;91:415–23.
30. Nahser HC, Henkes H, Weber W, Berg-Dammer E, Yousry TA, Kuhne D. Intracranial vertebrobasilar stenosis: angioplasty and follow-up. AJNR Am J Neuroradiol. 2000;21:1293–301.
31. Alazzaz A, Thornton J, Aletich VA, Debrun GM, Ausman JI, Charbel F. Intracranial percutaneous transluminal angioplasty for arteriosclerotic stenosis. Arch Neurol. 2000;57:1625–30.

32. Gress DR, Smith WS, Dowd CF, Van Halbach V, Finley RJ, Higashida RT. Angioplasty for intracranial symptomatic vertebrobasilar ischemia. Neurosurgery. 2002;51:23–7. discussion 27–29.
33. Gupta R, Schumacher HC, Mangla S, Meyers PM, Duong H, Khandji AG, Marshall RS, Mohr JP, Pile-Spellman J. Urgent endovascular revascularization for symptomatic intracranial atherosclerotic stenosis. Neurology. 2003;61:1729–35.
34. Marks MP, Wojak JC, Al-Ali F, Jayaraman M, Marcellus ML, Connors JJ, Do HM. Angioplasty for symptomatic intracranial stenosis: clinical outcome. Stroke. 2006;37:1016–20.
35. Marks MP, Marcellus ML, Do HM, Schraedley-Desmond PK, Steinberg GK, Tong DC, Albers GW. Intracranial angioplasty without stenting for symptomatic atherosclerotic stenosis: long-term follow-up. AJNR Am J Neuroradiol. 2005;26:525–30.
36. Cruz-Flores S, Diamond AL. Angioplasty for intracranial artery stenosis. Cochrane Database Syst Rev. 2006;3:CD004133.
37. Dumont TM, Kan P, Snyder KV, Hopkins LN, Siddiqui AH, Levy EI. Revisiting angioplasty without stenting for symptomatic intracranial atherosclerotic stenosis after the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) study. Neurosurgery. 2012;71(6):1103–10.
38. Dumont TM, Sonig A, Mokin M, Eller JL, Sorkin GC, Snyder KV, Nelson Hopkins L, Levy EI, Siddiqui AH. Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective phase I study. J Neurosurg. 2016;125(4):964–71.
39. Bose A, Hartmann M, Henkes H, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. Stroke. 2007;38:1531–7.
40. Zaidat OO, Klucznik R, Alexander MJ, Chaloupka J, Lutsep H, Barnwell S, Mawad M, Lane B, Lynn MJ, Chimowitz M, NIH Multi-center Wingspan Intracranial Stent Registry Study Group. The NIH registry on use of the Wingspan stent for symptomatic 70–99% intracranial arterial stenosis. Neurology. 2008;70:1518–24.
41. Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard-Kienitz B, Hanel RA, Woo H, Rasmussen PA, Hopkins LN, Masaryk TJ, McDougall CG. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke. 2007;38:881–7.
42. Chimowitz MI, Lynn MJ, Derdeyn CP, et al., SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993–1003. https://doi.org/10.1056/NEJMoa1105335.
43. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014;383(9914):333–41.
44. Fiorella D, Derdeyn CP, Lynn MJ, et al. Detailed analysis of periprocedural strokes in patients undergoing intracranial stenting in stenting and aggressive medical Management for Preventing Recurrent stroke in intracranial stenosis (SAMMPRIS). Stroke. 2012;43:2682–8.
45. Bliden KP, Dichiara J, Lawal L, Singla A, Antonino MJ, Baker BA, Bailey WL, Tantry US, Gurbel PA. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. J Am Coll Cardiol. 2008;52:531–3.
46. Waters MF, Hoh BL, Lynn MJ, Kwon HM, Turan TN, Derdeyn CP, Fiorella D, Khanna A, Sheehan TO, Lane BF, Janis S, Montgomery J, Chimowitz MI, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial Investigators. Factors associated with recurrent ischemic stroke in the medical group of the SAMMPRIS trial. JAMA Neurol. 2016;73(3):308–15.
47. Derdeyn CP, Fiorella D, Lynn MJ, Barnwell SL, Zaidat OO, Meyers PM, Gobin YP, Dion J, Lane BF, Turan TN, Janis LS, Chimowitz MI, SAMMPRIS Trial Investigators. Impact of operator and site experience on outcomes after angioplasty and stenting in the SAMMPRIS trial. J Neurointerv Surg. 2013;5(6):528–33.

48. Zaidat OO, Castonguay AC, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, Gupta R, Kirshner H, Eliasziw M, Thomas Megerian J, Shetty S, Yoklavich Guilhermier M, Barnwell S, Smith WS, Gress DR, VISSIT Trial Investigators. Design of the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial in symptomatic intracranial stenosis. J Stroke Cerebrovasc Dis. 2013;22(7):1131–9.
49. Zaidat OO, Fitzsimmons B, Woodward B, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. 2015;313(12):1240–8.
50. Lutsep HL, Barnwell SL, Larsen DT, Lynn MJ, Hong M, Turan TN, Derdeyn CP, Fiorella D, Janis LS, Chimowitz MI, SAMMPRIS Investigators. Outcome in patients previously on antithrombotic therapy in the SAMMPRIS trial: subgroup analysis. Stroke. 2015;46(3):775–9.
51. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. N Engl J Med. 1985;313:1191–200.
52. Hopkins LN, Budny JL. Complications of intracranial bypass for vertebrobasilar insufficiency. J Neurosurg. 1989;70:207–11.
53. Chimowitz MI, Derdeyn CP. Endovascular therapy for atherosclerotic intracranial arterial stenosis: back to the drawing board. JAMA. 2015;313:1219–20.
54. Hess DC, Blauenfeldt RA, Andersen G, Hougaard KD, Hoda MN, Ding Y, Ji X. Remote ischaemic conditioning-a new paradigm of self-protection in the brain. Nat Rev Neurol. 2015;11(12):698–710.
55. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology. 2012;79:1853–61.
56. Meng R, Ding Y, Asmaro K, Brogan D, Meng L, Sui M, et al. Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. Neurotherapeutics. 2015;12(3):667–77.
57. Gonzalez NR, Dusick JR, Connolly M, Bounni F, et al. Encephaloduroarteriosynangiosis for adult intracranial arterial steno-occlusive disease: long-term single-center experience with 107 operations. J Neurosurg. 2015;123:654–61.
58. Gonzalez NR, Dusick JR, Connolly M, Bounni F, et al. Encephaloduroarteriosynangiosis for adult intracranial arterial steno-occlusive disease: long-term single-center experience with 107 operations. J Neurosurg. 2015;12:1–8.

Chapter 29
Counseling and Management of Patients with Intracranial Atherosclerosis Disease

Abdul R. Tarabishy, Maurice M. Miller, and Ansaar T. Rai

Management of "intracranial atherosclerotic disease" (ICAD) represents an evolving area of neurovascular medicine. A neurointerventionalist is often faced with ICAD either emergently as part of acute ischemic stroke (AIS) treatment or electively in a symptomatic but stable patient. This chapter presents a practical evidence-based guide on the management of ICAD patients.

Epidemiology

Counseling starts with an understanding of the epidemiology and natural history of this pathology. ICAD is an infrequent cause of stroke in the western population accounting for about 10% of AIS patients [1]. However, it is one of the most common causes of stroke worldwide and is associated with a higher risk of recurrent stroke compared with other ischemic stroke subtypes [1, 2]. ICAD is particularly prevalent in black, Asian, Hispanic, and Indian populations, and in some Arabic countries [2, 3]. It is the cause of 5–10% of strokes in whites, 15–29% in blacks, and 30–50% of strokes in Asians [1, 4]. The global burden of stroke from ICAD is likely to grow as populations continue to expand in regions most affected by this disease process [1, 2].

A. R. Tarabishy (✉)
Department of Radiology, West Virginia University, Morgantown, WV, USA
e-mail: artarabishy@hsc.wvu.edu

M. M. Miller · A. T. Rai
Department of Interventional Neuroradiology, West Virginia University, Morgantown, WV, USA
e-mail: mmiller@hsc.wvu.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_29

Risk Factors

The risk factors for ICAD include the typical risk factors for vascular disease, i.e., hypertension, diabetes mellitus, smoking, and hyperlipidemia [5]. The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial (discussed more in the treatment section) identified hypertension and hyperlipidemia as the most important modifiable risk factors associated with an increased risk of recurrent stroke in patients with ICAD [6]. In a study of asymptomatic patients with underlying risk factors for vascular disease, transcranial Doppler revealed about a 7% prevalence of middle cerebral artery (MCA) stenosis in patients with one risk factor rising to almost 30% in patients with four risk factors [7]. The major risk factors in the studied population were advancing age, hyperlipidemia, hypertension, and diabetes [7]. The three main hypothesized mechanisms of ICAD leading to AIS include hypoperfusion [8], artery-to-artery embolism [9], and plaque occlusion of a penetrating artery ostia [9].

Diagnostic Imaging

There has been significant progress in noninvasive high-resolution intracranial vascular imaging. Even though transcranial Doppler (TCD) [10] and intravascular ultrasound (IVUS) [11] have been studied, operator dependence for TCD and the invasive technical challenges associated with IVUS preclude them as optimal imaging tests. Vessel wall imaging with MRI can potentially assess the plaque itself [12] mitigating the problem of positive wall remodeling and may be useful in the future as technology evolves. At present, high-resolution CT and MR angiography have emerged as the preferred noninvasive means of assessing the cerebral vasculature [13], while catheter angiography remains the gold standard for more detailed and dynamic vascular analysis.

Assessment of cerebral tissue level perfusion provides a physiologic correlate to an anatomic abnormality and can add help assess the functional impact of a stenotic vessel. Acetazolamide-challenged SPECT CT is valuable in assessing regional cerebrovascular reserve (rCVR) in patients with intra- and extracranial atherosclerotic disease [14]. Acetazolamide-induced decrease in the rCVR in the vascular territory of interest unmasks the brain's dependence on collateral circulation indicating a functionally severe stenosis that is being maximally compensated.

Quantitative phase contrast MRA has been utilized to stratify patients with symptomatic vertebrobasilar disease based on the presence of normal or compromised distal blood flow [15]. To a similar degree, blood oxygen level-dependent (BOLD) MRI techniques can show reduced cerebrovascular reserve corresponding to severity of stenosis based on catheter angiography [16]. Perfusion imaging utilizing CT and MRI is another important tool in assessing hemodynamic insufficiency associated with intracranial stenosis [17, 18], when combined with a concurrently

performed CTA or MRA, these tests can yield simultaneous anatomic and functional information. Alexander et al. [19] demonstrated that lesions causing symptoms as a result of reduced perfusion have more favorable outcomes after stent placement.

Management

Management decisions are based on neurological presentation, age, comorbidities, and the degree of stenosis. Plaque morphology and downstream hemodynamics may be additional considerations [20] before planning an intervention. Morphology influences the embolic potential of an atherosclerotic plaque, and collateralization influences downstream hemodynamics [20]. The location of the stenotic lesion is also important as MCA atherosclerosis has been shown to confer a lower mortality than vertebrobasilar or internal carotid artery terminus lesions [21].

Outcomes on Medical Management

Optimum medical management remains an essential first step in the treatment of ICAD. This includes aggressive control of risk factors supplemented by antiplatelet therapy. Before going into the details of antiplatelet therapy, it is useful to consider the natural history of ICAD on optimized medical management:

- In the WASID trial [6], the recurrent stroke risk with severe symptomatic intracranial stenosis (≥70%) was as high as 23% at 1 year, despite medical therapy.
- In the GESICA study, the ischemic stroke or TIA rate was 38% in patients with a single large artery atherosclerotic disease (stenosis ≥50%) followed over 2 years with medical management [22].
- In a study with an almost 4-year mean follow-up, about 27% of the patients experienced an ischemic event if the stenosis was ≥50% [23].

Optimal Medical Management: Control of Risk Factors

Hypertension

Medical therapy in patients with cardiovascular disease is associated with reduced incidence of stroke [24]. The practice of maintaining higher blood pressure in patients with symptomatic stenosis of a major intracranial artery to protect against hypoperfusion and stroke is not supported by Turan et al. [25] that showed higher systolic and diastolic blood pressures were associated with increased risk of ischemic stroke overall and an increase in stroke in the territory of the stenotic vessel.

Systolic blood pressure (SBP) ≥140 mmHg predicted recurrent ischemic stroke in a multivariate analysis (hazard ratio 1.58, 95% CI 1.07–2.32).

Hypercholesterolemia

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) [24] was a prospective, double-blind international trial (n = 4731) randomized to either atorvastatin (80 mg) or placebo and showed significant reduced relative risks of stroke and TIA and TIA alone in the atorvastatin group.

Diabetes

The AHA has a class IIa level of evidence and C level recommendation [26] for screening in patients with stroke or TIA for diabetes and has a class I level B recommendation for treating diabetic patients with a stroke or TIA according to the ADA glycemic guidelines [26]. Detailed glycemic control addressing the two different types of diabetes is beyond the scope of this review. Pioglitazone (reduces insulin resistance in the liver and peripheral tissues) therapy among patients with a history of stroke who entered the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was associated with a 47% RR reduction in recurrent stroke and a 28% RR reduction in stroke, MI, or vascular death [27]. In the Barcelona-AsIA study [28] among patients with asymptomatic intracranial atherosclerosis, diabetes and metabolism syndrome significantly increased the risk of intracranial atherosclerosis.

Optimal Medical Management: Antiplatelet Therapy

Aspirin and Clopidogrel

Aspirin irreversibly inhibits cyclooxygenase-1 thereby inhibiting the production of thromboxane A_2, a potent activator of platelets [29]. Clopidogrel is a potent antithrombotic agent that irreversibly inhibits ADP-induced platelet aggregation by blocking the $P2Y_{12}$ surface receptors [30]. The primary aim of the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) [6] trial was to compare the efficacy and safety of warfarin with high-dose aspirin for preventing ischemic or hemorrhagic stroke and vascular death in patients with ≥50% stenosis of a major intracranial artery. The study was stopped early because of increased adverse outcomes among the group randomized to warfarin and also failed to show any difference in the primary endpoint of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke, 21.8% for warfarin versus 22.1% in the aspirin group ($P = 0.83$).

There is a lack of data regarding the use of dual antiplatelet therapy (DAPT) versus aspirin only for ICAD. There is indirect evidence extrapolated from extracranial carotid stenosis trials that may have some bearing on the role of antiplatelet

therapy in stroke prevention from ICAD. The CHANCE [31] trial was a randomized, double-blind, placebo-controlled trial conducted in 114 centers in China randomizing 5170 patients with 24 h of minor stroke or TIA to either clopidogrel plus aspirin or placebo plus aspirin. The study found a reduced stroke rate of 8.2% in the clopidogrel plus aspirin group versus a stroke rate of 11.7% in the aspirin-only group (OR 0.68, 95%CI 0.57–0.81, $p < 0.001$) with a similar rate of hemorrhage (0.3%) in each group and concluded that in patients with TIA or minor stroke treated within 24 h of symptoms onset, DAPT was superior to aspirin alone in reducing the risk of stroke without increasing the risk of hemorrhage [31]. Clopidogrel plus aspirin was also superior to aspirin alone in reducing microembolic signals in the CLAIR trial in patients with AIS or TIA who had symptomatic ICAD [32]. A similarly designed trial evaluating Clopidogrel plus aspiring versus aspirin alone (CARESS) for symptomatic extracranial carotid stenosis showed DAPT to be more effective than aspirin alone in reducing asymptomatic microembolization [33].

On the other hand, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial [34], which was a randomized, double-blind, placebo-controlled trial that compared clopidogrel plus aspirin versus aspirin alone in 3020 patients who had a symptomatic lacunar (perforator artery) infarction confirmed by magnetic resonance imaging within 6 months of onset, failed to show any difference in the risk of recurrent between the two groups, but DAPT was associated with a significantly higher major bleeding rate than the aspirin monotherapy [34]. Similarly, the MATCH trial [35], which randomized 7599 patients within 3 months of ischemic stroke or TIA to clopidogrel plus aspirin versus clopidogrel alone, failed to show a significant benefit for DAPT over monotherapy for the primary composite endpoint of ischemic stroke, myocardial infarction, vascular death, or hospitalization for cerebral or systemic ischemia. The MATCH trial did not show a significant difference in fatal bleeding or symptomatic intracranial hemorrhage, but there was a significant risk of life-threatening bleedings with DAPT [35]. The SPS3 and the MATCH trials did not exclusively focus on patients with documented ICAD but primarily on those with lacunar infarcts. It is possible that symptomatic ICAD (70–99% stenosis) has a significantly higher risk of recurrent ischemic stroke than lacunar causes of stroke, and therefore the benefits of DAPT on recurrent ischemic stroke prevention in ICAD may outweigh the potential increased risk of major bleeding.

Cilostazol

Cilostazol (a phosphodiesterase-3 inhibitor) is classified as an antiplatelet agent because of its inhibitory effects on platelet aggregation induced by collagen, 5'-adenosine diphosphate, epinephrine, and arachidonic acid. However, unlike other antiplatelet agents, it not only inhibits platelet function but also improves endothelial cell function [36]. In the Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS-2) [37], a randomized, double-blind, multicenter clinical trial conducted at 20 centers in 4 Asian countries, combination antiplatelet therapies were compared for efficacy in preventing the progression of symptomatic ICAD among 457 AIS patients with symptomatic stenosis in the MCA or in the basilar artery. Patients were randomized to

either the aspirin (75–150 mg daily) plus cilostazol (100 mg twice daily) versus clopidogrel 75 mg daily. Although the trial failed to show a significant difference in preventing progression of ICAD and new ischemic lesions between the two combination antiplatelet therapies, the overall cardiovascular event rate (nonfatal stroke, nonfatal myocardial infarction, and vascular death) in this study (5.5%) was significantly lower than in the WASID trial, perhaps due to the extensive use of statins and aggressive risk factor control. A longer observation study of cilostazol, CATHARSIS [38], demonstrated that progression of ICAD during the 2-year observation period was less frequent than previously reported in stroke patients on antiplatelet agents after the acute phase. A possible explanation could be the adequate control of risk factors and exclusion of patients within 2 weeks of an acute stroke. The results of the CATHARSIS trial suggested a potential utility of pharmacotherapies with cilostazol plus aspirin as well as of strict control of risk factors for the management of symptomatic ICAD.

Endovascular Therapy: Indications and Techniques

While medical management remains the mainstay of ICAD treatment, randomized trials as early as WASID indicate that stroke risk in ICAD patients may be high enough to justify consideration for endovascular intervention.

Stenting for ICAD

- The "Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis" (SAMMPRIS) [39] trial showed that aggressive medical therapy alone was superior to aggressive medical therapy plus angioplasty and stent placement with an absolute difference of 8.9% at 30 days and 9.0% at 3 years in the primary outcome (stroke or death within 30 days after enrollment or after the revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days). The device used in the trial was the Gateway® angioplasty balloon and the Wingspan® self-expanding stent. Following the conclusion of the trial, the FDA revised its indications for ICAD (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm): Wingspan® is now approved only for patients who are between 22 and 80 years old *and* who meet *all* of the following criteria:
  - Who have had two or more strokes despite aggressive medical management.
  - Whose most recent stroke occurred more than 7 days prior to planned treatment with Wingspan.
  - Who have 70–99% stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes.
  - Who have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is used to measure the degree of disability in stroke patients. Lower scores indicate less disability.

- The Wingspan stent system should not be used for the treatment of stroke with an onset of symptoms within 7 days or less of treatment or for the treatment of transient ischemic attacks (TIA).

Case 1

A 74-year-old gentleman presented with acute aphasia; imaging showed high-grade stenosis of the mid-left middle cerebral artery with accompanying significant perfusion abnormalities characterized by markedly increased mean transit time over the entire left middle cerebral distribution (Fig. 29.1). His symptoms of aphasia and confusion were also pressure-dependent, making him symptomatic whenever his blood pressure dropped. This patient failed best medical therapy. The patient successfully underwent angioplasty followed by stenting.

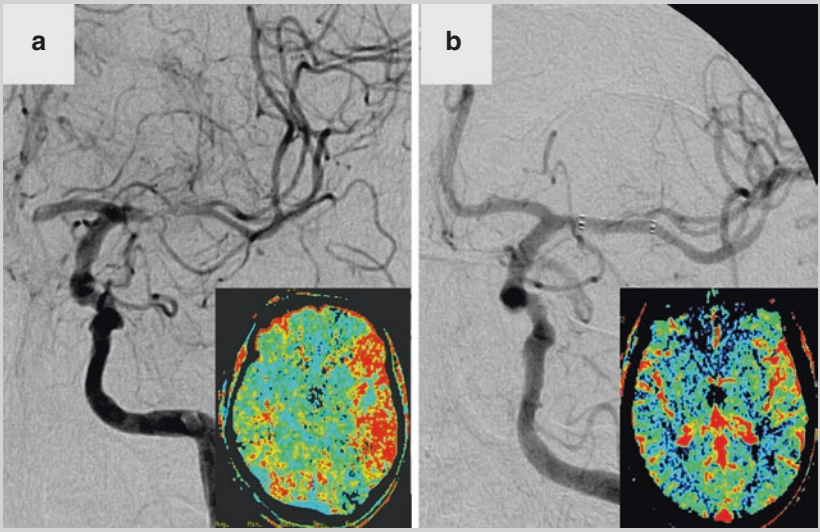


Fig. 29.1 ICAD presenting with symptomatic stenosis. 74 M presented with acute aphasia. (**a**) AP DSA projection showed high-grade stenosis of the mid-left middle cerebral artery. A: DSA AP projection shows severe irregular left M1 stenosis. Inset A: mean transit time (MTT) perfusion map demonstrates an accompanying significant perfusion abnormalities characterized by markedly increased mean transit time over the entire left middle cerebral distribution. (**b**) Post-angioplasty and stenting with 3.5 × 12 Wingspan. Inset B: improved perfusion with normalization on the MTT map with symmetric perfusion to the left MCA

- The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) [40] trial was a prospective, nonrandomized, multicenter phase I trial of a bare metal stent (Neurolink, Guidant Corp, Menlo Park, CA, USA) for symptomatic single artery intracranial stenosis of >50%. At 30 days, 6.6% of the patients had a stroke, and no deaths occurred, and 7.3% of the patients had a stroke later than 30 days. Despite 95% initial technical success rates, angiographic restenosis of >50% was observed in almost one-third of the patients.

The FDA granted a humanitarian device exemption for treatment of significant symptomatic intracranial stenosis by balloon angioplasty and stent placement.

- The VISSIT Intracranial Stent Study for Ischemic Therapy [41] showed that the use of a balloon-expandable stent for 70–99% intracranial stenosis resulted in an increased 12-month risk of added stroke or TIA in the same territory and increased 30-day risk of any stroke or TIA compared to the same aggressive medical therapy regimen used in the SAMMPRIS trial. The trial results did not support the results of a balloon-mounted stent for ICAD.
- As mentioned previously, Asians have a higher incidence of ICAD and large-vessel strokes secondary to underlying ICAD. Data from Asian countries favors early endovascular therapy in symptomatic patients [42]. The Hong Kong Society of Interventional and Therapeutic Neuroradiology endorses intracranial angioplasty and stenting for patients with ≥70% stenosis who are symptomatic despite medical therapy [43]. They also advocate performance of these procedures in high-volume centers with experienced operators.
- ICAD and large-vessel strokes: intracranial angioplasty and stenting are currently not approved in the USA for AIS secondary to a large-vessel occlusion. A small single-center study [44] for ICAD patients presenting as large-vessel strokes reported comparable safety and functional outcomes with angioplasty and stenting to achieve revascularization when compared with non-ICAD large-vessel strokes.

Case 2

A 55-year-old gentleman presented with acute basilar artery occlusion (Fig. 29.2). On the first day, recanalization was achieved with tPA and clot retrieval. The vessel recanalized afterward and improved after overnight heparin, and then angioplasty was performed on post-intervention day 3 followed by stent placement.

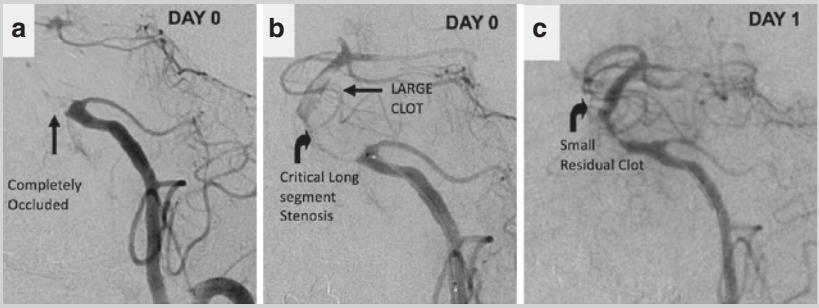


Fig. 29.2 ICAD presenting as large vessel stroke. 55 M presented with acute basilar artery occlusion. AP projections of DSA runs performed at different time points. (**a**): Acute basilar artery occlusion. (**b**): Recanalization after tPA, mechanical thrombectomy with angioplasty. (**c**): Overnight heparin. (**d**): Third day preintervention. (**e**): 3 × 9 mm angioplasty on day 3 and then stent placement (3.5 × 15 Wingspan). (**f**): Coronal view of a post stenting CT

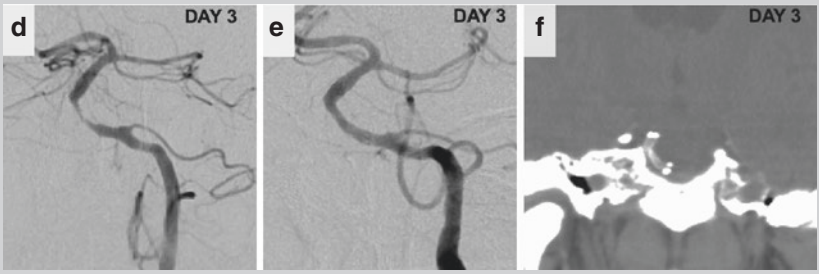


Fig. 29.2 (continued)

Angioplasty Alone

Intracranial angioplasty without stent placement is technically less challenging and could be a first-line endovascular option for ICAD. Multiple studies have reported the technical safety and low complication rate of primary intracranial angioplasty [45, 46, 47]. Marks et al. [46] described a 91% success rate with primary angioplasty and an annual rate of 3% for strokes in the territory appropriate to the site of angioplasty over a mean follow-up of 35.4 years. One important contribution to the safety of balloon angioplasty was the concept of "submaximal angioplasty" first promoted by Connors et al. [48], by a modified technique of slight undersizing and slow prolonged inflation. Another worthwhile consideration was hypothesized by Mori et al. [49] regarding morphology and its effect on lesion response to angioplasty. The study categorized atherosclerotic lesions as short, concentric and <5 mm long (Mori A), 5–10 mm long and possibly eccentric (Mori B), and >10 mm with excessive tortuosity (Mori C) (Fig. 29.3). As predicted, the paper found higher rates of death and ipsilateral stroke for longer and more tortuous lesions.

Summary

Optimizing management of intracranial atherosclerosis (Fig. 29.4) is an evolving aspect of neurovascular care in which medical management remains the mainstay of treatment. Endovascular therapy is reserved for patients who fail best medical management with adequate control of associated risk factors and despite dual antiplatelet therapy. Primary submaximal angioplasty is a safe first-line endovascular treatment followed by stenting if necessary.

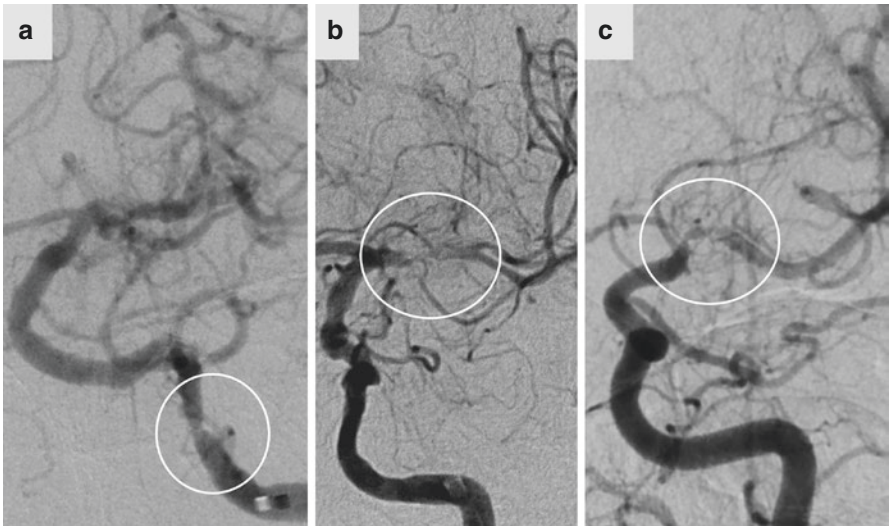


Fig. 29.3 Classification of stenosis based on lesion length (Mori Classification). (**a**) (Mori A): short, concentric, and <5 mm long. (**b**) (Mori B): 5–10 mm long and possibly eccentric. (**c**) (Mori C): >10 mm with excessive tortuosity

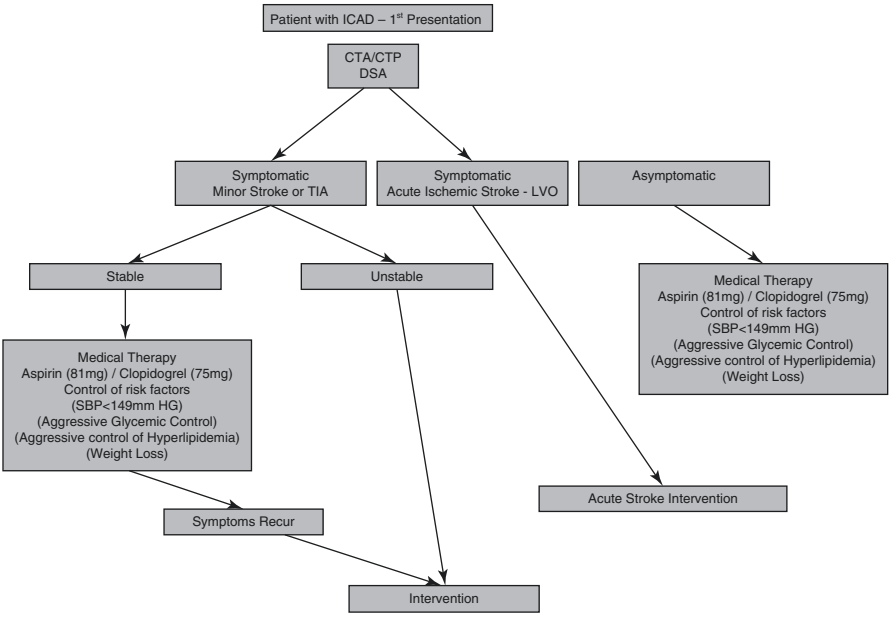


Fig. 29.4 Proposed management algorithm for a patient with intracranial atherosclerotic disease. *CTA/CTP* CT angiogram and perfusion imaging, *DSA* digital subtraction angiography. Stable: resolved TIA or minor stroke. Unstable: recurring labile symptoms that could be blood pressure-dependent symptoms

References

1. Gorelick PB, Wong KS, Bae HJ, et al. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke. 2008;39(8):2396–9.
2. Wong LK. Global burden of intracranial atherosclerosis. Int J Stroke. 2006;1(3):158–9.
3. Sacco RL, Kargman DE, Gu Q, et al. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995;26(1):14–20.
4. De Silva DA, Woon FP, Lee MP, et al. South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. Stroke. 2007;38(9):2592–4.
5. Rincon F, Sacco RL, Kranwinkel G, et al. Incidence and risk factors of intracranial atherosclerotic stroke: the Northern Manhattan Stroke Study. Cerebrovasc Dis. 2009;28(1):65–71. https://doi.org/10.1159/000219299.
6. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352(13):1305–16.
7. Wong KS, Ng PW, Tang A, et al. Prevalence of asymptomatic intracranial atherosclerosis in high-risk patients. Neurology. 2007;68(23):2035–8.
8. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. Ann Neurol. 2011;69(6):963–74.
9. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology. 1989;39(9):1246–50.
10. Alexandrov AV, Sloan MA, Tegeler CH, et al. Practice standards for transcranial Doppler (TCD) ultrasound. Part II. Clinical indications and expected outcomes. J Neuroimaging. 2012;22(3):215–24.
11. Hussain AS, Hussain NS. Intravascular ultrasound for intracranial and extracranial carotid artery stent placement. Cureus. 2016;8(8):e732. https://doi.org/10.7759/cureus.732.
12. Turan TN, Bonilha L, Morgan PS, et al. Intraplaque hemorrhage in symptomatic intracranial atherosclerotic disease. J Neuroimaging. 2011;21(2):e159–61.
13. Bash S, Villablanca JP, Jahan R, et al. Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. AJNR Am J Neuroradiol. 2005;26(5):1012–21.
14. Ozgur HT, Kent Walsh T, Masaryk A, et al. Correlation of cerebrovascular reserve as measured by acetazolamide-challenged SPECT with angiographic flow patterns and intra- or extracranial arterial stenosis. AJNR Am J Neuroradiol. 2001;22(5):928–36.
15. Amin-Hanjani S, Du X, Zhao M, et al. Use of quantitative magnetic resonance angiography to stratify stroke risk in symptomatic vertebrobasilar disease. Stroke. 2005;36(6):1140–5.
16. Donahue MJ, Dethrage LM, Faraco CC, et al. Routine clinical evaluation of cerebrovascular reserve capacity using carbogen in patients with intracranial stenosis. Stroke. 2014;45(8):2335–41.
17. Dubow JS, Salamon E, Greenberg E, et al. Mechanism of acute ischemic stroke in patients with severe middle cerebral artery atherosclerotic disease. J Stroke Cerebrovasc Dis. 2014;23(5):1191–4.
18. Jeon P, Kim BM, Kim DI, et al. Emergent self-expanding stent placement for acute intracranial or extracranial internal carotid artery dissection with significant hemodynamic insufficiency. AJNR Am J Neuroradiol. 2010;31(8):1529–32.
19. Alexander MD, Meyers PM, English JD, et al. Symptom differences and pretreatment asymptomatic interval affect outcomes of stenting for intracranial atherosclerotic disease. AJNR Am J Neuroradiol. 2014;35(6):1157–62.
20. Leng X, Wong KS, Liebeskind DS. Evaluating intracranial atherosclerosis rather than intracranial stenosis. Stroke. 2014;45(2):645–51.
21. Komotar RJ, Kellner CP, Raper DM, et al. Update on the natural history of intracranial atherosclerotic disease: a critical review. World J Radiol. 2010;2(5):166–71.
22. Mazighi M, Tanasescu R, Ducrocq X, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66(8):1187–91.

23. Marzewski DJ, Furlan AJ, St Louis P, et al. Intracranial internal carotid artery stenosis: long-term prognosis. Stroke. 1982;13(6):821–4.
24. Huisa BN, Stemer AB, Zivin JA. Atorvastatin in stroke: a review of SPARCL and subgroup analysis. Vasc Health Risk Manag. 2010;6:229–36.
25. Turan TN, Cotsonis G, Lynn MJ, et al. Relationship between blood pressure and stroke recurrence in patients with intracranial arterial stenosis. Circulation. 2007;115(23):2969–75.
26. 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(7):2160–236.
27. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–89.
28. Lopez-Cancio E, Dorado L, Millan M, et al. The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study: prevalence and risk factors. Atherosclerosis. 2012;221(1):221–5.
29. Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res. 2003;110(5–6):255–8.
30. Herbert JM, Savi P. P2Y12, a new platelet ADP receptor, target of clopidogrel. Semin Vasc Med. 2003;3(2):113–22.
31. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9.
32. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9(5):489–97.
33. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111(17):2233–40.
34. Investigators SPS, Benavente OR, Hart RG, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012;367(9):817–25.
35. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9431):331–7.
36. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. Atheroscler Suppl. 2005;6(4):3–11.
37. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke. 2005;36(4):782–6.
38. Uchiyama S, Sakai N, Toi S, et al. Final results of Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis (CATHARSIS). Cerebrovasc Dis Extra. 2015;5(1):1–13.
39. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365(11):993–1003.
40. Investigators SS. Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): study results. Stroke. 2004;35(6):1388–92.
41. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. 2015;313(12):1240–8.
42. Tang CW, Chang FC, Chern CM, et al. Stenting versus medical treatment for severe symptomatic intracranial stenosis. AJNR Am J Neuroradiol. 2011;32(5):911–6.
43. Yu SC, Cheng HK, Cheng PW, et al. Angioplasty and stenting for intracranial atherosclerotic stenosis: position statement of the Hong Kong Society of Interventional and Therapeutic Neuroradiology. Hong Kong Med J. 2013;19(1):69–73.

44. Yoon W, Kim SK, Park MS, et al. Endovascular treatment and the outcomes of atherosclerotic intracranial stenosis in patients with hyperacute stroke. Neurosurgery. 2015;76(6):680–6. discussion 86.
45. McTaggart RA, Marks MP. The case for angioplasty in patients with symptomatic intracranial atherosclerosis. Front Neurol. 2014;5:36. https://doi.org/10.3389/fneur.2014.00036.
46. Marks MP, Marcellus M, Norbash AM, et al. Outcome of angioplasty for atherosclerotic intracranial stenosis. Stroke. 1999;30(5):1065–9.
47. Nahser HC, Henkes H, Weber W, et al. Intracranial vertebrobasilar stenosis: angioplasty and follow-up. AJNR Am J Neuroradiol. 2000;21(7):1293–301.
48. Connors JJ 3rd, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. J Neurosurg. 1999;91(3):415–23.
49. Mori T, Fukuoka M, Kazita K, et al. Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty. AJNR Am J Neuroradiol. 1998;19(8):1525–33.

Chapter 30
Imaging Selection of Acute Ischemic Stroke

Anthony D. Kuner and Howard A. Rowley

Time Versus Imaging-Based Stroke Triage

When a patient presents with the signs and symptoms of an acute ischemic stroke, it is crucial to make the correct diagnosis and determine the most appropriate course of therapy in a rapid but accurate manner. The purpose of an acute stroke workup algorithm is to identify the patients that would benefit from thrombolysis or thrombectomy while excluding those in whom these interventions would be futile or harmful.

Whether based on clinical assessment or imaging, the acute stroke assessment attempts to quantify the volume of likely irreversible "core" infarct and identify any ischemic tissue that is at risk of infarction if left untreated (i.e., "penumbra"). Reperfusion of the penumbra can reduce the loss of neurologic function, while restoration of flow to the infarcted core tissue provides no benefit and can result in parenchymal hemorrhage. The potential benefit of penumbra revascularization decreases with time in a nonlinear fashion [1]. Therefore, the acute stroke evaluation must provide a rapid but accurate assessment.

Traditionally, candidacy for intravenous thrombolytic therapy has been determined using a time-based method of evaluation and non-contrast CT features. This approach is based on the assumption that the degree of tissue ischemia can be estimated by the time elapsed from symptom onset. There are, however, significant limitations with this method. Using time as a surrogate measure for tissue infarction operates on the false assumptions that ischemic infarction starts at the time of symptom onset and that all strokes progress at the same rate. This method

A. D. Kuner · H. A. Rowley (✉)
Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: akuner@uwhealth.org; hrowley@uwhealth.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_30

specifically excludes individual factors that influence infarction including the presence or absence of a large vessel occlusion and collateral flow, among others. Studies evaluating the determinants of final infarct size have shown that time alone does not accurately predict final infarct volume and thus is a poor predictor of patient outcome [2]. Time-based stroke assessment is overly simplistic and insufficient in the current era of stroke intervention, driving the need for imaging-based triage.

The presence of a proximal large vessel occlusion (LVO) has recently emerged as one of the most important factors in determining how a patient is best treated for ischemic stroke [3]. It is now clear that properly selected patients with this type of vascular event have better outcomes with intra-arterial intervention rather than with intravenous thrombolysis alone [4]. It has also been established that the presence or absence of an LVO cannot accurately be predicted based only on clinical assessment, even when utilizing an NIHSS cutoff threshold. Imaging studies are needed to accurately make this diagnosis [3]. Vascular imaging not only accurately detects a thrombus amenable to endovascular intervention but also provides additional details including thrombus length, location, feasible access routes, and the degree of collateral flow. These additional factors have been shown to influence the effectiveness of a particular stroke therapy in a given patient [2, 5–8]. Consequently, the diagnostic and prognostic information obtained with the use of neuroimaging have significantly improved patient outcomes.

There are currently several accepted imaging pathways to the evaluation of the acute ischemic stroke patient, and the optimal methods are an ongoing area of research and debate. The benefits and limitations of the imaging modalities and techniques will be discussed in detail in the following sections.

Considerations and Contraindications to Intra-arterial Therapy

Given the heterogeneity of recent positive clinical trials supporting the use of intra-arterial mechanical thrombectomy, there are somewhat varied patient selection criteria [9–15]. Despite these differences, all of the current evidence supporting the intra-arterial treatment of acute ischemic stroke converges on the presence of a large-vessel occlusion. An appropriate and accessible endovascular target must be identified to consider intra-arterial therapy.

Additionally, it is generally accepted that patients with a large preprocedural infarct core volume (70–100 mL) will have a poor outcome regardless of reperfusion, and thus intra-arterial therapy would be futile in these patients [16]. The imaging methods to determine the size of the infarct core are multiple and the subject of debate. MRI diffusion-weighted sequences (with quantitative ADC maps) are considered optimal for detection of acute ischemia, but given the practical considerations, CT metrics are now more commonly employed in the emergency setting.

The infarct can be directly visualized or inferred from perfusion imaging and/or collateral assessment [17]. The ideal intra-arterial candidate will have a proximal large-vessel intracranial arterial occlusion and a small infarct size with large penumbra. Automated post-processing methods using quantitative thresholds to objectively estimate penumbra are increasingly available and considered well supported using trial data [18].

Intra-arterial therapy is also supported in the setting of a tandem carotid stenotic lesion located in the carotid artery in the neck. The proximal carotid lesion can be initially treated with angioplasty and stenting prior to treatment of the more distal intracranial vessel occlusion [17].

Evolving Considerations in Triage and Intra-arterial Therapy

There are many factors entering into the decision-making process for intra-arterial stroke therapy, and current evidence leaves room for several topical debates. While mechanical thrombectomy within 6 h or less of symptom onset was first shown to be beneficial in multiple pivotal trials, positive results at later timeframes (e.g., 6–24 h) have only recently become available [9–15]. Positive results from the DAWN and CRISP trials now support late treatment using advanced imaging, with a level 1A evidence-based recommendation from the American Heart Association. Time from symptom onset is heterogeneous in the currently completed trials, and more data are needed before firm recommendations will be made in the sub-6 h window [18, 19].

Another area still incompletely understood is the role of patient age. An upper age limit has been implemented in some but not all of the trials supporting the use of intra-arterial therapy. There has been no significant difference in the outcomes of these groups, and thus, exclusion of a patient from endovascular therapy on age alone is not currently warranted [20]. Some analyses have even suggested a relatively greater benefit for older patients (above 80–85 years), suggesting there should be no arbitrary older age cutoff. Data for patients at the younger and pediatric end of the age spectrum also remains incompletely assessed [21].

There is also debate regarding the optimal modality for stroke triage – CT versus MRI. Both are excellent options, capable of providing the critical "4Ps of stroke imaging" in 10 min or less: comprehensive assessment of the parenchyma, pipes, perfusion, and penumbra [22]. Given the recent positive endovascular trials, which predominantly used CT, and the practical limitations of MRI in most facilities (screening, 24/7 access, length of exam, and reader comfort/preferences), CT has become the dominant triage modality. MRI tends to play a larger role in late-arriving patients, follow-up after the acute phase, in pediatric patients (avoiding radiation), and in posterior fossa ischemia.

Further investigation of these factors will play a role in selection criteria for patients who are candidates for intra-arterial intervention in the future.

Imaging Triage Using Non-contrast CT

Evaluation of the stroke patient with non-contrast (native) CT remains the initial step in most imaging-based workup algorithms. The study is fast, readily available, and an excellent way to differentiate ischemic from hemorrhagic stroke. The examination can also assess for classic stroke mimics such as intracranial neoplasm.

In the setting of acute ischemic stroke, the non-contrast CT examination can be used to assess for ischemic changes in an attempt to assess the size of the infarct. In order to improve the reliability of this type of assessment, the Alberta Stroke Program Early CT Score (ASPECTS) was developed [23]. ASPECTS is a 10-point scoring system that assesses for evidence of ischemic changes in the distribution of the MCA (Fig. 30.1). This offers a reproducible and quantitative method to assess the extent of early ischemic changes in stroke. It has been shown that those with low

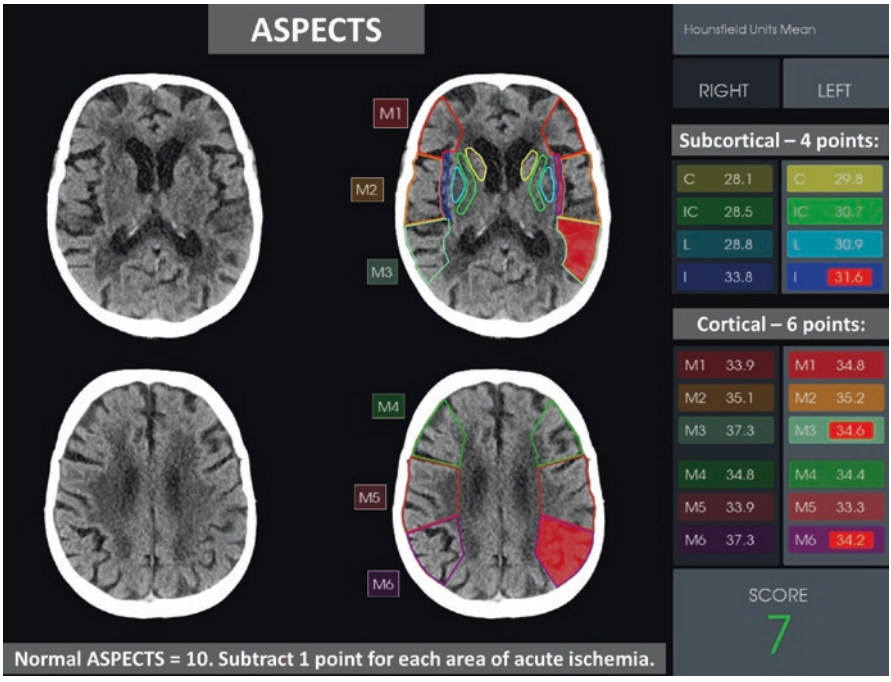


Fig. 30.1 ASPECTS (Alberta Stroke Program Early CT Score), acute left MCA ischemia. On all 5 mm non-contrast axial images from basal ganglia to the centrum semiovale, four subcortical areas (caudate, internal capsule, lentiform nucleus, and insula) and six MCA sectors (M1–M6) are reviewed for signs of low attenuation suggesting acute MCA ischemia. A normal scan or one with only old lesions receives ASPECTS = 10. A point is subtracted for each of the ten areas showing acute changes, with low scores predicting less favorable outcome. Software packages are being developed to automate ASPECTS scoring, as shown here (ASPECTS = 7) (RAPID software images modified from PD Dr. Med. Carlo Cereda Medico Caposervizio, Neurocentro (EOC) della Svizzera Italiana, Stroke Center, Servizio di Neurologia, Ospedale Civico, Lugano, Switzerland)

ASPECTS scores (approximately 7 or less) have a sharp increase in dependence and death. Routine use of the scale for "stroke codes" is recommended to help align decisions with clinical trials, to provide shorthand communication among the stroke team, and to improve documentation. Although ASPECTS creates a reproducible method to assess the acute stroke patient, the method is intrinsically limited by the low sensitivity of CT to early ischemic changes. Machine learning and artificial intelligence methods are being introduced to provide preliminary automated ASPECT scoring.

The finding of a hyperdense artery sign (HDAS; or HDMCA if middle cerebral artery) on non-contrast CT can also give evidence for thrombus presence and length. Thin section images and reconstructions improve the sensitivity and specificity compared to 5 mm sections. However, sensitivity of detection is only about 70% in proven clots, likely due to variable clot composition and state of retraction. Once detected, the HDAS indicates LVO and predicts intravenous TPA alone will not adequately recanalize the vessel – so immediately the patient is moved into IA triage. Even when proceeding to IA therapy, multiple trials and most neurovascular experts agree that, if the patient is a good IV TPA candidate, TPA be immediately given while IA triage decisions are finalized and the angio suite is prepared. This is based on the proven utility of IV TPA in improving stroke outcomes in patients screened without consideration of vascular data and may theoretically have the advantage of partial clot lysis and preservation of tenuous collaterals during the bridge from IV to IA therapy.

The major limitation of non-contrast CT in the current era of stroke treatment, however, is the lack of direct assessment of the intracranial vasculature. A large-vessel occlusion (LVO) is a prerequisite for endovascular therapy, and non-contrast CT is inadequate for definitive confirmation of this finding. Additionally, there is no information regarding collateral flow, perfusion, or penumbra.

CT Angiography and CT Perfusion: Benefits and Limitations

CTA Benefits

As discussed in the previous sections, assessment of the vascular system has become an essential part of the acute stroke workup, rendering evaluation with non-contrast CT alone inadequate. CT angiography provides a comprehensive view of the arterial system in a short amount of time utilizing a modality that is readily available. This technique has been shown to be highly effective at identifying intracranial large vessel thrombus, with an accuracy of 99% in one representative study [24]. Thus, this rapidly acquired, readily available modality is an ideal choice for imaging assessment of the vasculature in the setting of acute ischemic stroke.

In patients where a proximal intracranial thrombus is identified, CT angiography provides for additional information to be extracted from the study to further determine

the appropriateness of endovascular therapy. Characteristics of the thrombus (length, location, and number) as well as procedure-related information (e.g., vascular anatomy for appropriate catheter selection, potential stent-based device deployment zones) can be determined [3]. One of the most critical of these additional factors potentially assessed on CTA is the degree of collateral flow observed in the affected vascular territory, estimated by filling of vessels distal to site of occlusion (Fig. 30.2). There is a strong correlation between the collateral status in the distribution of the occluded vessel and the end infarct size [2]. Furthermore, the collateral grade is an independent predictor of outcome in acute ischemic stroke, particularly when reperfusion is achieved [25, 26].

CT angiography is a rapid method of vascular imaging that is readily available in most healthcare facilities, with only a modest increase in technical complexity relative to a non-contrast CT of the head. When undertaken, this should include both the head and neck for comprehensive assessment, such that causes of underlying stroke (e.g., carotid stenosis) and feasibility of access to the LVO site can be determined.

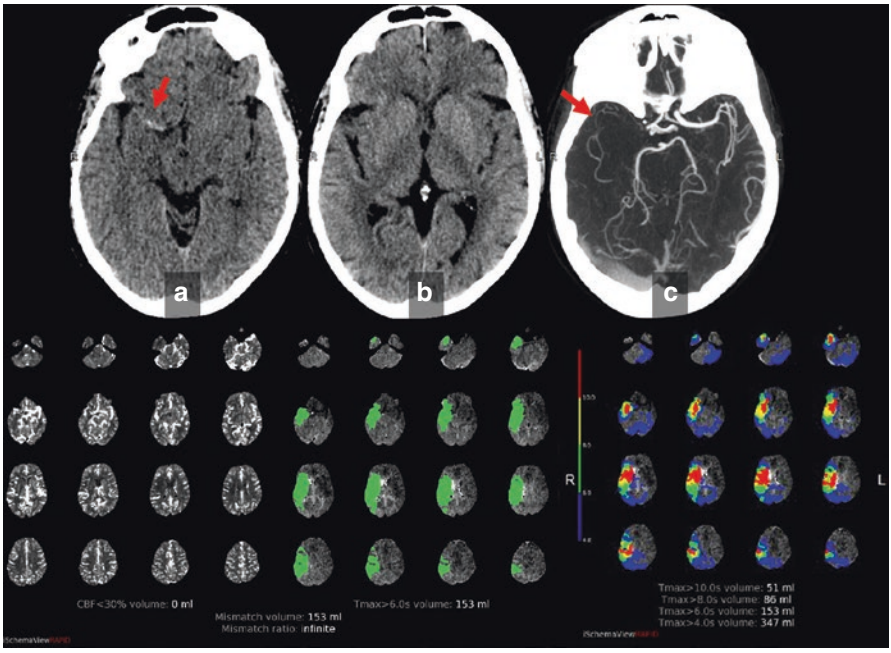


Fig. 30.2 75-year-old woman with acute right M1 MCA occlusion due to cardiac embolism. A, hyperdense MCA sign (arrow); B, normal CT (ASPECTS = 10); C, CTA confirms right MCA occlusion with poor distal collaterals (arrow). Quantitative CT perfusion (RAPID software, lower panel) shows no estimated core infarct (CBF < 30%), but a 153 ml area of poor perfusion (Tmax >6 s) therefore essentially completes "target mismatch." Gradations in Tmax or shown in rainbow color. The patient underwent urgent thrombectomy with excellent recovery

CTA Limitations

There are a few disadvantages to the use of CT angiography. The main limitation of this technique is that a typical single-phase CTA provides a static view of a complex hemodynamic process. This can lead to the underestimation of collateral flow and in turn overestimation of the infarct core. These findings can potentially lead to the erroneous exclusion of a patient from receiving beneficial therapy [27]. One approach is to simply acquire a second set of CTA images immediately after the initial run, in order to see late collateral filling. Another technique offers the ability to correct for this known shortcoming by creating a timing-invariant CT angiogram of the intracranial vasculature from the dynamic CT perfusion data set [28].

Additional drawbacks with CT angiography include the modality's intrinsic use of ionizing radiation with the typical scan covering the upper chest, neck, and head. As with all CT studies, the clinical presentation must appropriately warrant the examination. Another disadvantage intrinsic to CT angiography is the dependence on iodinated contrast to image the vasculature. There is small risk of both allergy and contrast-induced nephrotoxicity. The concern for contrast-induced nephropathy, however, has been assessed in the setting of acute stroke in patients with unknown renal function and has not been found to be associated with excess risk of acute kidney injury, dialysis, or death, despite predisposing risk factors [29, 30]. It is therefore acceptable – and likely best practice – to perform CTA in the assessment of an acute stroke without prior knowledge of renal function [31].

Finally, there has been concern that the acquisition of any additional imaging in conjunction with the non-contrast CT of the head at the time of initial acute stroke assessment would cause a meaningful delay in treatment; however, this has subsequently been disproven [13, 32].

CT Perfusion Benefits

CT perfusion can also be performed as part of the initial stroke evaluation, usually acquired directly before or after the CT angiogram. The examination uses serial dynamic IV contrast-enhanced imaging over the brain in order to capture the wash-in and wash-out patterns of parenchymal contrast enhancement, typically acquired over a period of 45–60 s. In essence, the bolus of iodine serves as a proxy for blood delivery, and mathematical modeling schemes are used to produce color maps reflecting various parameters related to perfusion. Through post-processing, this time-resolved data set is used to calculate perfusion parameters including mean transit time (MTT), time to peak (TTP), relative cerebral blood flow (rCBF), and relative cerebral blood volume (rCBV) that are typically displayed as color-coded maps that can be interpreted both qualitatively and quantitatively. The twofold use of perfusion imaging in the evaluation of acute stroke is to attempt to more accurately define both the core infarct volume and also identify any surrounding ischemic penumbra. As

defined by DEFUSE investigators and others, the ideal or "target" perfusion pattern supporting endovascular therapy is a patient with small core (thresholded low CBF) in conjunction with putative penumbra (very long transit times) seen beyond the core. Post-processing algorithms are critical, since CT perfusion images are inherently noisy, and reliability has been questioned by some authors [33]. Perfusion imaging with the demonstration of penumbra has however been a part of the inclusion criteria in many of the recent endovascular treatment studies, and this newer data suggests that it has a positive role in outcomes [12, 14, 15, 20].

An underappreciated but large benefit of CTP is its general utility in clinical practice for emergency cases and the complementary role it plays with CT and CTA. CTP refines the differential diagnosis of cases beyond acute ischemia, for example, stroke mimics such and migraine or tumors. A wedge of long transit times seen on CTP may redirect the reader's search to identify an initially overlooked small distal branch occlusion, then seen in retrospect on CTA (Fig. 30.3). As part of a standard comprehensive neurovascular protocol, it also plays a role in triage and intervention for aneurysms, hemorrhage, and complications such as vasospasm. A normal CTP also helps provide further diagnostic confidence for negative cases. Having CTP as a routine tool in practice provides benefits beyond the stroke triage indications usually highlighted.

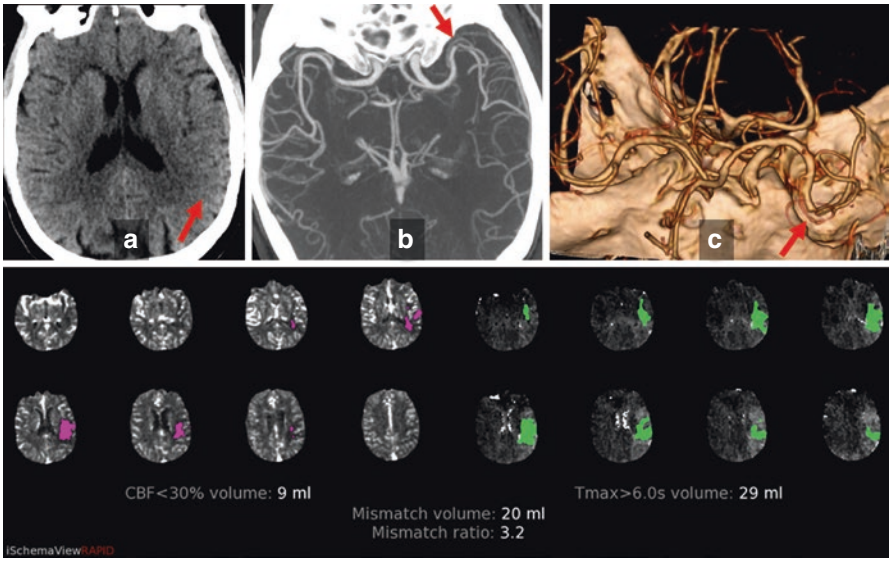


Fig. 30.3 74-year-old man 4 days after cardiac bypass surgery with abrupt aphasia and right hemiparesis. A, non-contrast CT has ASPECTS = 9, with subtle loss of gray-white distinction in the left angular region (arrow). B, a subtle filling defect is seen on thick multiplanar reconstructions from the CTA (arrow). CT perfusion (below) shows a large area of ischemia and small mismatch, suggesting a more significant stenosis or occlusion is likely present. CTA was post-processed in 3D to show a proximal M2 occlusion (arrow), missed on initial CTA review due to tortuous overlapping vessels on 2D images. The occlusion site was proven during successful thrombectomy procedure, with good clinical recovery

CT Perfusion Limitations

CT perfusion shares the same modality-related limitations as CT angiography including the use of ionizing radiation and iodinated contrast. CT perfusion-related radiation exposure has gained increased attention in recent years with both the medical community and general public but can be easily managed and is considered well justified in the context of stroke [34]. There are a few additional limiting factors specific to the CT perfusion examination. Until recently, there was a lack of post-processing standardization, resulting in significant variability between examinations. Even with standardization, there are confounding factors that can affect the accuracy of the perfusion maps. This includes the intrinsically low contrast-to-noise ratio of the examination as well as factors relating to altered vascular flow, including collateral vessels [33, 35].

The use of CT perfusion imaging remains controversial but is routine practice in many stroke centers for evaluation and triage of acute ischemic stroke patients. Although some recent studies have begun to demonstrate that patients with penumbra and infarct mismatch on CT perfusion imaging have more favorable outcomes with revascularization [12–14], this type of evaluation has not yet been fully validated. Continued research is needed to further assess the role of this method and which components (core, penumbra, or both) play in directing patient treatment. Recent data suggest CTP and other advanced methods (DWI, perfusion MRI) may have particular utility in the 6–24 h time windows, where such refined selection criteria can lead to improved outcomes after IA therapy [14, 15] (Fig. 30.4). One of

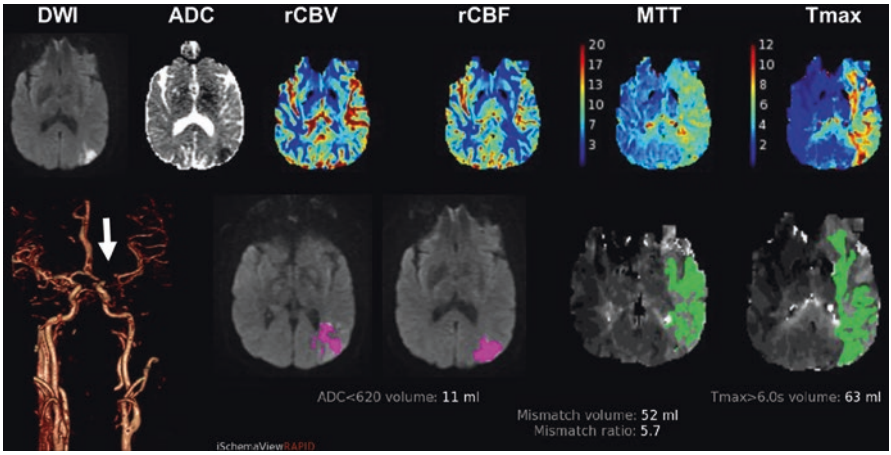


Fig. 30.4 MRI-based triage in a 46-year-old man with global aphasia and right hemiparesis for more than 4.5 h. Upper row shows a small diffusion lesion with low ADC, with much larger perfusion defect by qualitative "eyeball" method. Lower panel shows left carotid terminus near-total occlusion on TRICKS MRA (arrow), with good access via patent cervical carotid. Quantitative thresholded maps made using RAPID software show a favorable "target mismatch" pattern: a small estimated core infarct (ADC <620 = 11 mL, in pink) but large significant perfusion defect (Tmax >6 s = 63 mL, in green), for an estimated mismatch volume/penumbra = 52 mL. He underwent successful endovascular therapy and made a complete clinical recovery

the points of contention with the utilization of this technique is the limited accuracy of infarct volume and penumbra measurement. It has been shown that if a lesion volume is found to be 70 mL on DWI, the same lesion on CTP with relative CBV and CBF can vary +/− ≥55 mL within a 95% confidence interval [33]. Variability this large has the potential to exclude patients that would benefit from intra-arterial therapy based on erroneous data. In fact, this is one of the criticisms of the EXTEND-IA trial in which perfusion data was utilized for patient selection. The trial screened 1044 patients but enrolled only 70 for therapy [4]. This debate does not discount the value of identifying penumbra but raises the issue of the most appropriate thresholds to avoid "cherry picking" of just those most likely to benefit – rather than all those with some likelihood of benefit. In contrast, some who believe that CT perfusion imaging is not accurate enough to make treatment decisions instead advocate for the use of "clinical penumbra." This is a method that infers the degree of salvageable tissue by correlation of the NIHSS with the presence and location of a proximal large vessel thrombus. A low stroke score with the presence of a proximal large vessel occlusion would imply that there is salvageable brain parenchyma that has not yet infarcted [36]. The late (6–24 h) time window DAWN trial successfully combined advanced imaging and clinical stroke scale metrics for selection [15].

Just as the role of endovascular therapy in the treatment of acute ischemic stroke has been revised over time, so too it is likely that the role of perfusion imaging will continue to evolve and see an expanded role. Some promising areas that may provide the greatest potential utility of CT perfusion imaging include the evaluation of "wake up" stroke or strokes where the time of symptom onset is otherwise unknown, and in patients with a low NIHSS with a large vessel occlusion. Management in these patients could potentially best be based upon the size of infarct and presence of penumbra. Currently, however, there is no consensus on the utilization of perfusion imaging in the assessment of acute ischemic stroke.

References

1. Fransen PS, et al. Time to reperfusion and treatment effect for acute ischemic stroke: a randomized clinical trial. JAMA Neurol. 2016;73:190–6.
2. Cheng-Ching E, et al. Degree of collaterals and not time is the determining factor of core infarct volume within 6 hours of stroke onset. Am J Neuroradiol. 2015;36:1272–6.
3. McTaggart RA, et al. Initial hospital management of patients with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the Society of NeuroInterventional Surgery. J Neurointerv Surg. 2017;9:316–23.
4. Liebeskind DS, et al. Computed tomography perfusion in acute ischemic stroke: is it ready for prime time? Stroke. 2015;46:2364–7.
5. del Zoppo GJ, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol. 1992;32:78–86.
6. Riedel CH, et al. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke. 2011;42:1775–7.

7. Vendrell J-F, et al. Evaluation of an intravenous-endovascular strategy in patients with acute proximal middle cerebral artery occlusion. AJNR Am J Neuroradiol. 2013;34:603–8.
8. Vogt G, Laage R, Shuaib A, Schneider A. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: an analysis of the Virtual International Stroke Trials Archive (VISTA) database. Stroke. 2012;43:1266–72.
9. Berkhemer OA, et al. A randomized trial of Intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11–20.
10. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.
11. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
12. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285–95.
13. Campbell BCV, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
14. Lansberg MG, et al. Computed tomographic perfusion to predict response to recanalization in ischemic stroke. Ann Neurol. 2017;81:849–56.
15. Nogueira RG, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2017; https://doi.org/10.1056/NEJMoa1706442.
16. González RG, et al. The Massachusetts General Hospital acute stroke imaging algorithm: An experience and evidence based approach. J Neurointerv Surg. 2013;5 https://doi.org/10.1136/neurintsurg-2013-010715.
17. Akbik F, et al. The evolution of mechanical thrombectomy for acute stroke. Curr Treat Options Cardiovasc Med. 2016;18:1–17.
18. Powers WJ, et al. 2018 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. 2018;49:e46–e110.
19. Albers GW. Late window paradox. Stroke. 2018;49:768–71.
20. Campbell BCV, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol. 2015;14:846–54.
21. Goyal M, et al. Endovascular therapy in acute ischemic stroke: challenges and transition from trials to bedside. Stroke. 2016;47:548–53.
22. Rowley HA. The four Ps of acute stroke imaging: parenchyma, pipes, perfusion, and penumbra. Am J Neuroradiol. 2001;22:599–600.
23. Pexman JHW, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. Am J Neuroradiol. 2001;22:1534–42.
24. Lev MH, 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;25:520–8.
25. Miteff F, et al. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain. 2009;132:2231–8.
26. Menon BK, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. Am J Neuroradiol. 2011;32:1640–5.
27. Yoo AJ, et al. CT angiography source images acquired with a fast-acquisition protocol overestimate infarct core on diffusion weighted images in acute ischemic stroke. J Neuroimaging. 2012;22:329–35.
28. Smit EJ, et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke. 2013;44:2194–9.
29. McDonald RJ, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology. 2014;273:714–25.
30. Josephson SA, Dillon WP, Smith WS. Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging. Neurology. 2005;64:1805–6.

31. Krol AL, et al. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. Stroke. 2007;38:2364–6.
32. Vagal A, et al. Multimodal CT imaging: time to treatment and outcomes in the IMS III trial. Am J Neuroradiol. 2016;37:1393–8.
33. Schaefer PW, et al. Limited reliability of computed tomographic perfusion acute infarct volume measurements compared with diffusion-weighted imaging in anterior circulation stroke. Stroke. 2015;46:419–24.
34. Boone JM, Hendee WR, McNitt-Gray MF, Seltzer SE. Radiation exposure from CT scans: how to close our knowledge gaps, monitor and safeguard exposure—proceedings and recommendations of the radiation dose summit, sponsored by NIBIB, February 24–25, 2011. Radiology. 2012;265:544–54.
35. Copen WA, et al. Exposing hidden truncation-related errors in acute stroke perfusion imaging. Am J Neuroradiol. 2015;36:638–45.
36. Boxerman JL, Jayaraman MV, Mehan WA, Rogg JM, Haas RA. Clinical stroke penumbra: use of National Institutes of Health stroke scale as a surrogate for CT perfusion in patient triage for intra-arterial middle cerebral artery stroke therapy. Am J Neuroradiol. 2012;33:1893–900.

Chapter 31
Role for Intra-arterial Therapy for Acute Ischemic Stroke

Hazem Shoirah and J. Mocco

The Burden of Stroke

Stroke is a leading cause of mortality, ranking second worldwide and fourth in the United States, as well as being the second leading cause of disability in the United States [1]. There are more than 700,000 new or recurrent stroke patients annually in the United States, 85% of which are acute ischemic strokes (AIS), with an annual economic burden of $70 billion [2]. An estimated 25–30% of patients with acute ischemic stroke have a large vessel occlusion (LVO) at the time of presentation. An additional 10% of acute stroke patients have underlying symptomatic carotid disease. Studies of natural history reveal that LVO is resistant to systemic thrombolysis with a 20% rate of recanalization [3] with many of those recanalized vessels eventually reoccluding. Thus, LVO patients have significantly higher morbidity and mortality [4, 5] and are at risk for poor neurological outcome even when their symptoms are minor on presentation. Between the morbid outcomes of large vessel pathologies, be them occlusion or symptomatic atherosclerotic stenosis, endovascular management is redefining the field of acute and hyperacute stroke management.

History of Catheter-Based Revascularization

The history of intra-arterial, catheter-directed therapy has always been at the forefront of stroke therapy, with the first trials evaluating its use dating back to the 1980s. The Prolyse in Acute Cerebral Thromboembolism (PROACT) and PROACT-I trials set the stage for the evaluation of endovascular thrombolytic use, by

H. Shoirah · J. Mocco (✉)
Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: hazem.shoirah@mountsinai.org; j.mocco@vanderbilt.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_31

demonstrating the safety of using prourokinase in patients with M1 and M2 occlusions, treated within 6 h from their last-known-well (LKW) times. In 1999, PROACT-II trial, a randomized controlled trial in 180 patients comparing placebo with 9 mg of IA prourokinase, demonstrated the safety and efficacy of intra-arterial (IA) prourokinase with 40% good clinical outcome in the treated group vs 25% in the control arm (p 0.04) [6]. Following specific logistical and financial reasons, those trials were not succeeded with clinical translation into practice and endovascular therapy for AIS fell out of favor till the introduction of mechanical devices for treatment. The early years of the twenty-first century witnessed an expansion in the scope of mechanical devices used for stroke treatment. Several approaches including microwire clot disruption, saline injection within the clot, and manual aspiration implemented nonspecialized techniques of recanalization. None of those techniques were robustly successful, and none was evaluated rigorously in a randomized trial. The first mechanical device to be systemically evaluated was the EKOS microcatheter system (EKOS, Bothell, WA) which implemented a combination of IA thrombolysis and ultrasonographic waves to disrupt clot. This was evaluated in the Inteventional Management of Stroke (IMS)-I and IMS-II trials, but the device was largely abandoned by the time of the conduction of IMS-III. In 2004, MERCI retriever (Concentric Medical, Mountain View, CA) was cleared by the FDA for removal of thrombus based on the 510 K pathway, and in 2008, Penumbra clot aspiration system (Penumbra Inc., Alameda, CA) followed suit. Those early-generation devices had low recanalization rates (46.0–87.0%), poor impact on functional independence (25.0–41.0%), and high mortality (20.0–43.5%) [7–11]. Those were the devices that were used in the majority of cases in what was later to be deemed as the "old-generation trials" [12–14]. The trials demonstrated no significant benefit from thrombectomy compared to standard care. In spite of their negative results, the trials highlighted the challenges facing the field. They were specifically criticized for using outdated devices, poor patient selection, delayed treatment, and slow enrollment rates. By the time the results of those studies were published, the technology has already moved on, and a new, "second" generation of retrievable intracranial stents, known as the stent retrievers, were in wide use. Building upon the experience from the old-generation trials, five seminal randomized, controlled trials evaluated Intra-arterial Therapy (IAT) using new-generation devices for carefully selected patients, in comparison with standard-of-care treatment. The results of all five trials were overwhelmingly positive in favor of thrombectomy [12, 14–17], setting the field for thrombectomy to become the standard of care for LVO treatment.

Thrombectomy

A patient-level, pooled meta-analysis of the five seminal trials (HERMES) included 1287 patients (634 in IAT and 653 in the medical arm) and demonstrated that IAT results in a reduction in modified Rankin score (mRS), a score of functional independence after stroke, when compared with standard treatment (adjusted odds ratio 2.49, 95% CI 1.76–3.53, $p < 0.0001$) with nearly double the patients achieving neurological independence (mRS 0–2) at 90 days (46% vs 26.5%, $p < 0.0001$) [18].

The number needed to treat to achieve at least one point reduction in mRS was 2.6; one of the most robust treatment effects in medicine. This positive effect was sustained in multiple subgroup analyses including pretreatment with tPA, different age groups including octogenerians, tandem lesions, or time to revascularization within or beyond 300 min. Uncertainty remains regarding patients with extensive ischemic changes on CT defined as having an Alberta Stroke Program Early CT changes (ASPECTS) <5, patients with distal occlusions (M2) or patients with mild stroke symptoms (NIHSS <10).

Time to Revascularization

The physiological principle of a time-dependent outcome in post-thrombolysis stroke patients is concretely accepted with better odds of good outcome associated with shorter onset to start of treatment [19]. One of the hallmarks of the HERMES trials was the implementation of rapid reperfusion strategies with an average time from symptom onset to reperfusion of 286 min [20], as opposed to 325 min in IMS-III [21]. Each 30-min delay was associated with a decreased likelihood of a good clinical outcome with an adjusted relative risk of 0.88 (95% CI 0.80–0.98) in the IMS-III population, and each 1-h delay to reperfusion in the HERMES population was associated with a less favorable degree of disability with a common odds ratio of 0.84 (95% CI 0.76–0.93). Thus, early revascularization is universally associated with better outcomes. In spite of that, there remains a great deal of individual variability in the rate of progression of stroke volume. The presence of good collaterals, evidenced by the presence of penumbral tissue on perfusion imaging, has been demonstrated to be associated with smaller final infarct volumes [13], and patients with such good penumbral patterns may undergo slower ischemic progression. Several trials are underway evaluating the expansion of the rigidly defined "clock-based" treatment window using a collateral-dependent "tissue-based" model.

Imaging-Based Patient Selection

Noncontrast head imaging with computed tomography is required for all patients presenting with AIS to exclude hemorrhage and evaluate the extent of early ischemic changes. This is commonly assessed using the Alberta Stroke Program Early CT Score (ASPECTS), with lower scores indicating more extensive ischemic changes and worse outcome. More than 90% of the patients enrolled in the HERMES trials had ASPECTS >5. Unlike the old-generation trials, all HERMES trials required the use of noninvasive angiographic imaging (CTA or MRA) to confirm the presence of LVO. CT perfusion (CTP) was a prerequisite for enrollment in only two of the five trials [12, 16], and its ultimate role in the selection of patients presenting within 6 hours from their symptom onset remains controversial. Thus, the ideal protocol for imaging selection will remain a topic of debate and discussion and should be tailored to each center's demands and resources.

Procedural Techniques

First-generation devices are no longer used in their original format. Currently, there are numerous configurations of catheter-based intervention for LVO that comprise of a retrievable stent, or stentriever (Trevo; Stryker, Kalamazoo, MI) (Solitaire; Covidien, Minneapolis, MN); an aspiration catheter, which should be flexible and with a large internal diameter; or a combination of the two. Aspiration, when used as first-pass techniques, is also known as ADAPT (a direct aspiration first pass technique) in which aspiration can be achieved mechanically via a pump-based aspiration system (Penumbra, Inc., Alameda, CA) (Fig. 31.1).

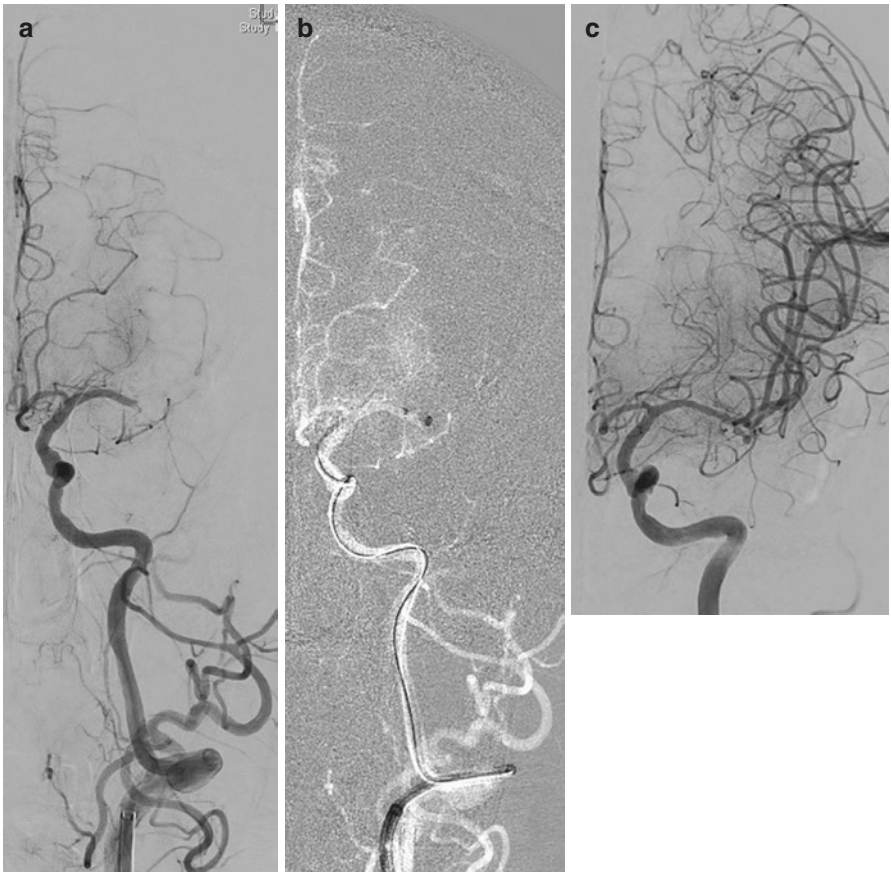


Fig. 31.1 (**a**) A subtracted, anteroposterior projection of the left common carotid artery, demonstrating an abrupt cutoff at the left M1 segment of the MCA. (**b**) A road map overlay of the previously displayed run. With the assistance of a microwire (Fathom-16; Boston Scientific, Marlborough MA) and a microcatheter (3MAX; Penumbra, Alameda CA), the aspiration catheter (ACE68; Penumbra) was brought in contact with the clot. Pump-assisted aspiration (Penumbra) was performed. (**c**) Angiographic run after the first pass, showing successful recanalization (Thrombolysis in Cerebral Infarction - TICI 3)

Alternatively aspiration can be achieved using a large-volume vacuum syringe using the Manual Aspiration Technique (MAT) [22]. Stentriever-mediated thrombectomy is usually achieved under aspiration via a pump-based aspiration system (Fig. 31.2) but can also be achieved with manual aspiration, a technique known as stentriever-mediated manual aspiration thrombectomy (SMAT) [23]. There is no

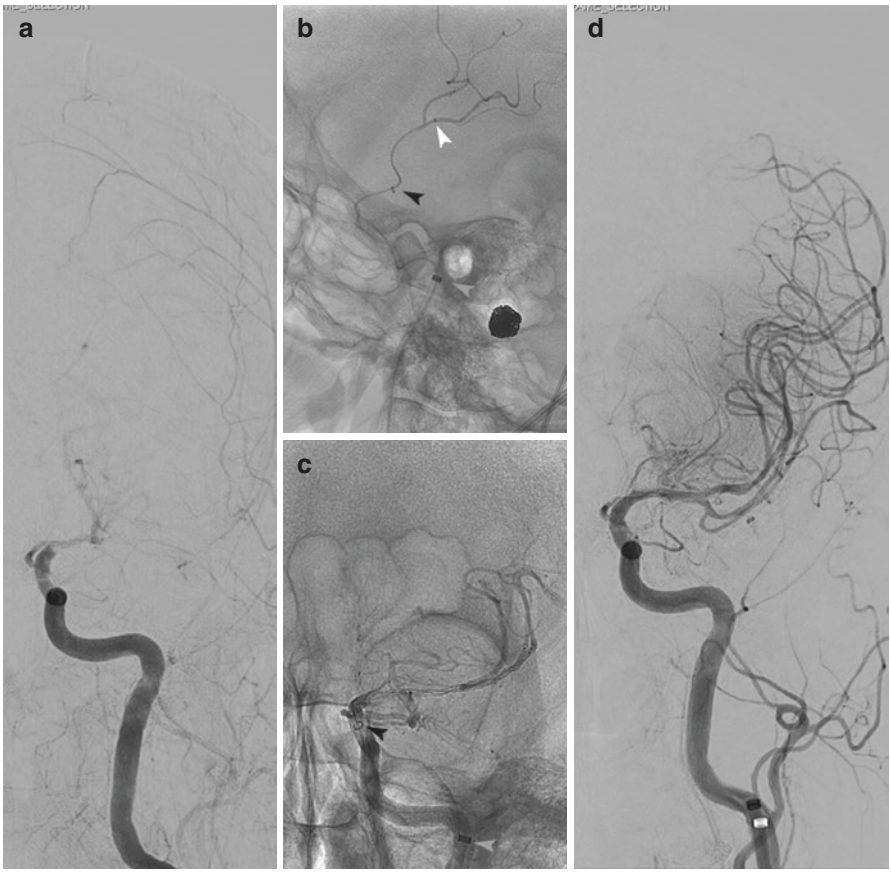


Fig. 31.2 (**a**) A subtracted, anteroposterior projection of the left internal carotid artery, demonstrating an abrupt cutoff at the ICA terminus. (**b**) An unsubtracted, lateral projection: the guide catheter (grey arrowhead) has been brought up to the vertical petrous ICA. The aspiration catheter (black arrowhead) is seen at the interface of the clot. The microcatheter (white arrowhead) has traversed the clot. This angiographic run through the microcatheter confirms the correct positioning of the microcatheter in a patent vessel, distal to the point of occlusion. (**c**) An unsubtracted, anteroposterior projection, through the guide catheter (gray arrowhead). The stentriever (Trevo 6 × 25 mm; Stryker) has been deployed, and contrast can be seen opacifying the ICA terminus and the subsequent left MCA. Four minutes later, the stentriever will be retrieved. (**d**) Final run through the guide catheter demonstrates recanalization of the previously occluded ICA terminus and the left M1 with its subsequent territories (TICI 3). Notice the lack of visualization of the left A1 with a residual clot at its origin. Subsequent runs from the right ICA revealed excellent flow across the anterior communicating artery, and it was elected to not pursue the left A1 clot

consensus on which primary approach is more favorable. Preliminary data from randomized, controlled trials recently demonstrated no difference in recanalization rate between the two techniques (85.4% aspiration, 83.1% stentriever, $p = 0.53$), though final data is yet to be published [24] and other head-to-head trials are underway. In theory, distal emboli may be reduced by the use of aspiration or a balloon-guide catheter with proximal flow arrest, but this is yet to be proven systemically.

Management of Tandem Occlusions

Tandem disease of the ICA and occlusion of the MCA (TIM) occur in 20% of patients with LVO of the anterior circulation. Those cases are poorly responsive to systemic thrombolysis with low recanalization rates <5% [25, 26] and, if not procedurally treated, pose significant morbidity and mortality with rates as high as 70% and 55%, respectively [27]. Although TIM patients were generally excluded from the HERMES trials, several surgical and endovascular approaches have been proposed to overcome the limitation of systemic thrombolysis in TIM. Most commonly, a combination of emergent carotid angioplasty with stenting and endovascular thrombectomy is performed in either an anterograde (treating proximal then distal lesion) or a retrograde approach. Management of TIM has limitations including technical difficulties, prolonged time to flow restoration, and higher rates of symptomatic ICH [28], possibly related to emergent loading with antithrombotic agents necessary during angioplasty and stenting.

Anesthesia Management

The choice of sedation for the procedure depends on multiple factors. General anesthesia (GA) may be mandated by patient's inability to protect their airway or extreme agitation [29]. In many occasions, however, it is dependent on the operator preference and the availability of anesthesia team. General anesthesia has been found in multiple retrospective studies to be associated with worse neurological outcome when compared with conscious sedation (CS) [30, 31]. Potential explanations include longer procedural time, anesthesia-related hypotension, and hypocapnia-induced vasoconstriction. Recently, a randomized controlled trial, comparing conscious sedation to general anesthesia, found no difference in outcome between the two groups in terms of rapid neurological improvement (−3.2 for GA vs −3.6 for CS, p 0.82) [32], in spite of higher rates of periprocedural pneumonia and delayed extubations. Although it is the only randomized controlled trial evaluating sedation modalities, this study was a single-center study with impressively lower rates of good outcome in either arm, compared to the outcomes of any of the HERMES trials.

Carotid Stenting and Angioplasty

Epidemiology of Carotid Disease

Carotid artery atherosclerotic stenosis is responsible for 10–20% of all acute ischemic strokes [33]. Carotid artery atherosclerosis carries the highest risk of short-term recurrent stroke among all stroke etiologies (OR 3.3 and 2.9 at 7 and 30 days) [34]. Four percent of patients with large artery atherosclerosis will experience a recurrent stroke in the first 7 days after their index event, 12.6% in the first 30 days, and 19.2% in the first 90 days. Asymptomatic carotid artery stenosis (ACAS) also carries a significant risk of causing stroke, with a 1-year risk of ipsilateral symptoms as high as 20% in patients with severe ACAS (>70%) [35]. This risk is higher when microemboli are detected on transcranial Doppler (TCD) or when there is contralateral carotid occlusion [36, 37]. With the advances in medical therapy, especially with high-potency statins, the risk of recurrent stroke with an underlying symptomatic or asymptomatic carotid disease has been significantly reduced. Concurrently, the technology and experience with revascularization surgery have witnessed impressive improvements in the last 2 decades, making them safer than previously reported in earlier experience.

