Current Clinical Neurology
Series Editor: Daniel Tarsy

Randall C. Edgell *Editor*
Sean I. Savitz
John D. Dalfino *Associate Editors*

Neurointervention in the Medical Specialties

A Comprehensive Guide

Humana Press

Current Clinical Neurology

More information about this series at http://www.springer.com/series/7630

Series Introduction

Neurointervention in the Medical Specialties provides a remarkably detailed and comprehensive review of the state of the art in this very innovative and burgeoning field. As stated by the editors, neurointervention is a coming together of the fields of neurology, neurosurgery, and neuroradiology which, in a relatively short period of time, has greatly expanded therapeutic options for a number of previously untreatable conditions. More than a manual concerning vascular neurointerventions of one type or another, it also covers important areas of interest to other medical and surgical subspecialties such as preoperative tumor embolization, interventional approaches to ophthalmological and otolaryngological disorders, the role of Wada testing in epilepsy surgery, the role of neurointervention in Cushing's Syndrome, and even the potential future for catheter delivery of stem cell therapy. The opening chapter concerning "the neurointerventional tool kit" sets the stage for the very specific and highly useful information which characterizes all of the chapters in this volume. Ample numbers of illustrative figures and case discussions are provided which greatly enhance the delivery of this material. This is a highly useful and down to earth overview of the field which will be of great interest to all practitioners in the field.

Daniel Tarsy, MD
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA, USA

Editor Randall C. Edgell, MD

Associate Editors Sean I. Savitz, MD and John D. Dalfino, MD

Neurointervention in the Medical Specialties

A Comprehensive Guide

Springer

Editor
Randall C. Edgell, MD
Department of Neurology and Psychiatry
Saint Louis University
St. Louis, MO, USA

Associate Editors
Sean I. Savitz, MD
Department of Neurology
University of Texas Health Science Center, UT-HEALTH
Houston, TX, USA

John D. Dalfino, MD
Department of Neurosurgery
Albany Medical Center
Albany, NY, USA

ISBN 978-1-4939-1941-3 ISBN 978-1-4939-1942-0 (eBook)
DOI 10.1007/978-1-4939-1942-0
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014955061

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

Neurointervention was developed over 30 years ago to deal with a specific clinical challenge: intraoperative hemorrhage associated with intracerebral arteriovenous malformations. Improvised techniques were developed to deal with this clinical challenge, and eventually elegant solutions were obtained. Shortly thereafter the second great clinical challenge was met and elegantly overcome: treatment of intracerebral aneurysms.

Now, several decades later, *neurointervention* is still an evolving clinical field overlapping several other specialties. The discipline, however, is still incompletely understood in the medical world. Neurointerventional procedures rarely exist in a vacuum and are intrinsically related to preexisting specialties. Many medical professionals in these other arenas are unaware of possible ancillary procedures or therapeutic solutions that this new specialty now offers that can aid them and their patients. Further, management or treatment of various disorders is typically assessed from a singular viewpoint, and neurointervention offers a unique and new perspective.

Neurointervention and the medical specialties outlines the scope of this new field with particular attention to the interdisciplinary overlap. Attention is paid to actual clinical conditions and possible solutions offered by neurointervention. In this way, light is shed on the symbiosis between various specialties and neurointervention with the goal of facilitating interdisciplinary collaboration for the benefit of patients. Many procedures might be obvious or commonplace among some of the various neurological and head/neck specialties, while others might be unknown. In addition to delineating these multiple solutions to numerous clinical situations and resulting

diagnostic and therapeutic problems, the authors give in-depth description of the procedures themselves.

In a quarter of a century of practicing in this arena, I still meet people, including physicians, who have never heard of our profession. Neurointervention has much to offer and this book will be enlightening.

JOHN J. (BUDDY) CONNORS, MD
Professor and Director;
Interventional Neuroradiology;
Dept of Radiology
Professor of Neurology
Professor of Neurosurgery
Vanderbilt University Medical Center
Nashville, TN 37203

Preface: Neurointervention—An Evolving Specialty

The field of neurointervention is in many ways a microcosm of the many trends shaping modern medicine. It is a point of convergence among several traditionally distinct fields: neurology, neurosurgery, and radiology. The "giants" upon whose shoulders the field has been built include Portuguese neurologist Egas Moniz, who first introduced cerebral angiography in 1927; Swedish radiologist Sven-Ivar Seldinger, who enhanced the safety of vascular access and navigation in 1953; and Russian neurosurgeon Fedor Serbinenko, who invented one of the first therapeutic neurointerventional techniques in 1969. The knowledge base and perspective of each field have resulted in a subspecialty that is able to provide highly complex, multidimensional patient care.

Technological advances have served as a constant and powerful driving force within neurointervention. The introduction of detachable coils, liquid embolic materials, intracranial stents, and stroke thrombectomy devices has all occurred within the last two decades. Indeed, the rate of innovation seems to increase with each passing year. This relentless creativity opens windows of therapeutic opportunity but also presents challenges for both neurointerventional practitioners and referring physicians. The pace of innovation has outstripped our ability to rigorously test emerging devices and treatment paradigms. There have been some disappointments when randomized clinical trial data has caught up with a promising new treatment, but this process of creative destruction also has led to great leaps forward in therapeutic safety and efficacy.

As this fast moving field grows, it is important for practitioners of neurointervention to understand their role in the profession as a whole. Where can we be most useful to our medical colleagues and patients? This book serves as a bridge between the neurointerventionalist and the physicians who most frequently look to us for answers to some of the most intractable problems they face. It provides background on the diseases treated through neurointervention along with the indications and alternatives to such treatments.

The book is grouped into four parts: an introduction to the tools and anatomical structures that are integral to the field; disease processes most often encountered by neurologists, cardiologists, and vascular surgeons; those more frequently treated by

neurosurgeons; and finally those first seen by several other specialties including ophthalmologists and head and neck surgeons.

Importantly, each chapter includes details of neurointerventional techniques and case discussions that are sufficiently granular to provide a treatment template and guidance to the neurointerventionalist in training and practice. At the same time these descriptions will provide the referring physician with insight into how neurointerventional procedures are performed. Finally, there are several chapters at the end of the text that attempt to look into the crystal ball of neurointervention at what new opportunities await us just over the horizon.

St. Louis, MO, USA Randall C. Edgell

Contents

Contributors

Alex Abou-Chebl, M.D. University of Louisville School of Medicine, Louisville, KY, USA

Michael J. Alexander, M.D. Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Kaiz S. Asif, M.D., M.S. Department of Neurology, Froedtert Hospital & Medical College of Wisconsin, Milwaukee, WI, USA

Vibhav Bansal Department of Neurology, Michigan State University, Park, IL, USA

Lee A. Birnbaum, M.D. Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Alan S. Boulos, M.D. Albany Medical College, Albany, NY, USA boulosa@mail.amc.edu

Mark D. Calayag, M.D. Department of Neurosurgery, Albany Medical Center, Albany, NY, USA

Alicia C. Castonguay, Ph.D. Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

Peng R. Chen, M.D. Assistant Professor, The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School, Houston, TX, USA

Yanjun Chen, M.D., Ph.D. Ophthalmology and Visual Sciences, University of Wisconsin Hospitals and Clinics, Madison, WI, USA

Sophia Chung, M.D. Saint Louis University School of Medicine, St. Louis, MO, USA

Jeroen R. Coppens, M.D. Department of Neurosurgery, St. Louis University, St. Louis, MO, USA

John C. Dalfino Department of Neurosurgery, Albany Medical Center, Albany, NY, USA

Mark Dannenbaum, M.D. Department of Neurosurgery, The University of Texas Houston Medical School & Memorial Hermann, Houston, TX, USA

Eric M. Deshaies, M.D. Associate Professor of Neurosurgery, Neuroscience & Physiology, SUNY Upstate Medical University, Neurosurgery, East Adams St., Syracuse, NY, USA

Doniel Drazin, M.D., M.A. Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Paula Eboli, M.D. Department of Neurosurgery, Cedars Sinai Medical Center, Los Angeles, CA, USA

Randall C. Edgell, M.D. Department of Neurology and Psychiatry, Saint Louis University, St. Louis, MO, USA

Eliahu Feen Department of Neurology and Psychiatry, Saint Louis University, St. Louis, MO, USA

Ahmed Galal, M.D. Assistant Professor, Ain Shams University, Department of Neurosurgery, Cairo, Egypt

Ravi H. Gandhi, M.D. Department of Neurosurgery, Albany Medical Center, Winter Park, FL, USA

George T. Griffing, M.D. Department of Endocrinology, St. Louis University, St. Louis, MO, USA

Diogo C. Haussen, M.D. Neurology—Neurosurgery, University of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, FL, USA

Syed I. Hussain, M.D. Department of Neurology & Ophthalmology, B401 Msu Clinical Center, Michigan State University and Sparrow Hospital, East Lansing, MI, USA

Mouhammad A. Jumaa, M.D. Department of Neurology, University of Toledo Medical Center, Toledo, OH, USA

Junaid Siddiq Kalia, M.D. Department of Neurology, Saint Louis University Hospital, St. Louis, MO, USA

Joanna Kemp, M.D. Department of Neurosurgery, Saint Louis University, St. Louis, MO, USA

Abhay Kumar, M.D. Department of Neurology, Saint Louis University, St. Louis, MO, USA

David S. Liebeskind, M.D. Department of Neurology, UCLA, Los Angeles, CA, USA

Sonal Mehta, M.D. Department of Neurology, St. Louis University Hospital, St. Louis, MO, USA

Osman Mir, M.D. Department of Neurology, Texas A&M University, Baylor University Medical Center, Dallas, TX, USA

Vivek Misra, M.D. Department of Neurology, University of Texas Health Science Center San Antonio, San Antonio, TX, USA

Ashish Nanda, M.D. Neurology and Neurosurgery, University of Missouri, Columbia, MO, USA

Anmar Razak, M.D. Department of Neurology, Michigan State University, B401 MSU Clinical Center, East Lansing, MI, USA

Sean I. Savitz, M.D. Department of Neurology, University of Texas Health Science Center, UT-HEALTH, Houston, TX, USA

Amit Singla, M.D. Resident Physician, SUNY Upstate Medical University, Department of Neurosurgery, Syracuse, NY, USA

Parul Sinha, M.D., M.B.B.S., M.S. Otolaryngology-Head & Neck Surgery, Washington University School of Medicine, St. Louis, MO, USA

Aaron P. Tansy, M.D. Department of Neurology, UCLA, Los Angeles, CA, USA

Mohamed S. Teleb, M.D. Department of Neurology, Froedtert Hospital & Medical College of Wisconsin, Milwaukee, WI, USA

Ali Hassoun Turkmani, M.D. Department of Neurosurgery, University of Texas at Houston, Houston, TX, USA

Mark A. Varvares, M.D., F.A.C.S. Department of Otolaryngology, Head and Neck Surgery, Saint Louis University School of Medicine, St. Louis, MO, USA

Anantha Vellipuram, M.D. Department of Neurology, University of Missouri, Columbia, MO, USA

Mohammad Wasay, M.B.B.S., M.D., F.R.C.P. Department of Neurology, Aga Khan University, Karachi, Pakistan

L. James Willmore, M.D. Saint Louis University School of Medicine, St. Louis, MO, USA

Dileep R. Yavagal, M.D., M.B.B.S. Neurology/Neurosurgery, University of Miami, Miami, FL, USA

Osama O. Zaidat, M.D., M.S. Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

Chapter 1
The Neurointerventional Toolkit

Paula Eboli, Doniel Drazin, and Michael J. Alexander

Introduction

Neurointerventional procedures employ the use of various specialized products and devices. This chapter presents an overview of the contrast agents, catheters, coils, liquid and particulate embolic materials, stents, clot retrievers, and closure devices commonly used by neurointerventionalists. An understanding of the basic differences in the uses and actions of these products is intended to assist providers in choosing from the many options.

Contrast Agents

Nonionic Contrast Agents

Iohexol, trade name Omnipaque, is currently the most widely used contrast media for neurointerventional procedures. Iohexol is a low-osmolality contrast agent available in various concentrations ranging from 140 to 350 milligrams of iodine per milliliter. Iohexol is safer and less allergenic than ionic preparations. Patients with normal renal function can tolerate as much as 5–8 cm^3/kg of contrast for the duration of the interventional procedure for a maximum of 400–800 cm^3 [1]. Patients with impaired renal function should have reduced contrast load and periprocedural precautions taken to reduce the risk of contrast-induced nephropathy.

P. Eboli, M.D. (✉) • D. Drazin, M.D., M.A. • M.J. Alexander, M.D.
Department of Neurosurgery, Cedars-Sinai Medical Center, Advanced Health Sciences Pavilion, 127 South San Vicente Boulevard, Sixth Floor, Suite A-6600, Los Angeles, CA 90048, USA
e-mail: paula.eboli@cshs.org; ddrazin@gmail.com; michael.alexander@cshs.org

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_1

Femoral Artery Sheath Types

Smaller access 4- and 5-French catheters and sheaths are used in diagnostic cerebral angiography (4 French in children). For interventional procedures, larger catheters are used, which therefore require a larger femoral sheath, usually 5 French to 9 French [2] (Fig. 1.1). A longer sheath is needed for cases of significant ilio-femoral artery tortuosity to facilitate catheter navigation. Similarly, in interventional cases with significant vascular tortuosity, in which more support is necessary, a long sheath (80–90 cm) can be placed distally into the carotid or vertebral artery, and then a guiding catheter or intermediate catheter is coaxially inserted to create a "triaxial" support system. Once a sheath is inserted into the groin, it is usually continuously flushed during the procedure with a solution of 2,000 U heparin in 500 ml of normal saline [3]. Other common sheath lengths include the 35 cm bright-tip sheath.

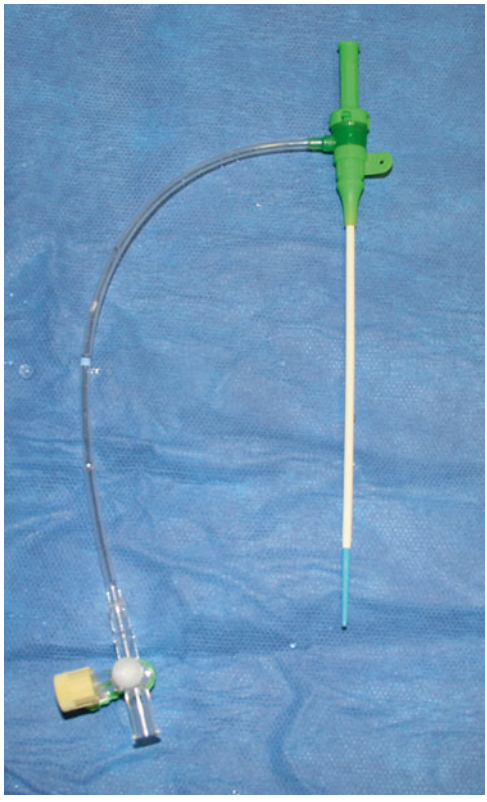

Fig. 1.1 6F femoral sheath

Wires and Catheters

Diagnostic Cerebral Angiography

Diagnostic catheters are usually advanced over a hydrophilic wire. The wire acts as a guide to prevent the catheter tip from damaging vessel walls and/or causing a dissection.

Hydrophilic wires vary from soft and flexible to slightly stiffer. Selection of the wire for a procedure depends on how much wire support is needed to navigate the catheter. With stiffer catheters, there is a greater risk of vessel dissection [1]. Arterial dissections are an uncommon complication with prevalence reported in the literature at around 0.4 % [4].

Typically, a 5-French standard catheter is used for cerebral angiography (4 French in children). Catheters should have good torque control, be soft and non-traumatic, be radiopaque, and have a smooth surface to prevent thrombus formation. A standard angled catheter is the workhorse of most diagnostic cases. However, in cases of tortuous anatomy, more complex-shaped catheters can be used such as Simmons II shaped, Headhunter, or Mikaelsson [5].

Guide Catheter and Microcatheters

For intracranial aneurysm embolization procedures, a large-lumen 6-French guide catheter (Fig. 1.2) or long 6-French sheath is typically used. Once the guide catheter is in position, a microcatheter is advanced under road-mapping guidance over a

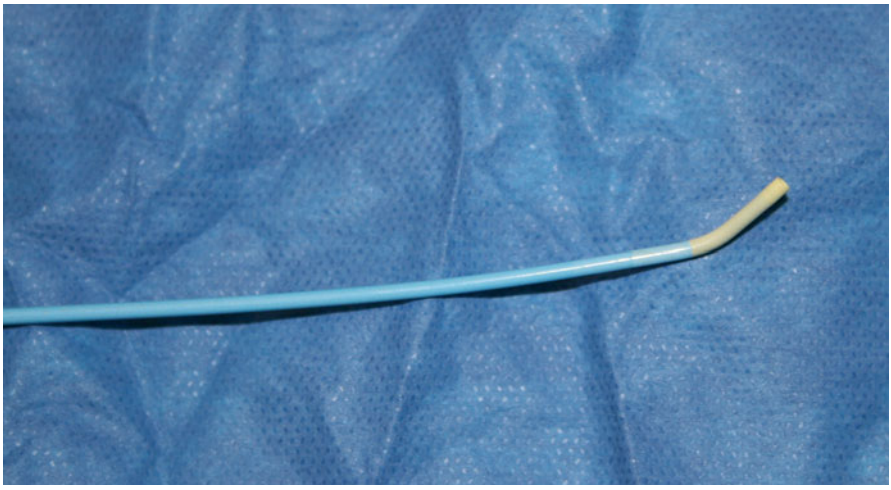

Fig. 1.2 6F Envoy guide catheter. Credit: DePuy Companies, used with permission

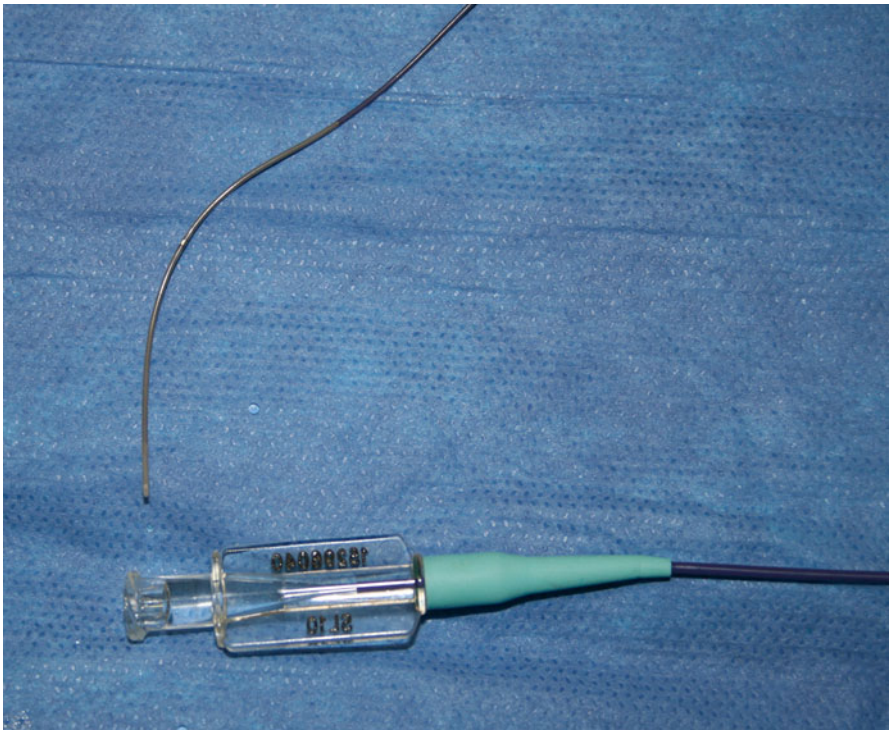

Fig. 1.3 Excelsior® SL-10® microcatheter. Credit: Stryker, used with permission

micro-guidewire into the aneurysm. Subsequently, coils are advanced and detached inside the aneurysm [6]. In tortuous anatomy, a long sheath may be used, in coordination with a guide catheter or an intermediate distal access catheter, and a microcatheter. This system is termed a triaxial system.

Microcatheters can be hydrophilic or nonhydrophilic, but only hydrophilic microcatheters are recommended since they are proven to be less thrombogenic [7]. Microcatheters come in different sizes, and in general, the smallest catheter for the desirable coils should be used [1] (Fig. 1.3). The inner diameter of the microcatheter may range in size for coil delivery from 0.015 to 0.025 in., so close attention must be paid to coil size compatibility during aneurysm embolization.

Coils

Platinum coils for the treatment of brain aneurysms were introduced in the 1990s as an alternative to surgical clipping [8]. Platinum coils consist of a platinum thread looped around a thicker platinum wire. Once deployed inside the aneurysm, they regain their original shape and are subsequently detached from the wire by a low current (Fig. 1.4) or other mechanism.

Fig. 1.4 Low-current detachment system. Credit: Boston Scientific, used with permission

Coils can be "filling," "framing," or "finishing." They have different diameters, stiffness profile, and geometry that influence their stability within the aneurysm [9].

Framing coils are three-dimensionally designed coils to frame the circumference of the aneurysm, while *filling coils* pack the aneurysm once it has been framed. *Finishing coils*, on the other hand, are soft coils designed for final packing of the aneurysm and neck [1].

Achieving an adequate packing density of the coils within the aneurysm is one of the most important factors in avoiding aneurysm recanalization [10]. Recanalization and coil compaction are determined by many factors; however, notably, smaller and softer coils generally have a higher risk for coil compaction.

An effort to minimize recanalization led to the introduction of *bioactive coils*. Bioactive coils consist of platinum coils with adjunctive polymers that have the properties affecting the thrombosis, inflammation, and healing processes within the aneurysm [11]. Theoretically, bioactive coils are expected to produce a more prominent healing response within the aneurysm and therefore result in less recanalization. Longer follow-up, however, is needed for validation [11].

Recently, a randomized trial showed no angiographic difference between Cerecyte coils and bare platinum coils [12].

Liquid Embolic Materials

Liquid embolic material is mainly used for embolization of cerebral or spinal arteriovenous malformations (AVMs) and pial or dural arteriovenous fistulas (AVFs). It is used less frequently for cerebral aneurysms. Most of these materials are supplied in a liquid state and delivered using microcatheters. Currently, there are few liquid embolic agents commercially available.

Ethylene-vinyl alcohol copolymer (Onyx) is supplied by the manufacturer in a liquid form dissolved in an organic solvent, dimethyl sulfoxide (DMSO), with tantalum powder added for radiopacity. Onyx is nonadhesive and has an even flow pattern. When Onyx contacts blood, the DMSO rapidly diffuses causing precipitation and solidification of the polymer [13]. The solidification occurs more slowly than cyanoacrylates, and it usually does not adhere to the walls of the microcatheter, thereby allowing a slower injection and better AVM nidus and/or fistula penetration [13]. Reflux of the Onyx around the distal microcatheter, however, is often encountered the longer the injection of the copolymer, which can make the microcatheter difficult to retrieve.

Cyanoacrylate (*n*-BCA TRUFILL) is an acrylic agent that polymerizes when it contacts blood or saline solutions. Due to its strong adhesive characteristics, it is possible to cause adhesion between the tip of the microcatheter and the vessel or glue cast [14]. The polymerization rate can be adjusted by varying the concentration of the monomer in Ethiodol or by adding glacial acetic acid to the mixture.

Particulate Embolics

Polyvinyl alcohol particles are small solid particles of various sizes which are radiolucent and need to be mixed with contrast material to make them radiopaque. Particles are commonly used for permanent small-vessel occlusion. They produce occlusion by thrombus formation, and when the particles are too large, they can clog the microcatheter. Particles can be carried out by flow; this means that flow can take them to the lesion or may cause them to land more distally than intended. For this reason, particles are not effective for high-flow fistulas. Embospheres (BioSphere Medical, Rockland, MA) of various sizes may also be used for deliberate small-vessel occlusions in AVMs, tumors, and epistaxis.

Stents

Stent-assisted coiling is used in the setting of a wide-neck aneurysm. Stent-assisted coiling requires the use of dual antiplatelet therapy, and therefore, they are generally used for unruptured cases. Their use in the setting of subarachnoid hemorrhage (SAH) has been described as a viable option in the literature but still remains

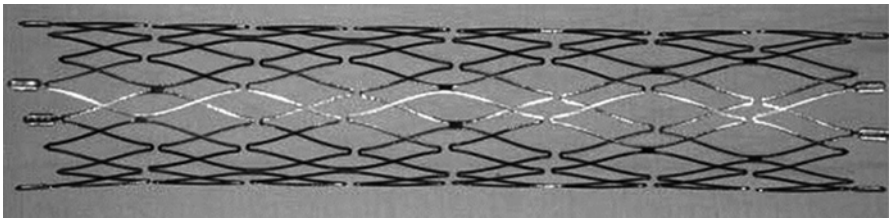

Fig. 1.5 Neuroform® stent system. Credit: Stryker, used with permission

controversial [15]. Stents or vascular remodeling devices designed for aneurysm treatment are self-expandable nitinol meshes of thin-strut density deployed across the neck aneurysm and followed by coil packing of the aneurysm [16]. They provide more stability to the coil mass by holding it in place, and theoretically, they reduce the possibility of recanalization [16]. Early complications include thromboembolism, and, in a late setting, stent stenosis and occlusion of the parent vessel can rarely occur [17] (Fig. 1.5). These come in open-cell and closed-cell designs. The open-cell design has somewhat more vessel conformity in small vessels, on a turn, and allows for a Y-stent configuration. The closed-cell design has somewhat more protection from the stent herniating into aneurysm or coils herniating through the stent.

Flow diverters are self-expandable, flexible stent-like devices with a dense mesh that once expanded, covers a large surface area. Flow diverters are mainly used for the treatment of wide-neck, fusiform, large, and giant aneurysms and are typically constructed of nitinol and cobalt chromium. They are designed to offer aneurysm occlusion due to flow disruption, and for large and giant side-wall aneurysms, the preliminary angiographic results have been superior to coil embolization alone [17, 18]. This occlusion is delayed following treatment, based on the size and location of the aneurysm. With this device, most patients demonstrate very good long-term angiographic results [17]. The potential complications reported have been embolic events, stent thrombosis, delayed aneurysm rupture, and in-stent stenosis [17, 19].

Cervical carotid stenting is a 4-stage procedure for reestablishing luminal diameter in high-grade carotid atherosclerotic disease. Following access and placement of a 6-French sheath in the common carotid artery, an embolic protection device is inserted across the stenosis. The insertion is followed by an angioplasty procedure performed to the stenotic area of the vessel to permit the advancement of the stent. The third stage is insertion of the stent. Once the stent is deployed, it should be followed by a second angioplasty procedure to fully expand the stent [1].

Mechanical Clot Retrievers

Mechanical clot retrievers are used as an alternative or in combination with pharmacological thrombolytic agents in the setting of acute ischemic stroke. This is a promising treatment, especially in patients ineligible to receive or nonresponders to the

use of intravenous tPA [20]. There are currently a few devices available commercially, and they can be categorized according to their mode of action into two main groups, aspiration vs. retrieval devices.

Aspiration devices use a proximal approach and act by applying a vacuum force to the proximal aspect of the thrombus. These systems use (1) a microcatheter which is attached to a power aspiration pump and (2) an additional soft wire with a teardrop-shape tip to separate the clot. The tip of the wire is inserted through the microcatheter to physically break up the clot and prevent it from becoming occluded. A major advantage of these devices is that they work at the proximal edge of the clot, and therefore, there is no need to distally pass the thrombus. They are effective with soft or intermediate clot but have more difficulty with firm fibrinous clots.

Retrieval devices, on the other hand, consist of a microcatheter containing a retrieval device which is passed distal to the thrombus. The microcatheter is then retracted, and the retrieval device is either a wire that adopts a coil or basket-like shape which ensnares the clot as it is unsheathed or a stent-like device that traps the clot within its struts and removes it from the vessel [20]. The use of a balloon catheter in association with this technique can reduce the risk of losing the clot during retrieval to embolized to otherwise unaffected vessels.

Stent retrievers are mainly used in acute ischemic stroke as thrombectomy devices to promote higher recanalization rates. Different studies have shown that patients with acute ischemic stroke treated with stent retrievers had better revascularization rates and clinical outcomes with lower complications when compared to those treated with the Merci retriever device [21].

Trevo (Concentric Medical, Mountain View, California) and Solitaire (eV3, Irvine, California) are examples of available stent retrievers in the United States. Trevo is a stent-like device designed to integrate the clot into its structure, allowing to retract both the device and clot from the blood vessel. The Solitaire is a self-expanding stent that can be fully deployed and/or completely retrieved if it has not been detached [22]. In 2012, Mendaca et al. published their results comparing both devices, and their study showed no significant differences between them [22].

Closure Devices

Percutaneous femoral artery closure devices are commonly used to close the punctured artery in the groin after endovascular cases. These closure devices allow patients to ambulate sooner than when standard compression techniques are used. Two of these products are Perclose (Abbott Vascular, Redwood City, CA) and Angio-Seal (St. Jude Medical, St. Paul, MN).

Perclose places a prolene stitch, which is placed in the arteriotomy site percutaneously (Fig. 1.6). There are 6-French and 8-French varieties.

Angio-Seal places a mechanical seal, produced by a bioabsorbable anchor and a collagen sponge, which dissolves within 60–90 days. With this device, the same artery can be re-punctured [1].

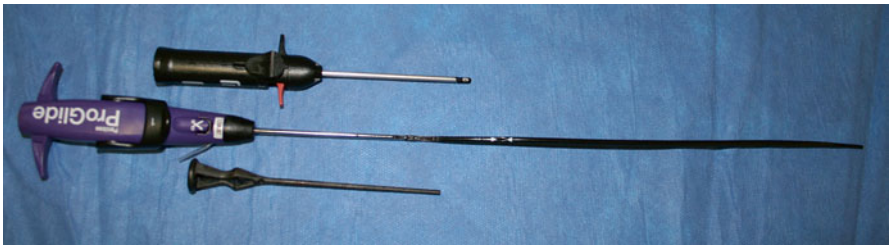

Fig. 1.6 Perclose closure device. Credit: Abbott, used with permission

References

1. Harrigan M. Handbook of cerebrovascular disease and neurointerventional technique. New York: Springer; 2012.
2. Koenigsberg R, Wysoki M, Weiss J, Faro S, Tsai F. Risk of clot formation in femoral arterial sheaths maintained overnight for neuroangiographic procedures. AJNR Am J Neuroradiol. 1999;20:297–9.
3. Krings T, Willmes K, Becker R, Meister I, Hans F, Reinges M, Mull M, Thron A. Silent microemboli related to diagnostic cerebral angiography: a matter of operator's experience and patient's disease. Neuroradiology. 2006;48:387–93.
4. Cloft H, Jensena M, Kallmesa D, Diona J. Arterial dissections complicating cerebral angiography and cerebrovascular interventions. AJNR Am J Neuroradiol. 2000;21:541–5.
5. Thiex R, Norbash A, Frerichs K. The safety of dedicated-team catheter-based diagnostic cerebral angiography in the era of advanced noninvasive imaging. AJNR Am J Neuroradiol. 2010; 31:230–4.
6. Rabinstein A, Nichols D. Endovascular coil embolization of cerebral aneurysm remnants after incomplete surgical obliteration. Stroke. 2002;33:1809–15.
7. Kallmes D, McGraw K, Mathis J, Hergenrother R, Jensen M. Thrombogenicity of hydrophilic and nonhydrophilic microcatheters and guiding catheters. AJNR Am J Neuroradiol. 1997; 18:1243–51.
8. Guglielmi G. History of the genesis of detachable coils. A review. J Neurosurg. 2009; 111:1–8.
9. Schloesser PE, Pakbaz RS, Levy DI, Imbesi SG, Wong WH, Kerber CW. Analysis of complex framing coil stability in a wide-necked aneurysm model. AJNR Am J Neuroradiol. 2007; 28:387–9.
10. Sluzewski M, Van Rooij WJ. Packing performance of helical Guglielmi detachable coil (GDC) 18 in intracranial aneurysms: a comparison with helical GDC 10 coils and complex Trufill/ Orbit coils. AJNR Am J Neuroradiol. 2007;28:1384–7.
11. Berenstein A, Song JK, Niimi Y, Namba K, Heran NS, Brisman JL, Nahoum MC, Madrid M, Langer DJ, Kupersmith MJ. Treatment of cerebral aneurysms with hydrogel-coated platinum coils (HydroCoil): early single-center experience. AJNR Am J Neuroradiol. 2006;27:1834–40.
12. 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.
13. Nogueira RG, Dabus G, Rabinov JD, Eskey CJ, Ogilvy CS, Hirsch JA, Pryor JC. Preliminary experience with onyx embolization for the treatment of intracranial dural arteriovenous fistulas. AJNR Am J Neuroradiol. 2008;29:91–7.

14. Oowaki H, Matsuda S, Sakai N, Ohta T, Iwata H, Sadato A, Taki W, Hashimoto N, Ikada Y. Non-adhesive cyanoacrylate as an embolic material for endovascular neurosurgery. Biomaterials. 2000;21:1039–46.
15. Amenta PS, Dalyai RT, Kung D, Toporowski A, Chandela S, Hasan D, Gonzalez LF, Dumont AS, Tjoumakaris SI, Rosenwasser RH, Maltenfort MG, Jabbour PM. Stent-assisted coiling of wide-necked aneurysms in the setting of acute subarachnoid hemorrhage: experience in 65 patients. Neurosurgery. 2012;70:1415–29.
16. 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.
17. Deutschmann HA, Wehrschuetz M, Augustin M, Niederkorn K, Klein GE. Long-term follow-up after treatment of intracranial aneurysms with the Pipeline embolization device: results from a single center. AJNR Am J Neuroradiol. 2011;33:481–6. doi:10.3174/ajnr.A2790 AJNR 2011.
18. Lubicz B, Collignon L, Raphaeli G, Pruvo JP, Bruneau M, De Witte O, Leclerc X. Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke. 2010;41:2247–53.
19. Lubicz B, Collignon L, Raphaeli G, De Witte O. Pipeline flow-diverter stent for endovascular treatment of intracranial aneurysms: preliminary experience in 20 patients with 27 aneurysms. World Neurosurg. 2011;76(1–2):114–9.
20. Benmira S, Banda ZK, Bhattacharya V. The start of a new era for stroke treatment: mechanical thrombectomy devices. Curr Neurovasc Res. 2011;8(1):75–85.
21. Broussalis E, Trinka E, Hitzl W, Wallner A, Chroust V, Killer-Oberpfalzer M. Comparison of stent-retriever devices versus the Merci retriever for endovascular treatment of acute stroke. AJNR Am J Neuroradiol. 2013;34(2):366–72.
22. Mendonça N, Flores A, Pagola J, Rubiera M, Rodríguez-Luna D, Miquel MA, Cardona P, Quesada H, Mora P, Alvarez-Sabín J, Molina C, Ribó M. Trevo versus solitaire a head-to-head comparison between two heavy weights of clot retrieval. J Neuroimaging. 2012;24:167–70.

Chapter 2
Neurovascular Anatomy

Sonal Mehta and Randall C. Edgell

Arterial Supply of the Head and Neck

The Aortic Arch

The three main branches of the aortic arch are the brachiocephalic artery, the left common carotid artery (CCA), and the left subclavian artery (LSCA). The best angiographic visualization of the origins of the great vessels is obtained from an LAO position at an angle between 20 and 30° [1] (Fig. 2.1). There is significant variation in the anatomy of these vessels, and the usual order is only seen in about two-thirds of patients. The most commonly seen anatomic variant is a "bovine arch" (Fig. 2.2) in which there is a shared origin of the brachiocephalic and LCCA. Other variants that are seen include the LCCA arising from the brachiocephalic artery, the LCCA and LSCA sharing a common trunk, and the LVA originating directly from the arch. There are also several anomalies of the arch. The most common among these is the left aortic arch with an aberrant RSCA. Some of these anomalies may cause symptoms by forming a compressive vascular ring [2].

S. Mehta, M.D. (✉)
Assistant Professor, Department of Neurology, University of South Carolina School of Medicine, 8 Medical Park, Suite 420, SC 29203, Columbia
e-mail: sonal.mehta@uscmed.sc.edu

R.C. Edgell, M.D.
Department of Neurology and Psychiatry, Saint Louis University, 1438 S. Grand Blvd, Saint Louis, MO 63104, USA
e-mail: redgell@slu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*, Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_2

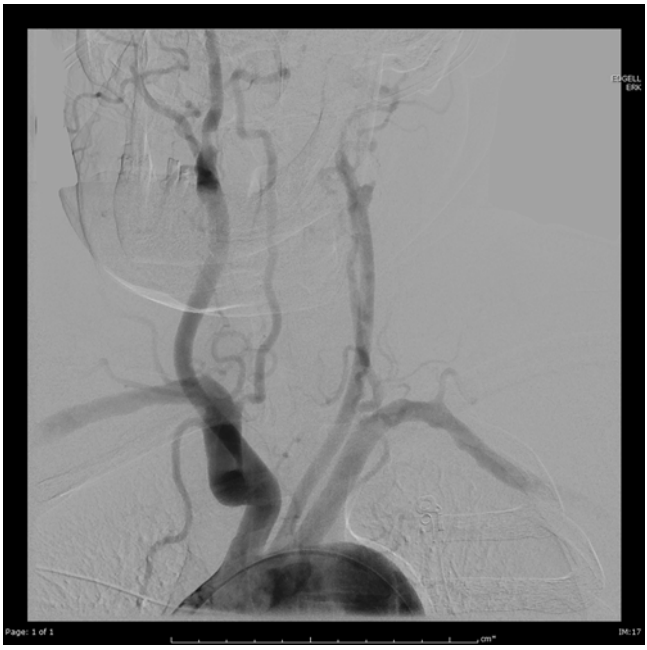

Fig. 2.1 Left anterior oblique projection of the standard aortic arch configuration

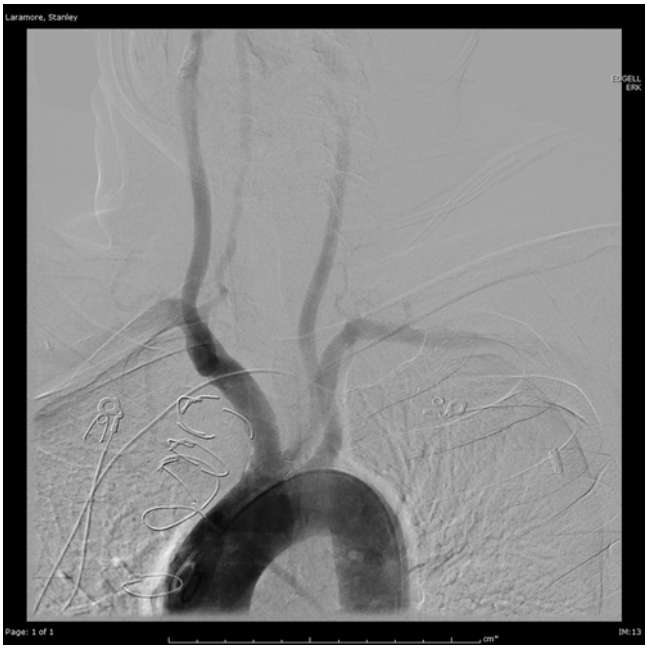

Fig. 2.2 Left anterior oblique projection of the bovine aortic arch variant

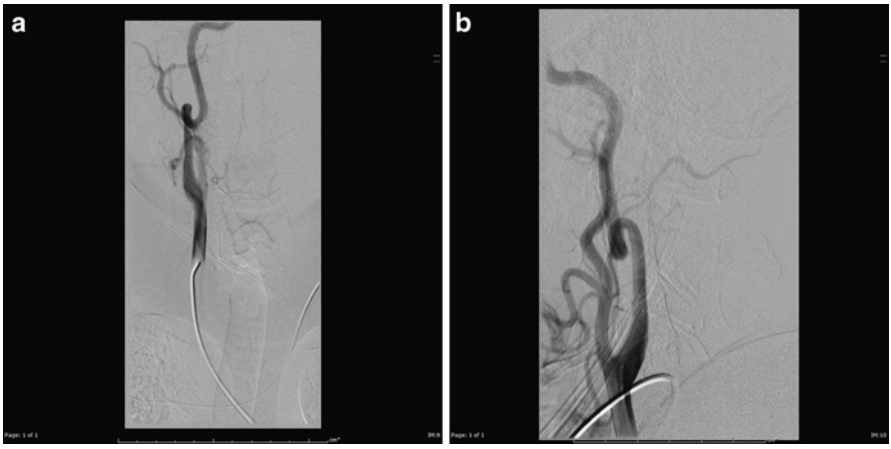

Fig. 2.3 External carotid artery in the anteroposterior (**a**) and lateral (**b**) projections

The External Carotid Artery

The external carotid artery (ECA) originates from the bifurcation of the common carotid artery at about the C4 vertebral level (Fig. 2.3a, b). It lies anteromedial to the internal carotid artery and then courses posterolaterally. Multiple angiographic projections may be required to view the ECA and its branches well.

The ECA has eight branches (Fig. 2.4):

1. The superior thyroid artery—usually the first ECA branch, it supplies the larynx and superior aspect of the thyroid gland.
2. Ascending pharyngeal artery [3]—it is the first posterior branch and supplies the pharynx and middle ear.
3. Lingual artery—supplies the tongue and the oral cavity and anastomoses with other ECA branches.
4. Facial artery—supplies the face and courses superolaterally to terminate near the medial canthus where it forms the angular artery. In about 26 % of cases, it may terminate in the lateral nasal (or alar) branch [4].
5. Occipital artery—courses posterosuperiorly to supply the scalp and posterior aspect of the neck. It may anastomose with the vertebral artery or on occasion, may arise directly from it.
6. Posterior auricular artery—small branch that supplies the scalp and the pinna.
7. Superficial temporal artery—it is one of the terminal ECA branches and supplies the scalp.
8. Internal maxillary artery—it is the larger of the two terminal branches of the ECA and supplies the nose. It can further be subdivided into three segments. The mandibular segment is where the largest branch of the IMA, the middle

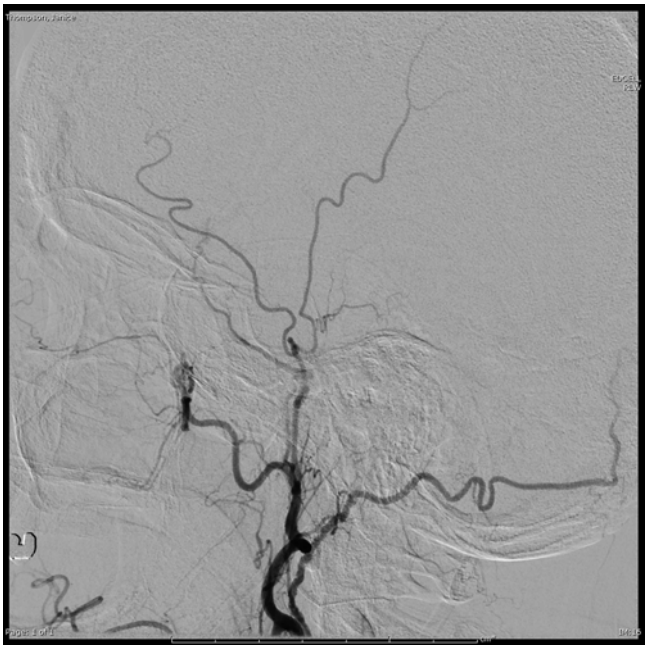

Fig. 2.4 Lateral projection images of the external carotid artery branches

meningeal artery, originates. The pterygoid segment gives rise to the deep temporal arteries. The pterygopalatine segment is the terminal segment and supplies the nose through the sphenopalatine artery. It also gives rise to the infraorbital artery that supplies the lower eyelid and parts of the cheek and nose. The greater palatine artery also arises from this segment and supplies the soft palate and palatine tonsils [5].

External Carotid: Internal Carotid Anastomoses

1. The ascending pharyngeal artery anastomoses with the ICA through the inferolateral trunk, the Vidian artery, and the caroticotympanic artery.
2. Facial artery anastomoses with the ophthalmic artery through branches of the angular artery near the medial canthus (Fig. 2.5).
3. The stylomastoid branch of the posterior auricular artery anastomoses with the caroticotympanic branch of the internal carotid artery.
4. The internal maxillary artery (IMAX) is an important source of potential collateral flow between the ECA and ICA. It may anastomose with the petrous ICA through the Vidian artery, the cavernous ICA through the artery of the foramen rotundum, and the supraclinoid ICA through the ophthalmic artery. These are important channels that need to be kept in mind to prevent ischemic complications

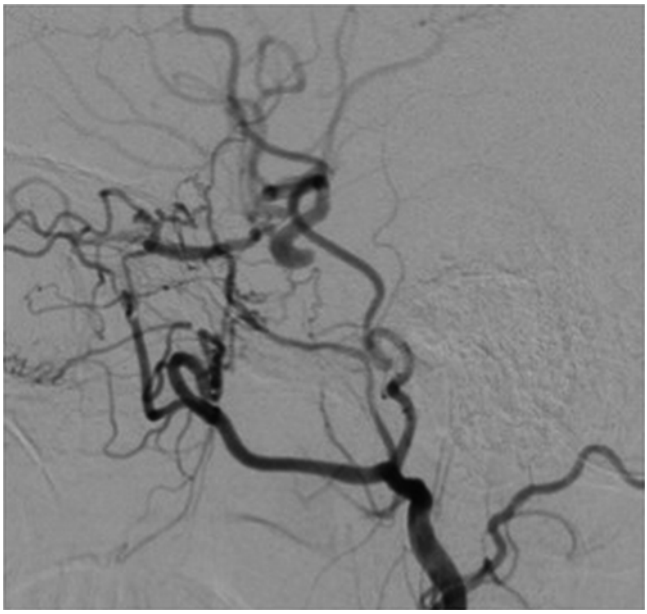

Fig. 2.5 Lateral projection images demonstrating the anastomotic connection between the angular branch of the facial artery and the ophthalmic artery

during head and neck embolization procedures. The middle meningeal artery may anastomose with branches from the cavernous segment of the ICA and can be an important source of collateral flow in carotid bulb atherosclerosis.

5. The STA anastomoses with the ICA via the ophthalmic artery via the supratrochlear artery [6, 7].

The Internal Carotid Artery

There are various classification systems of the segments of the ICA. One widely adopted system proposed by Bouthillier [8] is utilized in this chapter. This system divides the ICA into the following seven segments.

C1: Cervical ICA

The ICA usually originates from the CCA at C3–4 level. This segment has two distinct parts:

- The carotid bulb—a dilated segment with a complex flow dynamic, this is a frequent site for the development of atherosclerotic disease.
- The ascending cervical segment—from the bulb it courses upward within the carotid space.

There are no named branches that arise from the cervical segment. There can be considerable variation in the level of the carotid bifurcation. A medial origin of the ICA is common and may require an oblique projection to view the bifurcation clearly. Tortuosity and looping of the ICA are also visualized frequently and may present technical challenges to endovascular procedures.

Anomalies of the cervical ICA are uncommon with a congenital absence of the ICA being an extremely rare example. An absent or hypoplastic bony carotid canal on CT scan can present a clue to distinguish a developmentally hypoplastic ICA rather than an occlusion of a normally developed vessel [9]. Two important anastomotic channels that can originate from the cervical ICA are the persistent hypoglossal artery, which may connect it to the basilar artery, and the proatlantal intersegmental artery, which could anastomose with the vertebral artery.

C2: Petrous ICA

The petrous ICA has a vertical subsegment, a genu, and a horizontal subsegment. It may give off two small branches. The first of these is the Vidian artery (artery of the pterygoid canal) that more often arises from the ECA. As described in the previous section, it is an important anastomotic connection between the ICA and the IMAX, a branch of the ECA. The second is the caroticotympanic artery that supplies the middle ear cavity and may anastomose with the inferior tympanic artery, a branch of the APA.

Anomalies of the petrous ICA are rare but of clinical importance. An aberrant ICA may rarely be seen and can present as a retrotympanic pulsatile mass or can be found incidentally where significant bleeding from ear surgery may be encountered (see Chap. 16). The artery may also be mistaken for a middle ear tumor. A persistent otic artery is another anastomotic connection between the ICA and the basilar artery, which is extremely rare [10].

C3: Lacerum ICA

This segment begins at the end of the petrous carotid canal, courses above the foramen lacerum, and ends at the petrolingual ligament. Usually, it has no branches, although rarely the Vidian artery may originate from the C2–C3 segment junction.

C4: Cavernous ICA

The cavernous ICA begins at the petrolingual ligament and ends as it leaves the cavernous sinus through the dural ring. It is the most medial structure in the cavernous sinus, and the CN III, IV, and V1 and V2 run lateral to it, whereas CN VI runs inferolaterally. It is visualized well on a lateral view where it can be seen to have a posterior genu, a horizontal segment, and an anterior genu. This segment gives off

three branches. The posterior trunk or the meningohypophyseal trunk (MHT) arises from the posterior genu and is often seen on angiography. Its branches include the inferior hypophyseal artery which supplies the pituitary gland, the marginal tentorial artery (MTA) which supplies the tentorium, and the clival branches to the clivus. The MTA, also known as the artery of Bernasconi–Cassinari, is sometimes involved in the pathologic supply of arteriovenous malformations or tumors, typically associated with tentorial meningiomas [11]. The lateral trunk or the inferolateral trunk (ILT) supplies the CN III, IV, and VI and dura of the cavernous sinus. It anastomoses with branches of the internal maxillary artery and the middle meningeal artery. In addition to these the cavernous ICA also gives off small capsular branches, which supply the pituitary gland. Anatomical variants of the cavernous ICA include increased tortuosity in this segment and paramedian ICAs. The latter, also known as "kissing" ICAs, occurs when the two ICAs course medially through the sella turcica. An important anomalous connection is a persistent trigeminal artery, which is the most common carotid–basilar anastomosis [12]. It arises from the posterior genu and is associated with increased prevalence of other vascular anomalies and aneurysms. The posterior genu is also often the site of direct carotid–cavernous fistulae formation [13].

C5: Clinoid ICA

This is the shortest ICA segment and lies between the proximal and distal dural ring, making it an interdural structure. It has no named branches but may give off small capsular arteries. Rarely, the ophthalmic artery may arise from this segment.

C6: Ophthalmic ICA

The first intradural segment of the ICA, the ophthalmic segment is surrounded by CSF. The first major intracranial ICA branch, the ophthalmic artery arises from this segment. It runs anteriorly through the optic canal and gives off three types of branches. The ocular branches provide arterial supply to the choroid and retina and include the central retinal artery and the ciliary arteries. Orbital branches of the ophthalmic artery supply the extraocular muscles and the orbit periosteum [14]. An important orbital branch is the lacrimal artery which may anastomose with the middle meningeal artery through the recurrent meningeal artery. An important but rare anatomic variant is a middle meningeal artery which may arise from the ophthalmic artery [15]. Extraorbital branches of the ophthalmic are also important sites of anastomoses with the ECA circulation through ethmoidal and facial arteries. The other important ICA branches from the C6 segments are the superior hypophyseal arteries which may be one or more in number. The C5 and 6 segments together make up the carotid siphon and are best visualized on lateral views on angiography [16].

C7: Communicating ICA

The C7 segment is the terminal ICA segment and begins proximal to the origin of the posterior communicating artery (PCom) and ends at the ICA bifurcation into the anterior and middle cerebral arteries. The first major branch from this segment is the PCom that arises from the posterior aspect of the ICA, runs above CN III, and gives off several small perforating branches. An important anatomical variant of the PCom is when it may supply the entire PCA territory in the absence of a P1 segment, also called a "fetal PCA" (Fig. 2.6). Another frequently encountered variant is a dilatation at the origin of the PCom called an infundibulum. It is important to distinguish these structures from true aneurysms. The second major branch of this segment is the anterior choroidal artery (AChA), which arises from the posteromedial aspect of the C7 segment. It has two segments, the cisternal and intraventricular. It has a variable but important territory of vascular supply including the optic tract, the posterior limb of the internal capsule, cerebral peduncle, medial temporal lobe, and choroid plexus. Rarely, a hypoplastic or hyperplastic AChA may be present. Another rare anomaly is when an AChA may arise proximal to the PCom.

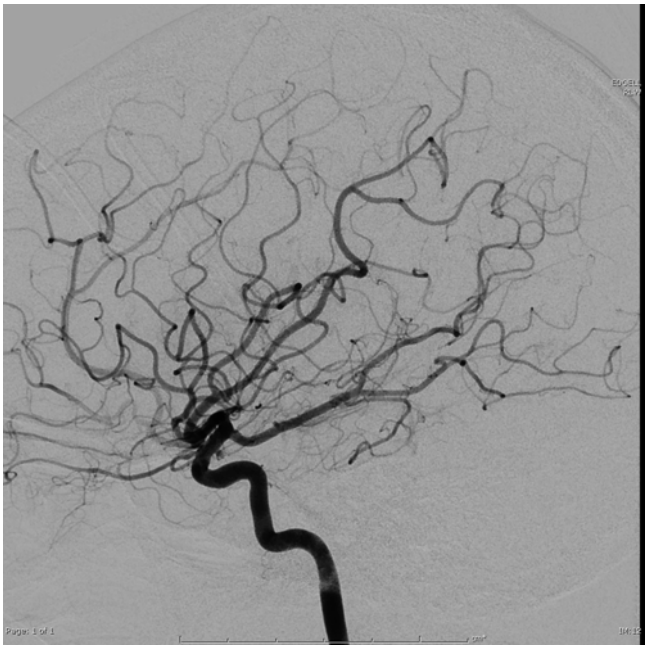

Fig. 2.6 Lateral projection images of a fetal posterior cerebral artery anatomical variant

The Circle of Willis

The circle of Willis (COW) is a polygonal anastomotic ring that connects the anterior circulation with its contralateral counterpart as well as with the posterior circulation. It lies in the suprasellar cistern. Its contributing arteries are:

The internal carotid arteries, right and left
The anterior cerebral arteries (A1), right and left
The posterior communicating arteries, right and left
The posterior cerebral arteries (P1), right and left
The basilar artery
The anterior communicating artery

A complete COW is present in less than 50 % of all cases, and anatomic variants are extremely common [17]. The A1 segment may be hypoplastic (10 %) or absent (1–2 %). There may be duplicated or fenestrated anterior communicating arteries. A plexiform ACom is one where multiple channels may be present. A hypoplastic P1 segment may be seen with a fetal PCA. An anatomically isolated ICA occurs when there is an absent A1 and an ipsilateral fetal PCA. The entire COW is rarely visualized on a single angiogram, and different views and injections may be required to view it. There are important small perforating branches, which arise from the vessels in the COW. The ACA gives rise to the recurrent artery of Heubner, an artery that may inadvertently be clipped with an anterior communicating aneurysm due to its variable origin [18], and the medial lenticulostriate arteries. The anterior communicating artery itself gives rise to small perforating branches that supply the optic chiasm and parts of the corpus callosum. The posterior communicating arteries give rise to the anterior thalamoperforating arteries, which supply the thalamus and the optic tracts. The posterior thalamoperforators arise from the distal BA and the proximal PCAs, which supply the midbrain and the thalamus.

Anterior Cerebral Artery

The ACA is the smaller of the two terminal branches of the ICA. It is subdivided into three segments, the A1 or the precommunicating segment, the A2 or the postcommunicating segment, and the A3 or the distal ACA. The precommunicating segment is visualized well on a straight AP projection on angiography as it courses over the optic chiasm and below the anterior perforated substance and extends from the ACA origin to the junction of the ACA and the ACoA. The A2 segment extends from this point to the genu of the corpus callosum and is well visualized on the lateral projection. The proximal ACA segments give rise to perforating arteries, which supply parts of the anterobasal forebrain, corpus callosum, fornix, and septum pellucidum. The largest among these is the recurrent artery of Heubner, which has a variable origin [18]. It arises most often from the proximal A2 segment or the A1 segment. Less frequently it may arise from the ACoA. The ACA cortical branches

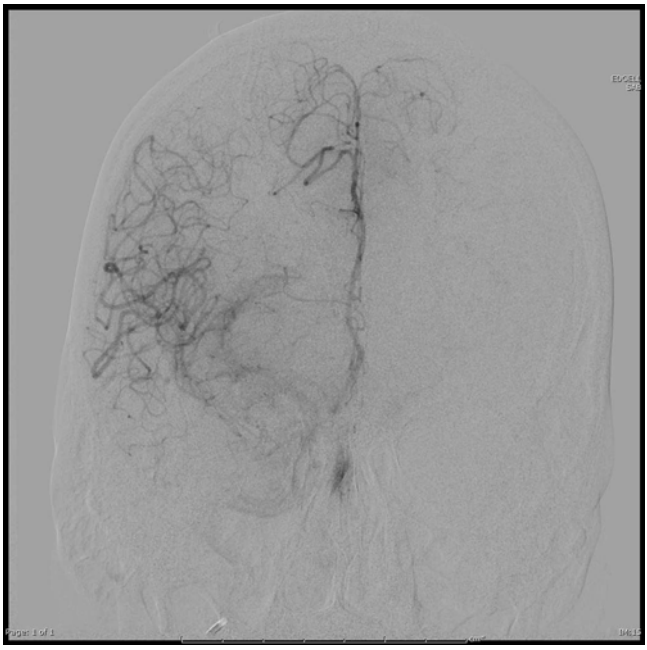

Fig. 2.7 Anteroposterior projection images of the pericallosal and callosomarginal branches of the anterior cerebral artery

are grouped according to their vascular territory. The first such group is the orbital branches, which includes the orbitofrontal artery. This group largely supplies the orbital surface of the frontal lobe. The second group is the frontal branches, which includes the frontopolar artery.

Distally, the ACA curves around the corpus callosum and bifurcates into two main branches, the pericallosal artery and the callosomarginal artery, and gives off the last group of cortical branches, the parietal branches. The distal ACA is also well visualized on a lateral projection. However on AP projection the pericallosal and callosomarginal arteries have a characteristic "smile and mustache" appearance in the late arterial phase [19] (Fig. 2.7).

While anatomical variations are common, true anomalies of the ACAs are rare. An absent or hypoplastic A1 segment is a common variation. Rarely, an anomalous origin of the ACA may be seen, arising from the level of the ophthalmic artery from the ICA. Other anomalies include an accessory, bihemispheric, or azygous ACA.

Middle Cerebral Artery

The MCA (Fig. 2.8) is subdivided into four anatomical segments. The M1 segment originates at the ICA bifurcation and courses laterally till the limen insulae where the MCA branches turn upwards. It is here that the M2 segments start and are

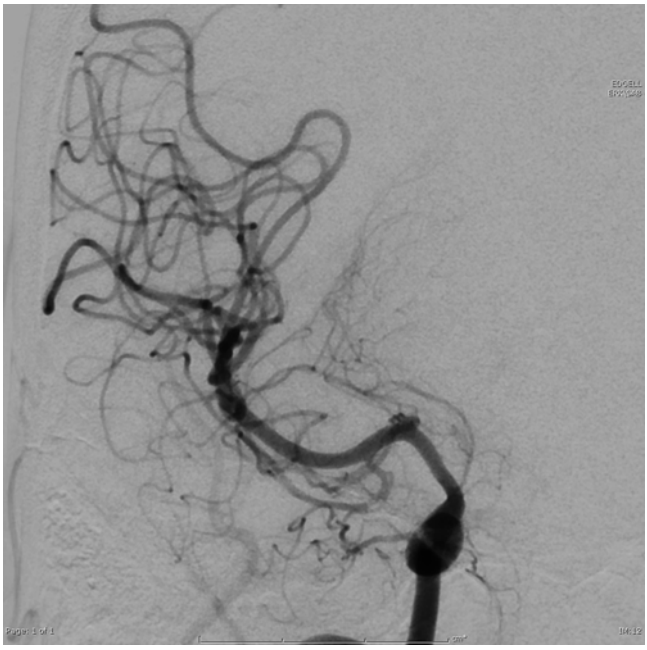

Fig. 2.8 Anteroposterior projection images of the middle cerebral artery

comprised of 6–8 MCA branches that lie over the insula. The M2 segments then end by coursing laterally at the top of the Sylvian fissure, where the M3 segments begin. The M3 segments end at the lateral cerebral fissure. The M4 segments then begin and the distal branches then take varying courses to the cortical areas they supply [20].

The M1 segment gives off two groups of penetrating branches, the medial and lateral lenticulostriate arteries, which then supply the lentiform nucleus, caudate nucleus, and internal capsule.

The first cortical MCA branch is the anterior temporal artery, which arises from the M1 segment. The cortical branches arising from the M4 segments are divided into anterior, central, or posterior groups depending on their vascular territory. The anterior branches include the orbitofrontal and prefrontal arteries, which supply the inferior and lateral frontal lobes, respectively. The central or intermediate branches include the pre-Rolandic, Rolandic, and anterior parietal arteries that supply the posterior frontal lobe and anterior parietal lobes including the pre- and post-central gyri. The posterior parietal artery, the angular artery, the temporooccipital artery, and the posterior temporal artery make up the posterior branches. Of these, the angular artery is the major terminal branch and is of importance during intracranial neurointerventional procedures as its relatively straight course allows for better distal wire access during thrombectomies of the middle cerebral artery.

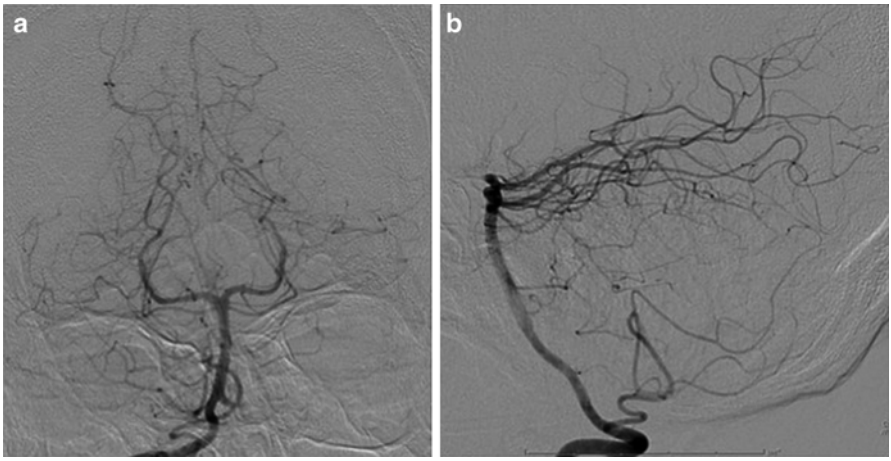

Fig. 2.9 Anteroposterior (**a**) and lateral projection (**b**) images of the posterior cerebral arteries

While true anomalies of the MCA are rare, there is significant variation in the branching patterns. A true MCA bifurcation is only seen in about 50 % of cases, whereas in other cases there may be a trifurcation or multiple branches. Rare anomalies include an accessory MCA that arises from the ACA, a duplicated MCA that arises from the terminal ICA, hypoplastic or aplastic MCAs, fenestrated MCAs, and a single nonbifurcating MCA trunk [21].

Posterior Cerebral Artery

The PCA originates from the basilar artery bifurcation (Fig. 2.9a) in the interpeduncular cistern and is divided into four segments [22]. The P1 or precommunicating segment starts at the basilar bifurcation and extends to its junction with the PCoA. From this point, the P2 (ambient) segment extends to the posterior aspect of the midbrain, coursing in the ambient cistern, and is well visualized on the lateral projection on angiography (Fig. 2.9b). The P3 (quadrigeminal) segment extends from the quadrigeminal plate to the calcarine fissure. The P4 segment is the terminal segment within the calcarine fissure and includes the cortical branches of the PCA. Several perforating branches arise from the PCA. The thalamoperforators arise from the P1 segment, the thalamogeniculates, and the peduncular perforators from the P2 segment. Two main choroidal arteries are the medial posterior choroidal artery and the lateral posterior choroidal artery, both of which arise from the P2 segment and are well visualized on the lateral projection. The lateral posterior choroidal arteries anastomose with the medical posterior choroidal artery as well as the anterior choroidal artery, a branch of the ICA. The first cortical branches arising from the P2 segment are the anterior temporal artery, followed by the posterior

temporal artery. The P3 segment then continues within the perimesencephalic cistern, and then the P4 segment bifurcates into the medial occipital artery and the lateral occipital artery. The medial occipital artery further divides into the parietooccipital artery that supplies the brain adjacent to the parietooccipital sulcus and also provides accessory supply to the visual cortex. The other division of the medial occipital artery is the calcarine artery, which supplies the visual cortex. The lateral occipital artery has several branches that supply the inferior temporal lobe.

The Vertebrobasilar System

Vertebral Artery

The vertebral artery (Fig. 2.10) is divided angiographically into four segments [23]. The V1 (extraosseous) segments arise from the subclavian arteries and ascend posteriorly to enter the C6 transverse foramen. The origin of vertebral arteries may be variable, as most often they tend to arise from the superior aspect of the subclavian but may arise from other aspects as well. Thus the subclavian artery may overlap with the vertebral artery origin on a straight AP projection, and the origin may be difficult to visualize angiographically. Multiple-angled projections may be required

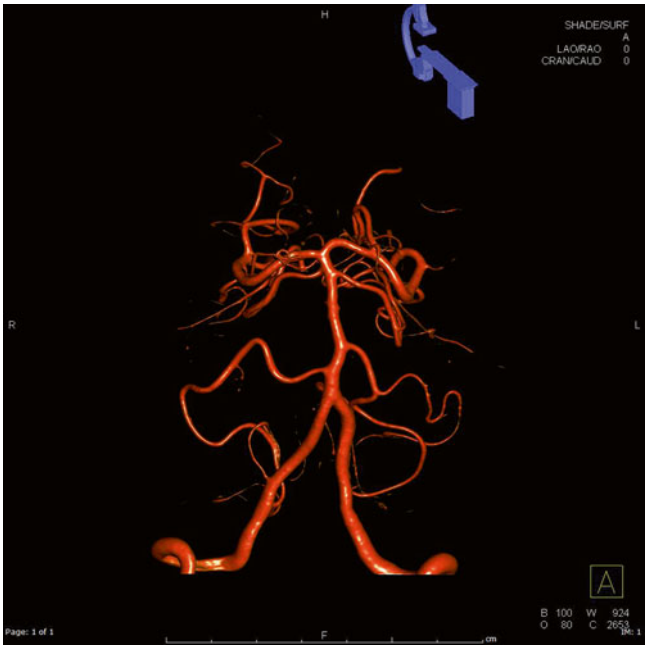

Fig. 2.10 3D angiogram of the vertebrobasilar system

to visualize the origin clearly. The V2 (foraminal) segment then ascends cephalad from the C6 to the C2 transverse foramina and turns laterally as it exits from C1. The anterior meningeal artery is a branch that arises from the distal V2 segment and supplies the dura around the foramen magnum. This segment is well visualized on a straight AP projection. The V3 (extraspinal) segment extends from the VAs exit point from C1 to their entry into the dura. This segment is well visualized on both AP and lateral projections. The V4 (intradural) segment begins at the dura, courses through the foramen magnum, and ends by uniting with its contralateral counterpart to form the basilar artery (BA) near the pontomedullary junction. The distal vertebral artery is frequently an area affected by atherosclerotic disease in posterior circulation strokes [24]. The intracranial branches of the VA arise from the V4 segment. The first of these is the posterior spinal artery, which is a small vessel that forms a vascular network that continues inferiorly along the spinal cord. The anterior spinal artery (ASA) also arises from the distal VA and runs inferiorly giving off a small number of perforators that supply the pyramid.

The most important intracranial branch of the VA is the posterior inferior cerebellar artery (PICA). It arises from the V4 segment near the olive and has four segments [25]. The first (anterior medullary) segment runs posteriorly in the medullary cistern. The second (lateral medullary) segment continues posteriorly in the cerebellomedullary fissure. The third (posterior medullary) segment ascends behind the posterior medullary velum, and the fourth (supratonsillar segment) is the second loop of the PICA, formed by its course above the cerebellar tonsils. The PICA is well visualized on lateral projections. Anatomical variants of the VA are common as there is a significant asymmetry in the sizes of the two VAs, with the left being dominant in the majority of people. Other common variations include a shared AICA–PICA trunk, as well as extradural origin of the PICA, which is of important consideration during posterior fossa surgeries. More rare variants include a duplicated PICA and a vertebral artery ending in a PICA. The most common anomaly of the vertebral artery is an origin from the aortic arch, which may be seen in 5 % of cases. Other anomalies include duplicated and fenestrated VAs, which may be associated with increased risk of aneurysms.

Basilar Artery

The basilar artery (Fig. 2.10) is formed by the unification of the two vertebral arteries and is a rare example of two arteries uniting to form one vessel in the human body. It ascends cephalad from its origin at the pontomedullary junction to its bifurcation in the interpeduncular cistern. It has extensive perforating arteries, which form the vascular supply to the pons. These are further divided into the median and paramedian pontine perforators which course posteriorly from the BA and penetrate the pons and the lateral pontine arteries which course around the brainstem, giving off small perforators that penetrate the pons to supply it. It also gives rise to two major cerebellar arteries. The anterior inferior cerebellar artery (AICA) (Fig. 2.10) takes

origin from the proximal BA and courses posterolaterally. It is an important source of labyrinthine branches, and an AICA stroke may present with unilateral sensorineural hearing loss [26]. The AICA supplies the anterolateral surface of the cerebellum. The superior cerebellar arteries (SCAs) arise just proximal to the BA bifurcation (Fig. 2.10). The SCAs course posterolaterally and divide into a lateral branch that supplies the superolateral surface of the cerebellar hemispheres and a medial branch that supplies the superomedial cerebellar surface and vermis. Duplicated SCAs are a common anatomical variation. Anomalies of the BA are rare but include duplication or fenestration of the vessel. Persistent embryonic connections may result in carotid–basilar anastomotic channels that are discussed elsewhere.

Venous Drainage of the Head and Neck

Extracranial Veins

Venous drainage of the head and neck is through several veins and plexuses. The superior and inferior ophthalmic veins drain the orbit posteriorly [27]. The face is drained predominantly by the anterior facial vein, which is joined by the deep facial vein along its course. Submental veins and anterior facial vein join to form the common facial vein. Veins from the scalp, pinna, and deep face drain into the external jugular vein, whereas the internal jugular vein drains blood from the skull and brain and subsequently forms the brachiocephalic vein in combination with the subclavian vein [28].

Dural Venous Sinuses (See Chap. 8)

These endothelium-lined channels are located between the dural layers. They are valveless vessels without any muscular tissue and have complex trabeculae, rather than being a single large channel. The dural sinuses are the major routes of drainage for the brain.

The superior sagittal sinus (Fig. 2.11) originates anteriorly at the crista galli and courses posteriorly, joined by many cortical parasagittal veins along its course, which also results in an increase in diameter as it runs caudally [29]. It terminates to form the torcula or sinus confluence as it joins with the straight sinus near the internal occipital protuberance. It is well visualized angiographically in the venous phase on lateral view.

The inferior sagittal sinus is a smaller channel that courses posteriorly along the inferior edge of the falx cerebri, above the corpus callosum. It drains the falx, corpus callosum, cingulum, and medial cerebral hemispheres. The ISS then joins with the vein of Galen (great cerebral vein) to form the straight sinus [30] (Fig. 2.11) which then courses posteroinferiorly and receives tributaries draining the vermis.

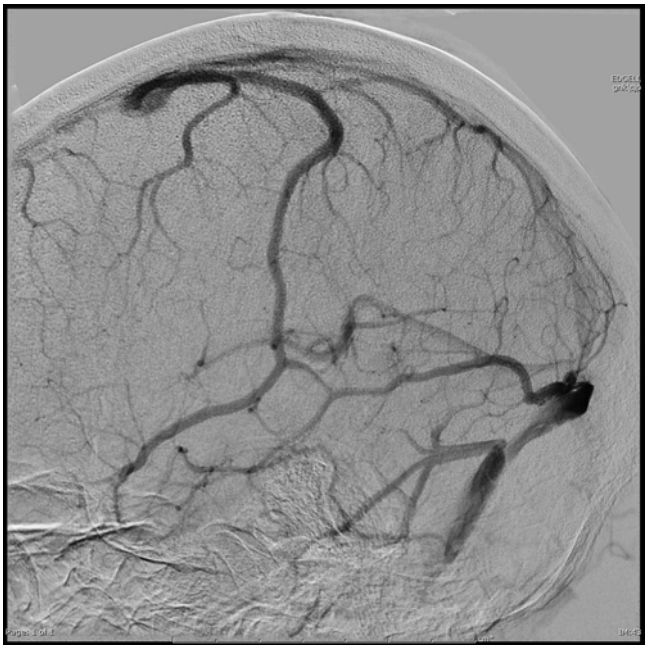

Fig. 2.11 Lateral projection images of the dural sinuses, cortical veins, and deep cerebral veins

The SS also terminates in the torcular Herophili, which is formed by the confluence of SS, SSS, and transverse sinuses, and is well visualized on the AP projection. The TSs receive blood from SS and SSS as well as tributaries from the cerebellum and temporal and occipital lobes. It also receives the vein of Labbe. The two TSs are frequently asymmetrical with the right one being larger in 75 % cases. The TSs continue anteroinferiorly as the sigmoid sinuses and then the internal jugular veins.

The cavernous sinuses (Fig. 2.12; see Chap. 17) lie lateral to the sphenoid body and are usually made of multiple small veins, extending from the superior orbital fissure to the petrous apex, and also house the CN III, IV, V1, and VI and the cavernous segment of the ICA. The CS then drains into the superior and inferior petrosal sinuses.

Considerable variation is seen in the anatomy of the dural sinuses. These include an absent SSS or an SSS that deviates to the right in its descent. It may rarely drain directly into a TS, where the torcula may be hypoplastic or absent. There may be absence or hypoplasia of a TS. The IJV has a normal dilatation at its origin called the jugular bulb. There may be rare occasions where the bulb may be higher than normal, and this may be of clinical significance, causing tinnitus. True anomalies of dural venous sinuses are rare but may be associated with congenital brain malformations such as Chiari II and Dandy–Walker malformations.

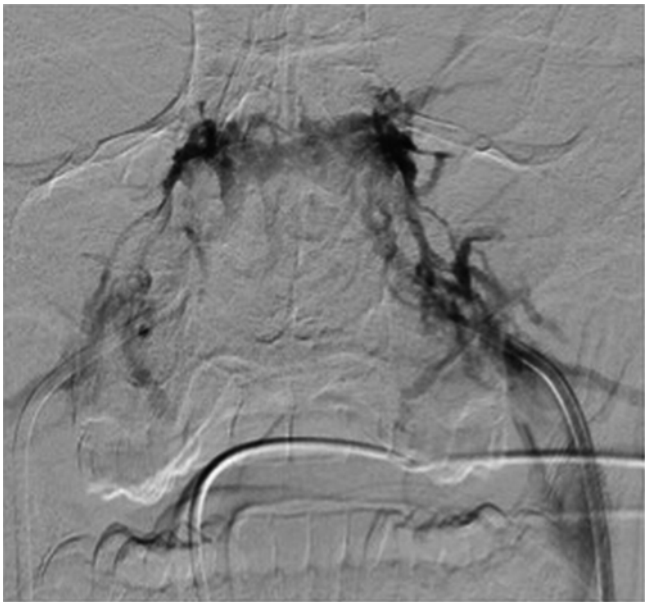

Fig. 2.12 Anteroposterior images of the cavernous and circular sinuses

The Cerebral Veins

The cerebral veins are further subdivided into:

1. Superficial cerebral veins
   These are several veins which course along the superficial sulci and drain the cortex. Cortical veins are well visualized on lateral view in the venous phase of a cerebral angiogram and appear to radiate outwards like spokes of a wheel. They are very variable and are, by and large, unnamed. There are however three prominent veins which are named:
   (a) The superficial middle cerebral vein—it courses along the Sylvian fissure and drains the operculum to ultimately drain into the cavernous or sphenoparietal sinus [31].
   (b) The vein of Trolard (Fig. 2.11)—also known as the superior anastomotic vein, it connects the SMCV with the SSS.
   (c) The vein of Labbe—also known as the inferior anastomotic vein, it connects the SMCV with the transverse sinus. The superior and inferior anastomotic veins have a reciprocal relationship whereby if one is dominant, the other is usually small or even absent [32].
2. Deep Veins
   The deep veins drain blood from the deep white matter and can be visualized better on lateral view of the venous phase of a cerebral angiogram. They include [33]:

(a) Medullary veins—small deep veins which course along the walls of the lateral ventricles. They are sometimes visualized on lateral views and are perpendicular to the ventricular ependymal.
(b) Subependymal veins—they receive the medullary veins and together form important larger tributaries. The major deep tributaries are the septal vein, the thalamostriate vein, and the internal cerebral vein. The septal veins receive tributaries from the corpus callosum and frontal white matter. They then unite with the internal cerebral vein. The thalamostriate veins form by the joining together of the anterior caudate veins and the terminal vein. They too unite with the septal veins to form the internal cerebral veins, which are the largest of the deep cerebral veins. They course posteriorly and continue to receive small subependymal veins. They terminate by joining with each other as well as the basal veins to form the vein of Galen (great cerebral vein). The basal veins of Rosenthal are deep veins that are formed by the coming together of anterior and deep middle cerebral veins. The ICVs and BVRs form the great cerebral vein of Galen that terminates by joining the inferior sagittal sinus to form the straight sinus.

3. Posterior fossa draining veins [34]
The majority of the posterior fossa draining veins are well visualized on the lateral projection, with the exception of the petrosal vein, which can be seen on the AP projection. The main systems draining the posterior fossa are classified as [35]:

(a) The superior or Galenic veins—these include the precentral cerebellar vein, the superior vermian vein, and the anterior pontomesencephalic vein.
(b) The anterior or petrosal veins—these include the petrosal vein, which is formed by multiple small tributaries from the cerebellum, pons, and medulla and drains into the superior petrosal sinus.
(c) Posterior or tentorial veins—the important posterior veins are the inferior vermian veins.

References

1. Harrigan MR, Deveikis JP. Diagnostic cerebral angiography. In: Harrigan MR, Deveikis JP, editors. Handbook of cerebrovascular disease and neurointerventional technique. 2nd ed. New York: Humana Press; 2013. p. 128.
2. Osborn AG. The aortic arch and great vessels. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 16–27.
3. Hacein-Bey L, Daniels DL, Ulmer JL, Mark LP, Smith MM, Strottmann JM, Brown D, Meyer GA, Wackym PA. The ascending pharyngeal artery: branches, anastomoses, and clinical significance. AJNR Am J Neuroradiol. 2002;23(7):1246–56.
4. Niranjan NS. An anatomical study of the facial artery. Ann Plast Surg. 1988;21(1):14–22.
5. Tanoue S, Kiyosue H, Mori H, Hori Y, Okahara M, Sagara Y. Maxillary artery: functional and imaging anatomy for safe and effective transcatheter treatment. Radiographics. 2013;33(7): e209–24. doi:10.1148/rg.337125173.

6. Geibprasert S, Pongpech S, Armstrong D, Krings T. Dangerous extracranial-intracranial anastomoses and supply to the cranial nerves: vessels the neurointerventionalist needs to know. AJNR Am J Neuroradiol. 2009;30(8):1459–68. doi:10.3174/ajnr.A1500.
7. Osborn AG. The external carotid artery. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 38.
8. Bouthillier A, van Loveren HR, Keller JT. Segments of the internal carotid artery: a new classification. Neurosurgery. 1996;38(3):425–32. discussion 432–3.
9. Cohen JE, Gomori JM, Leker RR. Internal carotid artery agenesis: diagnosis, clinical spectrum, associated conditions and its importance in the era of stroke interventions. Neurol Res. 2010;32(10):1027–32. doi:10.1179/016164110X12767786356273.
10. Vasović L, Arsić S, Vlajković S, Jovanović I, Jovanović P, Ugrenović S, Andjelković Z. Otic artery: a review of normal and pathological features. Med Sci Monit. 2010;16(5):RA101–9.
11. Shane Tubbs R, Nguyen HS, Shoja MM, Benninger B, Loukas M, Cohen-Gadol AA. The medial tentorial artery of Bernasconi–Cassinari: a comprehensive review of its anatomy and neurosurgical importance. Acta Neurochir. 2011;153(12):2485–90.
12. Alcalá-Cerra G, Tubbs RS, Niño-Hernández LM. Anatomical features and clinical relevance of a persistent trigeminal artery. Surg Neurol Int. 2012;3:111. doi:10.4103/2152-7806.101798.
13. 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.
14. Lang J, Kageyama I. The ophthalmic artery and its branches, measurements and clinical importance. Surg Radiol Anat. 1990;12(2):83–90.
15. Dilenge D, Ascherl Jr GF. Variations of the ophthalmic and middle meningeal arteries: relation to the embryonic stapedial artery. AJNR Am J Neuroradiol. 1980;1(1):45–54.
16. Osborn AG. The internal carotid artery. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 97.
17. Krabbe-Hartkamp MJ, van der Grond J, de Leeuw FE, de Groot JC, Algra A, Hillen B, Breteler MM, Mali WP. Circle of Willis: morphologic variation on three-dimensional time-of-flight MR angiograms. Radiology. 1998;207(1):103–11.
18. El Falougy H, Selmeciova P, Kubikova E, Haviarová Z. The variable origin of the recurrent artery of Heubner: an anatomical and morphometric study. Biomed Res Int. 2013;2013:873434. doi:10.1155/2013/873434.
19. Osborn AG. The anterior cerebral artery. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 132–3.
20. Gibo H, Carver CC, Rhoton Jr AL, Lenkey C, Mitchell RJ. Microsurgical anatomy of the middle cerebral artery. J Neurosurg. 1981;54(2):151–69.
21. Umansky F, Dujovny M, Ausman JI, Diaz FG, Mirchandani HG. Anomalies and variations of the middle cerebral artery: a microanatomical study. Neurosurgery. 1988;22(6 Pt 1):1023–7.
22. Zeal AA, Rhoton AL. Microsurgical anatomy of the posterior cerebral artery. J Neurosurg. 1978;48:534–59.
23. Osborn AG. The vertebrobasilar system. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 173–5.
24. Caplan LR. The intracranial vertebral artery: a neglected species. The Johann Jacob Wepfer Award 2012. Cerebrovasc Dis. 2012;34(1):20–30.
25. Osborn AG. The vertebrobasilar system. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 177–8.
26. Lee H, Sohn SI, Jung DK, Cho YW, Lim JG, Yi SD, Lee SR, Sohn CH, Baloh RW. Sudden deafness and anterior inferior cerebellar artery infarction. Stroke. 2002;33(12):2807–12.
27. Spektor S, Piontek E, Umansky F. Orbital venous drainage into the anterior cavernous sinus space: microanatomic relationships. Neurosurgery. 1997;40(3):532–9. discussion 539–40.
28. Braun JP, Tournade A. Venous drainage in the craniocervical region. Neuroradiology. 1977;13(3):155–8.
29. Andrews BT, Dujovny M, Mirchandani HG, Ausman JI. Microsurgical anatomy of the venous drainage into the superior sagittal sinus. Neurosurgery. 1989;24(4):514–20.

30. Browder J, Kaplan HA, Krieger AJ. Anatomical features of the straight sinus and its tributaries. J Neurosurg. 1976;44(1):55–61.
31. Galligioni F, Bernardi R, Pellone M, Iraci G. The superficial sylvian vein in normal and pathologic cerebral angiography. Am J Roentgenol Radium Ther Nucl Med. 1969;107(3):565–78.
32. Sener RN. The occipitotemporal vein: a cadaver, MRI and CT study. Neuroradiology. 1994;36(2):117–20.
33. Friedman DP. Abnormalities of the deep medullary white matter veins: MR imaging findings. AJR Am J Roentgenol. 1997;168(4):1103–8.
34. Galligioni F, Bernardi R, Pellone M, Iraci G. The veins of the posterior cranial fossa: an angiographic study under pathologic conditions. Am J Roentgenol Radium Ther Nucl Med. 1970; 110(1):39–49.
35. Osborn AG. The cerebral veins. In: Osborn AG, editor. Diagnostic cerebral angiography. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 233–5.

Chapter 3
Intensive Care of the Neurointerventional Patient

Junaid Siddiq Kalia, Eliahu Feen, and Abhay Kumar

Introduction

The fields of neurointervention and neurocritical care have both grown and evolved rapidly over the last 10–20 years. The variety and severity of patients treated by neurointerventionalists has increased dramatically. The neurointensivist must be familiar with the spectrum of such patients in order to manage both anticipated and unanticipated events effectively. The neurointensivist's goal should be to maintain lines of communication between the various teams involved in order to coordinate and direct excellent care of the patient in a collaborative environment. This chapter focuses on neurocritical care pertaining to common neurointerventional procedures. Table 3.1 provides a summary of intensive care of the neurointerventional patients.

J.S. Kalia, M.D. • E. Feen, M.D. • A. Kumar, M.D. (✉)
Department of Neurology and Psychiatry, Saint Louis University,
1438 South Grand Blvd, Saint Louis, MO 63104, USA
e-mail: jskalia@gmail.com; efeen@slu.edu; akumar22@slu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_3

Table 3.1 Summary of intensive care of the neurointerventional patient

Condition	Synopsis of clinical condition and monitoring	Synopsis of management
Pre-procedure renal protection	Absolute increase by 0.5 mg/dl or 25 % relative increase from baseline seen 2–7 days after contrast exposure	If ≥2 risk factors for contrast nephropathy, NAC 600–1,200 mg PO Q6 h× 4 doses pre-procedure and/or 1 ml/kg/h normal saline or sodium bicarbonate 6–12 h pre- and post-procedure
Vascular access site complications Local hematoma Retroperitoneal hematoma Pseudoaneurysm Arteriovenous fistula	Local growth; margins should be demarcated Flank and abdominal pain, painful and cold extremity. Potentially life threatening due to acute anemia and shock Ecchymosis, pulsatile palpable mass and presence of bruit. Untreated source of emboli and infection and potential rupture Rare iatrogenic communication between femoral artery and vein Most resolve spontaneously; in rare cases chronic AVF may cause cardiac failure, limb edema, or degeneration of the artery	Local compression Frequent marking and serial checks Frequent hemoglobin checks CT abdomen; aggressive management of shock Progressive worsening—consider blood transfusion, reversal of anticoagulation, surgical/angiographic exploration of arteriotomy site Duplex ultrasound or CT/MR angiography in some cases If small (<2 cm), observe. Larger pseudoaneurysm could be treated using ultrasound-guided compression or rarely open surgical repair Serial duplex ultrasound. USGC or endovascular/open surgical repair for chronic AVF
Stroke thrombectomy Blood pressure management Intracranial hemorrhage (ICH) Increased ICP management Herniation or ICP crisis	Frequent neurological examination Signs of increased intracranial pressure with change in neurological exam Risk factors: onset-to-reperfusion time >270 mins, initial larger stroke >1/3 of MCA, or severe deficits at presentation (NIHSS >20) Sustained ICP >20 mmHg with neuro worsening Sustained ICP >25 mmHg for prolonged period Unilateral pupil dilation	CT scan with or without CT angiogram if exam changes Complete recanalization—SBP range 120–140 mmHg Partial recanalization—BP range more liberal up to 180/105 Prompt reversal of anticoagulation; consider checking fibrinogen levels with FFP ± platelet transfusion Consider prophylactic hypernatremia Neurosurgery consultation for potential decompression or EVD placement Elevation of bed to 30° Mannitol (average 1 g/kg) Q6 h +/− hypertonic saline Monitor osmolar gap and renal function Hyperventilate to maintain $PaCO_2 \sim 30$ mmHg Bolus mannitol 1–1.5 g/kg or 23.4 % NaCl 0.67 cc/kg

(continued)

Table 3.1 (continued)

Condition	Synopsis of clinical condition and monitoring	Synopsis of management
Subarachnoid hemorrhage Blood pressure management Vasospasm	Frequent neurological examination Commonly seen 3–21 days post-aSAH Neurological deterioration	Incidence of rebleed is 5–10 % in first 72 h Maintain SBP <160 and MAP <110 prior to securing aneurysm Daily transcranial Doppler (TCD); maintain euvolemia Diagnostic angiogram or CT/MR angiography Induce hypertension using boluses with or without vasopressor Sustained vasospasm intra-arterial vasodilator and/or angioplasty
Carotid artery stenting Cardiovascular complications Bradycardia Myocardial infarction Ischemic stroke Intracerebral hemorrhage Cerebral hyperperfusion syndrome	Frequent neurological examination Avoid sedation and pain medication, may mask symptoms Persistent heart rate below 60 beats per minute Risk of periprocedural MI high (~1.3 %) Periprocedural risk is ~3.5 % New neurological deficit Ipsilateral headache, seizure, and transient neurological deficit in the absence of ischemic or hemorrhagic injury	Dual antiplatelet therapy should be started in all patients pre-procedure Atropine IV 0.5–0.75 mg if symptomatic Continue pre-procedure beta-blocker at reduced dose Start or continue statins Optimize electrolytes K >4, Mg >2, calcium >8 Cardiology consult if new onset arrhythmia and troponin leak CT brain rules out ICH CT angiography or conventional angiography to investigate in-stent thrombosis versus intraluminal occlusive Consider emergent intra-arterial tPA or mechanical thrombectomy Maintain blood pressure close to normal Symptomatic headache therapy Symptomatic seizure therapy with antiepileptics
Intracranial embolization procedures Hemorrhagic complications Ischemic complications Seizure	Frequent neurological examination Neurological deterioration Iatrogenic secondary to catheter-induced emboli Common ~8 %	Blood pressure regulation is extremely important post-procedurally All patients should be kept normotensive and euvolemic CT brain to rule out ICH Prevented with systemic heparinization First-line antiepileptic

AVF arteriovenous fistula, *SBP* systolic blood pressure

Pre-procedural Care

Fasting

Pre-procedural fasting (NPO or *nulla per os*) reduces the risk of gastric regurgitation. Usually, patients are kept "NPO after midnight" in anticipation of a planned procedure during the daytime. Care must be taken to avoid starvation, dehydration, and electrolyte imbalance in this situation. The American Society of Anesthesiologists practice guidelines recommend abstaining from clear liquids (should not contain alcohol) for at least 2 h prior to elective procedures, 6 h or more from light meals, and ≥8 h from larger meals with high fat content [1]. These recommendations are meant for healthy individuals only and may need to be modified for patients with conditions that affect gastric emptying (as in diabetes, gastroesophageal reflux disease, or enteral feeding) or those who are at high risk for regurgitation or tracheobronchial aspiration.

Hydration

Patients undergoing neurointerventional procedures that have intact thirst mechanisms may be able to maintain euvolemia by ingesting fluids while in the intensive care unit. Those with neurological injuries that impair swallowing, with thirst, or who are intubated should be administered fluids in the event of adequate renal function at the rate of 30 ml/kg/day. Usually crystalloids are sufficient. Colloids may occasionally be used for rapid intravascular volume replacement, although they are much more expensive and may cause unwarranted side effects [2].

Renal Protection

Patients undergoing angiograms, especially those with renal insufficiency, diabetes, and congestive heart failure, are at risk for contrast nephropathy due to regional hypoxia or acute tubular necrosis. It is usually diagnosed based on an absolute increase of serum creatinine of 0.5 mg/dl or by a 25 % relative increase from the baseline value. The rise is usually seen 2–7 days after contrast exposure and may persist for 2 weeks or longer. This can be a serious event, resulting in prolonged hospitalization, dialysis, or even death. The risk of contrast nephropathy appears to be smaller with iso-osmolar, dimeric, nonionic contrast agents than low-osmolar, nonionic, monomeric contrast agents [3]. If the patient requires a dye-based study, risk factors should be considered. If ≥2 risk factors for contrast nephropathy are present, nephroprotection using *N*-acetylcysteine 600–1,200 mg orally for four doses periprocedurally should be considered. Otherwise, hydration with 1 ml/kg/h

of intravenous normal saline for 6–12 h before and after the procedure should be administered while minimizing the use of contrast dye during the procedure. Sodium bicarbonate likely has a similar protective effect to normal saline, although some believe its alkalinizing action on the renal tubular fluid provides additional protection [4].

Post-procedural Care

Vascular Access Site Complications

Vascular access site (VAS) care is important in post-procedural care, and neurointensivists should be familiar with the prevention and management of related complications. The rate of percutaneous VAS complications due to neurointervention is reported to be between 0.3 and 4.2 % [5, 6]. Improved closure devices have contributed to decreased morbidity and mortality in recent years [7]. A detailed hand-off communication [8] helps in early detection and prompt management [9]. Femoral access is commonly employed in neurointerventional cases, and related complications will be discussed.

- *Hematoma*
  A localized hematoma remains the most common complication in any endovascular procedure. The adverse consequences range from minimal to life threatening if retroperitoneal space is involved. A high puncture level above the inguinal ligament is an important risk factor for the development of retroperitoneal hematoma.

  A hematoma will cause pain and swelling, while a retroperitoneal hematoma may result in flank/abdominal pain, a painful/cold limb, loss of peripheral pulses, acute anemia, and hemorrhagic shock in extreme cases. Management with local compression, serial groin/flank checks marking hematoma growth, and frequent follow-up of hemoglobin is the first line of treatment. There should be a low threshold to get CT of the abdomen and pelvis in patients with falling hematocrit and physical signs consistent with shock. Progressive blood loss and hypovolemic shock necessitate reversal of anticoagulation, blood transfusion, and aggressive management of shock. Continued bleeding with evidence of retroperitoneal bleeding requiring multiple transfusions may necessitate surgical/endovascular management to explore the arteriotomy site for active bleeding and repair.

  Long-term complications of these hematomas include compressive femoral neuropathy/lumbar plexopathy causing weakness, numbness, and pain.

- *Pseudoaneurysm*
  A pseudoaneurysm is a contained vascular rupture (hematoma) within the elements of the surrounding tissue at the arteriotomy site that creates turbulent flow between the vessel and soft tissue space. Diagnosis is suspected based on a groin examination that shows ecchymosis, a pulsatile palpable mass, and/or bruit.

If left untreated, the pseudoaneurysm can serve as a source of emboli, infection, or rupture [10]. Duplex ultrasound shows a hypoechoic region, either lobulated or cystic, adjacent to the artery with color flow map that demonstrates turbulent, swirling flow ("yin-yang sign") [11]. Obese patients may need CT or MR angiography for diagnosis. Retroperitoneal extension may be investigated using a CT of the abdomen to identify the arterial injuries.

Management and treatment of a pseudoaneurysm depends on the size, location, and progression of the lesion. Smaller pseudoaneurysms (<2 cm) can be observed with frequent Doppler exams. Larger pseudoaneurysms are treated using ultrasound-guided compression (USGC), ultrasound-guided thrombin injection (USGTI), or less commonly open surgical repair.

- *Arteriovenous fistula (AVF)*
  Iatrogenic fistulas (communication between femoral artery and vein) are a rare VAS complication. Most cases resolve spontaneously, but rarely long-standing fistula may give rise to cardiac failure, limb edema, or degeneration of the artery. Treatment should be pursued using USGC or endovascular or open surgical repair.

- *Infection*
  Infection is a low-frequency complication in percutaneous interventions (including diagnostics, angioplasty, stenting, and/or embolization procedures). There is no need to use prophylactic antibiotics [12].

Stroke Thrombectomy (See Chap. 7)

Only about 7 % of acute ischemic stroke patients receive intravenous (IV) thrombolysis. Clinical recovery depends on recanalization of the affected blood vessel(s) but occurs in only 20–30 % of large artery occlusions treated with IV tPA [13, 14]. Mechanical thrombectomy with stent retriever devices has better rates of recanalization and fewer complications (e.g., intracerebral hemorrhage) than other methods even though its clinical efficacy has not yet been fully proven [15–17]. While some trials (e.g., REVASCAT) are attempting to establish the clinical utility of mechanical thrombectomy in prespecified settings, it is currently offered on a case-by-case basis to eligible patients. Medical management of such patients in the neurocritical care unit remains an important task for the neurointensivist.

- *Blood pressure management*
  Blood pressure (BP) should be frequently monitored along with the neurologic examination for the first 24 h in patients receiving mechanical thrombectomy. BP parameters are similar to management following IV thrombolysis, although experts suggest different titration strategies based on the extent of recanalization [18, 19]. Sudden changes in BP with worsening of neurological examination should immediately be investigated for spontaneous intracranial hemorrhage. In

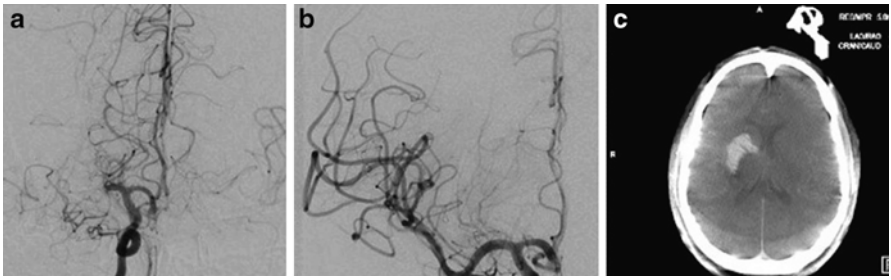

Fig. 3.1 Reperfusion hemorrhage following successful treatment of MCA occlusion. Cerebral angiogram shows a MCA-M1 occlusion (**a**), which was successfully recanalized (**b**). Post-thrombectomy computed tomography (CT) shows intracerebral hemorrhage (**c**)

the event of full recanalization, BP should be kept in the systolic 120–140 mmHg range to minimize the risk of reperfusion hemorrhage. Those receiving mechanical thrombectomy alone with only partial recanalization may benefit from a higher BP target—up to 180/105 mmHg.

- *Intracranial hemorrhage*
  Small volume intracranial hemorrhage (ICH) after thrombolysis is frequently seen on follow-up imaging studies (Fig. 3.1). This may be a marker of early successful recanalization that has been shown to be associated with reduced infarct size and improved clinical outcome [20]. On the other hand, deterioration in neurological examination with ICH or symptomatic ICH (sICH) is a feared complication that results in worsened outcomes and increased mortality. This risk may increase with longer onset-to-reperfusion times (>270 min) [21]. In addition, more severe deficits at presentation (NIHSS > 20), the presence of cerebral edema on initial imaging, involvement of >1/3 of the MCA territory, as well as deviation from thrombolysis protocols may increase the risk of sICH. Guidelines regarding management of sICH following thrombolysis/thrombectomy are currently lacking, and empirical treatment is done based on the clinician's judgment. Some strategies are based on fibrinogen levels—if <100 mg/dl, cryoprecipitate is administered at 0.15 U/kg. Alternatively, fresh frozen plasma along with platelets (6–8 U, if platelet dysfunction is suspected) is relied upon at some centers [22]. A neurosurgical consultation should be obtained for potential decompression or clot evacuation in the event of a life-threatening decline, while remaining vigilant for secondary cardiorespiratory failure. Seizure prophylaxis in the event of sICH is not generally recommended, although this area also is lacking in high-level evidence.

- *Intracranial Pressure (ICP) management*
  Large hemispheric infarcts complicated by hemorrhagic conversion or cerebral edema can result in elevated ICP. There is no benefit in routine ICP monitoring as patients may develop pupillary abnormalities and signs of brainstem compression even with normal ICP values [23]. Patients with high NIHSS (>15) on

presentation and large territorial involvement due to a large vessel occlusion are at risk for developing malignant MCA infarction.

While sICH generally occurs in the first 24 h after presentation, cytotoxic edema and ICP elevation often peak 3–4 days after the initial injury. Patients with large hemispheric infarcts that involve >50 % MCA territory with greater than 66 % perfusion deficit are at risk of developing life-threatening malignant brain edema within 24 h [24]. Hemicraniectomy provides definitive treatment for malignant brain edema while medical management is at best temporizing in such situations.

– *Hemicraniectomy*
  Decompressive hemicraniectomy (DHC) is the definitive treatment for malignant cerebral edema due to middle cerebral artery (MCA) infarcts. It normalizes the intracranial pressure, improves the cerebral blood flow, and reverses the herniation impacting the contralateral hemisphere and midline structures.

  The pooled analysis of three European hemicraniectomy trials proved the efficacy of DHC performed up to 48 h from the onset of symptoms. A reduction in mortality was seen in patients up to 60 years of age (number needed to treat =2) [25]. These trials included patients with MCA strokes on either side. Similar benefits may be seen in patients up to 70 years of age based on the findings from the recently completed DESTINY II trial [26]. The impact of DHC on functional outcomes was not as robust in this age group. Despite this fact, patients reported satisfaction with their quality of life even in the setting of a high degree of physical disability and depression [27].

  Patients benefit from DHC irrespective of the hemisphere involved. The benefit is most pronounced if surgery is performed within 24 h. It is unclear whether the benefit would persist if surgery were performed beyond 48 h. Since not all large territory MCA infarctions lead to malignant edema requiring DHC, vigilant neuromonitoring is needed. Infarct volumes >145 cm^3 at 14 h seen on magnetic resonance diffusion-weighted imaging were shown to have 100 % sensitivity and 94 % specificity in predicting malignant edema [28]. Infarct volumes >82 cm^3 at 6 h have 98 % specificity but lower (52 %) sensitivity [28].

  An adequate DHC should be 14 cm in anteroposterior diameter as well as 9 cm in vertical diameter (Fig. 3.2). The neurointensivist should watch for the complications of an undersized craniectomy that may result in mushrooming herniation of the brain through the craniectomy leading to further ischemia. Additional care should be paid to the development of subdural hygromas, hydrocephalus, and hemorrhage at the craniectomy site as well as any signs of infection at the site of surgery.

– *Medical*
  The first priority in ICP management is ensuring adequate airway, breathing, and circulation. Other medical interventions in the management of ICP in malignant MCA infarction are temporizing measures. Mortality can be up to

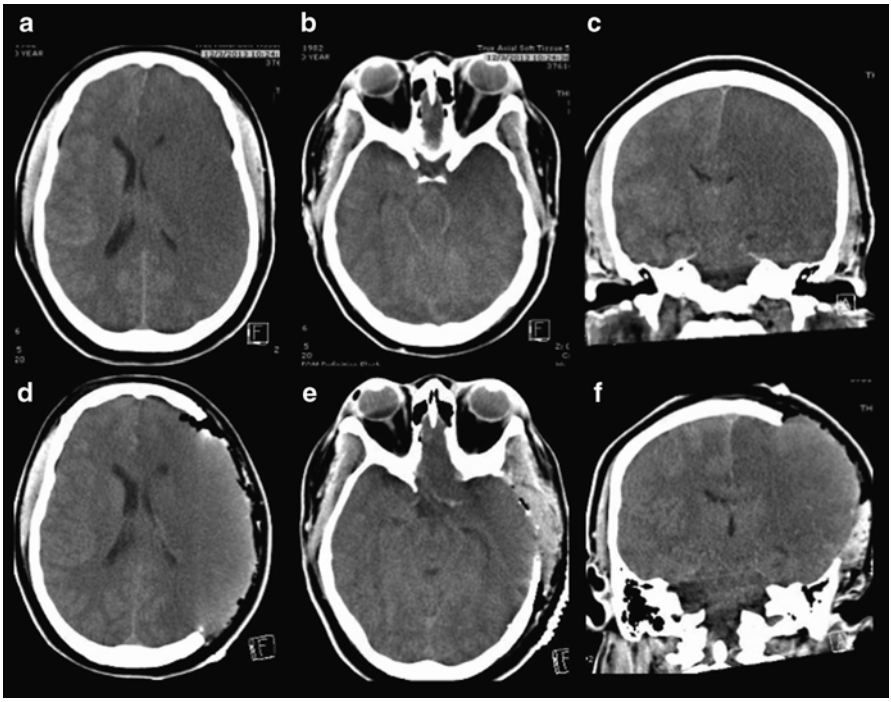

Fig. 3.2 Malignant MCA infarction requiring decompressive craniectomy. Computed tomography (CT) shows malignant right middle cerebral artery (MCA) infarction with extension into the temporal lobe (**a**–**c**). Post-surgical resolution of subfalcine herniation with overlying scalp expanded to accommodate expanding brain (**d**–**f**)

70 % when relying upon medical management only in this population. Medical management of ICP includes elevation of bed to 30°; use of mannitol (average 1 g/kg) every 6 h while maintaining euvolemia, monitoring osmolar gap (should reconsider mannitol if gap >15) and renal function; hypertonic saline; and intubation with hyperventilation. There is currently insufficient evidence to advocate the use of prophylactic hypernatremia in preventing the development of cerebral edema following ischemic stroke [29].

- *Antithrombotic use post-thrombectomy*
  Initiation of anticoagulation and/or antiplatelet agents is an individualized decision post-thrombectomy given the absence of formal guidelines. Initial studies and clinical trials (NINDS and PROACT II) excluded patients with infarct volume >1/3 MCA territory due to concerns of hemorrhagic reperfusion injury. In general if reperfusion hemorrhage has occurred, antithrombotic therapy should be held for 1–4 weeks.

Subarachnoid Hemorrhage (See Chap. 11)

Aneurysmal subarachnoid hemorrhage (aSAH) patients should be cared for in a high-volume center. The neurointensivist acts as the linchpin to ensure appropriate care in this high morbidity and mortality disease. Various organ systems may be affected through the course of the patient's presentation. Knowledge of these conditions is required to provide the best possible care.

- *BP management*
  Aneurysmal rupture is associated with a sympathetic surge and resultant increase in blood pressure. The incidence of rebleeding is 5–10 % in the first 72 h. The exact blood pressure beyond which the risk of rebleeding significantly rises is not clear; however, systolic blood pressures up to 160 mmHg or mean blood pressure up to 110 mmHg is generally acceptable. Short-acting BP medications (e.g., labetalol or hydralazine) may be used intermittently or continuously (e.g., nicardipine). Premorbid blood pressure should be taken into consideration while hypotension should be avoided. Hypertension that is accompanied by bradycardia should raise concern for increased intracranial pressure and may require osmotic therapy to treat cerebral edema or extraventricular diversion of cerebrospinal fluid if hydrocephalus is diagnosed.

  BP is commonly elevated in the acute phase following aSAH. After the aneurysm is secured, strict BP control is not required. BP goals should be relaxed to allow for cerebral perfusion. Strict BP control may mask the early warning signs of vasospasm during which BP typically increases. BP should be titrated in the event of signs and symptoms of end-organ damage.

- *Vasospasm*
  Arterial narrowing or vasospasm as evidenced on angiography is seen between 3 and 21 days post-aneurysmal rupture with the peak being around 7–10 days. It is seen in two-thirds of patients presenting with aSAH, and in approximately 30 % of such cases, arterial vasospasm results in focal neurological deficits also known as delayed cerebral ischemia (DCI). If not treated appropriately, DCI can result in cerebral infarction—a feared complication that can greatly affect the long-term outcome. Vasospasm risk increases with the thickness of SAH as measured by the modified Fisher scale [30]. Nimodipine (60 mg every 4 h), a dihydropyridine calcium channel antagonist, is the only agent shown to reduce cerebral ischemia and mortality when used prophylactically. It is used for 21 days in aSAH. Sometimes due to its hypotensive effect, it may need to be given at a reduced dose but greater frequency (30 mg every 2 h).

  In the event of neurological worsening, potential confounders (fever, hypotension, hyponatremia, seizures, etc.) should be ruled out. In parallel, vasospasm should be investigated using catheter angiography. While catheter angiography is the preferred modality in cases at high risk for vasospasm where intra-arterial

intervention may be required, CT/MR angiograms with/without perfusion maybe reasonable alternatives in select situations. CT/MR angiograms are less sensitive in detecting mild–moderate vasospasm compared to catheter angiography. While planning for a catheter angiogram, hemodynamic augmentation should be attempted using a fluid bolus with/without a vasopressor (Neo-Synephrine or norepinephrine) in order to up-titrate mean arterial pressure by 15–20 %. Occasionally, an inotropic agent may be useful in this setting. If vasospasm on angiogram is diagnosed, it may require treatment with intra-arterial vasodilator agents or angioplasty. Only the induced hypertension component of the conventional "triple H" therapy should be used as hypervolemia and hemodilution do not improve cerebral blood flow or oxygen delivery and may even cause cardiopulmonary complications.

- *Medical management*
  The SAH patient requires comprehensive medical management as various physiologic derangements can result in worsened outcomes. The commonly encountered medical problems in an SAH patient are anemia, fever, cardiopulmonary complications, and electrolyte abnormalities. Anemia is multifactorial in nature in SAH patients and predictive of adverse outcome. Conversely, patients with higher hemoglobin levels have been observed to have better outcomes [32]. However, it is also known that a liberal transfusion strategy (hemoglobin >10 g/dl) is fraught with complications. Blood transfusion should thus be carefully considered in anemic patients with ongoing vasospasm. Fever is frequent in SAH and may be associated with vasospasm, further leading to poor functional and cognitive outcomes. Noninfectious/central etiologies can cause fever in the early phase (<72 h) in approximately half of these patients [33]. It is, however, important to rule out infectious causes in such cases. Treatment of fever with cooling strategies can cause shivering that should be managed through non-pharmacologic (surface warming) as well as pharmacologic (antipyretics, NSAIDs, buspirone, etc.) means.

  Cardiopulmonary function can be affected by a catecholamine surge-induced dysfunction leading to cardiac arrhythmias, "stunned" myocardium, and hypoxemia due to pulmonary edema or acute respiratory distress syndrome. Supportive cardiopulmonary management should be utilized. Careful fluid balance with a goal of euvolemia should be employed in SAH as hypervolemia is not beneficial and hypovolemia is associated with cerebral ischemia and infarction [34]. Central venous pressure (CVP) monitoring is not a reliable marker of intravascular volume and hence should be avoided. Patients develop hyponatremia with hypovolemia, which may be mistakenly construed as syndrome of inappropriate antidiuretic hormone secretion (SIADH). Even in these situations fluid restriction should be avoided. Instead, euvolemia with hypertonic fluids should be the goal in the vasospasm period.

Carotid Stenting (See Chap. 4)

- *Cardiovascular complications*
  Post-procedural care after carotid artery stenting (CAS) involves close neurologic observation and careful hemodynamic monitoring due to the subacute complications that may develop within hours to days of surgery. Bradycardia and hypotension are commonly seen in CAS patients due to mechanical stretching of the carotid baroreceptor [35]. Cerebral perfusion should be maintained, as prolonged hypotension can result in expansion of ipsilateral stroke or new ischemic stroke [36]. Hypotension unresponsive to gentle fluid boluses should be treated with vasopressors as required. Midodrine may be used in some patients with prolonged hypotension.

  CAS is most often performed in patients at high risk for carotid endarterectomy. These patients are disproportionately affected by premorbid conditions such as diabetes or advanced age and are prone to cardiac ischemia. Careful preprocedure risk assessment should be performed in all patients. Perioperative myocardial infarction (PMI) may result from unstable coronary plaque and prolonged myocardial oxygen supply–demand imbalance. Even though the risk of PMI is real (~1.3 %), prophylactic initiation of beta-blockers is not advised due to the incidence of hypotension and bradycardia in CAS [37]. Those already on beta-blockers should be continued on a reduced dose. Statins (HMG-CoA reductase inhibitors) have been shown to reduce perioperative cardiac events [38, 39]. Dual antiplatelet therapy must be started prior to the procedure in all patients [40]. Optimization of electrolytes is recommended to prevent arrhythmia that may lead to PMI. Typically, serum potassium >4 mEq/l, magnesium >2 mg/dl, and calcium >8 mg/dl are recommended.

- *Ischemic stroke*
  Periprocedural ischemic stroke risk is ~3.5 % and typically occurs during or within a few days of carotid stenting [41]. About two-thirds of periprocedural strokes are due to thromboembolism; other causes include arterial spasm and intraluminal thrombosis or occlusion [42]. After an emergent CT of the brain rules out ICH, CT angiography (CTA) or standard angiography may be appropriate to investigate in-stent thrombosis or other intraluminal occlusive processes for which emergent intra-arterial tPA or mechanical thrombectomy may be needed (Fig. 3.3). Intravenous tPA may be used if large artery embolization is seen on CT angiography [43]. Other options for thrombolysis include IV GP IIb/IIIa inhibitors (e.g., eptifibatide, abciximab, integrilin), platelet-rich thrombus, or anticoagulation for dissection. The decision to perform stroke intervention is challenging as patient may have a subacute preexisting stroke that creates a high risk of reperfusion hemorrhage.

- *Intracerebral hemorrhage*
  Reperfusion of the brain may lead to significant complications including cerebral hyperperfusion syndrome, intracerebral hemorrhage (ICH), and contrast

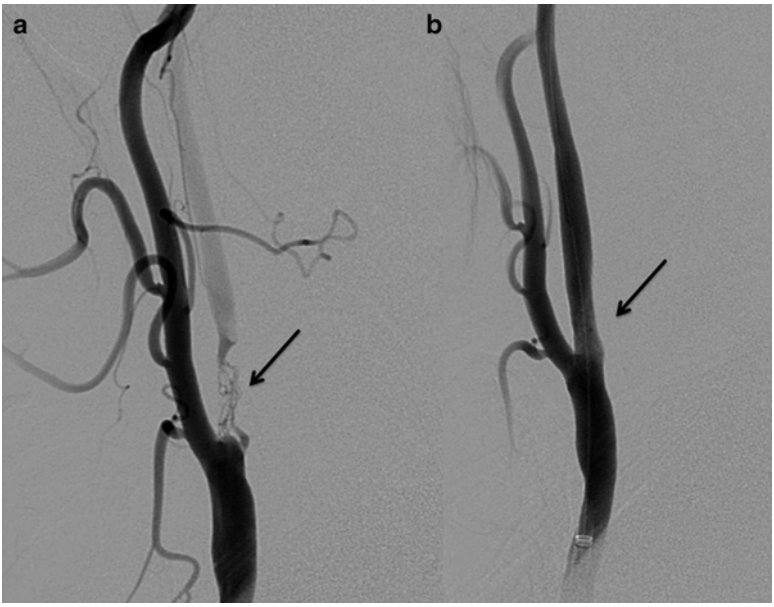

Fig. 3.3 Right common carotid stenosis; pre-stenting showing significant stenosis (**a**). Post-stenting flow void representing acute in-stent thrombosis (**b**)

encephalopathy. Cerebral autoregulation involves an intimally mediated physiological response of smooth muscles in the large vessels. Normal cerebral autoregulatory processes that ensure consistent cerebral blood flow (CBF) within 60–150 mmHg of mean arterial pressure are impaired in the ischemic brain [44]. Ischemic insult also disrupts the blood–brain barrier (BBB) so that when flow is restored in impaired cerebral autoregulation, luminal hydrostatic pressure is directly transmitted to brain parenchyma resulting in hemorrhagic transformation (Fig. 3.4) [45]. The incidence of ICH post-CAS is 0.36–4.5 % [46]. The risk of hemorrhagic transformation is greater with larger preexisting infarct volumes [47]. Once ICH is identified; immediate reversal of anticoagulation should be initiated with protamine. The reversal of antiplatelet medication must be weighed against the risk of in-stent platelet aggregation and intracranial embolism. Management otherwise involves treatment of increased intracranial pressure and consideration of surgical intervention such as ventriculostomy and craniectomy.

- *Cerebral hyperperfusion syndrome (CHS)*
  Sundt initially defined cerebral hyperperfusion syndrome (CHS) as a clinical triad of ipsilateral headache, seizure, and focal neurological deficit in the absence of ischemic or hemorrhagic injury after CEA [48]. These symptoms typically present within hours after CAS [49]. Besides hypertension post-CAS, preoperative risk factors are microangiopathy, diabetes mellitus, recent contralateral carotid intervention, poor collateral flow, and an incomplete circle of

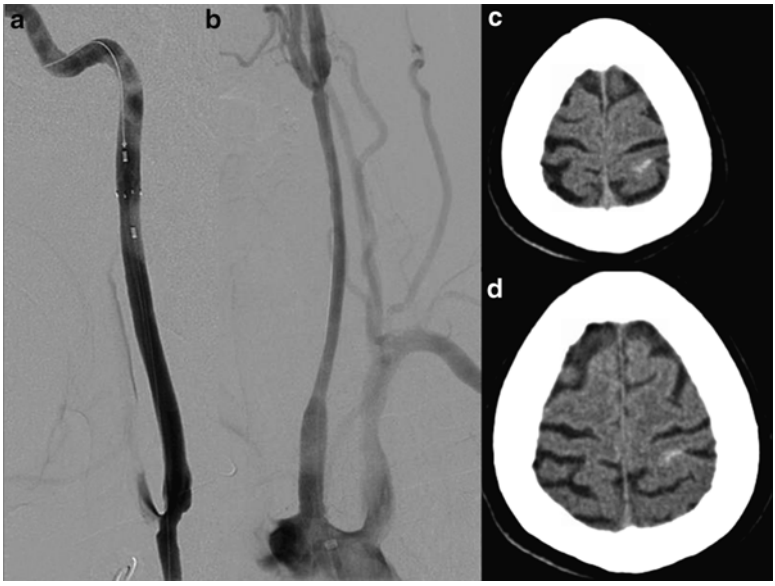

Fig. 3.4 Right common carotid stenosis (**a**) post-stenting (**b**). CT scan showing subarachnoid hemorrhage (SAH) secondary to reperfusion injury post-stenting in ipsilateral cerebral hemisphere (**c**, **d**)

Willis [50]. Diagnosis of CHS is made on the basis of clinical presentation with radiographic presence of cerebral edema. Management of CHS is not standardized. Blood pressure should be controlled in these patients. Symptomatic management of headache, which is usually self-limited, is recommended since pain may increase blood pressure and pulse. Seizures should be treated with a first-line antiepileptic.

- *Contrast encephalopathy*
  Contrast encephalopathy is a rare, self-limited condition, in which contrast material causes disruption of blood–brain barrier. Patients typically present with visual symptoms or focal neurological deficits. A CT of the brain will show cortical enhancement, edema, and rarely subarachnoid hemorrhage [51, 52].

Intracranial Embolization Procedures

Endovascular embolization procedures are done in many intracranial pathologies including arteriovenous malformation (AVM), arteriovenous fistula (AVF), bleeding intracranial vessel (traumatic or iatrogenic), and tumors. These may be standalone therapies or part of multimodality treatment to increase procedural safety and efficacy.

Blood pressure regulation is extremely important post-procedurally. All patients should be monitored in neuro ICU with close blood pressure monitoring preferably via an arterial catheter [53, 54]. Patient should be kept normotensive and euvolemic [55]. Some interventionalists advocate maintaining sedation and intubation to regulate blood pressure posttreatment. This is especially true in cases of multistage embolization. Post-procedure, headache is a common complaint. A CT of the brain should be obtained to rule out hemorrhage in patients with unusually severe headache, especially when accompanied by a neurological change. All patients should have serial neurological examination, and any change should prompt immediate brain imaging. Besides hemorrhage, venous infarction, hydrocephalus, venous thrombosis, and arterial infarction may occur.

Ischemic complications secondary to catheter-induced emboli or reflux of embolic material may also occur. While not widely utilized, some practitioners advocate the use of post-procedural anticoagulation to prevent venous thrombosis when angiographic venous stasis is noted [56].

The incidence of new seizure after therapy is about 8 %. New seizures post-procedure should be treated with a first-line antiepileptic.

Vasospasm is a very rare complication of ruptured AVMs. It is usually self-limiting but in some cases may require intervention [57, 58].

References

1. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology. 2011;114:495–511. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21307770.
2. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2(CD000567). Available from: http://www.ncbi.nlm.nih.gov/pubmed/23450531.
3. Aspelin P, Aubry P, Fransson S-G, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med. 2003;348:491–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12571256.
4. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA. 2006;295:2765–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16788132.
5. Fifi J, Meyers P, Lavine S. Complications of modern diagnostic cerebral angiography in an academic medical center. J Vasc Interv Radiol. 2009;20:442–7. Available from: http://www.sciencedirect.com/science/article/pii/S1051044309000141.
6. Cloft H, Joseph G, Dion J. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. Stroke. 1999;30(2):317–20. Available from: http://stroke.ahajournals.org/content/30/2/317.short.
7. Piper W, Malenka D. Predicting vascular complications in percutaneous coronary interventions. Am Heart J. 2003;145(6):1022–9. Available from: http://www.sciencedirect.com/science/article/pii/S0002870303000796.
8. Merriweather N, Sulzbach-Hoke LM. Managing risk of complications at femoral vascular access sites in percutaneous coronary intervention. Crit Care Nurse. 2012;32:16–29. quiz first page after 29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23027788.

9. Omoigui N, Califf R, Pieper K. Peripheral vascular complications in the coronary angioplasty versus excisional atherectomy trial (CAVEAT-I). J Am Coll Cardiol. 1995;26:922–30. Available from: http://www.sciencedirect.com/science/article/pii/0735109795002634.
10. Kronzon I. Diagnosis and treatment of iatrogenic femoral artery pseudoaneurysm: a review. J Am Soc Echocardiogr. 1997;10:236–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9109690.
11. Hendricks NJ, Saad WE. Ultrasound-guided management of vascular access pseudoaneurysms. Ultrasound Clin. 2012;7:299–307. Available from: http://www.ultrasound.theclinics.com/article/S1556-858X(12)00040-0/abstract.
12. Kelkar PS, Fleming JB, Walters BC, Harrigan MR. Infection risk in neurointervention and cerebral angiography. Neurosurgery. 2013;72:327–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23151621.
13. Linfante I, Llinas RH, Selim M, Chaves C, Kumar S, Parker RA, et al. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activato. Stroke. 2002;33:2066–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12154264.
14. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38:948–54.
15. 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. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3651875&tool=pmcentrez&rendertype=abstract.
16. 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. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3708480&tool=pmcentrez&rendertype=abstract.
17. 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. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3690785&tool=pmcentrez&rendertype=abstract.
18. Leslie-Mazwi TM, Sims JR, Hirsch JA, Nogueira RG. Periprocedural blood pressure management in neurointerventional surgery. J Neurointerv Surg. 2011;3:66–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21990793.
19. Tarlov N, Nien YL, Zaidat OO, Nguyen TN. Periprocedural management of acute ischemic stroke intervention. Neurology. 2012;79:S182–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23008396.
20. Molina CA, Alvarez-Sabín J, Montaner J, Abilleira S, Arenillas JF, Coscojuela P, et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. Stroke. 2002;33:1551–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12052990.
21. Mosimann PJ, Sirimarco G, Meseguer E, Serfaty J-M, Laissy J-P, Labreuche J, et al. Is intracerebral hemorrhage a time-dependent phenomenon after successful combined intravenous and intra-arterial therapy? Stroke. 2013;44:806–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23370204.
22. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. Arch Neurol. 2010;67:965–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3690951&tool=pmcentrez&rendertype=abstract.
23. Poca MA, Benejam B, Sahuquillo J, Riveiro M, Frascheri L, Merino MA, et al. Monitoring intracranial pressure in patients with malignant middle cerebral artery infarction: is it useful? J Neurosurg. 2010;112:648–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19663552.

24. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. Cerebrovasc Dis. 2008;25:176–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18212524.
25. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6:215–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17303527.
26. Juttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370:1091–100.
27. Rahme R, Zuccarello M, Kleindorfer D, Adeoye OM, Ringer AJ. Decompressive hemicraniectomy for malignant middle cerebral artery territory infarction: is life worth living? J Neurosurg. 2012;117:749–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22920962.
28. Oppenheim C, Samson Y, Manaï R, Lalam T, Vandamme X, Crozier S, et al. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. Stroke. 2000;31:2175–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10978048.
29. Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt F-G, Köhrmann M, et al. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. Ann Neurol. 2010;68:435–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20865766.
30. Ryu JH, Walcott BP, Kahle KT, Sheth SA, Peterson RT, Nahed BV, et al. Induced and sustained hypernatremia for the prevention and treatment of cerebral edema following brain injury. Neurocrit Care. 2013;19:222–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23468135.
31. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59:21–7. discussion 21–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16823296.
32. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, et al. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2004;62:-1468–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15136667.
33. Naidech AM, Jovanovic B, Wartenberg KE, Parra A, Ostapkovich N, Connolly ES, et al. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. Crit Care Med. 2007;35:2383–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17717494.
34. Rabinstein AA, Sandhu K. Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors. J Neurol Neurosurg Psychiatry. 2007;78:1278–80. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2117587&tool=pmcentrez&rendertype=abstract.
35. Wijdicks EF, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: is fluid restriction harmful? Ann Neurol. 1985;17:137–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3977297.
36. McKevitt FM, Sivaguru A, Venables GS, Cleveland TJ, Gaines PA, Beard JD, et al. Effect of treatment of carotid artery stenosis on blood pressure: a comparison of hemodynamic disturbances after carotid endarterectomy and endovascular treatment. Stroke. 2003;34:2576–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14593127.
37. Ito Y, Kato N, Matsumura A, Sonobe M. Hemodynamic instability increases new ischemic brain lesions on diffusion-weighted imaging after carotid artery stenting. Neurol Med Chir (Tokyo). 2013;53:375–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23803615.
38. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med. 2005;353:349–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16049209.
39. Durazzo AES, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leão P, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial.

J Vasc Surg. 2004;39:967–75. discussion 975–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15111846.
40. Feringa HHH, Schouten O, Karagiannis SE, Brugts J, Elhendy A, Boersma E, et al. Intensity of statin therapy in relation to myocardial ischemia, troponin T release, and clinical cardiac outcome in patients undergoing major vascular surgery. J Am Coll Cardiol. 2007;50:1649–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17950146.
41. Schleinitz MD, Olkin I, Heidenreich PA. Cilostazol, clopidogrel or ticlopidine to prevent sub-acute stent thrombosis: a meta-analysis of randomized trials. Am Heart J. 2004;148:990–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15632883.
42. Touzé E, Trinquart L, Chatellier G, Mas J-L. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. Stroke. 2009;40:e683–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19892997.
43. Radak D, Popovic AD, Radicević S, Nesković AN, Bojić M. Immediate reoperation for perioperative stroke after 2250 carotid endarterectomies: differences between intraoperative and early postoperative stroke. J Vasc Surg. 1999;30:245–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10436443.
44. Cazorla García R, Martínez Sánchez P, Frutos Martínez R, Marín Aguilera B, Díez Tejedor E. Simultaneous carotid angioplasty and intracraneal thrombectomy in acute stroke. Neurologia. 2012;27:249–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21658821.
45. Strandgaard S, Paulson OB. Cerebral blood flow and its pathophysiology in hypertension. Am J Hypertens. 1989;2:486–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2757806.
46. Hamann GF, Okada Y, del Zoppo GJ. Hemorrhagic transformation and microvascular integrity during focal cerebral ischemia/reperfusion. J Cereb Blood Flow Metab. 1996;16:1373–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8898714.
47. Cheung RTF, Eliasziw M, Meldrum HE, Fox AJ, Barnett HJM. Risk, types, and severity of intracranial hemorrhage in patients with symptomatic carotid artery stenosis. Stroke. 2003;34:1847–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12829862.
48. Eriksen N, Rasmussen RS, Overgaard K, Johansen FF, Pakkenberg B. Comparison of quantitative estimation of intracerebral hemorrhage and infarct volumes after thromboembolism in an embolic stroke model. Int J Stroke. 2012;9(6). Available from: http://www.ncbi.nlm.nih.gov/pubmed/22928632.
49. Sundt TM, Sandok BA, Whisnant JP. Carotid endarterectomy. Complications and preoperative assessment of risk. Mayo Clin Proc. 1975;50:301–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1127994.
50. Meyers PM, Higashida RT, Phatouros CC, Malek AM, Lempert TE, Dowd CF, et al. Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. Neurosurgery. 2000;47:335–43. discussion 343–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10942006.
51. Moulakakis KG, Mylonas SN, Sfyroeras GS, Andrikopoulos V. Hyperperfusion syndrome after carotid revascularization. J Vasc Surg. 2009;49:1060–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19249185.
52. Dangas G, Monsein LH, Laureno R, Peterson MA, Laird JR, Satler LF, et al. Transient contrast encephalopathy after carotid artery stenting. J Endovasc Ther. 2001;8:111–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11357968.
53. Fang H-Y, Kuo Y-L, Wu C-J. Transient contrast encephalopathy after carotid artery stenting mimicking diffuse subarachnoid hemorrhage: a case report. Catheter Cardiovasc Interv. 2009;73:123–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19089972.
54. 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;13:140–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7355377.
55. Ogilvy CS, Stieg PE, Awad I, Brown RD, 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;103:2644–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11382737.
56. 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;62:1213–25. discussion 1225–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18824988.
57. Dorothea Strozyk, Carlos E. Baccin JCP, RGN. Textbook of Interventional Neurology Chapter: 13 Intracranial arteriovenous malformations. 2011. p. 255.
58. Gross BA, Du R. Vasospasm after arteriovenous malformation rupture. World Neurosurg. 2012;78:300–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22381269.
59. Pendharkar AV, Guzman R, Dodd R, Cornfield D, Edwards MSB. Successful treatment of severe cerebral vasospasm following hemorrhage of an arteriovenous malformation. Case report. J Neurosurg Pediatr. 2009;4:266–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19772412.

Chapter 4
Endovascular Treatment of Extracranial Atherosclerotic Disease

Alex Abou-Chebl and Mouhammad A. Jumaa

Cervical Carotid Artery Disease

Internal carotid artery arteriosclerosis at its origin is an important single cause of TIA and stroke of arterial origin. Carotid endarterectomy (CEA) has been shown to be the treatment of choice in patients with symptomatic stenoses measuring >50 % luminal narrowing. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), CEA was superior to medical therapy in patients with >70 % stenosis, reducing the ipsilateral stroke rate from 26 to 9 % at 2 years. Even patients with 50–69 % luminal narrowing benefited from surgery with a decrease in 5-year ipsilateral stroke rates from 22.2 to 15.7 % [1]. This then is the gold standard therapy against which newer therapies must be measured. CEA is not ideal in all circumstances, however, as its benefits are counterbalanced by significant drawbacks. The margin of benefit in NASCET was dependent on a low perioperative stroke and death rate of 5.8 %. Higher surgical complication rates reduce the benefit from surgery for the population as a whole. The NASCET results do not accurately reflect the real population of symptomatic patients with ICA arteriosclerosis for two major reasons. First, the low perioperative complication rates attained by the specialized centers involved in the trial are much lower, by as much as a factor of three, than those obtained in everyday practice. Second, the patients enrolled in the trial were highly selected and did not include those with major medical comorbidities [renal, pulmonary, and especially coronary artery disease (CAD)], those aged 80 and older,

A. Abou-Chebl, M.D. (✉)
Stroke Program, Baptist Health Hospital, 3900 Kresge Way, Louisville 40207, KY, USA
e-mail: achebl@yahoo.com

M.A. Jumaa, M.D.
Department of Neurology, University of Toledo Medical Center,
3000 Arlington Avenue, Mail Stop 1195, Toledi, OH 43614, USA
e-mail: Mouhammad.jumaa@utoledo.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_4

Table 4.1 Indications for CAS: high-surgical-risk criteria

• Congestive heart failure (class III/IV) and/or known severe left ventricular dysfunction LVEF <30 %
• Open heart surgery within 6 weeks
• Recent MI (>24 h and <4 weeks)
• Unstable angina (CCS class III/IV)
• Coexistent severe coronary artery disease requiring carotid and coronary revascularization
• Severe pulmonary disease (FEV <1.0)
• Contralateral carotid occlusion
• Contralateral laryngeal nerve palsy
• Post-cervical radiation treatment
• Previous CEA (i.e., recurrent stenosis)
• High cervical ICA lesions (C2 or higher)
• CCA lesions below the clavicle
• Severe tandem lesions

or those with a history of prior endarterectomy, radical neck dissection, or radiation therapy to the neck. In addition to the risk of stroke and death noted in NASCET, there were a 7.6 % incidence of cranial neuropathy and an 8.9 % incidence of surgical wound hematoma or infection.

Carotid angioplasty and stenting is an attractive alternative to CEA for several reasons. It is potentially less risky to perform in patients with medical comorbidities especially those with CAD since it is performed without general anesthesia. CAS is a less invasive procedure and does not carry a risk of cranial nerve palsies or surgical wound hematomas and infection, the frequency and clinical significance of which are not minor. CAS may also be applied to patients at particularly high risk of complications from CEA including patients who have major medical comorbidities, those who have had prior CEA or neck exploration or neck irradiation, as well as individuals who have high carotid bifurcations, contralateral carotid occlusion, or tandem stenoses (Table 4.1). Early investigators performed ICA angioplasty only and later used stents only as a rescue if a dissection developed. As stent technology improved, it became possible to deliver stents into the ICA with a significant improvement in acute outcomes compared with angioplasty alone. Currently, stenting following PTA of the ICA is the standard practice. Additional experience has shown that carotid artery stenting (CAS) is best performed with an embolic protection device (EPD). Many non-randomized but large series (300–400 patients each) have shown that cerebral embolic events are greatly reduced using these "filter devices" with a decrease in stroke rates from approximately 5–8.6 to 2–3 % (Fig. 4.1). World experts in CAS have published position statement that the use of embolic prevention devices should be the standard practice.

Following the development of stent and then filter technology, a clinical trial comparing CEA and CAS was needed. Protected stenting (i.e., stenting with the use an EPD) had not been validated outside of registries [2–4]. Several small and poorly conducted trials were initiated [5, 6], but to date the only large randomized trial of

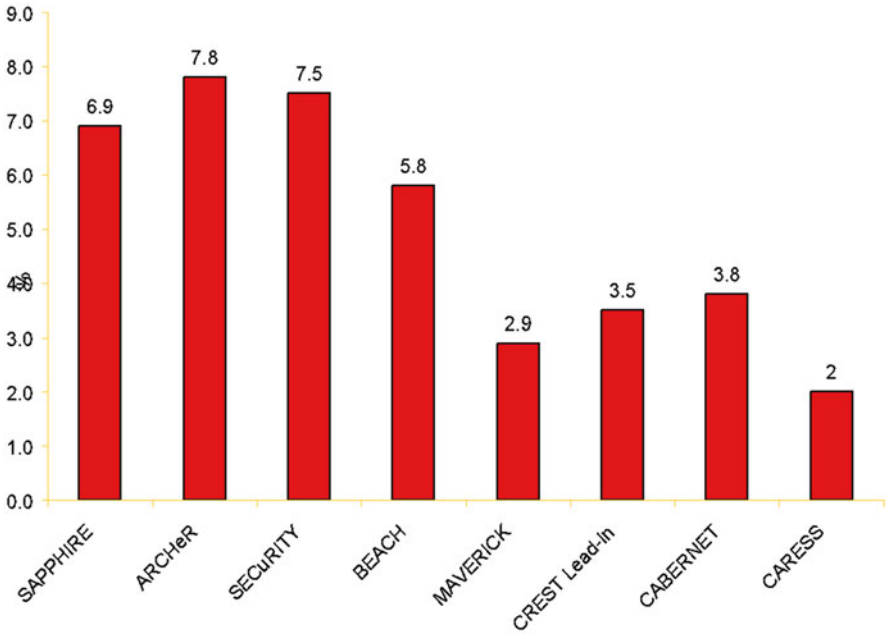

Fig. 4.1 Bar chart illustrating the steady reduction in procedural morbidity and mortality over time

protected CAS vs. CEA in high-surgical-risk patients has been completed: the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study [7]. This non-inferiority study evaluated the Cordis PRECISE™ stent and the ANGIOGUARD™ filter and was sponsored by the manufacturer Cordis Endovascular Inc. The primary study endpoint of stroke, myocardial infarction, or death at 30 days and ipsilateral stroke to 1 year was 12.2 % with CAS and 20.1 % with CEA, $p = 0.05$ for non-inferiority. The 30-day perioperative stroke/MI/death was lower in the CAS group as compared with the CEA group, 4.4 % vs. 9.9 %, respectively, but the difference was not statistically significant ($p = 0.06$) in the on-treatment analysis. The CEA complication rates were much higher than those noted in the "low-risk" studies NASCET (5.8 %) and ACAS (<3 %) [1, 8]. The 3-year results continued to show non-inferiority of CAS to CEA with a cumulative major adverse event rate (stroke, death, or MI) of 20.1 % in the stenting arm and 30.3 % in the CEA arm ($p = 0.231$). Additionally, the need for reoperation at 1 year was significantly lower in the CAS group than in the CEA group, 0.7 % vs. 4.6 %, respectively, $p = 0.04$.

In addition to the randomized data from SAPPHIRE, two data sets from large post-marketing studies, CAPTURE and CASES-PMS [9, 10], show continued good outcomes with CAS in high-surgical-risk patients. Both of these registries consisted of real-world experience with commercially available stent and embolic prevention systems as well as *independent neurological adjudication* of outcomes and events.

The much larger follow-up registry, the SAPPHIRE Worldwide Registry, has enrolled more than 15,000 patients since October 2006. The periprocedural results were presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference on October 23, 2012, on the first 15,003 patients, 4,569 of whom (30 %) were symptomatic and 10,433 (70 %) were asymptomatic. The 30-day stroke/MI/death rate was 4.5 % (death 1.2 %, MI 0.6 %, stroke 3.3 %). There was a significant difference in the "NASCET" 30-day endpoint (stroke/death) between symptomatic (5.6 %) and asymptomatic (3.5 %) patients ($p<0.0001$). This registry also confirmed that patients 75 years of age and older had a higher complication rate (5.6 % vs. 2.9 %) compared to younger patients ($p<0.0001$). These results compare favorably with the results of the CEA arm in the SAPPHIRE trial, the only randomized data set to define the outcomes of CEA in this patient population. These results also compare favorably with ACAS and ACST surgical results of approximately 3 % 30-day stroke/death in low-surgical-risk patients who are also at lower risk of stroke or death perioperatively. Based on these data, it is clear that in the high-risk patient with symptomatic ICA stenosis, CAS with EPD is the treatment of choice.

The SAPPHIRE study results clearly showed that CEA carries a markedly elevated risk to asymptomatic high-risk patients. Although it appears that in asymptomatic high-surgical-risk patients CAS has similar complication rates to low-surgical-risk CEA patients, the overall benefit in the high-surgical-risk population is not clear, and therefore, a definitive statement cannot be made on the best treatment option for these patients. For some of these patients, medical therapy may be the best treatment. A clinical trial evaluating CAS vs. medical therapy in asymptomatic high-risk patients may help to answer this question.

Four recent studies have greatly clouded the issue of CEA vs. CAS in standard-surgical-risk patients. The CaRESS trial was a non-randomized study with "real-world allocation" of 397 primarily asymptomatic patients that found no statistical difference in death/stroke/MI at 30 days (4.4 % vs. 2.1 %) or 1 year (14.3 % vs. 10.9 %) with CEA compared to protected CAS, respectively [11]. The SPACE trial was a randomized comparison of CEA vs. CAS in 1,183 symptomatic patients [12]. Not surprisingly, since less than 30 % of patients were treated with embolic prevention devices contrary to the accepted standard of care, there was no difference in outcomes at 30 days (6.34 % vs. 6.84 %, $p=0.09$). This study effectively replicated the results of the earlier CAVATAS trial and adds no new data except to confirm that CAS without embolic prevention devices is not safe. The most problematic study was the EVA-3S study of 527 randomized patients with symptomatic stenosis [13]. This study was conducted with poor standardization of CAS technique including the inconsistent use of dual antiplatelet therapy, incomplete use of EPD, no angiographic exclusion criteria for CAS patients but with high-risk exclusion for CEA patients, and most importantly very low CAS operator experience with some operators having performed only five cases prior to randomizing patients. Not surprisingly, the complication rates were unacceptably high in the CAS arm compared to the CEA arm, 9.6 % vs. 3.9 %, respectively. The final study was the International Carotid Stenting Study (ICSS), which was a randomized trial of CEA vs. CAS in symptomatic normal-surgical-risk patients [14]. In that trial the use of EPD was the

discretion of the operator and approximately 20 % of patients were treated without an EPD. Also operators did not have to have extensive experience in performing CAS. They could be supervised by an experienced operator, and experience was defined having performed 50 stent procedures anywhere in the body, of which a minimum of 10 were required to be carotid artery procedures. That trial showed that the 30-day stroke/MI/death rate was 8.5 % with CAS and 5.1 % with CEA ($p = 0.004$).

The most important trial of CAS, the **C**arotid **R**evascularization **E**ndarterectomy vs. **S**tent **T**rial (CREST), was actually started in 2000 but took 10 years to complete [15]. The initial purpose of CREST was to compare protected CAS vs. CEA in low-surgical-risk symptomatic patients, but due to slow enrollment it was expanded to include asymptomatic low-surgical-risk patients in 2005. Both the National Institutes of Health (NIH) and Guidant (now Abbott Vascular) sponsored CREST. It was designed as a 2,500-patient superiority trial with equal randomization between CEA and protected CAS using the Accunet™ embolic prevention device ("whenever feasible") and Acculink™ carotid stenting system (Abbott Vascular Inc.). Symptomatic patients with a carotid bifurcation stenosis ≥50 % in severity on angiography, ≥70 % on ultrasonography, or ≥70 % on computed tomography angiography or magnetic resonance angiography were enrolled. Asymptomatic patients were enrolled with a stenosis ≥60 % by angiography, ≥70 % on ultrasonography, or ≥80 % on computed tomography angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50–69 %. In addition to the exclusion of high-surgical-risk patients, the study excluded patients who had contraindications to CAS such as severe tortuosity, extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery, an intraluminal filling defect, ipsilateral intracranial or extracranial arterial stenosis more severe than the lesion to be treated, and occlusion or "string sign" >1 cm of the ipsilateral common or ICA. Aspirin in the CEA arm and dual antiplatelet therapy (aspirin 325 mg plus clopidogrel 75 mg or ticlopidine) in the CAS arm were mandated for at least 30 days, with aspirin in all patients thereafter.

Importantly, the study included a rigorous vetting of interventionists with a lead-in/credentialing phase of approximately 20 patients per interventionist [16]. In fact only 225 (52 %) of 429 interventionists were approved for randomization. Those who were refused outright had a median case experience of 12, range 1–56; these operators would have qualified for EVA-3S and ICSS.

The study primary endpoint consisted of the composite of any periprocedural (i.e., within 30 days) stroke, MI, or death and ipsilateral stroke within 4 years of randomization. Patients underwent independent neurological evaluations.

A total of 2,522 patients were enrolled (1,271 CAS and 1,251 CEA) with a median follow-up of 2.5 years. Approximately 5.4 % of the CAS patients and 8.8 % of the CEA patients were lost to follow-up or withdrew consent. The patients were very well matched other than a slightly higher preponderance of patients with dyslipidemia in the CEA group (85.8 % vs. 82.9 %, $p = 0.05$) and more smoking in the CAS group during follow-up (21.8 % vs. 13.8 %, $p = 0.03$). The median time to treatment from randomization was similar (6 days for CAS and 7 days for CEA).

The majority of the CEA were performed under general anesthesia (90 %) and most had a patch (62.4 %) or shunt (56.7 %). The overwhelming majority of CAS were performed with embolic protection device (96.1 %), and most had pre-dilatation before stenting (67.7 %). There were a high rate (12.1 %) of CAS patients not taking dual antiplatelet agents for the full 4 weeks and a high rate of no aspirin use among CEA patients (8.9 %).

CREST showed no difference in the primary study endpoint of stroke/MI/death within 30 days [CAS 5.2 ± 0.6 vs. CEA 4.5 ± 0.6, hazard ratio (HR) 1.18 (0.82 to 1.68), $p = 0.38$] or up to 4 years [CAS 7.2 ± 0.8 vs. CEA 6.8 ± 0.8, HR 1.11 (0.81 to 1.51), $p = 0.51$]. There was no difference in the individual endpoint of periprocedural death (CAS 0.7 ± 0.2 vs. CEA 0.3 ± 0.2, $p = 0.18$), but there was a difference for any periprocedural stroke [CAS 4.1 ± 0.6 vs. CEA 2.3 ± 0.4, HR 1.79 (1.14 to 2.82), $p = 0.01$] or MI [CAS 1.1 ± 0.3 vs. CEA 2.3 ± 0.4, HR 0.50 (0.26 to 0.94), $p = 0.03$]. Following the periprocedural period, the incidence of ipsilateral stroke was similar (CEA 2.4 % vs. CAS 2.0 %, $p = 0.85$) as was the risk of fatal stroke (CAS $N = 7$ vs. CEA $N = 6$). There was no difference in the primary endpoint during the perioperative period among symptomatic patients [CAS 6.7 % vs. CEA 5.4 %, HR 1.26 (0.81–1.96)] or asymptomatic patients [CAS 3.5 % vs. CEA 3.6 %, HR 1.02 (0.55 to 1.86)]. There was no interaction between sex and symptomatic status and treatment effect although there was an interaction between age and efficacy ($p = 0.02$). The crossover point for age was at approximately 70 years with greater efficacy with CAS in younger patients and greater efficacy with CEA for older patients. The risk of cranial neuropathy was significantly higher in the CEA group (0.3 % vs. 4.7 %).

The CREST trial, the first trial to compare protected CAS vs. CEA in standard-surgical-risk symptomatic and asymptomatic patients, has shown that both procedures are equivalent in perioperative morbidity and mortality as well as long-term stroke prevention. There was a clear difference however in the risk of perioperative stroke with an increased risk in the endovascular group; most of these strokes were minor.

Conversely, there was a higher risk of MI in the surgical group. Importantly, the 30-day outcomes were similar for both procedures to the accepted thresholds for clinical benefit compared to medical therapy, i.e., <6 % for symptomatic (6 % stroke/death with CREST CAS and 3.2 % for CREST CEA) and <3 % for asymptomatic patients (in CREST the rate of 30-day stroke/death with CAS was 2.3 % for ACAS-eligible patients). It is important to note that the stroke rate declined over time in the CREST trial and if the results from the latter half of the study were utilized there would have been no difference in stroke rate with CEA. This highlights the importance of case experience and improved patient selection.

These results contradict the results of the three randomized European trials discussed earlier [12–14]. The EVA-3S, ICSS, and SPACE trial results have greatly reduced the enthusiasm for CAS and have blocked the expansion of CMS coverage for CAS. Taken at face value, this cooling of enthusiasm is understandable; however, all randomized trials are not created equal, and the results of these trials have to be reconciled with those of the CREST trial and the registries. As with the early

Table 4.2 Comparison of CAS trial protocols

	SAPPHIRE	CAVATAS	EVA-3S	SPACE	ICS	CREST
Stenting	✓	X	✓	✓	✓	✓
EPD mandatory	✓	X	✓	X	X	✓
Experienced operators	✓	X	X	X	X	✓
Dual antiplatelet Tx	✓	X	X	✓	✓?	✓
Angiographic exclusions	✓	X[a]	X	X	✓	✓
Independent neurologist	✓	✓?[b]	✓	✓	✓?[b]	✓
No general anesthesia	✓?	✓?	X	X	✓?	√
Symptomatic definition	3 months	>6 months	4 months	6 months	12 months	6 months
Angiography in all patients	X	X	X	X	X	X

[a]Only if known pre-procedure, no crossovers allowed
[b]Neurologist or "physician interested in stroke"

Table 4.3 Contraindications to CAS

Severe vascular tortuosity
Poor arterial access
Coagulation or platelet disorder that precludes adequate antithrombotic agent use
Severe, circumferential target lesion calcification
Target lesion length >15 mm

trials of CEA, the differences in outcomes have to do with patient and operator selection as well as procedural techniques. Several editorials have highlighted the many limitations of these trials and (Table 4.2) highlighted the differences and possible explanations for the differing results.

Carotid artery stenting can be performed in nearly all patients (98.6 % in SAPPHIRE). The remainder may be better treated medically or surgically (Table 4.3 lists the relative contraindications to CAS). There are two groups of patients for whom the ideal therapy is unknown. The first are patients who have an intraluminal filling defect (i.e., thrombus) within the stenotic segment. In NASCET these patients had an 18–22 % risk of perioperative stroke. Such patients have not been enrolled in the trials of CAS, and it is generally agreed that they may also have a high stroke risk with CAS. In these patients a short period of anticoagulation may be appropriate followed by CEA or CAS when the thrombus resolves. The other and far larger group of patients is those over the age of 80. These patients were mostly excluded from the trials of CEA and are known to have a higher perioperative complication rate than younger patients. With CAS, however, the elderly appear to have a higher

rate of complications [9, 15]. In the CREST trial lead-in phase ($N = 1{,}246$), octogenarians had a 12.1 % 30-day stroke/death rate. At this time therefore a conclusion cannot be drawn on the optimal treatment for octogenarians, but medical therapy alone should be given strong consideration since CEA also carries a nearly 12 % complication rate in those over age 75.

The long-term patency of the two procedures appears comparable. In a 2-year follow-up period of the CREST population, severe restenosis and occlusion were infrequent (approximately 6 %), and rates were similar between the CEA and CAS groups [17].

There are several issues that have not yet been addressed by the published results, e.g., newer embolic prevention devices and stents are available; might one or several of them be associated with lower stroke rates? There have been debates about the type of stent used with some suggestion that closed-cell stents are associated with lower periprocedural stroke [18]. Proximal occlusion EPDs have also been touted as superior at stroke prevention, but they have some limitations such as larger bore femoral access and increased probability of intolerance to the occlusion of antegrade flow. In a large single-center registry of 1,300 patients treated with proximal occlusion, the 30-day stroke/death rate was 1.38 % with independent neurological assessment at 24 h and 30 days [19]. In a meta-analysis of 2,397 patients from 6 independent databases, Bersin et al. found that the composite of stroke/MI/death occurred in 2.25 % of cases [20]. So while these data are tantalizing, there are no definitive randomized trial data that show one type of EPD device is superior to another. Clinicians should, in the author's opinion, become familiar with one or two devices/approaches and use them exclusively until there are definitive data on superiority of one approach or device over another.

Also studies on which other factors predict complications are also needed. One such study pooled data on 2,104 patients from four Cordis Endovascular Inc.-sponsored registries [21]. In that analysis the median age was 74 years (24 % >80 years), 36 % were female and 24.2 % of the patients were symptomatic. Multivariate predictors of the 4.2 % neurological deaths or strokes included older age (continuous), African-American race, angiographically visible thrombus in symptomatic patients, procedural use of glycoprotein IIb/IIIa inhibitor, procedural transient ischemic attack, final residual stenosis >30 %, and periprocedural use of protamine or vasopressors.

Of particular interest is that in symptomatic patients, the risk of a neurological event declined with increasing time between incident event and CAS [22]. The issue of timing of CAS in symptomatic patients has been a major unanswered question. The vast clinical experience with CEA has clearly shown that earlier intervention is superior to delayed intervention in preventing recurrent ischemic stroke but comes at the cost of increased intracerebral hemorrhage [23]. The fear of reperfusion/hyperperfusion ICH is perhaps more justified with CAS since patients are treated with dual antiplatelet agents and are theoretically more likely to have ICH. The available literature has not corroborated those fears. To the contrary with adequate blood pressure control, the risk of the hyperperfusion syndrome can be mitigated [24, 25]. Early CAS can also be performed safely in selected patients [26].

To conclude, in high-surgical-risk patients, CAS is at least as safe as CEA and is the preferred treatment option in patients eligible for revascularization. Furthermore, the CREST trial has shown that protected CAS and CEA are both good options for the treatment of low-surgical-risk patients with carotid atherosclerosis with CAS better in younger patients and CEA better in older patients.

General Technique

CAS is performed under moderate sedation in order to avoid mental status impairment and allow neurological assessment. The procedure includes five steps: embolic protection device placement, pre-stenting angioplasty to facilitate passing the stent, stent delivery and deployment, post-stenting angioplasty, and retrieval of the protection device. Pre-procedural planning is essential for optimal outcome; planning can be based on noninvasive or angiographic imaging.

- *Preoperative Preparation*
  Antiplatelet therapy should be started at least 48 h before carotid artery stenting. In CREST patients received aspirin at a dose of 325 mg twice daily and clopidogrel at a dose of 75 mg twice daily at least 48 h prior to CAS. When carotid artery stenting was scheduled within 48 h, 650 mg of aspirin and 450 mg of clopidogrel were given 4 or more hours before the procedure. After the procedure, patients received one or two 325 mg doses of aspirin daily for 30 days and either clopidogrel, 75 mg daily, or ticlopidine, 250 mg twice daily, for 4 weeks. The continuation of antiplatelet therapy for more than 4 weeks after the procedure was recommended for all patients who had undergone carotid artery stenting [15]
- *Anesthesia*
  Sedation should be minimized in CAS. A brief neurological examination should be performed immediately prior to the procedure and after the post-dilatation angioplasty. Patients are asked to repeat a sentence, smile, squeeze with both hands, and wiggle toes. A complete neurological exam should be performed after the procedure.
- *Procedural Steps*
  - *Anticoagulation:* A loading dose of IV heparin should be given after femoral arterial access is obtained to keep the activated clotting time (ACT) between 250 and 300 s.
  - *Hemodynamic changes:* Mechanisms of brain injury in CAS include both embolic and hemodynamic events. In a retrospective series of 500 patients who underwent CAS, hemodynamic depression defined as systolic blood pressure of <90 mmHg or bradycardia (heart rate of <60 beats/s) during 42 % of all procedures and was persistent in 17 % of patients. This was more common when the lesion involved the carotid bulb or was calcified and was less common in patients with prior CEA. Patients who developed persistent HD

were at a significantly increased risk of a periprocedural major adverse clinical event [OR 3.05 (range 1.35–5.23), $p<0.02$] or stroke [OR 3.34 (range 1.13–9.90), $p<0.03$] [27]. Close monitoring of blood pressure and heart rate is recommended during and after CAS; self-expanding stents can continue to expand in the first 24 h after implantation and can result in persistent hypotension and/or bradycardia in some patients. Premedication with atropine may occasionally be needed in patients at risk of hemodynamic depression. Periprocedural hypertension should also be avoided, especially in patients at risk of hyperperfusion syndrome.

– A three-vessel diagnostic arteriogram is recommended to evaluate the contralateral internal carotid artery and the intracranial anterior and posterior circulation. The diagnostic catheter is then exchanged to a 90-cm shuttle sheath over an exchange length 300-cm wire without contacting the atherosclerotic plaque. Alternatively, these steps can be achieved using the telescoping technique with a diagnostic 5-French catheter within a 6-French, 90-cm shuttle sheath, and a Glidewire. Securing the position of the shuttle sheath in the CCA is essential for adequate support during the five stages of the procedure.

- *Embolic protection devices (EPD):* Using proximal carotid occlusion or distal protection can decrease the risk of cerebral embolization during CAS. Théron et al. described the first protection device in 1990; their technique involved temporary occlusion of the cervical ICA distal to the lesion by a nondetachable latex balloon [28].

  Many EPDs have been introduced since then; adequate selection of a protection device requires good knowledge of their functions and shortfalls. In the updated review of the global carotid artery stent registry, the rate of strokes and procedurally related deaths was 5.29 % in the 6,753 cases done without protection and 2.23 % in the 4,221 cases with cerebral protection [29].

  – Distal balloon occlusion: This technique is not commonly used in the USA. The best-known off-label distal balloon occlusion system is the GuardWire Temporary Occlusion and Aspiration System (Medtronic AVE, Santa Rosa, CA).
  – Filter devices: The most commonly used EPDs; they are filtration membranes placed beyond the ICA lesion in a straight segment and can capture medium to large (>100-μm) debris. Their performance depends on their "crossing profile" or delivery system and "capturing profile" which depend on filter wall opposition and the size of pores. Table 4.4 summarizes the main features of the currently available filter devices. The limitations of filter devices include: crossing the lesion prior to protection which can result in distal embolization, generating spasm in the ICA if the device cannot be advanced to petrous ICA segment, emboli can be dislodged from the filter during filter retrieval, and emboli may pass the device due to poor wall opposition or through the pores of the device (microemboli).

Table 4.4 Filter devices

	Delivery system	Crossing profile	Pore size (μm)	Trials	FDA approved
Accunet	Wire mounted	3.5–3.7 Fr	120	ARCHeR, CREST, CAPTURE	Yes
SpideRX	Bare wire	2.9 Fr	50–300	CREATE II	No
ANGIOGUARD	Wire mounted	3.2–3.9 Fr	100	SAPPHIRE, CASES	No
Emboshield	Bare wire	3.7–3.9 Fr	120	EXACT, SECURITY	No
FilterWireEX	Wire mounted	3.2 Fr	110	BEACH, CABERNET	No
Rubicon	Wire mounted	2.1 Fr	100		No
Interceptor PLUS	Wire mounted	2.7 Fr	1,400	MAVERIC III	No

  - Proximal balloon occlusion: This technique involves inflation of a balloon in the CCA and a balloon in the ECA with the advantage of providing protection before crossing the lesion. It does not require a distal landing zone for the EPD and could potentially minimize the risk of ICA dissection and retrieval complications. The MO.MA device (Invatec, Roncadelle, Italy) requires a minimum sheath size of 8 French and a 0.035″ guidewire. The balloon occlusion range is up to 13 mm in the CCA balloon and 6 mm in the ECA balloon with the goal of providing static blood column at the carotid bifurcation. At the end of procedure, aspiration with at least three 20-cm^3 syringes is performed before deflating the balloons. The Parodi Anti-Emboli System (W. L. Gore & Associates, Flagstaff, AZ) requires an 11-Fr. sheath. This technique cannot be used in patients with severe ECA disease and can be limited sometimes by occlusion intolerance.

- *Pre-dilatation:* The aim of this step is to allow the passage of the stent; a low-profile coronary balloon is usually used. Oversizing should be avoided as it can increase the risk of embolic events.
- *Stents:* The majority of stents in use for CAS are self-expanding. Balloon-expandable stents have fallen out of favor due to their propensity to deform and their difficult delivery. The stent should be sized appropriately to allow complete opposition to the CCA lumen. Stents can have an open-cell or closed-cell design and can be tapered to accommodate the difference in size between the CCA and the ICA if the stent is intended to extend between the two vessels. All stents are made of nitinol except for Wallstent (Boston Scientific; Natick, MA), which are made of stainless steel. Slow stent deployment is essential to optimize the stent position; nitinol stents can store energy and slide forward during deployment. The following stents are the most commonly used in the USA:

Open-Cell Design

- Acculink (Abbott Laboratories, Abbott Park, IL): tapered
- PRECISE (Cordis Neurovascular, Miami Lakes, FL): auto-taper
- Protégé (Covidien, Irvine, CA): tapered

Closed-Cell Design

- Xact (Abbott Laboratories, Abbott Park, IL): tapered
- Wallstent (Boston Scientific Scimed, Maple Grove, MN): tapered

The stent diameter is usually selected based on the diameter of the ICA; the distal end of the stent is usually oversized by 1–2 mm. High frame rate cine is usually used to deploy the stent with the vertebral anatomy used for landmarks after a cine run is obtained.

Post-dilatation: This is usually performed using monorail peripheral balloons sized at 1.5 mm less than the diameter of the stent used. A residual stenosis of 20 % is acceptable in most cases.

- *Management of Complications During CAS*
  Complications of carotid artery stenting are largely preventable [30]. Secure shuttle sheath access to the distal CCA, and adequate selection of EPD can minimize the risk of embolic complications. Hemodynamic monitoring during and after the procedure can also minimize the risk of hemodynamic depression and reperfusion injury.
  - *Hemodynamic depression:* Timely administration of atropine or glycopyrrolate prior to balloon dilatation helps in preventing baroreceptor stimulation leading to severe bradycardia and hypotension in patients at risk of hemodynamic depression. Mild hypotension is commonly seen after the procedure and should only be treated if symptomatic.
  - *In-stent filling defect*: This can be due to thrombus formation or plaque prolapse. A thrombus can result in diffuse haziness or a filling defect inside or at the edge of the stent. Incidence of this complication ranges from 0.04 to 2 % [31, 32]. This can be treated with intra-arterial administration of abciximab or recombinant tissue plasminogen activator (r-tPA). These treatments can theoretically increase the risk of intracranial hemorrhage especially in patients with recent cerebral infarcts. Thrombus formation is more frequently seen in patients who were not adequately treated with dual antiplatelet therapy prior to the procedure but can also indicate resistance to clopidogrel or aspirin.
  - *Plaque prolapse*: It can be treated with in-stent balloon inflation or implantation of a second stent.
  - *Emboli:* Cerebral emboli can occur despite meticulous CAS technique; a rapid neurological evaluation should be performed if this complication is suspected. Symptomatic large emboli should be treated with mechanical embolectomy if the MCA or the ACA is occluded. Small symptomatic emboli to distal ACA or MCA branches can be treated with intra-arterial recombinant tissue plasminogen activator or a bolus of GpIIb/IIIa inhibitors.

- *Inadequate stent placement:* This can be due to inadvertent stent migration or technical error. Placement of a second stent is usually necessary for adequate plaque coverage.
- *Carotid dissection:* This is more common in the ICA and usually occurs during EPD placement or retrieval. A flow-limiting or spiral dissection should be treated with stent placement. A non-flow-limiting dissection can be monitored with a follow-up carotid ultrasound or CT angiography.
- *Filter-related complications:* EPD-induced spasm can occur in up to 3.8 % of patients when a filter device is used [33]. This is usually self-limited but can be treated with intra-arterial spasmolytic administration if it persisted or is thought to be symptomatic. Filter occlusion was seen in 4.9 % of patients in one series; it is usually due to the entrapment of a large load of embolic material in the basket and does not seem to correlate with the type of the filter used [34]. If managed appropriately, most patients with this complication do not suffer any neurological complications. This is usually managed by aspiration with special catheters at the filter site and retrieval of the device into the aspiration catheter or EPD recovery without full withdrawal into the retrieval catheter to avoid migration of the debris.
- Filter retrieval can sometimes be difficult due to tortuous anatomy or altered configuration of the ICA after stent placement. This has to be managed carefully to avoid filter disruption; forceful pulling of the EPD should be avoided as it can lodge into the stent struts. Neck rotation and swallowing can sometimes facilitate advancing the retrieval sheath. Adequate shuttle sheath or guide catheter support is necessary to pass the retrieval sheath through the stent. A diagnostic 5-Fr. catheter with a mild shape can also be used to retrieve the EPD.
- *Hyperperfusion syndrome:* see Chap. 3.
- *Contrast encephalopathy:* see Chap. 3.

Illustrative Case 1

A 70-year-old man presented with sudden-onset right arm weakness and speech impairment. His symptoms improved after several days of hospitalization, but a small middle cerebral artery territory stroke was seen on MRI. MR angiography showed high-grade left internal carotid artery stenosis and occlusion of the right internal carotid artery. Given this high-risk feature (contralateral carotid occlusion), the patient was loaded with clopidogrel (300 mg) and started on aspirin in preparation for carotid artery stenting.

The procedure was performed under monitored anesthesia care. Central venous access was obtained to facilitate the use of vasopressor agents post-procedurally as needed. An arterial line was placed for continuous hemodynamic monitoring.

An aortic arch angiogram was performed utilizing a 5-Fr. 100-cm pigtail catheter. A 7-Fr. 90-cm Flexor Shuttle guiding sheath (Cook Medical; Bloomington, IN) and 6-Fr. 125-cm Simmons II Slip Cath (Cook Medical; Bloomington, IN) along with a stiff 0.035-in. Glidewire (Terumo; Somerset, NJ) were used to select the left common carotid artery. Once arterial access was obtained, 100 U/kg of unfractionated heparin was administered to achieve an activated clotting time (ACT) of ≥250 s. The Glidewire and Slip Cath were removed and a baseline cervical and cerebral angiogram was performed (Fig. 4.2a). A 0.014-in. Transcend Floppy (Stryker, Kalamazoo, MI) wire was used to cross the stenosis and was positioned within the petrous carotid segment. A 6-mm SpideRX (Covidien; Irvine, CA) EPD was navigated across the stenosis and deployed within the distal cervical carotid artery. Over the filter wire a 2 mm × 20 mm Maverick (Boston Scientific; Natick, MA), monorail, angioplasty balloon was navigated and inflated to nominal pressure within the stenosis. The balloon was removed and an 8 mm to 6 mm × 40 cm Xact (Abbott; Chicago, IL) carotid stent was deployed. The patient's heart rate was in the 50 s, and 0.6 mg of atropine was administered intravenously prior to post-stent angioplasty. A 5 mm × 20 mm, monorail AVIATOR balloon catheter was positioned with the residual stenotic lesion and inflated to nominal pressure. A post-angioplasty angiogram of the neck and head was performed (Fig. 4.2b).

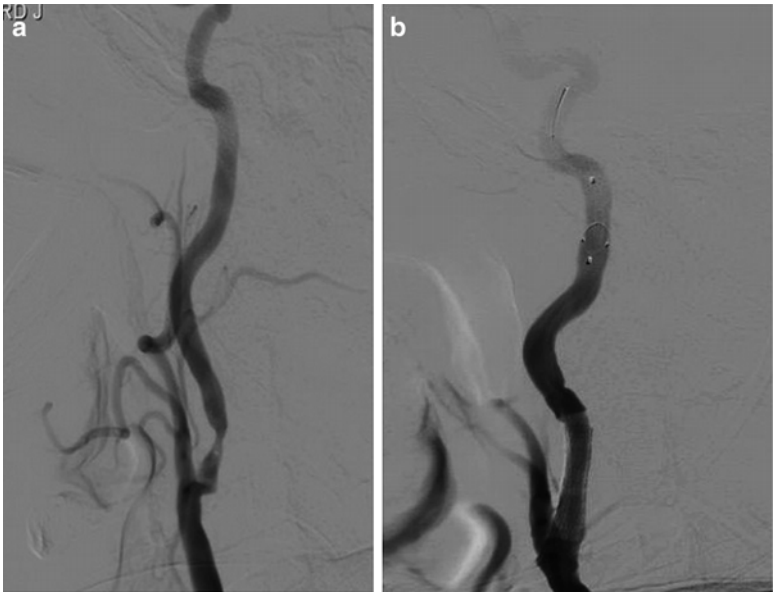

Fig. 4.2 Lateral projection angiogram showing high-grade carotid bulb stenosis (**a**) and resolution post-stenting with EPD (**b**)

Extracranial Vertebral Artery Stenosis

Extracranial vertebral artery (VA) stenosis and great vessel (i.e., ostial common carotid, innominate and subclavian arteries) stenosis are less common but important causes of stroke that are often overlooked in the evaluation of patients with stroke. Of vertebrobasilar territory strokes, VA origin (ostial) disease accounts for approximately 20 %. Most often VA stenosis is a source of emboli to the basilar and posterior artery territories; however, in cases of bilateral severe VA stenoses or in situations in which one VA is hypoplastic and the other severely stenotic, symptoms of true vertebrobasilar insufficiency (VBI) may occur. The clinical presence of true VBI associated with extracranial VA stenosis mimics intracranial basilar artery stenosis both in symptomatology and the high risk of stroke as noted in the WASID trial. Much like cervical ICA stenosis, VA stenosis can be treated with endarterectomy, angioplasty, and stenting, as well as surgical bypass. The former is uncommonly performed because of the high surgical morbidity associated with the surgical exposure. Angioplasty and stenting can be generally easily performed with extremely low complication rates of approximately 1–2 % in experienced hands. The drawback to VA ostial intervention is a high rate of restenosis of 30–50 %. This can be overcome with the use of drug-eluting coronary stents used off-label. In fact all VA ostial stenting is off-label as there are no FDA-approved devices for this location.

General Technique

- *Preoperative preparation:* As with all neurovascular stenting, patients must be pretreated with dual antiplatelet therapy. Aspirin 325 mg for 3 days and clopidogrel 75 mg daily for 5 days is one effective regimen.
- *Anesthesia:* These brief, minimally stimulating procedures are done under local anesthesia with light sedation.
- *Procedural steps:* VA origin stenting is usually performed through 6-Fr. guiding catheter placed in the subclavian artery. A buddy wire can be place into the brachial artery to provide support in patients with tortuous anatomy. A microcatheter can facilitate passing a 0.014-in. wire through the lesion but is usually unnecessary. An EPD can be used although the retrieval process can be challenging at times. Once the microwire tip is positioned at the v2/V3 junction, a monorail, balloon-mounted stent is positioned across the lesion and deployed at nominal or supra-nominal pressures. The ideal stent position allows for 1–2-mm overhang into the subclavian artery.
- *Post-procedural considerations:* Dual antiplatelet agents must be continued for a minimum of 6 weeks post-stenting. When drug-eluting stents are utilized, aspirin and clopidogrel should be continued for a minimum of 12 months. Close angiographic follow-up at 6 months, 12 months, and 24 months should be performed to detect in-stent stenosis.

Illustrative Case 2

A 58-year-old man with a history of multiple coronary artery stents was admitted with sudden-onset dizziness, nausea, and visual impairment. MRI revealed several punctate acute infarcts affecting the left cerebellar hemisphere and left occipital lobe. A CT angiogram showed a hypoplastic right vertebral artery ending in PICA and a focal stenosis at the left V1 segment. The patient was started on dual antiplatelet therapy in preparation for catheter angiography and possible stenting.

The procedure was performed under conscious sedation under the supervision of the interventionalist. Right femoral access was obtained with a 6-Fr. 35-cm BRITE TIP introducer sheath (Cordis; Bridgewater, NJ). Heparin is administered to obtain an activated clotting time 1.5–2.0 times the baseline value. A 6-Fr. MPC ENVOY (Codman Neurovascular; Raynham, MA) guiding catheter is then positioned in the subclavian artery in proximity to the vertebral artery origin (Fig. 4.3a). A 0.014-in. Transcend Floppy microwire was used to cross the stenotic lesion under roadmap guidance. A 3.5 mm×23 mm, monorail, balloon-mounted XIENCE everolimus-eluting stent (Abbott; Chicago, IL) was used to navigate across the stenosis. The stent was deployed across the stenosis allowing for 2 mm of stent overhang into the subclavian artery to ensure coverage of the ostium of the vertebral artery (Fig. 4.3b). Dual antiplatelet therapy was continued for 12 months and aspirin was continued for life.

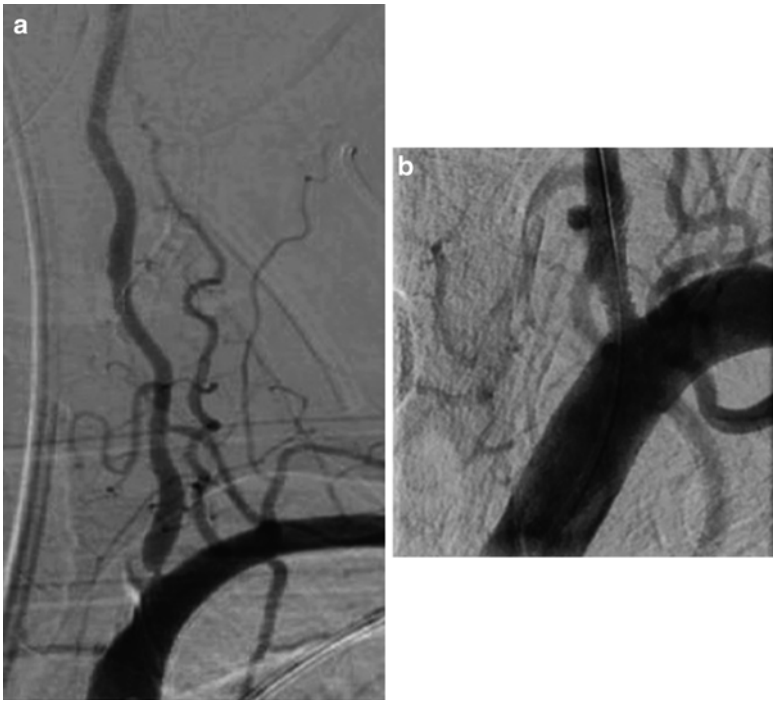

Fig. 4.3 Left anterior oblique angiogram showing high-grade vertebral artery origin stenosis (**a**) with resolution post-stenting (**b**)

Great Vessel Stenosis

It is not clear what percent of stroke is due to great vessel stenosis but it is thought to be <5 % (Fig. 4.4a). Common carotid artery ostial stenoses may cause cerebral ischemia via embolization or more often hemodynamic compromise. Subclavian stenosis is well recognized as a cause of the subclavian steal syndrome, but innominate disease may also cause arm ischemia, TIA, and embolic stroke. Since stenoses in these locations may be treatable, it is important to search for them as potential causes. Ultrasonography is a poor modality for imaging these vessels, and they are best evaluated with computerized tomography angiography (CTA) or contrast-enhanced magnetic resonance angiography (MRA). Surgery on the great vessels typically consists of arterial bypasses but is associated with significant morbidity.

General Technique

Angioplasty and stenting of great vessel stenosis can be performed with low morbidity and mortality:

- *Preoperative considerations:* Once again, dual antiplatelet therapy is essential to safe neurovascular stenting. Pre-procedural planning with a separate catheter angiogram should be considered to allow selection of the optimal approach and equipment.
- *Anesthesia:* Most procedures are performed under conscious sedation. However, general anesthesia may facilitate treatment through mechanically induced apneic periods and enhanced imaging clarity.

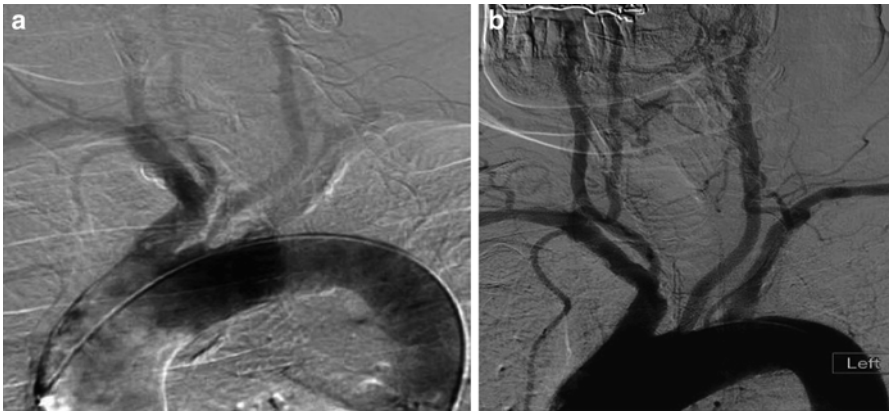

Fig. 4.4 Left anterior oblique angiogram showing severe proximal left common carotid artery stenosis (**a**) with resolution post-stenting (**b**)

- *Procedural steps*: All procedures are done under therapeutic heparinization with a goal activated clotting time of ≥250 s. Selection of a large, stable base system is essential to great vessel stenting. The guiding catheter or sheath will remain in the aortic arch and lacks the buttress of a vessel wall to support its position. An angled tip or headhunter tip 8-Fr. guide catheter is often suitable. The use of a "buddy" wire creates additional stability and can be positioned within the external carotid artery (common carotid stenosis) or brachial artery (innominate or subclavian stenosis). The use of an EPD within the internal carotid artery is recommended in CCA stenting procedures, but these devices may not be compatible with the 0.035-in. peripheral balloon-expandable stents most commonly required (Fig. 4.4b).
- *Post-procedural care*: Dual antiplatelet therapy is maintained for a minimum of 6 weeks. Perioperative cardiac events are less common than post-carotid bulb stenting, but perioperative stroke and hemorrhage remain a concern.

References

1. North American Symptomatic Carotid Endarterectomy Trial C. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445–53.
2. Group SC, Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, 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.
3. Henry M, Amor M, Henry I, Klonaris C, Chati Z, Masson I, et al. Carotid stenting with cerebral protection: first clinical experience using the PercuSurge GuardWire system. J Endovasc Surg. 1999;6(4):321–31.
4. Parodi JC, La Mura R, Ferreira LM, Mendez MV, Cersosimo H, Schonholz C, et al. Initial evaluation of carotid angioplasty and stenting with three different cerebral protection devices. J Vasc Surg. 2000;32(6):1127–36.
5. Jordan Jr WD, Schroeder PT, Fisher WS, McDowell HA. A comparison of angioplasty with stenting versus endarterectomy for the treatment of carotid artery stenosis. Ann Vasc Surg. 1997;11(1):2–8.
6. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. J Vasc Surg. 1998;28(2):326–34.
7. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med. 2008;358(15):1572–9.
8. Young B, Moore WS, Robertson JT, Toole JF, Ernst CB, Cohen SN, et al. An analysis of perioperative surgical mortality and morbidity in the asymptomatic carotid atherosclerosis study. ACAS Investigators. Asymptomatic Carotid Atherosclerosis Study. Stroke. 1996;27(12):2216–24.
9. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. Catheter Cardiovasc Interv. 2007;69(3):341–8.
10. Katzen BT, Criado FJ, Ramee SR, Massop DW, Hopkins LN, Donohoe D, et al. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. Catheter Cardiovasc Interv. 2007;70(2):316–23.

11. Ca RSC. Carotid revascularization using endarterectomy or stenting systems (CaRESS) phase I clinical trial: 1-year results. J Vasc Surg. 2005;42(2):213–9.
12. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, 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.
13. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, 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.
14. International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, 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.
15. Brott TG, Hobson 2nd RW, 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.
16. Hopkins LN, Roubin GS, Chakhtoura EY, Gray WA, Ferguson RD, Katzen BT, et al. The Carotid Revascularization Endarterectomy versus Stenting Trial: credentialing of interventionalists and final results of lead-in phase. J Stroke Cerebrovasc Dis. 2010;19(2):153–62.
17. Lal BK, Beach KW, Roubin GS, Lutsep HL, Moore WS, Malas MB, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. Lancet Neurol. 2012;11(9):755–63.
18. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg. 2007;33(2):135–41. discussion 42–3.
19. Stabile E, Salemme L, Sorropago G, Tesorio T, Nammas W, Miranda M, et al. Proximal endovascular occlusion for carotid artery stenting: results from a prospective registry of 1,300 patients. J Am Coll Cardiol. 2010;55(16):1661–7. Epub 2010/04/17.
20. Bersin RM, Stabile E, Ansel GM, Clair DG, Cremonesi A, Hopkins LN, et al. A meta-analysis of proximal occlusion device outcomes in carotid artery stenting. Catheter Cardiovasc Interv. 2012;80(7):1072–8.
21. Giri J, Kennedy KF, Weinberg I, Hawkins BM, Press MC, Drachman D, et al. Comparative effectiveness of commonly used devices for carotid artery stenting: an NCDR Analysis (National Cardiovascular Data Registry). J Am Coll Cardiol Intv. 2014;7(2):171–7.
22. Aronow HD, Gray WA, Ramee SR, Mishkel GJ, Schreiber TJ, Wang H. Predictors of neurological events associated with carotid artery stenting in high-surgical-risk patients: insights from the Cordis Carotid Stent Collaborative. Circ Cardiovasc Interv. 2010;3(6):577–84.
23. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists C. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet. 2004;363(9413):915–24.
24. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol. 2004;43(9):1596–601.
25. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. Catheter Cardiovasc Interv. 2007;69(5):690–6.
26. Lin R, Mazighi M, Yadav J, Abou-Chebl A. The impact of timing on outcomes of carotid artery stenting in recently symptomatic patients. J Neurointerv Surg. 2010;2(1):55–8.
27. Gupta R, Abou-Chebl A, Bajzer CT, Schumacher HC, Yadav JS. Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. J Am Coll Cardiol. 2006;47(8):1538–43.
28. 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 75–7.

29. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv. 2003;60(2):259–66.
30. Veeraswamy RK, Rubin BG, Sanchez LA, Curi MA, Geraghty PJ, Parodi JC, et al. Complications of carotid artery stenting are largely preventable: a retrospective error analysis. Perspect Vasc Surg Endovasc Ther. 2007;19(4):403–8.
31. Roubin GS, New G, Iyer SS, Vitek JJ, Al-Mubarak N, Liu MW, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. Circulation. 2001;103(4):532–7.
32. Terada T, Tsuura M, Matsumoto H, Masuo O, Yamaga H, Tsumoto T, et al. Results of endovascular treatment of internal carotid artery stenoses with a newly developed balloon protection catheter. Neurosurgery. 2003;53(3):617–23. discussion 23–5.
33. Reimers B, Corvaja N, Moshiri S, Sacca S, Albiero R, Di Mario C, et al. Cerebral protection with filter devices during carotid artery stenting. Circulation. 2001;104(1):12–5.
34. Maldonado TS, Loh S, Fonseco R, Poblete H, Adelman MA, Cayne NS, et al. Incidence and outcome of filter occlusion during carotid artery stent procedure. Ann Vasc Surg. 2008;22(6):756–61.

Chapter 5
Endovascular Treatment of Intracranial Atherosclerosis

Mohamed S. Teleb, Kaiz Asif, Alicia C. Castonguay, and Osama O. Zaidat

Introduction

One of the most common causes of ischemic stroke worldwide is intracranial atherosclerotic disease (ICAD). However, our understanding of the most appropriate treatment of this complex disease with a high recurrence rate of stroke remains limited. Although medical therapy has lowered the risk of stroke, the recurrence of stroke rate still remains overall high at 1 and 2 years follow-up. Certain high-risk ICAD patients may derive benefit from endovascular therapy. We will review the natural history, epidemiology, and current treatment options including surgical, medical, and endovascular management of ICAD while highlighting the recent literature in the field. We will concentrate and conclude with an in-depth look at endovascular treatment options including equipment and methods.

Natural History/Epidemiology

Intracranial atherosclerotic disease (ICAD) is a common cause of stroke worldwide, afflicting the Black, Asian, and Hispanic populations at a higher rate than Whites with strokes [1, 2]. ICAD is found in an estimated 10 % of stroke patients in the USA, while in Asia, it accounts for approximately 30–50 % of all strokes [3, 4]. Age, hypertension, smoking, diabetes mellitus, hypercholesterolemia, and metabolic syndrome are all risk factors for ICAD [5, 6]. Although the high rate of certain uncontrolled risk factors partially accounts for the increased incidence of ICAD in

M.S. Teleb, M.D. (✉) • K. Asif, M.D. • A.C. Castonguay, Ph.D. • O.O. Zaidat, M.D., M.S.
Department of Neurology, Neurointerventional Division, Froedtert Hospital and Medical College of Wisconsin, 9200 W Wisconsin Avenue, Milwaukee, WI 53226, USA
e-mail: mteleb@mcw.edu; kasif@mcw.edu; acastonguay@mcw.edu; szaidat@mcw.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_5

African-Americans [7–10], the rates of these risk factors do not differ significantly in the Chinese population and do not account for the significant burden of ICAD in this population [11–13].

The warfarin versus aspirin for symptomatic intracranial disease (WASID) trial data revealed that patients with symptomatic ICAD carry a high risk of subsequent stroke [14–16]. Despite the use of aspirin and management of risk factors, patients with a recent transient ischemic attack or stroke and a stenosis of ≥70 % had a 23 % risk of stroke at 1 year [15, 17–19]. Currently the risk with best medical therapy and lifestyle modification including blood pressure reduction, smoking cessation, weight loss, cholesterol reduction, and dual antiplatelet therapy remains at a high 12.2–15 % [16, 20].

Clinical Presentations

Ischemic stroke or transient ischemic attack (TIA) is the classic presenting symptom of ICAD [21, 22]. There can be various clinical presentations including isolated motor or sensory involvement and/or cortical function impairments depending on the location of ischemia [16, 23–25]. Cognitive deficits, like impairment of executive function and anterograde amnesia, can occur with infarcts involving the anterior-medial thalamus, caudate nucleus, or cerebral cortical or white matter areas [26–28]. White matter degeneration, hypoperfusion, and hypometabolism may lead to cognitive changes in the absence of infarcts [1, 29].

Diagnosis

Imaging is used to detect intracranial stenosis; to ascertain the degree and length of stenosis; to differentiate the atherosclerotic stenosis from mimics such as a recanalized partial thrombus, intracranial dissection, or non-atherosclerotic vasculopathy; and to assess the state of collateral circulation.

Differential Diagnosis

Anatomic arterial narrowing detected on imaging studies may be due to a variety of pathologies, and determining which is causal in a specific patient can be challenging. Mimics include partially recanalized thrombus, intracranial dissection, vasculitis, vasculopathy, and vasospasm. A careful analysis of the clinical scenario along with repeated multimodal imaging may be required to distinguish between these mimics. A detailed history regarding prior peripheral atherosclerotic disease, diagnosis of coronary disease, or the presence of atherosclerotic risk factors can help in

identifying non-atherosclerotic etiologies of stenosis [3, 30]. In the setting of acute stroke, partially recanalized thrombus mimics intracranial atherosclerosis but will usually have resolved on repeat imaging [5, 31, 32]. The presence of a severe headache and diffuse intracranial narrowing might also suggest reversible vasoconstrictive syndrome. Overall, limited data exists on the radiopathologic correlations for intracranial arterial stenotic diseases, but studies of extracranial vessel imaging with pathologic correlation have shown inflammatory conditions to be associated with concentric, circumferential wall thickening and enhancement, while atherosclerotic disease is frequently eccentric [7, 9, 33].

Mechanisms of Symptoms

Ischemia from ICAD can be due to hypoperfusion, in situ thromboembolism, or perforator orifice occlusion [11, 13, 34, 35]. A combination of local branch occlusion and embolism, with or without hemodynamic compromise, can occur concurrently [11, 14, 16]. Similarly, in situ thrombosis followed by distal arterial embolism, in addition to delayed washout of emboli due to hypoperfusion, can be present at the same time.

Imaging may help in delineating the stroke mechanisms though sometimes one imaging pattern can be produced by a combination of mechanisms. Border zone infarcts are suggestive of hypoperfusion, territorial infarcts point to peripheral embolism, and deep subcortical infarcts are indicative of perforator artery orifice occlusion [17, 18, 36]. In a study investigating lesion patterns on diffusion-weighted imaging (DWI) for middle cerebral artery atherosclerotic disease, 15 (83.3 %) of 18 patients with border zone infarcts had concomitant infarcts suggestive of either peripheral embolism (territorial infarcts) or perforator artery involvement (subcortical infarcts), indicating the coexistence of multiple mechanisms [16, 37]. Inferring the initial stroke mechanism is important, as it could be predictive of the risk of recurrent stroke or the mechanism of the next ischemic event. In an analysis of patients presenting with an index stroke in the WASID trial, the risk of recurrent stroke was similar in patients who presented with lacunar and non-lacunar strokes, and recurrent strokes in patients presenting with lacunar stroke were typically non-lacunar [21, 38].

Quantification of Stenosis

Digital subtraction angiography (DSA) is considered the standard for the evaluation of intracranial stenosis. Excellent quantification of luminal stenosis is allowed with high-resolution DSA. Calculation of the degree of stenosis on DSA uses the following equation: $[1-(D_{\text{stenosis}}/D_{\text{normal}})]\times 100$, where D_{stenosis} = the diameter of the artery at the site of most severe degree of stenosis and D_{normal} = the diameter of the proximal normal artery (see Table 5.1 and Fig. 5.1) [23, 38].

Table 5.1 Measurement of intracranial stenosis using the WASID method

1. The diameter of the proximal part of the artery at its widest, non-tortuous, normal segment is chosen (first choice)
2. If the proximal artery is diseased, the diameter of the distal portion of the artery at its widest, parallel, non-tortuous normal segment is substituted (second choice)
3. For the internal carotid artery disease involving the pre-cavernous, cavernous, and postcavernous segments, the petrous carotid segment with parallel margins is measured at its widest, non-tortuous, normal portion
4. If the entire petrous carotid is diseased, the most distal, parallel part of the extracranial internal carotid artery is substituted (second choice)

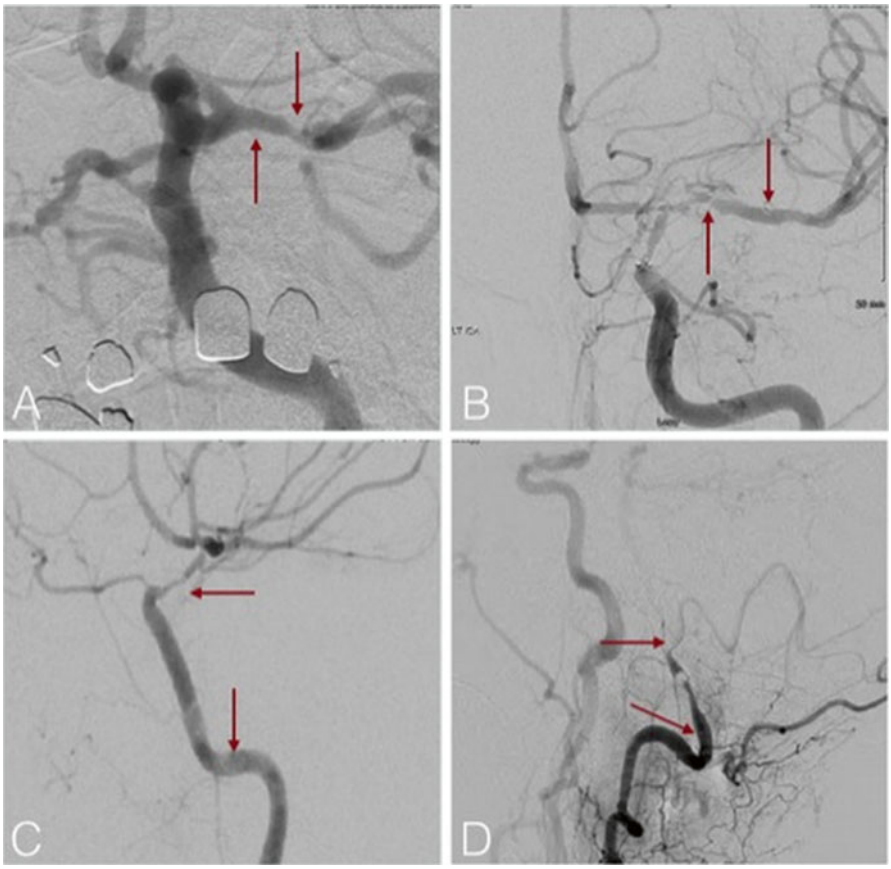

Fig. 5.1 Measurement of intracranial stenosis using the WASID method. (**a**) The diameter of the proximal part of the artery at its widest, non-tortuous, normal segment is chosen (first choice). (**b**) If the proximal artery is diseased, the diameter of the distal portion of the artery at its widest, parallel, non-tortuous normal segment is substituted (second choice). (**c**) For the internal carotid artery disease involving the pre-cavernous, cavernous, and postcavernous segments, the petrous carotid segment with parallel margins is measured at its widest, non-tortuous, normal portion. If the entire petrous carotid is diseased, the most distal, parallel part of the extracranial internal carotid artery is substituted (second choice)—not shown. (**d**) If the entire intracranial artery is diseased, the most distal, parallel, non-tortuous normal segment of the feeding artery is measured (third choice)

For noninvasive modalities of evaluating ICAD, a study assessing the accuracy of TCD and MRA compared with DSA showed the TCD and MRA to have good negative predictive values of 86–91 % but low positive predictive values of 36–59 % [15, 26]. Another study comparing CTA with MRA, using DSA as the reference standard, CTA was shown to have a higher sensitivity, specificity, and positive predictive value [29, 39]. The higher sensitivity and specificity of CTA have been observed specifically for stenosis which is 50 % or higher [30]. As far as the evaluation of small intracranial arteries, a study comparing multidetector CT (MDCT) angiography to DSA concluded that MDCT depicted ≥90 % of all examined small intracranial arteries compared to DSA, and the smallest arterial size reliably detected with CTA was 0.7 mm versus 0.4 mm for DSA.

Imaging of Vessel Wall

Vessel wall imaging can be achieved with high-resolution 3T MRI, intravascular ultrasound, and fat-suppressed T1-weighted MRI. High-resolution MRI can identify the thickness and pattern of protrusion [31, 32]. Intravascular ultrasound can be used for plaque components like calcium and lipid but is limited in its use due to its invasive nature [33]. Identification of recent intra-plaque hemorrhage and inflammation can be made with fat-suppressed T1-weighted MRI on which these plaques show increase in signal and enhancement after contrast injection [34, 35, 40, 41].

Collateral Assessment

The degree of collateral circulation is a powerful predictor of recurrent stroke in the setting of medical therapy for symptomatic ICAD [11, 42]. Impaired distal territory perfusion can be compensated for with good leptomeningeal collaterals. The ASITN collateral score (Table 5.2) is the most commonly used grading system [36, 43].

Table 5.2 ASITN collateral score grade description

0 = no collaterals visible to the ischemic site
1 = slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2 = rapid collaterals to periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3 = collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4 = complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

Surgical Treatment of Intracranial Stenosis

Multiple surgical treatments such as direct and indirect bypass surgeries have been developed and used for over 40 years in treatment of intracranial stenosis. Most recently, the Carotid Occlusion Surgery Study (COSS) evaluated patients with ipsilateral ischemic events within 120 days in the setting of cervical carotid occlusion. Patients were randomized if they exhibited an increased oxygen extraction fraction and were randomized to medical treatment versus EC/IC (extracranial to intracranial) bypass surgery. Stroke and death at 30 days and 2-year ipsilateral stroke rates were not statistically different between the surgical and medical group (21 % versus 23 %) [37, 43–45]. Interestingly, the surgical group did experience decreased oxygen extraction fraction but no cognitive outcomes testing was conducted.

Prior to the COSS trial, the EC/IC bypass study showed no benefit of surgical bypass versus medical therapy for the reduction of overall ipsilateral major strokes or death. This trial included patients with both intracranial and extracranial stenotic and occlusive diseases [38, 46]. Surgical treatment used a direct bypass from the superficial temporal artery to the middle cerebral artery at one of the M2 branches. The medical arm was limited to single antiplatelet use (aspirin 325 mg, four times daily) and blood pressure reduction but no specific lifestyle modification regimen [38, 46–48]. Due to the results of these studies, EC/IC bypass is not generally recommended in the setting of ICAD.

Medical Treatment of Intracranial Atherosclerotic Stenosis

The medical treatment or ICAD has evolved over the years. The WASID trial was the first major trial to evaluate medical treatments and compared aspirin versus warfarin in patients with ICAD. The overall risk was similar in the warfarin and aspirin arms, with the primary endpoint of ischemic stroke, brain hemorrhage, or vascular death occurring in 22.1 % of patients assigned aspirin versus 21.8 % in the warfarin group. However, the warfarin cohort had significantly more adverse events defined as death, major hemorrhage, and myocardial infarction or sudden death [15, 49]. Next, the GEISCA study demonstrated that despite medical treatment, the 2-year rate of ischemic events in the territory of the stenotic artery was 38.2 % with the highest risk of stroke in clinically significant hemodynamic stenosis [39, 50]. Most recently, the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial revealed much better outcomes with medical treatment. At 1 year, the event rate was 17.6 % in the stenting arm and 12.2 % in the medical management arm [2, 6, 51]. The medical arm of SAMMPRIS is now considered the standard of care for first-time symptomatic ICAD patients. The regimen was aspirin 325 mg and Plavix 75 mg daily for 3 months, followed by aspirin only. Additionally, patients were treated with a “statin” medication, blood pressure control, and were enrolled in a lifestyle modification program. Goal systolic blood

pressure was less than 140 mmHg and LDL was less than 70 mg per deciliter (1.81 mmol/L). In addition to the above regimen, management of secondary risk factors [diabetes, elevated non-high-density lipoprotein (non-HDL) cholesterol levels, smoking, excess weight, and insufficient exercise] was included.

Endovascular Treatment of Intracranial Atherosclerotic Stenosis

Endovascular treatment of intracranial stenosis can be divided up into three possible treatments: balloon angioplasty alone (BA), balloon-mounted stenting (BMS), and self-expanding stent (SES) placement. Indications for each procedure (Table 5.3), outcomes from literature, and example case presentations are provided in the chapter.

Intracranial Balloon Angioplasty Without Stenting

Stand-alone intracranial balloon angioplasty has been advocated by some over stenting, based on case series with low periprocedural complication rates [40, 41, 52]. Balloon angioplasty was first used in the coronary circulation. The goal of angioplasty is to reduce luminal stenosis and increase perfusion to downstream tissue. The proposed mechanisms include plaque redistribution and dilatation of the actual vessel diameter [40, 42, 53, 54]. This was initially described with percutaneous transluminal angioplasty (PTA) of the coronary arteries.

Initially there was some enthusiasm for the use of balloon angioplasty in the intracranial circulation with the first reported cases in the 1980s [40, 41, 43, 53–57]. There were cases of basilar followed by cavernous segment carotid and then middle cerebral artery stenosis treated with angioplasty [40, 43–45]. Unfortunately due to higher rates of complications, the use was limited until new techniques and technologies were developed [46, 56]. Dissections, emboli, and rupture were not uncommon

Table 5.3 Possible indications and FDA indications for endovascular treatment

1.	Hemodynamic symptoms
2.	Poor collaterals
3.	Large mismatch on imaging with signs of collateral failure
4.	Recurrent symptoms despite best medical therapy
5.	FDA Wingspan use criteria: (1) age 22–80 years (2), two or more strokes despite aggressive medical management (3), most recent stroke occurring more than 7 days prior to planned intervention (4), 70–99 % stenosis due to atherosclerosis of the related intracranial artery, and (5) good recovery from previous stroke and modified Rankin score of ≤3 prior to intervention [65, 66]

with a complication rate of up to 50 % reported in one study [46–48, 53]. These complications were attributed to the large size of balloons and the rapid rate of inflation. Unlike coronary vessels, the intracranial circulation is surrounded by brain and cerebrospinal fluid in the subarachnoid space. A muscular myocardium as well as a pericardial sac surrounds the coronary arteries. A small rupture or dissection is usually not significant in the coronary circulation. On the other hand, a subarachnoid hemorrhage can be fatal with morbidity and mortality reported in up to 40–50 % of patients [49, 58–60]. Intraparenchymal hemorrhages also carry a high rate of morbidity and mortality [50, 61]. Dissections can cause ischemic strokes that can also cause a high morbidity. Stroke, largely ischemic, remains the number 1 cause of disability [52, 62]. With slow inflation over minutes as opposed to seconds and undersized balloons, complication rates have been reported as low as 5 % [40, 53, 54, 63] (see Fig. 5.2).

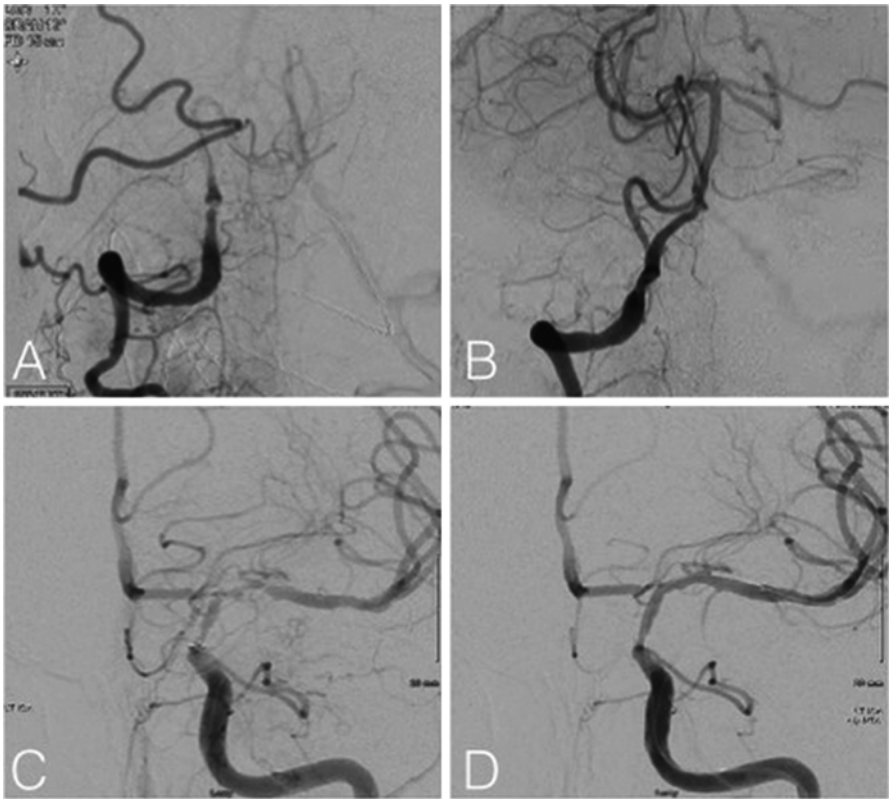

Fig. 5.2 (**a**, **b**) Patient with vertebral artery stenosis with recurrent strokes on optimal medical therapy before and after balloon angioplasty cerebral angiogram in AP projections, (**c**, **d**) patient with in-stent intimal hyperplasia before and after balloon angioplasty cerebral angiogram in AP projections

There have been multiple recent case reports of balloon angioplasty for intracranial stenosis with low complication rates and technical success rates to above 90 %. Defining technical success as less than 50 % stenosis (established by the Practice Guideline Committee of the Society of Neurointerventional Surgery) puts modern series at a technical success rate of 60 to above 90 % [3, 40, 41, 53–57, 64, 65]. The largest study by Marks et al. included 120 patients [3, 20, 40]. Some studies have suggested that restenosis and outcomes in balloon angioplasty without stenting versus stenting are similar as was demonstrated by a comparison paper of angioplasty alone versus stenting by Siddiq et al. [56, 66].

Balloon Types

There are several intracranial balloons that have been approved for use, but only one for the treatment of ICAD. These include the Scepter (MicroVention; Tustin, CA, USA), HyperForm (Covidien, Irvine, CA), and Transform (Stryker, Kalamazoo, Michigan, USA). These devices are designed for balloon-assisted coil embolization of aneurysms. The Gateway (Stryker, Kalamazoo, Michigan, USA) balloon is the only FDA-approved device for intracranial angioplasty. Coronary angioplasty balloons have been used off label to treat ICAD [51, 53].

Drug-Eluting Stents

Drug-eluting stents (DES) have been used off label in the intracranial circulation, and multiple reports have been published on their use. DES have been used in both the anterior and posterior circulation with periprocedural complication rates ranging from 0 to 25 % [3, 58–60]. A design limitation of DES is that most are balloon mounted and difficult to track in the intracranial circulation. Other criticisms include the need for dual antiplatelet therapy for 6 months or longer as suggested by some of the cardiac literature [61, 67]. There is some literature on newer DES that points to a lower incidence of delayed thrombotic events, but research is still ongoing [54, 62]. The lack of long-term follow-up in patients treated with DES has limited their acceptance. However, recent small case series ($n = 11$) with a mean follow-up period of 67 months has shown no patient with greater than 50 % restenosis [63, 68].

Balloon-Mounted Stents

Balloon-mounted stents (BMS) have also been used in ICAD with similar success as seen with balloon angioplasty alone. Most of the reported literature has used coronary BMS. The only published data on a dedicated intracranial BMS system is

from the SYLLVIA trial that used the NeuroLink system. The difficulty with the current BMS systems is that they are stiff and, therefore, harder to track in the tortuous intracranial circulation. The SYLLVIA trial also showed a 35 % restenosis rate although 61 % were asymptomatic.

Self-Expanding Stents

Self-expanding, nitinol, stents have been the main of intracranial stenting ever since the FDA approval of the Wingspan Stent (Stryker, Kalamazoo, Michigan, USA). They have had high technical success rate ranging from the 98.8 to 96.7 % in the two large reported registries and 94.6 % (12/224) in the SAMMPARIS randomized control trial with seven patients having procedure aborted and five having only angioplasty for technical reasons [3, 56, 64, 65]. It has been argued that this system is more appropriate for use in the intracranial circulation due to its small outward radial force (<0.1 atm). It also does not need a balloon and can be delivered thru a microcatheter, making it more trackable. Despite these advantages, the SAMMPRIS trial, short- and long-term outcomes, revealed better outcomes in the rate of stroke and death in the medically treated group. At a median follow-up of 32.4 months, 34 (15 %) of 227 patients in the medical group and 52 (23 %) of 224 patients in the stenting group had a primary endpoint event [3, 20, 57] (Fig. 5.3).

Procedural Considerations

Patient Selection

Patients with recurrent symptoms in the setting of high-grade intracranial stenosis (≥70 %) and maximal medical therapy (dual antiplatelet agents, high-dose statin treatment, glycemic control, normotension, regular aerobic exercise, and smoking cessation) may be candidates for endovascular therapy. Other considerations include the location of stenosis and mechanism of stroke. Stenosis in non-perforator-rich locations (intracranial internal carotid and vertebral arteries) is likely lower risk during endovascular treatment than perforator-rich locations (basilar and proximal middle cerebral arteries). Also, patients with hypoperfusion-related events would seem, based on physiology, most likely to benefit from improvement in luminal diameter. However, this later point has not been confirmed in the most rigorous clinical trials to date.

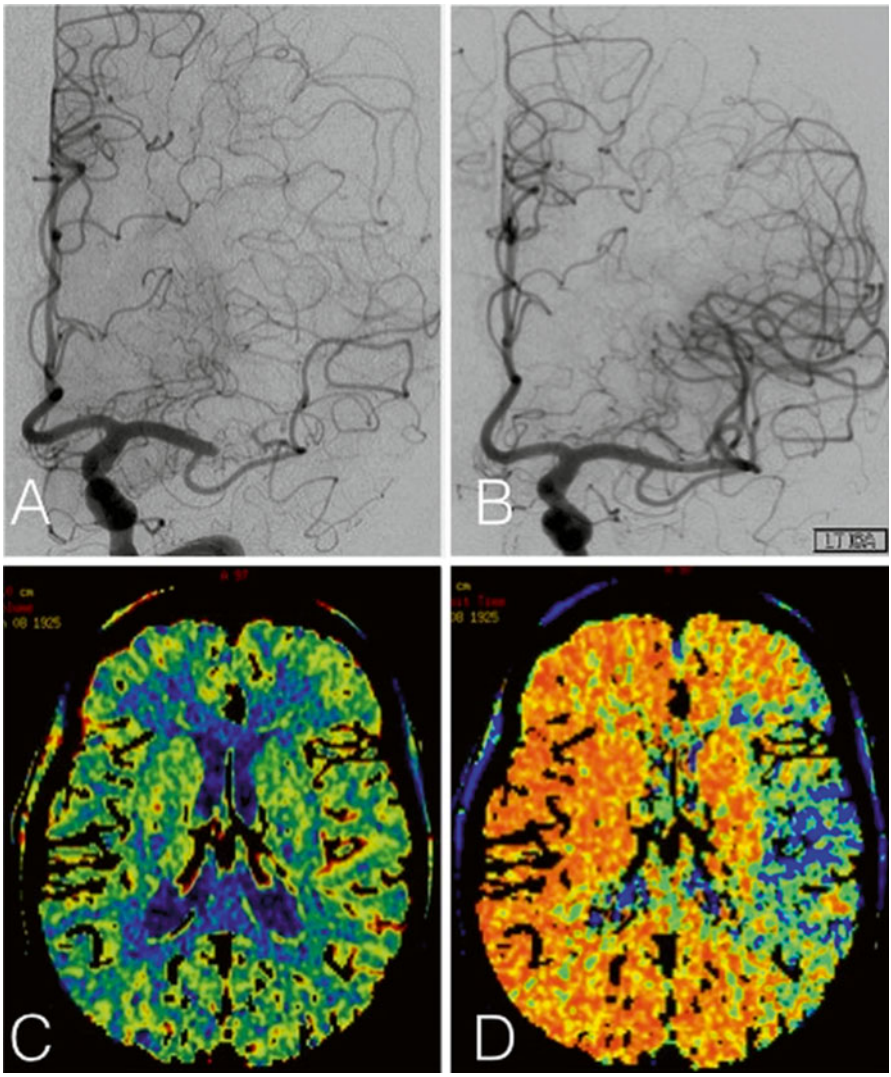

Fig. 5.3 Patient with near occlusion of M1 MCA who is symptomatic when her blood pressure is dropped. (**a**) Cerebral angiogram demonstrating the M1 MCA near occlusion before angioplasty and stenting, (**b**) cerebral angiogram after treatment with improved stenosis, (**c**) CBV (cerebral blood volume) increased in corresponding area, (**d**) MTT (mean transit time) decreased in corresponding area of symptoms and stenosis

Pre-procedure

Once stenosis has been identified on noninvasive imaging, it is important to perform a stand-alone catheter angiogram for presurgical planning. A three-dimensional image is sometimes helpful to further characterize the lesion and optimal imaging

angle to utilize during endovascular surgery. This diagnostic procedure also allows risk stratification by characterizing the proximal vessels and aortic arch as well as the degree of intracranial tortuosity that needs to be navigated in order to deliver the angioplasty balloon and/or stent to the desired location. The degree of angulation of the posterior and anterior genus of the cavernous carotid is a key determinant of success. Highly angulated carotid genus may prohibit the navigation of a stent distally. It is important to remember that endovascular treatment of ICAD is one of the highest-risk procedures an interventionalist will perform, and the strategy must be tailored to the patient and his/her individual anatomy.

As noted above, all patients being considered for endovascular treatment will have failed a course of dual antiplatelet agents (aspirin and clopidogrel) along with high-dose statin therapy. It is essential that these agents be continued pre- and post-procedure. Consideration should be given to pre-procedural platelet function testing to screen for aspirin or clopidogrel resistance. The utility of these tests in reducing procedurally related stroke is controversial, but given the high-risk nature of this treatment, all potential methods of risk reduction must be considered.

Anesthesia

Most neurointerventionalists currently perform intracranial angioplasty and stenting under general anesthesia. The arguments for this approach include the need for high-resolution imaging that is enhanced by decreased patient motion and mechanically induced apnea when needed. Elimination of the risk of sudden patient movement during a high-risk portion of the procedure is also achieved with general anesthesia. On the other hand, proponents of moderate sedation argue that the ability to monitor neurological function during the course of the procedure is invaluable. Additionally, the potential for medication-induced hypotension and subsequent hypoperfusion-related stroke may be less with moderate sedation. An arterial line should be in place both for procedural purposes and, just as importantly, for post-procedure blood pressure monitoring.

Sheaths

A 6F or larger sheath is needed to perform these procedures. A sheath length (35 cm or greater) that bypasses the ileac artery and distal abdominal aorta is recommended due to the high incidence of femoroiliac stenosis/tortuosity and abdominal aortic aneurysms in this population. When treating posterior circulation lesions, a radial access site may be advantageous. In this case a 6F 10 cm or shorter sheath is recommended. When intracranial stenting is planned, a 90 cm guiding sheath positioned in the distal common carotid artery or proximal internal carotid artery provides excellent support and allows the use of a “triaxial” system (guiding sheath, guiding catheter, and microcatheter) in the setting of difficult balloon/stent navigation.

Guiding Catheters

A 6F or larger guiding catheter is generally recommended. Standard guiding catheters can be safely positioned within the distal cervical carotid artery or at the V2/3 junction (e.g., Envoy XB; Codman Neurovascular; Raynham, MA). A 45-degree tip catheter may help guide the force vector during the procedure. Alternatively, a more flexible, atraumatic tip guide catheter may be navigated into the petrous/cavernous carotid (e.g., Neuron; Penumbra Inc; Alameda, CA). Some practitioners believe this more distal position outweighs the less supportive design of such catheters.

Intermediate Catheters

A relatively recent addition to the endovascular armamentarium is the intermediate or distal access catheter (DAC). These catheters can be routinely navigated into the cavernous or supraclinoid segment. This can greatly facilitate accessing middle cerebral artery stenotic lesions by bypassing the cavernous segment.

Microcatheters

A low-profile microcatheter and microwire are used to cross the stenotic segment. There are many equally effective microcatheters available for this purpose such as the SL 10 (Stryker; Kalamazoo, MI).

Microwires

Two microwires are often used. The first is a standard length 0.014″ wire that, along with a low-profile microcatheter, is used to cross the stenosis. Ideal wire characteristics include 1:1 torque and a soft tip (e.g., Synchro 14; Stryker; Kalamazoo, MI). A headhunter shape to the distal wire tip often facilitates crossing the lesion. The second wire is an exchange length 0.014″ wire. This wire should be supportive proximally and highly shapable distally (e.g., X-Celerator; Covidien; Irvine, CA). A J- or C-shaped wire tip will reduce the risk of micro-branch wire migration and perforation.

Balloons

Over-the-wire, semi-compliant balloons are generally preferred over monorail systems due to the greater trackability of the former through tortuous vessels. There is only one FDA-approved (HDE pathway) balloon for intracranial angioplasty in the setting of ICAD. The Gateway balloon (Stryker; Kalamazoo, MI) is an over-the-wire, low-profile, and highly navigable balloon. It comes in a variety of diameters and lengths. Coronary angioplasty balloons have also been used off label for this purpose (e.g., Maverick; Boston Scientific; Natick, MA). With the use of balloon-mounted stents, a pre-dilation with a smaller balloon may facilitate stent passage.

With self-expanding stents, pre-stenting balloon diameters are generally sized to 80 % or less of the normal luminal diameter. Balloon lengths are generally 5–10 mm greater than the lesion length. Extreme care must be taken to avoid overdistention of the vessel, as the fragile angio-architecture of the circle of Willis makes vessel rupture a real and catastrophic possibility.

Stents

The Wingspan Stent System is the only FDA-approved (HDE pathway) device for intracranial stenting in the setting of ICAD. It is used in conjunction with the Gateway balloon. These nitinol, slotted tube, self-expanding stents are housed within a delivery catheter. The delivery catheter is generally navigated over an exchange wire and across the lesion. The delivery catheter is then withdrawn, allowing the stent to flower open. The diameter of the stent is generally close to that of the normal luminal diameter. The length is generally 5–10 mm greater than the lesion length. Over-the-wire, balloon-mounted coronary stents, both bare metal and drug-eluting, have been used off label to treat ICAD. These devices are less navigable, but with a highly supportive proximal system, can generally cross the stenotic lesion. Stent sizing with these devices is 80 % or less of the normal luminal diameter.

Procedural Steps

Anesthesia is induced. A sheath is placed within the access site. Heparin is administered to achieve an activated clotting time of >250 seconds and rechecked hourly. The guide catheter is navigated into the parent vessel. A low-profile microcatheter and standard length microwire are navigated intracranially and, under high-resolution road map guidance, used to cross the stenotic lesion. These devices are positioned in a large branch, a sufficient distance distal to the stenosis to allow support and access during subsequent steps (e.g., in the M3 angular branch or P2/3 segment). The standard length microwire is removed and replaced by an exchange

length microwire. The microcatheter is then removed over the exchange wire. This step takes extreme care in order to avoid sudden movement of the wire. Sudden forward movement is most dangerous as this may lead to wire perforation. A J- or C-shaped wire tip will reduce the tendency of the wire to enter small branch vessels in this circumstance. If the wire migrates proximally, trans-lesional access may be lost, or insufficient distal access may make balloon/stent navigation impossible. These exchanges generally require two operators. At this point a repeat high-resolution road map is helpful to illustrate any changes in vessel angulation caused by the microwire. Next an over-the-wire angioplasty balloon is navigated across the lesion and inflated (see discussion above for balloon sizing tips), slowly deflated, then removed from the arterial system.

If the Wingspan Stent System is being utilized, the delivery catheter is advanced over the exchange wire and across the lesion. Despite the hydrophilic coating and flexible design of this device, it is often a slow and laborious process to achieve the desired stent position across the stenotic lesion. The stent is deployed and the delivery catheter is removed (see above for stent sizing tips). An angiogram through the existing catheter is then performed. If insufficient luminal improvement is seen, a post-stent angioplasty can be performed, but is discouraged by the manufacturer.

If an over-the-wire, balloon-mounted coronary stent system is being utilized; a pre-stent angioplasty may not be needed, depending on the severity of the baseline lesion. Once the stent is navigated across the lesion, the balloon upon which it is mounted is inflated to nominal pressure (see above for stent sizing tips). A post-stent angioplasty can be performed if the desired luminal enlargement is not achieved. A final control angiogram will screen for thromboembolic complications or extravasation.

Post-procedural Considerations

It is important to carefully monitor and guard against spikes in blood pressure during the post-procedural period. High-risk points include awakening from anesthesia and extubation. Such spikes in blood pressure may precipitate hyperperfusion syndrome and ICH. Additionally, it is essential that dual antiplatelet therapy be maintained for at least 3 months. In the case of drug-eluting coronary stent use, 12-month to lifelong dual antiplatelet therapy is recommended.

Endovascular ICAD Studies

We have reviewed the literature on PTA, DES, BMS, and SES above. Despite having many options for treatment of ICAD with endovascular techniques, none has been established as primary treatment. Table 5.4 outlines some of the major literature on these approaches.

Table 5.4 Major[a] studies on endovascular treatment of intracranial atherosclerotic disease

Study	Groups compared	Endovascular txt, *location*	Pre- and post-txt stenosis	Restenosis rate (>50 %)	Periprocedural complication rate	Outcome stroke or death
Miao[b] (2012) [51, 64]	Medical	PTA, stent *MCA*	84 → NR	NR	8.3 %	19.4 % stent 17.6 % med
SAMMPRIS[b] (2011) [3, 40]	Aggressive medical	SES *A and P circulation*	80 → NR	NR	19.2 %	14.7 % stent 5.8 % med
Yu et al. (2011) [67, 69]	MCA versus other locations	SES *MCA, ICA, BA, VA*	78 → NR	10 %	2.4 %—MCA 4 %—other	5.7 % MCA 12 % other
Nguyen et al. (2011) [54]	None	PTA *I, M, and ACA, B and VA*	79 → 34 %	NR	5	8.5 %
INTRASTENT (2010) [68]	None	Stenting (NR) *ICA, MCA, BA, VA*	NR	NR	NR	12.4 %
Siddiq et al. (2008) [56]	PTA versus stent placement	PTA, stent (NR) *A and P circulation*	89 → NR 90 → NR	15 % 4 %	8 % PTA 9 % stent	8 % PTA 11 % stent
Mazighi et al. (2008) [57]	None	PTA, DES, BMS *ICA, MCA, BA, VA*	85 → 0 %	16 %	NR	10.1 %
Zaidat et al. (2008) [65]	None	SES *ICA, MCA, BA, VA*	82 → 20 %	25 %	6.2 %	14 %
Fiorella et al. (2007) [64]	None	SES *ICA, MCA, BA, VA*	75 → 27 %	NR	15.3 %	6.1 %
Marks et al. (2006) [40]	None	PTA, stent (NR) *I, M, and PCA, B and VA*	82 → 36 %	NR	NR	5.8 %
SSLYVIA (2004) [69]	None	BMS *I, M, and PCA, B and VA*	NR	32 %	NR	9.3 %

Txt treatment, *SES* self-expanding stent, *DES* drug-eluting stent, *BMS* balloon-mounted stent, *PTA* percutaneous transluminal angioplasty, *NR* not reported, *MCA* middle cerebral artery, *ICA* internal cerebral artery, *BA* basilar artery, *VA* vertebral artery, *ACA* anterior cerebral artery

[a]Major study has been defined as randomized, highly referenced, national registries, or greater than 100 patients

[b]Indicates studies that were randomized and prospective

There have been positive results from non-randomized registries and case series, but there have been no positive trials to indicate its use as primary treatment of symptomatic patients with ICAD. In fact, the SAMMPRIS trial argues that it is likely harmful as first-line treatment [3, 8, 10]. Despite this many neurovascular practitioners and academics still believe that there is a role for endovascular treatment of ICAD as evidenced by a survey at the international stroke meeting [12, 66]. In fact, subsequent analysis of SAMMPRIS periprocedural strokes revealed that perhaps perforator-rich areas, location (basilar), and close monitoring of hemorrhages from wire perforation, Plavix loading, and an activated clotting time above the target range could possibly help us produce better results from endovascular treatment [15, 70, 71]. Although SAMMPRIS was a well-designed trial and some of the initial criticisms have been addressed, there are some concerns. These initial critiques including lack of inclusion of patients that failed best medical therapy once, the time to treatment, and stenting in perforator-rich areas have been addressed well by the investigators in separate articles [15, 19, 72]. Having said that, SAMMPRIS did not use perfusion or collateral imaging to screen patients. There was no set criteria for hemodynamic or perioperative ICU care. Given these limitations and potential patients that can benefit from this treatment, it would be judicious to evaluate every patient individually for intracranial endovascular revascularization.

Summary and Future Directions

Currently endovascular treatment is reserved for patients who have failed medical treatment. There is a need for future trials as even medical treatment has a 12 % stroke rate at 1 year and an increasing rate of stroke at follow-up [3, 20]. Recent surveys revealed that most neurovascular doctors including neurologist, neurosurgeons, and interventionalist would enroll ICAD patients in endovascular trials [22, 66]. Perhaps patients with poor collaterals, hemodynamic symptoms, and recurrence despite medical therapy will benefit from endovascular treatment. Another treatment option may be indirect bypass surgery as recently proposed [16, 24, 25, 73]. Finally, it is possible that the type of stenosis and vessel affected (perforator rich or not) may play a role in patient selection for future endovascular versus surgical versus medical therapy trials [27, 28, 67, 70, 71, 74].

Disclosures Funding sources: None.

Conflict of Interest None.