Assessing Degree of Stenosis

The degree of stenosis could be evaluated by multiple modalities, including carotid Doppler, CT angiography, MR angiography, or conventional angiography. Carotid Doppler is a low-risk, noninvasive tool that is widely used in carotid disease screening. While it may provide helpful data about plaque morphology and offers dynamic assessment, it is operator-dependent and is often unable to distinguish high-grade stenosis from complete occlusion. Time-of-flight MR angiography infamously overestimates the degree of stenosis, a problem that may be mitigated by using gadolinium-enhanced MRA. In CT angiography, two methods could be used to assess the degree of stenosis. In the NASCET trial method, the degree of carotid stenosis was assessed by comparing the residual, stenotic lumen to the diameter of the non-stenosed distal segment of the vessel. The European Carotid Surgery Trial (ECST) assessed the degree of stenosis by comparing the residual, stenotic lumen to the estimated diameter of the disease-free carotid bulb. Conventional angiography is the gold standard of assessing degree of stenosis. It can reliably demonstrate a *string sign,* differentiating critical stenosis from occlusion, and can be used to assess collateral circulation as that seen from the external carotid artery (ECA) via the many ECA-ICA collateral circulations that exist, for example in relation to the inferolateral trunk or the ophthalmic artery. The limitation of conventional angiography is its invasive nature which poses a small risk for complications. However, it offers the advantage of combination with angioplasty and/or stenting in selected patients as will be detailed below.

Evidence for Efficacy

Like many technology-dependent procedures, the early experience with CAS is not immediately translatable to today's practice. Early trials were limited by less advanced techniques, lack of embolic protection devices (EPDs), and pharmacological regimens that would nowadays be considered inadequate. This likely contributed to the higher incidence of stroke in CAS compared to carotid endarterectomy (CEA) [38]. However, following the trend of technological and pharmacological advancements, more recent studies have shifted the view on CAS. Two seminal trials have set the field for carotid revascularization. In 2010, the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) randomized 2502 patients with symptomatic (>50%) or asymptomatic (>60%) carotid disease to either CEA or CAS [39, 40]. There was no significant difference in a composite of stroke, MI, or death in the first 30 days (7.2% in CAS vs 6.8% in CEA, $p = 0.51$). There was a trend for better outcomes with CEA in patients older than 70. Periprocedural risk of stroke was 4.1% in CAS vs 2.3% in CEA, but risk of MI was 2.3% in CEA vs 1.1% in CAS. The International Carotid Stenting Study (ICSS), a randomized controlled study of 1713 exclusively symptomatic patients, found no difference between CAS and CEA in death or disabling stroke in the first 120 days (4.0% vs 3.2%, HR 1.28, 95% CI 0.77–2.11) [41] or after 5 years of follow up (6.4% vs 6.5%, HR 1.06, 95% CI 0.72–1.57, $p = 0.77$) [42]. ICSS also showed that CAS was associated with a small, but significant increased risk of periprocedural stroke (65 events vs 35 events, HR 1.92, 1.27–2.89); however those were nondisabling strokes that had no impact on the long-term functional outcome endpoints. The increased risk of stroke with CAS is limited to the immediate periprocedural period. After the immediate periprocedural period, the incidence of stroke is very low and demonstrably similar between CAS and CEA (0.4–0.7% and 0.5–0.6% annual risk, respectively) [43, 44].

Timing of Revascularization

The benefit of revascularization is tightly tied to the time of surgery after index event. When performed within 2 weeks of index event, there is no increased procedural incidence of stroke or death. On the contrary, revascularization within 2 weeks resulted in an absolute risk reduction (ARR) in stroke recurrence of 30.2% with a number needed to treat of 3 [45]. After 4 weeks, the NNT was 9, markedly reducing its potential benefit over time, especially in women.

Treating Asymptomatic Disease

The Endarterectomy for Asymptomatic Carotid Artery Stenosis (ACAS) study showed a significant reduction in 5-year risk of ipsilateral stroke in CEA vs medically treated patients with >60% asymptomatic stenosis (5.1% vs 11.0%, aggregate

risk reduction of 53%, 95% CI 22%–72%). Similarly, the Asymptomatic Carotid Surgery Trial (ACST) found a 10-year risk of 13.4% vs 17.9% in the CEA and medical arms, respectively [46]. The Asymptomatic Carotid Trial (ACT I) which randomized 1453 patients with asymptomatic, severe carotid stenosis found that undergoing protected CAS was noninferior to standard CEA in a primary composite endpoint of 30-day death, stroke, or MI (p 0.01) [43]. The 5-year rate of stroke-free survival was 93.1% and 94.7% with no statistically significant difference in CAS and CEA. Arguably, those trials do not respond to the trend of improved outcomes of medically treated patients on current-day high potency statins. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2) is an ongoing trial that is enrolling patients with asymptomatic carotid disease into CAS, CEA, or high intensity medical arms that will help elucidate some of the important questions lingering in this domain.

Practical Implications for Patient Selection

To accommodate for interprovider experience, the American Heart Association/American Stroke Association has set a benchmark of tolerable 30-day risk of stroke or death of 3% and 6% for asymptomatic and symptomatic patients, respectively. This reflects the event rates in medically treated patients in the two cohorts, respectively, which have been arguably reduced further with the advent of high potency statins, since those guidelines were set. In 2011, 14 organizational bodies, including the AHA and ASA, released a joint and updated guidelines statement recommending revascularization procedures, for patients with symptomatic carotid disease with more than 50% stenosis or asymptomatic patients who have more than 70% stenosis, with CAS recommended as a possible alternative to surgery [47]. The Center for Medicare and Medicaid Services (CMS), however, still bases its reimbursement policies on the old CAS trials. In its current policies, CAS is only approved for patients with symptomatic carotid stenosis of more than 70% (or more than 80% asymptomatic stenosis) who are at high risk for CEA, using FDA-approved embolic protection devices (EPDs). It is a matter of active discussion, whether the reimbursement patterns will change following published and ongoing trials demonstrating the noninferiority of CAS to CEA. The current CMS definition of high surgical risk criteria includes procedural conditions, such as recurrent stenosis, contralateral carotid occlusion, previous radical neck radiation or dissection, or high-risk cardiac conditions, such as unstable angina, left ventricular ejection fraction <30%, congestive heart failure, or recent MI.

Technique

The hallmark of the technique of performing carotid stenting is system stability. A 7F sheath catheter (Shuttle; Cook, Bloomington IN) (Neuron Max; Penumbra,

Alameda CA) is usually used to access the descending aorta, and then the target vessel is selected by using a 5F catheter (VTK, Thorocon NB, Cook, Bloomington IN). The 5F catheter is then advanced to the external carotid artery, and the 7F sheath is advanced over it till the common carotid artery. Predilation is achieved using premeasured 0.018-inch compatible balloons (Sterling; Boston Scientific, Marlborough MA) after the lesion is successfully crossed with a steerable 0.014-inch guidewire (Synchro; Stryker, Fremont CA). Predilation is performed only once per balloon, but a serial, stepwise predilation may be performed in pre-occlusive lesions. We usually use closed-cell, self-expanding stents (Carotid WALLSTENT; Boston Scientific, Marlborough MA), which is deployed as the next step (Fig. 31.3).

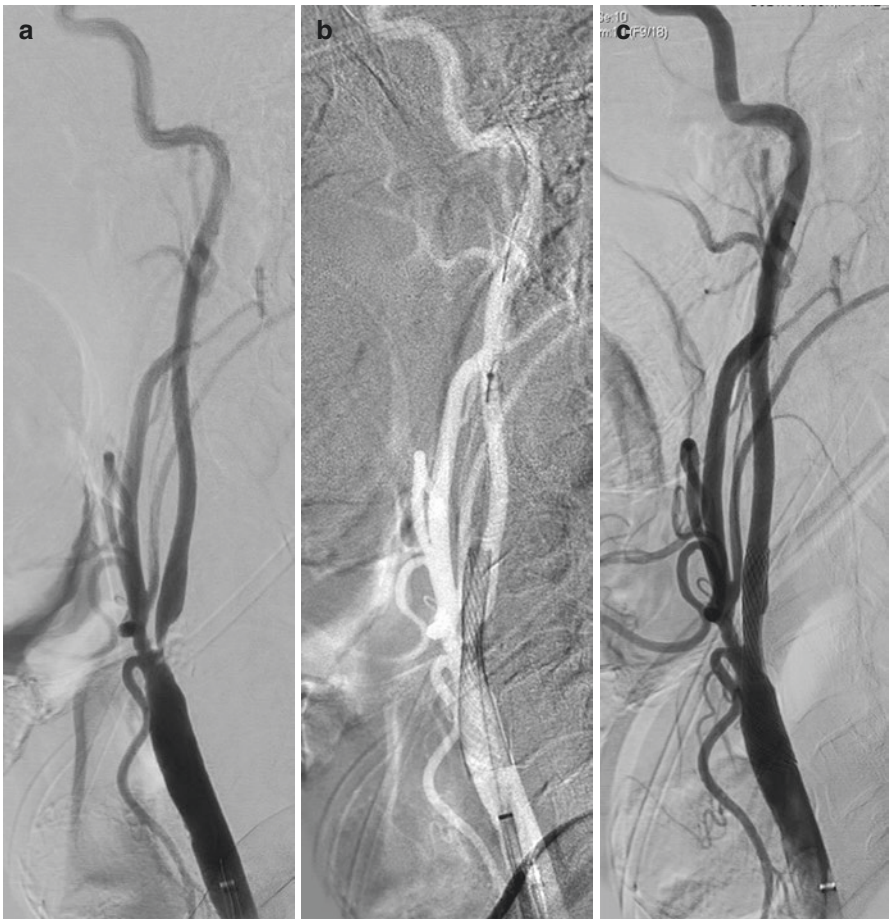


Fig. 31.3 (**a**) A subtracted, lateral projection of the right common carotid artery revealing an atheromatous plaque at the origin of the internal carotid artery, causing severe stenosis. (**b**) A road map overlay of the post-dilatation run. You can see the distally placed embolic protective device (FilterWire EZ; Boston Scientific, Marlborough, MA) and the placement of the stent (10 mm × 24 mm Carotid WALLSTENT; Boston Scientific). (**c**) Post-stenting subtracted projection reveals significant improvement in the caliber of the previously stenosed right ICA

Post-deployment dilatation may be performed, if necessary. A meta-analysis of 12,263 protected and 11,198 unprotected CAS procedures found that the use of embolic protection devices reduces the risk of perioperative stroke compared to unprotected CAS with a relative risk of 0.62 (95% CI 0.54–0.72) [48]. Embolic protection could be proximal, by using balloon-guided catheter and flow arrest, or distal, by using distal embolic capture devices. To date, there has been no demonstrable difference in the efficacy of either approach on clinical outcome [49], although some studies suggest that proximal protection is associated with less microembolic signals and asymptomatic DWI lesions [50, 51].

Anesthesia Management

The majority of CAS procedures are performed under local analgesia and conscious sedation. As opposed to GA, the use of conscious sedation is associated with less hemodynamic changes and allows for intra-procedural neurological assessment. The use of GA in the CREST population undergoing CEA was found to double the risk of myocardial infarction (MI) compared to the use of conscious sedation in the same patient population [52], further promoting the avoidance of GA in carotid revascularization procedures.

Role of Diagnostic Angiography

Beside the many therapeutic roles for endovascular procedures, diagnostic cerebral angiography remains the gold standard of cerebrovascular imaging. It may be used to assess the degree of stenosis, the patterns of collateral flow, and the identification of underlying disease, like dissection or vasculitic changes. While the information obtained from a diagnostic angiogram could be helpful, its benefit should be weighed against the small procedural risk of angiography given its invasive nature.

Conclusion and Future Considerations

Endovascular approach has established itself as a cornerstone in the acute and subacute management of strokes related to large vessel disease. The recent strides achieved in the field of hyperacute interventions have impacted the systems of stroke care and provision. Networks are realigning their triaging protocols, and primary stroke centers are increasingly affiliating with tertiary, thrombectomy-capable centers. There is ongoing debate in the field about the value of systemic thrombolysis in patients with suspected LVO and an inclination to bypass primary stroke centers in favor of thrombectomy-capable hospitals in these cases.

While thrombectomy benefits have been elucidated in large populations, refining patient selection, advancement of procedural techniques, and the prevention of procedural complications continue to be targets of ongoing research. New clot retrieval devices, catheters, EPDs, and implantable stents are being developed and produced at higher rates than ever in the history of this field. With the advent of revascularization therapy, it will become imperative to investigate and develop neuroprotective treatments to curb the incidence of revascularization and reperfusion injury and further improve neurological recovery. Locally infused neuroprotectants, focal cerebral hypothermia and endovascular implantation of stem cells are all topics of highly anticipated clinical impact in the future.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the global burden of disease study 2010. Lancet. 2014;383(9913):245–54.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322.
3. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41(10):2254–8.
4. Beumer D, Saiedie G, Fonvile S. Intra-arterial occlusion in acute ischemic stroke: relative frequency in an unselected population. Cerebrovasc Dis. 2013;35(Suppl):66.
5. Rai AT, Seldon AE, Boo S, Link PS, Domico JR, Tarabishy AR, et al. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. J Neurointerv Surg. BMJ Publishing Group Ltd; 2016 Jul 15;neurintsurg–2016–012515.
6. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-Urokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. American Heart Association, Inc. 1998;29(1):4–11.
7. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke. American Heart Association, Inc. 2005;36(7):1432–8.
8. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. Stroke. American Heart Association, Inc. 2008;39(4):1205–12.
9. The 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. American Heart Association, Inc. 2009;40(8):2761–8.
10. Hussain SI, Zaidat OO, Fitzsimmons BFM. The Penumbra system for mechanical thrombectomy in endovascular acute ischemic stroke therapy. Neurology. Lippincott Williams & Wilkins. 2012;79(13, Suppl. 1):S135–41.
11. Tarr R, Hsu D, Kulcsar Z, Bonvin C, Rufenacht D, Alfke K, et al. The POST trial: initial postmarket experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. J Neurointerv Surg. British Medical Journal Publishing Group. 2010;2(4):341–4.
12. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of Intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20.

13. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013;368(10):914–23.
14. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
15. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–306.
16. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–18.
17. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30.
18. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31.
19. Hacke W, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363(9411):768–74.
20. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279–89.
21. Khatri P, Yeatts SD, Mazighi M, Broderick JP, Liebeskind DS, Demchuk AM, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the interventional management of stroke (IMS III) phase 3 trial. Lancet Neurol. 2014;13(6):567–74.
22. Pierot L, Soize S, Benaissa A, Wakhloo AK. Techniques for endovascular treatment of acute ischemic stroke. Stroke. 2015;46(3):909–14.
23. Jadhav AP, Aghaebrahim A, Horev A, Giurgiutiu DV, Ducruet AF, Jankowitz B, et al. Stent retriever-mediated manual aspiration thrombectomy for acute ischemic stroke. Intervent Neurol Karger Publishers. 2016;6(1–2):16–24.
24. Lapergue B. ASTER: contact aspiration versus stent retriever front line for recanalization in acute cerebral infarction. Houston; 2017. http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_492110.pdf
25. Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke. 2006;37(9):2301–5.
26. Endo S, Kuwayama N, Hirashima Y, Akai T, Nishijima M, Takaku A. Results of urgent thrombolysis in patients with major stroke and atherothrombotic occlusion of the cervical internal carotid artery. AJNR Am J Neuroradiol. 1998;19:1169–75.
27. Meyer FB, Sundt TMJ, Piepgras DG, Sandok BA, Forbes G. Emergency carotid endarterectomy for patients with acute carotid occlusion and profound neurological deficits. Ann Surg. 1986;203(1):82–9.
28. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. J Neurointerv Surg. 2015;7(3):170–5.
29. Froehler MT, Fifi JT, Majid A, Bhatt A, Ouyang M, McDonagh DL. Anesthesia for endovascular treatment of acute ischemic stroke. Neurology. Lippincott Williams & Wilkins. 2012;79(13, suppl. 1):S167–73.
30. Anastasian ZH. Anaesthetic management of the patient with acute ischaemic stroke. Br J Anaesth. Oxford University Press. 2014;113(suppl 2):ii9–ii16.
31. Abou-Chebl A, Yeatts SD, Yan B, Cockroft K, Goyal M, Jovin T, et al. Impact of general anesthesia on safety and outcomes in the endovascular arm of interventional management of stroke (IMS) III trial. Stroke. American Heart Association, Inc. 2015;46(8):2142–8.
32. Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy. JAMA. 2016;316(19):1986–96.

33. Flaherty ML, Kissela B, Khoury JC, Alwell K, Moomaw CJ, Woo D, et al. Carotid artery stenosis as a cause of stroke. Neuroepidemiology. 2013;40(1):36–41.
34. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology. 2004;62(4):569–73.
35. Conrad MF, Michalczyk MJ, Opalacz A, Patel VI, LaMuraglia GM, Cambria RP. The natural history of asymptomatic severe carotid artery stenosis. J Vasc Surg. 2014;60(5):1218–26.
36. Spence JD. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol. 2010;67(2):180–6.
37. AbuRahma AF, Metz MJ, Robinson PA. Natural history of ≥60% asymptomatic carotid stenosis in patients with contralateral carotid occlusion. Trans Meet Am Surg Assoc. 2003;121:244–55.
38. Noiphithak R, Liengudom A. Recent update on carotid endarterectomy versus carotid artery stenting. Cerebrovasc Dis. 2017;43(1–2):68–75.
39. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11–23.
40. Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG, for the CREST Investigators. The carotid revascularization endarterectomy versus stenting trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke. American Heart Association, Inc; 2010;41(10, suppl. 1):S31–4.
41. International Carotid Stenting Study Investigators. 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(9719):985–97.
42. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, 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(9967):529–38.
43. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med. 2016;374(11):1011–20.
44. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374(11):1021–31.
45. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. Stroke. American Heart Association, Inc. 2004;35(12):2855–61.
46. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet. 2010;376(9746):1074–84.
47. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation. American Heart Association, Inc; 2011;124(4):489–532.
48. Garg N, Karagiorgos N, Pisimisis GT, Sohal DPS, Longo GM, Johanning JM, et al. Cerebral protection devices reduce Periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. J Endovasc Ther. 2009;16(4):412–27.

49. Iyer V, de Donato G, Deloose K, Peeters P, Castriota F, Cremonesi A, et al. The type of embolic protection does not influence the outcome in carotid artery stenting. J Vasc Surg. 2007;46(2):251–6.
50. Montorsi P, Caputi L, Galli S, Ciceri E, Ballerini G, Agrifoglio M, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. J Am Coll Cardiol. 2011;58(16):1656–63.
51. Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFI study (prevention of cerebral embolization by proximal balloon occlusion compared to filter protection during carotid artery stenting). J Am Coll Cardiol. 2012;59(15):1383–9.
52. Hye RJ, Voeks JH, Malas MB, Tom M, Longson S, Blackshear JL, et al. Anesthetic type and risk of myocardial infarction after carotid endarterectomy in the carotid revascularization endarterectomy versus stenting trial (CREST). J Vasc Endovasc Surg. 2016;64(1):3–8.e1.

Chapter 32
Evolution of Thrombectomy Approaches, Philosophy, and Devices for Acute Stroke

Alejandro M. Spiotta and Ferdinand K. Hui

Since its approval in 1995–2015, the administration of systemic intravenous tissue plasminogen activator (tPA) was the only FDA-approved treatment modality for acute ischemic stroke [1, 2], despite rapid advances in thrombectomy devices. However, the restrictive time window after symptom onset (up to 3–4.5 h) and educational, sociocultural, and geographical barriers to accessing rapid care resulted in only a small minority of patients with ischemic stroke receiving treatment with intravenous tPA [3, 4]. In addition, intravenous tPA was demonstrated to be less effective in large vessel occlusions [5]. Intra-arterial techniques were attempted to treat large vessel occlusions, initially using urokinase and prourokinase as described in the PROACT I and II trials [6, 7], which were followed by the development of devices designed for intra-arterial thrombectomy and thromboaspiration. Despite the initially futile thrombectomy trials [8–11], which failed to show a benefit over intravenous tPA of intra-arterial intervention using devices available at the time, patients outside the intravenous tPA window were still considered candidates for intra-arterial procedures. One of the critiques of these trials was that the lack of imaging identification of actual large vessel occlusions in both arms likely masked any treatment effect. Another was the long enrollment course, and they did not employ modern revascularization devices to achieve safe, efficacious, and expedient vessel revascularization. As such their results did not reflect modern practice at the time they were reported.

A. M. Spiotta
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: spiotta@musc.edu

F. K. Hui (✉)
Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD, USA

Carey School of Business, Johns Hopkins University, Baltimore, MD, USA

Department of Interventional Stroke, Johns Hopkins National Capital Region, Baltimore, MD, USA

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_32

Fortunately, the "negative trials" did not temper the enthusiasm of interventionalists committed to improving stroke care but rather served as a rallying call to improve thrombectomy techniques further, streamline stroke triaging processes with an emphasis on LVO identification, and learn from the lessons of the past "futile" trials. Under mounting pressure to have evidence in support of thrombectomy over iv-tPA, five randomized controlled trials [12–16] were launched shortly after the release of the negative trials. An impressive collective effort and rapid enrollment culminated in the halting of the trials in 2015 due to overwhelming statistical efficacy of thrombectomy over medical management. That year marked the largest improvement in the therapeutic options for acute ischemic stroke care since the NINDs trial in 1995 and armed us for the first time with a mechanical thrombectomy device, the stent retriever, with level 1A evidence supporting its use. We now review the technological advances that led to these developments and review next-generation thrombectomy approaches.

Intra-arterial Thrombolysis

Historically, the mainstay of intra-arterial therapy for clot lysis in acute ischemic stroke was the administration of a thrombolytic agent into the vessel of interest [6, 17, 18]. The PROACT II study was a randomized trial of intra-arterial infusion of recombinant prourokinase (r-proUK) versus placebo (heparinized saline) in patients with angiographically documented proximal middle cerebral artery occlusion [7]. Thrombolytic infusion was associated with significantly higher recanalization rates and improved patient outcomes with acceptable complication rates [6, 7]. Despite this significant difference, the FDA did not approve prourokinase for this indication. Local thrombolytic infusions have been performed since the PROACT II study in "off-label" fashion to treat both anterior and posterior circulation occlusions [4, 17–20]. In addition, some operators employed intra-arterial infusions of tPA or abciximab to further promote clot lysis [21]. Despite the lack of evidence supporting its use, many operators adopted thrombolysis as an adjunct to mechanical thrombectomy. Anecdotally, it became commonplace to administer small doses of either tPA or abciximab intra-arterially to treat smaller, more distal vessel occlusions following a thrombectomy attempt [22–25].

Adjunctive Endovascular Thrombectomy Strategies

To overcome the limitations of intra-arterial thrombolytic infusions alone, neurointerventionalists initially began attempting clot disruption with microwire manipulation. Shaping the microwire into a "J" or "C" shape and repeatedly advancing it through the thrombus were sometimes successful at recanalizing an occluded vessel. For more aggressive attempts, the microcatheter could be repeatedly advanced

through the thrombus while leaving the microwire purchased in the distal vasculature to "plow" through the thrombus. The hope was that any mechanical disruption of the thrombus, however rudimentary, may promote its lysis especially in the setting of systemic or intra-arterial thrombolysis [26–29]. Early methods of thrombectomy included the use of the gooseneck snare for clot capture and removal [30, 31].

In 2005, flexible intracranial balloon catheters were introduced. They were initially designed for vessel angioplasty and later for balloon remodeling during aneurysm coil embolization. Shortly thereafter, these balloons were used to achieve mechanical clot disruption by repeated angioplasty of the thrombus itself [32]. The introduction of intracranial stents presented another potential tool to achieve thrombectomy [33]. The Enterprise vascular reconstructive device (Codman, Raynham, Massachusetts, USA) is a retrievable closed-cell design stent that could be partially deployed within the segment of the occluded vessel to achieve both mechanical disruption and partial flow restoration without committing to permanent stent deployment [34, 35]. Some operators reported deploying intracranial stents in the occluded vessel, even in cases not involving underlying intracranial stenosis [36, 37]. The SARIS trial [35, 38] was an FDA-approved pilot study of stent placement within occluded vessels in acute stroke that showed high recanalization rates and good functional outcomes; however, the technique was limited by the need for dual antiplatelet therapy and the concern for hemorrhagic complications including conversions of core infarcts.

All of these devices were not primarily designed for stroke intervention and therefore were used in acute ischemic stroke in an "off-label" fashion. However, these devices and creative strategies set the stage for the design and development of dedicated thrombectomy devices. The following section outlines the various approaches, with a recognition that iterative improvements of each approach continue to be made.

Thrombectomy Techniques

Acute stroke thrombectomy approaches have evolved rapidly. Spurred primarily by advances in catheter technology as well as the thrombectomy device itself, we are now able to achieve higher recanalization rates than ever before. We review the key technological advances and design modifications that have allowed for navigation around the ophthalmic turn for more distal delivery of larger-bore catheters providing more aspiration force directly applied at the thrombus interface.

The First Device: The Merci Retriever

In 2004 the Merci retriever (Concentric Medical, Mountain View, California, USA) became the first mechanical thrombectomy device cleared for human use in

the USA by the FDA [39]. The Merci device primarily works by engaging the thrombus with a "corkscrew" distal wire and suture tip deployed from within the clot and then removing the thrombus en bloc to achieve recanalization. The device itself is delivered within a microcatheter (18 L, Concentric Medical). The original iterations of the Merci X series included the 2.5, 3.0, and 3.5 mm diameters. Later, the L series was introduced in 2006 and the V series in 2008. All of these systems were employed using a balloon guide catheter that was positioned at the carotid bifurcation or internal carotid artery. Balloon inflation was intended to cause temporary flow reversal, allowing the Merci to be retrieved into the guide catheter while mitigating the possibility of emboli showering to distal territories. However, clot retrieval into the guide catheter still required a long distance to be traveled while maintaining purchase on the thrombus, most commonly from the M1 segment of the middle cerebral artery to the proximal cervical internal carotid artery. The vector force applied while pulling on the thrombus was suboptimal (downward along the long axis of the cervical carotid artery, not horizontally along the axis of the middle cerebral artery). This caused considerable torqueing, stretching, and distortion of the parent vessel and presented a biomechanical disadvantage to thrombus removal. Traction on the vasculature results in pain for the patient. To avoid the inevitable movement that is induced, many operators chose to perform thrombectomy under general anesthesia. In addition, the Merci technique required a long distance to be traveled while remaining engaged with the thrombus.

Revascularization rates in the Merci studies range from 43% to 55% [40–42] and as such represented a vast improvement to thrombolysis alone for LVO, with the caveat that distal embolization rates were incompletely captured by recanalization scales. However, thrombectomy with the Merci device as frontline therapy was not associated with a higher percentage of good functional outcomes (defined as modified Rankin Scale score$\leq$ 2 at 90 days), reported in up to 36% of patients [42]. Recanalization rates with the Merci system are thought to have increased since the initial trial from design refinements as well as increased operator experience [43].

A landmark advancement came in 2010 with the approval of the outreach distal access catheter (DAC; Concentric Medical), which would have repercussions for the application of the Merci device and also for future iterations of thrombectomy approaches. The DAC was designed for the purpose of buttressing access for the Merci thrombectomy device, affording stable access to the target vessel. Use of the DAC optimized the vectors at play during pulling of the device. With further understanding of clot fragmentation and distal embolization, the DAC was used as an intermediate aspiration device which aided in preventing showering of distal emboli during clot retrieval, increased the aspiration power applied directly to the thrombus [44, 45]. The development of large-bore flexible catheters that could be delivered into the intracranial circulation represented a major advancement in thrombectomy technology and also in intermediate catheter technology [45, 46]. The DAC has a flexible distal shaft with increased proximal shaft strength and axial load-bearing

characteristics as well as good hoop strength, allowing it to be delivered to the intracranial circulation around the ophthalmic bend when navigated over a coaxial catheter system. A major drawback to the Merci retrieval system was that it necessitated navigating past the ophthalmic bend with every pass, decreasing the efficiency of the system and adding to procedure times.

The EKOS MicroLysUS Catheter

The EKOS microcatheter system (Bothwell, Washington, USA) and family of devices were designed to provide ultrasonic vibration to facilitate thrombolysis. Earlier studies employed a 2.5 F infusion catheter with an ultrasound-generating 2 mm transducer ring [47]. The current EndoWave system (Bothwell) is a 5.2 F 106-cm-long device using ultrasonic waves delivered via core wire and designed to be used in conjunction with intra-arterial tPA [48]. Data regarding this device remain limited, but further development and experience may prove the approach beneficial. Indeed, transcranial ultrasonic disruption remains an approach undergoing research and development [49, 50].

Second Generation: Penumbra Aspiration System

The Penumbra aspiration system introduced in 2008 involves maceration of the thrombus with a separator which is repeatedly introduced and withdrawn from the thrombus under direct aspiration to prevent showering of fragments [51]. While the Merci system relied primarily on a delivery microcatheter (the 18 L; Stryker, Kalamazoo, Michigan, USA) to the site of occlusion, the Penumbra aspiration system relied on the delivery of a relatively large-bore catheter to the thrombus (up to effectively a 5 F device). The introduction of highly flexible lubricious polymers with good hoop strength allowed for safe placement of large intermediate-class catheters directly into the large intracranial vessels. While the later introduction of the DAC catheter resulted in similar catheter profiles in the distal vasculature, the development of large-bore flexible catheters was essential to the function of the Penumbra system.

The original iteration of the Penumbra reperfusion catheter system included several different sized catheters (internal diameter 0.026″, 0.032″, and 0.041″) and accompanying separators to maximize clot interaction and force of aspiration in vessels of differing diameters (internal carotid artery terminus, M1, M2, M3) to address both proximal and distal thrombi [52]. The largest device had a lumen diameter of 0.041 inch, and it tracked suboptimally and required a median 45 min to achieve acceptable recanalization [53]. In 2009, the reperfusion catheter 054 became available which dramatically improved the aspiration efficiency

to a median 20 min [53] due to its much larger tapered lumen. As the aspiration force is proportional to the square of the diameter of the catheter, the 054 catheter provided an estimated 4× aspiration force over the next smaller catheter, the 041 [53].

Despite the improved technology, the 054 still required a coaxial catheter for delivery to the middle cerebral artery. Although a larger catheter lumen provides higher suction and more rapid removal of material, it also results in a larger catheter profile and more difficult distal navigation. Owing to its size, the 054 catheter often required the use of a coaxial technique to facilitate navigation to the site of occlusion. When navigated over a 0.014 inch microwire alone, a significant ledge would get held up at the origin of the ophthalmic artery. To overcome this obstacle to the target lesion, access with the 054 catheter can be optimized with a coaxial technique (Fig. 32.1). The smaller 032 and 026 reperfusion catheters can be delivered simply over either a 0.014 or 0.016 inch wire and the larger 054 delivered over those. One of the major advantages of the Penumbra aspiration system was that once the catheter system was delivered to the target vessel, separator clot maceration could be performed without having to reaccess (additional "passes"), as was the case for the Merci device [54].

Despite these advances in catheter technology, navigating past the carotid siphon was still a relative challenge during thrombectomy cases. In patients with very acute angulation in the ophthalmic segment, adjunctive techniques could be performed to obtain the necessary distal access. One approach used the Merci retriever system as an adjunct to improve the trackability of the 054 reperfusion catheter by altering the angle with which the catheter engages the ophthalmic segment and M1 origin. By deploying an appropriately sized Merci retriever (Concentric Medical), such as a V.2.0 or V.2.5 soft, in the mid-M1 segment through either the 032 catheter or an 18 L microcatheter and then applying gentle traction on the Merci retriever, the course of the wire straightens, approximating the inner curve of the vasculature, pulling the catheter complex away from the ledge of the vessel origins ("grappling hook" technique) [44, 55], an approach now used routinely using stent retrievers and intermediate catheters. The 054 catheter can then be more readily advanced into the target vessel. Once the 054 reperfusion catheter is in place, the retriever is resheathed into the 18 L microcatheter and then removed prior to separator placement and aspiration.

The next iteration of the Penumbra aspiration catheter family (Max series) was introduced in 2012 and included larger inner diameters at the distal end as well as the proximal end to increase the aspiration power. The larger proximal lumen reduces resistance to flow and therefore increases aspiration force at the catheter tip. Improvements in polymer and braid and ring reinforcement provide more catheter tip flexibility and an increased number of transition zones to improve trackability while maintaining hoop strength. The newly introduced intermediate catheters were named 5Max, 4Max, and 3Max. An increased number of transition zones in the catheter design and manufacturing allowed these catheters to be delivered primarily over either a 0.014 or 0.016 inch microwire, even past the ophthalmic origin.

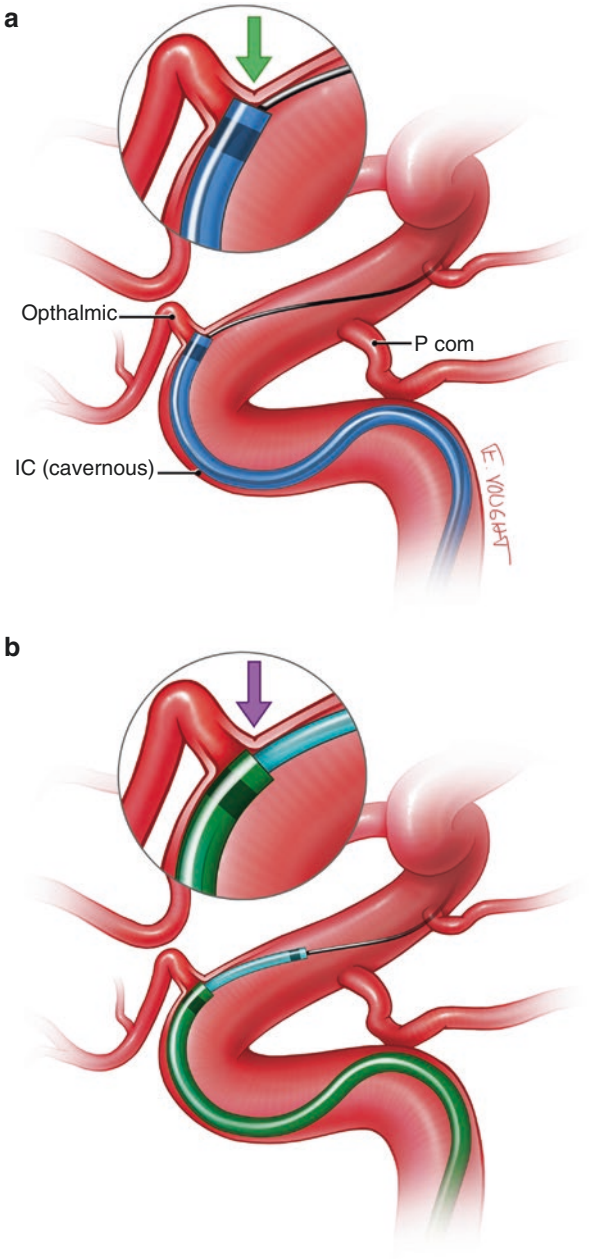


Fig. 32.1 (**a**) While a larger catheter lumen provides higher suction and more rapid removal of thrombus, it results in a larger catheter profile and "ledge effect" which renders navigation past the ophthalmic artery origin challenging. (**b**) To overcome this obstacle, access with an intermediate catheter is optimized with a coaxial technique resulting in a more tapered construct that minimizes the "ledge effect"

Third Generation: Stent Retrievers

The next generation of mechanical thrombectomy devices includes the "stent retriever" family: Solitaire (ev3 Endovascular, Plymouth, Minnesota, USA), Trevo Pro (Stryker Neurovascular, Kalamazoo Michigan, USA), and arguably the Penumbra 3D separator (Penumbra, Alameda, California, USA). The formal stent retrievers are literally stents that are fully recapturable and fused to the delivery microwire. Differences in cell design and lubricity and end portion variations have also been introduced in pre-market stent retrievers and are beyond the scope of this article. The Penumbra 3D separator differs from formal stent retrievers in that there is no "stent." A larger portion of the separator design by mass is designed to engage at the center of the vessel lumen rather than in an actual stent where the material is primarily at the outer margins of the vessel near the intima. These devices have the advantage of efficacious recanalization like a stent but are able to be removed, which obviates the need for clopidogrel and aspirin. While the Solitaire was the first to be released, all major device manufacturers produce similar devices [56]. The design differences in these devices have yet to show statistical differences in efficacy or safety.

Stent retrievers (SR) capitalize on the advantages observed with partial stent deployment and recapture during thrombectomy. The microcatheter is delivered across the thrombus, and the SR is unsheathed from within the thrombus itself. The outward radial force of the SR as it deploys promotes engaging the clot. While doing so, cerebral blood flow to the involved territory is temporarily restored, functioning as an "endovascular bypass." Once the SR has engaged the thrombus, it is pulled back ("retrieved") into a guide catheter. Application of suction with either a pump or manual syringe aspiration during retrieval may promote clot purchase and reduce the showering of emboli. Operators may also opt to employ a balloon guide catheter as an adjunct to decrease the likelihood of emboli to new territory. Recanalization rates with SR were found to be superior to the Merci device in several studies [49, 51], leading to rapid and widespread adoption.

To minimize the distance, the SR must travel while engaging the thrombus, especially into larger-caliber vasculature such as the internal carotid artery from the middle cerebral artery, and mitigating the possibility of losing purchase of the clot, variations to the SR technique have been employed with incorporation of Penumbra reperfusion catheters. For example, a 5Max catheter can be advanced over an 025 microcatheter and microwire up to the site of occlusion and left at the face of the thrombus. The SR is then deployed and the microcatheter is removed, leaving the SR in place. The SR is then pulled directly into the 5Max while maintaining aspiration (the so-called "Solumbra" technique since it combines a stent retriever (Solitaire) with a Penumbra aspiration catheter), and both are removed together (Fig. 32.2), much in the same way as the Merci retriever device was removed with a DAC. However, traction is minimized as compared with the Merci system since the force vectors are horizontal in orientation from the aperture of the aspiration catheter in parallel to the M1. This eliminated the painful stimulus that patients were formerly experiencing. Thus, in addition to representing a more effective technique,

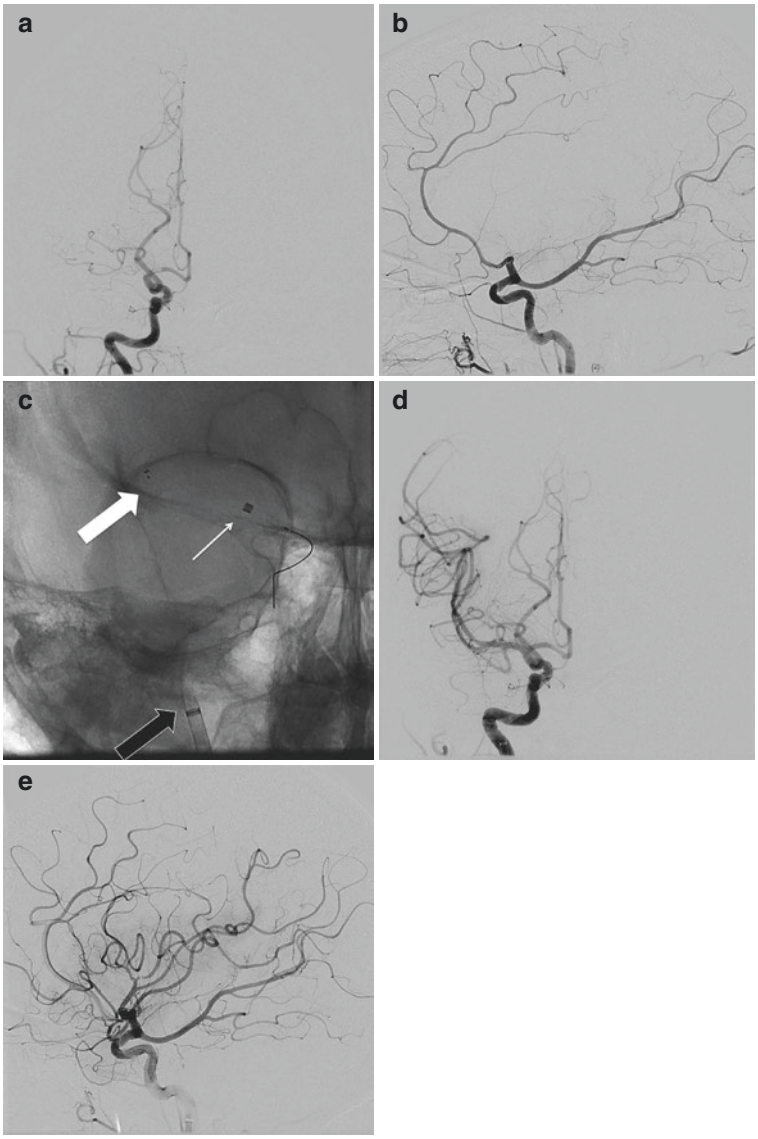


Fig. 32.2 "Solumbra" (Solitaire and Penumbra) technique. (**a**) Anteroposterior (AP) and (**b**) lateral digital subtraction angiography (DSA) demonstrates an M1 occlusion. (**c**) A Solitaire stent retriever (SR) is deployed across the M1 segment occlusion (large white arrow), with the aspiration catheter in the proximal M1 segment (small white arrow) and the guide catheter in the distal cervical internal carotid artery (black arrow). (**d**) The SR is then withdrawn back into the aspiration catheter under direct aspiration applied locally at the M1. Operator may choose to withdraw the SR entirely into the aspiration catheter or to partially withdraw and then pull both the SR and the aspiration catheter together back to the guide catheter. Aspiration can also be applied at the guide catheter. Some may choose to perform this technique with a balloon guide catheter to affect flow reversal for added protection against distal emboli in the event of thrombus fragmentation. (**e**) AP and lateral DSA demonstrates recanalization of the M1 occlusion (TICI 2B) with showering of distal fragments and small vessel occlusions

the now painless procedure had the added advantage of reintroducing the concept of the awake thrombectomy, with many operators now electing to perform the procedure with minimal conscious sedation. Advantages included the ability to examine the patient's neurological status throughout the procedure, shorter CT to groin stick times, and avoiding the imminent risk of systemic hypotension from induction of general anesthesia. In refractory cases in which the thrombus cannot be extracted using a standard SR approach, two SR deployed in "Y" configuration (coined "Y-stent retriever") have been described (Figs. 32.3 and 32.4).

SR technology was employed exclusively in the ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT trials. While the MR CLEAN trial did not dictate which thrombectomy device was to be utilized, the majority of cases were also SR based. Given that SR were used in the overwhelming majority of patients enrolled in the positive trials, they have often been referred to as the "Stent Retriever trials," which are reflected in the updated June 2015 American Heart Association/American Stroke Association guidelines recommending thrombectomy to be performed with a

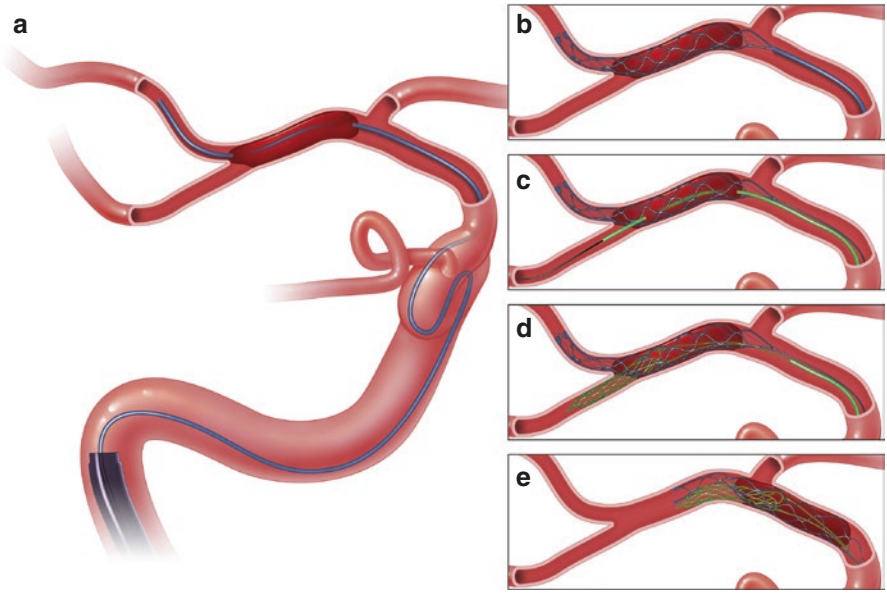


Fig. 32.3 Illustration of the "Y-stent retriever" technique with schematic illustrations to depict the procedure. (**a**) A Headway 27 microcatheter (MicroVention Terumo) was navigated into the occluded vessel. (**b**) A 4 × 20 mm Solitaire SR (Covidien) was deployed from the right superior M2 branch to M1. (**c**) The microcatheter is removed to leave more space in the lumen of the guide catheter for another system and for more potent aspiration. Another system is navigated using a Headway 21 microcatheter is advanced to the right inferior M2 artery passing through the interstices of the stent previously deployed. (**d**) Once in this "Y" configuration, a 4 × 20 mm Catch stent retriever (Balt) is deployed from the right inferior M2 artery to M1, leaving the proximal tip of the Catch SR inside the Solitaire SR, thus forming the "Y-stent retriever." (**e**) Both devices are slowly recovered by simultaneously pulling them together into guide catheter under continuous aspiration and fluoroscopic imaging control

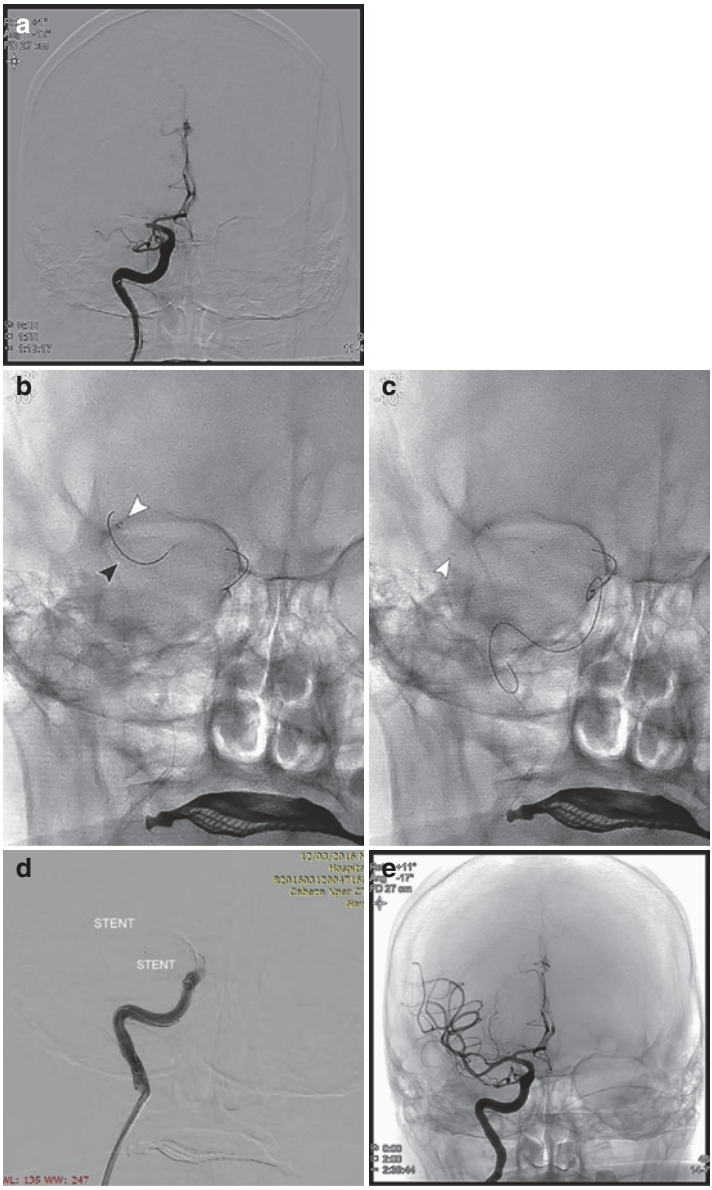


Fig. 32.4 (**a**) Anteroposterior projection of right internal carotid digital subtraction angiography. An occlusion at the level of the right proximal MCA-M1 is detected, TICI 0. (**b**) Angiographic imaging of the Y-SR technique procedure: front projection showing 4 × 20 mm Solitaire SR (Covidien) already deployed from the right superior M2 branch to M1 (white arrow). Another system is advanced to the right inferior M2 artery passing through the interstices of the stent previously deployed (black arrow). (**c**) Once in this "Y" configuration, a 4 × 20 mm Catch stent retriever (Balt) is deployed from the right inferior M2 artery to M1 (white arrow), leaving the proximal tip front projections of right internal carotid angiography. This resulted in complete recanalization of the branch with normal antegrade flow, Thrombolysis in Cerebral Infarction (TICI) scale 3, of the Catch SR inside the Solitaire SR. (**d**) AP view showing the stent retrievers in place. (**e**)

SR. However, thrombectomy techniques evolved even while those trials were enrolling, setting the stage for the next-generation strategy as detailed below. Although controversial, it is the belief of many stroke experts that it's more important that the LVO *is* recanalized quickly and effectively (outcome specific), rather than *how* it is recanalized (device specific). This philosophy has allowed continued improvements in thrombectomy techniques which are now being tested in a randomized controlled trial setting (COMPASS), as detailed in the next section.

New Generation: Direct Aspiration

Direct aspiration [57–60] has become possible due to advances in catheter technology that allow large-caliber aspiration catheters to be advanced intracranially to the thrombus. In general, the largest size aspiration catheter that the vessel can accommodate should be utilized. In the first iteration, this was most commonly a Penumbra 5Max reperfusion catheter (Penumbra, Oakland, CA) for M1 or carotid terminus occlusions. The 5Max can be advanced to the level of the thrombus over any microcatheter and microwire the operator chooses but most commonly a Velocity microcatheter (Penumbra, Oakland, CA) over a 0.016 inch Fathom wire (Boston Scientific Corp., Naidich, MA). The microcatheter and wire are removed, and aspiration is applied by either a 20 or 60 cc syringe or the use of the Penumbra aspiration pump that is part of the Penumbra thrombectomy/aspiration system [38]. Inability to draw back blood on aspiration confirms optimal position of the 5Max catheter abutting the thrombus. The next iteration involved advancing the catheter slightly to ensure firm engagement with the thrombus. The 5Max catheter is then slowly withdrawn while maintaining aspiration. Aspiration is also applied to the side port of the guide catheter to prevent dislodging the thrombus from the 5Max aperture as it is withdrawn into the sheath. Clots are typically removed en bloc, minimizing the risk of downstream emboli (Fig. 32.5). When this technique is successful, it eliminates the need to introduce stent retriever or Penumbra separator devices, leading to an overall much lower procedure device cost. [57, 58] Thus, we have found the initial application of this technique to provide the highest cost-effective value in acute stroke treatment.

This approach was facilitated by the development of the Penumbra Max aspiration catheter technology which significantly increased the ease and speed of navigation of a large-bore catheter into the intracranial circulation. The direct aspiration technique differs from prior thrombectomy methods, as it focuses on engaging and removing the clot in its entirety rather than the use of the separator that was designed to macerate the thrombus and clear the tip of the aspiration catheter [40]. Historically, due to the challenges with tracking an aspiration catheter into the intracranial circulation, catheters had to be telescoped with other catheters together or other tricks employed to advance through the siphon [32, 34, 41, 54, 55]. However, the superior trackability of the Penumbra Max catheters has given us the confidence to attempt direct aspiration alone without the fear that it will be a significant time and danger

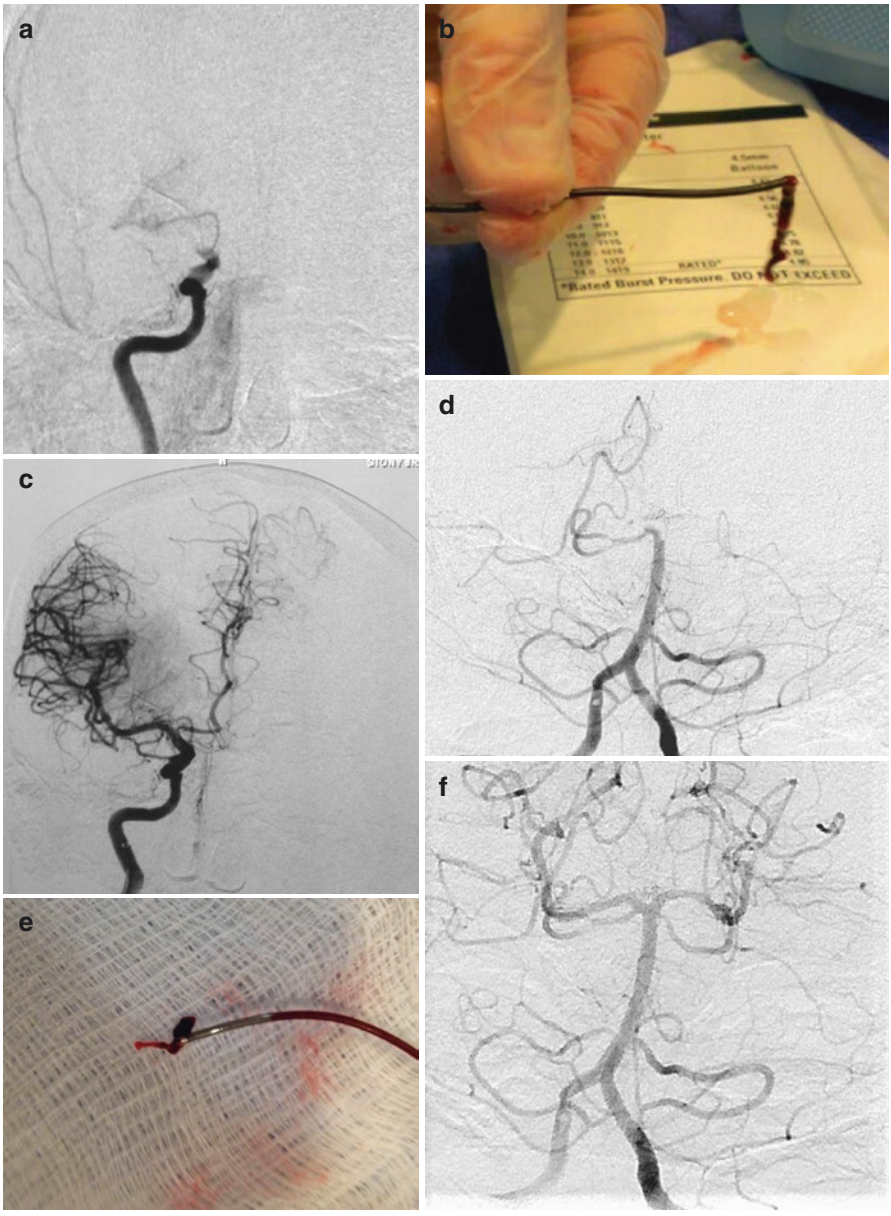


Fig. 32.5 ADAPT illustrations. Direct aspiration typically removed the thrombus en bloc, minimizing the risk of distal emboli. The largest-bore aspiration catheter that the occluded vessel will accommodate is advanced to the level of the thrombus. Aspiration is applied to engage the thrombus, which is then removed as demonstrated in the illustrations. (**a**,**b**,**c**) Carotid terminus occlusion recanalized in 15 min from groin puncture with direct aspiration thrombectomy in a single pass. (**d**, **e**, **f**) Basilar apex occlusion recanalized in 10 min with two passes of direct aspiration thrombectomy. (**g**, **h**, **i**) MCA bifurcation occlusion recanalized in 12 min with a single pass direct aspiration. (**j**, **k**, **l**) MCA bifurcation occlusion recanalized in 7 min with a single pass direct aspiration

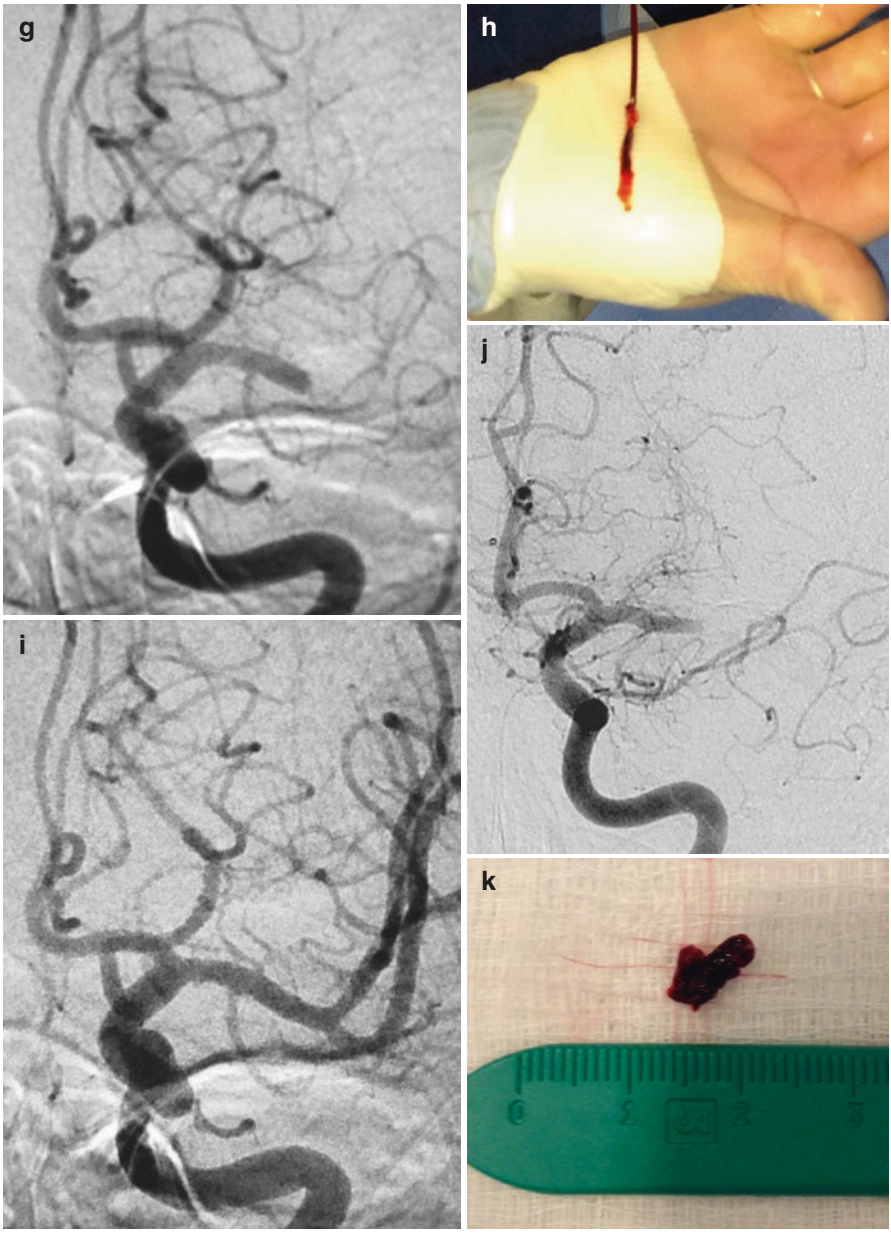
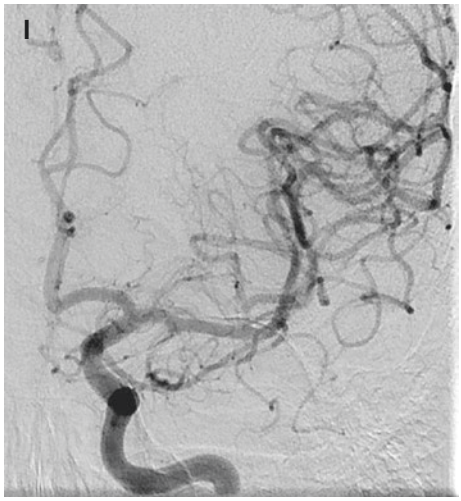


Fig. 32.5 (continued)

Fig. 32.5 (continued)



impediment to the patient if intracranial access is lost. The second iteration of the aspiration catheter, the 5Max ACE, has an increased inner diameter of 0060 at the distal 30 cm while housing a 0.068 proximal end for larger aspiration forces. Advances in catheter technology would soon follow, allowing for even larger-bore catheters to be safely delivered to the intracranial circulation. With the introduction of the ACE 064 and the ACE 068 (Penumbra, Oakland, CA), the direct aspiration technique was refined further. Owing to the larger aperture of these catheters, the aspiration catheter can now be advanced over the thrombus, to "ingest" the thrombus which is now typically aspirated directly into the catheter without having to remove it (Fig. 32.6).

Perhaps most importantly, if aspiration alone is not successful at revascularizing the occluded vessel, the Penumbra 5Max catheter can also function as a distal conduit for other devices such as a smaller 3Max catheter for direct aspiration in more distal branches (e.g., M2, P2, or P3) or stent retrievers, balloons or stents. This forms the basis of the "ADAPT" technique (a direct aspiration first pass technique) which is gaining popularity. If direct aspiration attempts are unsuccessful, other attempts including SR thrombectomy can then be performed. At the time of this writing, enrollment is well on the way for the COMPASS trial, a randomized controlled trial of anterior circulation LVO treated within 6 h of symptom onset with thrombectomy technique randomized to either SR or direct aspiration first. If unsuccessful after three attempts, another technique is then allowed. Trial completion is expected in early 2017.

The newest iteration of direct aspiration involves its application in more distal vasculature. In smaller-caliber vessels, the technique can be employed with either a 4 Max or 3Max reperfusion catheter (Penumbra Inc., Oakland, CA). In principle, the largest-bore catheter that the occlude vessel can accommodate is selected for aspiration (Fig. 32.7), with effective (TICI ≥2B 97.1%) and fast recanalization (mean 35.7 min) achieved safely [59].

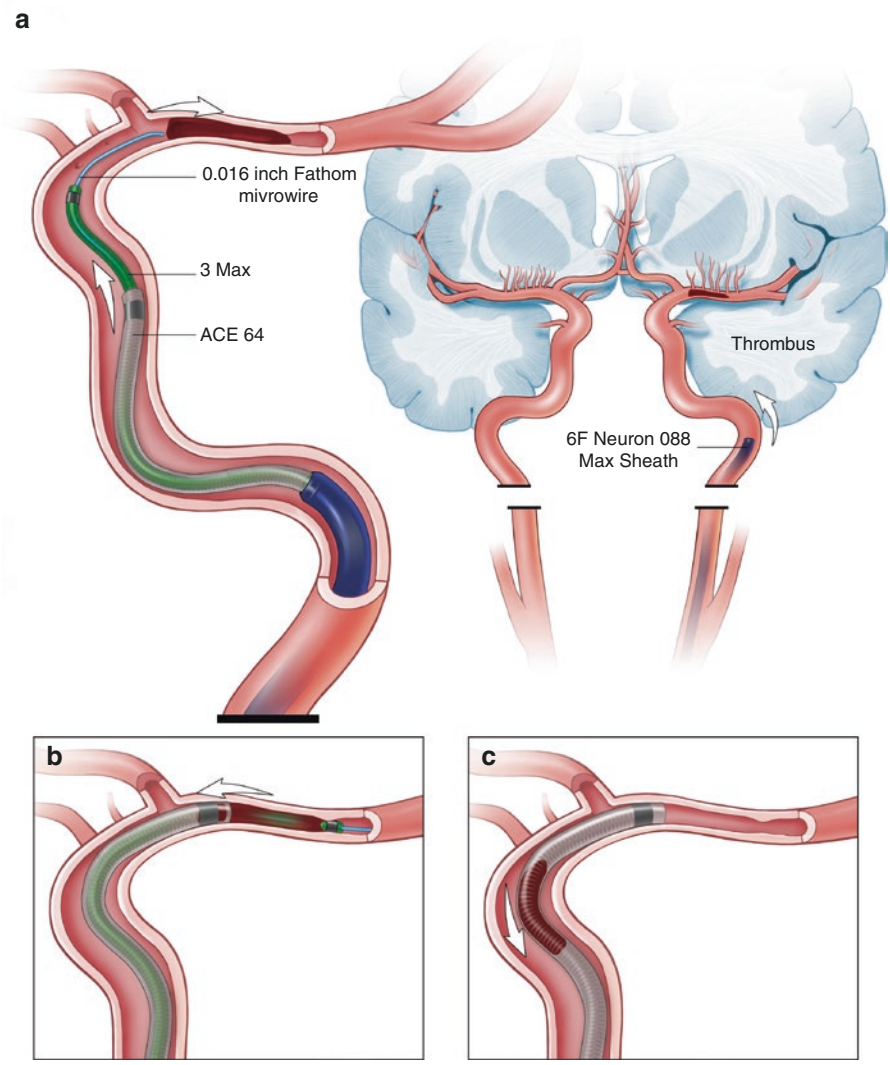


Fig. 32.6 Aspiration catheter technology has rapidly advanced. With the introduction of the ACE 064 and the ACE 068 (Penumbra, Oakland, CA), the direct aspiration technique has been refined further. Owing to the larger aperture of these catheters, the aspiration catheter can now be advanced directly over the thrombus to "ingest" the thrombus under aspiration. The thrombus is now typically aspirated directly into the catheter aspiration tubing without having to remove it

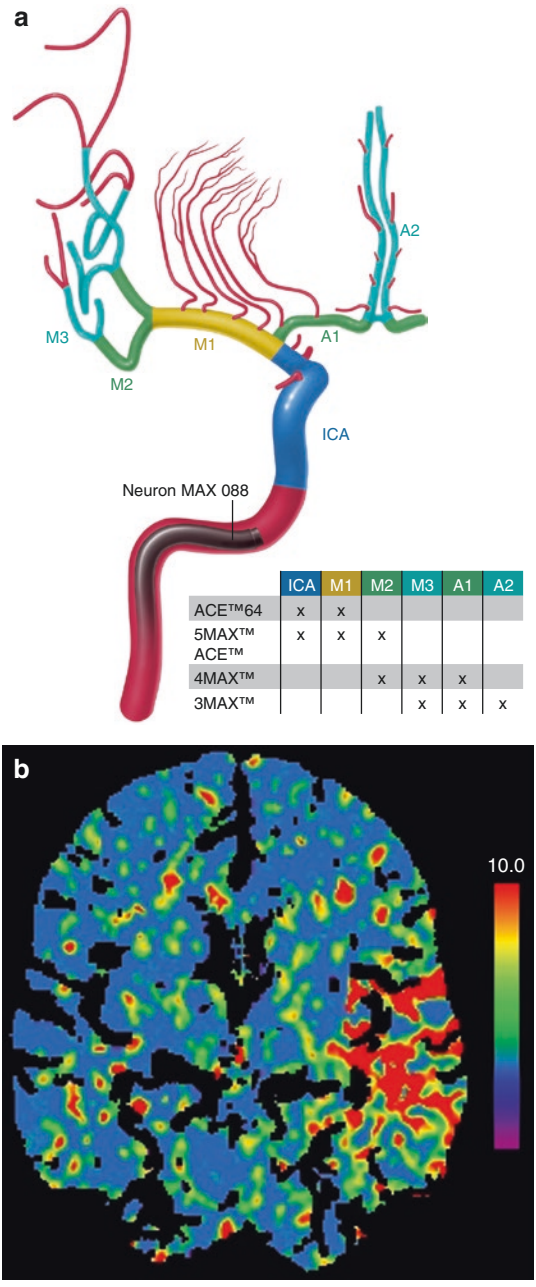


Fig. 32.7 (**a**) Illustration demonstrating aspiration catheter size recommendations for anterior circulation thrombectomy. The guide catheter is positioned in the ICA, providing a platform for thrombectomy with aspiration catheters. (**b**) CT perfusion imaging demonstrating elevated mean transit time in the left frontal lobe consistent with a left M2 occlusion. (**c**) AP and (**d**) lateral projection cerebral angiogram during a left internal carotid injection demonstrating M2 occlusion with no flow past the site of thrombus (arrows). (**e**). AP and (**f**) lateral projection cerebral angiogram during a left internal carotid injection following thrombectomy demonstrating resolution of M2 occlusion and opacification of distal branches. (**g**) CT perfusion imaging demonstrating elevated mean transit time consistent with a left A2 occlusion. (**h**) Lateral projection cerebral angiogram demonstrating A2 occlusion (arrow), (**i**) post-thrombectomy lateral projection cerebral angiogram with resolution of A2 occlusion and complete opacification of distal branches. (**j**) CT perfusion imaging demonstrating elevated mean transit time in the right occipital lobe consistent with right P2 ischemia. (**k**) Cerebral angiogram with AP projection from a left vertebral artery injection demonstrating right P2 occlusion and no opacification distal to the thrombus (arrow). (**l**) Post-thrombectomy cerebral angiogram with AP projection from a left vertebral artery injection demonstrating resolution of the thrombus with opacification of the distal PCA branches

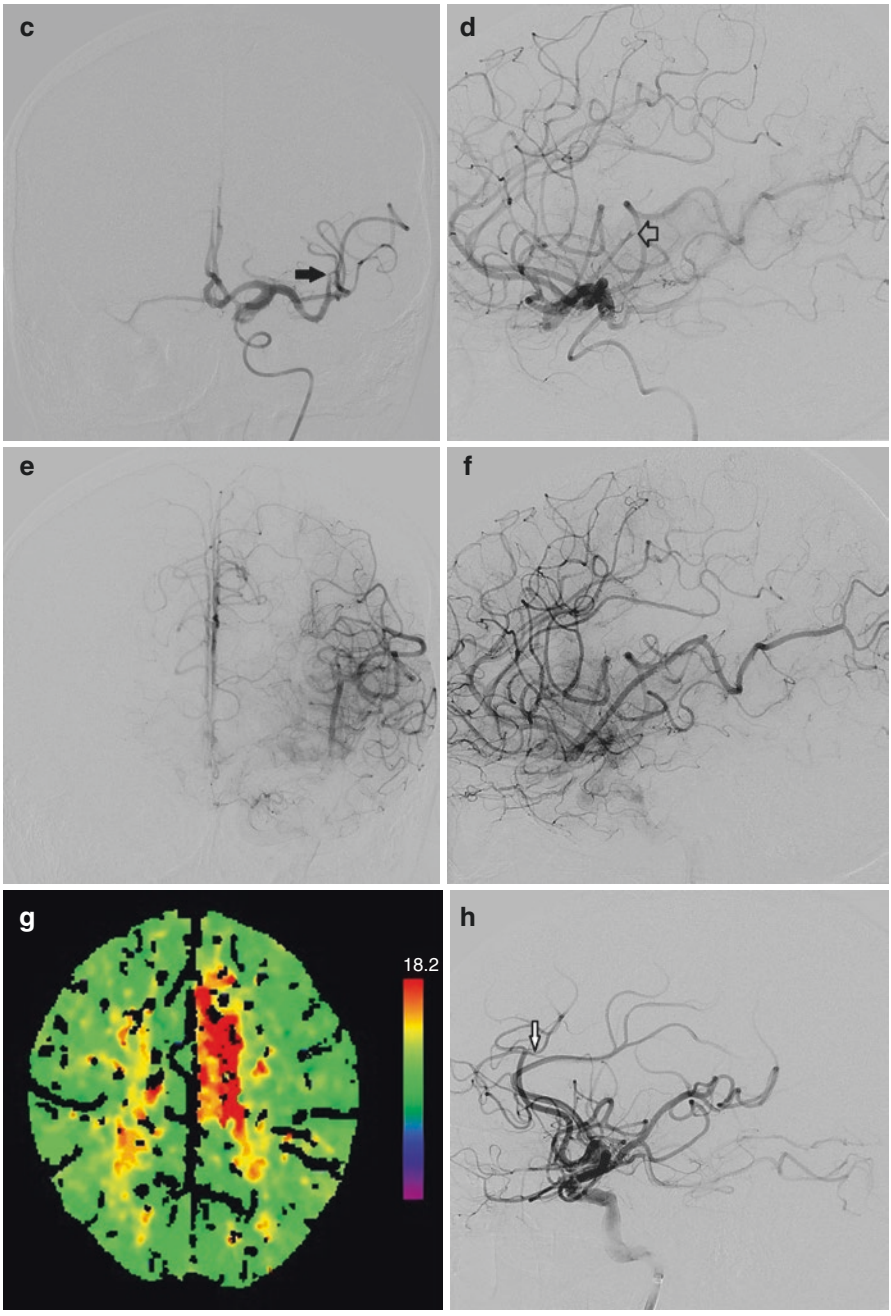


Fig. 32.7 (continued)

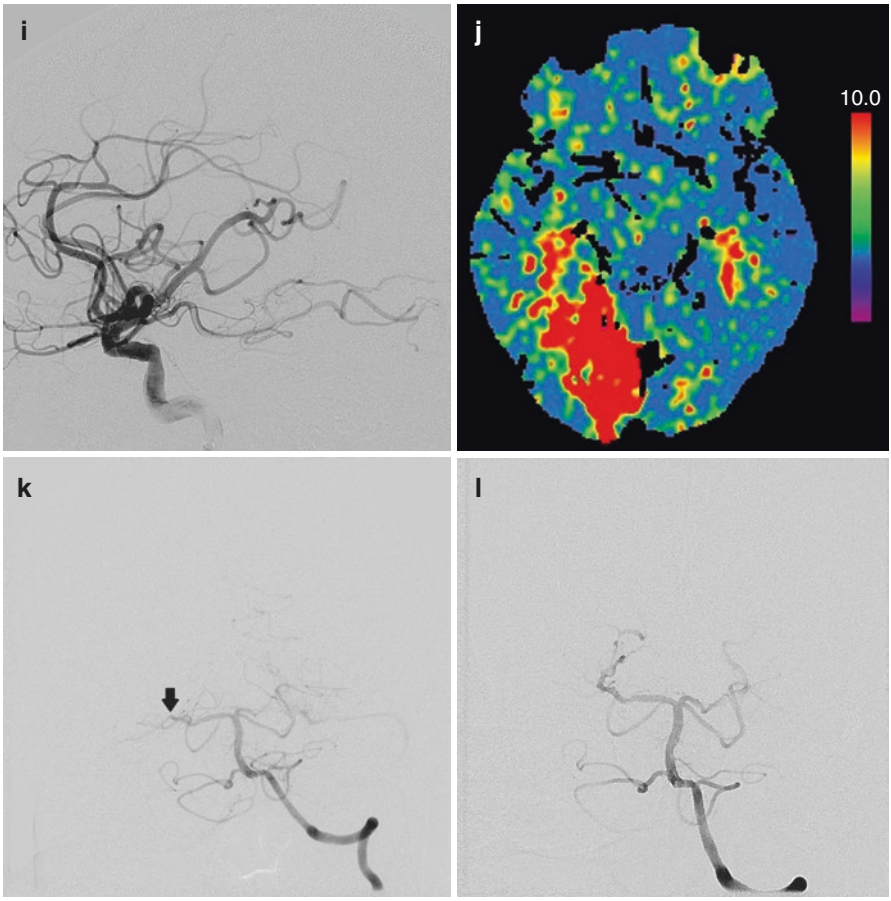


Fig. 32.7 (continued)

Future Devices

On-label intra-arterial devices for acute stroke intervention are developing rapidly with the introduction of both iterative changes and new classes of devices. With new generations of devices, increasingly high rates of recanalization are being reported. It is likely new techniques and devices will continue to evolve offering a more robust tool set and combination of devices for interventional management of acute stroke. However, futile recanalization remains a problem [43].

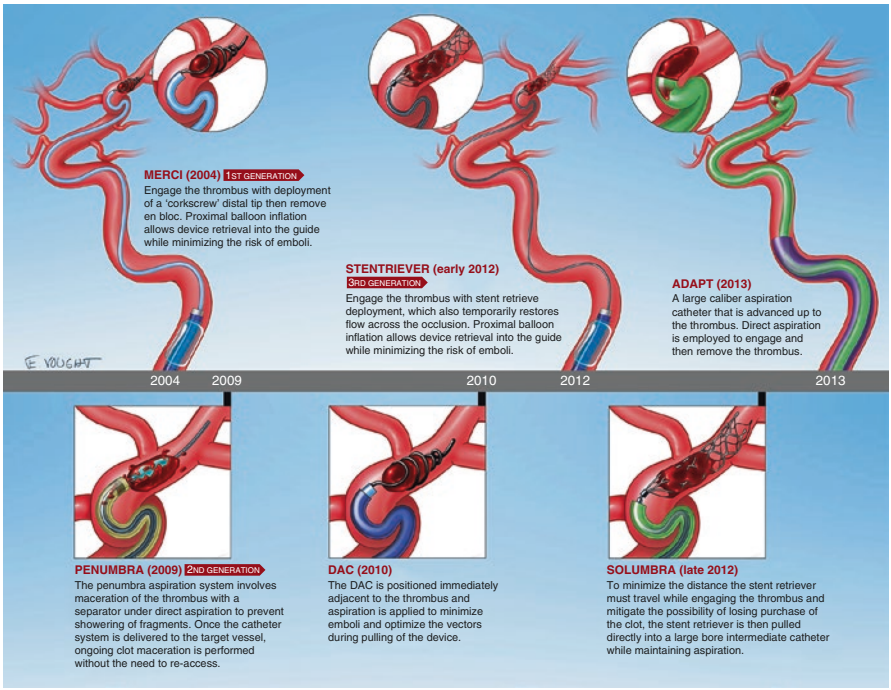


Fig. 32.8 Illustration depicting the major steps in evolution of thrombectomy devices, beginning from the first-generation concept to the state-of-the-art approaches

Conclusion

There have been rapid advances in thrombectomy devices and approaches over the past decade, from rudimentary mechanical disruption, followed by intra-arterial thrombolytic infusions to increasingly effective thrombectomy devices (Fig. 32.8) [61]. While it remains unknown what combinations of techniques, devices, selection criteria, and medicines will yield the best outcomes, ongoing improvements in the devices and techniques are yielding improved angiographic and clinical outcomes. Device technology, selection strategies, and medical management will likely evolve in tandem, and we look forward to the continued evolution of thrombectomy approaches for acute stroke in the future. We remind our colleagues in the neurointerventional field that high enrollment in clinical trials will be required to secure the role of intra-arterial therapy in the management of stroke.

References

1. 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;333:1581–7.

2. Jauch EC, Saver JL, Adams HP, et al. American Heart Association Stroke C, Council on Cardiovascular N, Council on Peripheral Vascular D, Council on Clinical C: 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.
3. Hirsch JA, Yoo AJ, Nogueira RG, Verduzco LA, Schwamm LH, Pryor JC, Rabinov JD, Gonzalez RG. Case volumes of intra-arterial and intravenous treatment of ischemic stroke in the USA. J Neurointerv Surg. 2009;1:27–31.
4. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Timeliness of tissue-type plasminogen activator therapy in acute ischemic Stroke Clinical perspective patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011;123:750–8.
5. Wechsler LR, Roberts R, Furlan AJ, Higashida RT, Dillon W, Roberts H, Rowley HA, Pettigrew LC, Callahan AS, Bruno A. Factors influencing outcome and treatment effect in PROACT II. Stroke. 2003;34:1224–9.
6. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators Prolyse in Acute Cerebral Thromboembolism. Stroke. 1998;29:4–11.
7. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM. Intra-arterial prourokinase for acute ischemic stroke. JAMA. 1999;282:2003–11.
8. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013;368:914–23.
9. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med. 2013;368:904–13.
10. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. N Engl J Med. 2013;368:893–903.
11. Chimowitz MI. Endovascular treatment for acute ischemic stroke--still unproven. N Engl J Med. 2013;368:952–5.
12. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20. https://doi.org/10.1056/NEJMoa1411587. Erratum in: N Engl J Med. 2015 Jan 22;372(4):394
13. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30.
14. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM, EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–18.

15. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R, SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
16. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A, REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015 Jun 11;372(24):2296–306.
17. Suarez J, Sunshine J, Tarr R, Zaidat O, Selman W, Kernich C, Landis D. Predictors of clinical improvement, angiographic recanalization, and intracranial hemorrhage after intra-arterial thrombolysis for acute ischemic stroke. Stroke. 1999;30:2094–100.
18. Ernst R, Pancioli A, Tomsick T, Kissela B, Woo D, Kanter D, Jauch E, Carrozzella J, Spilker J, Broderick J. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. Stroke. 2000;31:2552–7.
19. Hacke W, Zeumer H, Ferbert A, Bruckmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. Stroke. 1988;19:1216–22.
20. Brandt T, von Kummer R, Muller-Kuppers M, Hacke W. Thrombolytic therapy of acute basilar artery occlusion. Variables affecting recanalization and outcome. Stroke. 1996;27:875–81.
21. Abou-Chebl A, Bajzer CT, Krieger DW, Furlan AJ, Yadav JS. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. Stroke. 2005;36:2286–8.
22. Gobin YP, Starkman S, Duckwiler GR, Grobelny T, Kidwell CS, Jahan R, Pile-Spellman J, Segal A, Vinuela F, Saver JL. MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke. 2004;35:2848–54.
23. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, Lutsep HL, Nesbit GM, Grobelny T, Rymer MM. Safety and efficacy of mechanical embolectomy in acute ischemic stroke results of the MERCI trial. Stroke. 2005;36:1432–8.
24. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke emergency management of stroke (EMS) bridging trial. Stroke. 1999;30(12):2598–605.
25. Zeumer H, Freitag HJ, Zanella F, Thie A, Arning C. Local intra-arterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (r-TPA). Neuroradiology. 1993;35(2):159–62.
26. Smith W. 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. Am J Neuroradiol. 2006;27:1177–82.
27. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS. Merci, multi MWC: mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and multi MERCI part I trials. Stroke. 2007;38:1274–80.
28. Qureshi AI, Siddiqui AM, Suri MFK, Kim SH, Ali Z, Yahia AM, et al. Aggressive mechanical clot disruption and low-dose intra-arterial third-generation thrombolytic agent for ischemic stroke: a prospective study. Neurosurgery. 2002;51(5):1319–29.
29. Barnwell SL, Clark WM, Nguyen TT, O'Neill OR, Wynn ML, Coull BM. Safety and efficacy of delayed intraarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke. Am J Neuroradiol. 1994;15(10):1817–22.
30. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, Lutsep HL, Rymer MM, Higashida RT, Starkman S. Mechanical thrombectomy for acute ischemic stroke final results of the multi MERCI trial. Stroke. 2008;39:1205–12.
31. Chopko BW, Kerber C, Wong W, Georgy B. Transcatheter snare removal of acute middle cerebral artery thromboembolism: technical case report. Neurosurgery. 2000;46(6):1529–31.

32. Spiotta AM, Hussain MS, Sivapatham T, Bain M, Gupta R, Moskowitz SI, Hui FK. The versatile distal access catheter: the Cleveland Clinic experience. Neurosurgery. 2011;68:1677.
33. Jankowitz B, Aghaebrahim A, Zirra A, Spataru O, Zaidi S, Jumaa M, Ruiz-Ares G, Horowitz M, Jovin TG. Manual aspiration thrombectomy adjunctive endovascular recanalization technique in acute stroke interventions. Stroke. 2012;43:1408–11.
34. Turk A, Manzoor MU, Nyberg EM, Turner RD, Chaudry I. Initial experience with distal guide catheter placement in the treatment of cerebrovascular disease: clinical safety and efficacy. J Neurointerv Surg. 2013;5(3):247–52.
35. Mahon BR, Nesbit GM, Barnwell SL, Clark W, Marotta TR, Weill A, Teal PA, Qureshi AI. North American clinical experience with the EKOS MicroLysUS infusion catheter for the treatment of embolic stroke. Am J Neuroradiol. 2003;24:534–8.
36. Kuliha M, Roubec M, Fadrná T, Šaňák D, Herzig R, Jonszta T, Czerný D, Krajča J, Procházka V, Školoudík D. Endovascular sono-lysis using EKOS system in acute stroke patients with a main cerebral artery occlusion–a pilot study. Pers Med. 2012;1:65–72.
37. Clark W, Lutsep H, Barnwell S, Nesbit G, Egan R, North E, Yanase L, Lowenkopf T, Petersen B, Grunwald I. 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;40:2761–8.
38. Yoo AJ, Frei D, Tateshima S, Turk AS, Hui FK, Brook AL, Heck DV, Hirsch JA. The penumbra stroke system: a technical review. J Neurointerv Surg. 2012;4:199–205.
39. Frei D, Gerber J, Turk A, McPherson M, Heck D, Hui F, Joseph G, Jahan R, Miskolczi L, Carpenter J, Grobelny T, Goddard J, Turner RD, Huddle D, Bellon R, Chaudry I. The SPEED study: initial clinical evaluation of the Penumbra novel 054 Reperfusion Catheter. J Neurointerv Surg. 2013;5(Suppl 1):i74–6.
40. Tarr R, Hsu D, Kulcsar Z, Bonvin C, Rufenacht D, Alfke K, Stingele R, Jansen O, Frei D, Bellon R. The POST trial: initial post-market experience of the penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. J Neurointerv Surg. 2010;2:341–4.
41. Hui FK, Hussain MS, Spiotta A, Bhalla T, Toth G, Moskowitz SI, Elgabaly M, Sivapatham T, Rasmussen PA. Merci retrievers as access adjuncts for reperfusion catheters: the grappling hook technique. Neurosurgery. 2012;70:456–60.
42. Ringer AJ, Qureshi AI, Fessler RD, Guterman LR, Hopkins LN. Angioplasty of intracranial occlusion resistant to thrombolysis in acute ischemic stroke. Neurosurgery. 2001;48:1282–90.
43. Levy EI, Siddiqui AH, Crumlish A, Snyder KV, Hauck EF, Fiorella DJ, Hopkins LN, Mocco J. First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke SARIS (stent-assisted recanalization in acute ischemic stroke). Stroke. 2009;40:3552–6.
44. Kelly ME, Furlan AJ, Fiorella D. Recanalization of an acute middle cerebral artery occlusion using a self-expanding, reconstrainable, intracranial microstent as a temporary endovascular bypass. Stroke. 2008;39:1770–3.
45. Levy EI, Ecker RD, Horowitz MB, Gupta R, Hanel RA, Sauvageau E, Jovin TG, Guterman LR, Hopkins LN. Stent-assisted intracranial recanalization for acute stroke: early results. Neurosurgery. 2006;58:458–63.; discussion 458–463.
46. Mocco J, Hanel RA, Sharma J, Hauck EF, Snyder KV, Natarajan SK, Linfante I, Siddiqui AH, Hopkins LN, Boulos AS. Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods: clinical article. J Neurosurg. 2010;112:557–62.
47. Levy EI, Rahman M, Khalessi AA, Beyer PT, Natarajan SK, Hartney ML, Fiorella DJ, Hopkins LN, Siddiqui AH, Mocco J. Midterm clinical and angiographic follow-up for the first food and drug administration-approved prospective, single-arm trial of primary stenting for stroke: saris (stent-assisted recanalization for acute ischemic stroke). Neurosurgery. 2011;69:915–20.
48. Roth C, Papanagiotou P, Behnke S, Walter S, Haass A, Becker C, Fassbender K, Politi M, Körner H, Romann M-S. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. Stroke. 2010;41:2559–67.

49. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO. Solitaire flow restoration device versus the Merci retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. 2012;380(9849):1241–9.
50. Schellinger PD, Alexandrov AV, Barreto AD, Demchuk AM, Tsivgoulis G, Kohrmann M, et al. Combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator for emergent revascularization in acute ischemic stroke (CLOTBUST-ER): design and methodology of a multinational phase 3 trial. Int J Stroke. 2015;10(7):1141–8.
51. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, Liebeskind DS, Smith WS, Trialists T. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. 2012;380:1231–40.
52. Turk AS, Spiotta A, Frei D, Mocco J, Baxter B, Fiorella D, Siddiqui A, Mokin M, Dewan M, Woo H. Initial clinical experience with the ADAPT technique: a direct aspiration first pass technique for stroke thrombectomy. J Neurointerv Surg. 2014;6(3):231–7.
53. Turk AS, Campbell JM, Spiotta A, Vargas J, Turner RD, Chaudry MI, Battenhouse H, Holmstedt CA, Jauch E. An investigation of the cost and benefit of mechanical thrombectomy for endovascular treatment of acute ischemic stroke. J Neurointerv Surg. 2014 Jan;6(1):77–80.
54. Park MS, Stiefel MF, Fiorella D, Kelly M, McDougall CG, Albuquerque FC. Intracranial placement of a new, compliant guide catheter: technical note. Neurosurgery. 2008;63:E616–7.
55. Chaudhary N, Pandey AS, Thompson BG, Gandhi D, Ansari SA, Gemmete JJ. Utilization of the neuron 6 French 0.053 inch inner luminal diameter guide catheter for treatment of cerebral vascular pathology: continued experience with ultra distal access into the cerebral vasculature. J Neurointerv Surg. 2012;4:301–6.
56. Molina CA. Futile recanalization in mechanical embolectomy trials a call to improve selection of patients for revascularization. Stroke. 2010;41:842–3.
57. Turk AS, Frei D, Fiorella D, Mocco J, Baxter B, Siddiqui A, Spiotta A, Mokin M, Dewan M, Quarfordt S, Battenhouse H, Turner R, Chaudry I. ADAPT FAST study: a direct aspiration first pass technique for acute stroke thrombectomy. J Neurointerv Surg. 2014;6(4):260–4. https://doi.org/10.1136/neurintsurg-2014-011125.
58. Turk AS, Turner R, Spiotta A, Vargas J, Holmstedt C, Ozark S, Chalela J, Turan T, Adams R, Jauch EC, Battenhouse H, Whitsitt B, Wain M, Chaudry MI. Comparison of endovascular treatment approaches for acute ischemic stroke: cost effectiveness, technical success, and clinical outcomes. J Neurointerv Surg. 2015 Sep;7(9):666–70. https://doi.org/10.1136/neurintsurg-2014-011282.
59. Vargas J, Spiotta A, Fargen K, Turner R, Chaudry I, Turk A. Long term experience using the ADAPT technique for the treatment of acute ischemic stroke. J Neurointerv Surg. 2016; pii: neurintsurg-2015-012211. doi: https://doi.org/10.1136/neurintsurg-2015-012211.
60. Vargas J, Spiotta AM, Fargen K, Turner RD, Chaudry I, Turk A. Experience with ADAPT for thrombectomy in distal cerebral artery occlusions causing acute ischemic stroke. World Neurosurg. 2017;99:31–6.
61. Spiotta AM, Chaudry MI, Hui FK, Turner RD, Kellogg RT, Turk AS. Evolution of thrombectomy approaches and devices for acute stroke: a technical review. J Neurointerv Surg. 2015;7(1):2–7. https://doi.org/10.1136/neurintsurg-2013-011022.

Chapter 33
Tandem Occlusions

Don Heck and Christina Roels

Tandem occlusion of the cervical internal carotid artery and the internal carotid artery terminus or middle cerebral artery represents a special, and more challenging, type of emergent large vessel occlusion. Unlike the more straightforward case of cardiogenic embolism, the tandem occlusion presents the simultaneous problem of an intracranial embolus and an acute thrombotic event in the cervical carotid artery (Fig. 33.1). In the coronary circulation where hemorrhage of the end organ is not a consideration, plaque rupture and thrombosis are ideally treated with stent placement, anticoagulation, and aggressive intravenous antiplatelet therapy. Such aggressive medical treatment in the setting of acute stroke is obviously at odds with the goal of safely removing the intracranial embolus without causing hemorrhage and generally not recommended in acute stroke. Tandem occlusions challenge us to balance the competing priorities.

Tandem occlusion is not uncommon, representing between 13% and 32% of patients with ELVO [1–3]. Outcomes in the ESCAPE trial were similar between patients with and without tandem occlusion [4]. Emergent endovascular treatment should in general be recommended based on similar criteria used for patients with other intracranial large vessel occlusions, e.g., evidence of an ischemic penumbra large enough to justify intervention, the probability of success, and the possibility of complications. Two disclaimers are appropriate: First, in most cases *emergent* treatment of extracranial carotid disease is *not* recommended in the *absence* of a large vessel intracranial occlusion (i.e., when the carotid terminus and middle cerebral artery are patent by antegrade flow in the internal carotid artery or by circle of Willis collaterals). While *early* treatment may be indicated for secondary stroke preven-

D. Heck (✉)
Novant Health Forsyth Medical Center,
Winston-Salem, NC, USA

C. Roels
Department of Pharmacy, Novant Health Forsyth Medical Center,
Winston-Salem, NC, USA

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_33

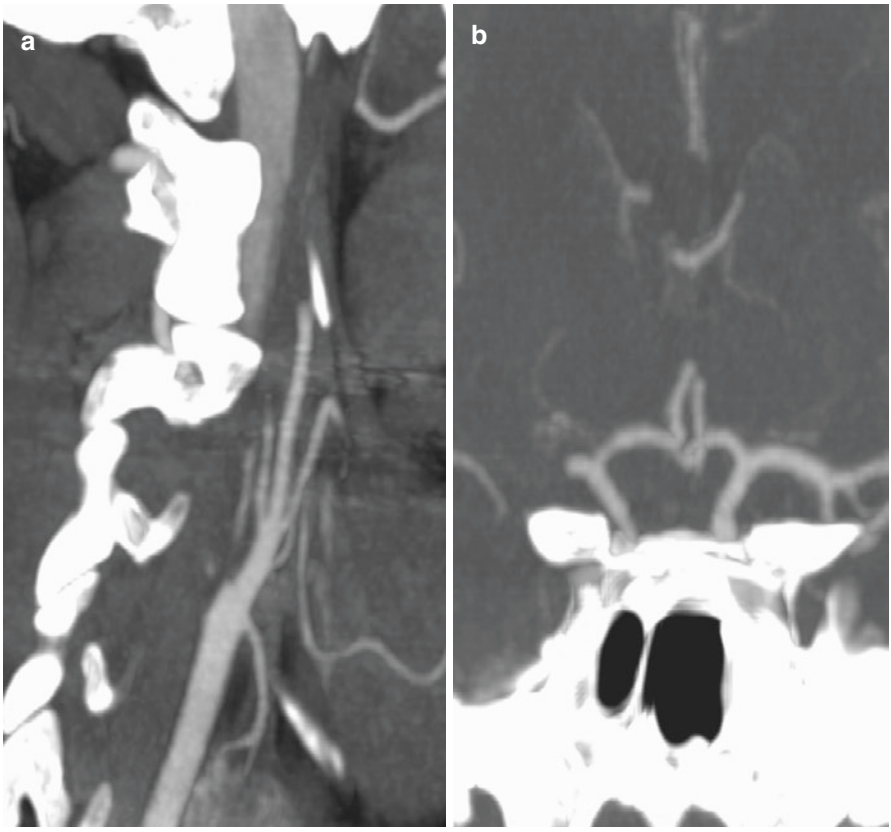


Fig. 33.1 (**a**) Lateral CTA image demonstrating an atherosclerotic occlusion of the right internal carotid artery. (**b**) CTA showing right middle cerebral artery embolus

tion in such cases of severe carotid stenosis, this usually can be done more safely after at least a brief period to stabilize the patient and optimize conditions for a carotid revascularization procedure, such as institution of optimal medical therapy prior to the intervention. There does exist the exception of a patient with an acute extracranial occlusion without an intracranial occlusion who is symptomatic because of hypoperfusion, but this is a relatively uncommon situation. Second, if the internal carotid artery is diseased, but it is possible to perform the intracranial embolectomy without treating the extracranial disease, removal of the intracranial embolus and delayed treatment of the extracranial disease under more optimal conditions are usually preferable. On the other hand, a patient with a true tandem occlusion must be treated emergently, hence the added challenge of dealing with the extracranial atherosclerotic carotid occlusion, or near occlusion, in order to perform the more important part of the procedure—the intracranial embolectomy.

Ideally tandem endovascular treatment would safely reestablish a normal intracranial circulation and preserve the internal carotid artery, without causing hemorrhage or embolization to a new territory (the anterior cerebral artery, posterior

cerebral artery, or ophthalmic artery). Optimal conditions for carotid stenting include therapeutic dual antiplatelet therapy and anticoagulation. Unfortunately, such conditions increase the risk of intracranial hemorrhage in the setting of acute stroke, and hence compromises must be made. In general, following a successful intracranial embolectomy, extracranial carotid reocclusion is not always associated with neurologic deterioration. On the other hand, hemorrhagic conversion of an infarct usually does result in neurologic decline, hence avoiding the latter must be the primary consideration. However, it is also true that reocclusion of the internal carotid artery may be associated with repeat embolization and that achieving direct carotid inflow to support pial collaterals is likely also beneficial in some cases, for example, with less than TICI 3 results of the thrombectomy. Judicious steps to establish and preserve the patency of the internal carotid artery are therefore reasonable.

Technique

Proximal to Distal

The "proximal to distal" technique advocates treating the carotid lesion with stenting prior to performing the mechanical embolectomy. This technique has advantages. First, a passage through the diseased carotid artery is immediately established for larger devices, such as guide catheters, distal aspiration catheters, and larger microcatheters used to deliver retrieval devices. Second, in a minority of cases, establishing direct carotid inflow may be enough to relieve the intracranial occlusion [5]. Third, establishing direct carotid inflow may help support pial collaterals. There are also potential disadvantages. First, performing the additional intervention such as a stent may cause a delay (although usually brief) of the intracranial embolectomy. Second, the presence of a stent in the artery may limit some options for embolectomy. For example, a stent retriever cannot be safely pulled through a carotid stent due to the risk of entanglement and hence must be recaptured by a guide or large-bore aspiration catheter advanced above the stent. Catheters may also "catch" on a stent in the artery making it more difficult to advance devices through the stent. With regard to the latter, the use of a closed cell design may ease the ability to pass other devices through the stent if a proximal to distal approach is chosen. A stent should not be placed in the setting of dense and concentric calcification, as the stent may not open properly, which can hinder the intracranial embolectomy and make thrombosis after the procedure more likely.

Distal to Proximal

The "distal to proximal" approach advocates performing the mechanical embolectomy first and treatment of the carotid lesion second. Practically speaking, in a true tandem occlusion, the extracranial carotid severe stenosis or occlusion usually must

be treated with angioplasty or "dottering" with a guide sheath in order to facilitate passage of the necessary devices intracranially (Fig. 33.2). The distal to proximal approach also has advantages. First, there is potentially less delay in performing the intracranial embolectomy. Second, immediate institution of antiplatelet therapy may be less critical as no foreign body has been implanted. Third, catheters and devices do not need to be maneuvered through a stent. Of course there are possible disadvantages. Maneuvering devices through a fresh angioplasty site or a severely stenotic lesion may cause additional embolization. Also, the incidence of elastic recoil may be high, and there may be a delay in establishing direct carotid inflow compared with the "stent-first" approach. In the distal to proximal approach, once the intracranial embolectomy is complete, one must decide whether to perform any additional intervention, such as placing a stent. Angioplasty alone may require less aggressive antiplatelet therapy to maintain patency of the artery, which is a potential advantage. Placing a stent, on the other hand, usually requires immediate institution of antiplatelet therapy to reduce the risk of platelet aggregation and thrombosis. The appearance of the carotid artery and whether or not there is normal flow in the internal carotid artery at the end of the procedure are also considerations. The decision to use angioplasty alone, or place a stent at the end of the procedure, will involve all of the above considerations, and both approaches are reasonable.

Cerebral "Protection"

In the event of emergent carotid angioplasty or stenting, the interventionalist must decide whether, and if so how, to utilize cerebral protection. In the setting of *elective* carotid stenting, cerebral protection is generally recommended. All of the FDA-approved carotid stents are approved for use in conjunction with some form of cerebral protection. In the United States, reimbursement for carotid stenting requires the use of cerebral protection. Notably, the use of cerebral protection devices has never been rigorously established superior to "unprotected" carotid stenting, but the most rigorous trial establishing the safety and efficacy of carotid stenting compared with carotid endarterectomy used a carotid filter for protection [6]. However, data also exist supporting carotid stenting without "protection," even in the elective setting [7]. The landscape in emergent carotid stenting is even more uncertain. Therapeutic anticoagulation is recommended for usage of both filter and flow-reversal cerebral protection strategies, which is obviously problematic for stroke intervention. Additionally, in the case of an occlusion, one does not always know the status of the cervical internal carotid artery in terms of its course or clot burden. Also, many filter devices are not optimal for crossing complete occlusions. Lastly, transfemoral flow-reversal systems can be cumbersome and time-consuming and do not utilize the optimal guide catheter for the intracranial intervention to come. Hence, it is reasonable and often preferable to perform emergent carotid stenting in the setting of acute stroke intervention without the use of cerebral protection.

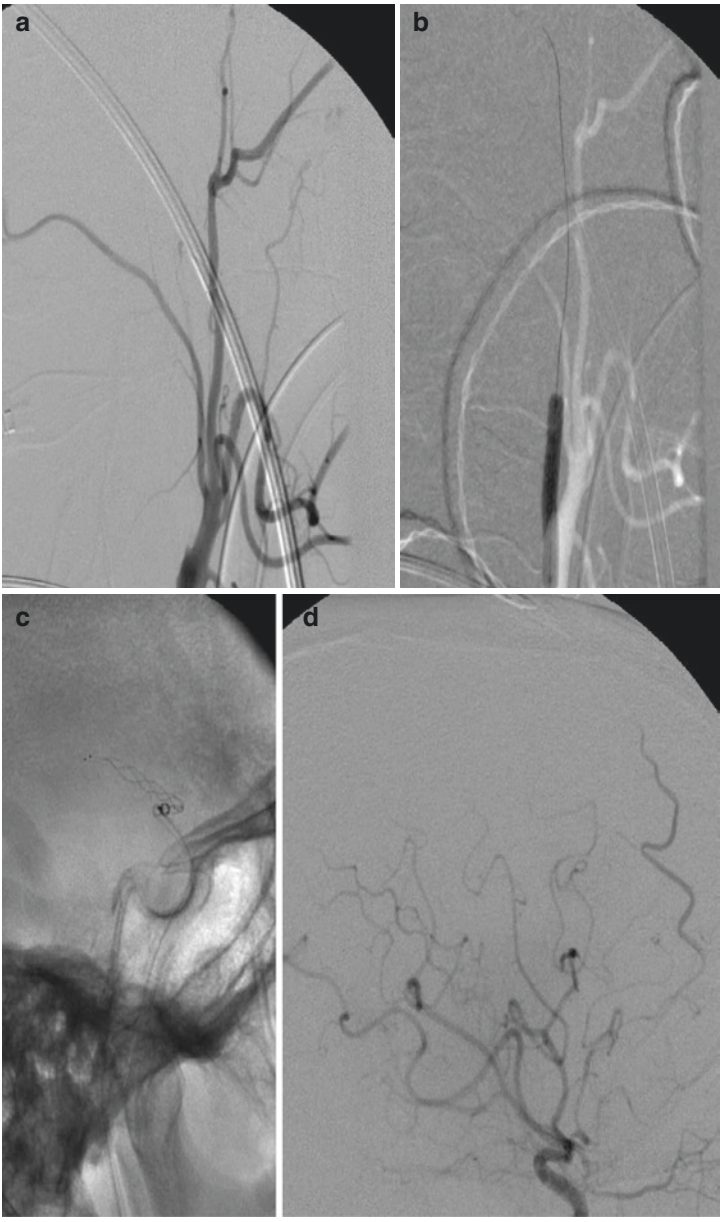


Fig. 33.2 (**a**) Angiogram of the patient in Fig. 33.1a, demonstrating an atherosclerotic occlusion of the right internal carotid artery. (**b**) Wiring of the occlusion and angioplasty. (**c**) Advancement of the guide catheter above the occlusion for embolectomy (with a distal aspiration catheter and stent retriever). (**d**) Lateral angiogram after embolectomy showing reperfusion. (**e**) Frontal angiogram after embolectomy showing reperfusion. (**f**) Placement of a carotid stent after the embolectomy

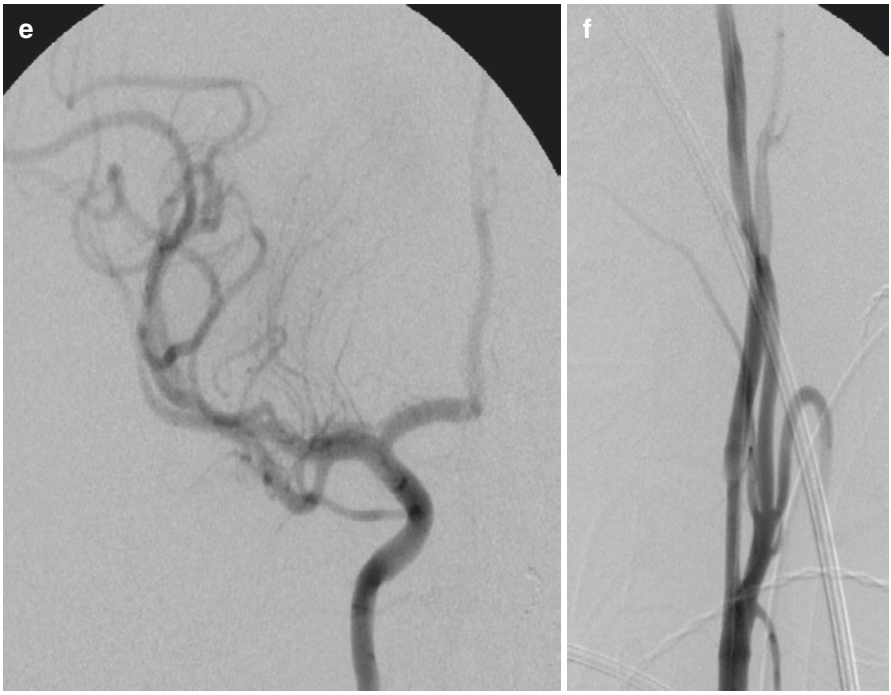


Fig. 33.2 (continued)

There are some circumstances, however, when cerebral protection may confer benefit. In the setting of a carotid terminus occlusion, when there is no antegrade flow from the carotid artery to any cerebral vessel, cerebral protection seems to have no theoretical benefit. On the other hand, in the setting of a severe carotid stenosis with antegrade flow to a cerebral artery (usually the ipsilateral anterior cerebral artery), using cerebral protection has the theoretical advantage of preventing a large embolus to the anterior cerebral artery, which could be disastrous. One approach is to utilize cerebral protection only in this situation and to perform the procedure quickly and without therapeutic anticoagulation, but there is no data that this strategy is safer than an "unprotected" procedure.

Given the lack of data, the decision to utilize or not utilize cerebral protection devices is best left to the judgment of the treating physician.

Medical Therapy and Review of Literature

Patients with tandem occlusions included in the randomized trials of mechanical embolectomy for intracranial occlusion benefited similar to patients without extracranial carotid occlusion [1–4]. No randomized trials comparing techniques or medical

therapies for treatment of tandem occlusions exist. The literature mainly consists of relatively small single-center case series where the techniques and medical therapies even within those case series are often heterogeneous. In general, the risk of SICH seems to be slightly higher than is the case with mechanical embolectomy alone. Some series have shown much higher rates when more aggressive antiplatelet regimens were utilized [8, 9], and some series have shown lower rates of SICH [10]. A 2017 review and meta-analysis of 11 case series with a total of 237 patients reported 81% successful revascularization (TICI 2B or TICI 3), 7% risk of SICH, and good clinical outcomes in 44% (MRS 0–2) [11]. These numbers again are based on heterogeneous treatment strategies, and heterogeneous medical therapy, but definitely support catheter intervention for tandem occlusion when there is an intracranial embolus causing cerebral ischemia with salvageable brain tissue. Reporting of acute in-stent thrombosis, or longer-term patency, has not been routine among case series, and therefore the incidence of acute or subacute stent thrombosis is difficult to discern.

Treatment of a tandem occlusion, assuming a carotid angioplasty or stent was performed, mandates consideration of antiplatelet therapy. If possible, the first step is determining the patient's active medications. A patient already on dual antiplatelet therapy, for example, may not require additional medication. One should note that the recommendation for patients receiving intravenous t-PA is withholding antiplatelet therapy for 24 h, but this recommendation is clearly not based on outcomes for the tandem occlusion population [12].

A range of antiplatelet protocols have been employed in tandem patients with acute ICA stenting. The optimal medical therapy to maximize the chance of preserving carotid patency while minimizing the risk of hemorrhagic transformation of the core infarct has not been defined, and no one approach has been shown superior to another. In the setting of uncertainty, at a minimum aspirin-administered pre-procedure seems reasonable. Most published case series employed a periprocedural dose of aspirin (oral, PR, or IV, dose range 250–650 mg) [8–10, 13–22]. The timing of initiation of clopidogrel varied with the following administration strategies reported: (1) prior to stent deployment [18–20, 23], (2) immediately following a post-procedure CT negative for hemorrhage [16, 17], (3) after 24-h CT negative for hemorrhage [13, 14], or (4) using an intravenous glycoprotein IIb/IIIa inhibitor until 24-h CT negative for hemorrhage with subsequent transition to clopidogrel [11, 20, 24–26].

The choice of antiplatelet agent and timing of administration require consideration of the properties of each agent in this patient subset. Clopidogrel use acutely may be challenged by uncertain absorption from the enteric route and the fact that placing a nasogastric tube in the setting of intravenous thrombolysis has a risk of serious bleeding. Additionally, clopidogrel has delayed onset, nonuniform response, lack of reversibility, and long duration of antiplatelet effect if intracranial hemorrhage occurs.

Intravenous medications such as the glycoprotein IIb/IIIa inhibitors abciximab, tirofiban, and eptifibatide may also be used. These medications have the advantage of immediate onset, reliable platelet inhibition, and shorter duration of antiplatelet effect; however, they may increase the risk of hemorrhagic conversion. Among the glycoprotein IIb/IIIa inhibitors, eptifibatide and tirofiban may be advantageous

being reversible at the IIb/IIIa site and therefore quicker offset of antiplatelet effect compared to abciximab if intracranial hemorrhage occurs. Full-dose intravenous abciximab alone increased the risk of bleeding over placebo in acute stroke, even in the absence of thrombolytic therapy or mechanical embolectomy [27]. Intra-arterial low-dose abciximab has been reported successful in a small retrospective cohort, although dosing was not standardized [28]. Low-dose eptifibatide and tirofiban have been shown safe in the setting of acute stroke and thrombolysis, but safety and efficacy have not been proven for intervention in tandem occlusions [29–32].

Cangrelor is an intravenous P2Y12 inhibitor approved in the United States in 2015 as an adjunct for percutaneous coronary intervention and may be considered in the tandem patients with acute ICA stenting. There is currently no data for use in the stroke population. It has immediate onset and quick offset of return of antiplatelet activity 1 h after infusion stopped if intracranial hemorrhage were to occur. If considered, judicious efforts for timing of transition to oral therapy would be needed as offset is quick, and giving clopidogrel while cangrelor is infusing renders clopidogrel ineffective [33].

Statin therapy has possible benefit in carotid stenting and may be considered when a safe enteric route has been established. High-dose statin therapy to statin-naïve patients, or as a reload strategy, would be reasonable; however this strategy has not been studied specifically in the acute tandem occlusion population [34–38].

As previously noted, a 2017 meta-analysis of tandem occlusion patients treated with acute ICA stenting (n = 193) using various medication regimens reported a relatively low rate of SICH (7%), despite the majority of patients receiving concomitant IV thrombolysis and early use of antiplatelet therapy [11].

Clearly optimal medication management is an area that requires study. It is worth repeating, however, that re-thrombosis of the extracranial carotid artery is not always associated with neurologic deterioration, whereas intracranial hemorrhage usually is, which mandates that antithrombotic therapy be judicious.

Post-procedure Care

Blood Pressure

The blood pressure must be attentively managed after any mechanical embolectomy but especially after a tandem occlusion intervention. The presumptive cause of hypertension in acute stroke is autoregulation attempting to support collateral brain perfusion, and the presumptive benefit is improved flow through pial collateral vessels. On one hand, consider that acute carotid revascularization may be exposing the brain to flow dynamics that have not been present for years (and hence the rare complications of intracranial hemorrhage and hyper-perfusion syndrome with elective carotid revascularization) [39]. Also, consider that a successful procedure has reperfused not only the penumbra but also the established core infarct. Given these considerations, the patient may benefit from a lower blood pressure to prevent hemorrhage. On the

other hand, in the setting of an imperfect angiographic result where substantial brain tissue is still supplied by pial collaterals, the patient may benefit from hypertension to support collateral flow. Aggressive therapy to correct hypertension in acute stroke is usually not recommended [12]. However, that recommendation applies to a population where the status of the collateral vessels is not known, which is not the case after mechanical embolectomy. For patients treated with acute carotid revascularization and mechanical embolectomy with a TICI 3 or near TICI 3 result, there should be little benefit to hypertension, and steps to lower the blood pressure to the normal range seem reasonable. On the contrary, if substantial brain tissue is still perfused by pial collaterals, a higher pressure may be beneficial along the lines of what is generally recommended after intravenous thrombolysis [12].

Post-procedure Care: Imaging

In addition to imaging the brain at 24 h to establish the size of the infarct and the presence or absence of hemorrhage, carotid ultrasound is recommended at 24 h to determine the patency of the carotid artery (the artery will not in all cases be patent at 24 h, even if the angiogram demonstrated normal flow immediately post-procedure). These two critical data points can help guide medical therapy in the initial days following the intervention. For example, for a patient with a patent artery and a small, nonhemorrhagic stroke, antiplatelet loading seems reasonable. In distinction, for a patient with a large infarct, one might want to be more cautious, and there is probably no benefit beyond aspirin if the artery is reoccluded. After the initial hospitalization, carotid ultrasound at 30 days seems reasonable to establish a baseline for follow-up, similar to what is generally practiced for elective carotid revascularization procedures.

Summary

Tandem occlusion presents a challenging scenario for acute cerebral revascularization. The interventionalist must balance managing the acute intracranial embolus and the acute extracranial thrombosis. Successful intervention requires attention to patient selection, technique, and intra-procedural and post-procedural medical care.

References

1. Berkhemer OA, Eransen PS, Beumer D, van den Bert LA, Lingsma HF, et al. A randomized trial of intraarterial treatment of acute ischemic stroke. N Engl J Med. 2015;372:11–20.
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.

3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
4. Assis Z, Menon BK, Goyal M, Demchuk AM, Shankar J, et al. J Neurointerv Surg. 2017; https://doi.org/10.1136/neurintsurg-2017-013316.
5. Malik A, Vora N, Lin R, Zaidi S, Aleu A, et al. Endovascular treatment of tandem extracranial/intracranial anterior circulation occlusions: preliminary single center experience. Stroke. 2011;42:1653–7.
6. Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. N Engl J Med. 2010;363:11–23.
7. Bonati LH, Jongen LM, Haller S, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a sub-study of the international carotid stenting study. Lancet Neurol. 2010;9:355–62.
8. Dorado L, Castano C, Millan M, Aleu A, de la Osa N, et al. Hemorrhagic risk of emergent endovascular treatment plus stenting in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22(8):1326–31.
9. Heck D, Brown M. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. J Neurointerv Surg. 2015;7:170–5.
10. Spiotta A, Lena J, Vargas J, Hawk H, Turner R, et al. Proximal to distal approach in the treatment of tandem occlusions causing an acute stroke. J Neurointerv Surg. 2015;7(3):164–9.
11. Sivan-Hoffman R, Gory B, Armoiry X, Goyal M, Riva R, et al. Stent-retriever thrombectomy for acute anterior ischemic stroke with tandem occlusion: a systematic review and meta-analysis. Eur Radiol. 2017;27(1):247–54.
12. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, 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(3):870–947.
13. Fahed R, Redjem H, Blanc R, Labreuche J, Robert T, Ciccio G, et al. Endovascular management of acute ischemic strokes with tandem occlusions. Cerebrovasc Dis. 2016;41(5–6):298–305.
14. Papanagiotou P, Roth C, Walter S, Behnke S, Grunwald IQ, Viera J, et al. Carotid artery stenting in acute stroke. J Am Coll Cardiol. 2011;58(23):2363–9.
15. Maurer CJ, Joachimski F, Berlis A. Two in one: endovascular treatment of acute tandem occlusions in the anterior circulation. Clin Neuroradiol. 2015;25(4):397–402.
16. Cohen JE, Gomori JM, Rajz G, Itshayek E, Eichel R, Leker RR. Extracranial carotid artery stenting followed by intracranial stent-based thrombectomy for acute tandem occlusive disease. J Neurointerv Surg. 2015;7(6):412–7.
17. Puri AS, Kühn AL, Kwon HJ, Khan M, Hou SY, Lin E, et al. Endovascular treatment of tandem vascular occlusions in acute ischemic stroke. J Neurointerv Surg. 2015;7(3):158–63.
18. Son S, Choi DS, Oh MK, Kim SK, Kang H, Park KJ, et al. Emergency carotid artery stenting in patients with acute ischemic stroke due to occlusion or stenosis of the proximal internal carotid artery: a single-center experience. J Neurointerv Surg. 2015;7(4):238–44.
19. Machi P, Lobotesis K, Maldonado IL, Costalat V, Vendrell JF, Riquelme C, et al. Endovascular treatment of tandem occlusions of the anterior cerebral circulation with solitaire FR thrombectomy system. Initial experience. Eur J Radiol. 2012;81(11):3479–84.
20. Stampfl S, Ringleb PA, Möhlenbruch M, Hametner C, Herweh C, Pham M, et al. Emergency cervical internal carotid artery stenting in combination with intracranial thrombectomy in acute stroke. Am J Neuroradiol. 2014;35(4):741–6.
21. Soize S, Kadziolka K, Estrade L, Serre I, Barbe C, Pierot L. Outcome after mechanical thrombectomy using a stent retriever under conscious sedation: comparison between tandem and single occlusion of the anterior circulation. J Neuroradiol. 2014;41(2):136–42.
22. Yoon W, Kim BM, Kim DJ, Kim DI, Kim SK. Outcomes and prognostic factors after emergent carotid artery stenting for hyperacute stroke within 6 hours of symptom onset. Neurosurgery. 2015;76(3):321–9.

23. Lescher S, Czeppan K, Porto L, Singer OC, Berkefeld J. Acute stroke and obstruction of the extracranial carotid artery combined with intracranial tandem occlusion: results of interventional revascularization. Cardiovasc Intervent Radiol. 2015;38(2):304–13.
24. Grigoryan M, Haussen DC, Hassan AE, Lima A, Grossberg J, Rebello LC, et al. Endovascular treatment of acute ischemic stroke due to tandem occlusions: large multicenter series and systematic review. Cerebrovasc Dis. 2016;41(5–6):306–12.
25. Mpotsaris A, Bussmeyer M, Buchner H, Weber W. Clinical outcome of neurointerventional emergency treatment of extra- or intracranial tandem occlusions in acute major stroke: antegrade approach with wallstent and solitaire stent retriever. Clin Neuroradiol. 2013;23(3):207–15.
26. Lockau H, Liebig T, Henning T, Neuschmelting V, Stetefeld H, Kabbasch C. Mechanical thrombectomy in tandem occlusion: procedural considerations and clinical results. Neuroradiology. 2015;57(6):589–98.
27. Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke. 2008;39(1):87–99.
28. Al-Mufti F, Amulur K, Manning NW, Khan I, Peeling L, et al. Emergent carotid stenting and intra-arterial abciximab in acute ischemic stroke due to tandem occlusion. Br J Neurosurg. 2017;31(5):573–57.
29. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, et al. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. Stroke. 2008;39(12):3268–76.
30. Pancioli AM, Adeoye O, Schmit PA, Khoury J, Levine SR, Tomsick TA, et al. Combined approach to lysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen stroke trial. Stroke. 2013;44(9):2381–7.
31. Adeoye O, Sucharew H, Khoury J, Vagal A, Schmit PA, Ewing I, et al. Combined approach to lysis utilizing Eptifibatide and recombinant tissue-type plasminogen activator in acute ischemic stroke-full dose regimen stroke trial. Stroke. 2015;46(9):2529–33.
32. Li W, Lin L, Zhang M, Wu Y, Liu C, Li X, Huang S, et al. Safety and preliminary efficacy of early Tirofiban treatment after Alteplase in acute ischemic stroke patients. Stroke. 2016;47(10):2649–51.
33. Cangrelor [package insert on the Internet]. Cary, NC: Chiesi Farmaceutici S.p.A. 2016. [cited 2018 Jan 9]. Available from: https://resources.chiesiusa.com/Kengreal/KENGREAL_US_PI.pdf.
34. Hong JH, Sohn SI, Kwak J, Yoo J, Chang HW, Kwon OK, et al. Dose-dependent effect of statin pretreatment on preventing the periprocedural complications of carotid artery stenting. Stroke. 2017;48(7):1890–4.
35. Patti G, Tomai F, Melfi R, Ricottini E, Macrì M, Sedati P, et al. Strategies of clopidogrel load and atorvastatin reload to prevent ischemic cerebral events in patients undergoing protected carotid stenting. Results of the randomized ARMYDA-9 CAROTID (Clopidogrel and Atorvastatin Treatment During Carotid Artery Stenting) study. J Am Coll Cardiol. 2013;61(13):1379–87.
36. Tadros RO, Vouyouka AG, Chung C, Malik RK, Krishnan P, Ellozy SH, et al. The effect of statin use on embolic potential during carotid angioplasty and stenting. Ann Vasc Surg. 2013;27(1):96–103.
37. Reiff T, Amiri H, Rohde S, Hacke W, Ringleb PA. Statins reduce peri-procedural complications in carotid stenting. Eur J Vasc Endovasc Surg. 2014;48(6):626–32.
38. Verzini F, De Rango P, Parlani G, Giordano G, Caso V, Cieri E, et al. Effects of statins on early and late results of carotid stenting. J Vasc Surg. 2011;53(1):71–9.
39. Moulakakis K, Mylonas S, Sfyroeras G, Andrikopoulos V. Hyperperfusion syndrome after carotid revascularization. J Vasc Surg. 2009;49:1060–8.

Chapter 34
The Angiographic Suite: A One-Stop Shop for the Triage and Treatment of Large Vessel Occlusive Acute Ischemic Strokes

Charles M. Strother and Guang-Hong Chen

The motivation for development of imaging techniques that can transform the angiographic suite into a facility which is suitable not only for treatment guidance but also for comprehensive imaging of patients with an acute ischemic stroke (AIS) is, simply, to shorten the interval between stroke onset and treatment. Full realization of this goal requires a significant improvement in both the imaging capabilities of the C-arm CT systems and in current postprocessing algorithms. In this chapter we (1) propose a workflow for the "one-stop shop" approach, (2) discuss how this approach should add value, (3) describe current limitations impacting full execution of the one-stop shop, (4) describe the technology that will provide the improvements necessary for implementation of the one-stop shop concept, and (5) discuss and illustrate the imaging capabilities that can be derived from application of this technology.

Our belief in the feasibility of the one-stop shop workflow and its value added is based on the use of technology which has not been fully validated or tested in a clinical environment. However, our belief and confidence in the proposed workflow are well supported by preliminary results from our initial clinical studies and basic imaging science researches.

C. M. Strother (✉)
Department of Radiology, UW School of Medicine and Public Health, Madison, WI, USA
e-mail: CStrother@uwhealth.org

G.-H. Chen
Departments of Medical Physics and Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: gchen7@wisc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_34

One-Stop Shop Workflow

Workflows for patients arriving at a comprehensive stroke center (CSC) vary widely in details. Many of these variations are due to differences in the imaging algorithms which are used to triage patients following a clinical diagnosis of an AIS. Variations in the current workflows thus depend on differences not only in where the ED patients are transferred for imaging, e.g., to CT or MRI or imaging in the ED or at a different site, but also on the selected imaging goals, e.g., only exclude hemorrhage and obtain an ASPECTS score or both of these plus CTA and CTP. After imaging, patients typically then return to the ED where consents are signed, and, if not already done, IV tPA is started. Patients thought to be appropriate for endovascular treatment are then transferred to the angiography suite.

Current guidelines for CSCs call for the time from a patient's arrival at the ED to the start of CT imaging to be shorter than 15 min and for the door to CT interpretation to be less than 45 min [1]. Although the proposed one-stop shop workflow may offer an opportunity to further reduce the time between the clinical diagnosis of an AIS and image interpretation, this is not the primary goal. Instead, it is the interval between imaging and the start of treatment in the angiographic suite that we believe can be significantly reduced by adoption of the one-stop shop concept. This so-called "picture to puncture (P2P)" interval has been identified as being highly correlated with clinical outcome [2].

Patient Selection for the One-Stop Shop Workflow

One key to the success of the one-stop shop workflow is proper patient selection. The following discussion assumes that patients arrive at a hospital that is a comprehensive stroke center (CSC) and also that there is adherence to the recently published AHA/ASA statement regarding inclusion and exclusion criteria for IV tPA and endovascular therapy [3]. Of millions of people worldwide who annually suffer AISs, only a relatively small fraction will be candidates for endovascular treatment. This number is, however, still very large and will likely increase as the average age of the population in developed countries increases. As we test the feasibility of this concept, we will initially limit selection of patients to be brought directly to the angiography suite from the ED to those who (1) have a pre-stroke mRS of 0–1; (2) meet the criterion of having IA treatment initiated within 8 h after stroke onset; and (3) have an NIHSS of at least eight with a clearly defined onset of their stroke [4] (Fig. 34.1). Almost all such patients will have a large vessel occlusion (LVO).Use of the NIHSS of ≥ 8 will yield few false positives but will fail to identify a significant number of suitable patients, especially ones with LVOs in the posterior circulation or the right cerebral hemisphere (because of the heavy weighting of the SS to the anterior circulation and to language rather than to agnosias) [5]. Ultimately, the number of appropriate patients denied the one-stop shop option because this bias

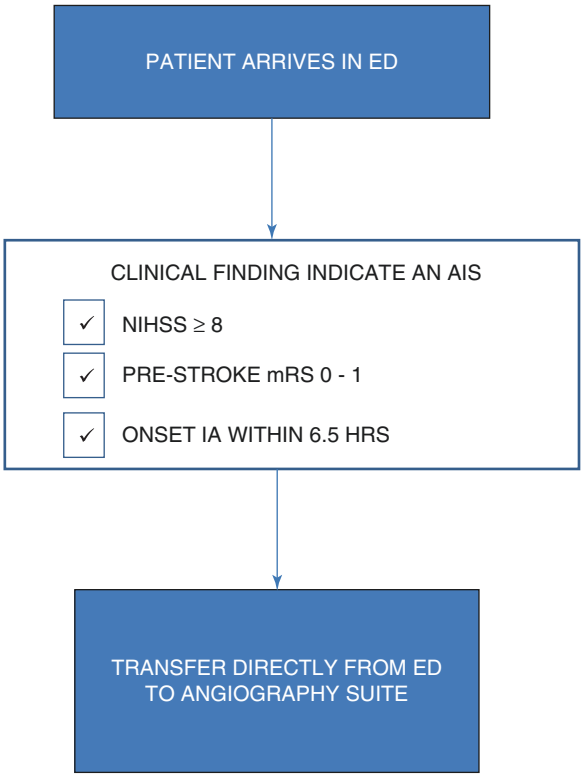


Fig. 34.1 Proposed workflow and patient selection criterion for the one-stop shop model

can almost surely be reduced by adding to the stroke score criterion the presence of clinical findings which are usually indicative of a LVO, e.g., a gaze palsy or involvement of the face and arm greater than the lower extremity. Evaluations of proposed "clinical" scores aimed at identification of patients with a LVO are underway. At least one of these is suitable for use both by physicians and emergency responders [6, 7]. The use of such methods should also help to increase the ability to identify patients with a LVO.

Does the One-Stop Shop Approach Add Value?

We believe that, in at least three ways, it does. First, and most importantly, it offers the opportunity to significantly reduce the interval between comprehensive imaging and the initiation of treatment. This P2P interval is not only one that has been shown to account for a very significant amount of time but also is one where the duration has been more highly correlated with clinical outcome than in any other times in the workflow of patients from the ED to treatment [2, 8, 9]. Given the magnitudes of

how time delays impact the odds of good clinical outcomes (decreases of 15–26% for each 30-min delay), the significance of shortening the overall door to puncture interval can hardly be overstated.

Second, eliminating the time cost associated with comprehensive imaging also addresses the reluctance of many clinicians to forgo obtaining CTAs and CTPs because of the associated delay in treatment initiation [10]. There is a consensus that the information provided by CTP and CTA helps in recognizing patients that are suitable for thrombectomy. Unfortunately, however, there is also general recognition that acquiring this information comes with a significant time cost. Although data acquisition necessary for CTP and CTA may be done very quickly, there are inherent delays associated with transfer to the CT facility, movement from transfer gurney to the CT table, and then back to the transfer gurney (the sicker the patient, the larger this delay is likely to be). There may also be delays in data processing, interpretation, and decision-making. We believe that utilization of the one-stop shop workflow will eliminate or significantly reduce all of these delays.

It is interesting that, of the five trials reported in 2015 showing efficacy of endovascular therapy over medical management, the two in which CTP was available to aid in patient selection [SWIFT-PRIME (81%), EXTEND-IA (100%)] both had better recanalization percentages and good outcome percentages than did the other three where CTP was not available (MR CLEAN, REVASCAT, ESCAPE) [10–14]. CTP is not only helpful in patient selection but also in optimizing management during and after treatment, e.g., blood pressure management, and in outcome predictions [15, 16]. One may wonder as to the extent to which delays related to comprehensive imaging might account for the significantly greater percentages of recanalization compared to good clinical outcomes in all of these trials (Table 34.1).

The imaging proposed in our one-stop-shop concept is done using a single IV injection of contrast medium and multi-rotational acquisitions of the angiographic C-arm cone-beam CT (CBCT) data acquisition system. From a ten-rotation acquisition, a non-contrast CBCT (NC-CBCT), a contrast-enhanced CBCT (CE-CBCT), dynamic perfusion maps (CBV, CBF, MTT), and a time-resolved CBCT angiogram (TR-CBCTA) can be derived (Fig. 34.2). The accumulated radiation dose from the acquisition is currently estimated to be a DLP of 1914 mGy-cm (4.4 mSv). This is an equivalent dose to the radiation exposure received from natural sunlight and other cosmic background radiations by a person taking a flight from New York to Los Angeles. In our institution it represents almost a threefold decrease in the radiation exposure from a conventional CTP, CTA protocol (12.6 mSv).

Table 34.1 Summary of the percentages of successful revascularizations and good clinical outcome of five stroke trials published in 2015 showing significant benefit of thrombectomy and IV tPA over tPA alone

MR CLEAN	ESCAPE	EXTEND-IA	SWIFT-PRIME	REVASCAT
RECAN 75%	RECAN 72%	RECAN 100%	RECAN 88%	RECAN 66%
mRS 0–1 33%	mRS 0–1 53%	mRS 0–1 71%	mRS 0–1 60%	mRS 0–1 44%
Difference 42%	Difference 19%	Difference 29%	Difference 28%	Difference 22%

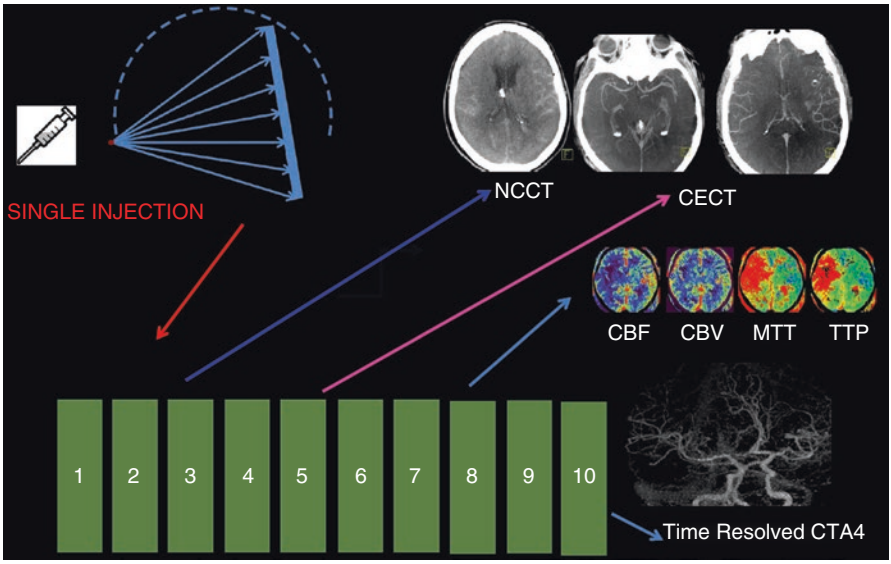


Fig. 34.2 Diagram showing the protocol used for data acquisition in the one-stop shop concept. After a single intravenous injection of contrast multiple rotations of the C-arm gantry acquires data over approximately 1 min. From these data a NCCT, CECT, time-resolved CTAs, and dynamic perfusion maps may be derived

Finally, in the current workflow, assessment of perfusion is only obtainable prior to treatment. Thus, only a snapshot of a dynamically changing physiologic process is available. In contrast, because of its availability at the point of treatment, the very small x-ray exposure, and the low-contrast dose required, the one-stop shop workflow allows the treating physicians to obtain additional perfusion information when/if needed during the endovascular treatment.

Current Limitations of the One-Stop Shop Concept

There are three major technical hurdles that currently prevent full implementation of the one-stop shop concept: (1) the limited low-contrast resolution of the CBCT images due to the limited dynamic range of the current flat-panel detectors; 2) the limited temporal resolution of CBCT imaging due to limited C-arm gantry rotation speed; and (3) obstructing image artifacts such as beam hardening artifact, scatter artifacts, metal artifacts, and view angle aliasing streaking artifacts. As a result, both low-contrast resolution and the temporal resolution of multi-detector CT (MDCT) are significantly better than that of the current angiographic C-arm cone-beam CT systems. Both [1] and [3] limit the currently achievable low-contrast resolution which is important for the detection of hemorrhages, while [2] limits the achievable temporal resolution which is important for obtaining accurate perfusion data.

Detection of Hemorrhage

Because of the risk of inducing new bleeding when IV tPA is given, identification of patients with an intracranial hemorrhage is obviously very important prior to its use. The magnitude of this risk or the extent to which it exists when recanalization is done with mechanical means alone is, to our knowledge, not known. In the one-stop shop concept, a NC-CBCT is part of the imaging sequence. Still, currently, the sensitivity of C-arm CBCT for hemorrhage detection has not been proven to be equal to that of MDCT. It is thus unknown whether or not the current low-contrast resolution of C-arm CBCT is sufficient for a NC-CBCT to be used as a screening tool for exclusion of hemorrhage in AIS patients. Recently C-arm angiographic systems with 16-bit flat detectors have become available, in contrast to the 14-bit detectors used in most of the current C-arm CBCT systems. This substantially improves the ability to visualize low-contrast details. Further improvements in low-contrast detectability have been provided by adding new data preprocessing methods and new image reconstruction and postprocessing algorithms to reduce image artifacts such as those listed in limitation [3].

In studies of stroke chameleons, intracranial hemorrhages are not included as a mimic. A review of 2200 AIS patients over an 8.25-year period at a university hospital found only 5 in which an AIS was misdiagnosed as a hemorrhage (subarachnoid hemorrhage or subdural hematoma). No information is given whether any of the patients correctly diagnosed also had intracranial hemorrhage [17, 18]. There is evidence, however, that nontraumatic convexal subarachnoid hemorrhages concomitant with AISs are rare [19]. Based on these observations, we strongly believe that the capabilities of the new detector discussed above, together with new image processing algorithms and the following patient selection criteria, will enable the one-stop shop concept to be safely employed. We would advise its use only for (1) patients with an anterior circulation stroke who also have a known clinical presentation (the presentation of patients with intracranial bleeding, either parenchymal or subarachnoid, and patients with an AIS is usually quite distinct) and (2) have no associated trauma.

Acquiring Accurate Perfusion Data

Using a steady-state concept based on a tailored injection/acquisition protocol, it is currently possible to measure CBV with C-arm CBCT at a level of accuracy that is comparable to that obtained with MDCT [20–22]. Because of the current availability to obtain ten sequential rotations of the C-arm and thus to potentially obtain dynamic perfusion maps, this single rotation, single parameter method, for evaluation of patients with AIS, is not widely used.

Perfusion data using current MDCTs are acquired with continuous rotation of a detector having temporal resolution that is better than 1.0 s. In stark contrast, it takes much longer for a current C-arm CBCT system to acquire data to reconstruct a

CBCT image volume. For example, when acquired with a commercially available biplane angiographic system (Artis zee, Siemens Healthineers, Forchheim, Germany), the time needed to acquire a single CBCT data set is about 5 s which results in the native temporal resolution of about 6 s (there is about 1 s pause time needed to reverse the C-arm gantry without data acquisition). Additionally, temporal sampling is also quite limited. For example, for a given total data acquisition time of about 60 s, one can only acquire ten rotation acquisitions to obtain ten data points to delineate the contrast uptake curve: one data point from each rotation. Together, these limitations decrease the accuracy of perfusion imaging using current cone-beam CT technology. Nonetheless, the feasibility of obtaining dynamic CBCTP maps which qualitatively compare well with CTP and MRP maps has been shown both in animals and in humans [23, 24].

These limitations can be addressed by the recent advances in both hardware and software developments. The hardware approach is to increase C-arm gantry rotation speed and thus to shorten the needed time to acquire a complete CBCT data set. The software approach is to introduce novel image processing algorithms such as TERESAR [25] and PICCS [26] to reduce noise and to improve temporal resolution and temporal sampling, or some other newer development in reconstruction algorithm [27] to comprehensively address the technical hurdles in temporal resolution, temporal sampling, and image artifacts simultaneously. Using these innovative software approaches, the temporal resolution of the cone-beam CT system can be reduced to less than 1 s. Applications of these algorithms also greatly improve the temporal sampling [25, 27] and reduce image artifacts [28]. In a retrospective study of human data, dynamic perfusion maps reconstructed with these techniques were shown to be not inferior to maps obtained with MDCT [26]. From these perfusion data, it is also possible to create time-resolved CBCTAs. These have been shown to provide information which allows accurate determination of the site of a LVO and assessments of collateral score and thrombus burden [29–31].

Emerging Imaging Capabilities Enabling the One-Stop Shop Concept

A joint statement from the ASNR, ACR, and SNIS published in 2013 suggested a variety of imaging protocols for patients presenting with acute stroke symptoms [32]. A user's choice of an imaging strategy was to be based on the specifics of the clinical scenario and the available therapeutic options under consideration. Regardless of the selected imaging strategy, emphasis was placed on the need for imaging to be performed in as few sessions as possible. The one-stop shop concept allows this goal to be met better than any imaging strategy suggested in these guidelines.

Currently, a NC-CBCT and a CE-CBCT can be derived from the mask and fill run of a 20 s C-arm CBCT. The image quality of the NC-CBCT is such that for supratentorial parenchymal hemorrhages, it compares well with that of a NC-CBCT done with MDCT. The sensitivity for detection of subarachnoid hemorrhage using

CBCT is not yet determined. A NC-CBCT and a CE-CBCT can also be derived from a multi-rotational acquisition designed to capture perfusion data. The sensitivity of these images for bleeding detection, collateral and thrombus burden assessments has also not yet been fully tested. Our personal experiences along with the new detector capabilities, new reconstruction algorithms, and the use of new artifact reduction algorithms (motion, scatter, and beam hardening) combined give us confidence that the NC-CBCT derived from a multi-rotational CBCT acquisition will be adequate for screening AIS patients for intracranial bleeding (Fig. 34.3).

A comparison of CBCT-derived dynamic perfusion maps with MR perfusion (MRP) was described by Struffert and colleagues in 2013. Although the series was small (12 subjects), in a qualitative comparison the CBCT maps compared well with those obtained with MRP [24]. In a retrospective study, we compared dynamic perfusion maps reconstructed using novel in-house temporal recovery and noise reduction algorithms with MDCTP maps obtained using commercial software. In this small study, both qualitative and quantitative image quality assessments showed that the CBCTP maps were not inferior to the ones obtained with MDCTP [29] (Fig. 34.4).

From the CBCTP acquisitions, time-resolved CBCTAs may also be derived. Using the same patient data described in the paragraphs above, we looked at the utility of the CBCTAs as tools to evaluate collateral score and thrombus burden [30, 31] (Fig. 34.5). It is increasingly clear that the status of collaterals is a critical (perhaps the most critical) variable in determining the rate of ischemic core growth and thereby of penumbra preservation. Collateral score is also a reliable predictor of both clinical and imaging outcomes [33]. Because of variations in patient's cardiac function, size, and velocity of collateral flow, collateral assessment with single-phase

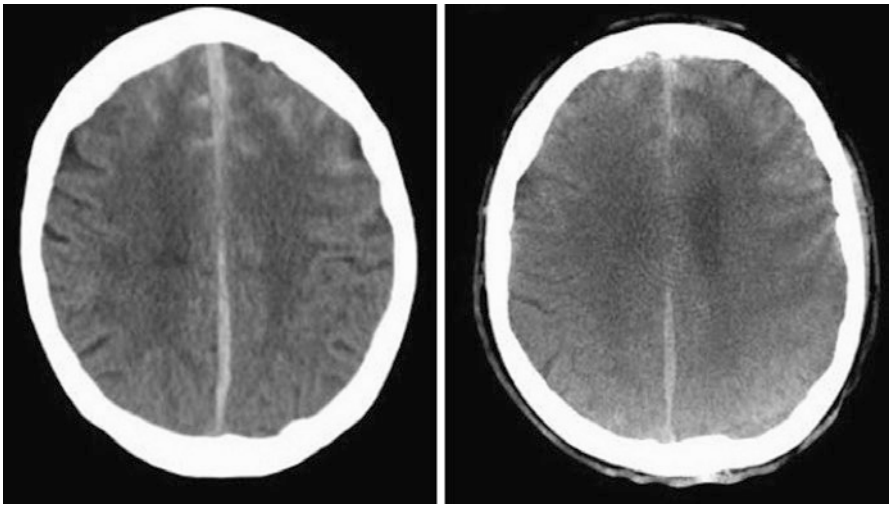


Fig. 34.3 Multidetector CT (left) and flat detector CBCT (right). (Courtesy of Professor Martin Skalej and Dr. Oliver Beuing Institute of Neuroradiology, Otto-von-Guericke University, Magdeburg, Germany)

CT is not a reliable predictor of collateral status. While multiphase CT resolves some issues with the use of single-phase CT, because it is not time resolved, it does not allow assessment of whether an artery is filling retrograde or antegrade [34, 35]. It is likely that the superior spatial resolution of CBCT compared with that of MDCT will result in an improved ability to visualize small collateral arteries.

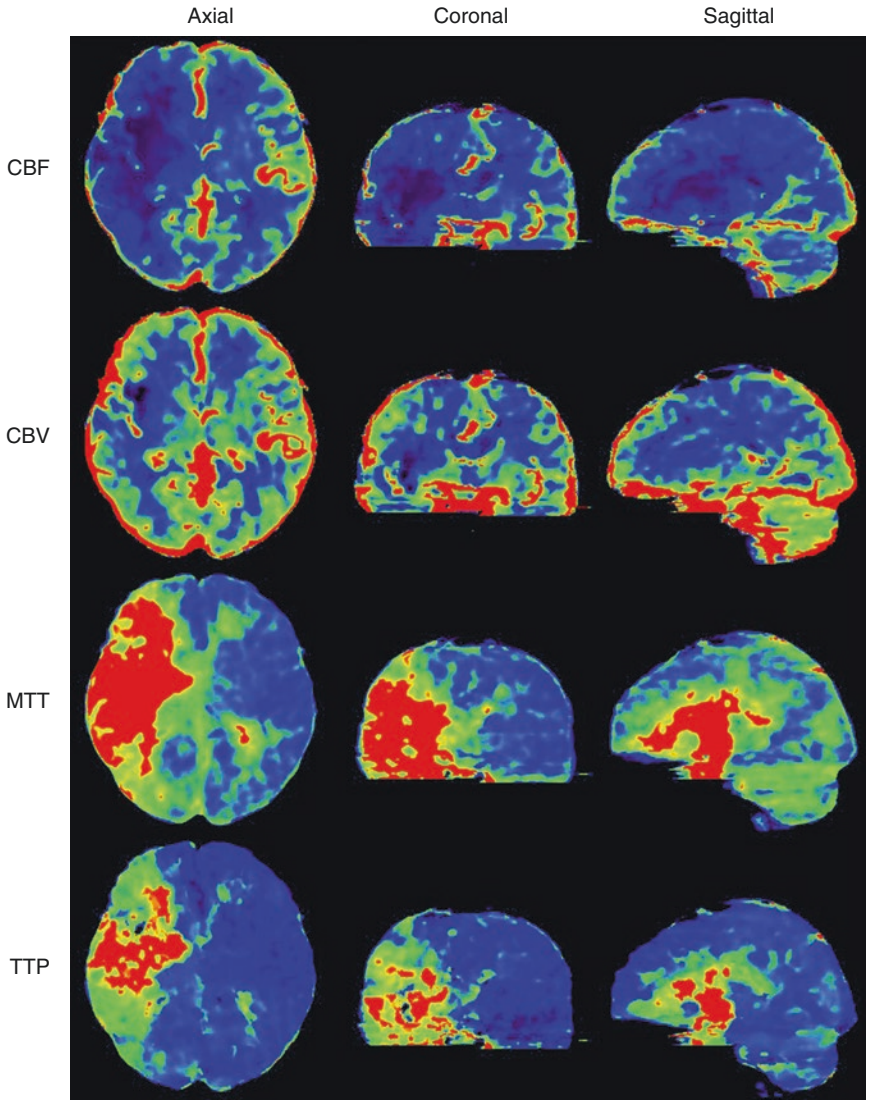


Fig. 34.4 CBCTP-derived perfusion maps (CBF, CBV, MTT, TTP) from a patient with an AIS. There is a mismatch between the extent of the CBF and CBV abnormalities. This figure illustrates well the ability of CBCTP to provide whole brain coverage and visualization of maps in axial, sagittal, and coronal planes. (From Niu et al. [29], with permission)

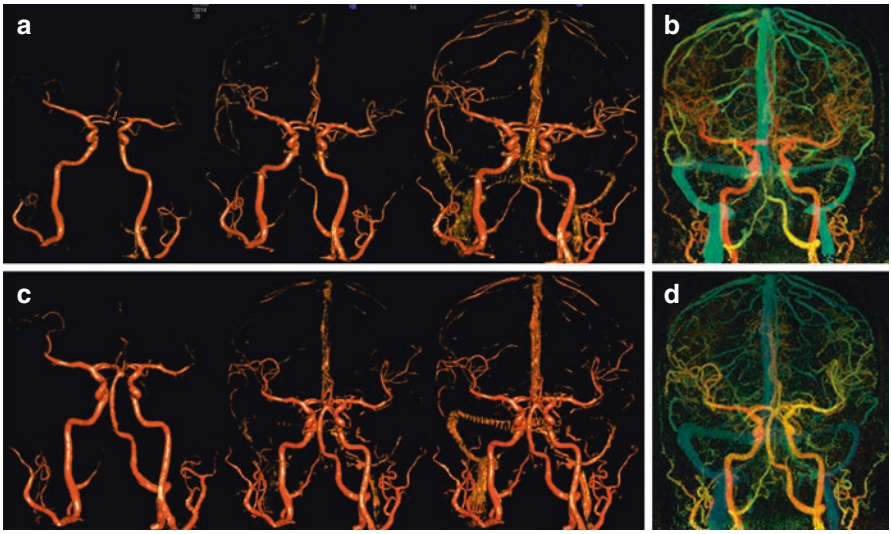


Fig. 34.5 Time-resolved CTAs derived from CTP acquisitions. Volume-rendered (**a** and **c**) and color-coded (**b** and **d**) before (top row) and after (bottom row) revascularization of a mid-basilar artery occlusion. There is a residual stenosis in the distal right vertebral artery. (From Yang et al. [30], with permission)

Summary

C-arm cone-beam CT technology is now at a point where it is feasible to perform comprehensive imaging of carefully selected patients with an AIS in the angiography suite. The ability to do this should result in a significant reduction in the picture to puncture time. This, in turn, should improve clinical outcomes following successful recanalization.

Acknowledgment We wish to acknowledge the very important contributions made to the one-stop shop concept by Professors Arnd Dörfler and Tobias Struffert and their colleagues in the Department of Neuroradiology at the University of Nuremberg Erlangen. Their cooperation in sharing human subject data derived from their initial efforts in performing comprehensive imaging in the angiography suite has been extremely helpful in demonstrating the feasibility of the one-stop shop concept.

References

1. 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(3):870–947.
2. Ribo M, Molina CA, Cobo E, et al. Association between time to reperfusion and outcome is primarily driven by the time from imaging to reperfusion. Stroke. 2016;47:999–1004.

3. Demaerschalk BM, Kleindorfer DO, Opeolu MA, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:581–641.
4. Powers WJ, Derdeyn CP, Jose B, et al. American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:3024–39.
5. Hacke W, Furlan AJ, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomized, double-blind, placebo-controlled study. Lancet Neurol. 2009;8:141–50.
6. Gupta R, Manuel M, Owada K, et al. Severe hemiparesis as a prehospital tool to triage stroke severity: a pilot study to assess diagnostic accuracy and treatment times. J Neurointerv Surg. 2016;8:775–7.
7. Ossa NP, Carrera D, Montse G, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. Stroke. 2014;45:87–91.
8. Sun CH, Nogueira RG, Glenn BA, Connelly K, Zimmermann S, Anda K, et al. "Picture to puncture": a novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke. Circulation. 2013;127:1139–48.
9. Pfaff J, Herweh C, Pham M, et al. Mechanical thrombectomy using a combined CT/C-arm X-ray system. J Neurointerv Surg. 2016;8:621–5.
10. Berkhemer OA, Fransen PSS, Beumer FD, et al. A randomized trial of Intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;272:11–22.
11. Jovin TG, Chamorro E, Coba MA, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
12. Goyal M, Demchuck BK, Menon M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.
13. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
14. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs t-PA alone in stroke. N Engl J Med. 2015;372:2285–98.
15. Sheth KN, Terry JB, Nogueira RG, et al. Advanced modality imaging evaluation in acute ischemic stroke may lead to delayed endovascular reperfusion therapy without improvement in clinical outcomes. J Neurointerv Surg. 2013;5:i62–5.
16. Lev MH. Acute stroke imaging: what is sufficient for triage to endovascular therapy? AJNR Am J Neuroradiol. 2010;33:789–94.
17. Richoz B, Hugli O, Dami F, et al. Acute stroke chameleons in a university hospital: risk factors, circumstances, and outcomes. Neurology. 2015;85:505–11.
18. Scott PA, Silbergleit R. Misdiagnosis of stroke in tissue plasminogen activator-treated patients: characteristics and outcomes. Ann Emerg Med. 2003;42:611–8.
19. Nakajima M, Inatomi Y, Yonehara T, et al. Nontraumatic convexal subarachnoid hemorrhage concomitant with acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23:1564–70.
20. Bley T, Strother CM, Pulfer K, et al. C-arm CT measurement of cerebral blood volume in ischemic stroke: an expeerimental study in canines. AJNR Am J Neuroradiol. 2010;31:536–40.
21. Struffert T, Deuerling-Zheng Y, Kloska S, et al. Cerebral blood volume imaging by flat detector computed tomography in comparison to conventional multislice perfusion CT. Eur Radiol. 2011;21:882–90.
22. Fiorella D, Turk A, Chaudry I, et al. A prospective multicenter pilot study investigating the utility of flat detector derived parenchymal blood volume maps to estimate cerebral blood volume in stroke patients. J Neurointerv Surg. 2014;6:451–6.

23. Royalty K, Manhart M, Pulfer K, et al. C-arm CT measurement of cerebral blood volume and cerebral blood flow using a novel high-speed acquisition and a single intravenous contrast injection. AJNR Am J Neuroradiol. 2013;34:2131–8.
24. Struffert T, Deuerling-Zheng Y, Kloska S, et al. Dynamic angiography and perfusion imaging using flat detector CT in the angiography suite: a pilot study in patients with acute middle cerebral artery occlusion. Am J Neuroradiol. 2015;36:1964–70.
25. Tang J, Xu M, Niu K, et al. A novel temporal recovery technique to enable cone beam CT perfusion imaging using an interventional C-arm system. Proc SPIE. 2013;8668:86681A.
26. Chen GH, Tang J, Leng S. Prior image constrained compressed sensing (PICCS): A method to accurately reconstruct dynamic CT images from highly undersampled projection data sets. Med Phys. 2008;35:660.
27. Chen GH, Li Y. Synchronized multiartifact reduction with tomographic reconstruction (SMART-RECON): a statistical model based iterative image reconstruction method to eliminate limited-view artifacts and to mitigate the temporal-average artifacts in time-resolved CT. Med Phys. 2015;42:4698–707.
28. Li Y, Garrett J, Chen GH. Reduction of beam hardening artifacts in cone-beam CT imaging via SMART-RECON algorithm. Proc SPIE. 2016;9783:97830W.
29. Niu K, Yang P, Wu Y, et al. C-arm conebeam CT perfusion imaging in the angiographic suite: a comparison with multidetector Ct perfusion imaging. AJNR Am J Neuroradiol. 2016;37:1303–9.
30. Yang P, Niu K, Wu Y, et al. Time-resolved C-arm computed tomographic angiography derived from computed tomographic perfusion acquisition: new capability for one-stop-shop acute ischemic stroke treatment in the Angiosuite. Stroke. 2015;46:3383–9.
31. Yang P, Niu K, Wu Y, et al. Evaluation of collaterals and clot burden using time-resolved C-arm cone beam CT angiography in the angio-suite: a feasibility study. AJNR Am J Neuroradiol. 2017;38(4):747–52.
32. Wintermark M, Sanell PC, Albers GW, et al. Imaging recommendations for acute stroke and transient ischemic attack patients: a joint statement by the American Society of Neuroradiology, the American College of Radiology and the Society of NeuroInterventional Surgery. AJNR Am J Neuroradiol. 2013;34:117–27.
33. Fanou EM, Knight J, Aviv RI, et al. Effect of collaterals on clinical presentation, baseline imaging, complications, and outcome in acute stroke. AJNR Am J Neuroradiol. 2015;36:2285–91.
34. Frölich AM, Wolff SL, Psychogios MN, et al. Time-resolved assessment of collateral flow using 4D CT angiography in large-vessel occlusion stroke. Eur Radiol. 2014;24:390–6.
35. Smit EJ, Vonken EJ, van Seeters T, et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. Stroke. 2013;44:2194–9.

Chapter 35
Mobile Stroke Units: Field Imaging and Triage for Acute Stroke Emergencies

Anne W. Alexandrov, Nitin Goyal, Abhi Pandhi, Sarah McCormick, Andrei V. Alexandrov, and Adam Arthur

Stroke is a pandemic affecting people of all populations and ages. In the past few decades, the global stroke burden has increased significantly worldwide especially between the years 1990 and 2013 [1]. Currently available acute ischemic stroke (AIS) treatments are intravenous recombinant tissue plasminogen activator (rtPA) and, in the case of emergent large vessel occlusion (ELVO), mechanical thrombectomy (MT) [2–7]; however, few patients receive these time-dependent treatments. The concept of taking stroke care to the patient by deployment of mobile stroke units (MSU) is gaining momentum. In this chapter, we explore the use of AIS treatments, management of contributors to treatment delays, and the history and utility of MSUs to support acute stroke treatment.

A. W. Alexandrov
Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

College of Nursing, University of Tennessee Health Science Center, Memphis, TN, USA
e-mail: aalexa33@uthsc.edu

N. Goyal · A. Pandhi · S. McCormick · A. V. Alexandrov
Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA
e-mail: ngoyal@uthsc.edu; apandhi@uthsc.edu; smccorm@uthsc.edu; aalexa30@uthsc.edu

A. Arthur (✉)
Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Semmes-Murphy Neurologic and Spine Clinic, Memphis, TN, USA
e-mail: aarthur@semmes-murphey.com

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_35

Time-Dependent Benefits of Acute Stroke Treatments

Intravenous rtPA was approved in the United States in 1996 [2]. Subsequent approval in other countries occurred in 1999 (Canada, South America, and Asia) [8, 9], 2002 (Europe) [9], and 2007 (the United Kingdom) [10]. But despite the increasing burden of the disease, only 5.2% of eligible US patients receive rtPA due to the narrow time frame for administration and the concern for hemorrhagic complications [11, 12]. The benefits of thrombolysis are time-dependent [13–15], and earlier thrombolysis is associated with better functional outcome [16–18]. A pooled analysis of early rtPA trials as well as the ECASS III and EPITHET trials showed that the greatest benefit from rtPA use in AIS comes from earlier treatment [18], with number needed to treat ranging from 4.5 to 14 as time from symptom onset increases [19]. However, clinical trial data fail to provide information about "ultra-early" rtPA administration due to the majority of patients being treated after 60 min from stroke symptom onset. Apart from clinical efficacy, early thrombolysis is also cost-effective [20], with the early use of rtPA reducing hospital length of stay, with higher discharge rates to homes instead of inpatient rehabilitation or nursing homes [19–22].

Five major randomized, controlled clinical trials recently demonstrated that timely MT for ELVO patients is safe and improves functional outcomes [3–7]. Good clinical outcome following successful angiographic reperfusion is also time dependent [23]. A recent meta-analysis of pooled individual patient data from 1287 adults in these trials demonstrated that MT up to 7.3 h after symptom onset was associated with improved outcomes. However, rates of functional independence after thrombectomy were as high as 64% with reperfusion at 3 h versus 46% with reperfusion at 8 h [24].

Factors Leading to Delayed Treatments

The Get with the Guidelines–Stroke program showed that less than 1000 of the 58,353 patients treated with rtPA were treated within 60 min of symptom onset [25]. Similarly, only 11% of rtPA-treated patients in the International Stroke Thrombolysis Registry received treatment within the first 90 min after symptom onset [26]. Delays to thrombolysis can be divided into prehospital and in-hospital factors [27]. Prehospital factors include stroke symptom recognition, decision time to call emergency services, and emergency medical service (EMS) arrival on scene, as well as scene time and hospital transport times. In-hospital treatment delay factors include emergency department (ED) triage, registration, history and evaluation, testing including computed tomography (CT) scanning, and blood laboratory studies, with some providers taking additional time to ponder consideration for rtPA treatment and/or referral for thrombectomy [28].

Various strategies have been implemented to address both prehospital and in-hospital delays over the years, each with varying degrees of success. Stroke

awareness campaigns may improve patient, family or lay responder times to EMS call [26, 29, 30], and also EMS recognition and response to acute stroke [31], but the effects of these campaigns are only temporary, requiring frequent repetition and widespread community engagement. In-hospital delay factors have been addressed by strategies that include the addition of point-of-care testing, implementation of an all-points alarm stroke team response [27, 32], or implementation of a multidisciplinary approach which includes EMS personnel, ED physicians, nursing staff, CT technologists, and vascular neurologists [33]. Although considerable improvements have been achieved, stroke onset-to-treatment times often remain unsatisfactory because prehospital delays are widely unaffected.

Mobile stroke units (MSU) were first proposed as a method to expedite acute stroke diagnosis and treatment, by bringing rtPA and other acute treatments to the patient in the prehospital setting [34]. MSU care may provide a robust strategy to treat patients significantly earlier, thereby saving brain tissue and reducing stroke-related morbidity or mortality.

History of Mobile Stroke Unit Development and Technological Advancements

Several factors previously made use of MSUs impractical, including the qualifications of the prehospital provider on board, access to ambulance-based CT, and laboratory testing capabilities to exclude coagulopathy. Walter and colleagues overcame these limitations, launching the first MSU in 2010 in Saarland, Germany, with a Mercedes-Benz Vario 815D ambulance that included conventional ambulance equipment: a small portable 8 slice CT scan; a telemedicine system for transmission of digital imaging, communication, and real-time video of patient clinical examination; and a point-of-care laboratory system [35, 36]. The Saarland MSU included a radiologist on board for immediate CT image interpretation, and once imaging was completed and treatment initiated, the patient was transferred to the hospital by regular ambulance [35]. These authors conducted a single-center randomized trial to compare the time from alarm (emergency call) to therapy decision between prehospital MSU-managed patients and conventional hospital-based treatment [37]. Prehospital stroke treatment in the MSU reduced the median time from alarm to therapy decision substantially: 35 min (IQR 31–39) versus 76 min (63–94), $p < 0.0001$; median difference 41 min (95% CI 36–48 min). Similarly, times from alarm to end of CT, alarm to end of laboratory analysis, and to intravenous thrombolysis bolus were also reduced. Although there were substantial differences in stroke management times, findings showed no significant differences between the two study groups in the number of patients who received thrombolysis or in neurological outcomes [37].

The second MSU emerged in Berlin, Germany, in 2011. The *Pre-Hospital Acute Neurological Therapy and Optimization of Medical care in Stroke patients*

(PHANTOM-S) study featured a newly designed ambulance, the so-called stroke emergency mobile unit (STEMO) [38]. The STEMO unit was designed as a mobile intensive care unit equipped with a CT scan, a point-of-care laboratory with an i-STAT portable clinical analyzer, and a telemedicine infrastructure for remote image reading, as well as videoconferencing support for evaluation of suspected stroke patients. The unit was staffed with a neurologist trained in emergency medicine, a paramedic, and a radiology technologist. In comparison with the Saarland MSU, STEMO was deployed in an urban area, with a high number of patients potentially eligible for treatment. Additionally, teleradiology was used instead of having a radiologist on board, and patients with acute emergencies were transported in STEMO to the hospital [38]. With a single STEMO prototype and total service time of less than 1 year, these investigators treated almost 1500 patients in a catchment area of 1.3 million inhabitants. A post hoc analysis of the PHANTON-S study demonstrated higher rates of thrombolysis once STEMO was deployed (32.6%) compared to conventional care (22.0%, $p < 0.001$). In addition, the proportion of patients who received thrombolysis within 60 min from symptom onset was sixfold higher after STEMO deployment (31.0% STEMO versus 4.9% with conventional care; $p < 0.01$) [39]. Moreover, patients receiving "golden hour" thrombolysis were more likely to be discharged home (adjusted odds ratio, 1.93 [95% CI, 1.09–3.41]; $p = 0.02$) [40, 41].

The first MSU in the United States was developed and implemented by James Grotta, MD at the University of Texas Health Science Center at Houston (UT-H) in 2014 with the aim of achieving better stroke onset-to-treatment times and improved patient outcomes [42] (Fig. 35.1a, b). The UT-H MSU operates in parallel with the Houston Fire Department EMS, so that when an emergency 9-1-1 call is received, the MSU is dispatched along with the nearest available EMS ambulance team. The operation is funded through research grants and operates on 50% of weeks in a given year according to a block randomization schedule. Data are also collected on stroke patients managed on non-MSU dispatch weeks (standard management weeks) to provide control group subjects. In a 26-patient pilot study conducted over their first 8 weeks, 12 patients received rtPA; 4 of these were treated within the first 60 min, another 4 were treated between 61 and 80 min, and 4 were treated within 81–270 min. There were no hemorrhagic or other clinical complications and no technical malfunctions of the CT scan or the MSU ambulance. Ninety-day modified Rankin Scale (mRS) scores were 0 or 1 in all 4 patients treated within 60 min of onset and were within 1 point of baseline mRS in 3 who had baseline mRS score of >1; 1 of the 12 treated patients died because of causes unrelated to stroke, and 1 was lost to follow-up [43].

The Cleveland Clinic deployed the second US MSU in 2014, dispatching alongside Cleveland Fire Department EMS when a distress call/stroke alert is received and a stroke is suspected [44]. The MSU wirelessly transmits CT and point-of-care data to Cleveland Clinic where a neurologist assesses the data, consults with the MSU team, diagnoses the patient, and orders treatment including rtPA remotely via telemedicine [45, 46]. Patients are then transported to the closest hospital with the resources to meet their clinical needs. The MSU is also capable of initiating

anticoagulation reversal therapy as indicated. On average, patients received rtPA 40 min faster in the MSU, compared to ED treatment. In addition, the proportion of suspected AIS patients who received thrombolysis was higher (26%) than those managed conventionally in the emergency department (14%) [45]. Importantly, the Cleveland Clinic MSU was the first in the world to report completion of both noncontrast CT and CT angiography (CTA), providing the capability to perform accurate prehospital triage of ELVO patients to a Comprehensive Stroke Center (CSC) [47].

Other MSUs have emerged throughout the United States using models similar to those developed in Berlin, Houston, and Cleveland. The University of Tennessee Health Science Center (UT-M) chose an MSU strategy that amplifies imaging quality and speed. The UT-M MSU is the first in the world to install a Siemens SOMATOM® Scope 16 slice CT scan (Fig. 35.1c, d) capable of providing high-resolution imaging, with a CTA auto-injection arm and a dedicated gantry that automatically moves the patient to obtain images from the aortic arch through the brain. The SOMATOM® Scope enables rapid scanning, with noncontrast imaging completed in under a minute, followed rapidly by CTA for a total imaging and reconstruction time of 3.5 min. Additionally, unlike scans produced by predecessor MSU CTs, UT-M images are of such high quality that additional admission CT imaging is not required, enabling direct transport to the catheterization lab, operating theater, neurointensive care unit, or stroke unit.

Fig. 35.1 Mobile stroke units in the United States: original vs. newer imaging technology. (**a**) University of Texas at Houston (UT-H), 1st MSU in the USA; (**b**) Interior of UT-H MSU with CereTom® computed tomography (CT) system; (**c**) University of Tennessee Health Sciences Center (UTHSC) MSU; (**d**) Interior of UT-M MSU with Siemens SOMATOM® Scope CT system

The UT-M MSU was designed with academic teaching in mind, providing a total of nine passenger seats, and expanded internal cab space making it the largest MSU in operation worldwide, although smaller cab layouts would also adequately support the Siemens SOMATOM® Scope CT if desired. An internal power source capable of matching regular electrical outlet access supports the system enabling up to a total of 20 CTs before recharging is necessary.

Imaging Technologies for Mobile Stroke Units

There are several portable CT scanners on the market, including the CereTom (Neurologica, Danvers, MA, USA), the Tomoscan (Philips Medical Systems, Best, the Netherlands), the xCAT ENT (Xoran Technologies, Ann Arbor, MI, USA), the OTOscan (NeuroLogica), and the SOMATOM® Scope (Siemens), each of which varies somewhat in their designs and intended uses. Historically, the first and most commonly utilized MSU CT is the Samsung CereTom, an 8-slice unit limited to head imaging because of the small size of the "donut," whereas the latest generation MSUs in operation at UT-M and Cadence Northwestern (Winfield, Illinois) utilize the 16-slice Siemens SOMATOM® Scope CT with capabilities of imaging from the aortic arch through the head. Table 35.1 provides characteristics of the CereTom and SOMOTOM® Scope systems. Despite differences in image quality, both scanners are similar in price, although repeat hospital admission imaging with the CereTom system carries additional hidden costs, as well as an increased dose of radiation for the patient.

Staffing the Mobile Stroke Units

Staffing models for MSUs are developed based on prehospital care requirements, radiation safety and imaging management needs, and available work force. Most countries and individual states/regions require that vehicles classified as ambulances be staffed with prehospital care educated and credentialed staff, such as emergency medical technicians (EMTs) and EMT-paramedics (EMT-P) [48, 49]. Drivers of vehicles classified as ambulances must also hold special drivers' licenses that verify competency in high-speed emergency transport [48].

Vascular neurology specialists must also supplement, or be accessible to, the required EMT/EMT-P crew. Vascular neurologists sometimes serve as members of the MSU crew, but the limited supply of these physicians often makes this unfeasible. Telemedicine has become an important alternative to onboard vascular neurologists, enabling imaging interpretation, the clinical exam, and provision of treatment orders [45, 50]. Most MSUs that operate with telemedicine are also supported by registered nurse crew members that are experienced in emergency stroke assessment and management. However, nurses that lack nurse practitioner (NP) licensure

Table 35.1 Characteristics of the CereTom® and SOMATOM® Scope CT systems

Imaging modality	Samsung CereTom®	Siemens SOMATOM® Scope
System hardware	8 slice per rotation (1cm coverage); axial; helical (spiral); dynamic Scanning 32 cm gantry Rapid scan time: 1-, 2-, and 4-second rotation Real-time image viewing Angiogram and perfusion capabilities with automatic bolus tracking and perfusion mapping	16 slice per rotation (from 24 row adaptive detector array); 70 cm gantry, tilt disabled Use of UFC (Ultra Fast ceramics) in detector Small footprint for optimal use of space Small focal spot size Angiogram and perfusion capabilities
System software	Easy to use interface Advanced visualization software allowing for 2D, 3D, and MPR viewing Easy integration with PACS; 3.1 dicom compliant; XR-29 compliant Wireless communication capability 1000 watt max load for energy saving	Easy to use interface Advanced visualization software allowing for 2D, 3D, and MPR viewing Easy integration with PACS Wireless communication capability Automatic system shutdown when ambulance is turned on Flying focal spot technology Energy saving functions enable saving on air conditioning due to low heat emissions **eCockpit SE** mode enables scanner to select optimum scan parameters, curbing wear and tear on hardware **eStart** feature extends the life span of the system's X-ray tube through gradual warm-up process following long periods of standby status **eSleep** mode puts gantry to sleep during inactivity
Ambulance hardware	Standard-sized ambulance with options for extended space 360° patient access around ambulance cot Comes with a radiolucent scan board and adaptor, which can transform any ambulance cot into a safe and stable scanning platform Optistat Power Injector Samsung PT60 Ultrasound Mounting system (not CT) is crash test certified to 150% with 0 damage to module or mount	Uses hospital grade CT table Auto-injector Ultrasound

(continued)

Table 35.1 (continued)

Imaging modality	Samsung CereTom®	Siemens SOMATOM® Scope
Reconstruction features	Statistical IR noise reduction Metal artifact reduction MIP, MinIP, AVG sliding slab 3D MIP, volume tender, MinIP Oblique and curved MPR Automatic exposure control Cine Import for MRI, PET, SPECT and X-ray viewing Side-by-side viewing Jpeg, cine, and Dicom 3.1 output	SureView™ reconstruction algorithm: pitch value selection from defined coverage and scan time chosen to retain slice thickness and image quality Uses **IRIS** (iterative reconstruction in image space) technology that performs image reconstruction and reduces noise Adaptive signal boosts improve weak signals during high attenuation **FAST** (fully assisting scanner technology) detects the anatomic region of interest and sets the scan parameters accordingly **CARE** (combined applications to reduce exposure) helps automate the imaging process and reduce radiation dose delivered to the patients
Need for repeat imaging	CT/CTA usually repeated once patient is admitted to hospital	Repeat imaging is not required for patient management, except when serial imaging is desired (e.g., intracerebral hemorrhage serial imaging for hematoma expansion assessment)

and credentialing are unable to independently order medications and testing. Without an active telemedicine connection to a physician or NP for orders and oversight, registered nurses' contributions are constrained [51–54].

The UT-M program is staffed by fellowship trained [55], vascular neurology board certified NPs [56] capable of localizing clinical findings, reviewing noncontrast CT and CTA source images, and ordering/delivering acute treatments including rtPA in the field. Because the process is not dependent on a telemedicine video connection and/or image transfer, and the program uses the rapid SOMATOM® Scope CT/CTA scan, scene arrival to rtPA bolus times is typically quite short at a median of 16 min (range 8–38 min), compared to 25–30 min reported by telemedicine-based CereTom scan-supported MSU programs. A strict quality improvement process supports NP staffing, including telephone availability of medical command, and 100% case review to assess accuracy in diagnosis and treatment decision-making.

Safe management of MSU CT imaging requires a CT technologist as crewmember. In the United States, radiology technologists (RTs) undergo additional education and training for registration as a CT technologist, and most US states also require RTs to be licensed [57]. Additionally, most CT technologists are also proficient in obtaining intravenous access, and some may be cross trained in other forms of vascular imaging such as transcranial Doppler or duplex ultrasound. Radiation safety must be continuously monitored to ensure patient, bystander, and crew safety.