References

1. Lee JS, Im DS, An Y-S, Hong JM, Gwag BJ, Joo IS. Chronic cerebral hypoperfusion in a mouse model of Alzheimer's disease: an additional contributing factor of cognitive impairment. Neurosci Lett. 2011;489(2):84–8. doi:10.1016/j.neulet.2010.11.071.
2. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995;26(1):14–20.
3. 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. doi:10.1056/NEJMoa1105335.
4. Wong LKS. Global burden of intracranial atherosclerosis. Int J Stroke. 2006;1(3):158–9. doi:10.1111/j.1747-4949.2006.00045.x.
5. Choi H-Y, Ye BS, Ahn SH, et al. Characteristics and the fate of intraluminal thrombus of the intracranial and extracranial cerebral arteries in acute ischemic stroke patients. Eur Neurol. 2009;62(2):72–8.
6. Chaturvedi S, Turan TN, Lynn MJ, et al. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology. 2007;69(22):2063–8. doi:10.1212/01.wnl.0000279338.18776.26.
7. Adams GJG, Greene JJ, Vick GWG, et al. Tracking regression and progression of atherosclerosis in human carotid arteries using high-resolution magnetic resonance imaging. Magn Reson Imaging. 2004;22(9):1249–59. doi:10.1016/j.mri.2004.08.020.
8. Carson AP, Howard G, Burke GL, Shea S, Levitan EB, Muntner P. Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension. 2011;57(6):1101–7. doi:10.1161/HYPERTENSIONAHA.110.168005.
9. Bley TA, Uhl M, Venhoff N, Thoden J, Langer M, Markl M. 3-T MRI reveals cranial and thoracic inflammatory changes in giant cell arteritis. Clin Rheumatol. 2007;26(3):448–50. doi:10.1007/s10067-005-0160-7.
10. Waddy SP, Cotsonis G, Lynn MJ, et al. Racial differences in vascular risk factors and outcomes of patients with intracranial atherosclerotic arterial stenosis. Stroke. 2009;40(3):719–25. doi:10.1161/STROKEAHA.108.526624.
11. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collaterals dramatically alter stroke risk in intracranial atherosclerosis. Ann Neurol. 2011;69(6):963–74. doi:10.1002/ana.22354.
12. Stevens J, Truesdale KP, Katz EG, Cai J. Impact of body mass index on incident hypertension and diabetes in Chinese Asians, American Whites, and American Blacks: the People's Republic of China Study and the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2008;167(11):1365–74. doi:10.1093/aje/kwn060.
13. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology. 1989;39(9):1246–50.
14. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998;55(11):1475–82. doi:10.1001/archneur.55.11.1475.
15. 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.
16. Lee DK, Kim JS, Kwon SU, Yoo S-H, Kang D-W. Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: early diffusion-weighted imaging study. Stroke. 2005;36(12):2583–8. doi:10.1161/01.STR.0000189999.19948.14.
17. Ryoo S, Park JH, Kim SJ, et al. Branch occlusive disease: clinical and magnetic resonance angiography findings. Neurology. 2012;78(12):888–96. doi:10.1212/WNL.0b013e31824c4699.
18. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2013;12(11):1106–14. doi:10.1016/S1474-4422(13)70195-9.

19. Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113(4):555–63. doi:10.1161/CIRCULATIONAHA.105.578229.
20. 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;383:333–41. doi:10.1016/S0140-6736(13)62038-3.
21. Khan A, Kasner SE, Lynn MJ, Chimowitz MI. Risk factors and outcome of patients with symptomatic intracranial stenosis presenting with lacunar stroke. Stroke. 2012;43(5):1230–3. doi:10.1161/STROKEAHA.111.641696.
22. Ois A, Gomis M, Rodriguez-Campello A, et al. Factors associated with a high risk of recurrence in patients with transient ischemic attack or minor stroke. Stroke. 2008;39(6):1717–21. doi:10.1161/STROKEAHA.107.505438.
23. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol. 2000;21(4):643–6.
24. Kang D-W, Kwon SU, Yoo S-H, et al. Early recurrent ischemic lesions on diffusion-weighted imaging in symptomatic intracranial atherosclerosis. Arch Neurol. 2007;64(1):50–4. doi:10.1001/archneur.64.1.50.
25. Cho K-H, Kang D-W, Kwon SU, Kim JS. Location of single subcortical infarction due to middle cerebral artery atherosclerosis: proximal versus distal arterial stenosis. J Neurol Neurosurg Psychiatry. 2009;80(1):48–52. doi:10.1136/jnnp.2007.143354.
26. Feldmann EE, Wilterdink JLJ, Kosinski AA, et al. The stroke outcomes and neuroimaging of intracranial atherosclerosis (SONIA) trial. Neurology. 2007;68(24):2099–106. doi:10.1212/01.wnl.0000261488.05906.c1.
27. de Andrade SPC, Brucki SMD, Bueno OFA, Siqueira Neto JI. Neuropsychological performance in patients with subcortical stroke. Arq Neuropsiquiatr. 2012;70(5):341–7.
28. Saczynski JS, Sigurdsson S, Jonsdottir MK, et al. Cerebral infarcts and cognitive performance: importance of location and number of infarcts. Stroke. 2009;40(3):677–82. doi:10.1161/STROKEAHA.108.530212.
29. 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.
30. Nguyen-Huynh MN, Wintermark M, English J, et al. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? Stroke. 2008;39(4):1184–8. doi:10.1161/STROKEAHA.107.502906.
31. Swartz RH, Bhuta SS, Farb RI, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology. 2009;72(7):627–34. doi:10.1212/01.wnl.0000342470.69739.b3.
32. Ryu C-WC, Jahng G-HG, Kim E-JE, Choi W-SW, Yang D-MD. High resolution wall and lumen MRI of the middle cerebral arteries at 3 tesla. Cerebrovasc Dis. 2009;27(5):433–42.
33. Diethrich EB, Margolis MP, Reid DB, et al. Virtual histology intravascular ultrasound assessment of carotid artery disease: the Carotid Artery Plaque Virtual Histology Evaluation (CAPITAL) study. J Endovasc Ther. 2007;14(5):676–86. doi:10.1583/1545-1550(2007)14[676:VHIUAO]2.0.CO;2.
34. Xu W-H, Li M-L, Gao S, et al. Middle cerebral artery intraplaque hemorrhage: prevalence and clinical relevance. Ann Neurol. 2012;71(2):195–8. doi:10.1002/ana.22626.
35. Vergouwen MDIM, Silver FLF, Mandell DMD, Mikulis DJD, Swartz RHR. Eccentric narrowing and enhancement of symptomatic middle cerebral artery stenoses in patients with recent ischemic stroke. Arch Neurol. 2011;68(3):338–42. doi:10.1001/archneurol.2011.20.
36. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34(8):e109–37. doi:10.1161/01.STR.0000082720.85129.0A.
37. Powers WJ, Clarke WR, Grubb RL, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. JAMA. 2011;306(18):1983–92. doi:10.1001/jama.2011.1610.

38. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. N Engl J Med. 1985;313(19):1191–1200. doi:10.1056/NEJM198511073131904.
39. Mazighi M, Tanasescu R, Ducrocq X, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66(8):1187–91. doi:10.1212/01.wnl.0000208404.94585.b2.
40. Marks MP, Wojak JC, Al-Ali F, et al. Angioplasty for symptomatic intracranial stenosis: clinical outcome. Stroke. 2006;37(4):1016–20. doi:10.1161/01.STR.0000206142.03677.c2.
41. Marks MP, Marcellus ML, Do HM, et al. Intracranial angioplasty without stenting for symptomatic atherosclerotic stenosis: long-term follow-up. AJNR Am J Neuroradiol. 2005;26(3):525–30.
42. Castaneda-Zuniga WR, Formanek A, Tadavarthy M, et al. The mechanism of balloon angioplasty. Radiology. 1980;135(3):565–71.
43. Sundt TM, Smith HC, Campbell JK, Vlietstra RE, Cucchiara RF, Stanson AW. Transluminal angioplasty for basilar artery stenosis. Mayo Clin Proc. 1980;55(11):673–80.
44. O'Leary DHD, Clouse MEM. Percutaneous transluminal angioplasty of the cavernous carotid artery for recurrent ischemia. AJNR Am J Neuroradiol. 1984;5(5):644–5.
45. Purdy PDP, Devous MDM, Unwin DHD, Giller CAC, Batjer HHH. Angioplasty of an atherosclerotic middle cerebral artery associated with improvement in regional cerebral blood flow. AJNR Am J Neuroradiol. 1990;11(5):878–80.
46. Takis C, Kwan ES, Pessin MS, Jacobs DH, Caplan LR. Intracranial angioplasty: experience and complications. AJNR Am J Neuroradiol. 1997;18(9):1661–8.
47. Connors JJ, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. J Neurosurg. 1999;91(3):415–23.
48. Terada T, Tsuura M, Matsumoto H, et al. Endovascular therapy for stenosis of the petrous or cavernous portion of the internal carotid artery: percutaneous transluminal angioplasty compared with stent placement. J Neurosurg. 2003;98(3):491–7.
49. Johnston S, Selvin S. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology. 1998;50(5):143–8.
50. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38(6):2001–23. doi:10.1161/STROKEAHA.107.183689.
51. Miao Z, Jiang L, Wu H, et al. Randomized controlled trial of symptomatic middle cerebral artery stenosis: endovascular versus medical therapy in a chinese population. Stroke. 2012;43(12):3284–90. doi:10.1161/STROKEAHA.112.662270.
52. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6–245. doi:10.1161/CIR.0b013e31828124ad.
53. Wojak JC, Dunlap DC, Hargrave KR, DeAlvare LA, Culbertson HS, Connors JJ. Intracranial angioplasty and stenting: long-term results from a single center. AJNR Am J Neuroradiol. 2006;27(9):1882–92.
54. Nguyen TN, Zaidat OO, Gupta R, et al. Balloon angioplasty for intracranial atherosclerotic disease: periprocedural risks and short-term outcomes in a multicenter study. Stroke. 2011;42(1):107–11. doi:10.1161/STROKEAHA.110.583245.
55. Hussain MS, Fraser JF, Abruzzo T, et al. Standard of practice: endovascular treatment of intracranial atherosclerosis. J Neurointerv Surg. 2012;4(6):397–406. doi:10.1136/neurintsurg-2012-010405.
56. Siddiq F, Vazquez G, Memon MZ, et al. Comparison of primary angioplasty with stent placement for treating symptomatic intracranial atherosclerotic diseases: a Multicenter study. Stroke. 2008;39(9):2505–10. doi:10.1161/STROKEAHA.108.515361.

57. Mazighi M, Yadav JS, Abou-Chebl A. Durability of endovascular therapy for symptomatic intracranial atherosclerosis. Stroke. 2008;39(6):1766–9. doi:10.1161/STROKEAHA.107.500587.
58. Qureshi AI, Kirmani JF, Hussein HM, et al. Early and intermediate-term outcomes with drug-eluting stents in high-risk patients with symptomatic intracranial stenosis. Neurosurgery. 2006;59(5):1044–51. doi:10.1227/01.NEU.0000245593.54204.99. discussion 1051.
59. Abou-Chebl A, Bashir Q, Yadav JS. Drug-eluting stents for the treatment of intracranial atherosclerosis: initial experience and midterm angiographic follow-up. Stroke. 2005;36(12):e165–8. doi:10.1161/01.STR.0000190893.74268.fd.
60. Boulos AS, Agner C, Deshaies EM. Preliminary evidence supporting the safety of drug-eluting stents in neurovascular disease. Neurol Res. 2005;27 Suppl 1:S95–102. doi:10.1179/016164105X35459.
61. Roy PP, Bonello LL, Torguson RR, et al. Temporal relation between clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009;103(6):801–5. doi:10.1016/j.amjcard.2008.11.038.
62. Palmerini T, Biondi-Zoccai G, Riva Della D, et al. Stent thrombosis with drug-eluting stents: is the paradigm shifting? J Am Coll Cardiol. 2013;62(21):1915–21. doi:10.1016/j.jacc.2013.08.725.
63. Park S, Lee D-G, Chung W-J, Lee DH, Suh DC. Long-term outcomes of drug-eluting stents in symptomatic intracranial stenosis. Neurointervention. 2013;8(1):9. doi:10.5469/neuroint.2013.8.1.9.
64. Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke. 2007;38(3):881–7. doi:10.1161/01.STR.0000257963.65728.e8.
65. Zaidat OO, Klucznik R, Alexander MJ, et al. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. Neurology. 2008;70(17):1518–24. doi:10.1212/01.wnl.0000306308.08229.a3.
66. Zaidat OO, Castonguay AC, Nguyen TN, et al. Impact of SAMMPRIS on the future of intracranial atherosclerotic disease management: polling results from the ICAD symposium at the International Stroke Conference. J Neurointerv Surg. 2014;6:225–30. doi:10.1136/neurintsurg-2013-010667.
67. Yu SCHS, Leung TWHT, Lee KTK, Hui JWYJ, Wong LKSL. Angioplasty and stenting of atherosclerotic middle cerebral arteries with Wingspan: evaluation of clinical outcome, restenosis, and procedure outcome. AJNR Am J Neuroradiol. 2011;32(4):753–8. doi:10.3174/ajnr.A2363.
68. Kurre W, Berkefeld J, Brassel F, et al. In-hospital complication rates after stent treatment of 388 symptomatic intracranial stenoses: results from the INTRASTENT multicentric registry. Stroke. 2010;41(3):494–8. doi:10.1161/STROKEAHA.109.568063.
69. The SSYLVIA Study Investigators. Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA): study results. Stroke. 2004;35(6):1388–92. doi:10.1161/01.STR.0000128708.86762.d6.
70. Derdeyn CP, Fiorella D, Lynn MJ, et al. Mechanisms of stroke after intracranial angioplasty and stenting in the SAMMPRIS trial. Neurosurgery. 2013;72(5):777–95. doi:10.1227/NEU.0b013e318286fdc8. discussion 795.
71. 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(10):2682–8. doi:10.1161/STROKEAHA.112.661173.
72. Chimowitz MI, Fiorella D, Derdeyn CP, et al. Response to critique of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial by Abou-Chebl and Steinmetz. Stroke. 2012;43(10):2806–9. doi:10.1161/STROKEAHA.112.661041.
73. Gonzalez NR, Liebeskind DS, Dusick JR, Mayor F, Saver J. Intracranial arterial stenoses: current viewpoints, novel approaches, and surgical perspectives. Neurosurg Rev. 2013;36(2):-175–84. doi:10.1007/s10143-012-0432-z.
74. Mori T, Fukuoka M, Kazita K, Mori K. Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty. AJNR Am J Neuroradiol. 1998;19(8):1525–33.

Chapter 6
Clinical and Radiographic Considerations in Acute Stroke Triage

Ashish Nanda and Anantha Vellipuram

Introduction

The saying "time is brain" captures the time-sensitive evolution of ischemic penumbral brain tissue into core infarct. The rationale behind acute stroke therapy is to reduce the infarct size by reperfusing the ischemic penumbral tissue. Both intravenous and intra-arterial therapies aim to achieve this common goal. Despite approaching 90 % recanalization rates, good clinical outcomes are seen in only 50 % of the patients who undergo acute stroke intervention [1–4]. This indicates that the recanalization of the artery does not necessarily always result in good clinical outcome. Earlier recanalization may improve patient outcomes [5–7] but the majority of the patients do not get access to these therapies in the early hours of stroke onset. There are also time lapses associated with transfer to tertiary care centers with endovascular capabilities. Selecting patients who may benefit from revascularization despite these delays is key. Finally, certain patients will not have any significant clinical improvement despite achieving early recanalization [8] due to the great variability in time to irreversible infarction. Here too, selection tools are needed.

A. Nanda, M.D. (✉)
Neurology and Neurosurgery, University of Missouri, Columbia, MO 65212, USA
e-mail: nandaa@health.missouri.edu

A. Vellipuram, M.D.
Department of Neurology, University of Missouri, Columbia, MO 65212, USA
e-mail: vellipurama@health.missouri.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_6

Tools Review

Clinical Assessment

Clinical information at the time of patient presentation should be emphasized as a key factor when interventional treatment is being considered. Interventionalists should have information regarding the patient's age, time of stroke onset, baseline NIHSS, baseline functional status, etiology of stroke (if possible), any contraindications to IV t-PA, and patient/family wishes before proceeding with stroke intervention. Intra-arterial (IA) therapy has shown benefit up to 6–8 h after stroke onset [3, 9].

NIHSS score is the most widely used stroke scale for initial assessment and can reliably measure stroke severity in acute stroke patients. Baseline NIHSS score may also help predict the clinical course and patient outcome [10–12]. Better outcomes have been noted with initial NIHSS score ≤7 [13], while a NIHSS score >20 predicts a less than 20 % chance of good outcome [14]. The scale can also help to predict the incidence of intracranial hemorrhage [15]. The majority of interventional stroke trials have enrolled patients with NIHSS >7.

Other scales like the Houston Intra-arterial Therapy (HIAT) score can help estimate the chances of poor outcomes in recanalized patients [16]. The HIAT (Table 6.1) score can be calculated by allocating 1 point each for age over 75 years, admission NIHSS score greater than 18, and admission glucose greater than 150 mg/dL. In the study, 100 % of patients with a HIAT score of 3 had a poor outcome compared with 97 % with a score of 2, 67 % with a score of 1, and 44 % with a score of 0 [16].

Calculating these clinical scores can help predict the outcome and possible risks vs. benefit of endovascular therapy in acute stroke patients.

Neuroimaging

Neuroimaging techniques can help identify vascular anatomy of the acute stroke patient, location of vascular occlusion, and potentially salvageable tissue. The most commonly used techniques include computerized tomography (CT) of the head without contrast, CTA/CTP, MRI/MRA, and magnetic resonance (MR) perfusion.

Table 6.1 HIAT score

Age
≥75 = 1
<75 = 0
NIHSS
≥18 = 1
<18 = 0
Admission glucose
≥150 mg/dl = 1
<150 mg/dl = 0

Identification of the penumbral tissue remains the "Holy Grail" of acute stroke imaging. Astrup et al. proposed the initial concept of penumbra in 1981 [17]. Penumbral tissue is described as the ischemic hypoperfused area surrounding the core infarct zone that is at risk of irreversible damage. As proposed by Hakim, penumbra is an ischemic tissue that is potentially reversible with timely intervention [18]. Cerebral blood flow (CBF) levels between 10–15 mL/100 g/min and 25 mL/100 g/min are likely to identify the penumbral tissue [19].

The rationale behind acute stroke therapy is to reduce infarct size by reperfusing the ischemic penumbral tissue, thereby improving patient outcomes. Initial brain perfusion studies have been done with the PET by mapping CMRO2 and OEF and with use of ligands that preferentially binds to the penumbral tissue [20–23]. But PET scanners are not used for emergent clinical triage due to their limited availability and the time required for studies to be performed. Other modalities relied upon in clinical practice are described below. Perfusion imaging provides physiologic information about the penumbral tissue at a given time. However, it is important to remember the dynamic physiological changes that occur between the time of perfusion imaging acquisition and actual stroke intervention.

Non-contrast CT

Acute stroke imaging begins with a non-contrast computed tomography (NCCT) scan [24, 25]. This imaging modality has become the first-line diagnostic test because of its acquisition speed, widespread availability, accuracy, and cost-effectiveness. In the acute setting, it not only accurately excludes subarachnoid and intracranial hemorrhage but also detects subacute infarct and occasionally identifies other conditions that may mimic acute cerebral ischemia. These findings play a very important role in selecting therapeutic options as well as predicting outcomes. The advent of multi-detector technology has considerably cut down the CT image acquisition time to 1–2 min and produces a better quality image with superior tissue differentiation [26]. The NCCT imaging is based on X-ray beam attenuation values that are expressed in Hounsfield units (HU). Substances denser than water have higher HU and are gray to white in appearance on NCCT, whereas lower density substances have negative HU value and appear dark on the scans. The physiological derangement causing edema (cytotoxic and vasogenic) in ischemic brain tissue is represented as hypodense areas on NCCT [27–29]. When an area is noted as hypodense on NCCT, the probability of it being infarcted is nearly 97 % [30]. As per current guidelines, any patient with stroke-like symptoms who is eligible for IV t-PA should have a NCCT done within 25 min of arrival to the hospital with results to be interpreted within 45 min of arrival [31]. The usual findings of early acute stroke on NCCT are hyperdense artery signs, loss of gray-white matter differentiation, loss of insular ribbon, compression of ventricles, and sulcal effacement. The occlusion of major vessels is sometimes seen as hyperdense artery signs, e.g., hyperdense MCA sign or MCA dot sign. Usually, a hyperdense MCA sign is seen

in proximal segments, whereas the dot sign is seen in the distal segments of MCA [32]. These signs usually disappear within a few days after recanalization and resolution of the thrombus [33]. The hyperdense MCA sign is a sensitive indicator of thrombus as is seen in nearly one-half of all cases of angiographically proven larger artery thrombosis [34].

The sensitivity of NCCT in the setting of acute stroke depends on many factors including the time of the scan, the area of infarct, technical specifications of scanner, the viewing methodology, and expertise of the interpreters. The studies have shown that stroke recognition rates are nearly 67 % if the scan is done within 3 h of symptom onset [35, 36]. In a post-hoc analysis of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, NCCT had a 31 % sensitivity in detecting early signs of stroke that increased to 82 % at 6 h [37]. There is some evidence indicating patients showing extensive parenchymal hypodensity or involvement of more than one-third of the MCA territory on NCCT should be excluded from treatment with IV rt-PA due to dismal outcomes [24].

The Alberta Stroke Program Early CT Score (ASPECTS) was designed to standardize the detection and reporting of the extent of ischemic hypodensity on NCCT. It is an effective clinical tool that is practical, reliable, and reproducible. ASPECTS is a topographic scoring system that divides the MCA territory into ten segments on two NCCT axial cuts, including: caudate, insula, lenticular nucleus, internal capsule, and M1–M6 cortical regions. The score is obtained by subtracting a point for apparent ischemia in each area from the total score of 10. A score of 0 represents completely infarcted area and a score of 10 indicates normal MCA territory respectively. The patients with ASPECT score of 8–10 have shown less infarct burden and better clinical outcomes [32]. The limitations with ASPECTS application are presence of preexisting white matter disease and interobserver variability [38].

CT Angiography

CT angiography (CTA) is performed through the intravenous administration of a rapid bolus of contrast. Helical CT scan images are acquired to visualize the intracranial and extracranial vasculature. These raw CT images can be reconstructed into three-dimensional images of the circle of Willis and extracranial cerebral arteries. This provides a noninvasive method for rapid evaluation of the cerebral vasculature and can be performed within minutes after NCCT head. Direct visualization of cerebral vasculature provides information about the site of vessel occlusion, vessel tortuosity, and clot size. This information is valuable in planning interventional therapy and achieving recanalization. CTA has sensitivities of about 92–100 % and specificities of 82–100 % for the detection of intracranial large vessel stenosis and occlusion [39]. Clot size exceeding 8 mm in length is associated with poor response to IV t-PA [40]. CTA images also provide visualization of collateral flow to the occluded vessel that can be a marker of penumbral tissue and possibly good outcomes [41]. CTA images are more sensitive than NCCT in visualizing areas of hypoattenuation and correlate well to final MRI DWI images for assessing infracted tissue [42].

CT Perfusion

CT perfusion imaging is widely used for identification of penumbra in acute stroke patients. The images are acquired on ultrafast CT scan by repetitive scanning of a defined area after injection of intravenous contrast. Semiquantitative CBV, CBF, and MTT maps can be generated from the arterial and tissue enhancement curves after administration of bolus of iodinated contrast. Ischemic penumbra is generally defined as areas with reduced CBF and elevated MTT with CBV values above threshold for ischemia [43, 44]. In comparison with MRI perfusion, widespread availability of CT perfusion makes it the more commonly used imaging modality to identify penumbra in acute stroke patients. Perfusion CT color maps can lead to fourfold increase in stroke diagnosis when compared to non-contrast CT alone [45].

Magnetic Resonance Imaging

The magnetic resonance imaging (MRI) is regarded as a most accurate tool in detecting cerebral infarction. The MRI demonstrates high rates of sensitivity and specificity in the diagnosis of acute ischemia [46, 47]. An American Academy of Neurology position statement states that MRI is more diagnostic than NCCT in the first 12 h of acute stroke and also plays a very important role in predicting the clinical prognosis [48]. During acute cerebral ischemia, there is disruption of energy metabolism, leading to failure of the Na^+/K^+ ATP pump which leads to loss of ionic gradient and net influx of water from extracellular to intracellular environment causing restricted diffusion of water molecules. These areas are readily identified as hyperintense lesions on DWI sequences of MRI. The lesions are correlated with apparent diffusion coefficient (ADC) sequences that demonstrate restricted diffusion as hypointense lesion [49–52].

Treatment outcomes are closely related to the volume of infarct on DWI imaging [53]. Studies have shown that there is nearly a sixfold increase in the risk of ICH when the infarct core volume exceeds 100 ml [54]. The existence of DWI lesion reversal still remains controversial. In a recent study, Labeyrie et al. demonstrated sizeable DWI reversal in patients who had undergone thrombolysis within ≤4.5 h of symptom onset [55]. In a *post-hoc* analysis of the EPITHET trial, only 6.4 % of patients demonstrated true DWI reversal [56]. DWI hyperintensity is also seen in other conditions like abscesses, aggressive viral infections (e.g., ADEM), and certain tumors.

MR Perfusion

MR perfusion or MR perfusion-weighted imaging is a technique in which the first pass of a bolus of gadolinium-based contrast agent through brain tissue is monitored by a series of T2-weighted MR images. The susceptibility effect of paramagnetic

agents like gadolinium leads to a signal loss in the time-to-signal intensity curve. Parametric maps of cerebral blood volume (CBV) and flow (CBF) can be derived from the concentration–time curve using this signal information.

It is generally believed that the DWI lesion reflects core infarct while PWI shows the area of hypoperfused ischemic tissue. Therefore, the combined use of PWI with DWI can visually help identify the penumbral area at risk by measuring volume difference referred to as "PWI-DWI mismatch."

Studies have shown some benefits of using the MRI diffusion–perfusion imaging-based mismatch for identifying patients for IV thrombolytic [57, 58]. Early changes suggestive of ischemic stroke can be noted on the DWI and ADC images within a few minutes of stroke onset. Stroke patients have been shown to have favorable outcome rate for patient treated with IV t-PA when selected with based on imaging with DWI-PWI mismatch vs. non-contrast CT scan [59, 60].

In DEFUSE trial, patients who were treated with IV t-PA within 3–6-h window were also screened with DWI-PWI imaging. Perfusion abnormality was defined as T max delay of >2 s and greater than 20 % mismatch of PWI-DWI lesion. In DWI-PWI mismatch group, early reperfusion was associated with favorable outcome in 56 %, while only a 19 % favorable outcome was achieved when reperfusion was not achieved. In the group with no DWI-PWI mismatch, lack of early reperfusion was associated with a more favorable outcome [57].

Another randomized trial, EPITHET, intravenous t-PA in the 3–6-h window along with MRI imaging, was used to assess for infarct growth at 90 days. Perfusion abnormalities were defined as T max delay of >2 s and greater than 20 % mismatch of PWI-DWI lesion, similar to DEFUSE trial. 56 % of t-PA patients were noted to have >90 % reperfusion of initial PWI lesion, as compared to 26 % in the placebo group [60].

Pooled analysis of DEFUSE and EPITHET trials showed that patient who had mismatch and had successful reperfusion had better 90-day outcomes compared with unsuccessful reperfusion (OR = 5.6). Reperfusion did not improve favorable outcomes in non-mismatch patients [61].

Based on these trials, patients that have MR perfusion imaging with T max delay of >2 s and greater than 20 % mismatch of PWI-DWI lesion might benefit from revascularization therapies.

When considering triaging patients using advanced neuroimaging, the potential benefits must be weighed against the time required to perform the test. While this loss of time may be justified in patients nearing the end or outside of the commonly accepted therapeutic time window, it may not be justified in patients presenting early in the course.

Transcranial Doppler

The role of Transcranial Dopplers (TCDs) in acute stroke therapy is debatable. Some studies have shown some benefits in using TCD in conjunction with intravenous t-PA therapy [62]. It is a quick, bedside, noninvasive imaging modality to

assess blood flow in major intracranial vessels. It is useful in detecting cerebral flow velocity, direction of flow, collateral supply, flow obstruction, and degree of vasospasm. The major vessels that are visualized are MCA, ACA, carotid siphon, vertebral artery, basilar artery, and ophthalmic artery [63, 64]. TCDs are more sensitive and specific in detecting stenosis in anterior circulation when compared to posterior circulation [65]. It also detects microemboli in patients with certain underlying conditions (e.g., carotid artery disease, atrial fibrillation, patients with cardio-embolic source of thrombus) in the form of transient high-intensity signal [66]. The most important use of TCD is monitoring for development of vasospasm in subarachnoid hemorrhages. The parameters which indicate vasospasm are flow velocities more than 200 cm/s, elevated Lindegaard ratios, and a rapid increase in flow velocities [67–69]. TCD's findings do however depend on bony windows, vessel anatomy, and operator/interpreter.

Assessment of Collaterals

As mentioned, CT or MRI techniques provide us with important information regarding the status of collateral blood flow to the ischemic area. Collaterals can provide flow to the ischemic or penumbral areas when the primary source of arterial inflow is blocked. The presence or absence of collaterals can be critical in predicting patient outcomes and aid in selecting patient that will benefit from endovascular recanalization [70]. The presence of collaterals is shown to be one of the most important predictors of clinical outcome and arterial recanalization [71].

The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale (Table 6.2) quantifies and characterizes collaterals on angiography with description of collateral filling, arterial flow, and venous phase of the ischemic territory [72]. Interestingly, beneficial effects were not observed in patients with poor collaterals even when revascularization was achieved [73].

Table 6.2 The ASITN/SIR Collateral Flow Grading System for determining angiographic collateral grade on pretreatment angiography

ASITN/SIR collateral grade	Definition
0	No collaterals visible to ischemic site
1	Slow collaterals to the periphery of ischemic site, with persistence of some of the defect
2	Rapid collaterals to the periphery of ischemic site, with persistence of some of the defect, and to only a portion of the ischemic territory
3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

Summary

Acute revascularization therapies for acute stroke hold the promise of improving patient outcomes. However, patient selection remains a challenge to the successful implementation of these therapies. We still are unclear as to which patients are most likely to benefit from this treatment approach. A combination of clinical and imaging-based selection is currently the best strategy to maximize benefit by combining baseline characteristics with a dynamic physiological assessment of penumbra.

Case Vignettes

Illustrative Case 1: A 79-year-old, right-handed Caucasian female with past medical history of HTN, HLD, and paroxysmal atrial fibrillation presents with sudden onset of right-sided weakness and speech difficulty 4 h ago. A CT perfusion study was performed to delineate the ischemic penumbra (Fig. 6.1). A large region of salvageable tissue was identified, and the patient was taken to the angiography suite where a right middle cerebral artery occlusion was found (Fig. 6.2a) and successfully recanalized with the aid of a Solitaire stent retriever (Fig. 6.2b) (Covidien, Irvine, CA). A post-procedural repeat NCCT shows only the core infarct (Fig. 6.3).

Illustrative Case 2: A 74-year-old, right-handed man woke up with moderate dysarthria, left hemianopsia, left facial paresis, and sensory loss. He arrived in the emergency department 9 h into his stroke symptom onset with NIHSS score of 8. MRI diffusion imaging showed only small punctate areas of restricted diffusion in the RMCA territory (Fig. 6.4a), while perfusion-weighted imaging showed a large region at risk (Fig. 6.4b). MR angiography showed a distal M1 occlusion (Fig. 6.5). The patient was taken for mechanical thrombectomy with the MERCI clot retriever and achieved complete restoration of flow (Fig. 6.6). Follow-up NCCT showed no large territorial infarction (Fig. 6.7).

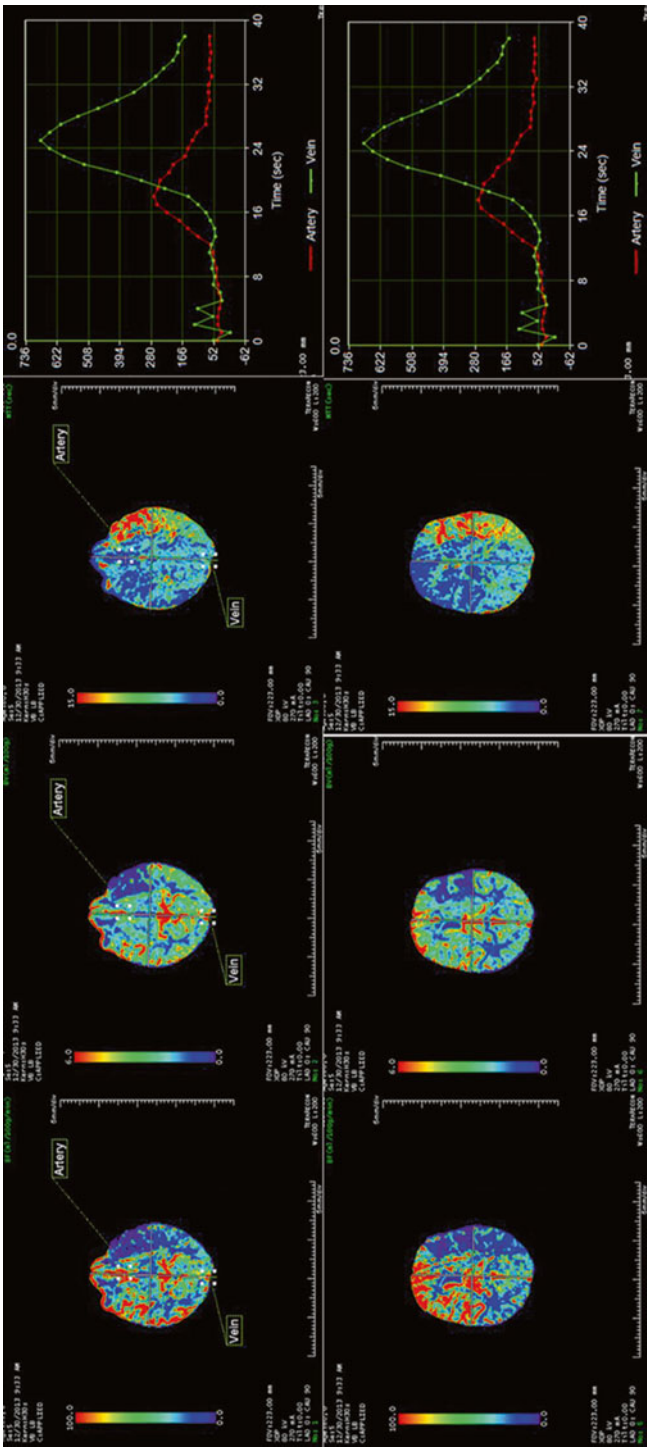

Fig. 6.1 A large left hemispheric MCA territory stroke with large frontal core infarct and a moderate frontoparietal penumbra (perfusion mismatch) with increased mean transit time and decreased blood flow. These images show both the area of core infarct and area of mismatch suggestive of penumbra in posterior division of the MCA territory

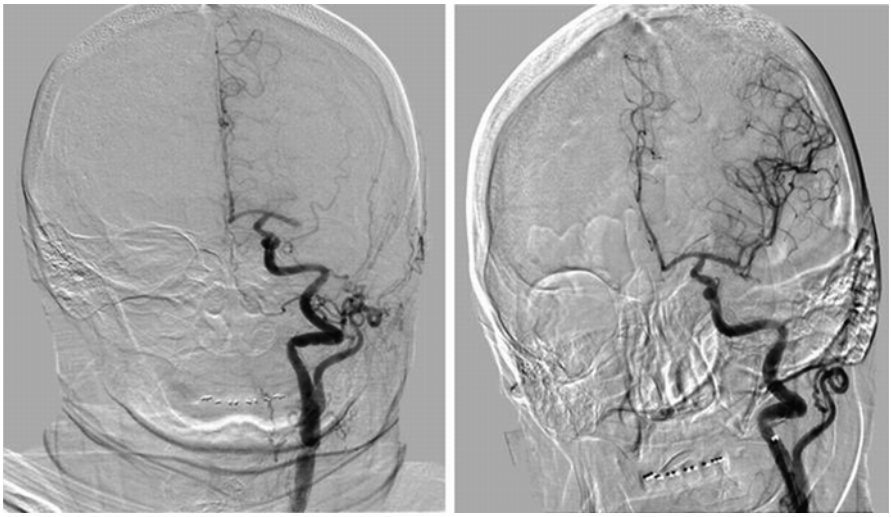

Fig. 6.2 Acute thrombus in the proximal left MCA with no flow to either the superior or inferior division before intervention (a), with restoration of TICI 2B flow post-thrombectomy with the Solitaire device

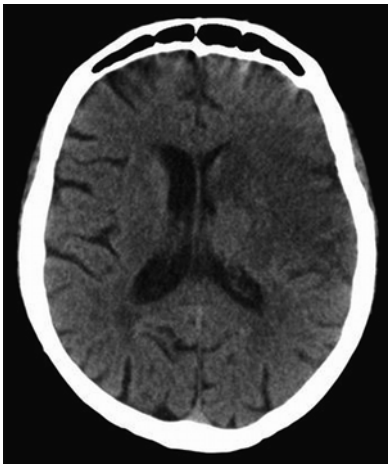

Fig. 6.3 CT head 2 days later shows hypodensity in the left frontoparietal region which correlates with the area of core infarct on CT perfusion images, while the posterior division with mismatch on CT perfusion was salvaged with mechanical intervention

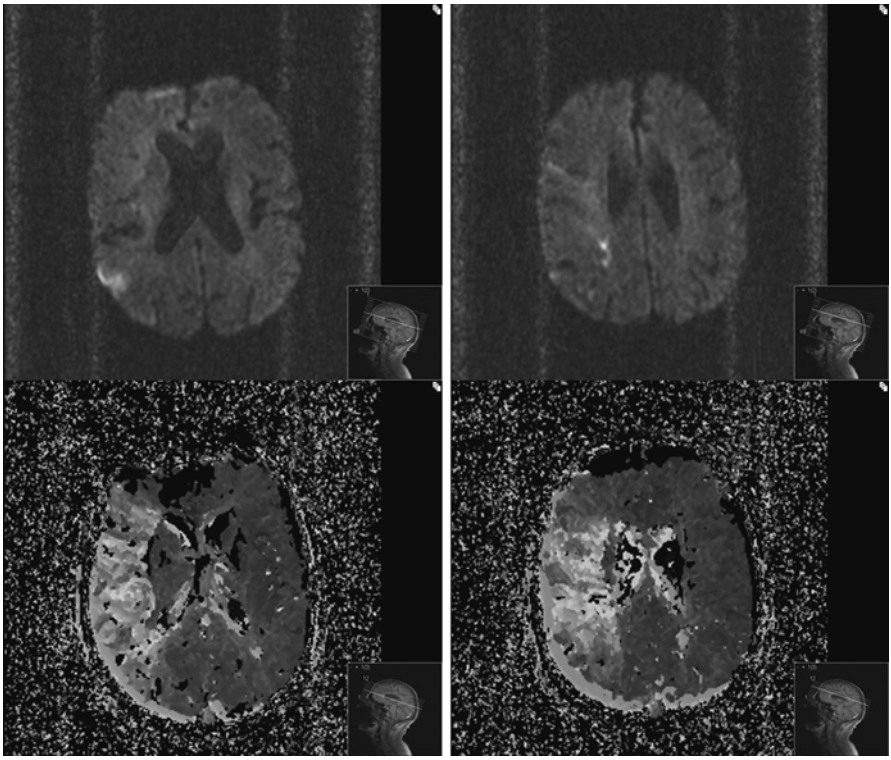

Fig. 6.4 MRI diffusion–perfusion imaging with small area of diffusion positive area noted in right hemisphere suggestive of core infarct. MRI perfusion shows almost the entire right MCA territory at risk with large area of penumbra

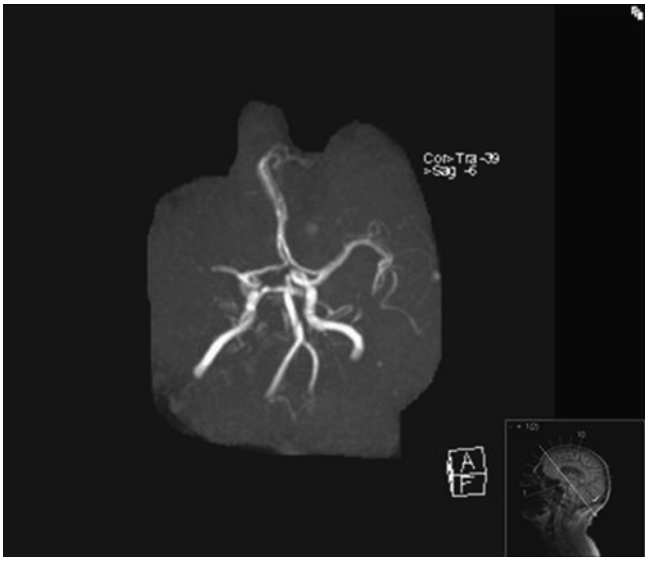

Fig. 6.5 MRA head shows occlusion of the right MCA

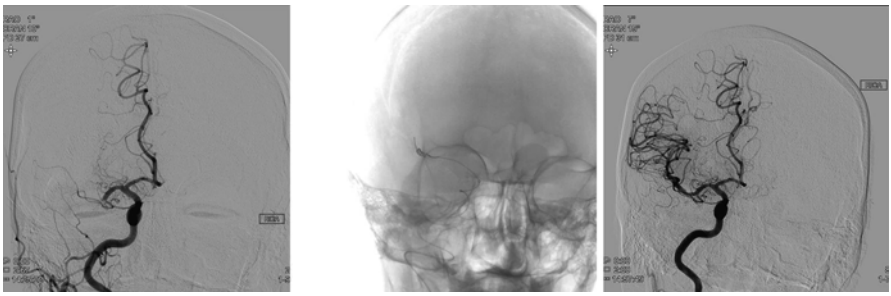

Fig. 6.6 Occlusion of the proximal right M1 MCA. Post mechanical intervention, successful TICI 3 recanalization of right MCA was achieved

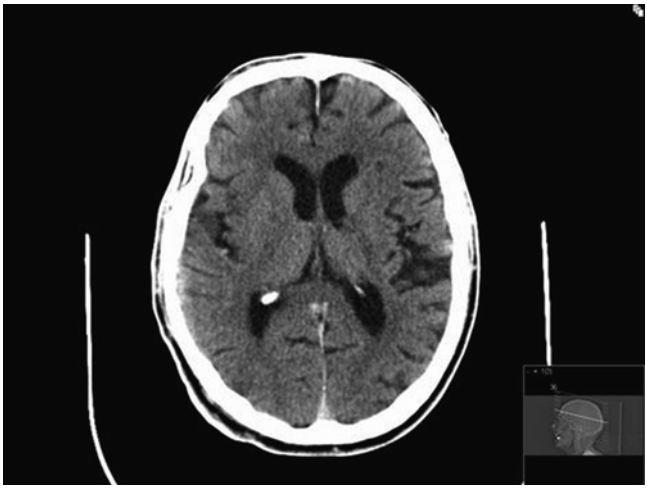

Fig. 6.7 CT head 2 days later shows no areas of hypodensity with patient NIHSS = 0 at time of discharge

References

1. Saver J, Jahan R, Levy E. 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.
2. Nogueira R, Lutsep H, Gupta G, 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.
3. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke. 2008;39(4):1205–12.
4. 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(8):2761–8.

5. Broderick J, Palesch Y, Demchuk A, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368:893–903.
6. Khatri P, Abruzzo T, Yeatts S, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009;73(13):1066–72.
7. Lansberg M, Straka M, Kemp S, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol. 2012;11(10):860–7.
8. Chelsea K, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013;368:914–23.
9. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.
10. Muir KW, Weir CJ, Murray G, et al. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke. 1996;27:1817–20.
11. Frankel MR, Morgenstern LB, Kwiatkowski T, et al. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. Neurology. 2000;55:952–9.
12. Adams Jr HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org10172 in Acute Stroke Treatment (TOAST). Neurology. 1999;53:126–31.
13. DeGraba TJ, Hallenbeck JM, Pettigrew KD, et al. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. Stroke. 1999;30(6): 1208–12.
14. Fonarow G, Saver J, Smith E, et al. Relationship of National Institutes of health stroke scale to 30-day mortality in medicare beneficiaries with acute ischemic stroke. J Am Heart Assoc. 2012;1:42–50.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke. 1997;28:2109–18.
16. Hallevi H, Barreto AD, Liebeskind DS, et al. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. Stroke. 2009;40(5):1780–5.
17. Ann Neurol. 1994; 36:557–60.
18. Hakim AM. The cerebral ischemic penumbra. Can J Neurol Sci. 1987;14:557–9.
19. Fisher M, Bastan B. Identifying and utilizing the ischemic penumbra. Neurology. 2012;79(13 Suppl 1):S79–85.
20. Baron J. Mapping the ischemic penumbra with PET. Implications for acute stroke treatment. Cerebrovasc Dis. 1999;9:193–201.
21. Heiss WD. Ischemic penumbra. Evidence from functional imaging I man. J Cereb Blood Flow Metab. 2000;20:1276–93.
22. Heiss W, Kracht L, Thiel A, Grond M, et al. Penumbral probability thresholds of flumazenil binding and blood flow predicting outcome in patients with cerebral ischemia. Brain. 2001;124:20–9.
23. Read S, Hirano T, Abott D, et al. The fate of hypoxic tissue on 18-F fluoromisonidazole PET after ischemic stroke. Ann Neurol. 2000;48:228–35.
24. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017–25.
25. The National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
26. Scharf J, Brockmann MA, Daffertshofer M, et al. Improvement of sensitivity and interrater reliability to detect acute stroke by dynamic perfusion computed tomography and computed tomography angiography. J Comput Assist Tomogr. 2006;30:105–10.
27. Von Kummer R, Bourquain H, Bastianello S, et al. Early prediction of irreversible brain damage after ischemic stroke at CT. Radiology. 2001;219:95–100.
28. Marks MP, Holmgren EB, Fox AJ, et al. Evaluation of early computed tomographic findings in acute ischemic stroke. Stroke. 1999;30:389–92.

29. Grond M, von Kummer R, Sobesky J, et al. Early X-ray hypoattenuation of brain parenchyma indicates extended critical hypoperfusion in acute stroke. Stroke. 2000;31:133–9.
30. Von Kummer R, Bourquain H, Manelfe C, et al. Predictive value of early CT in acute ischemic stroke. Stroke. 1999;30:250.
31. Jauch EC, Cucchiara B, Adeoye O, et al. Part 11: adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122(18 Suppl 3):S818–28.
32. Barber P, Demchuk A, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355(9216):1670–4.
33. Leys D, Pruvo JP, Godefroy O, et al. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. Stroke. 1992;23(3):317–24.
34. Tomsick T, Brott T, Barsan W, et al. Prognostic value of the hyperdense middle cerebral artery sign and stroke scale score before ultra early thrombolytic therapy. Am J Neuroradiol. 1996;17:79–85.
35. Von Kummer R, Holle R, Gizyska U, et al. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. Am J Neuroradiol. 1996;17:1743–8.
36. Schriger DL, Kalafut M, Starkman S, et al. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA. 1998;279:1293–7.
37. Von Kummer R, Nolte P, Schnittger H, et al. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6h of stroke. Neuroradiology. 1996;38:31–3.
38. Gupta A, Schaefer P, Chaudhry Z, et al. Interobserver reliability of baseline noncontrast CT Alberta Stroke Program Early CT Score for intra-arterial stroke treatment selection. Am J Neuroradiol. 2012;33(6):1046–9.
39. Latchaw R, Alberts M, Lev M, et al. American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke. 2009;40(11):3646.
40. Riedel C, Zimmermann P, Jensen-Kondering U, et al. Successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke. 2011;42:1775–7.
41. Menon B, Smith E, Modi J, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. AJNR Am J Neuroradiol. 2011;32:1640–5.
42. Schramm P, Schellinger P, Fiebach J, et al. Comparison of CT and CT angiography source images with diffusion-weighted imaging in patients with acute stroke within 6 hours after onset. Stroke. 2002;33(10):2426.
43. Wintermark M, Flanders A, Velthuis B, et al. Perfusion CT assessment of infract core and penumbra. Stroke. 2006;37:979–85.
44. Murphy B, Fox A, Sahlas D, et al. Identification of penumbra and infarct in acute stroke using CT perfusion derived blood flow and blood volume measurements. Stroke. 2006;37:1771–7.
45. Hopvan J, Ciarallo A, Dowlatshahi D, et al. Certainty of stroke diagnosis: incremental benefit with CT perfusion over non contrast CT and CT angiography. Radiology. 2010;255:142–53.
46. González RG, Schaefer PW, Buonanno FS, et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology. 1999;210:155–62.
47. Barber PA, Darby DG, Desmond PM, et al. Identification of major ischemic change: diffusion-weighted imaging versus computed tomography. Stroke. 1999;30:2059–65.
48. Schellinger PD, Bryan RN, Caplan LR, et al. Evidence based guideline: the role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010;75(2):177–85.

49. Chien D, Kwong KK, Gress DR, et al. MR diffusion imaging of cerebral infarction in humans. AJNR Am J Neuroradiol. 1992;13:1097–102.
50. Mintorovitch J, Yang GY, Shimizu H, et al. Diffusion-weighted magnetic resonance imaging of acute focal cerebral ischemia: comparison of signal intensity with changes in brain water and Na+, K(+)-ATPase activity. J Cereb Blood Flow Metab. 1994;14:332–6.
51. Kucharczyk J, Vexler ZS, Roberts TP, et al. Echo-planar perfusion-sensitive MR imaging of acute cerebral ischemia. Radiology. 1993;188:711–7.
52. Matsumoto K, Lo EH, Pierce AR, et al. Role of vasogenic edema and tissue cavitation in ischemic evolution on diffusion-weighted imaging: comparison with multiparameter MR and immunohistochemistry. AJNR Am J Neuroradiol. 1995;16:1107–15.
53. Gonzalez RG. Clinical MRI of acute ischemic stroke. J Magn Reson Imaging. 2012;36(2): 259–71.
54. Singer OC, Humpich MC, Fiehler J, et al. Risk for symptomatic intracerebral hemorrhage after thrombolysis assessed by diffusion-weighted magnetic resonance imaging. Ann Neurol. 2008;63(1):52–60.
55. Labeyrie MA, Turc G, et al. Diffusion lesion reversal after thrombolysis: a MR correlate of early neurological improvement. Stroke. 2012;43:2986–91.
56. Chemmanam T, Campbell BC, Christensen S, et al. Ischemic diffusion lesion reversal is uncommon and rarely alters perfusion–diffusion mismatch. Neurology. 2010;75(12):1040–7.
57. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508–17.
58. Mishra NK, Davis S, et al. Mismatch-based delayed thrombolysis: a meta-analysis. Stroke;41.
59. Wintermark M, Meuli R, Browaeys P, et al. Comparison of CT perfusion and angiography and MRI in selecting stroke patients for treatment. Neurology. 2007;68:694–7.
60. Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3h after stroke onset in echoplanar imaging thrombolytic evaluation trial (EPITHET): a placebo-controlled randomized trial. Lancet Neurol. 2008;7:299–399.
61. Lansberg MG, Lee J, Christensen S, et al. RAPID automated patient selection for reperfusion therapy. A pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. Stroke. 2011;42:1608–14.
62. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med. 2004;351:2170–8.
63. Newell DW, Aaslid R. Transcranial Doppler: clinical and experimental uses. Cerebrovasc Brain Metab Rev. 1992;4:122–43.
64. Babikian VL, Pochay V, Burdette DE, et al. Transcranial Doppler sonographic monitoring in the intensive care unit. J Intensive Care Med. 1991;6:36–44.
65. Sloan MA, Alexandrov AV, Tegeler CH, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2004;62:1468–81.
66. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus detection by TCD: International Consensus Group on Microembolic Detection. Stroke. 1998;29:725–9.
67. Aaslid R. Transcranial Doppler assessment of cerebral vasospasm. Eur J Ultrasound. 2002; 16:3–10.
68. Lindegaard KF. The role of transcranial Doppler in the management of patients with subarachnoid haemorrhage: a review. Acta Neurochir Suppl. 1999;72:59–71.
69. Grosset DG, Straiton J, McDonald I, Cockburn M, Bullock R. Use of transcranial Doppler sonography to predict development of a delayed ischemic deficit after subarachnoid hemorrhage. J Neurosurg. 1993;78:183–7.
70. Liebeskind DS. Collaterals in acute stroke: beyond the clot. Neuroimaging Clin N Am. 2005;15:553–73.

71. Jo KD, Saver JL, Starkman S, et al. Predictors of recanalization with mechanical thrombectomy for acute ischemic stroke. Stroke;39. Abstract.
72. Liebeskind DS, Nogueira RG. Angiographic scales in acute ischemic stroke: the MERCI/Multi MERCI experience. Stroke. 2008;39.
73. Kim G, Chung C, Ovbiagel B, et al. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. Stroke. 2011;42:693–9.
74. Kidwell C, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013;368:914–23.

Chapter 7
Intra-arterial Thrombolysis in Acute Ischemic Stroke

Vivek Misra and Lee A. Birnbaum

Introduction

Intra-arterial (IA) thrombolysis in acute ischemic stroke was first reported in the early 1980s [1, 2] when endovascular recanalization was performed as a lifesaving measure in patients with acute vertebrobasilar arterial occlusions. Subsequently, investigators also reported the feasibility, technical, and clinical success of IA thrombolysis in acute occlusions within the internal carotid distribution [3, 4]. The availability of newer thrombolytic agents and significant advancements in device technology eventually resulted in rapid expansion of utilization of IA thrombolysis in the management of acute stroke patients with intracranial large artery occlusions. With the evolution of primary and comprehensive stroke centers and the increasing number of patients receiving intravenous thrombolysis, IA thrombolysis remains an important therapeutic modality in patients who may be ineligible for or resistant to recanalization with IV thrombolytics.

V. Misra, M.D. (✉)
Department of Neurology, University of Texas Health Science Center,
8300 Curl Drive, San Antonio, TX 78229, USA
e-mail: misrav@uthscsa.edu

L.A. Birnbaum, M.D., M.S.
Department of Neurology, University of Texas Health Science Center,
8300 Floyd Curl Dr., MSC 7883, San Antonio, TX 78229, USA
e-mail: birnbaum@uthscsa.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_7

Endovascular Recanalization Techniques

Intra-arterial Fibrinolysis

This technique involves infusion of a thrombolytic agent through a microcatheter advanced intracranially into or immediately proximal to the occlusive thrombus. It was the traditional technique utilized before the evolution of mechanical thrombectomy devices. The PROACT II-Prolyse in Acute Cerebral Thromboembolism II trial demonstrated improved outcomes in patients with acute middle cerebral artery occlusions treated with intra-arterial infusion of prourokinase compared to controls when treated within 6 h of onset [5] despite the increased incidence of symptomatic intracranial hemorrhage (ICH). This agent did not receive FDA approval. Numerous other thrombolytic agents including urokinase, reteplase, recombinant tissue plasminogen activator, and tenecteplase have subsequently been used in IAT for acute stroke. It has been suggested that the use of intra-arterial thrombolytics is safe after the administration of IV t-PA [6–9]. There is however no dose equivalence among different thrombolytic agents in terms of safety or efficacy [10, 11].

Aggressive mechanical clot disruption with a microwire has also been utilized safely in conjunction with IA infusion of thrombolytic agents [12, 13]. Intra-arterial injection of thrombolytics alone is becoming less common with the availability of safe and effective dedicated clot retrieval devices.

Mechanical Thrombectomy Devices

Merci Retriever

The Merci retriever (Stryker, Kalamazoo, MI) was approved by FDA in 2004 after demonstrating safety and improved recanalization of intracranial arterial occlusions in the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial [14]. It is a corkscrew-shaped device with helical loops made of nitinol that engage the clot when deployed through a microcatheter. The device and the clot are subsequently pulled out through a balloon guide catheter positioned in the proximal parent artery. Up to six passes with the retriever were permitted to achieve recanalization in the occluded artery. The next generation Merci retrievers [15] showed further improved recanalization rates in the subsequent Multi-MERCI trial. Though this was the first FDA-approved device for mechanical thrombectomy, it did have certain limitations. The location of an occlusive clot in a tortuous arterial segment and with the thrombus extending into the arterial branches negatively impacted recanalization rates and outcomes in M1 occlusions [16]. Furthermore, arteries occluded by fibrin-rich clots had lower recanalization rates with Merci retrievers [17] as well as prolonged

times to reperfusion when compared to arteries with erythrocyte-rich occlusive thrombi. Investigators also demonstrated that up to three passes with the Merci retriever are optimal and further passes are unlikely to achieve recanalization and potentially increase risks of complications [18].

Penumbra System

The Penumbra System (Penumbra, Inc., Alameda, CA) is a suction thrombectomy device that received FDA approval in 2008 for use within 8 h of onset in patients with acute intracranial arterial occlusions following a study demonstrating its feasibility and safety [19]. While there has been no study comparing it to the Merci retriever, it has shown better recanalization rates [20, 21] than those reported in the MERCI trials.

Retrievable Stents (Stent Retrievers)

These are the latest generation mechanical thrombectomy devices that have demonstrated significant improvement in recanalization rates and time to recanalization, when compared to prior devices [22]. There are presently two FDA-approved stent-retriever devices: Solitaire FR (Covidien, Irvine, CA) and Trevo (Stryker, Kalamazoo, MI). Both of these devices showed significantly improved rates of recanalization in randomized trials when compared to the Merci retriever [23, 24] and have become the preferred neurointerventional devices for achieving reperfusion in acute stroke.

Technical Considerations

Pre-procedural Preparation (See Chap. 6)

It is important to review the treatment plan and equipment being used with the support personnel including the anesthesiology team. There is often a delay in obtaining thrombolytic agents and glycoprotein IIB/IIIA agents prepared and delivered from the pharmacy. If the use of these agents is being considered, it is advisable to notify the pharmacy prior to beginning the intervention.

Tool Review (See Chap. 1)

Chemical Thrombolysis

- *Sheath*: A 6-French sheath is generally adequate. You may up-size the sheath to allow continuous intra-arterial blood pressure monitoring if a radial arterial line is not available. A long (35 cm or greater) sheath is recommended given the high incidence of femoroiliac tortuosity and abdominal aortic aneurysms in this patient population.
- *Guiding Catheter*: We generally select a 6-French guiding catheter. A 45° angle (default) or Simmons II (patients with more severe arch angulation) tip catheters are adequate in most cases. A heparinized flush is connected to the guiding catheter via a three-way stopcock and Y adaptor.
- *Access Wires*: A standard hydrophilic 0.035-in. access wire is used to select and catheterize the great vessels. At times a wire with more body such as a 0.035″ stiff Glidewire (Terumo, Somerset, NJ) is useful to access tortuous vessels.
- *Microcatheter*: A 0.010-in. diameter or larger microcatheter is generally used to infuse t-PA once the clot is accessed.
- *Microwire*: A variety of 0.014″ microwires may be used to navigate the intracranial vessels. If vessel selection becomes difficult, the Synchro 14 microwire (Stryker, Kalamazoo, MI) allows excellent 1:1 torque.
- *Thrombolytic/Antiplatelet Agents*:
  - t-PA: Up to 30 mg intra-arterially is typically utilized, with several milligrams administered distal to the clot and several within the clot. The remainder is slowly infused into the proximal 1/3 of the clot. It is important to frequently image the thrombus and to advance the microcatheter as the clot lyses.

Mechanical Devices

- *Sheath*: For most modes of mechanical thrombolysis, an 8- or 9-F sheath is needed. If you anticipate attempting to place an intracranial stent, using a long sheath (90 cm) may provide additional support.
- *Guiding catheter*:
  - *Balloon guide*: These especially design guiding catheters come in 8 and 9F. They have a balloon at the distal tip allowing the operator to produce flow arrest by inflating the balloon in the proximal internal carotid. Attaching a large volume syringe and aspirating while withdrawing the thrombectomy device can then achieve flow reversal. There are currently two products on the market: the Stryker balloon guide (Stryker, Kalamazoo, MI) and the Cello balloon guide (Covidien, Irvine, CA).
  - A Neuron Max Guide (Penumbra, Inc., Alameda, CA): Designed for distal cervical carotid access. This catheter has a 6F OD and 0.088″ ID. It is often used in conjunction with the Penumbra aspiration system (see below).

- *Access wire*: A standard hydrophilic 0.035″ is typically used to select and catheterize the great vessels. It is sometimes easiest to select the target vessel with a diagnostic catheter and use an exchange-length (300 cm) 0.035″ wire to exchange for the guiding catheter. This is especially true when using the balloon guide catheters.
- *Microwire*: As described above, there are a variety of 0.014″ microwires that may be used to access and cross the target clot.
- *Devices*
  - *The Penumbra System*™ (Penumbra, Inc., Alameda, CA) is a mechanical clot disruptor utilizing a reperfusion catheter and a separator wire (optional). The ACE reperfusion catheter is the largest available, and the inner diameter allows higher rates of clot extraction. It is delivered either over a microwire or through the use of a triaxial system (microwire, smaller microcatheter, and ACE catheter). Once the clot is crossed with the microwire, the ACE catheter is positioned at the proximal clot face. The wire and smaller delivery catheter can then be removed and suction is applied to the clot. The clot may be successfully aspirated or "corked" in the distal tip or the ACE with both the clot and the ACE then removed from the body.
  - *Stent retrievers*: These revolutionary devices hold great promise to achieve the "Holy Grail" of endovascular stroke treatment: rapid, complete, and safe reperfusion. They are currently marketed by Covidien Medical (Solitaire) and Stryker Neurovascular (Trevo) and consist of a nitinol, slotted tube, stent attached to a microwire. The Solitaire device comes in 4 mm and 6 mm diameters and 15 mm and 20 mm lengths. It has the unique feature of a longitudinal gap that allows the stent to fold upon itself, potentially creating greater clot engagement. It is delivered through the Marksman microcatheter (Covidien, Irvine, CA). The Trevo device is 4 mm in diameter and 20 mm in length. It has two unique characteristics: a radio-opaque filament within the struts that allows greater visualization and deeper struts potentially allowing greater clot engagement. It is packaged with a dedicated delivery microcatheter. The delivery catheter is positioned across the clot, and the microwire is removed. Next the stent retriever is inserted within the microcatheter and pushed to its distal end. The device is unsheathed while taking care to maintain the stent retriever across the clot. A period of 5 min is allowed to pass, permitting the stent to become fully enmeshed in the clot. The stent retriever is then pulled out of the arterial system. It is recommended that a proximal balloon guide be used in conjunction with these devices and used to achieve flow reversal as described above.

Acute Middle Cerebral Artery Occlusion

Occlusions of the middle cerebral artery (MCA) account for the majority of acute intracranial large artery distribution ischemic strokes. Proximal MCA (M1) occlusions have reported recanalization rates of 30 % within 2 h of IV t-PA [25].

Illustrative Case 1 (MCA Occlusion)

A 50-year-old woman underwent balloon-assist coiling of a ruptured cerebral aneurysm. During the procedure, she developed a right MCA occlusion. With the aid of a microwire, a microcatheter was advanced into the right MCA beyond the clot burden. A Solitaire device was deployed across the clot and resulted in immediate restoration of distal flow. After a 5-min deployment, the Solitaire device was removed while continuously aspirating through the guide catheter with a 60-cm^3 syringe. Subsequent angiographic imaging demonstrated recanalization of the right middle cerebral artery (Fig. 7.1).

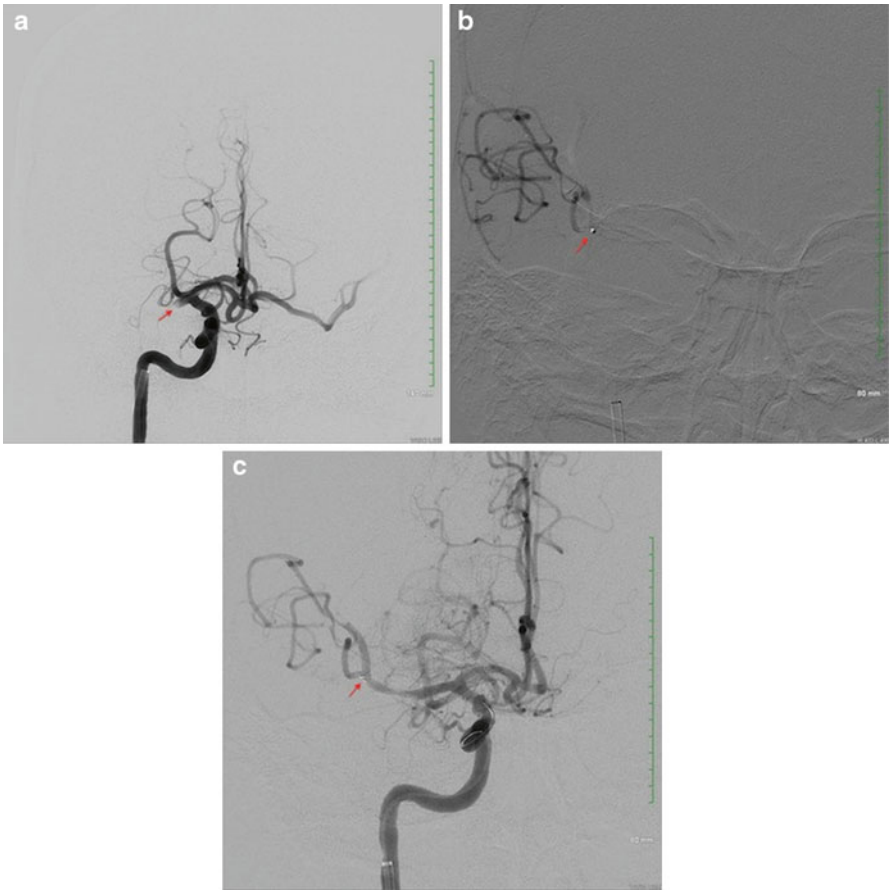

Fig. 7.1 Right MCA thrombectomy. (**a**) Right MCA is occluded at its origin (*arrow*). (**b**) Superselective microcatheter injection demonstrates placement of the microcatheter tip (*arrow*) distal to the clot burden. (**c**) The distal tines (*arrow*) of the stent retriever are seen at the level of the right MCA bifurcation. (**d**) The right MCA remains patent after retrieval of the stent retriever

Acute Vertebrobasilar Occlusion

Vertebrobasilar occlusions account for about 3 % of all acute intracranial large artery strokes [25] with high mortality rates ranging 40–80 % in some studies as well as a high likelihood of poor functional outcome among survivors [26, 27]. Achieving recanalization results in significant reduction in mortality [28]. In one study, the length of the occluded segment and extent of collaterals were independent predictors of survival. Even though the time window for achieving recanalization could be longer in the posterior circulation, one study reported higher recanalization rates if treatment was initiated within 6 h of onset [29].

Illustrative Case 2 (Basilar Occlusion)

A 67-year-old man with a history of hypertension, hyperlipidemia, and diabetes acutely developed dizziness with nausea and vomiting. His neurological exam progressively worsened, and the patient required intubation for altered mental status and respiratory compromise. He underwent a CT angiogram that demonstrated occlusion of the basilar and extracranial left vertebral arteries. The patient underwent a cerebral angiogram that confirmed basilar thrombosis. A 6-French guiding catheter was advanced into the right vertebral artery. With the aid of a microwire, a microcatheter was successfully navigated through the basilar thrombosis. Distal positioning of the microcatheter tip was confirmed with a superselective injection. A Solitaire device was then successfully deployed across the basilar thrombus and immediately improved flow. After a 5-min deployment, the Solitaire device was removed. Subsequent imaging demonstrated patency of the basilar artery with an unintended branch occlusion of the right posterior inferior cerebellar artery (Fig. 7.2).

Carotid-T Occlusions

Terminal internal carotid artery (ICA) occlusions with the thrombus extending into the origin of ipsilateral A1 and M1 segments are associated with high clot burden, poor collateral flow, and poor outcomes. Earlier studies investigating intra-arterial infusion of thrombolytic agents reported poor recanalization and unfavorable outcomes in carotid-T occlusions [30, 31]. A recent study reported significant improvement in recanalization rates with mechanical thrombectomy using Solitaire in patients with ICA-T occlusions without any additional increase in symptomatic intracranial hemorrhage [32].

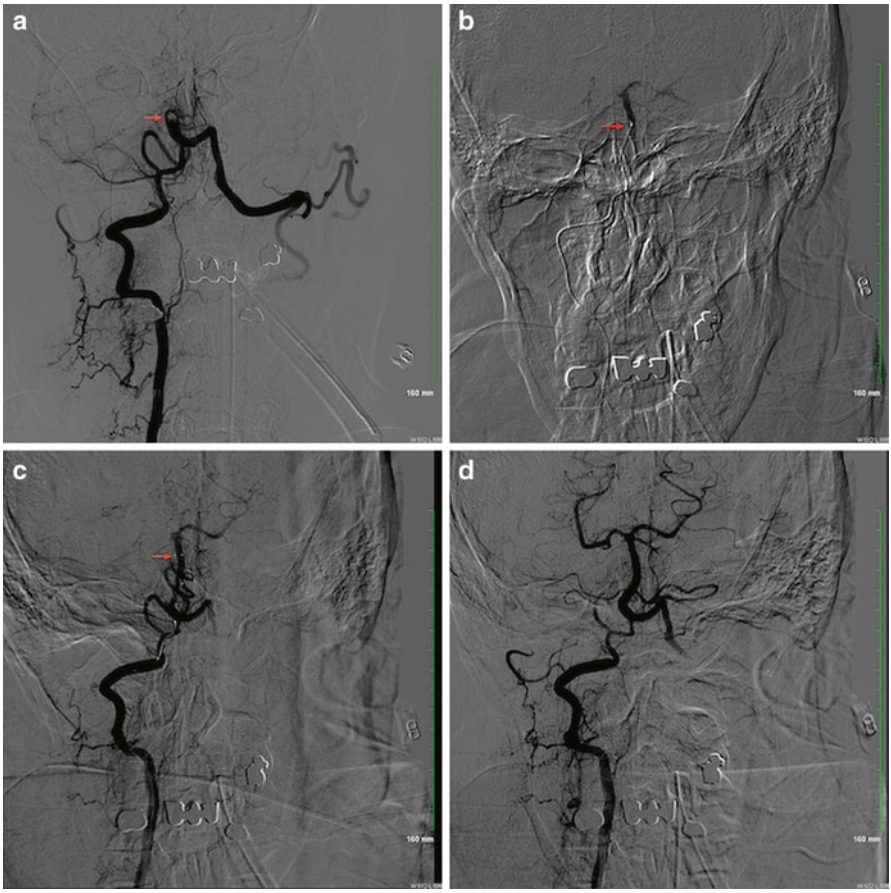

Fig. 7.2 Basilar artery thrombectomy. (**a**) Complete occlusion of the basilar artery is seen at the level of AICA (*arrow*). (**b**) Super-selective microcatheter injection demonstrates placement of the microcatheter tip (*arrow*) distal to the clot burden. (**c**) The distal tines (*arrow*) of the stent retriever are seen at the level of the distal basilar artery. (**d**) The basilar artery remains patent after retrieval of the stent retriever

Illustrative Case 3 (Carotid-T Occlusion)

A 42-year-old man with recently diagnosed renal infarct presented with the acute onset of aphasia and right-sided weakness. He was administered IV thrombolytics and his symptoms transiently improved but then returned. CT angiogram and perfusion studies were performed that demonstrated a left intracranial ICA occlusion with significant penumbra in the left hemisphere. A cerebral angiogram was then performed which demonstrated a left carotid-T occlusion with no flow beyond the posterior communicating artery segment. A Penumbra reperfusion catheter was advanced into the occluded intracranial carotid, and a thrombectomy was

performed with continuous aspiration and a separator wire. After recanalization of the left ICA, the reperfusion catheter was advanced into the distal left MCA, and an additional thrombectomy was performed with continuous aspiration and a separator wire. Subsequent angiographic imaging from the guide sheath demonstrated recanalization of the left MCA. There was unintended branch occlusion of the ipsilateral anterior cerebral artery that resolved spontaneously. The stroke evaluation also included an echocardiogram that demonstrated severe stenosis of the aortic valve with left atrial enlargement secondary to childhood rheumatic heart disease (Fig. 7.3).

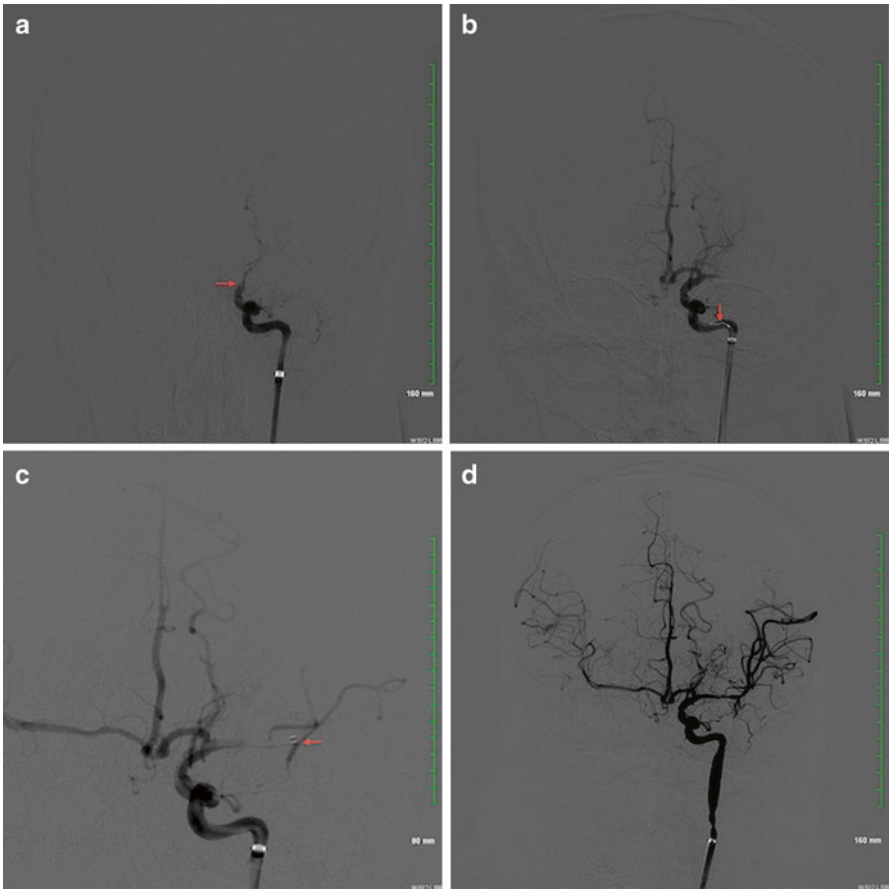

Fig. 7.3 Carotid-terminus thrombectomy. (**a**) Complete occlusion of the left ICA is seen at the level of the posterior communicating artery segment (*arrow*). (**b**) The left ICA is recanalized with the aid of the separator wire (*arrow*) and reperfusion catheter. (**c**) The reperfusion catheter (*arrow*) is advanced into the occluded left MCA and aspiration is performed. (**d**) The left MCA remains patent after removal of the reperfusion catheter

Tandem ICA/MCA Occlusions

Occlusions of cervical ICA and ipsilateral MCA comprise about 7 % of all acute intracranial large artery ischemic strokes [25]. Tandem ICA/MCA occlusions are associated with poor outcomes after intravenous thrombolysis [33]. Revascularization of the proximal ICA with stent placement and angioplasty followed by mechanical thrombectomy to achieve recanalization of the intracranial arterial occlusion has been demonstrated as safe and feasible with reported good recanalization rates and functional outcomes [34–36]. This technique has also been reported to be safe and feasible in tandem ICA/MCA occlusions in the setting of acute ICA dissection [37].

Illustrative Case 4 (Tandem ICA/MCA Occlusion)

A 52-year-old man without significant past medical history acutely developed vision loss in the right eye and left hemiparesis. He received intravenous thrombolytics in the emergency room, but his deficits persisted. A subsequent cerebral angiogram demonstrated a flame-shaped taper of the right ICA most consistent with a dissection. A Penumbra reperfusion catheter was successfully navigated distal to the carotid dissection. Subsequent super-selective angiographic imaging demonstrated complete occlusion of the right MCA at its origin. A carotid stent was deployed across the dissected segment of the cervical ICA. We did not administer heparin or antiplatelet agents since IV thrombolytics had been administered. A Penumbra reperfusion catheter was then advanced into the right MCA, and the thrombectomy was performed with continuous aspiration and a separator wire (Fig. 7.4).

Acute Large Artery Occlusion in Anticoagulated Patients

Patients with acute ischemic stroke receiving coumadin (with INR > 1.7) or newer anticoagulants are considered ineligible for IV thrombolysis due to perceived risks of ICH. Case series have reported safety and feasibility of IAT in patients receiving therapeutic doses of anticoagulants [38, 39]. The American Heart Association/American Stroke Association (AHA/ASA) guidelines also recently suggested endovascular therapies as a reasonable approach to treat patients with acute large artery occlusions in whom IV thrombolysis is contraindicated [40].

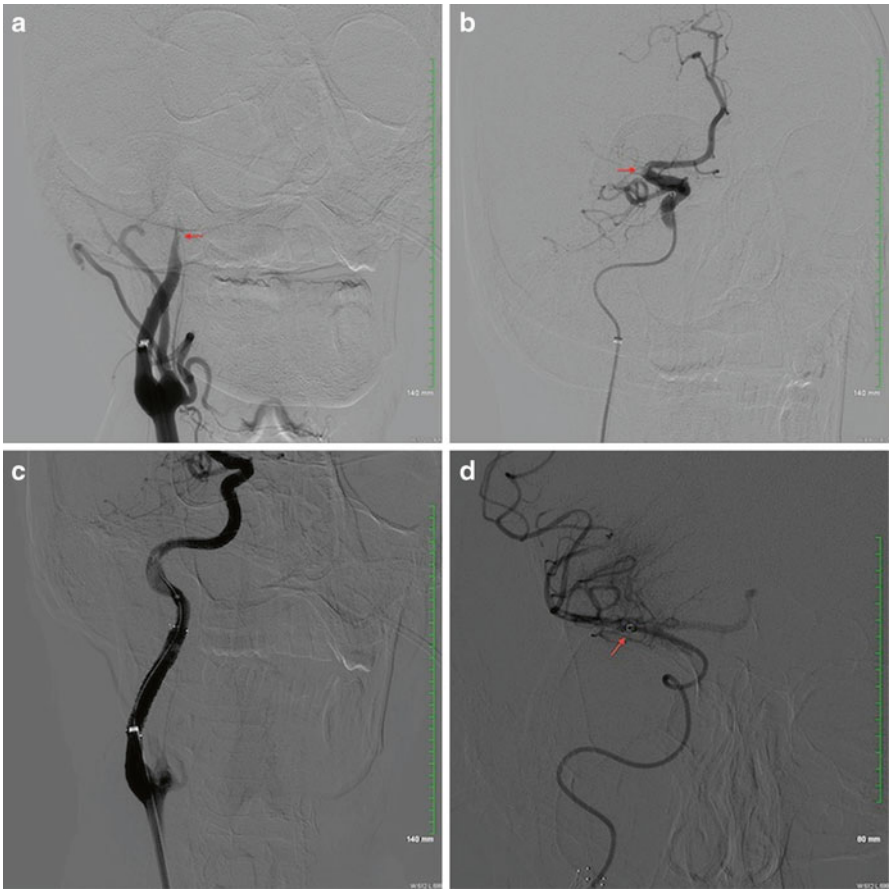

Fig. 7.4 Endovascular treatment for tandem occlusion—carotid artery stenting followed by MCA thrombectomy. (**a**) The cervical right ICA demonstrates a flame-shaped taper (*arrow*) consistent with a dissection. (**b**) Super-selective angiogram distal to the carotid dissection demonstrates occlusion of the right MCA (*arrow*). (**c**) Successful deployment of a carotid stent across the dissection results in recanalization of the right ICA. (**d**) The reperfusion catheter (*arrow*) is successfully advanced into the right MCA for thrombectomy

Complications Associated with IAT in Ischemic Stroke (See Chap. 3)

Certain complications such as arterial dissections/perforations, contrast-induced renal dysfunction, and groin hematomas can occur in any endovascular procedure. However intracranial hemorrhage occurring post-procedure is specifically associated with IA thrombolysis for ischemic stroke. Earlier studies reported an incidence of

ICH on follow-up CT scans in almost 50 % patients following IA thrombolysis [41]. However majority of these patients (43 %) had an asymptomatic ICH that was considered a marker of reperfusion and did not adversely affect outcomes. The recently concluded IMS-III and MR RESCUE trials [42, 43] reported rates of symptomatic ICH in the range of 4–6.2 % indicating that IA thrombolysis can be performed safely. Reducing the number of microcatheter contrast injections during the procedure has been suggested as a way to reduce the risk of hemorrhagic conversion [44].

Periprocedural Management (See Chap. 3)

The role of general anesthesia (GA) and intubation pre-procedure is controversial. In one retrospective study, poorer neurologic outcomes and higher mortality were noted in patients receiving GA when compared to conscious sedation [45]. It has been postulated that treatment delays associated with intubation and blood pressure changes associated with induction of GA could be factors affecting overall prognosis. Many centers therefore prefer conscious sedation whenever possible to minimize delays in therapy. Patients should be observed closely in an intensive care unit with close attention to the neurologic as well as hemodynamic monitoring following protocols similar to post-IVT.

Conclusions

As evident from the results of recently concluded clinical trials [42, 43], avoiding delays, achieving rapid recanalization, and identifying patient subgroups (see Chap. 6) that will benefit from IA thrombolysis are the key to optimizing outcomes.

References

1. Nenci GG, Gresele P, Taramelli M, Agnelli G, Signorini E. Thrombolytic therapy for thromboembolism of vertebrobasilar artery. Angiology. 1983;34(9):561–71.
2. Brückmann H, Ferbert A, del Zoppo GJ, Hacke W, Zeumer H. Acute vertebral-basilar thrombosis. Angiologic-clinical comparison and therapeutic implications. Acta Radiol Suppl. 1986;369:38–42.
3. del Zoppo GJ, Ferbert A, Otis S, Brückmann H, Hacke W, Zyroff J, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke. A pilot study. Stroke. 1988;19(3):307–13.
4. Theron J, Courtheoux P, Casasco A, Alachkar F, Notari F, Ganem F, et al. Local intraarterial fibrinolysis in the carotid territory. AJNR Am J Neuroradiol. 1989;10(4):753–65.
5. 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.

6. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr RW, Paras VH, et al. Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. Stroke. 2002;33(7):1821–6.
7. Lee KY, Kim DI, Kim SH, Lee SI, Chung HW, Shim YW, et al. Sequential combination of intravenous recombinant tissue plasminogen activator and intra-arterial urokinase in acute ischemic stroke. AJNR Am J Neuroradiol. 2004;25(9):1470–5.
8. Shaltoni HM, Albright KC, Gonzales NR, Weir RU, Khaja AM, Sugg RM, et al. Is intra-arterial thrombolysis safe after full-dose intravenous recombinant tissue plasminogen activator for acute ischemic stroke? Stroke. 2007;38(1):80–4.
9. Misra V, El Khoury R, Arora R, Chen PR, Suzuki S, Harun N, et al. Safety of high doses of urokinase and reteplase for acute ischemic stroke. AJNR Am J Neuroradiol. 2011;32(6):998–1001.
10. Eckert B, Kucinski T, Neumaier-Probst E, Fiehler J, Röther J, Zeumer H. Local intra-arterial fibrinolysis in acute hemispheric stroke: effect of occlusion type and fibrinolytic agent on recanalization success and neurological outcome. Cerebrovasc Dis. 2003;15(4):258–63.
11. Sugg RM, Noser EA, Shaltoni HM, Gonzales NR, Campbell MS, Weir R, et al. Intra-arterial reteplase compared to urokinase for thrombolytic recanalization in acute ischemic stroke. AJNR Am J Neuroradiol. 2006;27(4):769–73.
12. Qureshi AI, Siddiqui AM, Suri MF, 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):1319–27. discussion 1327–9.
13. Yoon W, Park MS, Cho KH. Low-dose intra-arterial urokinase and aggressive mechanical clot disruption for acute ischemic stroke after failure of intravenous thrombolysis. AJNR Am J Neuroradiol. 2010;31(1):161–4.
14. 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. 2005; 36(7):1432–8.
15. 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.
16. Zhu L, Liebeskind DS, Jahan R, Starkman S, Salamon N, Duckwiler G, et al. Thrombus branching and vessel curvature are important determinants of middle cerebral artery trunk recanalization with Merci thrombectomy devices. Stroke. 2012;43(3):787–92.
17. Yuki I, Kan I, Vinters HV, Kim RH, Golshan A, Vinuela FA, et al. The impact of thromboemboli histology on the performance of a mechanical thrombectomy device. AJNR Am J Neuroradiol. 2012;33(4):643–8.
18. Loh Y, Jahan R, McArthur DL, Shi ZS, Gonzalez NR, Duckwiler GR, et al. Recanalization rates decrease with increasing thrombectomy attempts. AJNR Am J Neuroradiol. 2010; 31(5):935–9.
19. 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. AJNR Am J Neuroradiol. 2008;29(7):1409–13.
20. 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(8):2761–8.
21. Almekhlafi MA, Menon BK, Freiheit EA, Demchuk AM, Goyal M. A meta-analysis of observational intra-arterial stroke therapy studies using the merci device, penumbra system, and retrievable stents. AJNR Am J Neuroradiol. 2013;34(1):140–5.
22. Broussalis E, Trinka E, Hitzl W, Wallner A, Chroust V, Killer-Oberpfalzer M. Comparison of stent-retriever devices versus the merci retriever for endovascular treatment of acute stroke. AJNR Am J Neuroradiol. 2013;34(2):366–72.
23. 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.

24. 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.
25. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38(3):948–54.
26. Schonewille WJ, Algra A, Serena J, Molina C, Kappelle LJ. Outcome in patients with basilar artery occlusion treated conventionally. J Neurol Neurosurg Psychiatry. 2005;76(9):1238–41.
27. Hacke W, Zeumer H, Ferbert A, Brückmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. Stroke. 1988;19(10):1216–22.
28. Brandt T, von Kummer R, Müller-Küppers M, Hacke W. Thrombolytic therapy of acute basilar artery occlusion. Variables affecting recanalization and outcome. Stroke. 1996;27(5):875–81.
29. Arnold M, Nedeltchev K, Schroth G, Baumgartner RW, Remonda L, Loher TJ, et al. Clinical and radiological predictors of recanalisation and outcome of 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. J Neurol Neurosurg Psychiatry. 2004;75(6):857–62.
30. Urbach H, Ries F, Ostertun B, Solymosi L. Local intra-arterial fibrinolysis in thromboembolic "T" occlusions of the internal carotid artery. Neuroradiology. 1997;39(2):105–10.
31. Arnold M, Nedeltchev K, Mattle HP, Loher TJ, Stepper F, Schroth G, et al. Intra-arterial thrombolysis in 24 consecutive patients with internal carotid artery T occlusions. J Neurol Neurosurg Psychiatry. 2003;74(6):739–42.
32. Möhlenbruch M, Seifert M, Okulla T, Wüllner U, Hadizadeh DR, Nelles M, et al. Mechanical thrombectomy compared to local-intraarterial thrombolysis in carotid T and middle cerebral artery occlusions: a single center experience. Clin Neuroradiol. 2012;22(2):141–7.
33. 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.
34. Ozdemir O, Bussière M, Leung A, Gulka I, Lee D, Chan R, et al. Intra-arterial thrombolysis of occluded middle cerebral artery by use of collateral pathways in patients with tandem cervical carotid artery/middle cerebral artery occlusion. AJNR Am J Neuroradiol. 2008;29(8):1596–600.
35. Malik AM, Vora NA, Lin R, Zaidi SF, Aleu A, Jankowitz BT, et al. Endovascular treatment of tandem extracranial/intracranial anterior circulation occlusions: preliminary single-center experience. Stroke. 2011;42(6):1653–7.
36. 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.
37. Lavalleé PC, Mazighi M, Saint-Maurice JP, Meseguer E, Abboud H, Klein IF, et al. Stent-assisted endovascular thrombolysis versus intravenous thrombolysis in internal carotid artery dissection with tandem internal carotid and middle cerebral artery occlusion. Stroke. 2007; 38(8):2270–4.
38. Linfante I, Reddy AS, Andreone V, Caplan LR, Selim M, Hirsch JA. Intra-arterial thrombolysis in patients treated with warfarin. Cerebrovasc Dis. 2005;19(2):133–5.
39. Janjua N, Alkawi A, Georgiadis A, Suri MF, Ibrahim MS, Kirmani JF, et al. Feasibility of IA thrombolysis for acute ischemic stroke among anticoagulated patients. Neurocrit Care. 2007; 7(2):152–5.
40. Jauch EC, Saver JL, Adams Jr HP, 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.
41. IMS Study Investigators. Hemorrhage in the interventional management of stroke study. Stroke. 2006;37(3):847–51.

42. 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.
43. 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.
44. Khatri P, Broderick JP, Khoury JC, Carrozzella JA, Tomsick TA, IMS I and II Investigators. Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk. Stroke. 2008;39(12):3283–7.
45. Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. Stroke. 2010;41(6):1175–9.

Chapter 8
Endovascular Treatment of Cerebral Sinus Thrombosis

Randall C. Edgell, Mohammad Wasay, Doniel Drazin, Sonal Mehta, and Afshin Borhani-Haghighi

Introduction

Cerebral venous thrombosis was first recognized in 1825 by Ribes, who described the autopsy of a patient with sagittal sinus thrombosis [1]. It is an infrequent form of stroke, accounting for 0.5 % of all cases, but is increasingly recognized [2]. Certain populations may be at especially high risk, with rates as high as 20 % in young, Asian women [3, 4]. Finally, there is increasing diagnosis of CVT in children [5].

R.C. Edgell, M.D. (✉) • S. Mehta, M.D.
Department of Neurology and Psychiatry, Saint Louis University,
1438 S. Grand Blvd, Saint Louis, MO 63104, USA
e-mail: redgell@slu.edu

M. Wasay, M.B.B.S., M.D., F.R.C.P.
Department of Neurology, Aga Khan University, Stadium Road, Karachi 74800, Pakistan
e-mail: mohammad.wasay@aku.edu

D. Drazin, M.D., M.A.
Department of Neurosurgery, Cedar Sinai Medical Center,
Advanced Health Sciences Pavilion, 127 S. San Vicente Blvd, Suite A-6600, Los Angeles, CA 90048, USA
e-mail: ddrazin@gmail.com

A. Borhani-Haghighi, M.D.
Clinical Neurology Research Center, Shiraz University of Medical Sciences,
Motahhari Clinic, Nemazee Square, Shiraz 71847, Iran
e-mail: aborhani@sums.ac.ir

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_8

Anatomy/Pathophysiology (See Chap. 2)

CVT can affect three types of cerebral venous structures: the dural sinuses, the cortical veins, and the deep cerebral veins. The sagittal (60–75 %) and lateral sinuses (70–85 %) are involved more frequently than the deep venous system. In about 75 % of cases, multiple veins or sinuses were affected [6]. The location of venous thrombosis is an important factor because deep cerebral and cerebellar vein thrombosis is associated with a higher mortality than thrombosis of superficial veins [7].

The exact trigger for CVT is usually unknown, but factors such as dehydration, hypercoagulable states, and inflammation—either local or systemic—are consistently associated. Infection is one of the most commonly seen inflammatory states [8] (Table 8.1).

Occlusion of the cerebral veins causes localized edema and venous infarction. Microscopic examination shows enlarged, swollen veins, edema, ischemic neuronal damage, and petechial hemorrhages. These petechial hemorrhages can merge to become large hematomas. Both cytotoxic (cellular swelling in the setting of apoptosis) and vasogenic (blood-brain barrier breakdown and extravascular extravasation of fluid) edemas occur [9].

A second, less dramatic cause of clinical symptoms in CVT is increased intracranial pressure (ICP). This is generally caused by isolated or predominant dural sinus thrombosis. Thrombus in this location leads to poor CSF drainage and absorption by the arachnoid granulations. A combination of these two mechanisms is often present in the most severe cases [10].

Table 8.1 Risk factors for cerebral venous thrombosis

Pregnancy
Puerperium
Infection related
Direct septic trauma
Cerebral abscess
Subdural empyema
Meningitis
Tuberculous meningitis
Otitis media
Orbital cellulitis
Tonsillitis
Dental infections
Stomatitis
Cellulitis
Septicemia
Pulmonary tuberculosis
Endocarditis
Measles

Table 8.1 (continued)

Hepatitis
Herpes simplex
Varicella zoster
Cytomegalovirus
HIV
Malaria
Trichinosis
Toxoplasmosis
Aspergillosis
Cryptococcosis
Hypercoagulable disorders
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden mutation
Prothrombin gene mutation
Homocystinemia/homocystinuria
Essential thrombocythemia
Primary polycythemia
Plasminogen deficiency
Tissue plasminogen deficiency
Elevated plasminogen activator inhibitor-1
Dysfibrinogenemia
Heparin-induced thrombocytopenia (HIT)
Increased factor VIIIc
Medication related
Oral contraceptive pills
Androgens
Antiestrogen therapy
Antineoplastic agents: cisplatin, L-asparaginase
Sildenafil
Carbamazepine
Malignancy
Squamous cell metabolic cervical cancer
Non-Hodgkin's lymphoma
Bilateral glomus tumors
Colorectal cancer
Epidermoid carcinoma of tongue
Dysgerminoma
Ewing's sarcoma
Allogenic transplant for acute lymphoblastic leukemia
Paraneoplastic syndrome
Meningioma
Rheumatologic disease
Behcet's disease

Table 8.1 (continued)

Antiphospholipid antibody syndrome
Systemic lupus erythematosus
Wegener's granulomatosis
Churg–Strauss syndrome
Other conditions
Nephrotic syndrome
Paroxysmal nocturnal hemoglobinuria
Iron deficiency anemia
Sickle cell anemia
Inflammatory bowel disease
Trauma
Lumbar puncture
Endocrine disorders: diabetes, thyroid disease
Renal allograft
Dehydration
Anemia
Prolonged airline flights

Clinical Presentation

Consistent with the variations in the underlying pathophysiology, clinical presentations also vary significantly, depending of the type and extent of venous thrombosis. This variability makes diagnosis, at times, challenging. There are three large categories of clinical features [11]:

- Headache with/without papilledema: headache is by far the most common symptom in CVT, occurring in 90 % of cases. It may occur suddenly, but more commonly is gradual in onset. The triad of headache, vomiting, and papilledema occurs in only 20–40 % of CVT patients, but is the most consistently identified clinical pattern.
- Focal brain irritation/injury: focal neurologic signs, including sensory and motor deficits, aphasia, or hemianopia, develop in 40–60 % of patients with CVT. Seizures occur in about 40 % of patients. Seizures may be focal or generalized. Status epilepticus is one of the more damaging manifestations of CVT.
- Obtundation/coma: found in 15–19 % of patients at presentation. These signs are usually seen in patients with extensive thrombosis of the deep venous system and bilateral thalamic involvement or with generalized seizures. This presentation can also be seen in patients with large unilateral lesions causing mass effect and herniation. Coma at presentation is the strongest predictor of poor outcome in CVT [10, 12].

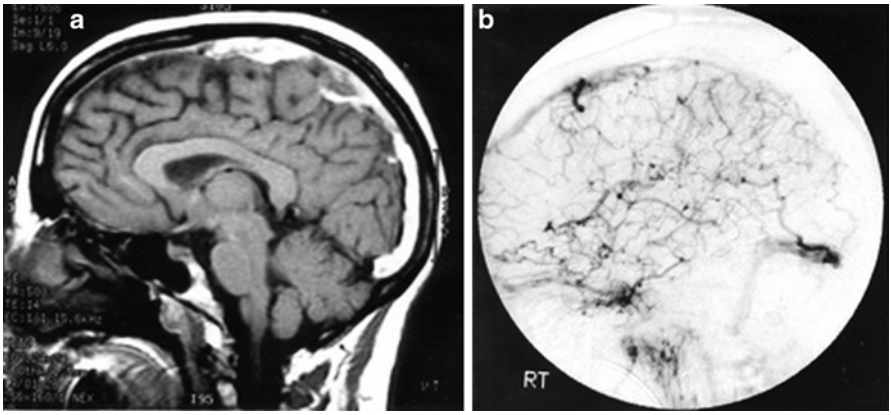

Fig. 8.1 (**a**) Gadolinium-enhanced sagittal MRI showing thrombus within the superior sagittal sinus (SSS). (**b**) Lateral projection cerebral angiogram confirming SSS thrombosis and demonstrating the collateral venous drainage patterns

Radiological Features

The most commonly utilized neuroimaging studies, non-contrast head CT and MRI, may be normal in CVT patients. Hyperdensity of the dural sinuses may be detected by the meticulous neuroimager but is only 25 % sensitive for this condition [13]. The famous "empty delta" sign is seen on contrast CT or MRI. An axial or coronal image through the torcular Herophili or superior sagittal sinus will show the triangular enhancement of the dural walls, but no contrast enhancement within the lumen due to clot. However, even this sign is only found in 30 % of CVT [14]. For this reason, venography is crucial to rule out CVT. MR venography and CT venography are both effective tools to image the dural sinuses, but are less sensitive for cortical vein and deep vein thrombosis. The sensitivity may be increased with catheter angiography, but must be accompanied by a high index of suspicion on the part of the angiographer. Catheter angiography also has the advantage of providing a dynamic assessment of venous flow/flow restriction [15] (Fig. 8.1).

Medical and Surgical Management

Once CVT has been diagnosed, the first line of therapy should include aggressive hydration and anticoagulation. The evidence base for anticoagulation in the setting of CVT is not deep, but the two published, prospective, randomized trials point to its benefit [16, 17]. A meta-analysis showed over 50 % reduction in death and disability compared to placebo [18]. It is important to emphasize that anticoagulation appears effective even in the setting of intracerebral hemorrhage (ICH).

Both unfractionated (UFH) and low molecular weight heparin (LMWH) have been used to achieve anticoagulation in the acute setting [16, 17]. UFH has the advantage of rapid normalization of coagulation parameters once the intravenous drip is turned off LMWH, on the other hand, maintains a more consistent therapeutic effect. In a mildly affected patient (i.e., headache and papilledema), LMWH may be relied upon. However, in the unstable or deteriorating patient, UFH should be utilized. This is especially true in the setting of ICH where hematoma expansion would necessitate prompt cessation of the anticoagulant effect. Although clinical trial evidence is lacking, it is common practice to transition from UFH or LMWH to oral anticoagulation once clinical stabilization/improvement is noted. The duration of oral agent use can be tailored to the particular patient. Typically, it is maintained until clot resolution is visualized on follow-up imaging (3–6 months). In patients with ongoing risk (e.g., a hypercoagulable condition), lifetime treatment may be required [19].

Seizure prophylaxis in CVT patients is somewhat controversial, but should be considered when significant cortical edema or hemorrhage has occurred [20]. Once seizures have occurred, however, initiation of an antiepileptic agent (AED) is universally recommended [21]. Status epilepticus is a not uncommon and particularly deadly manifestation of CVT and requires the use of intravenous agents. Fosphenytoin and levetiracetam are effective agents with good side effect profiles. It is reasonable to continue oral AED treatment for up to 1 year to prevent delayed seizure activity.

Surgical therapies are also effective and at times life saving in CVT. Extraventricular drain (EVD) placement is particularly effective in patients with a predominant involvement of the dural sinuses and impaired CSF drainage due to venous hypertension and obstruction of the arachnoid granulations by clot. In patients with significant preexisting parenchymal injury and/or a herniation syndrome, however, EVD placement is generally not helpful [22]. However, decompressive surgery (i.e., hemicraniectomy) does appear to be effective in preventing death under these dire circumstances. Such surgeries may also reduce long-term disability [23, 24].

Endovascular Treatment

Patient Selection

Due to the low incidence of CVT and high rate of favorable outcomes following medical therapy alone, endovascular therapy's role has taken only incremental steps forward over time. Current indications include:

- Progression of neurological deficits despite therapeutic anticoagulation: the failure of medical management in this setting has been defined using various criteria. A progression of neurological symptoms despite therapeutic anticoagulation

is one common definition. Some authors feel that the neurological deterioration must be severe or even life threatening in nature to justify this approach. However, if neurological damage is allowed to occur, these patients may be too profoundly affected to respond successfully to recanalization [25].

- Intracranial hypertension refractory to first-line treatment: in refractory patients, rapid recanalization using endovascular techniques may be beneficial in lowering ICP before irreversible vision loss occurs.
- Involvement of deep cerebral veins: as mentioned above, there is an emerging belief that delayed intervention reduces the chance of favorable recovery due to already irreversible neurological injury. This is especially true when the deep cerebral veins are involved due to the delicate nature of their adjacent structures (e.g., thalami and brainstem). Two studies identified involvement of deep cerebral veins as a predictor of poor outcome suggesting that earlier, more aggressive treatment may be justified in this population [10, 11].

Tool Review (See Chap. 1)

- *Sheath*: A 6- or 7-F venous sheath is generally recommended. A 4–6F arterial sheath is also utilized (the larger sizes allow continuous blood pressure monitoring if needed). The authors favor a 90-cm guide sheath on the venous side to allow maximum support to subsequently used devices.
- *Guiding catheter*: We generally select a 6-F, 100-cm guiding catheter, with a 45-degree angled tip. It can be used in conjunction with a 35-cm sheath or at times through a 90-cm guiding sheath to provide extra support.
- *Access wires*: A stiff hydrophilic 0.035″ Glidewire (Terumo, Somerset, NJ) is used to select and catheterize the internal jugular vein. A stiffer wire is more effective in crossing the valves of the internal jugular vein.
- *Microcatheter*: A 0.010-in. or larger microcatheter is generally used to infuse tPA once the clot is accessed. The Penumbra System™ (Penumbra, Inc., Alameda, CA) is a mechanical clot disruptor utilizing a reperfusion catheter and a separator wire (optional). The ACE reperfusion catheter is the largest available in the Penumbra System; the large inner diameter allows higher rates of clot extraction. It is delivered either over a microwire or through the use of a triaxial system (microwire, smaller microcatheter, and ACE catheter). Once the clot is crossed with the microwire, the ACE catheter is positioned at the proximal clot face. The wire and smaller delivery catheter can then be removed, and suction is applied to the clot. The clot may be successfully aspirated or “corked” in the distal tip or the ACE with both the clot and the ACE then removed from the body.
- *Microwire*: A variety of 0.014 microwires may be used to navigate the intracranial vessels. Larger wires up to 0.035 in. may assist in navigating the larger catheters, such as the ACE, across a clot.

- *Thrombolytic/antiplatelet agents*:
  - *tPA*: There is a great variation in the technique used to administer tPA in the setting of CVT. Generally a bolus dose (based on clot length—1 mg/1 cm of clot, or simply 10 mg) is administered along the length of the clot. This is followed by a prolonged infusion ranging from a total of 50 mg up to 100 mg/day for several days [26–28].
  - *Urokinase*: While favored in the early application of catheter thrombolysis to CVT, this agent has largely fallen out of use in intracranial thrombolysis.
- *Mechanical devices*:
  - Balloons: A variety of compliant over-the-wire balloons have been utilized in the treatment of CVT, as have off-label semi-compliant coronary and peripheral vascular balloons. The dural sinuses are robust structures and able to withstand such techniques. However, care must be taken to avoid smaller venous channels [29].
  - Stent retrievers: Consist of a nitinol, slotted tube, stent attached to a microwire. The Solitaire device (Covidien, Irvine, CA) comes in a 4-mm and 6-mm-diameter and 15-mm to 30-mm lengths. It has the unique feature of a longitudinal slice that allows the stent to be folded upon itself, potentially creating greater clot engagement. It is delivered through the Marksman microcatheter (Covidien, Irvine, CA). The Trevo device (Stryker, Kalamazoo, MI) is 4 mm in diameter and 20 mm in length. It has two unique characteristics: a radio-opaque filament within the struts that allows greater visualization and deeper struts, potentially allowing greater clot engagement. It is packaged with a dedicated delivery microcatheter. The delivery catheter is positioned across the clot, and the microwire is removed. Next the stent retriever is inserted within the microcatheter and pushed to its distal end. The device is unsheathed while taking care to maintain the stent retriever across the clot. A period of 5 min is allowed to pass, permitting the stent to become fully enmeshed in the clot. The stent retriever is then pulled out of the arterial system. The diameter of the dural sinuses typically exceeds 6 mm, making even the largest Solitaire device a bit undersized. However, significant mechanical disruption can be achieved [30].

Procedural Steps

Arterial access is obtained and an arterial angiogram is performed to identify the site of occlusion within the cerebral veins and to characterize alternate venous drainage pathways. It is important to attach the diagnostic catheter to heparinized flush if it will be maintained in place during the thrombolysis procedure. The use of therapeutic systemic heparinization varies among practitioners.

A 6- or 7-F, 90-cm venous guiding sheath is favored by the authors for the therapeutic portion of the procedure. This is due to the greater support a sheath

provides during the sometimes-difficult navigation across an organized thrombus. Other practitioners routinely use a guiding catheter, however. The sheath is introduced over a 0.035-in. stiff guidewire and angle-tipped catheter into the common femoral and iliac veins and subsequently advanced through the inferior vena cava, right atrium, and superior vena cava under fluoroscopic guidance. The guide sheath is advanced into the brachiocephalic vein and internal jugular vein. Arterial injections with delayed venous roadmap imaging of the internal jugular veins may be necessary to identify their origins and anatomical configuration. With the guiding sheath in the internal jugular vein, there are a number of strategies that can be employed:

- *Lytic infusion*: A microcatheter is advanced over a microwire under roadmap guidance. The microcatheter is guided to the site of the occlusion. The thrombus is crossed with the microwire utilizing a rotating motion. The microcatheter is then advanced over the wire. Care must be taken to remain in the main channel of the dural sinus. Microcatheter venography will help confirm that the microcatheter is in the desired location. The lytic agent, most commonly tPA, can be delivered at an interval along the length of the clot if desired. An infusion pump is then attached to the microcatheter and lytic agent is slowly infused over the desired time window.
- *Mechanical disruption*:
  - *Wire maceration*: It is possible to use a shaped 0.014- or 0.035-in. wire to fragment the clot to a limited extent. However, this technique alone is rarely successful in the large dural sinuses.
  - *Angioplasty*: Coronary and peripheral vascular over-the-wire balloons have been used to disrupt large clots and potentiate thrombolysis. The use of these devices should be limited to the large dural sinuses in order to avoid vessel rupture.
  - *Stent retrievers*: These relatively new devices have also been used with some success to disrupt large volume thrombi and allow suction thrombectomy or potentiate thrombolytics.
- *Suction thrombectomy*: Until recently, the ability to suction thrombus out of the large dural sinuses has been limited. One limiting factor was the relative stiffness of the existing peripheral vascular rheolytic catheters (e.g., AngioJet, Possis Medical, Minneapolis, MN). The more flexible catheters designed for arterial thrombectomy lacked a sufficiently large inner diameter to ingest the large clots present in the dural sinuses. With the introduction of up to 0.060-in. inner diameter, highly flexible, suction catheters (e.g., ACE catheter, Penumbra Inc., Alameda, CA), there is great potential for improved speed and safety through the use of direct thrombus aspiration. The ACE catheter along with a 3MAX (Penumbra, Inc; Alameda, CA) telescoped catheter and 0.014-in. microwire (ADAPT technique) are used to access the clot. The microwire and 3MAX devices are removed once the ACE catheter is at the clot face. Either manual or mechanical suction is then applied. The clot is either ingested into the catheter or "corked" at the tip. If corking occurs, both the ACE and clot are removed as a unit [31].

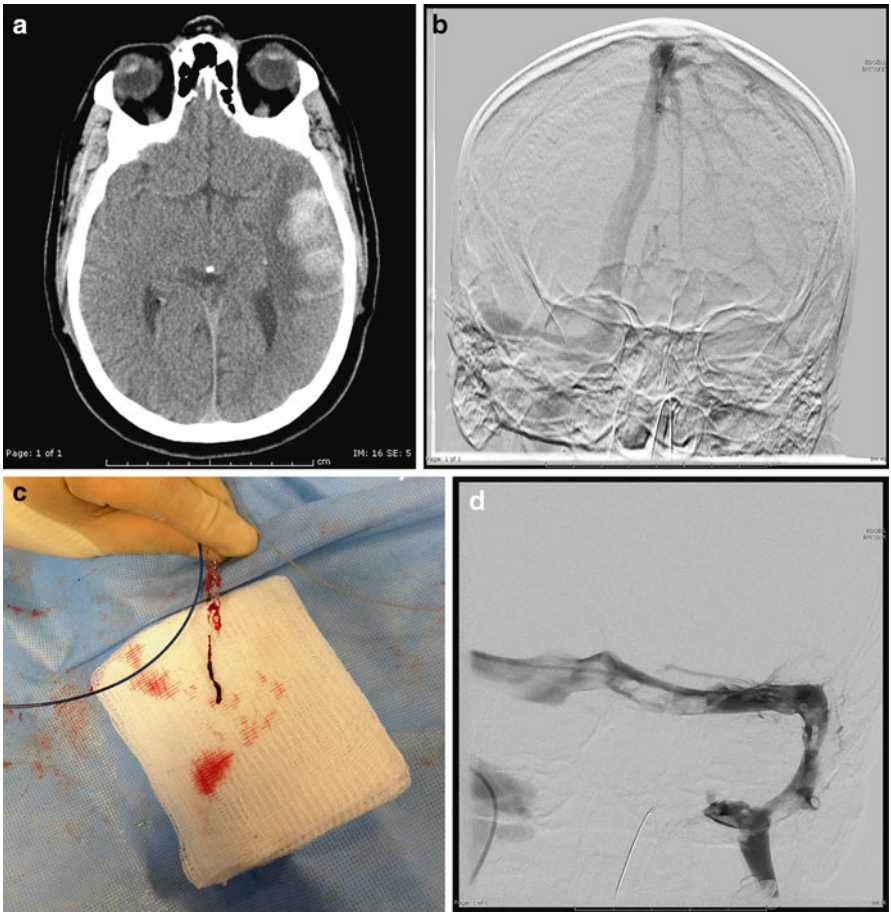

Fig. 8.2 (**a**) Axial, non-contrast head CT shows a left temporal venous infarct with hemorrhagic transformation. (**b**) Anterior–posterior projection angiogram showing occlusion of the left transverse sinus (TS) and sigmoid sinus (SS). (**c**) Extensive clot extracted with the aid of the Solitaire stent retriever. (**d**) High-magnification retrograde venogram showing restoration of venous drainage in the left TS and SS

Illustrative Case 1

A 35-year-old man with no past medical history presented with acute-onset abdominal pain to the local emergency room. He also complained of headache of 1 week's duration. An abdominal CT scan showed superior mesenteric vein thrombosis, and neuroimaging (Fig. 8.2a) showed a left temporal lobe venous infarct with hemorrhagic transformation. He was started on a therapeutic heparin drip but his headache continued to progress with development of mild expressive aphasia and agitation. An angiogram was obtained with the intention to perform a mechanical thrombectomy if amenable.

The angiogram revealed complete occlusion of the left transverse sinus, left sigmoid sinus, and left internal jugular vein (Fig. 8.2b). Because the patient had worsened while on therapeutic anticoagulation, a decision was made to attempt mechanical thrombectomy. This was performed through a transvenous approach using a 6-F 80-cm guiding sheath placed in the right femoral vein and navigated to the right internal jugular vein. A 0.054″ guiding catheter was then navigated into the right transverse sinus and then into the left transverse sinus across the torcular Herophili. A microcatheter was then navigated through the guiding catheter over a 0.014-in. microwire into the left transverse sinus and then the left internal jugular vein. After removing the microwire a 6×20 mm Solitaire thrombectomy device was deployed and clot retrieved (Fig. 8.2c). A total of eight passes of the Solitaire device were performed serially in a distal-to-proximal manner. Control angiograms showed interval recanalization of the left transverse sinus and left internal jugular vein following thrombectomy (Fig. 8.2d). The patient continued to have a complicated hospital course due to systemic venous thrombosis and was diagnosed with catastrophic antiphospholipid antibody syndrome (CAPS). He recovered well on therapeutic anticoagulation and immunosuppressive therapy and was ultimately discharged home.

References

1. Ribes MF. Des recherches faites sur la phlebite. Revue Medicale Francaise et Estrangere et Journal de Clinique de l'Hotel-Dieu et de la Charite de Paris. 1825;3:5–41.
2. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2): 162–70.
3. Borhani Haghighi A, Ashjazadeh N, Safari A, Cruz-Flores S. Cerebral venous sinus thrombosis in Iran: cumulative data, shortcomings and future directions. Iran Red Crescent Med J. 2012;14(12):805–10.
4. Wasay M, Kaul S, Menon B, Venketasubramanian N, Gunaratne P, Khalifa A, Poungvarin N, Saadatnia M, Gan RN, Dai A, Mehndiratta MM. Ischemic stroke in young Asian women: risk factors, subtypes and outcome. Cerebrovasc Dis. 2010;30(4):418–22.
5. de Veber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald EA, Gillett J, Meaney B, Shevell M, Sinclair DB, Yager J. Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345(6):417–23.
6. Sutton D, Stevens J. Vascular imaging in neuroradiology. In: Textbook of radiology and imaging, vol. 2. New York: Churchill Livingstone; 2003. p. 1682–7.
7. Bousser MG, Chiras J, Bories J, Castaigne P. Cerebral venous thrombosis—a review of 38 cases. Stroke. 1985;16(2):199–213.
8. Canhão P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F, ISCVT Investigators. Causes and predictors of death in cerebral venous thrombosis. Stroke. 2005; 36(8):1720–5.
9. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791–8.
10. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664–70.
11. de Bruijn SF, de Haan RJ, Stam J. Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients. For The Cerebral Venous Sinus Thrombosis Study Group. J Neurol Neurosurg Psychiatry. 2001;70(1):105–8.

12. Borhani Haghighi A, Edgell RC, Cruz-Flores S, Feen E, Piriyawat P, Vora N, Callison RC, Alshekhlee A. Mortality of cerebral venous-sinus thrombosis in a large national sample. Stroke. 2012;43(1):262–4.
13. Virapongse C, Cazenave C, Quisling R, Sarwar M, Hunter S. The empty delta sign: frequency and significance in 76 cases of dural sinus thrombosis. Radiology. 1987;162(3):779–85.
14. Vogl TJ, Bergman C, Villringer A, Einhäupl K, Lissner J, Felix R. Dural sinus thrombosis: value of venous MR angiography for diagnosis and follow-up. AJR Am J Roentgenol. 1994; 162(5):1191–8.
15. Wasay M, Azeemuddin M. Neuroimaging of cerebral venous thrombosis. J Neuroimaging. 2005;15(2):118–28.
16. Einhäupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, Haberl RL, Pfister HW, Schmiedek P. Heparin treatment in sinus venous thrombosis. Lancet. 1991;338(8767): 597–600.
17. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke. 1999;30(3):484–8.
18. Stam J, De Bruijn SF, DeVeber G. Anticoagulation for cerebral sinus thrombosis. Cochrane Database Syst Rev. 2002;4, CD002005.
19. Einhäupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, Masuhr F, European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol. 2010;17(10):1229–35.
20. Ferro JM, Correia M, Rosas MJ, Pinto AN, Neves G, Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport). Seizures in cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2003;15(1-2):78–83.
21. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin. 1992;10(1):87–111.
22. Lobo S, Ferro JM, Barinagarrementeria F, Bousser MG, Canhão P, Stam J, ISCVT Investigators. Shunting in acute cerebral venous thrombosis: a systematic review. Cerebrovasc Dis. 2014; 37(1):38–42.
23. Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, Derex L, Lichy C, Masjuan J, Massaro A, Matamala G, Poli S, Saadatnia M, Stolz E, Viana-Baptista M, Stam J, Bousser MG, Second International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT 2) Investigators. Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. Stroke. 2011;42(10):2825–31.
24. Borhani Haghighi A, Mahmoodi M, Edgell RC, Cruz-Flores S, Ghanaati H, Jamshidi M, Zaidat OO. Mechanical thrombectomy for cerebral venous sinus thrombosis: a comprehensive literature review. Clin Appl Thromb Hemost. 2013;20(5):507–15.
25. Curtin KR, Shaibani A, Resnick SA, Russell EJ, Simuni T. Rheolytic catheter thrombectomy, balloon angioplasty, and direct recombinant tissue plasminogen activator thrombolysis of dural sinus thrombosis with preexisting hemorrhagic infarctions. AJNR Am J Neuroradiol. 2004;25(10):1807–11.
26. Kim SY, Suh JH. Direct endovascular thrombolytic therapy for dural sinus thrombosis: infusion of alteplase. AJNR Am J Neuroradiol. 1997;18(4):639–45.
27. Frey JL, Muro GJ, McDougall CG, Dean BL, Jahnke HK. Cerebral venous thrombosis: combined intrathrombus rtPA and intravenous heparin. Stroke. 1999;30(3):489–94.
28. Yamini B, Loch Macdonald R, Rosenblum J. Treatment of deep cerebral venous thrombosis by local infusion of tissue plasminogen activator. Surg Neurol. 2001;55(6):340–6.
29. Chaloupka JC, Mangla S, Huddle DC. Use of mechanical thrombolysis via microballoon percutaneous transluminal angioplasty for the treatment of acute dural sinus thrombosis: case presentation and technical report. Neurosurgery. 1999;45(3):650–6. discussion 656–7.
30. Froehler MT. Successful treatment of cerebral venous sinus thrombosis with the Solitaire FR thrombectomy device. J Neurointerv Surg. 2013;5(6):e45.
31. Raychev R, Tateshima S, Rastogi S, Balgude A, Yafeh B, Saver JL, Vespa PM, Buitrago M, Duckwiler G. Successful treatment of extensive cerebral venous sinus thrombosis using a combined approach with Penumbra aspiration system and Solitaire FR retrieval device. J Neurointerv Surg. 2014;6(5):e32.

Chapter 9
The Role of Wada Testing in Contemporary Epilepsy Surgery

John C. Dalfino, L. James Willmore, and Mark D. Calayag

Introduction

Juhn Atsushi Wada first described intracarotid injection of the short-acting barbiturate, sodium amytal, to anesthetize one-half of the brain in 1949 [1]. This was originally described as a way to protect the dominant hemisphere during electroconvulsive therapy but was later developed as a tool to evaluate the lateralization of speech dominance [1]. Brenda Milner et al. [2], who described this technique as way to evaluate memory, expanded the utility of hemispheric anesthesia. Currently, intracarotid amytal injection (Wada test) is used to help determine the laterality of speech and memory prior to temporal lobe resection for medically refractory epilepsy or tumors. Unlike functional MRI (fMRI) that demonstrates what parts of the brain are active during a particular task, the Wada more directly demonstrates how residual brain might compensate after a surgical resection. In this way, the Wada gives information similar to grid mapping only with less spatial resolution. In fact, Wada testing, grid mapping, and fMRI are complementary studies in assessing the resectability of the eloquent cortex.

J.C. Dalfino, M.D. (✉)
Department of Neurosurgery, Albany Medical Center,
43 New Scotland Avenue, Albany NY 12208, USA
e-mail: john.dalfino@gmail.com

L.J. Willmore, M.D.
Neurology and of Pharmacology and Physiology, Saint Louis University School of Medicine,
1420 S. Grand Boulevard Suite 130, Saint Louis, MO 63104, USA
e-mail: Willmore@slu.edu

M.D. Calayag, M.D.
Neurosurgery, Albany Medical Center, 47 New Scotland Avenue, Albany NY 12208, USA
e-mail: calayam@mail.amc.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_9

The Wada starts by placing a standard diagnostic catheter into the internal carotid artery via a sheath in the femoral artery in a fully awake patient. A short-acting barbiturate or other anesthetic agent is then administered through the arterial catheter to anesthetize the ipsilateral hemisphere while a neurologist and/or neuropsychologist tests the patient's speech function and shows them a number of items to remember. Once the medication effect has worn off, the patient is asked to recall the items that were shown during the test. The injection is then repeated on the other side. Data from each hemisphere are compared to determine the laterality of speech and memory (right, left, or codominant). Intra-procedural EEG recordings can be used to both monitor the effectiveness of the anesthetic injection, to determine when the anesthetic has worn off so that testing can resume, or to be sure the patient has not had a seizure during the procedure.

Procedural Steps

Patient Preparation

Wada testing is performed with the patient awake. Conscious sedation with either narcotics or anxiolytics is avoided to allow the patient to be alert during the testing. Intravenous access should be secured prior to testing to help administer medications quickly should the patient have a seizure, stroke, or vascular injury. Patients are required to fast overnight in the rare event that emergent intubation is required due to excessive barbiturate sedation.

Patient Positioning and Access

The patient is positioned supine on an angiographic table. Scalp electrodes can be placed if EEG recording during testing will be performed. The skin over the femoral artery is prepped with antiseptic solution and draped with a commercially available femoral angiography drape. A few milliliters of 1 % lidocaine is injected over the femoral artery at the level of the femoral head. Access to the femoral artery is obtained using a 21-gauge micropuncture needle. The Seldinger technique is used to insert a 10 cm long 4- or 5-French sheath into the common femoral artery.

Pre-procedure Angiography

A 4F or 5F diagnostic catheter is guided into the proximal internal carotid artery using standard angiographic techniques. The goal of pre-procedure angiography is to identify anatomical variants, such as a fetal PCA, a persistent carotid-basilar

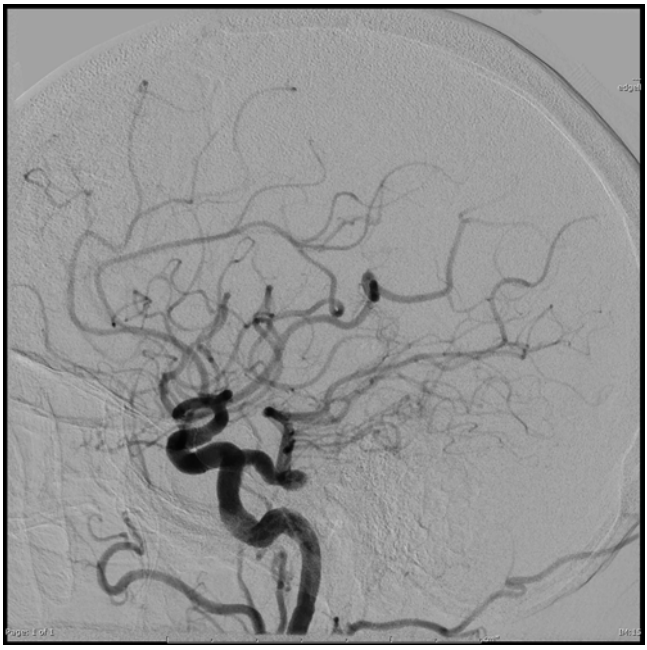

Fig. 9.1 Lateral projection image of a persistent trigeminal artery. These fetal remnants may allow intra-arterial injections to affect the brainstem and thalami, potentially leading to impairment of consciousness and respiratory depression

anastomosis, or absent ACA, that might require special accommodations during testing (Fig. 9.1). The hemisphere giving rise to seizures should be tested first so that if the full procedure must be interrupted, some clinically useful information would have been obtained.

A standard anterior–posterior (AP) and lateral cerebral angiogram is performed on both sides to identify any relevant anatomical variations in the cervical or cranial vasculature. Angiography of the posterior circulation is not performed routinely, except when needed to further define unusual vascular anatomy in the carotid distribution or if selective PCA barbiturate injections will be performed.

Special Anatomical Considerations (See Chap. 2)

Fetal PCA

Patients with a fetal-type PCA may have filling of the basilar artery during routine angiographic injections (Fig. 9.2). In these patients, a rapid infusion of barbiturates may result in respiratory suppression, lethargy, and even autonomic instability due

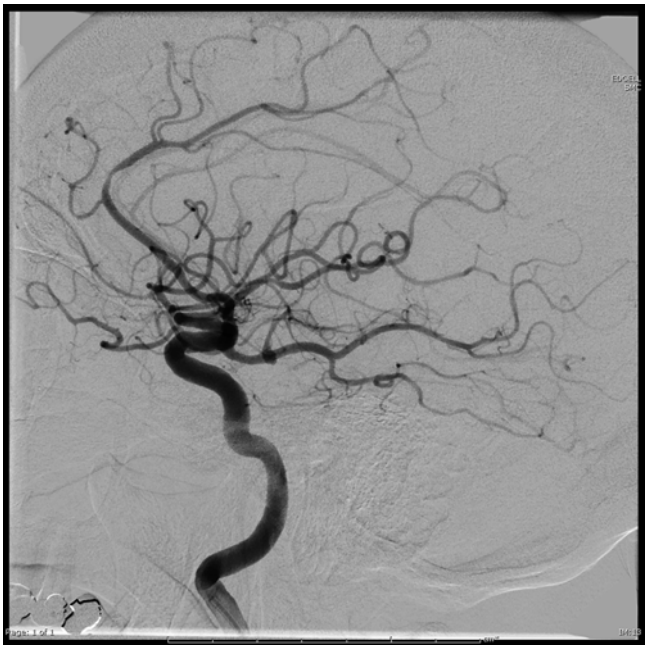

Fig. 9.2 Lateral projection image of a fetal posterior cerebral artery. This common anatomical variant does not preclude carotid injection, but care must be taken to administer the agent gradually in order to avoid filling of the posterior circulation

to brainstem compromise. Wada testing can be performed safely in patients with a fetal PCA provided the barbiturates are injected slowly, as competitive flow from the basilar artery will usually prevent the drug from flowing into the posterior circulation. This can be confirmed by doing a control run using contrast prior to drug infusion. In the rare case where a slow injection is not sufficient to prevent reflux into the basilar artery, the drug can be injected directly into the MCA using a microcatheter.

Persistent Carotid–Basilar Anastomosis

Persistent carotid–basilar (PCB) anastomoses are an uncommon anatomical variant of the circle of Willis in which there is a direct connection between the carotid artery and the vertebrobasilar system (Fig. 9.1). Unlike the more common fetal PCA variant, patients with a PCB anastomosis often will have unavoidable filling of most if not the entire basilar artery during a routine cervical carotid contrast injections. Consequently, cervical carotid injections of barbiturates during Wada testing may result in severe respiratory depression, lethargy, and even autonomic instability.

Wada testing can be safely performed in patients with a PCB anastomosis if the barbiturates are injected into the carotid artery distal to the anastomosis using a microcatheter or balloon microcatheter.

Absent or Atretic A1

Patients with an absent or atretic ACA artery may have nearly all of the blood to the frontal lobes supplied by one carotid artery. Injections on the side of the dominant ACA will often cause bilateral frontal lobe suppression leading to behavioral changes such as dysinhibition and confusion. This effect may be particularly profound when the dominant A1 is on the right side. In patients with an atretic but functional contralateral ACA, a softer injection will help to prevent the reflux of barbiturates into the contralateral hemisphere. In patients with absence of the contralateral ACA, direct injection of barbiturates into the MCA with a microcatheter on the side of the dominant A1 can be considered.

Carotid Occlusion

Rarely, a patient will be found to have an asymptomatic carotid artery occlusion or high-grade stenosis. In cases where testing from the ipsilateral carotid is not possible, barbiturate injections can be performed from the PCAs using a microcatheter.

Intracarotid Barbiturate Injections

A diagnostic cerebral angiogram is performed in the hemisphere giving rise to seizures. If there are no complicated vascular anatomical features, the catheter is then flushed with heparinized saline, and the C-arm is repositioned to allow the neurologist and neuropsychologist free access to the patient's head and arms. The patient is then given a brief tutorial regarding the testing procedure.

The test is initiated by having the patient raise both arms (braced by the neurology team to avoid contamination of the sterile field). As the patient counts backward from 100 aloud, a bolus of the anesthetic of choice is administered through the diagnostic catheter until the patient's contralateral upper extremity becomes flaccid. Once the neurologist determines the bolus was effective, the neuropsychological testing is performed. During neuropsychological testing, the neurologist continuously assesses the efficacy of the anesthetic dose by looking for the return of muscle tone or movement in the affected extremity and by inspecting the EEG pattern. Once the neuropsychological testing is complete, the catheter is removed from the body and flushed. After the patient recovers from the effects of the anesthetic, the

second phase of neuropsychological testing of memory is completed along with assessment to ensure the patient has not had a stroke. The process is then repeated on the other side.

Potential Pitfalls

The Wada test has all the inherent risks associated with diagnostic cerebral angiography including arterial dissection, stroke, and complications from bleeding but also has some unique consequences that may not be encountered in routine diagnostic testing.

Embolus

Emboli during Wada testing can occur as the result of clot formation on wires or catheters used for access, by dislodging plaque in the carotid artery or arch, or due to introduction of foreign particulate matter during contrast or drug injections. When an embolus is observed, whether symptomatic or not, the test must be discontinued. The catheter should be bled back and flushed to remove any particulate material. For small, distal emboli that cannot be reached with a clot retriever, consider administration of IA abciximab (0.25 mg/kg) through the arterial catheter or IA tPA (1–2 mg). A retrospective study of 677 patients showed that the incidence of stroke and the incidence of transient ischemic attack were both 0.6 % [3].

Seizure

A complex partial or generalized tonic–clonic seizure during Wada testing is a rare but not completely unexpected event with an incidence of 1.2 % [3]. Supportive care includes removing the diagnostic catheter and turning the head to the side to avoid aspiration. The use of lorazepam (2–4 mg) depends upon the patient's history of isolated or serial seizures. Since the postictal state following a seizure may influence the results of neuropsychological testing, the Wada is typically discontinued.

Pediatric Patient Testing

Wada testing of children 13 years and older is generally well tolerated without special accommodations. Testing of preteen children as young as 6 years has been shown to be safe and effective provided appropriate pre-procedure training is performed.

Mild sedation with propofol during femoral access and control angiography in these young patients have been used to help improve comfort and compliance during Wada testing [4–6].

Pharmacology

Methohexital (Brevital)

Methohexital (JHP Pharmaceuticals, Parsippany, NJ) is supplied as a lyophilized powder. The powder is reconstituted in sterile water or normal saline to a concentration of 10 mg/ml. It is then passed through a syringe filter onto the sterile field where it is further diluted with preservative-free saline to a final concentration of 1 mg/ml. An amount of 10 ml of methohexital (1 mg/ml) is drawn into a 10 ml syringe in preparation for injection.

The onset of action is nearly immediate (2–3 s). In most cases, 3–4 mg of methohexital is needed to initiate anesthesia. Boluses of 1–2 mg of methohexital every 90–120 s will be needed to maintain anesthesia during neurological testing. Full clinical and EEG recovery will take around 5–7 min [7].

Amobarbital (Amytal)

Amobarbital (Marathon Pharmaceuticals, Deerfield, IL) is supplied as a lyophilized powder. It is traditionally the first-line agent for these procedures but has been subject to supply shortages. The drug is diluted in 5 ml of sterile water and is dissolved by rotating the vial—not shaking. It may take several minutes to completely dissolve. Additional saline is added to achieve a final concentration of 25 mg/ml. The final solution is then passed through a syringe filter on the field to remove any particulate matter. Amobarbital should be used within 30 min of preparation.

Amytal dosing in adults is 125 mg, 5 ml administered at 1–2 ml/min. Up to an additional 50 mg (1–2 ml) may be administered, if needed, to induce hemiparesis. Lower doses of amobarbital (75 mg) have also been used effectively in adults in experienced centers, despite conflicting results from historical reports [8].

Etomidate (Amidate)

Etomidate (Hospira, Lake Forest, IL) is a nonbarbiturate hypnotic drug with a rapid onset of action. The liver rapidly metabolizes it. Etomidate is supplied as a sterile solution at a concentration of 2 mg/ml and can be diluted with saline. The onset of action after IA injection is approximately 45 s to 1 min, and its effects last approximately 5 min [9].

A protocol for using etomidate for Wada testing was first published by Jones-Gotman [9]. Etomidate was administered as a 2 mg bolus in 4 ml of saline via infusion pump followed by a rate of 6 ml/h. The patients were observed to be at baseline within 4–5 min of infusion cessation. A revised protocol using a single dose of 2 mg of etomidate diluted with 4 ml of saline delivered by hand injection over 60 s shows similar efficacy and resulted in a reduction in induced seizures and myoclonus [10].

Propofol (Diprivan)

Propofol (AstraZeneca) is a short-acting nonbarbiturate hypnotic-sedative drug. Its short duration of action is due primarily to redistribution, but the liver eventually metabolizes it. It is available as a ready-to-use liquid oil-water emulsion in a concentration of 10 mg/ml per the manufacturer, propofol should be diluted with 5 % dextrose, although most published reports suggest diluting it with saline. Propofol can be filtered through a syringe filter with a pore size of 5 μm or greater.

Propofol is diluted to a final concentration of 1 mg/ml with sterile saline. It should be noted that the manufacturer recommends diluting to no less than 2 mg/ml. Initial dosing is 10 mg per side. An additional 3–5 mg of propofol per side can be administered as necessary to achieve hemiplegia [11, 12]. A single bolus of 20 mg of propofol has also been shown to be safe and effective [13]. It has been suggested, however, that higher doses of propofol may be associated with more side effects. Pretest administration of 500 mg of methylprednisolone immediately prior to testing has been suggested to reduce the incidence of tonic posturing and rhythmic movements that are sometimes observed during intracarotid propofol injections [12].

Lidocaine

It has been suggested that white matter structures are resistant to barbiturate anesthetics like amytal due to their lack of GABA receptors. As a result, lidocaine, which acts on sodium channels that are present in both white and gray matter, has been used as a complementary anesthetic agent during superselective Wada testing (also referred to as provocative testing) of both the spinal cord and brain [14]. Provocative testing with intra-arterial lidocaine has also been used to detect the blood supply of cranial nerves and the presence of dangerous anastomoses in the external carotid circulation [15]. It has been reported that lidocaine testing in addition to barbiturates can reduce the incidence of a false-negative result during provocative testing when compared to barbiturate injection alone [16].

Lidocaine HCl injection (Hospira, Inc., Lake Forest, IL) is available in a 1 % (10 mg/ml) or 2 % (20 mg/ml) solution. Typically 10–20 mg is injected into each pedicle, depending on its size and flow characteristics. No more than 200–300 mg of lidocaine should be administered within 1 h.

Superselective Wada Testing

Injecting barbiturates and other anesthetics into the posterior cerebral arteries (PCAs) and middle cerebral arteries (MCAs) can be used in patients with anatomical contraindications to a cervical ICA injection. Superselective Wada tests have also been used to assess for eloquent branches prior to AVM and aneurysm embolizations [17].

Superselective P2 Injections

The P2 segment of the posterior cerebral artery has been suggested as an alternative to the intracarotid Wada [18]. CT SPECT scans have confirmed that microcatheter injections of amobarbital into the PCA are distributed to the hippocampus and amygdala and can be used to test for memory dominance without significantly affecting speech [19].

Superselective PCA injections are performed through a 0.018″ to 0.021″ microcatheter that has been advanced into the P2 segment using standard microcatheterization techniques. The patient should be fully heparinized prior to advancing the guide catheter to prevent thromboembolic events. After performing a control microcatheter angiogram demonstrating that the catheter is in the P2 segment, the anesthetic of choice in injected. Dosages should mirror those used for standard WADA testing.

Superselective MCA Injections

Superselective M1 injections have been suggested as an alternative to intracarotid Wada testing in patients with fetal-type PCAs or a hypoplastic A1 to avoid somnolence and mood changes [20]. Selective MCA injections have been shown to be effective in determining the laterality of speech and motor function in patients undergoing hemispherectomy, but it has been suggested that it may be ineffective for lateralizing memory due to the fact that the drug does not reach the anterior choroidal artery [20].

Superselective MCA injections are performed using a 0.018″ to 0.021″ microcatheter advanced into the M1 segment of the middle cerebral artery. As with other superselective catheterizations, the patient should be fully heparinized prior to advancing the guide catheter into the carotid artery. After performing a control angiogram through the microcatheter to ensure that both MCA branches are filled and that the tip of the microcatheter is not in a perforator, the anesthetic of choice is injected. Dosages should mirror those used for standard WADA testing.

Illustrative Case 1

The patient is a 28-year-old right-handed female with a history of partial complex seizures since age 12. The events typically consist of behavioral arrest and a "glassy-eyed look" for a minute followed by confusion, fatigue, and amnesia. No aura is reported. Inpatient long-term monitored scalp EEG recordings suggest a left temporal focus, although right parasagittal sharp waves were noted on rare occasion. MRI and PET scans show no focal abnormality.

The patient is currently managed on carbamazepine 400 mg TID and topiramate 200 mg bid but still has 1–2 episodes per day. She has previously failed management of her epilepsy with Vimpat, Trileptal, Keppra, Zonegran, Dilantin, and Lamictal.

Access was obtained to the right femoral artery using a micropuncture needle. The Seldinger technique was used to cannulate the right femoral artery with a 5-French 10 cm vascular sheath. The left internal carotid artery was catheterized using a 5F angled Glidecath (Terumo, Somerset, NJ, USA) diagnostic catheter. A standard angiographic run of the brain from the left ICA revealed filling of the top of the basilar artery via a fetal PCA (Fig. 9.3a). Reflux into the top of the basilar artery is prevented by a more gentle injection of contrast (Fig. 9.3b). Using a relatively slow rate of injection, 7 mg of Brevital (JHP Pharmaceuticals, Rochester, MI) was injected into the left ICA over approximately 10 s, and the clinical portion of

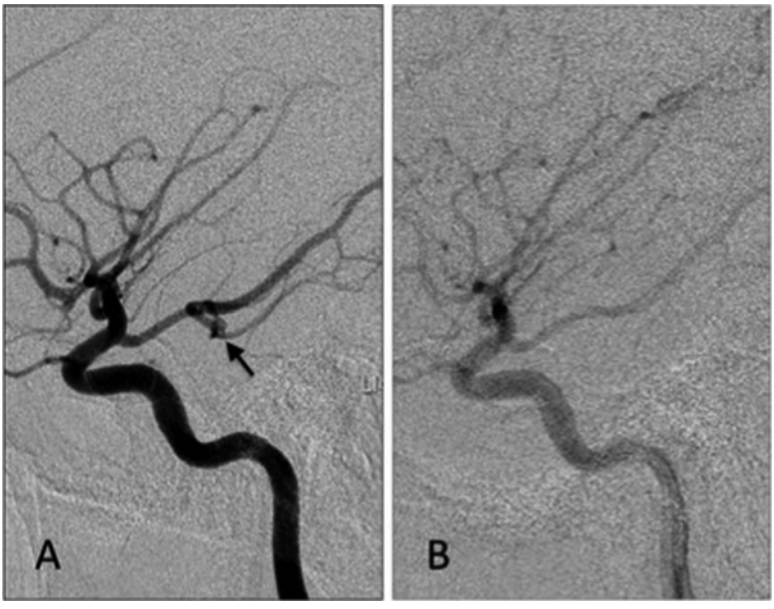

Fig. 9.3 (**a**) Cerebral run from the left ICA at standard injection rate shows filling of the top of the basilar artery (*arrow*). (**b**) Injecting at a slower rate prevents reflux into the basilar artery suggesting that slow injection of the barbiturate will not likely result in significant brainstem anesthesia

the Wada test was performed by a neurologist and neuropsychologist. The Brevital was redosed at 1-minute intervals as needed to maintain hemiparesis (up to 10 mg total). The process was then repeated on the right side. A 5-French Mynx closure device (AccessClosure, Santa Clara, CA, USA) was used to close the arteriotomy.

The results of the Wada test suggested that the left hemisphere was dominant for speech. Memory was not significantly affected by either the right or left carotid injections. EEG monitoring performed during the test showed left parietal sharp waves at P3 and P7. No EEG abnormalities were noted in the right hemisphere. Based on the results of the Wada test, further seizure mapping was performed using bilateral subdural grid monitoring. A vagal nerve stimulator was later inserted.

References

1. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960. J Neurosurg. 2007;106(6):1117–33.
2. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium amytal. Trans Am Neurol Assoc. 1962;87:224–6.
3. Loddenkemper T, Morris HH, Möddel G. Complications during the Wada test. Epilepsy Behav. 2008;13(3):551–3.
4. Binner Jr RA, Ginsberg B, Bloch EC, Mason DG. Anesthetic management of a pediatric Wada test. Anesth Analg. 1992;74(4):621–2.
5. Hinz AC, Berger MS, Ojemann GA, Dodrill C. The utility of the intracarotid Amytal procedure in determining hemispheric speech lateralization in pediatric epilepsy patients undergoing surgery. Childs Nerv Syst. 1994;10(4):239–43.
6. Masters LT, Perrine K, Devinsky O, Nelson PK. Wada testing in pediatric patients by use of propofol anesthesia. AJNR Am J Neuroradiol. 2000;21(7):1302–5.
7. Willmore LJ, Wilder BJ, Mayersdorf A, Ramsay RE, Sypert GW. Identification of speech lateralization by intracarotid injection of methohexital. Ann Neurol. 1978;4(1):86–8.
8. Fedio P, August A, Patronas N, Sato S, Kufta C. Semantic, phonological, and perceptual changes following left and right intracarotid injection (Wada) with a low amytal dosage. Brain Cogn. 1997;33(1):98–117.
9. Jones-Gotman M, Sziklas V, Djordjevic J, Dubeau F, Gotman J, Angle M, Tampieri D, Olivier A, Andermann F. Etomidate speech and memory test (eSAM): a new drug and improved intracarotid procedure. Neurology. 2005;65(11):1723–9.
10. Andelman F, Kipervasser S, Maimon S, Fried I, Parmet Y, Neufeld MY. A revised intracarotid etomidate memory (Wada) procedure. Acta Neurol Scand. 2013;127(2):97–102.
11. Takayama M, Miyamoto S, Ikeda A, Mikuni N, Takahashi JB, Usui K, Satow T, Yamamoto J, Matsuhashi M, Matsumoto R, Nagamine T, Shibasaki H, Hashimoto N. Intracarotid propofol test for speech and memory dominance in man. Neurology. 2004;63(3):510–5.
12. Mikuni N, Yokoyama Y, Matsumoto A, Kikuchi T, Yamada S, Hashimoto N, Miyamoto S. Intravenous methylprednisolone reduces the risk of propofol-induced adverse effects during Wada testing. Neurol Med Chir (Tokyo). 2010;50(8):622–6.
13. Mikati MA, Naasan G, Tarabay H, El Yamen S, Baydoun A, Comair YG. Intracarotid propofol testing: a comparative study with amobarbital. Epilepsy Behav. 2009;14(3):503–7.
14. Niimi Y, Sala F, Deletis V, Setton A, de Camargo AB, Berenstein A. Neurophysiologic monitoring and pharmacologic provocative testing for embolization of spinal cord arteriovenous malformations. AJNR Am J Neuroradiol. 2004;25(7):1131–8.
15. Deveikis JP. Sequential injections of amobarbital sodium and lidocaine for provocative neurologic testing in the external carotid circulation. AJNR Am J Neuroradiol. 1996;17(6):1143–7.

16. Fitzsimmons BF, Marshall RS, Pile-Spellman J, Lazar RM. Neurobehavioral differences in superselective Wada testing with amobarbital versus lidocaine. AJNR Am J Neuroradiol. 2003;24(7):1456–60.
17. Rajpal S, Moftakhar R, Bauer AM, Turk AS, Niemann DB. Superselective Wada test for ruptured spontaneous fusiform middle cerebral artery aneurysm: a technical case report. J Neurointerv Surg. 2011;3(3):237–41.
18. Jack Jr CR, Nichols DA, Sharbrough FW, Marsh WR, Petersen RC, Hinkeldey NS, Ivnik RJ, Cascino GD, Ilstrup DM. Selective posterior cerebral artery injection of amytal: new method of preoperative memory testing. Mayo Clin Proc. 1989;64(8):965–75.
19. Urbach H, Klemm E, Linke DB, Behrends K, Biersack HJ, Schramm J, Schild HH. Posterior cerebral artery Wada test: sodium amytal distribution and functional deficits. Neuroradiology. 2001;43(4):290–4.
20. Fujii M, Miyachi S, Matsubara N, Kinkori T, Takebayashi S, Izumi T, Ohshima T, Tsurumi A, Hososhima O, Wakabayashi T, Yoshida J. Selective propofol injection into the M1 segment of the middle cerebral artery (MCA Wada test) reduces adverse effects and enhances the reliability of the Wada test for determining speech dominance. World Neurosurg. 2011;75(3–4):503–8.

Chapter 10
Unruptured Intracranial Aneurysms

Eric M. Deshaies, Amit Singla, Ravi H. Gandhi, and Alan S. Boulos

Introduction

Unruptured intracranial aneurysms (UIA) are those in which there is no evidence of a breach in the aneurysm wall. These aneurysms are most commonly found incidentally or in the setting of aneurysm-related mass effect. With the increasing utilization and quality of noninvasive cerebral imaging, the detection of UIAs has become more frequent. Treatment decisions surrounding UIAs can be complex and fall into three general categories: observation, endovascular treatment, or open surgical repair. In order to advise a patient on the best option, it is important for the involved physicians to understand the natural history, risk factors for rupture, and risks of treatment.

Cerebral aneurysms measuring more than 25 mm in diameter are considered giant intracranial aneurysms (GIAs) [1]. Despite the many surgical options and advances in endovascular therapies, treatment of GIAs remains challenging. The

E.M. Deshaies, M.D.
Associate Professor of Neurosurgery, Neuroscience & Physiology, SUNY Upstate Medical University, Neurosurgery, 750 East Adams St., Syracuse, NY 13202, USA
e-mail: eric.m.deshaies@gmail.com

A. Singla, M.D.
SUNY Upstate Medical University, Department of Neurosurgery,
750 E. Adams St., Syracuse, NY 13210, USA

R.H. Gandhi, M.D.
Department of Neurosurgery, Indiana University, Indianapolis, IN, USA

Department of Neurosurgery, Albany Medical Center,
1544 Holts Grove Circle, Winter Park, FL 32789, USA
e-mail: rhgandhi@gmail.com

A.S. Boulos, M.D. (✉)
Albany Medical Center, 43 New Scotland Avenue, Albany, NY 12208, USA
e-mail: boulosa@mail.amc.edu; alan.boulos@gmail.com

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_10

goal of treatment is to isolate the aneurysm from the circulation while maintaining patency of the parent vessel and the distal arterial tree. This can be particularly challenging for GIAs not only because of their size but also because they frequently (a) are wide necked, (b) incorporate arterial branches into the sac, (c) harbor thrombus in the dome risking thromboembolic events, (d) cause mass effect, and (e) obscure anatomical features important for intervention. In addition to removing the risk of rupture, treatment goals specific to GIAs include reduction in mass effect and prevention of thromboembolic complications [2] (see Chap. 15 for ophthalmologic presentations of UIAs).

Natural History

The most rigorous medical literature on the natural history of UIAs consists of retrospective or prospective cohort studies. Such studies have significant limitations including selection bias. Aneurysms followed in these trials may be those in which surgical risk is thought to be high or the need for treatment low. An additional limitation is the lack of a control arm. Never the less, certain factors have been consistently associated with rupture risk in these studies:

Size has been identified as a predictor of rupture risk. The International Study of Unruptured Intracranial Aneurysms (ISUIA) is the most referenced study of the natural history of UIAs. This study consisted of a retrospective and prospective cohort. In the prospective cohort, 4,060 patients were included of which 1,692 patients were not treated. The patients were divided into group 1 (no previous SAH) and group 2 (previous SAH from another aneurysm). The average follow-up was 4.1 years. They found a progressively increasing risk of rupture with increasing aneurysm size. Overall, it appeared that posterior circulation aneurysms ≥5 mm (including posterior communicating artery aneurysms) had a high enough rupture risk to warrant preventative treatment. In the anterior circulation, aneurysms ≥7 mm (excluding the extradural carotid artery where rupture risk was extremely low) were thought to warrant treatment. Aneurysms <7 mm found in the setting of a prior SAH (group 2) also showed higher rates of rupture justifying treatment [3]. In the Unruptured Cerebral Aneurysm Study (UCAS) of Japan, 6,697 aneurysms were included. Using the 3–4-mm size as a reference, the hazard ratios for rupture were 3.35, 9.09, and 76.26 for 7–9-mm, 10–24-mm, and >25-mm aneurysms, respectively [4]. While aneurysm size is clearly an important factor, it cannot be used in isolation to determine whether an UIA should be treated.

Location of an aneurysm is also related to the risk of rupture. The prospective ISUIA cohort identified a relative risk of rupture (with the intradural internal carotid artery as the reference) of 2.3, 2.1, and 0.15 for aneurysms of the basilar apex, posterior communicating artery, and cavernous carotid, respectively [3]. The UCAS of Japan identified the anterior communicating artery (ACoA) to be the

location with highest rupture risk followed by the posterior communicating artery (PCom) artery, basilar apex/superior cerebellar artery (SCA), middle cerebral artery (MCA), vertebral artery/posterior inferior cerebellar (PICA)/vertebrobasilar junction, and internal carotid artery in descending order. They found that ACoA and PCom aneurysms had a relatively high rate of rupture even when smaller than 7 mm. Posterior circulation aneurysms excluding PCom aneurysms were not more prone to rupture [4]. A meta-analysis by Wermer et al. found the posterior circulation (not including the PCom) had the greatest relative risk of rupture followed by PCom, MCA, and non-PCom ICA aneurysms, with cavernous sinus aneurysms having the lowest relative risk [5].

The **morphology** of an aneurysm such as the presence of daughter sacs, the ratio of aneurysm height to neck width (aspect ratio), and the anatomical relationship to the parent vessel may contribute to the risk of rupture. Multiple studies have compared morphological characteristics of ruptured to unruptured aneurysms and found an association between lobulation or daughter sacs and rupture [6, 7]. The UCAS Japan is the only prospective study to identify a daughter sac as a factor that increases the relative risk of rupture. The presence of a daughter sac was associated with a hazard ratio of 1.63 [4]. There has also been a suggestion that the presence of branching vessels adjacent to the aneurysm, the angle at which the aneurysm arises from the parent vessel, and the aspect ratio may increase the risk of rupture [8, 9]. The aspect ratio has also been shown to be significantly higher in ruptured when compared to unruptured aneurysms in several studies [10, 11], while Esharkway et al. found only a height to width ratio >1, an irregular wall, and location at the main MCA bifurcation predicted rupture in MCA aneurysms [12].

Presenting symptoms and comorbidities of patients with UIA are also associated with rupture risk [5, 13]. A history of SAH contributes to the risk of rupture from UIAs. In the retrospective cohort study of ISUIA, there was a tenfold increase in the risk of rupture in the group of patients with a history of SAH and aneurysms less than 10 mm (group 2). However, this difference was not noted in larger aneurysms [3, 14]. Patient age, sex (females are more likely to have a ruptured aneurysm), smoking, and hypertension increase the risk of rupture [13, 15]. Of all the modifiable risk factors, smoking has been found to have the greatest association with multiple aneurysms [16, 17], growth of UIAs [18], and to independently increased risk of rupture [19]. In the meta-analysis by Wermer et al., both Japanese and Finnish descent increased the risk of rupture [5].

Although the natural history of an individual aneurysm cannot be predicted with precision, the above factors should be considered when weighing the risk of rupture. The formula for calculating the risk of hemorrhage in a lifetime is 1 − (annual chance of not bleeding) × expected years of life. If a 30-year-old has a 5-mm basilar apex aneurysm (.5 %/year based on ISUIA data), their lifetime risk is 22 % based on an expected lifespan of 80 years. The aneurysm morphology, including the presence of geometric irregularity, and patient factors such as smoking, hypertension, alcohol use, and previous history of SAH also have to be taken into consideration.

Noninvasive Management

Noninvasive or "conservative" management is often equated with doing nothing. However, patient education, modification of risk factors, and routine screening can improve the outcomes in patients with UIAs. Smoking increases the risk of SAH from a UIA 2.1–3 times. Although former smokers still have a higher risk of SAH than never smokers, the risk is lower than for active smokers [16, 17]. Hypertension increases the risk of SAH by 2.5 times [20]. Patient education, immediate steps to modify lifestyle, and general medical health are imperative to reducing the risk of rupture and new aneurysm formation.

Change in aneurysm morphology or growth may imply an increased risk of rupture. Therefore routine observation with noninvasive imaging to evaluate for increasing size, change in symptoms, or morphology should be considered in selected cases. Yasui et al. evaluated 25 aneurysms that were initially treated conservatively and went on to rupture. A majority of these aneurysms increased in diameter at the time of rupture [21]. The initial size of the aneurysm has been identified as a risk for growth on noninvasive imaging [22].

Surgical Management

Small and Large Aneurysms

The goal of surgery is to exclude the treated aneurysm from the circulation. The options for surgery include direct clip ligation, aneurysm trapping and bypass, and rarely wrapping of a dysplastic vessel or aneurysm.

After primary clipping of an aneurysm, the risk of residual aneurysm is 4–8 % [23–26]. In a series of 715 aneurysms that were clipped, there were 3.8 % (28 aneurysms) with residual aneurysm sac of which 1 aneurysm rebled [24]. In a series by David et al., late angiographic follow-up was performed in 160 aneurysms. They found 2 recurrent aneurysms (1.5 %) out of 135 completely occluded aneurysms. Of the group with residual aneurysm, they found an annual hemorrhage rate of 1.9 % in those with a dog-ear residual. In those with broad-based residuals, there was a 75 % rate of growth. Grouping all incompletely clipped aneurysms, they found a risk of recurrence of 2.9 % per year and 1.5 % risk of hemorrhage per year [23].

Based on the ISUIA prospective cohort of 1,917 patients who underwent surgical clipping of UIAs, the 1-year mortality was 2.3 % and 1-year morbidity 12.1 %. Age >50 years was a strong predictor of poor outcome. Other factors that were predictive of poor surgical outcome were diameter greater than 12 mm, location in the posterior circulation, previous ischemic disease, and aneurysm symptoms other than rupture [3]. The Cleveland Clinic looked at their series of 449 UIAs treated by 10 neurosurgeons. They compared the baseline modified Rankin Scale scores (mRS) with 6-month mRS and found that 94 % of patients showed no functional worsening.

They found that surgeons with greater than 5 years experience prior to the onset of the study achieved better outcomes. Increasing patient age and aneurysm size were predictors of worsened functional outcome [27].

Giant Aneurysm

The surgical approach to GIAs is significantly more challenging than the approach to smaller aneurysms. Stand-alone clip ligation is often impossible to perform safely due to difficulty in visualizing the aneurysm neck and inflow/outflow vessels due to the large size of the aneurysm sac. Several alternative and adjunctive techniques have been utilized in this setting:

- *Clip ligation*: Anterior circulation GIAs are approached from a standard pterional approach often including frontal-orbitozygomatic extensions and orbital osteotomies, to improve exposure of the clinoidal, cavernous, and ophthalmic segments of the ICA. Additionally, proximal control frequently requires exposure of the cervical carotid artery, particularly if an EC-IC bypass is required. These more complex anterior skull base approaches provide additional exposure to the undersurface of the frontal lobes, temporal lobes, and Sylvian fissure [28].

  Approaches to the basilar artery vary depending on the segment in question. Subtemporal or orbitozygomatic trans-Sylvian approaches provide access to the basilar apex and upper third of the basilar artery. The mid-basilar artery requires a transpetrosal or an extended retrosigmoid skull base approach; these approaches are associated with higher morbidity due to the venues needed for access [29]. The lower third of the basilar artery and the vertebrobasilar junction are better approached through a far-lateral suboccipital craniotomy [30]. Aneurysm treatment in the posterior circulation is particularly challenging given the anatomical features of the skull base and soft tissue structures in the surrounding area, in addition to the smaller working space, increased difficulty of obtaining proximal and distal vascular control, and morbidity associated with manipulation of the brainstem and its vascular supply.

  Once the GIA has been exposed and adequate proximal and distal vascular control is achieved, debulking of the aneurysm sac for better visualization is often performed. To extend occlusive working times, techniques such as hypothermia, barbiturate-induced burst suppression, and circulatory arrest have been employed. Hypothermic circulatory arrest is associated with a morbidity rate of 13 % and a mortality rate of 8 % [29].

  The most common complications with surgical clip ligation of the GIA include major vessel occlusion, incomplete aneurysm obliteration, and damage to the perforating arteries resulting from clip migration. Lawton et al. reported a surgical mortality of 7 % and neurological morbidity of 11 % in their series of 242 patients operated for GIAs [28].

- *Parent vessel occlusion (PVO)*: Proximal occlusion of the vessel giving rise to a GIA can induce auto-thrombosis [31]. The success of this surgery is dependent on the thorough assessment of collateral circulation. This can be achieved through preoperative balloon occlusion testing (see Chap. 16) and/or the measurement of "stump pressure" [32]. If the mean stump pressure decreases by 30–70 % of the mean pre-clamping pressure on the ICA, and EEG monitoring does not change during the 15 min of temporary CCA occlusion; abrupt ligation of the CCA is performed with multiple 3-0 silk ligatures just below the CCA bifurcation. On the other hand, if the stump pressure is less than 30 %, an adjunctive bypass is recommended. If the stump pressure is >70 %, the chance of auto-thrombosis is low, and aneurysm trapping or direct clipping is needed.
- *Aneurysm trapping*: Aneurysm "trapping" involves permanent occlusion of the inflow and outflow of the aneurysm. EC-IC bypass to the distal vasculature allows for continued arterial flow after trapping. Patients who have a balloon test occlusion (BTO) prior to surgery and tolerate BTO with a hypotensive challenge are at low risk (<10 %) for stroke from arterial occlusion, and EC-IC bypass may not be required (see Chap. 16). In either case, it does provide an added level of safety long term.
- *EC-IC bypass*: Unclippable aneurysms require alternative techniques (e.g., trapping, parent artery occlusion, excision, and aneurysmorrhaphy) that compromise parent arteries and may require revascularization to restore adequate cerebral blood flow. Several bypass grafts are available for direct cerebral revascularization, and selection depends on whether low-flow bypass (superficial temporal artery (STA) or occipital artery (OA)) or a high-flow interposition free graft (saphenous vein (SV) or radial artery (RA)) is needed to establish adequate perfusion. The largest report on EC-IC bypass comes from the trial conducted in 1985 which involved 663 STA-MCA bypass procedures performed for symptomatic ICA or MCA narrowing or occlusion. The morbidity from major stroke and mortality rates following surgery were 2.5 % and 0.6 %, respectively, at 30 days [33].

Endovascular Management

Endovascular surgery is an increasingly utilized option for the treatment of UIAs. At a large number of centers, it has overtaken open surgery as the primary treatment modality. To best evaluate endovascular treatment, it is important to critically assess the initial occlusion, recanalization, and re-rupture rates. The standard endovascular therapy for aneurysms with a favorable neck to dome ratio is coil embolization. The advent of balloon remodeling and stent-assisted coiling as well as flow-diverting stents has enabled the extension of endovascular techniques to treat less favorable aneurysms such as wide-neck aneurysms or GIAs.

Equipment Review (See Chap. 1)

- *Sheath*: A 6-F sheath is the minimum size required for UIA coiling. A 35-cm or longer sheath is recommended to bypass tortuous ileac and femoral vessels and enhance guide catheter control. At times a guide sheath positioned in the common carotid artery or proximal internal carotid artery may be needed to provide support or a larger inner diameter.
- *Guide catheter*: A 6-F guide catheter is recommended in most instances. Several varieties are currently on the market. The traditional iteration has a fixed angle tip designed to be positioned in the distal cervical carotid artery (e.g., MPC ENVOY; Codman Neurovascular; Raynham, MA). Newer guide catheters have a flexible straight tip that can be positioned in the petrous segment safely (e.g., Neuron MAX; Penumbra Inc.; Alameda, CA). While the distal purchase is helpful at times, the trade-off is less stability/support.
- *Microcatheter*: A wide range of microcatheters is available for intracranial use. Optimal design features include trackability, stability within the aneurysm, and the ability to accommodate both 0.010-in. and 0.018-in. coil sizes. Most catheters are available in both pre-shaped and straight (may be steam shaped if desired) varieties.
- *Microwire*: Most practitioners employ a 0.014-in. 200-cm microwire for intracranial navigation and aneurysm entry. Ideal wire characteristics include 1:1 extracranial/intracranial torquability, a soft distal tip, and a supportive proximal shaft.
- *Coils*:
  - *Framing*: Creates a shell that conforms to the inner surface of the aneurysm and bridges the aneurysm neck. Longer coil lengths may enhance neck coverage and reduce the number of coils needed.
  - *Filling*: Used to occlude the body of an aneurysm, these coils are usually helical in shape and flexible.
  - *Finishing*: The softest family of coils, designed to occlude the aneurysm neck without pushing the coiling catheter out of position.
  - *Coated*: Several coil types are coated with materials designed to enhance initial filling (e.g., HydroCoil; MicroVention-Terumo; Tustin, CA) or aneurysm healing (PRESIDIO; Codman Neurovascular; Raynham, MA).
  - *Bigger and better?*: The Penumbra Coil 400 (Penumbra Inc.; Alameda, CA) is the largest diameter coil on the market at 0.020 in. It has the potential advantage of more rapid aneurysm occlusion and less compaction in the setting of large or giant aneurysm. These claims are still being evaluated in practice.
- *Compliant balloon*
  - *Single lumen*: The HyperGlide and HyperForm balloons (Covidien; Irvine, CA) have the longest track record in balloon-assisted coiling (BAC). The HyperForm is the most compliant and effectively herniates into an aneurysm neck. The HyperGlide is somewhat less deformable but also can be used in BAC. These catheters require the use of 0.010-in. microwires (X-Pedion 10; Covidien; Irvine, CA).

  - *Dual lumen*: Newer BAC catheters are designed with central lumen compatible with a 0.014-in. wire and an outer parallel noncommunicating lumen that allows inflation of a compliant balloon at the distal tip of the microcatheter. The inner lumen is designed to deliver compatible therapeutic agents. The Ascent catheter (Codman Neurovascular; Raynham, MA) has a proximal marker band 3 cm from the tip that facilitates the use of detachable coils. The Scepter catheter (MicroVention-Terumo; Tustin, CA) is designed for delivering coils but is somewhat more navigable and is compatible with Onyx liquid embolic (Covidien; Irvine, CA).

- *Coiling scaffold stents*: Two such stents are currently available. Both are nickel-titanium (Nitinol), laser slotted-tube stents. These stents are approved under the Food and Drug Administration's Humanitarian Device Exemption. Hence, their use requires approval and monitoring by the local Institutional Review Board. The Neuroform EZ stent delivery system (Stryker; Kalamazoo, MI) can be delivered through an included 3-F microcatheter that is first positioned across the aneurysm neck. It is an open-cell design, which may allow for greater flexibility and facilitates complex multi-stent configurations. It comes in multiple sizes that can be tailored to the target vessel. The ENTERPRISE stent (Codman Neurovascular; Raynham, MA) comes in 4.5-mm diameters only. It is delivered through a PROWLER SELECT Plus microcatheter (Codman Neurovascular; Raynham, MA). Its closed-cell design may more effectively prevent coil herniation into the parent vessel; however, concern has been raised about its tendency to "ovalize" on sharp turn, which may lead to stasis and clot formation. The ENTERPRISE stent can also be repositioned if partially deployed.
- *Liquid embolics*: Onyx HD-500 (ethylene vinyl alcohol; Covidien; Irvine, CA) has specific applications for aneurysm treatment and is the only FDA-approved liquid embolic agent for the treatment of intracranial aneurysms, as the primary curative strategy (HDE approval). Its use has decreased with the rise of flow-diverting stents.
- *Flow diverters*: The Pipeline Embolization Device (PED; Covidien; Irvine, CA), the first flow-diverting stent to receive FDA approval, is one such device designed to treat intracranial aneurysms via flow diversion. Ultimately, neointimal hyperplasia across the aneurysm neck results in arterial wall reconstruction and aneurysm sac occlusion [34]. The flow-diverting properties of the PED come from its design which is composed of 48 individual cobalt, chromium, and platinum strands providing 30–35 % metal surface area coverage when fully deployed [35]. This stands in stark contrast to the only 6–9.5 % wall coverage with conventional bare metal stents such as Neuroform EZ (Stryker; Kalamazoo, MI) and ENTERPRISE (Codman Neurovascular; Raynham, MA) [36]. PEDs are available with a nominal diameter from 2.5 to 5 mm in 0.25-mm increments. At the nominal diameter, the pore size is 0.02–0.05 mm^2, and the radial force is approximately 2.0 mN/mm (3.0-mm vessel diameter). The PED is premounted on a stainless steel wire with a radiopaque 15-mm platinum tip extending beyond the end of the PED and is delivered via a 0.027-in. inner-diameter microcatheter [37].

Small and Large Aneurysms

- *Coil embolization*: Given the rapid evolution of endovascular techniques and technology, it is important to give greater weight to more recent literature. The ISUIA prospective cohort of 451 patients treated endovascularly found 55 % complete obliteration, 24 % incomplete obliteration, and no obliteration in 18 %. Naggara et al. performed a meta-analysis of 71 studies between January of 2003 and July of 2008 that demonstrated a complete obliteration rate of 86 % [38]. This indicates that there has been an increased rate of complete or near-complete aneurysm obliteration over the last 10 years.
  - *Pretreatment*: The practice of pretreating elective coiling patients with antiplatelet agents is gaining popularity based on the much higher incidence of thromboembolic complications than intra-procedural ruptures. Some groups use aspirin alone, while others use a combination of aspirin and clopidogrel [39]. This practice also facilitates the safe use of balloon assistance or stent assistance if the need arises during the case.
  - *Illustrative case 1*: A 47-year-old female was seen by her cardiologist for evaluation of syncope. During the evaluation, the patient underwent an MRI and MRA of the brain that showed an unruptured 7-mm posterior communicating artery aneurysm. She underwent diagnostic cerebral angiography that showed a favorable neck to dome ratio, and coil embolization was selected as the treatment modality (Fig. 10.1a). The patient was started on 3 days of aspirin 325 mg daily and 5 days of clopidogrel 75 mg daily.

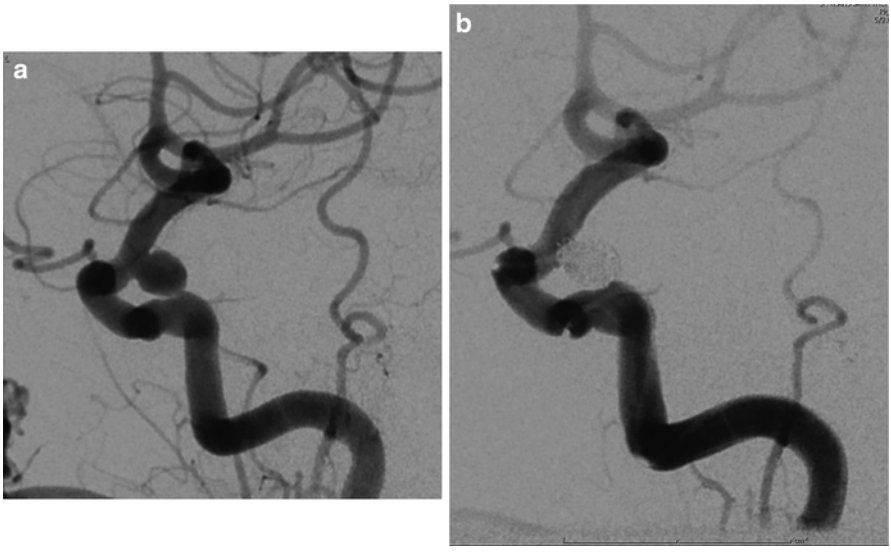

Fig. 10.1 A 7-mm right posterior communicating artery UIA with a favorable neck to dome ratio (**a**) treated with unassisted coil embolization (**b**)

A 6-F 35-cm BRITE TIP sheath (Cordis; Bridgewater, NJ) was placed in the right femoral artery, and intravenous unfractionated heparin was administered to achieve an activated clotting time of ≥250 s. A 6-F 100-cm MPC ENVOY guide catheter along with a 0.035-in. Glidewire (Terumo; Somerset, NJ) was navigated into the distal cervical carotid artery on the right. An Excelsior 1018 microcatheter (Stryker; Kalamazoo, MI) and a Synchro 0.014-in., 200-cm microwire (Stryker; Kalamazoo, MI) were then navigated into the intracranial circulation and used to select the aneurysm. A roadmap image at the previously selected coiling angles was obtained. The microwire was removed and a 7-mm PRESIDIO framing coil was deployed. Several HydroSoft (MicroVention-Terumo; Tustin, CA) filling coils and HyperSoft (MicroVention-Terumo; Tustin, CA) finishing coils were used to completely occlude the aneurysm (Fig. 10.1b). She spent 48 h in the hospital and was discharge home off antiplatelet agents.

- *Balloon-assisted coiling*
  Advanced techniques such as balloon remodeling, stent-assisted coiling (SAC), and flow diversion have increased the scope of endovascular treatment in UIAs. These techniques allow endovascular treatment in aneurysms with less favorable morphology such as wide-neck aneurysms. Although a few small series have suggested an increased risk of thromboembolic complications with the use of balloon remodeling, the ATHENA study did not show a statistically significant difference [40]. In addition to a similar safety profile, balloon remodeling has a better immediate and follow-up anatomical result than coiling alone [41].

  – *Case study 2*: A 42-year-old woman who underwent MRI of the brain after a first ever seizure showed a 1-cm carotid terminus aneurysm. The patient was unable to tolerate prolonged dual antiplatelet therapy due to prior life-threatening gastrointestinal bleeding. The patient was started on 3 days of aspirin 325 mg. Bilateral femoral arteries were accessed with 6-F 35-cm BRITE TIP sheaths, and intravenous unfractionated heparin was administered to achieve an activated clotting time of ≥250 s. Two 6-F 100-cm MPC ENVOY guide catheters along with a 0.035-in. Glidewire were navigated into the bilateral distal cervical carotid arteries. A Scepter XC 4 mm × 11 cm balloon and a Synchro 14 microwire were navigated into the left anterior cerebral artery, across the anterior communicating artery, and into the right middle cerebral artery. An Excelsior 1018 microcatheter and a Synchro 14 200-cm microwire were then navigated into the intracranial right internal carotid artery used to select the aneurysm. A 9 mm × 33 cm PRESIDIO framing coil, followed by 7 mm × 30 cm PRESIDIO framing coil, was deployed in a "Russian doll" manor, while the Scepter XC balloon was inflated from the proximal MCA to proximal ACA. The remaining aneurysm was filled with a combination of HydroSoft filling coils and HyperSoft finishing coils (Fig. 10.2a, b).

- *Stent-assisted coiling*
  Hong et al. performed a meta-analysis of ten retrospective cohort studies comparing standard coiling to SAC and concluded that although there was a slightly lower initial occlusion rate in the SAC group (57.6 % vs. 68.7 %), there was a

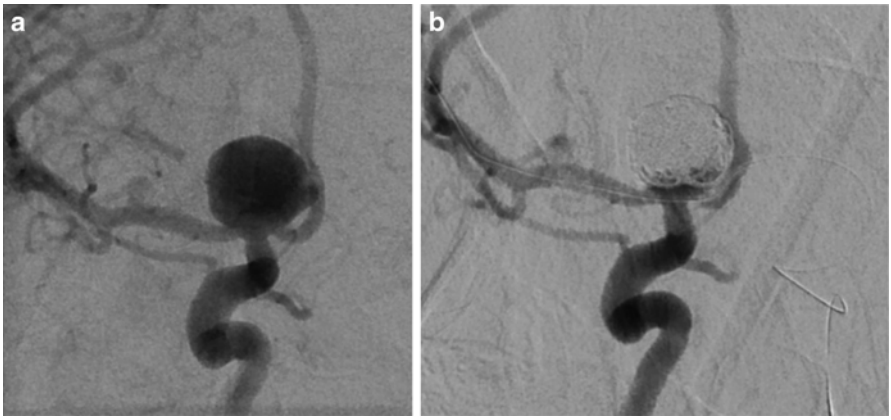

Fig. 10.2 A 1-cm right carotid terminus UIA with a wide neck (**a**) treated with balloon-assisted coiling (**b**)

significantly lower recurrence rate (16.2 vs. 34.4 %) and a higher progressive thrombosis rate (37.5 % vs. 19.4 %). There was no statistical difference in the complication rate between the two groups [42].

– *Illustrative case 3*: The patient was a 49-year-old female who presented with a wide-neck basilar tip aneurysm found on CTA performed in the setting of severe headache (Fig. 10.3a). Given the basilar tip location and wide-neck configuration, stent-assisted coiling was selected as the treatment modality. The patient was started on 3 days of aspirin 325 mg daily and 5 days of clopidogrel 75 mg daily.

Diagnostic angiography showed a large posterior communicating artery on the left. The bilateral femoral arteries were accessed with a 6-F, 35-cm BRITE TIP sheath on the right and a 6-F 90-cm Flexor Shuttle guiding sheath (Cook Medical; Bloomington, IN) on the left. Unfractionated heparin was administered to achieve an ACT of ≥250 s. A 6-F Simmons II Slip-Cath (Cook Medical; Bloomington, IN) and 0.035-in. stiff Glidewire were inserted within the Shuttle sheath and used to position it within the proximal left internal carotid artery, just distal to the bulb. A 6-F, 100-cm MPC ENVOY guide catheter was then inserted within the BRITE TIP sheath and, with the aid of a 0.035-in. Glidewire, navigated to the V2/V3 junction of the left vertebral artery. A PROWLER SELECT Plus microcatheter and a Synchro 14 microwire were then navigated into the intracranial left internal carotid artery and used to select the left posterior communicating artery. The microcatheter was used to enter the ipsilateral P1 segment, across the basilar tip, and was positioned within the contralateral P1 segment. A 4.5 mm × 20 cm ENTERPRISE stent was inserted within the microcatheter and advanced to its distal tip. An SL-10 microcatheter (Stryker; Kalamazoo, MI) and a Synchro 14 microwire were then inserted within the guide catheter and navigated into the basilar tip aneurysm.

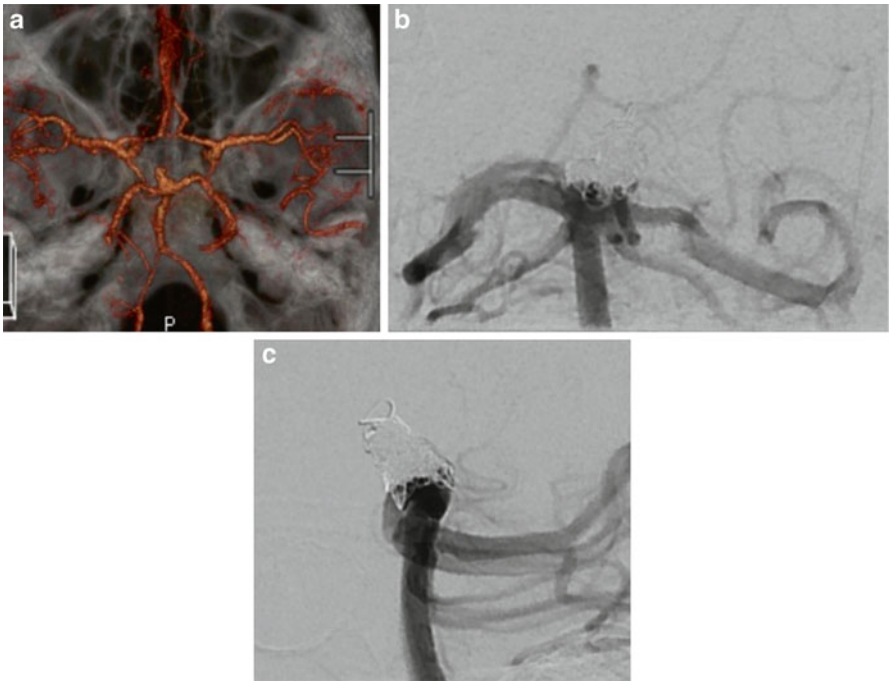

Fig. 10.3 A wide-neck basilar tip UIA (**a**) treated with P1 to P1 ENTERPRISE stent-assisted coil embolization. Shows coils conforming to outer surface of the stent on anterior–posterior (**b**) and lateral (**c**) projections

The PROWLER SELECT Plus microcatheter microcatheter was then withdrawn, deploying the ENTERPRISE stent from P1 to P1 segments, across the neck of the aneurysm. Coiling then commences through the "trapped" SL-10, with excellent aneurysm occlusion, conforming to the stent surface (Fig. 10.3a, b).

Dual antiplatelet agents were used for 6 weeks, followed by aspirin only for life.

Giant Aneurysms

In one of the earlier reports on coil embolization of GIAs, 69 % of aneurysms were incompletely occluded at 6-month follow-up angiography (range, 1–11 months). These recurrences have been attributed to thrombus dissolution, coil compaction, or coil migration into preexisting thrombus. GIAs frequently require retreatment, sometimes more than once [43]. Even the use of BAC and SAC has not adequately addressed these high rates of recanalization [44, 45].

- *Liquid embolics*
  Liquid embolic agents, such as Onyx HD-500, were introduced in an attempt to reduce the high recanalization rates seen described above. The CAMEO trial (Cerebral Aneurysm Multicenter European Onyx) was the largest study on the use of Onyx HD-500, the only FDA-approved liquid embolic agent for the treatment of intracranial aneurysms, as the primary curative strategy. Out of the 100 aneurysms treated, 19 were classified as GIAs. All had complete (100 %) or subtotal (90–99 %) initial occlusion. Of the 19 GIAs, one (5 %) was reported to need retreatment for recurrence at 3-month follow-up angiography. However, four patients did not have 3- to 6-month follow-up outcomes reported, and three patients had complete or subtotal occlusion that progressed to incomplete or indeterminate occlusion [46].

  Liquid embolic delivery requires balloon inflation across the aneurysm neck. The balloon must remain inflated for at least 3 min after injection of the embolic agent, allowing the agent to precipitate inside the aneurysm. If the balloon is let down too soon, the liquid embolic agent can leak into the parent artery causing embolic occlusions. Additionally, the embolic agent can leak into the parent artery around the balloon if it is not inflated adequately, yet if inflated too much, arterial dissection or rupture can occur with devastating consequences. In the CAMEO trial, procedure- or device-related permanent neurological deficits, including hemorrhage (ICH), ischemic stroke, or worsening cranial nerve deficit, were present in 8/97 patients, and seven died, two of which were procedure related (one groin complication and one ICH from vessel dissection), one death was disease related, and four others were from unrelated causes.

  These risks, along with concerns about long-term durability, have limited the use of liquid embolic agent use to treat GIAs.

- *Parent vessel occlusion*
  Parent vessel occlusion (PVO) to treat GIAs of the carotid artery dates back to the eighteenth century when it was first described by Cooper in 1809 [47]. From historical experience on surgical clamp occlusion, approximately 75 % of patients can tolerate surgical clamp occlusion of the ICA [48]. Surgical PVO has been discussed earlier in this chapter, and we will further discuss endovascular treatment here.

  PVO can be performed by several techniques including coil embolization and/or Onyx HD-500 embolization. In most patients with unruptured aneurysms presenting with mass effect on the cranial nerves, symptoms are improved soon after therapy [48]. Complications from endovascular PVO therapy for GIAs include: (a) increased local mass effect from aneurysm thrombosis or the devices used to achieve aneurysm occlusion, (b) subarachnoid hemorrhage, and (c) stroke from thromboembolic events. In a series of 15 patients undergoing endovascular PVO one patient developed new sixth cranial nerve palsy, three patients had access site complications, and one died from aneurysm rupture [49].

  Due to the recent developments in endovascular technology, there is a paradigm shift toward vessel-preserving treatments such as the use of flow-diverting stents.

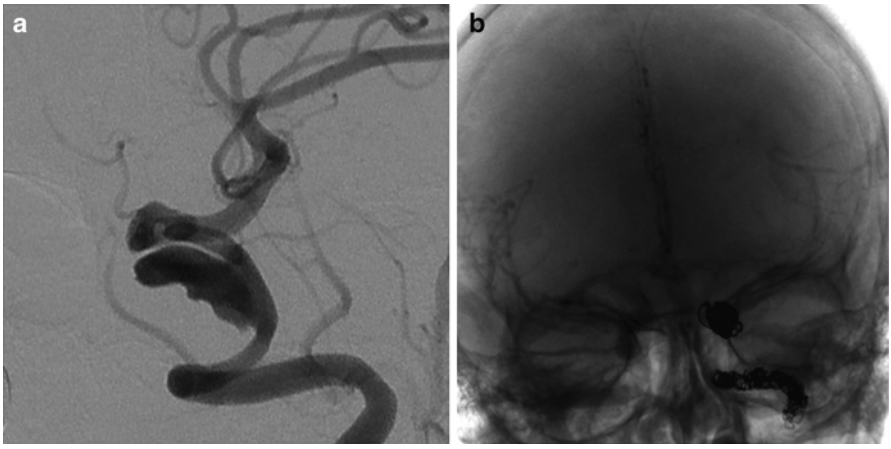

Fig. 10.4 An example of vessel sacrifice to treat a partially thrombosed giant cavernous carotid artery aneurysm (**a**) with adequate collateral supply via the anterior communicating artery post-occlusion (**b**)

  - *Illustrative case 4*: A 45-year-old woman presented with severe headache and ophthalmoparesis progressing rapidly to ophthalmoplegia. She underwent diagnostic angiography that showed a large partially thrombosed cavernous carotid artery aneurysm encompassing a large portion of the parent vessel (Fig. 10.4a). Given the difficulty in treating the aneurysm with vessel-preserving strategies and progressive nature of her symptoms, it was decided that parent vessel sacrifice should be considered. She underwent balloon test occlusion with hypotensive challenge without neurological deficits (see Chap. 16). Robust filling through the anterior communicating artery was observed. Venous phase delay was <1 s. She subsequently underwent successful vessel sacrifice with long-term near-total resolution of her ocular symptoms (Fig. 10.4b).

- *Flow diversion*
  Flow diversion is a highly promising, emerging technology that was initially developed to treat aneurysms with morphologies not amenable to coil embolization. Flow diversion results in disruption of flow near the aneurysm neck, inducing thrombosis in the aneurysm sac while keeping the physiological blood flow in the parent vessel and adjacent branches intact.

  Reports on the use of the PED include aneurysms of all sizes. A literature review on the outcomes of aneurysmal flow diverters showed immediate angiographic aneurysm occlusion in only 8–21 % of patients [36-7, 50]. However, over time the aneurysm occlusion rates were higher than conventional treatments with complete occlusion ranging from 69 % at 6 months [51] to >90 % at 1 year [36], even with large and giant aneurysms. The PITA trial (Pipeline for the Intracranial Treatment of Aneurysms) included 31 aneurysms, nine were large and two were GIA's. Follow-up complete aneurysm occlusion was observed in

28 of 30 (93.3 %) patients, and residual aneurysm filling was noted in two (6.7 %) [52]. Some users have used a coil-assisted flow-diverter technique, whereby coils are placed into the aneurysm to promote better aneurysm sac occlusion, particularly for large or acutely ruptured aneurysms. This has not been found to be associated with increased aneurysm occlusion rate [50]. Lubicz et al. advocates the use of additional coiling only in aneurysms with high risk of rupture or to restrict the PED coverage to a single device in order to minimize the risk of side branch occlusion [51]. If there is residual aneurysm after placing the PED, some interventionalists will place a second stent across the first one to further increase the metal coverage of the aneurysm neck.

The main limitation of the PED is the potential latency period before aneurysm thrombosis takes place; this is particularly challenging for ruptured aneurysms [34]. Complications of the PED include in-stent thrombosis (6 %), in-stent stenosis (1 %), intracranial hemorrhage (3.8 %), and perforator vessel occlusion [37]. Szikora reported a 1.75 % rate of severe hemorrhagic complications (mostly delayed ipsilateral parenchymal or subarachnoid hemorrhage) after using the PED, resulting in a 0.75 % permanent morbidity rate and a 1 % mortality rate [53]. In PITA, two patients had periprocedural stroke, and no other neurologic deterioration was observed in any of the patients at discharge [52].

Siddiqui et al. [54] recently reported their experience with flow-diverting stents in the treatment of large or giant intracranial vertebrobasilar aneurysms in seven patients. Pipeline devices were placed in six patients and the Silk Device (Balt Extrusion; Montmorency, France) in one patient. Four of seven patients treated with the PED died on follow-up, the other three had mRS scores of 5 (severe disability), 1, and 0. The deaths resulted from aneurysmal rupture in two patients and poor neurological status related to presenting brainstem infarcts and subsequent withdrawal of care in the other two patients. This report has raised questions about the safety of flow diversion in the posterior circulation.

– *Case study 5*: A 51-year-old woman presented with new-onset cranial nerve III palsy. MRI imaging revealed a giant right cavernous carotid artery aneurysm. The PED was selected to treat the aneurysm. The patient was started on 3 days of aspirin 325 mg daily and 5 days of clopidogrel 75 mg daily. Platelet aggregometry was performed to ensure adequate platelet inhibition.

A 6-F sheath was placed in the right common femoral artery. Unfractionated heparin was administered to achieve an ACT $\geq$ 250. A 5-F Simmons II Glidecatheter was navigated into the right internal carotid artery with the aid of a 0.035-in. Glidewire. The diagnostic catheter was then exchanged over a 0.035-in. Bentson wire (Boston Scientific; Natick, MA) for a 7-F Shuttle sheath that was positioned within the proximal right internal carotid artery. A Navien (Covidien; Irvine, CA) 0.058-in. intracranial support catheter, a Marksman (Covidien; Irvine, CA) microcatheter, and a Synchro 14 microwire were navigated past the aneurysm under roadmap guidance (Fig. 10.5a). The microwire was removed and a 3.5 mm $\times$ 25 mm PED was deployed across the aneurysm neck creating stagnation of flow within the aneurysm (Fig. 10.5b). The 6-month follow-up angiography showed complete remodeling of the parent vessel with resolution of the patient's cranial neuropathy (Fig. 10.5c).

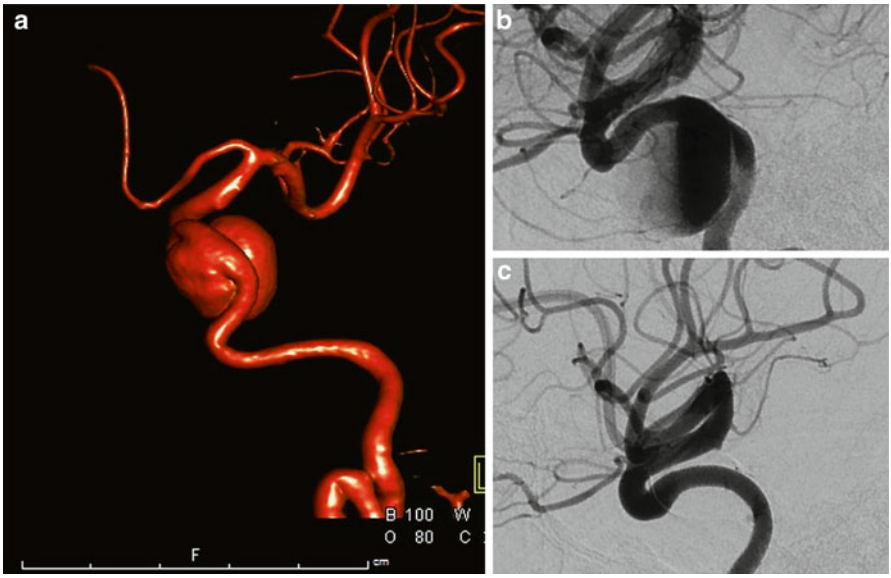

Fig. 10.5 A GIA of the left cavernous carotid artery (**a**) treated with PED leading to immediate intra-aneurysmal stasis (**b**) and 6-month complete vessel remodeling (**c**)

References

1. Sundt Jr TM, Piepgras DG. Surgical approach to giant intracranial aneurysms. Operative experience with 80 cases. J Neurosurg. 1979;51(6):731–42.
2. Sharma BS, Gupta A, Ahmad FU, Suri A, Mehta VS. Surgical management of giant intracranial aneurysms. Clin Neurol Neurosurg. 2008;110(7):674–81.
3. Wiebers DO, Whisnant JP, Huston 3rd J, Meissner I, Brown Jr RD, 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 Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103–10.
4. UCAS Japan Investigators, 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.
5. 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(4):1404–10.
6. Beck J, Rohde S, el Beltagy M, Zimmermann M, Berkefeld J, Seifert V, Raabe A. Difference in configuration of ruptured and unruptured intracranial aneurysms determined by biplanar digital subtraction angiography. Acta Neurochir (Wien). 2003;145(10):861–5. Discussion 865.
7. Hademenos GJ, Massoud TF, Turjman F, Sayre JW. Anatomical and morphological factors correlating with rupture of intracranial aneurysms in patients referred for endovascular treatment. Neuroradiology. 1998;40(11):755–60.
8. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(5):E2.

9. Rahman M, Smietana J, Hauck E, Hoh B, Hopkins N, Siddiqui A, Levy EI, Meng H, Mocco J. Size ratio correlates with intracranial aneurysm rupture status: a prospective study. Stroke. 2010;41(5):916–20.
10. Sadatomo T, Yuki K, Migita K, Taniguchi E, Kodama Y, Kurisu K. Morphological differences between ruptured and unruptured cases in middle cerebral artery aneurysms. Neurosurgery. 2008;62(3):602–9. Discussion 602–9.
11. Ujiie H, Tamano Y, Sasaki K, Hori T. Is the aspect ratio a reliable index for predicting the rupture of a saccular aneurysm? Neurosurgery. 2001;48(3):495–502. Discussion 502–3.
12. Elsharkawy A, Lehečka M, Niemelä M, Kivelev J, Billon-Grand R, Lehto H, Kivisaari R, Hernesniemi J. Anatomic risk factors for middle cerebral artery aneurysm rupture: computed tomography angiography study of 1009 consecutive patients. Neurosurgery. 2013;73(5):825–37. Discussion 836–7.
13. Weir B. Unruptured intracranial aneurysms: a review. J Neurosurg. 2002;96(1):3–42.
14. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. N Engl J Med. 1998;339(24):1725–33.
15. Nahed BV, DiLuna ML, Morgan T, Ocal E, Hawkins AA, Ozduman K, Kahle KT, Chamberlain A, Amar AP, Gunel M. Hypertension, age, and location predict rupture of small intracranial aneurysms. Neurosurgery. 2005;57(4):676–83. Discussion 676–83.
16. Juvela S. Risk factors for multiple intracranial aneurysms. Stroke. 2000;31(2):392–7.
17. Qureshi AI, Suarez JI, Parekh PD, Sung G, Geocadin R, Bhardwaj A, Tamargo RJ, Ulatowski JA. Risk factors for multiple intracranial aneurysms. Neurosurgery. 1998;43(1):22–6. Discussion 26–7.
18. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. Stroke. 2001;32(2):485–91.
19. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg. 2008;108(5):1052–60.
20. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773–80.
21. Yasui N, Magarisawa S, Suzuki A, Nishimura H, Okudera T, Abe T. Subarachnoid hemorrhage caused by previously diagnosed, previously unruptured intracranial aneurysms: a retrospective analysis of 25 cases. Neurosurgery. 1996;39(6):1096–100. Discussion 1100–1.
22. Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. J Neurosurg. 2004;101(6):908–14.
23. David CA, Vishteh AG, Spetzler RF, Lemole M, Lawton MT, Partovi S. Late angiographic follow-up review of surgically treated aneurysms. J Neurosurg. 1999;91(3):396–401.
24. Feuerberg I, Lindquist C, Lindqvist M, Steiner L. Natural history of postoperative aneurysm rests. J Neurosurg. 1987;66(1):30–4.
25. Sindou M, Acevedo JC, Turjman F. Aneurysmal remnants after microsurgical clipping: classification and results from a prospective angiographic study (in a consecutive series of 305 operated intracranial aneurysms). Acta Neurochir (Wien). 1998;140(11):1153–9.
26. Thornton J, Bashir Q, Aletich VA, Debrun GM, Ausman JI, Charbel FT. What percentage of surgically clipped intracranial aneurysms have residual necks? Neurosurgery. 2000;46(6):1294–8. Discussion 1298–300.
27. Chyatte D, Porterfield R. Functional outcome after repair of unruptured intracranial aneurysms. J Neurosurg. 2001;94(3):417–21.
28. Lawton MT, Spetzler RF. Surgical strategies for giant intracranial aneurysms. Neurosurg Clin N Am. 1998;9(4):725–42.
29. Lawton MT, Daspit CP, Spetzler RF. Technical aspects and recent trends in the management of large and giant midbasilar artery aneurysms. Neurosurgery. 1997;41(3):513–20. Discussion 520–1.

30. Heros RC. Lateral suboccipital approach for vertebral and vertebrobasilar artery lesions. J Neurosurg. 1986;64(4):559–62.
31. Elhammady MS, Wolfe SQ, Farhat H, Ali Aziz-Sultan M, Heros RC. Carotid artery sacrifice for unclippable and uncoilable aneurysms: endovascular occlusion vs common carotid artery ligation. Neurosurgery. 2010;67(5):1431–6. Discussion 1437.
32. Swearingen B, Heros RC. Common carotid occlusion for unclippable carotid aneurysms: an old but still effective operation. Neurosurgery. 1987;21(3):288–95.
33. Anon. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. N Engl J Med. 1985;313(19):1191–200.
34. D'Urso PI, Lanzino G, Cloft HJ, Kallmes DF. Flow diversion for intracranial aneurysms: a review. Stroke. 2011;42(8):2363–8.
35. 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. Discussion 1120–1.
36. Lylyk P, Miranda C, Ceratto R, et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. Neurosurgery. 2009;64(4):632–42. Discussion 642–3; quiz N6.
37. Tse MMY, Yan B, Dowling RJ, Mitchell PJ. Current status of pipeline embolization device in the treatment of intracranial aneurysms: a review. World Neurosurg. 2013;80(6):829–35.
38. Naggara ON, White PM, Guilbert F, Roy D, Weill A, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. Radiology. 2010;256(3):887–97.
39. Yamada NK, Cross 3rd DT, Pilgram TK, Moran CJ, Derdeyn CP, Dacey Jr RG. Effect of antiplatelet therapy on thromboembolic complications of elective coil embolization of cerebral aneurysms. AJNR Am J Neuroradiol. 2007;28(9):1778–82.
40. Pierot L, Cognard C, Spelle L, Moret J. Safety and efficacy of balloon remodeling technique during endovascular treatment of intracranial aneurysms: critical review of the literature. AJNR Am J Neuroradiol. 2012;33(1):12–5.
41. Shapiro M, Babb J, Becske T, Nelson PK. Safety and efficacy of adjunctive balloon remodeling during endovascular treatment of intracranial aneurysms: a literature review. AJNR Am J Neuroradiol. 2008;29(9):1777–81.
42. Hong Y, Wang YJ, Deng Z, Wu Q, Zhang JM. Stent-assisted coiling versus coiling in treatment of intracranial aneurysm: a systematic review and meta-analysis. PLoS One. 2014;9(1):e82311. doi:10.1371/journal.pone.0082311. eCollection 2014.
43. 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.
44. 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 1201–2.
45. Gao X, Liang G, Li Y, Wu Z. Neuroform stent-assisted coiling of large and giant intracranial aneurysms: angiographic and clinical outcomes in 71 consecutive patients. Neurol India. 2010;58(6):825–32.
46. Molyneux AJ, Cekirge S, Saatci I, Gál G. 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.
47. Cooper A. A case of aneurism of the carotid artery. Med Chir Trans. 1809;1:1–12.1.
48. Linskey ME, Jungreis CA, Yonas H, et al. Stroke risk after abrupt internal carotid artery sacrifice: accuracy of preoperative assessment with balloon test occlusion and stable xenon-enhanced CT. AJNR Am J Neuroradiol. 1994;15(5):829–43.
49. de Gast AN, Sprengers ME, van Rooij WJ, Lavini C, Sluzewski M, Majoie CB. Midterm clinical and magnetic resonance imaging follow-up of large and giant carotid artery aneurysms after therapeutic carotid artery occlusion. Neurosurgery. 2007;60(6):1025–9. Discussion 1029–31.

50. Szikora I, Berentei Z, Kulcsar Z, 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.
51. Lubicz B, Collignon L, Raphaeli G, et al. Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke. 2010; 41(10):2247–53.
52. 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.
53. Szikora I. Results using flow-diverter devices: ongoing or reported studies. Presented at the 2nd European Society of Minimally Invasive Neurological Therapy (ESMINT) congress, Nice, France; 2010.
54. Siddiqui AH, Abla AA, Kan P, 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.

Chapter 11
Ruptured Cerebral Aneurysms

Vibhav Bansal and Syed I. Hussain

Introduction

Subarachnoid hemorrhage (SAH) has a worldwide incidence of 10:100,000 [1, 2]. The vast majority, approximately 85 %, occurs as a result of ruptured cerebral aneurysms. This estimate has remained fairly constant over the past two decades, despite the decreasing incidence of most other stroke types due to aggressive modification of vascular risk factors. The average age of aneurysmal subarachnoid hemorrhage (aSAH) is 60.5 years [3, 4].

While women outnumber men by 2:1 in overall prevalence, men under the age of fifty are more likely than their counterpart to suffer an aSAH as estrogen is likely protective [5]. This effect diminishes as women approach menopause; the risk of aSAH is higher in women than men by the age of sixty [6, 7]. The higher overall incidence in women may be partly due to their longer life expectancy as the risk of aSAH increases with age. The risk for women increases by 2 % every 5 years [1].

The incidence of aSAH among Caucasian Americans, Black Americans, and Hispanics is 8.2, 10.9, and 12.8 per 100,000, respectively [2]. The incidence in certain countries significantly differs from the worldwide average. Japan and Finland have

V. Bansal, M.D.
Department of Neurology, Michigan State University, East Lansing, MI, USA

Neurology, Michigan State University, 1760 Orchid Ct, Highland Park, IL 60035, USA
e-mail: bansalv@cooley.edu

S.I. Hussain, M.D. (✉)
Department of Neurology, Michigan State University, East Lansing, MI, USA

Neurology & Ophthalmology, Michigan State University & Sparrow Hospital,
B401 MSU Clinical Center, 804 Service Road, East Lansing, MI 48824, USA
e-mail: syed.hussain@hc.msu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_11

much higher rates of aSAH; annual occurrences are 22 and 19:100,000, respectively [6]. The reasons for this have not been fully elucidated; however, hypertension and smoking are more common in the Japanese and Finnish people [6, 8]. Moreover, the median life expectancy in these countries is higher than in most others. Consistent with this, certain Central American countries report lower rates of aSAH (0.5:10,000), and these countries have lower median life expectancies [6, 8].

Risk Factors

It is well established that in most instances aneurysms are not present from birth but rather develop during the lifetime. Risk factors have been identified that influence the susceptibility to aneurysm formation and rupture. The latter is especially critical as the incidence of aneurysms outnumbers aSAH by an order of magnitude, and the bulk of morbidity and mortality stem from rupture.

Hypertension has consistently been found to increase risk for aSAH. The attributed risk may be as high as 20 % [9]. There is a linear relationship between elevated systolic blood pressures, greater than 140 mmHg, and risk for aneurysmal rupture. A similar trend has also been noted for diastolic blood pressure [4]. Furthermore, mean systolic blood pressures in aSAH patients may be 20 mm Hg greater than in controls [10]. The increased risk related to hypertension may contribute to African Americans more frequently suffering from aneurysms and their complications [11].

Cigarette smoking is also associated with a substantial risk of aSAH [4]. This increased risk applies to current and former smokers with attributed risks of 29 % and 10 %, respectively [4, 9]. In one case-controlled study, the proportion of current smokers in the SAH group was significantly greater than in the control group, 73.1 % vs. 41.3 %, respectively [10]. This may be related to nicotine's inhibition of antiproteases, such as alpha-1-antitrypsin [12], which inhibit collagenases that breakdown collagen in vascular walls and destabilize the vascular framework. Higher levels of collagenases facilitate the formation of aneurysms. Nicotine also has a proinflammatory effect on the immune system resulting in the activation of macrophages and their release of metalloproteinases which also degrade vessel walls [13]. Cigarette smoking's profound effect is underscored by a study that found for every 20 pack-years of tobacco use, there is a threefold higher risk of aneurysms in family members of patients with SAH [14].

A more recently recognized risk factor for aSAH is excessive caffeine consumption. Namely, it has been found that patients who drink more than five cups of coffee daily have a significantly higher risk [10]. This may in part stem from its effect on blood pressure [15]. Interestingly, body mass index (BMI) has a negative correlation with aSAH [16]. The risk of aneurysmal rupture is also increased in patients with prior aSAH. In one study, the incidence of new aneurysm development and rupture in patients with a previous aneurysm ruptured was 11 times as high [17].

Other risk factors are less compelling as a number of studies have offered contradictory conclusions. For example, while there is evidence that patients who completely abstain from alcohol have a lower risk for aSAH [4], other data indicates a J-shaped trend for aSAH risk and alcohol consumption [18, 19]. The latter implies that low levels of alcohol consumption may actually be protective.

Hereditary conditions predispose certain families to aneurysm. These conditions (e.g., Marfan's syndrome, Ehlers–Danlos syndrome type IV, neurofibromatosis type 1, and adult polycystic kidney disease) may be responsible for 5 % of aneurysms. It is also well known that family members of patients with aSAH have a higher risk of aneurysms and rupture. Risk of aneurysms and rupture in families with two or more first-degree relatives is 20 % [14, 20]. Patients with a single first-degree relative have a 4 % risk of rupture [20]. Aside from these rare genetic diseases, siblings, especially older females with other aforementioned risk factors such as smoking and hypertension, are especially at risk for aneurysms and their complications [14].

Risk of Rupture

Aneurysm size appears to be one of the main factors influencing rupture rates. Most studies have verified that aneurysms with a diameter <1 cm have a 0.5 % annual risk of rupture, whereas those >1 cm have a 7 % annual rate of rupture [17]. Moreover, symptomatic aneurysms tend to have a higher rate of rupture. This increased risk may simply be a manifestation of the inherent larger size of most symptomatic aneurysms. Location of aneurysms is also important [21]. Anterior communicating artery (ACOM) aneurysms appear most prone to rupture. There are three times more ruptured than unruptured ACOM aneurysms [22]. Posterior circulation aneurysms are at increased risk of rupture compared to the ones in the anterior circulation (1.8 % annually vs. 0.49 %, respectively) [21, 23]. As the posterior circulation has less robust autoregulation, it is less suited for adapting to elevated blood pressures resulting in more significant hemodynamic stress (Table 11.1).

Table 11.1

	NC-ICA, MCA, AC/COM (%)	VB, PC/COM (%)	Cavernous carotid artery (%)
<7 mm group 1	0	2.5	0
<7 mm group 2	1.5	3.4	0
7–12 mm	2.6	14.5	0
13–24 mm	14.5	18.4	3
>24 mm	40	50	6.4

Group 1: no prior history of aneurysm rupture. Group 2: prior history of aneurysm rupture (of a different blood vessel)

NC-ICA non-cavernous internal carotid artery, *MC* middle cerebral artery, *AC/COM* anterior cerebral artery and anterior communicating artery, *VB* vertebrobasilar arterial system, *PC/COM* posterior cerebral artery and posterior communicating artery

Pathogenesis

It was previously thought that aneurysms were the result of impaired smooth muscle and endothelial migration during embryonic development. It is now widely accepted that a cascade of inflammatory events result in both aneurysm formation and rupture [24]. It is not a coincidence that certain risk factors for atherosclerotic disease, namely, hypertension, overlap those of aneurysmal development as vascular injury, especially to the internal elastic lamina, occurs in both. Macrophages respond to this injury with the secretion of inflammatory mediators including interleukins and proteases, i.e., MMP. Macrophages also create a highly oxidative state injuring and killing the smooth muscle cells within the vicinity. There is ultimately loss of the structural integrity of the vessel wall with apoptosis of smooth muscle and endothelial cells, the breakdown of collagenous extracellular matrix (ECM), and disorganized and dysregulated vascular remodeling [25, 26]. This has been corroborated by evidence suggesting that macrophage-depleted mice have lower incidence of aneurysms. Moreover, mice with knockout genes for monocyte chemotactic protein-1 also have lower incidences of aneurysm formation [25].

The process is accentuated at artery bifurcations that are common locations for aneurysms. The multidirectional shear stress and turbulent flow applied to vessel walls result in nonuniform remodeling. Moreover, areas of persistently increased stress continue to undergo chronic disorganized remodeling. This results in segments of weaker structural framework between intimal pads—areas of thickened and inelastic tissue—predisposing aneurysms for rupture [26]. This predisposition is especially notable in cerebral arteries as these vessels lack an external elastic lamina and have only a thin internal lamina.

Pathologic evaluation of unruptured and ruptured aneurysms indicates a continuum of inflammatory changes from disorganized replacement of smooth muscle cells to unstable plaques [27]. Turbulent flow ruptures these plaques, triggering further inflammatory infiltration. This accounts for the consistent presence of leukocytes present in the peri-aneurysmal region. The end result is very fragile vascular walls prone to rupture. The lack of structural integrity is underscored by the leaky connections between smooth muscle and endothelial cells, where intercalated red blood cells are frequently identified [27]. The lack of adhesion results also acts as a potent apoptotic signal to the few remaining smooth muscle cells [28]. Ruptured aneurysmal walls frequently demonstrate the absence of smooth muscle cells and collagen type IV, with membranous hyaline replacement. Smooth muscle cells provide the plasticity and malleability of blood vessels to withstand changes in hemodynamic pressures. The loss of smooth muscle cells results in poor compliance and provides an explanation for the increased pulsatility of ruptured aneurysms [29].

Clinical Presentation

When a patient presents to the emergency room with the "worst headache ever," a dilated pupil, and a focal neurologic examination, the diagnosis of subarachnoid hemorrhage is obvious. However, such a fulminant presentation does not always occur. Instead, patients frequently present with only a headache that may even be transient. This headache is unusually severe. However, this sensitive symptom has a very low specificity for aneurysmal rupture, accounting for 1 % of all nontraumatic headache visits to the emergency room [30–33]. Headache features that are more suggestive of aSAH include acute onset of a very severe headache that is different in quality from the patient's usual headache pattern. An atypical and severe headache occurs in more than 75 % of patients [3, 34]. The positive predictive value increases when nausea, vomiting, and/or meningismus is also present [33, 35–37]. Their presence is noted in 61–77 % of patients [3, 34]. Nausea and vomiting result from elevated intracranial pressures; the degraded blood products also stimulate the area of postrema.

Sentinel symptoms, such as headaches, occurring days to weeks prior to fulminant aneurysm rupture, are present in 10–40 % of patients [38–40]. The onset of headache during exertion or a Valsalva maneuver may also suggest aSAH. Physical activity, defecation/voiding, and sexual intercourse may precipitate rupture by causing an abrupt rise in intracranial pressure [3, 41, 42]. Although helpful when present, the onset of symptoms during exertional activity occurs in less than half of patients [3].

Physical exam findings including neurologic deficits may help clinicians hone in on patients with the highest likelihood of aSAH. Nuchal rigidity results from intrathecal inflammation caused by degraded blood products in the subarachnoid space. Elevated systolic blood pressure greater than 200 mmHg is present in 32 % of patients [3]. This is likely a manifestation of the hyperautonomic state that immediately precedes rupture. The presence of either nuchal rigidity or hypertension may occur in roughly 40 % of patients [3].

An altered sensorium occurs in up to 40 % of patients [3, 34]. This results from impaired cerebral perfusion during periods of elevated intracranial pressure (ICP). Brief losses of consciousness, coma, and confusion or lethargy occur in 36 %, 17 %, and 28 % of patients, respectively [3].

Focal neurologic deficits are present in 10–13 % of patients [3, 34]. These deficits, when present, may be helpful in identifying the aneurysm's location. For example, patients with diplopia and an unreactive large pupil are frequently due to ipsilateral posterior communicating and less commonly superior cerebellar artery aneurysms. Similarly, patients with facial-brachial weakness are likely to have aneurysms around the contralateral middle cerebral artery (MCA). Nonmotor signs including aphasia and visual spatial deficits may localize to the dominant and nondominant MCAs, respectively.

Diagnosis

Despite the poor specificity of a severe headache as the presenting symptom of aSAH, cost-benefit analyses favor early and prompt recognition with a diagnostic evaluation as this results in improved outcomes [33, 43]. This is a testament to the potentially devastating morbidity and mortality of delayed diagnosis of aSAH.

Once the decision to rule out aSAH is made, patients should undergo a complete evaluation. This begins with an emergent non-contrast computerized tomography (CT) of the head which has a sensitivity approaching 100 % if performed within the first 6 h of headache/symptom onset [33, 44]. Its sensitivity drops dramatically with time to 85, 50, and 30 % at 5, 7, and 14 days, respectively [33, 45, 46]. Conversely, the yield of lumbar puncture increases with time. In fact, the negative predictive value for SAH is 100 % when a lumbar puncture is performed from 12 h of symptom onset to 14 days [47, 48]. The diagnostic finding of xanthochromia, yellowish-colored cerebrospinal fluid (CSF), results from the oxidation of lysed erythrocyte hemoglobin. This oxidative reaction takes 12 h—accounting for its high sensitivity beyond this time period [33]. The absence of xanthochromia after the first 12 h excludes SAH [48]. CT of the head followed by spectrophotometric analyses of CSF is the gold standard for diagnosing SAH [48].

Lumbar punctures, however, are not very specific and may yield false-positive results for several reasons. Namely, CSF from a traumatic tap with red blood cells >10,000 may appear xanthochromic. The common teaching that a sequential decline in the number of RBCs from tube 1 to tube 4 as being consistent with a traumatic tap has a sufficient negative predictive value to exclude aSAH is incorrect. Heasley et al. reported that 25 % of patients may demonstrate this clearing despite having aSAH [49]. Moreover, if there is a delay in the spinning and analysis of CSF, oxidation of RBCs may occur in vitro resulting in xanthochromia [50]. Hospitals/institutions frequently rely upon visual inspection alone for reporting CSF xanthochromia as spectrophotometers are uncommon devices. This results in significant interobserver variability and misdiagnosis. Visual inspection of CSF for detection of xanthochromia cannot reliably exclude SAH [51]. Other imaging modalities aside from plain CT scan may also be used to evaluate patients with possible SAH. Magnetic resonance imaging (MRI) scans have received a great deal of attention. MRI has been studied for its utility in the hyperacute setting. Wiesmann et al. [52] found that in a cohort of 13 patients who underwent an MRI within 12 h of headache, SAH was detected in all cases with either FLAIR or proton density sequences. Similarly, in the acute time period (within the first 96 h), gradient echo and FLAIR series have been found to have sensitivities of 94 and 100 % [53, 54].

MRI is also very sensitive at detecting subacute SAH. In fact, the sensitivity of gradient echo MRI sequences at days 4–6 approaches 100 %, while that of CT is 45.5 % [53, 54]. This may preclude the need for lumbar puncture in the subacute setting.

At this time MRI is impractical as the study of choice for patients presenting with possible SAH as it takes significantly longer to perform and is poorly tolerated by claustrophobic patients. However, MRI can be utilized in cases where the initial

workup is nondiagnostic or equivocal. For example, patients with erythrocytes in the CSF due to a traumatic tap who have a negative head CT could avoid an invasive cerebral angiogram if MRI demonstrates no abnormal signal on GRE and FLAIR. Furthermore, an MRA may be performed at the same time to evaluate for any aneurysms >5 mm as these have higher likelihood of rupture [55]. A normal MRA would provide further evidence to exclude SAH.

Angiographic Detection and Evaluation

Once subarachnoid hemorrhage has been diagnosed, the search for potential causes is undertaken. Typically this includes vascular imaging to assess for ruptured cerebral aneurysms that account for 85 % of nontraumatic SAH. Digital subtraction angiography (DSA) remains the gold standard for this as the accuracy and depth of diagnostic information it provides remain unsurpassed [56]. This minimally invasive procedure has a low but definite risk of complications including stroke, femoral artery injury, and acute kidney injury related to iodinated contrast. The risk of complications leading to permanent neurologic disability is typically cited between 0.06 and 0.33 % [56–58].

Interestingly, cerebral angiograms may fail to identify ruptured aneurysms in the first 14 days. Thrombus at the site of rupture or cerebral vasospasm may prevent their detection during the acute setting. Thus, an angiogram must be repeated in 3–4 weeks, especially in patients with an aneurysmal pattern of hemorrhage, when these have resolved. Repeat cerebral angiogram may detect 17 % of aneurysms that were undetected on the first angiogram [59].

Recently, noninvasive imaging modalities have been utilized in lieu of cerebral angiography. These include MRA and CTA. MRA allows assessment of cerebral vasculature without the risks of radiation and iodinated dye. However, the resolution is suboptimal at visualizing small aneurysms (<5 mm) [55]. Moreover, it fails to provide sufficient anatomical detail for surgical intervention. It has a limited role in the acute setting and serves better as a screening modality in patients at higher risk for aneurysms [60].

Computerized tomography angiography (CTA) has been more successful than MRA at not only detecting aneurysms but also providing surgeons with enough anatomical detail to proceed with definitive therapy without the need for DSA. While some studies have reported no discrepancies between CTA and DSA for surgical planning, others have provided examples illustrating its limitations. Anderson et al. [61] reported that preoperative CTA provided sufficient information to directly proceed to surgery in only 48 % of aneurysms—predominately those coming off the middle cerebral artery. While the anatomic details including size, shape, neck characteristics, and orientation were sufficient in these cases, bony artifact limited visualization of the posterior circulation. Anderson's study also demonstrated CTA's poor sensitivity to detect small (<4 mm) aneurysms as twenty-four such aneurysms (16 %) were missed by CTA. One patient underwent surgery for an asymptomatic aneurysm as the ruptured aneurysm (3 mm) was not visualized on CTA.

At our institution, CTA of the head/neck is performed when aSAH is suspected on the basis of CT scan or lumbar puncture. This provides two types of important information: It allows for early noninvasive detection of cerebral aneurysms with a sensitivity approaching 99.2 % and a specificity of 100 % [62]. If the culprit aneurysm is identified and its anatomy and configuration can be adequately discerned then these patients are taken to the angiography suite or operating room for treatment under general anesthesia. Secondly, the CTA of the neck offers the interventionists an opportunity to appreciate the proximal tortuosity and prepare for potential complications or difficulties related to vascular access. If, however, no aneurysm is detected on CTA or if the anatomy is not well defined, the patient is taken to angiography suite for a diagnostic angiogram under conscious sedation. If an aneurysm is then identified, the patient is subsequently intubated and the aneurysm subsequently treated if technically feasible. Thus, the benefits of this rapidly obtainable, noninvasive modality cannot be ignored. CTA may become the imaging modality of choice for SAH with DSA being performed in equivocal cases and in cases where CTA fails to identify a culpable source [63].

Acute Management

The patient's neurologic status at time of presentation offers the best prognostic information in aSAH patients. This is not only important for these patients' families but also in determining aggressiveness of care and therapeutic measures best fit for patients. The Hunt and Hess classification schema (Table 11.2) of aSAH patients provides a quick and accurate method for predicting outcome of patients with ruptured aneurysms [64, 65]. This 5-point scale has been validated for its reproducibility.

The World Federation Neurosurgery (WFNS) scale is another scale that may be employed to help prognosticate. This scale utilizes both the Glasgow Coma Scale (GCS) and the presence of focal neurologic deficits, i.e., hemiparesis and/or aphasia, to predict longer-term outcomes. While utilized by some centers, its interobserver variability has prevented its wider acceptance. The major issue being the characterization of focal neurologic deficits; for example, some clinicians may score the presence of pronator drift with a GCS of 7–12 as grade 3, while others may fail to characterize the pronator drift as a major focal deficit and thus score the patient as grade 2.

Table 11.2 Classification schema of aSAH patients

Grade	Description	Mortality (%)
I	Headache, no neurologic impairment	30
II	Nuchal rigidity, drowsiness, mild impairment (i.e., forgetfulness), moderate to severe headache, cranial neuropathy	40
III	Lethargy or confusion, mild impairment of power/tone/sensation	50
IV	Unconsciousness with marked changes in tone and power	80
V	Unresponsive	90

Stabilization (See Chap. 3)

aSAH patients should be admitted to an intensive care unit to closely monitor for any deterioration (AHA). A majority of complications occur within the acute and subacute setting.

- *Airway management*
  In patients with higher-grade SAH, rapid sequence intubation and mechanical ventilation may be necessary [66]. Indications for this include aspiration, acute cardiopulmonary failure, and impaired mental status (GCS of 8 or less). Short-acting anesthetic agents should be utilized when possible to allow for frequent accurate neurologic checks. Thiopental and etomidate are preferred agents. Lidocaine and fentanyl may also be utilized for their potential to lower intracranial pressure (ICP). In very agitated patients, early intubation may be necessary to avoid precipitous rises in ICP which may increase the risk of rebleeding [67].

- *Blood pressure*
  Blood pressure is another parameter that needs to be closely monitored. The range is best determined by the physicians involved, as it needs to be tailored to patients' medical problems and other comorbid conditions. As a rule of thumb though, normotension with systolic pressures less than 140 mmHg should be maintained prior to securing the aneurysm. Systolic pressures up to 200 mmHg may be tolerated, if necessary, after the aneurysm has been definitively treated [68].

- *Analgesia*
  Pain control should be managed with reversible short-acting agents. This would allow for frequent neurologic evaluations. Acetaminophen is typically favored. However, if this fails to provide adequate pain control, morphine or codeine may be administered [68].

- *Hydrocephalus*
  Obstructive hydrocephalus usually occurs within the first week. This risk significantly decreases with time. In fact, the risk may be as low as 3 % after day 3 of SAH if no evidence of ventricular enlargement was present on admission [69].

  Obstructive hydrocephalus may occur in approximately 19 % of nontraumatic SAH patients, usually presenting with an acute deterioration of mental status [70]. Thus, patients who deteriorate in the hospital undergo emergent CT of the head to evaluate for hydrocephalus. If new/worsening hydrocephalus is present, an external shunt is placed.

  The degree of hydrocephalus on CT has a poor clinical correlation with mental status and neurologic dysfunction. Thus, when incidental hydrocephalus is found in alert and awake patients, no interventions are undertaken. A converse situation frequently arises when patients present to the hospital with a high-grade aSAH with radiographic evidence of hydrocephalus. It is often unclear if the mental status changes are a direct result of the aSAH or due to the secondary hydrocephalus. Some authors recommend a period of monitoring for 24 h. If the patient does not improve, an external ventricular device (EVD) is placed; however, if the

patient's clinical status deteriorates, this is performed earlier. This delay in drain placement may not affect mortality [69]. However in our institution we favor early placement of a ventricular drain.

There is a theoretical concern of increased risk of rebleeding prior to securing the aneurysm in patients with early EVD placement. This is believed to be due to the rapid decrease in the intracranial pressure (ICP) immediately after the implantation of the EVD. This decline in ICP may result in a significant rise in the transmural pressure transmitted to the cerebral vasculature including the weak site of aneurysm rupture. This concern has not materialized in the scientific studies, however. The Mayo Clinic in 2002 found a trend toward less rebleeding in patients with preoperative ventriculostomy [71].

- *Vasospasm*

Vasospasm accounts for approximately 20 % of the morbidity and mortality associated with subarachnoid hemorrhage [70]. There is evidence that vasospasm may occur within the first 48 h of rupture [72]. Angiographic evidence of vasospasm occurs in 70 % of aSAH, and clinical deterioration is seen in as many as two-thirds of these patients [73]. Signs and symptoms suggestive of this include decreased mentation and fluctuating neurologic deficits.

The pathophysiology of vasospasm is unclear; however, the presence of oxidized hemoglobin, oxyhemoglobin, is necessary [74, 75]. Free radicals formed during this oxidative process damage vascular membranes—eliciting an inflammatory response. This results in both decreased nitric oxide (NO) production and decreased sensitivity of its receptors. Potent vasoconstrictors including prostacyclins and cytokines such as endothelin-1 are also secreted [76]. These synergistically contribute to vasospasm [77, 78]. Histological changes also result from the inflammatory response. These include degeneration within the media and elastica layers, concentric thickening of the intima, and an abundance of myofibroblasts and type V collagen [79, 80].

Certain features are predictive of vasospasm, especially the amount of subarachnoid hemorrhage initially present on a CT scan of the head. Patients with more subarachnoid blood and those with thicker and larger cisternal clots tend to have more severe vasospasm than patients in whom the blood is minimal or distributed diffusely [81, 82]. Moreover, patients under the age of 20 and those who rebleed carry a higher risk for vasospasm [82]. The modified Fischer scale (Table 11.3) incorporates many of these imaging findings to predict prognosis and risk of DID. This scale uses a scoring system where each unit increase is associated with an incremental risk for vasospasm and stroke [83].

Vasospasm typically occurs during days 4–14 and usually peaks at days 7–8 [81]. It may result in permanent neurologic deficits and death due to delayed ischemic deterioration (DID). Patients are monitored very closely during this period as early detection and intervention are crucial for a favorable prognosis [66].