A recent report from the UT-H program showed that the cumulative occupational deep dose equivalent for the CT technologist that remains in the truck during the scan was 1.14 mSv, well below 10% of the current United States occupational dose limit [58].

The most important aspect of sound MSU performance is recognition and respect for each provider's unique qualifications and expertise. Oversight and security on scene should be the focus of the EMT and EMT-P crewmembers who bring considerable expertise to this aspect of MSU management. When EMT and EMT-P crew are integrated with local EMS systems, the protocols and experience managing medical emergencies other than stroke (including extreme events such as cardiac arrest) will further benefit the team. Collaborative relations with EMS personnel and CT technologists allow vascular neurology experts to focus solely on diagnosis and treatment, thereby optimizing patient management. Lastly, the prehospital environment can be highly unpredictable, chaotic, and even dangerous [59]. MSU administrators should cautiously vet staff interested in the project, for appropriate fit in this challenging environment.

Emergency Medical System Integration

While different models for MSU housing exist (hospital-based, community center-based, vs. fire station-based), successful MSU deployment requires integration with local EMS, including the ability to initiate MSU dispatch directly from 9-1-1 or other emergency system calls. Fundamental to this is the requirement that the MSU be classified as an ambulance. This classification enables the MSU to transport patients with lights and sirens to ensure timely access to – and transport of – acute stroke patients. Ambulance classification mandates that standard equipment, personnel, and drugs are on board so that all encountered emergencies can be appropriately managed [48].

Focusing solely on the needs of vascular neurology patients, without an understanding of how the MSU fits into the regional EMS system, will limit acceptance of the program in the region and slow the ambulance classification approval process. The most successful strategy to expedite both acceptance and approvals involves hiring a MSU operations director that possesses EMS and Fire Department employment/expertise along with the required EMT and/or EMT-P credentials. Fire Department/EMS personnel have ready access to leaders that can guide and promote the MSU within the EMS system. Additionally, these individuals bring significant knowledge and expertise to the process of securing regional and state licensing.

Quality Improvement and MSU Registry Data

The PRE-hospital Stroke Treatment Organization (PRESTO) is an international consortium of medical practitioners involved in MSU programs that was formed in 2016 to improve stroke outcomes by supporting research and advocacy for MSU

prehospital stroke treatment [60]. The organization has developed a minimum dataset for collection among all MSU teams that will enable aggregation of registry data across all programs. The dataset includes elements in the following categories: (1) demographics, (2) vital signs, (3) pretreatment medications, (4) clinical scores, (5) critical times, (6) MSU treatments, (7) in-hospital treatment, (8) MSU CT imaging, (9) in-hospital imaging, (10) MSU and final diagnoses, (11) complications/course, and (12) outcomes. Use of the minimum dataset should benefit our ability to understand the impact of MSU care.

Mobile Stroke Unit Management of Specific Acute Stroke Subtypes and Neuroemergencies

Acute Ischemic Stroke

Several studies have demonstrated that MSUs achieve faster onset-to-needle time with no increase in mortality or sICH compared to hospital-based thrombolysis programs. Additionally, the proportion of suspected AIS patients receiving thrombolysis has been shown to be higher on MSUs then in EDs during the same time period [35–47]. Long-term follow-up data are not yet available, and it is unknown how much improvement in functional outcome may occur with MSU care. Nevertheless, there is theoretical support for MSU care due to the inverse relation between time of thrombolysis and clinical outcomes [18, 19, 21–26]. In addition to achieving faster thrombolysis, MSUs can provide hemodynamic and neurologic monitoring as an integral part of pre- and post-thrombolysis care. MSU crewmembers are capable of detecting deterioration or improvement in the neurological exam post-rtPA treatment, as well as monitoring and treating arterial blood pressure with continuous infusion medications that provide more precise control.

Emergent Large Vessel Occlusion

In MSUs with CTA capability, prehospital detection of ELVO promotes early triage to a Comprehensive Stroke Center (CSC) or neurointerventional-capable hospital. Direct CSC transport provides a distinct time to treatment advantage and ensures rapid access to thrombectomy. In contrast, the time to transfer from a Primary Stroke Center (PSC) to a CSC increases time to treatment and may jeopardize patient outcomes. Onboard CTA also offers the opportunity for prehospital notification of endovascular staff, facilitating rapid assembly of the endovascular team and preparation of the interventional suite. Well-organized MSU care supported by onboard CTA allows patients to bypass the ED entirely and proceed directly to the endovascular suite, contributing to the potential for improved functional outcomes.

Hemorrhagic Stroke

Hematoma expansion occurs early after ictus in spontaneous intraparenchymal hemorrhage (IPH), most commonly within 4.5–6 h from onset [61]. Whether early aggressive reduction systolic blood pressure in the MSU could effectively improve functional outcome in IPH remains unknown, but the MSU provides a unique environment to test this hypothesis. Other than blood pressure lowering, MSUs may serve as a powerful platform for study of hemorrhage control agents [62] as well as neuroprotective drugs in the management of IPH, alongside well-controlled arterial pressure. The BEST-MSU study reported enrolling 4 IPH cases from their first 26 patients, and aggressive BP lowering was provided within the first hour of symptom onset [63]. The use of continuous infusion antihypertensive agents by MSU teams promotes improved blood pressure control of these fragile cases while ensuring provision of close hemodynamic monitoring. Additionally, MSU teams that stock reversal agents for coagulopathic ICH are well suited to rapidly support hemostasis alongside standard management while alerting both neurosurgery and neurocritical care teams of CT/CTA findings and pending patient needs [43, 63].

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) and its structural source may be rapidly detected by MSUs equipped with CT/CTA capabilities. In accordance with guidelines [64], blood pressure control can be achieved and smoothly maintained to less than 160/90 mm Hg in these cases using continuous infusion antihypertensive agents which are typically stocked on MSUs, and patients are advantaged by direct triage to a CSC for definitive management. En route, the neuroendovascular team can be notified to facilitate direct transfer to the endovascular suite. While it is expected that the incidence of aneurysmal SAH cases transported by MSU will be low, the MSU provides a distinct advantage to these patients by ensuring rapid diagnosis, triage, stabilization, and direct access to definitive management.

Seizure

Seizures may occur with either ischemic or hemorrhagic stroke, may be idiopathic, or may produce persisting focal clinical findings that mimic stroke. But, MSUs with both CT and CTA capabilities provide the advantage of vascular imaging to assist in diagnosing stroke events. While almost all ambulance services are stocked with at

least one dose of a benzodiazepine agent, MSUs may be equipped with larger quantities of these medications to support improved seizure control. Of the first 100 cases transported by the UT-M MSU, one patient was diagnosed with status epilepticus and rapidly managed in the field. The BEST-MSU study showed that three out of four ICH patients had seizures and were treated with antiepileptic drugs while on MSU [43].

Mobile Stroke Unit Program Limitations

Program Costs

Numerous costs are associated with MSU program start-up and continuation [65]. Vehicle development, including CT scan installation and lead lining, commonly runs $600,000 to $1.4 million USD. Costs are similar between smaller ambulances equipped with the Samsung CereTom® and larger ambulances equipped with Siemens SOMATOM® Scope CT/CTA systems, making the choice of vehicle/CT systems solely dependent on imaging preferences. Annual staffing for programs that run 12 h/day, 7-days/week, can cost up to $2 million USD, with the use of a full-time vascular neurologist physician staffing model being the most expensive option. Insurance and licensing costs must also be factored into start-up expenses, as well as additional equipment common to all ambulances to meet country, state, and regional requirements. Telemedicine costs, both within the ambulance and at the remote center, also contribute to overall expense. Point-of-care lab systems are relatively inexpensive, whereas the use of standard laboratory equipment may be costly and also carries the requirement of CLIA certification which mandates that this equipment only be used by individuals holding at least a bachelor's degree. Many programs choose to limit lab testing to blood glucose in patients without a history of anticoagulation or coagulopathy, thereby reducing equipment costs and improving efficiency. To date, there are no data suggesting that a scaled down approach to labs on the MSU is unsafe. Additional medical equipment may be included on an MSU depending on program resources and interests. For example, the UTHSC MSU program also stocks a transcranial Doppler (TCD) for monitoring ELVO recanalization and duplex ultrasound for extracranial vascular imaging as well as assisting with difficult intravenous access; the cost of these devices ranges from $50 K to $90 K. Drugs unique to the management of stroke can add considerable expense, including alteplase tPA and premixed nicardipine or clevidipine infusions. Lastly, initial and ongoing supply costs need to be included in overall program expense, although if the ambulance is operated as a city or county government operated/integrated vehicle, these authorities will manage many supply expenses, excluding drugs unique to the stroke mission. Despite these expenses, MSU programs may prove to be a vital tool in reduction of disability and overall economic burden associated with stroke, increasing quality-adjusted life-years and reducing mortality.

Traffic

Traffic patterns within the targeted city or region may limit service availability and should be considered when initiating a MSU program. Use of emergency system data to determine where to house the MSU for improved scene response times can be valuable, although the disease-specific accuracy of this information may limit identification of the best housing location. Traffic should also be considered when determining the size of the vehicle selected for the stroke mission. For example, a larger truck chassis with an expanded cab would likely perform poorly in busy urban environments. However, while the size of the truck used to house the CT could potentially limit scene access, even the larger sized UT-M MSU has never experienced difficulty with street access to complete its mission despite being housed in a city with old, often historic, narrow intercity streets. Generally, streets accessible by any size fire truck will accommodate all sizes of MSU ambulances.

Concerns About Treatment of Stroke Mimics

The need for rapid decision-making, combined with the somewhat chaotic, limited-resource, prehospital environment, increases the potential for treatment of patients with stroke mimics or patients with exclusions for intravenous alteplase. Ebinger and colleagues reported treatment of only 2% of stroke mimic cases with alteplase on the MSU [36]. Importantly, thrombolysis treatment has been shown to be safe in large studies [66, 67]. Overall, rates for symptomatic intracerebral hemorrhage are low among alteplase-treated MSU cases, despite having limited time and resources to vet exclusions for alteplase treatment.

Conclusion

Mobile stroke units enable time-sensitive diagnosis and delivery of ultra-early stroke treatment. Advancements in imaging technology, telemedicine, and innovative staffing methods position MSUs as pivotal field triage machines capable of reducing time to treatment, with subsequent rapid transfer to the neuroendovascular suite, the operating room, the neurocritical care unit, or the stroke unit.

References

1. Feigin VL, Norrving B, George MG, et al. Prevention of stroke: a strategic global imperative. Nat Rev Neurol. 2016;12(9):501–12.
2. 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(24):1581–7.

3. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20.
4. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30.
5. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–18. https://doi.org/10.1056/NEJMoa1414792.
6. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
7. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–306.
8. Heart and Stroke. www.heartandstroke.ca/stroke/treatments/medications. Accessed 15 Jan 2017.
9. Millan M, Dorado L, Davalos A. Fibrinolytic therapy in acute stroke. Curr Cardiol Rev. 2010;6(3):218–26.
10. Robinson T, Zaheer Z, Mistr AK. Thrombolysis in acute ischemic stroke. Ther Adv Chronic Dis. 2011;2(2):119–31.
11. Adeoye O, Hornung R, Khatri P, et al. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke. 2011;42(7):1952–5.
12. Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol. 2009;8(3):261–9.
13. Meretoja A, Weir L, Ugalde M, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology. 2013;81(12):1071–6.
14. Gladstone DJ, Rodan LH, Sahlas DJ, et al. A citywide prehospital protocol increases access to stroke thrombolysis in Toronto. Stroke. 2009;40(12):3841–4.
15. O'Brien W, Crimmins D, Donaldson W, et al. FASTER (Face, Arm, Speech, Time, Emergency Response): experience of Central Coast Stroke Services implementation of a pre-hospital notification system for expedient management of acute stroke. J Clin Neurosci. 2012;19(2):241–5.
16. Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in contemporary stroke trials. Int J Stroke. 2009;4(3):200–5.
17. Haass A, Walter S, Ragoschke-Schumm A, et al. "Time is brain". Optimizing prehospital stroke management. Nervenarzt. 2014;85(2):189–94.
18. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010;375(9727):1695–703.
19. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363(9411):768–74.
20. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. Neurology. 1998;50(4):883–90.
21. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology. 2000;55(11):1649–55.
22. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. Stroke. 2009;40(6):2079–84.
23. Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009;73(13):1066–72.
24. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279–88.
25. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA. 2013;309(23):2480–8.

26. Cheng NT, Kim AS. Intravenous thrombolysis for acute ischemic stroke within 3 hours versus between 3 and 4.5 hours of symptom onset. Neurohospitalist. 2015;5(3):101–9.
27. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011;123(7):750–8.
28. Herlitz J, Wireklintsundström B, Bång A, et al. Early identification and delay to treatment in myocardial infarction and stroke: differences and similarities. Scand J Trauma Resusc Emerg Med. 2010;18:48.
29. Dombrowski SU, Mackintosh JE, Sniehotta FF, et al. The impact of the UK 'Act FAST' stroke awareness campaign: content analysis of patients, witness and primary care clinicians' perceptions. BMC Public Health. 2013;13:915.
30. Ragoschke-Schumm A, Walter S, Haass A, et al. Translation of the 'time is brain' concept into clinical practice: focus on prehospital stroke management. Int J Stroke. 2014;9(3):333–40.
31. Wojner-Alexandrov AW, Alexandrov AV, Rodriguez D, Persse D, Grotta JC. Houston paramedic and emergency stroke treatment and outcomes study (HoPSTO). Stroke. 2005;36(7):1512–8.
32. Walter S, Kostopoulos P, Haass A, et al. Point-of-care laboratory halves door-to-therapy-decision time in acute stroke. Ann Neurol. 2011;69:581–6.
33. Middleton S, Grimley R, Alexandrov AW. Triage, treatment and transfer: evidence-based clinical practice recommendations and models of nursing care for the first 72 hours of admission to hospital for acute stroke. Stroke. 2015;46(2):e18–25.
34. Ebinger M, Lindenlaub S, Kunz A, et al. Prehospital thrombolysis: a manual from Berlin. J Vis Exp. 2013;81:e50534.
35. Walter S, Kostpopoulos P, Haass A, et al. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. PLoS One. 2010;5(10):e13758.
36. Ebinger M, Fiebach JB, Audebert HJ. Mobile computed tomography: prehospital diagnosis and treatment of stroke. Curr Opin Neurol. 2015;28(1):4–9.
37. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. Lancet Neurol. 2012;11(5):397–404.
38. Wendt M, Ebinger M, Kunz A, et al. Improved prehospital triage of patients with stroke in a specialized stroke ambulance: results of the pre-hospital acute neurological therapy and optimization of medical care in stroke study. Stroke. 2015;46(3):740–5.
39. Ebinger M, Kunz A, Wendt M, et al. Effects of golden hour thrombolysis: a Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) substudy. JAMA Neurol. 2015;72(1):25–30.
40. Ebinger M, Rozanski M, Waldschmidt C, et al. PHANTOM-S: the prehospital acute neurological therapy and optimization of medical care in stroke patients – study. Int J Stroke. 2012;7(4):348–53.
41. Weber JE, Ebinger M, Rozanski M, et al. Prehospital thrombolysis in acute stroke: results of the PHANTOM-S pilot study. Neurology. 2013;80(2):163–8.
42. Parker SA, Bowry R, Wu TC, et al. Establishing the first mobile stroke unit in the United States. Stroke. 2015;46(5):1384–91.
43. Bowry R, Parker S, Rajan SS, et al. Benefits of stroke treatment using a mobile stroke unit compared with standard management: the BEST-MSU study run-in phase. Stroke. 2015;46(12):3370–4.
44. John S, Stock S, Cerejo R, et al. Brain imaging using mobile CT: current status and future prospects. J Neuroimaging. 2016;26(1):5–15.
45. Itrat A, Taqui A, Cerejo R, et al. Telemedicine in prehospital stroke evaluation and thrombolysis: taking stroke treatment to the doorstep. JAMA Neurol. 2016;73(2):162–8.
46. Rasmussen PA. Stroke management and the impact of mobile stroke treatment units. Cleve Clin J Med. 2015;82(12 Suppl 2):S17–21.
47. Cerejo R, John S, Buletko AB, et al. A mobile stroke treatment unit for field triage of patients for Intraarterial revascularization therapy. J Neuroimaging. 2015;25(6):940–5.

48. National Association of Emergency Medical Technicians (NAEMT). http://www.naemt.org. Accessed 15 Dec 2016.
49. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology, 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(3):870–947.
50. Wu T-Z, Parker SA, Jagolino A, Yamal JM, Bowry R, Thomas A, et al. Telemedicine can replace the neurologist on a mobile stroke unit. Stroke. 2017;48:493. https://doi.org/10.1161/STROKEAHA.116.015363.
51. APRN Consensus Work Group & the National Council of State Boards of Nursing APRN Advisory Committee. Consensus Model of APRN Regulation: Licensure, Accreditation, Certification & Education. 2008. http:///www.ncsbn.org/Consensus_Model_for_APRN_Regulation_July_2008.pdf. Accessed 15 Dec 2016.
52. American Nurse Credentialing Center. ANCC Certification Center. 2013. http://www.nursecredentialing.org/certification. Accessed 16 Dec 2016.
53. U.S. Drug Enforcement Agency. Mid-Level Providers Authorization by State. 2013. http://www.deadiversion.usdoj.gov/drugreg/practioners/. Accessed 15 Dec 2016.
54. National Council of State Boards of Nursing I. NCSBN's APRN Campaign for Consensus: State Progress toward Uniformity. 2013. https://www.ncsbn.org/2567.htm. Accessed 15 Dec 2016.
55. Health Outcomes Institute, NET SMART. www.learnstroke.com. Accessed 15 Dec 2016.
56. Association of Neurovascular Clinicians. www.anvc.org. Accessed 15 Dec 2016.
57. American Registry of Radiologic Technologists. https://www.arrt.org. Accessed 15 Dec 2016.
58. Gutiérrez JM, Emery RJ, Parker SA, et al. Radiation monitoring results from the first year of operation of a unique ambulance-based computed tomography unit for the improved diagnosis and treatment of stroke patients. Health Phys. 2016;110(5 Suppl 2):S73–80.
59. Pourshaikhian M, Gorji HA, Aryankhesal A, Khorasani-Zavareh D, Barati A. A systematic literature review: workplace violence against emergency medical services personnel. Arch Trauma Resusc. 2016;5(1):e28734.
60. Audebert H, Fassbender K, Hussein S, Ebinger M, Turc G, Davis S, Alexandrov AW, Grotta JC, on Behalf of the PRESTO Group. The PRE-hospital Stroke Treatment Organization (PRESTO). Int J Stroke. 2017;12(9):932–40.
61. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032–60.
62. Frontera JA, Lewin JJ, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar M, Peerschke EIB, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. Guideline for reversal of antithrombotics in intracranial hemorrhage: executive summary, a statement for healthcare professionals from the Neurocritical care society and Society of Critical Care Medicine. Crit Care Med. 2016;44:2251–7.
63. Gomes JA, Ahrens CL, Hussain MS, et al. Prehospital reversal of warfarin-related coagulopathy in intracerebral hemorrhage in a mobile stroke treatment unit. Stroke. 2015;46(5):e118–20.
64. Bederson JB, Connolly ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare providers from a special writing group of the stroke council. Am Heart Assoc Stroke. 2009;40:994–1025.
65. Rajan SS, Baraniuk S, Parker S, et al. Implementing a mobile stroke unit program in the United States: why, how, and how much? JAMA Neurol. 2015;72(2):229–34.
66. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology. 2010;74(17):1340–5.
67. Tsivgoulis G, Zand R, Katsanos AH, et al. Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis. Stroke. 2015;46(5):1281–7.

Chapter 36
Role of Decompressive Hemicraniectomy for Intracranial Hypertension Following Stroke

Seby John, James Scozzafava, and Muhammad Shazam Hussain

Elevated intracranial pressure (ICP) is a frequently encountered problem in neurological and neurosurgical patients in the intensive care unit. When it is severely or persistently elevated and unresponsive to aggressive medical therapy, it is sometimes referred to as malignant intracranial hypertension and can lead to severe consequences including brain herniation and death. The most common cause of raised ICP is traumatic brain injury (TBI). As a result, much of the management is extrapolated from TBI experience and literature. In TBI, elevations in ICP have been shown to be associated with worse outcome [1]. Furthermore, the degree of elevation and duration of elevation have both been shown to negatively impact outcome [2]. Similar findings have been noted in other causes of raised ICP, including stroke and aneurysmal subarachnoid hemorrhage [3–5]. Secondary issues like cerebral edema, impaired autoregulation, hydrocephalus, and secondary ischemia can lead to more significant and life-threatening consequences. As a result, regardless of the cause or severity of the initial injury to the brain, a great deal of attention must often be focused on the monitoring and the management of ICP in acute neurological patients.

S. John
Neurology and Neurointerventional Surgery, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
e-mail: JohnS5@ClevelandClinicAbuDhabi.ae

J. Scozzafava
Department of Adult Critical Care Medicine, Saskatoon Health Region, Saskatoon, Saskatchewan, Canada

Division of Stroke Neurology, Neurosciences Program, Department of Medicine, University of Alberta, Edmonton, AB, Canada

M. Shazam Hussain (✉)
Cerebrovascular Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: HUSSAIS4@ccf.org

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_36

Physiology

The brain is enclosed within an inelastic container (the skull) or "closed box," and the sum of volumes of intracranial contents is relatively constant. The intracranial contents include blood, cerebrospinal fluid (CSF), and brain [6]. In the average adult, the total volume of the intracranial contents is approximately 1450 mL [7]. The brain takes up the largest proportion of this volume with approximately 1300 mL while blood typically takes up approximately 110 mL. CSF is constantly being circulated and takes up approximately 65 mL of the intracranial volume. Given the limited compliance of the cranial vault, an increase in volume must be offset by a decrease in one or more of the contents or an increase in ICP will result. Although CSF is the most accommodating of the intracranial contents, its compensatory capabilities are limited, and once exhausted, small increases in intracranial volume result in large increases in ICP. This is best described by the Monro-Kellie hypothesis (Fig. 36.1).

Elevations in ICP can lead to a compromise in cerebral perfusion and cerebral blood flow (CBF). Typically CBF is about 750 ml/min, but this is impaired in the setting of raised ICP through increased cerebral vascular resistance (CVR). The result of impaired cerebral perfusion and decreased CBF can be cerebral ischemia and infarction. CBF is closely related to cerebral perfusion pressure (CPP) and CVR [8].

$$\text{CBF} = \frac{\text{CPP}}{\text{CVR}}$$

Although CBF and CVR are not easily accessible, CPP can be calculated from mean arterial pressure (MAP) and ICP.

$$\text{CPP} = \text{MAP} - \text{ICP}$$

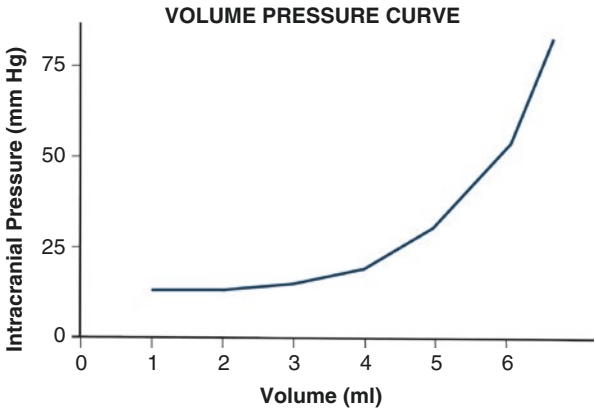


Fig. 36.1 ICP – volume curve showing exponential increases in ICP as skull compensatory mechanisms exhaust in the face of increasing intracranial volume

As a result, CPP is often used as a surrogate for CBF and is often closely monitored along with ICP in patients with raised ICP from various causes.

Cerebral edema can be a significant contributing factor in many causes of raised ICP and can occur from various causes in neurological patients. It can accumulate intracellular or extracellular, and depending on the cause and location, it can be a bigger factor on ICP than the primary injury. Intracellular edema is usually the result of cytotoxic edema damaging the cell membranes often destroying the sodium/potassium exchange pump. This leads to unregulated passage of sodium and water into neuronal cells. It can occur as the result of many factors including toxins, trauma, hypoxia, and hypothermia. It can also occur in the context of cerebral ischemia as a lack of oxygen and glucose destroys cell membrane. In the case of cerebral ischemia, it is often the sodium/calcium pumps on the cell membrane that are destroyed, but inevitably the unregulated passage of sodium with water leads to cell swelling. In many causes of brain injury, including cerebral ischemia, initial cerebral edema is intracellular and cytotoxic; however extracellular vasogenic edema can occur soon after.

Extracellular edema often results from capillary injuries at specific areas. This leads to breakdown of the blood-brain barrier (BBB) and leakage of protein and fluids into the extracellular space affected. It can occur from direct disruption of the BBB as in the case of trauma, hemorrhage, and severe hypertension. In the case of severe hypertension, it is often referred to as hydrostatic-type vasogenic edema and is felt to be the result of excess direct hydrostatic pressure across overwhelmed cerebral capillary. Vasogenic edema can also occur as a result of release of vasoactive compounds as in the case of tumors and various causes of neuro-inflammation. A more recent subtype of vasogenic edema has been suggested as a result of hypoxia at a mitochondrial level on the cells of the BBB. It is sometimes seen in the context of altitude sickness and is sometimes referred to as high-altitude cerebral edema (HACE) [9].

A third category of edema is sometimes referred to as interstitial hydrostatic edema. It is seen in acute obstructive hydrocephalus but can also be seen in nonobstructive hydrocephalus. It can also occur from meningitis and subarachnoid hemorrhage. It is felt to result from increased intraventricular pressures, which disrupt the ventricular ependymal lining (Table 36.1).

Considerations Specific to Ischemic Stroke

Issues regarding raised ICP are encountered less in ischemic stroke compared to hemorrhagic stroke. Similarly, the challenges in management of malignant intracranial hypertension are not as frequently encountered in ischemic stroke patients compared to hemorrhagic stroke or other neurology and neurosurgery patients presenting with mass lesions. This is because in the case of ischemic stroke, a new mass or volume is not immediately introduced into our “closed box” model of intracranial contents like with other causes of brain injury like hemorrhage or tumor. However,

Table 36.1 Types of cerebral edema

Type of edema	Pattern	Mechanism	Differential diagnosis	Potential therapies
Vasogenic	Extracellular spaces in white matter	Blood-brain barrier breakbown secondary to capillary injury near focal lesions	Tumors Hemorrhage Infection Inflammation Trauma Hypoxia/HACE	Surgery Antibiotics Steroid
Hydrostatic	Extracellular spaces in white matter and gray matter. Often diffuse. Can favor posterior circulation in PRES. Can be unilateral in CHS	Increased cerebral capillary water influx across blood-brain barrier because of elevated pressure states	Hypertensive Emergencies Hyperperfusion Syndromes Hepatic Encephalopathy	Antihypertensives
Interstitial	Prefers periventricular white matter, especially frontal and occipital lobes	Transependymal flow of cerebrospinal fluid	Acute Obstructive Hydrocephalus NPH Meningitis SAH	Shunt or EVD
Cytotoxic	Often intracellular prefers gray matter	Na/K pump breakdown and damaged cell membranes leading to water entry into cells and cellular swelling	Toxins Trauma Hepatic Encephalopathy Hypoxic Severe hypothermia Ischemia/ Infarction	Mannitol Hypertonic Saline

immediately after the onset of ischemia, changes to the brain begin to occur including cerebral edema.

It has been estimated that anywhere from 1% to 10% of supratentorial ischemic strokes can cause rapid neurological deterioration from space-occupying cerebral edema. Although ischemic strokes display some vasogenic edema as part of the inflammatory phase, the primary swelling is the result of cytotoxic edema. Cytotoxic edema is the result of damaged cell membranes during ischemia. The result is that neuronal cells fill with plasma ultrafiltrate. Although this usually occurs between the second and fifth day after stroke, it can occur as early as 24 h. Such a presentation following an ischemic stroke involving the entire middle cerebral artery (MCA) territory is called "malignant MCA infarction" (MMI). The term MMI was first introduced in 1996 and has also become known as large hemispheric infarction (LHI). This is often a consequence of occlusion of the internal carotid artery or the proximal portion of the middle cerebral artery. MMI is associated with cerebral edema, increased ICP, and a high rate of herniation. The prognosis of MMI is poor, and mortality is as high as 80%, with most deaths occurring during the first week from cerebral edema and brain herniation [10].

Management of MMI

Medical Management

Management of patients with large infarction of the MCA territory is still a controversial topic in neurology and neurosurgery. Medical management options to treat cerebral edema from MMI are limited. They include hyperosmolar agents like glycerol, mannitol, or hypertonic saline solutions and other ICP-lowering strategies such as hyperventilation and sedation. However, none of these therapies have been proven effective by clinical trials, and their effects on patient outcomes remain largely unknown or unimpressive. The limited effectiveness of the above strategies may be explained from the fact that shift in brain tissue is the main pathophysiological process in MMI, and ICP elevation occurs only later, if at all.

Both mannitol and hypertonic saline are safe therapeutic options, without causing tissue shifts as assessed by imaging end points [11–13]. These agents are best used in MMI, only when there is clinical evidence of cerebral edema. Caution must be exercised when using mannitol in patients with acute renal impairments and hypertonic saline solutions in patients with volume overload states such as congestive heart failure. Osmotherapy may also be beneficial to bridge the time to surgical intervention [14]. The use of corticosteroids [15] and barbiturates [16] is not recommended for treatment of cerebral edema in MMI [guidelines paper]. Prophylactic hyperventilation is also not recommended, but may be used as a rescue maneuver in patients with MMI showing clinical signs of brain herniation [14]. Backrest elevation to 30 degrees may be employed in patients with raised ICP [14].

In regard to other general conservative measures, evidence does exist that induced hypothermia lowers ICP, likely through decreasing cerebral metabolic rate. However this has not always been shown to correlate to a decreased rate of secondary brain injury. A large randomized controlled trial in severe closed head injury failed to show any significant benefit of induced hypothermia on outcome [17]. One study in stroke patients with MMI showed that maintaining core temperature at 33 ° C for 48–72 h reduced mortality to 44% with an outcome on Barthel index of 70 at 3 months [18], though the benefit was less in comparison with decompressive hemicraniectomy (DCH) (mortality with hypothermia was 47% compared to 12% with DCH) [19]. In combination with hemicraniectomy, hypothermia may have some additional beneficial effect (slightly improved outcome after 6 months without additional side effects) [20]. A controlled study to assess this is still in progress [21]. Although the quality of evidence is low, hypothermia may be considered in patients who are ineligible for surgical interventions, with a target temperature of 33–36 ° C for 24–72 h [14]. Potential side effects such as pneumonia, coagulopathy, and electrolyte derangement should be kept in mind. Caution should also be exercised in the rewarming phase as rebound increase in ICP can be observed.

Surgical Management

Given the consequences of malignant intracranial hypertension and the limitations of the medical therapies, DCH has been proposed as an alternative or adjunct strategy for treatment of cerebral edema in MMI. Craniectomy for prevention of fatal brain herniation has been around for almost 100 years. The rationale for surgery is to change the inelastic container or "closed box" and provide a mechanical outlet for the edematous brain to stretch beyond the skull, thereby preventing herniation. As a consequence, secondary benefits include rapid reduction of intractable ICP and restoration of cerebral perfusion.

Multiple non-randomized studies have shown that DCH, consisting of a hemicraniectomy and duraplasty, reduces mortality in patients with MMI [22–24]. However, its popularity decreased because clinicians were concerned as to whether survival was at the expense of poor functional outcome. In the midst of uncertainty regarding functional outcome, three European trials addressed the role of DCH on functional outcome since 2000: the French DECIMAL (decompressive craniectomy in malignant middle cerebral artery infarcts) trial, the German DESTINY (decompressive surgery for the treatment of malignant infarction of the middle cerebral artery) trial, and the Dutch HAMLET (hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial) trial. A pooled analysis of all three trials was also performed that confirmed suggestions from earlier non-randomized trials and demonstrated the robust effect of DCH on mortality [25–28].

The above trials were both praised and criticized on many points. Analysis of all the trials was assumed possible due to similar design and use of the modified Rankin Scale (mRS) as a common primary outcome measure. Significant difference between the trials included imaging modalities and longer treatment window allowed in HAMLET, which allowed patients to be treated up to 96 h after onset of stroke symptoms. However, the pooled analysis included only the patients randomized and treated within 48 h. The primary outcome measure for the pooled analysis was the mRS dichotomized between "favorable" (defined as mRS 0–4) and "unfavorable" (mRS 5–6). There was clearly a difference between the two treatment arms, with 75% achieving a favorable outcome in the hemicraniectomy group as compared to 24% in the medical treatment alone arm, an absolute risk reduction of 51%. The most robust effect was seen on survival, which increased from 29% to nearly 78% with DCH, translating to an absolute risk reduction of 49% and a number needed to treat of 2 to avoid one fatal outcome. Another significant result was the proportion of patients who were independent with disability (mRS 2), which increased more than five times with DCH from 2.5% to 14%. Forty-three percent of patients had a good clinical outcome with mRS 2–3 after a DCH compared to 21.5% of patients who received conservative therapy. However, the proportion of patients surviving with moderate-to-severe disability (mRS 4) was increased more than 12-fold (31% vs. 2.5%), but the rate of very severe disability (mRS 5) was not increased after DCH (4%vs. 5%).

Despite the evidence provided by these trials, the questions remained regarding the selection of patients for surgery because not all middle cerebral infarctions lead to MMI and no single prognostic factor has been identified as a consistent and accurate predictor of fatal outcome in MMI. Neuroimaging combined with clinical examination does provide valuable information to identify patients at risk. Early ischemic changes (less than 6 h) on CT scan that involves greater than 50% of the MCA territory have been associated with fatal outcomes. This included such early CT changes as localized cerebral edema causing sulcal effacement or compression of the lateral ventricle [29]. The DECIMAL trial used a critical stroke volume of 145 mL on diffusion-weighted MRI and confirmed this cutoff value suggested by previous authors. Analysis showed 78% mortality in strokes with >145 mL volume and no deaths when the stroke volume was less than 145 mL. NIHSS >20 (dominant hemisphere) or >15 (non-dominant hemisphere) within 6 h of symptom onset along with CT findings of hypodensity >50% were also associated with high risk for developing malignant cerebral edema [29].

The optimal timing of surgery is also debated. One approach is to wait for signs of neurological deterioration, brainstem herniation, and/or major midline shift, and the other approach emphasizes early intervention with surgical decompression after the diagnosis of large MCA infarction is made. From the individual results and pooled analysis of DECIMAL and DESTINY, patients who were surgically treated with decompressive hemicraniectomy within 48 h did better when compared to the HAMLET trial in which there was no improvement in functional outcome despite decrease in mortality in patients who received delayed surgical treatment (up to 96 h after symptoms onset). As such, early decompressive hemicraniectomy (within 24–48 h of symptom onset) is recommended for all patients with MMI and prior to signs of herniation syndrome in order to achieve the best neurological outcome [14].

Another important variable relates to the surgical procedure itself and specifically the size of the DCH. Suboptimal DCH with a size less than 12 cm has been associated with increased cerebral complications and decreased survival rates. Most reports recommend a diameter for DCH of at least 12 cm, and it appears that a larger size DCH of 14–16 cm may be associated with better outcomes [14]. There is little evidence to support a duraplasty after DCH. Although it is mandatory to open the dura in order to achieve maximal decompressive effect of the DCH, whether to close it with or without a duraplasty remains controversial. In most cases, closure of the dura was performed with the help of a duraplasty, and the material used did not affect outcomes or complication rates. Similarly, the effect of temporal lobectomy on outcome and survival rates has not been addressed.

Age is another important consideration in this population following MMI. The upper age limit in the above randomized trials was 60 years, and therefore the results are not easily transferable to individuals older than 60 years of age. Until the recent publication of the DESTINY II trial [30], the benefits of DCH in patients older than 60 years were uncertain. The DESTINY II study was a randomized controlled trial in patients 61 years of age and older with MMI. The results showed a decrease in

mortality rate from 70% to 33% in the DCH group. It also demonstrated a significant increase in the proportion of patients who achieved survival without severe disability (mRS 0–4) in the DCH group compared to controls (38% vs. 18%). However, 32 and 28% of patients that survived with DCH remained in a very poor neurological status quantified as mRS of 4 and 5, respectively. Only 7% of DCH patients showed a mRS of 3 as the best outcome that could be achieved.

Two recent meta-analyses have been published looking at the six randomized controlled trials comparing DCH with standard medical therapy in patients who develop malignant cerebral swelling after MCA territory infarction [31, 32]. Both analyses again demonstrate that DCH can reduce mortality. With the availability of all the above information, we can now recommend DCH as a potential therapy for patients with MMI irrespective of age and hemispheric dominance to improve survival [14]. However, long-term outcomes, patient selection, and ethical issues still require consideration. This is especially pertinent in patients older than 60 years of age, in whom there is a higher likelihood of survival with severe disability. As such, the wishes of the patient and family should be carefully weighed while discussing this treatment option. This is important because only the patient and family can decide what is a "desirable outcome" [33]. Definitions of poor outcome by dichotomizing mRS scores of 4–6 or 5–6 is a crude categorization of outcomes, and the disputes regarding the results of the previous trials can be distilled down to whether one considers an mRS of 4 acceptable or not.

Investigators have asked patients whether they regret having had the DCH and whether they would provide consent if they had known their eventual outcome (retrospective consent) [34]. Several studies have demonstrated a high level of retrospective consent, and this may provide some further support to justify use of DCH. This position however is problematic. The ethical concept of critical interest must be appreciated – the idea that one's most important values ought to be made when in full command of one's faculties [35]. Obtaining a positive response to such retrospective consents cannot be considered as relevant as the consenting process, particularly in the stroke patient. It is possible that some of the positive responses may reflect a degree of adaptation or recalibration on the part of the patient to the new neurological disability, which previously might have been deemed unacceptable. As a result, retrospective consent cannot merit the same weight as the wishes of truly informed individual while in sound mind to deliberate about their values. A recent study on healthcare workers at two major public neurosurgical centers in Western Australia (ORACLE Stroke Study) aimed to assess their opinions regarding consent for surgery if they were unfortunate enough to develop MMI and what level of disability they would deem acceptable or otherwise for themselves [36]. The authors found that most participants felt survival with dependency to be unacceptable. However, many patients would be willing to provide consent for surgery in the hopes that they may survive with some degree of independence. Resolving the ethical issue of "favorable long-term outcome" involving the patients and family members should be a goal of future studies.

In contrast to supratentorial ischemic strokes, there is less uncertainty as to the potential value of surgical intervention in large cerebellar strokes. Fatal space-occu-

pying edema can develop in 17–54% of cerebellar strokes resulting in obstructive hydrocephalus, cerebellar tonsillar herniation, and brainstem compression. Although lacking evidence from randomized clinical trials, it is widely accepted that surgical intervention with suboccipital decompressive craniectomy or insertion of an external ventricular drainage can be lifesaving in large cerebellar infarctions and with the potential for good clinical outcomes. In the long term, survivors also do well, especially if there is no associated brainstem injury or infarction [37]. As a result, similar to the case with cerebellar hematoma/hemorrhage, patients with large cerebellar ischemic stroke should be considered for early decompression.

Conclusion

Over the last two decades, there has been resurgence in the use of DCH for a number of neurological emergencies. This includes large-territory ischemic strokes with an increased risk of swelling, herniation, and death. A number of prospective randomized controlled trials, pooled analysis, and meta-analysis have shown strong evidence that the use of DCH reduces mortality in patients who develop MMI. This result is seen irrespective of age, and DCH improves mortality even in patients >60 years of age. However, long-term outcomes, patient selection, and ethical issues still require consideration. Perhaps the most important and yet controversial question that arises when considering DCH for MMI is what constitutes a favorable outcome for the patient. As such, although we can now recommend DCH as a potential therapy for patients with MMI to improve survival, the values and preferences of patients and family must be carefully weighed while arriving at a decision. This is especially pertinent in patients older than 60 years of age, in whom there is a higher likelihood of survival with severe disability. Addressing the issue of "favorable long-term outcome" involving patients and family members should always be a goal of care and should be a goal of future studies. In cases where DCH is considered, early surgery (within 24–48 h of symptom onset) is recommended, prior to onset of any herniation syndrome in order to achieve the best neurological outcome.

References

1. Mak CHK, Lu YY, Wong GK. Review and recommendations on management of refractory raised intracranial pressure in aneurysmal subarachnoid hemorrhage. Vasc Health Risk Manag. 2013;9:353–9.
2. Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. Neurocrit Care. 2007;6(2):104–12.
3. Diringer MN, Bleck TP, Claude Hemphill J 3rd, et al. Neurocritical care society: critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations

from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15:211–40.
4. Wang DZ, Nair DS, Talkad AV. Acute decompressive hemicraniectomy to control high intracranial pressure in patients with malignant MCA ischemic strokes. Curr Treat Options Cardiovasc Med. 2011;13:225–32.
5. Heiss WD, Malignant MCA. Infarction: pathophysiology and imaging for early diagnosis and management decisions. Cerebrovasc Dis. 2016;41:1–7.
6. Rangel-Castillo L, Gopinath S, Robertson CS. Management of intracranial hypertension. Neurol Clin. 2008;26(2):521–41.
7. Doczi T. Volume regulation of the brain tissue—a survey. Acta Neurochir. 1993;121:1–8.
8. Scozzafava J, Shazam Hussain M, John S. In: Balestrino M, editor. Medical and surgical management of intracranial hypertension, Advances in the treatment of ischemic stroke: InTech; 2012. https://doi.org/10.5772/32754.
9. Van Osta A, Moraine JJ, Mélot C, Mairbäurl H, Maggiorini M, Naeije R. Effects of high altitude exposure on cerebral hemodynamics in normal subjects. Stroke. 2005;36(3):557–60.
10. Carter BS, Ogilvy CS, Candia GJ, et al. One-year outcome after decompressive surgery for massive non-dominant hemispheric infarction. Neurosurgery. 1997;40:1168–76.
11. Hauer EM, Stark D, Staykov D, Steigleder T, Schwab S, Bardutzky J. Early continuous hypertonic saline infusion in patients with severe cerebrovascular disease. Crit Care Med. 2011;39(7):1766–72.
12. Koenig MA, Bryan M, Lewin JL, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70(13):1023–9.
13. Manno EM, Adams RE, Derdeyn CP, Powers WJ, Diringer MN. The effects of mannitol on cerebral edema after large hemispheric cerebral infarct. Neurology. 1999;52(3):583–7.
14. Torbey MT, Bösel J, Rhoney DH, et al. Evidence-based guidelines for the management of large hemispheric infarction. Neurocrit Care. 2015;22(1):146–64.
15. Qizilbash N, Lewington SL, Lopez-Arrieta JM. Corticosteroids for acute ischaemic stroke. Cochrane Database Syst Rev. 2002;2:CD000064.
16. Schwab S, Spranger M, Schwarz S, Hacke W. Barbiturate coma in severe hemispheric stroke: useful or obsolete? Neurology. 1997;48(6):1608–13.
17. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med. 2001;344:556–63.
18. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke. 1998;29:2461–6.
19. Georgiadis D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. Stroke. 2002;33:1584–8.
20. Els T, Oehm E, Voigt S, Klisch J, Hetzel A, Kassubek J. Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. Cerebrovasc Dis. 2006;21:79–85.
21. Neugebauer H, Kollmar R, Niesen WD, et al. DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS): a protocol of a multicenter randomized controlled clinical trial and a literature review. Int J Stroke. 2013;8:383–7.
22. Robertson SC, Lennarson P, Hasan DM, et al. Clinical course and surgical management of massive cerebral infarction. Neurosurgery. 2004;55:55–61. discussion 61–2.
23. Walz B, Zimmermann C, Böttger S, et al. Prognosis of patients after hemicraniectomy in malignant middle cerebral artery infarction. J Neurol. 2002;249:1183–90.
24. Schwab S, Steiner T, Aschoff A, et al. Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke. 1998;29:1888–93.
25. Juttler 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;38:2518–25.

26. 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;38:2506–17.
27. 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(4):326–33.
28. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant middle cerebral artery infarction: a pooled analysis of three randomized controlled trials. Lancet Neurol. 2007;6:215–22.
29. von Kummer R, Meyding-Lamade U, Forsting M, et al. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. Am J Neuroradiol. 1994;15:9–15. discussion 16–8.
30. Juttler E, Unterberg A, Woitzik J, Bosel J, Amiri H, Sakowitz OW, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370(12):1091–100.
31. Yang MH, Lin HY, Fu J, Roodrajeetsing G, Shi SL, Xiao SW. Decompressive hemicraniectomy in patients with malignant middle cerebral artery infarction: a systematic review and meta-analysis. Surgeon. 2015;13:230–40.
32. Back L, Nagaraja V, Kapur A, Eslick GD. Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a metaanalysis of randomised trials. Intern Med J. 2015;45:711–7.
33. Puetz V, Campos CR, Eliasziw M, Hill MD, Demchuk AM, Calgary Stroke Program. Assessing the benefits of hemicraniectomy: what is a favourable outcome? Lancet Neurol. 2007;6:580. author reply 580–581
34. Honeybul S, Ho KM, Gillett G. Outcome following decompressive hemicraniectomy for malignant cerebral infarction. Stroke. 2015;46(9):2695–8.
35. Dworkin R. Ch 8. Life past reason. In: Life's dominion: an argument about abortion, euthanasia, and individual freedom. New York: Alfred A. Knopf; 1993. p. 218–37.
36. Honeybul S, Ho KM, Blacker DW. ORACLE stroke study: opinion regarding acceptable outcome following decompressive hemicraniectomy for ischemic stroke. Neurosurgery. 2016;79(2):231–6.
37. Pfefferkorn T, Eppinger U, Linn J, et al. Long-term outcome after suboccipital decompressive craniectomy for malignant cerebellar infarction. Stroke. 2009;40(9):3045–50.

Chapter 37
Neurovascular Carotid and Vertebral Arterial Dissection and Blunt Vessel Injury

G. Lee Pride Jr. and Babu G. Welch

Carotid and vertebral arterial dissections are vascular lesions that manifest clinically with symptoms related to local mass effect, cerebral ischemia, or cerebral hemorrhage depending on the involved segment of the vessel. The damage or injury to the wall of a cervical or intracranial artery occurs through an interplay of environmental and intrinsic influences. Early diagnosis, possible with noninvasive screening using various imaging modalities, provides opportunity for effective medical or invasive treatment to prevent disastrous early or late clinical sequelae. Physicians involved in the management of cerebrovascular diseases can expect to encounter these lesions on a relatively frequent basis in both emergency and outpatient environments.

Demographics/Epidemiology

Extracranial dissections are somewhat arbitrarily divided into spontaneous and traumatic lesions based upon a history of a significant inciting traumatic event. Most are probably related to a variably recalled inciting mechanical trigger, including trauma of varying degree, with or without an underlying predisposing condition. While spontaneous lesions account for only 2% of strokes, they account for up to 10–25% of strokes in young- to middle-aged patients [1]. A peak in incidence occurs in the

G. L. Pride Jr. (✉)
Departments of Radiology and Neurosurgery, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Lee.Pride@UTSouthwestern.edu

B. G. Welch
Departments of Neurological Surgery and Radiology, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: babu.welch@utsouthwestern.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_37

fifth decade of life, with no reliable sex predilection. Their annual incidence is estimated to be 1.72/100,000 population for cervical carotid and 0.97/100,000 population for cervical vertebral dissections [2]. A seasonal variation occurs, with carotid dissection, more than vertebral dissection, clustering more frequently in the fall or winter [3]. This seasonal increase led some to suggest infection as a cause of dissection. An underlying inflammatory process has been implicated and supported by the finding of leukocytosis in more patients with acute cervical arterial dissection than in controls [4]. Hypertension, migraine, hyperhomocysteinemia, along with various connective tissue disorders including Marfans syndrome, Ehlers-Danlos syndrome (particularly type IV), osteogenesis imperfecta, and fibromuscular dysplasia have all been associated with spontaneous dissection [5]. There is an inverse relationship with hypercholesterolemia [6]. Lesions identified as traumatic dissections are generally more severe given the inciting mechanism. Their incidence has been reported to have increased by as much as 72% in the last decade secondary to more widespread noninvasive imaging screening of trauma patients [7].

Intracranial dissections of the carotid and vertebral arteries are more rare than extracranial dissections, particularly in reports from non-Asian countries. There is overlap with extracranial dissections regarding conditions associated with a propensity to dissection. Hypertension may be slightly more common with intracranial dissection. There is less clear association with trauma. Rare monogenic connective tissue disorders such as Loeys-Dietz syndrome have been associated, as well as loose associations with connective tissue disorders such as Marfan's syndrome, fibromuscular dysplasia, and segmental arterial mediolysis. Intracranial dissections tend to involve the posterior circulation more than the anterior circulation with the intradural segment of the vertebral artery being the most common location of involvement [8]. The subarachnoid location of the vessel segments allows presentation with hemorrhage. Autopsy series suggest that between 4.5% and 10.5% of fatal non-traumatic subarachnoid hemorrhages had intracranial dissections as their etiology [9, 10].

Pathophysiology

The combination of intrinsic susceptibility and environmental triggers involving the cervical or intracranial vessels is implicated in the genesis of neurovascular dissection. This may explain the frequent occurrence of dissection on the most mobile segments of the vessels.

For extracranial dissection, several individual predisposing conditions, including vascular tortuosity, connective tissue disorders, bony anatomical variation or pathology, infection, and associated medical conditions, influence the degree of trauma or mechanical manipulation, ranging from significant to trivial, required to produce injury. Regardless of the trigger or underlying susceptibility, all involve formation of mural hematoma resulting from either intimal injury or vasa vasorum related neoangiogenetic capillary rupture at the medial/adventitial interface [11]. Mural

hematoma expansion toward the intima or adventitia leads to symptom production through thromboembolism, vascular luminal impairment, vascular perineural irritation, or aneurysmal dilatation with mass effect (Fig. 37.1a–c). Intimal involvement leads to an intimal flap with formation of a false, 2nd lumen of the vessel. Adventitial involvement may lead to vessel wall weakening and the formation of dissecting pseudoaneurysm (Fig. 37.1d).

While the intracranial arteries have well-developed internal elastic lamina, there is a paucity of elastic fibers in the media, little adventitial tissue, and no external elastic lamina [8]. This, coupled with the subarachnoid vessel location of the V4 segments of the vertebral arteries and the C6 and C7 segments of the internal carotid arteries, allows hemorrhagic presentations due to dissection-related vessel wall compromise [12]. Vasa vasorum are not always seen in the intracranial arteries and are more prevalent in the adventitia in the proximal segments [13]. Thus, a mechanism for dissection involving vasa vasorum rupture in the intracranial vessels is more speculative. Granulation tissue replacement of mural hematoma and resultant neovascularization in the vessel wall may contribute to the progressive fusiform

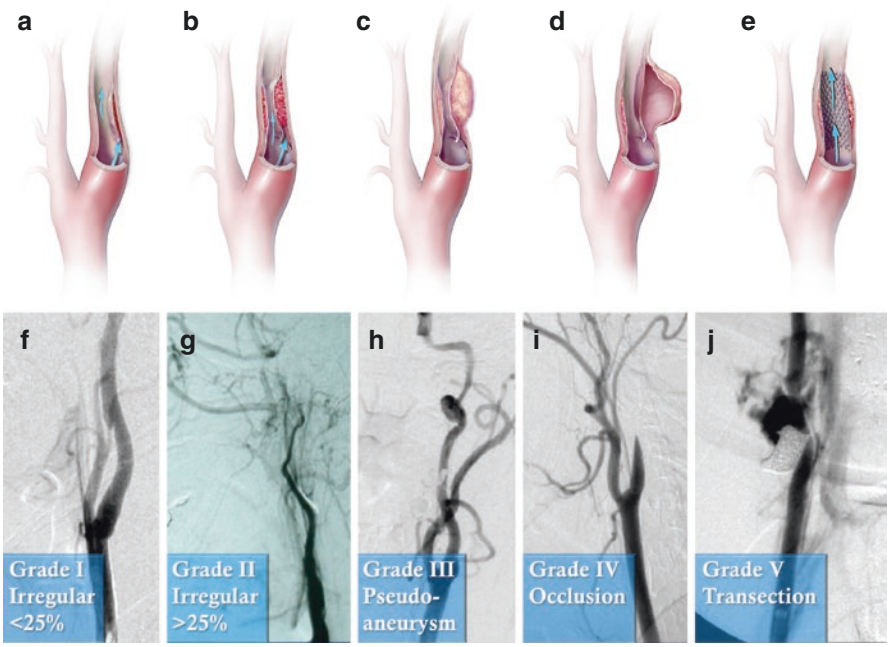


Fig. 37.1 Dissection pathophysiology. Mural hematoma and intimal injury leading to potential thromboembolus generation, hemodynamic stenosis (**a**–**c**), or dissecting pseudoaneurysm formation (**d**). Effective treatment of dissection with endovascular stent (**e**). Denver scale for traumatic cervical dissection: five grades of dissection: grade 1 (**f**) shows irregularity of the vessel wall with less than 25% stenosis; grade 2 (**g**) shows intraluminal thrombus, or intimal flap, or mural thrombus with luminal narrowing by more than 25%; grade 3 (**h**) involves pseudoaneurysm formation; grade 4 (**i**) shows vascular occlusion; and grade 5 (**j**) shows transection of the vessel with active extravasation or fistula formation (Courtesy of Pam Curry UTSW Medical Illustration)

dilatation, more common with intracranial dissections [14]. The association with trauma is not as strong as with extracranial dissection [8].

Possible ischemic stroke mechanisms in neurovascular dissection include distal embolization, stenosis or occlusion-related critical hemodynamic insufficiency in the absence of sufficient collaterals, perforating vessel compromise, or combinations of these [15].

Clinical Presentation/Imaging Evaluation

Symptoms of carotid and vertebral arterial dissections are dependent upon the location and severity of vascular involvement. Local effects caused by the injury (pain, mass effect, loss of vascular flow or integrity, pulsatile tinnitus) and remote effects (thromboembolic phenomena) account for clinical manifestations. Headache and localized pain are common to all locations. Cervical carotid dissections cause pain localized to the ipsilateral anterior neck and head. Pain associated with vertebral dissections localizes more to the occipital or suboccipital region. Intracranial dissections may produce retro-orbital pain or sudden headache syndromes associated with subarachnoid hemorrhage. Pain onset may be of relatively rapid onset, unilateral, constant, and throbbing. Local mass effect can affect sympathetic and cranial nerves, leading to Horner's syndrome, hypoglossal or multiple lower cranial nerve palsies (Collet-Sicard syndrome) [16], or extraocular cranial nerve palsies. There is enough overlap with other headache syndromes that arterial dissection should be considered in the initial evaluation of unilateral headaches.

Extracranial carotid dissections are less likely to produce ischemic symptoms. Only about 20% of extracranial carotid dissections present with ischemic stroke without any warning signs [1, 17]. Extracranial vertebral artery dissections commonly present with posterior circulation ischemic symptoms (up to 77% of patients) [18]. Ischemic symptoms are more commonly of thromboembolic than hemodynamic etiology.

Intracranial dissections present with hemorrhage, cerebral ischemic symptoms, or symptoms of local mass effect. Approximately 50–60% of intracranial dissections present with hemorrhage [8]. Posterior circulation intracranial dissections, particularly involving the intradural vertebral arteries, are more likely to present with hemorrhage from aneurysmal morphology, while anterior circulation dissections are more likely to present with ischemic symptoms from steno-occlusive morphology [19].

Diagnosis is typically confirmed with noninvasive imaging using ultrasound, computed tomography, or magnetic resonance imaging (Figs. 37.2, 37.3 and 37.4). CT and MR angiographic techniques provide adequate vascular evaluation, with axial fat-saturated T1-weighted imaging allowing direct visualization of the mural hematoma (Fig. 37.3b). The gold standard technique of cerebral angiography has largely been replaced with noninvasive techniques.

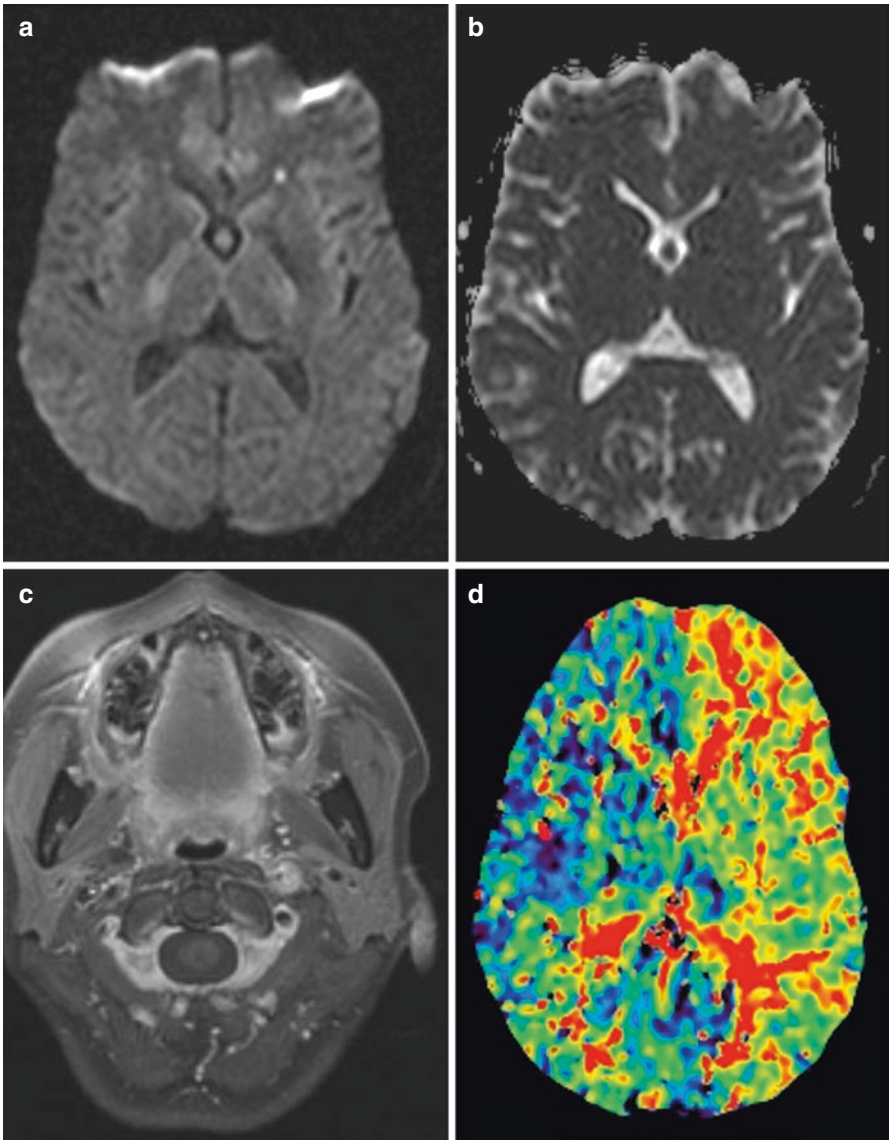


Fig. 37.2 Case 1: a 40-year-old woman with left cervical ICA dissection presented with headache, left neck pain, and transient right arm/leg numbness. She experienced recurrent episodes of right-sided weakness and numbness despite medical therapy with anticoagulation. MRI brain with DWI and ADC map showed small left frontal white matter infarct (**a**, **b**). Axial fat-suppressed T1-weighted MRI showed mural hematoma in distal cervical left ICA (**c**). CT perfusion showed delayed time to peak in the left hemisphere (**d**)

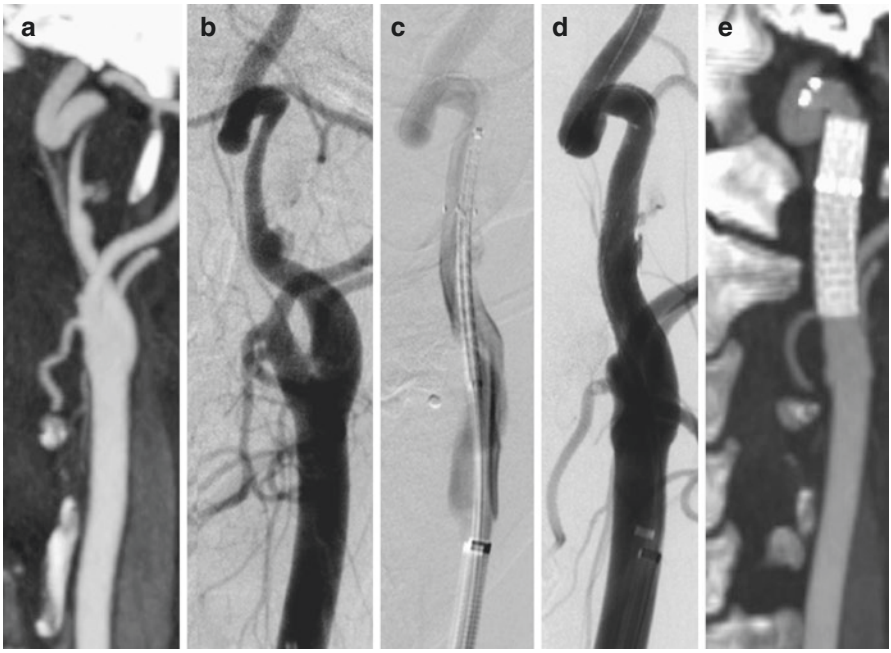


Fig. 37.3 Same patient shown in Fig. 37.2. Endovascular treatment with overlapping stents. Sag MIP CTA (**a**) and catheter angiogram (**b**) show left cervical ICA dissection-related stenosis with flow into largely thrombosed dissecting pseudoaneurysm. Angiograms during treatment (**c**, **d**) show positioning and deployment of overlapping self-expanding stents (Wingspan Stent (Stryker Neurovascular) superiorly placed around curve, Precise Stent (Cordis Endovascular) coaxially placed inferiorly). (**e**) Six-month follow-up Sag MIP CTA shows adequate reconstruction of the lumen with stents

Classification

A classification scheme for traumatic cervical carotid dissections was described in Denver, subsequently becoming known as the "Denver scale" [20]. This scale categorizes five grades of dissection (Fig. 37.1): grade 1 shows irregularity of the vessel wall with less than 25% stenosis; grade 2 shows intraluminal thrombus, or intimal flap, or mural thrombus with luminal narrowing by more than 25%; grade 3 involves pseudoaneurysm formation; grade 4 shows vascular occlusion; and grade 5 shows transection of the vessel with active extravasation or fistula formation. Stroke risk increases, and incidence of spontaneous resolution decreases with increasing grade. Although described for carotid dissections, this scale has been applied to cervical vertebral dissections as well. This scale is not to be confused with the Denver criteria, defined to determine clinical and historical risk factors for blunt cerebrovascular injury (BVCI) [21].

A proposed diagnostic grading scale for intracranial dissection has recently been introduced [8]. This scale defines categories of definite, probable, and possible to imaging findings in suspected intracranial dissection. The important imaging

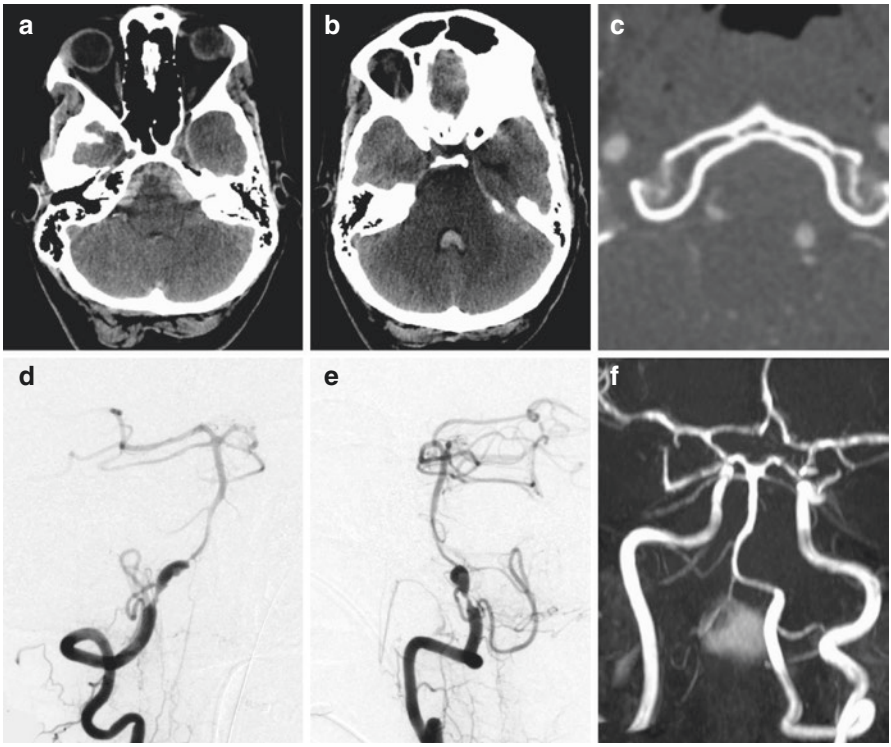


Fig. 37.4 Case 2: a 42-year-old female with history of methamphetamine abuse who presented with sudden onset severe headache. Non-contrast head CT (**a**, **b**) shows subarachnoid hemorrhage in the prepontine cistern and intraventricular hemorrhage in the fourth ventricle. Axial CTA image (**c**) and bilateral oblique angiography views (**d**, **e**) show partially thrombosed dissecting aneurysm of the V4 segment of the right vertebral artery. (**f**) Follow-up TOF MRA 1 month after treatment with proximal vertebral artery sacrifice with coils shows T1 shortening in the thrombosed aneurysm sac and retrograde flow-related enhancement of the intracranial vertebral artery

findings allowing progressive diagnostic certainty regarding intracranial dissection include fusiform dilatation, irregular stenosis, mural hematoma, and rapid change over time.

Natural History

The natural history of neurovascular dissection depends somewhat on location, the mode of symptomatic presentation, and the degree of associated historical trauma. The overall annual recurrent stroke risk from symptomatic cervical arterial dissection ranges from 0.3% to 3.4%. This stroke risk and thus subsequent prognosis depends upon the arterial morphologic outcome. Stenotic lesions seem to resolve without significant abnormality on follow-up imaging in up to 70% of cases in a few

months [22]. Recanalization of occlusion in the presence of mural hematoma is also frequent. When occlusions or stenoses persist, they seem to be associated with a relatively low long-term stroke risk with medical therapy (annual ipsilateral stroke risk 0.7%) [23]. Although low, this stroke risk is approximately double the 0.3% annual ipsilateral stroke risk in those initially stenotic or occluded lesions that resolve. Dissecting aneurysms persist in up to 2/3rd of carotid lesions, resolving more often in vertebral lesions. Transcranial Doppler emboli detection monitoring has been used to predict stroke risk with those patients exhibiting a TCD emboli detection rate of greater than 8 per hour having a statistically higher subsequent risk of stroke [24].

Dissecting aneurysms or pseudoaneurysms seem to be associated with a relatively favorable prognosis [25, 26]. In one series following 112 patients with 122 dissecting extracranial or intracranial pseudoaneurysms over a mean follow-up period of 29.3 months, 3.3% of the patients had recurrent TIA, but none had strokes. Imaging follow-up showed that 13.8% enlarged; 30.2% resolved, and 56% remained stable. Predictors of dissecting pseudoaneurysm enlargement on follow-up include smoking, history of trauma, petrous carotid location, hyperlipidemia, and large initial pseudoaneurysm size [27]. The reported mortality for spontaneous carotid dissection is around 3–4% [22] and that from traumatic dissection approximates 10% [28, 29]. The risk of recurrent dissection is relatively high in the first 2 months after a spontaneous dissection [30, 31], decreasing thereafter.

Intracranial dissection is reported to have a relatively high (33%) overall risk of symptomatic recurrence [14]. Three phases are described: early recurrence within 1 month predominately consisting of hemorrhagic presentations in those presenting with bleeding, late recurrence after 30 days where nonhemorrhagic symptoms predominate, and late fusiform aneurysm formation. It is rare for initially nonhemorrhagic lesions to produce later hemorrhage.

Medical Treatment

Medical treatment is effective for extracranial dissection to prevent stroke, with randomized data revealing low stroke rates of 1–3% on medical therapy [32]. Nonrandomized studies have suggested a higher recurrent stroke risk for those patients initially presenting with ischemic symptoms as opposed to those who are asymptomatic or have only local symptoms (6.2% vs 1.1%) [33]. For traumatic dissection discovered through imaging screening based on mechanism or associated injuries, medical therapy with anticoagulants or antiplatelet agents reduced the incidence of ischemic neurological events in single center series from large urban trauma centers [34, 35]. Despite these promising single center findings, population data from 2001 to 2012 Medicare claims failed to show decreasing stroke rates associated with diagnoses of dissection in trauma patients [7].

The choice of between anticoagulant and antiplatelet therapy to prevent thromboembolic stroke represented a past point of contention. No difference between

anticoagulant and antiplatelet therapy was found in the CADISS trial [32], leading to the general acceptance of antiplatelet therapy as a medical treatment regimen. Treatment of hypertension is also advisable.

For intracranial dissections, medical treatment is most appropriate for symptomatic presentations other than hemorrhage. Treatment regimens are directed toward the prevention of thromboembolic stroke. Both antithrombotic and anticoagulant regimens have been used, but no randomized data exist to definitively guide therapy. Hemorrhagic presentations often lead to interventional treatment to prevent recurrent hemorrhage.

Interventional Treatment

While interventional treatment is common with hemorrhagic presentations to prevent rebleeding, the effectiveness of medical therapy for nonhemorrhagic dissections obviates the need for consideration of invasive interventional treatment in most cases. Modern treatment paradigms reserve interventional treatment for relatively specific indications.

Indications

Suggested indications for interventional treatment of cervical arterial dissections include (1) recurrent ischemic symptoms despite medical therapy; (2) hemodynamic hypoperfusion secondary to stenosis, poor collaterals, or involvement of multiple vessels; (3) persistent stenosis imparting ongoing stroke risk; (4) expanding or symptomatic dissecting or pseudoaneurysms; (5) contralateral occlusion or high-grade stenosis; and (6) contraindications to anticoagulation due to intracranial or systemic hemorrhage [36, 37]. Interventional treatment generally involves more risk in the acute phase of a dissection. The indications for treatment of nonhemorrhagic intracranial dissections have most commonly included acute/crescendo ischemia/infarction due to a critical hemodynamic insufficiency or recurrent ischemic symptoms despite adequate medical treatment [15].

Surgical Treatment

Open surgical treatment of carotid and vertebral dissections has been largely supplanted by endovascular treatment given the relative surgical inaccessibility of these lesions and the efficacy of modern endovascular techniques and tools. Prior surgical series for cervical carotid dissecting aneurysms were associated with high permanent neurological morbidity, approaching 9–10% [38, 39]. Although some cases

may be amenable to vessel sparing procedures, many surgical approaches involve vessel sacrifice. Surgical bypass may be used to support deconstructive techniques in the absence of adequate collateral flow and occasionally to bypass diseased segments of cervical vessels.

Endovascular Treatment

Endovascular treatment of neurovascular dissections has become the mainstay of interventional therapy over the past two decades. Both deconstructive and reconstructive modes of therapy have been employed.

Vessel sacrifice is an effective means of treating acute hemorrhagic dissection or to prevent embolic ischemic sequelae. Collateral circulation should be adequate for consideration of a deconstructive strategy. Balloon occlusion testing can be used to assess collateral adequacy. The most common indications for sacrifice involve hemorrhagic presentations of intracranial dissections or contraindications to anticoagulant or antiplatelet therapy due to intracranial or systemic hemorrhage in the setting of cervical dissection. Mechanisms of achieving vessel occlusion include coils, liquid embolic agents (n-BCA, Onyx), and vascular plugs of various sizes. Due to widespread reported success of reconstructive techniques of treatment involving various stenting strategies, deconstructive vessel sacrifice is becoming less common.

Reconstructive techniques share common goals of preservation of luminal flow, restoration of vessel integrity, exclusion of injured vascular segments, and elimination of flow-restricting lesions. The current state of endovascular technology includes treatment with bare metal self-expanding or balloon-expandable stents with or without concomitant coil embolization, covered stent grafts, and flow-diverting stents. Stent placement may serve to limit the extension of dissection and reduce perforating vessel involvement in intracranial vessels. The mobility of involved cervical segments of the carotid and vertebral arteries favors the use of devices that resist compression or permanent deformity. Such a detail would favor self-expanding stents in the cervical vasculature. Clinical outcomes for aneurysmal and stenotic forms of cervical dissection are generally good [26, 40]. A meta-analysis of stenting or stent-graft supported angioplasty to treat carotid dissection demonstrated a high technical success rate of 99.1% with only 3.3% restenosis rates over 16-month follow-up and recurrent stroke rates over 20.9 months of only 2.1% [37]. Flow diversion therapy with low porosity woven stents, when applied to carotid dissections, may offer advantages with tortuosity encountered in the high cervical and skull base region [41–44]. This strategy has been applied in small series with good result for both carotid and vertebral dissection, with or without additional anchoring stents to prevent migration.

Successful treatment of cervical carotid dissection in the setting of acute stroke has been described using mechanical thrombectomy for distal thromboembolic occlusion with or without primary stent treatment of the offending cervical dissection. Good outcomes (MRS ≤ 2) have been obtained in up to 70% of selected

acute stroke patients with cervical carotid dissection with or without tandem intracranial occlusion [24, 45].

Intracranial dissections in the anterior circulation can be effectively and safely treated using self-expanding stents [15]. In the posterior circulation, reports on flow diversion technology frequently included the V4 segment of the vertebral artery in the same category as the basilar. High reported complication rates, particularly related to perforator infarcts [46], initially discouraged neurointerventionalists from pursuing flow diversion strategies for vertebral dissections or dissecting aneurysms not amenable to deconstructive techniques. Multiple subsequent case series demonstrate good results and improved morbidity when flow diversion is used in this area, where there are fewer perforators than in the basilar artery. The V4 segment of the vertebral artery should be considered an exception to the rule of higher morbidity when flow diversion is used in the posterior circulation [47, 48]. Flow diversion strategies have been applied successfully for hemorrhagic presentations of intracranial vertebral dissection [48].

Follow-up and medication therapy to prevent thrombosis become important with usage of stents to treat dissection. In-stent stenosis, a problem for intracranial atherosclerotic disease, may not present as significant of a problem when stents are used to treat dissection. Much lower restenosis rates are seen [37]. Most practitioners use a posttreatment regimen after stenting to prevent thromboembolic complications consisting of dual antiplatelet therapy, most commonly using clopidogrel and aspirin for a variable period from 1 to 6 months followed by indefinite aspirin monotherapy [37].

Summary

The discussion surrounding dissection of arteries that supply the cerebral vasculature is one primarily focused on the prevention of stroke once a diagnosis is identified. Antiplatelet therapies are now understood to provide stroke reduction comparable to anticoagulation. Early medical failure or recurrent ischemia continue to be the indications for more aggressive endovascular or surgical repair. Through significant developments in endovascular technology, vessel reconstruction has supplanted prior approaches that involved vessel sacrifice and surgical bypass. The application of flow diversion to the treatment paradigm continues to evolve.

References

1. Schievink W. Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med. 2001;344(12):898–906.
2. Lee VH, Brown RD, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. Neurology. 2006;67(10):1809–12. https://doi.org/10.1212/01.wnl.0000244486.30455.71.

3. Schievink WI, Wijdicks EF, Kuiper JD. Seasonal pattern of spontaneous cervical artery dissection. J Neurosurg. 1998;89(1):101–3. https://doi.org/10.3171/jns.1998.89.1.0101.
4. Grond-Ginsbach C, Giossi A, Aksay SS, et al. Elevated peripheral leukocyte counts in acute cervical artery dissection. Eur J Neurol Off J Eur Fed Neurol Soc. 2013;20(10):1405–10. https://doi.org/10.1111/ene.12201.
5. Blum CA, Yaghi S. Cervical artery dissection: a review of the epidemiology, pathophysiology, treatment, and outcome. Arch Neurosci. 2015;2(4) https://doi.org/10.5812/archneurosci.26670.
6. Debette S, Metso T, Pezzini A, et al. Association of vascular risk factors with cervical artery dissection and ischemic stroke in young adults. Circulation. 2011;123(14):1537–44. https://doi.org/10.1161/CIRCULATIONAHA.110.000125.
7. Newhall K, Gottlieb DJ, Stone DH, Goodney PP. Trends in the diagnosis and outcomes of traumatic carotid and vertebral artery dissections among Medicare beneficiaries. Ann Vasc Surg. 2016;36:145. https://doi.org/10.1016/j.avsg.2016.06.001.
8. Debette S, Compter A, Labeyrie M-A, et al. Epidemiology, pathophysiology, diagnosis, and management of intracranial artery dissection. Lancet Neurol. 2015;14(6):640–54. https://doi.org/10.1016/S1474-4422(15)00009-5.
9. Sasaki O, Ogawa H, Koike T, Koizumi T, Tanaka R. A clinicopathological study of dissecting aneurysms of the intracranial vertebral artery. J Neurosurg. 1991;75(6):874–82. https://doi.org/10.3171/jns.1991.75.6.0874.
10. Ro A, Kageyama N, Abe N, Takatsu A, Fukunaga T. Intracranial vertebral artery dissection resulting in fatal subarachnoid hemorrhage: clinical and histopathological investigations from a medicolegal perspective. J Neurosurg. 2009;110(5):948–54. https://doi.org/10.3171/2008.11.JNS08951.
11. Völker W, Dittrich R, Grewe S, et al. The outer arterial wall layers are primarily affected in spontaneous cervical artery dissection. Neurology. 2011;76(17):1463–71. https://doi.org/10.1212/WNL.0b013e318217e71c.
12. Ramgren B, Cronqvist M, Romner B, Brandt L, Holtås S, Larsson E-M. Vertebrobasilar dissection with subarachnoid hemorrhage: a retrospective study of 29 patients. Neuroradiology. 2005;47(2):97–104. https://doi.org/10.1007/s00234-005-1346-z.
13. Takaba M, Endo S, Kurimoto M, Kuwayama N, Nishijima M, Takaku A. Vasa vasorum of the intracranial arteries. Acta Neurochir. 1998;140(5):411–6.
14. Ono H, Nakatomi H, Tsutsumi K, et al. Symptomatic recurrence of intracranial arterial dissections: follow-up study of 143 consecutive cases and pathological investigation. Stroke. 2013;44(1):126–31. https://doi.org/10.1161/STROKEAHA.112.670745.
15. Kim DJ, Kim BM, Suh SH, Kim DI. Self-expanding stent placement for anterior circulation intracranial artery dissection presenting with ischemic symptoms. Neurosurgery. 2015;76(2):158–64. discussion164. https://doi.org/10.1227/NEU.0000000000000582.
16. Smith R, Tassone P, Saada J. Collet-Sicard syndrome as a result of unilateral carotid artery dissection. BMJ Case Rep. 2013;2013:bcr2013200358. https://doi.org/10.1136/bcr-2013-200358.
17. Redekop GJ. Extracranial carotid and vertebral artery dissection: a review. Can J Neurol Sci. 2008;35(2):146–52.
18. Arnold M. Vertebral artery dissection: presenting findings and predictors of outcome. Stroke. 2006;37(10):2499–503. https://doi.org/10.1161/01.STR.0000240493.88473.39.
19. Kwak JH, Choi JW, Park HJ, et al. Cerebral artery dissection: spectrum of clinical presentations related to angiographic findings. Neurointervention. 2011;6(2):78–83. https://doi.org/10.5469/neuroint.2011.6.2.78.
20. Biffl WL, Moore EE, Offner PJ, Brega KE, Franciose RJ, Burch JM. Blunt carotid arterial injuries: implications of a new grading scale. J Trauma Inj Infect Crit Care. 1999;47(5):845–53.
21. Burlew CC, Biffl WL, Moore EE, Barnett CC, Johnson JL, Bensard DD. Blunt cerebrovascular injuries: redefining screening criteria in the era of noninvasive diagnosis. J Trauma Acute Care Surg. 2012;72(2):330–5. discussion336–7–quiz539. https://doi.org/10.1097/TA.0b013e31823de8a0.

22. Touzé E, Gauvrit J-Y, Meder J-F, Mas J-L. Prognosis of cervical artery dissection. Front Neurol Neurosci. 2005;20:129–39. https://doi.org/10.1159/000088157.
23. Kremer C, Mosso M, Georgiadis D, et al. Carotid dissection with permanent and transient occlusion or severe stenosis: long-term outcome. Neurology. 2003;60(2):271–5.
24. Delgado F, Bravo I, Jiménez E, et al. Endovascular treatment in the acute and non-acute phases of carotid dissection: a therapeutic approach. J NeuroIntervent Surg. 2016. neurintsurg–2016–012475.; https://doi.org/10.1136/neurintsurg-2016-012475.
25. Guillon B, Brunereau L, Biousse V, Djouhri H, Lévy C, Bousser MG. Long-term follow-up of aneurysms developed during extracranial internal carotid artery dissection. Neurology. 1999;53(1):117–22.
26. Touzé E, Randoux B, Méary E, Arquizan C, Meder JF, Mas JL. Aneurysmal forms of cervical artery dissection: associated factors and outcome. Stroke. 2001;32(2):418–23.
27. Daou B, Hammer C, Chalouhi N, et al. Dissecting pseudoaneurysms: predictors of symptom occurrence, enlargement, clinical outcome, and treatment. J Neurosurg. 2016;125(4):936–42. https://doi.org/10.3171/2015.10.JNS151846.
28. Miller PR, Fabian TC, Bee TK, et al. Blunt cerebrovascular injuries: diagnosis and treatment. J Trauma Inj Infect Crit Care. 2001;51(2):279–85. discussion285–6.
29. Miller PR, Fabian TC, Croce MA, et al. Prospective screening for blunt cerebrovascular injuries: analysis of diagnostic modalities and outcomes. Annals of Surgery. 2002;236(3):386–93. discussion393–5. https://doi.org/10.1097/01.SLA.0000027174.01008.A0.
30. Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. N Engl J Med. 1994;330(6):393–7. https://doi.org/10.1056/NEJM199402103300604.
31. Dittrich R, Nassenstein I, Bachmann R, et al. Polyarterial clustered recurrence of cervical artery dissection seems to be the rule. Neurology. 2007;69(2):180–6. https://doi.org/10.1212/01.wnl.0000265595.50915.1e.
32. CADISS trial investigators, Markus HS, Hayter E, et al. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol. 2015;14(4):361–7. https://doi.org/10.1016/S1474-4422(15)70018-9.
33. Georgiadis D, Arnold M, von Buedingen HC, et al. Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. Neurology. 2009;72(21):1810–5. https://doi.org/10.1212/WNL.0b013e3181a2a50a.
34. Cothren CC, Moore EE, Ray CE, et al. Screening for blunt cerebrovascular injuries is cost-effective. Am J Surg. 2005;190(6):845–9. https://doi.org/10.1016/j.amjsurg.2005.08.007.
35. Eastman AL, Muraliraj V, Sperry JL, Minei JP. CTA-based screening reduces time to diagnosis and stroke rate in blunt cervical vascular injury. J Trauma. 2009;67(3):551–6. discussion555–6. https://doi.org/10.1097/TA.0b013e3181b84408.
36. Asif KS, Lazzaro MA, Teleb MS, Fitzsimmons B-F, Lynch J, Zaidat O. Endovascular reconstruction for progressively worsening carotid artery dissection. J NeuroIntervent Surg. 2015;7(1):32–9. https://doi.org/10.1136/neurintsurg-2013-010864.
37. Xianjun H, Zhiming Z. A systematic review of endovascular management of internal carotid artery dissections. Interv Neurol. 2013;1(3–4):164–70. https://doi.org/10.1159/000353124.
38. Schievink WI, Piepgras DG, McCaffrey TV, Mokri B. Surgical treatment of extracranial internal carotid artery dissecting aneurysms. Neurosurgery. 1994;35(5):809–15. discussion815–6.
39. Müller BT, Luther B, Hort W, Neumann-Haefelin T, Aulich A, Sandmann W. Surgical treatment of 50 carotid dissections: indications and results. J Vasc Surg. 2000;31(5):980–8. https://doi.org/10.1067/mva.2000.104586.
40. Lee W-J, Jung K-H, Moon J, et al. Prognosis of spontaneous cervical artery dissection and transcranial Doppler findings associated with clinical outcomes. Eur Radiol. 2016;26(5):1284–91. https://doi.org/10.1007/s00330-015-3944-4.
41. Brzezicki G, Rivet DJ, Reavey-Cantwell J. Pipeline embolization device for treatment of high cervical and skull base carotid artery dissections: clinical case series. J NeuroIntervent Surg. 2016;8(7):722–8. https://doi.org/10.1136/neurintsurg-2015-011653.

42. Fischer S, Perez MA, Kurre W, Albes G, Bäzner H, Henkes H. Pipeline embolization device for the treatment of intra- and extracranial fusiform and dissecting aneurysms: initial experience and long-term follow-up. Neurosurgery. 2014;75(4):364–74. discussion374. https://doi.org/10.1227/NEU.0000000000000431.
43. Zeleňák K, Zeleňáková J, Deriggo J, Kurča E, Kantorová E, Poláček H. Treatment of cervical internal carotid artery spontaneous dissection with pseudoaneurysm and unilateral lower cranial nerves palsy by two silk flow diverters. Cardiovasc Intervent Radiol. 2012;36:1147. https://doi.org/10.1007/s00270-012-0472-3.
44. Rahal JP, Dandamudi VS, Heller RS, Safain MG, Malek AM. Use of concentric solitaire stent to anchor pipeline flow diverter constructs in treatment of shallow cervical carotid dissecting pseudoaneurysms. J Clin Neurosci. 2014;21(6):1024–8. https://doi.org/10.1016/j.jocn.2013.10.017.
45. Marnat G, Mourand I, Eker O, et al. Endovascular management of tandem occlusion stroke related to internal carotid artery dissection using a distal to proximal approach: insight from the RECOST study. Am J Neuroradiol. 2016;37(7):1281–8. https://doi.org/10.3174/ajnr.A4752.
46. Phillips TJ, Wenderoth JD, Phatouros CC, et al. Safety of the pipeline embolization device in treatment of posterior circulation aneurysms. Am J Neuroradiol. 2012;33(7):1225–31. https://doi.org/10.3174/ajnr.A3166.
47. Chalouhi N, Tjoumakaris S, Dumont AS, et al. Treatment of posterior circulation aneurysms with the pipeline embolization device. Neurosurgery. 2013;72(6):883–9. https://doi.org/10.1227/NEU.0b013e31828ba984.
48. Dmytriw AA, Martinez JL, Marotta T, Montanera W, Cusimano M, Bharatha A. Use of a flow-diverting stent for ruptured dissecting aneurysm treatment in a patient with sickle cell disease. Interv Neuroradiol. 2016;22(2):143–7. https://doi.org/10.1177/1591019915617323.