Angiography remains the gold standard in diagnosing vasospasm. However, its invasive nature prevents its daily use for vasospasm monitoring. Transcranial Doppler ultrasound (TCD) is frequently used to monitor for evidence of early

Table 11.3 Modified Fischer scale

Score	Description	Vasospasm (%)	Delayed infarction/ poor outcome (%)
0	No SAH or IVH	0	
1	Focal or diffuse, thin SAH, no IVH	6	
2	Focal or diffuse, thin SAH, IVH		
3	Focal or diffuse, thick SAH, no IVH		
4	Focal or diffuse, thick SAH, IVH		

vasospasm for this noninvasive bedside test can be performed without potential harm to patients. TCDs have good sensitivity and specificity for clinically significant vasospasm—equal to that of cerebral angiography in the detection of symptomatic spasm [84]. TCDs measure basal cerebral artery flow velocities as surrogates for vasospasm. This correlation, derived from Poiseuille's equation, notes an exponential indirect relationship between vessel diameter and flow velocity. Frequent use during the peak period of vasospasm allows for monitoring of flow velocities and their trends (which is more sensitive for critical vasospasm) [85]. In so doing, treatment of vasospasm can be promptly initiated prior to clinical deterioration. This is important as TCD evidence of vasospasm may precede clinical deterioration by 24 h [84].

Effective prophylactic and therapeutic measures to treat vasospasm are very limited. In fact, prophylactic administration of oral nimodipine for 21 days remains the only treatment showing significant reduction in DID and poor outcome in a randomized double-blinded placebo-controlled study. Nimodipine reduces the risk of cerebral infarction and poor outcome at 3 months by 33 % and 40 %, respectively [86]. In addition to its potential for reducing cerebral vasospasm, nimodipine is known to inhibit other cellular-mediated processes that require calcium as cofactors, i.e., apoptosis. Administration of nimodipine is a class A recommendation by the American Heart Association (AHA) for aSAH [66].

Triple-H therapy, which refers to combination of hypervolemia, hemodilution, and hypertension, has traditionally been utilized in the setting of vasospasm; however, only hypertension is now utilized. In fact, a recent meta-analysis of these treatments found no evidence to support the use of hemodilution [87]. A few studies demonstrating the efficacy of hypertension and triple H for therapeutic and prophylactic use in SAH patients, respectively, were cited. However, these studies used cerebral perfusion rather than clinical outcomes as primary endpoints [88, 89].

Early studies also seemed promising for magnesium. Magnesium may prevent vasospasm by competitively inhibiting calcium channels in smooth muscle cells. Moreover, magnesium may have neuroprotective effects. Recent meta-analysis failed to demonstrate a benefit from magnesium infusion in reducing DCI or in improving neurologic outcomes [90].

Endovascular treatment is effective in preventing DID in patients who have failed medical management of vasospasm. It is also beneficial in patients who are

otherwise unable to tolerate these therapies. For example, patients with systolic dysfunction or those with neurogenic pulmonary edema would be precluded from hypervolemic therapy. In such cases, transluminal balloon angioplasty and intra-arterial infusion of vasodilators including nicardipine, verapamil, and verapamil and nicardipine have been found to be very effective. The complication rates of these procedures are low, and the reported outcomes have been promising, with 61 % of patients demonstrating a good outcome at follow-up [91]. Balloon angioplasty tends to have a longer-lasting and more robust effect as it may lead to permanent endothelial changes but may be associated with up to a 5 % risk of vessel rupture.

Complications

Complications related to endovascular coiling in aSAH are mainly those related to rebleeding and/or ischemia related to the catheter or from thromboembolism. The former necessitates reversal of any anticoagulation, such as immediate protamine administration. The latter may necessitate permissive hypertension to maintain cerebral perfusion or thrombectomy in cases of thromboembolism [92].

The results of International Subarachnoid Aneurysm Trial (ISAT), a multicenter randomly controlled trial, suggested that coiling was superior to clipping in reducing mortality and short-term morbidity. Both treatment modalities had their benefits and risks. Coiling was associated with a lower risk of dependence and mortality at 1 year. This advantage has carried out to at least 7 years. The risk of epilepsy and vasospasm after coiling was significantly lower than in patients who had undergone clipping [93–96].

These results have been reproduced in subsequent studies. In Barrow Ruptured Aneurysm Trial (BRAT), the safety and efficacy comparing surgical clipping with endovascular coiling of acutely ruptured aneurysms found that at 1 year posttreatment, coil embolization resulted in significantly fewer poor outcomes [97]. At 3 years posttreatment, this trend favoring coil embolization, however, was not statistically significant [98].

While the rate of rebleeding was slightly higher in the endovascular group, this did not reach statistical significance. Patients requiring retreatment was higher in the endovascular group; however, this too did not have any impact on the outcome [93, 95, 99].

Rebleeding and Treatment of the Ruptured Aneurysm

Surgery to secure a ruptured aneurysm should be performed expeditiously. Rebleeding is a feared complication that carries a high mortality rate. This risk is greatest early on. The risk of rebleeding during the first 24 h and 2 weeks is between 4 and 17 %, respectively [100–102]. Approximately half of patients presenting with aSAH will rebleed in the first 6 months if their aneurysms are left unsecured [103, 104].

The mortality rate in this group approaches 75 %, with less than 20 % demonstrating a good outcome [105]. Thus, early endovascular or surgical intervention is recommended, usually within 72 h [106]. More recent data suggests even better outcomes with lower rebleeding when treatment is performed within the first 24 h [107].

Aneurysm Repair

There are currently two approaches for treating aneurysm, surgical and endovascular. In the past, definitive management typically involved surgical clipping of the aneurysm. This microsurgical technique involves the placement of a small metal clip along the neck of the aneurysm. This prevents blood from entering the aneurysm. Moreover, this precludes any further transmission of hemodynamic stress to aneurysm fundus where growth and destabilization occurs.

Endovascular Treatment

Endovascular coiling has become the most common treatment for aneurysms in the past decade. Dr. Guido Guglielmi popularized this technique with his invention of the Guglielmi detachable coil (GDC). GDCs are platinum coils that are directed into the aneurysm via a stainless steel guidewire. The coil is electrolytically detached from the guidewire and is believed to promote thrombosis and thus cessation of flow into the aneurysm [108].

Coiling was initially reserved for patients with high surgical risk and for posterior circulation aneurysms. However, with several randomized prospective trials demonstrating similar efficacy and possibly superiority to clipping, this minimally invasive technique has gained widespread attention and is supplanting the routine use of clipping [93].

Procedural Considerations

Patient Selection

A majority of ruptured aneurysms are amenable to endovascular treatment. The aneurysm characteristic that most influences the choice between endovascular coiling and open surgical clipping is the dome/neck ratio. Aneurysms that are best suited for coiling have a dome/neck ratio of at least 2. Aneurysms with larger necks have a higher risk for coil herniation and coil mass migration distally if endovascular treatment is pursued. Those aneurysms with ratios greater than 1 but less than 2 may be successfully coiled with balloon remodeling. In the unruptured setting, wide neck aneurysms are treated with stent-assisted coiling which requires the use of

aspirin and clopidogrel. Given the potential for neurosurgical intervention in aSAH patients (i.e., external ventricular drain placement, etc.), most centers only perform stent-assisted coiling in the setting of aSAH when the risks of microsurgical clipping are exceedingly high.

Anesthesia

Endovascular coil embolization for ruptured aneurysms is almost always performed under general anesthesia. This has the advantages of optimal patient comfort, minimal patient movement during angiography that ensures better picture quality, elimination of the risk of sudden movement during delicate portions of the intracranial microcatheterization, and control of the patient's airway and hemodynamics for the duration of the procedure.

Tools Review

- *Sheaths*: A 6 French sheath is typically necessary to perform coiling. At our institution a 23 cm sheath is utilized in patients older than 50 years of age, while a shorter 11 cm sheath is used in younger patients. A 6 French × 90 cm guiding sheath may also be advanced from the groin to the distal common carotid artery for more support. Longer sheaths provide greater stability and improve the pushability of other catheters through tortuous proximal vessels.
- *Guiding catheters*: A 6 Fr × 90 cm (0.070″ ID) guiding catheter is best suited for aneurysmal coiling. The ID allows for two microcatheters (one for coiling and one for balloon remodeling).
  The 6 Fr guiding catheter is usually advanced over a 0.035″ guidewire. If there is significant tortuosity or an unfavorable arch, the guiding catheter may alternatively be advanced over a diagnostic 5F catheter.
- *Microcatheters*: There is a greater degree of variability regarding ID/OD of microcatheters. Several different companies manufacture these; typically, at least 1.7 Fr/.017″ ID microcatheter is preferred (Excelsior SL-10; Stryker; Kalamazoo, MI).
- *Microwires*: A 0.014″ microwire is preferred. As mentioned in the prior chapter, favorable characteristics of the microwire include torquability (requiring proximal stiffness) with a soft and malleable distal tip to avoid injury to the delicate intracranial vasculature. Microwires come in at least two sizes, a standard 200 cm and an exchange length 300 cm.
- *Balloons*: A balloon may be advanced through a microcatheter and temporarily inflated during the coiling process to preclude herniation of coils into either the parent or branch vessels, respectively.

Compliant balloons are typically employed during coiling procedures when there is concern that the aneurysm neck may be wide. Several different balloons can be used for vessel remodeling. These include the more compliant Hyperform^{R} and Hyperglide^{R} (Covidien, Irvine, CA) that use a 0.010″ microwire. The Hyperform balloon is more compliant and adapts better to the surrounding vessel anatomy. The Hyperglide balloon is slightly stiffer and thus provides greater stability. These two balloons are both advanced using a 0.010″ wire.

Double-lumen balloon microcatheters have also been recently utilized allowing a single microcatheter to accomplish both balloon remodeling and coiling, i.e., Scepter balloon (Microvention-Terumo; Tustin, CA) using a 0.014″ wire. Balloons are typically inflated with a 50:50 or 70:30 mixture of contrast and saline.

- *Medications*: The use of heparin during coiling of ruptured aneurysms is variable. Those who do utilize it administer it after different steps in the procedure: sheath insertion, guiding catheter positioning, and aneurysm access with a microcatheter or after deploying the first coil.

Procedural Steps A sheath is placed within the access site. Heparin is administered to achieve an activated clotting time of >250 s and rechecked hourly (assuming the aneurysm has already been secured). The guiding catheter is navigated into the parent vessel (i.e., proximal internal carotid artery or vertebral artery). Baseline angiography is performed (usually including three-dimensional angiography) to clarify the angioarchitecture and to obtain the best working projection for visualization of the aneurysm neck and parent vessel.

Under roadmap angiography, a microcatheter is advanced over a microwire to the aneurysm. Ideally, the microcatheter should land approximately halfway into the aneurysm. At this point, the microwire is removed from the microcatheter and coiling is undertaken. There are a number of different coils to choose from for endovascular aneurysm treatment. In ruptured aneurysms, a softer coil is usually preferred to frame the aneurysm as it decreases the risk of aneurysm perforation/rupture. Subsequently, coils are deployed in a sequential fashion into this framing coil with progressively smaller diameters and increasing softness. After being completely deployed into the aneurysm, each coil is detached either electrolytically or mechanically, and subsequently the coil pusher is removed. During the coiling procedure, control angiograms are performed intermittently to evaluate the progressive occlusion of the aneurysm and to rule out the development of thromboembolism, perforation, or encroachment of coils on the normal parent vessel. Once the aneurysm is satisfactorily filled with coils, the microcatheter is slowly removed from the aneurysm.

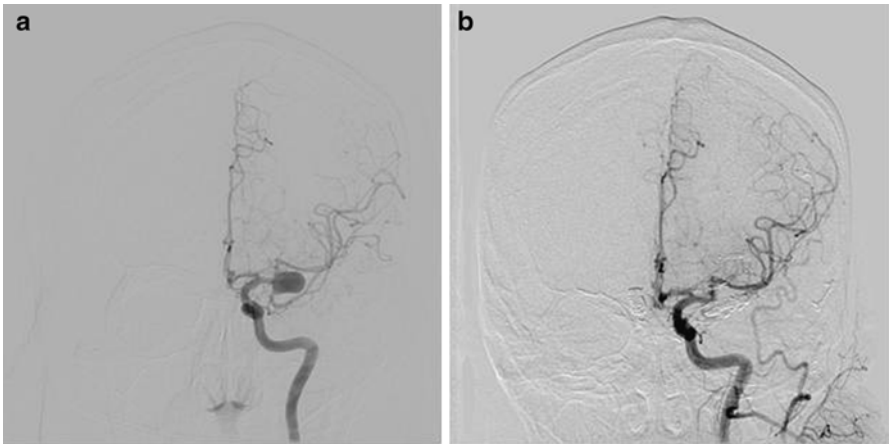

Fig. 11.1 (**a**) Left middle cerebral artery (MCA) aneurysm. (**b**) Same patient after surgical clipping of the left MCA aneurysm

Illustrative Case 1

A 75-year-old woman presented was brought to the emergency department after being found down by her family. Her initial Hunt and Hess (HH) grade was IV. A non-contrast head CT (NCCT) revealed diffuse SAH with hydrocephalus, and CTA showed a left MCA bifurcation aneurysm. Her exam improved to HH 3 after EVD placement, and a decision was made to secure the aneurysm with endovascular coiling. The initial angiogram confirmed the left MCA bifurcation aneurysm (Fig. 11.1a). The aneurysm was successfully coiled with complete aneurysm occlusion (Fig. 11.1b).

Illustrative Case 2

A 45-year-old male smoker presented to the emergency department with a severe headache (HH II) and diffuse SAH on NCCT. A basilar tip aneurysm was identified on CTA, and endovascular coiling was selected as the treatment modality given the high risk associated with open surgical clipping in this location. Catheter angiography confirmed a favorable aneurysm configuration (Fig. 11.2a), and successful coil embolization was performed (Fig. 11.2b).

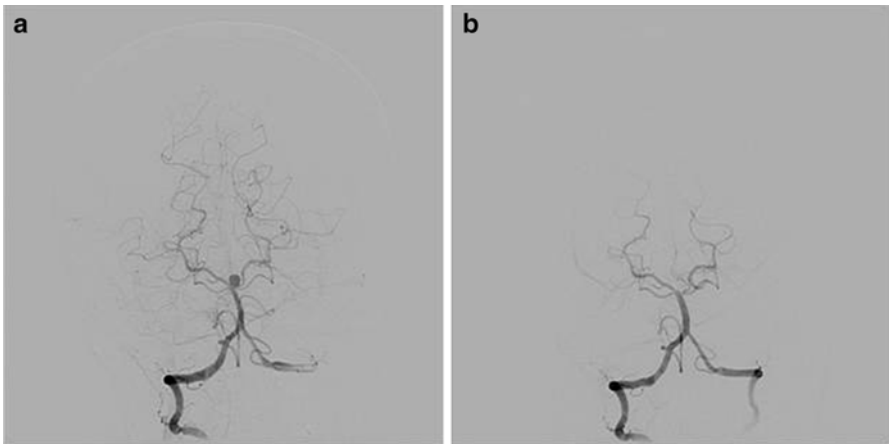

Fig. 11.2 (**a**) Tip of the basilar artery (BA) aneurysm. (**b**) Same patient after endovascular coiling of the BA aneurysm

Endovascular Management of Cerebral Vasospasm

Patient Selection

aSAH patients are monitored for 14–21 days (depending on the Hunt and Hess score) using several different noninvasive modalities. These include daily transcranial Dopplers, CT perfusion, EEG, and clinical exam. When a significant change is noted (see "vasospasm" section), select patients with a high likelihood of decline are taken to the angiography suite for further treatment.

Anesthesia

Endovascular vasospasm treatment is usually performed under general anesthesia if angioplasty is planned or possible. In cooperative or sedated patients, intra-arterial catheterization and injection of spasmolytic agents can be performed with moderate sedation.

Tools Review (See Chap. 1)

- *Sheaths*: A 6 French sheath is typically necessary to perform either angioplasty and/or intra-arterial infusion of vasodilators. At our institution a 23 cm sheath is utilized in patients older than 50 years of age while a shorter 11 cm sheath is used in younger patients.

- *Guiding catheters*: A 6 Fr × 90 cm (0.070″ ID) guiding catheter is best suited for the treatment of vasospasm. The ID allows for two microcatheters as well as ample space for performing intraprocedural angiographic runs (one for angioplasty and one for intra-arterial infusion of vasodilators).
- *Microcatheters*: A 0.010 in. or greater microcatheter is typically utilized to spasmolytic agents.
- *Microwires*: A 0.014 in. microwire is preferred. As mentioned in the prior chapter, favorable characteristics of the microwire include torquability (requiring proximal stiffness) with a soft and malleable distal tip to avoid injury to the delicate intracranial vasculature. Lengths of 180–200 cm are typically used.
- *Balloons*: Several different balloons can be used for angioplasty. These include the Hyperglide^{R} that uses a 0.010″ microwire. As the arteries that are typically angioplastied are ≤4 mm (i.e., M1 or M2/A1), balloon dimensions range from 2 to 4 mm × 7 to 10 mm.

  More recently, double-lumen balloons such as the Scepter XC^{R} and the Ascent^{R} (Codman Neurovascular; Raynham, MA) that utilize a 0.014″ microwire can be used. These compliant balloons have a double lumen through which vasodilators may be infused in addition to performing balloon angioplasty.
- Balloons are typically inflated with a 50:50 or 70:30 mixture of contrast and saline.

  Some operators may also use semicompliant coronary balloons (off label) that advance over a 0.014″ microwire system, e.g., TREK (Abbott; Chicago, IL) or Maverick (Boston Scientific; Natick, MA). These balloons should be used very carefully, and typically a submaximal angioplasty of up to 70 % of the diameter should be performed.
- *Medications*: Several different vasodilators have been infused intra-arterially to reduce vasospasm. Verapamil and nicardipine are our drugs of choices. These can be diluted and infused intra-arterially especially when treating vasospasm that is distal and not amenable to balloon angioplasty.

Procedural Steps (See Fig. 11.3)

A sheath is placed within the access site. Heparin is administered to achieve an activated clotting time of >250 s and rechecked hourly (assuming the aneurysm has already been secured). The guiding catheter is navigated into the parent vessel (i.e., proximal internal carotid artery or vertebral artery). Baseline angiography is performed to evaluate the vasculature. If significant vasospasm is noted proximally, then balloon angioplasty may be performed. The balloon occlusion catheter can either be advanced primarily or in some instances utilizing an exchange technique. The balloon is slowly inflated (submaximally) and then deflated. This can be repeated several times. For more distal spasm a microcatheter can be tracked into the parent vessel MCA, ACA, or PCA, and intra-arterial nicardipine or verapamil may be infused into the territory. Typically these infusions are diluted over several minutes to minimize the systemic hypotensive effects.

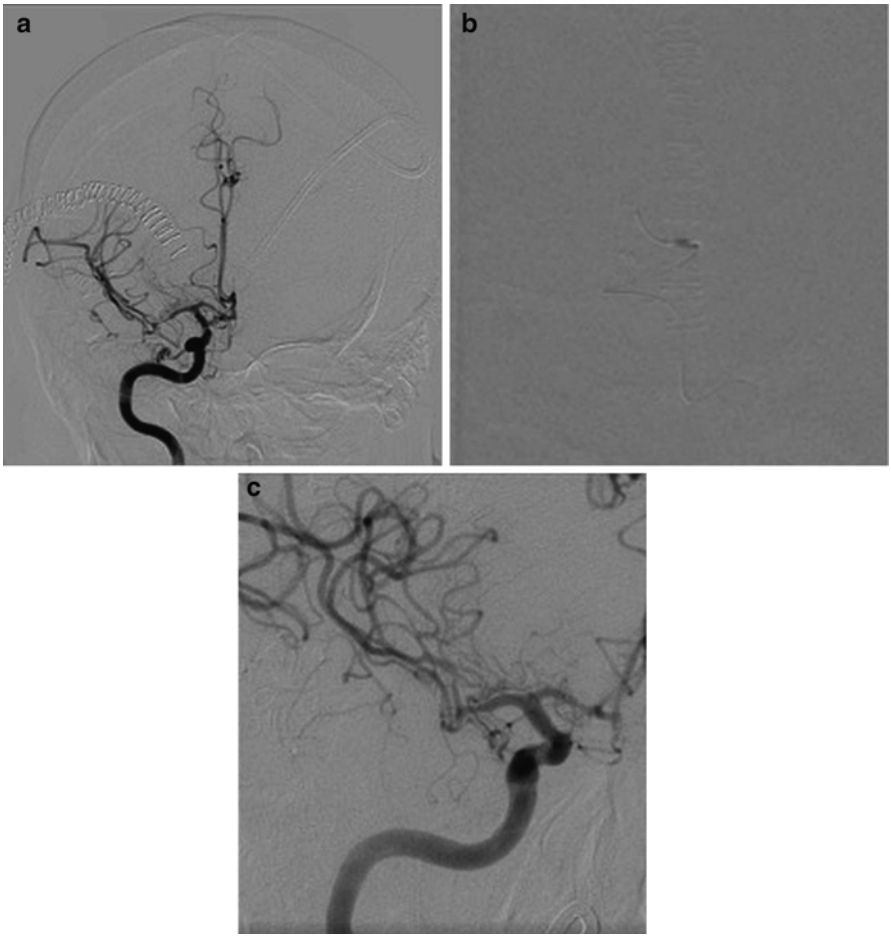

Fig. 11.3 (**a**) Right middle cerebral artery (MCA) with evidence of vasospasm involving the distal right M1 segment of the MCA. (**b**) A Hyperglide balloon is inflated **within** the right MCA (magnified view) within the stenotic segment. Contrast is seen filling the lumen of the balloon. (**c**) A magnified view of the right MCA after angioplasty

Post-procedural Considerations

While balloon angioplasty tends to have more prolonged effects, the therapeutic/beneficial effects of intra-arterial vasodilators are ephemeral typically lasting 24 h. Thus, it is important to continue close monitoring of these patients as they may require repeated treatments. We typically will leave the femoral access sheath in place up to 24 h after vasospasm treatment for potential retreatment.

Illustrative Case 3

A 38-year-old woman presented with sudden severe headache and transient loss of consciousness (HH II). She underwent open surgical clipping of an anterior communicating artery aneurysm and on post-bleed day 5 developed elevations of velocities on TCD and a left arm drift. Catheter angiography revealed severe right middle cerebral artery spasm. Given the early onset of severe spasm, angioplasty was selected as the most dural treatment. This was successfully performed (Fig. 11.3a, b) with greatly improved vessel diameter posttreatment (Fig. 11.3c).

References

1. Sandvei MS, et al. Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984-2007. Neurology. 2011;77(20):1833–9.
2. Labovitz DL, et al. Subarachnoid hemorrhage incidence among Whites, Blacks and Caribbean Hispanics: the Northern Manhattan Study. Neuroepidemiology. 2006;26(3):147–50.
3. Fontanarosa PB. Recognition of subarachnoid hemorrhage. Ann Emerg Med. 1989;18(11): 1199–205.
4. Sandvei MS, et al. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. Stroke. 2009;40(6):1958–62.
5. Young AM, Karri SK, Ogilvy CS. Exploring the use of estrogen & progesterone replacement therapy in subarachnoid hemorrhage. Curr Drug Saf. 2012;7(3):202–6.
6. de Rooij NK, et al. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365–72.
7. Mhurchu CN, et al. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: an international population-based, case-control study. Stroke. 2001;32(3):606–12.
8. Ohkuma H, Fujita S, Suzuki S. Incidence of aneurysmal subarachnoid hemorrhage in Shimokita, Japan, from 1989 to 1998. Stroke. 2002;33(1):195–9.
9. Feigin V, et al. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke. 2005;36(7):1360–5.
10. Isaksen J, et al. Risk factors for aneurysmal subarachnoid haemorrhage: the Tromso study. J Neurol Neurosurg Psychiatry. 2002;73(2):185–7.
11. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290(2):199–206.
12. Schievink WI, et al. Alpha-1-antitrypsin phenotypes among patients with intracranial aneurysms. J Neurosurg. 1996;84(5):781–4.
13. Nordskog BK, et al. Matrix-degrading and pro-inflammatory changes in human vascular endothelial cells exposed to cigarette smoke condensate. Cardiovasc Toxicol. 2003;3(2):101–17.
14. Brown Jr RD, et al. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. J Neurosurg. 2008;108(6):1132–8.
15. Jee SH, et al. The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. Hypertension. 1999;33(2):647–52.
16. Sandvei MS, et al. Risk factors for aneurysmal subarachnoid hemorrhage – BMI and serum lipids: 11-year follow-up of the HUNT and the Tromso Study in Norway. Acta Neurol Scand. 2012;125(6):382–8.
17. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. N Engl J Med. 1998;339(24):1725–33.

18. Longstreth Jr WT, et al. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke. 1992;23(9):1242–9.
19. Juvela S, et al. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke. 1993;24(5):639–46.
20. Schievink WI, et al. Familial aneurysmal subarachnoid hemorrhage: a community-based study. J Neurosurg. 1995;83(3):426–9.
21. Clarke G, Mendelow AD, Mitchell P. Predicting the risk of rupture of intracranial aneurysms based on anatomical location. Acta Neurochir (Wien). 2005;147(3):259–63. Discussion 263.
22. Aarhus M, Helland CA, Wester K. Differences in anatomical distribution, gender, and sidedness between ruptured and unruptured intracranial aneurysms in a defined patient population. Acta Neurochir (Wien). 2009;151(12):1569–74.
23. Rinkel GJ, et al. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29(1):251–6.
24. Chyatte D, et al. Inflammation and intracranial aneurysms. Neurosurgery. 1999;45(5):1137–46. Discussion 1146–7.
25. Kanematsu Y, et al. Critical roles of macrophages in the formation of intracranial aneurysm. Stroke. 2011;42(1):173–8.
26. Hashimoto T, Meng H, Young WL. Intracranial aneurysms: links among inflammation, hemodynamics and vascular remodeling. Neurol Res. 2006;28(4):372–80.
27. Kataoka K, et al. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. Stroke. 1999;30(7):1396–401.
28. Pera J, et al. Gene expression profiles in human ruptured and unruptured intracranial aneurysms: what is the role of inflammation? Stroke. 2010;41(2):224–31.
29. Jayaraman T, et al. TNF-alpha-mediated inflammation in cerebral aneurysms: a potential link to growth and rupture. Vasc Health Risk Manag. 2008;4(4):805–17.
30. Dhopesh V, Anwar R, Herring C. A retrospective assessment of emergency department patients with complaint of headache. Headache. 1979;19(1):37–42.
31. Leicht MJ. Non-traumatic headache in the emergency department. Ann Emerg Med. 1980;9(8):404–9.
32. Ramirez-Lassepas M, et al. Predictors of intracranial pathologic findings in patients who seek emergency care because of headache. Arch Neurol. 1997;54(12):1506–9.
33. Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physicians. J Emerg Med. 2008;34(3):237–51.
34. Seet CM. Clinical presentation of patients with subarachnoid haemorrhage at a local emergency department. Singapore Med J. 1999;40(6):383–5.
35. Edlow JA. Diagnosis of subarachnoid hemorrhage in the emergency department. Emerg Med Clin North Am. 2003;21(1):73–87.
36. Edlow JA. Diagnosis of subarachnoid hemorrhage. Neurocrit Care. 2005;2(2):99–109.
37. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306–18.
38. Locksley HB. Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. J Neurosurg. 1966;25(3):321–68.
39. Ball MJ. Pathogenesis of the "sentinel headache" preceding berry aneurysm rupture. Can Med Assoc J. 1975;112(1):78–9.
40. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. Cephalalgia. 2003;23(10):935–41.
41. Schievink WI, et al. Circumstances surrounding aneurysmal subarachnoid hemorrhage. Surg Neurol. 1989;32(4):266–72.
42. Matsuda M, et al. Circumstances, activities, and events precipitating aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2007;16(1):25–9.
43. Schievink WI. Intracranial aneurysms. N Engl J Med. 1997;336(1):28–40.
44. Perry JJ, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. BMJ. 2011;343:d4277.

45. Kassell NF, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73(1):18–36.
46. van Gijn J, van Dongen KJ. The time course of aneurysmal haemorrhage on computed tomograms. Neuroradiology. 1982;23(3):153–6.
47. Perry JJ, et al. Is the combination of negative computed tomography result and negative lumbar puncture result sufficient to rule out subarachnoid hemorrhage? Ann Emerg Med. 2008; 51(6):707–13.
48. Vermeulen M, et al. Xanthochromia after subarachnoid haemorrhage needs no revisitation. J Neurol Neurosurg Psychiatry. 1989;52(7):826–8.
49. Heasley DC, Mohamed MA, Yousem DM. Clearing of red blood cells in lumbar puncture does not rule out ruptured aneurysm in patients with suspected subarachnoid hemorrhage but negative head CT findings. AJNR Am J Neuroradiol. 2005;26(4):820–4.
50. Graves P, Sidman R. Xanthochromia is not pathognomonic for subarachnoid hemorrhage. Acad Emerg Med. 2004;11(2):131–5.
51. Arora S, Swadron SP, Dissanayake V. Evaluating the sensitivity of visual xanthochromia in patients with subarachnoid hemorrhage. J Emerg Med. 2010;39(1):13–6.
52. Wiesmann M, et al. Detection of hyperacute subarachnoid hemorrhage of the brain by using magnetic resonance imaging. J Neurosurg. 2002;96(4):684–9.
53. Yuan MK, et al. Detection of subarachnoid hemorrhage at acute and subacute/chronic stages: comparison of four magnetic resonance imaging pulse sequences and computed tomography. J Chin Med Assoc. 2005;68(3):131–7.
54. Mitchell P, et al. Detection of subarachnoid haemorrhage with magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2001;70(2):205–11.
55. Huston 3rd J, et al. Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: importance of aneurysm size. AJNR Am J Neuroradiol. 1994; 15(9):1607–14.
56. Kaufmann TJ, Kallmes DF. Diagnostic cerebral angiography: archaic and complication-prone or here to stay for another 80 years? AJR Am J Roentgenol. 2008;190(6):1435–7.
57. Mani RL, Eisenberg RL. Complications of catheter cerebral arteriography: analysis of 5,000 procedures. II Relation of complication rates to clinical and arteriographic diagnoses. AJR Am J Roentgenol. 1978;131(5):867–9.
58. Earnest 4th F, et al. Complications of cerebral angiography: prospective assessment of risk. AJR Am J Roentgenol. 1984;142(2):247–53.
59. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001;124(Pt 2):249–78.
60. Ronkainen A, et al. Intracranial aneurysms: MR angiographic screening in 400 asymptomatic individuals with increased familial risk. Radiology. 1995;195(1):35–40.
61. Anderson GB, et al. Computed tomographic angiography versus digital subtraction angiography for the diagnosis and early treatment of ruptured intracranial aneurysms. Neurosurgery. 1999;45(6):1315–20. Discussion 1320–2.
62. Chen W, et al. Cerebral aneurysms: accuracy of 320-detector row nonsubtracted and subtracted volumetric CT angiography for diagnosis. Radiology. 2013;269(3):841–9.
63. Lai PH, et al. Detection and assessment of circle of Willis aneurysms in acute subarachnoid hemorrhage with three-dimensional computed tomographic angiography: correlation with digital substraction angiography findings. J Formos Med Assoc. 1999;98(10):672–7.
64. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968;28(1):14–20.
65. Hunt WE, Kosnik EJ. Timing and perioperative care in intracranial aneurysm surgery. Clin Neurosurg. 1974;21:79–89.
66. Bederson JB, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 2009;40(3):994–1025.
67. Lemonick D. Subarachnoid hemorrhage: state of the artery. Am J Clin Med. 2010;7(2): 61–73.

68. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med. 2006;354(4):387–96.
69. Hasan D, et al. Management problems in acute hydrocephalus after subarachnoid hemorrhage. Stroke. 1989;20(6):747–53.
70. Haley Jr EC, Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. Stroke. 1992;23(2):205–14.
71. McIver JI, et al. Preoperative ventriculostomy and rebleeding after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;97(5):1042–4.
72. Seiler RW, et al. Cerebral vasospasm evaluated by transcranial ultrasound correlated with clinical grade and CT-visualized subarachnoid hemorrhage. J Neurosurg. 1986;64(4):594–600.
73. Wang HC, et al. Time course of cerebral hemodynamics in aneurysmal subarachnoid hemorrhage. J Clin Ultrasound. 2012;40(2):91–8.
74. Harrod CG, Bendok BR, Batjer HH. Prediction of cerebral vasospasm in patients presenting with aneurysmal subarachnoid hemorrhage: a review. Neurosurgery. 2005;56(4):633–54. Discussion 633–54.
75. Suzuki H, et al. Intracranial heme metabolism and cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2003;34(12):2796–800.
76. Rodriguez y Baena R, et al. Cisternal and lumbar CSF levels of arachidonate metabolites after subarachnoid haemorrhage: an assessment of the biochemical hypothesis of vasospasm. Acta Neurochir (Wien). 1987;84(3–4):129–35.
77. Fuwa I, et al. Enhanced secretion of endothelin by endothelial cells in response to hemoglobin. Neurol Med Chir (Tokyo). 1993;33(11):739–43.
78. Kessler IM, et al. Endothelin-1 levels in plasma and cerebrospinal fluid of patients with cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Surg Neurol. 2005;64 Suppl 1:S1:2–5. Discussion S1:5.
79. Schianchi PM, Hughes JT. Cerebral artery spasm: histological changes in necropsies of cases of subarachnoid hemorrhage. Adv Neurol. 1978;20:521–34.
80. Smith RR, et al. Arterial wall changes in early human vasospasm. Neurosurgery. 1985;16(2): 171–6.
81. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm – the clinical manifestations. Neurosurgery. 1977;1(3):245–8.
82. Rabb CH, et al. A statistical analysis of factors related to symptomatic cerebral vasospasm. Acta Neurochir (Wien). 1994;127(1–2):27–31.
83. Kramer AH, et al. A comparison of 3 radiographic scales for the prediction of delayed ischemia and prognosis following subarachnoid hemorrhage. J Neurosurg. 2008;109(2):199–207.
84. Suarez JI, et al. Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. Crit Care Med. 2002;30(6):1348–55.
85. Naval NS, Thomas CE, Urrutia VC. Relative changes in flow velocities in vasospasm after subarachnoid hemorrhage: a transcranial Doppler study. Neurocrit Care. 2005;2(2):133–40.
86. Pickard JD, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989;298(6674):636–42.
87. Dankbaar JW, et al. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. Crit Care. 2010;14(1):R23.
88. Origitano TC, et al. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. Neurosurgery. 1990;27(5):729–39. Discussion 739–40.
89. Hoff R, et al. Blood volume measurement to guide fluid therapy after aneurysmal subarachnoid hemorrhage: a prospective controlled study. Stroke. 2009;40(7):2575–7.
90. Wong GK, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage: an updated systemic review and meta-analysis. Crit Care. 2011;15(1):R52.
91. Jun P, et al. Endovascular treatment of medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2010;31(10):1911–6.

92. Byrne JV. Tutorials in endovascular neurosurgery and interventional neuroradiology. New York: Springer; 2012.
93. Molyneux AJ, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809–17.
94. 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.
95. Qureshi AI, et al. Comparison of endovascular and surgical treatments for intracranial aneurysms: an evidence-based review. Lancet Neurol. 2007;6(9):816–25.
96. Natarajan SK, et al. Outcomes of ruptured intracranial aneurysms treated by microsurgical clipping and endovascular coiling in a high-volume center. AJNR Am J Neuroradiol. 2008;29(4):753–9.
97. McDougall CG, et al. The Barrow Ruptured Aneurysm Trial. J Neurosurg. 2012;116(1): 135–44.
98. Spetzler RF, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. J Neurosurg. 2013;119(1):146–57.
99. Molyneux A, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267–74.
100. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. Neurosurgery. 1983;13(5):479–81.
101. Rosenorn J, et al. The risk of rebleeding from ruptured intracranial aneurysms. J Neurosurg. 1987;67(3):329–32.
102. Winn HR, Richardson AE, Jane JA. The long-term prognosis in untreated cerebral aneurysms: I. The incidence of late hemorrhage in cerebral aneurysm: a 10-year evaluation of 364 patients. Ann Neurol. 1977;1(4):358–70.
103. Wirth FP. Surgical treatment of incidental intracranial aneurysms. Clin Neurosurg. 1986;33:125–35.
104. Jane JA, Winn HR, Richardson AE. The natural history of intracranial aneurysms: rebleeding rates during the acute and long term period and implication for surgical management. Clin Neurosurg. 1977;24:176–84.
105. Juvela S. Rebleeding from ruptured intracranial aneurysms. Surg Neurol. 1989;32(5): 323–6.
106. Whitfield PC, Kirkpatrick PJ. Timing of surgery for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2001;(2):CD001697.
107. Wong GK, et al. Ultra-early (within 24 hours) aneurysm treatment after subarachnoid hemorrhage. World Neurosurg. 2012;77(2):311–5.
108. Horowitz MB, et al. Endovascular therapy for intracranial aneurysms: a historical and present status review. Surg Neurol. 2002;57(3):147–58. Discussion 158–9.

Chapter 12
Arteriovenous Malformations of the Brain

Anmar Razak, Syed I. Hussain, Joanna Kemp, and Jeroen R. Coppens

Introduction

Most AVMs are sporadic lesions. The underlying cell biology of this phenomenon has been studied, and while considerable progress has been made, it is still not completely understood [1, 2]. It has been postulated that AVMs are congenital lesions related to failure of embryogenesis during the differentiation of vascular channels into mature arteries, capillaries, and veins [1, 3, 4]. These alterations in development lead to fistulous connections between arteries and veins. The lack of a capillary bed creates a low resistance system, resulting in high-flow shunting with subsequent arterial dilatation and venous arterialization. This high-flow state also appears to be related to the development of aneurysms in a variety of locations associated with the AVM [1, 5–9].

AVMs have been shown to be dynamic lesions with a variety of morphologies. Niazi et al. [4] separated these morphologies into three major groups: the most common high-flow variant with a compact nidus and few arterial feeders and draining veins; the rarer diffuse variant with low-flow and multiple en-passage arterial feeders and draining veins; and the more recently described linear vein-based configuration with multiple arterial feeders draining into a single, usually superficial, vein. The latter two types are more frequently seen in the pediatric population, but can

A. Razak, M.D. • S.I. Hussain, M.D.
Department of Neurology and Ophthamology, Michigan State University,
B401 MSU Clinical Center, 804 Service Road, East Lansing, MI 48824, USA
e-mail: anmar.razak@hc.msu.edu; syed.hussain@hc.msu.edu

J. Kemp, M.D. • J.R. Coppens, M.D. (✉)
Department of Neurosurgery, Saint Louis University,
3635 Vista Avenue, St. Louis, MO 63104, USA
e-mail: kempjm@slu.edu; coppensj@slu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_12

grow, develop, and even recur after therapy due to flow characteristics, growth factors, and remodeling secondary to small hemorrhages (evidenced by hemosiderin deposition) and pressure differentials [1, 4, 5, 10, 11]. These factors can all impact the ultimate management strategy.

Epidemiology

AVMs are relatively uncommon lesions whose true prevalence and incidence are unknown. Based on hospital autopsy data, it has been estimated that the prevalence is up to 500–600 AVMs per 100,000 people [12–14]. Based on the incidence of hemorrhage, however, the calculated prevalence ranges from 4 to 19 per 100,000 adults [15]. This is largely thought to be due to lesions that remain clinically silent over the lifetime of some patients, though some have questioned the accuracy of such high numbers produced by the autopsy series [13, 15–18]. However, with the increasing use of various imaging modalities, the ability to detect incidental or unruptured AVMs has also increased. Reported total detection rates range from 0.82 to 1.42 per 100,000 person-years [12, 13, 15–21].

The majority of patients present in their second to fourth decades of life, but children comprise between 3 and 20 % of sporadic AVM patients. Most studies report equal occurrence in males and females. Approximately 90 % of identified AVMs are supratentorial, and 10 % are infratentorial [1, 4, 15, 16, 18, 20–26].

The vast majority of AVMs are sporadic, but 2–5 % of AVMs are associated with genetic syndromes: hereditary hemorrhagic telangiectasia (HHT or Osler–Weber–Rendu syndrome), Wyburn–Mason syndrome, and other cerebrofacial arteriovenous metameric syndromes (CAMSs). HHT is a rare autosomal dominant vascular dysplasia caused by gene mutations at 9q33–q34.1 cr9 (HHT1) or 12q11–q14 cr12 (HHT2). Four to 13 % of HHT patients will have cerebral AVMs in addition to lesions in other organ systems (i.e., nasal, pulmonary, GI, hepatic). One third of HHT patients with cerebral AVMs will have multiple AVMs, compared to 1 % of sporadic AVM patients. Wyburn–Mason syndrome is one of the several neurocutaneous disorders associated with AVMs. Specifically the constellation of findings includes cutaneous vascular nevi, optic nerve or retinal AVMs, and mesencephalic intracranial AVMs that can be bilateral or ipsilateral to lesions in the visual pathway. The genetics is unknown [1, 3, 4, 23].

Natural History

The overall rate of hemorrhage from an AVM has been reported to range from 2 to 4 % per year [1, 7, 12, 21, 23, 25, 27–31]. AVMs are responsible for 1–2 % of strokes [20]. The multiplicative law of probability can be used to calculate the lifetime risk of hemorrhage: $1-(1-\text{risk of hemorrhage})^n$, where n is the number of

expected years of life remaining [1, 23]. Alternatively, estimating lifetime risk can be simplified using lifetime risk (percentage) = 105 minus the patient's age in years. These formulas however do not take into consideration factors that may predict a higher risk of hemorrhage [1, 23, 27].

Multiple factors have been associated with predicting AVM rupture: previous hemorrhage, size, location, pattern of venous drainage, and presence of associated aneurysms. Ethnicity seems to play a role, with Hispanic patients at significantly higher risk for hemorrhage (~3.1-fold). African patients also had a trend of increased risk, though this did not achieve statistical significance [25]. Pediatric patients over the age of 2 are more likely to present with hemorrhage, though the overall risk of hemorrhage does not appear to be any higher than adults [1, 4, 24]. Older age has been shown in many studies to be a risk factor due to increased likelihood of the presence of some of the aforementioned risk factors.

Previous hemorrhage is the most consistent predictor of subsequent hemorrhage [1, 7, 12, 21, 23, 25–32]. The risk of recurrent hemorrhage seems to be the highest in the first year and range from 6 to 17 % [7, 23, 27]. Some evidence supports even higher risk, up to 25 %, after a second hemorrhage. This risk appears to decrease over time if the patient remains hemorrhage-free, with the risk of hemorrhage returning to baseline by the third year [6, 27].

The impact of AVM size has been controversial, with some studies supporting increased risk with small size [1, 21, 23, 33], while others saw higher rates of hemorrhage in larger AVMs [28, 29]. Others have shown no association with AVM size [14]. Some theories have been put forth to explain these observations. First is small size may be related to increased transnidal pressure, resulting in a propensity to hemorrhage [1, 9, 33]. Another theory suggests that small AVMs are more likely to present with hemorrhage as they are unlikely to cause other neurologic symptoms based on size. Therefore, the increased rates of hemorrhage seen in some studies from small AVMs may be more related to a history of previous rupture [1, 28].

Location has been shown to impact the risk of hemorrhage risk. Both deep and infratentorial lesions have higher hemorrhage rates [1, 7, 14, 17, 21, 23, 28, 34, 35]. For example, Fleetwood et al. demonstrated an annualized hemorrhage risk of 9.8 % per patient-year in basal ganglia and thalamic AVMs [35]. This association may be related to angioarchitecture of the AVM with perforating vessels less tolerant to high flow, or simply that presentation with other neurologic symptoms is less likely due to their subcortical location [1, 28].

Deep and compromised venous drainage is also thought to increase hemorrhage risk. Stenosis, occlusion, turbulent flow, and deep drainage have been postulated to result in increased nidal pressure through various mechanisms. This increased pressure may result in AVM rupture [1, 5–7, 11, 14, 23, 27, 28, 33].

AVM-associated aneurysms have also been found to increase risk of hemorrhage. The rate of aneurysm occurrence in AVMs has been highly variable (2–58 %) and may be located on feeding arteries, intranidal, or in the venous drainage system [1, 6, 7, 14, 36]. In a paper by Brown et al., risk of intracranial hemorrhage among patients with coexisting aneurysm and AVM was found to be 7 % per year at 5 years following diagnosis compared to 1.7 % for patients with AVM alone [36].

Morbidity/Mortality

Mortality reported from an initial hemorrhage ranges from 4 to 29 %. Risk for mortality was higher in patients presenting with hemorrhage compared to other presentations. Recurrent hemorrhage is not associated with an increase in mortality rate that is as great as the first event [1, 6, 12, 27, 35]. Risk of mortality is higher for patients with hemorrhage in the infratentorial compartment (~66 %) [34, 37]. Morbidity in patients with AVMs is also variable. Studies report higher rates of significant disability in those who experience hemorrhage (23–85 %) compared to those with other presentations (7 %) [1, 6, 7, 12, 27–29, 37]. Risk of long-term morbidity is higher in those with parenchymal hemorrhage (versus subarachnoid or intraventricular location), involvement of the basal ganglia or thalamus, and location in the posterior fossa [1, 6, 12, 27, 34, 35].

Clinical Presentation

Patients with AVMs can present in a variety of ways. The most common presentation is hemorrhage (38–71 %). Most hemorrhages are intraparenchymal, followed by subarachnoid, intraventricular, and rarely subdural hemorrhage. The second most common presentation is seizure (15–35 %). Mechanisms for this include cortical irritation from mass effect and steal syndrome resulting in ischemia and gliosis of surrounding tissues. Less common presentations include a headache (5–15 %) that mimics migraine, neurologic deficit (up to 10 %, including focal deficits, learning disability, and cognitive impairment which may be related to steal phenomenon), and pulsatile tinnitus. Children may present with hydrocephalus or heart failure [4]. Finally, many more AVMs are being found incidentally due to increased use of cross-sectional imaging, which accounts for 2–15 % of presentations [1, 12, 14, 27].

Diagnosis

Cerebral digital subtraction angiography (DSA) remains the gold standard for the accurate diagnosis of AVMs. Angiography also helps to characterize the size, location, and hemodynamic behavior of the AVM including the anatomy and flow rates of their arterial blood supply and venous drainage and their relationship to the surrounding cerebral vascular environment.

CT- and MR-based imaging are also important in the diagnosis of AVMs both in the acute setting of symptomatic lesions and in elective pretreatment planning. Both modalities are frequently done as the initial diagnostic tests since the majority of AVMs are discovered after nonspecific presentations such as hemorrhage, seizures,

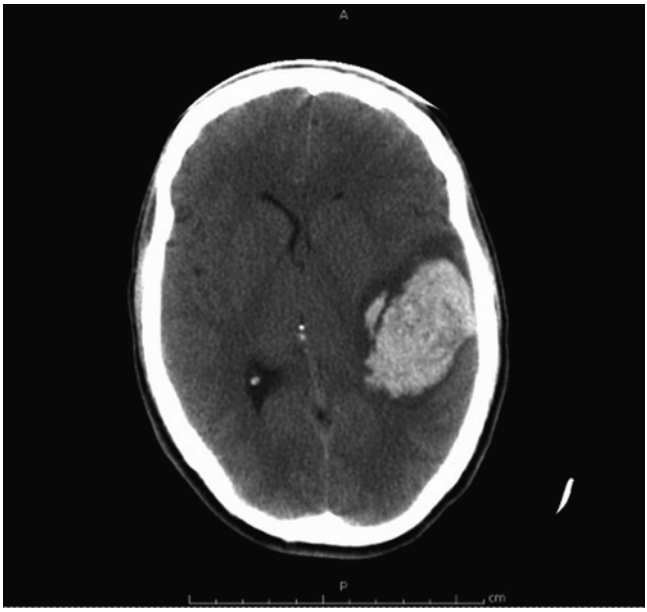

Fig. 12.1 Non-contrast axial CT of brain showing a large intracerebral hemorrhage at time of presentation

focal neurologic deficits, or even headaches [27, 38]. Non-contrast CT scans are usually the initial testing of choice for evaluation of hemorrhage (Fig. 12.1). In the absence of a bleed, CT scans may suggest the presence of an AVM by showing hyperattenuating structures with or without calcifications representing the nidus or one of its feeding or draining vessels. These can also be visualized on MR images as flow voids on T2-weighted sequences. An enhancing nidus can frequently be appreciated on contrast-enhanced MRI T1 sequence (Fig. 12.2) [39]. An advantage of MRI over other imaging modalities is its unique high resolution ability to visualize the surrounding brain parenchyma and delineate any mass effect or gliosis associated with the abnormality as well as proximity to eloquent brain structures (Fig. 12.3). Diffusion tensor imaging (DTI) and functional MRI (fMRI) can further define the relationship of an AVM to critical cortical and white matter structures [40, 41]. MRI also plays an important role in pre-radiosurgery planning and post-treatment follow-up [39, 42].

Noninvasive vascular imaging such as CT angiography (CTA) and MR angiography (MRA) is also a widely used diagnostic testing for evaluation of AVMs. They are both more sensitive and specific than plain CT and MRI in visualizing AVM's angioarchitecture. They remain however inferior to DSA in their ability to demonstrate the temporal flow relationship of the lesion to its surrounding vasculature. They can also miss low-flow small AVMs, which can only be confirmed with DSA [27, 39].

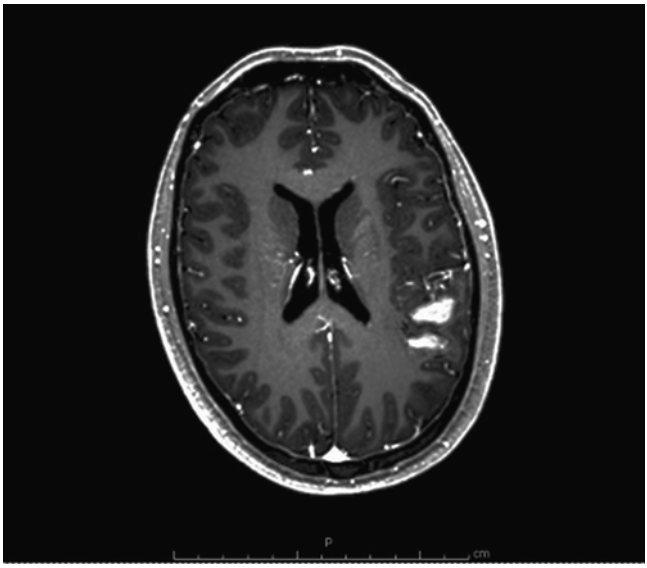

Fig. 12.2 Axial T1 MRI of the brain with gadolinium demonstrating a ruptured left frontoparietal AVM with associated hematoma

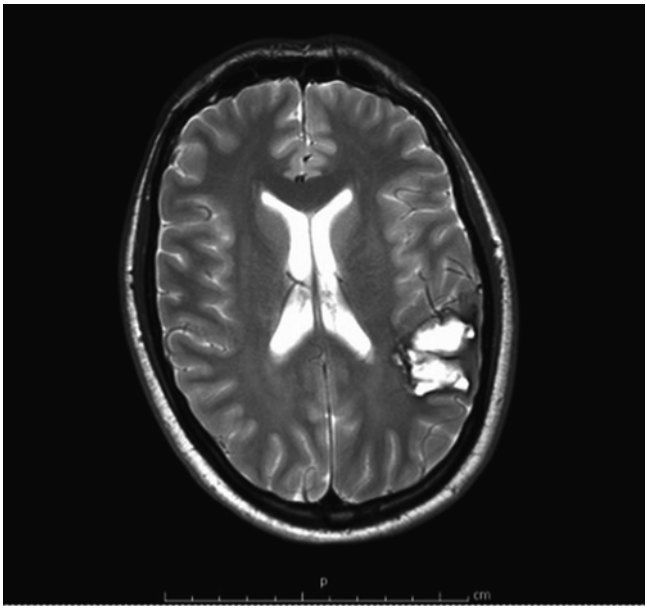

Fig. 12.3 Axial T2 MRI of the brain demonstrating a ruptured AVM with associated hematoma. Small vascular flow voids can be seen representing feeding vessels

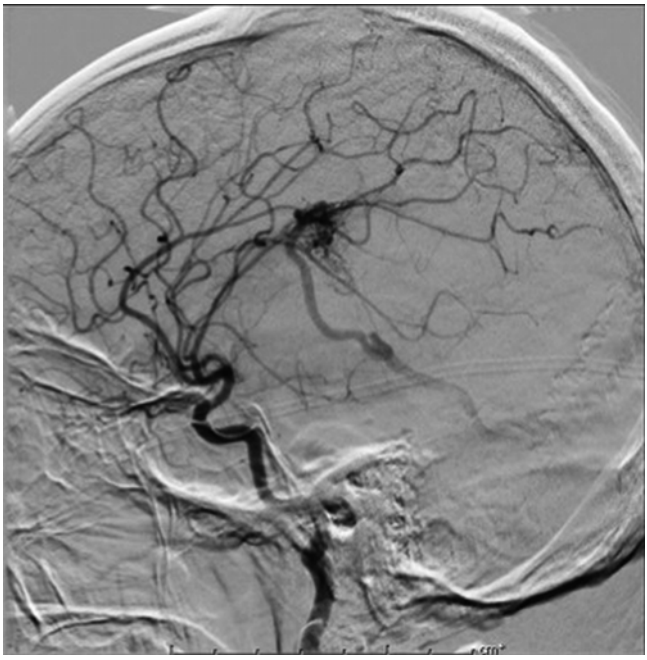

Fig. 12.4 A conventional DSA showing left frontoparietal AVM nidus supplied by feeders from the middle and anterior cerebral arteries. A single draining vein can also be seen flowing inferiorly and posteriorly

The flow dynamics of an AVM can be significantly altered by an acute hematoma. This may cause the size of the AVM to be underestimated or for the lesion to be missed entirely. Repeating the imaging after 6–8 weeks (after the hematoma resolves) may improve visualization [16, 43].

Noninvasive imaging techniques are inferior to conventional DSA in their ability to accurately characterize the hemodynamic behavior of an AVM including the exact location and size of its nidus, the number and flow rates of its various arterial feeders, and the location and characteristics of its draining veins relative to the normal vasculature (Fig. 12.4). All of these characteristics have huge therapeutic and prognostic implications, and their precise knowledge is crucial prior to any planned treatment. Moreover, DSA is superior in its ability to identify associated vascular anomalies such as extranidal and intranidal aneurysms, intranidal arteriovenous fistulas, and any associated vascular occlusive disease that may alter the treatment plan. DSA can also be used diagnostically in the preoperative planning of AVM treatment to test eloquence and map for potential posttreatment neurological deficits. This is done using provocative or superselective Wada testing (see Chap. 9) by locally delivering agents such as amobarbital and propofol among others intra-arterially into the AVM vasculature resulting in transient arrest of brain function in the region of local infusion. This is of particular importance in lesions lying in close

proximity to language centers in the dominant hemisphere [44, 45]. Although invasive in nature, modern DSA has been shown to be extremely safe with a very low risk of complications and long-term sequelae [46].

Therapeutic Decision Making

Multiple variables must be considered when choosing the best course of treatment, including: Spetzler–Martin grade (accounting for size, venous drainage, and eloquence), lenticulostriate supply, compactness of the nidus, the history of previous hemorrhage, and the patient's clinical condition. Available options for treatment include microsurgery, radiosurgery, and endovascular therapy, as well as conservative management.

Classification

Multiple means of grading AVMs have been proposed with focus on using these methods to help guide therapeutic decision making. The most widely used system is the Spetzler–Martin scale (Table 12.1). This grading system was originally designed for risk stratification regarding surgical resection and is based on AVM size (<3 cm nidus, 3–6 cm, >6 cm), pattern of venous drainage (deep versus superficial), and eloquence of surrounding brain tissue (including sensorimotor, language, and visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei). AVMs are graded on a scale of I–V. Higher grades indicate a higher degree of surgical difficulty, with some AVMs classified as grade VI or inoperable [47].

Table 12.1 Spetzler–Martin grading system for AVMs

Characteristic	Points
Size of nidus	
<3 cm	1
3–6 cm	2
>6 cm	3
Venous drainage pattern	
Superficial only	0
Deep	1
Eloquence of adjacent brain	
Non-eloquent	0
Eloquent	1

Adapted from Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83

Evaluation of this grading system has been correlated with patient outcomes [1, 48–54]. A study by Hamilton et al. determined the permanent major neurological morbidity rates for grades I through III were 0 %, increasing to 21.9 % in patients with grade IV and 16.7 % in patients with grade V AVMs [48]. Comparable results were noted in a paper by Spears et al., with early disability (within 7 days) as follows: grade I, 2.1 %; II, 9.4 %; III, 17.3 %; and IV, 39.1 % (no grade V patients). Permanent disability was seen in 2.1 % of grade I patients, 5.7 % in grade II, 1.9 % in grade III, and 21.7 % in grade IV. Statistical analysis did not reveal a difference between outcomes in grades I–III in long-term outcomes [54]. Significant differences between lower grade AVMs were seen in a study by Hartmann et al., in which the study showed any long-term deficits (both mild and disabling) postoperatively in 8 % of grade I patients, 36 % in grade II, 32 % in grade III, and 65 % in grade IV [49]. Similarly, Heros et al. found morbidity in 1.9 % in grade I, 6.5 % in grade II, 23 % in grade III, 32 % in grade IV, and 69 % in grade V [50]. The overall trend does point to correlation with Spetzler–Martin grading; however, variations in the literature between each group have lead to proposed modifications in the system, ranging from expanding the classification to identify differences within groups [55] to simplifying the system into low-risk, moderate-risk, and high-risk categories to aid in capturing larger groups for statistical analysis as well as making application of the system easier [56, 57]. However, none of these modifications are currently widely used.

Microsurgery

Due to low risk of associated morbidity and mortality, surgery is generally recommended in lower grade AVMs. High-grade AVMs are less likely to be treated with surgical intervention due to perceived surgical risk. However, with advancements in surgical techniques and equipment, imaging and neuronavigation, and implementation of multimodality treatment, surgery in high-grade AVMs is becoming safer and more successful [58]. The primary of goal of surgery is the prevention of hemorrhage. Secondary goals are alleviation of seizures and preoperative neurological deficits; however, the efficacy of surgery with these indications is less clear since both can be complications of surgery as well [1, 58].

Surgery for AVMs is typically performed in an elective manner. While there are some reports of acute resection of AVMs after hemorrhage [1, 59, 60], it has been shown that allowing resolution of surrounding edema and removing the AVM in a planned, controlled fashion with a good understanding of its angioarchitecture are more likely to produce favorable outcomes. An ideal compromise can usually be accomplished with the presence of liquefied hematoma surrounding the AVM and absence of significant brain edema. The time between initial rupture and resection of the AVM usually increases in proportion to the size of the hematoma at time of rupture.

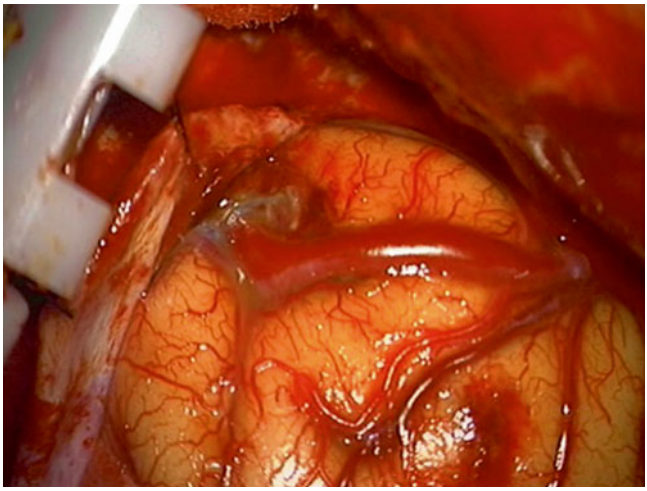

Fig. 12.5 Intraoperative photograph showing large superficial feeding artery

Exceptions may have to be made in cases of large hematomas causing significant mass effect and midline shift. An urgent craniotomy or craniectomy may be necessary. The appropriate approach has to be individualized in those cases, and the primary goal of the operation consists of maximal decompression. It is recommended not to resect the nidus in these cases unless a craniectomy and duraplasty are not sufficient [1, 59, 60].

Approach and positioning of the patient are dependent upon the location of the AVM, and skull-based approaches may be required for the best exposure. Surgery is greatly facilitated when it is possible to access the main arterial feeders early in the procedure and disconnect them prior to mobilizing the nidus (Fig. 12.5). Deep-seated AVMs are best approached with the assistance of frameless stereotactic navigation, which aids in planning optimal trajectory and size of craniotomy and confirms margins during resection. Its use has also shown decreased operative times and blood loss [61].

The craniotomy should be designed to achieve identification of superficial feeding vessels. Correlation with angiography is essential to help distinguish arteries from arterialized draining veins. Careful dissection of sulci, fissures, and subarachnoid cisterns should be performed to secure the more proximal portions of feeding vessels. These vessels should then be followed towards the nidus, where they are coagulated and divided, or clips can be applied (Fig. 12.6). Care should be taken to identify en-passage vessels, which supply normal brain tissue distal to the AVM. Small feeding branches to the AVM from these vessels should be identified and taken with the main artery preserved [1, 58].

Once the feeding vessels have been controlled, a circumferential dissection of the nidus is performed. The nidus should be separated from the underlying brain by taking advantage of the rim of gliosis that surrounds the nidus (Fig. 12.7).

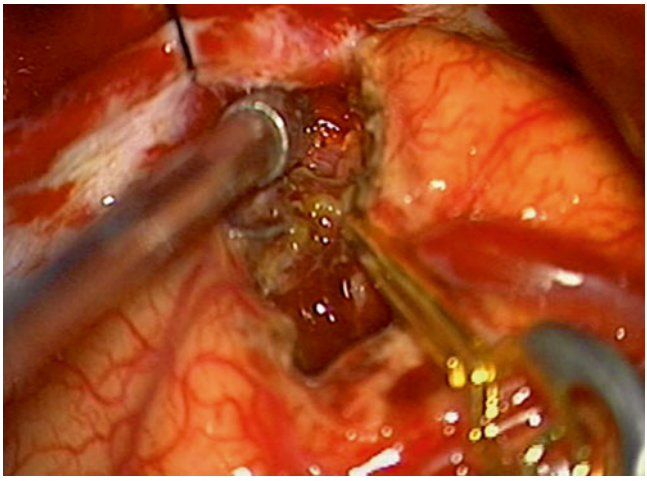

Fig. 12.6 Intraoperative photograph. Initial dissection of nidus with temporary clip placed on feeding vessel

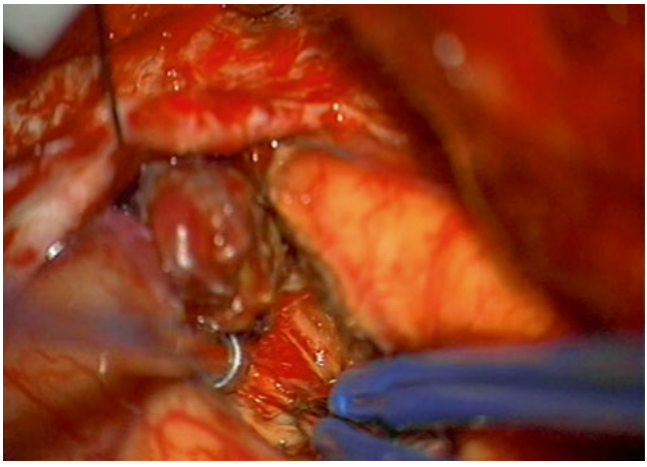

Fig. 12.7 Intraoperative photograph. Deep dissection of AVM with nidus retracted superiorly

Initially the nidus is still under high pressure, so direct coagulation of the nidus can result in hemorrhage and should be avoided. Therefore, it is recommended to avoid coagulation of the nidus until sufficient numbers of feeding vessels have been disconnected and the nidus decreases in size and turgor. Deep perforators and feeding vessels can be a source of hemorrhage, and use of mini clips can be helpful to control those vessels and prevent them from retracting in the surrounding brain after incomplete anticoagulation. After the nidus has been disconnected from its

inflow, it will appear deflated, and the venous drainage will have become darker. At this time, disconnection from the venous drainage system is indicated, and the nidus can be removed en bloc [1, 58].

Meticulous hemostasis is critical to the microsurgical resection of AVMs. Coagulating high-flow vessels is more difficult and requires longer application of cautery. After removal of the nidus, the cavity should be inspected for any potential sources of bleeding. Increasing the patient's systolic blood pressure by 15–20 mmHg can assist in identifying points of breakthrough [1, 58].

Intraoperative confirmation of complete resection is desirable and can be achieved by either conventional digital subtraction angiography or intraoperative near-infrared indocyanine green (ICG) angiography. Use of conventional angiography requires placement of an arterial catheter and use of fluoroscopy and a radiolucent head holder, whereas ICG angiography requires intravenous administration of ICG and a microscope with integrated function. ICG angiography may have limited capacity to identify deep vessels or nidus hidden by surrounding parenchyma, but both have capability of identifying residual nidus and differentiating normal from residual AVM vessels and are useful tools for assessment of total resection [1, 58, 62].

Endovascular Treatment

Introduction

The endovascular approach to treatment of AVMs consists of percutaneous transarterial delivery of therapeutic embolic agents that are introduced locally into the AVM nidus or its feeding and draining vessels with the ultimate goal being hemodynamic shutdown of the AVM. The site of entry into the body is usually the femoral artery or in some instances the brachial or radial arteries. Endovascular embolization of AVM has been shown to be an invaluable tool in the pre- and post-microsurgical and radiosurgical management of AVMs and in certain cases can serve as the definitive curative treatment [63–65].

Embolization Strategy

Endovascular treatment of AVMs assumes one of three roles: adjunctive, curative, or palliative. The extent of embolization desired or achieved depends on a number of factors including: (1) lesion characteristics including size, accessibility, and the number and size of feeding vessels, (2) experience of the operating interventionalist, (3) available technology in terms of access systems and embolic agents, and in some instances (4) a therapeutic decision is sometimes taken to only partially obliterate the AVM if it is felt that complete obliteration carries more risk of morbidity or mortality.

Endovascular embolization is typically performed in multiple stages spanning weeks or even months. This approach reduces the risk of intracerebral hemorrhage as a complication that may result from treatment-related alteration in cerebral flow dynamics within the AVM and the surrounding normal parenchyma in the immediate vicinity. A mechanism known as normal perfusion pressure breakthrough explains this risk in which a sudden occlusion of a major AVM feeder leads to diversion of blood to adjacent parenchymal tissue that has been hypoperfused prior to treatment with maximally dilated normal vessels that in turn fail to autoregulate the sudden increase in diverted flow, leading to dangerous hyperperfusion and probable hemorrhage [66, 67].

- *Adjunctive embolization*
  Endovascular therapy is often utilized as part of a multimodality treatment approach to AVMs that also includes microsurgery and radiosurgery. This approach enables more successful treatment of deeply seated and large AVMs and has been shown to improve patient outcome [68–70]. The purpose of adjunctive embolization is to supplement to other modalities through reduction of the AVM nidus by shutting down some of its feeders. This can facilitate surgical excision of accessible lesions, help in preparation for radiosurgery of lesions that are initially too large to respond to radiation, and also be used to treat associated vascular lesions such as aneurysms [71–73]. As an adjunct to microsurgical resection, endovascular embolization has proven very helpful in cases of AVMs with a large nidus, deep-feeding vessels, and high-flow shunts (Figs. 12.8 and 12.9). This approach has allowed for safe treatment of AVMs with higher Spetzler–Martin grades as compared to surgical resection alone while at the same time shortening operative time and minimizing blood loss intraoperatively (Fig. 12.10) [63, 74, 75].

  Endovascular embolization is one of the highest risk neurointerventional procedures and should not be offered without careful consideration. Some architecturally simple and small AVMs (Spetzler–Martin grades I and II) can be safely removed using surgical excision alone. On the other hand, embolization should be strongly considered in AVMs with a Spetzler–Martin grade of III, IV, and sometimes V and, as mentioned above, generally any AVMs with deep feeders that are hard to access through microsurgery [76]. As an adjunctive treatment, the degree of nidal occlusion does not always need to be 100 %. The work by Vinuela et al. suggests that while endovascular embolization is most useful to the surgeon when the AVM nidus has been occluded by at least 75 %, lesser degrees of occlusion were also helpful if they removed deep inaccessible feeders [77].

  For AVMs that are large and deeply seated in eloquent cortex, multimodal treatment consists of endovascular embolization and radiosurgery. The goal of endovascular embolization in these cases is to reduce the size of the AVM in addition to treating associated vascular lesions that are not responsive to radiation, such as intra- and extranidal aneurysms and fistulas. Radiosurgery generally becomes more likely to achieve a cure as the size of the AVM nidus decreases. There is data to suggest that radiosurgical cure is more likely when the AVM

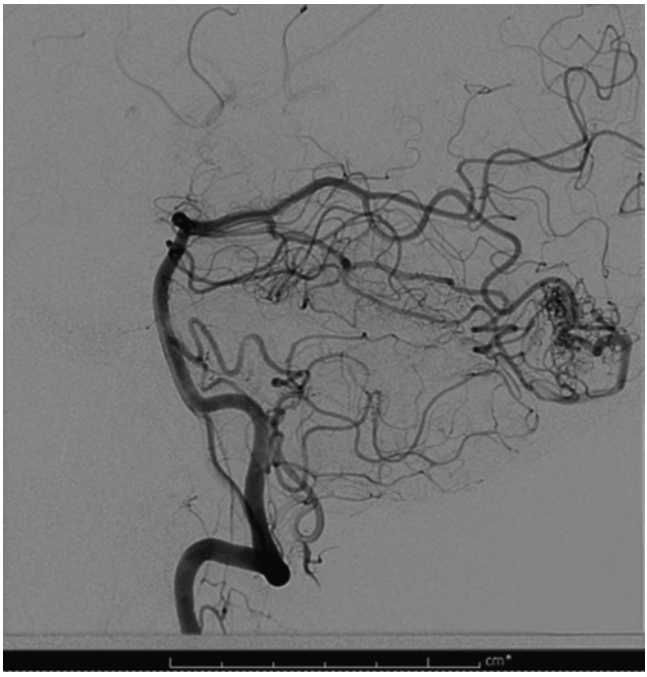

Fig. 12.8 A pre-embolization conventional angiogram showing occipital AVM with feeders from the posterior cerebral artery

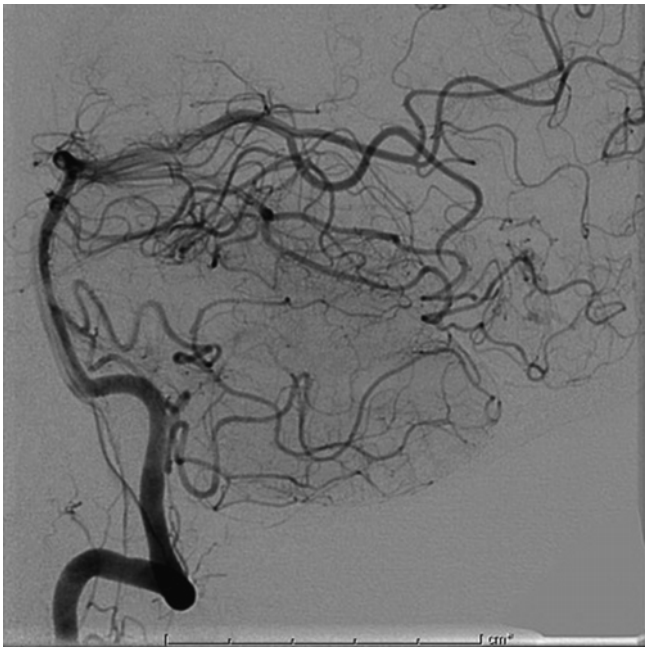

Fig. 12.9 Post-embolization conventional angiogram of the same patient demonstrating near-complete shutdown of the AVM nidus

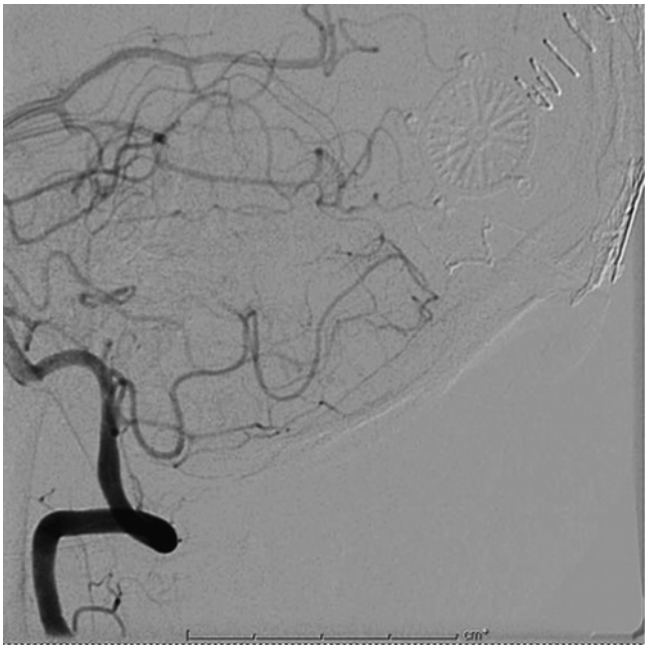

Fig. 12.10 Postsurgical resection angiogram of embolized occipital AVM

nidus volume is reduced to less than 10 ml (diameter < 3 cm). Gobin et al. showed that embolization was most helpful as adjunct to radiosurgery in treatment of AVMs with a nidus size of 4–6 cm in diameter [78–81]. In some cases, endovascular embolization is used post-radiosurgery, in AVMs that fail to obliterate after radiosurgery [72, 81].

- *Curative*
  The concept of embolization as a curative modality is somewhat controversial. However, there is an increasing belief among interventionalists that complete angiographic obliteration leads to elimination of hemorrhage risk. Achieving this goal is challenging. The main reason for this is the difficulty in superselectively catheterizing and obliterating all of the small feeders that most AVMs have. In case series of AVMs destined for multimodal treatment with endovascular embolization as the initial therapy, only 10–20 % of these lesions were declared cured with embolization alone with no further treatment modality required [63, 79, 82]. However, and with the continuing evolution of endovascular equipment, technique, and tools for lesion accessibility and obliteration, data from more recent series demonstrated higher cure rates of 27–49 % [64, 83]. When specific criteria were used to select AVMs to undergo primarily curative endovascular embolization as opposed to its use as an adjunctive treatment, even higher cure rates were reported. These criteria included AVMs with a single nidus, with few prominent feeders, and with more fistulous rather than nidal arteriovenous shunting. Cure rates with

endovascular embolization alone approaching 75 % were reported in such selected subcohorts [65, 82]. Wikhom et al. also suggest that the cure rate depends heavily on the volume of the nidus, with those smaller than 4 ml having over 70 % chance of cure as opposed to a 15 % cure rate for those larger than 4 ml [84].

- *Palliative treatment*
  In certain AVMs that are surgically inoperable or cannot be obliterated with multimodal treatment, palliative embolization may be offered to reduce the risk of recurrent hemorrhage posed by perinidal aneurysms or to alleviate neurological symptoms caused by local mass effect or steal phenomenon [85, 86]. Whether palliative treatment of AVMs that are asymptomatic improves the natural history of these lesions is controversial with strong data suggesting that it does not alter the natural history of these lesions [27, 86] and with some studies suggesting it may actually increase the risk of intracerebral hemorrhage [84, 87].

Tools Review: Embolic Agents (See Chap. 1)

Several embolic agents have been developed over the years to treat AVMs. Some of these are now almost obsolete due primarily to poor nidal penetration, higher recurrence rates, and an increased overall complication rate. Examples of such agents are silk sutures and polyvinyl alcohol particles (PVA) [88, 89]. The success of any embolic treatment lies mainly in the embolic agent's ability to penetrate and durability. Proximal feeding vessel embolization without penetration into the nidus typically results in nidal recurrence via a phenomenon known as nidal recruitment in which the AVM nidus, over time, recruits new arterial feeders [90, 91].

This section will focus on the two most widely used, Food and Drug Administration (FDA) approved liquid embolic agents. These are *N*-butyl cyanoacrylate (n-BCA) (TRUFILL, Codman Neurovascular, Raynham, MA) and ethylene vinyl alcohol copolymer (Onyx, Covidien, Irvine, CA). Other embolic materials such as platinum coils are sometimes used in treatment of AVMs or associated aneurysms, but these are discussed elsewhere in this book.

- *N-butyl cyanoacrylate (n-BCA)*
  Approved by the FDA in 2000 for treatment of brain AVMs, n-BCA is marketed in the USA under the name TRUFILL® n-BCA Liquid Embolic System (Codman Neurovascular, Raynham, MA). It is also commonly referred to in the medical literature as "glue."

  Chemically, n-BCA is a liquid adhesive monomer that is clear and free flowing in its pure form. Upon contact with body fluids and tissues including blood, the monomer undergoes a rapid polymerization reaction via an anionic mechanism transforming it into a solid state that forms a hard cast inside the lumen of the containing structure or vessel.

  The monomer is carefully injected under fluoroscopic guidance via superselective catheterization of the target vessel or nidus. The catheter is placed as

close as possible to the nidus of the AVM in order to avoid hardening inside the feeding vessel prior to reaching and penetrating the nidus [92, 93].

Prior to its delivery, n-BCA is usually mixed in various ratios with an ethiodized oil compound to retard the polymerization reaction and to allow the injected mixture to travel some distance and achieve better nidal penetration before polymerization sets it. Once injected, the operator should be ready to retract the delivery microcatheter within seconds to prevent hardening of the mixture around the catheter tip and trapping the catheter tip within the artery, which can lead to retention of a catheter fragment upon attempted retrieval [67]. In addition to its role as an occlusive agent, it is also shown that n-BCA induces an inflammatory reaction in situ, promoting fibrotic remodeling and involution over time, thus aiding in the obliteration process [94].

- *EVOH (Onyx)*
  Onyx® LES is made of ethylene vinyl alcohol copolymer (EVOH) (Covidien, Irvine, CA). It is a liquid nonadhesive copolymer that received its FDA approval in 2005 for endovascular embolic treatment of AVMs. It solidifies inside the vessels from the outside inward, creating a semisolid shell. This process is analogous to the hardening of lava and led to its trade name, Onyx.

  Onyx was mainly developed to address one main shortcoming of n-BCA: its rapid polymerization in contact with tissue. This property is not optimal for many users due to the perceived risk of trapping the delivery catheter within the embolic mass. The Onyx solidification process occurs over minutes to hours in a cohesive rather than adhesive manner. This allows more time and control for the operator treating the AVM while at the same time promoting more complete nidal penetration. Once it solidifies, the end product is a spongy cast within the injected lumen.

  Onyx is delivered into the target vessel dissolved in dimethyl sulfoxide (DMSO). DMSO allows the copolymer to travel some distance once injected before it precipitates out of the solvent and begins the solidification process. The distance it travels depends on the final viscosity of the mixture (EVOH plus DMSO). Onyx is supplied in two different concentrations producing two different viscosities. Onyx 18 is composed of 6 % EVOH and 94 % DMSO producing a viscosity of 18 centipoises, and Onyx 34 is composed of 8 % EVOH and 92 % DMSO and has a viscosity of 34 centipoises. Onyx 34 therefore is more viscous, making it useful in the treatment of high-flow AVMs with large feeders or fistulous connections. Onyx 18 has the ability to travel farther in low-flow situations given its lower viscosity [95].

  Once the injection process starts, fluoroscopic visualization of the injection must be attained to ensure anterograde flow of the injected material. Thanks to its nonadhesive nature, the injection and delivery process can be performed slowly, and the injection can be stopped and restarted several times if needed. Initially, a small Onyx cast is allowed to form around the catheter tip (the “plug”). Once created, subsequent injections of Onyx travel into the AVM nidus, and large volumes of nidus can be occluded.

EVOH produces minimal to no inflammatory reaction upon precipitation in tissue in contrast to n-BCA. On the other hand, its solvent DMSO is capable of inducing severe vasospasm and even angionecrosis and rupture if injected too quickly. Slow controlled injection is therefore prudent when using Onyx [96, 97]. Patients also notice a garlic-like taste and a characteristic odor to their breath for several hours to days after Onyx treatment due to DMSO.

EVOH vs. n-BCA

In a prospective, multicenter, randomized trial comparing n-BCA to Onyx for presurgical endovascular embolization of AVM, there was no significant difference between the two agents in terms of AVM volume reduction, amount of surgical blood loss, and surgical resection time. Adverse events between the two agents also showed no statistical significance in the 117 patients' study [98]. On the other hand, Akin et al., in a swine model experiment, demonstrated easier post-embolization surgical resection of AVMs when Onyx is used compared to n-BCA [99]. This however comes on the expense of a prolonged endovascular procedure time and increased radiation exposure with Onyx [100]. Finally, some evidence suggests that Onyx may be associated with AVM recanalization due to its lower inflammatory-induced angiofibrosis [101]. Which of the two liquid embolic systems to use in which particular clinical situation remains largely an operator preference.

AVM-Associated Aneurysms

There is a strong association between AVMs and intracranial aneurysms resulting from the altered flow dynamics. The reported prevalence of intracranial aneurysms in AVM population varies widely and ranges from 3 % up to 58 % [102–105]. Presence of AVM-related aneurysms significantly increases the risk of hemorrhagic presentations [7, 36, 106].

These aneurysms can simply be classified into intranidal (IN) and extranidal (EN). EN aneurysms can be located in the territory of the AVM (i.e., on a direct feeding artery) or outside this territory in a typical location such as the circle of Willis. Most aneurysms found in hemorrhagic AVM presentations are located intranidally or on a distal feeder close to the AVM nidus, suggesting a higher likelihood that these aneurysms are the source of the bleed [102, 107, 108]. Multiple aneurysms are frequently found as well; however, these are not associated with additional risk versus single aneurysms [102, 104]. No data exists with regard to the size of AVM-related aneurysms at which they pose a critical risk of rupture. However, it is generally agreed that the larger the aneurysm, the higher is its risk of rupture.

The modality as well as timing of treatment for these AVM-associated aneurysms depends on their location as well as presentation. Most of AVM-associated

aneurysms (IN and those located within the territory of AVM feeders) are preferentially treated via endovascular coil embolization or liquid embolization, usually prior to treating the AVM itself to avoid any risk of rupture associated with sudden changes in flow dynamics related to AVM treatment [102, 104, 108]. There is some evidence on the other hand to suggest that AVM-associated aneurysms spontaneously regress when the AVM lesion is treated, especially for proximally located aneurysms, and they therefore do not have to be dealt with prior to definite AVM treatment [103, 107]. This is of course unless they are determined to be the source of hemorrhage, in which case urgent treatment of the aneurysm is recommended regardless of its precise location since aneurysmal bleed has a higher early recurrence rate than non-aneurysm-related AVM nidal hemorrhage [102].

Complications and Risks of Endovascular Treatment

Complications of endovascular embolization of AVMs include nonspecific complications such as access site bleeding, contrast allergy, and contrast-related nephrotoxicity. We will focus our discussion here, however, on the specific complications related to endovascular AVM treatment.

The most feared complication of AVM embolization is neurological injury with permanent morbidity or mortality related to ischemia or hemorrhage. Ischemic complications occur when blood clots develop around the delivery and access catheters and wires, when a small artery is mechanically dissected, or when air is introduced accidentally into the system. This is typically minimized with careful manipulation and catheterization of vessels, judicious administration of systemic heparin intravenously during the procedure, and meticulous attention to maintain a closed and continuously flushed access system. More commonly, ischemic injury results from inadvertent embolization or reflux of embolic material into an eloquent vessel [77, 109]. Careful planning of the procedure and proper visualization of target vessels coupled with appropriate choice of embolic agent and its concentration help minimize these potentially catastrophic complications. Pre-embolization provocative testing may also help determine which arterial feeders also serve normal brain function, the so-called en-passage vessels [44, 45, 110].

Hemorrhagic complications can occur either intraoperatively or postoperatively and are related to changes in flow dynamics induced by occlusive embolization of arterial pedicles leading to diversion of flow to areas that cannot withstand the sudden increase in perfusion pressure (normal perfusion pressure breakthrough phenomenon, NPPB) [66]. Hemorrhage can also result from inadvertent embolization of draining veins leading to venous congestion with subsequent hemorrhage [111]. Catheter and wire manipulation can sometimes cause mechanical rupture or perforation of the vessel wall, also precipitating acute hemorrhagic complications. These complications can be minimized by careful visualization of the embolization target with the appropriate choice of the embolization agent concentration to prevent inadvertent venous embolization. Staged embolization over weeks or months may

decrease the risk of overwhelming the cerebral autoregulatory mechanism allowing it time to recalibrate and thus preventing NPPB [67, 75, 109].

A number of characteristics are associated with higher rates of morbidity and mortality related to endovascular AVM treatment. These include AVMs with higher Spetzler–Martin grades (grades III–V), those having deep venous drainage, older patients, and those having a normal neurological exam at baseline [67, 109]. Overall, the rate of treatment-related disabling neurological morbidity ranges from 1.6 to 11 % with mortality rates of less than 2 %, with ischemia being a slightly more common cause than hemorrhages [67, 109, 112, 113].

Procedural Considerations

- *Patient selection*: Ruptured AVMs are generally treated with embolization, resection, or a combination of these modalities. The decision to treat unruptured AVMs is more controversial. Young age, low operative risk, high-risk features, and refractory symptoms may argue for aggressive treatment with embolization, resection, radiosurgery, or a multimodality approach. Whether ruptured or unruptured, AVM treatment decisions should be made as part of a multidisciplinary team.
- *Pre-procedure*: A complete diagnostic catheter angiogram must be performed in all cases. This provides information on the location and structure of the nidus, the size and number of its feeders, the venous drainage, and the presence of flow-related stenoses or aneurysms. Digital subtraction angiography at higher frame rates is usually employed to help identify dominant feeders to the AVM and help stratify the most accessible feeders. Pre-embolization microcatheter angiography with or without provocative testing (see Chap. 9) is performed at some centers to select arterial pedicles for embolization but is associated with an elevated risk compared to extracranial catheterization. A three-dimensional image is sometimes helpful to further characterize the lesion and select the optimal imaging angle to utilize during endovascular surgery.
- *Anesthesia*: General anesthesia is the preferred modality in lengthy AVM embolization procedures. It improves image quality through mechanically induced apnea and decreased patient movement. Eliminating the risk of sudden unexpected patient movement during delicate microcatheterization enhances safety. Finally, general anesthesia allows for greater hemodynamic stability and control.
- *Sheaths*: A 6F or larger sheath is generally required. In patients older than 50, we recommend using a femoral sheath length (35 cm or greater) that bypasses any proximal aortoiliac tortuosity. When treating posterior circulation lesions, radial access may be advantageous. In this case, a 6F 11 cm or shorter sheath is recommended.
- *Guiding catheters*: A 6F or larger guiding catheter is generally recommended; however, in some instances, a 5F guiding catheter may suffice. Standard guiding

catheters can be safely positioned within the distal cervical carotid artery or at the V2/3 junction. Alternatively, a more flexible, atraumatic tipped guiding catheter may be navigated into the petrous/cavernous carotid or V3/4 junction (e.g., Neuron, Penumbra Inc., Alameda, CA).

- *Intermediate catheters*: Distal access catheters can act as intermediate catheters and help navigate the intracranial circulation. A DAC 038 or 044 by Stryker Neurovascular (Kalamazoo, MI) can be used as an intermediate catheter. They can help provide support to help direct flow-guided microcatheters towards the AVM and additionally can help perform superselective angiograms or roadmap images of a limited territory. DAC also helps in retrieval of the microcatheter by changing the angle of extraction and reducing the risk of extraction-related hemorrhage.
- *Microcatheters*: The size of the arterial feeder and the embolic agent being used dictates the type of microcatheter that is used. If Onyx is the embolic agent that is to be used, then 2.1/1.7 F Echelon 10, 2.4/1.9 F Echelon 14, or Marathon 2.7/1.3F (Covidien) flow-directed catheters are compatible. The advantage of using the Echelon platform is that these catheters can also be used to deploy coils if desired. For distal AVMs with small feeding vessels, typically a flow-directed Marathon catheter is preferable. These catheters are also compatible with n-BCA.

  Recently the Scepter balloon tip microcatheter (Microvention-Terumo, Tustin, CA), a dual lumen balloon microcatheter, has been used to inject Onyx. The balloon around the microcatheter is inflated before injecting Onyx and allows for more distal penetration into the AVM nidus without retrograde or branch artery reflux. This microcatheter does not have the flow-directed properties that are required for more distal AVMs, and the 4 mm nominal diameter precludes inflation in small vessels.
- *Microwires*: Depending on the type of microcatheter used, either a 0.010″ or 0.014″ microwire is used to help navigate the intracranial circulation. The 0.008″ Mirage wire is atraumatic and facilitates the safe selection of distal AVM vessels.
- *Embolic agents*: As described earlier in this chapter, the mainstays of liquid embolic agents are n-BCA and EVOH. Coils (see Chaps. 1, 10, and 11) may also be used if needed to slow down passage of the embolic agent into the AVM (typically with n-BCA) or if treating an associated aneurysm.

Procedural Steps

Anesthesia is induced, and intravascular access is obtained. Typically heparin is administered to maintain an ACT > 250 and checked hourly thereafter. The guide catheter is advanced into position. The presurgical angiogram should be accessible to help plan the best working projection. After obtaining baseline angiograms, a working projection roadmap is obtained to elucidate access to the AVM nidus via the most dominant and least risky feeder. We typically will use a 038 or 044 DAC

intermediate catheter to help advance our microcatheter towards the AVM in a coaxial fashion. The DAC is also useful to perform a focused roadmap of the territory of concern. To keep our options open on the type of embolic agent being used, we typically advance either an Echelon 10 or a Marathon microcatheter over a 0.014″ or 0.010″ microwire respectively to the most distal position obtainable. Subsequently a superselective microcatheter angiogram is performed paying attention to the transit time through the nidus, any additional branches coming off the feeder that supply tissue adjacent to the nidus and the venous outflow. The goal of liquid embolic (LE) injection is to maximize nidal penetration while minimizing adjacent normal brain and venous outflow obstruction. Once satisfied with the position of the microcatheter, a decision is made to use either Onyx or n-BCA based on the distance the agent needs to travel and the rate of flow through the AVM as described previously. The microcatheter is then flushed with either dextrose solution in the case of n-BCA or DMSO in the case of Onyx. The LE is then injected under a negative roadmap, paying particular attention to the dead space of the microcatheter being used so as to know when to expect the embolic agent to leave the catheter and so that the material is well visualized as it penetrates the vascular bed. It is desirable to have reference images up on the screen to remind the operator where the embolic agent should not go (i.e., adjacent vessels supplying brain tissue or venous outflow).

With n-BCA, the duration of injection is very short (5–15 s depending on concentration) during which optimal penetration of the nidus is achieved without obstructing venous outflow. For fast flowing fistulas, the flow may need to be slowed down by inducing hypotension, partially inflating a balloon proximally, or deploying a coil next to the nidus in addition to using a more viscous mixture of n-BCA. After the injection, the microcatheter has to be extracted immediately to prevent it from permanently adhering to tissue.

Onyx injections can last anywhere from 15 min up to an hour and still allow for safe catheter extraction. Initially a plug is created around the catheter tip. During this time, small microinjections are performed under negative roadmap to monitor the amount of reflux and direction of Onyx accumulation. A “plug” typically takes about 10–15 min to form. Once complete, subsequent Onyx injection will proceed into the nidus. If Onyx 34 is initially employed, subsequent use of Onyx 18 may achieve deeper penetration into the nidus. Recently the Scepter balloon microcatheter has allowed more effective Onyx injections while the balloon is inflated in the pedicle. Deflation of the balloon tip may also promote catheter disengagement with the cast and facilitate catheter removal.

Post embolization and extraction of the catheter, control angiography is performed to rule out vascular injury or inadvertent embolization of normal territories. Additional embolization may be performed through other arterial feeders depending on the scope of treatment, i.e., adjunctive, curative, or palliative. As a rule, grade IV–V AVMs should be embolized in stages to allow gradual redistribution of flow and to prevent breakthrough bleeding.

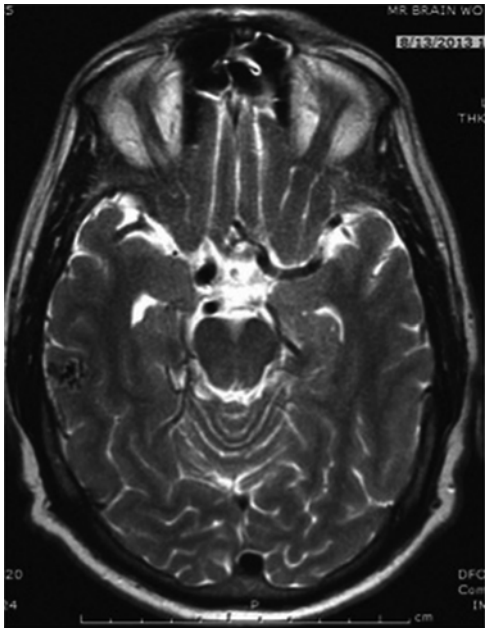

Fig. 12.11 T2-weighted axial MRI image showing a small right temporal AVM

Illustrative Case 1

A 54-year-old left-handed man presented with a several-year history of left-sided parkinsonian symptoms and facial twitching. Given the atypical unilateral nature of his symptoms, a brain MRI was performed (Fig. 12.11). This study showed a right temporal lobe AVM. The possibility of a vascular steal syndrome causing his symptoms was raised, and the patient elected to undergo treatment of the lesion in hopes that his parkinsonism would improve or stabilize. As part of his preoperative evaluation, a functional MRI was performed to screen for language function in the right temporal lobe. This study indicated language was represented bilaterally (Fig. 12.12). In order to minimize risk to the language area, endovascular embolization was selected as the treatment modality.

A 6F 35 cm sheath was placed in the right femoral artery. A 6F MPC Envoy guiding catheter (Codman Neurovascular, Raynham, MA) was navigated along with a 0.035-in. Glidewire (Terumo, Somerset, NJ) into the right distal internal carotid artery. A 0.038-in. DAC and Marathon microcatheter were coaxially inserted along with a mirage wire and used to microcatheterize the AVM (Fig. 12.13a). Two pedicles were injected with Onyx using the "plug and push" technique. Complete angiographic cure was achieved (Fig. 12.13b).

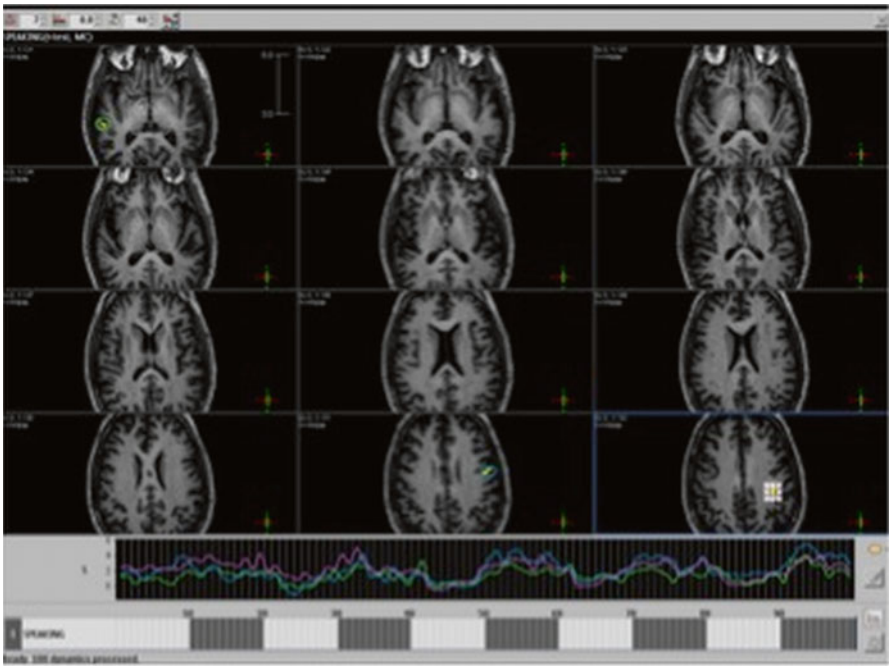

Fig. 12.12 Functional MRI showing bilateral, temporal language representation

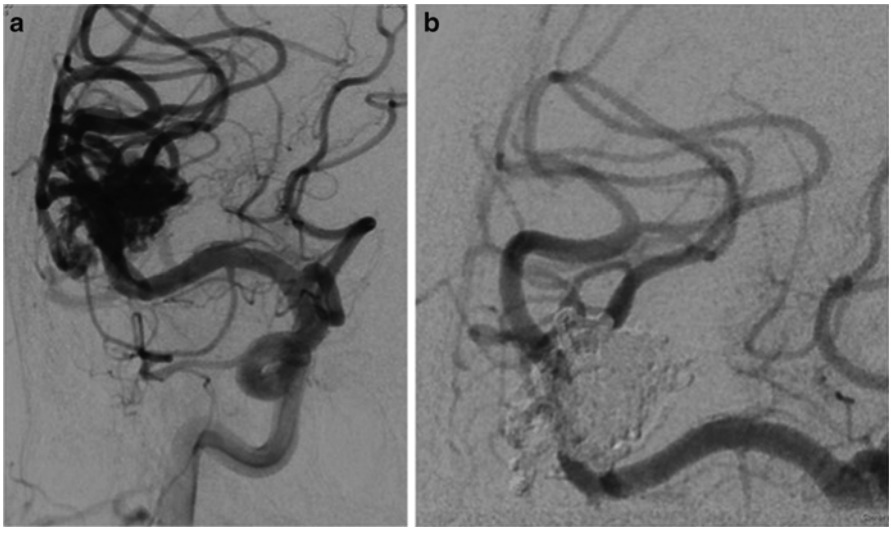

Fig. 12.13 Anterior–posterior projection, high-magnification angiogram showing the right temporal AVM pre (**a**) and post (**b**) embolization

Post-procedural Considerations

It is important to carefully monitor and guard against spikes in blood pressure during the post-procedural period. High-risk points include awakening from anesthesia and extubation. Such spikes in blood pressure may precipitate hyperperfusion syndrome, cerebral edema, and/or ICH. We typically recommend monitoring the patient in the neurointensive care unit with continuous arterial blood pressure monitoring. A systolic blood pressure less than 140 after a staged partial or adjunctive embolization or less than 120 for the first 24–48 h if an AVM is completely obliterated is desirable. Some operators may use perioperative steroids to minimize inflammation, pain, and edema after embolization. Continued attention to a patient's blood pressure even after discharge is important for the first couple of weeks to prevent breakthrough bleeding after AVM embolization, and we judiciously use antihypertensive medications in patients with either known or borderline hypertension in the postoperative period.

Stereotactic Radiosurgery

Introduction

Stereotactic radiosurgery (SRS) is a nonsurgical procedure in which a precise beam of high-dose radiation is delivered to a lesion causing damage and necrosis at the cellular level. Its application in treatment of intracranial lesions dates back to the 1950s with subsequent use in AVM treatment beginning in the late 1960s [114]. SRS works by inducing cellular necrosis and ultimately causing obliteration of flow to the AVM nidus. Its main advantage is that it delivers a focused beam of high-dose radiation to a stereotactically defined target while only exposing the surrounding tissue to minimal radiation, essentially sparing it from any long-term effect. Histopathologically, Schenieder et al. described the changes at the cellular levels of SRS-treated lesions; these changes included endothelial layer damage, intimal thickening due to smooth muscle proliferation, and subsequent stenosis and obliteration of vascular channels [115]. The process of lesion obliteration is gradual and prolonged, taking months to years before the desired effect is achieved [116–118].

Three types of stereotactic radiosurgery have been used in the treatment of brain AVMs: Gamma Knife radiosurgery which uses cobalt as a radiation source, linear accelerator radiosurgery, and proton or helium ion beam therapy. There is no proven difference in efficacy among these modes of SRS.

SRS Treatment Strategy

As with other AVM treatment modalities, the main goal of SRS treatment is complete AVM obliteration to reduce the risk of hemorrhage and to help control AVM-related symptoms such as intractable seizures [119–121]. SRS is used primarily to treat AVMs when microsurgery is not feasible and endovascular embolization is not curative. Examples include large AVMs or AVMs located in the brain stem or basal ganglia. Radiation treatment may also be offered to patients with low S–M grade AVMs who refuse to undergo surgical resections [120, 122–124]. SRS is sometimes offered to treat large AVMs either as a palliative measure or as part of a multimodal treatment plan in combination with microsurgical resection or endovascular embolization or both, and this is sometimes done in a staged fashion [125, 126].

When SRS is used to treat AVM, it is important to understand the "latency period" associated with it, that is, the period from the start of SRS treatment until obliteration, partial or complete, is achieved. This latency period takes on average 2–3 years during which time the risk of AVM hemorrhage persists, though it might be decreased [127, 128]. It is therefore not recommended to offer SRS as a primary treatment modality to treat AVMs that present with hemorrhage, as these have a higher risk of subsequent hemorrhage, or to AVMs that are assessed as having an aggressive course with a high initial hemorrhage risk (e.g., having associated aneurysms or complex high-flow nidus) [120, 129].

The main factor that predicts the success of SRS in achieving nidal obliteration is the size of the nidus itself. Multiple published case series report obliteration rates of 80 % or more when the AVM nidus diameter was 3 cm or less [120, 130–132]. Other factors found to favor SRS success were younger patients, hemispheric AVM location, and smaller number of draining veins [131]. SRS outcomes in treatment of large AVMs that were unsuitable for surgery have been less impressive with obliteration rates of less than 60 % and often requiring longer and more frequent SRS treatment and with higher doses of radiation [132, 133].

The effect and outcome of SRS treatment and degree of AVM obliteration are usually monitored with noninvasive imaging such as MRI and MR angiogram of the brain [39, 134, 135]. However, conventional angiography remains the gold standard in its ability to confirm complete nidus obliteration post radiosurgery, and this is recommended as a confirmatory method once the MRI suggests obliteration to rule out any false negatives (residual nidus) or early recanalization [135].

Complications and Risks of SRS Treatment

Complications of SRS therapy can include adverse events that arise from radiation exposure of normal tissue adjacent to the target lesion. This can range from inconsequential and transient local scalp alopecia to more serious parenchymal brain edema

or even radiation necrosis with varying degrees of neurological manifestations ranging from headaches, seizures, and focal neurological deficits to death [132, 136, 137]. Transient abnormal signal in the peri-AVM region on brain MRI following treatment is also seen [138].

Risks specific to the target lesion include the continued risk of hemorrhage during the treatment latent period, although recent published data suggest that this risk may be reduced from the original hemorrhage risk by approximately 60 % [117, 128]. Finally, rare recanalization or reappearance of the AVM several years after conclusion of SRS therapy and declared obliteration has also been reported [139].

Conclusion

Management of AVMs has evolved to include multiple available treatment modalities. Microsurgical, endovascular, and radiosurgical approaches should all be considered on a case by case basis, and often the best course of action involves a multimodality approach. Progress in the field of medical technology has markedly improved understanding of pathophysiology as well as improved patient outcomes. As technology advances, the hope is that AVMs will be even better treated with fewer risks. In any case, collaboration between the neurosurgeon, interventionalist, and radiation oncologist is critical to the best patient outcomes from diagnosis to treatment of AVMs.

References

1. Winn HR. Youmans neurological surgery. 6th ed. Philadelphia, PA: Elsevier; 2011.
2. Moftakhar P, et al. Cerebral arteriovenous malformations. Part 1: cellular and molecular biology. Neurosurg Focus. 2009;26(5):E10.
3. Vanaman MJ, Hervey-Jumper SL, Maher CO. Pediatric and inherited neurovascular diseases. Neurosurg Clin N Am. 2010;21(3):427–41.
4. Niazi TN, et al. Diagnosis and management of arteriovenous malformations in children. Neurosurg Clin N Am. 2010;21(3):443–56.
5. Turjman F, et al. Correlation of the angioarchitectural features of cerebral arteriovenous malformations with clinical presentation of hemorrhage. Neurosurgery. 1995;37(5):856–60. Discussion 860–2.
6. Brown Jr RD, et al. The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg. 1988;68(3):352–7.
7. da Costa L, et al. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. Stroke. 2009;40(1):100–5.
8. Kondziolka D, et al. Cerebral arteriovenous malformations with associated arterial aneurysms: hemodynamic and therapeutic considerations. Can J Neurol Sci. 1988;15(2):130–4.
9. Moftakhar P, et al. Cerebral arteriovenous malformations. Part 2: physiology. Neurosurg Focus. 2009;26(5):E11.
10. Kader A, et al. Recurrent cerebral arteriovenous malformations after negative postoperative angiograms. J Neurosurg. 1996;85(1):14–8.

11. Young WL, et al. Arteriovenous malformation draining vein physiology and determinants of transnidal pressure gradients. The Columbia University AVM Study Project. Neurosurgery. 1994;35(3):389–95. Discussion 395–6.
12. Brown Jr RD, et al. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intracranial vascular malformations in Olmsted County, Minnesota. J Neurosurg. 1996;85(1):29–32.
13. Ohaegbulam SC. The epidemiology of brain arteriovenous malformations. Neurosurgery. 2001;49(1):226–8.
14. Stapf C, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology. 2006;66(9):1350–5.
15. Berman MF, et al. The epidemiology of brain arteriovenous malformations. Neurosurgery. 2000;47(2):389–96. Discussion 397.
16. Al-Shahi R, et al. Prevalence of adults with brain arteriovenous malformations: a community based study in Scotland using capture-recapture analysis. J Neurol Neurosurg Psychiatry. 2002;73(5):547–51.
17. ApSimon HT, et al. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. Stroke. 2002;33(12):2794–800.
18. Stapf C, et al. The New York Islands AVM Study: design, study progress, and initial results. Stroke. 2003;34(5):e29–33.
19. Al-Shahi R, et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke. 2003;34(5):1163–9.
20. Gabriel RA, et al. Ten-year detection rate of brain arteriovenous malformations in a large, multiethnic, defined population. Stroke. 2010;41(1):21–6.
21. Stapf C, et al. Epidemiology and natural history of arteriovenous malformations. Neurosurg Focus. 2001;11(5):e1.
22. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain. 2001;124(Pt 10):1900–26.
23. Buis DR, et al. Brain arteriovenous malformations: from diagnosis to treatment. J Neurosurg Sci. 2011;55(1):39–56.
24. Fullerton HJ, et al. Long-term hemorrhage risk in children versus adults with brain arteriovenous malformations. Stroke. 2005;36(10):2099–104.
25. Kim H, et al. Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. Stroke. 2007;38(9):2430–7.
26. Stapf C, et al. Effect of age on clinical and morphological characteristics in patients with brain arteriovenous malformation. Stroke. 2003;34(11):2664–9.
27. Brown Jr RD, et al. Natural history, evaluation, and management of intracranial vascular malformations. Mayo Clin Proc. 2005;80(2):269–81.
28. Hernesniemi JA, et al. 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 829–31.
29. Laakso A, et al. 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 378.
30. Ondra SL, et al. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg. 1990;73(3):387–91.
31. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg. 1983;58(3):331–7.
32. Kondziolka D, McLaughlin MR, Kestle JR. Simple risk predictions for arteriovenous malformation hemorrhage. Neurosurgery. 1995;37(5):851–5.
33. Kader A, et al. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. Neurosurgery. 1994;34(5):801–7. Discussion 807–8.
34. Arnaout OM, et al. Posterior fossa arteriovenous malformations. Neurosurg Focus. 2009;26(5):E12.

35. Fleetwood IG, et al. Deep arteriovenous malformations of the basal ganglia and thalamus: natural history. J Neurosurg. 2003;98(4):747–50.
36. Brown Jr RD, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. J Neurosurg. 1990;73(6):859–63.
37. Fults D, Kelly Jr DL. Natural history of arteriovenous malformations of the brain: a clinical study. Neurosurgery. 1984;15(5):658–62.
38. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. Lancet Neurol. 2005;4(5): 299–308.
39. Mossa-Basha M, Chen J, Gandhi D. Imaging of cerebral arteriovenous malformations and dural arteriovenous fistulas. Neurosurg Clin N Am. 2012;23(1):27–42.
40. Okada T, et al. Diffusion tensor fiber tractography for arteriovenous malformations: quantitative analyses to evaluate the corticospinal tract and optic radiation. AJNR Am J Neuroradiol. 2007;28(6):1107–13.
41. Latchaw RE, et al. Functional magnetic resonance imaging as a management tool for cerebral arteriovenous malformations. Neurosurgery. 1995;37(4):619–25. Discussion 625–6.
42. Yu C, et al. Study of magnetic resonance imaging-based arteriovenous malformation delineation without conventional angiography. Neurosurgery. 2004;54(5):1104. Discussion 1108–10.
43. Arteriovenous malformations of the brain in adults. N Engl J Med. 1999;340(23):1812–8.
44. Barr JD, Mathis JM, Horton JA. Provocative pharmacologic testing during arterial embolization. Neurosurg Clin N Am. 1994;5(3):403–11.
45. Feliciano CE, et al. Provocative test with propofol: experience in patients with cerebral arteriovenous malformations who underwent neuroendovascular procedures. AJNR Am J Neuroradiol. 2010;31(3):470–5.
46. Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. Stroke. 1999;30(2):317–20.
47. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83.
48. Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. Neurosurgery. 1994;34(1):2–6. Discussion 6–7.
49. Hartmann A, et al. Determinants of neurological outcome after surgery for brain arteriovenous malformation. Stroke. 2000;31(10):2361–4.
50. Heros RC, Korosue K, Diebold PM. Surgical excision of cerebral arteriovenous malformations: late results. Neurosurgery. 1990;26(4):570–7. Discussion 577–8.
51. Morgan MK, et al. Surgery for cerebral arteriovenous malformation: risks related to lenticulostriate arterial supply. J Neurosurg. 1997;86(5):801–5.
52. Morgan MK, et al. Surgical risks associated with the management of Grade I and II brain arteriovenous malformations. Neurosurgery. 2004;54(4):832–7. Discussion 837–9.
53. Pikus HJ, Beach ML, Harbaugh RE. Microsurgical treatment of arteriovenous malformations: analysis and comparison with stereotactic radiosurgery. J Neurosurg. 1998;88(4):641–6.
54. Spears J, et al. A discriminative prediction model of neurological outcome for patients undergoing surgery of brain arteriovenous malformations. Stroke. 2006;37(6):1457–64.
55. Lawton MT. Spetzler-Martin Grade III arteriovenous malformations: surgical results and a modification of the grading scale. Neurosurgery. 2003;52(4):740–8. Discussion 748–9.
56. Ponce FA, Spetzler RF. Arteriovenous malformations: classification to cure. Clin Neurosurg. 2011;58:10–2.
57. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations. Clinical article. J Neurosurg. 2011;114(3):842–9.
58. Hashimoto N, et al. Surgery of cerebral arteriovenous malformations. Neurosurgery. 2007;61(1 Suppl):375–87. Discussion 387–9.
59. Ashley Jr WW, Charbel FT, Amin-Hanjani S. Surgical management of acute intracranial hemorrhage, surgical aneurysmal and arteriovenous malformation ablation, and other surgical principles. Neurol Clin. 2008;26(4):987–1005.