Chapter 38
Moyamoya Disease: Indications for Revascularization and Techniques

Rabia Qaiser and Gary K. Steinberg

Moyamoya disease (MMD) is a rare, idiopathic, chronic, steno-occlusive cerebrovascular disease involving the bilateral terminal internal carotid or proximal middle and anterior cerebral arteries. Less frequently, the proximal posterior cerebral arteries are affected. The stenosis or complete occlusion, in turn, results in the characteristic development of fragile collateral vessels. MMD was first described in 1957 by Takeuchi and Shimizu as "hypoplasia of internal carotid arteries." [1] The term moyamoya was coined later by Suzuki and Takaku in 1969 in describing the angiographic finding of collateral blood vessels as appearing like a "haziness" or "puff of smoke" [2]. This chapter presents an overview of MMD, its natural history, indications for revascularization, and the various techniques utilized to achieve it.

Epidemiology and Genetics

MMD is mostly prevalent in Asian populations; however, it is increasingly reported in people of diverse ethnicities. In our Stanford MMD series, 53% are Caucasian, 32% Asian, 7% Hispanic, 5% black, and 3% others. There is an estimated prevalence of 3 cases per 100,000 children in Japan [3] and the annual Japanese incidence overall of MMD has been reported as 0.54/100,000 [4].

A study in France found the incidence of MMD to be 0.065 per 100,000 children per year, with an overall prevalence of 0.39 per 100,000 children [5]. The overall incidence in the USA was previously reported to be 0.086 per 100,000/year [6], but a more recent study demonstrated an incidence of 0.57/100,000 persons/year, similar to that of Japan [7]. MMD has a bimodal age distribution with a first peak at 5–9 years of age and a second peak at 45–49 years of age [8]. In children younger

R. Qaiser (✉) · G. K. Steinberg
Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA
e-mail: rqaiser@stanford.edu; gsteinberg@stanford.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_38

than 10 years, it occurs with equal frequency in boys and girls; however, after 10 years of age, the male-to-female ratio is 2:1 [8, 9].

In Japan, the presentation in the younger age group is mostly as ischemic strokes and TIAs, while in adults is mostly as hemorrhagic strokes. Interestingly, the demographics of MMD in the USA differ, with a predominance of ischemic symptoms dominating both pediatric and adult populations.

The incidence of affected first degree relatives is 10% in Japan and 6% in the USA [10]. Pedigree analysis has revealed an autosomal dominant pattern in families with MMD [11]. Genetic linkage analysis by multiple groups has identified five distinct chromosomal regions linked to MMD [12]. The primary region is at chromosome position 17q25.3. Exome analysis of this region identified RNF213 as a susceptibility gene for MMD. It was found to be mutated in 95% of Japanese familial MMD, 73% of nonfamilial MMD, and 1.4% of controls [13]. Other genes have also been implicated in predisposing Asian and other ethnic groups to MMD [14–16].

Pathophysiology and Grading

The progressive stenosis of the vessels is a result of hyperplasia of smooth muscle cells and thickening of the tunica media from fibrous tissue accumulation, loss of elastic lamina, and regression of the media [17]. As the stenosis progresses, thrombosis can occur leading to complete occlusion of the vessel. Moyamoya vessels then form as a response to the ischemia that results from this progressive stenosis and finally occlusion of the carotid arteries. These vessels are histologically abnormal with dilatation at the origin, fragmented elastic lamina, fibrin deposition in the proximal orifice, loss of vessel wall media, and microaneurysm formation in the media [17]. Thus, these vessels carry a higher risk of bleeding and thrombus formation. As the collateral circulation from leptomeningeal sources develops and improves the perfusion, or after a revascularization procedure, these moyamoya vessels may regress [18].

Suzuki et al. developed a staging system based on the progression of the stenosis, the neovascularization resulting in the formation of the "puff of smoke," and the development of collateral circulation (Table 38.1) [2, 10, 19].

Natural History and Prognosis

MMD is well documented as a progressive disease. Unilateral disease has a rate of 30–39% progression into bilateral disease over 2–3 years [20, 21]. In one study, disease progression occurred in 66% of MMD patients with poor outcome without surgical treatment over a 5-year period [22]. In another study, patients with bilateral symptomatic moyamoya disease had an 82% incidence of recurrent symptoms within 5 years of first symptom onset with best medical management [23]. Therefore,

Table 38.1 Suzuki staging of moyamoya disease based on carotid angiography

Stage	Angiographic description
Stage I	Isolated narrowing of the supraclinoid carotid (C1–C2 segment)
Stage II	Progressive narrowing of the carotid, dilatation of native cerebral arteries, early formation of moyamoya vessels in the basal carotid circulation
Stage III	Intensification of moyamoya vasculature in the basal regions, exuberant moyamoya vessel formation, severe carotid stenosis with decreased flow in middle and anterior cerebral arteries
Stage IV	Minimization of moyamoya vessels, severe carotid stenosis with impaired filling of middle, anterior and posterior cerebral arteries
Stage V	Further minimization of moyamoya vessels, complete cessation of flow in ipsilateral middle, anterior, and posterior cerebral arteries
Stage VI	Disappearance of moyamoya vessels, filling of cerebral vasculature by external carotid supply via leptomeningeal anastomoses

there is a clear need for better treatment for MMD and surgical management has become the mainstay of therapy. While there has never been a controlled trial of surgical revascularization versus medical therapy for ischemic MMD, numerous surgical series have demonstrated a much lower rate of subsequent stroke than for medical therapy alone [9, 10, 23–25]. Until recently, the evidence that hemorrhagic MMD benefited from surgical revascularization was suggestive, but less compelling than for ischemic MMD [26]. However, a landmark prospective randomized trial published in 2014 demonstrated that direct surgical revascularization in MMD patients who present with hemorrhagic stroke decreased both the recurrent hemorrhage risk and the combined neurologic morbidity [27].

Workup and Imaging

Clinical Evaluation

The preoperative workup includes a thorough history and clinical examination to determine medical and cardiac risk factors and a baseline neurological exam. In addition, routine preoperative labs and several imaging studies are obtained.

Imaging

Barring any contraindications, we obtain a 6-vessel digital subtraction angiogram (DSA) including bilateral internal carotid arteries, bilateral external carotid arteries, and bilateral vertebral arteries (Fig. 38.1). This is the gold standard for disease staging and surgical planning. For some Majewski osteodysplastic primordial dwarfism type II (MOPD II) patients, we have used either magnetic resonance angiography

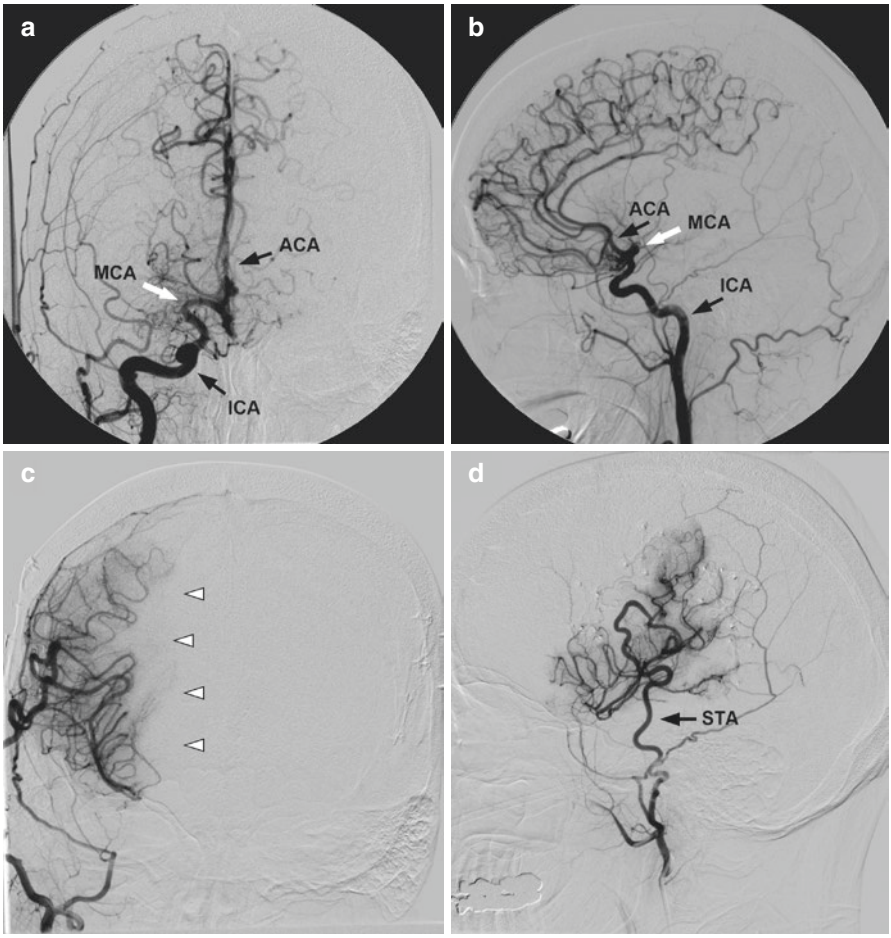


Fig. 38.1 Pre- and postoperative angiograms after direct EC-IC bypass. (**a**) AP view, preoperative right internal carotid artery (ICA) injection showing right middle cerebral artery (MCA) occlusion (white arrow). (**b**) Lateral view, preoperative right ICA injection showing MCA occlusion (white arrow). (**c**) AP view, postoperative right external carotid artery (ECA) injection showing areas of superficial temporal artery (STA) perfusion (white arrowheads). (**d**) Lateral view, postoperative right ICA injection showing enlarged STA (arrow)

(MRA) or computed tomography angiography (CTA) for visualization of the external and internal carotid arteries, given the high risk of DSA [28]. In addition, MRI of the brain and quantitative MRI perfusion studies with and without Diamox are obtained preoperatively to determine cerebrovascular reserve. Patients with impaired cerebrovascular reserve and maximally vasodilated vascular territory, as shown by decreased or absent augmentation after Diamox administration, are at higher risk for perioperative strokes. Thus, they need very strict management of their baseline mean arterial pressures (MAPs) and to avoid hypotension. In addition to these studies,

PET, SPECT, and Xenon scans, and transcranial Dopplers can also be helpful and are used at various institutions. CT angiograms and CT perfusion scans can be helpful for preoperative as well as postoperative monitoring in patients in whom MRI is contraindicated or MR perfusion is not available.

Medical Management

Medical management is not a mainstay of treatment in MMD but a supportive measure to prevent strokes or transient ischemic attacks that result from microthrombi at the vessel stenosis sites or at the origin of the moyamoya vessels that can cause hypercoagulable states. We place all of our patients on acetylsalicylic acid (ASA), both preoperatively and postoperatively for life, despite no proven benefit in preventing strokes in MMD as a standalone therapy. We hypothesize that ASA helps to maintain patency of the extracranial-intracranial grafts. Stronger anticoagulation using clopidogrel or warfarin is not recommended due to the hemorrhagic risk in these patients. Hypotension or hypoventilation is avoided as it can also increase the risk of strokes [10].

Decision-Making in Revascularization

- The goal of surgery is to restore blood flow to the ischemic hemisphere using direct, indirect, or a combination of both revascularization techniques. At our institute, we have performed 1470 revascularization procedures in 921 patients from 1991 through February 2017. Ages have ranged 7 months–69 years. Of the 1470 procedures, 200 (14%) were indirect, and 1270 (86%) were direct. Direct revascularization has the advantage of immediate restoration of blood flow and hemodynamic reserve. In contrast, indirect revascularization techniques depend on stimulation of neovascularization from adjacent vascularized tissues. This can take from a few months to years and thus indirect techniques do not decrease the immediate risk of stroke [29]. Deciding between direct versus indirect bypass is based on several factors. (Tables 38.2 and 38.3).

Table 38.2 Decision-making for direct vs indirect revascularization

	Indirect	Direct
Donor vessel availability	No	Yes
Donor vessel size	<0.8 mm	>0.8 mm
ICA/MCA occlusion	No	Yes
ICA/MCA/ACA stenosis (moderate to severe)	Yes	No
Robust filling from collaterals	Yes	No

Table 38.3 Revascularization techniques

Direct	Indirect
STA-MCA	EDAS
Posterior auricular Artery-MCA	EDAMS/EMS/EGPS
Occipital Artery-MCA	MBH
	Omental transposition

STA superficial temporal artery, *MCA* middle cerebral artery, *EDAS* encephaloduroarteriosynangiosis, *EDAMS* encephaloduroarteriomyosynangiosis, *EGPS* encephalogaleoperiosteosynangiosis, *MBH* multiple burr holes

- Internal carotid artery or middle cerebral artery occlusion versus stenosis: We prefer to do a direct bypass in cases of complete vessel occlusion as there is less chance of competing flows between the graft and native collaterals, compared with ICA or M1 stenosis, where the direct graft might compete directly with the anterograde flow through the stenosed (but not occluded) arteries. Also, in cases of complete occlusion, direct bypass provides immediate augmentation of blood flow. Long term, there is more collateral vessel formation as confirmed with angiography, as well as fewer ischemic events and higher stroke-free survival by about 95% over 5 years [27, 29, 30]. In some cases of ICA or M1 stenosis competing flows between the graft and the native flow can predispose to stasis of blood flow, potentially causing perioperative transient neurologic deficits (TNEs) and ischemic strokes. We prefer to perform an indirect bypass for patients with ICA or MCA moderate to severe stenosis.
- Vessel availability and size: We attempt direct revascularization for patients with angiographic occlusion of the ICA or M1, except in pediatric patients who are less than 4 years of age or when donor or recipient vessels are less than 0.8 mm in diameter. However, we have successfully performed direct bypasses with vessel diameters as small as 0.6 mm [9]. A smaller diameter of donor or recipient vessel risks occlusion from stenosis and/or thrombus.
- Previous surgeries: If a patient has had previous surgeries, including craniotomies, head injuries, or even prior revascularization attempts, then the decision to do a direct versus indirect bypass depends upon the availability of a donor vessel. If an adequate donor vessel is identified then a direct bypass is undertaken, otherwise an indirect bypass is performed.
- Intraoperative blood flow analysis of direct revascularization procedures in patients with MMD: Cerebrovascular reserve and augmentation based on perfusion studies after Diamox can predict the outcome after revascularization procedures. Poor or absent augmentation preoperatively indicates maximized flow with the current collaterals. These patients are also at a higher risk of perioperative strokes [31]. The intraoperative blood flow analysis showing increased flow after direct bypass in the recipient vessels indicates the increased likelihood of competing flows. In these instances meticulous management of blood pressure postoperatively is maintained, using maneuvers to increase systemic blood pressure [32].

Direct Bypass: EC–IC Bypass

Direct bypass has been the preferred choice for revascularization in MMD patients at Stanford (86%). Based on the preoperative imaging, which includes an angiogram and in some cases an MRA or a CTA, mostly the parietal, and less commonly a frontal branch of the superficial temporal artery (STA), is chosen for anastomoses (Fig. 38.1). In some circumstances, due to previous craniotomies, trauma, or agenesis of the STA, the occipital artery or the postauricular artery or occasionally even the middle meningeal artery might be chosen as an alternative. The patient remains on ASA until the day of surgery. Preoperatively the patient is placed under anesthesia while strictly maintaining MAPs between 90 and 110. The pCO_2 is maintained normally and hypoventilation is avoided. A central line, arterial line, and Foley catheter are placed. We also use a frontal scalp Bispectral index (Medtronic) monitor for assessing burst suppression after propofol infusion for the short M4 occlusion period. Patients are placed under mild hypothermia to 33 °C with a cooling blanket. An STA branch measuring up to 8–10 cm in length is mapped using ultrasound. This is marked for the incision. In the case of a frontal branch, the incision is marked behind the hairline, and the vessel is dissected under the skin flap. We have recently started using the SonoSite Ultrasound Doppler, in which we increase the gain and decrease the depth to visualize the vessel in its entirety. The patient is then placed in a Mayfield head clamp with 3-point fixation. The patient is supine with the head turned laterally such that the operative site marking the STA is parallel to the floor. The patient is prepped and draped in the usual fashion.

The STA harvest is performed using a microscope under magnification, starting 1 cm above the tragus and continuing until 8–10 cm of STA has been harvested, along with a cuff of vascular fascia. The vessel is left intact until the anastomoses is about to be undertaken. At this point the microscope is removed from the operating field, and the temporalis fascia and temporalis muscle are cut using monopolar cautery and retracted out of the way. Two burr holes are drilled using an M8 bit of the Midas Rex drill under the proximal and distal ends of the STA. Then a 7 cm × 7 cm craniotomy is completed to maximize the area for finding a recipient artery and positioning it over or slightly posterior to the Sylvian fissure. Once the craniotomy is complete the microscope is again brought back into the field. The dura is opened in a stellate fashion. The fascial cuff along the STA is dissected out at the proximal and distal ends for placement of the clip and for anastomosis, respectively. A recipient M4 branch, preferably oriented perpendicular to the surgeon, is selected for the recipient, but it is most important to isolate the largest M4 branch. Arachnoid dissection is done to expose an approximately 7 mm segment of this M4 branch. A high-visibility background is placed underneath the vessel. The flows are measured in the MCA as well as STA, and at this point if the flow in the recipient M4 vessel is high, then an indirect bypass is undertaken; otherwise we proceed with a direct bypass. Also, the STA and M4 diameters are measured. A temporary clip is applied to the proximal STA followed by transecting the donor vessel at a 45° angle in

preparation for an end-to-side anastomosis to "fish-mouth" it. The STA is then flushed with heparinized saline. MAPs are raised to 90–110, the patient is cooled to 33 °C, and burst suppression is achieved by giving propofol. Specially designed Lazic temporary aneurysm clips (Peter Lazic GmbH, Tuttlingen, Germany) are then placed at the proximal and distal ends of the M4 recipient segment, and any branches arising from this segment are included in the clip to control bleeding during the anastomosis. The diameter of the recipient vessel is matched to the donor vessel by making a diamond-shaped arteriotomy using scissors. The donor vessel is then brought back into the field. Diameters above 0.8 mm are better for an anastomosis technically and to decrease risk of occlusion; however, we have used as small as 0.6 diameter vessels successfully with reliable flows and long-term patency [9]. The ends of recipient and donor vessels are stained with indigo carmine or methylene blue for better visibility. Using a 10/0 monofilament suture (Monosof, Covidien, Dublin, Ireland), the vessels are anastomosed using heel and toe stitches first, followed by suturing the front and back wall. Great care is taken to avoid catching the back wall of the vessel and to pass the sutures from outside the donor to inside the recipient and then tied on the outer surface of the anastomosis. Once the anastomosis is complete, the temporary clips are taken off first from the M4, followed by the STA. Sometimes additional stitches are applied during which the M4 arterial segment is usually not clamped. Minor oozing is controlled with mild pressure using Surgicel or Gelfoam. Microdoppler is utilized to confirm flow through the anastomoses. We then measure the flows in the distal and proximal M4, as well as the distal STA using Charbel transonic flow probes (Charbel Micro-Flow-probe; Transonics Systems, Inc., Ithaca, NY). Indocyanine green (ICG) angiography is then performed to further confirm patency and good flow through the anastomosis. The dura is then approximated over the graft, taking great care that the entry point for the STA and the anastomosis are not compromised. A dural graft is also laid over the dura. The burr hole on the skull plate at the entry point of the STA is enlarged to accommodate the entry of STA, and the bone is secured in place using titanium plates and screws. The temporalis and temporal fascia are also approximated, again ensuring that the STA entry is not compromised. We continue to assess the STA by Doppler throughout the closure to confirm that the flow is not compromised at any point. The galea and skin are then closed (Fig. 38.2).

MAPs are kept between 90 and 110 throughout the case in order to avoid any episodes of hypotension that can precipitate an ischemic stroke. The patient is warmed, extubated, and then transferred to the ICU for postoperative management.

Indirect Bypass

Encephaloduroarteriosynangiosis

Encephaloduroarteriosynangiosis (EDAS) was initially introduced by Matsushima in 1979 [34]. The general principal is the same, that is, to harvest the superficial temporal artery and lay it in close proximity with the cortical surface in order to

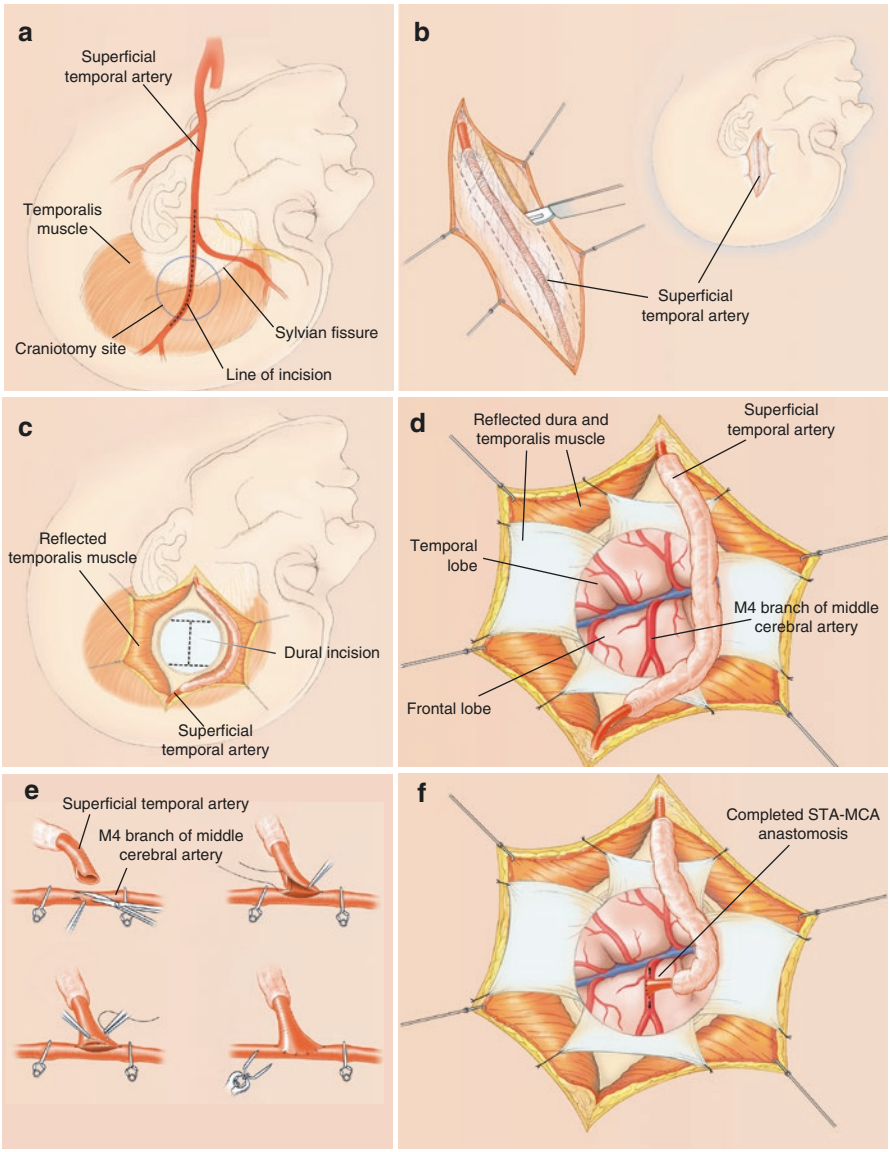


Fig. 38.2 Direct bypass. Each step of the direct bypass surgery. (**a**) Starting in front of the tragus within the hairline the STA is mapped for 7–8 cm. (**b**) The STA is prepared under the surgical microscope, leaving an approximately 8-mm tissue cuff around the vessel. (**c**) A 4 × 4-cm craniotomy is performed over the Sylvian fissure and (**d**) the size of the M4 branches of the MCA evaluated at high magnification. (**e**) The largest M4 branch is chosen as recipient. The STA is fishmouthed and the wall of the MCA cut using microscissors, removing a tiny elliptical piece of the superior wall. Under high magnification a bypass between the STA and MCA is performed using 10.0 interrupted sutures. (**f**) After completing the direct anastomosis, the STA with its cuff of soft tissue is laid on the cortical surface to induce an additional indirect revascularization. (From [33] with permission)

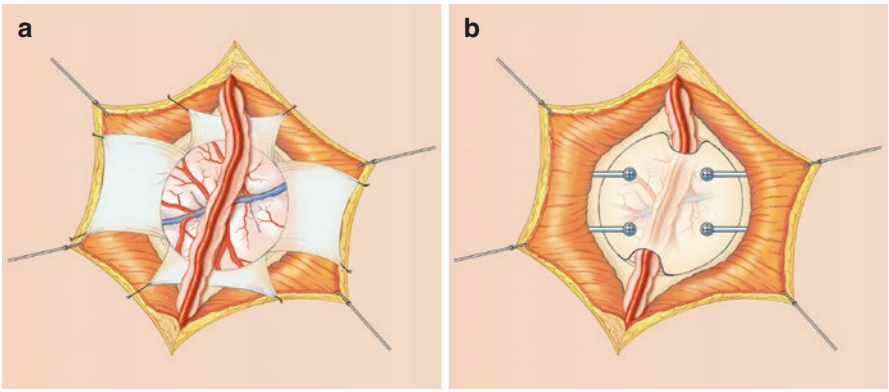


Fig. 38.3 Indirect bypass. The indirect bypass procedure is similar to the direct bypass up to Fig. 38.2a–d, The last two steps are as follows: (**a**) The STA along with the tissue cuff is placed in close approximation to the underlying brain. The pia is also opened to encourage ingrowth of new blood vessels. (**b**) A generous opening is made at the entry and exit sites of the STA to avoid any compression of the vessel. Bone flap is then replaced and attached to the skull using plates and screws

encourage growth of new blood vessel formation over time. A variant of this procedure called pial synangiosis was developed by Scott in 1985 [10]. The STA is not only laid on the cortex after widely opening the arachnoid but is also sutured to the pia. At Stanford, we harvest the STA as done with a direct bypass, widely opening the arachnoid, but do not suture the STA to the pia. We usually do not place a central line, or induce hypothermia or burst suppression, as there is no M4 occlusion required for this procedure. An arterial line is placed in order to ensure strict blood pressure control by keeping the MAPs between 90 and 110. In the pediatric population we keep blood pressure close to baseline MAPs. After the STA is harvested, a craniotomy and dural opening are performed in a similar fashion. We do measure blood flows in the M4. Great care is taken to enlarge both the burr holes to easily accommodate the STA entry and exit from the craniotomy. The donor vessel undergoes Doppler throughout the closure to confirm patency (Fig. 38.3).

EMS/EDAMS/EGPS

Encephalomyosynangiosis (EMS) was initially introduced by Karasawa and colleagues in 1970 [35]. The temporalis muscle is dissected and laid over the brain to encourage growth of arteries into the underlying brain. Additional variations of this procedure include encephaloduroarteriomyosynangiosis (EDAMS) and encephalogaleoperiosteosynangiosis (EGPS). In these two procedures, the dura, artery, periosteum, and/or galea, in addition to the temporalis muscle, are laid on the brain surface to encourage neovascularization [36, 37].

Dural Inversion

This procedure was introduced by Dauser et al. in 1997. The middle meningeal artery is used as the feeding artery for ingrowth of blood vessels. The craniotomy is done while trying to preserve the middle meningeal artery (MMA). The dura is then divided on either side of the MMA, and the well-vascularized dural surface that was adjacent to the bone is laid over the brain. The bone is fixed using plates and screws prior to skin closure [38].

Multiple Burr Holes In 1984 Endo et al. introduced this technique [39] where 10–20 burr holes are placed with opening of the dura and stripping of the arachnoid to promote neovascularization [40].

Omental Bypass

Karasawa performed the first intracranial transplantation of omentum for MMD in February 1978 [41]. A frontoparietooccipital skin incision is fashioned, similar to a "reverse question-mark." In cases where there was a previous bypass, the STA branch and bone overlying it are preserved. Removal of the anterior inferior border of the new bone flap is performed for insertion of the omentum. At our institute, we have been collaborating with general surgery colleagues who harvest the omentum laparoscopically, along with the vascular pedicle containing the gastroepiploic artery and vein. The omental graft is then tunneled under the skin taking care not to twist or kink the vessels. It is then passed retroauricularly to the craniotomy site. The omental graft is held in place by suturing it to the edges of the resected dura, thus forming the dural closure. The inner table of the craniotomy bone flap is removed by drilling to accommodate the omental graft. The bone is then secured in place using plates and screws. Prior to placing the bone, we perform an ICG angiogram to visualize the vascularity of the omental graft (Fig. 38.4). The skin is then closed over the bone, and the patient is monitored in the ICU. There is expected swelling in the neck, which resolves over time [42].

Postoperative Angiographic Grading

The postoperative evaluation is based on DSA and MRI/MRI perfusion studies. The angiograms take into account a patient with EC−IC bypass, if direct, and also the percentage of area supplied by the donor vessel. MRI and MRI perfusion studies assess the perfusion of the hemisphere post bypass.

A: Area perfused by the synangiosis is greater than 2/3 of the MCA territory.
B: Area perfused by the synangiosis is between1/3 and 2/3 of the MCA territory.
C: Area perfused by the synangiosis is less than 1/3 of the MCA territory [43].

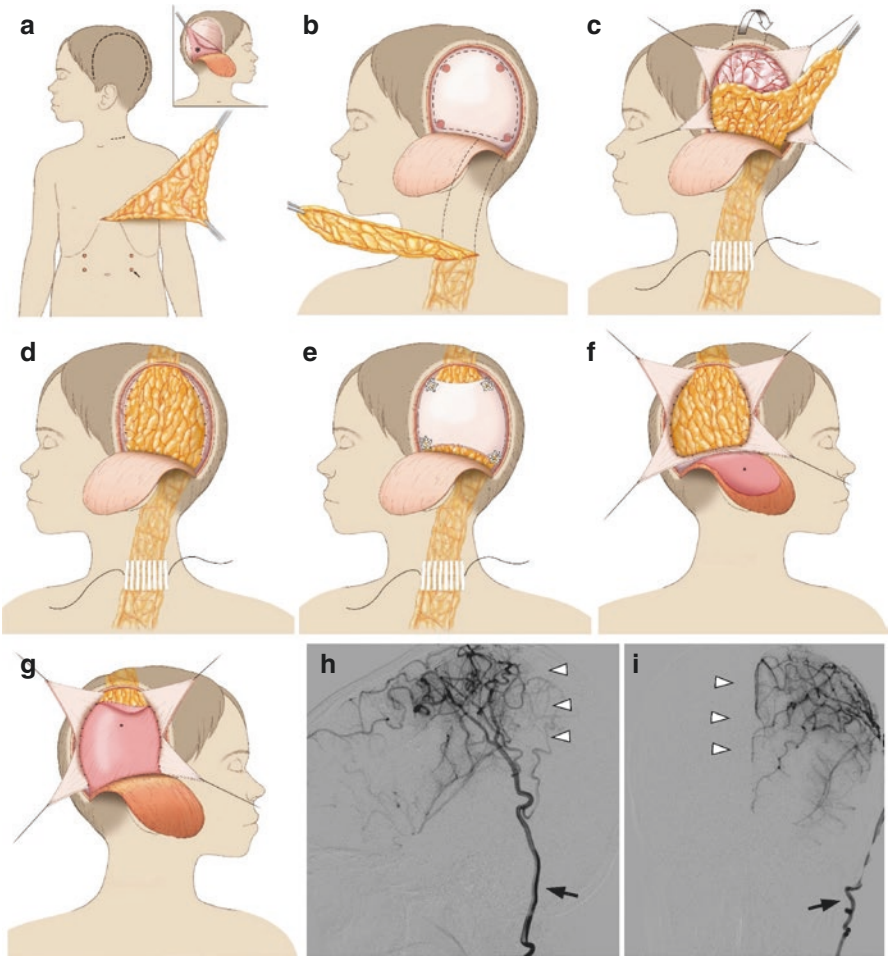


Fig. 38.4 Omental bypass. Artist's rendition of steps involved in bilateral cranial revascularization using a single laparoscopically harvested, pedicled omental flap. (**a**) Hair-sparing incisions are marked on both sides of the head to allow for craniotomies to be done over ischemic areas. The head is kept on a donut rest so that it can be turned during the procedure. The entire head and left side of the neck are prepared and draped, leaving out the face. First, the right-sided craniotomy is performed, leaving the dura unopened. Because the right side is the far side, the pericranium (asterisk) is preserved as a backup indirect flap in case the omental flap cannot reach entirely. The scalp is loosely reapproximated with a few staples and covered with a sterile drape. The head is then turned to the right to perform the exposure on the left side. In parallel to our cranial work, the pediatric general surgeons harvest the omentum, working through four laparoscopic ports (orange dots; small black arrow pointing to one example). The omentum is first separated from the transverse, descending and then ascending colon. Next, it is taken off the stomach and proximal small bowel. The gastroepiploic artery, which runs close to the greater curvature of the stomach and supplies the omentum, is carefully preserved. The omental flap is brought out of the abdomen via a 1.5-inch transverse incision in the epigastrium. The flap is inspected to ensure that the exit incision is wide enough, and that it has adequate blood supply. To increase the flap to its maximum possible length so that it can reach the contralateral hemisphere, the omentum is dissected in such a way that the vascular arcades are preserved, but the flap can be unfolded and extended. (**b**) A long

0-silk suture is tied to the tip of the omentum. A copious amount of KY jelly is applied to the omentum. A 1.5-inch incision is then made in the left neck area. The epigastric and neck incisions are connected with blunt dissection, aided by long, lighted blade retractors. The omentum is then pulled through the wide, subcutaneous tunnel, by the use of the silk suture, out the neck incision. In a similar way, the omentum is tunneled to the left craniotomy site. (**c**) The exposed dura is excised, and the microscope is brought in to widely dissect open the arachnoid, including that in the deep sulci and fissures. A subgaleal tunnel connecting the bilateral craniotomies is made. The omentum is then pulled up as far as possible, and the proximal portion laying over the left-sided craniotomy is trimmed. The pediatric surgeons have closed the abdominal and neck incisions at this point. (**d**) Next, the omentum is sutured to the dural edge. The remaining omentum is pulled through the subgaleal tunnel to the right side of the head. (**e**) Before replacing the bone flap, the inner table is shaved off to reduce the mass effect caused by the omentum on the brain. The bone at the inlet and outlet for the omentum is also widely removed with a craniotome drill to accommodate the flap. Then, the bone is fixed to the rest of the skull with titanium plates. (**f**) The dura is then opened widely on the right side. Through similar steps, the omental flap is secured to the dura and laid over the exposed brain. (**g**) To provide an additional source for indirect revascularization, the previously harvested pericranium (asterisk) is laid on top of the omental flap and secured to the dura. The bone is contoured as described above and secured to the skull with plates. The galea is closed with interrupted, absorbable suture (3–0 Vicryl). The skin is closed with a dissolvable, running 4–0 Monocryl suture. (**h**, **i**) Angiogram, lateral view (**h**) and AP view (**i**), abdominal aorta injection. Omental pedicle artery (arrow). Perfusion area (white arrowheads). (Panels **a**–**g** and legend from Navarro et al. [41], with permission)

Our protocol is usually 3 days of hospitalization postoperatively with the first day in the ICU. Patients are placed on daily 81 mg of ASA for life. They are encouraged to avoid medications that might induce hypotension. In patients at higher risk of TIAs in the perioperative period or in whom there is a risk of hypotension, we have used midodrine and/or fludrocortisone to maintain MAPs and intravascular volume in the safe range. We recommend that patients remain well hydrated with 2–3 liters of non-caffeinated beverages each day. There are usually no restrictions to activities of daily life.

For long-term follow-up, patients undergo DSA and MRI perfusion studies as well as neuropsychological testing at 6 months, 3 years, 10 years, and 20 years after surgery. Patients who have unilateral MMD are followed with annual CTAs or MRI/MRAs to observe progression on the contralateral side.

Complications

Complications can include perioperative transient neurologic deficits, ischemic strokes, bleeding, infection, and wound dehiscence. In our series, the complication risk was very low. Of 1100 procedures that were followed for 4.9 years, we found rates of 3.5% morbidity and 1.5% permanent neurological morbidity. Modified Rankin scores improved in 71% of patients [9]. A recent meta-analysis of perioperative complications and long-term outcomes showed that direct bypass was better than indirect bypass at preventing hemorrhage and ischemia and is associated with favorable outcomes [44].

Conclusions

MMD is a rare but important cause of strokes in the young population. The natural course of the disease follows a progressive pattern leading to increasing strokes and neurologic dysfunction. This mandates surgical intervention, as medical management has not proven to be beneficial. Surgical management options include direct and indirect bypass procedures. Decision-making is based on several factors including degree of vessel stenosis, that is, stenosis of varying degrees versus occlusion, availability of donor and recipient vessels, and previous interventions. In one study at our institution we reported the cumulative 5-year risk of any stroke or hemorrhage after revascularization surgery was 5.6% in 329 patients undergoing 557 revascularization procedures, as compared to 65% in symptomatic patients over 5 years and 3.2% per year in asymptomatic patients treated medically in other studies [9]. Surgical intervention carries relatively small risk of complications and the benefits far outweigh the natural course of the disease. We strongly recommend surgical intervention for symptomatic patients and close monitoring for disease progression in unilateral disease.

Acknowledgments We thank Butch Colyear for Fig. 38.3. We also thank Cindy Harrymon Samos for the editing. This work was supported in part by the Josef Huber Family Moyamoya Fund, the Reddy Lee Moyamoya Fund, Russell and Elizabeth Siegelman, Bernard Lacroute, Ronni Lacroute, and the William Randolph Hearst Foundation (GKS).

References

1. Takeuchi K, Shimizu K. Hypoplasia of the bilateral internal carotid arteries. Brain Nerve. 1957;9:37–43.
2. Suzuki J, Takaku A. Cerebrovascular “moyamoya” disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;20(3):288–99.
3. Wakai K, Tamakoshi A, Ikezaki K, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg. 1997;99(Suppl 2):S1–5.
4. Kuriyama S, Kusaka Y, Fujimura M, et al. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. Stroke. 2008; 39(1):42–7.
5. Kossorotoff M, Herve D, Toulgoat F, et al. Paediatric moyamoya in mainland France: a comprehensive survey of academic neuropaediatric centres. Cerebrovasc Dis. 2012;33(1):76–9.
6. Uchino K, Johnston SC, Becker KJ, Tirschwell DL. Moyamoya disease in Washington State and California. Neurology. 2005;65(6):956–8.
7. Starke RM, Crowley RW, Maltenfort M, et al. Moyamoya disorder in the United States. Neurosurgery. 2012;71(1):93–9.
8. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry. 2008;79(8):900–4.
9. Guzman R, Lee M, Achrol A, et al. Clinical outcome after 450 revascularization procedures for moyamoya disease Clinical article. J Neurosurg. 2009;111(5):927–35.
10. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg. 2004;100(2 Suppl Pediatrics):142–9.

11. Mineharu Y, Takenaka K, Yamakawa H, et al. Inheritance pattern of familial moyamoya disease: autosomal dominant mode and genomic imprinting. J Neurol Neurosurg Psychiatry. 2006;77(9):1025–9.
12. Achrol AS, Guzman R, Lee M, Steinberg GK. Pathophysiology and genetic factors in moyamoya disease. Neurosurg Focus. 2009;26(4):E4.
13. Kamada F, Aoki Y, Narisawa A, et al. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. J Hum Genet. 2011;56(1):34–40.
14. Milewicz DM, Kwartler CS, Papke CL, Regalado ES, Cao J, Reid AJ. Genetic variants promoting smooth muscle cell proliferation can result in diffuse and diverse vascular diseases: evidence for a hyperplastic vasculomyopathy. Genet Med. 2010;12(4):196–203.
15. Miskinyte S, Butler MG, Herve D, et al. Loss of BRCC3 deubiquitinating enzyme leads to abnormal angiogenesis and is associated with syndromic moyamoya. Am J Hum Genet. 2011;88(6):718–28.
16. Shoemaker LD, Clark MJ, Patwardhan A, et al. Disease variant landscape of a large multiethnic population of moyamoya patients by exome sequencing. G3 (Bethesda). 2015;6(1):41–9.
17. Yamashita M, Oka K, Tanaka K. Histopathology of the brain vascular network in moyamoya disease. Stroke. 1983;14(1):50–8.
18. Wang MY, Steinberg GK. Rapid and near-complete resolution of moyamoya vessels in a patient with moyamoya disease treated with superficial temporal artery-middle cerebral artery bypass. Pediatr Neurosurg. 1996;24(3):145–50.
19. Suzuki J, Kodama N. Moyamoya disease – a review. Stroke. 1983;14(1):104–9.
20. Kelly ME, Bell-Stephens TE, Marks MP, Do HM, Steinberg GK. Progression of unilateral moyamoya disease: a clinical series. Cerebrovasc Dis. 2006;22(2–3):109–15.
21. Smith ER, Scott RM. Progression of disease in unilateral moyamoya syndrome. Neurosurg Focus. 2008;24(2):E17.
22. Takeuchi S, Tsuchida T, Kobayashi K, et al. Treatment of moyamoya disease by temporal muscle graft 'encephalo-myo-synangiosis'. Childs Brain. 1983;10(1):1–15.
23. Hallemeier CL, Rich KM, Grubb RL Jr, et al. Clinical features and outcome in North American adults with moyamoya phenomenon. Stroke. 2006;37(6):1490–6.
24. Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst. 2005;21(5):358–64.
25. Nakashima H, Meguro T, Kawada S, Hirotsune N, Ohmoto T. Long-term results of surgically treated moyamoya disease. Clin Neurol Neurosurg. 1997;99(Suppl 2):S156–61.
26. Kawaguchi S, Okuno S, Sakaki T. Effect of direct arterial bypass on the prevention of future stroke in patients with the hemorrhagic variety of moyamoya disease. J Neurosurg. 2000;93(3):397–401.
27. Miyamoto S, Yoshimoto T, Hashimoto N, et al. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan adult moyamoya trial. Stroke. 2014;45(5):1415–21.
28. Bober MB, Khan N, Kaplan J, et al. Majewski osteodysplastic primordial dwarfism type II (MOPD II): expanding the vascular phenotype. Am J Med Genet A. 2010;152A(4):960–5.
29. Thines L, Petyt G, Aguettaz P, et al. Surgical management of Moyamoya disease and syndrome: current concepts and personal experience. Rev Neurol (Paris). 2015;171(1):31–44.
30. Arias EJ, Dunn GP, Washington CW, et al. Surgical revascularization in North American adults with moyamoya phenomenon: long-term angiographic follow-up. J Stroke Cerebrovasc Dis. 2015;24(7):1597–608.
31. So Y, Lee HY, Kim SK, et al. Prediction of the clinical outcome of pediatric moyamoya disease with postoperative basal/acetazolamide stress brain perfusion SPECT after revascularization surgery. Stroke. 2005;36(7):1485–9.
32. Lee M, Guzman R, Bell-Stephens T, Steinberg GK. Intraoperative blood flow analysis of direct revascularization procedures in patients with moyamoya disease. J Cereb Blood Flow Metab. 2011;31(1):262–74.

33. Guzman R, Steinberg GK. Direct bypass techniques for the treatment of pediatric moyamoya disease. Neurosurg Clin North America. 2010;21(3):568.
34. Matsushima Y, Fukai N, Tanaka K, et al. A new surgical treatment of moyamoya disease in children: a preliminary report. Surg Neurol. 1981;15(4):313–20.
35. Karasawa J, Kikuchi H, Furuse S, Sakaki T, Yoshida Y. A surgical treatment of "moyamoya" disease "encephalo-myo synangiosis". Neurol Med Chir (Tokyo). 1977;17(1 Pt 1):29–37.
36. Kim DS, Huh PW, Kim HS, et al. Surgical treatment of moyamoya disease in adults: combined direct and indirect vs. indirect bypass surgery. Neurol Med Chir (Tokyo). 2012;52(5):333–8.
37. Reis CV, Safavi-Abbasi S, Zabramski JM, Gusmao SN, Spetzler RF, Preul MC. The history of neurosurgical procedures for moyamoya disease. Neurosurg Focus. 2006;20(6):E7.
38. Dauser RC, Tuite GF, McCluggage CW. Dural inversion procedure for moyamoya disease. Technical note. J Neurosurg. 1997;86(4):719–23.
39. Endo M, Kawano N, Miyaska Y, Yada K. Cranial burr hole for revascularization in moyamoya disease. J Neurosurg. 1989;71(2):180–5.
40. Sainte-Rose C, Oliveira R, Puget S, et al. Multiple bur hole surgery for the treatment of moyamoya disease in children. J Neurosurg. 2006;105(6 Suppl):437–43.
41. Karasawa J, Kikuchi H, Kawamura J, Sakai T. Intracranial transplantation of the omentum for cerebrovascular moyamoya disease: a two-year follow-up study. Surg Neurol. 1980;14(6):444–9.
42. Navarro R, Chao K, Gooderham PA, Bruzoni M, Dutta S, Steinberg GK. Less invasive pedicled omental-cranial transposition in pediatric patients with moyamoya disease and failed prior revascularization. Neurosurgery. 2014;10(Suppl 1):1–14.
43. Matsushima Y, Inaba Y. Moyamoya disease in children and its surgical treatment. Introduction of a new surgical procedure and its follow-up angiograms. Childs Brain. 1984;11(3):155–70.
44. Sun H, Wilson C, Ozpinar A, et al. Perioperative complications and long-term outcomes after bypasses in adults with Moyamoya disease: a systematic review and meta-analysis. World Neurosurg. 2016;92:179–88.

Chapter 39
Vasculitis and Strokes

Tarun Girotra and Wuwei Feng

Systemic vasculitis is one of the most perplexing categories of diseases known to the medical field. Since the early twentieth century, the involvement of central nervous system (CNS) has been known to occur in systemic inflammatory conditions of the blood vessels. Over the past several decades, we have increased our knowledge in understanding more about the pathogenesis, natural course, and treatment of such disorder. However, several key questions are still unanswered, making a timely accurate diagnosis of vasculitis as an etiology for stroke remains one of the biggest challenges in the world of cerebrovascular diseases.

It is important to understand that CNS vasculitis is a heterogeneous group of disorders. Several attempts have been made to classify inflammatory vascular processes by subtypes. For the purpose of this discussion, we would classify vasculitis as shown in Table 39.1. The classification of the primary vasculitides is adapted from the revised Chapel Hill classification, which uses the caliber of the vessels primarily affected as the primary classification point with immunopathogenesis for subclassification [1].

Epidemiology

Systemic vasculitides are a rare group of disorders. Several studies from Europe placed an annual incidence rate of systemic vasculitis to be around 2 cases per 100,000 population [2–4]. A few additional studies have noted the maximal

T. Girotra (✉)
Department of Neurology, University of New Mexico, Albuquerque, NM, USA
e-mail: Tagirotra@salud.unm.edu

W. Feng
Department of Neurology, Duke University School of Medicine, Durham, NC, USA
e-mail: wayne.feng@duke.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_39

Table 39.1 Classification of vasculitis

1. Autoimmune vasculitis
(a) Primary vasculitis conditions
1. Large vessel vasculitis
(i) Takayasu arteritis (TAK)
(ii) Giant cell arteritis (GCA)
2. Medium vessel vasculitis
(i) Polyarteritis nodosa (PAN)
(ii) Kawasaki disease (KAW)
3. Small vessel vasculitis
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
1. Microscopic polyangiitis (MPA)
2. Granulomatosis with polyangiitis (Wegener's) (GPA)
3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
4. Variable vessel vasculitis
(i) Behçet's disease
5. Single-organ vasculitis
(ii) Primary angiitis of CNS (PACNS)
(b) Vasculitis associated with systemic autoimmune conditions
1. Systemic lupus erythematosus
2. Rheumatoid arthritis and Sjogren's disease
3. Sarcoid disease
2. Infectious vasculitis
3. Drug-induced vasculitis
4. Neoplasm-associated vasculitis

incidence occurs between the age of 55 and 75 years [4, 5]. Overall, the incidence rate of cerebral vasculitis is estimated to be about 1–2 cases per million population [6].

Epidemiology of specific vasculitides will be discussed under their respective sections, but it is interesting to note that geographical, racial, and ethnic factors have been noted to play an important part in the epidemiology of certain types of vasculitides. For example, the incidence of PAN was noted to be greater in Alaskan Indians (~77 cases per million population) and Kuwaiti populations (~16 cases per million population) [7, 8] and incidence of GCA was noted to increase with higher latitudes [6].

Exposure to environmental factors such as silica, solvent, metal, herbicide, and pesticide has been associated with autoimmune vasculitides. Silica exposure is one of the most studied environmental factors, and one study investigating 75 patients with primary systemic vasculitis (PSV) demonstrated an increased odd of developing PSV (OR 3.0; 95% CI, 1.0–8.4) and eosinophilic granulomatosis with

polyangiitis (EGPA) (OR 5.6; 95% CI, 1.3–23.5) in population with high silica exposure [9]. Various theories have been proposed in an attempt to explain the role of silica in the pathogenesis of autoimmune vasculitides which includes activation of T cell lymphocytes in a superantigen-like mechanism, in vitro observations of silica activating macrophages and monocytes, and apoptosis induction which dysregulates the immune system and increases the risk of development of autoimmune conditions [10].

Clinical Presentation

The relative paucity of disease-specific symptoms makes clinical diagnosis a challenge with CNS vasculitides. New or recurrent strokes and transient ischemic attacks (TIA) may occur in approximately 30–50% of the patients [11–13]. In addition to the focal deficits associated with acute ischemic or hemorrhagic stroke, common neurological symptoms include headaches, acute or subacute encephalopathy, seizures, and optic and cranial neuropathies. Table 39.2 shows the frequency of these symptoms observed with various CNS vasculitides [14–19]. There also can be non-specific systemic symptoms such as fever, malaise, night sweats, cutaneous rash, hematuria, and arthralgia which can confound the working differential diagnoses.

Table 39.2 Frequencies of common CNS symptoms in various cerebral vasculitides

	PACNS [12] (%)	GPA [14] (%)	GCA [15] (%)	EGPA [16] (%)	Behçet's disease [17] (%)	Sjogren's syndrome [18] (%)	SLE [19] (%)
Symptoms	*N* = 101	*N* = 341	*N* = 161	*N* = 96	*N* = 200	*N* = 82	*N* = 2049Δ
Headache	63	NR	87	NR	95[a] 49[b]	NR	28.3
Stroke	40	14.6	2.4	6	NR	NR	8
TIA	28	NR	NR	NR	NR	NR	
Hemorrhage	NR	NR	NR	NR	NR	NR	
Seizure	16	9	NR	NR	4	8.5	9.9
Cognitive impairment	50	NR	NR	1	70 (*n* 74)	11	19.7
Cranial neuropathy	NR	19.2	NR	4	<1	19.5	1
Visual symptoms	42	NR	26.1	NR	NR	ON 16	NR

[a]Nonvascular Behçet's disease; [b]vascular Behçet's disease; *Δ* meta-analysis study, *EGPA* eosinophilic granulomatosis with polyangiitis, *GCA*, giant cell arteritis, *GPA* granulomatosis with polyangiitis, *NR*, not reported, *ON* optic neuritis, *PACNS* primary angiitis of CNS, *SLE* systemic lupus erythematosus, *TIA* transient ischemic attack

Clinical Investigations

If the etiology for stroke is suspected to be vasculitis, there are certain non-specific blood tests that may provide clue(s) suggesting an ongoing, underlying systemic process. These processes could include normocytic anemia, leukocytosis, thrombocytosis, and elevated acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Additionally, depending on the extent of involvement of other organ systems, abnormal renal and liver function tests should also be made. Although these tests are usually non-specific, they do provide valuable information in the clinical context, for example, ESR and CRP are important diagnostic investigations for suspected GCA cases. The sensitivity of ESR and CRP in GCA has been noted to be 84% and 86%, respectively, in a study of 764 patients with biopsy-proven diagnosis of GCA [20].

To further investigate the etiology for vasculitis, an autoimmune panel is commonly performed. Many tests are typically included: rheumatoid factor (RF), antinuclear antibodies (ANA), dsDNA antibodies, histone antibodies, complement levels, anti-Ro (SS-A) and anti-La (SS-B) antibodies, antineutrophil cytoplasmic antibodies (c- and p-ANCA), anticardiolipin antibodies, lupus anticoagulant, serum/urine electrophoresis, and angiotensin convertase enzyme (ACE). Importantly, cerebrospinal fluid (CSF) assessment should be performed, and it usually shows a lymphocytic pleocytosis with elevated proteins [12, 21]. Salvarani et al. analyzed 75 CSF samples from PACNS patients. They observed a median leukocyte count of 5/ml (range, 0–535) and a median protein level of 98 mg/dl (range, 44–1034 mg/dl) [12]. They also observed that any abnormality in the CSF had a sensitivity of 88%. Cultures and viral studies are done in the CSF to exclude certain infections that mimic autoimmune CNS vasculitis as explained in the other sections of this chapter.

Radiographic studies including brain magnetic resonance imaging (MRI) should be performed in all patients if there are no contraindications (Fig. 39.1). Depending on the caliber of the vessel affected, the size and the location of stroke may vary. For example, stroke from carotid artery disease secondary to TAK would typically yield a large hemispheric stroke affecting the cortex, whereas small vessel vasculitides like PAN may cause subcortical infarct in the deep gray and white matter. Popmer et al. [22] analyzed MRI findings of 18 patients with angiographically proven CNS vasculitis and noted that 78% of the patients had bilateral lesions, and all of 18 patients had supratentorial lesions with 72% having exclusively supratentorial lesions. In Popmer's study, the average number of lesions per patient ranged from 2 to 6 with a mean volume of 11.3 cm^3 per lesion. The authors noted, among all the lesions, 27% were in the subcortical white matter, 21% in the deep gray matter, and 21% in the superficial gray matter. Uncommon CNS vasculitis can also be associated with intraparenchymal hemorrhage, subarachnoid hemorrhage, and microbleeds. Sometimes, patients may only have leptomeningeal enhancement on the MRI and such cases may represent a subset of PACNS with favorable prognosis. Salvarani et al. described eight such cases from their cohort of 101 PACNS patients; all had

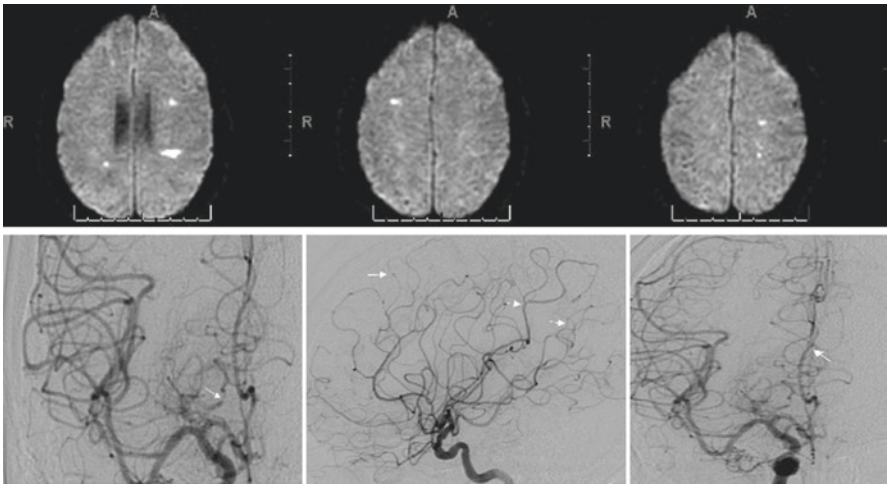


Fig. 39.1 56-year-old female presented with progressive subacute encephalopathy and right hemiparesis. Patient's MRI (**a**) and angiography (**b**) are shown. The patient received the final diagnosis of primary angiitis of CNS based on a brain biopsy. Top row shows multiple supratentorial and bilateral lesions with restricted diffusion on a diffusion-weighted image (DWI) sequence commonly encountered in patients with CNS vasculitis. Bottom row shows the digital subtraction angiography (DSA) showing multiple sites of intracranial vessel stenosis (arrows)

milder clinical presentations and better treatment outcomes including corticosteroids with or without cyclophosphamide, five patients recovered completely and three left with mild to moderate disability [23].

Vascular imaging workup is often pursued with different modalities including magnetic resonance angiography (MRA), computed tomography angiography (CTA), and digital subtraction angiography (DSA). The classical imaging finding CNS vasculitis includes segmental, multifocal areas of stenosis with areas of localized dilatation. DSA has a greater sensitivity and specificity for detecting areas of stenosis and for assessment of smaller vessels when compared with MRA. Differentiating between atherosclerotic narrowing and vasculitic narrowing is always a challenge. However, contrast-enhanced high-resolution (3.0 T) MR imaging may help differentiation based on enhancement patterns which can be either eccentric in the vessel wall (atherosclerotic plaque) or concentric (vasculitis) according to Swartz et al. [24]. These authors identified systematic differences between patients with atherosclerotic disease ($n = 13$) and vasculitis ($n = 3$). Not surprisingly, vessel imaging can appear to be normal in up to one-third of biopsy-proven cases when only very small vessels were affected [25].

Brain biopsy is "the gold standard" for diagnosing CNS vasculitis; despite the best efforts, up to one-fourth of autopsy-proven cases can display false-negative biopsies [26, 27]. These false negatives are due to the segmental nature of the disease which often appears in inaccessible lesions. The diagnostic yield can be improved if care is taken to ensure that radiologically affected areas and leptomeninges are

biopsied. Importantly, biopsies can yield an alternate diagnosis of vasculitis mimics. Alwari et al. analyzed the pathology reports of 61 patients that underwent brain biopsy for suspected vasculitis [28]. These authors found that 39% of the biopsies had non-vasculitis etiologies – infections (toxoplasmosis, herpes, and abscesses), neoplasm (CNS lymphoma), or atypical demyelinating plaques of multiple sclerosis.

Diagnostic Approaches

There is no universal diagnostic approach that can be applied to patients with suspected CNS vasculitis. With the current resources available, brain biopsy is the most specific test but has limitations discussed above. Subjecting the patient to an invasive procedure like the brain biopsy, however, would require a certain degree of confidence in the minds of the treating neurologists. Needless to say, brain biopsies should be avoided in patients where histological diagnoses can be obtained from sites elsewhere, e.g., the skin or peripheral nerves. Unfortunately, that is not possible for most patients. The present authors propose the following diagnostic scheme (Fig. 39.2) for patients with suspected CNS vasculitis. The differential diagnosis of CNS vasculitis can be found in Table 39.3 [29].

Large Vessel Vasculitis

Giant Cell Arteritis

Giant cell arteritis (GCA) is a granulomatous, large vessel vasculitis with a predilection for affecting superficial temporal, ophthalmic, occipital, posterior ciliary, and vertebral arteries. GCA is believed to be a primarily cell-mediated autoimmune condition which produces a transmural and segmental inflammation of the vessel wall with infiltration of macrophages, lymphocytes, and multinucleated giant cells. A local maladaptive endothelial response leads to hyperplasia and occlusion of the vessel causing distal ischemia and its associated symptoms. Salvarani et al. reported an annual incidence of 17.8 cases per 100,000 population and a prevalence for active or remitted GCA cases to be 200 per 100,000 population over 50 years old. These data were from records collected over a 42-year period in Olmsted County, MN [30].

Common symptoms of GCA include headaches, jaw claudication, pain in the neck, shoulder and pelvic girdle region (associated polymyalgia rheumatica), and tenderness over the superficial temporal artery. The most frequent CNS ischemic complication is monocular vision loss which is seen in up to 15–20% of patients [31]. Most of the cases of visual disturbances are secondary to anterior ischemic

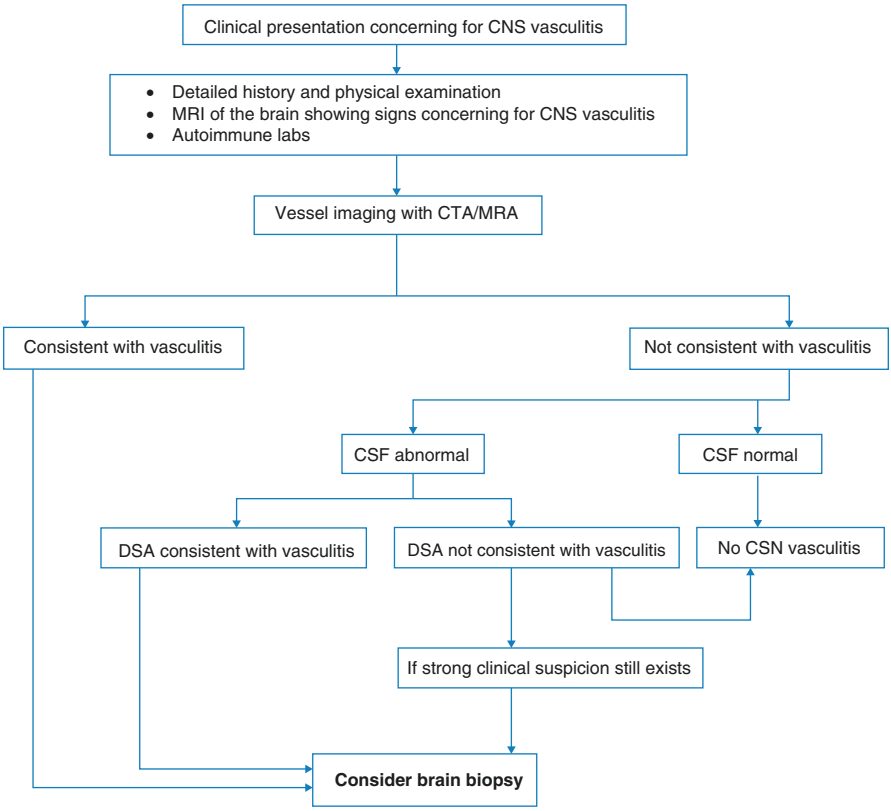


Fig. 39.2 Proposed diagnostic scheme for suspected cases of CNS vasculitis

Table 39.3 Differential diagnosis of CNS vasculitis

Conditions with multifocal cerebral thromboembolism	Brain diseases with MRI lesions that can mimic CNS vasculitis	Conditions with cerebral angiographic abnormalities that can mimic CNS vasculitis
Atrial fibrillation Cholesterol atheroembolism Endocarditis Left atrial myxoma and other cardiac tumors	Intravascular lymphoma Gliomatosis cerebri Genetic conditions, (e.g., CADASIL, HERNS, COL4A1 mutation) Posterior reversible encephalopathy syndrome Susac syndrome Chronic hypertension (microvascular cerebral ischemia) Demyelinating diseases including multiple sclerosis, acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy	Reversible cerebral vasoconstriction syndrome Premature intracranial atherosclerosis Fibromuscular dysplasia Moyamoya disease Angiotropic and intravascular lymphoproliferative disorders Radiation vasculopathy

From Hajj-Ali and Calabrese [29], with permission

optic neuritis (AION) due to posterior ciliary arteritis. Strokes and TIAs have also been observed in 4–6% of cases [32, 33], and they tend to preferentially occur in the vertebrobasilar system rather than the internal carotid system [34]. These vessels are affected just proximal to the dura entry points. The presence of traditional vascular risk factors and absence of severe systemic inflammatory responses – fever, weight loss, anemia, and elevated ESR – are associated with a greater risk of stroke, TIA, and ocular symptom [15, 35].

Common lab findings in GCA include elevated ESR (usually >50 mm/h) and CRP. A large study of 724 patients undergoing biopsy for suspected GCA by Kermani et al. identified sensitivities of ESR, CRP, and the combination of ESR and CRP at 84%, 86%, and 96%, respectively. The specificity of these markers ranged up to 30% [20]. On Doppler examination of the superficial temporal artery (STA), a diffusely thickened hypoechoic arterial wall ("halo sign") can be pathognomonic for GCA. Temporal artery biopsy (TAB) is currently "the gold standard" for diagnosis of GCA with a specificity of 100%. However, the sensitivity has been observed to be 81–91% due to the segmental nature of the disease [36]. Some argue that STA Doppler could be a more sensitive test than TAB to diagnose GCA. "Temporal artery biopsy *vs* ultrasound (TABUL)" is an ongoing study in Oxford University that will analyze 400+ patients with suspected GCA and compare TAB with STA Doppler results in terms of sensitivity and specificity of diagnosing GCA [37].

Corticosteroid is the mainstay of treatment. Improvement of systemic symptoms usually occurs rapidly (within 72 h) after IV steroids. After improvement, dosage should be a slow prednisone taper down to the minimum dosage required to suppress symptoms. Additionally, it has been noted that a concomitant use of low-dose aspirin can decrease the occurrence of visual loss and stroke [38]. Untreated cases have poor prognosis and may suffer permanent blindness, stroke, myocardial infarction, and peripheral vascular disease. Prompt diagnosis and treatment can dramatically improve the prognosis with often complete recovery, and survival rate of treated patients has been the same as that of the general population [39]. Relapse occurs as high as in 40–60% of patients; relapse symptoms primarily consist of headaches and systemic complaints but less commonly visual symptoms [40].

Takayasu Arteritis

Takayasu arteritis (TAK) is a systemic granulomatous inflammation of the aorta and its major branches including carotid and vertebral arteries. The annual incidence of TAK is reported to be about 2.6 cases per million population in the United States [41]. The incidence is higher in Japan, India, and other Asian countries with a higher incidence in females of childbearing age. Constitutional symptoms such as fever, malaise, and weight loss are common. Non-specific neurological complaints including headaches and lightheadedness are commonly reported. Strokes or TIAs have been reported to occur in 3% or 5%, respectively [42]. The etiology for the stroke is usually large vessel stenosis/occlusion of the carotid or vertebral artery.

Other etiologies are small vessel atherosclerosis due to long-standing hypertension from renal artery stenosis and cardioembolism from cardiomyopathy as result of a dilated aortic root and subsequent aortic regurgitation.

In the early stages of TAK, high-resolution ultrasound depicts increased intimal-medial thickness which is a reliable marker for active disease [43]. There are ongoing studies in the United States and Europe aiming to establish the carotid Doppler diagnostic criteria. Intimal-medial thicknesses and carotid neovascularization can be measured periodically to monitor disease progression [44, 45]. T2-weighted imaging can show subtle wall thickening and hyperintense signal in and around an inflamed vessel. During the acute phase, vessel wall contrast enhancement and peri-adventitious soft tissues can be helpful, and during the late phase, there is segmental dilatation with stenotic regions of the common carotid and subclavian arteries associated with dilatation of the ascending aorta.

Again, corticosteroids are the initial treatment of choice, followed by long-term use of immunosuppressant including cyclophosphamide, azathioprine, methotrexate, tacrolimus, mycophenolate mofetil, rituximab, tocilizumab, or antitumor necrosis factor (TNF) agents to achieve remission (Fig. 39.3). Twenty percent of patients have a monophasic self-limiting course, but the remaining 80% require long-term immunosuppression therapy [46]. Ishikawa et al. followed 120 TAK patients for a median 13-year duration observing that the 15-year survival rate averaged 83% [47].

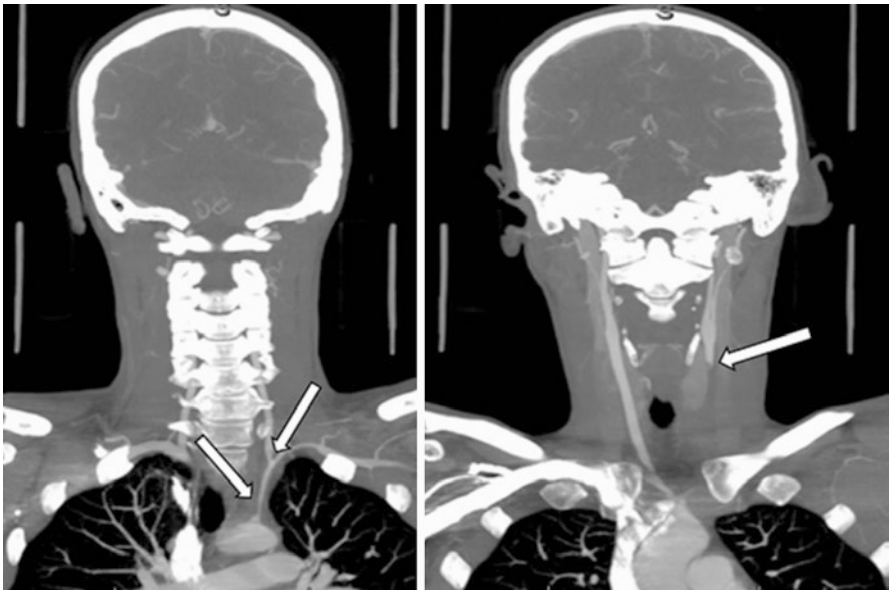


Fig. 39.3 A 26-year-old female with history of acute onset right hemiparesis and aphasia noted to have occlusion of left common carotid artery with severe stenosis of left subclavian and left vertebral artery origin (**arrows**). She was diagnosed with Takayasu arteritis based on vascular imaging. She was placed on a prolonged course of oral corticosteroids with disease stabilization determined by multiple, repeat vascular imaging over the following 2 years

Multivariate cox analysis showed that the presence of major complications (retinopathy, hypertension, aortic regurgitation, and aneurysm) and progressive course of the disease were associated with poorer prognosis.

Medium Vessel Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a systemic, medium vessel, necrotizing vasculitis which was first described in the nineteenth century and is well known to be associated with hepatitis B virus (HBV) infection. Prevalence ranges from 2 to 25 cases per million population [48, 49]. PAN typically affects the medium vessels at branch points where inflammation originates in the intima and spreads to the entire vessel wall causing necrotizing vasculitis. Distal ischemia can occur due to thrombus formation or intimal proliferation resulting in subsequent vascular occlusion. Hemorrhage also happen due to aneurysmal rupture as a result of compromised vessel wall integrity.

Common PAN symptoms include non-specific systemic symptoms, renal symptoms (hematuria, flank pain, or symptoms of acute renal failure), gastrointestinal tract symptoms (abdominal pain, GI bleeding, nausea, or vomiting), and cutaneous manifestations (rash, purpura, or gangrene). Peripheral nervous system involvement occurs in 60% of cases with mononeuritis multiplex being the most common manifestation, but CNS involvement can also occur. A recent analysis of data from 1963 to 2005 in 348 PAN patients revealed that only 4.6% of patients had CNS involvement [50].

PAN-associated strokes typically occur in the late stages of the disease, usually 2–3 years after onset [51]. Strokes occur despite vasculitis quiescence via corticosteroids treatments and other immunosuppression. This has led some to believe that strokes are rather due to accelerated atherosclerosis from chronic corticosteroid use. A recent study with 11 patients actually observed a shorter interval between the initiation of corticosteroids and the stroke onset (mean latency of 6.5 months with 50% occurring within 3 weeks) [52]. The authors proposed a theory that there is an imbalance with greater inhibition of prostacyclin PGI2 (*a vasodilator and platelet aggregation inhibitor*) as compared to thromboxane A_2 (*a vasoconstrictor and platelet activation/aggregation stimulator*) resulting from corticosteroids use. It is from this theoretical imbalance in platelet activation/aggregation that aspirin use is justified in PAN.

Laboratory investigations reveal non-specific findings such as elevated creatinine, ESR, and CRP along with normocytic anemia and proteinuria. Patients should be tested for both hepatitis B and C because both are frequently associated with PAN. Cryoglobulins, circulating immune complexes, and low complement C3 and C4 may be observed in patients with HBV-associated PAN. Angiographic findings include segmental stenosis and focal aneurysms of the medium-caliber

vessels. Histologic examination is the gold standard for the diagnosis of PAN with tissue typically obtained from clinically affected organs like the skin, kidney, or sural nerve.

Treatment of mild PAN cases involves administration of corticosteroids. More severe cases of PAN with CNS involvement require treatment with cyclophosphamide in addition to corticosteroids. In cases associated with HBV, in addition to the treatment regimen above, a combination of plasmapheresis and antivirals, such as lamivudine and interferon alpha-2b, have been shown to be beneficial. Additionally, remission can be maintained using other immunosuppressive agents including methotrexate, azathioprine, and mycophenolate mofetil.

The prognosis is poor if not treated. The 5-year survival rate is only 13% [53]. Treatment with immunosuppressive medications significantly improves the survival rate to 80% [50]. Prognosis and mortality for PAN can be predicted by the five-factor score (FFS) which was proposed in 1996 by Guillevin et al. [54]. These factors included proteinuria, elevated creatinine, cardiomyopathy, GI involvement, and CNS involvement. The FFS criteria were revised in 2011 when additional data from the French Vasculitis Study Group (FVSG) became available [55]. The revised FFS scores one point each for age $\geq$ 65 years, cardiac symptoms, gastrointestinal symptoms, and renal insufficiency. The 5-year mortality based on the revised criteria is 12%, 18%, and 29% with FFS scores of 0, 1, and $\geq$ 2, respectively.

Kawasaki Disease

Kawasaki disease (KAD) occurs primarily in the pediatric age group with 85–90% of cases under the age of 5 years [61]. It affects acute, medium-sized vessels with a strong mucocutaneous symptomatology. Strokes are a very rare complication of KAD and only 14 cases have been reported in children with active KAD. Most of these cases occurred before the era of using intravenous immunoglobulins (IVIG) in KAD treatment [56]. Proposed stroke etiology theories in KAD patients include a cardioembolic mechanism (from cardiomyopathy due to coronary artery involvement), vasculitis, or acquired hypercoagulable state from IVIG. Currently, IVIG and aspirin are the primary treatment.

ANCA-Associated Small Vessel Vasculitis

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) was initially considered to be a microscopic version of PAN but has more recently been identified as a separate disease with immunopathogenic similarities to GPA and EGPA. It is further distinguished from the latter two diseases by the lack of granuloma formation and a presence of necrotizing

vasculitis. The annual incidence rate of MPA in the United Kingdom (UK) is about five cases per million population [57], though incident rates are higher in Japan (14.8 per million population [57]) and Kuwait (24 per million population [8]). Common clinical manifestations of MPA include constitutional symptoms, skin lesions, upper respiratory symptoms, renal impairment, and pulmonary involvement. Neurological symptoms commonly occur with MPA in the form of mononeuritis multiplex in up to 58% of affected patients, whereas CNS involvement occurs in ~12% of cases [58]. Though review of the literature did not elaborate on the frequency of ischemic or hemorrhagic strokes among the "CNS manifestations," it is accepted that strokes are not a common manifestation of CNS involvement, and only a handful of cases have been reported. ANCA is positive in most patients with perinuclear or pANCA against myeloperoxidase (MPO) being the predominant positive serology, unlike GPA which has cytoplasmic or cANCA positivity against PR3. Sensitivity of the ANCA in MPO is estimated to be about 75% [58]. Tissue biopsy of the skin, lung, kidney, or peripheral nerve is the gold standard for diagnosis. Remission is induced by a combination therapy of corticosteroids with either cyclophosphamide or rituximab. Remission is maintained by steroid-sparing immunosuppressive agents. With these treatment options, the remission rate has been estimated to be 75–89% [59]. A large French study monitored the clinical course of 85 patients and noted that the relapse rate was 34% by 70 months [58]. The 5-year survival rate is 45–76% in MPA; renal impairment affected survival adversely (HR 3.69; 95% CI, 1.01–13.4) [59].

Granulomatosis with Polyangiitis (Wegener's) (GPA)

GPA is a rare systemic disease characterized by granulomatous vasculitis affecting small and medium vessels, especially in the respiratory and renal systems. The annual incidence of GPA in the United Kingdom was 8.4 cases per million population when 1990–2005 data were analyzed [60]. This same study showed that GPA prevalence increased from 29 cases per million population in 1990 to 65 cases in 2005. Common clinical manifestations include constitutional symptoms, upper respiratory tract symptoms (chronic rhinosinusitis, nasal ulcerations, or saddle nose), pulmonary manifestations (cough, hemoptysis, pulmonary infiltrates, or diffuse alveolar hemorrhage), and also renal involvement. About two out of three patients have peripheral nervous system involvement in the form of peripheral neuropathy or mononeuritis multiplex. CNS manifestations have been reported in 7–11% of patients via direct CNS vasculitis, remote intracerebral granuloma formations, or contiguous invasion of the nasal and paranasal sinus granulomas into the adjacent structures like orbit, optic nerve, optic chiasm, and pituitary gland [61]. TIA, ischemic stroke, intracerebral or subarachnoid hemorrhage, cerebral venous thrombosis, seizure, and cognitive decline can all occur as a result of CNS vasculitis which reportedly affects 3–5% of patients [62]. Other non-vasculitic CNS manifestations include cranial neuropathies [62] with optic and olfactory neuropathies

being common [14]. Chronic hypertrophic pachymeningitis can occur which produces severe, steroid-responsive headaches and a diffusely thickened dura mater with gadolinium-enhanced MRIs. Pituitary gland involvement has been noted as well. This involvement can cause diabetes insipidus and prolactinoma. Finally, direct invasion of the granulomas from the nasal and paranasal sinuses into the orbit and brain can produce local mass effect.

Cytoplasmic or cANCA directed against PR3 antigen is the most specific blood test for GPA as 87% of patients had cytoplasmic staining upon immunofluorescence (IF) testing for ANCA, but a slightly fewer, 76%, had positivity for ANCA against PR3 on enzyme immunoassays (EIA) [63]. Though pANCA is typically positive in MPA, the same study observed that 12% of patients with GPA can also have this antibody when tested either with IF or EIA. Combining all methods, the sensitivity and specificity of ANCA positivity are ~98% in active systemic disease, but the sensitivity drops to 60–70% in limited or atypical GPA [64]. Brain MRI may demonstrate ischemic or hemorrhagic lesions, dural thickening, pituitary involvement, or enhancement of inflamed orbital and paranasal mucosa. Tissue biopsy is required for a definite diagnosis for most cases.

Disease remission is induced by combination of corticosteroids with cyclophosphamide or rituximab though plasmapheresis can also be considered in patients with severe renal or pulmonary involvement [65]. Agents that can be used for remission maintenance include azathioprine, methotrexate, rituximab, and leflunomide. Prognosis is poor if untreated with a mean survival of 5 months and a 2-year mortality of 93% [66]. Immunosuppressive therapies have significantly changed the outlook with a recent 155-patient study showing a mean survival of 21+ years [67]. Factors associated with decreased survival include age > 52 years (HR 3.4; 95% CI, 1.03–11.21), dependency on dialysis at the time of diagnosis (HR 8.2; 95% CI, 2.03–33.11), and vasculitis damage index (VDI) ≥ 1 (HR 5.54; 95% CI, 1.28–24.05) [59]. Relapses are common and occur in 40% of patients at 24 months [68]. Predictors of relapse include ANCA positivity (RR 2.89; 95% CI, 1.12 to 7.45), fourfold increase in cANCA levels from baseline (RR 42.5; 95% CI, 9.48–180.8), maintenance of high-dose prednisolone (>20 mg/day) for <2.8 months (RR 2.87; 95% CI, 1.09–7.58), and chronic nasal carriage of *Staphylococcus aureus* (RR 7.16; 95% CI, 1.63–31.50). Interestingly, concomitant use of trimethoprim/sulfamethoxazole with the remission maintenance therapy has been noted to decrease the relapse rate (RR 0.32; 95% CI, 0.13–0.79) [59].

Eosinophilic Granulomatosis with Polyangiitis (EGPA or Churg-Strauss)

EGPA is the rarest of the three ANCA-associated vasculitides. It is characterized by the triad of asthma, hypereosinophilia, and necrotizing vasculitis. The annual incidence rate for EGPA is 0.1–0.3 case per 100,000 population [69, 70]. Systemic vasculitis typically occurs 8–10 years after the development of asthma and allergic rhinitis

[16]. Other common clinical manifestations include non-specific systemic symptoms, pulmonary symptoms, GI symptoms, cardiac arrhythmias or failure, and rash. Neurological manifestations are very common and observed in 60–70% of patients. EGPA predominantly affects the peripheral nervous system, but CNS involvement has been noted in 8–13% of patients [16, 71]. Ischemic stroke is the most commonly reported CNS complication, but intracerebral hemorrhage has also been described.

Relevant positive lab findings include eosinophilia, elevated Ig-E levels, hypergammaglobulinemia, and pANCA positivity in up to 40% of patients [72]. MRI findings vary, and the cerebral lesions (infarcts, microbleeds, or macrobleeds) are similar to those seen in other vasculitides. Like other aforementioned vasculitides, EGPA diagnosis frequently requires tissue biopsies. Treatment for EGPA is typically based on the severity of the disease and the five-factor score (FFS). Mild cases (FFS = 0) can be treated with corticosteroids only, but CNS involvement necessitates combination of corticosteroids and cyclophosphamide. Remission can be maintained with several agents including azathioprine, methotrexate, leflunomide, mycophenolate mofetil, and rituximab.

With treatment, remission is achieved in 81–91% of patients, but 15–35% of patients experience relapses within 2 years [59]. The FFS described with PAN has also been used to predict mortality in EGPA by adding the absence of ENT symptoms into the scoring system. The absence of ENT symptoms is associated with greater mortality with 5-year mortality rate (84%, with ENT symptoms; 92%, without such symptoms) [55].

Variable Vessel Vasculitis

Behçet's Disease

Behçet's disease (BD) is a remarkable condition which can affect all caliber vessels. BD has a symptomatology that has been classically described as including recurrent oral aphthous ulcers, genital ulcers, and iridocyclitis. Calamia et al. estimated the annual incidence was 0.38 per 100,000 population, respectively, in Olmsted County, MN [73]. BD is more prevalent in countries on the Silk Road with the highest prevalence in Turkey with 420 per 100,000 population [73]. BD is considered to be an autoimmune disease which develops as a result of an aberrant immune response to bacteria (streptococcus species) and tends to occur more commonly in genetically predisposed individuals with carriers of HLA-B51/HLA-B5 [74]. Common BD symptoms include recurrent, painful oral ulcers, cutaneous symptoms (acneiform lesions, pustules, erythema nodosum, palpable purpura, etc.), genital ulcers, ocular manifestations (uveitis, retinal vasculitis), and arthritis. Pathergy test is characteristic for BD which involves the formation of a sterile erythematous papule ≥2 mm in diameter within 48 h following a skin prick with a sterile needle.

Neurological involvement in BD is reported to occur in the range of 5.3–14.3% [75, 76]. Neuro-Behçet's disease (NBD) occurs more commonly in males especially when other systemic features are already present. NBD has been observed as the first

manifestation in <6% of BD cases [77]. There are two broad categories of NBD including "non-parenchymal or vascular" and the "parenchymal." Non-parenchymal or vascular NBD consists mostly of central venous sinus thrombosis (CVST) which occurs at a frequency of 18% [77]. Uncommon strokes from arterial thrombosis and dissections are also reported in NBD cases though are less common than CVSTs. Parenchymal NBD is more common than the non-parenchymal form of NBD. Parenchymal NBD presents as an intense meningoencephalitis reaction. Presenting symptoms are dependent on the part of the brain and can include ophthalmoparesis, pyramidal dysfunction, cerebellar dysfunction, encephalopathy, aphasia, seizures, etc. Common areas affected include the brainstem, basal ganglia, thalamus, diencephalon, cerebral hemisphere, and the spinal cord. Up to one-fifth of affected patients can have both parenchymal and non-parenchymal BD manifestations. The MRI findings for parenchymal NBD include leptomeningeal enhancement and T2-hyperintense, isolated, or confluent lesions that predominantly affect the brainstem and are typically larger and more extensive than those of multiple sclerosis. The presence of brainstem atrophy is also noted in chronic NBD cases. The presence of this atrophy can be useful in differentiating NBD from multiple sclerosis.

Diagnosis of BD is clinical though can be supported by radiologic and CSF findings. In one of the largest series, Akman-Demir et al. [17] noted that in 49 patients with abnormal CSF, there existed a neutrophilic or lymphocytic predominance with the median lymphocyte count of 30/mm^3 (mean, 63; range, 0–485) and the median neutrophil count of 10/mm^3 (mean, 98; range, 0–1100). When evaluated, the immunoglobulin G (IgG) index was elevated in 73% of cases and median CSF protein level of 60 mg/dl (maximum 150 mg/dl).

BD CNS disease is usually treated with systemic corticosteroids, interferon alpha, azathioprine, cyclophosphamide, methotrexate, or TNF-α antagonists. For the treatment of sinus thrombosis, corticosteroids in combination with oral anticoagulation are recommended [78]. A French study observed that in their single-center cohort of 817 patients, overall mortality was 5% after a median follow-up of 7.7 years [79]. They also observed that male sex (hazard ratio [HR] 4.94; 95% CI, 1.53–16.43); systemic arterial involvement such as aneurysms, Budd-Chiari syndrome (HR 2.51; 95% CI, 1.07–5.90); and a high number of BD flares (HR 2.37; 95% CI, 1.09–5.14) were independently associated with the risk of mortality. The non-parenchymal form of NBD is less likely to result in disease progression, disability, or premature death compared to parenchymal NBD.

Single-Organ Vasculitis

Primary Angiitis of CNS (PACNS)

The vessels involved in PACNS are restricted to the CNS. It is a rare disorder with an estimated annual incidence of 2.4 cases per million population in North America [12], with a preponderance of males. PACNS is considered to be an autoimmune disease, but the exact pathogenesis is unknown. PACNS typically involves

medium-caliber arteries and/or veins with typical histopathological findings consisting of the infiltrating T-lymphocytes and macrophages, which later undergo granulomatous differentiation with giant cell formation. Miller et al. [80] reviewed 29 PACNS-positive biopsies and revealed that besides the typical granulomatous morphology (n = 17. 58%), a purely lymphocytic (n = 8, 28%) and acutely necrotizing (n = 4, 14%) morphology can also occur. Salvarani et al. [12] noted that headaches (63%) were the most common clinical manifestation followed by encephalopathy (50%), hemiparesis (43%), and persistent neurological deficits or stroke (40%). Seizures (16%), intracranial hemorrhage (8%), and TIA (28%) were other manifestations seen in this 101-patient cohort. A recently published paper increased the patient count to 163 and noted similar findings [81]. The overall clinical pattern of PACNS can be either a progressive, subacute encephalopathy or a series of recurrent focal symptoms similar to those seen in multiple sclerosis.

Routine blood tests including CBC, ESR, and CRP are typically normal, and antibody titers such as ANA, ANCA, dsDNA, and RF are also typically not detected. CSF studies show some abnormalities in about 90% of patients [12, 81] and can include mild lymphocytic leukocytosis and elevated protein levels. Salvarani et al. [81] observed the median WBC count of 6/ml (range, 0–615/ml) and the median total protein of 72 mg/dl (range, 15–1034 mg/dl). Cultural and serological CSF examinations are essential to exclude infections. MRI brain findings are non-specific but can include infarcts in up to 50% and discrete or diffuse supratentorial or infratentorial lesions involving the deep white matter, superficial white matter, cortex, and deep gray matter [22]. Additionally, gadolinium-enhanced intraparenchymal lesions and leptomeninges can also be seen in up to 40% of cases [81]. Other uncommon MRI findings include mass-like lesions in up to 15% of cases (these can be mistaken as neoplasms), confluent white matter lesions, cortical laminar necroses, subarachnoid hemorrhage, and intraparenchymal hemorrhage [82]. The overall sensitivity of catheter angiography varies from 40% to 90%, whereas its specificity has been shown to be as low as 30% [83]. When an abnormality is noted, in the majority of instances, both small and large vessels are involved. Small vessel changes were more common occurring in 91% of cases as compared to 66% of cases with large vessel changes in the 163-patient cohort [81]. Again, brain biopsy is the gold standard for diagnosis of PACNS. Miller et al. [80] analyzed 53 tissue samples from patients with suspected PACNS and detected vasculitis in 63%. Biopsies of radiologically abnormal regions or leptomeninges yielded greater sensitivities than "blind biopsies." Calabreses and Mallek proposed a diagnostic criterion in 1988 which gave equal weight to angiographic and histological findings and has been widely accepted [84]. In 2009, Birnbaum and Hellmann proposed another diagnostic criterion in view of the non-specificity of the angiographic findings compared to the histopathological findings. They stratified the level of certainty as "definite" and "probable" based on the presence or absence of tissue confirmation [82]. Both diagnostic criteria are shown in Table 39.4.

There have been no randomized clinical trials that compared the existing treatment options. Based on the experience of treating other severe systemic vasculitides, a combination of corticosteroids with cyclophosphamide is often used after

Table 39.4 Diagnostic criteria for proposed for PACNS

Diagnostic criteria for PACNS proposed by Calabreses and Mallek [84]	Diagnostic criteria for PACNS proposed by Birnbaum and Hellmann [82]
A history of an unexplained neurologic deficit that remains after a vigorous diagnostic workup, including lumbar puncture and neuroimaging studies Either classic angiographic evidence of vasculitis or histopathologic evidence of vasculitis within the CNS No evidence of systemic vasculitis or any other condition to which the angiographic or pathologic evidence can be attributed	*Definite diagnosis*: confirmation of vasculitis on analysis of a tissue biopsy specimen *Probable diagnosis*: in the absence of tissue confirmation, if there are high probability findings on an angiogram with abnormal findings on MRI and a CSF profile consistent with PCNSV

diagnosis is reasonably certain. Less toxic immunosuppressant such as azathioprine or methotrexate can be used once remission is achieved. Salvarani et al. found 27% of patients who were treated with immunosuppression relapsed during the mean follow-up period of 12 months (range from 0 to 13.7 years). The relapse rate was higher in the corticosteroid-only cohort ($n = 75$) compared to the cohort treated with both corticosteroid and cyclophosphamide ($n = 72$; 39% vs 18%; $p = 0.006$) [81]. Older age (OR 1.44; 95% CI, 1.11–1.86) and the presence of infarct on brain MRI at the time of diagnosis (OR 3.74; 95% CI, 1.55–9.06) were associated with higher disability scores (modified Rankin scale 4–6) at the end of study [81].

Secondary Vasculitis Associated with Systemic Autoimmune Conditions

CNS vasculitis is rarely the first manifestation of the systemic autoimmune diseases described here. As a rule of thumb, by the time CNS involvement occurs, patients are usually in the midst of a systemic flare-up and are exhibiting other symptoms and signs of the primary disease affecting other organ systems. The presence of these flare-ups aids in diagnosing the cause of the CNS symptoms.

Systemic Lupus Erythematosus (SLE)

Neuropsychiatric SLE (NPSLE) has been described as 19 discrete syndromes by the American College of Rheumatology (ACR) [85]. These syndromes include cerebrovascular disease, demyelinating syndromes, myelopathy, seizures, mood disorders, psychosis, peripheral neuropathy, plexopathy, etc. About 30–40% of SLE patients are reported to have at least one of these syndromes [19, 86]. Cerebrovascular disease incidence ranges from 4.5% to 14.3% [19]. Patients with SLE have a higher risk for developing strokes when compared to the general population with a recent meta-analysis reporting individuals with SLE carrying a twofold higher risk of

ischemic stroke, a threefold higher risk of intracerebral hemorrhage, and an almost fourfold higher risk of subarachnoid hemorrhage [87]. It is important to note that most of the increased risk of strokes is secondary to accelerated atherosclerosis, antiphospholipid antibody syndrome, and cardioembolism from Libman-Sacks endocarditis instead of cerebral vasculitis. Autopsy studies have shown the presence of true angiitis in patients with SLE and strokes is only at a rate of 0–7% [88, 89]. Currently, FDA has approved the use of aspirin, hydroxychloroquine, and corticosteroids for the treatment of NPSLE, but severe cases with CNS involvement (including vasculitis) have been treated with cyclophosphamide. Anecdotally other treatment options include IVIG, methotrexate, plasmapheresis, and rituximab. The presence of antiphospholipid syndrome necessitates the use of systemic anticoagulation.

Sarcoidosis

The incidence of neurological involvement in patients with sarcoidosis is reported to be 5–15% [90]. Common presentations of neurosarcoidosis include cranial neuropathy (especially, facial nerves), myelopathy, and meningitis with stroke as a rare and late complication. There are only a handful of case reports/series which have reported strokes in patients with sarcoidosis. One theory for sarcoid-related vasculitis is that inflammatory granulomas tend to originate in the leptomeninges and spread perivascularly into the Virchow-Robin spaces [91]. These inflammatory granulomas may invade vessel walls resulting in vasculitis and subsequent stenosis and occlusion.

Sjogren's Syndrome (SS)

The true prevalence of CNS manifestations in Sjogren's disease is not clear. Studies have shown a prevalence between 0% and 60% with wide variability possibly due to the involvement of the psychiatric symptoms in some studies, a lack of uniform SS diagnostic criteria, and involvement of secondary SS in patients with another primary autoimmune disease like SLE in some studies [92]. A more recent study has noted that the incidence rate of strokes in patients with SS is 5.1 per 1000 person-year [93]. Other CNS manifestations of SS include myelopathy, cranial neuropathies, and focal (such as hemiparesis) or diffuse (such as confusion, seizures) cerebral dysfunction. Alexander et al. observed that a subset of SS with Ro antibody positivity has higher odds of developing small vessel vasculitis and focal progressive CNS symptoms [94]. There are a few case reports of non-atherosclerotic, large vessel disease which resembles moyamoya in patients with SS [95, 96], but the etiology is not established yet, and vasculitis is considered to be one potential cause.

Rheumatoid Arthritis (RA)

Cerebral vasculitis from RA is a rare phenomenon that is usually associated with non-specific, systemic, and extra-articular manifestations [97]. The overall annual incidence rate of systemic vasculitis in patients with RA was noted to be seven cases per million population in a retrospective analysis from the United Kingdom [98]. Vasculitis in RA commonly affects the skin and peripheral nerves, but cerebral parenchymal vasculitis is a rare complication [99]. Similar to other vasculitides, the treatment for RA-associated cerebral vasculitis is a combination of steroids and a cytotoxic agent. Interestingly, Pons et al. [99] observed that cases treated with corticosteroids had poorer outcomes compared with cases treated with a combination of drugs.

CNS Vasculitis Associated with Infections

Neurosyphilis

In the post-antibiotic era, neurosyphilis is a rare phenomenon. Meningovascular syphilis occurs about 5–12 years after initial infection. The most common form of syphilitic vasculitis, Heubner's arteritis, is a crescentic endarteritis obliterans affecting large- and medium-sized arteries which lead to fibrous and inflammatory changes in the adventitia, thinning of the media, and fibroblastic proliferation of the intima leading to progressive stenosis. The other form of vasculitis that can be seen in these cases is a less common small vessel vasculitis, Nissl arteritis, characterized by a proliferation of endothelium and adventitial cells. Symptoms associated with meningovascular neurosyphilis include headaches, psychiatric symptoms (personality changes, emotional lability, and dementia), seizures, and strokes with the middle cerebral artery being the most commonly affected vessel. The diagnosis of syphilitic vasculitis depends on obtaining a reliable clinical history of prior symptoms consistent with primary and secondary syphilis, positive syphilis serology (VDRL, RPR), and non-specific CSF markers of vasculitis (lymphocytic pleocytosis with elevated proteins). CSF VDRL is a highly specific test but with a low sensitivity as demonstrated by one study in which 43% of 241 patients with neurosyphilis display false-negative CSF VDRL [100]. Intravenous penicillin remains the mainstay of treatment for neurosyphilis.

Tuberculosis (TB)

TB has resurfaced as an important entity in the last 3 decades due to the widespread prevalence of HIV/AIDS. Mycobacterium tuberculosis initially establishes itself in the lungs and then spreads to the brain at various sites (so-called Rich foci)

including meninges, subpial or subependymal regions, or the spinal cord. Subsequently, these foci rupture and can produce a thick, exudative meningitis around the base of the brain. This exudate can frequently affect the middle cerebral artery and lenticulostriate arteries [101]. Patients can present with symptoms of meningitis, focal neurological dysfunction, behavior changes, or decreased alertness. History of prior exposure to TB, positive skin tuberculin tests, or the presence of high-risk factors for TB should raise concerns. Typical CSF findings include elevated protein (100–500 mg/dl), low glucose (<40 mg/dl), and lymphocytic pleocytosis (100–500 cells/μl) [102]. Identifying acid-fast bacilli (AFB) in the CSF remains the most important investigative tool to diagnose TB infection, but it has a poor sensitivity (≤ 20%) noted in several studies [103]. CSF adenosine deaminase (ADA) has been an area of interest recently. A meta-analysis revealed a mean sensitivity of 79% and mean specificity of 91% in cases of TB meningitis [104]. MRI typically shows strokes in the area surrounding the affected vessels. Other less common findings include hydrocephalus, leptomeningeal enhancement, tuberculomas, or noncaseating granulomas which can appear isointense to hypointense on both T1- and T2-weighted images. Antitubercular drugs should be started as soon as the diagnosis is suspected. An initial 2-month induction therapy regimen includes isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 7–10 additional months of isoniazid and rifampin as maintenance therapy with adjunctive corticosteroid use.

Human Immunodeficiency Virus (HIV) Infection

HIV infection can result in stroke via several mechanisms including opportunistic infection, vasculopathy, cardioembolism, and coagulopathy. A South African study found that most strokes observed were ischemic and occurred predominantly in young patients without any atherosclerotic risk factors. HIV-associated vasculopathy is identified as a causative etiology in 20% of patients [105]. Roughly half of the patients had extracranial involvement. Patients with extracranial vasculopathy typically had a preserved CD4 count (mean 479 cells/μl) compared to those with intracranial vasculopathy who had lower CD4 counts (mean 112 cells/μl). Vasa vasorum involvement is believed to play an important role in extracranial vasculopathy. An autopsy was performed in one of the patients and showed occlusion of extracranial ICA with microscopic evidence of neovascularization as well as vessel wall inflammation. The pathogenesis of HIV-associated vasculopathy is unclear though it is theorized that endothelial dysfunction originates from contact with HIV-infected cells (CD4+ T cells, monocytes, and macrophages), circulating HIV viruses, viral proteins, and viral-induced proinflammatory cytokines which cause endothelial dysfunction [106]. The treatment of HIV-induced vasculitis includes the use of antiretroviral treatment, but the role of corticosteroids is unclear.

Fungal Infections

Typically, fungal infections occur in immunocompromised patients and present as a subacute meningoencephalitis. Aspergillus is one of the few fungal organisms which presents with chronic paranasal sinusitis that can spread to the adjacent skull base causing osteomyelitis and the fungal hyphae can directly invade the cerebral blood vessels causing hemorrhagic stroke. Cryptococcal meningitis is rarely associated with vasculitis, but when strokes occur, they typically affect subcortical regions supplied by small, deep vessels supplying the basal ganglia, internal capsule, and thalamus [107]. India ink stain and agglutination test for polysaccharide antigen in CSF are available to aid in the diagnosis. Treatment of fungal-associated vasculitides includes amphotericin B and flucytosine for 6 weeks and fluconazole in the case of CNS cryptococcal infection.

Varicella-Zoster Virus (VZV)

Over the past few decades, VZV has emerged as an important cause of vasculopathy and strokes. As matter of fact, VZV vasculopathy now accounts for 31% of all arterial ischemic strokes in the pediatric population [108]. The exact pathogenesis is under debate, but it is thought that the virus directly invades the vessels from existing latent infection of cranial nerves [109]. Some investigators have examined the retrograde axonal spread of the virus from the sensory ganglia to the blood vessels intracranially with anatomical evidence provided by animal models showing these afferent fibers extending from trigeminal ganglia to intracranial blood vessels [110, 111]. The infected arteries contained Cowdry A inclusion bodies, multinucleated giant cells, herpes virions, and both VZV DNA and antigen [112]. Stroke risk is increased not only acutely [113, 114], but also long-term risk of having stroke and TIA is shown recently by a large retrospective observational study from the United Kingdom. This study showed that the risk of TIA and strokes can persist up to 24 years after the infection in the population between the age 18–40 years with an adjusted hazard ratio of 1.74 (95% CI: 1.13–2.66) for stroke and 2.42 (95% CI: 1.34–4.36) for TIA. Clinically, vesicular rash can be seen preceding the stroke symptoms but can be absent in 40% of patients when the stroke is closely associated with the infection [115]. CSF analysis shows modest pleocytosis which is predominantly mononuclear, as seen in a study analyzing 30 cases of VZV vasculopathy [115]. A characteristic image finding for VZV vasculopathy is the presence of MRI lesions at the gray-white matter junction. Regarding virological confirmation, CSF VZV IgG and elevated CSF/serum VZV IgG are more sensitive than VZV DNA PCR in CSF as studies have noted that PCR can be negative in up to 70% of cases [115, 116]. Acyclovir is used for the treatment because of the concept that vasculopathy is due to a productive viral infection in the artery as demonstrated by the presence of multinucleated giant cells, Cowdry A inclusion bodies, VZV antigens, and VZV DNA in the cerebral vessels [112]. The benefits of concurrent steroid treatment remain unclear.

Vasculitis Associated with Neoplasm

Certain malignancies have been associated with systemic vasculitis including cranial vasculitides such as hairy cell leukemia and reticulohistiocytoma cutis [117]. It is rarely seen as a direct complication of treatment modalities such as immunosuppression or bone marrow transplant. Lymphomatoid granulomatosis is a rare, systemic angiodestructive lymphoproliferative disease which can cause transmural angiitis and neurological manifestations in up to 20% of patients [118]. Intravascular lymphomas comprising CD20-positive B-cell neoplasms confined intravascularly are also known to mimic vasculitis but rarely cause strokes.

Vasculitis Associated with Drugs

There are numerous medications that have been associated with vasculitis including TNF inhibitors, propylthiouracil, cocaine/levamisole, hydralazine, minocycline, rituximab, montelukast, and statins. Drug-induced vasculitis typically affects the cutaneous tissue, but CNS manifestations have been rarely reported. A few drugs such as amphetamines, cocaine, ephedrine, and phenylpropanolamine have been reported as causes of CNS vasculitis, but only a handful of case reports are backed up by the results of tissue diagnosis. Test results have shown pathological changes ranging from perivascular cuffing to frank necrotizing vasculitis [119]. Cocaine is one such drug which has been reported to be associated with cerebral vasculitis in all forms of its usage, including inhalation and intravenous administration. The exact pathogenesis is unknown, but animal models have shown that intravascular administration of cocaine can cause not only structural damage to the vessel wall but also promote the release of chemical mediators and cytokines that can initiate cascades which eventually culminate in endothelial inflammation [120]. One should be careful in labeling abnormal angiographic studies in stroke patients post consumption of such drugs since CNS vasculitis can be due to any of several confounding factors which include vasospasm, coexisting infections such as syphilis, HIV, hepatitis B, hepatitis C, and endocarditis which can produce imaging changes through other mechanisms.

Summary

Due to the paucity of vasculitis cases, large-scale studies have been lacking. To solve this issue, an international, multicenter research infrastructure was created in 2003 by the National Institutes of Health (NIH) known as the "Vasculitis Clinical Research Consortium (VCRC)." VCRC provides a knowledge base and resource for researchers worldwide. Use of this database has resulted in translational and clinical studies focusing on vasculitis. There are currently several ongoing studies assessing

various aspects of several vasculitic syndromes. A giant clinical data and bio-sample repository have also been established. It already contains over 48,000 patient samples of serum, plasma, DNA, and urine invaluable for biomarkers research. There are several ongoing studies in the area of noninvasive diagnostic methods such as the TABUL study in GCA. Additionally, several ongoing studies on the topic of neuropsychiatric SLE assess the utility of several advanced neuroimaging methods including diffusion tensor imaging and PET scans with novel glutamate receptor ligands. A vast majority of ongoing trials are investigating the therapeutic options and searching for safer immune modulators. For example, *plasma exchange and glucocorticoid dosing in the treatment of antineutrophil cytoplasm antibody-associated vasculitis: an international randomized controlled trial* (PEXIVAS) study is examining a combination of plasmapheresis and corticosteroids in treating ANCA-associated vasculitides. Abatacept is currently being studied in two clinical trials – *abatacept in treating adults with giant cell arteritis and temporal arteritis* (AGATA) and *abatacept for the treatment of relapsing, non-severe, granulomatosis with polyangiitis* (ABROGATE). It is hoped that such collaborative activities on a global scale will advance the understanding of diseases mechanism and improve outcomes for the thousands of lives affected.

Acknowledgment We would like to thank Drs. Forrest Lowes and James Sawers for their generous inputs and comments to this book chapter. We also thank Drs. Angelos Katramados and Daniel Miller, MD, for providing case images.

References

1. Jennette JC, et al. 2012 revised international Chapel Hill consensus conference nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11.
2. Watts RA, et al. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum. 2000;43(2):414–9.
3. Gonzalez-Gay MA, Garcia-Porrua C. Epidemiology of the vasculitides. Rheum Dis Clin N Am. 2001;27(4):729–49.
4. Tidman M, et al. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975–95: organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. J Intern Med. 1998;244(2):133–41.
5. Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. Ann Rheum Dis. 2000;59(3):161–3.
6. Watts RA, Scott DG. Classification and epidemiology of the vasculitides. Baillieres Clin Rheumatol. 1997;11(2):191–217.
7. McMahon BJ, et al. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. Hepatology. 1989;9(1):97–101.
8. el-Reshaid K, et al. The spectrum of renal disease associated with microscopic polyangiitis and classic polyarteritis nodosa in Kuwait. Nephrol Dial Transplant. 1997;12(9):1874–82.
9. Lane SE, et al. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 2003;48(3):814–23.
10. Tervaert JW, Stegeman CA, Kallenberg CG. Silicon exposure and vasculitis. Curr Opin Rheumatol. 1998;10(1):12–7.
11. Hajj-Ali RA, et al. Primary angiitis of the CNS. Lancet Neurol. 2011;10(6):561–72.

12. Salvarani C, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol. 2007;62(5):442–51.
13. Lie JT. Angiitis of the central nervous system. Curr Opin Rheumatol. 1991;3(1):36–45.
14. Nishino H, et al. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. Ann Neurol. 1993;33(1):4–9.
15. Gonzalez-Gay MA, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore). 2000;79(5):283–92.
16. Guillevin L, et al. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore). 1999;78(1):26–37.
17. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. The Neuro-Behcet Study Group. Brain. 1999;122(Pt 11):2171–82.
18. Delalande S, et al. Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients. Medicine (Baltimore). 2004;83(5):280–91.
19. Unterman A, et al. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum. 2011;41(1):1–11.
20. Kermani TA, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Semin Arthritis Rheum. 2012;41(6):866–71.
21. Stone JH, et al. Sensitivities of noninvasive tests for central nervous system vasculitis: a comparison of lumbar puncture, computed tomography, and magnetic resonance imaging. J Rheumatol. 1994;21(7):1277–82.
22. Pomper MG, et al. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. AJNR Am J Neuroradiol. 1999;20(1):75–85.
23. Salvarani C, et al. Primary central nervous system vasculitis with prominent leptomeningeal enhancement: a subset with a benign outcome. Arthritis Rheum. 2008;58(2):595–603.
24. Swartz RH, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology. 2009;72(7):627–34.
25. Calabrese LH, et al. Primary angiitis of the central nervous system: diagnostic criteria and clinical approach. Cleve Clin J Med. 1992;59(3):293–306.
26. Lie JT. Classification and histopathologic spectrum of central nervous system vasculitis. Neurol Clin. 1997;15(4):805–19.
27. Parisi JE, Moore PM. The role of biopsy in vasculitis of the central nervous system. Semin Neurol. 1994;14(4):341–8.
28. Alrawi A, et al. Brain biopsy in primary angiitis of the central nervous system. Neurology. 1999;53(4):858–60.
29. Hajj-Ali RA, Calabrese LH. Diagnosis and classification of central nervous system vasculitis. J Autoimmun. 2014;48–49:149–52.
30. Salvarani C, et al. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med. 1995;123(3):192–4.
31. Cid MC, et al. Five clinical conundrums in the management of giant cell arteritis. Rheum Dis Clin N Am. 2007;33(4):819–34. vii
32. Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology. 1988;38(3):352–9.
33. Gonzalez-Gay MA, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 1998;41(8):1497–504.
34. Gonzalez-Gay MA, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore). 2009;88(4):227–35.
35. Cid MC, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum. 1998;41(1):26–32.
36. Niederkohr RD, Levin LA. A Bayesian analysis of the true sensitivity of a temporal artery biopsy. Invest Ophthalmol Vis Sci. 2007;48(2):675–80.
37. https://clinicaltrials.gov/ct2/show/NCT00974883., T.A.B.v.U.i.D.o.G.T.C.g.I.N.A.f.
38. Nesher G, et al. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum. 2004;50(4):1332–7.

39. Andersson R, Malmvall BE, Bengtsson BA. Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study of 90 patients treated with corticosteroids. Acta Med Scand. 1986;220(4):361–4.
40. Gonzalez-Gay MA, Pina T. Giant cell arteritis and polymyalgia rheumatica: an update. Curr Rheumatol Rep. 2015;17(2):6.
41. Hall S, et al. Takayasu arteritis. A study of 32 North American patients. Medicine (Baltimore). 1985;64(2):89–99.
42. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56(3):1000–9.
43. Garg A. Vascular brain pathologies. Neuroimaging Clin N Am. 2011;21(4):897–926. ix
44. Carotid Artery Neovascularization in Takayasu's and Giant Cell Arteritis. https://clinicaltrials.gov/ct2/show/NCT01795456. Accessed 30 Jan 2019.
45. Magnetic Resonance Angiography vs Ultrasonography in Systemic Large vEssel vasculitiS (MUSES). https://clinicaltrials.gov/ct2/show/NCT02042092. Accessed 30 Jan 2019.
46. Kerr GS, et al. Takayasu arteritis. Ann Intern Med. 1994;120(11):919–29.
47. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. Circulation. 1994;90(4):1855–60.
48. Mahr A, et al. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum. 2004;51(1):92–9.
49. Haugeberg G, et al. Primary vasculitis in a Norwegian community hospital: a retrospective study. Clin Rheumatol. 1998;17(5):364–8.
50. Pagnoux C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum. 2010;62(2):616–26.
51. Cohen RD, Conn DL, Ilstrup DM. Clinical features, prognosis, and response to treatment in polyarteritis. Mayo Clin Proc. 1980;55(3):146–55.
52. Reichart MD, Bogousslavsky J, Janzer RC. Early lacunar strokes complicating polyarteritis nodosa: thrombotic microangiopathy. Neurology. 2000;54(4):883–9.
53. Balow JE. Renal vasculitis. Kidney Int. 1985;27(6):954–64.
54. Guillevin L, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore). 1996;75(1):17–28.
55. Guillevin L, et al. The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90(1):19–27.
56. Sabatier I, et al. Stroke by carotid artery complete occlusion in Kawasaki disease: case report and review of literature. Pediatr Neurol. 2013;49(6):469–73.
57. Watts RA, et al. Renal vasculitis in Japan and the UK--are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant. 2008;23(12):3928–31.
58. Guillevin L, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42(3):421–30.
59. Mukhtyar C, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European league against rheumatism systemic vasculitis task force. Ann Rheum Dis. 2008;67(7):1004–10.
60. Watts RA, et al. Prevalence and incidence of Wegener's granulomatosis in the UK general practice research database. Arthritis Rheum. 2009;61(10):1412–6.
61. Seror R, et al. Central nervous system involvement in Wegener granulomatosis. Medicine (Baltimore). 2006;85(1):54–65.
62. Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. Curr Opin Rheumatol. 2011;23(1):7–11.
63. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2003;48(8):2299–309.

64. Vassilopoulos D, Hoffman GS. Clinical utility of testing for Antineutrophil. Clin Diagn Lab Immunol. 1999;6(5):645–51.
65. Mukhtyar C, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68(3):310–7.
66. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J. 1958;2(5091):265–70.
67. Reinhold-Keller E, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum. 2000;43(5):1021–32.
68. Stegeman CA, et al. Trimethoprim–sulfamethoxazole (Co-Trimoxazole) for the prevention of relapses of Wegener's granulomatosis. N Engl J Med. 1996;335(1):16–20.
69. Eustace JA, Nadasdy T, Choi M. Disease of the month. The Churg Strauss syndrome. J Am Soc Nephrol. 1999;10(9):2048–55.
70. Greco A, et al. Churg-Strauss syndrome. Autoimmun Rev. 2015;14(4):341–8.
71. Sinico RA, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum. 2005;52(9):2926–35.
72. Sable-Fourtassou R, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med. 2005;143(9):632–8.
73. Calamia KT, et al. Epidemiology and clinical characteristics of Behcet's disease in the USA: a population-based study. Arthritis Rheum. 2009;61(5):600–4.
74. de Menthon M, et al. HLA-B51/B5 and the risk of Behcet's disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis Rheum. 2009;61(10):1287–96.
75. Al-Araji A, Sharquie K, Al-Rawi Z. Prevalence and patterns of neurological involvement in Behcet's disease: a prospective study from Iraq. J Neurol Neurosurg Psychiatry. 2003; 74(5):608–13.
76. Serdaroglu P, et al. Neurologic involvement in Behcet's syndrome. A prospective study. Arch Neurol. 1989;46(3):265–9.
77. Al-Araji A, Kidd DP. Neuro-Behcet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol. 2009;8(2):192–204.
78. Barnes CG. Treatment of Behcet's syndrome. Rheumatology (Oxford). 2006;45(3):245–7.
79. Saadoun D, et al. Mortality in Behcet's disease. Arthritis Rheum. 2010;62(9):2806–12.
80. Miller DV, et al. Biopsy findings in primary angiitis of the central nervous system. Am J Surg Pathol. 2009;33(1):35–43.
81. Salvarani C, et al. An update of the Mayo clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. Medicine (Baltimore). 2015;94(21):e738.
82. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol. 2009;66(6):704–9.
83. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis: an update. Curr Opin Rheumatol. 2012;24(1):46–52.
84. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore). 1988;67(1):20–39.
85. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42(4):599–608.
86. Borowoy AM, et al. Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort. Semin Arthritis Rheum. 2012;42(2):179–85.
87. Holmqvist M, et al. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. RMD Open. 2015;1(1):e000168.
88. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann Neurol. 1988;23(4):380–4.

89. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. Semin Arthritis Rheum. 1979;8(3):212–21.
90. Hamzeh N. Sarcoidosis. Med Clin North Am. 2011;95(6):1223–34.
91. Meyer JS, Foley JM, Campagna-Pinto D. Granulomatous angiitis of the meninges in sarcoidosis. AMA Arch Neurol Psychiatry. 1953;69(5):587–600.
92. Soliotis FC, Mavragani CP, Moutsopoulos HM. Central nervous system involvement in Sjogren's syndrome. Ann Rheum Dis. 2004;63(6):616–20.
93. Yurkovich M, et al. OP0212 the risk of myocardial infarction and cerebrovascular accident in patients with SjÖGren's syndrome: a general population-based cohort study. Ann Rheum Dis. 2014;73(Suppl 2):142–3.
94. Alexander EL, et al. Anti-Ro(SS-A) autoantibodies in central nervous system disease associated with Sjogren's syndrome (CNS-SS): clinical, neuroimaging, and angiographic correlates. Neurology. 1994;44(5):899–908.
95. Sakata H, et al. Efficacy of extracranial-intracranial bypass for progressive middle cerebral artery occlusion associated with active Sjogren's syndrome: case report. J Stroke Cerebrovasc Dis. 2014;23(8):e399–402.
96. Nagahiro S, et al. Multiple cerebral arterial occlusions in a young patient with Sjogren's syndrome: case report. Neurosurgery. 1996;38(3):592–5; discussion 595.
97. Mrabet D, et al. Cerebral vasculitis in a patient with rheumatoid arthritis. Joint Bone Spine. 2007;74(2):201–4.
98. Watts RA, et al. Rheumatoid vasculitis: becoming extinct? Rheumatology (Oxford). 2004;43(7):920–3.
99. Caballol Pons N, et al. Isolated cerebral vasculitis associated with rheumatoid arthritis. Joint Bone Spine. 2010;77(4):361–3.
100. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. JAMA. 1972;219(6):726–9.
101. Gupta RK, et al. MR imaging and angiography in tuberculous meningitis. Neuroradiology. 1994;36(2):87–92.
102. Marx GE, Chan ED. Tuberculous meningitis: diagnosis and treatment overview. Tuberc Res Treat. 2011;2011:798764.
103. Rock RB, et al. Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin Microbiol Rev. 2008;21(2):243–61.
104. Xu HB, et al. Diagnostic value of adenosine deaminase in cerebrospinal fluid for tuberculous meningitis: a meta-analysis. Int J Tuberc Lung Dis. 2010;14(11):1382–7.
105. Tipping B, et al. Stroke in patients with human immunodeficiency virus infection. J Neurol Neurosurg Psychiatry. 2007;78(12):1320–4.
106. Benjamin LA, et al. HIV infection and stroke: current perspectives and future directions. Lancet Neurol. 2012;11(10):878–90.
107. Lan SH, et al. Cerebral infarction in chronic meningitis: a comparison of tuberculous meningitis and cryptococcal meningitis. QJM. 2001;94(5):247–53.
108. Askalan R, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke. 2001;32(6):1257–62.
109. Linnemann CC Jr, Alvira MM. Pathogenesis of varicella-zoster angiitis in the CNS. Arch Neurol. 1980;37(4):239–40.
110. Mayberg M, et al. Perivascular meningeal projections from cat trigeminal ganglia: possible pathway for vascular headaches in man. Science. 1981;213(4504):228–30.
111. Saito K, Moskowitz MA. Contributions from the upper cervical dorsal roots and trigeminal ganglia to the feline circle of Willis. Stroke. 1989;20(4):524–6.
112. Gilden DH, et al. Varicella zoster virus, a cause of waxing and waning vasculitis: the New England journal of medicine case 5-1995 revisited. Neurology. 1996;47(6):1441–6.
113. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. Neurology. 2010;74(10):792–7.

114. Sundström K, et al. Incidence of herpes zoster and associated events including stroke—a population-based cohort study. BMC Infect Dis. 2015;15(1):1–10.
115. Nagel MA, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. Neurology. 2008;70(11):853–60.
116. Nagel MA, et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. Neurology. 2007;68(13):1069–73.
117. Mertz LE, Conn DL. Vasculitis associated with malignancy. Curr Opin Rheumatol. 1992;4(1):39–46.
118. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. Cancer. 1979;43(1):360–73.
119. Calabrese LH, Duna GF. Drug-induced vasculitis. Curr Opin Rheumatol. 1996;8(1):34–40.
120. Merkel PA, et al. Cocaine-associated cerebral vasculitis. Semin Arthritis Rheum. 1995;25(3):172–83.

Part IV
Miscellaneous

Chapter 40
Cerebral Venous Sinus Thrombosis

Benjamin Atchie and Don Frei

Cerebral venous sinus thrombosis (CVST) describes focal or diffuse clot formation within the intracranial venous sinuses of the brain. The diagnosis of CVST is rare with a reported rate ranging from 3 to 15 patients per million people per year. As such, there is sparse evidence available to help guide therapeutic strategies. It is therefore important to have a well-developed understanding of the pathophysiology, the myriad of potential underlying causes, and clinical features and imaging features that may be helpful in determining the best treatment options. Additionally, as is true with most other cerebrovascular disorders, cerebral venous sinus thrombosis management is best guided by a multidisciplinary team of providers including neurologists, neurosurgeons, and neuroradiologists, with a treatment plan tailored to the individual patient.

Epidemiology

Recent reports indicate an absolute incidence of CVST as high as 15.7 cases per million people per year [1]. Observationally this is consistent with an increasing trend over the past 3 decades with a rate of 13.2 per million people per year identified in a multicenter study from the Netherlands from 2008 through 2010 and an estimated rate of <10 per million people per year in a retrospective analysis from Saudi Arabia from 1985 through 1994 [2, 3]. Whether this trend reflects a true increase in incidence of CVST or increased awareness and availability of improved noninvasive imaging remains unclear. Though these new reports suggest a significantly higher incidence than the widely accepted 3–4 cases per million people per year, CVST still remains a relatively uncommon diagnosis with the reported ratio of venous to arterial strokes being 1:62.5 [3, 4].

B. Atchie · D. Frei (✉)
Department of Neuro-Interventional Surgery, RIA Neurovascular, Englewood, CO, USA
e-mail: Benjamin.atchie@riaco.com; don.frei@riaco.com

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_40

Patient demographics are not homogenous with regard to the prevalence of CVST development. Unlike many other cerebral vascular diseases, CVST generally affects an otherwise healthy subset of younger adults; however, it is worth noting that this claim is heavily influenced by the incidence of CVST in young females of childbearing age. In fact, females are more likely to be diagnosed than males at a rate of 3:1, a statistic believed to reflect the hypercoagulable state induced by pregnancy and even more so by the frequency of oral contraceptive use [5]. To further emphasize this point, a publication by Ameri and Bousser has reported a uniform age distribution in men presenting with CVST, whereas 61% of women with CVST were between the ages of 20 and 35 [6, 7].

Etiology

There are a number of risk factors associated with the development of CVST. In the majority of patients, approximately 70–80%, an underlying etiology will be found. Most commonly, a hypercoagulable condition is the instigating cause, and this may either be inherited or acquired. Over 100 predisposing hypercoagulable conditions have been identified; a list of common inherited and acquired hypercoagulable conditions is provided (Table 40.1). As stated previously, OCP use is one of, if not, the most frequently encountered risk factors; however, retrospective reviews have demonstrated more than one underlying cause in over a third of all patients presenting with cerebral venous thrombosis [8]. As such, a thorough investigation and a broad hypercoagulability work-up are mandated in every patient in order to uncover any and all predisposing risk factors and guide management.

Other less frequently encountered but well-established etiologies of CVST include head trauma and infection. With regard to head trauma, acute posttraumatic CVST is almost always associated with skull fractures that extend to the sinus or jugular foramen; however, there are case reports describing the delayed development of CVST even in the absence of a fracture [9, 10]. Similarly, CVST produced by local infection is rare in the modern era of antibiotics. When thrombophlebitis of the dural venous sinuses is suspected, the source is from the trans-osseous extension by a local infection, usually of the paranasal sinuses or middle ear, and it is in most cases readily identifiable.

Recently there has been an increasing awareness of the apparent effects of altitude on the development of CVST as well as venous thrombosis in other locations, but the data is limited to isolated case reports. Commonalities between these case reports suggest that the risk for CVST is increased in climbers who reach altitudes of about 5000 meters. Potential causalities include hypobaric hypoxia at extreme altitude, which can precipitate thrombosis through increased blood viscosity due to a secondary polycythemia, as well as an induced hypercoagulable state from increased factor VIIa activity and platelet activation [11–13].

Not to be understated is the risk dehydration may play. There are several reports citing a seasonal variation in the development of CVST, with increased incidence of

Table 40.1 Risk factors for the development of CVST

Hormones
Oral contraceptives
Pregnancy and puerperium
Steroids
Hormone replacement therapy
Thyroid disease
Prothrombotic hematologic disorders
Antithrombin lll deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid and anticardiolipin antibodies
Hyperhomocysteinemia
Systemic conditions
Cancer (local compression or hypercoagulable state)
Local infections (mastoiditis, sinusitis, the neck, etc.)
Nephrotic syndrome
Systemic lupus erythematosus
Behcet's disease
Inflammatory bowel disease
Sarcoidosis
Mechanical
Trauma
Lumbar puncture
Epidural blood patch

CVST during high-temperature months which indirectly implicates dehydration as a contributing factor [14]. Caution is advised however in labeling dehydration as the sole culprit when no other etiologies can be found as there is little direct evidence to support that dehydration alone is enough to potentiate venous thrombus formation [15].

Pathogenesis

Vasogenic edema, venous infarct, and hemorrhage are directly related to cortical cerebral venous thrombosis and impaired venous outflow. Vasogenic edema is a result of the disruption of the blood-brain barrier and leaking of plasma into the intercellular space. This can present clinically with headaches, as a focal neurologic deficit, or with seizure, but is generally considered reversible. If prolonged or severe, the obstruction to venous outflow can eventually lead to irreversible cytotoxic edema as a result of local ischemia leading to cell death. MRI has been demonstrated as a useful tool in differentiating these two, often overlapping, phenomena [16] (Fig. 40.1). Cytotoxic edema in turn can predispose to petechial hemorrhages that can expand, often suddenly, into large lobar hemorrhages.

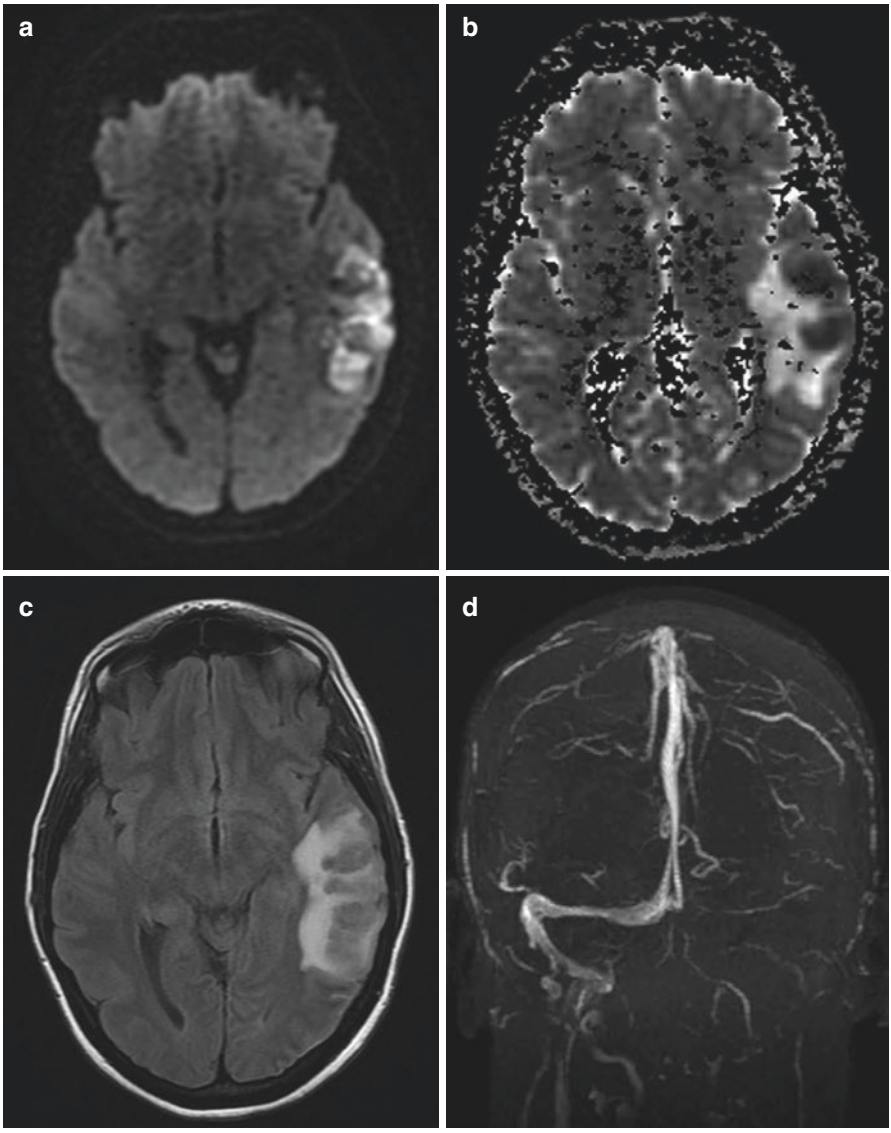


Fig. 40.1 Diffusion-weighted image (**a**) and apparent diffusion coefficient map (**b**) demonstrating restricted diffusion consistent with cytotoxic edema. A T2-FLAIR image (**c**) also shows the extent of surrounding, potentially reversible, vasogenic edema. MR venography (**d**) confirming the presence of a left transverse and sigmoid sinus thrombosis

The role cerebral venous thrombosis plays in the development of intracranial hypertension and dural arteriovenous fistula is less well established. It is believed that the obstruction to venous outflow caused by dural venous sinus thrombosis leads to increased venous pressures which decreases the absorption of cerebral spinal fluid and results in increased intracranial pressures [4]. The resulting venous

hypertension that develops after venous thrombosis is also postulated to cause enlargement of microvascular connections within the dura as the body attempts to reroute the venous flow around the occlusion. Physiologic arteriovenous shunts have been described within the dural walls of the venous sinuses, and as these microvascular connections within the dura enlarge, these shunts may inadvertently capture this rerouted venous flow and develop into large dural AV shunts, further pressurizing the venous system [17].

Clinical Presentation

The clinical presentation of CVST is often varied and nonspecific. It is not entirely surprising then that it often overlooked and commonly misdiagnosed in routine clinical practice. Small retrospective case reports demonstrate a "miss rate" of up to 45% [18].

Headache is the most frequent and often the only symptom at presentation, with an incidence of 75–95% in patients with CVST. These headaches range in severity but generally worsen over the course of a few days eventually becoming severe enough for patients to seek medical attention. Rarely they can present acutely, and occasionally patients report them as "the worst headache of my life," mimicking the presentation of subarachnoid hemorrhage. The source of these headaches is felt to be related to the resultant increased intracranial pressure, and not an inflammatory reaction to the thrombus or occlusion of the sinus itself. This is corroborated by the general inability of the headache to localize to the underlying thrombosed sinus. In fact, there appears to be almost no association between location of the headache and site of sinus thrombosis with the exception of the sigmoid sinus involvement, where 61% of patients with sigmoid sinus thrombosis report occipital headaches and neck pain [19]. Other nonspecific symptoms related to increased intracranial pressure are nausea and vomiting, which are also commonly seen in association with CVST.

Perhaps the most clinically apparent and readily available assessment of elevated intracranial pressure is the presence of papilledema which is observed in nearly a third of cases. Diplopia may also be present in 14% of patients when the intracranial pressure becomes so elevated that it produces downward displacement of the brain stem and stretches the sixth cranial nerves that are tethered in Dorello's canal [20].

Other frequently encountered symptoms that are not related to elevated intracranial pressure are instead related to parenchymal injury secondary to hemorrhage, infarct, or vasogenic edema. Typical manifestations include seizures and focal neurologic deficit which develop in as many as half of all patients. Seizures are usually self-limited and focal, rarely progressing to a more generalized seizure. Focal impairments such as hemiparesis and aphasia are present in a minority of patients but are characteristic and, not surprisingly, correlate to the location of the thrombus. A classically described presentation is that of unilateral hemiparesis that progresses to bilateral hemiparesis over the course of a few days due to the involvement of the sagittal sinus [21]. Deep venous sinus involvement is less common, but patients with thrombosis of the straight sinus or vein of Galen may exhibit symptoms related

to thalamic or basal ganglia injury such as lethargy, disorientation, amnesia, occasionally oculomotor disturbances, and often rapid neurological deterioration.

In the 624 patients included in international study on cerebral vein and dural sinus thrombosis (ISCVT), the superior sagittal sinus was the most commonly involved sinus (62%) followed by the transverse sinus (41–45%) and the straight sinus (18%). Thrombosis of more than one sinus was also frequently encountered (30%).

Diagnosis

Noninvasive imaging is paramount in establishing the diagnosis of CVST. Although a noncontrast head CT is typically the first study performed on patients with symptoms suggestive of CVST, it is insufficient to exclude the diagnosis and may be normal in more than two thirds of patients [22]. When positive, the most common findings include evidence of cerebral edema, hemorrhage, and a hyperdense cortical vein or venous sinus.

Due to wide availability, rapid acquisition, and ease of interpretation, the use of contrast-enhanced CT venography is becoming more widespread. It provides a highly detailed analysis of the cerebral venous system and provides equivalent sensitivity and specificity in making the diagnosis of dural sinus thrombosis, compared to non-enhanced "time-of-flight" MR venography [23] (Fig. 40.2). The same equivalency, however, has not yet been demonstrated in the comparison of CT venography to contrast-enhanced MR venography. Moreover, CT is inherently limited by the use of ionizing radiation and need for iodinated contrast [24].

MRI with the addition of MR venography is generally considered to be the gold standard in noninvasive imaging for the evaluation for CVST. MR venography delivers an accurate depiction of the intracranial dural venous sinuses and cortical veins. In addition to providing precise location and extent of sinus involvement, MRI and MRV can impart other clinically relevant information. Careful analysis can often suggest the age of the thrombus, and MRI can effectively evaluate the effects on the brain parenchyma. Parenchymal brain abnormalities have been identified in as many as 57% of patients with CVST and are more readily identified using MRI than CT. As eluded to previously, MRI provides valuable differentiation between potentially reversible vasogenic edema and irreversible cytotoxic edema using diffusion-weighted techniques. Similar to ischemic infarcts, cytotoxic edema will demonstrate restricted diffusion with decreased ADC values. MRI findings suggesting cytotoxic edema are generally considered a poor prognostic indication [16, 24].

Prognosis

Similar to the varied clinical presentation, there is an unpredictable progression of symptoms and wide diversity in ultimate clinical outcome. For instance, an isolated headache can suddenly worsen deteriorating into coma or death, while a

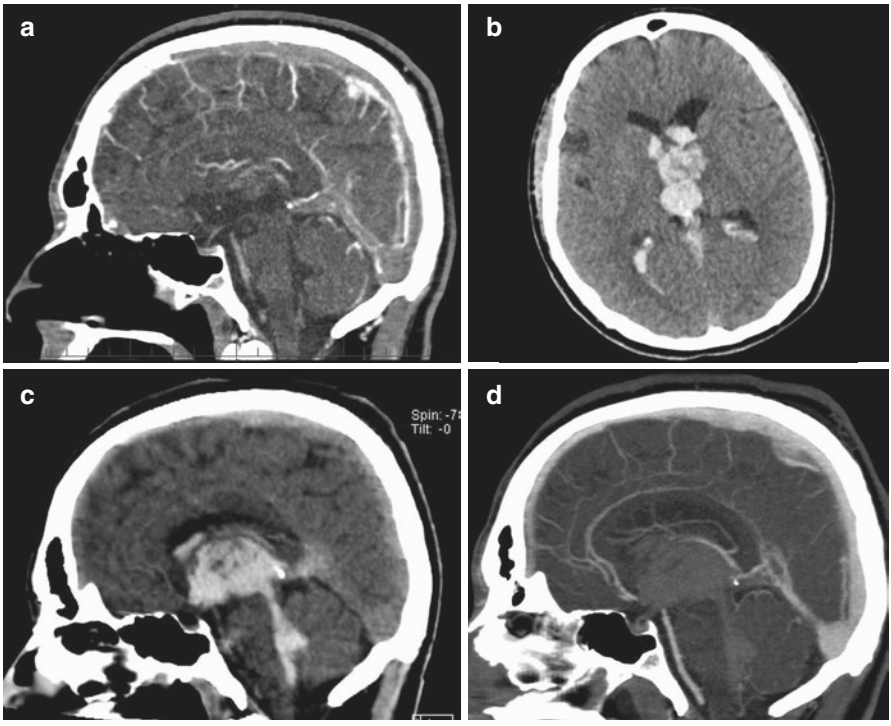


Fig. 40.2 CT venography (**a**) showing extensive thrombosis filling the superior sagittal sinus and straight sinus. Axial (**b**) and sagittal (**c**) noncontrast CT examination revealing delayed thalamic hemorrhage with intraventricular extension despite systemic anticoagulation. CT venography (**d**) showing recanalized dural sinuses post-mechanical thrombectomy

patient presenting with focal neurological deficits may make a prompt and complete recovery [25]. As such, it can be as much a challenge counseling the patient and their families as it is triaging them.

There are a few valuable prognostic indicators. The international study on cerebral vein and dural sinus thrombosis (ISCVT) identified 8 variables predictive of an unfavorable outcome: age >37 years, presenting GCS <9, male gender, ICH on admission, deep venous system thrombosis, any underlying malignancy, or CNS infection. These factors can double, or even triple, the risk of disability or death. It is important to note that despite the importance imagining plays in the diagnosis of CVST, its prognostic value is limited. Clinical improvement is often seen before vessel recanalization, and complete improvement may occur even in the event of persistent dural occlusion [26].

Overall mortality and morbidity rates range from 9% to 44% in small single-center series; however, in ISCVT, the largest multicenter observational study, a death and dependency rate of 13.4% was found and only approached 50% in cases of treatment failure [20]. The diagnosis of CVT generally carries with it a relative favorable outcome for the majority of patients who receive adequate treatment.

Treatment

Initial stabilizing and standard resuscitative measures should be provided to every patient presenting with CVST. Once recognized, a parallel process of symptomatic treatment (normalizing ICPs, seizure control, and pain relief) alongside investigation into predisposing causes should be rapidly initiated. The specific management of CVST, however, can be challenging given the variety of presenting symptoms, unique underlying causes, varying extent of disease, generally poor value prognostic indicators, and the wide range of clinical outcomes.

Prompt administration of anticoagulation therapy is a well-established treatment modality with a large observational dataset and is widely considered to be the current standard of care in most patients presenting with CVT. It should be noted, however, that there are only two available randomized controlled studies investigating the role of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in the treatment of CVT [27, 28]. It also should be pointed out that the study comparing LMWH to placebo did not show a statistical significance benefit of LMWH and the study comparing unfractionated heparin to placebo included only 20 patients. Criticism notwithstanding, these two studies did demonstrate one important point: the safety of anticoagulation in the treatment of CVT even in the setting of intracerebral hemorrhage. Since then a mountain of observational data has supported not only the safety of administering anticoagulation to patients with CVT, with and without ICH, but also a trend toward benefit [29]. This trend is so convincing that the likelihood for any future randomized controlled studies is low as they would probably be deemed unethical.

The rational for anticoagulation revolves mainly around its ability to prevent thrombus propagation and to facilitate recanalization. There are no current recommendations of one agent over the other with regard to UFH vs. LMWH; however, a large meta-analysis evaluating the two medications for treatment of pulmonary thromboembolism has showed a safety benefit with LMWH, which had a lower risk of major hemorrhage (1.2% versus 2.1%) and death (4.5% versus 6.0%) [30]. There is also no specific data to suggest the optimal long-term anticoagulation agent or guide the duration of management, but a typical time course ranges from 3 to 12 months depending on the underlying cause for CVST.

Despite the efficacy of anticoagulation, there are those patients who will deteriorate despite best medical management alone. For these cases, there is an increasing interest in the role endovascular thrombectomy and thrombolysis might play in the treatment of CVST as an adjunctive or stand-alone therapy. The potential advantage of endovascular therapy over systemic therapy alone is the rapid resolution of thrombus resulting in normalization of venous flow and associated decrease in ICPs. How this is achieved varies by institution, and a variety of different techniques have been described.

The most studied endovascular technique is that of direct catheter thrombolysis. This technique is employed through the placement of a microcatheter into the affected sinus and delivery of a thrombolytic agent directly to the thrombus. A meta-

analysis that included 169 patients with CVST treated with local thrombolysis demonstrated potential benefit to critically ill patients [31]. In a small retrospective cohort compiled by Wasay et al., 20 patients who received systemic thrombolysis were compared with 20 patients who received catheter-directed thrombolysis. They showed improved outcomes at discharge in those patients who underwent catheter-directed thrombolysis with urokinase, but at the cost of an increased risk of developing ICH [32].

Other promising techniques including rheolytic and mechanical thrombectomy have since been developed along with the advent of newer endovascular devices. In fact, the only prospective endovascular study included 20 patients, of which the majority [15] were treated with a rheolytic catheter in combination with chemical thrombolysis. Rheolytic catheters use high-velocity saline jets to create a Bernoulli effect for thrombus dissociation and evacuation. In this study, directed thrombolysis/thrombectomy was shown to be effective but again appeared to increase the risk of ICH, possibly related to small vessel injury [33]. Other potentially less traumatic methods include mechanical embolectomy using a Fogarty balloon catheter (Fig. 40.3); (Edwards Lifesciences Corp, Irvine, CA) or the newer Penumbra aspiration catheters (Penumbra Inc., Alameda, California), but information on the use of these devices is limited.

Whichever endovascular method is employed, it is generally considered wise to use it in conjunction with systemic anticoagulation as opposed to stand-alone therapy. There is an ongoing trial, the TOACT (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis) trial, which is directly comparing endovascular therapy alone to systemic anticoagulation with heparin, but it remains to be seen; however, this will affect the current consensus on this particular clinical practice.

Because current data on the efficacy and safety of endovascular therapy consists only of isolated case reports and small case series, it is currently recommended, in a scientific statement by the American Heart Association and American Stroke Association, as treatment reserved for those patients who continue to deteriorate despite the use of anticoagulation or in patients who develop mass effect from venous infarction or ICH that causes intracranial hypertension resistant to standard therapies [29]. Perhaps a more robust algorithm in determining the appropriate use of endovascular treatment has been outlined by Rahman et al., which also takes into consideration the severity of the patient's clinical presentation through the use of the Glasgow Coma Scale (GCS). In their interpretation of the currently available data, patients who present with a GCS score ≤ 8 are strongly considered for immediate catheter-directed thrombolysis/thrombectomy, patients with GCS scores between 9 and 12 may be considered for immediate endovascular treatment, and patients with a GCS >12 may be considered only after a trial of systemic anticoagulation [34]. Of course, as with the use of systemic medical management, neither of these recommendations have been validated with an appropriately designed randomized control trial and should be implemented cautiously.

Despite some interesting historical reports regarding the open surgical management of CVST, surgery has fallen from favor due to the emergence of effective medical and endovascular methods. It remains, however, an integral and critical

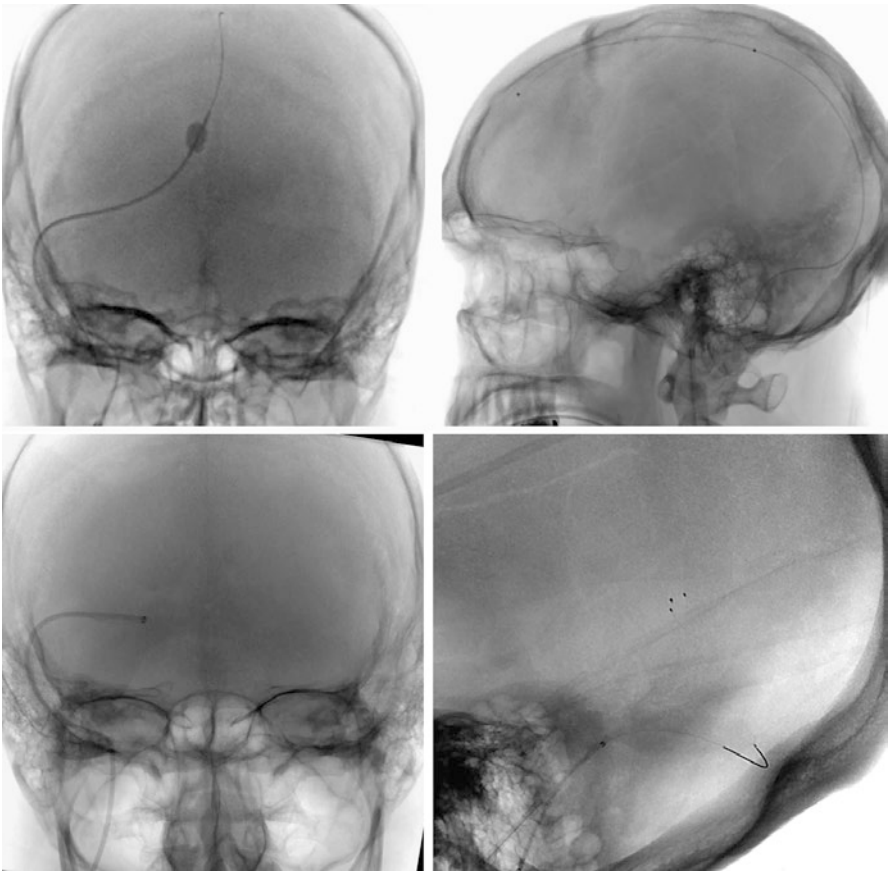


Fig. 40.3 AP fluoroscopic image demonstrating placement of a Fogarty balloon for mechanical thrombectomy of a sagittal sinus and right transverse sinus thrombosis

component in the comprehensive treatment of patients with CVST who require decompressive craniotomies for large venous infarctions with elevated ICPs and for decompression of large hematomas.

Summary

Cerebral venous sinus thrombosis is an uncommon diagnosis effecting as many as 15.7 patients per million people per year. It affects females more common than males on the order of 3:1, and in the majority cases, there is an underlying hypercoagulable state or underlying cause such as trauma or infection.

It has a varied clinical manifestation but common presenting symptoms, such as headache and seizures, which are generally nonspecific. Similarly, the natural his-

tory of cerebral venous sinus thrombosis varies widely from a benign self-limiting process to intracerebral hemorrhage and death. These potentially disastrous outcomes highlight the need for quick, accurate diagnosis and prompt management.

Though the mainstay of therapy for venous sinus thrombosis remains systemic anticoagulation, there is an increasing evidence to support adjunctive care with early endovascular treatment through catheter-directed thrombolysis and/or mechanical thrombectomy.

As with most cerebrovascular disorders, cerebral venous sinus thrombosis management is best guided by a multidisciplinary team of providers including neurologists, neurosurgeons, and neuroradiologists, with a treatment plan tailored to the individual patient.

References

1. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral venous sinus thrombosis incidence is higher than previously thought. Stroke. 2016;47:2180–2.
2. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. Stroke. 2012;43:3375–7.
3. Daif A, et al. Cerebral venous thrombosis in adults. Stroke. 1995;26:1193–5.
4. Bienfait HP, Stam J, Lensing AW, van Hilten JJ. Thrombosis of the cerebral veins and sinuses in 62 patients. Ned Tijdschr Geneeskd. 1995;139:1286–91.
5. Filippidis A, Kapsalaki E, Patramani G, Fountas KN. Cerebral venous sinus thrombosis: review of the demographics, pathophysiology, current diagnosis, and treatment. Neurosurg Focus. 2009;27:E3.
6. Siddiqui FM, Kamal AK. Incidence and epidemiology of cerebral venous thrombosis. JPak Med Assoc. 2006;56:485–7.
7. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin. 1992;10:87–111.
8. Yadegari S, Ghorbani A, Miri SR, Abdollahi M, Rostami M. Clinical features, risk factors, and outcome of cerebral venous thrombosis in Tehran, Iran. J Neurosci Rural Pract. 2016;7:554–8.
9. Delgado Almandoz JE, et al. Prevalence of traumatic dural venous sinus thrombosis in high-risk acute blunt head trauma patients evaluated with multidetector CT venography. Radiology. 2010;255:570–7.
10. Ghuman MS, Salunke P, Sahoo SK, Kaur S. Cerebral venous sinus thrombosis in closed head trauma: a call to look beyond fractures and hematomas! J Emerg Trauma Shock. 2016;9:37–8.
11. Song SY, et al. Cerebral thrombosis at altitude: its pathogenesis and the problems of prevention and treatment. Aviat Space Environ Med. 1986;57:71–6.
12. Bendz B, et al. Acute hypoxia and activation of coagulation. Lancet. 2003;362:997–8.
13. Shrestha P, Basnyat B, Küpper T, van der Giet S. Cerebral venous sinus thrombosis at high altitude. High Alt Med Biol. 2012;13:60–2.
14. Salehi G, Sarraf P, Fatehi F. Cerebral venous sinus thrombosis may follow a seasonal pattern. J Stroke Cerebrovasc Dis. 2016;25:2838–43.
15. Schreijer AJM, Reitsma PH, Cannegieter SC. High hematocrit as a risk factor for venous thrombosis. Cause or innocent bystander? Haematologica. 2010;95:182–4.
16. Yii IYL, Mitchell PJ, Dowling RJ, Yan B. Imaging predictors of clinical deterioration in cerebral venous thrombosis. J Clin Neurosci. 2012;19:1525–9.
17. Chaudhary MY, et al. Dural arteriovenous malformation of the major venous sinuses: an acquired lesion. AJNR Am J Neuroradiol. 1982;3:13–9.
18. Wang X, Sun X, Liu H. Clinical analysis and misdiagnosis of cerebral venous thrombosis. Exp Ther Med. 2012;4:923–7.

19. Wasay M, Kojan S, Dai AI, Bobustuc G, Sheikh Z. Headache in cerebral venous thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain. 2010;11:137–9.
20. Ferro JM, Canhão P, Stam J, Bousser M-G, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35:664–70.
21. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352:1791–8.
22. Linn J, et al. Noncontrast CT in deep cerebral venous thrombosis and sinus thrombosis: comparison of its diagnostic value for both entities. AJNR Am J Neuroradiol. 2009;30:728–35.
23. Ozsvath RR, et al. Cerebral venography: comparison of CT and MR projection venography. AJR Am J Roentgenol. 1997;169:1699–707.
24. Leach JL, Fortuna RB, Jones BV, Gaskill-Shipley MF. Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls. Radiographics. 2006;26:S19–41.
25. Bentley JN, Figueroa RE, Vender JR. From presentation to follow-up: diagnosis and treatment of cerebral venous thrombosis. Neurosurg Focus. 2009;27:E4.
26. Bousser M-G. Cerebral venous thrombosis. Stroke. 1999;30:481–3.
27. Einhäupl KM, et al. Heparin treatment in sinus venous thrombosis. Lancet. 1991;338:597–600.
28. de Bruijn SFTM, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke. 1999;30:484–8.
29. Saposnik G, et al. Diagnosis and management of cerebral venous thrombosis. Stroke. 2011;42:1158–92.
30. van Dongen CJ, van den Belt AG, Prins MH Lensing A. In: Prins MH, editors. Cochrane Database of Systematic Reviews. CD001100. John Wiley & Sons, Ltd; 2004. https://doi.org/10.1002/14651858.CD001100.pub2
31. Canhão P, Falcão F, Ferro JM. Thrombolytics for cerebral sinus thrombosis: a systematic review. Cerebrovasc Dis. 2003;15:159–66.
32. Wasay M, et al. Nonrandomized comparison of local Urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis. Stroke. 2001;32:2310–7.
33. Stam J, Majoie CBLM, van Delden OM, van Lienden KP, Reekers JA. Endovascular thrombectomy and thrombolysis for severe cerebral sinus thrombosis. Stroke. 2008;39:1487–90.
34. Rahman M, Velat GJ, Hoh BL, Mocco J. Direct thrombolysis for cerebral venous sinus thrombosis. Neurosurg Focus. 2009;27:E7.

Chapter 41
Venous Sinus Stenting for Idiopathic Intracranial Hypertension

Jan Vargas, Raymond D. Turner, Aquilla S. Turk, Alejandro M. Spiotta, Jonathan Lena, and M. Imran Chaudry

Idiopathic intracranial hypertension (IIH), historically termed pseudotumor cerebri, is a poorly understood entity characterized by an increase in intracranial pressures (ICP) without a known cause. Patients often present with headaches, visual disturbances and photophobia, occasionally tinnitus, nausea, and vomiting, and most have objective changes in vision. The term *benign* intracranial hypertension is misleading as papilledema may be present in up to 95% of patients, and as the disease progresses, optic atrophy can lead to permanent visual loss in 10% of cases [1–3].

This disease most commonly occurs in females and obese individuals, with reported female to male ratios ranging from 4:1 to 15:1, and the frequency of obesity in patients with IIH range from 71% to 94%. The overall prevalence of IIH in North America has been estimated to be 0.9–1.07/100,000 [4, 5]; however, in women with obesity between 20 and 44 years of age, the prevalence rises to 15–19/100,000 [6, 7].

Pathophysiology

Although the pathogenesis of IIH remains elusive, several hypotheses have been proposed including excess CSF production, reduced CSF absorption, excessive brain water content, increased cerebral venous pressure leading to reduced CSF reabsorption, or altered vasomotor control of the intracranial vascular bed [8, 9]. In a subset of patients, increased intracranial pressure may be due to a focal stenosis in a dural venous sinus. Recent studies have demonstrated that up to 93% of patients

J. Vargas · A. S. Turk · A. M. Spiotta · J. Lena · R. D. Turner · M. I. Chaudry (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: vargasma@musc.edu; Turk@musc.edu; spiotta@musc.edu; turnerrd@musc.edu; chaudry@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_41

with IIH can have focal venous sinus stenosis on MR venography, most commonly in the transverse or sigmoid sinuses [10]. CSF is normally absorbed by the pressure-sensitive arachnoid granulations, and a stenosis of any sinus may lead to impaired venous drainage resulting in decreased cerebral venous drainage, ultimately resulting in cerebral venous hypertension and impaired CSF reabsorption [5, 11–13]. However, dural venous sinus stenosis in the setting of IIH may represent a common presentation of a heterogenous group of underlying pathologies.

The proposed pathogenesis of cerebral venous sinus stenosis can be classified into extrinsic compression and intrinsic stenosis. High intracranial pressures can collapse the compliant or incompetent venous sinuses resulting in an extrinsic compression, which can cause venous congestion and worsening intracranial hypertension leading to a vicious cycle [14]. Another proposed cause is intrinsic stenosis within the sinuses themselves, caused by webs or hypertrophied granulations, which can also lead to venous congestion.

Diagnosis

The diagnosis of IIH is currently defined by [15]:

1. If signs or symptoms are present, they may only reflect those of generalized intracranial hypertension or papilledema.
2. Documented elevated ICP (greater than 25 cm of H_2O) measured in the lateral decubitus position.
3. Normal cerebral spinal fluid (CSF) composition.
4. No evidence of hydrocephalus and mass, structural, or vascular lesion on MRI or contrasted-enhanced CT for typical patients or MRI and MR venography.
5. No other cause of intracranial hypertension.

Treatment

Conservative Management

Many treatment modalities are available for the treatment of IIH. Conservative measures such as decreasing CSF production pharmacologically using acetazolamide or serial lumbar punctures are effective for patients without severe papilledema and intermittent symptoms. In the subset of obese patients with IIH, there is limited evidence that lifestyle modifications to target weight loss or even gastric bypassing can help with symptoms [16, 17].

Surgical Treatment

In patients with progressive visual symptoms, however, more aggressive surgical treatments have traditionally been the mainstay of management to prevent further loss of vision. Surgical options include CSF diversion with either a ventriculoperitoneal or lumboperitoneal shunt and optic nerve sheath fenestration. More recently, dural venous sinus stenting has emerged as a potentially effective treatment for IIH in select patients with radiographic cerebral sinus stenosis and evidence of pressure gradients [5, 18].

CSF Diversion

CSF diversion techniques, consisting of shunting from either the ventricular system or the lumbar cisterns into the peritoneum, atria of the heart, pleura, or even the gall bladder, are usually the first surgical interventions for medically refractive patients with IIH [11, 19–21]. Until recently, CSF flow diversion was the only option available for this patient population. CSF diversion is an invasive procedure with high rates of revisions [22, 23]. Forty-three percent of patients who underwent shunting required at least 1 additional surgery, with an average of 2.78 procedures for each failure and an overall complication rate of 40.5% [18]. As with any invasive procedure, serious complications have been described in the literature including shunt infections, subdural hematomas, and CSF fistulas. Repeated revisions have been associated with an increase in the risk of shunt infections and should be considered carefully when evaluating a patient for surgical candidacy [24–27].

Optic Nerve Sheath Fenestration

ONSF is considered the first-line treatment if patients have visual symptoms with minimal headaches [11, 19, 28–32]. ONSF is a good option in these patients as the procedure rapidly reduces pressure on the optic nerve. Limitations of the procedure include patients presenting with severe headaches as primary symptom and availability of ophthalmologists comfortable performing this technically challenging procedure. Optic nerve sheath fenestration is reportedly more successful in improving papilledema (80%) and visual fields (68%), but less patients reported an improvement in headaches (44%) when compared to CSF diversion. The total average complication rate for ONSF was 18% [18].

Dural Venous Sinus Stenting

Compared to traditional surgical treatments, endovascular stenting of the cerebral venous sinuses provides a minimally invasive treatment. Conventional cerebral venography with venous pressure measurements is performed with no sedation once the diagnosis of IIH is established. This is done by obtaining femoral venous access, navigating a guide catheter into the internal jugular veins, and then using a microcatheter connected to a pressure transducer to measure sinus pressures in the superior sagittal sinus, torcula, and bilateral sigmoid and transverse sinuses. If a pressure gradient of greater than 10 mmHg is detected, the patient is considered a candidate for stent placement and is brought back on an elective basis for stent placement under general anesthesia across the pressure gradient.

Preliminary studies have demonstrated significant success rates with venous sinus stenting, with 83–88% of patients reporting improvement of headaches, 97% of patients demonstrating improvement or resolution of papilledema, and overall complication of 6–7.4% [5, 18]. Given the low complication rate and comparable success rate of venous sinus stenting, there is a growing trend toward stenting as a first-line treatment for IIH.

Some caveats to this modality are worth mentioning, such as the need for antiplatelet therapy. Patients are initiated on full-dose aspirin and an antiplatelet agent such as clopidogrel for 3 months, exposing patients to the risks of antiplatelet therapy, as well as deferring any further elective procedures. Additionally, cerebral angiography and venography, while low risk, have been associated with retroperitoneal hematomas and ischemic events, and an overall complication of 6–7.4% has been reported, with one study citing a 2.9% rate of subdural hematomas following stent placement [5, 18].

The Conduit Technique

All patients undergo diagnostic venography with pressure measurements proximal and distal to the stenosis prior to intervention. All patients are premedicated with dual antiplatelet therapy. This procedure is performed under general anesthesia. Measurements of target sinus diameter and stenosis lengths are made from the initial diagnostic venogram. A 6 or 8 Fr Pinnacle sheath is placed into the right common femoral vein utilizing a Seldinger technique. All patients are heparinized after groin access.

Distal access across the target stenosis can be achieved either with a Neuron Max guide, advanced coaxially over a 6F diagnostic insert (Penumbra Inc., Alameda, CA, USA), or with a triaxial system composed of a 0.038-inch wire, a 5F diagnostic catheter, a 6F Neuron 070 guiding catheter (or 071 Chaperone guide catheter [Microvention Inc., Tustin, CA, USA]), and Neuron Max catheter (Figs. 41.1a and 41.2). Either the Neuron Max or 070 guide catheter is then left across the stenosis (Figs. 41.1b and 41.3). Traversing of the lesion is aided by the tapered design provided by the diagnostic insert and the smooth transition between diagnostic insert

and guide catheter. After achieving distal access, the diagnostic insert and guidewire are removed. With this large stable access platform, a self-expanding carotid stent (Cordis Precise ProRx [Codman Neurovascular, Raynham, MA, USA]) is advanced through the guide catheter across the stenosis (Fig. 41.4). The Neuron Max guide catheter is then gently withdrawn proximally (Figs. 41.1c and 41.5) and the stent delivered using standard technique across the stenosis (Figs. 41.1d and 41.6). Follow-up venography and pressure measurement can be performed to confirm both morphological and hemodynamic resolution of the stenosis. If there is a persistent stenosis, angioplasty was performed. At the conclusion all catheters are removed, and hemostasis is achieved with either a closure device or manual pressure.

The success of the conduit technique relies on the ability to obtain distal access, past the target stenosis. Before the availability of more modern guide catheters, venous sinus stent deployment relied on placement of a guide catheter proximally within the jugular bulb and then attempted to cross the target stenosis with a stent, which would often fail due to the rigidity of the stent. Using the conduit technique, the sharp turns of the venous sinus system are mitigated, allowing rapid and easy deployment of stents.

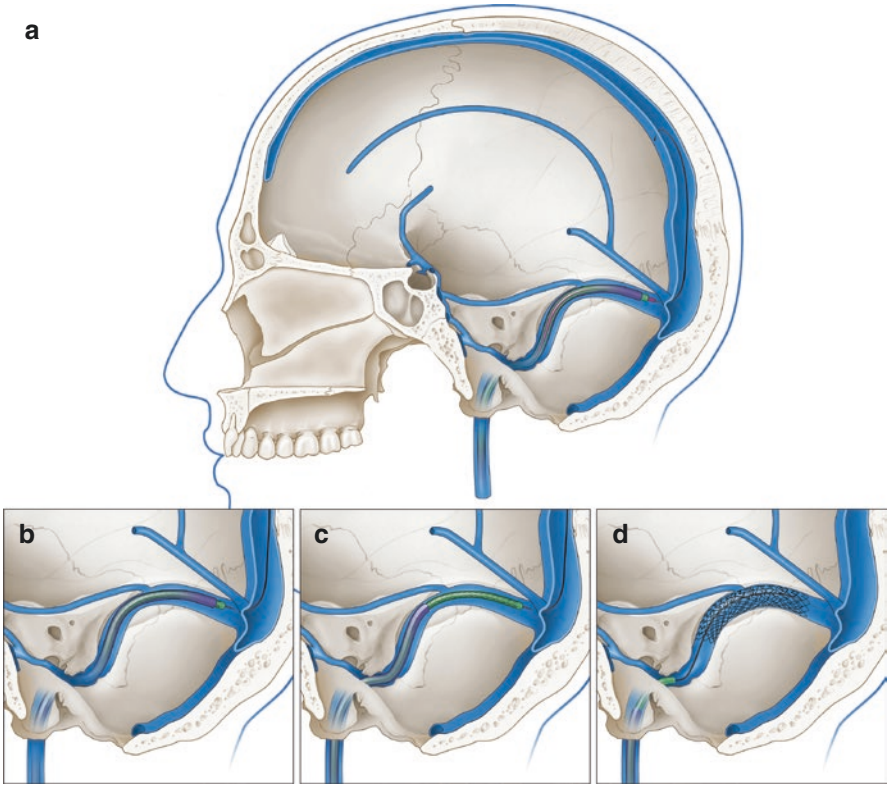


Fig. 41.1 (**a**–**d**) Coaxial or triaxial access across the transverse-sigmoid junction (see also Figs. 41.2, 41.3, 41.5 and 41.6)

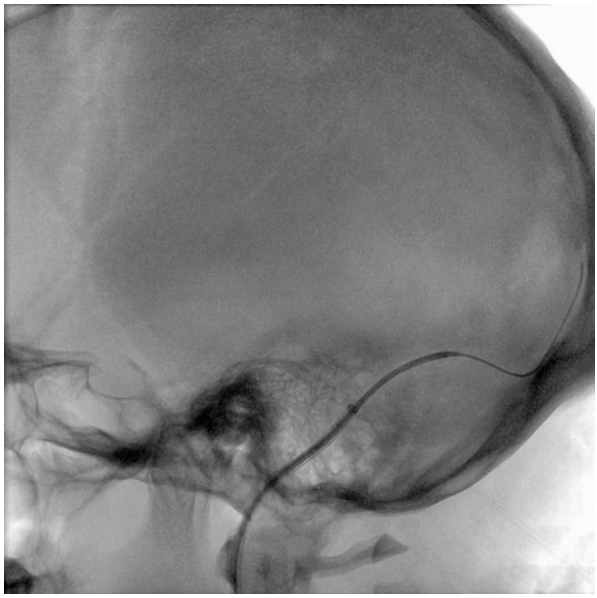


Fig. 41.2 Coaxial or triaxial access across the transverse-sigmoid junction can be achieved with a 6 fr. Neuron Max, 6 fr. Berenstein insert or 6 fr. Neuron Max, 071 Benchmark (or Chaperone), and 5 fr. Diagnostic insert (see Fig. 41.1)

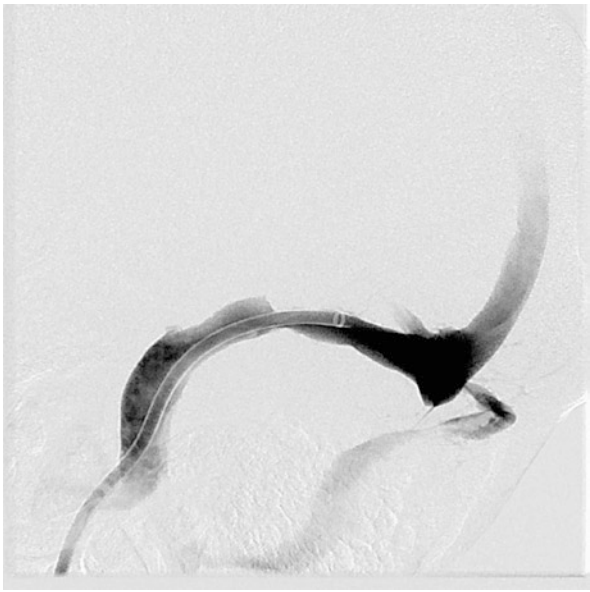


Fig. 41.3 The diagnostic insert is removed leaving a large catheter (either Neuron Max, Benchmark, or Chaperone) across the stenosis to deliver the stent (see Fig. 41.1b)

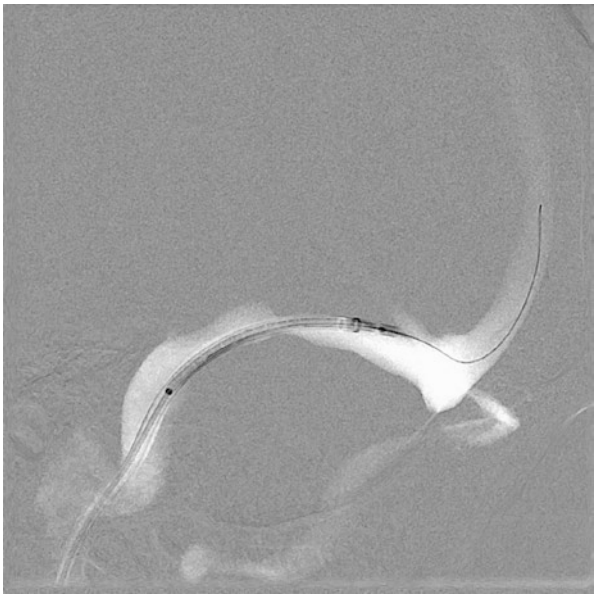


Fig. 41.4 The stent is advanced through the guide catheter across the stenosis

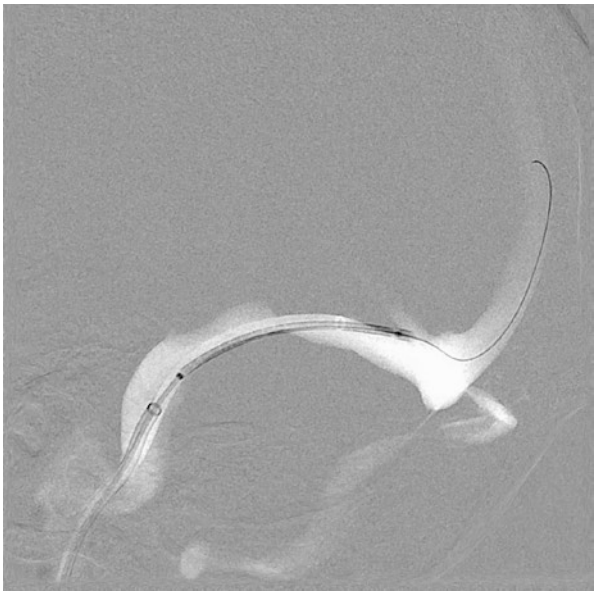


Fig. 41.5 The guide catheter is withdrawn unsheathing the stent across the stenosis (see Fig. 41.1c)

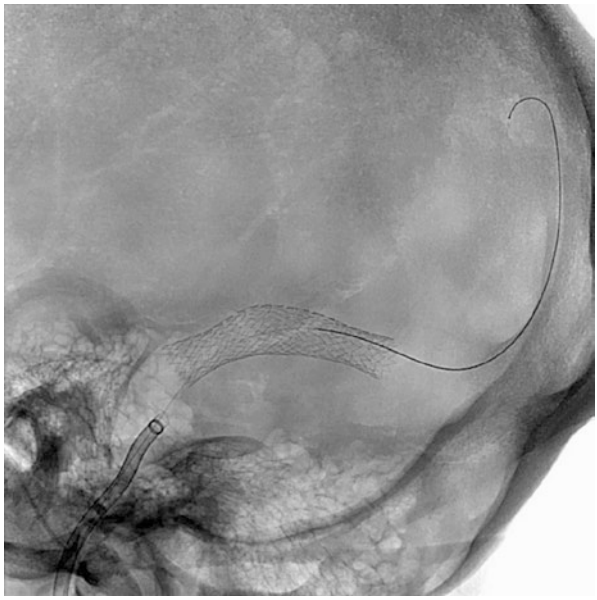


Fig. 41.6 Stent deployed across the stenosis (see Fig. 41.1d)

Follow-Up

Patients should be maintained on antiplatelet therapy for 3 months following stenting. If their symptoms have improved, these can be discontinued. For patients with persistent symptoms, or transient improvement followed by return, repeat venography and pressure measurements can reveal persistent pressure gradients or even new stenoses adjacent to the stented segment warranting re-treatment. Follow-up ophthalmological examinations can reveal improvement in papilledema.

Summary

IIH continues to be a diagnosis of exclusion, with a poorly understood pathogenesis. Despite few advances in the understanding of the causes of IIH, new treatment modalities have evolved with the advent of endovascular stenting that, in select patients, can lead to improvement in symptoms.

References

1. Rowe FJ, Sarkies NJ. Assessment of visual function in idiopathic intracranial hypertension: a prospective study. Eye (Lond). 1998;12(Pt 1):111–8.
2. Orcutt JC, Page NG, Sanders MD. Factors affecting visual loss in benign intracranial hypertension. Ophthalmology. 1984;91(11):1303–12.

3. Corbett JJ, Savino PJ, Thompson HS, et al. Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. Arch Neurol. 1982;39(8):461–74.
4. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. Arch Neurol. 1988;45(8):875–7.
5. Puffer RC, Mustafa W, Lanzino G. Venous sinus stenting for idiopathic intracranial hypertension: a review of the literature. J Neurointerv Surg. 2013;5(5):483–6.
6. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE. Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci. 1993;116(1):18–28.
7. Glueck CJ, Aregawi D, Goldenberg N, Golnik KC, Sieve L, Wang P. Idiopathic intracranial hypertension, polycystic-ovary syndrome, and thrombophilia. J Lab Clin Med. 2005;145(2):72–82.
8. Ball AK, Clarke CE. Idiopathic intracranial hypertension. Lancet Neurol. 2006;5(5):433–42.
9. Bandyopadhyay S. Pseudotumor cerebri. Arch Neurol. 2001;58(10):1699–701.
10. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology. 2003;60(9):1418–24.
11. Galgano MA, Deshaies EM. An update on the management of pseudotumor cerebri. Clin Neurol Neurosurg. 2013;115(3):252–9.
12. Higgins JN, Cousins C, Owler BK, Sarkies N, Pickard JD. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry. 2003;74(12):1662–6.
13. Albuquerque FC, Dashti SR, Hu YC, et al. Intracranial venous sinus stenting for benign intracranial hypertension: clinical indications, technique, and preliminary results. World Neurosurg. 2011;75(5–6):648–52. discussion 592-645
14. Lazzaro MA, Darkhabani Z, Remler BF, et al. Venous sinus pulsatility and the potential role of dural incompetence in idiopathic intracranial hypertension. Neurosurgery. 2012;71(4):877–83.
15. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology. 2002;59(10):1492–5.
16. Handley JD, Baruah BP, Williams DM, Horner M, Barry J, Stephens JW. Bariatric surgery as a treatment for idiopathic intracranial hypertension: a systematic review. Surg Obes Relat Dis. 2015;11(6):1396–403.
17. Fridley J, Foroozan R, Sherman V, Brandt ML, Yoshor D. Bariatric surgery for the treatment of idiopathic intracranial hypertension. J Neurosurg. 2011;114(1):34–9.
18. Satti SR, Leishangthem L, Chaudry MI. Meta-analysis of CSF diversion procedures and dural venous sinus stenting in the setting of medically refractory idiopathic intracranial hypertension. AJNR Am J Neuroradiol. 2015;36(10):1899–904.
19. Burgett RA, Purvin VA, Kawasaki A. Lumboperitoneal shunting for pseudotumor cerebri. Neurology. 1997;49(3):734–9.
20. El-Saadany WF, Farhoud A, Zidan I. Lumboperitoneal shunt for idiopathic intracranial hypertension: patients' selection and outcome. Neurosurg Rev. 2012;35(2):239–43. discussion 243–234
21. Rosenberg ML, Corbett JJ, Smith C, et al. Cerebrospinal fluid diversion procedures in pseudotumor cerebri. Neurology. 1993;43(6):1071–2.
22. Eggenberger ER, Miller NR, Vitale S. Lumboperitoneal shunt for the treatment of pseudotumor cerebri. Neurology. 1996;46(6):1524–30.
23. Sinclair AJ, Kuruvath S, Sen D, Nightingale PG, Burdon MA, Flint G. Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. Cephalalgia. 2011;31(16):1627–33.
24. Johnston I, Besser M, Morgan MK. Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. J Neurosurg. 1988;69(2):195–202.
25. McGirt MJ, Woodworth G, Thomas G, Miller N, Williams M, Rigamonti D. Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes. J Neurosurg. 2004; 101(4):627–32.