60. Pavesi G, et al. Acute surgical removal of low-grade (Spetzler-Martin I-II) bleeding arteriovenous malformations. Surg Neurol. 2009;72(6):662–7.
61. Russell SM, et al. Role of frameless stereotaxy in the surgical treatment of cerebral arteriovenous malformations: technique and outcomes in a controlled study of 44 consecutive patients. Neurosurgery. 2002;51(5):1108–16. Discussion 1116–8.
62. Killory BD, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green angiography during cerebral arteriovenous malformation surgery. Neurosurgery. 2009;65(3):456–62. Discussion 462.
63. Fournier D, et al. Endovascular treatment of intracerebral arteriovenous malformations: experience in 49 cases. J Neurosurg. 1991;75(2):228–33.
64. Mounayer C, et al. Nidal embolization of brain arteriovenous malformations using Onyx in 94 patients. AJNR Am J Neuroradiol. 2007;28(3):518–23.
65. Valavanis A, Yasargil MG. The endovascular treatment of brain arteriovenous malformations. Adv Tech Stand Neurosurg. 1998;24:131–214.
66. Spetzler RF, et al. Normal perfusion pressure breakthrough theory. Clin Neurosurg. 1978; 25:651–72.
67. Ledezma CJ, et al. Complications of cerebral arteriovenous malformation embolization: multivariate analysis of predictive factors. Neurosurgery. 2006;58(4):602–11. Discussion 602–11.
68. Sasaki T, et al. Arteriovenous malformations in the basal ganglia and thalamus: management and results in 101 cases. J Neurosurg. 1998;88(2):285–92.
69. Uno M, et al. Does multimodality therapy of arteriovenous malformations improve patient outcome? Neurol Res. 2004;26(1):50–4.
70. Chang SD, et al. Multimodality treatment of giant intracranial arteriovenous malformations. Neurosurgery. 2007;61(1 Suppl):432–42. Discussion 442–4.
71. Gailloud P. Endovascular treatment of cerebral arteriovenous malformations. Tech Vasc Interv Radiol. 2005;8(3):118–28.
72. Marks MP, et al. Endovascular treatment of cerebral arteriovenous malformations following radiosurgery. AJNR Am J Neuroradiol. 1993;14(2):297–303. Discussion 304–5.
73. Le Feuvre D, Taylor A. Target embolization of AVMs: identification of sites and results of treatment. Interv Neuroradiol. 2007;13(4):389–94.
74. Jafar JJ, et al. The effect of embolization with N-butyl cyanoacrylate prior to surgical resection of cerebral arteriovenous malformations. J Neurosurg. 1993;78(1):60–9.
75. Spetzler RF, et al. Surgical management of large AVM's by staged embolization and operative excision. J Neurosurg. 1987;67(1):17–28.
76. Ogilvy CS, 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.
77. Vinuela F, 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.
78. Mathis JA, et al. The efficacy of particulate embolization combined with stereotactic radiosurgery for treatment of large arteriovenous malformations of the brain. AJNR Am J Neuroradiol. 1995;16(2):299–306.
79. Gobin YP, et al. Treatment of brain arteriovenous malformations by embolization and radiosurgery. J Neurosurg. 1996;85(1):19–28.
80. Friedman WA, et al. Analysis of factors predictive of success or complications in arteriovenous malformation radiosurgery. Neurosurgery. 2003;52(2):296–307. Discussion 307–8.
81. Kwon Y, et al. Analysis of the causes of treatment failure in gamma knife radiosurgery for intracranial arteriovenous malformations. J Neurosurg. 2000;93 Suppl 3:104–6.
82. Yu SC, et al. Complete obliteration of intracranial arteriovenous malformation with endovascular cyanoacrylate embolization: initial success and rate of permanent cure. AJNR Am J Neuroradiol. 2004;25(7):1139–43.
83. Katsaridis V, Papagiannaki C, Aimar E. Curative embolization of cerebral arteriovenous malformations (AVMs) with Onyx in 101 patients. Neuroradiology. 2008;50(7):589–97.

84. Wikholm G, Lundqvist C, Svendsen P. Embolization of cerebral arteriovenous malformations: Part I – Technique, morphology, and complications. Neurosurgery. 1996;39(3):448–57. Discussion 457–9.
85. Kusske JA, Kelly WA. Embolization and reduction of the "steal" syndrome in cerebral arteriovenous malformations. J Neurosurg. 1974;40(3):313–21.
86. 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.
87. Miyamoto S, et al. Posttreatment sequelae of palliatively treated cerebral arteriovenous malformations. Neurosurgery. 2000;46(3):589–94. Discussion 594–5.
88. Sorimachi T, 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.
89. Song JK, et al. Preoperative embolization of cerebral arteriovenous malformations with silk sutures: analysis and clinical correlation of complications revealed on computerized tomography scanning. J Neurosurg. 2000;92(6):955–60.
90. Fournier D, et al. Revascularization of brain arteriovenous malformations after embolization with bucrylate. Neuroradiology. 1990;32(6):497–501.
91. Miyachi S, et al. Embolization of arteriovenous malformations prior to radiosurgery. Interv Neuroradiol. 2000;6 Suppl 1:131–7.
92. Gruber A, et al. Repermeation of partially embolized cerebral arteriovenous malformations: a clinical, radiologic, and histologic study. AJNR Am J Neuroradiol. 1996;17(7):1323–31.
93. Wikholm G. Occlusion of cerebral arteriovenous malformations with N-butyl cyano-acrylate is permanent. AJNR Am J Neuroradiol. 1995;16(3):479–82.
94. Brothers MF, et al. n-Butyl 2-cyanoacrylate – substitute for IBCA in interventional neuroradiology: histopathologic and polymerization time studies. AJNR Am J Neuroradiol. 1989; 10(4):777–86.
95. Ayad M, Eskioglu E, Mericle RA. Onyx: a unique neuroembolic agent. Expert Rev Med Devices. 2006;3(6):705–15.
96. Murayama Y, et al. Nonadhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile. Neurosurgery. 1998; 43(5):1164–75.
97. Chaloupka JC, et al. A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. AJNR Am J Neuroradiol. 1999;20(3):401–10.
98. Loh Y, Duckwiler GR, Onyx I. Trial, A prospective, multicenter, randomized trial of the Onyx liquid embolic system and N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations. Clinical article. J Neurosurg. 2010;113(4):733–41.
99. Akin ED, Perkins E, Ross IB. Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with N-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine. J Neurosurg. 2003;98(2):366–70.
100. Velat GJ, et al. Comparison of N-butyl cyanoacrylate and onyx for the embolization of intracranial arteriovenous malformations: analysis of fluoroscopy and procedure times. Neurosurgery. 2008;63(1 Suppl 1):ONS73–8. Discussion ONS78–80.
101. Natarajan SK, et al. 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 1225–6.
102. Piotin M, et al. Intracranial arterial aneurysms associated with arteriovenous malformations: endovascular treatment. Radiology. 2001;220(2):506–13.
103. Meisel HJ, et al. Cerebral arteriovenous malformations and associated aneurysms: analysis of 305 cases from a series of 662 patients. Neurosurgery. 2000;46(4):793–800. Discussion 800–2.
104. Thompson RC, et al. The management of patients with arteriovenous malformations and associated intracranial aneurysms. Neurosurgery. 1998;43(2):202–11. Discussion 211–2.

105. Turjman F, et al. Aneurysms related to cerebral arteriovenous malformations: superselective angiographic assessment in 58 patients. AJNR Am J Neuroradiol. 1994;15(9):1601–5.
106. Kim EJ, et al. The relationship of coexisting extranidal aneurysms to intracranial hemorrhage in patients harboring brain arteriovenous malformations. Neurosurgery. 2004;54(6):1349–57. Discussion 1357–8.
107. Redekop G, et al. Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. J Neurosurg. 1998;89(4):539–46.
108. Batjer H, Suss RA, Samson D. Intracranial arteriovenous malformations associated with aneurysms. Neurosurgery. 1986;18(1):29–35.
109. Hartmann A, et al. Risk of endovascular treatment of brain arteriovenous malformations. Stroke. 2002;33(7):1816–20.
110. Groden C, et al. Two-step presurgical endovascular treatment of five arteriovenous malformations partially fed by single vessels en passage. Surg Neurol. 1999;52(2):160–5. Discussion 165–6.
111. Hayashi K, et al. [A case of cerebral arteriovenous malformation complicated with intracerebral hemorrhage after endovascular embolization]. No Shinkei Geka. 2001;29(4):353–8.
112. Jayaraman MV, et al. Neurologic complications of arteriovenous malformation embolization using liquid embolic agents. AJNR Am J Neuroradiol. 2008;29(2):242–6.
113. Taylor CL, et al. Complications of preoperative embolization of cerebral arteriovenous malformations. J Neurosurg. 2004;100(5):810–2.
114. Lasak JM, Gorecki JP. The history of stereotactic radiosurgery and radiotherapy. Otolaryngol Clin North Am. 2009;42(4):593–9.
115. Schneider BF, Eberhard DA, Steiner LE. Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg. 1997;87(3):352–7.
116. 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.
117. Maruyama K, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med. 2005;352(2):146–53.
118. Yen CP, et al. Hemorrhage risk of cerebral arteriovenous malformations before and during the latency period after GAMMA knife radiosurgery. Stroke. 2011;42(6):1691–6.
119. Yang SY, et al. Radiosurgery for unruptured cerebral arteriovenous malformations: long-term seizure outcome. Neurology. 2012;78(17):1292–8.
120. Kano H, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 1: management of Spetzler-Martin Grade I and II arteriovenous malformations. J Neurosurg. 2012; 116(1):11–20.
121. Steiner L, et al. Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg. 1992;77(1):1–8.
122. Nagy G, et al. Stereotactic radiosurgery for arteriovenous malformations located in deep critical regions. Neurosurgery. 2012;70(6):1458–69.
123. Kurita H, et al. Results of radiosurgery for brain stem arteriovenous malformations. J Neurol Neurosurg Psychiatry. 2000;68(5):563–70.
124. Kano H, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 4: management of basal ganglia and thalamus arteriovenous malformations. J Neurosurg. 2012;116(1):33–43.
125. Amponsah K, et al. Staged gamma knife radiosurgery for large cerebral arteriovenous malformations. Stereotact Funct Neurosurg. 2011;89(6):365–71.
126. Murray G, Brau RH. A 10-year experience of radiosurgical treatment for cerebral arteriovenous malformations: a perspective from a series with large malformations. Clinical article. J Neurosurg. 2011;115(2):337–46.
127. Karlsson B, Lax I, Soderman M. Risk for hemorrhage during the 2-year latency period following gamma knife radiosurgery for arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2001;49(4):1045–51.

128. Maruyama K, et al. Radiosurgery to reduce the risk of first hemorrhage from brain arteriovenous malformations. Neurosurgery. 2007;60(3):453–8. Discussion 458–9.
129. Pollock BE, et al. Factors that predict the bleeding risk of cerebral arteriovenous malformations. Stroke. 1996;27(1):1–6.
130. 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.
131. Pollock BE, et al. Factors associated with successful arteriovenous malformation radiosurgery. Neurosurgery. 1998;42(6):1239–44. Discussion 1244–7.
132. Lunsford LD, et al. Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg. 1991;75(4):512–24.
133. Kano H, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. J Neurosurg. 2012;116(1): 54–65.
134. Pollock BE, et al. Magnetic resonance imaging: an accurate method to evaluate arteriovenous malformations after stereotactic radiosurgery. J Neurosurg. 1996;85(6):1044–9.
135. Gauvrit JY, et al. Three-dimensional dynamic magnetic resonance angiography for the evaluation of radiosurgically treated cerebral arteriovenous malformations. Eur Radiol. 2006; 16(3):583–91.
136. Flickinger JC, et al. A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. Int J Radiat Oncol Biol Phys. 1999;44(1):67–74.
137. Flickinger JC, et al. Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. Int J Radiat Oncol Biol Phys. 2000;46(5):1143–8.
138. Flickinger JC, et al. Analysis of neurological sequelae from radiosurgery of arteriovenous malformations: how location affects outcome. Int J Radiat Oncol Biol Phys. 1998;40(2): 273–8.
139. Lindqvist M, et al. Angiographic long-term follow-up data for arteriovenous malformations previously proven to be obliterated after gamma knife radiosurgery. Neurosurgery. 2000; 46(4):803–8. Discussion 809–10.

Chapter 13
Intracranial Dural Arteriovenous Fistulae

Ahmed Galal and John Dalfino

Introduction

Cranial dural arteriovenous fistulas (DAVFs) are vascular lesions in which an abnormal, direct arteriovenous connection forms typically between a meningeal artery and a dural venous sinus or cortical vein. The fistula causes a rise in the luminal pressure of the sinus and its contributing veins that may result in venous congestion, the formation of venous varices, and even hemorrhage. With the exception of the vein of Galen malformation, DAVFs are generally thought to be acquired lesions. It has been postulated that venous obstruction due to thrombosis or compression might cause small, preexisting microshunts in the dura to open and expand over time [1]. Alternatively, it has been proposed that venous obstruction causes the release of angiogenic growth factors that lead to the recruitment of collaterals from local arteries [2]. In either case, once the fistula forms, patients may experience tinnitus, headaches, neurological deficits, or even intracranial hemorrhage. This chapter will focus on the diagnosis and treatment of these lesions with a focus on endovascular approaches.

A. Galal, M.D.
Assistant Professor, Ain Shams University, Department of Neurosurgery, Cairo, Egypt
e-mail: ahmedoc2004@yahoo.com

J. Dalfino, M.D. (✉)
Department of Neurosurgery, Albany Medical Center,
43 New Scotland Ave, Albany NY 12208, USA
e-mail: john.dalfino@gmail.com

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_13

Tools Review (See Chap. 1)

Sheath A 6F sheath is generally employed for DAVF embolization procedures. For arterial access in young patients, a short sheath is sufficient, but a 35 cm sheath is recommended in older patients to avoid iliofemoral tortuosity. At times, a 6F, 90 cm guiding sheath may be useful for venous access in order to provide sufficient support and a large enough inner diameter to navigate subsequent devices.

Guide A 6F guide catheter is most commonly used for transarterial access. A 5F catheter may be helpful when accessing the external carotid artery due to its smaller diameter and tendency to develop catheter-induced spasm.

Microcatheter A wide variety of catheters are available; however, care must be taken to ensure these catheters are compatible with the liquid embolic agent selected. The manufacturer of Onyx liquid embolic (ethylene vinyl alcohol; Covidien; Irvine, CA) also produces a line of neurovascular microcatheters that are compatible with Onyx. The two most commonly used for this purpose are the Marathon (Covidien; Irvine, CA) and UltraFlow (Covidien; Irvine, CA). Both catheters are somewhat longer than average, allowing more distal navigation (165 cm). The UltraFlow has more flow-guided properties but is somewhat less robust than the braided Marathon design. These microcatheters require a 0.010 in. or smaller microwire. The Scepter (MicroVention-Terumo; Tustin, CA) dual-lumen balloon tip microcatheter is also Onyx compatible, and the ability to inflate the distal balloon can greatly facilitate injection of the agent as well as reduce the risk of catheter entrapment. However, care must be taken when inflating in a small vessel, as the nominal diameter is 4 mm. The Duo microcatheter (MicroVention-Terumo; Tustin, CA) is Onyx compatible and has the advantages of accepting larger microwires while having a smaller distal outer diameter than the Marathon.

Microwire A 0.010 in. microwire or smaller microwire is needed with most liquid embolic-compatible microcatheters. The Mirage microwire (Covidien; Irvine, CA) is often paired with the Marathon or UltraFlow catheters. It is a 0.008 in. wire and therefore is the least likely to cause arterial injury while accessing the small, distal vessels often involved in DAVF. However, it is not the most steerable, and a 0.010 in. wire is preferred in difficult vessel selection.

Liquid Embolic (see Chap. 12) Onyx and TRUFILL (*n*-butyl cyanoacrylate; Codman Neurovascular; Raynham, MA) liquid embolic agents are most commonly utilized in DAVF embolization. TRUFILL has the advantage of variable dilution parameters that can be tailored to the particular lesion but is limited by short working times.

Coil (see Chaps. 1, 10, and 11) These devices are useful in occluding larger venous structures or slowing a high-flow lesion prior to the use of a liquid embolic agent. However, their use in the dural sinuses can be costly due to the large number needed to achieve occlusion. There are several lower cost coils designed for "peripheral" use that can be considered, including the AZUR (MicroVention-Terumo; Tustin, CA) and Ruby (Penumbra; Alameda, CA) lines.

Clinical Presentation

The symptoms of a DAVF will vary depending on its location (Table 13.1). Most symptomatic DAVFs are high-flow lesions. They at least partially interfere with normal venous drainage and in many cases cause a compensated communicating hydrocephalus. As a result, patients with DAVF complain of headaches, pulsatile tinnitus, and blurry vision. In severe cases, intracranial hemorrhage can occur due to rupture of a venous varix or venous infarction. DAVF in the cavernous sinus will produce ocular palsies, chemosis, proptosis, and vision loss (see Chap. 15). DAVFs that occur in infants, such as vein of Galen malformations, may cause high output cardiac failure.

Imaging of DAVF

Non-contrast Computed Tomography

As with most vascular lesions, DAVFs are not typically visible by non-contrasted computed tomography (CT). In patients with a high clinical suspicion, the following features might be noted:

- The presence of intracranial hemorrhage, sometimes associated subdural hematoma
- Ventriculomegaly secondary to communicating hydrocephalus
- Hyperdensity of a dural sinus suggesting thrombosis

Table 13.1 Most common locations of DAVF [3]

Location (sinus)	Typical feeding arteries	Venous outlet	Typical symptoms
Transverse/sigmoid (50 %)	ICA, MMA, APA, PA, OA, VA	Transverse/sigmoid sinus	Pulsatile tinnitus, bruit, headaches
Cavernous sinus (10–16 %)	ICA, IMA, MMA, APA	Cavernous sinus, ophthalmic vein, inferior petrosal sinus	Chemosis, proptosis, bruit, vision loss
Tentorial incisura (8–12 %)	ICA, MMA, APA, OA, VA	Straight sinus, deep cerebral veins	ICH, tinnitus, headache
Convexity (SSS) (8 %)	OphA, MMA, OA, VA	Superior sagittal sinus	Headache, dementia, seizures
Anterior cranial fossa (5 %)	OphA, IMA, MMA	Olfactory vein, frontal veins	ICH, headache
Foramen magnum (5 %)	ICA, MMA APA, OA, VA	Clival plexus	Myelopathy, ICH, tinnitus

CT Angiography

Due to the high-flow nature of DAVF and the fact that they are commonly located near bone, the location of the fistulous connection is not generally visualized by CT angiography. Nevertheless, CT angiography can often identify some of the associated findings of the fistula including:

- Venous varices
- Dilation and/or occlusion of a venous sinus
- Dilation of the ophthalmic vein
- Abnormally enlarged subpial vessels

Magnetic Resonance Imaging

DAVFs are typically not well seen on magnetic resonance imaging (MRI). As with CT/CT angiography, MRI may identify dilated veins resulting from venous hypertension. In some cases, venous hypertension may cause focal areas of hyperintensity on T2 and FLAIR sequences. Dilated cortical veins may appear as flow voids within the cortical sulci but lack a true nidus within the brain parenchyma as would be found in a cortical AVM.

MR Angiography

Time-of-flight MR angiography, unlike CT angiography, is sensitive to the direction of blood flow. In some cases this will allow visualization of flow reversal in a dural sinus. As with other noninvasive imaging techniques, however, MR angiography often does not provide enough detail to aid in treatment planning.

Catheter Angiography

Catheter Angiography is the gold standard for the identification and staging of DAVF. In most cases, selective, bilateral injections the ECAs and ICAs as well as the VA should be performed to identify all of the arterial feeders. Often the fistula will have multiple feeders that supply a relatively short segment of the involved dural sinus. Retrograde flow from the arterialized sinus into the cortical veins (cortical venous reflux) is evidence of a hemodynamically significant change in local parenchymal venous drainage and has been associated with a more malignant

natural history, including a higher rate of intracranial hemorrhage. The goals of catheter angiography include:

- Locate arterial feeders.
- Identify the fistulous portion of the involved sinus.
- Look for evidence of venous sinus stenosis or reflux.
- Evaluate alternative venous drainage pathways.
- Look for evidence of cortical venous reflux.

Angiographic Classification of DAVF

Various classification methods have been adopted that attempt to explain the significance of the angiographic anatomy, namely, the pattern of venous drainage. The commonly used classifications are the Borden and Cognard classifications.

The Borden classification system is used to classify DAVF according to the patency of the affected dural sinus and the presence or absence of cortical venous reflux [4]. This classification system was initially proposed as a guide to help describe DAVF according to anatomical and physiological parameters and by doing so help in selecting the best surgical and/or endovascular approach. Later case series [5] confirmed that the Borden grade also correlates with the risk of intracranial hemorrhage or nonvisual neurological deficit. A summary of this classification system is presented in Table 13.2.

The Cognard classification system is more detailed (Table 13.3) and elaborates on the direction of flow, whether normal (antegrade) or retrograde, and the presence or absence of cortical venous retrograde drainage. In addition, spinal perimedullary venous drainage is recognized [6].

Table 13.2 The Borden classification system [4]

Borden type	Description	% of patients presenting with ICH or nonvisual neurological deficit
I	Flow into the affected sinus is antegrade with no evidence of cortical venous reflux	2 %
II	Flow in the affected sinus is antegrade, but there is evidence of cortical venous reflux	39 %
III	There is no antegrade flow through the affected sinus distal to the fistula. All venous outflow from the fistula is via subarachnoid veins	79 %
Subtype A	Fistula has one arterial feeder	–
Subtype B	Fistula has more than one arterial feeder	–

Table 13.3 Cognard classification system [6]

Cognard type	Pattern of venous drainage
I	Venous drainage into a sinus, normal antegrade flow
II	Venous drainage into a sinus, with insufficient antegrade flow and reflux:
IIa	– Retrograde venous drainage into a sinus only
IIb	– Retrograde venous drainage into a cortical vein only
IIa+b	– Retrograde venous drainage into a sinus and cortical veins
III	Venous drainage into a cortical vein without ectasia
IV	Venous drainage directly into a cortical vein with venous ectasia larger than 5 mm in diameter and three times larger than the diameter of the draining vein
V	Venous drainage into spinal perimedullary veins

Differential Diagnosis

Pial AVFs (PAVFs) arise from the arterial supply to the pia or cortex, and the abnormality does not lie with the dural leaflets. These rare lesions disproportionately affect pediatric patients and young adults. They present with similar symptoms and signs to DVAF, but intraparenchymal hemorrhage may be more common than subdural hemorrhages. The venous drainage is also cortical, and there may be an associate varix. Treatment modalities are similar to DAVF, but the more simple angioarchitecture makes transarterial embolization or surgical disconnection more feasible [7].

Arteriovenous malformations (AVMs) are distinguished from DAVF by the cobweb of fragile connecting blood vessels between the arterial input and the venous output present in the AVM. This network is known as the nidus (see Chap. 12).

Illustrative Case 1

A 27-year-old woman presented with sudden-onset headache and mild confusion. She was found to have a left, frontal lobe, intraparenchymal hemorrhage on noncontrast head CT (Fig. 13.1a). Diagnostic angiography showed a PAVF arising from the frontopolar branch of the left anterior cerebral artery (ACA) and draining into a cortical vein (Fig. 13.1b).

A 6F 10 cm Pinnacle introducer sheath (Terumo; Somerset, NJ) was inserted within the right femoral artery. A 6F MPC Envoy (Codman Neurovascular; Raynham, NJ) along with a 0.035 in. Glidewire (Terumo; Somerset, NJ) was then used to select the distal left cervical internal carotid artery. A Marathon microcatheter and Mirage microwire were then navigated to the site of the fistula, and a microcatheter angiogram was performed (Fig. 13.1c). Onyx 18 liquid embolic was then used to occlude the PAVF (Fig. 13.1d).

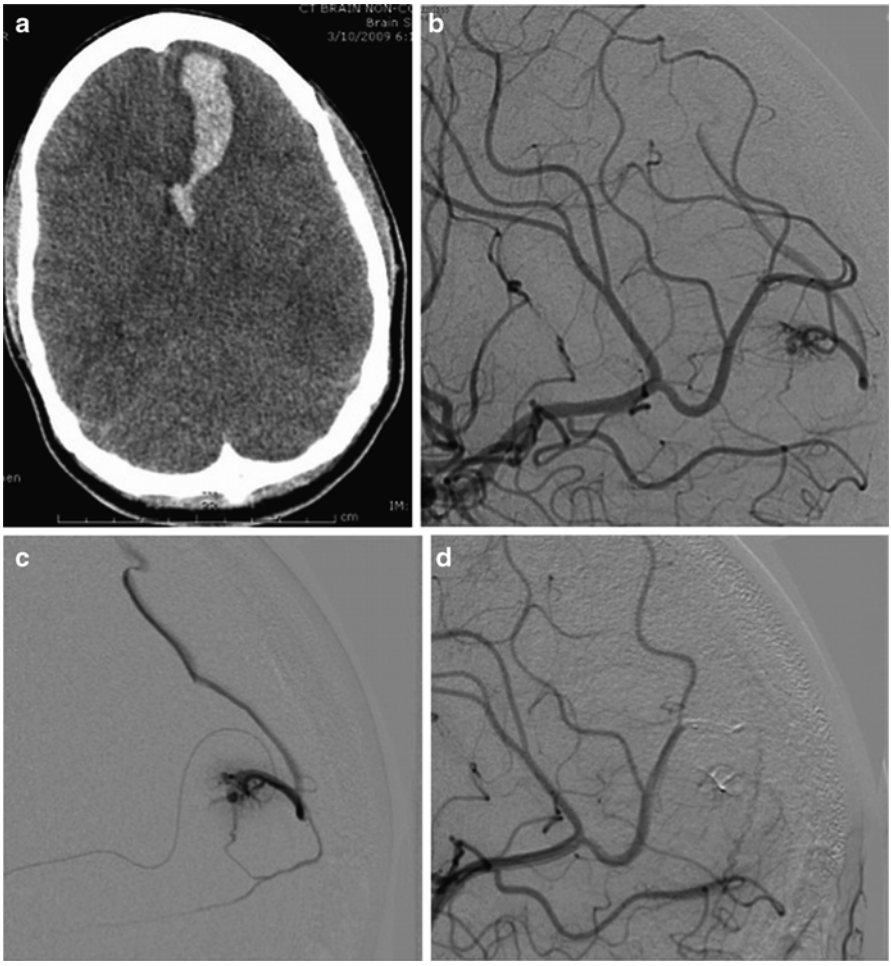

Fig. 13.1 Non-contrast head CT showing a left frontal lobe hemorrhage (**a**). Lateral projection angiogram showing a PAVF between the left frontopolar branch and a cortical vein (**b**), confirmed on microcatheter angiogram (**c**). Complete occlusion is shown after embolization with Onyx 18 (**d**)

The Natural History of DAVF

The natural history of a DAVF is primarily determined by its effect on local drainage patterns. Lesions that do not result in hemodynamically significant venous hypertension may produce only a bruit or pulsatile tinnitus. As the flow through the lesion increases, progressive venous hypertension develops. Depending on the location, this may lead to hydrocephalus, seizures, ocular edema, or myelopathy. High-flow lesions may eventually lead to cortical venous reflux causing the formation of venous varices and even intracranial hemorrhage.

The natural history of a DAVF is highly correlated with its Borden classification regardless of its location. Davies et al. [8] showed that both treated and untreated Borden grade I lesions had a benign clinical course. In 133 patient-years of follow-up, the following were observed:

- Most patient's symptoms improved with time with treatment (86 %) or without (81 %).
- The rate of ICH, neurological deficit, or death was low (<2 %) in both treated and untreated patients.
- Two patients out of 22 experienced a complication from embolization including a pulmonary embolus and an asymptomatic pericallosal artery embolus, but neither suffered permanent injury.

In contrast to Borden grade I lesions, Davies demonstrated that Borden grade II and III lesions are associated with a more malignant course [9].

- 29 % of untreated patients died during the 249 lesion-month follow-up period.
- Untreated patients had a 19.2 % risk of ICH, a 10.9 % risk of neurological deficit, and a 19.3 % risk of death per year.
- Endovascular cure was effective in avoiding symptoms, but patients with angiographic evidence of cortical venous reflux after treatment still had an aggressive clinical course.
- Surgical resection of the fistula was associated with a high rate of complications (33 %). Surgical disconnection of the sinus alone was safer (no complications in 16 patients) and effective.

Medical Decision-Making

Based on this data, the Borden classification can be used to help choose between observation and treatment.

- Incidental Borden grade I lesions can be safely observed. Endovascular embolization of these lesions is safe and may be considered for palliative treatment in symptomatic patients.
- Borden grade II and III lesions have an aggressive clinical course and should be treated. Endovascular treatment is effective only if cortical venous reflux is eliminated. Surgical disconnection of the sinus was another safe and effective alternative.

Treatment Strategies for DAVF

The treatment strategies for DAVF include transarterial embolization, transvenous embolization, dural sinus recanalization, surgical sinus skeletonization, and radiation. Often, more than one technique will be needed to treat a complex lesion.

As with any arteriovenous shunt, the most effective and durable treatment consists of occlusion of the venous recipient of the fistula [10], whether this is achieved by endovascular treatment or surgery. A proximal arterial occlusion is usually not sufficient, despite angiographic non-opacification of the fistula, as the fistulous site will still be active. With dural collaterals, the fistula in time will recruit other dural supply and will recur. Conversely, it is equally important to ensure that sufficient venous drainage is preserved to avoid venous infarction or intracerebral hemorrhage.

1. Transverse-Sigmoid Sinus DAVF

The transverse-sigmoid sinus is the most common location for cranial DAVF. These lesions are often Borden type 1 and therefore have a benign natural history. Treatment is only to alleviate symptoms such as pulsatile tinnitus. Lesions with high-risk features such as cortical venous reflux, however, should be treated.

Selection of the treatment strategy involves weighing several different factors including the significance of the patient's symptoms and their demand for treatment, as well as careful analysis of the angiogram. The angiogram may show that the affected sinus does not participate in normal venous drainage. In such cases venous occlusion has been shown to be effective and safe. Compartments of a sinus may be involved by the fistula, while others are free so that selective occlusion can be achieved while keeping the normal venous pathway patent [11]. When the targeted sinus is participating in normal cerebral drainage, cure by endovascular means is difficult, because in such cases the patent dural sinus is still a normal pathway for venous drainage, and its occlusion may risk a venous infarction. Palliative arterial embolization may thus be used for symptomatic relief. Arterial supply to fistulae of this region typically includes the petrous and petrosquamosal divisions of the middle meningeal artery, lateral division of the meningohypophyseal trunk off the ICA, transosseous branches of the posterior auricular artery, ascending pharyngeal artery, transosseous branches of the occipital artery, posterior meningeal arteries, and artery of the falx cerebelli.

In a large series of DAVFs of the transverse and sigmoid sinuses in 150 patients [12], the occlusion rate of transarterial embolization alone was 30 %, and multiple procedures were often required. Ideally, transarterial embolization with permanent liquid material (as Onyx) that closes only the AV shunts within the wall of the sinus is desirable. Some have proposed the use of transvenous balloon protection within the dural sinus to facilitate closure of the DAVF with preservation of the sinus [13]. Treatment of a transverse sinus DAVF by sinus recanalization by angioplasty and stenting together with transarterial embolization has also been reported [14].

Occasionally, the involved sinus is isolated by occlusions at both ends, making endovascular access difficult. In such cases a combined surgical-endovascular approach can be performed with a burr hole over the involved sinus followed by sinus occlusion under fluoroscopic guidance. This may be preceded by arterial embolization in high-flow lesions [15]. Depending on the angioarchitecture, reaching the

venous compartment with a liquid embolic agent from a transarterial approach may also be an option.

Radiosurgery to transverse-sigmoid DAVFs has also been reported [16, 17] from a total of 45 patients, symptomatic improvement has been reported to be 74–96 %, while angiographic cure rates were 55–87.5 %. It is to be noted that given the long time required for radiosurgery to exert an effect and the significant risk for a patient with cortical venous reflux during that period, radiosurgery is not recommended for high-risk DAVFs.

Illustrative Case 2

A 53-year-old female complained of 5 months of left-sided tinnitus and headaches. An ENT evaluation revealed no evidence of middle or inner ear pathology. Hearing acuity was normal. An MR angiogram revealed evidence of a vascular lesion adjacent to the transverse-sigmoid sinus junction. A catheter angiogram revealed a Borden grade I dural AVF fed primarily by branches of the left occipital and middle meningeal arteries that drained into the sigmoid sinus (Fig. 13.2a). Due to the complex and extensive anatomy of the arterial feeders, the decision was made to treat this fistula from the venous side.

The case was performed under general anesthesia. 5 French 10 cm sheaths were inserted into the right common femoral artery. A 4 F diagnostic catheter was navigated into the left occipital artery and connected to a continuous heparinized saline flush. The patient was then given an intravenous heparin bolus of 70 units/kg. A 100 cm, 6F Flexor Shuttle guiding sheath (Cook Medical; Bloomington, IN) was navigated into the distal sigmoid sinus over a 0.035″ stiff Glidewire using an arterial roadmap for visualization. A venous angiogram confirmed that the guide catheter was in the sigmoid sinus.

A Scepter balloon catheter and Synchro 14 microwire (Stryker; Kalamazoo, MI) were then advanced through the Shuttle sheath in the sigmoid sinus and into the fistula using an arterial roadmap for visualization.

Embolization started with coils. A total of 6 HydroSoft microcoils (MicroVention, Tustin, CA) were deployed in the fistula (Fig. 13.2b). An angiogram performed after coiling still demonstrated filling of the fistula. Using the same microcatheter, with the distal balloon inflated, 0.7 ml of Onyx 34 (ev3 Neurovascular, Irvine, CA) was injected behind the coil mass (Fig. 13.2b). A run following Onyx embolization confirmed that the fistula was completely closed (Fig. 13.2c). Follow-up imaging at 5 months and 1 year after embolization shows that the treatment was durable.

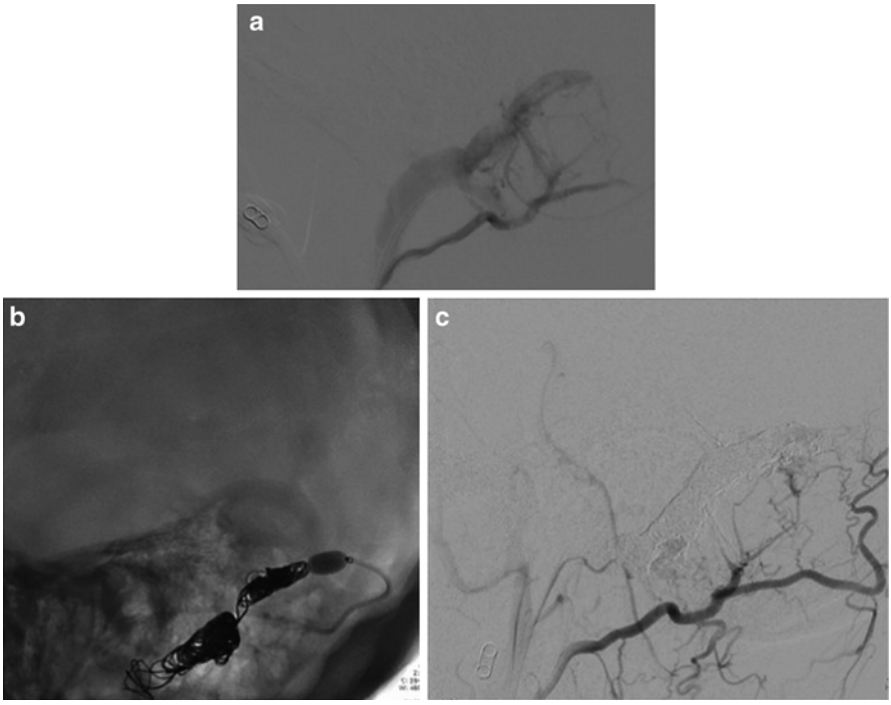

Fig. 13.2 Lateral projection angiogram of the left occipital artery showed a DAVF of the transverse sinus (**a**). Occlusion of the transverse sinus with coil deployment and Onyx 34 delivered through an inflated Scepter balloon catheter (**b**). Elimination of the DAVF after embolization (**c**)

2. Cavernous Sinus DAVFs (See Chap. 15)

DAVFs of the cavernous sinus are the second most common type of carotid-cavernous fistulae. Barrow et al. [18] established the following classification scheme:

- Type A: Direct fistula between ICA and cavernous sinus (i.e., traumatic CCF and ruptured cavernous carotid aneurysms)
- Type B: Indirect fistula between branches of the ICA and the cavernous sinus
- Type C: Indirect fistula between branches of the ECA and the cavernous sinus
- Type D: Indirect fistula between branches of both the ICA and ECA and the cavernous sinus

  Type D1: unilateral
  Type D2: bilateral

The presenting symptoms depend on the pattern of venous drainage. Drainage anteriorly into the superior and inferior ophthalmic veins most commonly causes ocular symptoms of chemosis, exophthalmos, diplopia, increased intraocular pres-

sure, and impaired vision. If both cavernous sinuses become involved in the venous drainage secondary to a change in the ipsilateral venous outflow of the affected cavernous sinus, the ocular findings may become bilateral. The so-called "white eye" cavernous sinus fistulas occur when posterior venous drainage predominates. Posterior drainage through the inferior petrosal sinus may cause pulsatile tinnitus, and venous hemorrhage or infarctions. Rarely, cortical venous reflux through the sphenoparietal sinus into the superficial and deep sylvian veins or veins in the posterior fossa can also lead to hemorrhage.

The vascular supply to the dura of the cavernous sinus is complex because of extensive regional anastomoses between dural branches of the internal carotid artery and branches of the internal maxillary artery. From the perspective of angiographic workup and embolization, these lesions can be divided into two groups:

- Anterolateral group: arising from the orbital apex and lateral cavernous sinus. The meningeal supply to the anterior division lesions may be considered as reflecting the hemodynamic balance between branches arising from the horizontal segment of the cavernous internal carotid artery (inferolateral trunk) and the meningeal branches of the internal maxillary artery.
- Posterior group: arising from the posterior cavernous sinus. The supply to posterior division lesions is derived primarily from the meningohypophyseal branches of the cavernous internal carotid artery and their potential anastomotic connections with branches of the middle meningeal artery and the ascending pharyngeal artery.

Treatment options

1. Manual compression
   Spontaneous thrombosis with subsequent closure occurs in 15 % of cavernous DAVFs; therefore, Borden type 1 lesions without increased intraocular pressure can be managed conservatively. Manual compression of the cervical carotid has been reported to facilitate spontaneous closure. The patient is instructed to use the opposite hand to locate and manually compress the carotid artery.

   A diagnostic angiogram is indicated for follow-up and to document complete closure of the fistula.

2. Embolization

   - Arterial embolization: This is rarely curative and should be used only as a palliative treatment in selected cases.
   - Venous embolization: This is the most effective route. Various transvenous routes have been reported; the two most commonly used are (1) the inferior petrosal sinus and (2) the superior ophthalmic vein from the angular and facial vein through the external jugular vein [19]. Dural AVF involving both cavernous sinuses are not uncommon. They are usually connected through the intercavernous sinuses and can be treated from a unilateral venous approach.

   A thrombosed inferior petrosal sinus can be traversed in some cases [20].

If femoral venous access is unsuccessful or difficult due to unnavigable anatomy, then direct percutaneous (or via open surgery) transorbital puncture can be performed. This may be done via a superior or inferior ophthalmic vein approach [21, 22].

In a large series of 141 patients diagnosed with cavernous DAVF [19], the initial cure rate was 81 %, with long-term follow-up cure rates of 94.5 %. The overall complication rate (including asymptomatic emboli and venous perforation) was 8 % without any permanent neurological sequelae. Detachable coils are the most commonly used materials, either alone or in combination with liquid embolics (n-BCA or Onyx).

3. Radiosurgery
   Several reports have been published on the use of radiosurgery for treatment of cavernous DAVFs. Obliteration rates are reported to be more than 80 % [23, 24].

3. Tentorial DAVFs

Tentorial DAVFs are also known as superior petrosal DAVFs. They are classified according to Picard et al. [25] into:

1. Marginal type: located along the free edge of the tentorium
2. Lateral type: located along the lateral venous sinuses
3. Medial type: located adjacent to the straight sinus and torcula

The angiographic anatomy typically shows multiple feeders arising from: middle meningeal artery, meningohypophyseal trunk, posterior cerebral artery, occipital artery, posterior meningeal artery, and superior cerebellar artery. Venous drainage is typically retrograde into cerebral and/or cerebellar veins, basal vein of Rosenthal, pontine and perimesencephalic veins, and cervical spinal perimedullary veins [26].

Tentorial DAVFs frequently are nearly all Borden II or III lesions and frequently present with hemorrhage and therefore are treated aggressively when diagnosed.

No single treatment strategy is ideal. Surgery and/or embolization treatment depends on the clinical status of the patient as well as the angioarchitecture of the fistula. In very complicated cases, radiosurgery combined with serial embolizations can be utilized.

1. Surgery

   In most cases coagulation and division of the arterialized draining vein or veins can accomplish obliteration of the lesion. Interruption of the draining vein may be effective when no other pathway of venous drainage exists [27]. Preoperative arterial embolization may facilitate surgery [26].

The surgical approach chosen depends on the location of the arterialized veins, but a supratentorial-infraoccipital approach is commonly used for exposure of tentorial sinus DAVFs.

2. Embolization
   - Venous embolization
   - Venous embolization should be done only when a venous drainage pouch that is separate from veins draining normal brain can be identified and accessed with a microcatheter [28]. Venous embolization is usually done with coils.
   - Arterial embolization
   - Arterial embolization can lead to angiographic cure only when the microcatheter tip is placed close enough to the fistulous connection to permit placement of liquid embolic material across the fistula to the venous side [28].
3. Radiosurgery
   The use of radiosurgery is generally not recommended due to the long latency of action and risk of injury of adjacent structures as the brainstem and cranial nerves and the <100 % obliteration rates [28]. On the other hand, successful radiosurgical obliteration of tentorial DAVFs has been reported [29] and may be reasonable in patients with no other options.

Illustrative Case 3

A 69-year-old woman presented to an outside hospital with sudden-onset dizziness and ataxia. A non-contrast head CT showed a right cerebellar hemisphere hemorrhage (Fig. 13.3a). CTA was suspicious for a vascular lesion. Diagnostic angiography revealed a medial-type tentorial AVF with involvement of the torcular Herophili (Fig. 13.3b) with the largest supply arising from the posterior division of the middle meningeal artery (MMA). Endovascular embolization was selected as the treatment modality.

The procedure was performed under general anesthesia. A 6F 35 cm BRITE TIP introducer sheath (Cordis; Bridgewater, NJ) was inserted within the right femoral artery. A 6F MPC ENVOY guide catheter along with a 0.035 in. Glidewire (Terumo; Somerset, NJ) was then used to select the right external carotid artery. A Marathon microcatheter and Mirage microwire were then navigated into the MMA. Onyx 18 liquid embolic was then used to create a dense plug at the catheter tip, with care taken to avoid >1 cm of reflux. Once anterograde embolization resumed, the entire fistulous connection was obliterated bilaterally (Fig. 13.3c). This result was stable at 6-month follow-up.

4. Superior Sagittal Sinus DAVF

Superior sagittal sinus DAVFs are uncommon. The lesions are typically located in the midportion of the superior sagittal sinus, and feeders are commonly bilateral: middle meningeal artery, superficial temporal artery, and occipital artery. Venous drainage is primarily to the superior sagittal sinus. These lesions can be Borden type II or III lesions with cortical venous reflux [30].

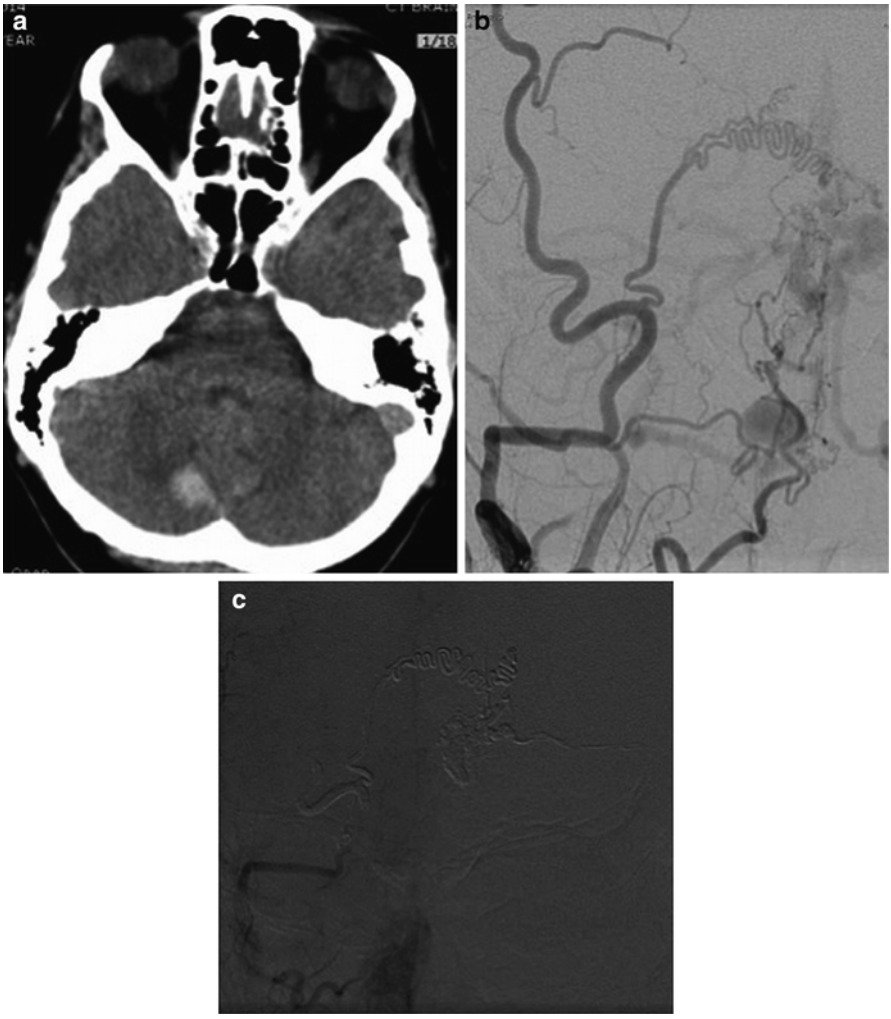

Fig. 13.3 Non-contrast head CT showing a right cerebellar hemisphere hemorrhage (**a**). Catheter angiogram showing a medial tentorial DAVF involving the torcular Herophili (**b**). Post-embolization Onyx cast within the arterial pedicles (**c**)

These lesions are often challenging to manage by endovascular techniques alone and are frequently managed by open surgical techniques. Superior sagittal sinus DAVFs requiring surgery are exposed with a midline craniotomy over the sinus and the fistula. Performing the craniotomy over the sinus requires careful preservation of the dura. A two-piece craniotomy may be needed to first expose one side of the sinus to allow sinus dissection from the inner table of the skull under direct

visualization before crossing the midline with the second craniotomy flap. Surgical techniques depend on the Borden grade:

- Grade I: skeletonizing the superior sagittal sinus, eliminating the arterial supply while preserving normal sinus flow
- Grade II: skeletonizing the superior sagittal sinus and interruption of arterialized veins, which is done by clipping, cauterizing, and dividing the fistulous vein
- Grade III: interrupting the fistula on its venous sinus as it exits the superior sagittal sinus

5. Anterior Cranial Fossa DAVFs (Ethmoidal DAVFs)

Anterior cranial fossa DAVFs (Ethmoidal DAVFs) are located on the floor of the anterior cranial fossa, adjacent to the cribriform plate. These lesions are unique in that unlike all the other dural AVFs, ethmoidal DAVFs are not associated with a venous sinus, and always have retrograde cortical venous drainage (Borden grade III lesions), and therefore have a propensity to hemorrhage. Nonhemorrhagic presentations include headache, decreased visual acuity, and diminished sense of smell and taste [31, 32].

Feeders are typically from the anterior ethmoidal artery off the ophthalmic artery in 84 % of cases. Other feeders may arise from the internal maxillary artery, middle meningeal artery, and superficial temporal artery [31, 32].

Surgery is the main form of treatment for these lesions, given the high hemorrhage risk and the difficulties associated with embolization [32]. Ethmoidal DAVFs are exposed through a bifrontal craniotomy and a subfrontal approach. The critical step is the interruption of the fistulous connection between the ethmoidal arteries perforating the dura around the cribriform plate and the draining veins. The cortical draining vein is identified early and followed retrograde to the fistulous connection. The vein just distal to the fistula is coagulated and divided. Excessive evacuation of a frontal hematoma is avoided to prevent bleeding from the varix before the fistula is controlled.

Disconnection of anterior cranial fossa DAVFs has also been reported by using transarterial catheterization of the ophthalmic artery and subsequent injection of n-BCA. In a report by Agid et al., the success rate was reported as 63.6 % [33]. The microcatheter tip should be positioned distal to the origin of the central retinal artery (identified through the choroidal blush of the adjacent posterior ciliary arteries in lateral view). Glue embolization is done with a diluted mixture injected in a forward direction toward the venous side. Therefore, reflux is not part of the technique, nor will there be any reflux toward normal collateral anastomoses [33].

Transvenous approaches have also been reported [34] but are technically more challenging, requiring navigation of the microcatheter to the anterior part of the superior sagittal sinus and then selective catheterization of the draining cortical vein. Coiling of the vein must be done as close as possible to the fistulous site and proximal to the venous pouch to avoid a catastrophic hemorrhage.

Conclusions

- Dural AVFs are acquired vascular lesions that can often have a benign clinical course provided that the venous outflow of the normal brain parenchyma is not impeded.
- While noninvasive imaging will sometimes suggest the presence of a DAVF, catheter angiography is often required to diagnose and classify these lesions.
- Endovascular cure of a dural AVF requires embolization of the venous pouch of the fistula and will rarely be achieved via proximal embolization of its arterial feeders.

References

1. Piton J, Guilleux MH, Guibert-Tranier F, et al. Fistulae of the lateral sinus. J Neuroradiol. 1990;72:839–50.
2. Rothbart D, Awad IA, Lee J, et al. Expression of angiogenic factors and structural proteins in central nervous system vascular malformations. Neurosurgery. 1996;38:915–24.
3. Mullan S. Reflections upon the nature and management of intracranial and intraspinal vascular malformations and fistulae. J Neurosurg. 1994;80:606–16.
4. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. J Neurosurg. 1995;82:166–79.
5. Davies MB, TerBrugge K, Willinsky R, Coyne T, Saleh J, Wallace MC. The validity of classification for the clinical presentation of intracranial dural arteriovenous fistulas. J Neurosurg. 1996;85:830–7.
6. Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. Radiology. 1995;194(3):671–80.
7. Hoh BL, Putman CM, Budzik RF, Ogilvy CS. Surgical and endovascular flow disconnection of intracranial pial single-channel arteriovenous fistulae. Neurosurgery. 2001;49(6):1351–63. Discussion 1363–4.
8. Davies MA, Saleh J, Brugge TK, Willinsky R, Wallace MC. The natural history and management of intracranial dural arteriovenous fistulae. Part I: benign lesions. Intervent Neuroradiol. 1997;3(4):295–302.
9. Davies MA, Saleh J, Brugge TK, Willinsky R, Wallace MC. The natural history and management of intracranial dural arteriovenous fistulae. Part 2: aggressive lesions. Intervent Neuroradiol. 1997;3(4):303–11.
10. Cognard C, Houdart E, Casaco AE, Jhaveri HS, Chapot R, Merland JJ. Endovascular therapy and long term results for intracranial dural arteriovenous fistulae. In: Connors JJ, Wojak JC, editors. Interventional neuroradiology. 1st ed. Philadelphia, PA: Saunders; 1999. p. 198–214.
11. Piske RL, Campos CM, Chaves JB, et al. Dural sinus compartment in dural arteriovenous shunts: a new angioarchitectural feature allowing superselective transvenous dural sinus occlusion treatment. Am J Neuroradiol. 2005;26:1715–22.
12. Kirsch RL, Liebig T, Kuhne D, Henkes H. Endovascular management of dural arteriovenous fistulas of the transverse and sigmoid sinus in 150 patients. Neuroradiology. 2009;51(7):477–83.
13. Shi ZS, Loh Y, Duckwiler GR, Jahan R, Vinuela F. Balloon-assisted transarterial embolization of intracranial dural arteriovenous fistulas. J Neurosurg. 2009;110(5):921–8.
14. Murphy KJ, Gailloud P, Venbrux A, Deramon H, Hanley D, Rigamonti D. Endovascular treatment of a grade IV transverse sinus dural arteriovenous fistula by sinus recanalization, angioplasty, and stent placement: technical case report. Neurosurgery. 2000;46(2):497–500.

15. Naito I, Iwai T, Shimaguchi H, et al. Percutaneous transvenous embolization through the occluded sinus for transverse-sigmoid dural arteriovenous fistulas with sinus occlusion. Neuroradiology. 2001;43(8):672–6.
16. Friedman JA, Pollock BE, Nicholas DA, Gorman DA, Foote RL, Stafford SL. Results of combined stereotactic radiosurgery and transarterial embolization for dural arteriovenous fistulas of the transverse and sigmoid sinus. J Neurosurg. 2001;94(6):886–91.
17. Pan DH, Chung WY, Guo WY, et al. Stereotactic radiosurgery for the treatment of dural arteriovenous fistulas involving the transverse-sigmoid sinus. J Neurosurg. 2002;96(5):823–9.
18. Barrow DL, Spector R, Braun IF, Landman JA, Tindall SC, Tindall GT. Classification and treatment of spontaneous carotid cavernous sinus fistulas. J Neurosurg. 1985;62(2):248–56.
19. Kirsch M, Henkes H, Leibig T, et al. Endovascular management of dural carotid-cavernous sinus fistulas in 141 patients. Neuroradiology. 2006;48(7):486–90.
20. Benndorf G, Bender A, Lehmann R, Lanksch W. Transvenous occlusion of dural cavernous sinus fistulas through the thrombosed inferior petrosal sinus: report of four cases and review of literature. Surg Neurol. 2000;54(1):42–54.
21. Dashti SR, Fiorella D, Spetzler RF, Albuquerque FC, McDougall CG. Transorbital endovascular embolization of dural carotid-cavernous fistula: access to cavernous sinus through direct puncture: case examples and technical report. Neurosurgery. 2011;58(1):75–83.
22. White JB, Layton KF, Evans AJ, et al. Transorbital puncture for the treatment of cavernous sinus dural arteriovenous fistulas. AJNR Am J Neuroradiol. 2007;28(7):1415–7.
23. Guo WY, Pan DH, Wu HM, et al. Radiosurgery as a treatment alternative for dural arteriovenous fistulas of the cavernous sinus. Am J Neuroradiol. 1998;19(6):1081–7.
24. Pollock BE, Nicholas DA, Garrity JA, et al. Stereotactic radiosurgery and particulate embolization for cavernous sinus dural arteriovenous fistulae. Neurosurgery. 1999;45(3):459–66.
25. Picard L, Bracard S, Islak C, et al. Dural fistulae of the tentorium cerebelli. Radioanatomical, clinical and therapeutic considerations. J Neuroradiol. 1990;17(3):161–81.
26. Zhou LF, Chen L, Song DL, et al. Tenorial dural arteriovenous fistulas. Surg Neurol. 2007; 67(5):472–81.
27. Thompson BG, Doppman JI, Oldfield EH. Treatment of cranial dural arteriovenous fistulae by interruption of leptomeningeal venous drainage. J Neurosurg. 1994;80(4):617–23.
28. Tomak PR, Cloft HJ, Kaga A, Cawley CM, Dion J, Barrow DL. Evolution of the management of tentorial dural arteriovenous malformations. Neurosurgery. 2003;52(4):750–60.
29. Soderman M, Edner G, Ericson K, et al. Gamma knife surgery for dural arteriovenous shunts:25 years of experience. J Neurosurg. 2006;104(6):867–75.
30. Kurl S, Saari T, Vanninen R, Hernesniemi J. Dural arteriovenous fistulas of superior sagittal sinus: case report and review of literature. Surg Neurol. 1996;45(3):250–4.
31. Gliemroth J, Nowak G, Arnold H. Dural arteriovenous malformation in the anterior cranial fossa. Clin Neurol Neurosurg. 1999;101(1):37–43.
32. Lawton MT, Chun J, Wilson CB, Halbach VV. Ethmoidal dural arteriovenous fistulae: an assessm9ent of surgical and endovascular management. Neurosurgery. 1999;45(4):805–10.
33. Agid R, Terbrugge K, Rodesch G, Anderson T, Soderman M. Management strategies for anterior cranial fossa (ethmoidal) dural arteriovenous fistulas with an emphasis on endovascular treatment. J Neurosurg. 2009;110:79–84.
34. Defreyne L, Vanlangenhove P, Vandekerckhove T, Deschrijver I, et al. Transvenous embolization of a dural arteriovenous fistula of the anterior cranial fossa: preliminary results. AJNR Am J Neuroradiol. 2000;21:761–5.

Chapter 14
Preoperative Tumor Embolization

Ali Hassoun Turkmani, Mark Dannenbaum, and Peng R. Chen

Introduction

Egas Moniz first performed cerebral angiography in 1927 and thus opened the door for the development of cerebral endovascular therapies [1]. Several years later, Brooks introduced a piece of muscle into the carotid artery intending to occlude a large carotid-cavernous fistula [2], giving birth to the therapeutic angiography. Luessenhop injected plastic beads in the internal carotid and vertebral arteries in an attempt to treat cerebral arteriovenous malformations [3]. In 1973, Djindjian et al. published a study of 50 cases of transfemoral, selective embolizations for a variety of intracranial pathologies [4]. In 1975, Hilal et al. published their experience with the embolization of head and neck tumors via common carotid artery direct puncture with the use of Silastic beads, gelatin foam, or liquid Silastic elastomers [5].

A.H. Turkmani, M.D. • M. Dannenbaum, M.D. (✉)
The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School, Houston, TX, USA
e-mail: dr.turkmani@yahoo.com; Mark.dannenbaum@memorialhermann.org; mjdannenbaum@gmail.com; Mark.Dannenbaum@uth.tmc.edu

P.R. Chen, M.D.
The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School, 6400 Fannin Suite 2800, Houston, TX 77030, USA

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_14

Tool Review (See Chap. 1)

Embolisates

Various embolic agents have been described in the successful embolization of tumors. The selection of appropriate embolic materials depends on the target, size of the feeding arteries, blood flow pattern, and the presence of any potentially dangerous anastomoses or collateral pathways [6]. Embolic agents can be grouped with regard to whether they are particles or liquid as well as whether they are temporary or permanent. Nonabsorbable materials, such as *N*-butyl cyanoacrylate (NBCA; TRUFILL; Codman Neurovascular; Raynham, MA) and ethylene vinyl alcohol copolymer (Onyx; Covidien; Irvine, CA), achieve more durable occlusion than absorbable materials, such as Gelfoam, and are well suited for the treatment of vascular lesions. For preoperative embolization of tumors, temporary, absorbable embolic agents are often less costly and are usually sufficient [7]. Absorbable agents may also be preferable when there is high potential for emboli to migrate to nontarget vessels during embolization, such as in vessels with EC-IC anastomoses, or when the arteries that supply the vasa nervorum of the lower cranial nerves are embolized [7]. Particle size is another important consideration. It has been suggested that particles of less than 100 μm should be avoided when the potential for dangerous EC-IC anastomoses or supply to the vasa nervorum exists.

- *Particle embolisates*
  - *Polyvinyl alcohol foam*
    Polyvinyl alcohol (PVA) foam is a sponge-like material formed when polyvinyl alcohol is mixed with foaming agents and hardened with formaldehyde [8]. PVA particles are radiolucent and require the addition of contrast solution in order to be visualized. While PVA embolization is long lasting, it is not permanent, with degradation generally occurring within a few weeks after embolization. It produces a vigorous inflammatory response that facilitates vessel occlusion through progressive thrombosis [9]. This inflammatory reaction may partially account for the associated peritumoral edema following PVA embolization.
  - *Microspheres*
    Trisacryl gelatin microspheres (Embosphere Microspheres; Merit Medical; South Jordan, UT) are hydrophilic, nonabsorbable, collagen-coated embolic agents. The spherical and deformable nature of microspheres enables easy injection and helps prevent catheter occlusion, while facilitating more distal tumor penetration. Microspheres have a unique role in patients undergoing palliative embolization without subsequent surgery. This therapy is indicated for symptomatic control in patients who are not surgical candidates. In these patients, permanent devascularization with deeper penetration is desired in order to obtain tumor necrosis and thus arrest tumor growth [10].

  - *Cellulose beads*
    C-cellulose beads are uniform, nonabsorbable particles that carry a positive charge and have a specific gravity close to that of whole blood. Unlike PVA, cellulose beads do not readily initiate an inflammatory reaction in the vessel wall but are thought to electrically promote thrombus formation, resulting in a more stable vessel occlusion [11].
  - *Gelatin foam*
    Gelatin foam particles are absorbable, easy to handle, and quickly degraded by the body, permitting rapid recanalization. For this reason it has been suggested that Gelfoam may be the embolic agent of choice whenever particle migration could result in nontarget embolization [7].

- *Liquid embolisates*
  Liquid agents are not frequently utilized for embolizing intracranial meningiomas as they are associated with increased risk for embolization of nontarget tissues and are often quite expensive to use [6]. Liquids embolisates can cross anastomotic channels and enter small nontarget arteries that are unseen during fluoroscopic imaging [12]. They penetrate deeper into the vascular bed than particles and, thus, may be more effective than small particles at inducing tumor necrosis.

  - *TRUFILL*
    TRUFILL (NBCA) is a commonly used, highly occlusive and permanent, liquid glue embolisate that polymerizes immediately upon contact with blood. NBCA penetrates quickly and deeply into tumor vasculature [13]. The relatively fast polymerization rate of NBCA can, however, increase the risk of catheter tip adherence to the vessel wall as well as the risk of occluding the feeding artery prematurely without nidal penetration.

  - *Onyx*
    Onyx is a permanent, radiopaque liquid embolic agent. It is commercially available as ethylene vinyl copolymer and micronized tantalum powder suspended in dimethyl sulfoxide. Onyx 18 and 34 are composed of 6 % and 8 % ethylene vinyl alcohol copolymer and 94 % and 92 % dimethyl sulfoxide (DMSO), respectively. When injected into blood, the DMSO diffuses out of the mixture and allows the copolymer to precipitate into a spongy embolus that is highly cohesive but not adhesive to the vessel wall or the microcatheter [14]. Onyx can be delivered more slowly and in a more controlled fashion than other liquid agents. This enables a longer working time and potentially deeper penetration of small- to medium-sized tumor vessels. The spongy composition of Onyx may also facilitate its handling during resection compared with the rigid, inflexible casts formed by NBCA.

  - *Fibrin glue*
    Fibrin glue is a radiopaque, liquid embolic material that has traditionally been used in various surgical fields for tissue sealing and hemostasis. Probst et al. embolized 80 patients with meningiomas using fibrin glue with good result and few complications [15].

- *Miscellaneous agents*
  A variety of other embolic agents have been utilized for tumor embolization, including homologous controlled-viscosity fibrin [16], microfibrillar collagen [17], lyophilized human dura mater [18], estrogen [19], and Silastic spheres [20]. More recently used agents include phenytoin [21], mannitol [22], and hydroxyapatite ceramics [23].

Provocative Testing (See Chap. 9)

Prior to embolization, pharmacological provocative testing with amobarbital and/or lidocaine has been described as a method for identifying the blood supply to brain regions and cranial nerves that are at risk for nontarget embolization [24].The development of temporary deficits in response to provocative testing suggests that there is the potential for ischemic complications if the catheterized vessel is embolized.

Amobarbital injection was first described as a method to detect hemispheric dominance for language in epilepsy patient evaluation by Wada et al. [25]. Amobarbital is an intermediate-acting barbiturate and has generalized depressant effects on the central nervous system. Acting through the GABA receptor, it inhibits cortical neuronal activity, producing transient neurologic deficits. For this reason, amobarbital may be useful for detection of direct supply and occult anastomoses to cerebral cortical structures [24].

Intra-arterial injection of lidocaine represses excitation of nerve cell membranes by blocking voltage-gated sodium channels in both white and gray matters. Lidocaine may be better than amobarbital for eliciting central nervous system dysfunction through vascular infusion [26]. It carries a risk of seizures and cardiopulmonary arrest. A dual challenge provocation test of amobarbital (50 mg) followed by 2 % lidocaine (10 mg) in order to minimize the possibility of false-negative result has been described [24].

In centers where the use of general anesthesia is preferred, provocative testing is necessarily precluded. For such cases, continuous neuromonitoring with somatosensory-evoked potentials and EEG is advocated [27].

Mechanical provocative testing in which a vessel is temporarily occluded using a balloon is another way to predict whether occlusion of the vessels will have negative hemodynamic consequences that can result in ischemic injury. Balloon test occlusion is generally performed in a preoperative setting when it is anticipated that one of the vessels supplying the brain will be sacrificed. Adjunctive maneuvers including hypotensive challenge [28], neuropsychological testing [29], somatosensory-evoked potentials [30], cerebral oximetry [31], and electroencephalography [32] may be considered to reduce the incidence of a false-negative result. In addition, the hemodynamic effects of occlusion can be assessed by measuring the stump pressure [69], angiographic control runs [33], transcranial Doppler [34], xenon 133 imaging [35], xenon CT [36], CT perfusion [37], PET [38], SPECT [39], and MR perfusion [40].

General Technique

A detailed cerebral angiogram that includes selective injections of the common carotid artery, internal carotid artery, external carotid artery, vertebral artery, and thyrocervical and costocervical trunks of the subclavian artery is first performed. Once the hypervascularity of the tumor and need for preoperative embolization have been confirmed, the patient is put under general anesthesia. Access and guide catheter placement is accomplished in the usual manner. A microcatheter and a microwire are then used to select the first vascular pedicle, and a microcatheter angiogram is performed to check for dangerous anastomoses between the ECA and ICA or vertebral arteries. The appropriate embolic agent is then injected using constant fluoroscopic monitoring, making sure to avoid reflux of embolic material. Proximal occlusion of the arterial feeders is inadequate because it allows arterial collateralization, and the goal should be penetration to the arteriolar/capillary level. This can be accomplished through the use of PVA particles in 150–250 μm range. Liquid embolic agents (e.g., NBCA or EVOH) are preferred by some practitioner, especially when direct percutaneous puncture of tumors is planned.

Risks

The risks associated with tumor embolization are similar to those seen in the treatment of epistaxis and include stroke due to reflux of the embolic agent into the cerebral vasculature or transit through external to internal or external to vertebral artery connections. There is also risk associated with unintentional devascularization of cranial nerves, skin, and mucosa. When large tumors are treated, perioperative edema and mass effect may occur. This risk can be minimized through the judicious use of postoperative steroids and timing the embolization procedure in close proximity to surgical resection.

Neoplastic Vascular Lesions

Hemangioma

Infantile hemangiomas are congenital vascular tumors comprised of rapidly dividing endothelial cells affecting up to 10 % of population with a greater incidence in Caucasians, female patients, and premature and low-birth-weight infants [41].Capillary hemangiomas proliferate during the first 9–12 months of life and subsequently involute at a variable course over many years [42]. The visible portion of hemangiomas on the skin often represents only an element of a larger subcutaneous component. The bright red discoloration is persistent until the onset of involution when resurfacing is observed as variable graying of the overlying skin. Rapid expansion can lead to adjacent skin

and soft tissue ischemia, necrosis, and ulceration. Ulceration and subsequent bleeding is common in watershed areas, such as the lip and ear, and will appear within the first few months of life during the rapid growth phase [43].

Conservative observation has been historically employed to allow the majority of lesions, in inconspicuous sites, to dissipate on their own. Medical and surgical therapies have been uncommon unless functional problems arose such as orbital obstruction, airway occlusion, and ulceration. Nonetheless, a recent paradigm shift in the management of these conditions has occurred. Many practitioners now advocate early intervention to circumvent immanent aesthetic squeal from residual scarring and fibrofatty distortion. Undisputed indications for treatment of hemangiomas still remain and include ulceration, bleeding, functional deficits, and congestive heart failure with massive disease [44]. Historic treatment options for infantile hemangiomas include systemic or intralesional corticosteroids, chemotherapeutic agents (vincristine, alpha interferon), surgery, lasers, or a combination of these therapies. Recently, the identification of orally administered propranolol as a novel therapy in hemangiomas has shed new light on their pathogenesis. The mechanism of propranolol, although controversial, in reducing or eliminating the hemangiomas seems to center around the control of cellular apoptosis [45].

Hemangioblastoma

Hemangioblastomas are highly vascular tumors of the central nervous system that have a predilection of the cerebellum. They may occur sporadically but also occur in the setting of genetic disorders such as von Hippel–Lindau syndrome. They occur more frequently in children and young adults. Resection may be curative but is complicated by the potential for large volume blood loss. Effective preoperative embolization with liquid embolic agents has been described in a variety of case reports [46, 47].

Meningioma

The blood supply to meningiomas is variable and is primarily dependent on the location of the tumor. The primary blood supply may be from the ECA, ICA, and/or vertebral arteries. The more common arterial feeders include the MMA, the accessory meningeal artery, the ascending pharyngeal artery, and the occipital transmastoid perforators of the ECA. Embolization exhibits the best risk–benefit profile when it is used for large tumors, primarily supplied by the ECA [7].

- *Anterior fossa and frontal meningiomas*
  The MMA and the falcine artery often supply high convexity and parasagittal lesions. The ethmoidal and anterior falcine arteries often supply fronto-polar and falcine tumors. The anterior and posterior ethmoidal branches of the ophthalmic artery typically feed olfactory groove meningiomas.

- *Middle fossa meningiomas*
  Branches from the external carotid artery including the artery of the foramen rotundum, the vidian artery, the ascending pharyngeal artery, the MMA, the accessory meningeal artery, and occipital transmastoid-perforating branches typically supply tumor of the middle fossa as well as branches of the petrous, cavernous, and supraclinoid segments of the ICA.

Illustrative Case 1

A 50-year-old female presented with a 3-month history of pulsatile tinnitus and a 1-week history of headache, nausea, and vomiting. She was found on gadolinium-enhanced MRI to have an enhancing right temporal pole mass (Fig. 14.1a). Angiography showed prominent tumor blush arising from the deep temporal branches of the internal maxillary artery (Fig. 14.1b, c). Post-embolization (PVA particles) intraoperative MRI shows no further tumor enhancement (Fig. 14.1d).

- *Posterior fossa meningioma*
  Posteromedially located posterior fossa meningioma often receives supply from meningeal branches of the vertebral arteries. More laterally located posterior fossa meingiomas commonly receives supply from transmastoid branches of the occipital artery as well as contribution from the ascending pharyngeal artery. Preoperative embolization of meningioma feeding arteries is usually confined to large tumors with high vascularity. Evidence of reduction in perioperative transfusion associated with embolization has been reported [48].

Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) is a benign tumor that tends to bleed and occurs in the nasopharynx of prepubertal and adolescent males. It originates from the posterolateral nasopharynx in the pterygopalatine fossa and extends through the sphenopalatine foramen to involve both the pterygopalatine fossa and the posterior nasal cavity [49]. It may extend laterally through the pterygomaxillary fissure into the infratemporal fossa. Anterior bowing of the posterior wall of the maxillary antrum is a result of remodeling and expansion of the bony wall of the pterygopalatine fossa. Occasionally, the greater wing of the sphenoid may be eroded, exposing the middle fossa dura. Sphenoid sinus involvement through its ostium may afford access into the medial portion of the middle fossa. Orbital extension via the inferior orbital fissure may occur in approximately one third of the patients [50].

Arterial supply for JNA arises initially from the pterygopalatine portion of the internal maxillary artery including the sphenopalatine, infraorbital, and descending palatine branches. Recruitment of adjacent vessels including the accessory meningeal,

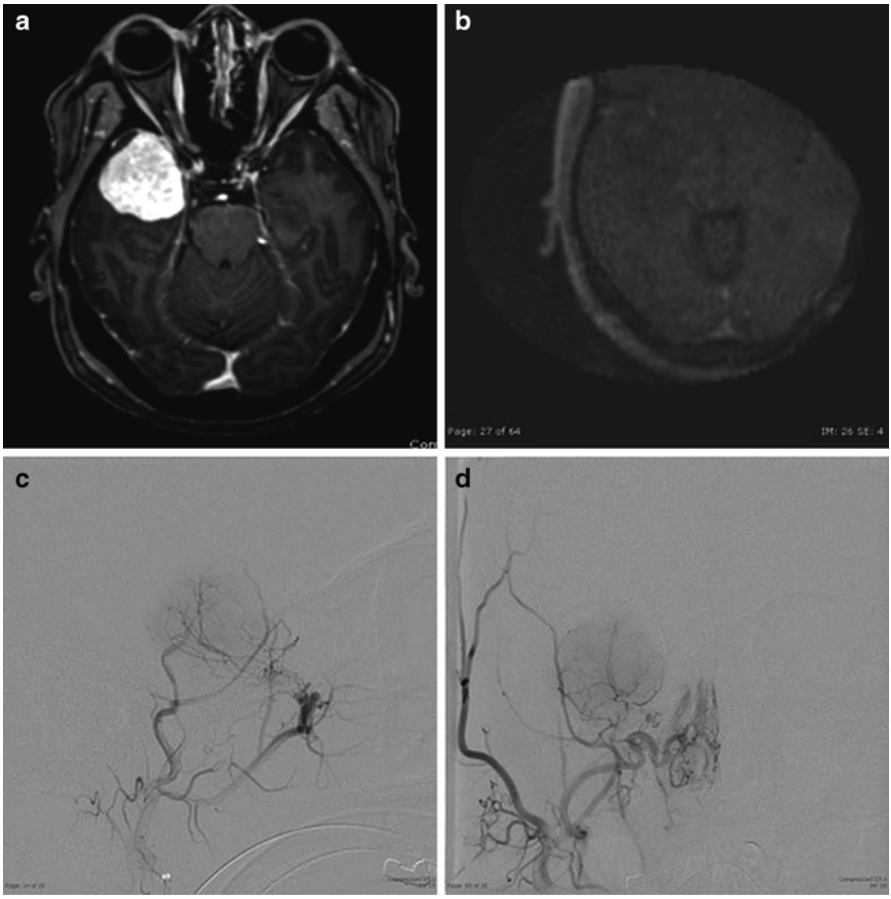

Fig. 14.1 Gadolinium-enhanced axial image showing avid enhancement of a right middle fossa meningioma (**a**). Catheter angiography demonstrates a significant tumor blush with microcatheter injection of the internal maxillary artery on anterior–posterior (**b**) and lateral (**c**) projections. No residual enhancement is seen on intraoperative gadolinium-enhanced MRI (**d**)

ascending pharyngeal, and ascending palatine arteries is common with larger tumors. Pial supply from the ICA, although uncommon, may exist, reflecting tumor extension into the anterior or middle fossa [51]. Bilateral blood supply is not uncommon, and when present, both branches should be embolized to prevent excessive hemorrhage at the time of resection [52].

Complete surgical resection is the therapy of choice. Preoperative embolization of JNA has been shown to reduce both perioperative blood loss and the duration of surgical resection [53]. Preoperative embolization has typically been performed via a transarterial route using a variety of embolic materials.

The JNA location and routes of extension mandate a particular attention to the possibility of orbital or intracranial anastomoses. Supply to cranial nerves is also of

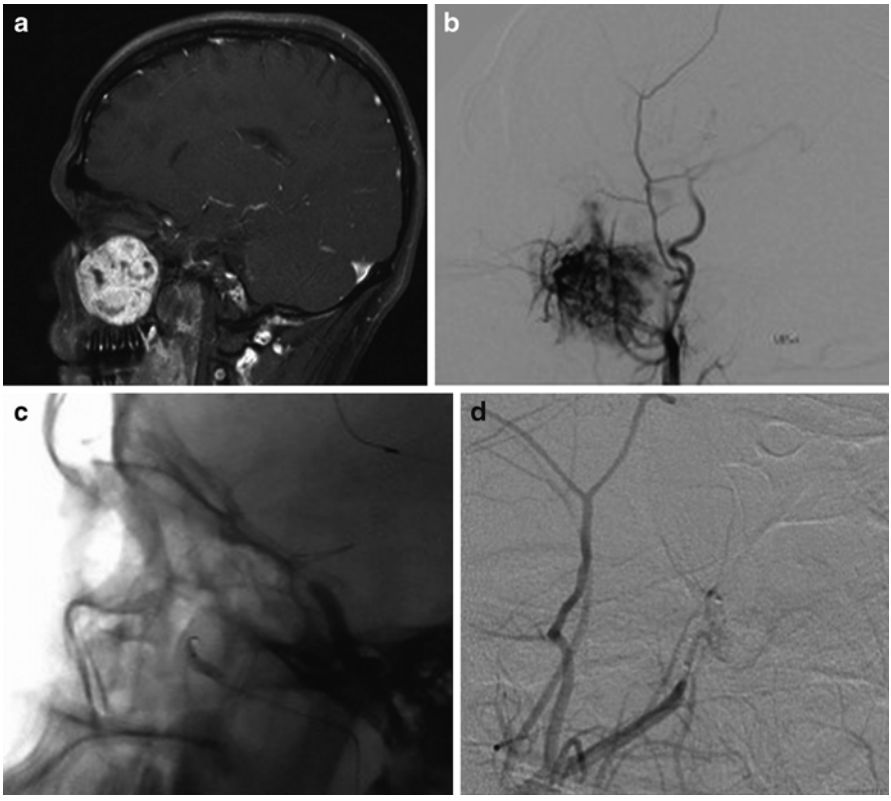

Fig. 14.2 Gadolinium-enhanced sagittal MRI showing avid enhancement of a maxillary sinus juvenile nasal angiofibroma (**a**). Microcatheter injection of the internal maxillary artery demonstrates significant tumor blush (**b**) that was treated with particle embolization (**c**), resulting in elimination of the previously seen blush (**d**)

concern when embolization is attempted for tumor involving the skull base [53]. Endoscopic assistance has been used for direct transnasal tumor puncture and intratumoral embolization using the liquid embolic agent Onyx [54].

Illustrative Case 2: Juvenile Nasal Angiofibroma

A 22-year-old man who presented with recurrent epistaxis was found to have a right maxillary sinus mass on MRI (Fig. 14.2a). A biopsy confirmed the diagnosis of JNA. The patient underwent diagnostic angiography revealing splaying of the right internal maxillary artery and tumor blush (Fig. 14.2b). The patient underwent successful embolization with PVA particles (Fig. 14.2c, d) followed by complete resection.

Glomus Tumors

Paragangliomas, also known as glomus tumors, are rare hypervascular neoplasms that arise from chemoreceptor organs derived from the neural crest [55].Carotid body location is the most common. Temporal bone paragangliomas are next in frequency and include glomus tympanicum tumors that involve the middle ear and are associated with the tympanic branch of the glossopharyngeal nerve. The glomus jugulare tumors involve the jugular fossa and thought to originate from the chief cell located within the jugular bulb adventitia. Paraganglioma associated with the auricular branch of the vagus nerve (glomus vagale) and those involving the larynx are less common [56].

Glomus tumors are found most commonly in women during the fifth and sixth decades. Wide age distribution is reported with earlier onset in familial cases. Due to the tumor's slow growing nature, the clinical presentation is often indolent and delayed. Clinical manifestations are usually related to the location of the tumor and the infiltration of adjacent structure. While the majority of paragangliomas show histological evidence of catecholamine production, clinical hypersecretion occurs in less than 5 % of cases. Hypersecretion of catecholamines can result in paroxysmal hypertension, headache, nausea, and excessive perspiration [57].

CT scans of the skull base will usually demonstrate the extent of bone thinning or bone erosion around the mass lesion. MR images are the mainstay of noninvasive images and typically demonstrate the characteristic "salt-and-pepper" appearance of high-velocity flow voids within the tumor. Complete surgical resection, usually with preoperative embolization of major external carotid artery feeding arteries, is the mainstay of therapy [58]. Preoperative embolization of the ECA supply usually gives the most favorable risk–benefit ratio for the vast majority of paragangliomas of the head and neck [59]. Balloon occlusion testing of the ICA may be necessary when carotid encasement is present or carotid sacrifice is anticipated. Superselective angiography is important to delineate cranial nerve supply or dangerous anastomoses with the intracranial circulation. Jugulotympanic paragangliomas receive major supply from ascending pharyngeal artery. Middle ear paragangliomas receive their blood supply from the inferior tympanic branch while the neuromeningeal branch supplies both the jugular fossa and hypoglossal canal. Additional ECA supply from the temporal branch of the middle meningeal artery, transmastoid branches of the occipital artery, or extradural ICA (caroticotympanic or cavernous branches) may contribute to the tumor blood supply. The musculospinal branches of the ascending pharyngeal artery supply vagal paraganglioma inferior to the skull base [60].

Hemangiopericytoma

The term hemangiopericytoma (HPC) was first described by Stout and Murray in 1942 as a distinct neoplasm of pericytic origin. The cell of origin is believed to be the pericyte of Zimmerman, a modified smooth muscle cell that is found in the capillary wall. Up to 25 % of HPCs involve the head and neck with the sinonasal region being the

most common location [61]. HPC intracranial involvement should be considered in the differential diagnosis of tumors involving the dura. They are most often supratentorial although posterior fossa location has been reported [62].

Typically presenting in the fifth and sixth decade of life, the tumor has been found in all age groups and affects both sex equally. Despite an apparently benign initial presentation, a propensity for local aggressiveness and metastases frequently characterizes HPC, leading to significant mortality rates [63].

Angiography often demonstrates high vascularity and may be considered when HPC is a differential consideration. Preoperative embolization has been recommended to aid in achieving a gross total resection [64].

Endolymphatic Sac Tumors

Endolymphatic sac tumors, first described in 1989 by Heffner et al., are rare lesions affecting females more commonly than males with a mean age of symptom onset in the fourth decade [65].They most often occur sporadically; nevertheless, they have also been described as a component of von Hippel–Lindau syndrome.

The tumors arise from the endolymphatic sac that is located in the bony vestibular aqueduct. It communicates with the endolymphic duct that in turn joins the utricular and saccular ducts. It is believed to be involved in the regulation of endolymphatic fluid volume [66].

CT scan will demonstrate an expansive, erosive soft tissue mass involving the temporal bone adjacent to the vestibular aqueduct. MR typically demonstrates a heterogeneous signal as a result from component of hemorrhage, cyst, residual bone, and cholesterol granuloma. Flow voids may be present suggesting high vascular flow [67].

The vascular nature of the neoplasm has led to the recommendations for preoperative embolization to aid in surgical resection [68].

References

1. Lowis GW, Minagar A. The neglected research of Egas Moniz of internal carotid artery occlusion. J Hist Neurosci. 2003;12(3):286–91.
2. Brooks B. The treatment of traumatic arteriovenous fistula. South Med J. 1930;23:100–6.
3. Luessenhop AJ, Gibbs M, Velasquez AC. Cerebrovascular response to emboli. Observations in patients with arteriovenous malformation. Arch Neurol. 1962;7:264–74.
4. Djindjian R, Cophignon J, Rey Theron J, Merland JJ, Houdart R. Superselctive arteriographic embolization by the femoral route in neuroradiology. Study of 50 cases. Neuroradiolgy. 1973;6(3):143–52.
5. Hilal SK, Michelsen JW. Therapeutic percutaneous embolization for extra-axial vascular lesions of the head, neck and spine. J Neurosurg. 1975;43(3):275–85.
6. Bruce JN, D'Amico R, Ellis JA, Lavine SD, McKhann GM, Meyers PM. Pre-operative intracranial meningioma embolization. Expert Rev Neurother. 2011;11(4):545.

7. Manelfe C, Lasjaunias P, Ruscalleda J. Preoperative embolization of intracranial meningiomas. AJNR Am J Neuroradiol. 1986;7(5):963–72.
8. Tadavarthy SM, Moller JH, Amplatz K. Polyvinyl alcohol(Ivalon) – a new embolic material. Am J Roentgenol Radium Ther Nucl Med. 1975;125(3):609–16.
9. Latchaw RE, Gold LH. Polyvinyl foam embolization of vascular and neoplastic lesions of the head, neck and spine. Radiology. 1979;131(3):669–79.
10. Bendszus M, Martin-Schrader I, Schlake HP, Solymosi L. Embolisation of intracranial meningiomas without subsequent surgery. Neuroradiology. 2003;45(7):451–5.
11. Hamada J, Kai Y, Kazekawa K, Tsukahara T, Hashimoto N, Iwata H. Embolization with cellulose porous beads, II: Clinical trial. AJNR Am J Neuroradiol. 1996;17(10):1895–9.
12. Gupta R, Thomas AJ, Horowitz M. Intracranial head and neck tumors: endovascular consideration, present and future. Neurosurgery. 2006;59(5 Suppl 3):S251–60. Discussion S3–13.
13. Gruber A, Killer M, Mazal P, Bavinzski G, Richling B. Preoperative embolization of intracranial meningiomas: a 17-years single center experience. Minim Invasive Neurosurg. 2000;43(1):18–29.
14. Gobin YP, Murayama Y, Milanese K, et al. Head and neck hypervascular lesions: embolization with ethylene vinyl alcohol copolymer – laboratory evaluation in swine and clinical evaluation in human. Radiology. 2001;221(2):309–17.
15. Probst EN, Grzyska U, Westphal M, Zeumer H. Preoperative embolization of intracranial meningioma with a fibrin glue preparation. AJNR Am J Neuroradiol. 1999;20(9):1695–702.
16. Richling B. Homologous controlled-viscosity fibrin for endovascular embolization. Part I. Experimental development of the medium. Acta Neurochir (Wien). 1982;62(3-4):159–70.
17. Kumar AJ, Kaufman SL, Patt J, Posey JB, Maxwell DD, White Jr RI. Preoperative embolization of hypervascular head and neck neoplasms using microfibrillar collagen. AJNR Am J Neuroradiol. 1982;3(2):163–8.
18. Richter HP, Schachenmayr W. Preoperative embolization of intracranial meningiomas. Neurosurgery. 1983;13(3):261–8.
19. Suzuki J, Komatsu S. New embolization method using estrogen for dural arteriovenous malformation and menigioma. Surg Neurol. 1981;16(6):438–42.
20. Hieshima GB, Everhart FR, Mehringer CM, et al. Preoperative embolization of meningiomas. Surg Neurol. 1980;14(2):119–27.
21. Kasuya H, Shimizu T, Sasahara A, Takakura K. Phenytoin as a liquid material for embolisation of tumors. Neuroradiology. 1999;41(5):320–3.
22. Feng L, Kienitz BA, Matsumoto C, et al. Feasibility of using hyperosmolar mannitol as a liquid tumor embolization agent. AJNR Am J Neuroradiol. 2005;26(6):1405–12.
23. Kubo M, Kuwayama N, Hirashima Y, Takaku A, Ogawa T, Endo S. Hydroxyapatite ceramics as a particulate embolic material: report of the clinical experience. AJNR Am J Neuroradiol. 2003;24(8):1545–7.
24. Deveikis JP. Sequential injections of amobarbital sodium and lidocaine for provocative neurologic testing in the external carotid circulation. AJNR Am J Neuroradiol. 1996;17(6):1143–7.
25. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960. J Neurosurg. 2007;106(6):1117–33.
26. Horton JA, Kerber CW. Lidocaine injection into external carotid branches: provocative test to preserve cranial nerve function in therapeutic embolization. AJNR Am J Neuroradiol. 1986; 7(1):105–8.
27. Kim LJ, Albuquerque FC, Aziz-Sultan A, Spetzler RF, McDougall CG. Low morbidity associated with the use of N-butyl cyanoacrylate liquid adhesive for preoperative transarterial embolization of central nervous system tumors. Neurosurgery. 2006;59(1):98–104. Discussion 98–104.
28. Marshall RS, Lazar RM, Pile-Spellman J, et al. Recovery of brain function during induced cerebral hypoperfusion. Brain. 2001;124(Part 6):1208–17.
29. Cloughesy TF, Nuwer MR, Hoch D, Vinuela F, Duckwiler G, Martin N. Monitoring carotid test occlusions with continuous EEG and clinical examination. J Clin Neurophysiol. 1993; 10(3):363–9.

30. Schellhammer F, Heindel W, Haupt WF, Landwehr P, Lackner K. Somatosensory evoked potentials: a simple neurophysiological monitoring technique in supra-aortal balloon test occlusion. Eur Radiol. 1998;8(9):1586–9.
31. Takeda N, Fujita K, Katayama S, Tamaki N. Cerebral oximetry for the detection of cerebral ischemia during temporary carotid artery occlusion. Neurol Med Chir. 2000;40(11):557–62. Discussion 62–3.
32. Kurata A, Miyasaka Y, Tanaka C, Ohmomo T, Yada K, Kan S. Stump pressure as a guide to the safety of permanent occlusion of the internal carotid artery. Acta Neurochir. 1996; 138(5):549–54.
33. Abud DG, Spelle L, Piotin M, Mounayer C, Vanzin JR, Moret J. Venous phase timing during balloon test occlusion as a criterion for permanent internal carotid artery sacrifice. AJNR Am J Neuroradiol. 2005;26(10):2602–9.
34. Giller CA, Mathews D, Walker B, Purdy O, Roseland AM. Prediction of tolerance to carotid artery occlusion using transcranial Doppler ultrasound. J Neurosurg. 1994;81(1):15–9.
35. Marshall RS, Lazar RM, Young WL, et al. Clinical utility of quantitative cerebral blood flow measurement during internal carotid test occlusions. Neurosurgery. 2002;50(5):996–1004. Discussion 5.
36. Mathis JM, Barr JD, Jungreis CA, et al. Temporary balloon test occlusion of the internal carotid artery: experience in 500 cases. AJNR Am J Neuroradiol. 1995;16(4):749–54.
37. Jain R, Hoeffner EG, Deveikis JP, Harrigan MR, Thompson BG, Mukherji SK. Carotid perfusion CT with balloon occlusion and acetazolamide challenge test: feasibility. Radiology. 2004;231(3):906–13.
38. Brunberg JA, Frey KA, Horton JA, Deveikis JP, Ross DA, Koeppe RA, Brunberg JA, Frey KA, Horton JA, Deveikis JP, Ross DA, Koeppe RA. [150]H2O positron emission tomography determination of cerebral blood flow during balloon test occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 1994;15(4):725–32.
39. Monsein LH, Jeffery PJ, van Heerden BB, et al. Assessing adequacy of collateral circulation during balloon test occlusion of the internal carotid artery with 99mTc-HMPAO cerebral perfusion SPECT imaging. AJNR Am J Neuroradiol. 1991;12(6):1035–41.
40. Michel E, Liu H, Remley KB, et al. Perfusion MRI neuroimaging in patients undergoing balloon test occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 2001;22(8): 1590–6.
41. Haggstrom AN, Drolet BA, et al. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr. 2007;150:291–4.
42. Ronchese F. The spontaneous involution of the cutaneous vascular tumor. Am J Surg. 1953; 86:376–86.
43. Haggstrom AN, Drolet BA, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics. 2006;118:882–7.
44. Buckmiller LM, Richter GT, Suen JY. Diagnosis and management of hemangiomas and vascular malformation of the head and neck. Oral Dis. 2010;16:405–18.
45. Frieden IJ, Drolet BA. Propranolol for infantile hemangiomas: promise, peril, pathogenesis. Pediatr Dermatol. 2009;26:642–4.
46. Dabus G, Pryor J, Spilberg G, Samaniego EA, Nogueira RG. Embolization of intra-axial hypervascular tumors with Onyx: report of three cases. J Neurointerv Surg. 2013;5(2): 177–80.
47. Seong Eom K, Won Kim D, Sung Choi S, Ha Choi K, Young Kim T. Preoperative embolization of a cerebellar haemangioblastoma using Onyx: case report and literature review. Neurol Neurochir Pol. 2011;45(3):292–6.
48. Alexiou GA, Gogou P, Markoula S, Kyritsis AP. Managment of meningiomas. Clin Neurol Neurosurg. 2010;112:177–82.
49. Onerci M, Ogretmenoglu O, Yucel T. Juvenile nasopharyngeal angiofibroma: a revised staging system. Rhinology. 2006;44:39–45.
50. Cruz AA, Atique JM, Melo-Filho FV, et al. Orbital involvement in juvenile nasopharyngeal angiofibroma: prevalence and treatment. Ophthal Plast Reconstr Surg. 2004;20:296–300.

51. Gill G, Rice D, Ritter F. Intracranial and extracranial nasopharyngeal angiofibroma. Arch Otolaryngol. 1976;102:371–7.
52. Wu AW, Mowry SE, Vinuela F, et al. Bilateral vascular supply in juvenile nasopharyngeal angiofibromas. Laryngoscope. 2011;121:639–43.
53. Davis K, Debrun G. Embolization of juvenile angiofibromas. Semin Interv Radiol. 1987; 4:309–20.
54. Aziz-Sultan MA, Moftakhar R, Wolfe SQ, Elhammady MS, Herman B, Farhat H. Endoscopically assisted intratumoral embolization of juvenile nasopharyngeal angiofibroma using Onyx. J Neurosurg Pediatr. 2011;7(6):600–3.
55. Zak F, Lawson W. The paraganglionic chemoreceptor system: physiology, pathology, and clinical medicine. New York: Springer; 1982.
56. Pellitteri PK, Rinaldo A, Myssiorek D, et al. Paragangliomas of the head and neck. Oral Oncol. 2004;40:563–75.
57. Young Jr WF. Paragangliomas: clinical overview. Ann N Y Acad Sci. 2006;1073:21–9.
58. Gujrathi CS, Donald PJ. Current trends in the diagnosis and management of head and neck paragangliomas. Curr Opin Otolaryngol Head Neck Surg. 2005;13:339–42.
59. Valavanis A. Preoperative embolization of the head and neck : indications, patient selection, goals, and precautions. AJNR Am J Neuroradiol. 1986;7:943–52.
60. Moret J, Lasjaunias P. Vascular architecture of tympanojugular glomus tumors. In: Vignaud J, editor. The ear. Diagnostic imaging. New York: Masson; 1986. p. 289–303.
61. Acioglu E, Cansiz H, Mercan H, Dervisoglu S. Head and neck hemangiopericytomas: diagnostic contradictions. J Craniofac Surg. 2009;20:930–5.
62. Tashjian VS, Khanlou N, Vinters HV, et al. Hemangiopericytoma of the cerebellopontine angle: a case report and review of the literature. Surg Neurol. 2009;72:290–5.
63. Rutkowski MJ, Sughrue ME, Kane AJ, et al. Predictors of mortality following treatment of intracranial hemangiopericytoma. J Neurosurg. 2011;113:333–9.
64. Craven JP, Quigley TM, Bolen JW, Raker EJ. Current management and clinical outcome of hemangiopericytomas. Am J Surg. 1992;163:490–3.
65. Diaz RC, Amjad EH, Sargent EW, et al. Tumors and pseudotumors of the endolymphatic sac. Skull Base. 2007;17:379–93.
66. Lo WW, Applegate LJ, Carberry JN, et al. The endolymphatic duct and sac. AJNR Am J Neuroradiol. 1997;18:881–7.
67. Joy HM, Barker CS, Millar JS, Davis A. Radiological consideration in the diagnosis of an endolymphatic sac tumor. Clin Radiol. 2002;57:652–4.
68. Bae CW, Cho YH, Chung JW, et al. Endolymphatic sac tumors: report of four cases. J Korean Neurosurg Soc. 2008;44:268–72.
69. Augusto E. Elias, Neeraj Chaudhary, Aditya S. Pandey, Joseph J. Gemmete. Intracranial Endovascular Balloon Test Occlusion: Indications, Methods, and Predictive Value. Neuroimag Clin N Am. 2013;23:695–702.

Chapter 15
Neurointervention in Ophthalmologic Disorders

Yanjun Chen, Sophia M. Chung, Diogo C. Haussen, and Dileep R. Yavagal

Cerebral Aneurysm

Introduction

Cerebral aneurysms are localized abnormal dilatation of the cerebral artery resulted from weakening of the vascular wall. Cerebral aneurysms most commonly involve the branching points of the major arteries at the skull base [1]. The overall prevalence of intracranial aneurysm varies from 0.8 to 6 % [1–4]. The majority of cerebral aneurysms remain unruptured with an average annual rate of rupture of

Y. Chen, M.D., Ph.D. (✉)
Department of Ophthalmology, Neurology and Neurosurgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Ophthalmology and Visual Sciences, University of Wisconsin Hospitals and Clinics, 2828 Marshall Ct. Suite 200, Madison, WI 53705, USA
e-mail: ychen@ophth.wisc.edu

S.M. Chung, M.D.
Department of Ophthalmology, Saint Louis University School of Medicine, 1755 South Grand Boulevard, Saint Louis, MO 63104, USA

Department of Neurology and Psychiatry, Saint Louis University School of Medicine, 1755 South Grand Boulevard, Saint Louis, MO 63104, USA
e-mail: chungsm@slu.edu

D.C. Haussen, M.D. • D.R. Yavagal, M.D.
Department of Neurology, University of Miami School of Medicine, Miami, FL, USA
e-mail: dhaussen@gmail.com; dyavagal@med.miami.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_15

approximately 1.3 %; patient age, smoking, and size of aneurysm are important risk factors for rupture [5, 6]. The annual rate of rupture increases to 3–8 % for aneurysms greater than 10 mm in diameter [7].

Clinical Manifestations

The ocular manifestations of cerebral aneurysms occur primarily in three different ways: (1) visual loss as a result of retinal/vitreal hemorrhage associated with subarachnoid hemorrhage, also called Terson syndrome, (2) visual field defects caused by aneurysmal compression of the anterior visual pathways, and (3) diplopia and ocular motility deficits caused by aneurysmal compression on the cranial nerves [8–10]. Other rare ocular manifestations have been reported, as a result of either the cerebral aneurysm or its related intervention, such as retinal arterial emboli [11], orbital compartment syndrome and blindness [12], and internuclear ophthalmoplegia [13].

Terson syndrome manifests as bleeding in the retina, subhyaloid space, and vitreous and occurs in more than 30 % of patients who survive subarachnoid hemorrhage [14]. The mechanism of intraocular bleeding is postulated to be rupture of the fine papillary and retinal capillaries when central retinal venous stasis develops as a result of suddenly elevated intracranial pressure from subarachnoid hemorrhage. Terson syndrome commonly affects both eyes, and severity of the visual loss depends on the extent of the bleeding and its relative location to the retina (Fig. 15.1). The visual outcome in Terson syndrome is usually favorable; complete visual recovery occurs within 12 months once the blood is reabsorbed. However, presence of Terson syndrome may predict poorer neurologic outcome from subarachnoid hemorrhage [15].

The intimate relationship between the anterior visual pathways and the circle of Willis makes visual loss a frequent presenting symptom of cerebral aneurysms. Cerebral aneurysms arising from intracranial carotid artery, middle cerebral artery, and anterior communicating arteries are more likely associated with visual loss than aneurysms arising from basilar and posterior communicating aneurysms [9]. Involvement of the optic nerve gives rise to decreased central vision and optic atrophy. Compression of the optic chiasm results in bitemporal field defects. Aneurysms growing posteriorly may cause homonymous hemianopia from involvement of the optic tract. Ophthalmic and supraclinoid segment carotid aneurysms constitute less than 10 % of all cerebral aneurysms [6, 16]. They may present with headache, orbital pain, and visual loss by compression and without rupture. Middle cerebral artery and anterior communicating artery aneurysms account for nearly half of all cerebral aneurysms. They tend to rupture and present with subarachnoid hemorrhage before enlarging sufficiently to affect visual function [17].

Diplopia and ocular motility abnormalities are commonly associated with aneurysms arising from carotid-cavernous segment, posterior communicating, and basilar arteries [18]. Posterior communicating artery aneurysm is a frequent cause of third nerve palsy, which presents with a symptom complex of ptosis, fixed and dilated

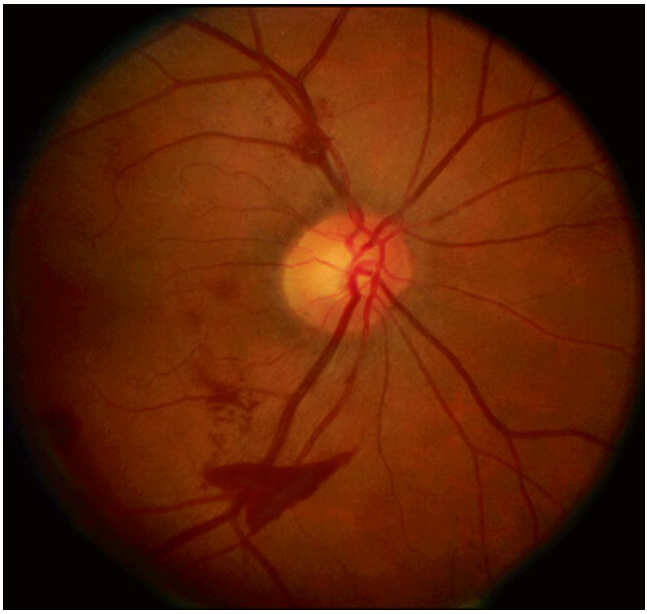

Fig. 15.1 Retinal and subhyaloid hemorrhage in a patient with Terson syndrome as result of a ruptured middle cerebral artery aneurysm. Note typical appearance of triangular-shaped hemorrhage to subhyaloid space in inferior retina

pupil, and the so-called down and out eye [19]. The pupil reactivity to light stimulus should be meticulously examined to help differentiate aneurysmal compression from an ischemic third nerve palsy. A complete third nerve palsy that spares the pupil is due to an ischemic third nerve palsy, while pupil involvement in combination with either a complete or an incomplete third nerve palsy raises a high suspicion for aneurysmal compression. An incomplete third nerve palsy without pupil involvement warrants close observation over the following 1 week for development of pupil abnormalities. Aneurysms within the cavernous sinus can affect the multiple cranial nerves that travel through cavernous sinus; the ocular motor abnormalities are sometimes associated with decreased sensation or pain along the V1 and V2 distributions of the trigeminal nerve [10]. Carotid-cavernous aneurysm may occasionally present with a sixth nerve palsy in combination with Horner syndrome, localizing the lesion to the cavernous sinus. Basilar aneurysms, while less common, constitute the majority of the cerebral aneurysms arising within the posterior fossa. Basilar artery aneurysms may cause diplopia via third, fourth, and sixth nerve involvement, skew deviation, and gaze palsy secondary to aneurysmal compression of the midbrain and pons. Basilar artery aneurysms can also cause homonymous visual field loss due to thromboembolic infarction to the occipital lobe [18].

The radiographic features and endovascular intervention for cerebral aneurysm are described in Chaps. 10 and 11.

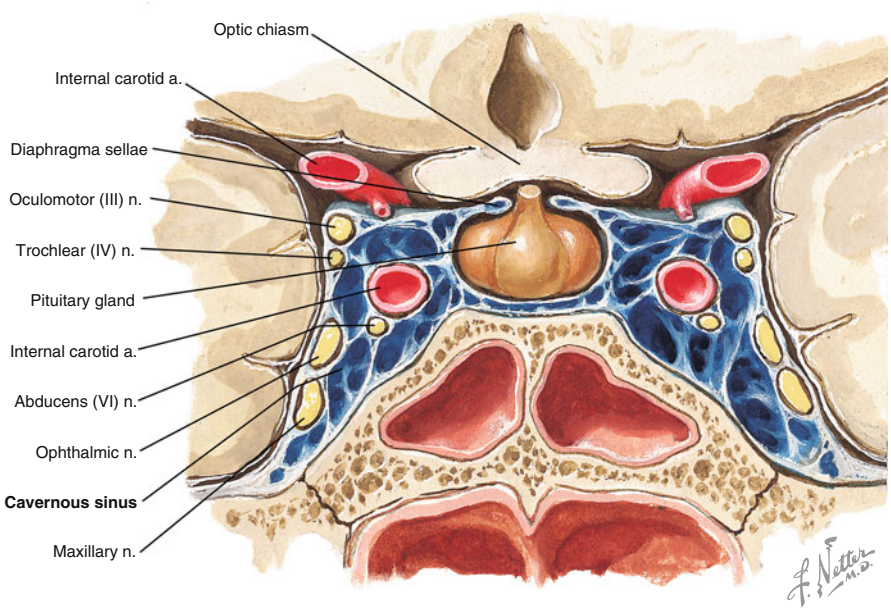

Fig. 15.2 Coronal view of the cavernous sinus demonstrating the passage of the third, fourth, fifth, and sixth cranial nerves and internal carotid artery inside the cavernous sinuses (permission from Netter's production)

Carotid-Cavernous Fistula

Introduction

The cavernous sinuses are a pair of cerebral venous sinuses located at the center of the skull base lateral to each side of the sella turcica (Fig. 15.2). They are bordered by the sphenoid and temporal bones. The cavernous sinus collects venous blood drained from the eye and orbit through the superior and inferior ophthalmic veins and then drains posteriorly to the internal jugular vein through the superior and inferior petrosal sinuses and the transverse sinus [20]. A number of cranial nerves and intracranial vessels travel through the cavernous sinus. The cavernous segment of the internal carotid artery is located in the medial aspect of the cavernous sinus and is surrounded by oculosympathetic fibers that form a fine plexus. Immediately lateral to the internal carotid artery is the sixth cranial nerve. The third and fourth cranial nerves and the first and second divisions of the trigeminal nerve (ophthalmic and maxillary nerve, respectively) travel along the lateral border of the cavernous sinus. The pituitary gland is located in the sella turcica between the pair of cavernous sinuses.

Carotid-cavernous fistula (CCF) is an abnormal communication between the cavernous sinus and the carotid arterial system. Meningeal branches arising from the internal carotid artery, external carotid artery, or both supply the dural sheath and anatomical structures contained in the cavernous sinus. When there is a breach in either the main trunk of the cavernous segment of the internal carotid artery or the meningeal branches from the internal or external carotid artery, an abnormal communication develops between the arterial and venous circulation [21]. Communication between the arterial and venous system results in elevated venous pressure thus elevated venous outflow resistance. Functional obstruction of the venous drainage from the eye and orbit ensues. The classification of CCF is based on anatomy (direct vs. indirect), cause (traumatic vs. spontaneous), or hemodynamic status (high flow vs. low flow). Each type of CCF is associated with specific clinical manifestations, treatment strategies, and outcomes. The most commonly used dichotomies in CCF classification are (1) *direct CCF* formed by direct connection between the cavernous segment of the internal carotid artery and cavernous sinus and (2) *indirect CCF* caused by a communication between the branches of the internal or external carotid arteries and the cavernous sinus.

Clinical Manifestation

A direct CCF is caused by a tear in the intra-cavernous segment of the internal carotid artery, usually in the setting of trauma, although in a small proportion of patients, it may occur spontaneously [22–26]. Direct CCF tends to affect younger patients and men are affected more than women, reflecting the higher incidence of trauma in these groups. The classic triad of proptosis, conjunctival chemosis, and orbital bruit is consequence of significantly elevated venous pressure in the superior ophthalmic vein and cavernous sinus system [26–28]. Typical ocular findings are prominent proptosis, chemosis, hyperemia, and irritating periorbital pain or headache. Elevated intraocular pressure and secondary glaucoma are caused by increased episcleral pressure and vortex venous pressure, anterior shift of the lens-iris diaphragm, as well as neovascular glaucoma secondary to ocular ischemia [24]. Ophthalmoplegia can be a consequence of either edema of the extraocular muscles or damage to the cranial nerves as they travel through the cavernous sinus. Vision loss is common and is usually severe in direct CCF, caused by exposure keratopathy, glaucoma, ischemia of the optic nerve, or coexisting traumatic optic neuropathy [29].

In contrast to direct CCF, indirect CCFs usually have a spontaneous onset and are slowly progressive. A history of minor trauma is reported in a small group of patients. When compared to direct CCF, indirect CCF tends to occur in an older age group (mean from 50 to 69 years of age), and women constitute 60–90 % of all indirect CCF cases. Vascular changes in a variety of systemic conditions such as postmenopausal hormonal changes, pregnancy, hypertension, and atherosclerosis are hypothesized to predispose patients to the development of indirect CCFs [27, 28, 30, 31].

Clinical manifestations of indirect CCFs include red eye, discomfort, ocular hypertension, or diplopia. Eye findings include engorged, "corkscrew" episcleral vessels from arterialized venous blood, ocular hypertension, and ophthalmoparesis. Less common presentations of indirect CCFs include headache, pulse-synchronous tinnitus, vision loss, and venous retinopathy [26, 27, 30, 32–47]. When indirect CCFs drain posteriorly to the superior or inferior petrosal sinuses, they may be asymptomatic or manifest as isolated cranial nerve palsies; symptoms and signs of orbital congestion become noticeable when indirect CCFs change its drainage from posterior to anterior draining indirect CCFs [48–51].

Importantly, significantly elevated venous pressure in the cavernous sinus may be transmitted retrograde to the cortical veins (cortical venous drainage), resulting in hemorrhagic venous infarction. Cortical venous drainage may lead to severe neurological dysfunction such as hemimotor or hemisensory deficits, necessitating prompt intervention to close the arterial venous shunt. Among various clinical manifestations, the presence of bilateral orbital signs and a postauricular bruit was found to have the most predictive value of cortical venous drainage [52].