26. Abubaker K, Ali Z, Raza K, Bolger C, Rawluk D, O'Brien D. Idiopathic intracranial hypertension: lumboperitoneal shunts versus ventriculoperitoneal shunts – case series and literature review. Br J Neurosurg. 2011;25(1):94–9.
27. Abu-Serieh B, Ghassempour K, Duprez T, Raftopoulos C. Stereotactic ventriculoperitoneal shunting for refractory idiopathic intracranial hypertension. Neurosurgery. 2007;60(6):1039–43. discussion 1043–1034
28. Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2012;83(5):488–94.
29. Feldon SE. Visual outcomes comparing surgical techniques for management of severe idiopathic intracranial hypertension. Neurosurg Focus. 2007;23(5):E6.
30. Kelman SE, Sergott RC, Cioffi GA, Savino PJ, Bosley TM, Elman MJ. Modified optic nerve decompression in patients with functioning lumboperitoneal shunts and progressive visual loss. Ophthalmology. 1991;98(9):1449–53.
31. Sergott RC, Savino PJ, Bosley TM. Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. Arch Ophthalmol. 1988;106(10):1384–90.
32. Brourman ND, Spoor TC, Ramocki JM. Optic nerve sheath decompression for pseudotumor cerebri. Arch Ophthalmol. 1988;106(10):1378–83.

Chapter 42
Microvascular Decompression for Trigeminal Neuralgia and Other Neurovascular Compression Syndromes

Jaime L. Martinez, Stephen R. Lowe, Alexander Vandergrift, and Sunil J. Patel

The most accepted etiology of trigeminal neuralgia is neurovascular compression of the trigeminal nerve root; hence the most definitive cure for trigeminal neuralgia is with microvascular decompression. In this chapter, we describe in detail the anatomy and pathophysiology of trigeminal neuralgia, describe our technique for microvascular decompression, and provide a brief overview of other cranial nerve neurovascular compression syndromes.

Anatomy of the Trigeminal Nerve

The trigeminal nerve (CN V) is the largest cranial nerve, with nuclei extending from the midbrain to the upper cervical spinal cord. It comprises three divisions or branches, one sensory ganglion ("Gasserian" or "semilunar" ganglia), one large sensory root (*portio major*), one motor root (*portio minor*), and four brainstem nuclei. The trigeminal nerve has mixed sensory and motor functions, innervating extensively the skin and mucosae of the head (general somatic afferent), and the muscles derived from the first branchial arch, including the muscles of mastication.

The CN V has four major nuclei in the brainstem. Three sensory nuclei comprise the mesencephalic nucleus (proprioception), the principal sensory nucleus in the pons, and the spinal nuclei (pain and temperature) in the medulla oblongata. The small motor nuclei of CN V are in the rostral pons.

The apparent nerve origin is in the ventrolateral pons. The nerve then occupies the prepontine cistern (this segment is called *plexus triangularis*) and travels anteriorly, and slightly laterally, to pierce the dura (*porus trigeminus*) over the anterior petrous temporal bone and enter Meckel's cave in the middle cranial fossa. Meckel's

J. L. Martinez · S. R. Lowe · A. Vandergrift · S. J. Patel (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: martinezj@musc.edu; lowesr@musc.edu; vandergr@musc.edu; patels@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_42

cave is a space lined by the dura mater that connects the middle and posterior cranial fossae and contains CSF (trigeminal cistern), the sensory and motor roots, ganglia, and proximal portions of the three main divisions of the nerve: the ophthalmic (V1), maxillary (V2), and mandibular (V3).

The spatial somatotopic relationship of the three divisions is maintained in its sensory root or *portio major* [1]; therefore, fibers coming from V1 are rostromedial and from V3 are caudolateral. From the brainstem nuclei, 2nd-order neurons ascend to the ventral posteromedial nucleus of the thalamus (3rd-order neuron) as the trigeminal lemniscus (ventral [crossed] and dorsal [uncrossed] trigeminothalamic tract), and then, via the thalamic radiation, terminate in layers 2 and 4 of the somatosensory cortex (4th-order neuron) in the parietal lobe.

Pathophysiology of Trigeminal Neuralgia

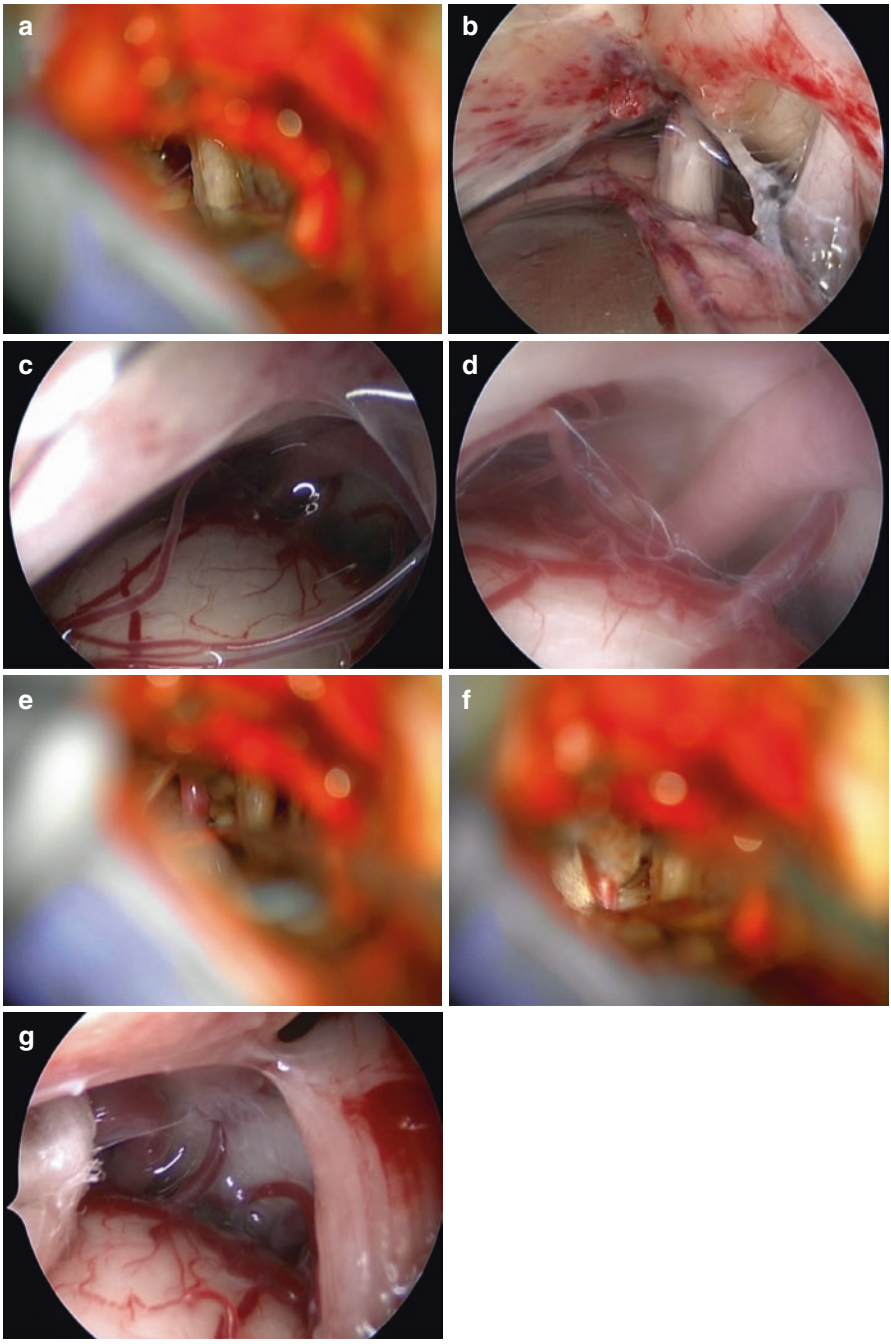
Trigeminal neuralgia (TGN), also known as *tic douloureux*, is an excruciating and disabling facial pain syndrome. The pain in TGN is characterized by recurring bouts of brief unilateral electric shock-like discharges in the distribution of one or more branches of the trigeminal nerve.

TGN is the most common facial pain syndrome and its incidence increases with age. Its annual incidence in the USA is 3.4/100,000 in men and 5.9/100,000 in women [2], and the right side tends to be involved more frequently.

Multiple theories attempt to explain the etiology of trigeminal neuralgia; in general, they can be divided into two main groups: (1) peripheral and (2) central mechanisms.

1. Peripheral: The most widely accepted peripheral mechanism is the neurovascular compression theory. A compressive arterial or venous loop is found in more than 96% of patients with typical trigeminal neuralgia [3, 4]. Compression can occur at any point in the cisternal segment of the trigeminal nerve, between the brainstem and Meckel's cave. The root entry zone or Obersteiner-Redlich zone – where central myelin transitions into peripheral myelin – is particularly vulnerable. The superior cerebellar artery (SCA) is responsible for 88% and the AICA for <25% [4] of cases. The most common intraoperative finding is a rostroventral loop of the superior cerebellar artery (SCA) (Figs. 42.1 and 42.2). As expected

Fig. 42.1 Right-sided microvascular decompression in a patient with trigeminal neuralgia. (**a**) Intraoperative photograph of the right trigeminal nerve. (**b**) Same view with the 0-degree neuroendoscope showing better illumination, wider field, and a more detailed anatomy. The cerebellum is being retracted inferiorly on its superolateral surface to avoid traction injury on cranial nerves VII and VIII. The internal acoustic meatus and VII–VIII cranial nerve complex are seen. It is important to preserve the arachnoidal trabeculae surrounding these nerves. Note the entry of the trigeminal nerve in Meckel's cave. This same corridor can be used to carefully visualize from the foramen magnum to the tentorium. (**c** and **d**) The endoscope is advanced between the tentorium and the trigeminal nerve to reveal the neurovascular conflict, in this case a rostral loop of the superior cerebellar artery. This view is facilitated by the endoscope. (**e**) The SCA loop is removed from under the trigeminal nerve. (**f**) A piece of Teflon felt is placed around the SCA, and the vessel is kept away from the nerve. (**g**) View with the neuro-endoscope showing successful decompression from the root entry zone to Meckel's cave (arrow)


a
b
c
d
e
f
g

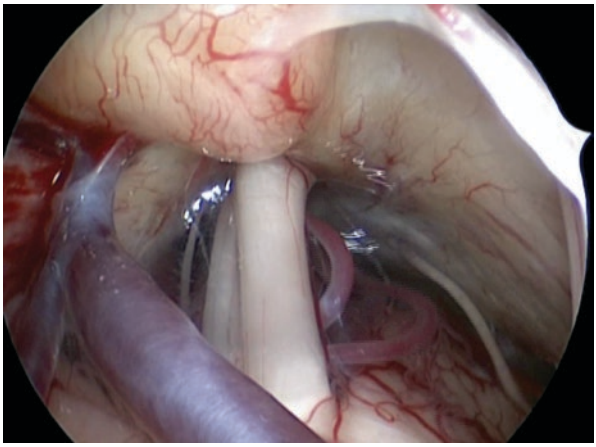


Fig. 42.2 Intraoperative endoscopic view showing a ventral-rostral loop of the superior cerebellar artery under the ipsilateral trigeminal nerve. This is the most commonly encountered neurovascular conflict in trigeminal neuralgia. Note the superior petrosal vein on the left

by the somatotopic arrangement of the fibers in portio major, in most cases (55%), symptoms are transmitted in the territory of V3, and in 32% both V2 and V3 are involved [5]. Venous compression is seen in 8–10% [6] – usually by the transverse pontine vein or the superior petrosal vein or its tributaries, usually near the porus trigeminus. However, it is important to note that not all vascular compression appears to be pathologic. A study using a 3 Tesla MRI found that neurovascular compression of the trigeminal nerve is a common finding, even in asymptomatic individuals [7].

This chronic vascular compression and the pulsatile effect of the vessels on the nerve cause focal demyelination and abnormal remyelination, which result in symptomatic ephaptic neurotransmission. Sensory signals coming from large myelinated sensory Type A fibers are aberrantly transmitted to small nociceptive type C and delta fibers. Therefore, innoxious stimuli such as chewing, teeth brushing, cold, etc. precipitate severe pain attacks.

2. Central: On the other hand, pain from central mechanisms arises from cells in the intra-axial trigeminal nerve pathway secondary to neuronal hyperactivity or focal epileptogenic discharges from these injured cells [8]. These injuries include compression, demyelination, micro-infarction, or infection.

Diagnosis and Classification of Trigeminal Neuralgia

The different treatment modalities for TGN include antiepileptic medications, minimally invasive percutaneous rhizotomies, radiation, and open microneurosurgery. The diagnosis of TGN is clinical, i.e., based on a stereotypical history. According to the International Headache Society [9], the diagnosis of TGN is made if at least three attacks of unilateral pain fulfill the following criteria:

1. No radiation beyond the territory of innervation of the trigeminal nerve
2. Pain with at least three of the following characteristics: (a) recurring pain paroxysms lasting from a fraction of a second to 2 min; (b) severe in intensity; (c) electric shock-like, shooting, stabbing, or sharp quality; and (d) triggered by innocuous stimuli

Burchiel [10] classified patients with trigeminal neuralgia into two types based on predominance of episodic (type I) or constant (type II) pain. Type I patients have a symptomatology more consistent with the "classical" descriptions of trigeminal neuralgia. Most of these patients have an identifiable vascular compression, and, therefore, surgery is very effective, with reported >84% excellent-to-good pain relief [11].

The natural history of trigeminal neuralgia has not been clearly described. The most common progression of symptomatology includes pain attacks becoming more frequent with fewer periods of remission, with a concomitant development of sensory disturbances or dysesthesias. For this reason, it has been postulated that typical trigeminal neuralgia, atypical trigeminal neuralgia, and trigeminal neuropathic pain may represent different degrees of injury to the trigeminal nerve [12]. This might explain why severe nerve damage can often be demonstrated upon exploration of trigeminal nerve in patients with an atypical syndrome.

Differential Diagnosis

Secondary causes of trigeminal neuralgia should be investigated in patients with associated focal neurological deficit, bilateral symptoms, young age, and absence of refractory period in-between attacks. The differential diagnosis of facial pain includes, but is not limited to, temporomandibular joint disease, post-traumatic (invasive dental procedures or fractures) or postherpetic neuralgia, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform attacks with cranial autonomic symptoms (SUNA), paroxysmal hemicrania, atypical facial pain syndrome, and occipital neuralgia.

Treatment of Trigeminal Neuralgia

Most neurovascular compression syndromes are initially treated medically with anticonvulsant medications, and patients usually respond well. First-line medical treatment is generally considered to be a trial of carbamazepine, gabapentin, or both. Clonazepam, baclofen (typically used in combination with a second drug), and phenytoin or fosphenytoin (in acute attacks) can all be tried in patients refractory or intolerant to carbamazepine or gabapentin.

Surgical treatment is considered when pain relief is inadequate from medications or when doses needed for pain relief are causing significant drug toxicity [13]. Surgical modalities are categorized as "destructive" (ablative) or "physiologic" (microvascular decompression). Ablative options are offered in patients who are not good surgical candidates and involve delivering an injury to the nerve's sensory fibers extracranially (peripheral neurectomy) or intracranially (rhizotomies). Rhizotomies of the preganglionic fibers intracranially can be achieved with one of the following: stereotactic radiosurgery of the nerve root or percutaneous procedures through the foramen ovale (radiofrequency ablation, glycerol injection, or balloon compression). Immediate pain relief as high as 87% has been reported in patients undergoing rhizotomies with 50% incidence of recurrence in 6 months in patients receiving their first balloon rhizotomy and 24 months in patients receiving their first glycerol rhizotomy [14]. Other modalities of treatment include motor cortex and peripheral nerve stimulators. Details on the different treatment modalities for trigeminal neuralgia and other neurovascular compression syndromes are not within the scope of this chapter.

Microvascular decompression has become the gold standard treatment for trigeminal neuralgia and other neurovascular compression syndromes. This approach is the least likely to require additional treatment [15]. Excellent surgical results are reported in the neurosurgical literature, with Barker and Jannetta first reporting a 70% rate of pain relief without medication 10 years after microvascular decompression [3]. In that study, the annual risk of pain recurrence was less than 2% at 5 years and less than 1% at 10 years after MVD. More recent series report long-term significant pain relief in 80–100% of patients if properly selected for surgery [16–18].

Other Vascular Compression Syndromes

These include hemifacial spam, glossopharyngeal neuralgia, intermediate neuralgia, disabling tinnitus, disabling positional vertigo, and medically refractory hypertension. A short overview of these syndromes is given in Table 42.1.

Microvascular Decompression

The surgical management of neurovascular compression syndromes, especially trigeminal neuralgia, has evolved tremendously. Initially, surgery for trigeminal neuralgia consisted of either performing a Gasserian ganglionectomy (Hartley and Krausse in 1892) or sectioning the sensory root "portio major" (Cushing and others in 1928) via a middle fossa subtemporal approach [19]. Years later, Dandy described a "cerebellar" posterior fossa suboccipital approach for partial nerve root sectioning, an approach he pioneered to reduce overall complication rates. Employing this

Table 42.1 Other neurovascular compression syndromes

	Hemifacial spasm	Vestibular paroxysmia	Geniculate neuralgia (*nervus intermedius* or nerve of Wrisberg)	Vagoglossopharyngeal neuralgia
Definition and clinical presentation	Involuntary spasms of the muscles of facial expression. Commonly around the orbit	Acute episodes of vertigo with or without tinnitus and hearing loss	Unilateral paroxysmal otalgia and prosopalgia (referred pain to deep viscero-cranial structures such as nasal cavity, palatal region, and orbits)	Severe and sharp pain in the sensory (GSA) distribution of the glossopharyngeal (CN IX) and vagus (CN X) nerves. The CN IX receives the posterior EAM, tragus, posterior 1/3 of the tongue, soft nasopharynx, tonsillar fossa, mastoid, tympanic membrane, and Eustachian tube. The CN X receives the posterior fossa dura; posterior pinna, external acoustic meatus, and external surface of the tympanic membrane (Arnold's nerve); and larynx. Deadly arrhythmias, cardiac arrest, and syncope can also occur
Differential diagnosis [2]	Cerebellopontine angle tumors and trauma	Meniere's, vestibular migraine, benign paroxysmal positional vertigo, and superior semicircular canal dehiscence	Herpetic ganglionitis (Ramsay-Hunt) and *tic convulsive* (geniculate neuralgia + hemifacial spasm)	Trigeminal neuralgia, superior laryngeal and geniculate neuralgia, Eagle's syndrome, and peritonsillar trauma
Compressive vessel [2]	AICA 43%, PICA 31%, VA 23%, and venous 3%. Multivessel 38%	AICA 75% and venous 10%	AICA [3] but also PICA or branches of the VA [4]	PICA 68%, VA 2%, and venous 6%. Multivessel 23%
Relief from microvascular decompression	>90%	One case reported [5]	72–90% [6, 7]	80–90% [8]
Postoperative complications	Facial palsy, hearing loss, dysgeusia, diplopia (CN IV), lower cranial nerves palsy, middle ear effusion, CSF leak, supratentorial SDH, and posterior circulation infarcts [9]	Imbalance, hearing loss, facial palsy, diplopia, etc.	Facial numbness, facial paresis, sensorineural hearing loss, vertigo, lower cranial nerve palsy, chemical meningitis, CSF leak, and wound infection [4]	Lower cranial nerve palsies, dysphagia, hoarseness, transient hypertension, and CSF leak

"relatively bloodless" operation, Dandy also inadvertently performed the first microvascular decompression by mobilizing arterial loops in contiguity to the nerve that was obstructing his view. He later observed alterations in the shape of the nerve at the point of vascular compression. Based on these direct intraoperative observations, he is credited for being the first to theorize that vascular compression of the trigeminal nerve could be the cause of trigeminal neuralgia. In the 1950s, Gardner at the Cleveland Clinic also hypothesized that gentle compression on the nerve is the pathophysiological mechanism responsible for the pain paroxysms in trigeminal neuralgia [19]. Finally, the microsurgical technique utilized today was developed and perfected by Jannetta, who confirmed this previously mentioned vascular compression in most cases of trigeminal neuralgia with the aid of magnification provided by the neurosurgical microscope.

Preoperative Workup

Neuroimaging is obtained in all patients. Thin-cut high-resolution 3D T2-weighted steady-state free precession sequences are obtained to assess the cisternal segment of the nerve and characterize the neurovascular conflict. In patients with classic medically refractory neuralgia, we advocate for posterior fossa exploration even if no apparent neurovascular conflict is noted in imaging. Very importantly, a volumetric T1-weighted sequence in combination with a TOF MR angiography helps rule out other pathologies, such as extra-axial tumors, vascular malformations, and aneurysms, and also demyelinating plaques [6]. The secondary causes of trigeminal neuralgia should be thoroughly investigated in all patients but especially in those with any associated neurological deficit, bilateral symptoms, young age, and absence of refractory or pain-free period.

Microvascular Decompression Technique

After general anesthesia is induced and the patient is intubated, the body is securely positioned in lateral decubitus using an inflatable bean bag with all pressure points padded in the customary way including the use of an axillary roll. Prior to securing the head to the table with a head holder (we use the Sugita head holder, Mizuho), the head of the patient is slightly rotated to the contralateral shoulder, and the neck is slightly flexed so that the mastoid process is parallel to the floor. It is important to position and tape the ipsilateral shoulder in such a fashion as not to obstruct the movements of the surgeon's hands. Preoperative lumbar drainage is not typically used in our institution but is an acceptable option. Others have described a supine position of the body, back elevated 30 degrees, with the head turned to the contralateral side, and secured in slightly flexed position.

Intraoperative Monitoring

Intraoperative neurophysiologic monitoring is useful in some of the procedures and not utilized for all of the syndromes.

Brainstem auditory evoked responses (BAER) can be used in all of the procedures to monitor for stretch injury to the cochlear nerve from direct manipulation or retraction of the cerebellum.

Vocal cord EMGs are useful when decompressing the lower cranial nerves and medulla. We monitor the vocal cord electromyogram with a nerve integrity monitor system (NIMS, Medtronics).

Facial EMGs are used primarily in cases of hemifacial spasm. The zygomatic branch is stimulated at baseline to look for pathologic responses – after-potentials (from the orbicularis oculi) or lateral spread (from the orbicularis oris). Post-decompression recordings are used to determine the need for further decompression if the pathologic responses do not resolve. Discussion with anesthesiology is important to ensure no long-acting muscle relaxation is used at the time of induction.

Any change in neuromonitoring parameters should prompt a quick response from the surgeon by unlocking and loosening the cerebellar retraction, repositioning the blades, draining CSF, irrigating, or decompressing an expanding hematoma.

Procedure

A point 3 cm posterior to the external acoustic meatus (EAM) in females and 3.5 cm in males is marked (Fig. 42.3). We center our incision at this point in all cases. For aesthetic purposes, we shave only what is necessary for the incision (usually no more than 1 cm behind the hairline). Additionally, the individual osseous and muscular anatomy is studied and major landmarks identified and marked. These include the tip of the mastoid and two very important lines (Fig. 42.3). The first line is measured from the root of the zygomatic process to the inion, across the EAM. The second line is measured perpendicular to the previous line and extends upward from the digastric notch. The point of intersection of these two lines generally correlates to the junction of the transverse and sigmoid sinuses. Our craniectomy is centered slightly caudal and posterior to this point for trigeminal root exposures. For the lower cranial nerves and facial and vestibulocochlear root exposures, the incision is made along the perpendicular line going up from the palpable digastric grove. Frameless neuronavigation can also be used to confirm the location of the major dural sinuses. The superior nuchal line, which usually corresponds to the transverse sinus, and the asterion, which usually corresponds to the transverse-sigmoid sinus junction, can also be used as landmarks.

A small incision is made, oriented obliquely down for decompressing the trigeminal nerve and vertically for decompressing the facial and lower cranial nerves. The scalp and musculature are dissected down using monopolar electrocautery, and

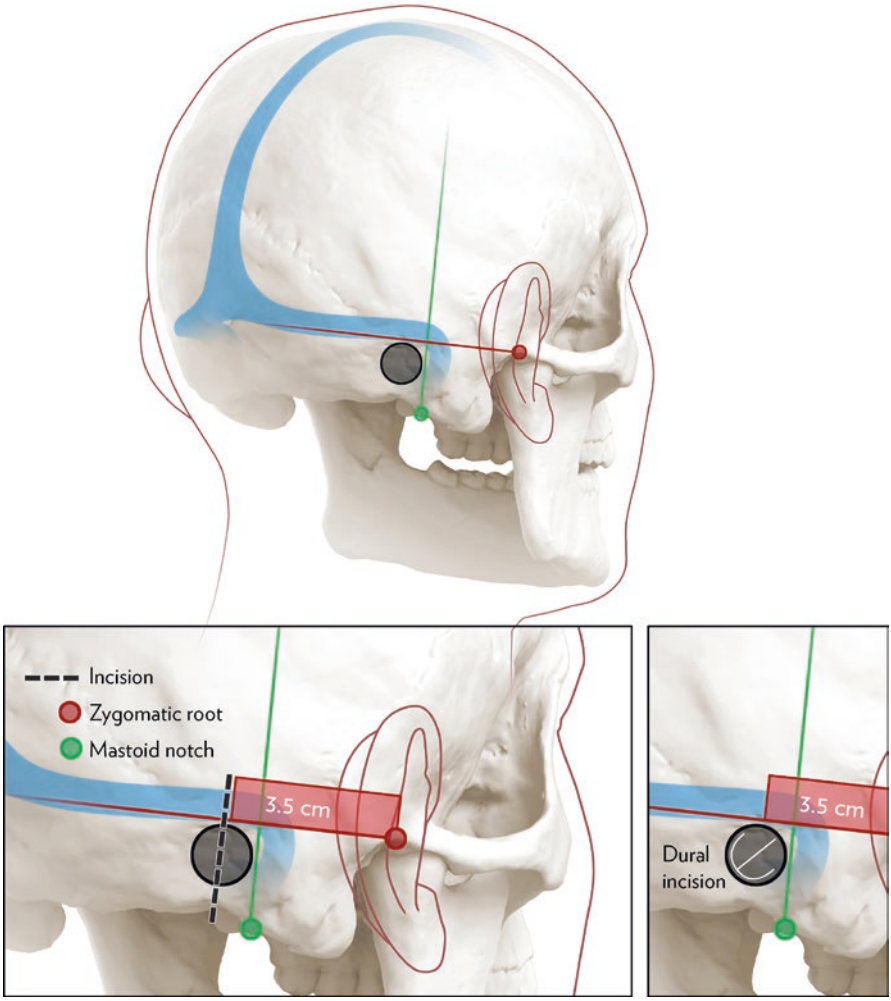


Fig. 42.3 *Upper*: The incision is made 3 cm posterior to the external acoustic meatus (EAM) in females and 3.5 cm in males. The transverse-sigmoid sinus junction is usually located at the point of intersection of two important reference lines. The first line (in red) is measured from the root of the zygomatic process to the inion, across the EAM. The second line (in green) is measured perpendicular to the previous line and extends upward from the digastric notch of the mastoid process. The craniectomy (*bottom left*) is made just caudal and posterior to this intersection when decompressing the trigeminal, facial, and vestibulocochlear nerves and more inferiorly when decompressing the lower cranial nerves and medulla. Once complete hemostasis is achieved, the dura is opened in "C" fashion inferior to the transverse sinus and posterior to the sigmoid sinus, and a T incision made across toward the transverse-sigmoid junction (*bottom right*)

a self-retaining retractor is placed. Care is taken to preserve the greater occipital, lesser occipital, and greater auricular nerves, given that injury to these nerves is the major cause for postoperative pain [20]. These nerves are not always easy to preserve and sometimes require proper recognition and transection to avoid partial

injury and a neuritis. The craniectomy is done slightly posteriorly and inferiorly to the junction of the sigmoid and transverse sinuses for trigeminal neuralgia and more inferiorly for decompression of more lower cranial nerves. A high-speed drill is used initially. A dissector is used to carefully separate the endosteal layer of the dura and dural sinuses from the bone, and the craniectomy is expanded using a Kerrison rongeur. For the trigeminal nerve, the craniectomy is extended as far as the margins of the junction of the transverse and sigmoid sinuses prior to opening the dura. For the lower cranial nerve explorations, the craniectomy is extended anteriorly to the posterior margin of the sigmoid sinus. All exposed mastoid air cells are completely filled with bone wax. Occasionally exposed emissary veins may be either cauterized with bipolar electrocautery or sealed with wax or oxidized cellulose or absorbable gelatin sponge. Profuse bleeding may occur with exposure of an emissary vein, and the surgeon should be prepared for this possibility. Complete hemostasis must be obtained before the dura is opened.

Prior to any dural opening, the anesthesiologist should be reminded during this approach to be sure that the end-tidal PCO2 is less than 35 mm Hg, with the head elevated above the heart.

The dura is opened in "C" fashion inferior to the transverse sinus and medial to the sigmoid sinus, and a T incision made across toward the transverse-sigmoid junction (Fig. 42.3). The dural edges are tacked up, and cerebrospinal fluid is slowly drained from under tentorium with very gentle traction on the cerebellum to achieve cerebellar relaxation. It is essential to patiently release cerebrospinal fluid early on to allow for easier retraction of the cerebellum. Sterilely draped operative microscope is then used for the rest of the operation. A malleable retractor is used to very gently inferiorly retract the superior surface of the cerebellum to visualize the tentorial edge and arachnoid. This arachnoid is then carefully opened sharply under increased magnification being mindful of cranial nerve IV – which in some cases could be mistaken for a thick arachnoid trabecula. Additional release of CSF allows for further relaxation of the cerebellum and better visualization of the petrosal vein and tributaries and ultimately the trigeminal nerve root. Patience and careful use of retraction must be exercised to avoid causing CN VIII traction or avulsion of the petrosal vein and tributaries (usually located in the path of the dissection at the tentorial-petrosal angle) or occasional veins draining into the tentorium. The superior petrosal vein and its tributaries (Figs. 42.4 and 42.5) must be visualized carefully as early as possible and most often may need to be cauterized and transected for best visualization of the medially located trigeminal root. Its tributaries often include the trigeminal vein, vein of the cerebellopontine fissure, pontotrigeminal vein, anterolateral marginal vein, and vein of the middle cerebellar peduncle. These veins can sometimes independently drain into the superior petrosal sinus in the petro-tentorial angle. It is for this reason also that the blade of the retractor should be placed initially laterally along the superior cerebellar surface parallel the tentorium. Then the blade of the retractor is repositioned more obliquely on the superolateral surface of the cerebellum which creates a nice corridor toward the trigeminal nerve. The arachnoid here is also dissected exposing the entire root of the trigeminal nerve. Once the trigeminal root is exposed and in view (Fig. 42.1a), further dissection of the arachnoid over the VII/VIII nerve complex should be avoided as much as

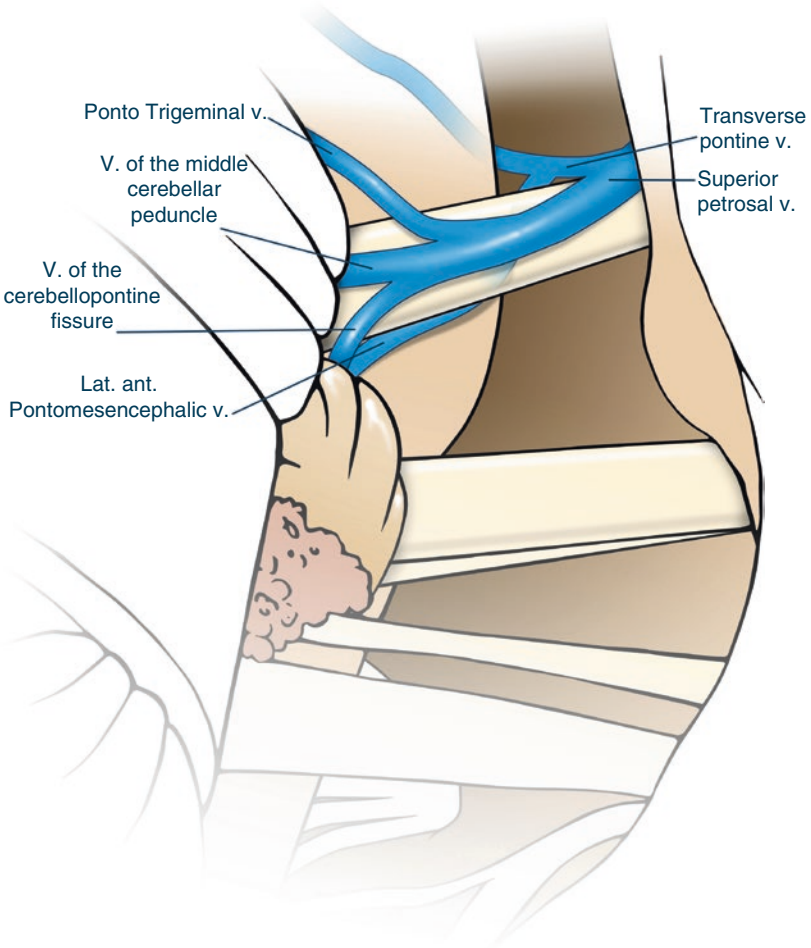


Fig. 42.4 This is an illustration of the right superior petrosal vein and its main tributaries in relationship with the trigeminal nerve. The tentorium was removed

possible to avoid either direct injury or traction on them. Frequently fixed retraction is no longer needed at this point often with the cerebellum relaxed with additional CSF removal.

Neurovascular compression can occur at any point along the nerve – from its root entry zone to Meckel's cave. The superior cerebellar artery (SCA) is the most common cause of neurovascular compression in trigeminal neuralgia (Fig. 42.2). The second segment of the SCA (lateral pontomesencephalic segment) bifurcates in the ambient cistern under the trochlear nerve (CN IV) and loops down near the trigeminal nerve root entry zone [21]. In trigeminal neuralgia, this vessel is usually found looped under the nerve (Figs. 42.1 and 42.2), and treatment consists of carefully mobilizing the SCA loop from under the nerve and

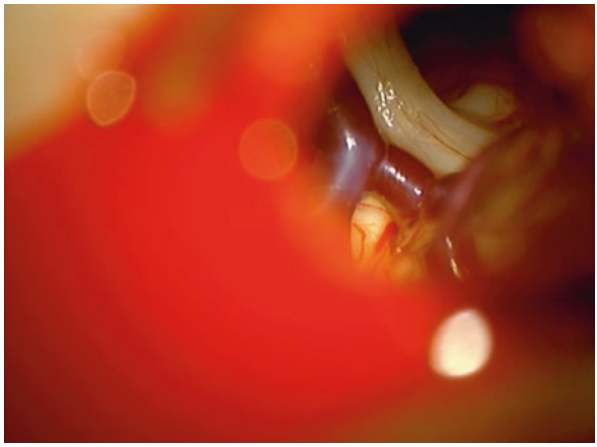


Fig. 42.5 Intraoperative picture illustrating a case of TGN from venous compression. Note the right trigeminal nerve being compressed by the superior petrosal vein and the vein of the cerebellopontine fissure

placing a piece of shredded Teflon felt to tuck the artery away from the nerve (Fig. 42.1). It is our experience that it is best to avoid any contact of the Teflon wool with the nerve root itself (Fig. 42.1g). The offending vessel can also be transpositioned away, in a sling fashion, from the nerve by using sutures [22] or surgical adhesive. The nerve is again inspected thoroughly to make sure there are no other compressive arteries or veins and that the offending vessel has been successfully mobilized.

Another vessel that could be found compressing the trigeminal nerve is the anterior inferior cerebellar artery (AICA). The lateral pontine segment of the AICA travels through the cerebellopontine angle above, below, or in-between the facial and vestibulocochlear nerves. This vessel can loop up and compress the nerve inferiorly (caudally). Less common vascular root compression can be from elongated dolichoectatic vertebral arteries, basilar artery, or both –that typically requires transposition of the arteries toward the clivus. Rarely observed vessels compressing the trigeminal root include pontine arterioles, aneurysms, or vascular malformations. At the time of surgery, it is important to carefully inspect the entire length of the nerve for any of these offending entities under microscopic magnification or using the neuro-endoscope.

A 0 or 30 degrees neuro-endoscope can be used to inspect the trigeminal nerve from the root entry zone to Meckel's cave for compressive vessels when the neurovascular conflict is not obvious (Fig. 42.1) and, at the end of the case, to verify that the nerve has been successfully decompressed.

Venous compression of the trigeminal nerve may also be encountered especially from one of the branches of the petrosal. Classically, the anatomical nomination of posterior fossa veins has been particularly complex. Matsushima and Rhoton [23] divided these veins in four groups: (1) superficial, (2) deep, (3) brainstem veins, and (4) bridging veins or major draining groups. Cerebellopontine angle and rostral pontine veins relevant for this procedure include mostly veins draining into the superior petrosal vein (Fig. 42.4), which then drains into the superior petrosal sinus. Compressive veins can either be bipolar-electrocoagulated and divided if small or

transpositioned if large or if in opposition to the brainstem to avoid complications associated with venous sacrifice – which are rare but can occur in ~ 4.8% [24]. Also keep in mind that it is very important to minimize nerve manipulation to reduce postoperative dysesthesias.

The technique for decompressing the lower cranial nerves is similar. The only variation is the direction of the incision, which is done vertically to allow easier muscle retraction, and obviously, the craniectomy is done more inferiorly.

Once the nerve is decompressed, the subarachnoid cistern is thoroughly irrigated with antibiotic solution and complete hemostasis achieved. The dura is closed in watertight fashion whenever possible. Synthetic dural substitute is layed on top of the durotomy and fibrin glue is applied. Any exposed mastoid air cells should be re-waxed. Bone dust and chips, preserved during the craniectomy portion of the procedure, are packed in a sheet of Surgicel and packed in the craniectomy defect. Burr hole cover is placed on top. The wound is closed anatomically, with attention to watertight musculofascial and skin closure.

Postoperatively, patients are monitored in the stepdown unit overnight and discharged home the next day. If the patient is on carbamazepine or other pharmacotherapy, these are slowly weaned off depending on symptom relief.

Outcomes and Complications

In experienced hands, microvascular decompression surgery is safe and effective, with mortality rates of <0.5% [25] and recurrence rates of 3–15.9% [15, 18] for trigeminal neuralgia. Despite being a safe and effective neurosurgical intervention, there are risks associated with all microvascular decompression surgeries for cranial nerve and brainstem compression hyperactivity syndromes. Procedure-associated risks comprise the standard complications of posterior fossa craniotomies such as cerebrospinal fluid leakage in up to 7% of cases, meningitis and wound infection, pontocerebellar edema, and supratentorial or posterior fossa hematoma and complications directly associated with neurovascular manipulation such as arterial or venous infarction and cranial neuropathies. The most frequent cranial neuropathies include facial numbness in around 4% of the patients, hearing deficits from cochlear nerve retraction while retracting the cerebellum in ~ 10% [26], and diplopia from trochlear nerve injury (usually transient). See Table 42.1 for complications of MVD in the other compression neuropathies.

Conclusions

Trigeminal neuralgia is, and has been historically, one of the most painful illnesses in medicine. Microvascular decompression surgery, done by experienced and caring hands, has proven to be safe and effective in attaining a complete and

definitive relief. Given its good outcomes, this elegant procedure is one of the most rewarding neurosurgical operations. As emphasized here, microvascular decompression is also highly effective for other neurovascular compression syndromes. As a final note, careful patient selection, profound anatomical knowledge, and diligent review of the patient's neuroimaging in preparation for the case are key.

References

1. Jannetta PJ, McLaughlin MR, Casey KF. Technique of microvascular decompression. Technical note. Neurosurg Focus. 2005;18(5):E5.
2. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ Clin Evid. 2014:1207. PMID: 25299564.
3. Barker FG 2nd, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med. 1996;334(17):1077–83.
4. Sindou M, Howeidy T, Acevedo G. Anatomical observations during microvascular decompression for idiopathic trigeminal neuralgia (with correlations between topography of pain and site of the neurovascular conflict). Prospective study in a series of 579 patients. Acta Neurochir. 2002;144(1):1–12. discussion 12–3.
5. Bangash TH. Trigeminal neuralgia: frequency of occurrence in different nerve branches. Anesth Pain Med. 2011;1(2):70–2.
6. Donahue JH, Ornan DA, Mukherjee S. Imaging of vascular compression syndromes. Radiol Clin N Am. 2017;55(1):123–38.
7. Peker S, Dincer A, Necmettin Pamir M. Vascular compression of the trigeminal nerve is a frequent finding in asymptomatic individuals: 3-T MR imaging of 200 trigeminal nerves using 3D CISS sequences. Acta Neurochir. 2009;151(9):1081–8.
8. Peker S, Sirin A. Primary trigeminal neuralgia and the role of pars oralis of the spinal trigeminal nucleus. Med Hypotheses. 2017;100:15–8.
9. Headache Classification Committee of the International Headache, S. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808.
10. Burchiel KJ. A new classification for facial pain. Neurosurgery. 2003;53(5):1164–6. discussion 1166–7.
11. Eller JL, Raslan AM, Burchiel KJ. Trigeminal neuralgia: definition and classification. Neurosurg Focus. 2005;18(5):E3.
12. Burchiel KJ, Slavin KV. On the natural history of trigeminal neuralgia. Neurosurgery. 2000;46(1):152–4. discussion 154–5.
13. Cohen J. Role of the neurologist in the evaluation and treatment of patients with trigeminal neuralgia. Neurosurg Focus. 2005;18(5):E2.
14. Kouzounias K, et al. Comparison of percutaneous balloon compression and glycerol rhizotomy for the treatment of trigeminal neuralgia. J Neurosurg. 2010;113(3):486–92.
15. Hitchon PW, et al. Options in treating trigeminal neuralgia: experience with 195 patients. Clin Neurol Neurosurg. 2016;149:166–70.
16. Tyler-Kabara EC, et al. Predictors of outcome in surgically managed patients with typical and atypical trigeminal neuralgia: comparison of results following microvascular decompression. J Neurosurg. 2002;96(3):527–31.
17. Meybodi AT, et al. Microvascular decompression for trigeminal neuralgia using the 'stitched sling retraction' technique in recurrent cases after previous microvascular decompression. Acta Neurochir. 2014;156(6):1181–7. discussion 1187.

18. Berger I, et al. Microvascular decompression versus stereotactic radiosurgery for trigeminal neuralgia: a decision analysis. Cureus. 2017;9(1):e1000.
19. Patel SK, Liu JK. Overview and history of trigeminal neuralgia. Neurosurg Clin N Am. 2016;27(3):265–76.
20. Tomasello F, et al. Microvascular decompression for trigeminal neuralgia: technical refinement for complication avoidance. World Neurosurg. 2016;94:26–31.
21. Rhoton AL Jr. The cerebellar arteries. Neurosurgery. 2000;47(3 Suppl):S29–68.
22. Masuoka J, et al. Outcome of microvascular decompression for trigeminal neuralgia treated with the stitched sling retraction technique. Neurosurg Rev. 2015;38(2):361–5. discussion 365.
23. Matsushima T, et al. Microsurgical anatomy of the veins of the posterior fossa. J Neurosurg. 1983;59(1):63–105.
24. Liebelt BD, et al. Superior petrosal vein sacrifice during microvascular decompression: perioperative complication rates and comparison to venous preservation. World Neurosurg. 2017;104:788–94.
25. Zakrzewska JM, Coakham HB. Microvascular decompression for trigeminal neuralgia: update. Curr Opin Neurol. 2012;25(3):296–301.
26. Li N, et al. Correlation between cerebellar retraction and hearing loss after microvascular decompression for Hemifacial spasm: a prospective study. World Neurosurg. 2017;102:97–101.

Chapter 43
Sickle Cell Disease: Considerations for the Cerebrovascular Neurosurgeon

Stephen R. Lowe, Mohammed Alshareef, Julie Kanter, and Alejandro M. Spiotta

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy first described in 1915 by James Herrick characterized by anemia, vaso-occlusive crises, autosplenectomy, and susceptibility to infection. It is a result of a single transversion mutation (adenosine to thymine), wherein glutamic acid is replaced by valine at the sixth position in the beta globin subunit of hemoglobin (HbS) [1]. Non-affected hemoglobin is soluble within the intracellular milieu, allowing red blood cells to maintain their flexible structural integrity. Affected hemoglobin, however, will polymerize into an insoluble precipitate when exposed to certain stressors such as hypoxia or dehydration, resulting in a process of red blood cell morphologic change commonly referred to as "sickling." Sickling can occur when erythrocytes pass through the capillaries, where oxygen saturation decreases, resulting in the alteration of the hemoglobin quaternary conformation, yielding the characteristic crescent morphology of affected RBCs [2]. In addition to this rigid structure of erythrocytes, studies indicate that sickled RBCs exhibit an affinity to vascular endothelium which promotes clot formation, ultimately ensuing vaso-occlusive crises [3].

A normal HbA molecule contains four globin subunits, two alpha and two beta, with interactions dictated by hydrogen and covalent bonds between the side chains of the amino acids within the subunits. These molecules exist in both oxygenated and deoxygenated states. Oxygen loading and unloading is dependent on each of the four molecules and relies upon the tetramer configuration of heme and the globin subunits in the physiologic mechanism, cooperativity, or heme-heme interaction. Once an oxygen molecule is loaded to a globin molecule, the configuration of the remaining

S. R. Lowe · M. Alshareef · A. M. Spiotta (✉)
Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
e-mail: lowesr@musc.edu; alsharee@musc.edu; spiotta@musc.edu

J. Kanter
Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA
e-mail: kanter@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_43

globin molecules is transformed to increase the affinity for binding oxygen. The reverse process occurs once an oxygen molecule is released, prompting reconfiguration and release of all the oxygen molecules within the hemoglobin tetramer [2].

Unaffected human hemoglobin undergoes numerous transformations during the progression of life. All forms of hemoglobin are comprised of four subunits that polymerize into a tetramer. In the adult form, two alpha (α) globin chains are paired with two other globin chains – β (Hb A), δ (Hb A_2), or γ (Hb F). In the intrauterine portion of development, embryonic hemoglobin is the primary form of the protein, where zeta (ζ) chains replace the alpha chains and are paired with epsilon (ε) chains. Affected infants are typically asymptomatic for the first few weeks of life and only begin to display signs of SCD as HbF is replaced by HbS. HbF concentration in SCD patients ranges from 2% to 20% as a compensatory mechanism. HbF acts to inhibit polymerization and therefore is resistant to sickling and improves longevity of erythrocytes in circulation. Levels of HbF cells have been shown to be inversely proportional to clinical severity of SCD [2].

Genetics

SCD is a heritable hemoglobinopathy that is transmitted through an autosomally recessive pattern. The mutation is a single nucleotide polymorphism that results in the transversion of adenosine to thymine at 11p15.5 on the short arm of chromosome 11. During translation, this mutation results in a valine being placed at the sixth amino acid position of the beta globin subunit in hemoglobin. Individuals with sickle cell disease genotypically possess two recessive alleles and express a phenotype of entirely sickled hemoglobin (HbSS). Carriers of the condition inherit one normal allele and one variant allele; this will result in sickle cell trait (HbAS).

Epidemiology

SCD is believed to have originated in regions of the world where malaria is endemic. It has subsequently spread through human migration. The heterozygotic genotype of SCD provides a survival advantage against malaria, particularly against *Plasmodium falciparum*. Five distinct haplotypes of HbS have been found around the world, which supports the hypothesis that separate mutations have occurred and were amplified regionally in response to an endemic process [4]. To further support this hypothesis, SCD was found to be most prevalent in sub-Saharan Africa, an area of higher rates of malaria. It is estimated that over 230,000 children are affected by SCD in that region, accounting for about 80% of the global disease prevalence [5].

The World Health Organization (WHO) reports a 7% prevalence of heterozygotic SCD carriers across the world and an incidence of 300,000–400,000 for true homozygotic SCD [6]. Domestically, the Centers for Disease Control and Prevention (CDC) reports that the prevalence of SCD within the United States is 100,000 (Table 43.1). SCD has an incidence of 1 in 365 African American newborns and 1 in 16,300 Hispanic newborns, and 1 in 13 African Americans inherit sickle cell trait [7].

Although SCD is encountered across the world, it has prevailed in tropical regions and in Africa due to its capacity to confer resistance to malaria in patients who are heterozygotic carriers. Conversely, malarial resistance is not found in those who are homozygotic for sickle cell disease, and the infection is oftentimes fatal [8].

Diagnosis

With newborn screening becoming ubiquitous throughout the United States, undiagnosed cases of SCD are increasingly unusual. Shortly after birth, a blood sample is obtained from the infant by heel prick and is sent for evaluation. A variety of hemoglobinopathy screening modalities are available, including cation-exchange high-performance liquid chromatography (HPLC), isoelectric focusing (IEF), capillary electrophoresis, and gel electrophoresis. The two most frequently used tests are IEF and HPLC due to their high sensitivity, specificity, and reproducibility.

In some instances, SCD is diagnosed later in life, due to immigration from foreign countries into the United States, for example. The best initial step in evaluation is governed by the index of suspicion; if the patient is not of an endemic area and does not meet the clinical picture for SCD, a CBC is ideal due to its low-cost and low-risk profile. A positive CBC will reveal a significant level of anemia and elevated reticulocytes. If a peripheral smear was done, crescent-shaped erythrocytes and Howell-Jolly bodies (in the presence of autosplenectomy) are virtually pathognomonic for SCD. In high-risk individuals, however, where the index of suspicion is high to begin with, more sensitive options should be performed to confirm the diagnosis, such as DNA sequencing, HPLC, hemoglobin electrophoresis, or PCR analysis.

Table 43.1 Epidemiology of SCD as of August 31, 2016 according to the Centers for Disease Control and Prevention

Population	Value
Entire American Population	Prevalence of SCD = 1 in 100,000
African American Population	Incidence of SCD = 1 in 365
African American Population	Incidence SCT = 1 in 13
Hispanic Population	Incidence of SCD = 1 in 16,3000

From Ref. [7]

Prognosis and Mortality

The effect of newborn screening has undoubtedly decreased the number of undiagnosed cases of SCD since being mandated by law. Its effect on mortality, however, is under debate; certain epidemiologic data supports an unchanged rate of mortality [9, 10], while others report a significant decrease in mortality after introduction of newborn screening [11]. While a 42% reduction in mortality was noted from age 0 to 3 years between 1999 and 2002, one study argues that this decrease in mortality coincides with the advent of the pneumococcal vaccine, introduced in 2000 (Table 43.2) [12].

A study published in 1994 reported that homozygous SCD patients died at a median age of 42 years in males and 48 years in females [13]. This has since improved, as illustrated in a 2014 publication reporting that the median age is now approximately 58 years [14]. However, it must be noted that this disease is still associated with a significantly reduced lifespan resulting from chronic complications of the disease.

The development of hydroxyurea has markedly decreased mortality and is considered one of the most effective interventions at this time. A 2015 retrospective study reported that in a group of 469 pediatric patients, hydroxyurea was considered to decrease mortality more effectively than hematopoietic stem cell therapy and prolonged survival substantially more than no therapy [15]. Pulmonary hypertension is a common comorbidity of SCD patients, present in 32% of all patients. It is postulated to be a result of chronic hemolysis and increases mortality substantially as it is resistant to mitigation by hydroxyurea [16].

Cerebrovascular Manifestations

Sickle cell disease is of importance to the cerebrovascular neurosurgeon due to the high incidence of associated cerebrovascular pathology, which is often unique in its pattern and age distribution as highlighted in the sections to follow. Intracranial aneurysms, intracranial hematomas, ischemic stroke, and in particular moyamoya syndrome and its sequelae are more common in patients with SCD as compared to those in the general population and often manifest at a much younger age. Below, we discuss these conditions as they relate to patients with SCD.

Table 43.2 A significant decrease in mortality in all ages, noted from 1999 to 2002[a]

Age group (years)	Decrease in mortality (%)
0–3	68.0
4–9	39.0
10–14	24.0

[a]This drop is suspected to be due to the introduction of the pneumococcal vaccine in 2000

Ischemic Stroke and Moyamoya Syndrome

Ischemic CNS events are extremely common in SCD patients and can result from variety of etiologies. Several types of unique neurosurgical pathology are common in sickle cell patients. Most commonly, moyamoya syndrome is noted to occur in a high number SCD patients. Up to 10% of children with SCD will have strokes by the age of 20, and half of these will have moyamoya-like collaterals on imaging [17]. It is important to note that while ischemic events can occur in the setting of a vaso-occlusive crisis or an acute chest episode, they are more often isolated events that can be clinically silent [18].

Moyamoya vasculopathy is an occlusive cerebrovascular disorder characterized by stenosis of the supraclinoid internal carotid arteries and subsequent formation of fragile collateral vessels in the cerebral hemispheres.

In semantic terms, the condition is referred to as moyamoya *disease* if it is idiopathic or not associated with other conditions and moyamoya *syndrome* if it is associated with other pathologic states. In this instance, in association with SCD, it is proper to refer to the condition as moyamoya syndrome. While the pathophysiologic etiologies of moyamoya syndrome and moyamoya disease have not been entirely elucidated in terms of differentiating the two conditions, at this time it is fair to consider the two equivalent in terms of discussion on surgical treatment strategies [19].

The most common cause of strokes in children is SCD. These are primarily associated with moyamoya-type vasculopathy in the distal internal carotid artery and proximal middle cerebral arteries [20]. Although the exact underlying pathogenesis is not completely understood, it is thought to result from chronic, repetitive vascular microtrauma from circulating sickled cells. However, much remains to be explained from an underlying insult that is systemic (abnormally shaped circulating erythrocytes), and the affected territories are segmental. Why is only the proximal carotid circulation (supraclinoid to terminus segments) involved and the posterior circulation not affected? Why are some cases symmetric while in others there is clear asymmetry (Figs. 43.1 and 43.2)?

The stroke risk is approximately 1% between ages 2 and 5 years and rises to 11% by age 20 [21]. Furthermore, the recurrence of a stroke is above 60%, although it can be reduced with blood transfusions. Radiographically, the rates of cerebral infarcts have been found to be higher, up to 20% in children. These infarcts tend to be in watershed regions and are often silent, although there are links to subtle neurocognitive deficits and increased susceptibility for more overt strokes [22]. Risk factors associated with cerebrovascular incidents include HbSS phenotype, previous transient ischemic attacks or strokes, low baseline hemoglobin concentration, high white blood cell counts, elevated blood pressure, and previous incidents of acute chest syndromes [23].

Cognitive deficits have also been found in the absence of cerebral infarcts, suggesting that the underlying hypoxia and anemia may promote a type of chronic, subthreshold ischemic injury without overt infarction [24]. Furthermore, the rate of seizures is higher in the SCD population than general population and may therefore be mistaken for transient ischemic attacks or acute infarcts [25].

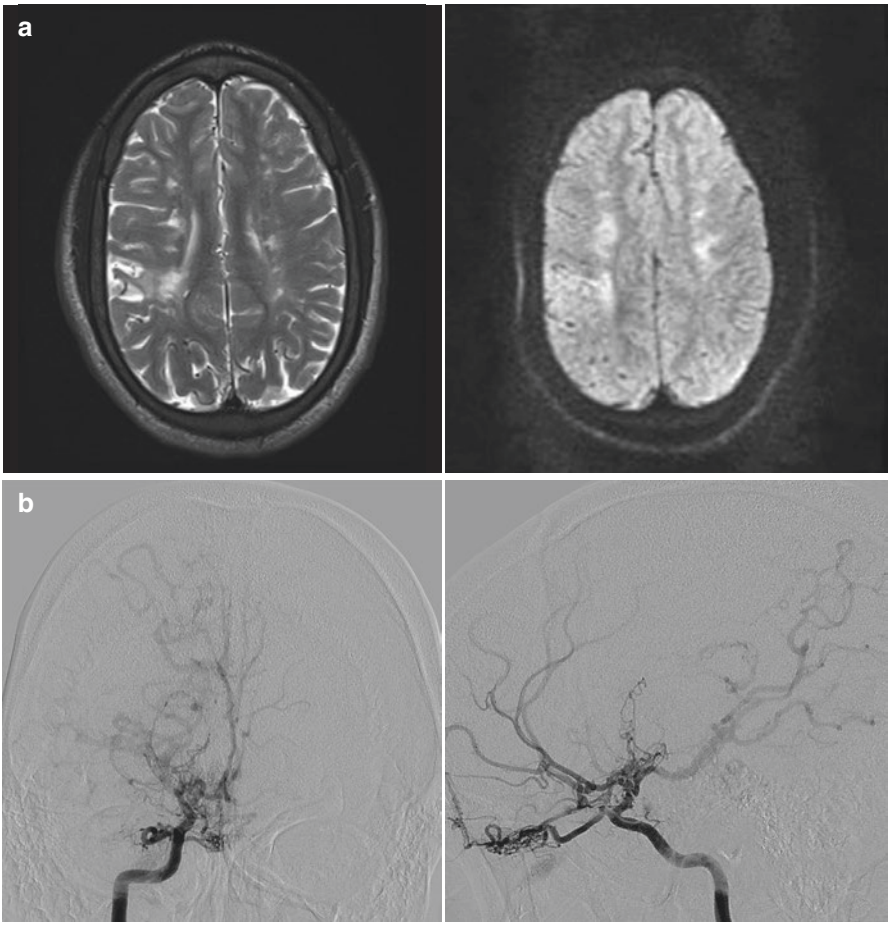


Fig. 43.1 Symmetric moyamoya syndrome in sickle cell disease (SCD): 17-year-old male with SCD and history of right hemispheric ischemic symptoms. (**a**) T2-weighted and DWI MRI brain demonstrates chronic watershed infarcts and a remote right parietal infarct. (**b**) Digital subtraction angiography (DSA) in the anteroposterior (AP) and lateral views demonstrates complete occlusion of the supraclinoid internal carotid artery (ICA) with moyamoya-like collaterals from the lenticulostriate arteries. Collateral supply from an enlarged ophthalmic artery across the anterior falcine artery and from the posterior circulation across pial collaterals from the posterior cerebral artery and the splenial artery. (**c**) Symmetric changes involving the left-sided anterior circulation. (**d**) Native AP view of the skull demonstrating the site of the cranial flap (black arrow) following indirect EC-IC bypass with an EDAMS procedure and (**e**) AP and lateral DSA 1 year following indirect bypass demonstrating faint opacification of the middle cerebral artery territory from this external carotid artery injection

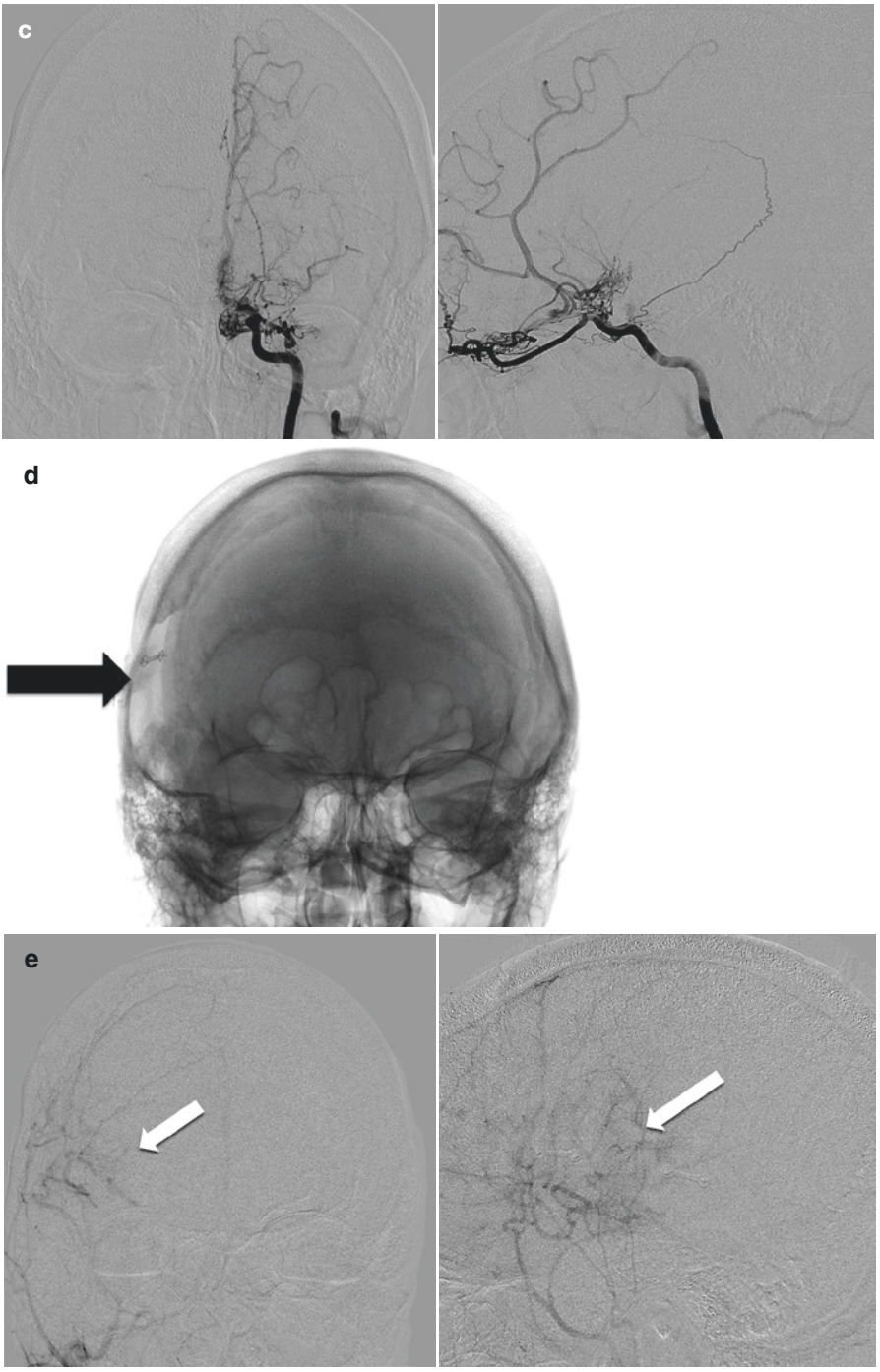


Fig. 43.1 (continued)

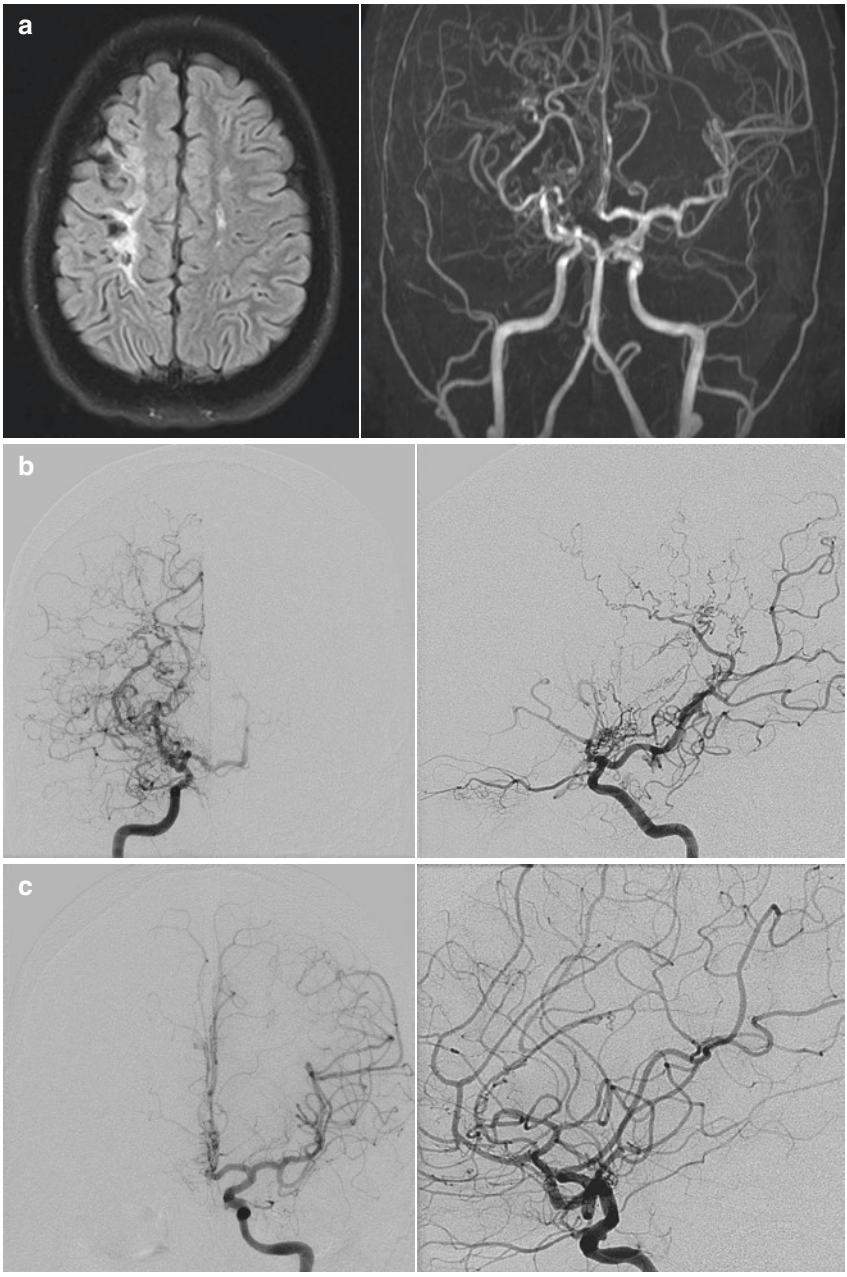


Fig. 43.2 Asymmetric moyamoya syndrome in sickle cell disease (SCD): 21-year-old male with SCD and a history of right hemispheric ischemic symptoms. (**a**) MRI of the brain FLAIR sequences demonstrates chronic watershed infarcts in the right hemisphere, and MRA demonstrates occlusion of the supraclinoid internal carotid artery (ICA) with moyamoya collaterals. (**b**) Right carotid digital subtraction angiography (DSA) in the anteroposterior (AP) and lateral views demonstrates complete occlusion of the supraclinoid internal carotid artery (ICA) with moyamoya changes, while (**c**) the left carotid DSA demonstrates no such changes. There is a small 1 mm paraophthalmic artery aneurysm projecting posteriorly and medially

Stroke Screening and Prevention

Assessment of transcranial Doppler velocities is one method of stroke prevention screening in this population [23]. Abnormal velocity measurements on a TCD carries a stroke risk of 10–15% per year as compared to a 0.5–1% per year risk in SCD HbS patients with normal velocities. Therefore, TCD is now recommended for children aged 2–16 years with HbS disease. MRI/MRA screening has also been adopted at some centers aiming to identify silent small or watershed infarcts and to allow for earlier detection of moyamoya changes in the carotid circulation.

Recent trials for neurological complications in SCD have focused on the reduction of stroke rates in this patient population with serial blood transfusions. The Stroke Prevention in Sickle Cell Anemia (STOP) trial aimed at reducing the HbS concentration to less than 30% using frequent blood transfusions. Preoperative transfusion in high-risk children (defined as children with peak MCA velocity > 200 cm/sec) reduced the risk of stroke in patients with elevated transcranial velocities by 90% [26]. Additionally, a follow-up trial (STOP II) showed that discontinuation of transfusions, even in patients with normalized TCD values, leads to reversion to a high risk of continuing infarction. The Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial, which compared the efficacy of blood transfusions and iron chelation to hydroxyurea with phlebotomy in children, was halted early due to larger number of strokes in the hydroxyurea group [27].

Hemorrhagic Pathology

Intracerebral Hemorrhage

In contrast to the higher incidence of strokes in children with SCD, intracerebral hemorrhage (ICH) occurs more commonly in the adult SCD population between the ages of 20 and 30 years. Around 20% of SCD-related strokes are hemorrhagic in nature and are more common in adults than children [18, 21]. There are multiple etiologies for hemorrhagic events in SCD patients. These intracranial hemorrhages tend to be secondary to other processes occurring from SCD such as cerebral aneurysms and moyamoya syndrome. ICH in this population tends to be devastating with a mortality of 26% within 2 weeks [21]. Histologic testing shows characteristic changes in the vasculature including intimal hyperplasia, fibroblast and smooth muscle proliferation, and thrombus formation [23].

Intracranial Aneurysms

Also of great interest to the cerebrovascular surgeon is the propensity toward intracranial aneurysm formation and subsequent subarachnoid hemorrhage in this patient population. While the pathophysiology of the increased formation of intracranial aneurysms is not entirely clear, Oyesiku et al. propose that increased

endothelial injury secondary to sickled erythrocytes increases propensity for aneurysm formation at sites of increased hemodynamic stress [28]. Similar histopathologic changes have been attributed to multiple cases of intracranial aneurysms found in SCD patients. It has been proposed that endothelial injury results in the breakdown of internal elastic lamina and degeneration of smooth muscle layers predisposes the arterial wall to breakdown and aneurysm formation [28]. Indeed, intracranial aneurysms have been shown to occur more often in SCD than the general population [29].

Thus, this hypothesis would support the notion that chronic, repetitive vascular microtrauma from circulating sickled cells yields aneurysms particularly at bifurcations, where shear stress is accentuated. It would stand to reason that diluting the causative agent, the sickled erythrocyte, from the circulation with transfusions would reduce injury. However, while frequent serial transfusions have been proven to decrease the likelihood of ischemic infarcts in SCD, transfusions have not been linked to a lower propensity to form, grow, or rupture intracranial aneurysms.

Interestingly, aneurysm formation does not appear to be related to the presence or absence of moyamoya syndrome; rather, it appears to be related to the HbSS genotype, with patients harboring this genotype being more likely to develop intracranial aneurysms [30]. The overall incidence of intracranial aneurysms is reported to be 1.2% in children and up to 10% in adults [29]. A large incidence of multiple aneurysms in this patient population with up to 57% of patients harboring multiple aneurysms [31]. In addition to multiplicity of aneurysms, these lesions aneurysms may also arise in atypical locations (Figs. 43.3, 43.4 and 43.5). Another distinguishing feature of this population is the prevalence of posterior circulation aneurysms is high, with estimated incidence as high as 38% [30].

Aneurysmal Subarachnoid Hemorrhage

There is evidence that aneurysms in the SCD population follow a more sinister natural history than the control population [32, 33]. Most cases of SAH in the overall population occur in 40–65-year-old patients, and only 10% occur in those less than 35 years of age (American Stroke Association). By comparison, SCD patients tend to present with ruptured aneurysms at a much younger age. Birkeland et al. found that women ages 30–39 are most at risk for subarachnoid hemorrhage, while Preul et al. reported a mean age range from 25 to 30 [30, 31]. There is also a suggestion that aneurysms in SCD tend to rupture at a smaller size than the general population, approaching a rupture risk profile comparable to those with familial rupture patterns [28]. Thus, due to a higher incidence of multiple aneurysms, younger age at presentation, propensity toward posterior circulation involvement, higher likelihood of rupture at a lower aneurysm size, and lower overall life expectancy, there is strong rationale for the aggressive approach toward treating identified unruptured aneurysms among patients with SCD. Some have proposed a low threshold for screening MRA or cerebral angiography for any SCD patient with neurologic symptoms [31], but there is currently no consensus on screening timelines for the asymptomatic patient [34].

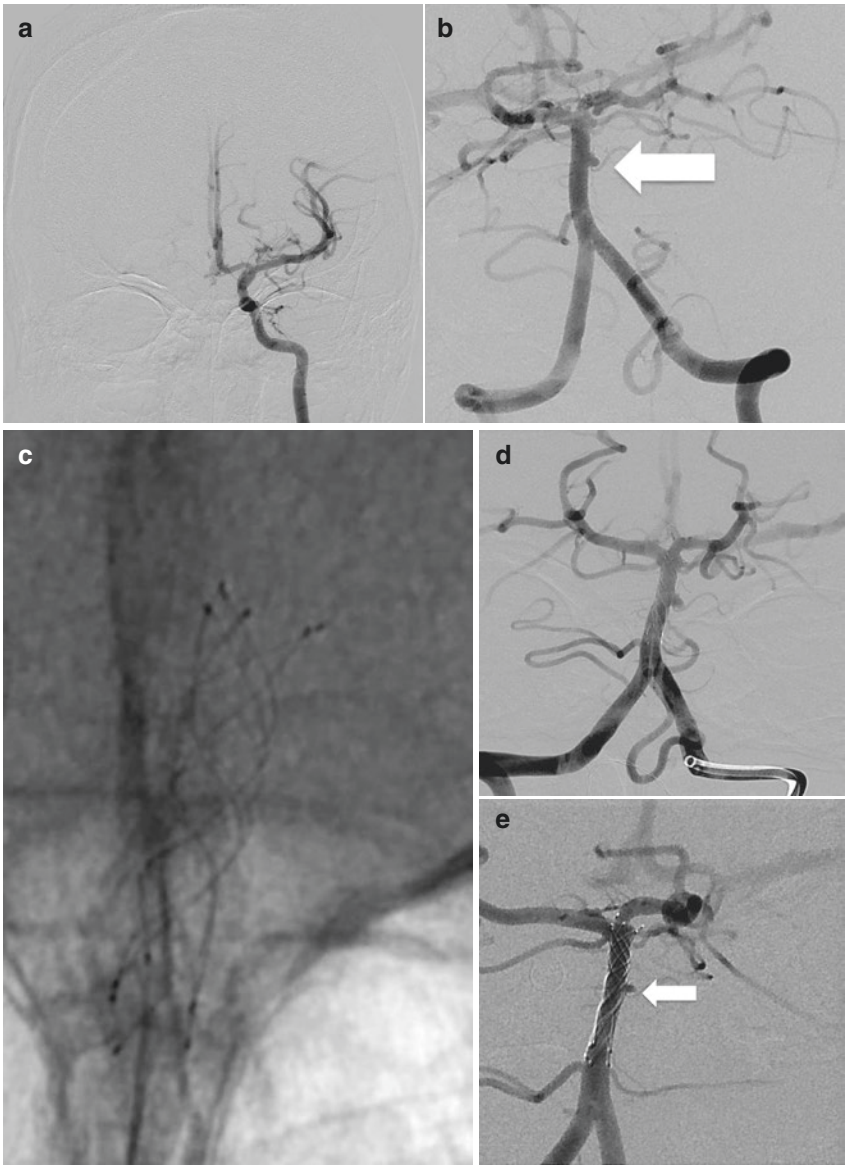


Fig. 43.3 15-year-old female with SCD found to have multiple aneurysms on screening MRI. (**a**) Left carotid digital subtraction angiography (DSA) in the anteroposterior (AP) and lateral views demonstrates normal anatomy. (**b**) Left vertebral artery DSA in the AP view demonstrates a mid-basilar trunk pontine perforator-associated aneurysm (white arrow) which (**c**) was treated with two overlapping LVIS Jr. stents (Microvention Inc., Tustin, CA) in overlapping fashion to achieve flow diversion. (**d**) Immediate post-stenting DSA demonstrates filling of the aneurysm, which has drastically decreased in size by 6-month follow-up (white arrow) (**e**). (**f**) Right carotid DSA demonstrates a 4 mm paraophthalmic aneurysm (white arrow) which was treated with a pipeline embolization device (ev3, Plymouth MN). (**g**) At 6-month follow-up AP and lateral DSA, there is no opacification of the aneurysm, but an asymptomatic stenosis at the carotid terminus just distal to the deployment of the pipeline device is noted (black arrow). Dual antiplatelet therapy was continued, and the patient remained asymptomatic and the stenosis remained stable on repeat DSA and transcranial Doppler ultrasonography

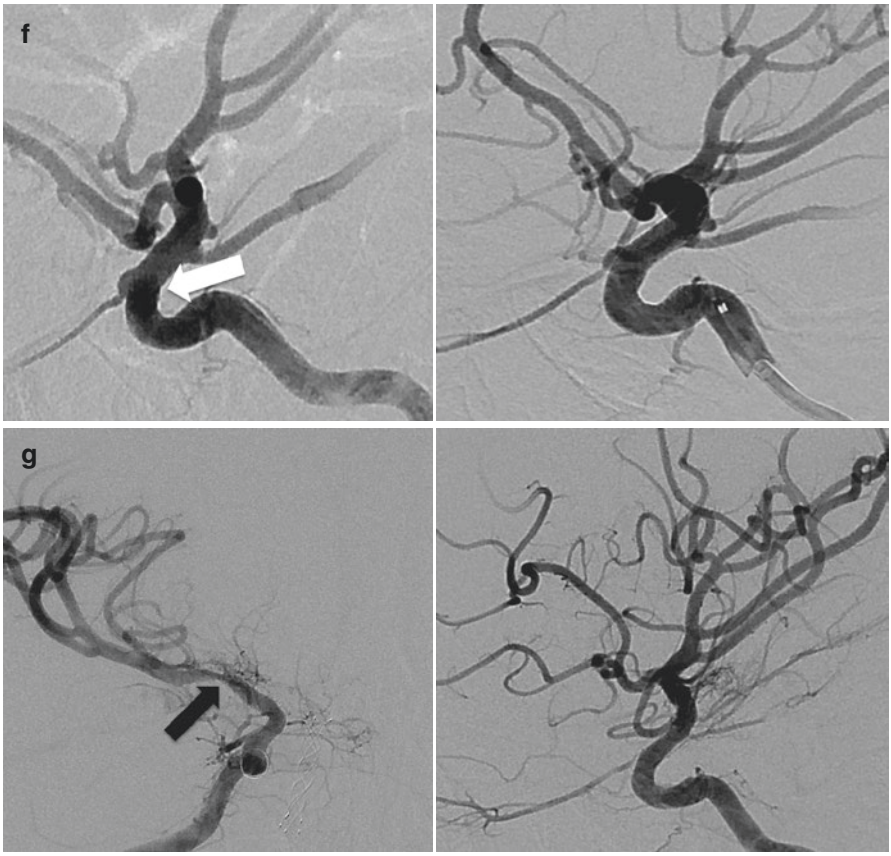
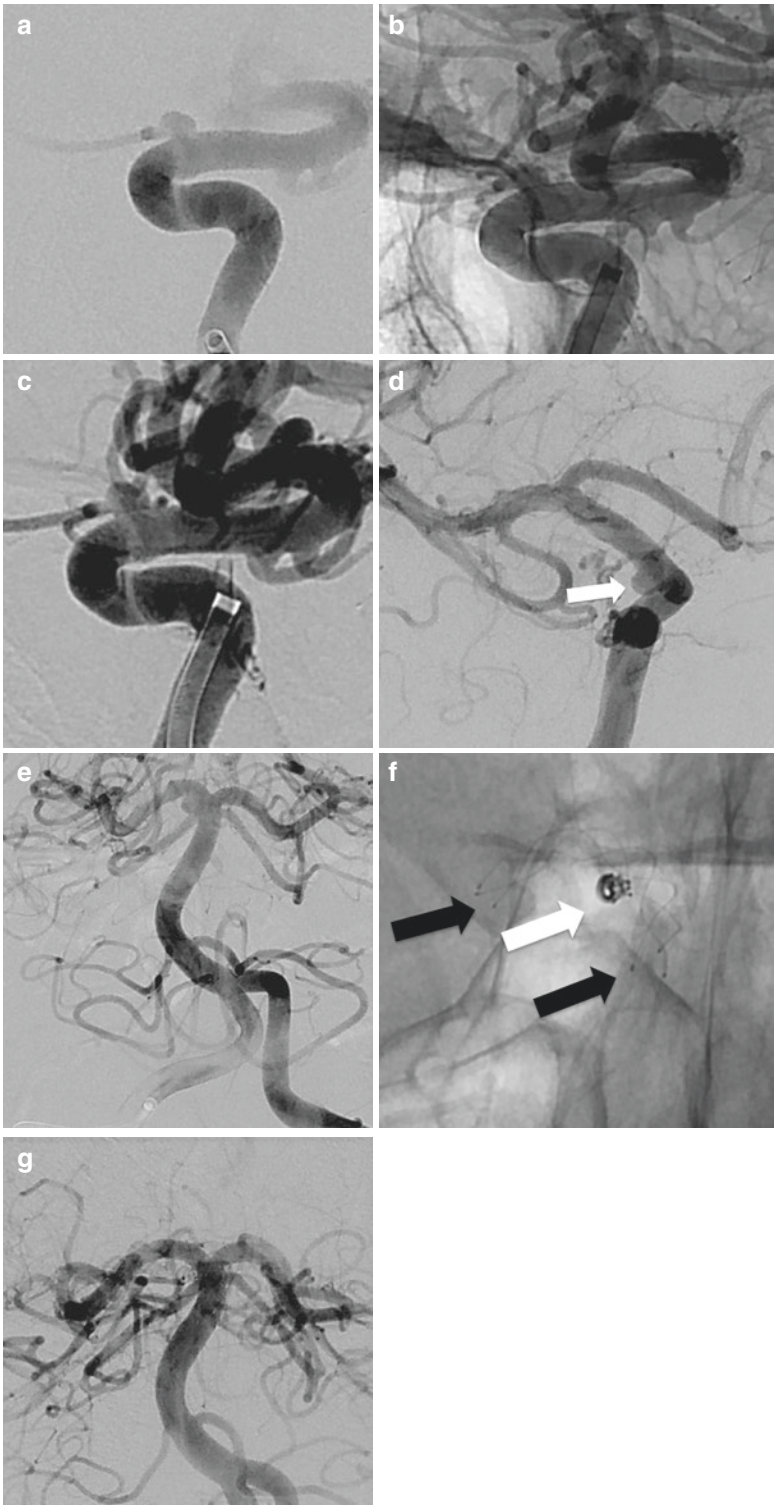


Fig. 43.3 (continued)

Fig. 43.4 19-year-old male with SCD and multiple intracranial aneurysms identified on MRI screening. (**a**) Right carotid digital subtraction angiography (DSA) in the lateral view demonstrates an ophthalmic artery aneurysm. Incidental note is made of infundibuli involving the origins of both the posterior communicating and anterior choroidal artery. (**b**) Native view showing the deployed Pipeline embolization device (ev3, Plymouth MN) spanning the neck of the aneurysm from the supraclinoid to the cavernous segment of the internal carotid artery. (**c**) Immediate post-pipeline deployment DSA. (**d**) A smaller paraophthalmic artery was also identified on right carotid DSA, which has been followed with serial imaging. (**e**) Right vertebral artery DSA identified a right-sided superior cerebellar artery (SCA) aneurysm which was treated with stent-assisted (LVIS Jr., Microvention, Tustin CA) coil embolization as seen on this native AP view. (**f**) Black arrows designate the proximal and distal ends of the stent; white arrow shows the coil mass within the aneurysm. (**g**) Immediate posttreatment DSA demonstrates near-complete occlusion of the aneurysm, with a small amount of opacification at the neck (Raymond I)


a
b
c
d
e
f
g

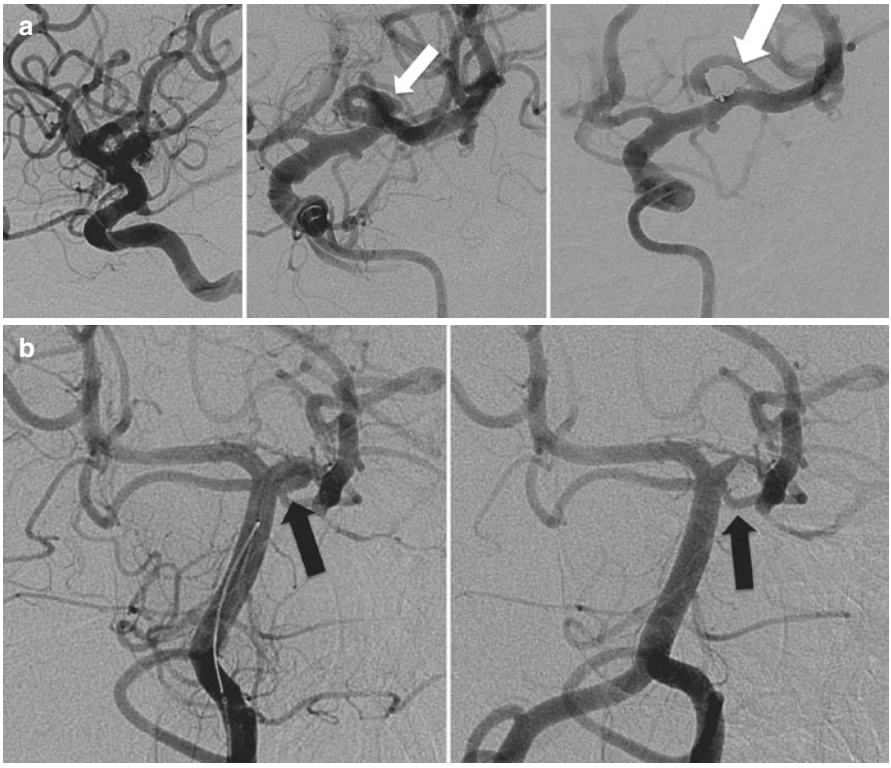


Fig. 43.5 22-year-old female with SCD and multiple intracranial aneurysms identified on MRI screening. (**a**) Left carotid digital subtraction angiography (DSA) in the lateral view demonstrates an infundibulum at the posterior communicating artery origin and a broad-based middle cerebral artery bifurcation aneurysm (white arrow) that was treated with balloon-assisted coil embolization to complete occlusion. (**b**) Left vertebral artery DSA demonstrates a left-sided superior cerebellar artery aneurysm that was also treated with balloon-assisted coil embolization to complete occlusion

There is also currently no evidence favoring open surgical or endovascular approaches for aneurysm treatment. The first successful clipping of an aneurysm in a sickle cell patient with SAH was described by Cheatham and Brackett in 1965 [34]. While they did not employ preoperative exchange transfusions, they carefully maintained oxygenation and avoided hypertonic agents such as urea. They also opted against their customary induction of hypothermia as a neuroprotective measure as it could increase blood viscosity. Awareness of the association between SCD and aneurysms grew in the 1980s with more reports of successful surgical treatment of ruptured intracranial aneurysms [35–37] most of which involved perioperative exchange transfusions to reduce the level of HbS to less than 40%.