Radiographic Features

The most prominent radiographic feature of direct CCF and indirect CCFs on computed tomography (CT) or magnetic resonance imaging (MRI) is a dilated superior ophthalmic vein, although enlargement of the EOMs, abnormal cavernous sinus flow voids, and sometimes engorgement of the cavernous sinus with a convexity of the lateral wall can also be observed [53, 54]. Orbital ultrasonography may also provide sensitive and reliable measurement by demonstrating dilatation of the superior ophthalmic vein and enlargement of the EOMs [55]. A high index of suspicion should be maintained in patients with symptomatology as above and a prompt imaging study of the brain and orbit using CT or magnetic resonance tomography done for screening. Catheter angiography remains the only definitive study to confirm or eliminate the diagnosis. Dural AVFs can be very difficult to diagnose with noninvasive imaging and sometimes is recognized only on catheter angiography.

Management of CCF

Spontaneous resolution of indirect CCFs has been reported in 20–60 % of indirect CCFs in the literature [28, 31, 37, 39, 56]. A nonsurgical management of indirect CCFs is carotid-jugular compression. The compression entails intermittent, seconds to a few minutes of compression of the ipsilateral cervical carotid artery and internal jugular vein using the contralateral hand for a period of a few weeks to a couple of months [26, 39, 57]. This maneuver should be considered in patients whose symptoms are too mild to warrant immediate surgical intervention or in those whose age or systemic comorbidities predispose them to higher surgical complications.

Endovascular Treatment

Although a conservative approach has been advocated for direct carotid-cavernous fistulas when there is no rapidly progressive visual deterioration or cerebral ischemia, intermittent compression of the jugular and carotid artery is very unlikely to be effective. Resolution without recurrence has been described in only 17 % of attempted cases [57].

Conversely, indirect carotid-cavernous fistulas commonly develop insidiously, and a conservative approach might be appropriate. Approximately 30–36 % of indirect (or "dural") CCFs may heal with conservative treatment utilizing manual external compression of the carotid artery and jugular vein [57, 58]. Close follow-up may be indicated to evaluate for the development of cortical venous drainage (which is correlated with higher risk of development of hemorrhagic complications or venous infarcts) [59]. Indications for treatment include persistently elevated intraocular pressure, visual deterioration, malignant proptosis, symptomatic ocular deviation, exposure keratopathy, severe pain, intolerable bruit, and/or diplopia.

Endovascular intervention has replaced intracranial surgery and is the treatment of choice when intervention is indicated. Endovascular treatment is typically the first-line approach for direct carotid-cavernous fistulas [60]. Compared to carotid artery surgery (trapping or ligation), endovascular intervention has significant lower risk of complications. The objective of the endovascular treatment is to eliminate the arteriovenous carotid-cavernous shunting. This leads to normalization of the venous pressures, reversing the ophthalmic and leptomeningeal venous retrograde flow and engorgement, as well as symptoms related to vascular steal.

The evaluation for feeding pedicles during catheter-based angiography is made through bilateral common, internal, and external carotid artery iodinated contrast injections. The endovascular therapy aiming to obliterate the fistulous connections may be performed through either trans-arterial or transvenous routes, and it is based on the arterial and venous angioarchitecture and flow patterns.

In indirect CCFs, trans-arterial embolization is technically difficult due to the small size and multiplicity of feeders. Therefore, transvenous embolization of CCF is the preferred approach for indirect CCFs. The cure rates have been reported between 70 and 90 %, with complication rates ranging between 2.3 and 5 % [60]. Technically, central venous access (femoral vein or internal jugular puncture) is obtained and followed by the introduction of a short vascular sheath. A 6-French guide catheter is introduced commonly through the common femoral vein and navigated into the distal internal jugular vein (sometimes directly into the internal jugular vein) and then into the jugular bulb, where a retrograde venogram is performed. The inferior petrosal sinus (IPS) may opacify and will constitute the path to reach the cavernous sinus. If the fistulous flow is high, the retrograde venogram may not opacify the IPS or any other cavernous sinus draining vein (such as the superior petrosal sinus). Therefore, a second diagnostic catheter (via a groin arterial puncture) is positioned in the common carotid artery ipsilateral to the side where the main arteriovenous shunting is present. This allows delineation of the venous outlets, which will fill early in the arterial phase, and guides the catheterization of the

cavernous sinus under overlay technique or venous-phase road mapping. It also allows intermittent arterial runs to evaluate for resolution of the arteriovenous shunting during embolization. As stated, the cavernous sinus is most commonly accessed through the IPS, utilizing a microcatheter that is navigated from the catheter previously positioned in the jugular bulb. However, at times the IPS may be either thrombosed or composed of a plexiform structure. The contralateral IPS can be cannulated and the microcatheter navigated through the contralateral cavernous sinus, across the intercavernous sinus, and into the targeted side. Other endovenous route options are available and include catheterization of the superior petrosal sinus or the facial vein takeoff from the internal jugular vein (which leads to the angular vein, and then into the superior ophthalmic vein, and finally into the cavernous sinus).

If the aforementioned routes are technically challenging, the arterialized superior ophthalmic vein (if dilated) can be directly accessed via an eyelid or eyebrow incision, with subsequent dissection of the orbicularis oculi muscle, orbital septum, and fat until an arterialized venous branch is noted. The branch is followed proximally until the main trunk is found. A small incision is made, a J wire is inserted, and a 4-French pediatric short sheath (or a micropuncture sheath) is advanced. A gentle intraoperative angiogram is performed through the sheath to confirm the proper positioning [61].

Another, less studied, option involves percutaneous transorbital puncture leading to the catheterization of the superior or inferior ophthalmic veins or the cavernous sinus directly [61].

Regardless of the access route, the technique, the microcatheter is optimally positioned within the cavernous sinus (typically more anteriorly, close to the proximal aspect of the superior ophthalmic vein) and embolization can ensue. Commonly used options are coiling and/or embolization with ethylene vinyl alcohol copolymer (Onyx). The sinus is filled with coils and/or liquid embolics until there is complete distribution of the embolic material within the cavernous cavity, and no early venous drainage is observed through arterial runs. Ocular symptoms tend to improve over the following hours. Paradoxical worsening of the symptoms has been described by tend to be transient [62]. Coil overpacking or direct liquid embolic local effects on nerves may generate posttreatment cranial nerve deficits (which commonly improve) [43]. Reported endovascular cure rates for indirect CCFs range around 70–90 %, with complication rates of 2.3–5 % [41, 60]. Radiosurgery has been demonstrated in small series to be effective; however, the latency period for the obliteration of the fistula is typically of several months. It may have an important role for incompletely treated indirect fistulas [60, 63].

In direct CCFs, trans-arterial embolization with different materials is generally needed. A guide catheter is advanced into the ICA, and a microcatheter navigated from the arterial side navigated across the cavernous carotid arterial tear into the cavernous sinus. We favor filling of the cavernous sinus initially with coils in order to slow flow. Subsequently, ethylene vinyl alcohol copolymer (or *N*-butyl cyanoacrylate) may be injected to fill the remaining space. The major concern is that once the embolic material starts filling the cavernous sinus—which surrounds the ICA—visualization of the tear becomes difficult, and protrusion of the coils or regurgitation

of embolic agent from the cavernous sinus back into the ICA may occur inadvertently. Therefore, extreme caution is required. Some operators advocate inflation of a compliant balloon in the ICA across the tear during embolization to avoid unintentional ICA embolization. Transvenous embolization may be performed; however, it is not preferred due to the risks of herniation of embolic material into the ICA. For direct CCFs, overall endovascular occlusion rates have been reported to be between 55 and 99 %, and the morbidity was described to be as high as 10–40 % [60]. Newer but less studied techniques include covered stents that obliterate the fistula through a direct physical barrier [60, 64].

Illustrative Case 1

A 60-year-old man presented with chemosis and increased intraocular pressures involving the left eye. Conventional angiography confirmed an indirect CCF, fed by bilateral internal and external carotid arteries (Fig. 15.3a, b). The cavernous sinus and the arterialized superior ophthalmic veins were clearly demonstrated (Fig. 15.3b). Although the inferior petrosal sinuses could not be visualized, the facial vein was clearly delineated (Fig. 15.3c). The microcatheter was advanced into the cavernous sinus through the facial vein (Fig. 15.3d), and Onyx was carefully injected. The left cavernous sinus was filled with the liquid embolic, and the fistulous point obliterated (Fig. 15.3e, f).

Idiopathic Intracranial Hypertension

Introduction

Idiopathic intracranial hypertension (IIH), also called pseudotumor cerebri or benign intracranial hypertension, refers to a condition of elevated intracranial pressure unrelated to a space-occupying lesion, cerebral venous thrombosis, meningitis, or hydrocephalus. IIH has a predilection for obese women of child-bearing age, although it can occur in children, at older age, and in males [65–68]. IIH has been associated with a variety of medications including antibiotics (tetracycline, minocycline, doxycycline, and nalidixic acid), growth hormone, lithium, retinoids (both topical and oral), Lupron, Norplant, and cyclosporine. Obstructive sleep apnea and recent weight gain may also contribute to an elevated intracranial pressure [69].

A number of mechanisms are thought to contribute to the development of IIH, including increased cerebrospinal fluid production, reduced cerebrospinal fluid absorption, the influence of hormones, abnormal vitamin A metabolism, as well as elevated cerebral venous pressure. The role of elevated intracranial dural venous pressure in the pathophysiology of IIH has gained increasing attention, as a potentially treatable cause of IIH. Although stenosis of the transverse and sigmoid sinus

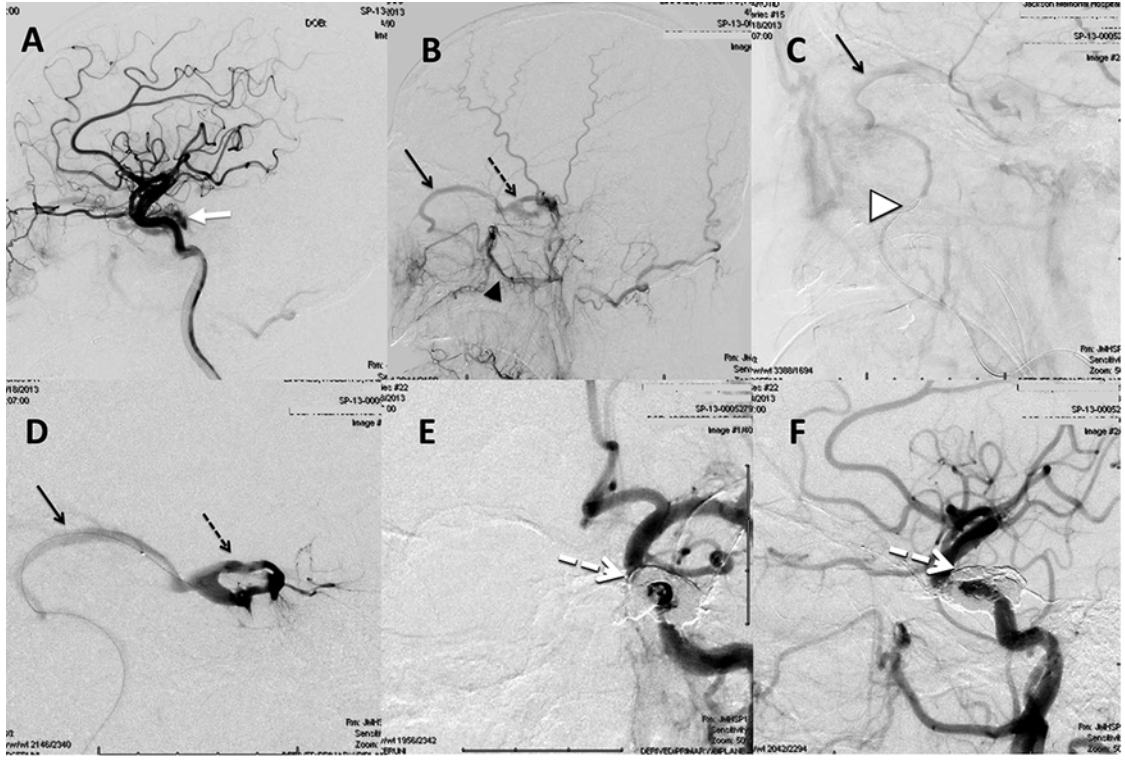

Fig. 15.3 (**a**) Lateral view of the left internal carotid artery injection revealing cavernous sinus early filling through the meningohypophyseal artery (*white arrow*). (**b**) Lateral view/mid-arterial phase left external carotid injection revealing internal maxillary (*arrowhead*) and ascending pharyngeal artery filling of the cavernous sinus (*dotted arrow*) and superior ophthalmic vein (*arrow*). (**c**) Lateral/late-arterial phase left external carotid injection revealing the microwire within the facial vein (*white arrowhead*). (**d**) Magnified lateral cavernous sinus (*dotted arrow*) venogram through the microcatheter. (**e**, **f**) AP and lateral final internal carotid angiograms revealing the Onyx cast (*dotted white arrow*) and no evidence of early venous drainage

is a common radiographic finding in IIH [70], it is unclear whether dural sinus stenosis is a cause of elevated intracranial pressure or a consequence of chronic compression of dural venous sinuses from persistently elevated intracranial pressure. Regardless of the etiology, increased resistance in cerebral venous outflow seems to be the common final pathway in the pathophysiology of IIH, suggested by elevated manometry measurements of the pre-stenotic vs. poststenotic pressure gradient [71–83].

Clinical Manifestation

The typical presentation of IIH includes headache, pulse-synchronous tinnitus, with varying degrees of vision loss, and papilledema. Headache occurs in about 90 % of IIH patients [84]. Pain in a nerve root distribution or retro-ocular pain with eye movement was found to be more specific, while all types of headaches can be seen [85, 86]. Pulse-synchronous tinnitus, described as a "whooshing" sound synchronized with the heart beat, is more specific for IIH if present. Patients may complain of transient visual obscurations and episodic and severe vision loss in both eyes lasting for seconds with complete recovery usually associated with activities that increase central venous pressure (such as Valsalva maneuver) or decrease systemic perfusion pressure (transition from supine or sitting to the upright position). Papilledema, manifested as hyperemia and elevation of the optic disc, engorgement of the central retinal veins, and obscuration of the central retinal vessels on the disc often with disc hemorrhage and exudates, is usually bilateral and symmetrical (Fig. 15.4). Most patients with IIH have mild vision loss that is reversible after appropriate treatment, although permanent vision loss can occur in about 25 % of patients [86]. A small proportion of patients (2–3 %) with IIH present with fulminant visual loss over days [87], necessitating aggressive intervention to salvage vision.

Investigation and Diagnosis

The diagnostic criteria of IIH was created by Dandy in 1937 and was last formulated by Friedman in 2002 [88]. The modified diagnostic criteria emphasize a normal cerebrospinal fluid composition as well as brain imaging study using MRI and MR venography (MRV) to rule out intracranial pathologies that may cause secondary intracranial hypertension. Typical symptoms of headache, pulse-synchronous tinnitus, and papilledema in overweight patients in the right demographic group make the diagnosis predictable. Diagnostic procedures include MRI and MRV of the brain and a lumbar puncture. Lumbar puncture provides information about the opening pressure as well as cerebrospinal fluid profile; the latter is essential in excluding secondary causes such as inflammation or infection. When performed without anesthesia with patients lying in the lateral decubitus position, the intracranial pressure in normal adults ranges from 100 to 250 mmH2O [88, 89].

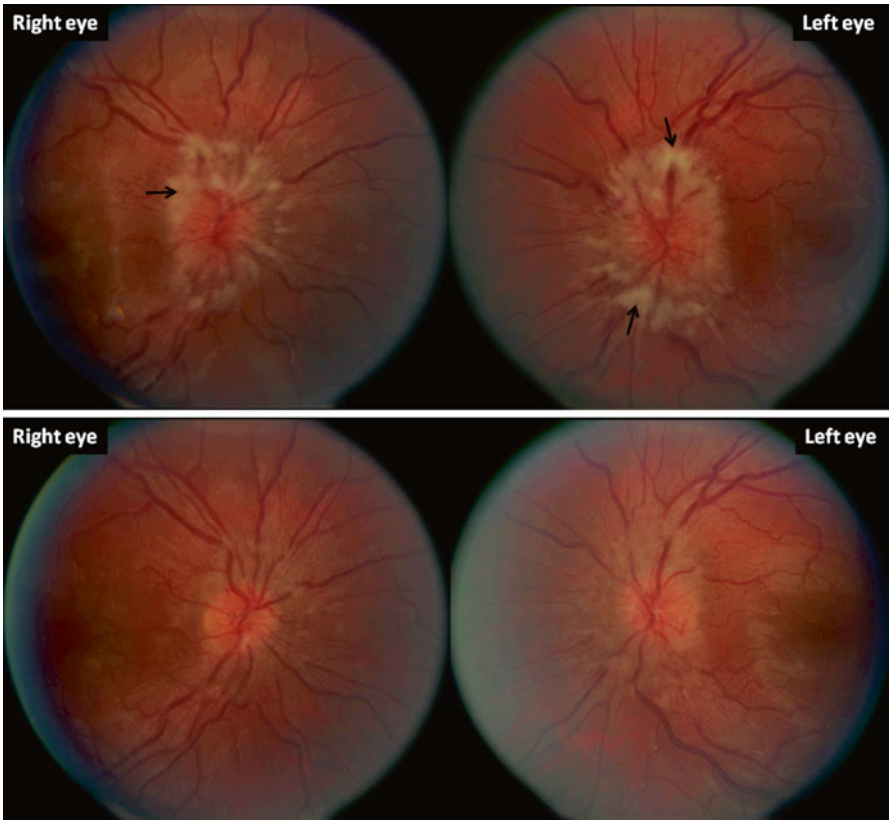

Fig. 15.4 Bilateral papilledema in a 26-year-old lady with a concurrent right sixth nerve palsy. Note the elevation of the optic disc, engorgement of the central retinal veins, and obscuration of the retina vessels both on the disc and as the vessels exit the disc margin (*top*). There are disc hemorrhages in the left eye. There are nerve fiber layer infarcts reflected by the white areas (*arrows*). The patient's visual acuity was 20/40 in the right eye and 20/60 in the left eye. The patient had been on oral minocycline for 2 months for acne treatment prior to presentation. Minocycline was discontinued and she was given acetazolamide 500 mg twice daily. One month later, both six nerve palsy and papilledema improved (*bottom*)

MRI and MRV of the brain provide information to rule out intracranial pathologies such as space-occupying lesions, hydrocephalus, Chiari malformation, and cerebral venous thrombosis. The radiographic findings suggesting IIH include posterior globe flattening, optic nerve sheath distension, and an empty sella [90]. One study using a specially designed MRV protocol found stenosis in the transverse and sigmoid sinuses to be both sensitive and specific for IIH [70].

Management

The severity of the vision loss in patients with IIH is the main determinant for treatment strategy. Treatment of patients with severe headache but intact visual function and mild papilledema is more variable across practitioners. Lumbar puncture, while serving as one of the mainstays of diagnosis, sometimes results in relief of headache for a prolonged period of time [91].

Weight loss serves as an important step in the management of IIH, and successful reduction of body weight of 5–15 % may have a significant impact on the evolution of both headache and papilledema [92, 93]. Pharmacologic treatment commonly includes carbonic anhydrase inhibitor and topiramate, or methazolamide or furosemide can be used when acetazolamide is poorly tolerated [94]. One must be aware that patients diagnosed with IIH may suffer from a headache disorder above and beyond that related to the elevated intracranial pressure, given the high predilection of headache disorder in the same demographic population.

When there is imminent visual loss, surgical intervention may be required. Optic nerve sheath fenestration creates a window or multiple slits on the intraorbital segment of the optic nerve sheath behind the globe to release cerebrospinal pressure [95]. Optic nerve sheath fenestration is generally regarded as a low-risk procedure, although serious complication may rarely occur such as central retinal artery occlusion, resulting in profound loss of vision. Lumboperitoneal and ventriculoperitoneal shunts divert cerebrospinal fluid from the spinal canal or cerebral ventricle into the abdomen via a catheter to lower the intracranial pressure. This allows treatment of both the papilledema and headache and leads to stabilization or improvement of visual acuity in a suboptimal proportion of patients. However, revision surgery is frequently necessary, and other complications (as low-pressure headache, infection, arachnoiditis of nerve roots) might develop [96, 97]. Cerebral shunting procedures are generally reserved as a last measure when other treatments have failed to halt progression of vision loss, or if there is a sign of rapid, fulminant vision loss at initial presentation.

Endovascular Treatment

The established surgical methods of treatment of idiopathic intracranial hypertension have limitations. As discussed, lumbar or ventriculoperitoneal shunting typically leads to stabilization or improvement of vision acuity in a proportion of patients, but revisional surgery is frequently necessary, and other complications (aforementioned) might develop. Likewise, optic nerve fenestration has been associated with deterioration of visual function years after an initial period of stabilization. Moreover, it does not treat the underlying mechanism that leads to headaches and tinnitus [98, 99].

Venous sinus stenting is an endovascular treatment option for IIH. Although a causal link between transverse-sigmoid venous sinus stenosis and IHH has never been definitively established, this abnormality is clearly more common in individuals with IHH than controls. Patients with IHH have been described to have substantial bilateral sinovenous stenoses in 27 of 29 (93 %) patients with IIH versus 4 of 59 (6 %) in control patients by MR gadolinium-enhanced venography [70]. Furthermore, significant pressure gradients have been demonstrated by direct venous manometry in patients with IHH and transverse-sigmoid junction stenosis: venous hypertension in the superior sagittal/transverse sinuses with a significant drop in venous pressures at pre-stenotic more caudal levels (sigmoid sinus/jugular bulb) [76]. Mounting evidence indicates that stenting of the stenotic dural venous sinus maintaining the drainage system fully patent is an effective approach for selected patients.

A systematic review published in 2010 included 40 stented individuals and had follow-up ranging from 4 to 60 months. Resolution or improvement was observed in 75 % of the cases with papilledema and in 82 % of the cases with headaches. Two patients required thrombolysis for in-stent thrombosis; however, the pre-procedural antiplatelet regimen was not clearly described; there were no reported cases of in-stent stenosis [72].

A recent series of 18 patients revealed 100 % technical success and similar rates of headache improvement/resolution; however, no formal ophthalmological follow-up data was available [100].

Another study of 52 patients revealed resolution of papilledema in 100 % of cases and of headaches in 84 %. In 12 % of patients, stenosis of adjacent stent segments was observed and required re-stenting [101].

The most recent published series included 15 cases, with a mean clinical follow-up of 14 months. Stents were unilaterally deployed in 87 % of cases, leading to improvement of papilledema in 100 % of cases, of headaches in 67 %, and of tinnitus in 79 % of patients. In regard to visual acuity, 93 % improved or stabilized, while 7 % worsened despite resolution of papilledema (which was posited to relate to sustained compression prior to stenting) [99]. Other rare but reported complications include stent migration and venous sinus perforation.

Procedural Steps

The first step in endovascular treatment involved angiographic confirmation of dural sinus stenosis and measurement of the transstenotic pressure gradient (typically $\geq$8 or 10 mmHg is considered clinically significant [99, 101]) between the superior sagittal sinus and the internal jugular bulb. A diagnostic catheter is advanced into the internal carotid artery ipsilateral to the suspected transverse-sigmoid stenosis. This allows robust opacification of the sagittal and transverse sinuses. Central venous access (femoral vein or internal jugular puncture) is obtained and followed by the introduction of a short vascular sheath. A 6-French guide catheter may be navigated into the jugular bulb. A retrograde venogram is performed, which should

opacify the venous sinuses. Under road map guidance, a microcatheter (such as a 0.027″)/microwire (0.016″) system is advanced into the superior sagittal sinus. The microwire is retracted and the microcatheter connected to a pressure transducer, and pressure is measured. The microcatheter is gently pulled into the torcula, distal transverse sinus, proximal transverse sinus, sigmoid sinus, and jugular bulb, and serial measurements are recorded.

Guide catheter navigation and venous sinus stretching during angioplasty and balloon inflation are very painful, and therefore, general anesthesia is required. Patients must be pretreated with aspirin and clopidogrel (3–5 days of 75 mg nightly or a 300 mg loading doses 24 h prior to stenting). Intraprocedurally, therapeutic heparin anticoagulation (ACT > 250s) is recommended. Via an ipsilateral femoral or IJ vein, a 6F is inserted, and a properly sized self-expanding stent (or balloon-expandable) is navigated into the venous sinus stenosis. Pre- and post-angioplasty may be performed, but typically not necessary. Dual antiplatelet therapy should be maintained for at least 3 months.

In summary, stenting in appropriately selected patients with refractory IHH might be reasonable. However, longer follow-up is critical for defining more clearly the role of this intervention, and further studies are needed for improvement of selection criteria.

Illustrative Case 2

A 37-year-old woman with history of rheumatoid arthritis presented with worsening frequency/intensity of headaches and blurry vision. Exam revealed papilledema. MRI brain was normal, and MRV was suspicious of venous stenosis bilaterally. Lumbar puncture revealed opening pressure of 24 cm H2O. Headache was refractory to acetazolamide and repeated therapeutic lumbar punctures. Her vision worsened, and she was referred optic nerve fenestration. Despite this therapy, headaches persisted.

Cerebral venous manometry and possible angioplasty/stenting were requested. Stenosis of the right transverse-sigmoid junction was observed (Fig. 15.5a, b). The mean venous pressure in the superior sagittal sinus was 41 mmHg (Fig. 15.5c), torcula 39 mmHg, transverse sinus (distal to stenosis) 36 mmHg, sigmoid sinus (proximal to stenosis) 29 mmHg, and jugular bulb 18 mmHg. Due to the gradient of 23 mmHg, the decision was made to intervene endovascularly. Angioplasty with a 6 × 40 mm Savvy balloon was performed. This was followed by the deployment of an 8 × 20 mm Precise self-expandable stent. Due to the development of stenosis immediately distal to the stent, an overlapping 8 × 30 mm Protégé self-expandable stent was placed. A good angiographic result was noted, and pressures in the superior sagittal sinus decreased to 22 mmHg, transverse sinus to 21 mmHg, and jugular bulb to 19 mmHg. Chronic daily headache and visual blurriness resolved within weeks. Follow-up angiogram at 2 months revealed patency of the stents. At 1 year, the optic disks were normal.

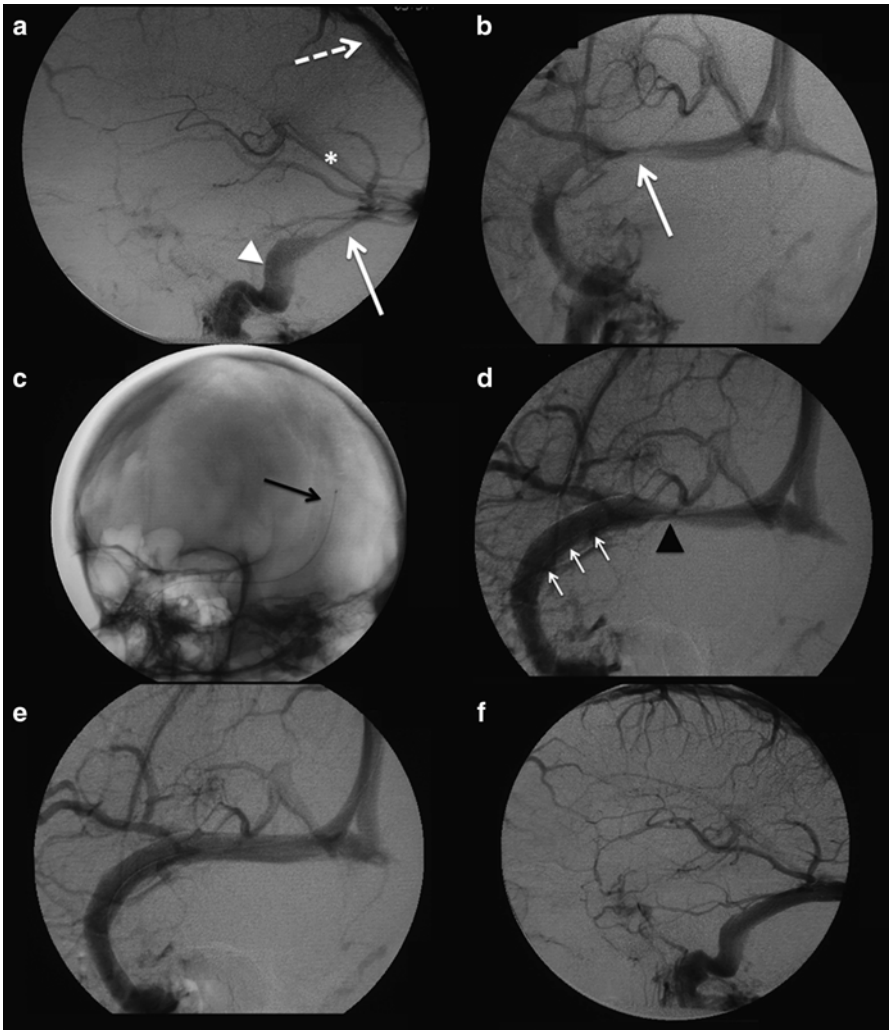

Fig. 15.5 (**a**) Lateral venous phase of arterial angiogram revealing stenosis of the transverse-sigmoid junction (*white arrow*). The sigmoid sinus is normal (*white arrowhead*), and the superior sagittal (*dashed arrow*) and straight sinuses are observed (*asterisk*). (**b**) An anterior–posterior projection reveals stenosis of the transverse-sigmoid junction (*white arrow*). (**c**) Oblique projection revealing the microcatheter positioned in the superior sagittal sinus. (**d**) A stent is depicted (*small white arrows*) and a residual segment of stenosis noted (*black arrowhead*). (**e**, **f**) Fully patent sinuses

References

1. Schievink WI. Intracranial aneurysms. N Engl J Med. 1997;336:28–40.
2. Agarwal N, Gala NB, Choudhry OJ, et al. Prevalence of asymptomatic incidental aneurysms: a review of 2685 computed tomographic angiograms. World Neurosurg. 2013.
3. Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol. 1990;34:361–5.

4. Sugar O. Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol. 1992; 37:158.
5. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg. 2000;93:379–87.
6. Loumiotis I, Wagenbach A, Brown Jr RD, Lanzino G. Small (<10-mm) incidentally found intracranial aneurysms, Part 1: reasons for detection, demographics, location, and risk factors in 212 consecutive patients. Neurosurg Focus. 2011;31:E3.
7. Lawson MF, Neal DW, Mocco J, Hoh BL. Rationale for treating unruptured intracranial aneurysms: actuarial analysis of natural history risk versus treatment risk for coiling or clipping based on 14,050 patients in the Nationwide Inpatient Sample database. World Neurosurg. 2013;79:472–8.
8. Biousse V, Mendicino ME, Simon DJ, Newman NJ. The ophthalmology of intracranial vascular abnormalities. Am J Ophthalmol. 1998;125:527–44.
9. Liu GV, Volpe NL, Galetta SL. Neuro-ophthalmology diagnosis and management. 2nd ed. New York: Saunders Elsevier; 2010.
10. Dailey EJ, Holloway JA, Murto RE, Schlezinger NS. Evaluation of ocular signs and symptoms in cerebral aneurysms. Arch Ophthalmol. 1964;71:463–74.
11. Yang HS, Joe SG, Yoon YH, Kim JG. A case of Purtscher retinopathy associated with stent-assisted coil embolization of a middle cerebral artery aneurysm. Eur J Ophthalmol. 2013; 23:262–6.
12. Takahashi Y, Kakizaki H, Selva D, Leibovitch I. Bilateral orbital compartment syndrome and blindness after cerebral aneurysm repair surgery. Ophthal Plast Reconstr Surg. 2010;26: 299–301.
13. Jacob JT, Burns JA, Dupont SA, Lanzino G, Wijdicks EF. Wall-eyed bilateral internuclear ophthalmoplegia after ruptured aneurysm. Arch Neurol. 2010;67:636–7.
14. Garfinkle AM, Danys IR, Nicolle DA, Colohan AR, Brem S. Terson's syndrome: a reversible cause of blindness following subarachnoid hemorrhage. J Neurosurg. 1992;76:766–71.
15. Schultz PN, Sobol WM, Weingeist TA. Long-term visual outcome in Terson syndrome. Ophthalmology. 1991;98:1814–9.
16. Loumiotis I, Brown Jr RD, Vine R, Cloft HJ, Kallmes DF, Lanzino G. Small (<10-mm) incidentally found intracranial aneurysms, Part 2: treatment recommendations, natural history, complications, and short-term outcome in 212 consecutive patients. Neurosurg Focus. 2011;31:E4.
17. Wiebers DO, Whisnant JP, Huston 3rd J, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003; 362:103–10.
18. McKinna AJ. Eye signs in 611 cases of posterior fossa aneurysms: their diagnostic and prognostic value. Can J Ophthalmol. 1983;18:3–6.
19. Hamer J. Prognosis of oculomotor palsy in patients with aneurysms of the posterior communicating artery. Acta Neurochir. 1982;66:173–85.
20. Blumenfeld H. Brainstem II: eye movements and pupillary control. In: Neuroanatomy through clinical cases. 2. Sunderland, MA: Sinauer; 2002.
21. Miller NR. Diagnosis and management of dural carotid-cavernous sinus fistulas. Neurosurg Focus. 2007;23:E13.
22. Brosnahan D, McFadzean RM, Teasdale E. Neuro-ophthalmic features of carotid cavernous fistulas and their treatment by endoarterial balloon embolisation. J Neurol Neurosurg Psychiatry. 1992;55:553–6.
23. Gupta AK, Purkayastha S, Krishnamoorthy T, et al. Endovascular treatment of direct carotid cavernous fistulae: a pictorial review. Neuroradiology. 2006;48:831–9.
24. Henderson JW, Schneider RC. The ocular findings in carotid-cavernous fistula in a series of 17 cases. Am J Ophthalmol. 1959;48:585–97.
25. Kobayashi N, Miyachi S, Negoro M, et al. Endovascular treatment strategy for direct carotid-cavernous fistulas resulting from rupture of intracavernous carotid aneurysms. AJNR Am J Neuroradiol. 2003;24:1789–96.

26. Kupersmith MJ, Berenstein A, Choi IS, Warren F, Flamm E. Management of nontraumatic vascular shunts involving the cavernous sinus. Ophthalmology. 1988;95:121–30.
27. Halbach VV, Higashida RT, Hieshima GB, Reicher M, Norman D, Newton TH. Dural fistulas involving the cavernous sinus: results of treatment in 30 patients. Radiology. 1987;163: 437–42.
28. Phelps CD, Thompson HS, Ossoinig KC. The diagnosis and prognosis of atypical carotid-cavernous fistula (red-eyed shunt syndrome). Am J Ophthalmol. 1982;93:423–36.
29. Sanders MD, Hoyt WF. Hypoxic ocular sequelae of carotid-cavernous fistulae. Study of the causes of visual failure before and after neurosurgical treatment in a series of 25 cases. Br J Ophthalmol. 1969;53:82–97.
30. Goldberg RA, Goldey SH, Duckwiler G, Vinuela F. Management of cavernous sinus-dural fistulas. Indications and techniques for primary embolization via the superior ophthalmic vein. Arch Ophthalmol. 1996;114:707–14.
31. Palestine AG, Younge BR, Piepgras DG. Visual prognosis in carotid-cavernous fistula. Arch Ophthalmol. 1981;99:1600–3.
32. Annesley-Williams DJ, Goddard AJ, Brennan RP, Gholkar A. Endovascular approach to treatment of indirect carotico-cavernous fistulae. Br J Neurosurg. 2001;15:228–33.
33. Barry RC, Wilkinson M, Ahmed RM, et al. Interventional treatment of carotid cavernous fistula. J Clin Neurosci. 2011;18:1072–9.
34. Chen ZQ, Deng DF, Gu BX, et al. [Treatment of dural arteriovenous fistula by transarterial embolization with low dose of N-butyl-2-cyanoacrylate]. Zhonghua yi xue za zhi. 2006; 86:157–9.
35. Jung KH, Kwon BJ, Chu K, et al. Clinical and angiographic factors related to the prognosis of cavernous sinus dural arteriovenous fistula. Neuroradiology. 2011;53:983–92.
36. Kai Y, Hamada J, Morioka M, Yano S, Kuratsu J. Treatment of cavernous sinus dural arteriovenous fistulae by external manual carotid compression. Neurosurgery. 2007;60:253–7. Discussion 257–8.
37. Keltner JL, Satterfield D, Dublin AB, Lee BC. Dural and carotid cavernous sinus fistulas. Diagnosis, management, and complications. Ophthalmology. 1987;94:1585–600.
38. Kirsch M, Henkes H, Liebig T, et al. Endovascular management of dural carotid-cavernous sinus fistulas in 141 patients. Neuroradiology. 2006;48:486–90.
39. Liu HM, Wang YH, Chen YF, Cheng JS, Yip PK, Tu YK. Long-term clinical outcome of spontaneous carotid cavernous sinus fistulae supplied by dural branches of the internal carotid artery. Neuroradiology. 2001;43:1007–14.
40. Luo CB, Teng MM, Chang FC, Chang CY. Traumatic indirect carotid cavernous fistulas: angioarchitectures and results of transarterial embolization by liquid adhesives in 11 patients. Surg Neurol. 2009;71:216–22.
41. Meyers PM, Halbach VV, Dowd CF, et al. Dural carotid cavernous fistula: definitive endovascular management and long-term follow-up. Am J Ophthalmol. 2002;134:85–92.
42. Miller NR, Monsein LH, Debrun GM, Tamargo RJ, Nauta HJ. Treatment of carotid-cavernous sinus fistulas using a superior ophthalmic vein approach. J Neurosurg. 1995;83:838–42.
43. Oishi H, Arai H, Sato K, Iizuka Y. Complications associated with transvenous embolisation of cavernous dural arteriovenous fistula. Acta Neurochir. 1999;141:1265–71.
44. Preechawat P, Narmkerd P, Jiarakongmun P, Poonyathalang A, Pongpech SM. Dural carotid cavernous sinus fistula: ocular characteristics, endovascular management and clinical outcome. J Med Assoc Thai. 2008;91:852–8.
45. Quinones D, Duckwiler G, Gobin PY, Goldberg RA, Vinuela F. Embolization of dural cavernous fistulas via superior ophthalmic vein approach. AJNR Am J Neuroradiol. 1997;18:921–8.
46. Yoshida K, Melake M, Oishi H, Yamamoto M, Arai H. Transvenous embolization of dural carotid cavernous fistulas: a series of 44 consecutive patients. AJNR Am J Neuroradiol. 2010;31:651–5.
47. Yu SC, Cheng HK, Wong GK, Chan CM, Cheung JY, Poon WS. Transvenous embolization of dural carotid-cavernous fistulae with transfacial catheterization through the superior ophthalmic vein. Neurosurgery. 2007;60:1032–7. Discussion 1037–8.

48. Hawke SH, Mullie MA, Hoyt WF, Hallinan JM, Halmagyi GM. Painful oculomotor nerve palsy due to dural-cavernous sinus shunt. Arch Neurol. 1989;46:1252–5.
49. Miller NR. Dural carotid-cavernous fistulas: epidemiology, clinical presentation, and management. Neurosurg Clin N Am. 2012;23:179–92.
50. Selky AK, Purvin VA. Isolated trochlear nerve palsy secondary to dural carotid-cavernous sinus fistula. J Neuroophthalmol. 1994;14:52–4.
51. Sempere AP, Menendez BM, Alvarez CC, Hoenigsfeld LC. Isolated oculomotor nerve palsy due to dural cavernous sinus fistula. Eur Neurol. 1991;31:2.
52. Stiebel-Kalish H, Setton A, Berenstein A, Kalish Y, Nimii Y, Kupersmith MJ. Bilateral orbital signs predict cortical venous drainage in cavernous sinus dural AVMs. Neurology. 2002;58:1521–4.
53. Chaudhry IA, Elkhamry SM, Al-Rashed W, Bosley TM. Carotid cavernous fistula: ophthalmological implications. Middle East Afr J Ophthalmol. 2009;16:57–63.
54. Rucker JC, Biousse V, Newman NJ. Magnetic resonance angiography source images in carotid cavernous fistulas. Br J Ophthalmol. 2004;88:311.
55. Spector RH. Echographic diagnosis of dural carotid-cavernous sinus fistulas. Am J Ophthalmol. 1991;111:77–83.
56. Haugen OH, Sletteberg O, Thomassen L, Krakenes J. Bilateral non-traumatic carotid cavernous sinus fistula with spontaneous closure. Acta Ophthalmol. 1990;68:743–7.
57. 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.
58. Barrow DL, Spector RH, Braun IF, Landman JA, Tindall SC, Tindall GT. Classification and treatment of spontaneous carotid-cavernous sinus fistulas. J Neurosurg. 1985;62:248–56.
59. Miyamoto N, Naito I, Takatama S, Shimizu T, Iwai T, Shimaguchi H. Clinical and angiographic characteristics of cavernous sinus dural arteriovenous fistulas manifesting as venous infarction and/or intracranial hemorrhage. Neuroradiology. 2009;51:53–60.
60. Gemmete JJ, Chaudhary N, Pandey A, Ansari S. Treatment of carotid cavernous fistulas. Curr Treat Options Neurol. 2010;12:43–53.
61. Wolfe SQ, Cumberbatch NM, Aziz-Sultan MA, Tummala R, Morcos JJ. Operative approach via the superior ophthalmic vein for the endovascular treatment of carotid cavernous fistulas that fail traditional endovascular access. Neurosurgery. 2010;66:293–9. Discussion 299.
62. Sergott RC, Grossman RI, Savino PJ, Bosley TM, Schatz NJ. The syndrome of paradoxical worsening of dural-cavernous sinus arteriovenous malformations. Ophthalmology. 1987;94:205–12.
63. Barcia-Salorio JL, Soler F, Barcia JA, Hernandez G. Stereotactic radiosurgery for the treatment of low-flow carotid-cavernous fistulae: results in a series of 25 cases. Stereotact Funct Neurosurg. 1994;63:266–70.
64. Tiewei Q, Ali A, Shaolei G, et al. Carotid cavernous fistulas treated by endovascular covered stent grafts with follow-up results. Br J Neurosurg. 2010;24:435–40.
65. Bruce BB, Biousse V, Newman NJ. Update on idiopathic intracranial hypertension. Am J Ophthalmol. 2011;152:163–9.
66. Bruce BB, Preechawat P, Newman NJ, Lynn MJ, Biousse V. Racial differences in idiopathic intracranial hypertension. Neurology. 2008;70:861–7.
67. Dessardo NS, Dessardo S, Sasso A, Sarunic AV, Dezulovic MS. Pediatric idiopathic intracranial hypertension: clinical and demographic features. Coll Antropol. 2010;34 Suppl 2:217–21.
68. Kesler A, Goldhammer Y, Gadoth N. Do men with pseudomotor cerebri share the same characteristics as women? A retrospective review of 141 cases. J Neuroophthalmol. 2001;21:15–7.
69. Thurtell MJ, Bruce BB, Rye DB, Newman NJ, Biousse V. The Berlin questionnaire screens for obstructive sleep apnea in idiopathic intracranial hypertension. J Neuroophthalmol. 2011;31:316–9.
70. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology. 2003;60:1418–24.

71. Arac A, Lee M, Steinberg GK, Marcellus M, Marks MP. Efficacy of endovascular stenting in dural venous sinus stenosis for the treatment of idiopathic intracranial hypertension. Neurosurg Focus. 2009;27:E14.
72. Bussiere M, Falero R, Nicolle D, Proulx A, Patel V, Pelz D. Unilateral transverse sinus stenting of patients with idiopathic intracranial hypertension. AJNR Am J Neuroradiol. 2010; 31:645–50.
73. Donnet A, Metellus P, Levrier O, et al. Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients. Neurology. 2008; 70:641–7.
74. 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: 1662–6.
75. Karahalios DG, Rekate HL, Khayata MH, Apostolides PJ. Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. Neurology. 1996;46:198–202.
76. King JO, Mitchell PJ, Thomson KR, Tress BM. Cerebral venography and manometry in idiopathic intracranial hypertension. Neurology. 1995;45:2224–8.
77. Ogungbo B, Roy D, Gholkar A, Mendelow AD. Endovascular stenting of the transverse sinus in a patient presenting with benign intracranial hypertension. Br J Neurosurg. 2003;17: 565–8.
78. Owler BK, Parker G, Halmagyi GM, et al. Cranial venous outflow obstruction and pseudotumor cerebri syndrome. Adv Tech Stand Neurosurg. 2005;30:107–74.
79. Paquet C, Poupardin M, Boissonnot M, Neau JP, Drouineau J. Efficacy of unilateral stenting in idiopathic intracranial hypertension with bilateral venous sinus stenosis: a case report. Eur Neurol. 2008;60:47–8.
80. Pickard JD, Czosnyka Z, Czosnyka M, Owler B, Higgins JN. Coupling of sagittal sinus pressure and cerebrospinal fluid pressure in idiopathic intracranial hypertension – a preliminary report. Acta Neurochir Suppl. 2008;102:283–5.
81. Rajpal S, Niemann DB, Turk AS. Transverse venous sinus stent placement as treatment for benign intracranial hypertension in a young male: case report and review of the literature. J Neurosurg. 2005;102:342–6.
82. Teleb MS, Rekate H, Chung S, Albuquerque FC. Pseudotumor cerebri presenting with ataxia and hyper-reflexia in a non-obese woman treated with sinus stenting. J Neurointerv Surg. 2012;4:e22.
83. Zheng H, Zhou M, Zhao B, Zhou D, He L. Pseudotumor cerebri syndrome and giant arachnoid granulation: treatment with venous sinus stenting. J Vasc Interv Radiol. 2010;21: 927–9.
84. Wall M. Idiopathic intracranial hypertension. Neurol Clin. 1991;9:73–95.
85. Bulens C, De Vries WA, Van Crevel H. Benign intracranial hypertension. A retrospective and follow-up study. J Neurol Sci. 1979;40:147–57.
86. 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;39:461–74.
87. Thambisetty M, Lavin PJ, Newman NJ, Biousse V. Fulminant idiopathic intracranial hypertension. Neurology. 2007;68:229–32.
88. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology. 2002;59:1492–5.
89. Corbett JJ, Mehta MP. Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. Neurology. 1983;33:1386–8.
90. Agid R, Farb RI. Neuroimaging in the diagnosis of idiopathic intracranial hypertension. Minerva Med. 2006;97:365–70.
91. De Simone R, Marano E, Fiorillo C, et al. Sudden re-opening of collapsed transverse sinuses and longstanding clinical remission after a single lumbar puncture in a case of idiopathic intracranial hypertension. Pathogenetic implications. Neurol Sci. 2005;25:342–4.

92. Johnson LN, Krohel GB, Madsen RW, March Jr GA. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthalmology. 1998;105:2313–7.
93. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ. 2010; 341:c2701.
94. Celebisoy N, Gokcay F, Sirin H, Akyurekli O. Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study. Acta Neurol Scand. 2007;116: 322–7.
95. Alsuhaibani AH, Carter KD, Nerad JA, Lee AG. Effect of optic nerve sheath fenestration on papilledema of the operated and the contralateral nonoperated eyes in idiopathic intracranial hypertension. Ophthalmology. 2011;118:412–4.
96. Brazis PW. Clinical review: the surgical treatment of idiopathic pseudotumour cerebri (idiopathic intracranial hypertension). Cephalalgia. 2008;28:1361–73.
97. Brazis PW. Surgery for idiopathic intracranial hypertension. J Neuroophthalmol. 2009;29: 271–4.
98. Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. J Neurol. 2011;258:874–81.
99. Fields JD, Javedani PP, Falardeau J, et al. Dural venous sinus angioplasty and stenting for the treatment of idiopathic intracranial hypertension. J Neurointerv Surg. 2013;5(1):62–8.
100. 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;75:648–52. Discussion 592–5.
101. Ahmed RM, Wilkinson M, Parker GD, et al. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. AJNR Am J Neuroradiol. 2011;32:1408–14.

Chapter 16
Neurointervention and the Otolaryngologist: Head and Neck Surgeon

Randall C. Edgell, Parul Sinha, and Mark A. Varvares

Introduction

The intersection of head and neck surgery and neurointervention dates to the turn of the twentieth century [1] when the endovascular devascularization of a tumor was first attempted. As neurointervention evolved toward greater safety with the introduction of the Seldinger technique [2] and the transfemoral approach [3], its application to disorders of the head and neck has also increased. Preoperative tumor embolization is now widely applied. Endovascular treatment of epistaxis has lessened the need for open vascular ligation [4] that, while effective, requires highly invasive and technically challenging surgery. Endovascular treatment with arterial embolization is now an accepted option for management of intractable epistaxis. In addition to these applications, neurointerventional techniques have been successfully applied to temporary and permanent vessel occlusion, treatment of carotid blowout syndrome, and treatment of iatrogenic vessel injuries to the head and neck.

R.C. Edgell, M.D.
Department of Neurology and Psychiatry, Saint Louis University,
1438 S. Grand Blvd, St. Louis, MO 63104, USA
e-mail: redgell@slu.edu

P. Sinha, M.D., M.B.B.S., M.S.
Department of Otolaryngology – Head and Neck Surgery, Washington University
School of Medicine, 660 S Euclid Avenue, Campus Box-8115, St. Louis, MO 63110, USA
e-mail: parul_50@yahoo.com

M.A. Varvares, M.D., F.A.C.S. (✉)
Department of Otolaryngology – Head and Neck Surgery, Saint Louis University
School of Medicine, 3635 Vista Avenue at Grand Blvd, St. Louis, MO 63130, USA
e-mail: varvares@slu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_16

Tools Review (See Chap. 1)

Coils

The coil consists of two components: a fine, soft, metal helix often made of platinum and a steel pusher wire. For intracranial application, these components are typically connected and must be mechanically or electrolytically detached. This connection allows for repositioning or removal of coils when the initial deployment is unsafe. For extracranial applications in which repositioning is rarely necessary, "pushable" coils are sometimes used. These coils are not attached to the pusher wire, and once deployed may not be retrieved. "Feathered" coils are not generally utilized intracranially, due to the perceived increased risk of thromboembolic complications. These coils are more often employed extracranially as the risk of cerebral ischemia is minimal, and their feathering may promote the desired vascular occlusion more rapidly.

Coils may be utilized in the treatment of a variety of head and neck disorders. They are perhaps most frequently used to sacrifice large cranial vessels in a controlled manner. They are less effective in devascularizing the nasal cavity or a tumor bed as they do not penetrate the microvasculature that is the target in these circumstances.

Particulate Embolics

Polyvinyl alcohol particles (PVA; Boston Scientific, Boston, MA) and tris-acryl microspheres (microspheres) are the most frequently used particulate embolics in the modern treatment of head and neck pathology. They are available in a range of diameters, allowing control over the depth of vascular penetration. Gelfoam pledgets have also been utilized but are not as effective in microvascular penetration and therefore provide less complete devascularization of tumor beds and the nasal cavity.

Liquid Embolics

Liquid *n*-butyl cyanoacrylate (*n*-BCA) (Trufill, Codman Neurovascular, Raynham, NJ) and ethylene-vinyl alcohol copolymer (EVOH) (Onyx, Covidien, Irvine, California) have both been utilized to treat a variety head and neck disorders. They are effective in treating extracranial vascular malformations, with EVOH gaining favor in recent years due to its ability to occlude large portions of these malformations. They have also been successfully utilized in the embolization of epistaxis and tumors.

Stents: The use of stent technology in extracranial head and neck disease is relatively uncommon. Radiation-induced carotid stenosis is one condition for which stenting is indicated. The stents utilized in this setting are self-expanding nickel-titanium alloy (Nitinol). For iatrogenic vascular injuries or carotid blowout, balloon-mounted stents with a microfilament layer (covered stents) may be utilized.

Balloon Test Occlusion

Indications

Giant aneurysms (see Chap. 10): These ≥25 mm aneurysms often involve the intracranial carotid artery. The open surgical approach to these lesions may involve a skull base approach, requiring collaboration between the head and neck surgeon and vascular neurosurgeon. Direct clip ligation of the aneurysm is often prohibitively risky due to adjacent cranial nerves, bony structures, and involvement of large portions of the parent vessel wall. Under these circumstances, vessel sacrifice may be contemplated through either open or endovascular means (discussed under "Carotid Blowout Syndrome" and "Case Study 1: Carotid Blowout"). Surgical occlusion involves trapping of the aneurysm through clip application to the cervical carotid artery proximal to the aneurysm and clip application distal to the aneurysm to prevent retrograde filling.

Prior to undertaking these technically challenging and high-risk procedures, it is important to test the competence of the circle of Willis through balloon test occlusion (BTO). Patients who fail the BTO may require extracranial to intracranial bypass surgery prior to vessel sacrifice.

Skull base tumors: Examples of these lesions include pituitary macroadenomas, craniopharyngiomas, meningiomas, chordomas, and esthesioneuroblastomas. They often are adjacent to, and at times surrounding, arterial structures, making vessel sacrifice intraoperatively possible or, at times, unavoidable. Again, it is essential to test the collateral circulation via BTO prior to surgical resection.

Cervical tumors: Vascular encroachment or encasement of internal carotid artery is most commonly associated with metastatic lymphadenopathy from head and neck squamous cell carcinoma or the direct extension of the primary tumor. A variety of less common tumors may also present in this manner. These tumors may be malignant with rare histologies such as chondrosarcoma, papillary carcinoma (thyroid), adenocarcinoma, or undifferentiated carcinoma. Benign neoplasms of the neck including carotid body tumor, vagal paragangliomas, and peripheral nerve neoplasms (e.g., schwannomas or neurofibromas) are other lesions which can cause carotid artery encroachment. It is imperative to include angiography and BTO in the preoperative workup of patients with strong clinical or radiological suspicion of vascular encasement from cervical tumors. The information from these two interventions helps to assess safety of carotid ligation and resection, which may be required for complete tumor removal if encroachment of the artery by malignant disease is 270° or more.

General Technique

The BTO is performed with no sedation in order to ensure that patient's neurological function is not pharmacologically impaired. Local anesthesia is applied followed by puncture of the femoral artery. Some neurointerventionalists prefer to utilize the femoral artery ipsilateral to the artery to be occluded. This eliminates the possibility that vascular injury or insufficiency associated with the femoral access site will be confused with a neurological deficit induced by balloon inflation. A diagnostic catheter is then used to perform a four-vessel angiogram. The patency of the circle of Willis is carefully evaluated. When no visible filling across the anterior communicating artery is present, manual carotid compression with firm dye injection may make this collateral evident. Next, systemic heparin is administered to achieve an activated clotting time >250 s. A 6 French guide catheter is then navigated into the target vessel. Through this catheter, a compliant non-detachable balloon-tipped catheter is navigated into the petro-cervical carotid. The L-shaped curve of the artery at this location reduces the tendency for distal migration of the balloon caused by the arterial pressure within the cervical carotid artery. Among modern balloon types, the Hyperform (ev3) 7×7 mm and Scepter (Codman) balloon catheters are frequently employed. The Scepter has the advantage of being a dual-lumen catheter. This allows for removal of the microwire and administration of continuous heparinized flush distal to the balloon. Next the balloon is inflated and angiography is performed to ensure the balloon is occlusive. At this point, it is useful to visualize the external carotid artery to look for external to internal collaterals and to assess the caliber of the superficial temporal artery (often utilized for external to internal bypass). Balloon inflation should be maintained for a minimum of 20 min. The patient's neurological function should be assessed in a standardized manor and at regular intervals of 2–5 min during balloon inflation. This examination often involves questioning of the patient for subjective symptoms, level of alertness, orientation, visual fields, language function, facial expression, and motor examination (drift and grip strength in upper extremities; movement of toes in lower extremities).

Predictive Value

When a circle of Willis collateral to the occluded carotid (posterior or anterior communicating artery) is angiographically visible, no neurological symptoms are noted during the period of occlusion, and cortical venous drainage is visible with less than a 1-s delay between hemispheres (venous phase assessment), the patient is said to have "passed" the balloon test occlusion. In one study, only 2 % of patients who passed their BTO went on to develop a neurological deficit postoperatively [5].

A variety of attempts have been made to improve upon the positive predictive value of the findings above, including stump pressure measurement [6, 7], induced hypotension [8, 9], single-photon emission computed tomography (SPECT) imaging, CT perfusion imaging with acetazolamide challenge [10], xenon CT perfusion

imaging [11–13], MR perfusion imaging [14, 15], transcranial Doppler [16], and neurophysiological monitoring [17, 18]. While some of these methods increase the sensitivity of the test, they have not been shown to improve surgical outcome.

Risks

The primary risk associated with BTO is thromboembolism. There is stasis of blood flow proximal to the balloon within the carotid artery and decreased/turbulent flow distal to the balloon. This risk may be reduced through the use of systemic heparin as described above. In patients in whom surgery is not imminent or in whom endovascular vessel sacrifice is anticipated, aspirin may be considered. Additionally balloon inflation may be associated with vessel dissection. If balloon inflation is performed at the carotid bulb or within the common carotid artery, it may trigger reflex bradycardia, hypotension, and, in extreme cases, asystole. While this should not occur if the balloon is inflated in the location described above, it is advisable to be prepared for the eventuality.

Technical Variations

Variations on the general approach to BTO include positioning of the balloon across the ophthalmic artery rather than at the petro-cervical junction. The purpose of this maneuver is to eliminate the possibility of external to internal carotid collateral recruitment that may cause a falsely normal test. Rarely, proximal basilar artery occlusion may be contemplated to treat large or giant basilar artery aneurysms or posterior fossa tumors. In these cases, the BTO is performed with the balloon in the proximal basilar artery. Some institutions have utilized the balloon guide catheter (Stryker Neurovascular) designed for use with the Solitaire thrombus retrieval system. The advantage of this catheter is that it allows robust delivery of heparinized saline distal to the balloon. The disadvantage is its large diameter and associated risk of vascular injury or baroreceptor stimulation.

Carotid Blowout Syndrome

Causes

Carotid blowout syndrome denotes rupture of the extracranial carotid artery or its major branches in the neck. It is mostly associated with local spread, treatment, or recurrence of squamous cell cancers of the head and neck. These tumors may arise from the nasopharynx, oral cavity, oropharynx, larynx, or the hypopharynx. Advanced, fungating tumors may directly encroach and at times invade the carotid artery, leading to imminent rupture. Though uncommon, carotid blowout is one of

the most dreaded complications after surgery for advanced head and neck carcinoma. Surgical resection may involve radical (en bloc removal of the lymph node-bearing tissues on one side of the neck, as well as the removal of the spinal accessory nerve, internal jugular vein (IJV), and sternocleidomastoid muscle) or modified radical (dissection with the goal of preserving the IJV, the sternocleidomastoid muscle, or the spinal accessory nerve) neck dissection. Impaired healing and wound breakdown are the main postoperative complications that precede carotid blowout. Predisposing factors for these postoperative complications are from infection, tumor recurrence, use of vertical limb and three-point junction incision for radical neck dissection, rough handling of the vessel adventitia during surgery, flap necrosis, and systemic factors such as malnourishment, anemia, and hypoproteinemia [19]. Pharyngocutaneous fistula is another known postoperative complication with a high risk for carotid rupture due to exposure of the carotid wall to direct salivary contamination and damage from salivary enzymes. Finally, treatment protocols including radiotherapy play an etiological role. Radiation has been associated with a sevenfold increased risk of carotid rupture in head and neck cancer [20, 21]. Thrombosis of the vasa vasorum, adventitial fibrosis, and fragmentation of tunica media elastic fibers following irradiation of carotid sheath lead to weakening of the vessel wall and subsequent rupture [22]. Carotid blowout will be accelerated in this setting if there is chronic carotid exposure or can occur if there is delayed wound healing since radiation also increases postoperative healing complications and pharyngocutaneous fistulae, thus, further predisposing to the risk of carotid blowout. Blunt or penetrating trauma to the neck is also reported in the literature as a rare cause of carotid blowout [23].

Epidemiology

Over 550,000 patients are diagnosed with head and neck cancers annually worldwide [24]. Carotid blowout has been reported to occur in 3–5 % of patients with major head and neck resections [25]. Among patients with head and neck squamous cell carcinoma, up to 20 % require radical neck dissection, and this procedure is associated with a 4 % incidence of carotid blowout [26]. The reported rates vary across series but the average mortality estimate from carotid blowout is 40 % (9–64 %) and severe neurological deficit occurs in about 60 % (9–84 %) [25, 27].

Clinical Presentation

Chaloupka et al. [27] have described three entities that fall within the carotid blowout syndrome:

- Exposed carotid: in which there is wound breakdown and direct exposure of the carotid artery postsurgical resection of tumor with or without irradiation. There may also be evidence of tumoral invasion of the carotid sheath or asymptomatic pseudoaneurysm of the carotid artery.

- Impending blowout: in which there is a "sentinel" hemorrhage presenting with nasal, oral, or transcervical hemorrhage that is self-limited. This may be due to an angiographically evident pseudoaneurysm or tumoral erosion into the vessel. Highly variable duration of sentinel bleeding from moments to months prior to hemorrhage has been described. Patients at high risk for potential blowout should be counseled to report such occurrences. Precautionary measures such as protection of airway with a cuffed tracheostomy tube and crossmatching in anticipation of blood transfusion are recommended.
- Acute carotid blowout: presenting with uncontrolled nasal, oral, or transcervical hemorrhage. There is often massive blood loss with the need to manual compression of the carotid and hemodynamic resuscitation.

Indications for Invasive Treatment

An *exposed carotid* requires adequate coverage of the weakened vessel wall with mobilization of a tissue flap and attempted wound closure to prevent both early and delayed rupture. Skin or fascial grafts are inadequate. Local flaps consisting of skin and subcutaneous tissue are required to provide sufficient healthy tissue for carotid coverage, particularly in postirradiated patients. The most reliable protection is provided by pedicled muscular flaps composed of well-vascularized muscle. If there is a skin defect overlying the carotid, a pedicled myocutaneous flap is recommended which comprises of the overlying skin, subcutaneous fat, and muscle. The most commonly utilized flap to prevent carotid rupture flaps is a pectoralis major myocutaneous flap which is mobilized from the chest and rotated above from the chest to the neck. Less commonly used are latissimus dorsi and deltopectoral flaps. The muscle paddle of the flap is sutured to the tissue around the carotid while the skin overlying the muscle is sutured to the edges of the cutaneous defect in the neck, thus providing complete carotid protection. In patients with pharyngocutaneous fistula with carotid exposure, reconstruction with the myocutaneous flap helps seal the salivary leak and promotes revascularization of the vessel wall, thus preventing rupture of the carotid.

When tumor invasion of the carotid or pseudoaneurysm formation is present, it is reasonable to proactively plan for possible carotid sacrifice. This would involve an elective cerebral angiogram to localize the arterial defect if present (common carotid, external carotid, or internal carotid) and assess collateral circulation. A BTO would also be helpful to assess the ability to safely sacrifice the affected vessel. The decision to prophylactically sacrifice the involved vessel could then be based on a thorough understanding of the clinical condition of the patient, native collateral circulation, and extent of tumoral involvement of the artery.

For patients with an *impending blowout* or *acute blowout*, the need for invasive treatment is more clear-cut. The difference in approach to these two entities is related to the speed with which treatment must occur. In cases of impending blowout, the steps of workup may be more measured with reliance on more technically elegant vessel-sparing strategies such as stent-assisted pseudoaneurysm coiling and

covered stent placement. For acute blowout syndromes, where control of bleeding must be obtained within minutes rather than hours, vessel sacrifice may be the only feasible option.

Risks

The most pressing risk associated with acute carotid blowout syndrome is the failure to control bleeding in time to prevent exsanguination and death due to hypovolemic shock. Vessel-preserving strategies may paradoxically increase this risk in the short term as they often involve the use of stent technology and the associated need for antiplatelet agents. Vessel occlusion and use of stents without antiplatelet agents carries a risk of thromboembolism and ischemic stroke.

Surgical Approach

Emergent treatment of carotid blowout requires expeditious transfer of the patient to the operating room for definitive control. Traditional surgical intervention has been exploration of the neck and ligation of the bleeding vessel. Pressure is maintained at the site of hemorrhage until the vessel is exposed. Skin incision is planned in order to achieve the best exposure of the carotid artery along its entire length in the neck. In previously operated patients, the incision is made along the scar and extended as required. Skin flaps are elevated followed by identification of the site of bleeding. Sternocleidomastoid muscle (in patients with no history of radical neck dissection) is retracted laterally to expose the carotid sheath. Dissection in postoperative cases is complicated due to distortion of the anatomy by edematous, granulation, or necrotic tissue. Once identified, the common carotid artery is carefully dissected to obtain vessel control both proximal and distal to the bleeding site. If the site of rupture is located in the internal or common carotid artery, vertical sutures are preferred instead of horizontal sutures in order to prevent compromise of the cerebral blood flow [25]. Such ligatures may not always be sufficient and there may be a need to ligate or to ligate and resect the carotid artery. Reconstruction of the artery with interpositional grafts with Gore-tex or saphenous vein may be undertaken. Reconstruction is avoided in presence of infected, irradiated tissue due to increased risk of postoperative disruption. Hemorrhage may also occur from blowout of the external carotid artery or one of its major branches in the neck; these are usually safe to ligate unilaterally. Pharyngocutaneous fistula, if present, should be repaired and salivary diversion be created as required. It is, however, rare that the fistula can be repaired directly. The safest option is repair of the pharyngeal defect with a myocutaneous flap. This reconstruction will also bring vascularized muscle into the wound to cover the ligated vessels. Pharyngeal diversion may then be established with wound packing and a salivary bypass tube. All necrotic or infected tissue is

thoroughly debrided and swabs are sent for microbiology. The wound is copiously irrigated after ensuring complete control of the hemorrhage. Vascularized muscular or myocutaneous flaps are mobilized to cover the wound especially in irradiated necks and in patients with pharyngocutaneous fistula.

Ligation of the internal or common carotid artery is a rapid technique to secure bleeding in carotid blowout, but the rate of neurological sequelae and death is high in patients with insufficient collateral circulation at the circle of Willis. Lower cerebral ischemic complication rates are reported in patients who are hemodynamically stable prior to the surgery [28]. Therefore, vigilant monitoring of vitals and maintenance of adequate blood pressure in the perioperative period is paramount. Surgical ligation should be ideally preceded with BTO and cerebral angiography, but the unstable disposition and the emergent need to prevent death from exsanguination usually do not allow planning for such interventions. Newer endovascular techniques, however, have been developed for management of carotid blowouts with lesser complications versus open surgery and are discussed below.

Endovascular Approach

- *Vessel sacrifice*: While at first blush, vessel sacrifice may appear to be the least sophisticated treatment for carotid blowout syndrome, there are in fact a number of challenges that must be overcome. Although time is short in most cases, it is important to gain a rapid assessment of the circle of Willis. This will allow assessment of the risk of hemispheric stroke after vessel sacrifice. The next goal of treatment is to significantly slow the loss of blood in acute blowout. To this end it may be useful to position a non-detachable balloon proximal to the point of vessel rupture, or across the rupture site itself. At this point detachable coils are used to permanently occlude the vessel as they are the most controllable tool currently available in the neurointerventional armamentarium. Despite this relative control, coil migration is a risk in the early stages of vessel sacrifice, especially in large-caliber vessels such as the common carotid artery. Proximal balloon inflation will serve to reduce or eliminate anterograde flow while the first coils are positioned and deployed. Using oversized, longer coils will further reduce the risk of coil migration intracranially, as will anchoring of the first coils in the rupture point of the vessel. Also key in this endeavor is occluding the vessel distal to the rupture point and working backward to a position proximal to that point. This strategy avoids the risk of retrograde filling of the occluded vessel and continued blood loss. While coils alone may achieve complete vessel occlusion, the matrix they create is not occlusive in all cases, especially in large-caliber vessels. In these cases, the high-density version of EVOH (Onyx 34) may be injected once significant flow reduction has been achieved to completely eliminate flow.
- *Stent-assisted coiling* (see Chaps. 10 and 11): In cases of exposed carotid with pseudoaneurysm formation or impending rupture with pseudoaneurysm formation, stent-assisted coiling is an effective treatment option. The safe use of stent technology requires dual antiplatelet therapy, and in controlled circumstances

this can be achieved via oral administration of aspirin (81 or 325 mg) and clopidogrel (300 mg loading dose followed by 75 mg daily) as long as there is no active bleeding and treatment is planned in close proximity to antiplatelet administration. An alternative strategy is to utilize IV antiplatelet agents (e.g., eptifibatide or abciximab) immediately after stent deployment followed by administration of oral agents at the conclusion of the procedure. The latter approach reduces the interval of time between platelet inhibition and pseudoaneurysm occlusion.

- *Covered stent placement*: The covered stent offers the potential for quick control of blood loss while preserving vessel patency. It requires the ability to navigate a large-diameter guide catheter or sheath (8F or larger) proximal to the point of rupture. These devices tend to be more stiff and difficult to navigate than uncovered stents, and therefore the target vessel must be free of significant tortuosity. The larger surface area created by the stent membrane also increases the risk of thromboembolism, making the use of antiplatelet agents more pressing. This need may be mitigated by the introduction of heparin-coated covered stents. It is essential to oversize the stent diameter and allow for a substantial landing zone on either side of the rupture point to ensure complete occlusion of the lesion.

Case Study 1: Carotid Blowout

A 62-year-old man with a history of squamous cell carcinoma of the larynx presented with hypovolemic shock and bleeding from tracheotomy site, nose, and mouth. He was found to have a recurrent mass with erosion into the esophagus and common carotid, creating a fistulous connection. While undergoing emergent hemodynamic resuscitation with manual compression being applied to the common carotid artery, the patient was brought to the interventional suit. Diagnostic angiography revealed a patent anterior communicating artery. A proximal balloon catheter was inflated to reduce bleeding and allow coiling placement within the vessel. Onyx 34 was used to seal the coil matrix. The patient was successfully resuscitated and stabilized (Fig. 16.1).

Epistaxis

Epidemiology

Idiopathic epistaxis affects at least 60 % of the adult population during a lifetime; however, only 6 % of epistaxis cases require medical attention. Males and females are equally affected with an increase in frequency over the age of 40. Most cases arise from the anterior septal area; however, 5 % of cases arise more posteriorly and are difficult to control [29].

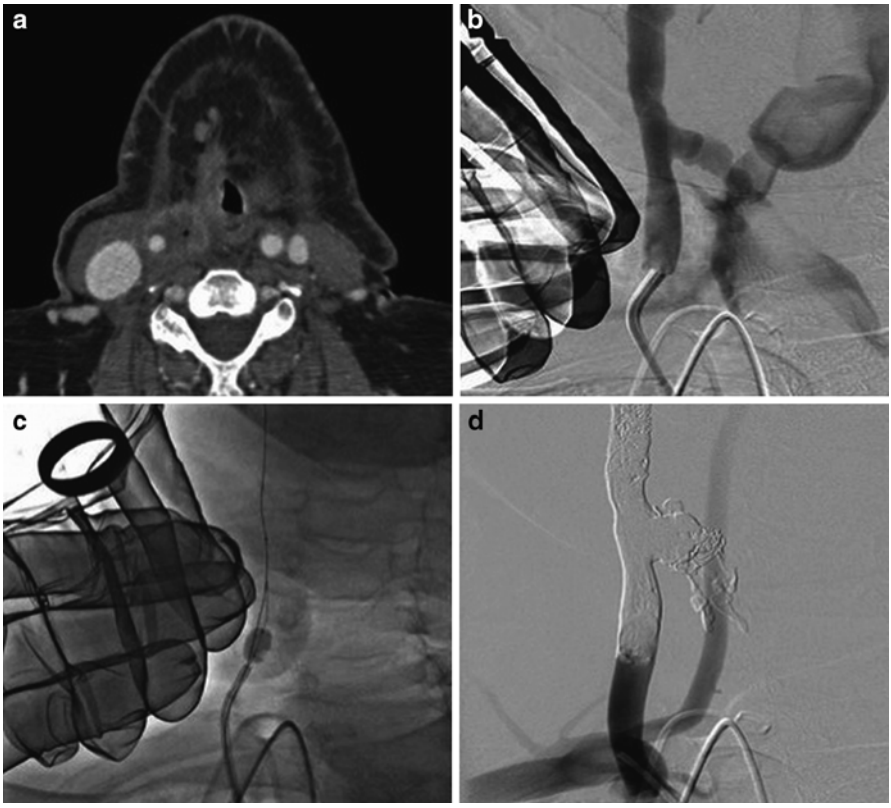

Fig. 16.1 Carotid blowout. (**a**) Contrast cervical axial CT scan showing recurrent laryngeal cancer encasing the right carotid artery (*arrow*). (**b**) Pretreatment angiogram showing a carotid-esophageal fistula with manual compression being applied. (**c**) Inflation of a balloon in the common carotid artery proximal to the fistula to slow flow and reduce blood loss. (**d**) Carotid occlusion with coil deployment distal, within the fistula, and proximal to the fistula with EVOH deposition to complete the occlusion

Associated Conditions

- Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu syndrome): a rare autosomal dominant, systemic disease in which epistaxis is caused by rupture of telangiectasias and is often refractory to treatment. While embolization will control an acute episode, symptoms generally recur over time [30].
- Eroding cavernous carotid aneurysms (see Chaps. 10 and 11): large and giant aneurysms of the cavernous carotid artery may erode into the sphenoid sinus, rupture, and present with epistaxis [31].

- Arteriovenous Malformation or Fistula (see Chaps. 12 and 13): is a rare cause of epistaxis but is the subject of several case reports [32].
- Trauma: Traumatic maxillofacial injury is sometimes associated with laceration of branches of the external carotid artery and massive oronasal blood loss. More rarely, skull base fractures are associated with laceration of the cavernous carotid artery. Generally this leads to symptoms of carotid cavernous fistulae (see Chap. 15). However, when there is rupture into the sphenoid sinus, oronasal bleeding may be seen [33].
- Sinonasal Neoplasm: Juvenile nasopharyngeal angiofibroma (see below) is the neoplasm most commonly associated with epistaxis. Other tumors that may present in this fashion include: hemangioma, hemangiopericytoma, acute myelogenous leukemia, pyogenic granuloma gravidarum, nasopharyngeal carcinoma, esthesioneuroblastoma, malignant fibrous histiocytoma, adenoid cystic carcinoma, and metastatic disease [34].

Stepwise Treatment Algorithm [29]

1. Nasal pressure
2. Topical hemostatic and vasoconstricting agents
3. Anterior packing
4. Reversal of underlying factors (i.e., platelet inhibition, anticoagulation, or hypertension)
5. Endoscopic cauterization: chemical, e.g., silver nitrate or electrocautery
6. Posterior packing with inpatient observation
7. Surgical or endovascular ligation of arterial supply to posterior nasal fossa

Angiographic Assessment

During the angiographic assessment of epistaxis, selective catheterization and angiography should be performed in bilateral internal and external carotid arteries. At least one vertebral artery injection may be useful to look for evidence of dural arteriovenous fistula or arteriovenous malformation.

Imaging of the internal carotid artery will rule out rare causes of epistaxis including aneurysms, AVMs, DAVF, or traumatic carotid cavernous fistula. In addition the ophthalmic artery provides important vascular supply to the superior nasal cavity via the anterior and posterior ethmoidal arteries. These arteries are not considered targets for endovascular therapy due to the risk of inadvertent embolization of cerebral or ophthalmic vessels.

Assessment of the external carotid artery is particularly important as the target vessels for endovascular treatment arise from it. Moving from the anterior to posterior nasal cavity, these include the superior labial artery (a branch of the facial artery)

and the greater palatine and sphenopalatine arteries (branches of the internal maxillary artery). It is also crucial to look for angiographically subtle external to internal anastomoses through the angular branch of the facial artery and branches of the internal maxillary artery (vidian, accessory meningeal, and middle meningeal). At times it may be feasible to remove nasal packing during angiography to look for extravasation of contrast and localize the side of bleeding more precisely.

Surgical Treatment

Surgical treatment is indicated in patients with epistaxis who continue to bleed despite conservative measures including decongestants, application of cautery, hemostatic agents, and short-term nasal packing. The origin of such intractable epistaxis is difficult to visualize and usually arises from the vessels in the posterior and superior nasal cavity, most commonly the sphenopalatine artery. Surgical intervention provides prompt treatment in these situations. It not only prevents pressure necrosis and infections in the nasal cavity but also reduces the hospital stay from prolonged packing. The nature of surgical interventions has evolved both in the technique and the target of ligation from open ligation of the external carotid artery (ECA) to transantral ligation of internal maxillary artery (IMA) to the endoscopic ligation of the sphenopalatine artery (SPA).

Ligation of the ECA through neck exploration is associated with risk of inadvertent injury to the hypoglossal nerve. It can also cause ischemic complications in atherosclerotic patients whose cerebral circulation is dependent on the external to internal carotid system anastomoses. Open ligation of ECA has been replaced by transantral ligation of IMA that is performed through a Caldwell-Luc approach. In this approach, a window is created through the anterior surface of the maxillary sinus via a gingivobuccal sulcus incision. Through this transantral window, the IMA is ligated in the pterygopalatine fossa which lies posterior to the maxillary sinus. A complication rate of 25–30 % is associated with this technique and mainly includes oroantral fistula, cheek and dental anesthesia, and injury to the nasolacrimal duct.

The most favored approach currently is endoscopic ligation of SPA that has less postoperative complications compared to transantral ligation of IMA [35]. A detailed endoscopic examination of the nasal cavity is performed under general anesthesia after adequately preparing the nasal cavity with topical decongestants. Nasal mucosa and, preferably, the greater palatine canal are injected with 1 % Xylocaine with 1:100,000 epinephrine for additional vasoconstriction. The middle turbinate is medialized and followed to its posteriormost aspect. The sphenopalatine foramen is situated just inferior to the posterior end of the middle turbinate and is accessed by a vertical mucoperiosteal incision on the lateral nasal wall. The SPA is clipped and/or cauterized as it exits the foramen, and the mucosal flap is reapproximated, thus completing the procedure. The success rate with this procedure is reported to be over 85 % [36]. The commonly reported complications include minor rebleeding, nasal crusting, palatal numbness, septal perforation, injury to

the nasolacrimal duct, and acute sinusitis. Postoperatively, nasal saline irrigation is recommended to reduce crusting.

Rarely, bleeding from the anterior ethmoidal artery (AEA) can be a source of intractable posterior epistaxis. This is seen mainly in patients with a history of midfacial trauma or iatrogenic injury during sinus surgery and often fails to subside with conservative measures. Surgical intervention requires ligation of AEA via either a traditional approach through an external Lynch incision placed over the medial orbital wall or an endoscopic approach. External approach achieves better control of AEA and also avoids the complications that may occur from an endoscopic approach such as cerebrospinal fluid leak and orbital injury.

Endovascular Treatment

Endovascular procedures to control epistaxis are most often performed under general anesthesia to reduce patient movement and protect the patient's airway from blood and saliva. Femoral artery access is obtained in the standard manor and a 5 or 6 F guide catheter is navigated into the origin of the external carotid. This vessel is prone to catheter-induced spasm, and consideration should be given to topical application of 1 inch of nitroglycerin to the angle of the ipsilateral jaw prior to catheterization. Intra-arterial nitroglycerine should also be available to relieve spasm that occurs during the case. A large inner diameter microcatheter (e.g., a 0.021 Rapid Transit, Codman) is then navigated over a microwire and positioned within the facial artery distal to the submandibular artery. The authors rely on microparticles for embolization of the ECA branches. We utilize 250–355 μm PVA particles suspended in a contrast slurry ipsilateral to the site of bleeding. Injection is performed under negative roadmap imaging. Brief puffs are administered with careful attention paid to anterograde penetration of the nasal cavity. Once reflux is noted, embolization of these vessels is complete. The particle-contrast slurry must be constantly agitated and attention must be paid to accumulation of microparticles within the hub or the microcatheter in order to avoid occlusion. A new microcatheter is utilized to select the contralateral ECA, is navigated in the internal maxillary artery, and is positioned distal to the deep temporal vessels. The process above is then repeated. The authors will embolize the contralateral ECA to reduce collateral supply to the area of hemorrhage. However, larger-diameter PVA particles (500–710 μm) are utilized in this case to avoid excessive penetration and devascularization of the nasal cavity and skin overlying the nose.

As described above, some interventionalists rely on proximal vessel occlusion of the IMAX through deployment of detachable or pushable coils rather than microparticles. Coils have the advantage of speed and simplicity but do not penetrate the capillary bed and obstruct re-treatment should symptoms recur. Liquid embolic agents are enjoying increasing favor but are higher cost, may be more prone to travel through external to internal collaterals, and also inhibit re-treatment if needed.

Some practitioners will have nasal packing removed in the angiography suite to assess the need for further treatment before concluding the procedure. Others will remove nasal packing the next day.

Efficacy

Embolization is associated with a 90–100 % efficacy in idiopathic epistaxis; however, eventual recurrence is the rule in HHT patients. When early rebleeding (within 30 days) is taken into account, rates of effective treatment are between 70 and 90 % [29].

Risks

While the overall risk of embolization for epistaxis is low, there is risk of serious adverse events such as blindness and stroke that may occur due to reflux of the embolic material into cerebral or ophthalmic collaterals. In addition, external to internal collateral may lead to inadvertent cerebral artery embolization, making the assessment of collaterals crucial. Finally, excessive devascularization of the nasal cavity may lead to erosion and ulceration of the nasal mucosa or skin overlying the nose.

Illustrative Case 2: Epistaxis

A 55-year-old woman was admitted with several days of epistaxis. Upon admission she underwent posterior nasal packing but upon removal once again experienced severe bleeding, requiring transfusion of two units of packed red blood cells. She was then brought to the angiography suit where she underwent PVA particle embolization of both distal facial and internal maxillary arteries. She tolerated the procedure well and was discharged, free of further bleeding, on postoperative day number 2 (Fig. 16.2).

Preoperative Tumor Embolization

General Technique

See Chap. 14.

Risks

The risks associated with tumor embolization are similar to those seen in the treatment of epistaxis and include stroke due to reflux of the embolic agent into the cerebral vasculature or transit through external to internal or external to vertebral artery connections. There is also risk associated with unintentional devascularization

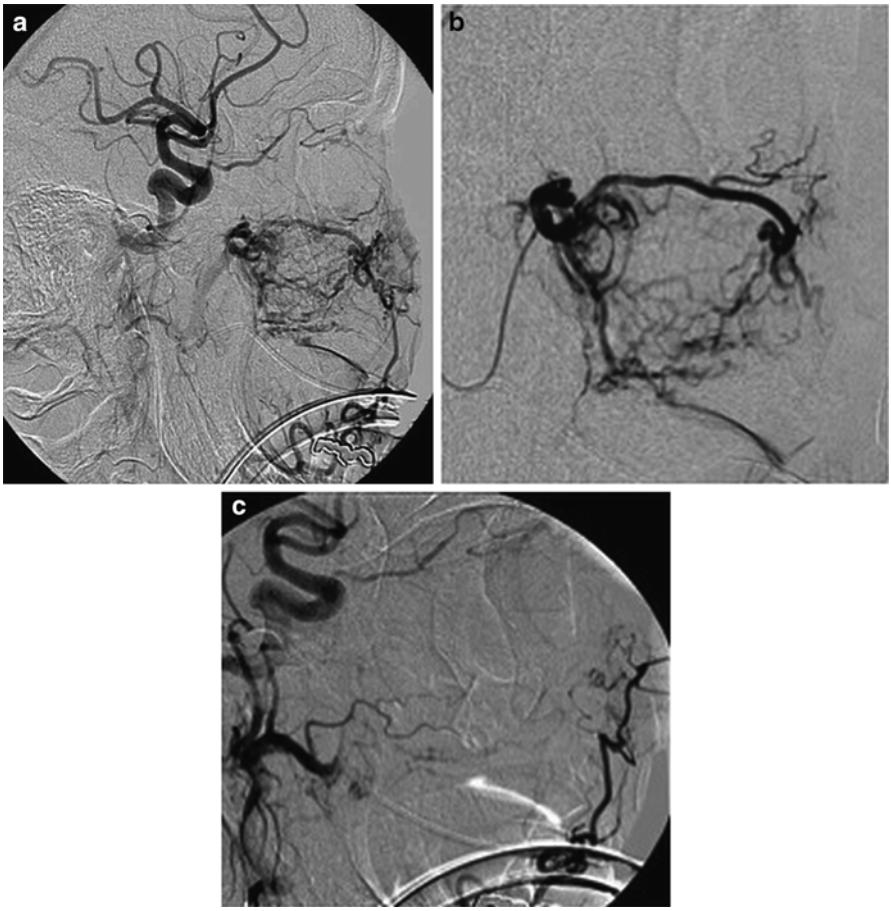

Fig. 16.2 Epistaxis. (**a**) Guide catheter angiogram showing vascular supply to the nasal cavity (sphenopalatine arteries: *bracket*, inferior orbital: *open arrow*, superior labial: *small arrow*). (**b**) Microcatheter angiogram of the distal internal maxillary artery (IMAX). (**c**) Post-PVA embolization showing occlusion of the distal IMAX

of cranial nerves, skin, and mucosa. When large tumors are treated, perioperative edema and mass effect may occur. This risk can be minimized through the judicious use of postoperative steroids and timing the embolization procedure in close proximity to surgical resection.

Vascular Tumors

- Meningiomas: benign tumors arising from the dura mater occurring more frequently in females and in advanced age. They may present incidentally, with headache, focal neurological deficits, or seizures. At the skull base, they arise

from the sphenoid wing, olfactory groove, and clivus. In these locations they may be supplied by dilated branches of the ophthalmic artery, cavernous carotid artery (meningohypophyseal trunk or inferolateral trunk), or branches of the posterior circulation. Preoperative embolization of large meningiomas has been shown to reduce blood loss and operative time compared to case-matched controls [37].

- Juvenile Nasopharyngeal Angiofibromas: represent 0.5 % of all head and neck tumors. They generally affect adolescent boys, presenting as a painless, unilateral nasal obstruction or epistaxis. They originate in the sphenopalatine foramen or pterygopalatine fossa. 10–20 % of JNAs have intracranial extension [38].
- Paragangliomas: represent 0.6 % of all head and neck neoplasms. They are vascular neoplasms arising from chemoreceptors of nerves. Women are more commonly affected with the peak incidence occurring between 30 and 60 years old. At times they are multiple, familial, and/or secretory. Patients may present with a mass lesion in the neck, a cranial nerve deficit, or pulsatile tinnitus. Cranial nerve deficits are sometimes associated with the glomus jugulare subtype. These tumors are most often supplied by branches of the ascending pharyngeal artery [39]. The following locations have been described:
  - Tympanic (glomus tympanicum)
  - Jugular bulb (glomus jugulare)
  - Vagal (glomus vagale)—11 %
  - Carotid body tumor—35 %
  - Aorta/larynx

Surgical resection with or without preoperative embolization provides the best chance of cure. Preoperative embolization may cause inflammation of the dissection plane of the carotid adventitia and is not always preferred prior to resection. However, radiation or observation with serial imaging is recommended in highly advanced or multicentric, bilateral tumors where surgery may lead to significant functional impairment from cranial nerve deficits or vascular complications.

Radiation-Induced Carotid Stenosis

Association of Carotid Stenosis and Radiation

There is a known association between head and neck irradiation and carotid stenosis. In a series of 240 patients treated with head and neck radiation, 12 % had >70 % stenosis at 5 years with a tenfold higher relative risk of stroke at 10 years [40–43].

Pathophysiology

Most authors attribute the stenotic lesions seen postradiation to accelerated atherosclerosis; however, endothelial hyperplasia has also been hypothesized [40].

Indications for Treatment (See Chap. 4)

Patients with symptomatic stenosis (TIA or stroke) >50 % should be considered for revascularization. Asymptomatic patients with 80 % stenosis or greater may also be candidates. Due to the obscuration of tissue planes and thickening of the tissues seen post-neck irradiation, endovascular treatment is generally preferred over carotid endarterectomy [44].

Endovascular Treatment

See Chap. 4.

Iatrogenic Carotid Injury

Persistent Stapedial Artery and Aberrant Course of the ICA

A persistent stapedial artery is seen in 0.5 % of temporal bone specimens at autopsy and is associated with an aberrant course of the internal carotid artery [45].

Illustrative Case 3: Aberrant ICA

An 88-year-old woman with what was thought to represent recurrent otitis media underwent elective myringotomy tube placement in an outpatient setting. Upon tube insertion, perfuse bleeding was encountered. CT angiography revealed a persistent stapedial artery with an aberrant course of the ICA and erosion into the middle ear cavity. The bleeding was controlled through navigation of an over-the-wire compliant balloon across the arteriotomy and occlusion of the middle ear cavity with Onyx 34 liquid embolic (Fig. 16.3).

Injury During Sinus Surgery

There is bulging of the internal carotid artery into the lateral wall of the sphenoid sinus in almost all patients with an up to 22 % incidence of dehiscence in the bony wall covering the artery. This makes the artery vulnerable to inadvertent laceration during sphenoidotomy.

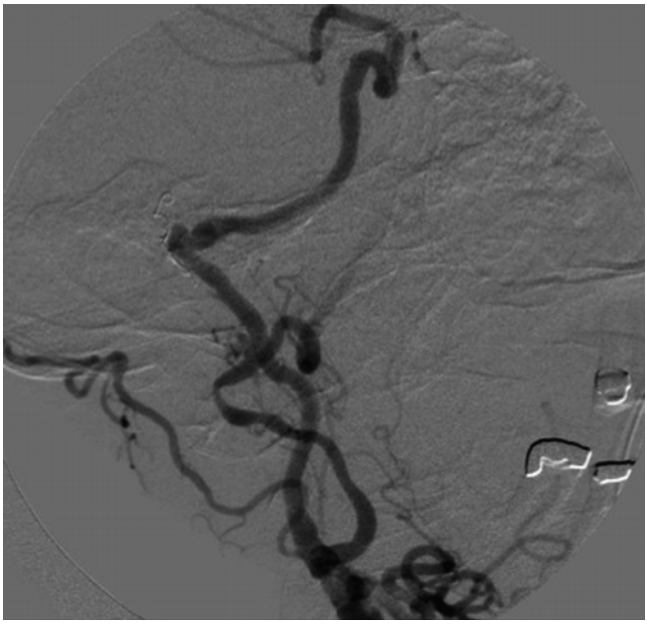

Fig. 16.3 Persistent stapedial artery

A clear understanding of the anatomy of the sphenoid sinus in relationship to the internal carotid artery (ICA) and proper training in the principles of endoscopic sinus surgery are fundamental to prevention of such a catastrophic injury. A careful review of preoperative CT scans before the procedure is of utmost importance to detect any variation in the sinus anatomy or vascular anomaly of the carotid artery. The carotid artery may bulge far into the lumen of the sphenoid sinus with a dehiscent bony wall. The sphenoidotomy should be made as medially toward the midline and inferiorly as possible. In addition, instruments like a microdebrider should be avoided in sphenoid sinus surgery to prevent any accidental injury. The ICA is at higher risk of injury during transsphenoidal and expanded endonasal approaches to the skull base. Use of micro-Doppler probe for carotid localization has been found to be a useful adjunct to prevent ICA injury in such surgeries.

Illustrative Case 4

A 59-year-old man with a past medical history significant for recurrent sinusitis underwent debridement of the ethmoid and sphenoid sinuses for a fungal infection. During sphenoidotomy, perfuse bleeding was encountered. Angiography revealed a cavernous carotid laceration. 4 mm × 12 mm Graftmaster stent was placed across the lesion with immediate cessation of bleeding (Fig. 16.4).

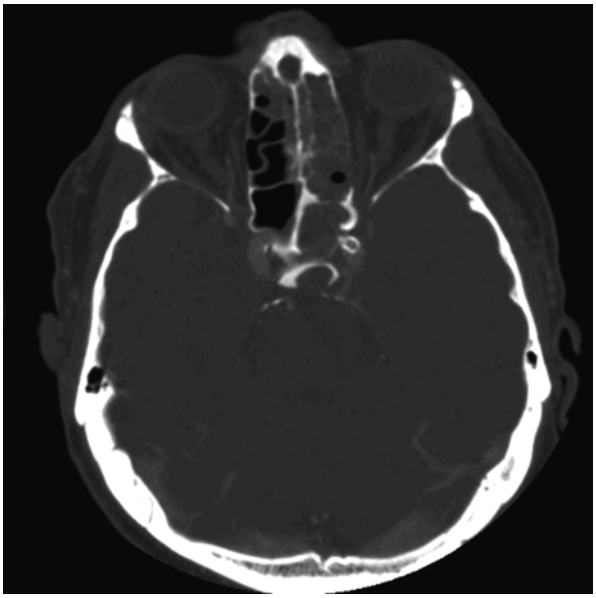

Fig. 16.4 Iatrogenic laceration of the left internal carotid artery. *Large arrow* shows damage to lateral wall of the sphenoid sinus. *Small arrow* shows covered stent deployment in the cavernous ICA

References

1. Dawbain RH. The starvation operation for malignancy in the external carotid area. JAMA. 1904;17:792–5.
2. Higgs ZC, Macafee DA, Braithwaite BD, Maxwell-Armstrong CA. The Seldinger technique: 50 years on. Lancet. 2005;366(9494):1407–9.
3. Rosenbaum AE, Eldevik OP, Mani JR, Pollock AJ, Mani RL, Gabrielsen TO. In re: Amundsen P. Cerebral angiography via the femoral artery with particular reference to cerebrovascular disease. Acta Neurol Scand 1967; Suppl. 31:115. AJNR Am J Neuroradiol. 2001;22(3):584–9.
4. Sokoloff J, Wickbom I, McDonald D, Brahme F, Goergen TC, Goldberger LE. Therapeutic percutaneous embolization in intractable epistaxis. Radiology. 1974;111(2):285–7.
5. van Rooij WJ, Sluzewski M, Metz NH, et al. Carotid balloon occlusion for large and giant aneurysms: evaluation of a new test occlusion protocol. Neurosurgery. 2000;47:116–21 (discussion: 122).
6. Tomura N, Omachi K, Takahashi S, et al. Comparison of technetium Tc 99m hexamethylpropyleneamine oxime single-photon emission tomograph with stump pressure during the balloon occlusion test of the internal carotid artery. AJNR Am J Neuroradiol. 2005;26:1937–42.
7. Barker DW, Jungreis CA, Horton JA, et al. Balloon test occlusion of the internal carotid artery: change in stump pressure over 15 minutes and its correlation with xenon CT cerebral blood flow. AJNR Am J Neuroradiol. 1993;14:587–90.
8. Dare AO, Chaloupka JC, Putman CM, et al. Failure of the hypotensive provocative test during temporary balloon test occlusion of the internal carotid artery to predict delayed hemodynamic ischemia after therapeutic carotid occlusion. Surg Neurol. 1998;50:147–55 (discussion: 155–6).

9. Standard SC, Ahuja A, Guterman LR, et al. Balloon test occlusion of the internal carotid artery with hypotensive challenge. AJNR Am J Neuroradiol. 1995;16:1453–8.
10. Okudaira Y, Arai H, Sato K. Cerebral blood flow alteration by acetazolamide during carotid balloon occlusion: parameters reflecting cerebral perfusion pressure in the acetazolamide test. Stroke. 1996;27:617–21.
11. Eskridge JM. Xenon-enhanced CT: past and present. AJNR Am J Neuroradiol. 1994;15: 845–6.
12. Kofke WA, Brauer P, Policare R, et al. Middle cerebral artery blood flow velocity and stable xenon enhanced computed tomographic blood flow during balloon test occlusion of the internal carotid artery. Stroke. 1995;26:1603–6.
13. Linskey ME, Jungreis CA, Yonas H, et al. Stroke risk after abrupt internal carotid artery sacrifice: accuracy of preoperative assessment with balloon test occlusion and stable xenon-enhanced CT. AJNR Am J Neuroradiol. 1994;15:829–43.
14. Michel E, Liu H, Remley KB, et al. Perfusion MR neuroimaging in patients undergoing balloon test occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 2001;22:1590–6.
15. Simonson TM, Ryals TJ, Yuh WT, et al. MR imaging and HMPAO scintigraphy in conjunction with balloon test occlusion: value in predicting sequelae after permanent carotid occlusion. AJR Am J Roentgenol. 1992;159:1063–8.
16. Eckert B, Thie A, Carvajal M, et al. Predicting hemodynamic ischemia by transcranial Doppler monitoring during therapeutic balloon occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 1998;19:577–82.
17. Brunberg JA, Frey KA, Horton JA, et al. [15O]H2O positron emission tomography determination of cerebral blood flow during balloon test occlusion of the internal carotid artery. AJNR Am J Neuroradiol. 1994;15:725–32.
18. Liu AY, Lopez JR, Do HM, et al. Neurophysiological monitoring in the endovascular therapy of aneurysms. AJNR Am J Neuroradiol. 2003;24:1520–7.
19. Mazumdar A, Derdeyn CP, Holloway W, Moran CJ, Cross 3rd DT. Update on endovascular management of the carotid blowout syndrome. Neuroimaging Clin N Am. 2009;19(2): 271–81.
20. Maran AG, Amin M, Wilson JA. Radical neck dissection: a 19-year experience. J Laryngol Otol. 1989;103(8):760–4.
21. Borsany SJ. Rupture of the carotids following radical neck surgery in irradiated patients. Ear Nose Throat J. 1962;41:531–3.
22. Huvos AG, Leaming RH, Moore OS. Clinicopathologic study of the resected carotid artery. Analysis of sixty-four cases. Am J Surg. 1973;126(4):570–4.
23. Maron BJ, Poliac LC, Ashare AB, et al. Sudden death due to neck blows among amateur hockey players. JAMA. 2003;290:599–601.
24. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–917.
25. Upile T, Triaridis S, Kirkland P, Archer D, Searle A, Irving C, Rhys Evans P. The management of carotid artery rupture. Eur Arch Otorhinolaryngol. 2005;262(7):555–60.
26. Vokes EE, Weischelbaum RR, Lippman SM, et al. Head and neck cancer. N Engl J Med. 1993;328(3):184–94.
27. Chaloupka JC, Putnam CM, Citardi MJ, et al. Endovascular therapy for the carotid blowout syndrome in head and neck surgical patients: diagnostic and managerial considerations. AJNR Am J Neuroradiol. 1996;17(5):843–52.
28. Moore OS, Karlan M, Sigler L. Factors influencing the safety of carotid ligation. Am J Surg. 1969;118:666–8.
29. Willems PW, Farb RI, Agid R. Endovascular treatment of epistaxis. AJNR Am J Neuroradiol. 2009;30(9):1637–45. Epub 2009 Apr 16.
30. Guttmacher AE, Marchuk DA, White Jr RI. Hereditary hemorrhagic telangiectasia. N Engl J Med. 1995;333:918–24.

31. Karkanevatos A, Karkos PD, Karagama YG, Foy P. Massive recurrent epistaxis from non-traumatic bilateral intracavernous carotid artery aneurysms. Eur Arch Otorhinolaryngol. 2005;262(7): 546–9.
32. de Tilly LN, Willinsky R, TerBrugge K, Montanera W, Marotta T, Wallace MC. Cerebral arteriovenous malformation causing epistaxis. AJNR Am J Neuroradiol. 1992;13(1):333–4.
33. Chen D, Concus AP, Halbach VV, Cheung SW. Epistaxis originating from traumatic pseudoaneurysm of the internal carotid artery: diagnosis and endovascular therapy. Laryngoscope. 1998;108(3):326–31.
34. Turowski B, Zanella FE. Interventional neuroradiology of the head and neck. Neuroimaging Clin N Am. 2003;13(3):619–45.
35. Feusi B, Holzmann D, Steurer J. Posterior epistaxis: systematic review on the effectiveness of surgical therapies. Rhinology. 2005;43(4):300–4.
36. Rudmik L, Smith TL. Management of intractable spontaneous epistaxis. Am J Rhinol Allergy. 2012;26(1):55–60.
37. Dean BL, Flom RA, Wallace RC, Khayata MH, Obuchowski NA, Hodak JA, Zabramski JM, Spetzler RF. Efficacy of endovascular treatment of meningiomas: evaluation with matched samples. AJNR Am J Neuroradiol. 1994;15(9):1675–80.
38. Radkowski D, McGill T, Healy GB, Ohlms L, Jones DT. Angiofibroma. Changes in staging and treatment. Arch Otolaryngol Head Neck Surg. 1996;122(2):122–9.
39. Wasserman PG, Savargaonkar P. Paragangliomas: classification, pathology, and differential diagnosis. Otolaryngol Clin North Am. 2001;34(5):845–62, v–vi.
40. Katras T, Baltazar U, Colvett K, et al. Radiation-related arterial disease. Am Surg. 1999;65(12):1176–9.
41. Cheng SWK, Wu LLH, Ting ACW, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. Am J Surg. 1999;178:323–8.
42. Dorresteijn LD, Kappelle AC, Boogerd W, Klokman WJ, Balm AJ, Keus RB, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. J Clin Oncol. 2002;20:282–8.
43. Murros KE, Toole JF. The effect of radiation on carotid arteries. Arch Neurol. 1989;46: 449–55.
44. 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, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351(15):1493–501.
45. Moreano EH, Paparella MM, Zelterman D, Goycoolea MV. Prevalence of facial canal dehiscence and of persistent stapedial artery in the human middle ear: a report of 1000 temporal bones. Laryngoscope. 1994;104(3 Pt 1):309–20.

Chapter 17
Neurointervention and the Endocrinologist: Inferior Petrosal Sinus Sampling

Sonal Mehta, Randall C. Edgell, and George T. Griffing

Introduction

Inferior petrosal sinus sampling (IPSS) is a major advance in the medical management of Cushing's syndrome (CS). The technique of inferior petrosal sinus (IPS) sampling for Cushing's syndrome was first published in 1977 by Corrigan at a time when transsphenoidal surgery (TSS) was becoming available to treat pituitary CS, or Cushing's disease (CD) [1]. Using this selective catheterization technique, it was possible to sample ACTH output centrally and peripherally and later even lateralize ACTH production. IPSS has continued to gain wide acceptance and now it is internationally considered the gold standard for diagnosing CD [2–12]. This chapter will explain IPSS including its applications, limitations, complications, and cost-effectiveness. It behooves all physicians involved in the medical management of CS to better understand this relatively new procedure.

S. Mehta, M.D. (✉)
Assistant Professor, Department of Neurology, University of South Carolina School of Medicine, 8 Medical Park, Suite 420, SC 29203, Columbia
e-mail: sonal.mehta@uscmed.sc.edu

R.C. Edgell, M.D.
Department of Neurology and Psychiatry, Saint Louis University, 1438 S. Grand Blvd, St. Louis, MO 63104, USA
e-mail: redgell@slu.edu

G.T. Griffing, M.D.
Division of Endocrinology, Department of Internal Medicine, Saint Louis University, St. Louis, MO USA
e-mail: George.griffing@slu.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*, Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_17

Clinical Features

CS is a result of excess glucocorticoids, either endogenous or exogenous. The majority among the corticotropin-dependent endogenous CS cases is due to pituitary adenomas, which is known as CD. A large percentage among these is caused by functional pituitary microadenomas producing excess ACTH, whereas macroadenomas are responsible for only 6 %.

The remainder is due to ectopic secretion of corticotropins, which is often a manifestation of a somatic endocrine tumor. Corticotropin-independent CS is often associated with adrenal adenomas or carcinomas.

The classic "cushingoid" habitus of obesity, facial plethora, and rounded ("moon") face is commonly seen. Other symptoms include hirsutism, weakness, menstrual irregularity, emotional lability, and easy bruising. Clinical manifestations often include glucose intolerance, hypertension, nephrolithiasis, and osteopenia, which may in turn lead to fractures.

General Principles of Screening and Diagnosis

1. **CS suspicion, screening, and diagnosis** (see Table 17.1): CS is a serious disease which if untreated has a 50 % 5-year mortality [13]. Although considered rare (2–4 per one million persons per year), CS is often curable, therefore worth the effort to diagnose and treat. The path to diagnosis begins with clinical suspicion. If suspected, at least two of the screening tests in Table 17.1 are performed. If one or more of the screening tests are positive, a referral to an endocrinologist for additional diagnostic testing is made to confirm the diagnosis [14–19].
2. **CS etiology and differential diagnostic testing** (Fig. 17.1): Appropriate therapy for CS requires an etiologic diagnosis between adrenal, pituitary, and an ectopic ACTH-producing tumor (EAS) [20, 21]. Understanding the tests used to establish the etiology requires knowledge of the hypothalamic–pituitary–adrenal (HPA) axis (see Fig. 17.1) [19, 22]. The first step to establishing the etiology is an ACTH level to determine ACTH dependency—either "independent" for adrenal nodule(s) or "dependent" for a CD or EAS (see Table 17.2) [23].

   (a) **ACTH-independent CS** (see Table 17.2): Approximately 10 % of CS is ACTH-independent including adrenal tumors (both benign and malignant) and primary nodular hyperplasia. IPSS is not indicated in cases of ACTH-independent CS where an adrenal etiology is likely [24–26]. Adrenal CS can be easily diagnosed by the combination of low ACTH levels and finding adrenal nodule(s) by CT or MRI.

   (b) **ACTH-dependent CS** (see Tables 17.2 and 17.3): The vast majority of CS is ACTH dependent—largely from two causes: CD (~80 %) and EAS (~10 %) [27]. Many different tumor types both benign and malignant can produce

Table 17.1 Establishing the diagnosis of Cushing's syndrome

Clinical suspicion for Cushing's syndrome
↓
Screening tests (first-line—perform at least 2)
• Urinary free cortisol (three 24 h collections)
• Low-dose (1 mg) overnight dexamethasone suppression
• Late-night salivary cortisol level
↓
Confirmatory testing
• Endocrinologist referral r/o physiologic hypercortisolism
• Confirmation of screening tests
• Second level testing if needed
1. Midnight plasma cortisol
2. Cortisol diurnal rhythm
3. 2 mg dexamethasone suppression test +/– CRH test

Adapted from Arnaldi G, Atkinson AB, Bertagna X, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003;88:5593–602

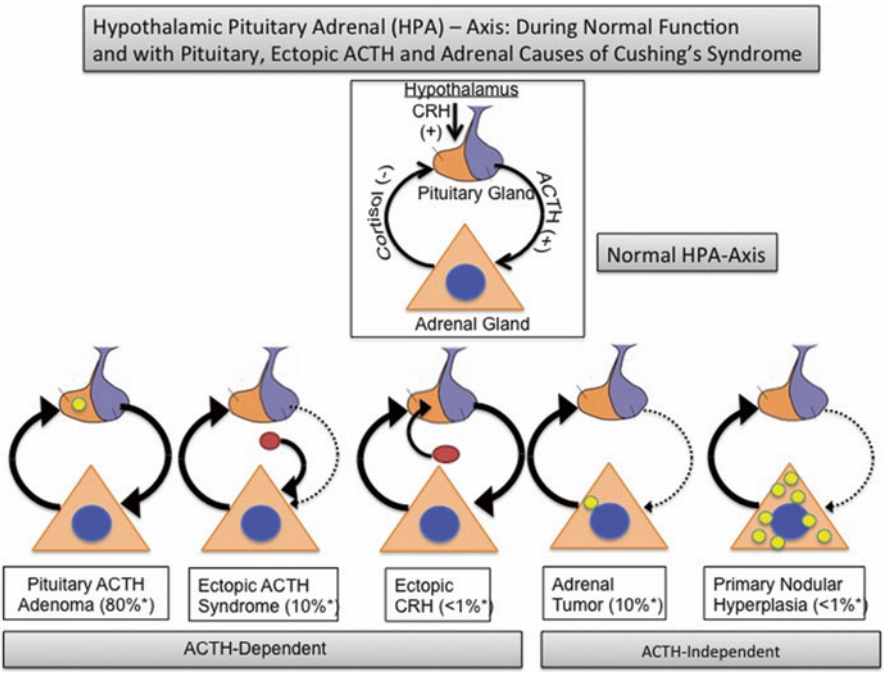

Fig. 17.1 Hypothalamic–pituitary–adrenal axis: during normal function and with various etiologies of Cushing's syndrome

Table 17.2 Differential diagnostic testing in patients with proven Cushing's syndrome

Test	Adrenal CS	Pituitary CS	Ectopic ACTH syndrome
ACTH level	Low	Normal/high	Normal/very high
CT/MRI adrenal g.	Mass(es)	Normal/hyperplasia	Normal/hyperplasia
HDDST[a]	No suppression	Suppression	Rare suppression
CRH test	No response	Response	Rare response
MRI pituitary	Normal[b]	Tumor (60 %)	Normal[b]
IPSS	Not applicable	Gradient (pit./peripheral)	No gradient (pit./peripheral)

The relative frequency of occurrence of the different CS etiologies is given in percentage inside the parentheses

Adapted from Arnaldi G, Atkinson AB, Bertagna X, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003;88:5593–602

[a]High-dose (8 mg) dexamethasone suppression test

[b]10–20 % pituitary "incidentalomas" up to 6 mm

Table 17.3 Examples of hormonally active tumors associated with ectopic ACTH secretion

Source	Biomarker(s)
Neuroendocrine/carcinoid tumors	5-HIAA, chromogranin A, and serotonin
Gastrinoma	Gastrin
Medullary thyroid carcinoma	Calcitonin
Pheochromocytoma	Catecholamines/metanephrines
Bronchogenic carcinoma	Hypercalcemia
Small cell lung carcinoma	ADH
Pancreatic carcinoma	GHRH

GHRH growth hormone-releasing hormone, *5-HIAA* 5-hydroxyindoleacetic acid

EAS, and many produce other ectopic biomarkers (see Table 17.3) [5, 27–29]. Historically, differentiating CD from EAS had been difficult but that changed when IPSS was introduced [1, 30, 31]. Since then, it has achieved a high level of diagnostic accuracy. This has improved with modifications including bilateral sampling [32, 33], CRH stimulation, and "normalizing" ACTH responses with prolactin measurements. To demonstrate how IPSS is used in clinical practice, a case is presented below.