The SAH state results in the activation of systemic inflammatory factors that result in a pro-thrombotic state. Endovascular approaches in the sickle cell patient will pose a higher theoretical risk of inducing intracranial thrombosis compared to conventional open surgical approaches as they require navigating small diameter intracranial

vessels with microcatheters and intermittent osmotic contrast administration for visualization. Strict adherence to catheter hygiene with maintenance with heparinized saline flushes is paramount (refer to section "Cerebral Angiography" below). Balloon remodeling has been widely adopted over the past decade as a very safe and effective method to treat geometrically complex and broad-based aneurysms that otherwise would have necessitated open surgical approaches. However, the intermittent balloon inflations of a few to several minute duration create conditions ripe for sickling. The temporary stasis in the vessel combined with the local hypoxia from flow arrest could precipitate a thrombosis. While we have used this technique at our center and we believe others have as well, no reports are available on the safety of balloon remodeling for aneurysm embolization in the SCD population. In addition, stenting as monotherapy [38] and flow diversion [39] has been reported to be feasible and safe in the immediate follow-up period for ruptured very small aneurysms.

Meticulous attention to detail and avoidance of factors predisposing to sickling have allowed both microsurgical clipping with craniotomy and coil embolization with endovascular techniques to be performed safely. However, long-term data does not exist on aneurysm occlusion and recurrences for either modality. In the absence of evidence-based guidelines, we recommend employing whatever modality is felt to be most safe and effective for each aneurysm following a multidisciplinary discussion among those with expertise in both modalities. Finally, given the above considerations, aneurysms should strongly be considered for treatment; only those in which the risk of treatment is unacceptably high should be monitored with imaging surveillance.

Once a ruptured aneurysm has been adequately secured, the SCD patient may face unique challenges in the neurocritical care setting. The general management principles of the neurocritically injured sickle cell patients involve adequate oxygenation, good ventilation to prevent respiratory acidosis, maintenance of circulating volume and tissue perfusion, and avoidance of hypothermia and venous stasis. In particular, SAH-induced cerebral vasospasm may be particularly challenging. Avoidance of intravascular depletion which would prove to be catastrophic and implementation of hypertensive-hypervolemic therapy supplemented with the early use of intra-arterial therapies such as calcium channel blocker administration and balloon angioplasty to restore the intracranial vasculature to its normal diameter and allow adequate cerebral perfusion make practical sense. Few reports have described their efficacy in the SCD population, so we must extrapolate from what we know to work in the normal population while taking the extra "sickle" precautions as outlined.

Arteriovenous Malformations

To date, no association between arteriovenous malformations and sickle cell disease exists. Indeed, only one case report exists describing co-occurrence of AVM and SCD [40]. When proceeding with an AVM resection in a SCD patient, meticulous adherence to sickle cell protocols and involvement of a multidisciplinary team in the perioperative period will be critical to ensure an adequate outcome (Fig. 43.6).

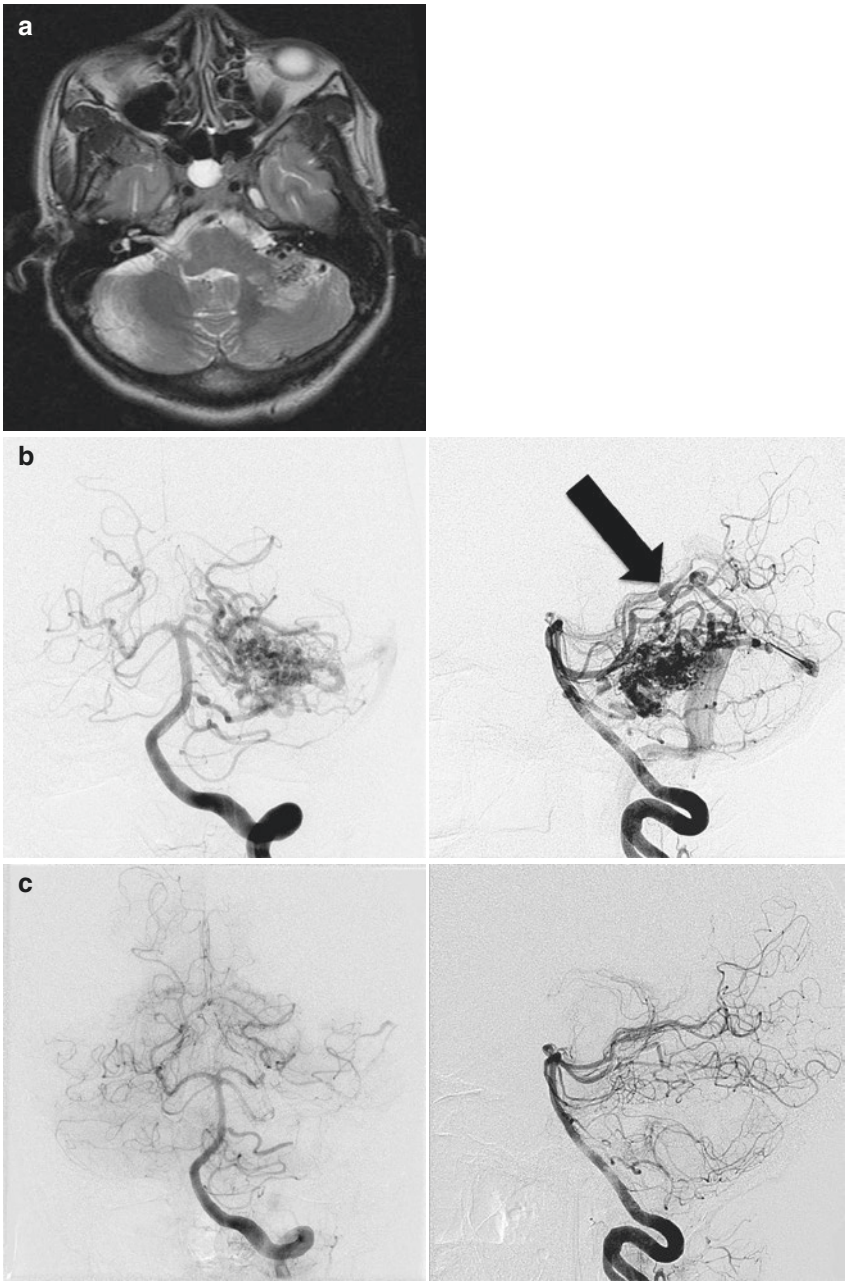


Fig. 43.6 Sickle cell patient with a complex arteriovenous malformation: (**a**) 33-year-old male with SCD and a history of headaches, ataxia, gait disturbance, and dizziness was found to have an arterial vascular malformation (AVM) involving the left cerebellum. (**b**) Left vertebral artery digital subtraction angiography (DSA) in the anteroposterior (AP) and lateral views to further interrogate the angioarchitecture of the AVM demonstrates supply from AICA and SCA, with a flow-related aneurysm (black arrow). Venous drainage is along cerebellar veins to the sigmoid sinus. Patient underwent balloon-assisted onyx embolization followed by surgical resection via a retrosigmoid craniotomy approach. (**c**) Postoperative DSA in the AP and lateral view demonstrates no residual AVM

Miscellaneous

Also of unique interest, spontaneous epidural hematoma is described in SCD. Hamm et al. describe a small number of SCD patients with spontaneous epidural hematoma formation. Interestingly, they note that approximately 70% of these patients are asymptomatic, with the remaining 30% of patients presenting with headache. However, it is worth noting that the overall mortality rate of approximately 20% in their series was compatible with Hettige et al., who also noted an association of calvarial infarction along with the formation of spontaneous EDH in this patient population. The mechanism, however, of this occurrence is unknown [41, 42]. The surgical management of this condition should proceed in the standard fashion.

Surgical Considerations

Preoperative Considerations

The success of surgical intervention in patients with SCD requires a thoughtful and methodical approach to proper perioperative care, anesthesia, and operative selection. Overall perioperative mortality rates are 1% in sickle cell patients [43], but this figure includes patients undergoing low-risk procedures, such as tonsillectomy and cholecystectomy, and is not specific to neurosurgical patients, where the overall procedural risk may be much higher. Overall operative morbidity is estimated to be 25–30% in sickle cell patients, while again noting this is not specific for neurosurgical patients [44]. It would be reasonable to suppose these risks are higher in a neurosurgical population, given overall increased surgical risk. Multidisciplinary involvement is paramount, in our opinion, and we involve the treating hematologist during the key perioperative period to optimize the likelihood of a good outcome. It must be remembered that this is a unique cohort of patients with a unique systemic milieu, and standard perioperative practices are generally not adequate.

Patients with SCD are at high risk for multiple intraoperative and postoperative complications, most notably acute chest syndrome, vaso-occlusive crisis, severe infections, renal impairment, deep venous thrombosis/pulmonary embolism, and, of the most interest to the neurosurgeon, ischemic CNS complications.

A mainstay of preoperative management has been preoperative blood transfusion or exchange transfusion. Proponents of transfusion argue that decreasing the overall proportion of HbS in the circulating blood decreases the overall viscosity of the blood, leading to a reduced risk of perioperative complication and ischemic cerebrovascular complications [45–47]. However, a recent Cochrane Review did not find evidence that transfusion (whether conservative or aggressive) significantly altered the risk of perioperative SCD-related complications while noting low-quality evidence suggested that conservative transfusion did reduce the risk of postoperative acute chest syndrome [48]. This data was not specific to CNS complications, and the authors noted the overall quality of evidence for the review was low. No work to date has specifically targeted preoperative management in neurosurgical patients.

Cerebral Angiography

Cheatham and Brackett [34] were concerned about an increased risk of thromboembolic complications during cerebral angiography in sickle cell patients. In their pioneering work in the 1960s around the time of their first reported clipping of a ruptured aneurysm in a SCD patient, they hypothesized that the osmotic angiographic contrast material could precipitate sickling. To test their hypothesis, they experimentally exposed progressive dilutions of contrast medium to blood from sickle cell patients in vitro. Mixing of contrast with HbSS erythrocytes resulted in significant sickling, but not with HbSC or HbAS. However, this risk may be mitigated by pretreatment blood transfusions as well as keeping contrast volume and concentrations to a minimum [49, 50].

Oyesiku et al. note that their standard practice prior to cerebral angiography is to perform partial exchange transfusion to reduce HbS percentage to less than 30%, with a goal hematocrit of 30–35%, the optimum range for cerebral blood flow, noting an increased propensity for sickling with administration of intravenous contrast media [28]. At our institution, we also transfuse prior to the procedure under the direction of our hematology colleagues as needed to optimize Hb3 concentrations. As the patients are made NPO overnight for conscious sedation with anxiolytics and are thus dehydrated by definition, we schedule them to be done early in the morning (avoiding late afternoon procedure times) and combat intravascular volume depletion by administering between 0.5 L and 1.0 L of crystalloid (normal saline) in the preprocedure holding area and continue the infusion during the angiogram. We also administer an intermediate dose of heparin (typically 1,000–2,000 IU) intravenously once percutaneous common femoral artery access is obtained and the sheath is placed and use judicious "double-flush" techniques with heparinized saline to optimize catheter hygiene and reduce the likelihood of sickling promoting intraluminal thrombus formation. The contrast concentration may also be diluted while maintaining images of diagnostic quality.

Intraoperative Considerations and Surgical Strategies

Anesthetic Considerations

In the context of a neurosurgical procedure, the goals of anesthesia are to prevent systemic complications of SCD and to prevent cerebral ischemia and other CNS complications. General tenets of intraoperative medical care involve prevention of erythrocyte sickling and painful vaso-occlusive crises. In the context of general care and maintenance of adequate hydration, supplementing oxygen to keep saturations above normal, avoiding acidosis, and avoiding extreme temperature shifts are of importance [51].

Apart from the considerations regarding preoperative transfusions already discussed, the surgeon and anesthesiologist should discuss, identify, and prevent the

causative risk factors for cerebral ischemia. These are elegantly summarized in a review by DeBaun et al [52]:

1. Low oxygen content which can be exacerbated by drops in hemoglobin or oxygen saturation
2. Presence of underlying cerebral vasculopathy, with subsequent loss of reserve
3. Fever
4. Underlying cardiovascular disease
5. Previous stroke within the preceding 3 years
6. Rapid rise in hemoglobin levels from iatrogenic transfusion or autotransfusion to >12 g/dL

While not all of these factors may be directly controlled at the time of the operation, understanding the mechanisms underlying cerebral ischemia is critical to mitigating potential complications, both in the preoperative and intraoperative arenas. In this context, neuroanesthetic considerations should follow the same principles as listed above, and anesthesia may proceed in the usual fashion with the surgeon and anesthesiologist bearing in mind the important factors.

At our institution, every surgery on patients with SCD is performed in conjunction with a neuroanesthesiology specialist who is a "champion" in the care of this patient population and with whom the goals and pitfalls to avoid during surgery are thoroughly discussed preoperatively. SCD with symptomatic moyamoya, for example, will have very little if any vascular reserve. Systemic hypotension during induction of general anesthesia should be avoided at all cost; the well-prepared neuroanesthesiologist will have place an invasive arterial pressure monitor and be equipped with vasopressors drawn up into syringes. A goal mean arterial pressure > 60–65 mm Hg is reasonable, and in addition to correcting for anemia and keeping up with any unexpected blood loss, the patient ought to be maintained slightly hyperoxygenated to maintain a safe PaO_2. In addition, hyperventilation and hypocarbia must also be avoided as cerebral vasoconstriction may not be tolerated. Optimization of arterial oxygen and carbon dioxide tensions may be verified with arterial blood gas analysis as needed (Table 43.3).

Specific to the neurosurgeon, discussion of the safety of intraoperative adjuncts to controlling intracranial pressure, such as administration of mannitol, is also relevant. While mannitol's immediate effect is to draw volume into the intravascular compartment, expanding this space and improving rheology, its secondary effects are to cause diuresis and intravascular depletion. Mannitol poses a theoretical risk of provoking a vaso-occlusive crisis secondary to this latter effect. While safe use of mannitol has been described in neurosurgical procedures for patients with SCD [32, 53], there are no large trials to provide quality data to support or refute this claim, and some authors state that the use of mannitol should be done with an appropriate caution [54]. Additionally, temporary hyperventilation to a PCO2 of 25–30 mmHg has been used safely [54], but again a paucity of data exists on this topic, preventing a more general recommendation on its use. For patients with concern for intraoperative brain swelling, preoperative placement of a ventriculostomy and the use of cerebrospinal fluid diversion is a viable option in lieu of therapies which may pose

Table 43.3 Illustrative case: Sickle cell disease patient with moyamoya syndrome; summary of the key parameters that must be optimized perioperatively, by highlighting the adverse cerebrovascular events that may occur when they are not meticulously managed[a]

Parameter	Adverse event	Pathophysiology	Alarming parameters	Monitor
Oxygenation	Hypoxia	Sickling and vaso-occlusion may lead to vessel occlusion	PaO_2 < 60 mmHg Oxygen saturation < 90% Respiratory rate > 30 cycles/min (Stankovic et al.)	Arterial Blood Gas Pulse Oximetry Respiratory rate
Blood pressure	Hypertension Hypotension	Ischemia Hemorrhage	Avoid SBP < 90 mmHg or a drop of >40 mmHg from baseline Maintain MAP ≥60 mm Hg, SBP < 160 mm Hg Avoid SBP > 180 mmHg	Arterial line
Lactate dehydrogenase	Metabolic acidosis Acute kidney injury	Sickling and vaco-occlusion Ischemia	LDH < 315 UI/L (100% sensitivity) LDH > 1000 UI/L (100% specificity) (Stankovic et al)	Lactate dehydrogenase level
Carbon dioxide	Cerebral edema Decreased cerebral blood flow	Failed cerebrovascular autoregulation Alkalosis and vasoconstriction	Maintain $PaCO_2$ between 35 and 45 mm Hg (Pianosi et al.)	End tidal CO_2, Arterial blood gas
Core temperature	Hypothermia Hyperthermia	Sickling and vaso-occlusion Increased metabolic demand with tenuous cerebral blood flow	Below 36° C Over 38.5° C (Sabota et al.)	Esophageal or bladder probe
Hemoglobin	Concentrated HbS	Sickling and vaso-occlusion	HbS > 30% Hgb < 7.8 g/dL (Cecchini et al.)	Hemoglobin and Hematocrit
Platelets	Thrombocytopenia	Postoperative hemorrhage	Platelet count <200,000 /mm [3] (Cecchini et al.)	Platelet count
Intravascular volume	Intravascular depletion	Precipitate sickle crisis	Generous intravenous crystalloid infusion	Central venous pressure, Urine output Strict in and out recordings

[a]Considerations given to other organ manifestations are included in Table 43.4

a risk of provoking a vaso-occlusive crisis. In any case, for patients with concern for life-threatening cerebral edema or impeding herniation, the benefits of any therapy to lower intracranial pressure or brain volume will likely outweigh the risks of such an intervention.

Patient Selection and Surgical Technique

Surgical intervention in the SCD cohort of patients will mostly revolve around revascularization procedures in patients with recurrent ischemia or moyamoya syndrome. While other procedures, such as decompressive craniectomy for a large-vessel territory infarction, craniotomy for evacuation of EDH, or craniotomy/endovascular therapy for aneurysm obliteration, will be common, there are no particular unique procedural factors in these patients that merit further discussion.

Revascularization procedures may be subdivided into "direct" and "indirect" vascular bypass techniques. Direct extracranial-to-intracranial (EC-IC) bypass techniques generally involve the transfer of a donor vessel, typically the superficial temporal artery, to a large intracranial recipient vessel, typically the middle cerebral artery (Fig. 43.7). Indirect EC-IC procedures will generally involve the overlay of a vascularized tissue with the goal of forming multiple small collateral vessels to enrich the overall microvascular tree of the cerebral tissue in question. Such procedures include encephaloduroarteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), encephaloduroarteriogaleosynangiosis (EDAGS), and encephaloduroarteriomyosynangiosis (EDAMS) (Fig. 43.8). Combined direct and indirect techniques are also possible. Both direct and indirect techniques have been shown to decrease the pathologic moyamoya vessels seen on angiographic imaging [55].

Direct Versus Indirect Intracranial Bypass

Direct EC-IC bypass techniques are well-studied in patients with moyamoya syndrome, although there is no high-level evidence for those with SCD. As such, we must extrapolate what is known from moyamoya disease to patients with SCD *and* moyamoya. There is level I evidence to show that direct bypass procedures are superior to medical management alone in preventing hemorrhagic strokes in adult patients with moyamoya disease [56]. In this study, Miyamoto and colleagues randomized adult patients with at least one intracranial hemorrhagic event to surgery or medical therapy alone, with 38 patients randomized to medical therapy only and 42 patients to direct or combined EC-IC bypass. This cohort was followed for 5 years postoperatively. A statistically significant benefit was seen in the reduction of further hemorrhagic events at 5 years in the surgical cohort [56]. Similarly, Jang et al. demonstrated a reduction in the frequency of hemorrhagic events in adult patients undergoing direct EC-IC bypass for moyamoya disease but did not note a decrease in ischemic events and a difference between direct and indirect methods [57]. Additionally, a large meta-analysis by Kim et al. failed to demonstrate a difference

in stroke risk reduction in the direct vs. indirect bypass groups while noting a non-statistically significant trend toward greater reduction in the direct bypass group [58]. A further meta-analysis by Qian et al. again demonstrated the effectiveness of EC-IC bypass in reducing hemorrhagic events in adult moyamoya patients as compared to medical therapy alone and showed a significant benefit of direct methods compared to indirect methods with no difference in complication rates [59]. The authors were unable to show a benefit for EC-IC bypass in ischemic symptoms in this patient cohort. This contrasts with Kim et al., who do show a benefit in reducing

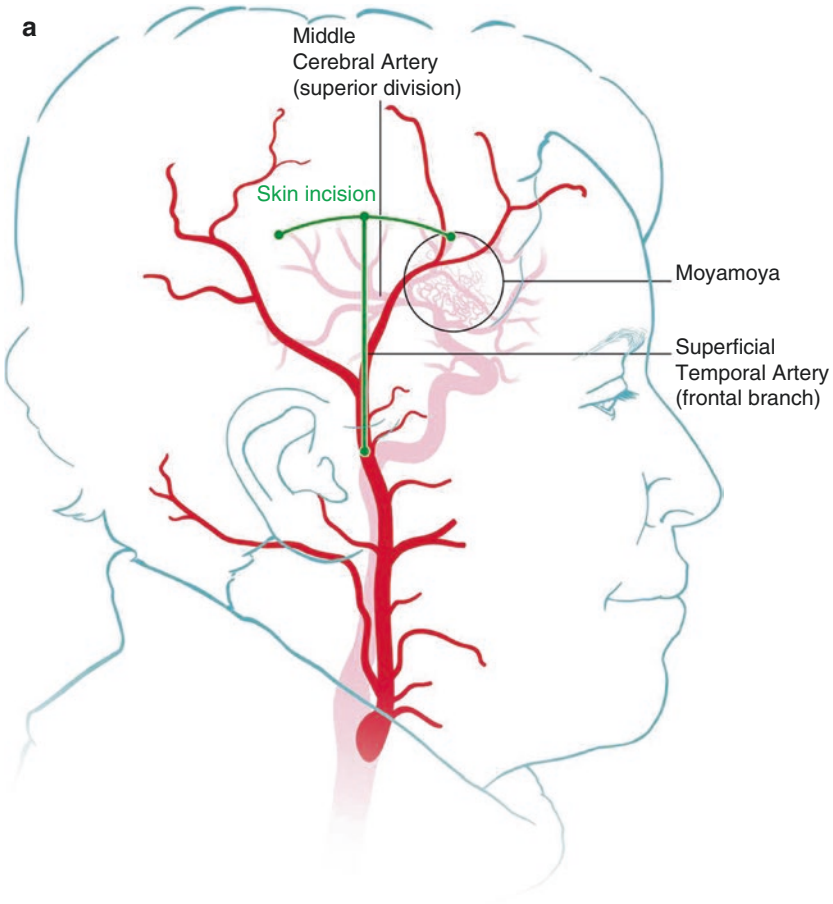


Fig. 43.7 Illustration of direct external carotid-internal carotid (EC-IC) bypass: direct EC-IC bypass consisting of a superficial temporal artery-middle cerebral artery bypass (STA-MCA). (**a**) Schematic demonstrating the planned incision, which is made after the paths of both the frontal and parietal branches of the STA are mapped out with a Doppler ultrasound on the scalp to avoid injuring them. (**b**) Once the cortical surface of the frontal lobe is exposed, a suitable recipient is identified and elevated from its arachnoid plane after the donor STA has been isolated, freed circumferentially, and mobilized to approximate it to the recipient and microsurgical anastomoses performed in an end-side "T" fashion

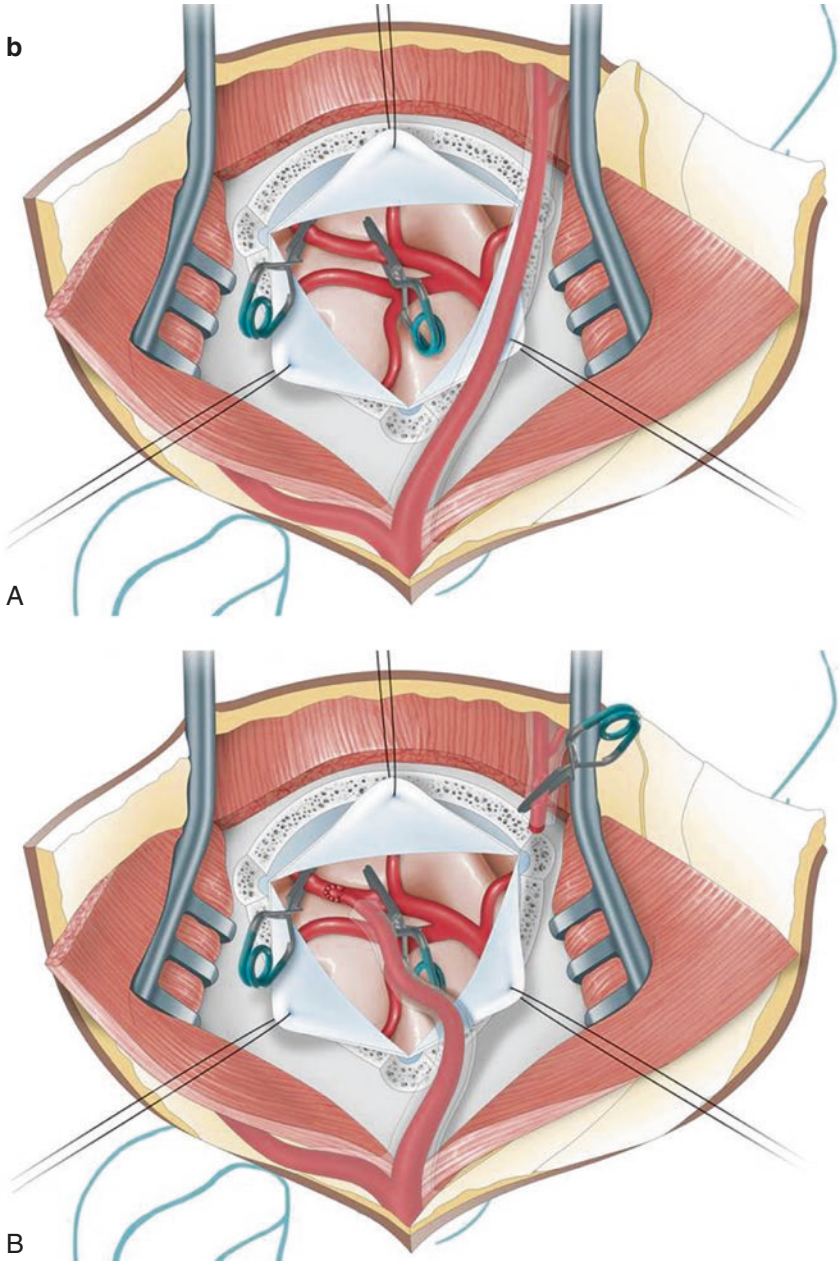


Fig. 43.7 (continued)

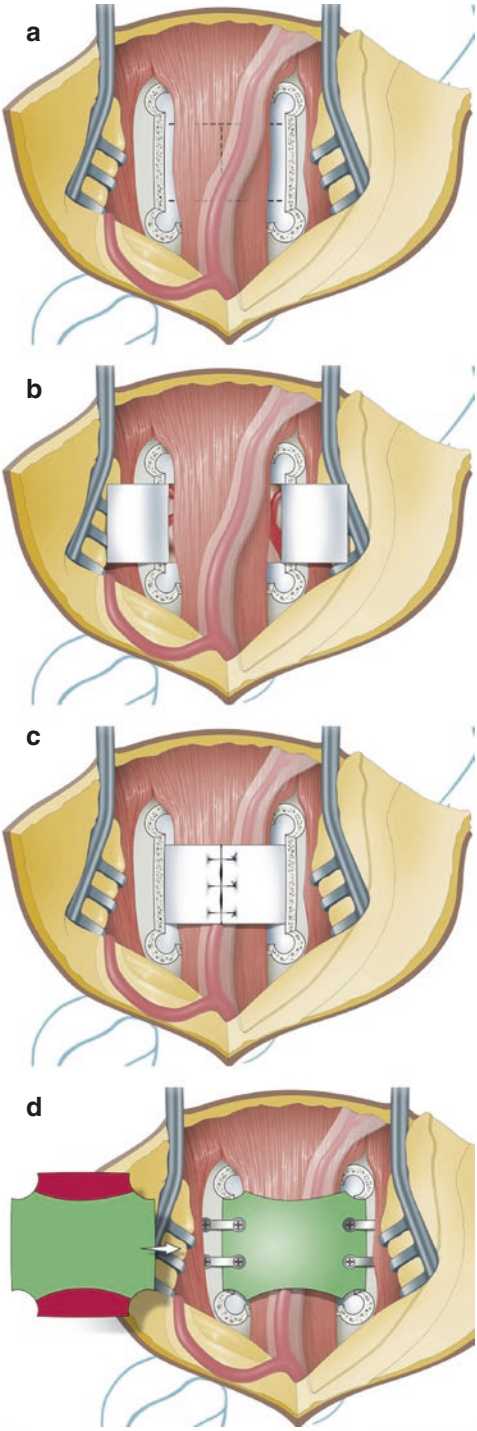


Fig. 43.8 Illustrations of indirect external carotid-internal carotid (EC-IC) bypass, encephaloduroarterio-myosynangiosis (EDAMS): (**a**) the superficial temporal artery is spared during the incision and scalp mobilization. Two vertical incisions are made in the temporalis muscle to expose the underlying skull and elevate the temporalis. Four small burr holes are inserted, and a craniotomy is made by with a Gigli Saw Wire connecting the horizontal segments and a B1 with a footplate connecting the vertical segments. (**b**) The dura is opened in an "H" fashion, and the underlying pia of the exposed cortical surface is disrupted with a beaver blade to promote angiogenesis. (**c**) The temporalis muscle is laid directly on the cortical surface, and the dura is reflected back and sutured to help appose the temporalis to the cortical surface. (**d**) The craniotomy flap is modified to prevent strangulation of the temporalis muscle as it dives under it and secured in a standard fashion

ischemic symptoms with direct or combined bypass methods [58]. In another meta-analysis, Sun et al. show that direct or combined techniques result in more favorable long-term outcomes and lower rates of long-term ischemia compared to indirect methods in adult patients with moyamoya disease. While these results are interesting, it is important to note that there are no randomized controlled trials comparing direct to indirect methods of EC-IC bypass for adult patients with moyamoya-like vessels on imaging.

Interestingly, radiologic data supports the notion that direct EC-IC bypass results in superior perfusion of the surgical hemisphere than indirect methods. Cheung et al. show significant increase in cerebrovascular reserve capacity on CT perfusion imaging in patients undergoing direct as opposed to indirect methods of revascularization [60–62]. The previously discussed study by Kim et al. also shows improved evidence of angiographic revascularization in symptomatic adult patients [59]. Direct procedures provide the advantage of achieving immediate revascularization and more reliable revascularization, given that indirect procedures result in angiogenesis in only half of all adult patients undergoing indirect bypass techniques [55, 63]. However, the indirect revascularization strategy is considered to have a lower overall complication rate [64].

Other sources counter that indirect methods can be effective in adult patients. Macyszyn and colleagues developed an analytical model to evaluate quality of life years in adult and pediatric patients undergoing bypass procedures for moyamoya syndrome and found indirect or combined techniques to be superior to direct techniques [65].

In pediatric patients, indirect methods are generally felt to be superior to direct methods of bypass [66]. Pial synangiosis has been shown to be very safe and effective in pediatric patients with SCD-related moyamoya in preventing stroke [67]. While direct bypass in children, particularly in young children, is often felt to be very technically challenging due to the small size of donor and recipient vessels, Rashad et al. showed good success with a combined technique [68].

While the debate on method of bypass will likely continue in the absence of a focused trial, it is certain that bypass improves outcomes in symptomatic patients with moyamoya-type vessels. The clinician must be certain to select a method with which they may optimize patient safety and achieve the goal of revascularization.

Postoperative Considerations, Including Common Complications in SCD Patients

Pain in Sickle Cell Disease

Pain crisis in patients with sickle cell disease is the most common cause of immediate morbidity. It indicates underlying ischemic attacks from micro-infarctions and vaso-occlusion. In general, while no correlation between mortality and rates of pain crises was found in patients between 10 and 19 years of age, higher pain rates were

correlated with mortality in patients over 20 years old [16]. Major risk factors for postoperative pain crises are low hematocrit and fetal HbF levels. Other risk factors include sibling history of asthma, nocturnal hypoxemia, and in general any factors leading to vaso-occlusion. Intraoperative hypoxemia and hypoperfusion can precipitate postoperative pain episode, along with increased postoperative immobility which leads to hypoventilation and acute chest syndrome [69]. Preventive measures instated include blood transfusions, reducing infectious episodes (vaccination), appropriate hydration, incentive spirometry, avoiding hypoxemic episodes, early ambulation, and adequate pain control [69]. The mainstay management for acute severe pain is opiate analgesia, with oral control being most appropriate [70]. It is imperative to note that many SCD patients have high degrees of narcotic tolerance and require large doses of narcotics for appropriate postoperative analgesia. In difficult cases, palliative care or pain management consultation is appropriate to ensure appropriate analgesic dosing. Corticosteroids have also been shown to reduce the length of acute pain episodes; however, lengthier use of corticosteroids has been associated with a high frequency of rebound pain and hospital readmission [71]. For a summary of noncentral nervous system complications that may occur in the postoperative period in patients with sickle cell disease, refer to Table 43.4.

Table 43.4 Summary of the predominant, noncentral nervous system complications that may occur in the postoperative period in patients with sickle cell disease, organized by organ system

Organ system	Pathophysiology	Complication	Epidemiology	Prevention
Renal system	HbS polymerizes once oxygen is unloaded which increases its likelihood to aggregate and causes a vaso-occlusive process The renal medulla is a region of low partial oxygen pressure, and low pH with high oxygen demand, inducing increased levels of oxygen unloading Higher rates of vaso-occlusion and thus renal infarction with papillary necrosis and medullary fibrosis	Nephrotic syndrome: Focal segmental glomerulosclerosis	Up to 30% of pediatric patients end up developing chronic renal failure as adults, a contributing factor to overall mortality Overall, SCD patients with proteinuria and a reduced GFR have an approximately 16–18% mortality	Maintaining appropriate hydration and minimizing intravenous contrast utilization are important in preventing acute kidney injury in this population

Table 43.4 (continued)

Organ system	Pathophysiology	Complication	Epidemiology	Prevention
Cardiopulmonary system	Vaso-occlusive events lead to ACS Chronic hypoxemia from multiple episodes of ACS leads to pulmonary hypertension which increases diastolic pressures Diastolic dysfunction from pulmonary hypertension eventually leads to left ventricular dilatation	Acute chest syndrome Pulmonary hypertension Congestive heart failure	20% of sickle cell patients who participated demonstrated mildly elevated pulmonary artery pressures Approximately 9% of patients displayed moderate to severe pulmonary hypertension (>45 mm Hg) Pulmonary hypertension can also lead to right heart failure in approximately 13% of patients Cardiac complications include left ventricular dysfunction in also 13% of patients	Reduction of the risk factors associated with exacerbation of pulmonary hypertension Sleep-associated breathing disorders should be treated regularly, with overnight oxygen and even continuous positive airway pressure Preoperative blood transfusions and exchange transfusion for reducing all the complications related to hypoxemia and micro-infarctions The use of incentive spirometry along with analgesia has been shown to significantly reduce the risk for atelectasis or infiltrates in the lungs

(continued)

Table 43.4 (continued)

Organ system	Pathophysiology	Complication	Epidemiology	Prevention
Immune system	The spleen is affected by the vaso-occlusive effect of sickled cells and blood sequestration leading to splenic infarctions. This results in an increased risk for infection, especially encapsulated organisms Infarcts of the spleen can become infected, leading to splenic abscess formation Other mechanisms of susceptibility include defective complement activation and nutritional deficiency Decreased erythrocyte production in the face of hemolysis predisposes to agents that halt hematopoietic production such as parvovirus B19	Functional asplenia and immunocompromise Splenic abscess Bacteremia and sepsis Aplastic crisis	Incidence of pediatric bacterial infection in SCD is 16% Incidence of bacteremia is 1.3%, with contribution from introduction of the conjugated vaccines (Bansil et al.) 94% of patients are functionally asplenic by age 5 years, with increased susceptibility to encapsulated bacteria Splenic sequestration occurs in 10–30% of children with SCD between 6 months and 3 years of age	Confirm administration of 7-Valent and 13-valent conjugated vaccines prior to any intervention Fever in immediate postoperative period should be thoroughly evaluated

Table 43.4 (continued)

Organ system	Pathophysiology	Complication	Epidemiology	Prevention
Musculoskeletal system	Micro-infarctions and vaso-occlusion causing bone marrow infarction which leads to musculoskeletal pain Joints may be involved with avascular necrosis leading to septic arthritis	Pain crisis Osteomyelitis Septic arthritis Osteopenia and Osteoporosis	Pain crisis in patients with sickle cell disease is the most common cause of immediate morbidity No correlation between mortality and rates of pain crises was found in patients between 10 and 19 years of age, but higher pain rates are correlated with mortality in patients over 20 years old Osteopenia and osteoporosis are present in 30–80% of patients with sickle cell anemia, with lumbar spine being most common site (Williams hematology book) 50% of patients have avascular necrosis of femoral head by age 33 years	Avoid intraoperative hypoxemia and hypoperfusion Preventative measures include blood transfusions, reducing infectious episodes (vaccination), appropriate hydration, incentive spirometry, avoiding hypoxemic episodes, early ambulation, and pain control (oral analgesia) Elevated inflammatory markers should raise suspicion for Septic arthritis and osteomyelitis

Conclusion

Sickle cell disease patients are complex with a host of unique factors and considerations that may affect virtually every organ system. Central nervous system considerations for the cerebrovascular neurosurgeon involve most commonly ischemic and hemorrhagic strokes. Stroke from vaso-occlusive disease in the absence of moyamoya changes is best managed medically with chronic transfusion therapy,

while strokes in the setting of progressive moyamoya changes are best managed with either direct or indirect revascularization. Intracranial hemorrhages are most often from aneurysms, and as compared to the general population, sickle cell patients tend to be younger and have smaller and multiple aneurysms with a posterior circulation predilection. Screening for both moyamoya and intracranial aneurysms with noninvasive is warranted, and surgical treatment should be offered in a multidisciplinary care setting to minimize complication risk.

References

1. Bunn HF, Aster JC. Pathophysiology of blood disorders. New York: McGraw-Hill Medical; 2011.
2. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med. 1997;337(11):762–9.
3. Kaul DK, Fabry ME, Costantini F, Rubin EM, Nagel RL. In vivo demonstration of red cell-endothelial interaction, sickling and altered microvascular response to oxygen in the sickle transgenic mouse. J Clin Invest. 1995;96(6):2845–53.
4. Williams TN, Mwangi TW, Wambua S, et al. Sickle cell trait and the risk of Plasmodium falciparum malaria and other childhood diseases. J Infect Dis. 2005;192:178–86.
5. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480–7. PMC. Web. 30 Nov 2016.
6. Guidelines for the control of haemoglobin disorders. Report of the VIth Annual Meeting of the WHO Working Group on Haemoglobinopathies, Cagliari, Sardinia, 8–9 April 1989. Geneva: World Health Organization, 1989.
7. Sickle cell disease: data & statistics. Centers for Disease Control and Prevention. 31 August 2016. Retrieved 19 November 2016.
8. Aluoch JR. Higher resistance to Plasmodium falciparum infection in patients with homozygous sickle cell disease in western Kenya. Tropical Med Int Health. 1997;2(6):568–71.
9. Wang Y, Liu G, Caggana M, et al. Mortality of New York children with sickle cell disease identified through newborn screening. Genet Med. 2015;17(6):452–9.
10. Sabarense AP, Lima GO, Silva LM, Viana MB. Characterization of mortality in children with sickle cell disease diagnosed through the Newborn Screening Program. J Pediatr. 2015;91(3):242–7.
11. Frempong T, Pearson HA. Newborn screening coupled with comprehensive follow-up reduced early mortality of sickle cell disease in Connecticut. Conn Med. 2007;71(1):9–12.
12. Yanni E, Grosse SD, Yang Q, Olney RS. Trends in pediatric sickle cell disease-related mortality in the United States, 1983–2002. J Pediatr. 2009;154(4):541–5.
13. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–44.
14. Elmariah H, Garrett ME, De castro LM, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 2014;89(5):530–5.
15. Cascieri MA, Goldenberg MM, Liang T. Biological activity of substance P methyl ester. Mol Pharmacol. 1981;20(3):457–9.
16. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004;350(9):886–95.
17. Smith ER, Scott RM. Moyamoya: epidemiology, presentation, and diagnosis. Neurosurg Clin N Am. 2010;21(3):543–51.
18. Alkan O, Kizilkilic E, Kizilkilic O, Yildirim T, Karaca S, Yeral M, Kasar M, Ozdogu H. Cranial involvement in sickle cell disease. Eur J Radiol. 2010;76(2):151–6. https://doi.org/10.1016/j.ejrad.2009.05.032.

19. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009; 360(12):1226–37.
20. Deane CR, Goss D, Bartram J, et al. Extracranial internal carotid arterial disease in children with sickle cell anaemia. Haematologica. 2010;95:1287–92.
21. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288–94.
22. Switzer JA, Hess DC, Nichols FT, Adams RJ. Pathophysiology and treatment of stroke in sickle-cell disease: present and future. Lancet Neurol. 2006;5:501–12.
23. Stuart ML, Nagel RL, et al. Sickle cell disease. Lancet. 2004;364(9442):1343–60.
24. Hogan AM, Pit-ten Cate IM, Vargha-Khadem F, Prengler M, Kirkham FJ. Physiological correlates of intellectual function in children with sickle cell disease: hypoxaemia, hyperaemia and brain infarction. Dev Sci. 2006;9:379–87.
25. Liu JE, Gzesh DJ, Ballas SK. The spectrum of epilepsy in sickle cell anemia. J Neurol Sci. 1994;123:6–10.
26. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339:5–11.
27. Ware HRW. SWiTCH investigators. Stroke with transfusions changing to hydroxyurea (SWiTCH). Blood. 2012;119(17):3925–32.
28. Oyesiku NM, Barrow DL, Eckman JR, Tindall SC, Colohan AR. Intracranial aneurysms in sickle-cell anemia: clinical features and pathogenesis. J Neurosurg. 1991;75(3):356–63.
29. Nabavizadeh SA, et al. Intracranial aneurysms in sickle cell anemia: clinical and imaging findings. J Neurointerv Surg. 2016;8:434–40. https://doi.org/10.1136/neurintsurg-2014-011572.
30. Birkeland P, Gardner K, Kesse-Adu R, et al. Intracranial aneurysms in sickle-cell disease are associated with the hemoglobin SS genotype but not with Moyamoya syndrome. Stroke. 2016;47(7):1710–3. https://doi.org/10.1161/STROKEAHA.116.012664. Epub 2016 Jun 14.
31. Preul MC, Cendes F, Just N, Mohr G. Intracranial aneurysms and sickle cell anemia: multiplicity and propensity for the vertebrobasilar territory. Neurosurgery. 1998;42(5):971–7; discussion 977–8.
32. Anson JA, Koshy M, Ferguson L, Crowell RM. Subarachnoid hemorrhage in sickle-cell disease. J Neurosurg. 1991;75(4):552–8.
33. Batjer HH, Adamson TE, Bowman GW. Sickle cell disease and aneurysmal subarachnoid hemorrhage. Surg Neurol. 1991;36:145–9.
34. Cheatham ML, Brackett CE. Problems in management of subarachnoid hemorrhage in sickle cell anemia. J Neurosurg. 1965;23:488–93.
35. Close RA, Buchheit WA. The management of ruptured intracranial aneurysm in sickle cell anemia. Case report. J Neurosurg. 1977;47:761–5.
36. Hitchcock ER, Tsementzis SA, Richardson SGN, et al. Subarachnoid hemorrhage in sickle-cell anemia. Surg Neurol. 1983;19:251–4.
37. Love LC, Mickle JP, Sypert GW. Ruptured intracranial aneurysms in cases of sickle cell anemia. Neurosurgery. 1985;16:808–12.
38. Ediriwickrema A, Williamson T, Hebert R, Matouk C, Johnson MH, Bulsara KR. Intracranial stenting as monotherapy in subarachnoid hemorrhage and sickle cell disease. J Neurointerv Surg. 2013;5(2):e4.
39. Dmytriw AA, Martinez JL, Marotta T, Montanera W, Cusimano M, Bharatha A. Use of a flow-diverting stent for ruptured dissecting aneurysm treatment in a patient with sickle cell disease. Interv Neuroradiol. 2016;22(2):143–7.
40. O'Shaughnessy BA, DiPatri AJ Jr, Parkinson RJ, Batjer HH. Development of a de novo cerebral arteriovenous malformation in a child with sickle cell disease and moyamoya arteriopathy. Case report. J Neurosurg. 2005;102(2 Suppl):238–43.
41. Hettige S, Sofela A, Bassi S, Chandler C. A review of spontaneous intracranial extradural hematoma in sickle-cell disease. Acta Neurochir. 2015;157(11):2025–9; discussion 2029. https://doi.org/10.1007/s00701-015-2582-6.

42. Hamm J, Rathore N, Lee P, LeBlanc Z, Lebensburger J, Meier ER, Kwiatkowski JL. Cranial epidural hematomas: a case series and literature review of this rare complication associated with sickle cell disease. Pediatr Blood Cancer. 2017;64(3). https://doi.org/10.1002/pbc.26237.
43. Koshy M, Weiner SJ, Miller ST, Sleeper LA, Vichinsky E, Brown AK, Khakoo Y, Kinney TR. Surgery and anesthesia in sickle cell disease. Cooperative Study of Sickle Cell Diseases. Blood. 1995;86(10):3676–84.
44. Buck J, Davies SC. Surgery in sickle cell disease. Hematol Oncol Clin North Am. 2005;19(5):897–902, vii.
45. Howard J. Sickle cell disease: when and how to transfuse. Hematology Am Soc Hematol Educ Program. 2016;2016(1):625–31.
46. Hulbert ML, Scothorn DJ, Panepinto JA, Scott JP, Buchanan GR, Sarnaik S, Fallon R, Chu JY, Wang W, Casella JF, Resar L, Berman B, Adamkiewicz T, Hsu LL, Smith-Whitley K, Mahoney D, Woods G, Watanabe M, MR DB. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr. 2006;149(5):710–2.
47. Rees DC, Robinson S, Howard J. How I manage red cell transfusions in patients with sickle cell disease. Br J Haematol. 180(4):607–17. First published: 29 January 2018. https://doi.org/10.1111/bjh.15115. February 2018.
48. Estcourt LJ, Fortin PM, Hopewell S, Trivella M, Doree C, Abboud MR. Interventions for preventing silent cerebral infarcts in people with sickle cell disease. Cochrane Database Syst Rev. 2016;(10). pii: CD012389. https://doi.org/10.1002/14651858.CD012389.
49. Mc Quaker IG, Jaspan T, Mcconachie NS, Dolan G. Coil embolization of cerebral aneurysm in patient with sickling disorders. Br J Haematol. 1999;106:388–90.
50. Vicari P, Choairy AC, Siufi GC, Arantes AM, Fonseca JR, Figueiredo MS. Embolization of intracranial aneurysms and sickle cell disease. Am J Hematol. 2004;76(1):83–4.
51. Firth PG, Peterfreund RA. Management of multiple intracranial aneurysms: neuroanesthetic considerations of sickle cell disease. J Neurosurg Anesthesiol. 2000;12(4):366–71.
52. DeBaun MR, Kirkham FJ. Central nervous system complications and management in sickle cell disease. Blood. 2016;127(7):829–38. https://doi.org/10.1182/blood-2015-09-618579.
53. Chong CT, Manninen PH. Anesthesia for cerebral revascularization for adult moyamoya syndrome associated with sickle cell disease. J Clin Neurosci. 2011;18(12):1709–12. https://doi.org/10.1016/j.jocn.2011.03.026.
54. Firth PG, Head CA. Sickle cell disease and anesthesia. Anesthesiology. 2004;101(3):766–85.
55. Houkin K, Kuroda S, Ishikawa T, Abe H. Neovascularization (angiogenesis) after revascularization in moyamoya disease. Which technique is most useful for moyamoya disease? Acta Neurochir. 2000;142(3):269–76.
56. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, Nakagawara J, Takahashi JC; JAM Trial Investigators. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan adult moyamoya trial. Stroke. 2014;45(5):1415–21. https://doi.org/10.1161/STROKEAHA.113.004386.
57. Jang DK, Lee KS, Rha HK, Huh PW, Yang JH, Park IS, Ahn JG, Sung JH, Han YM. Bypass surgery versus medical treatment for symptomatic moyamoya disease in adults. J Neurosurg. 2017;127(3):492–502. https://doi.org/10.3171/2016.8.JNS152875.
58. Kim DS, Huh PW, Kim HS, Kim IS, Choi S, Mok JH, Huh CW. Surgical treatment of moyamoya disease in adults: combined direct and indirect vs. indirect bypass surgery. Neurol Med Chir (Tokyo). 2012;52(5):333–8.
59. Kim T, Oh CW, Kwon OK, Hwang G, Kim JE, Kang HS, Cho WS, Bang JS. Stroke prevention by direct revascularization for patients with adult-onset moyamoya disease presenting with ischemia. J Neurosurg. 2016;124(6):1788–93. https://doi.org/10.3171/2015.6.JNS151105.
60. Sun H, Wilson C, Ozpinar A, Safavi-Abbasi S, Zhao Y, Nakaji P, Wanebo JE, Spetzler RF. Perioperative complications and long-term outcomes after bypasses in adults with moyamoya disease: a systematic review and meta-analysis. World Neurosurg. 2016;92:179–88. https://doi.org/10.1016/j.wneu.2016.04.083.

61. Cheung AH, Lam AK, Ho WW, Tsang CP, Tsang AC, Lee R, et al. Surgical outcome for moyamoya disease: clinical and perfusion computed tomography correlation. World Neurosurg. 2017;98:81–8. https://doi.org/10.1016/j.wneu.2016.10.117.
62. Kim H, Jang DK, Han YM, Sung JH, Park IS, Lee KS, et al. Direct bypass versus indirect bypass in adult moyamoya angiopathy with symptoms or hemodynamic instability: a meta-analysis of comparative studies. World Neurosurg. 2016;94:273–84. https://doi.org/10.1016/j.wneu.2016.07.009.
63. Mizoi K, Kayama T, Yoshimoto T, Nagamine Y. Indirect revascularization for moyamoya disease: is there a beneficial effect for adult patients? Surg Neurol. 1996;45(6):541–8; discussion 548–9.
64. Park SE, Kim JS, Park EK, Shim KW, Kim DS. Direct versus indirect revascularization in the treatment of moyamoya disease. J Neurosurg. 2017:1–10. https://doi.org/10.3171/2017.5.JNS17353.
65. Macyszyn L, Attiah M, Ma TS, Ali Z, Faught R, Hossain A, Man K, Patel H, Sobota R, Zager EL, Stein SC. Direct versus indirect revascularization procedures for moyamoya disease: a comparative effectiveness study. J Neurosurg. 2017;126(5):1523–9. https://doi.org/10.3171/2015.8.JNS15504.
66. Turhan T, Erşahin Y. Indirect bypass procedures for moyamoya disease in pediatric patients. Turk Neurosurg. 2011;21(2):160–6. https://doi.org/10.5137/1019-5149.JTN.3815-10.1.
67. Smith ER, McClain CD, Heeney M, Scott RM. Pial synangiosis in patients with moyamoya syndrome and sickle cell anemia: perioperative management and surgical outcome. Neurosurg Focus. 2009;26(4):E10. https://doi.org/10.3171/2009.01.FOCUS08307.
68. Rashad S, Fujimura M, Niizuma K, Endo H, Tominaga T. Long-term follow-up of pediatric moyamoya disease treated by combined direct-indirect revascularization surgery: single institute experience with surgical and perioperative management. Neurosurg Rev. 2016;39(4):615–23. https://doi.org/10.1007/s10143-016-0734-7.
69. Rees DC, Williams TN, Gladwin MT. Sickle cell disease. Lancet. 2010;376(9757):2018–31.
70. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. Am J Hematol. 2008;83(1):19–25.
71. Ataga KI, Moore CG, Jones S, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol. 2006;134(1):109–15.

Chapter 44
Neuroendovascular Surgery Medications

Ron Neyens

Antithrombotics

In order to minimize periprocedural thromboembolic complications, clinicians must understand the hematological system and targeted treatment strategies. The current physiology of hemostasis has evolved into a cell-based model with the platelet serving an integral role along all phases from clot initiation, amplification, and propagation [1, 2] (Fig. 44.1). In a traditional sense, endothelial injury/irritation occurs (plaque rupture, trauma, or catheter/balloon/stent interface), and the platelet immediately interacts with subendothelial proteins (tissue factor, von Willebrand factor, collagen matrix) *initiating* platelet adhesion and activation. It is followed by a thrombin-mediated *amplification* and release of soluble agonists (adenosine diphosphate, thromboxane A_2, serotonin) inducing recruitment, aggregation, and, finally, fibrinogen cross-linking with the glycoprotein (GP) IIb/IIIa receptor. Concomitantly, coagulation factors assemble on the surface of platelets, monocytes, and macrophages, *propagating* a tissue factor-initiated and thrombin-activated burst within both the prothrombinase complex and the intrinsic tenase. The magnitude of response and the strength of the formed clot depend upon the degree of endothelial injury as well as the concentration and activity of platelet/coagulation factors. In the absence of specific endothelial damage, endovascular-specific factors (composition of implants/tools, surface charge, contrast, and sheer stress) may initiate an inflammatory response to the "foreign body" and serve as the *initiating* phase of platelet activation and aggregation [3].

Therefore, the goal of pharmacological therapy is to prevent/minimize thrombus formation by decreasing platelet activity (via inhibiting adhesion/aggregation) and/

R. Neyens (✉)
Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC, USA
e-mail: neyens@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_44

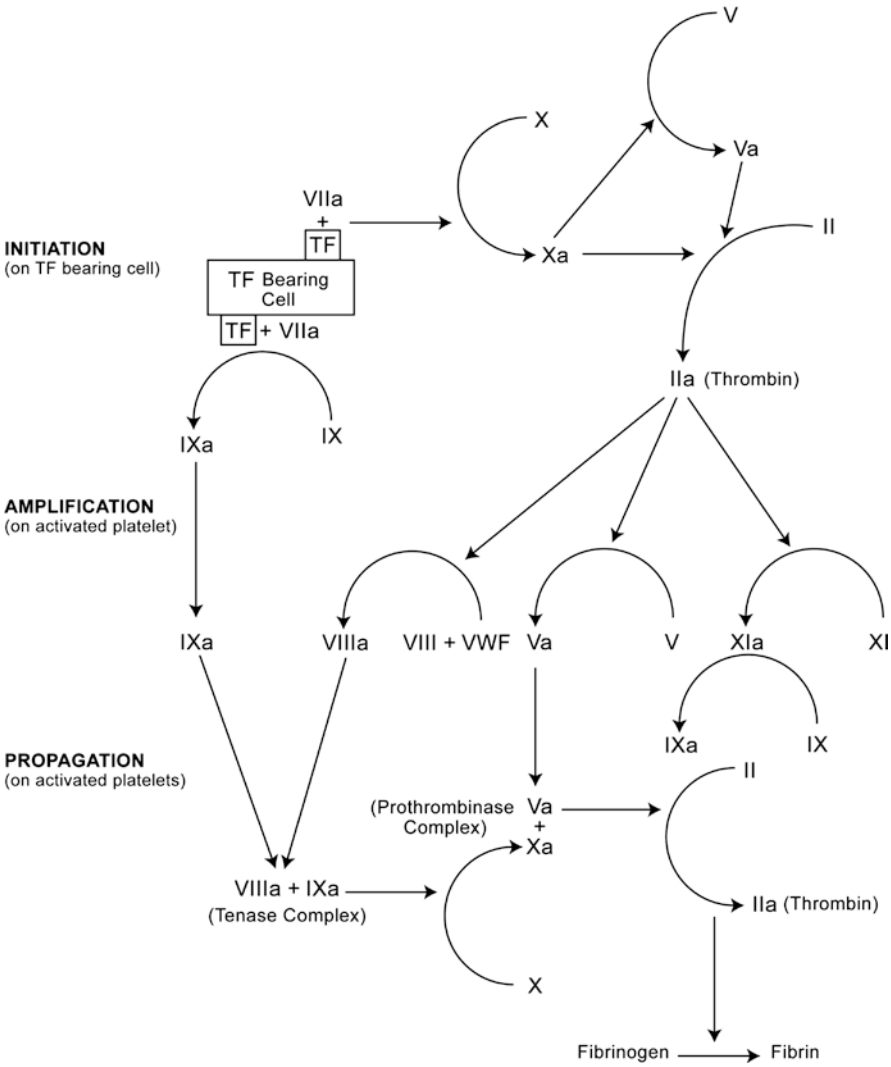


Fig. 44.1 Diagrammatic representation of cell-based model of hemostasis comprising initiation, amplification, and propagation. TF, tissue factor; a, activated [1]. (From Vine [1], with permission)

or thrombin-mediated propagation of fibrin formation. The greatest thrombosis risk ensues acutely over the initial 24 h following the NES procedure and/or endothelial injury and may maximally persist for up to 72 h until the local concentration of tissue factor and thrombin slowly dissipates [4]. If an implant is deployed, the thrombosis risk is extended into the subacute (within 30 days), late (within 1 year), and possibly the very late (greater than 1 year) phases [5]. It at least extends until neointimal endothelialization occurs, with the risk being device and location dependent, lasting at least a few weeks to several months.

Anticoagulation

Unfractionated Heparin (UFH)

Unfractionated heparin is the predominant anticoagulant utilized in the majority of neuroendovascular cases (Table 44.1). It carries a long history in interventional cardiology for the management of acute coronary syndrome (ACS) with clinical application extending to the management of NES cases. Of all current intravenous anticoagulants, it presently remains the most ideal given its vast clinical experience, ease of monitoring, and reversibility. It binds and forms an UFH-antithrombin III (AT-III) complex facilitating the inactivation of factors IIa, IX, Xa, XI, and XII [6]. By inhibiting factor IIa, it prevents the conversion of fibrinogen to fibrin, thus preventing clot propagation. In addition, it may inhibit thrombin-induced activation of platelets and factors V and VIII [10]. However, the clinical utility remains to be defined, and it must be carefully balanced with an observed UFH dose-dependent aggregation of platelets.

The dose of UFH for neuroendovascular procedures is not standardized and can be highly variable depending upon the amount of circulating AT-III, neutralizing acute-phase reactant proteins, degree of heparin clearance, and procedural hemorrhagic risk [7]. There is a myriad of reported doses, fixed at 3000–10,000 units, as

Table 44.1 Characteristics of anticoagulants and fibrinolytics for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ Pharmacodynamics	Considerations
Unfractionated heparin	IV: 3000–5000 units, titrate to ACT goal ACT: 1.5–2.5x baseline (200–350 s)	Onset: immediate T 1/2: 30–60 min (dose dependent)	Thrombocytopenia HIT (type I): little clinical significance HIT (type II): 1–2%, onset 4–10 days, prothrombotic Antidote Protamine: 1 mg/100 units UFH
Bivalirudin	IV: 0.6 mg/kg bolus and then 1.25 mg/kg/h (ACT 300–350 s) IV: 0.5 mg/kg bolus and then 0.8 mg/kg/h (ACT 200–300 s)	Onset: immediate T 1/2: 25 min (longer if renal impairment)	HIT history (preferred anticoagulant) Antidote None, may consider PCC in severe cases
Alteplase	IA: 2–5 mg aliquots up to max of 25 mg (total) IV: 1–2 mg/h (local catheter directed)	Onset: immediate T 1/2: 5 min 80% cleared within 10 min Lytic activity persists for ~1 h	Hypofibrinogenemia Lytic infusion: fibrinogen goal of 150–200 mg/dL Angioedema: <1% ACE-I increases risk

Data from Refs. [6–9]

well as weight-based doses ranging from 50 to 100 units/kg. The goal activated clotting time (ACT) is based on expert opinion, limited literature in carotid stenting, and often extrapolated from cardiac literature, which doesn't account for the technical difficulties encountered in NES procedures as well as the risk of dissections, thromboembolism, and vessel rupture. It is suggested to use a lower goal (ACT 200–300 s) for embolization of aneurysms and arteriovenous malformations (AVMs), whereas a higher goal (ACT 300–350 s) may be warranted for angioplasty and stenting [7]. It may be best to start with an UFH dose of 3000–5000 units (depending upon the procedural risk and patient weight) and then supplement to achieve the desired ACT. However, it is encouraged that each neuroendovascular group develop an appropriate UFH dose based on the utilized point-of-care ACT machine, reagent sensitivity, and desired ACT goal.

Direct Thrombin Inhibitors (DTIs)

There are currently two intravenous (IV) DTIs (bivalirudin and argatroban) in clinical use. In comparison with bivalirudin, argatroban has a longer half-life, which may not be an ideal agent for neuroendovascular procedures given the risk of hemorrhagic complications and the lack of a reversal antidote. In addition, argatroban dosing is often much less predictable provided its clearance is highly dependent upon hepatic blood flow and metabolic function. Bivalirudin has the majority of literature in both interventional cardiology and neuroendovascular procedures. In fact, it had gained traction as the preferred anticoagulant over UFH for percutaneous coronary intervention (PCI) given more predictable titration, the absence of platelet aggregation, and fewer periprocedural complications. However, most recent evidence for PCI stent deployment with the use of improved techniques, newer generation stents, and lower UFH doses now reveal that periprocedural complications are similar, which will possibly drive change back to UFH given the ease of reversibility and a much improved pharmacoeconomic profile [11]. Bivalirudin inhibits both free and clot-bound factor IIa, whereas UFH only inhibits free factor IIa; however, the clinical relevance of this is lacking in endovascular procedures. At present, given bivalirudin's similar efficacy/safety, high cost, and lack of reversibility, its clinical role is confined to cases of immune-mediated heparin-induced thrombocytopenia (HIT) or heparin resistance with the inability to reliably achieve targeted anticoagulation with UFH [12].

The dose of bivalirudin for neuroendovascular procedures is limited, but it is often lower than interventional cardiology procedures given the differing ACT goals. It is suggested that a dose of 0.6 mg/kg followed by a continuous infusion of 1.25 mg/kg/h is effective at maintaining an ACT of 300–350 s [8]. The bolus/maintenance dose would require incremental adjustments depending upon the procedural risk and the desired ACT. It does have some renal elimination (~10–20%) and will require dose adjustment in patients manifesting severe renal impairment (creatinine clearance <30 mL/min).

Fibrinolytics

Intra-arterial thrombolytics have been used for several years in the acute management of coronary and cerebrovascular ischemic disease (Table 44.2). Multiple agents are approved; however, only alteplase (tPA) is currently utilized clinically during neuroendovascular procedures. All serve as plasminogen activators, converting it into plasmin, which lyses fibrin-based clots into soluble degradation products. Pro-urokinase (first-generation thrombolytic) improved recanalization rates and functional outcome, but it also increased rates of intracranial hemorrhage [16]. Alteplase, being a newer-generation agent, is more clot/fibrin specific, targeting its dynamic action to the site of interest, thus improving the rates of clot dissolution with a theoretical lower risk of hemorrhage. It is currently utilized intra-procedurally for the management of ischemic stroke and for thromboembolic rescue treatment. However, its endovascular use in ischemic stroke has declined significantly as mechanical clot disruption techniques have advanced and rescue treatment is often considered to be inferior to glycoprotein (GP) IIB/IIIa inhibitors secondary to lower recanalization rates and higher hemorrhagic complications [9]. This is conceivable as acute, periprocedural clots tend to be very platelet rich with limited amounts of fibrin, thus mechanistically supporting a superior role for platelet inhibitors.

Antiplatelets

Cyclooxygenase Inhibitor

Aspirin has a long-standing history in interventional cardiology and was routinely utilized as mono-antiplatelet therapy alongside anticoagulation until the mid-1990s to early 1990s when it was discovered that local platelet deposition and activation were major periprocedural risk factors in thrombosis (Table 44.2 and Fig. 44.2) [13]. It was then delineated that dual antiplatelet therapy (DAPT) following PCI stent deployment is superior to aspirin/anticoagulation for preventing stent thrombosis, ischemic events, and hemorrhagic complications. This same finding has also been replicated in carotid artery stenting [18]. Initially, aspirin was combined with ticlopidine but later transitioned to combine with newer-generation P2Y12 inhibitors given the lower incidence of life-threatening hematological disorders. Aspirin irreversibly inhibits cyclooxygenase (COX), blocking the conversion of arachidonic acid to prostaglandins and thromboxane A_2, thereby inhibiting platelet aggregation [14].

P2Y12 Inhibitors

There are currently three oral P2Y12 inhibitors in clinical use (clopidogrel, prasugrel, and ticagrelor). Again, the majority of the literature is in interventional cardiology with extrapolated application to neuroendovascular procedures.

Table 44.2 Characteristics of antiplatelets for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ pharmacodynamics	Considerations
Aspirin	Oral Load: 325–650 mg Maintenance: 81–325 mg daily Rectal Load: 300–600 mg	Onset: 20–60 min (immediate release) T 1/2: 15–20 min (parent); 3–4 h (salicylate) Duration: 5–7 days	Resistance: 6–27% Hypersensitivity Urticaria-angioedema: 2–4% Bronchospastic: 10–15% of asthmatics
Clopidogrel	Oral Load: 300–600 mg Maintenance: 75 mg daily	Onset (time to 40–50% inhibition) 300 mg (6–10 h) 600 mg (2–6 h) T 1/2: 6 h (parent), 30 min (active) Duration: 5–10 days	Resistance: 10–48% ADRs: Hematological (rare) Hypersensitivity Anaphylaxis (rare) Rash: 3–5%, can attempt desensitization or substitute ticagrelor
Ticagrelor	Oral Load: 180 mg Maintenance: 90 mg BID	Onset (time to 70–80% inhibition) 180 mg (45–60 min) T 1/2: 7 h (parent), 9 h (active) Duration: 3–5 days	Resistance: n/a ADRs: Hematological (rare); dyspnea, 10–15%; hyperuricemia, 15–20%
Prasugrel	Oral Load: 60 mg Maintenance: 10 mg daily 5 mg (<60 kg)	Onset (time to 70–80% inhibition) 60 mg (45–60 min) T 1/2: 7–15 h (parent), 4–7 h (active) Duration: 5–10 days	Resistance: n/a ADRs: Hematological (rare) Black box: prior TIA or stroke
Abciximab	IV: 0.25 mg/kg bolus and then 0.125 mcg/kg/min IA: Variable 2–5 mg aliquots, up to max of 20–25 mg (total) 0.25 mg/kg	Onset (time to 70–80% inhibition) 0.25 mg/kg (10 min) T 1/2: 30 min Duration: variable ~75% platelet recovery at 48 h	Thrombocytopenia Actual: 0.5–5% Pseudo-(lab artifact): 1–2%, rule out by sending EDTA, citrate, and heparin tubes Hypersensitivity (rare) Immunogenicity Antibodies: ~5–7% with risk of infusion reactions and thrombocytopenia upon reexposure
Eptifibatide	IV: 180 mcg/kg bolus and then 0.5–2 mcg/kg/min IA: Variable 2 mg aliquots, up to max of 22 mg (total) 0.2 mg/kg	Onset (time to 70–80% inhibition) 180 mcg/kg (5–10 min) T 1/2: 2.5 h Duration: 4–8 h	Thrombocytopenia (rare)
Tirofiban	IV: 8–25 mcg/kg bolus and then 0.1–0.15 mcg/kg/min IA: Variable 0.2 mg aliquots, up to max of 1 mg (total) 0.3 mg aliquots, up to max of 1.2 mg (total)	Onset (time to 70–80% inhibition): 25 mcg/kg (5–10 min) T 1/2: 2 h Duration: 4–8 h	Thrombocytopenia (rare)

Data from Refs. [13–15]

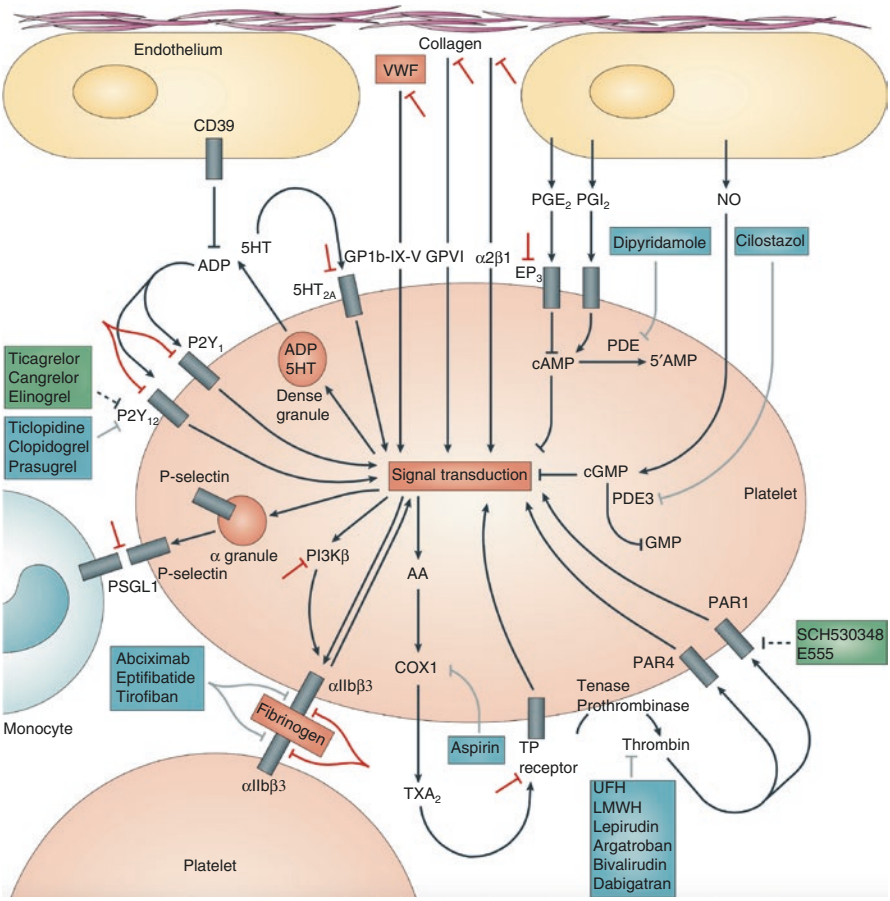


Fig. 44.2 Platelet function and molecular targets of antiplatelet agents. Initial platelet adhesion to damage vessel walls is mediated by the finding of exposed collagen to platelet surface glycoprotein Vl (GPVI) and integrin alpha2beta1 and the binding of von Willebrand factor (VWF) to the platelet surface glycoprotein 1b (GP1b)-IX-V complex. (From Michelson [17], with permission)

Clopidogrel was the first ticlopidine replacement and has been used for several years. Recently, newer-generation agents (prasugrel and ticagrelor) are being established as preferred therapy in acute coronary syndromes (ACS) following PCI stent deployment, especially in high-risk patients (large stent burden, diabetics) and those with high on-treatment platelet reactivity with clopidogrel [14]. The literature for novel antiplatelet agents in NES procedures is limited with the majority of case reports/series involving those expressing high on-treatment platelet reactivity with clopidogrel. All the P2Y12 inhibitors block ADP binding to the P2Y12 receptor, thereby inhibiting platelet aggregation [13]. However, they all have differing PK/PD, specifically in regard to the activation, onset, and/or potency of platelet inhibition. Clopidogrel and prasugrel are both irreversible

thienopyridine prodrugs requiring metabolic cytochrome P450 hepatic activation. Clopidogrel requires two-step activation and is more susceptible to drug-drug interactions (CYP2C19 inhibitors) and genetic polymorphisms exposing patients to a greater risk of hypo- or hyperresponse. Ticagrelor is an irreversible, (this should state, Ticagrelor is a reversible), direct-acting non-thienopyridine that does not require metabolic activation. Ticagrelor and prasugrel are both more potent than clopidogrel and superior in preventing coronary stent thrombosis and ischemic events. However, the trade-off is more hemorrhagic complications. Of importance to NES procedures, prasugrel carries an FDA black box warning for intracranial hemorrhage risk in patients with a prior transient ischemic attack (TIA) or stroke. It also requires weight-based dose adjustments adding to its dosing complexity. These specific factors have driven a shift toward the use of ticagrelor in situations requiring the use of a newer-generation P2Y12 inhibitor.

GP IIb/IIIa

There are currently three GP IIb/IIIa inhibitors in clinical use (abciximab, eptifibatide, and tirofiban). There are several years of experience with all three agents in interventional cardiology. Initially, abciximab was felt to be a superior agent theorized to be driven by its unique ability to inhibit endothelial and smooth muscle receptors preventing platelet adhesion and limiting inflammation [15]. Following dose optimization, evidence now suggests that the GP IIb/IIIa inhibitors have similar efficacy and safety outcomes after coronary revascularization. Abciximab has the majority of literature for neuroendovascular procedures; however, evidence for eptifibatide and tirofiban are accumulating. In fact, a recent meta-analysis suggested an improved recanalization rate with eptifibatide or tirofiban following aneurysm coil thrombosis rescue strategies [9]. The GP IIb/IIIa inhibitors block the final common pathway of fibrinogen cross-linking of platelets, thereby inhibiting platelet aggregation; however, they have different PK/PD. Abciximab is a large-molecule, monoclonal antibody that displays a long half-life and irreversibly binds the GP IIb/IIIa receptor [15]. Intermittent abciximab intravenous (IV)/intra-arterial (IA) bolus dosing strategies display a theoretical advantage in stent or flow-diverter deployment given the longer half-life and its potential to provide a longer duration of platelet inhibition while awaiting the onset of DAPT. However, the clinical application remains undefined but may be of relevance in emergent cases in which planned initiation of DAPT is not feasible. In comparison, eptifibatide and tirofiban are small-molecule, reversible inhibitors. The shorter half-lives may be attractive as bridge therapy post-procedural, before committing to DAPT, until the clinician is sure no open intracranial procedure or intracranial device is required. The relevance of each situation depends upon the case complexity, dose, route (IA vs IV), and mode of administration (bolus vs continuous) of the GP IIb/IIIa inhibitor.

Antiplatelet Monitoring

Antiplatelet monitoring started in interventional cardiology with "resistance" or high on-treatment platelet reactivity to aspirin and/or clopidogrel being associated with increased rates of stent thrombosis and recurrent ischemic events [13]. Point-of-care platelet inhibition assays were then utilized to identify an optimal target to direct dose individualization. Despite all these efforts, clopidogrel dose individualization in large randomized studies didn't result in improved cardiac outcomes. The new P2Y12 inhibitors were then found to be more clinically effective in PCI stent deployment, halting further studies for point-of-care-directed clopidogrel dose individualization. However, the increased hemorrhage risk with the more potent, newer-generation P2Y12 inhibitors has created some trepidation to use as standard of care in all high-risk neuroendovascular procedures requiring DAPT. Therefore, the NES realm still faces the difficult questions regarding the utility of antiplatelet monitoring, the most appropriate assay, the goal inhibition targets, and the dosing strategy.

The rates of actual "resistance" are variable and dependent upon the patient population, exposure time, methodology, assay, and interpretative criteria [19]. The reported rates for aspirin and clopidogrel are between 6–27% and 10–48%, respectively. It appears to be dose related, with higher doses able to achieve a greater degree of platelet inhibition, and susceptible to comorbidities (diabetes, atherosclerosis, myeloproliferative syndromes, etc.). It is clearly associated with clinical ischemic and thrombotic complications in interventional cardiology with accumulating evidence for associated thrombotic complications in neuroendovascular procedures [13].

There are several monitoring assays available, light transmission aggregometry (LTA), whole blood aggregometry (WBA), and various point-of-care tests: PFA-100, thromboelastography (TEG) platelet mapping, flow cytometry (VASP), and VerifyNow [20]. Each test has unique limitations regarding individual covariance and sensitivity/specificity. LTA is considered the "gold standard" and serves as the correlative comparator for alternative methods. The ideal assay would be readily available, rapidly performed with good sensitivity and specificity, with clearly defined targets to direct clinical decisions. LTA is very labor intensive (~3–4 h) and not logistically feasible in most NES procedures. WBA (multiplate) is not routinely available in the United States and is poorly correlated to LTA. PFA-100 also has poor correlation to LTA and is deemed not suitable for detection of platelet "resistance." TEG platelet mapping appears to have good correlation to LTA but presently has limited data for interpretive criteria and clinical application to interventional procedures. VASP is unique in its ability to isolate the effects of clopidogrel in the presence of GP IIb/IIIa inhibitors, which is an advantage over other point-of-care assays. However, it is not routinely available and is technically challenging to perform. VerifyNow is specifically designed to rapidly detect antiplatelet drug "resistance" at the bedside, allowing for rapid clinical decisions. It has been the most studied assay, with more well-established interpretive criteria (aspirin reaction units (ARU) for aspirin and P2Y12 reaction units (PRU) for P2Y12 inhibitors) for clinical

application in both interventional cardiology and neuroendovascular procedures. However, it is important to note that the ARU and PRU results are affected by certain factors: patient comorbidities, timing and dose of loading strategies, and the presence of circulating GP IIb/IIIa inhibitors.

As mentioned, there are no well-defined inhibition targets, specifically PRU, when utilizing VerifyNow to direct clopidogrel dose response during neuroendovascular procedures. The cardiology literature suggests a targeted PRU window between 95 and 208 to balance both safety and efficacy [21]. In general, much of the neuroendovascular literature replicates efforts in interventional cardiology. The exception is for more thrombotic implants (pipeline embolization devices) where the target PRU range may ideally fall between a range of 70 and 150 [22]. However, some suggest a PRU < 200 is not necessary for anterior circulation pipeline embolization devices [23]. The most optimal treatment strategy to overcome hyporesponsiveness (PRU > upper limit target) of clopidogrel lacks supported literature; however, one may consider reloading and increasing the maintenance dose (150 mg/day) or switch to an alternative P2Y12 inhibitor (ticagrelor). In a similar fashion, those expressing hyperresponsiveness (PRU < lower limit target) may benefit from a clopidogrel dose reduction (75 mg QOD) or switch to an alternative P2Y12 inhibitor [24]. It is the author's opinion given the known risk of thrombotic and hemorrhagic complications with higher and lower than target PRUs, respectively, to consider an alternative P2Y12 inhibitor, preferably ticagrelor, which is not a prodrug requiring metabolic activation.

Cerebrovascular Vasodilators

Intra-arterial vasodilating agents are predominantly utilized for the treatment of arterial vasospasm as a complication of aneurysmal subarachnoid hemorrhage (Table 44.3) [25]. In addition, they may be utilized to dilate vessels and assist with catheter/device advancement during endovascular procedures. Historically, papaverine, an opium-based phosphodiesterase inhibitor, had been utilized. It has fallen out of favor provided concerns for drug-induced intracranial hypertension, seizures, and neurotoxicity. There are currently three pharmacological agents in clinical use (verapamil, nicardipine, and milrinone). The first two agents are calcium-channel blockers (CCBs), while the latter is a phosphodiesterase inhibitor (PDE3-I). Nicardipine is a more vascular-selective agent in comparison with verapamil. It does appear to provide effective angiographic vasodilation with documented reductions in cerebral blood flow (CBF) velocities and associated neurologic improvement. The greatest concern is hypotension, which may be profound and potentially prolonged leading to a reduction in cerebral perfusion pressures. Verapamil is less selective for the cerebral vasculature yet has been shown to provide effective angiographic vasodilation and associated neurologic improvement. Although hypotension may occur, it may be less common than nicardipine given its lower degree of vascular selectivity. Milrinone has more limited literature but appears to quickly

Table 44.3 Characteristics of vasodilators for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ pharmacodynamics	Considerations
Nicardipine	IA: total dose (variable), 5–40 mg Dilute with NS to concentration of 1 mg/mL, administer 0.5–1 mL in an aliquot dosing strategy	Onset: 30–60 s Duration: 1–3 h	Hypotension (dose related)
Verapamil	IA: total dose (variable), 1–40 mg Dilute with NS to concentration of 1 mg/mL, administer 1–5 mL in an aliquot dosing strategy	Onset: 1–5 min Duration: 20–40 min	Hypotension/ bradycardia (dose related)
Milrinone	IA: total dose (variable), 4–15 mg Dilute with NS to concentration of 0.1 mg/mL, administer 2–4 mL in an aliquot dosing strategy	Onset: 1–5 min Duration: 2–4 h	Hypotension/ tachycardia (dose related)

Data from Refs. [25, 26]

improve angiographic vasodilation [26]. There is no comparative evidence documenting superiority; therefore, agent selection is largely based on clinician comfort and experience.

References

1. Vine AK. Recent advances in haemostasis and thrombosis. Retina. 2009;29:1–7.
2. Ferreira CN, Sousa MO, Sant'Ana Dusse LM, et al. A cell-based model of coagulation and its implications. Rev Bras Hematol Hemoter. 2010;32:416–21.
3. Palmaz JC. Intravascular stenting: from basic science to clinical application. Cardiovasc Intervent Radiol. 1992;15:279–84.
4. Ferns GA, Stewart-Lee AL, Anggard EE. Arterial response to mechanical injury: balloon catheter de-endothelialization. Atherosclerosis. 1992;92:89–104.
5. Klisch J, Turk A, Turner R, et al. Very late thrombosis of flow-diverting constructs after the treatment of large fusiform posterior circulation aneurysms. AJNR Am J Neuroradiol. 2011;32:627–32.
6. Hirsh J. Heparin. N Engl J Med. 1991;324:1565–74.
7. Hussein HM, Georgiadis AL, Qureshi AI. Point-of-care testing for anticoagulation monitoring in neuroendovascular procedures. Am J Neuroradiol. 2012;33:1211–20.
8. Georgiadis AK, Shah Q, Suri FK, et al. Adjunct bivalirudin dosing protocol for neuro-endovascular procedures. J Vasc Interv Neurol. 2008;1:50–3.
9. Brinjikji W, Morales-Valero SF, Murad MH, et al. Rescue treatment of thromboembolic complications during endovascular treatment of cerebral aneurysms: a meta-analysis. AJNR Am J Neuroradiol. 2015;36:121–5.
10. Mascelli MA, Kleiman NS, Marciniak SJ, et al. Therapeutic heparin concentrations augment platelet reactivity: implications for the pharmacologic assessment of the glycoprotein IIb/IIIa antagonist abciximab. Am Heart J. 2000;139:696–703.
11. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med. 2015;373:997–1009.
12. Hassan AE, Merron MZ, Georgiadis AL, et al. Safety and tolerability of high-intensity anticoagulation with bivalirudin during neurovascular procedures. Neurocrit Care. 2011; 15(1):96–100.

13. Gandhi CD, Bulsara KR, Fifi J, et al. Platelet function inhibitors and platelet function testing in neurointerventional procedures. J Neurointerv Surg. 2014;6:567–77.
14. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30–47.
15. Antoniucci D. Differences among GP IIb/IIIa inhibitors: different clinical benefits in non-ST segment elevation acute coronary syndrome percutaneous coronary intervention patients. Eur Heart J. 2007;9(Supp A):A32–6.
16. Del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. 1998;29:4–11.
17. Michelson AD. Antiplatelet therapies for the treatment of cardiovascular disease. Nat Rev. 2010;9:154–69.
18. Enomoto Y, Yoshimura S. Antiplatelet therapy for carotid artery stenting. Interv Neurol. 2013;1:151–63.
19. Oxley TJ, Dowling RJ, Mitchell PJ, et al. Antiplatelet resistance and thromboembolic complications in neurointerventional procedures. Front Neurol. 2011;2:1–9.
20. Le Quellec S, Bordet JC, Negrier C, et al. Comparision of current platelet functional tests for the assessment of aspirin and clopidogrel response. Thromb Haemost. 2016;116:638–50.
21. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicenter registry study. Lancet. 2013;382:614–23.
22. Daou B, Starke RM, Chalouhi N, et al. P2Y12 reaction units: effect on hemorrhagic and thromboembolic complications in patients with cerebral aneurysms treated with the pipeline embolization device. Neurosurgery. 2016;78:27–33.
23. Bender MT, Lin L, Colby GP, et al. (2016) P2Y12 hyporesponse (PRU > 200) is not associated with increased thromboembolic complications in anterior circulation pipeline. J Neurointerv Surg. 2017;9(10):978–81.
24. Goh C, Churilov L, Mitchell P, et al. Clopidogrel hyper-response and bleeding risk in neurointerventional procedures. AJNR Am J Neuroradiol. 2013;34:721–6.
25. Weant KA, Ramsey CN, Cook AM. Role of intraarterial therapy for cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage. Pharmacotherapy. 2010;30:405–17.
26. Shankar JS, dos Santos MP, Deus-Silva L, et al. Angiographic evaluation of the effect of intraarterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology. 2011;53:123–8.

Index

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3