3. **Illustrative case 1: A 24-year-old woman with weight gain and Cushing's features:**

   (a) **Clinical suspicion of CS:** A 24-year-old woman experienced a 100-lb. weight gain with Cushing's features, hyperglycemia, hypokalemia, hypertension, and psychoses requiring multiple psychiatric medications (Figs. 17.2 and 17.3). Her history was complicated by a series of undetermined quantities of Depo glucocorticoid injections over the last 2 years for back pain. Despite the history of exogenous glucocorticoids, CS testing was done because of the disproportionality of her findings. Exogenous CS

Fig. 17.2 A 24-year-old woman with Cushing's syndrome taken during first hospitalization for diagnostic testing

Fig. 17.3 (**a**) A 24-year-old woman with Cushing's syndrome taken during first hospitalization for diagnostic testing. (**b**) Same woman taken approximately 4 years earlier

Table 17.4 Diagnostic testing for Cushing's syndrome in a 24-year-old woman with Cushing's features

Date	DST (1 mg) 8 am Plasma cortisol	Plasma ACTH	24-h urine free cortisol values	Late-night salivary cortisol	Late-night plasma cortisol
Normal values	<2.0 μg/dl	7–63 pg/ml	0–50 μg/day	<0.112 μg/dl	<2.0 μg/dl
4/19/2013	35[a]		139[a]		
5/1/2013	22[a]			0.365[a]	
5/11/2013	13.6[a]				
5/12/2013			149[a]		16.8[a]
5/13/2013			169[a]		25.9[a]
5/14/2013					
5/15/2013	13.6[a]	16.6[a]			
5/16/2013	14.6[a]	29.1[a]			
7/22/2013			141[a]		

[a]Abnormal test result

was deemed an unlikely factor based on the rough assessment of dose, frequency, and remote history. In addition, normal cortisol responses to ACTH stimulation testing further diminished this possibility.

(b) **Diagnostic CS testing:** The diagnostic CS testing showed hypercortisolism based on late-night serum and salivary and 24-h urine cortisol values (see Table 17.4). Loss of the normal glucocorticoid feedback inhibition was found by dexamethasone suppression testing (DST). ACTH independence was excluded by non-suppressed plasma ACTH levels, thus ruling out adrenal CS.

(c) Differential diagnostic testing for CS etiology: Although an adrenal etiology of CS was ruled out by normal plasma ACTH levels (and later incidental abdominal CT imaging), the differentiation between CD and EAS was uncertain because of equivocal pituitary MRI findings and nondiagnostic hepatic mass pathology.

(i) **Ectopic ACTH syndrome evaluation:** The patient's abdominal CT scan showed multiple large masses most consistent with hepatic adenomas, which have not been associated with EAS. Consideration was given to hepatic carcinoid but the urinary 5-HIAA levels were normal.

(ii) **Pituitary MRI with gadolinium enhancement:** Nondiagnostic findings suggested a small 2×4 mm left-sided adenoma (Fig. 17.4). The pituitary MRI was repeated with the same result. Because of the likelihood of CD and the accuracy and possible lateralization, we proceeded with IPSS.

(iii) **IPSS:** Results of the IPSS angiography confirmed correct catheter placement (Fig. 17.5a, b). Increased ACTH production was localized to the pituitary gland confirming the diagnosis of CD (Tables 17.5 and 17.6). ACTH production within the pituitary body lateralized to the left side consistent with the MRI findings (Table 17.5).

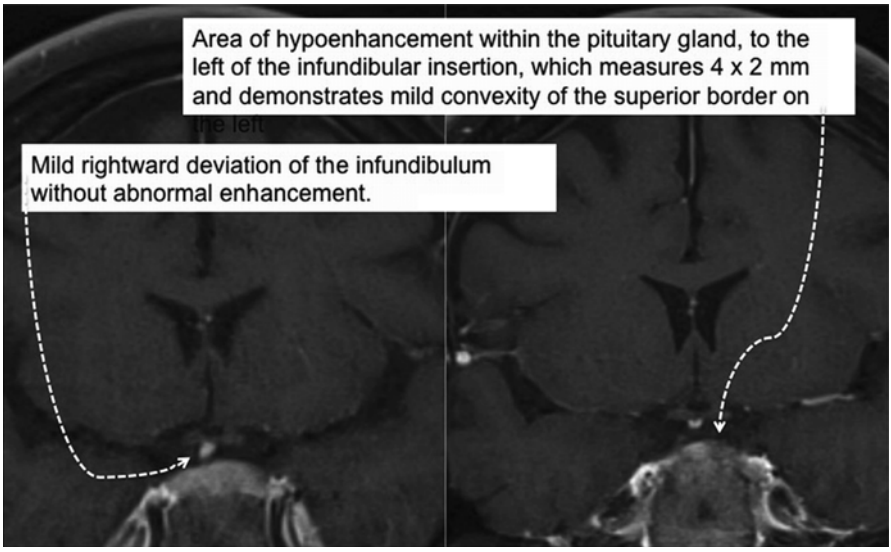

Fig. 17.4 Pituitary MRI findings in a 24-year-old woman with CS

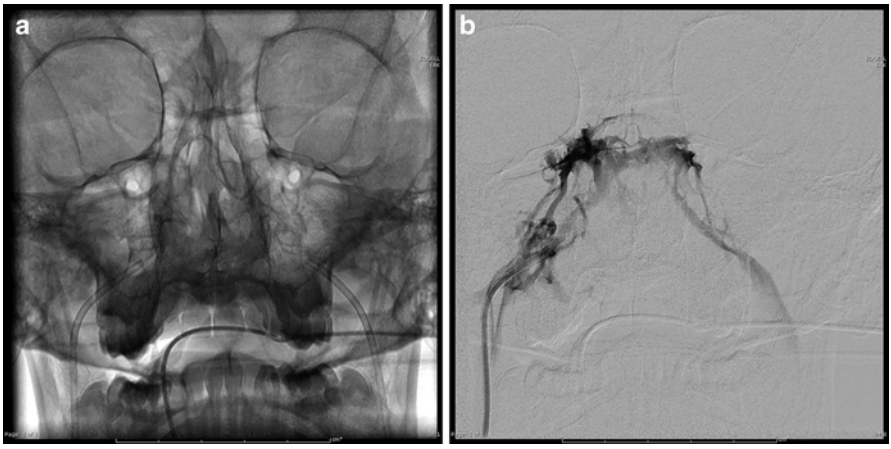

Fig. 17.5 (**a**) Fluoroscopic visualization of catheter placement in bilateral inferior petrosal sinuses. (**b**) Venogram of cavernous sinuses obtained from catheter in right inferior petrosal sinus

(d) **Summary:** This case summarizes the strategic use of IPSS in the medical evaluation of CS. Clinical suspicion to screen for CS was based on the rapidity and severity of her symptomatology disproportionate to her exogenous glucocorticoid exposure. The diagnosis of CS was made by multiple screening tests but the etiology was unclear because of equivocal pituitary MRI findings and the discovery of hepatic masses. Adrenal CS was unlikely based on non-suppressed plasma ACTH levels and normal adrenal gland imaging. On transs-

Table 17.5 IPSS testing in a 24-year-old woman with Cushing's syndrome to localize and lateralize the source of ACTH

Condition	Baseline-1	Baseline-1	Baseline-2	Baseline-2	CRH+15	CRH+15	CRH+30	CRH+30
Time	11:54 AM	11:54 AM	11:59 AM	11:59 AM	12:14 PM	12:14 PM	12:29 PM	12:29 PM
Test	ACTH	Prolactin	ACTH	Prolactin	ACHT	Prolactin	ACTH	Prolactin
Normal	7–63 pg/ml	4–23 ng/ml	7–63 pg/ml	4–23 ng/ml	7–63 pg/ml	4–23 ng/ml	7–63 pg/ml	4–23 ng/ml
Left IPS	648.9	58.7	540.5	57.2	1099	62.5	1,137	103.8
Right IPS	631.8	124.8	460.8	73.6	823.7	145.3	648.3	167.5
Peripheral	88.5	29.2	92.5	27.8	113.2	28.7	102.6	26.6

Table 17.6 Analysis of the IPSS testing in a 24-year-old woman with Cushing's syndrome to localize and lateralize the source of ACTH

Localization of ACTH source	Lateralization of ACTH within the pituitary
IPS:P ACTH basal (>2) = 6.6[a]	IPS ACTH L:R basal (>1.4) = 1.1
IPS:P ACTH CRH (>3) = 11.1[a]	IPS ACTH L:R CRH (>1.4) = 1.5[a]
IPS:P PROL basal (>1.8) = 2.0[a]	IPS PROL L:R basal (~1) = 0.5
IPS:P PROL CRH (>1.8) = 3.9[a]	IPS PROL L:R CRH (~1) = 0.5
IPS:P ACTH/PROL (>0.8) = 2.8[a]	IPS ACTH/PROL L:R basal = 1.8[a]
	IPS ACTH/PROL L:R CRH = 3.0[a]

IPS inferior petrosal sinus, *P* peripheral, *L* left, *R* right
IPS:P ACTH basal: if >2 indicates an ACTH source within the pituitary gland before CRH stimulation
IPS:P ACTH CRH: if >3 indicates an ACTH source within the pituitary gland after CRH stimulation
IPS:P PROL basal: if >1.8 validates the location of the IPS catheter before CRH stimulation
IPS:P CRH: if >1.8 validates the location of the IPS catheter after CRH stimulation
IPS:P ACTH/PROL: if >0.8 confirms a disproportionately high ACTH secretion relative to prolactin
IPS ACTH L:R basal: if >1.4 is suspicious for a left-sided pituitary adenoma before CRH stimulation
IPS ACTH L:R CRH: if >1.4 is suspicious for a left-sided pituitary adenoma after CRH stimulation
IPS PROL L:R basal: if ~1 indicates a non-lateralizing pituitary venous effluent before CRH stimulation
IPS PROL L:R CRH: if ~1 indicates a non-lateralizing pituitary venous effluent after CRH stimulation
IPS ACTH/PROL L:R basal: corrects ACTH lateralization for pituitary venous effluent before CRH stimulation
IPS ACTH/PROL L:R CRH: corrects ACTH lateralization for pituitary venous effluent after CRH stimulation
[a]High

phenoidal surgery she was found to have a left-sided pituitary adenoma that was resected, following which the cortisol levels returned to normal.

4. **Diagnostic accuracy of IPSS in ACTH-dependent CS:** As shown in this case, differentiating the etiology of CS between adrenal, pituitary, and EAS is essential for proper therapy. Adrenal CS has been relatively straightforward to diagnose with a combination of low ACTH levels and imaging showing adrenal mass(es) (see Table 17.2). Given the frequent small size of pituitary tumors and occasional occurrence of occult EAS tumors, differentiating CD and EAS can be difficult [34–37]. When IPSS has been used to confirm or exclude a pituitary source of ACTH in CS, it has been very successful with reports of diagnostic accuracy of around 90 % [38–43]. These tests are discussed below (see Table 17.2).

   (a) **Plasma ACTH:** This test will usually diagnose adrenal CS based on a low serum level (see Table 17.2). The combination of a low plasma ACTH with normal but autonomous urinary cortisol occurs in adrenal "incidentalomas." CD usually has normal or high ACTH levels, whereas EAS has the highest but considerable overlap occurrence.

   (b) **Adrenal gland CT or MRI:** The combination of hypercortisolism with low ACTH should prompt adrenal imaging. The usual finding is adrenal mass(es) usually unilateral but sometimes bilateral. The finding of an adrenal mass in CS without a low ACTH level, however, is not an evidence for an adrenal etiology since these patients may still have CD [44].

(c) **High-dose dexamethasone suppression testing (HDDST):** CD is based on the premise that most ACTH-secreting pituitary adenomas have an intact but relatively resistant negative feedback loop. In contrast, EAS has a negative feedback loop which is completely resistant to glucocorticoids with the exception of some carcinoid tumors. Unfortunately, using <50 % suppression "cut-point" yields false-positive and false-negative rates between 20 and 30 %, respectively [45].

(d) **CRH testing** (Ferring Pharmaceuticals, Limhamn, Sweden, under the tradename Acthrel): CRH can be difficult to procure for outpatient testing but it is considered second best for differentiating CD and EAS. The fact that most ACTH-secreting pituitary adenomas (85 %) respond to CRH with an increase in ACTH secretion and most EAS and adrenal CS do not is the basis for this test [46]. Dexamethasone is sometimes used in conjunction with CRH to improve the diagnostic accuracy, but the test has enough false-negative results to limit its use. The major use for this test is diagnosing pseudo-Cushing's and physiologic hypercortisolemic states (see Table 17.2) [47].

(e) **Pituitary MRI (with gadolinium enhancement):** Pituitary MRI has a diagnostic accuracy of only about 50 % largely as a result of two problems [48–51]. First, the small size of CD adenomas (sometimes ~1 mm) and second, lack of functional assessment, which is a problem with non-ACTH-secreting pituitary "incidentalomas." Pituitary incidentalomas have been found in 10–20 % of unselected MRIs and autopsies [52–54]. Co-lateralization of MRI findings with IPSS will further enhance not only diagnostic certainty but also lateralization within the pituitary body [55, 56].

(f) **IPSS (90 % diagnostic accuracy):** Of all of the etiologic tests for CS, IPSS has the best diagnostic accuracy as reported by high-volume referral centers [57]. The primary use of IPSS is to localize the source of ACTH (see Table 17.7). The secondary and less accurate use of IPSS is to lateralize the side of ACTH source within the pituitary body to allow for more selective and less invasive transsphenoidal surgery. It must be remembered that IPSS is not useful in diagnosing CS. IPSS has proven useful in both pregnancy [58] and young children [17, 59–61]. The diagnostic IPSS criteria to localize and lateralize the source of ACTH are seen in Table 17.8. Despite its successes IPSS still has inaccuracies in otherwise difficult cases [62, 63]. Furthermore, because IPSS requires a high degree of technical

Table 17.7 Utility of inferior petrosal sinus sampling (IPSS)

Primary
Differentiate the cause of Cushing's syndrome, i.e., pituitary disease versus ectopic ACTH
Secondary (less helpful)
Pituitary lateralization
Not helpful
Establishing diagnosis of endogenous CS

Table 17.8 IPSS criteria to localize and lateralize the source of ACTH

Purpose	Catheter	Test	Condition	Criteria
Localize ACTH	IPS:P	ACTH	Pre-CRH stim	>2
Localize ACTH	IPS:P	ACTH	Peak-CRH stim	>3
Catheter placement	IPS:P	Prolactin	Pre- or peak-CRH	>1.8
Excess ACTH	IPS:P	ACTH:prolactin	Pre-CRH stim	>0.8
Lateralize ACTH	IPS L:R	ACTH	Pre- or peak-CRH	>1.4
Lateralize prolactin	IPS L:R	Prolactin	Pre- or peak-CRH	~1.0
Corrected ACTH lateralization	IPS L:R	ACTH:prolactin	Pre- or peak-CRH	>1.4

IPS inferior petrosal sinus, *P* peripheral, *L* left, *R* right
Localize ACTH—confirm or exclude pituitary is source of ACTH
Catheter placement—validate the correct location of IPS catheter
Excess ACTH—confirms excess ACTH relative to prolactin control
Lateralize ACTH—lateralizes side of pituitary ACTH production
Lateralize prolactin—lateralize side of pituitary venous effluent
Corrected ACTH lateralization—corrects IPS ACTH for laterality of pituitary venous effluent

skill and expertise, results could vary widely. Anatomic variability precludes about 10 % of CS patients who cannot be successfully catheterized for IPSS. The principal reason for CRH stimulation is to correct for ACTH pulsatility [64]. Pulsatility is also a good reason to draw two baseline ACTH levels. CRH stimulation improves IPSS diagnostic accuracy from 60 to 90 % according to several reports [56, 65, 66]. A systematic analysis that included 21 studies and 569 patients found that IPSS with CRH stimulation achieved 96 % sensitivity and 100 % specificity in discriminating Cushing's disease from EAS [47]. Interestingly, CRH also stimulates AVP, prolactin, and other ACTH-related peptides [67–69]. CRH has also been combined with TRH (not commercially available) to dually stimulate both ACTH and prolactin [70]. Difficulty procuring CRH has led to the interest in alternatives such as naloxone, metyrapone, and vasopressin [71, 72]. A synthetic version of vasopressin and desmopressin (DDAVP; Ferring Pharmaceuticals) compared to CRH produces less ACTH stimulation [73–75]. Nevertheless, desmopressin stimulation improves diagnostic accuracy over 90 % and comparable to CRH [76]. Combined CRH and AVP stimulation also yields excellent diagnostic accuracy and perhaps better than either alone [77, 78]. The desmopressin technique is similar to CRH and 10 mg of desmopressin is used in place of the CRH. IPSS prolactin levels can be used to correct for venous effluent concentrations as they lateralize in the majority of non-CS subjects showing the need to correct for difference in venous effluent [79–84]. When petrosal-to-peripheral ACTH ratios are "normalized" to prolactin petrosal-to-peripheral ratios, the diagnostic accuracy for both localization and lateralization improves [82, 85]. "Normalization" of ACTH gradients improves accuracy not only prospectively but retrospectively using archived IPSS blood samples [79, 84]. In the current case,

ACTH gradients lateralized to the left (Table 17.6) only after prolactin normalization, which is where the CD adenoma was found. Beyond prolactin, other IPSS neuroendocrine biomarkers and pituitary hormones have yet to become useful [69, 86, 87]. **IPSS lateralization** refers to determining the side, either right or left, of the CD adenoma within the pituitary body. Lateralization unfortunately has not achieved the diagnostic accuracy of localizing the source of ACTH, either within the pituitary body or not. Some studies have shown that a gradient of ≥1.4 between the ACTH concentrations in the two sinuses predicted the side of the tumor with up to 71 % accuracy if catheters were appropriately placed [48, 49, 88–92]. However, others have not found such strong predictive values. Since there is a 50 % chance of correctly predicting the location without the aid of any anatomical data, this expensive procedure cannot be justified for lateralization alone [93–95]. If MRI lateralizes a pituitary lesion to the same side, the accuracy is much higher when it does not. If the IPPS lateralizes but the MRI does not, the whole pituitary body should still be explored at TSS since ~30 % have contralateral tumors [91]. The reasons for failing to lateralize are listed in Table 17.9. Besides the usual considerations of variations in venous drainage and catheter placement, an intrinsic lateralization of pituitary function favors the right of the time 80 %. This may explain why left-sided IPSS lateralization is most accurate for CD. Other causes are seen in the table and should be considered when evaluating the data.

(i) **Accuracy of IPSS localization—false positives:** A false-positive IPSS occurs when the ACTH source **is** localized to the pituitary body,

Table 17.9 Some rare difficulties in IPSS' ability to localize the source of ACTH (CD vs. EAS) and to lateralize CD within the pituitary

Failure to localize (pituitary vs. EAS) False (+) ~5 %; false (–) ~15 %	Failure to lateralize (right vs. left)
1. Anomalous venous drainage	1. Anomalous venous drainage
2. Incorrect catheter placement	2. Incorrect catheter placement
3. Ectopic CRH-secreting tumor (carcinoid)	3. Ectopic tumor secreting CRH
4. Cyclic hypercortisolism	4. Prior transsphenoidal surgery
5. Inadequate examination of surgical pathology	5. Inadequate examination of surgical pathology
6. Extrapituitary parasellar ACTH-secreting adenoma	6. Extrapituitary parasellar ACTH-secreting adenoma
7. Failure to employ CRH stimulation	7. Midline microadenoma
8. Inability to catheterize	8. Sample withdrawal was too rapid
9. Medical or surgical therapy: to decrease adrenal cortisol and/or pituitary ACTH secretion	9. Intrinsic functional laterality of hypothalamic–pituitary axis (80 % right-side dominant)
10. Failure to diagnose CS with certainty and exclude physiologic hypercortisolism	10. Mislabeling left and right sample tubes

but TSS neither finds the adenoma nor is curative. The IPSS false-positive rate is very low and in some studies approaching 0 %. Some causes of false-positive IPSS localization (as well as lateralization) results are seen in Table 17.9.

(1) **Normals and pseudo-Cushing's states:** The most important step to avoid a false-positive IPSS is to be certain of the diagnosis of CS. IPSS in normal subjects will localize ACTH secretion from the pituitary body. Therefore, IPSS is not helpful in confirming or establishing the diagnosis of CS only in its etiology. Particular concern occurs in pseudo-Cushing's states which can biochemically and/or clinically mimic true CS. In some of these conditions, all of the usual screening and diagnostic tests for CS will be positive [96, 97].

(2) **Extrapituitary parasellar ACTH-secreting adenomas:** One rare cause of a positive IPSS but negative pituitary surgery is an extrapituitary, parasellar ACTH-secreting (ectopic) adenoma [98, 99]. This occurs in ~1 % of CD cases and is sometimes associated with an empty sella. The extrapituitary adenomas probably develop from a remnant of Rathke's pouch, which failed to migrate to the anterior pituitary. The extrapituitary adenomas have been found in the sphenoid sinus, anterior cranial fossa, interpeduncular cistern, intraclival, and suprasellar locations. In most instances, careful examination of MRI images will reveal their location. It is important to consider the possibility of an extrapituitary adenoma especially if EAS is not found and before committing the patient to a total hypophysectomy and/or bilateral adrenalectomy [99–101].

(3) **Ectopic CRH:** Although very rare, ectopic tumors secreting CRH, especially bronchial carcinoids, will produce "eutopic" ACTH and cause IPSS localization to the pituitary body. Inhibiting adrenal corticosteroidogenesis (medical or surgical) in EAS will potentially restore pituitary ACTH secretion. Combined ectopic ACTH and CRH production has also been reported to give false-positive IPSS results [102].

(4) **MRI negative:** If IPSS is positive for a gradient (pituitary: peripheral) but the pituitary MRI is negative, TSS success drops almost in half (98–50 % in one study). In those unsuccessful cases, no pituitary tumor has subsequently been found in a 4-year follow-up suggesting an occult pituitary tumor was not missed [56, 103].

(5) **Other** causes of false-positive are in Table 17.10.

(ii) **Accuracy of IPSS localization—false negatives:** A false-negative IPSS occurs when the ACTH source **is not** localized to the pituitary body but later found that it is. **IPSS** has a larger problem with false-negative rates of up to 15 % [104]. A number of potential causes for false negatives are listed below (see Table 17.9):

Table 17.10 Basic steps in an IPSS protocol

Preparation
• Informed consent
• Prepare labeled tubes
• Late-night salivary cortisol to confirm pre-procedural hypercortisolism (optional)
Venous access (bilateral femoral vein)
• Secure venous access site and use 18G single-wall needle to puncture vein
• Placement of three catheters (2-IPSS and 1-peripheral) confirmed by angiography
Equipment
• Sheaths—90-cm shuttle sheath
• Catheters—5-F guide catheter navigated over guide wire
• Guide wire—stiff guide wire (Terumo)
• Microcatheters—2.8-F microcatheter
Medications
• Conscious sedation to allow real-time neurologic assessment
• 3–5,000 units of heparin (optional)
• CRH (Acthrel®, Ben Venue Laboratories Inc. Bedford, OH) 1 μg/kg IV
Collect blood ACTH and prolactin samples
• Baseline—two sets
• Post-CRH—3, 5, 10, and 15 min
Withdraw catheters, manually compress puncture site, and observe at least 4 h before discharge (usual time = 1–2 h; Deipolvi)

(1) **Improper catheter placement:** Venous angiography is needed to locate correct positioning of the catheters [105].
(2) **Anomalous drainage:** A unilateral hypoplastic or plexiform inferior petrosal sinus can result in anomalous drainage from the pituitary body that may lead to false-negative sampling results in ~1 % [106, 107]. Retrograde IPS blood flow and blood steal of the cavernous sinus associated with central vein stenosis has been described [108].
(3) **Microscopic adenomas (<1 mm) missed at surgical pathology examination:** Repeat examination with thinner sections and ACTH staining is advised.
(4) **Cyclic CS in remission:** Although rare, periodic hypercortisolism can be determined at the time of IPSS with a pre-procedure late-night salivary cortisol.
(5) **Pasireotide:** Is a somatostatin agonist that inhibits corticotroph ACTH secretion and is indicated for medical treatment of CD.

5. **IPSS—anatomy, tools, and procedural considerations**
The pituitary gland is divided into anterior (adenohypophysis) and posterior (neurohypophysis). It is drained by the lateral hypophyseal veins [94, 109]. It is surrounded by two venous compartments known as the cavernous sinuses.

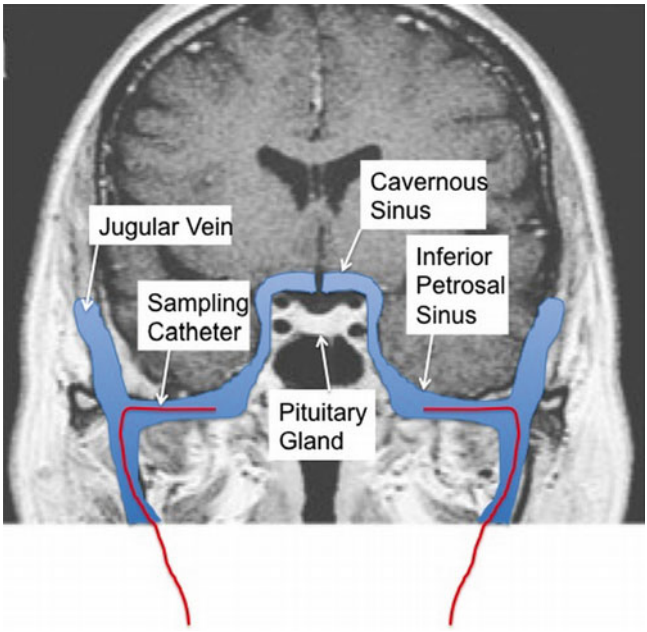

Fig. 17.6 Schematic diagram of pituitary venous drainage and placement of the inferior petrosal sinus sampling catheter

Three channels connect these compartments: the anterior intercavernous sinus, the posterior intercavernous sinus, and the inferior intercavernous sinus. These cavernous sinuses in turn drain via several channels including the IPS which empties into the internal jugular vein and from there into the subclavian vein. The IPS extends from the posterior aspect of the cavernous sinus posteriorly through the jugular foramen to the internal jugular vein.

A schematic diagram of pituitary venous drainage, fluoroscopic image of placement of the IPSS catheters, and an IPSS venogram are seen in Figs. 17.5 and 17.6.

Preparation

As Cushing's patients are often obese, venous access may be difficult. The abdomen must be taped to improve visualization of the groin. We recommend having multiple sampling lavender top tubes available and pre-labeled prior to beginning the procedure.

Venous access

An 18G single-wall needle may be used to gain venous access. Utilizing an over-the-wire approach, a sheath is used to access the inferior vena cava. Bilateral femoral venous access is required in order to sample both inferior petrosal sinuses.

Sheaths

A supportive sheath such as a 90-cm Shuttle Sheath (Cook Medical, Bloomington, IN) is often useful given the need for guide catheter support when passing through the valvular system of the jugular veins. Alternatively a shorter, 35-cm 6-F sheath may also be used. It is important to have at least one of the two sheaths of a larger diameter than the catheters being used to allow peripheral samples to be drawn from the sheath. Both sheaths should be continuously irrigated with heparinized saline. Once the femoral venous sheaths are in place, systemic heparin is administered intravenously.

Occasionally arterial access may be obtained in order to visualize the venous sinuses and internal jugular veins to provide a venous road map. For this purpose, a standard 5-F or 6-F sheath may be used.

Catheters

Once the sheath is in place, a 5-F guide catheter is navigated over a glide wire through each sheath into the ipsilateral jugular vein. Some authors recommend a cross catheterization approach, as it may be easier to catheterize the more difficult left jugular vein from the right femoral vein sheath, which is closer, thus offering a mechanical advantage [110]. The catheter is then directed superomedially toward the inferior petrosal sinuses. Typically the IPS drains directly into the jugular bulb and is easy to catheterize. However there is significant variation in the anatomy of the IPS. Shiu et al. described four distinct patterns of drainage of the IPS [111], with type 1 being the common one described above. Type II drainage is where the IPS anastomoses to a large anterior condylar vein. In type III there may be several small channels forming the IPS, whereas in type IV the IPS may not drain into the IJV at all and drain into the anterior condylar vein directly. Occasionally a venous road map may be useful to visualize the IPS. A 4-F or 5-F diagnostic catheter navigated into either common carotid artery, through which a cervico-cerebral angiogram is obtained through the venous phase. Alternatively a venous road map may be obtained through an arterial injection in which the images are obtained a few seconds after injecting in order to capture only the venous phase on fluoroscopy.

A variety of catheter shapes have been used to access the internal jugular vein. We find a 5-F Head Hunter catheter works most consistently in selecting the IPS. This catheter shape is able to hold the catheter stably against the IPS junction and may enter the IPS itself. This stability facilitates microcatheterization if needed. Other alternatives that may be used are a 5-F Davis catheter [109] or a 4-F Berenstein catheter (Cordis).

Guide wires

A stiff glide wire (Terumo) is often but not always needed to successfully cross the valves of the internal jugular vein. A regular 0.035″ in glide wire may routinely be used to navigate the catheter into the internal jugular veins.

Microcatheters

If selective microcatheterization of the IPS or cavernous sinus is desired, a larger microcatheter such as a Renegade HI-FLO (Boston Scientific) will facilitate aspiration. A 2.8-F microcatheter such as a Prowler Select Plus (Codman

Neurovascular) may alternatively be navigated further into the inferior petrosal sinus over a 0.014-in. microwire if required.

Corticotropin-releasing hormone (CRH)

Corticorelin ovine triflutate (Acthrel®, Ben Venue Laboratories Inc, Bedford, OH) is the commercially available synthetic form of CRH that is administered in a dose of 1 μg/kg intravenously [65].

Additional personnel

As multiple blood samples are drawn simultaneously from both petrosal sinuses and the femoral sheath, two additional team members may be required to scrub in, along with 1–2 other rotating non-sterile team members to ensure appropriate labeling, storage on ice, and transport of the specimens to the laboratory.

Collecting the samples

It is important to collect the three samples simultaneously. We recommend collecting at least three sets of baseline samples 5 min apart prior to the injection of CRH, as well as at least two, ideally four sets of samples at 1, 3, 5, and 10 min after CRH injection. Before each sample is obtained, a different syringe should be used to draw about 2 cc blood from all three sites, which should be discarded. Once each sample is collected, it should be handed to one of the circulating staff members who will place it in an appropriately pre-labeled lavender top tube. Alternatively, these tubes could also be color-coded. We recommend pre-labeling them with the site and the time, for example, "RIPS-10," "RIPS-5," "LIPS-3." These labels should then be placed on ice and transported to the lab.

An example of the basic steps in an IPSS protocol is summarized in Table 17.10. Documentation of hypercortisolism during the time of the procedure can be done with a late-night pre-procedure salivary cortisol to control for periodic hormonogenesis.

6. **Alternative pituitary sampling methods:** Interest in finding easier (jugular vein) and more accurate sampling locations (cavernous sinus) has resulted in a number of studies. In brief, the jugular vein while easier to perform is significantly less accurate, and the cavernous sinus is more accurate for lateralizing but also harder to perform.

   (a) **Jugular vein sampling** (JVS): The IPS passes through the jugular vein, which makes this an easier target but the diagnostic accuracy is less. The JVS values are lower than IPSS due to dilution and, therefore, not as reliable. A negative JVS must be confirmed by IPSS [112–115].

   (b) **Cavernous sinus sampling** (CSS): The cavernous sinus is closer to the pituitary body and theoretically a better place to sample. CSS localization is as good as IPSS, but may improve lateralization. On the other hand CSS is technically harder to reach and more invasive, thus increasing the risk of complications [116–126].

7. **Complications:** The incidence of serious complications, such as ischemic stroke, is 0.2 % when the procedure is performed by an experienced neurointerventionalist [127–135]. A list of reported IPSS complications is in Table 17.11. In one

Table 17.11 Reported complications of IPSS

0.2 % per year[a]
Groin hemorrhage (3 %)
Thromboembolism
Transient brain stem symptoms
Brain stem infarction
Hemiparalysis
Pontine hemorrhage
Isolated sixth nerve palsy
Venous subarachnoid hemorrhage
Subarachnoid extravasation of dye and blood

[a]At a center that does >50/year [135, 136]

series of 166 patients, transient cranial nerve palsy occurred in only one patient [38]. In another series of 44 patients, one developed hemiparesis and gaze palsy after the study [136]. Raymond's syndrome has been reported [137]. Pulmonary embolism and deep venous thrombosis have been reported, but their frequency in large series is not known [130, 138, 139]. The frequency of less serious complications, such as inguinal or jugular hematomas, is less common. Choice of catheters is probably also an important consideration to avoid complications [140].

8. **Recommendation guidelines**
   (a) **Successful TSS:** Hypocortisolism immediately post-TSS is the best measurement of success [141]. CD adenomas tend to be small and often are not well-localized preoperatively. As a result, even in the hands of an experienced medical, radiological, and surgical team, 25–35 % of patients with Cushing's disease are not in remission following surgical exploration of the sella turcica. A surgical technique removing the tumor along the plane of a histologic pseudocapsule facilitates more complete resection and over 90 % rates of remission [142].
   (b) **What to do if IPSS and EAS search are negative:** Following a negative IPSS study and negative EAS work-up (including chest and abdominal imaging), the possibility of either an occult EAS or CD must be considered [143–146]. Occult pituitary adenomas are sometimes found over time with repeat MRI [100, 147].
   (c) **When to avoid IPSS:** Given its cost and difficulty, avoiding IPSS when possible is desirable. Many authorities recommend going straight to TSS when MRI shows a pituitary lesion >6 mm without other confounding clinical findings. Given the relative high frequency of incidentalomas (up to 20 % in EAS), some of which are >6 mm, errors using these criteria alone will occur [148].
9. **Cost-effectiveness:** The timely and appropriate therapy for CS is critical to guarantee the best outcome. Delays in treatment take their toll in the progression of CS-associated diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoporosis, infections, psychoses, obesity, obstructive sleep apnea, NASH, hypokalemia, etc. [149]. The cost of an invasive technique like IPSS is

offset by the rapidity and accuracy of a timely therapeutic intervention such as TSS. The cost-effectiveness analyses, however, are sensitive to the pretest probability of Cushing's disease, test characteristics, and test costs which may change over time. At the present time most of the comparisons of cost-effectiveness favor IPSS, but this assessment can change as technology and our understanding of this disease evolves over time [150].

10. **Conclusion:** Cushing's syndrome is the pathophysiologic result of hypercortisolism, which if left untreated has up to a 50 % 5-year mortality. IPSS is a major advance and now gold standard for localizing and lateralizing the source of ACTH in CS. Because of its superior accuracy, IPSS has largely replaced other biochemical tests used for the same purpose. The two major diagnostic limitations are false-negative localization and false-positive lateralization. Both of these problems are largely attributed to technical problems, anomalous venous drainage, or pulsatile hormone production. Two innovations have addressed these limitations: first, the use of prolactin levels to "normalize" venous effluents and second, CRH stimulation to eliminate confounding ACTH pulsatility. Despite the advantages, physicians should use IPSS cautiously given the cost, invasiveness, required technical skill, and potential complications. Therefore, it has never been truer that with great medical advances comes even greater responsibility to understand and use them wisely.
11. **Abbreviations**

    (a) ACTH—adrenal corticotrophic hormone
    (b) CS—Cushing's syndrome
    (c) CD—Cushing's disease
    (d) EAS—ectopic ACTH syndrome
    (e) HDDST—high-dose dexamethasone suppression test
    (f) TSS—transsphenoidal surgery
    (g) CRH—corticotropin-releasing hormone
    (h) IPSS—inferior petrosal sinus sampling
    (i) HPA—hypothalamic–pituitary–adrenal
    (j) JVS—jugular venous sinus sampling
    (k) CSS—cavernous sinus sampling
    (l) AVP—arginine vasopressin
    (m) MRI—magnetic resonance imaging
    (n) HDD—high-dose dexamethasone (suppression test)

References

1. Corrigan DF, Schaaf M, Whaley RA, Czerwinski CL, Earll JM. Selective venous sampling to differentiate ectopic ACTH secretion from pituitary Cushing's syndrome. N Engl J Med. 1977;296:861–2.
2. Utz A, Biller BM. The role of bilateral inferior petrosal sinus sampling in the diagnosis of Cushing's syndrome. Arq Bras Endocrinol Metabol. 2007;51:1329–38.
3. Chan FL, Lam KS. Venous sampling: its role in localization of endocrine tumours. Ann Acad Med Singapore. 1993;22:707–13.

4. Deipolyi AR, Hirsch JA, Oklu R. Bilateral inferior petrosal sinus sampling. J Neurointerv Surg. 2012;4:215–8.
5. Huang TS. Bilateral inferior petrosal sinus sampling in the management of ACTH-dependent Cushing's syndrome. J Chin Med Assoc. 2007;70:1–2.
6. Lin LY, Teng MM, Huang CI, et al. Assessment of bilateral inferior petrosal sinus sampling (BIPSS) in the diagnosis of Cushing's disease. J Chin Med Assoc. 2007;70:4–10.
7. Norlisah R, Abdullah BJ, Hew FL, Chan SP. Petrosal sinus sampling in the diagnosis of Cushing's syndrome: preliminary experience in University of Malaya Medical Centre. Med J Malaysia. 2003;58:180–6.
8. Kalgikar AM, Chandratreya SA, Goel A, et al. Inferior petrosal sinus sampling in the diagnostic evaluation of Cushing's syndrome: K.E.M. experience. J Assoc Physicians India. 2005;53:685–8.
9. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003;88:5593–602.
10. Daousi C, Nixon T, Javadpour M, Hayden K, MacFarlane IA. Inferior petrosal sinus ACTH and prolactin responses to CRH in ACTH-dependent Cushing's syndrome: a single centre experience from the United Kingdom. Pituitary. 2010;13:95–104.
11. Martines V, Mansueto G, Tosi F, Caruso B, Castello R, Procacci C. Selective venous sampling in diagnosing ACTH-dependent hypercortisolism. Radiol Med. 2003;105:356–61.
12. Findling JW. Inferior petrosal sinus sampling: pros and cons; when and where. J Endocrinol Invest. 2000;23:193–5.
13. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. Am J Med. 1952;13:597–614.
14. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93:1526–40.
15. Nieman LK, Ilias I. Evaluation and treatment of Cushing's syndrome. Am J Med. 2005;118:1340–6.
16. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev. 1998;19:647–72.
17. Dias RP, Kumaran A, Chan LF, et al. Diagnosis, management and therapeutic outcome in prepubertal Cushing's disease. Eur J Endocrinol. 2010;162:603–9.
18. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30:729–47.
19. Findling JW, Raff H. Screening and diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34:385–402, ix–x.
20. Lindsay JR, Nieman LK. Differential diagnosis and imaging in Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34:403–21, x.
21. McCance DR, McIlrath E, McNeill A, et al. Bilateral inferior petrosal sinus sampling as a routine procedure in ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf). 1989;30:157–66.
22. Pecori Giraldi F, Invitti C, Cavagnini F. The corticotropin-releasing hormone test in the diagnosis of ACTH-dependent Cushing's syndrome: a reappraisal. Clin Endocrinol (Oxf). 2001;54:601–7.
23. Lindsay JR, Shanmugam VK, Oldfield EH, Remaley AT, Nieman LK. A comparison of immunometric and radioimmunoassay measurement of ACTH for the differential diagnosis of Cushing's syndrome. J Endocrinol Invest. 2006;29:983–8.
24. Magill SB, Raff H, Shaker JL, et al. Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. J Clin Endocrinol Metab. 2001;86:1066–71.
25. Ceral J, Solar M, Krajina A, Ballon M, Suba P, Cap J. Adrenal venous sampling in primary aldosteronism: a low dilution of adrenal venous blood is crucial for a correct interpretation of the results. Eur J Endocrinol. 2010;162:101–7.
26. Lau JH, Drake W, Matson M. The current role of venous sampling in the localization of endocrine disease. Cardiovasc Intervent Radiol. 2007;30:555–70.

27. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab. 2005;90:4955–62.
28. Luca PD, Oren A, Somers GR, Urbach SL. The search for ectopic ACTH production in a 9-year-old boy. J Pediatr Endocrinol Metab. 2013;26:781–3.
29. Isidori AM, Kaltsas GA, Pozza C, et al. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab. 2006;91:371–7.
30. Findling JW, Aron DC, Tyrrell JB, et al. Selective venous sampling for ACTH in Cushing's syndrome: differentiation between Cushing disease and the ectopic ACTH syndrome. Ann Intern Med. 1981;94:647–52.
31. Trainer PJ, Besser GM. Differential diagnosis in Cushing's syndrome: the role of inferior petrosal sinus sampling. Eur J Med. 1993;2:261–3.
32. Cuneo R, Ross D, MacFarlane M, Espiner E, Donald RA. Sequential inferior petrosal venous sampling for Cushing's disease. N Engl J Med. 1985;313:582.
33. McNally PG, Howlett TA. Investigation of Cushing's syndrome by inferior petrosal sinus sampling. Trends Endocrinol Metab. 1993;4:117–21.
34. Kaltsas GA, Giannulis MG, Newell-Price JD, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab. 1999;84:487–92.
35. Findling JW, Kehoe ME, Shaker JL, Raff H. Routine inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin (ACTH)-dependent Cushing's syndrome: early recognition of the occult ectopic ACTH syndrome. J Clin Endocrinol Metab. 1991;73: 408–13.
36. Tomycz ND, Horowitz MB. Inferior petrosal sinus sampling in the diagnosis of sellar neuropathology. Neurosurg Clin N Am. 2009;20:361–7.
37. Snow RB, Patterson Jr RH, Horwith M, Saint Louis L, Fraser RA. Usefulness of preoperative inferior petrosal vein sampling in Cushing's disease. Surg Neurol. 1988;29:17–21.
38. Colao A, Faggiano A, Pivonello R, Pecori Giraldi F, Cavagnini F, Lombardi G. Inferior petrosal sinus sampling in the differential diagnosis of Cushing's syndrome: results of an Italian multicenter study. Eur J Endocrinol. 2001;144:499–507.
39. Wiggam MI, Heaney AP, McIlrath EM, et al. Bilateral inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome: a comparison with other diagnostic tests. J Clin Endocrinol Metab. 2000;85:1525–32.
40. Findling JW, Raff H. Newer diagnostic techniques and problems in Cushing's disease. Endocrinol Metab Clin North Am. 1999;28:191–210.
41. Brew Atkinson A. The role of bilateral inferior petrosal sinus sampling in the investigation of ACTH-dependent hypercortisolism. Clin Endocrinol (Oxf). 1999;51:149–50.
42. Boscaro M, Rampazzo A, Paoletta A, et al. Selective venous sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome. Neuroendocrinology. 1992;55:264–8.
43. Swearingen B, Katznelson L, Miller K, et al. Diagnostic errors after inferior petrosal sinus sampling. J Clin Endocrinol Metab. 2004;89:3752–63.
44. Borretta G, Terzolo M, Cesario F, Meineri I, Pia A, Angeli A. Coexistence of unilateral adrenal macronodule and Cushing's disease. Report of two cases. J Endocrinol Invest. 1996; 19:131–5.
45. Shi X, Sun Q, Bian L, et al. Assessment of bilateral inferior petrosal sinus sampling in the diagnosis and surgical treatment of the ACTH-dependent Cushing's syndrome: a comparison with other tests. Neuro Endocrinol Lett. 2011;32:865–73.
46. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367:1605–17.
47. Newell-Price J, Morris DG, Drake WM, et al. Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab. 2002;87:1640–5.

48. Batista D, Gennari M, Riar J, et al. An assessment of petrosal sinus sampling for localization of pituitary microadenomas in children with Cushing disease. J Clin Endocrinol Metab. 2006;91:221–4.
49. Bonelli FS, Huston 3rd J, Meyer FB, Carpenter PC. Venous subarachnoid hemorrhage after inferior petrosal sinus sampling for adrenocorticotropic hormone. AJNR Am J Neuroradiol. 1999;20:306–7.
50. Patronas N, Bulakbasi N, Stratakis CA, et al. Spoiled gradient recalled acquisition in the steady state technique is superior to conventional postcontrast spin echo technique for magnetic resonance imaging detection of adrenocorticotropin-secreting pituitary tumors. J Clin Endocrinol Metab. 2003;88:1565–9.
51. Sun Y, Sun Q, Fan C, et al. Diagnosis and therapy for Cushing's disease with negative dynamic MRI finding: a single-centre experience. Clin Endocrinol (Oxf). 2012;76:868–76.
52. Coulon G, Fellmann D, Arbez-Gindre F, Pageaut G. Latent pituitary adenoma. Autopsy study. Sem Hop. 1983;59:2747–50.
53. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101:613–9.
54. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med. 1994;120:817–20.
55. Kaskarelis IS, Tsatalou EG, Benakis SV, et al. Bilateral inferior petrosal sinuses sampling in the routine investigation of Cushing's syndrome: a comparison with MRI. AJR Am J Roentgenol. 2006;187:562–70.
56. Yamada S, Fukuhara N, Nishioka H, et al. Surgical management and outcomes in patients with Cushing disease with negative pituitary magnetic resonance imaging. World Neurosurg. 2012;77:525–32.
57. Pecori Giraldi F, Invitti C, Cavagnini F. Inferior petrosal sinus sampling ten years down the road. J Endocrinol Invest. 2000;23:325–7.
58. Pinette MG, Pan YQ, Oppenheim D, Pinette SG, Blackstone J. Bilateral inferior petrosal sinus corticotropin sampling with corticotropin-releasing hormone stimulation in a pregnant patient with Cushing's syndrome. Am J Obstet Gynecol. 1994;171:563–4.
59. Calzolari F, Ambrosio MR, Trasforini G. Diagnosis of Cushing's disease in children: the role of inferior petrosal sinus sampling. Pediatr Radiol. 1995;25:575.
60. Lonser RR, Wind JJ, Nieman LK, Weil RJ, DeVroom HL, Oldfield EH. Outcome of surgical treatment of 200 children with Cushing's disease. J Clin Endocrinol Metab. 2013;98:892–901.
61. Lienhardt A, Grossman AB, Dacie JE, et al. Relative contributions of inferior petrosal sinus sampling and pituitary imaging in the investigation of children and adolescents with ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab. 2001;86:5711–4.
62. Invitti C, Pecori Giraldi F, Cavagnini F. Inferior petrosal sinus sampling in patients with Cushing's syndrome and contradictory responses to dynamic testing. Clin Endocrinol (Oxf). 1999;51:255–7.
63. Yamamoto Y, Davis DH, Nippoldt TB, Young Jr WF, Huston 3rd J, Parisi JE. False-positive inferior petrosal sinus sampling in the diagnosis of Cushing's disease. Report of two cases. J Neurosurg. 1995;83:1087–91.
64. Tabarin A, Greselle JF, San-Galli F, et al. Usefulness of the corticotropin-releasing hormone test during bilateral inferior petrosal sinus sampling for the diagnosis of Cushing's disease. J Clin Endocrinol Metab. 1991;73:53–9.
65. Oldfield EH, Doppman JL, Nieman LK, et al. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. N Engl J Med. 1991;325:897–905.
66. Zarrilli L, Colao A, Merola B, et al. Corticotropin-releasing hormone test: improvement of the diagnostic accuracy of simultaneous and bilateral inferior petrosal sinus sampling in patients with Cushing syndrome. World J Surg. 1995;19:150–3.

67. Colao A, Merola B, Di Sarno A, et al. Corticotropin-releasing hormone administration increases alpha-melanocyte-stimulating hormone levels in the inferior petrosal sinuses in a subset of patients with Cushing's disease. Horm Res. 1996;46:26–32.
68. Kalogeras KT, Nieman LK, Friedman TC, et al. Inferior petrosal sinus sampling in healthy subjects reveals a unilateral corticotropin-releasing hormone-induced arginine vasopressin release associated with ipsilateral adrenocorticotropin secretion. J Clin Invest. 1996;97:2045–50.
69. Schulte HM, Allolio B, Gunther RW, et al. Selective bilateral and simultaneous catheterization of the inferior petrosal sinus: CRF stimulates prolactin secretion from ACTH-producing microadenomas in Cushing's disease. Clin Endocrinol (Oxf). 1988;28:289–95.
70. Strack TR, Schild HH, Bohl J, Beyer J, Schrezemeir J, Kahaly G. Selective bilateral blood sampling from the inferior petrosal sinus in Cushing's disease: effects of corticotropin-releasing factor and thyrotropin-releasing hormone on pituitary secretion. Cardiovasc Intervent Radiol. 1993;16:287–92.
71. Cuneo RC, Lee W, Harper J, et al. Metyrapone pre-treated inferior petrosal sinus sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf). 1997;46:607–18.
72. Torpy DJ, Jackson RV, Grice JE, Hockings GI, Strakosch CR, Topliss DJ. Naloxone stimulation of ACTH secretion during petrosal sinus sampling in Cushing's syndrome. Clin Exp Pharmacol Physiol. 1993;20:299–302.
73. Deipolyi AR, Hirsch JA, Oklu R. Bilateral inferior petrosal sinus sampling with desmopressin. J Neurointerv Surg. 2013;5:487–8.
74. Machado MC, de Sa SV, Domenice S, et al. The role of desmopressin in bilateral and simultaneous inferior petrosal sinus sampling for differential diagnosis of ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf). 2007;66:136–42.
75. Gannage-Yared MH, Slaba S, Rizk T, Chidiac Wehbe RM. Use of desmopressin as an alternative to corticotropin-releasing hormone during inferior petrosal sinus sampling in a child with Cushing's disease. J Endocrinol Invest. 2007;30:434–8.
76. Newell-Price J, Perry L, Medbak S, et al. A combined test using desmopressin and corticotropin-releasing hormone in the differential diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1997;82:176–81.
77. Tsagarakis S, Kaskarelis IS, Kokkoris P, Malagari C, Thalassinos N. The application of a combined stimulation with CRH and desmopressin during bilateral inferior petrosal sinus sampling in patients with Cushing's syndrome. Clin Endocrinol (Oxf). 2000;52:355–61.
78. Tsagarakis S, Vassiliadi D, Kaskarelis IS, Komninos J, Souvatzoglou E, Thalassinos N. The application of the combined corticotropin-releasing hormone plus desmopressin stimulation during petrosal sinus sampling is both sensitive and specific in differentiating patients with Cushing's disease from patients with the occult ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab. 2007;92:2080–6.
79. Findling JW, Kehoe ME, Raff H. Identification of patients with Cushing's disease with negative pituitary adrenocorticotropin gradients during inferior petrosal sinus sampling: prolactin as an index of pituitary venous effluent. J Clin Endocrinol Metab. 2004;89:6005–9.
80. Tanaka K, Shimizu N, Nagata M, Seki T, Nagai J. Identification of source of excessive ACTH production by improved selective venous sampling: simultaneous assay of PRL as a pituitary marker. Endocrinol Jpn. 1984;31:195–200.
81. Lombardi G, Merola B, Miletto P, et al. Plasma prolactin levels in the inferior petrosal sinuses in various pituitary disorders during perihypophyseal phlebography. Neuroendocrinology. 1987;46:333–8.
82. Mulligan GB, Eray E, Faiman C, et al. Reduction of false-negative results in inferior petrosal sinus sampling with simultaneous prolactin and corticotropin measurement. Endocr Pract. 2011;17:33–40.
83. Sharma ST, Raff H, Nieman LK. Prolactin as a marker of successful catheterization during IPSS in patients with ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab. 2011;96:3687–94.

84. Vignati F, Berselli ME, Scialfa G, Boccardi E, Loli P. Bilateral and simultaneous venous sampling of inferior petrosal sinuses for ACTH and PRL determination: preoperative localization of ACTH-secreting microadenomas. J Endocrinol Invest. 1989;12:235–8.
85. Grant P, Dworakowska D, Carroll P. Maximizing the accuracy of Inferior petrosal sinus sampling: validation of the use of Prolactin as a marker of pituitary venous effluent in the diagnosis of Cushing's disease. Clin Endocrinol (Oxf). 2012;76:555–9.
86. McNally PG, Bolia A, Absalom SR, Falconer-Smith J, Howlett TA. Preliminary observations using endocrine markers of pituitary venous dilution during bilateral simultaneous inferior petrosal sinus catheterization in Cushing's syndrome: is combined CRF and TRH stimulation of value? Clin Endocrinol (Oxf). 1993;39:681–6.
87. Oklu R, Deipolyi AR, Wicky S, et al. Identification of small compound biomarkers of pituitary adenoma: a bilateral inferior petrosal sinus sampling study. J Neurointerv Surg. 2014; 6(7):541–6.
88. Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. N Engl J Med. 1985;312:100–3.
89. Yamada S, Shishiba Y, Sawano S, Aiba T. ACTH determination in a petrosal sinus venous specimen after corticotrophin releasing factor provides the best clue on the laterality of microadenoma in Cushing's disease. Endocrinol Jpn. 1989;36:269–74.
90. Manni A, Latshaw RF, Page R, Santen RJ. Simultaneous bilateral venous sampling for adrenocorticotropin in pituitary-dependent Cushing's disease: evidence for lateralization of pituitary venous drainage. J Clin Endocrinol Metab. 1983;57:1070–3.
91. Wind JJ, Lonser RR, Nieman LK, DeVroom HL, Chang R, Oldfield EH. The lateralization accuracy of inferior petrosal sinus sampling in 501 patients with Cushing's disease. J Clin Endocrinol Metab. 2013;98:2285–93.
92. Hendriks MJ, van't Verlaat JW, Koppeschaar HP, Croughs RJ. Inferior petrosal venous sinus sampling in lateralization of ACTH-secreting pituitary microadenomas. N Engl J Med. 1985;312:1457–8.
93. Booth GL, Redelmeier DA, Grosman H, Kovacs K, Smyth HS, Ezzat S. Improved diagnostic accuracy of inferior petrosal sinus sampling over imaging for localizing pituitary pathology in patients with Cushing's disease. J Clin Endocrinol Metab. 1998;83:2291–5.
94. Doppman JL, Oldfield E, Krudy AG, et al. Petrosal sinus sampling for Cushing syndrome: anatomical and technical considerations. Work in progress. Radiology. 1984;150:99–103.
95. Zovickian J, Oldfield EH, Doppman JL, Cutler Jr GB, Loriaux DL. Usefulness of inferior petrosal sinus venous endocrine markers in Cushing's disease. J Neurosurg. 1988;68:205–10.
96. Yanovski JA, Cutler Jr GB, Doppman JL, et al. The limited ability of inferior petrosal sinus sampling with corticotropin-releasing hormone to distinguish Cushing's disease from pseudo-Cushing states or normal physiology. J Clin Endocrinol Metab. 1993;77:503–9.
97. Yanovski JA, Nieman LK, Doppman JL, et al. Plasma levels of corticotropin-releasing hormone in the inferior petrosal sinuses of healthy volunteers, patients with Cushing's syndrome, and patients with pseudo-Cushing states. J Clin Endocrinol Metab. 1998;83:1485–8.
98. Kim LJ, Klopfenstein JD, Cheng M, et al. Ectopic intracavernous sinus adrenocorticotropic hormone-secreting microadenoma: could this be a common cause of failed transsphenoidal surgery in Cushing disease? Case report. J Neurosurg. 2003;98:1312–7.
99. Pluta RM, Nieman L, Doppman JL, et al. Extrapituitary parasellar microadenoma in Cushing's disease. J Clin Endocrinol Metab. 1999;84:2912–23.
100. Heppner C, Becker K, Saeger W, et al. Occult eutopic Cushing's syndrome – failure of simultaneous bilateral petrosal sinus sampling to diagnose pituitary-dependent Cushing's syndrome. Eur J Endocrinol. 1997;137:74–8.
101. Oldfield EH, Vance ML. A cryptic cause of Cushing's disease. J Clin Endocrinol Metab. 2013;98:4593–4.
102. Young J, Deneux C, Grino M, Oliver C, Chanson P, Schaison G. Pitfall of petrosal sinus sampling in a Cushing's syndrome secondary to ectopic adrenocorticotropin-corticotropin releasing hormone (ACTH-CRH) secretion. J Clin Endocrinol Metab. 1998;83:305–8.

103. Merola B, Colao A, Rossi R, et al. Bilateral and simultaneous inferior petrosal sinus sampling in the early diagnosis of an ACTH-producing pituitary microadenoma and its detection by magnetic resonance one year later. Horm Res. 1992;37:64–7.
104. Lopez J, Barcelo B, Lucas T, et al. Petrosal sinus sampling for diagnosis of Cushing's disease: evidence of false negative results. Clin Endocrinol (Oxf). 1996;45:147–56.
105. Mamelak AN, Dowd CF, Tyrrell JB, McDonald JF, Wilson CB. Venous angiography is needed to interpret inferior petrosal sinus and cavernous sinus sampling data for lateralizing adrenocorticotropin-secreting adenomas. J Clin Endocrinol Metab. 1996;81:475–81.
106. Doppman JL, Chang R, Oldfield EH, Chrousos G, Stratakis CA, Nieman LK. The hypoplastic inferior petrosal sinus: a potential source of false-negative results in petrosal sampling for Cushing's disease. J Clin Endocrinol Metab. 1999;84:533–40.
107. Crock PA, Pestell RG, Calenti AJ, et al. Multiple pituitary hormone gradients from inferior petrosal sinus sampling in Cushing's disease. Acta Endocrinol (Copenh). 1988;119:75–80.
108. Park JW, Park S, Kim JL, et al. Bilateral inferior petrosal sinus sampling by unilateral femoral venous approach. Neurointervention. 2011;6:23–6.
109. Deipolyi A, Karaosmanoglu A, Habito C, et al. The role of bilateral inferior petrosal sinus sampling in the diagnostic evaluation of Cushing syndrome. Diagn Interv Radiol. 2012;18:132–8.
110. Harrigan MR, Deveikis JP. Venous procedures. In: Harrigan MR, Deveikis JP, editors. Handbook of cerebrovascular and neurointerventional technique. 2nd ed. New York: Springer; 2013. p. 449–50.
111. Shiu PC, Hanafee WN, Wilson GH, Rand RW. Cavernous sinus venography. Am J Roentgenol Radium Ther Nucl Med. 1968;104:57–62.
112. Doppman JL, Oldfield EH, Nieman LK. Bilateral sampling of the internal jugular vein to distinguish between mechanisms of adrenocorticotropic hormone-dependent Cushing syndrome. Ann Intern Med. 1998;128:33–6.
113. Erickson D, Huston 3rd J, Young Jr WF, et al. Internal jugular vein sampling in adrenocorticotropic hormone-dependent Cushing's syndrome: a comparison with inferior petrosal sinus sampling. Clin Endocrinol (Oxf). 2004;60:413–9.
114. Ilias I, Chang R, Pacak K, et al. Jugular venous sampling: an alternative to petrosal sinus sampling for the diagnostic evaluation of adrenocorticotropic hormone-dependent Cushing's syndrome. J Clin Endocrinol Metab. 2004;89:3795–800.
115. Graham KE, Samuels MH, Nesbit GM, et al. Cavernous sinus sampling is highly accurate in distinguishing Cushing's disease from the ectopic adrenocorticotropin syndrome and in predicting intrapituitary tumor location. J Clin Endocrinol Metab. 1999;84:1602–10.
116. Aoki S, Okubo T, Sasaki Y, et al. Direct cavernous sinus sampling. Radiat Med. 1993;11:196–200.
117. Calzolari F. Evaluation of Cushing disease: cavernous or inferior petrosal sinus sampling? AJNR Am J Neuroradiol. 1998;19:1245–6.
118. Flitsch J, Ludecke DK, Knappe UJ, Grzyska U. Cavernous sinus sampling in selected cases of Cushing's disease. Exp Clin Endocrinol Diabetes. 2002;110:329–35.
119. Fujimura M, Ikeda H, Takahashi A, Ezura M, Yoshimoto T, Tominaga T. Diagnostic value of super-selective bilateral cavernous sinus sampling with hypothalamic stimulating hormone loading in patients with ACTH-producing pituitary adenoma. Neurol Res. 2005;27:11–5.
120. Hayashi N, Kurimoto M, Kubo M, et al. The impact of cavernous sinus drainage pattern on the results of venous sampling in patients with suspected Cushing syndrome. AJNR Am J Neuroradiol. 2008;29:69–72.
121. Kurata A, Suzuki S, Iwamoto K, et al. A new transvenous approach to the carotid-cavernous sinus via the inferior petrooccipital vein. J Neurosurg. 2012;116:581–7.
122. Lefournier V, Martinie M, Vasdev A, et al. Accuracy of bilateral inferior petrosal or cavernous sinuses sampling in predicting the lateralization of Cushing's disease pituitary microadenoma: influence of catheter position and anatomy of venous drainage. J Clin Endocrinol Metab. 2003;88:196–203.

123. Liu C, Lo JC, Dowd CF, et al. Cavernous and inferior petrosal sinus sampling in the evaluation of ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf). 2004;61:478–86.
124. Oldfield EH, Doppman JL. Petrosal versus cavernous sinus sampling. J Neurosurg. 1998;89:890–3.
125. Oliverio PJ, Monsein LH, Wand GS, Debrun GM. Bilateral simultaneous cavernous sinus sampling using corticotropin-releasing hormone in the evaluation of Cushing disease. AJNR Am J Neuroradiol. 1996;17:1669–74.
126. Teramoto A, Nemoto S, Takakura K, Sasaki Y, Machida T. Selective venous sampling directly from cavernous sinus in Cushing's syndrome. J Clin Endocrinol Metab. 1993;76:637–41.
127. Bonelli FS, Huston 3rd J, Carpenter PC, Erickson D, Young Jr WF, Meyer FB. Adrenocorticotropic hormone-dependent Cushing's syndrome: sensitivity and specificity of inferior petrosal sinus sampling. AJNR Am J Neuroradiol. 2000;21:690–6.
128. Doppman JL. There is no simple answer to a rare complication of inferior petrosal sinus sampling. AJNR Am J Neuroradiol. 1999;20:191–2.
129. Boolell M, Gilford E, Arnott R, McNeill P, Cummins J, Alford F. An overview of bilateral synchronous inferior petrosal sinus sampling (BSIPSS) in the pre-operative assessment of Cushing's disease. Aust N Z J Med. 1990;20:765–70.
130. Diez JJ, Iglesias P. Pulmonary thromboembolism after inferior petrosal sinus sampling in Cushing's syndrome. Clin Endocrinol (Oxf). 1997;46:777.
131. Ho FL, Cunanan EC, Wang SC, Mukherjee JJ. Contrast extravasation after bilateral inferior petrosal sinus sampling masquerading as venous subarachnoid haemorrhage. Singapore Med J. 2009;50:e380–3.
132. Kaltsas GA, Newell-Price JD, Trainer PJ, Besser GM, Grossman AB. Complications of inferior petrosal sinus sampling. J Clin Endocrinol Metab. 2000;85:1741.
133. Lefournier V, Gatta B, Martinie M, et al. One transient neurological complication (sixth nerve palsy) in 166 consecutive inferior petrosal sinus samplings for the etiological diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1999;84:3401–2.
134. Sturrock ND, Jeffcoate WJ. A neurological complication of inferior petrosal sinus sampling during investigation for Cushing's disease: a case report. J Neurol Neurosurg Psychiatry. 1997;62:527–8.
135. Miller DL, Doppman JL, Peterman SB, Nieman LK, Oldfield EH, Chang R. Neurologic complications of petrosal sinus sampling. Radiology. 1992;185:143–7.
136. Gandhi CD, Meyer SA, Patel AB, Johnson DM, Post KD. Neurologic complications of inferior petrosal sinus sampling. AJNR Am J Neuroradiol. 2008;29:760–5.
137. Seyer H, Honegger J, Schott W, et al. Raymond's syndrome following petrosal sinus sampling. Acta Neurochir (Wien). 1994;131:157–9.
138. Blevins Jr LS, Clark RV, Owens DS. Thromboembolic complications after inferior petrosal sinus sampling in patients with Cushing's syndrome. Endocr Pract. 1998;4:365–7.
139. Obuobie K, Davies JS, Ogunko A, Scanlon MF. Venous thrombo-embolism following inferior petrosal sinus sampling in Cushing's disease. J Endocrinol Invest. 2000;23:542–4.
140. Vandorpe RA, Fox AJ, Pelz DM, Lee DH. Direct sampling of the cavernous sinus in Cushing's disease. Can Assoc Radiol J. 1994;45:234–7.
141. Trainer PJ, Lawrie HS, Verhelst J, et al. Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment. Clin Endocrinol (Oxf). 1993;38:73–8.
142. Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. J Neurosurg. 2006;104:7–19.
143. Heaney A, Loughrey G, McCance D, et al. Is whole-lung CT scanning still necessary in all cases of ACTH-dependent Cushing's syndrome in the era of petrosal sinus sampling? QJM. 1999;92:335–40.
144. Hernandez I, Espinosa-de-los-Monteros AL, Mendoza V, et al. Ectopic ACTH-secreting syndrome: a single center experience report with a high prevalence of occult tumor. Arch Med Res. 2006;37:976–80.

145. Lad SP, Patil CG, Laws Jr ER, Katznelson L. The role of inferior petrosal sinus sampling in the diagnostic localization of Cushing's disease. Neurosurg Focus. 2007;23:E2.
146. Sugiyama M, Sugiyama T, Yamaguchi M, et al. Successful localization of ectopic ACTH-secreting bronchial carcinoid by selective pulmonary arterial sampling. Endocr J. 2010;57: 959–64.
147. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. J Clin Endocrinol Metab. 2006;91:3746–53.
148. Locatelli M, Vance ML, Laws ER. Clinical review: the strategy of immediate reoperation for transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab. 2005;90:5478–82.
149. Landolt AM, Schubiger O, Maurer R, Girard J. The value of inferior petrosal sinus sampling in diagnosis and treatment of Cushing's disease. Clin Endocrinol (Oxf). 1994;40:485–92.
150. Midgette AS, Aron DC. High-dose dexamethasone suppression testing versus inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome: a decision analysis. Am J Med Sci. 1995;309:162–70.

Chapter 18
Neurointervention and Neuroprotection in Stroke

Aaron P. Tansy and David S. Liebeskind

Introduction

Stroke results in brain injury within an affected vascular territory through a complex interplay and cascade of events that include oxygen deprivation, excitotoxicity, inflammation, and apoptosis causing injury to neurons, CNS supportive cells, and cerebrovascular structures [1]. Therapies that target and interfere with these various stages and pathways of the stroke cascade are considered neuroprotective.

Historically, such therapies have been systemically delivered pharmaceutical and medical agents, the great majority of which have not been proven of benefit in clinical trials [2–23]. With the advent of neurointervention, however, device therapies and options for selective, targeted delivery of medical agents have become available. The modalities continue to be developed and investigated with promising results for neuroprotection in stroke.

In this chapter, we review the major advances and therapies of neuroprotection relevant to the field of neurointervention in the management of stroke. We further look ahead to neurointervention's potential role in neuroprotection's impact on future stroke care.

A.P. Tansy, M.D. (✉)
Department of Neurology, Mount Sinai School of Medicine,
1 Gustave L. Levy Place, Box 1052, New York, NY, USA
e-mail: aaron.tansy@mountsinai.org

D.S. Liebeskind, M.D.
Department of Neurology, University of California, Los Angeles,
710 Westwood Plaza, Los Angeles, CA 90095, USA
e-mail: davidliebeskind@yahoo.com

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_18

Procedural Neuroprotection

Cerebral Embolic Protective Devices

- *Current practices*
  Carotid artery stenting (CAS) is an approved treatment for symptomatic internal carotid artery stenosis and is the preferred intervention in high-risk cardiac patients [24]. Procedure-associated cerebral embolization of plaque (PCEP) from the carotid lesion is a known complication of CAS [25–31]. To prevent distal embolization events (DEE), cerebral embolic protection devices (CEPD) were developed for use in CAS [32, 33]. Although no direct comparison exists between CAS with and without CEPD use, numerous registries and series support CEPD's neuroprotective benefit [34–37]. Historically, these devices were filter-based, but newer systems that utilize flow reversal technology have also become available [27]. Currently, three different types of CEPD are in routine use during CAS: filters, proximal occlusion balloons (POB), and distal occlusion balloons (DOB).

  All devices are introduced after sheath placement. Filters and DOB devices are positioned distally to the carotid lesion treatment area. POB devices with flow reversal are placed proximally to the lesion of interest and are consequently the only devices that provide protected crossing of the stenotic lesion [38]. Filters are commonly favored in practice because of their ease of use, preservation of anterograde flow, and allowance for contrast injection to enable excellent vessel and lesion visualization during CAS [37, 39]. DOB methods, on the other hand, are less in favor due to their associated limitations and risks: interruption of anterograde flow, preclusion of adequate lesion visualization after occlusion, and known procedural risk of severe ischemia [40]. If either balloon occlusion method is chosen, determination of appropriate collateral flow to the brain should first occur to reduce risk of intra-procedural ischemic complications [40].

  Device choice is operator dependent as it is undetermined which ones provide best protection and for which subpopulations of symptomatic internal carotid artery disease they are best indicated. Age, hypertension, lesion morphology, and aortic type have been found to be risk factors for DEE during CAS [41]. Additionally, stent type (open or closed) may also contribute differentially to DEE frequency and severity in CAS [30, 31].

  CEPD may not be considered neuroprotective in all CAS cases. The decision to use a CEPD should be individually based and take into consideration other factors that may lead to poor outcome [34, 37].
- *Investigative practices*
  There are multiple clinical trials currently underway and in the pipeline to investigate the long-term clinical effects of DEE and which device systems may most effectively reduce PCEP/DEE occurrence in CAS:

  – Effects of Carotid Stent Design on Cerebral Embolization [42]
  – Silent Cerebral Infarcts After Carotid Endarterectomy or Stenting and the Risk of Cognitive Decline [43]

- Effects of Cerebral Protection with Filters vs. Flow Reversal on Cerebral Embolization After Carotid Artery Stenting [44]
- Diffusion Weighted-MRI Based Evaluation of the Effectiveness of Endovascular Clamping During Carotid Artery Stenting with the Mo.Ma Device [45]

Magnesium Endovascular Therapy

- Investigative practices
  Magnesium functions in multiple capacities including as an antagonist to the *N*-methyl-D-aspartic acid (NMDA) and calcium channel receptors that aid in limiting ischemic effects. These, in addition to its excellent blood–brain barrier permeability and index of safety, have made it a potential neuroprotective therapy in hyperacute and acute stroke [46–48].

  Although past large trials [7, 8] have not found intravenously delivered magnesium to provide a definite neuroprotective benefit in stroke, targeted delivery through endovascular means may. A multicenter phase I/II safety and feasibility evaluation of intra-arterial delivery of magnesium in endovascular treatment of hyperacute large-vessel occlusive ischemic stroke is currently enrolling patients [49]. In this study, magnesium is locally infused via catheter to the affected vascular territory prior to revascularization. If endovascular delivery of magnesium is determined safe and feasible, its phase III evaluation on clinical outcome is expected. Such evaluations may help determine the role for neurointervention in neuroprotection therapies and approaches in management of hyperacute ischemic stroke.

Nimodipine

- Investigative practices
  Nimodipine's success as an oral/intravenous prophylaxis against subarachnoid hemorrhage (SAH)-related vasospasm has led to its investigative crossover use in the endovascular management of SAH with promising outcomes. In multiple small, single-center series, intra-arterial delivery of nimodipine has been associated with improved clinical and radiographic outcomes especially in cases of refractory vasospasm [50, 51]. Drug delivery is achieved through intra-arterial infusion to the affected cerebral arteries after catheter placement in the relevant internal carotid or vertebral artery. Future trials are necessary to determine the role neurointervention will play in the management of SAH-related vasospasm.

Periprocedural Neuroprotection

Glycemic Regulation

- *Current practices*
  Hyperglycemia in acute stroke carries multiple deleterious effects. It augments multiple neurotoxic pathways of the ischemic cascade exacerbating neuronal injury in acute stroke [1, 52–55]. Furthermore, it worsens stroke-related morbidity and mortality outcomes and may negatively impact clinical responses to and complications of thrombolytic therapies [52–54]. Consequently, euglycemic control has been incorporated into standardized management of acute stroke at stroke centers because of its neuroprotective potential. In line with this, neurointervention periprocedural management for acute ischemic stroke should include a euglycemic goal range. This may be accomplished through adherence to approved protocols of care that address proper diet, intravenous fluids, and indications for aggressive insulin therapy.
- *Investigative practices*
  Although a great deal of evidence supports the neuroprotective benefits of euglycemic maintenance in acute stroke, past large, multicenter trials have shown only nonsignificant clinical benefits of aggressive glycemic regulation [54, 55].

  The Stroke Hyperglycemia Insulin Network Effort (SHINE) is a phase III trial that may finally prove the neuroprotective benefits of euglycemia in acute stroke. The trial is currently enrolling patients to evaluate the role of euglycemic maintenance as a neuroprotective adjunctive therapy to thrombolytic and endovascular therapies in acute ischemic stroke [56, 57]. It is one of a few first-of-its-kind combination therapy studies in acute ischemic stroke and holds promise for improving on the clinical responses and complications seen with acute ischemic stroke therapies.

Hypothermia

- *Current practices*
  Hypothermia is protective against cellular injury through its reduction of energy requirements and limiting of neurotoxic processes [1, 58, 59]. Past trials have supported hypothermia's neuroprotective benefit [59–61] and have led to its use in critical care management of life-threatening neurological disease states such as SAH that may also require neurointervention. Hypothermia may be achieved and maintained through either device-based external or endovascular means. Critical care protocols guide hypothermic indication and management on a site-specific basis. Neurointervention periprocedural management may therefore necessarily include hypothermic regulation if clinically warranted.

- *Investigative practices*
  Although hypothermic regulation and neurointervention are used conjunctively in stroke management, it is undetermined how the two affect one another and clinical outcomes. Multiple clinical trials are currently underway to better understand hypothermia's neuroprotective role in acute stroke treatment apart from and in combination with thrombolytic and endovascular therapies:
  - Reperfusion with Cooling in Acute Cerebral Ischemia (ReCCLAIM) [62]
  - Hypothermia in Acute Ischemic Stroke—Surface Versus Endovascular Cooling (HAISE-SE) [63]
  - A Randomized Trial Comparing 2 Methods for Rapid Induction of Cooling in Stroke Patients (iCOOL 3) [64]
  - Controlled Hypothermia in Large Infarction (CHILI) [65]
  - The Intravascular Cooling in the Treatment of Stroke 2/3 Trial (ICTuS 2/3) [66]

In addition to systemic hypothermic regulation, selective cerebral hypothermic regulation has been considered of potential neuroprotective benefit and has become a possibility because of neurointervention. A single series demonstrated that rapid and effective cerebral hypothermia in isolation was safe and feasible with endovascular infusion of cold saline to a targeted ICA, setting the stage for further clinical testing [67].

Nimodipine Therapy

- *Current practices*
  Nimodipine is an L-type calcium channel antagonist that is one of the few well-established neuroprotective medical therapies in stroke. Indicated for the prevention of neurological injury related to vasospasm following SAH, it is a mainstay oral/intravenous therapy of critical care SAH management and should be used as clinically warranted in cases that include neurointervention therapies as well [68].
- *Investigative practices*
  Results support neuroprotective benefit on outcomes with periprocedural nimodipine in the neurointerventional management of SAH. One small case series showed reduced vasospasm and silent ischemia with long-term intravenous nimodipine after endovascular coiling [69]. Therefore, nimodipine in the periprocedural period appears to benefit neurointervention outcomes in SAH, but its indications and dosing require further evaluation.

Neuroprotection Success in the Future: Neurointervention's Role

Although the field of neuroprotection has made many promising advances at the basic science level, it has enjoyed few successes in the clinical realm. Many reasons likely account for this disparity and extend beyond the scope of this chapter, but certainly include past limitations in translational research design and methodology. Apart from improvements in its translational research, what are some other necessary keys to success for the field? Also, what role does neurointervention play in achieving this success for neuroprotection?

One likely key to neuroprotection's success is a multimodal, combined therapy approach to stroke treatment. As a complex disease state, stroke conceivably requires complex management. While one agent or therapy may not provide a clinically appreciable effect, its use in combination with any number of others may. Successful combined methods of treatment will presumably span not only the pharmacological but also the physiological and mechanical. In addition, the ongoing advent of singular and combined novel therapies and techniques affords a continuous source from which further to develop, refine, and build upon existing multimodal approaches.

Neurointervention appears poised to play an important role in this multimodal approach to neuroprotection. For one, neurointerventional therapies may be readily combined with other systemically delivered or externally based neuroprotective therapies in synergistic fashion. In fact, one recent study showed that intravenous delivery of the neuroprotective agent, NA-1, in the neurointerventional post-procedural period was not only feasible, but even provided a benefit in outcome [70]. Other trials currently investigating the benefits of combining neurointervention with other neuroprotective therapies include:

- SHINE [56, 57]
- Genervon-sponsored evaluation of the neurotropic GM6 [71–73]
- Field Administration of Stroke Therapy—Magnesium (FAST-MAG) [46, 74]

Notably, FAST-MAG is the first-of-its-kind large, multicenter site trial investigating the effects of prehospital administration of a putative neuroprotective agent, magnesium, on stroke outcomes including revascularization treatments. It recently completed enrollment with reported results expected in the near future.

Strategies which augment revascularization and cerebral perfusion may also feasibly be combined with neurointervention in future stroke care. While not traditionally considered neuroprotective, these strategies' promotion of tissue salvage justifies their consideration as such. A few of these in clinical evaluation include:

- Transcranial Doppler ultrasound [75–79]
- Thrombolytic adjunctive agents [80, 81]
- Enhanced external counterpulsation [82–84]
- NeuroFlo dual-balloon occlusive endovascular device [85, 86]

In addition to ease of combination with other therapies, neurointervention also may improve neuroprotection in stroke because it affords selective and targeted treatment strategies. Through endovascular delivery, potential neuroprotective therapies that were traditionally systemically delivered may now be administered to a targeted region of interest. Such precise means of delivery may allow for or enhance a neuroprotective benefit. Examples that have been reported or are under investigation include those previously described:

- Intra-arterial magnesium administration for acute stroke [49]
- Intra-arterial nimodipine administration for SAH-related vasospasm prevention [50, 51]
- Selective induction of cerebral hypothermia [67]

Neuroprotection in stroke management has and will continue to evolve as neurointervention's role in it expands. Current therapies and strategies provide promising support that the two will continue to influence, build upon, and advance one another through multimodal approaches that will improve the field and its impact on the future care of stroke.

References

1. Zukin RS, Jover T, Yokota H, et al. Molecular and cellular mechanisms of ischemia-induced neuronal death. In: Mohr JP, Choi DW, Grotta JC, Wolf P, editors. Stroke: pathophysiology, diagnosis, and management. Philadelphia, PA: Churchill Livingstone; 2004. p. 829–66. Chapter 42.
2. McLean MJ, MacDonald RL. Multiple action of phenytoin on mouse spinal cord neurons in cell culture. J Pharmacol Exp Ther. 1983;227:779–89.
3. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, Diener HC, Ashwood T, Wasiewski WW, Emeribe U, SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med. 2007;357(6):562–71.
4. The RANTTAS Investigators. A randomized trial of tirilazad mesylate in patients with acute stroke (RANTTAS). Stroke. 1996;27:447–53.
5. Rosenberg G, Bornstein N, Diener HC, Gorelick PB, Shuaib A, Lees K, MACSI Investigators. The Membrane-Activated Chelator Stroke Intervention (MACSI) Trial of DP-b99 in acute ischemic stroke: a randomized, double-blind, placebo-controlled, multinational pivotal phase III study. Int J Stroke. 2011;6(4):362–7.
6. Jensen BS. BMS-204352: a potassium channel opener developed for the treatment of stroke. CNS Drug Rev. 2002;8(4):353–60.
7. Muir KW, Lees KR. A randomized, double-blind, placebo-controlled pilot trial of intravenous magnesium sulfate in acute stroke. Stroke. 1995;26:1183–8.
8. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (intravenous magnesium efficacy in stroke trial): randomized controlled trial. Lancet. 2004;363:439–45.
9. The American Nimodipine Study Group. Clinical trial of nimodipine in acute ischemic stroke. Stroke. 1992;23:3–8.
10. Mohr JP, Ogogozo JM, Harrison MJG. Meta-analysis of oral nimodipine trials in acute ischemic stroke. Cerebrovasc Dis. 1994;4:197–203.
11. Horn J, de Haan R, Vermeulen M, Limburg M. Very early nimodipine use in stroke (VENUS). Stroke. 2001;32:461–5.

12. Becker KJ. Anti-leukocyte antibodies: LeukArrest (Hu23F2G) and Enlimomab (R6.5) in acute stroke. Curr Med Res Opin. 2002;18 Suppl 2:s18–22.
13. Bogousslavsky J, Victor SJ, Salinas EO, European-Australian Fiblast (Trafermin) in Acute Stroke Group, et al. Fiblast (trafermin) in acute stroke: results of the European-Australian phase II/III safety and efficacy trial. Cerebrovasc Dis. 2002;14(3–4):239–51.
14. Heiss WD, Brainin M, Bornstein NM, Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators, et al. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. Stroke. 2012;43(3):630–6.
15. Lang W, Stadler CH, Poljakovic Z, Fleet D, Lyse Study Group. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke. Int J Stroke. 2013;8(2):95–104.
16. Lyden P, Jacoby M, Schim J, et al. The clomethiazole acute stroke study in tissue-type plasminogen activator-treated stroke (CLASS-T): final results. Neurology. 2001;57:1199–205.
17. Hoyte L, Barber PA, Buchan AM, Hill MD. The rise and fall of NMDA antagonists for ischemic stroke. Curr Mol Med. 2004;4(2):131–6.
18. Ikonomidou C, Turski L. Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol. 2002;1(6):383–6.
19. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke. 2009;40(12):e647–56.
20. Teal P, Davis S, Hacke W, et al. Modified Randomized Exposure Controlled Trial Study Investigators, Fierus M; Bayer HealthCare AG. A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic effects of a targeted exposure of intravenous repinotan in patients with acute ischemic stroke: modified Randomized Exposure Controlled Trial (mRECT). Stroke. 2009;40(11):3518–25.
21. Kamei K, Maea N, Nomura K, et al. Synthesis, SAR studies, and evaluation of 1,4-benzoxazepine derivatives as selective 5-HT1A receptor agonists with neuroprotective effect: discovery of Piclozotan. Bioorg Med Chem. 2006;14(6):1978–92.
22. Schabitz W, Ali F, Irie K, Sandage Jr BW, Locke KW, Fisher M. Synergistic effects of a combination of low-dose basic fibroblast growth factor and citicoline after temporary experimental focal ischemia. Stroke. 1999;30:427–32.
23. Dávalos A, Alvarez-Sabín J, Castillo J, International Citicoline Trial on acUte Stroke (ICTUS) trial Investigators, et al. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). Lancet. 2012;380(9839): 349–57.
24. Gurm HS, Yadav JS, Fayad P, for the SAPPHIRE Investigators, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med. 2008;358(15):1572–9.
25. Schnaudigel S, Gröschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. Stroke. 2008;39(6): 1911–9.
26. Bonati LH, Jongen LM, Haller S, ICSS-MRI Study Group, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol. 2010;9(4):353–62.
27. Nikas D, Reith W, Schmidt A, Duda S, et al. Prospective, multicenter European study of the GORE flow reversal system for providing neuroprotection during carotid artery stenting. Catheter Cardiovasc Interv. 2012;80(7):1060–8.
28. 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): a prospective randomized trial. J Am Coll Cardiol. 2012;59(15):1383–9.
29. Montorsi P, Caputi L, Galli S, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. J Am Coll Cardiol. 2011;58(16):1656–63.

30. Grunwald IQ, Reith W, Karp K, et al. Comparison of stent free cell area and cerebral lesions after unprotected carotid artery stent placement. Eur J Vasc Endovasc Surg. 2012;43(1):10–4.
31. Tadros RO, Spyris CT, Vouyouka AG, et al. Comparing the embolic potential of open and closed cell stents during carotid angioplasty and stenting. J Vasc Surg. 2012;56(1):89–95.
32. Yadav JS, Wholey MH, Kuntz RE. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351:1493–501.
33. Sievert H, Rabe K. Role of distal protection during carotid stenting. J Interv Cardiol. 2002;15:499–504.
34. Zahn R, Mark B, Niedermaier N. Embolic protection devices for carotid artery stenting: better results than stenting without protection? Eur Heart J. 2004;25:1550–8.
35. Wholey MH, Al Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv. 2003;60:259–66.
36. Kastrup A, Groschel K, Krapf H, et al. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. Stroke. 2003;34:813–9.
37. Ohki T, Veith FJ. Carotid artery stenting: utility of cerebral protection devices. J Invasive Cardiol. 2001;13:47–55.
38. Ohki T, Parodi J, Veith FJ. Efficacy of a proximal occlusion catheter with reversal of flow in the prevention of embolic events during carotid artery stenting. An experimental analysis. J Vasc Surg. 2001;33:504–9.
39. Ohki T, Roubin GS, Veith FJ. Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: an ex vivo analysis. J Vasc Surg. 1999;30:1034–44.
40. Martin JB, Pache JC, Treggiari-Venzi M. Role of the distal balloon protection technique in the prevention of cerebral embolic events during carotid stent placement. Stroke. 2001;32:479–84.
41. Bijuklic K, Wandler A, Varnakov Y, Tuebler T, Schofer J. Risk factors for cerebral embolization after carotid artery stenting with embolic protection: a diffusion-weighted magnetic resonance imaging study in 837 consecutive patients. Circ Cardiovasc Interv. 2013;6(3):311–6.
42. Effects of carotid stent design on cerebral embolization. http://www.strokecenter.org/trials/clinicalstudies/effects-of-carotid-stent-design-on-cerebral-embolization
43. Silent cerebral infarcts after carotid endarterectomy or stenting and the risk of cognitive decline. http://www.strokecenter.org/trials/clinicalstudies/silent-cerebral-infarcts-after-carotid-endarterectomy-or-stenting-and-the-risk-of-cognitive-decline
44. Effects of cerebral protection with filters vs. flow reversal on cerebral embolization after carotid artery stenting. http://www.strokecenter.org/trials/clinicalstudies/effects-of-cerebral-protection-with-filters-vs-flow-reversal-on-cerebral-embolization-after-carotid-artery-stenting
45. Diffusion weighted-MRI based evaluation of the effectiveness of endovascular clamping during carotid artery stenting with the Mo.Ma device. http://www.strokecenter.org/trials/clinicalstudies/diffusion-weighted-mri-based-evaluation-of-the-effectiveness-of-endovascular-clamping-during-carotid-artery-stenting-with-the-moma-device
46. Saver JL, Kidwell C, Eckstein M, Starkman S, FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. Stroke. 2004;35(5):e106–8.
47. Izumi Y, Roussel S, Pinard E, Sylaz J. Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. J Cereb Blood Flow Metab. 1991;11:1025–30.
48. Marinov MB, Harbaugh KS, Hoopes PJ, et al. Neuroprotective effects of preischemia intraarterial magnesium sulfate in reversible focal cerebral ischemia. J Neurosurg. 1996;85:117–24.
49. Intra-arterial magnesium administration for acute stroke. http://www.strokecenter.org/trials/clinicalstudies/intra-arterial-magnesium-administration-for-acute-stroke
50. Wolf S, Martin H, Landscheidt JF, Rodiek SO, Schürer L, Lumenta CB. Continuous selective intraarterial infusion of nimodipine for therapy of refractory cerebral vasospasm. Neurocrit Care. 2010;12(3):346–51.

51. Dehdashti AR, Binaghi S, Uske A, Regli L. Intraarterial nimodipine for the treatment of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage: a preliminary study. Neurol India. 2011;59(6):810–6.
52. Woo J, Lam CW, Kay R, et al. The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Arch Neurol. 1990;47:1174–7.
53. Leigh R, Zaidat OO, Suri MF, et al. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolytic therapy. Stroke. 2004;35:1903–7.
54. Treatment of hyperglycemia in acute stroke. http://www.strokecenter.org/trials/clinicalstudies/treatment-of-hyperglycemia-in-ischemic-stroke/results
55. Gray CS, Hildreth AJ, Sandercock PA, GIST Trialists Collaboration, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6(5):397–406.
56. Southerland AM, Johnston KC. Considering hyperglycemia and thrombolysis in the Stroke Hyperglycemia Insulin Network Effort (SHINE) trial. Ann N Y Acad Sci. 2012;1268:72–8.
57. Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial. http://www.strokecenter.org/trials/clinicalstudies/stroke-hyperglycemia-insulin-network-effort-shine-trial
58. Campos F, Pérez-Mato M, Agulla J, et al. Glutamate excitotoxicity is the key molecular mechanism which is influenced by body temperature during the acute phase of brain stroke. PLoS One. 2012;7(8):e44191.
59. Linares G, Mayer SA. Hypothermia for the treatment of ischemic and hemorrhagic stroke. Crit Care Med. 2009;37(7 Suppl):S243–9.
60. Krieger D, De Georgia M, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, et al. Cooling for acute ischemic brain damage (COOL AID). Stroke. 2001;32:1847–54.
61. Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke. 2001;32:2550–3.
62. Reperfusion with cooling in cerebral acute ischemia II. http://www.strokecenter.org/trials/clinicalstudies/reperfusion-with-cooling-in-cerebral-acute-ischemia-ii
63. Hypothermia in acute ischemic stroke – surface versus endovascular cooling (HAIS-SE). http://www.strokecenter.org/trials/clinicalstudies/hypothermia-in-acute-ischemic-stroke-surface-versus-endovascular-cooling-hais-se
64. A randomized trial comparing 2 methods for rapid induction of cooling in stroke patients, cold infusions vs. EMCOOLS Brain.Pad (iCOOL 3). http://www.strokecenter.org/trials/clinicalstudies/a-randomized-trial-comparing-2-methods-for-rapid-induction-of-cooling-in-stroke-patients-cold-infusions-vs-emcools-brainpad-icool-3
65. Controlled hypothermia in large infarction (CHILI). http://www.strokecenter.org/trials/clinicalstudies/controlled-hypothermia-in-large-infarction
66. The Intravascular Cooling in the Treatment of Stroke 2/3 Trial (ICTuS2/3). http://www.strokecenter.org/trials/clinicalstudies/the-intravascular-cooling-in-the-treatment-of-stroke-23-trial
67. Choi JH, Marshall RS, Neimark MA, Konstas AA, Lin E, Chiang YT, Mast H, Rundek T, Mohr JP, Pile-Spellman J. Selective brain cooling with endovascular intracarotid infusion of cold saline: a pilot feasibility study. AJNR Am J Neuroradiol. 2010;31(5):928–34.
68. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm – a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308(11):619–24.
69. Mijailovic M, Lukic S, Laudanovic D, Folic M, Folic N, Jankovic S. Effects of nimodipine on cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage treated by endovascular coiling. Adv Clin Exp Med. 2013;22(1):101–9.
70. Hill MD, Martin RH, Mikulis D, Wong JH, Silver FL, Terbrugge KG, Milot G, Clark WM, Macdonald RL, Kelly ME, Boulton M, Fleetwood I, McDougall C, Gunnarsson T, Chow M, Lum C, Dodd R, Poublanc J, Krings T, Demchuk AM, Goyal M, Anderson R, Bishop J, Garman D, Tymianski M, ENACT Trial Investigators. Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2012;11(11):942–50.
71. http://www.genervon.com/genervon/science_development.php

72. Yu J, Zhu H, Ko D, Kindy MS. Motoneuronotrophic factor analog GM6 reduces infarct volume and behavioral deficits following transient ischemia in the mouse. Brain Res. 2008;1238:143–53.
73. Efficacy and safety study of GM602 in patients with acute middle cerebral artery ischemic stroke within 18 hours (GMAIS). http://www.strokecenter.org/trials/clinicalstudies/efficacy-and-safety-study-of-gm602-in-patients-with-acute-middle-cerebral-artery-ischemic-stroke-within-18-hours
74. The field administration of stroke therapy – magnesium phase 3 clinical trial. http://www.fastmag.info/
75. Alexandrov AV, Mikulik R, Ribo M, et al. A pilot randomized clinical safety study of sonothrombolysis augmentation with ultrasound-activated perflutren-lipid microspheres for acute ischemic stroke. Stroke. 2008;39(5):1464–9.
76. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med. 2004;351:2170–8.
77. Molina CA, Ribo M, Rubiera M, et al. Microbubble administration accelerates clot lysis during continuous 2-MHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. Stroke. 2006;37:425–9.
78. Nano-bubbles enhanced CLOTBUST treatment for acute ischemic stroke (NANOART). http://www.strokecenter.org/trials/clinicalstudies/nano-bubbles-enhanced-clotbust-treatment-for-acute-ischemic-stroke
79. Phase 3, randomized, placebo-controlled, double-blinded trial of the combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator (tPA) for emergent revascularization in acute ischemic stroke (CLOTBUST-ER). http://www.strokecenter.org/trials/clinicalstudies/phase-3-randomized-placebo-controlled-double-blinded-trial-of-the-combined-lysis-of-thrombus-with-ultrasound-and-systemic-tissue-plasminogen-activator-tpa-for-emergent-revascularization-in-acute-ischemic-stroke
80. Pancioli AM, Broderick J, Brott T, CLEAR Trial Investigators, 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.
81. Study of the combination therapy of rt-PA and eptifibatide to treat acute ischemic stroke (CLEAR-ER). http://www.strokecenter.org/trials/clinicalstudies/study-of-the-combination-therapy-of-rt-pa-and-eptifibatide-to-treat-acute-ischemic-stroke
82. Bonetti PO, Barsness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol. 2003;41(10):1761–8.
83. Luo C, Liu D, Wu G, et al. Effect of enhanced external counterpulsation on coronary slow flow and its relation with endothelial function and inflammation: a mid-term follow-up study. Cardiology. 2012;122(4):260–8.
84. Safety study of external counterpulsation as a treatment for acute ischemic stroke. http://www.strokecenter.org/trials/clinicalstudies/safety-study-of-external-counterpulsation-as-a-treatment-for-acute-ischemic-stroke
85. Hammer MD, Schwamm L, Starkman S, et al. Safety and feasibility of NeuroFlo use in eight- to 24-hour ischemic stroke patients. Int J Stroke. 2012;7(8):655–61.
86. http://www.coaxia.com/europe/neuroflo-product-information/

Chapter 19
Just Over the Horizon: Catheter Delivery of Stem Cell Therapy

Osman Mir and Sean I. Savitz

Introduction

The application of cell-based therapies to brain disorders is an emerging technology for which there is an urgent need [2, 3]. Cell-based therapies are being explored for cerebrovascular disorders such as ischemic stroke, neurodegenerative disorders such as Parkinson's disease and ALS, and traumatic brain and spinal cord injury. In this chapter, we will review studies focused on endovascular delivery of cell-based therapies for ischemic stroke. We then provide a brief overview of cell-based therapies under investigation for other neurological disorders.

Stroke

The only treatment approved by the FDA for acute ischemic stroke is IV tissue plasminogen activator (t-PA); however, only a minority of patients are eligible to receive it [4] because the drug must be administered within 3–4.5 h after symptom

O. Mir, M.D.
Department of Neurology, Texas A&M University, Baylor University Medical Center, 3600 Gaston Ave, Suite 1155, Dallas, TX 75246, USA
e-mail: osmanmir@gmail.com

S.I. Savitz, M.D. (✉)
Department of Neurology, University of Texas Health Science Center, UT-HEALTH, 6431 Fannin, Houston, TX 77030, USA
e-mail: Sean.I.Savitz@uth.tmc.edu

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0_19

onset, according to regulatory guidelines. There are no approved effective treatments to reverse or repair brain damage associated with stroke. New therapeutic approaches using cells, rather than drugs, hold the promise of promoting repair of the injured brain. A growing body of extensive animal data suggests that cell therapies derived from a range of tissues (whether they are embryonic, fetal, or adult) improve neurological outcome in rodent models of stroke [5–10].

Cell Therapies and Mechanisms

Among "cell therapies" there are different types of cells that fall into the categories of embryonic, fetal, and adult cell types, all of which are under development as potential new treatments for neurological disorders.

Multiple mechanisms of actions [11] have been described after intravenous and intra-arterial administration [12, 13] of cell therapies. These mechanisms can be dichotomized into paracrine and immunomodulatory actions. It is highly unlikely that any of the cells used in current cell therapies which are under development will actually differentiate into functional neurons. Therefore, cell transplantation and replacement of damaged tissue are not the principal mechanism of action of current cell therapies.

Most studies support the following mechanisms by which cell therapy works:

Neurogenesis and effects on astrocytes, oligodendrocytes, and axons Some types of cell therapies stimulate the brain parenchyma to secrete neurotropic factors such as basic fibroblast growth factor and brain-derived neurotrophic factor which activate pathways leading to enhanced survival, proliferation, differentiation, and migration of neural progenitor cells [14].

Angiogenesis and neurogenesis Several studies suggest that many types of cell therapies release growth factors that stimulate neurogenesis in the subventricular zone as well as the formation of new blood vessels in the peri-infarct area [15, 16]. Whether these processes underlie recovery promoted by stem cells is unknown. Angiogenesis and neurogenesis are closely interrelated and have been observed in the brains of patients with stroke. In a small study, there was a positive correlation between microvessel density and patient survival [15]. There is increased synthesis of angiogenic growth factors such as FGF-2, PDGF, and VEGF and their receptors in the brain after stroke [10, 16].

Immunologic mechanism In rodent models, the adrenergic response post stroke has been associated with the release of immunological cells from the spleen that contribute to secondary injury and exacerbation of the ischemic lesion. Intravenous umbilical cord blood cells prevent splenic release of immunological cells and decrease secondary injury in the brain [17]. Other cell types may exert similar mechanisms in the spleen [18]. Different types of cell therapies have also been shown to express anti-inflammatory cytokines that may reduce brain damage due to post-stroke inflammation [19].

Pros and Cons of Endovascular Delivery

There are currently multiple early phase studies employing different routes of cell therapy administration: intravenous, intra-arterial (IA), intrathecal, and direct intracerebral transplantation. In stroke, there is debate about which route is optimal. The intravenous route is least invasive, while the endovascular route (1) selectively targets cells to an area of injury within the brain, (2) delivers a more concentrated number of cells at a lower dose to the brain, and (3) bypasses the entrapment of cells in peripheral organs. Overall, IA could lead to better control of cell delivery and cover a greater surface area within the brain at a lower dose compared to other delivery routes. However, there are clear risks that need to be addressed. IA delivery of cells can lead to microvascular plugging and a reduction in cerebral blood flow. This risk likely depends on a number of factors including cell size, number of cells injected, the adhesiveness of the cells, the target arteries involved, and the infusion rate [20, 21].

Types of Stem Cell Therapies

Currently there are different types of stem cells under investigation for neurological disorders [6, 10, 13, 17, 22]. In this chapter we will focus mainly on bone marrow-derived cells as those are the most commonly studied cells in animal models of stroke and in early-stage clinical trials.

MNCs We begin with *bone marrow mononuclear cells* (MNCs). These cells are a mixture of various cell subpopulations including hematopoietic and mesenchymal stem cells as well as various mature cells. MNCs can be rapidly isolated from patients after bone marrow aspiration, permitting autologous applications for patients with acute to subacute stroke. MNCs have been found to reduce inflammatory processes and upregulate various repair mechanisms such as neurogenesis [14, 16, 23, 24]. Several small clinical studies have reported the safety of IA delivery of MNCs in patients with ischemic stroke [25, 26].

Aldehyde dehydrogenase bright (ALDH br) cells A Cytomedix sponsored randomized double-blind study to test the safety and efficacy of autologous ALDH bright cells in patients with recent ischemic stroke has recently completed enrollment. It could be described as the most advanced clinical trial of IA cell therapy to date. ALDH br cells are isolated and sorted from bone marrow MNCs based on the expression of aldehyde dehydrogenase. Stem cells within bone marrow are highly enriched with this enzyme, and therefore ALDH br cells represent a concentrated mixture of different types of stem cells. The trial was conducted in the USA, enrolled patients within 13–19 days after stroke onset, and involved a bone marrow harvest followed 2 days later by intracarotid infusion of autologous ALDH br cells. The control group underwent a sham bone marrow harvest and sham endovascular procedure. The site

of infusion was the distal ICA beyond the ophthalmic takeoff. Patients with greater than 50 % stenosis of the ipsilateral carotid were excluded, but patients who underwent carotid revascularization in the first few days after stroke were eligible for trial participation. After enrollment of 48 patients, there was sufficient power to determine if there was a significant difference in the mRS scale, the primary end point, between the two groups. Brain imaging performed within 24 h of the endovascular procedure assessed safety. The clinical results of this trial have not been released.

MSCs Mesenchymal stem cells are another population of cells with therapeutic activity that can be purified from bone marrow and other tissues such as adipose or umbilical cord blood. MSCs require growth in cell culture and are the main cell type that because of their large size can cause microvascular obstruction and reduced blood flow after intra-arterial injection to the CNS [20, 27]. Therefore, there are many preclinical variables and questions to address before the IA delivery of MSCs can advance to clinical trials for stroke [6, 20, 21, 27]. It will also be important to determine whether IA delivery is more effective at enhancing stroke recovery than IV delivery when procedural risk is taken into consideration. MSCs would have to be allogeneic for an acute study, autologous for delayed study.

Summary of Clinical Trials

1. Type of stem cells under investigation in stroke
   As seen from Table 19.1, most of the current clinical trials are investigating either bone marrow-derived stem cells whether BMMNCs or BMMSCs. There is one trial of adult-derived autologous adipose tissue, but it is unclear whether they will only investigate the endovascular route or will do a combination of IV and IA routes. Most of the ongoing studies to date have not demonstrated any safety concerns. However, they are in the early stages and caution must be used in interpreting these results.
2. Endovascular approach
   Most trials have targeted the MCA or distal internal carotid artery as the principal site of injection. The types of catheters and microcatheters used in these studies are not always reported. We believe that microcatheters should be studied for compatibility with the cell product. There had been initial concern that too small an inner diameter could lead to cell damage during the delivery process. Every clinical trial should complete validation runs to test for biocompatibility as part of regulatory requirements. Various catheters have been tested for their impact on cell viability [12, 27, 28]. However, the functional effects of catheter passage using different types of media and solutions are not very well defined. Our preliminary findings suggest that the media, catheter passage, and exposure to heparin/contrast can play a role in activating certain cytokines released from the cells, and these changes might lead to different functionality of the cells [28]. With regard to needles, based on published reports, it appears that one can use even a 26-gauge needle without damaging the cells [27].

Table 19.1 Neurological disorders in which IA cell delivery is under investigation

Author	Cell type	Patients	Stroke type	Timeline for infusion	Pretreatment/ infusion	Comments
Moniche F et al., Asturias, Spain [201]	Autologous CD34+ bone marrow cells	20	MCA infarct	5–9 days	None/intra-arterial	Phase I/II, single arm, evaluating safety and efficacy
Andre et al., Rio de Janeiro, Brazil [202]	Autologous BMMCs	12	MCA infarct	3 hours to 90 days	Intravenous/ intra-arterial	Phase I, 2 arms (nonrandomized), evaluating safety Completed, no safety issues
Habib et al., London, UK [203]	Autologous CD34+ bone marrow cells	10	Total anterior circulation infarct	Within 7 days 6 months to 5 years	None/Intra-arterial	Phase I/II, single arm, evaluating safety and tolerability Currently recruiting
Aldagen, USA [207]	ALD 401 cells derived from autologous bone marrow	48	MCA infarct	Within 2 weeks	None/intra-arterial	Phase I/II, randomized, double blind, evaluating safety Ongoing, currently recruited more than 25 patients
Morales V et al., Mexico	Autologous adipose-derived stromal cells	10	Ischemic and hemorrhagic stroke	None specified	None/intra-arterial	Open label, nonrandomized

Neurodegenerative Disorders

There are no large-scale trials using stand-alone endovascular approaches to deliver therapeutic cells in neurodegenerative disorders. There has been a randomized controlled trial of 33 patients with multisystem atrophy (MSA) in which MSCs were injected by intra-arterial and intravenous routes [29]. The trial suggested that MSA patients treated with MSCs had a delay in progression of their deficits compared with placebo. However, there were small ischemic lesions found on imaging in the intra-arterial group. Although the clinical significance is unknown, these findings validate concern that IA delivery of certain types of stem cells can cause tissue injury. Before expanding to new trials, further studies are needed to better understand the variables that contribute to tissue injury and how best to reduce these risks. There have also been a few reports of patients with Parkinson's disease (PD) receiving stem cells by IA delivery [30], and a clinical trial is listed on clinicaltrials.gov testing autologous, adipose-derived MSCs by IV and IA routes for patients with PD.

Conclusion

In summary, endovascular delivery of cell-based therapies is currently at an early, investigational stage. A number of practical, scientific, and translational issues need to be better studied, but we anticipate that this mode of delivery will become a preferred approach in the future to administer cells for a wide range of neurological disorders.

References

1. Ifejika-Jones NL, Barrett AM. Rehabilitation – emerging technologies, innovative therapies, and future objectives. Neurotherapeutics. 2011;8:452.
2. Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circ Res. 2011;109:923–40.
3. Chen J, Zhang ZG, Li Y, Wang L, Xu YX, Gautam SC, Lu M, Zhu Z, Chopp M. Intravenous administration of human bone marrow stromal cells induces angiogenesis in the ischemic boundary zone after stroke in rats. Circ Res. 2003;92:692–9.
4. Kleindorfer D, Lindsell CJ, Brass L, Koroshetz W, Broderick JP. National US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. Stroke. 2008;39:924–8.
5. Mattle HP, Savitz SI. Advances in emerging therapies 2010. Stroke. 2011;42:298–300.
6. Savitz SI, Chopp M, Deans R, Carmichael ST, Phinney D, Wechsler L. Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II. Stroke. 2011;42(3):825–9.
7. Honma T, Honmou O, Iihoshi S, Harada K, Houkin K, Hamada H, Kocsis JD. Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Exp Neurol. 2006;199:56–66.

8. Onda T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis JD. Therapeutic benefits by human mesenchymal stem cells (hMSCs) and Ang-1 gene-modified hMSCs after cerebral ischemia. J Cereb Blood Flow Metab. 2007;28:329–40.
9. Savitz SI. Stem cells and stroke: are we further away than anyone is willing to admit? Int J Stroke. 2012;7:34–5.
10. Burns TC, Steinberg GK. Stem cells and stroke: opportunities, challenges and strategies. Expert Opin Biol Ther. 2011;11:447–61.
11. Sahota P, Savitz SI. Investigational therapies for ischemic stroke: neuroprotection and neurorecovery. Neurotherapeutics. 2011;8:434–51.
12. Misra V, Lal A, El Khoury R, Chen PR, Savitz SI. Intra-arterial delivery of cell therapies for stroke. Stem Cells Dev. 2012;21:1007–15.
13. Miller RH, Bai L. Translating stem cell therapies to the clinic. Neurosci Lett. 2012;519:87–92.
14. Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol. 2009;8:491–500.
15. Krupinski J, Kaluza J, Kumar P, Kumar S, Wang JM. Role of angiogenesis in patients with cerebral ischemic stroke. Stroke. 1994;25:1794–8.
16. Font MÀ, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. Curr Cardiol Rev. 2010;6:238–44.
17. Walker PA, Harting MT, Shah SK, Day M-C, El Khoury R, Savitz SI, Baumgartner J, Cox CS. Progenitor cell therapy for the treatment of central nervous system injury: a review of the state of current clinical trials. Stem Cells Int. 2010;2010:369578.
18. Yang B, Schaar K, Hamilton J, Xi X, Mays R, Savitz SI. Abstract 198: The spleen is a pivotal target of functional recovery after treatment with multistem for acute ischemic stroke. Stroke [Internet]. 2014;43(2):A198. Available from: http://stroke.ahajournals.org/cgi/content/meeting_abstract/43/2_MeetingAbstracts/A198. Cited 30 Apr 2014.
19. Guzman R, Choi R, Gera A, De Los Angeles A, Andres RH, Steinberg GK. Intravascular cell replacement therapy for stroke. Neurosurg Focus. 2008;24:E15.
20. Janowski M, Lyczek A, Engels C, Xu J, Lukomska B, Bulte JWM, Walczak P. Cell size and velocity of injection are major determinants of the safety of intracarotid stem cell transplantation. J Cereb Blood Flow Metab. 2013;33:921–7.
21. Janowski M, Engels C, Gorelik M, Lyczek A, Bernard S, Bulte JWM, Walczak P. Survival of neural progenitors allografted into the cns of immunocompetent recipients is highly dependent on transplantation site. Cell Transplant. 2014;23:253–62.
22. Mir O, Savitz SI. Stem cell therapy in stroke treatment: is it a viable option? Expert Rev Neurother. 2013;13:119–21.
23. Bhasin A, Srivastava MVP, Kumaran SS, Mohanty S, Bhatia R, Bose S, Gaikwad S, Garg A, Airan B. Autologous mesenchymal stem cells in chronic stroke. Cerebrovasc Dis Extra. 2011;1:93–104.
24. Zhang R, Zhang Z, Wang L, Wang Y, Gousev A, Zhang L, Ho K-L, Morshead C, Chopp M. Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. J Cereb Blood Flow Metab. 2004;24:441–8.
25. Savitz SI, Misra V, Kasam M, Juneja H, Cox Jr CS, Alderman S, Aisiku I, Kar S, Gee A, Grotta JC. Intravenous autologous bone marrow mononuclear cells for ischemic stroke. Ann Neurol. 2011;70:59–69.
26. Moniche F, Gonzalez A, Gonzalez-Marcos J-R, Carmona M, Piñero P, Espigado I, Garcia-Solis D, Cayuela A, Montaner J, Boada C, Rosell A, Jimenez M-D, Mayol A, Gil-Peralta A. Intra-arterial bone marrow mononuclear cells in ischemic stroke: a pilot clinical trial. Stroke. 2012;43:2242–4.
27. Chua JY, Pendharkar AV, Wang N, Choi R, Andres RH, Gaeta X, Zhang J, Moseley ME, Guzman R. Intra-arterial injection of neural stem cells using a microneedle technique does not cause microembolic strokes. J Cereb Blood Flow Metab. 2010;31:1263–71.

28. Mir O, Parsha K, Yang B, Hanely P, Gee A, Aronowski J, Savitz S. Abstract T P219: customizing the secretomes of mesenchymal stem cells: implications for clinical trials. http://stroke.ahajournals.org (2014). ATP 219.
29. Lee PH, Lee JE, Kim H-S, Song SK, Lee HS, Nam HS, Cheong J-W, Jeong Y, Park H-J, Kim DJ, Nam CM, Lee JD, Kim HO, Sohn YH. A randomized trial of mesenchymal stem cells in multiple system atrophy. Ann Neurol. 2012;72:32–40.
30. Brazzini A, Cantella R, Cruz ADL, Yupanqui J, León C, Jorquiera T, Brazzini M, Ortega M, Saenz LN. Intraarterial autologous implantation of adult stem cells for patients with Parkinson disease. J Vasc Interv Radiol. 2010;21:443–51.

Index

R.C. Edgell et al. (eds.), *Neurointervention in the Medical Specialties*,
Current Clinical Neurology, DOI 10.1007/978-1-4939-1942-0