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Randall C. Edgell
Kara M. Christopher *Editors*

Neurointervention in the Medical Specialties

A Comprehensive Guide

Second Edition

Humana Press

Current Clinical Neurology

Series Editor

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Current Clinical Neurology offers a wide range of practical resources for clinical neurologists. Providing evidence-based titles covering the full range of neurologic disorders commonly presented in the clinical setting, the Current Clinical Neurology series covers such topics as multiple sclerosis, Parkinson's Disease and nonmotor dysfunction, seizures, Alzheimer's Disease, vascular dementia, sleep disorders, and many others. Series editor Daniel Tarsy, MD, is professor of neurology, Vice Chairman of the Department of Neurology, and Chief of the Movement Disorders division at Beth Israel Deaconness Hospital, Boston, Massachusetts.

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The Neurointerventional Toolkit

1

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, flow disruption devices, 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.

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 iliofemoral 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 2000 U heparin in 500 ml of normal saline [3].

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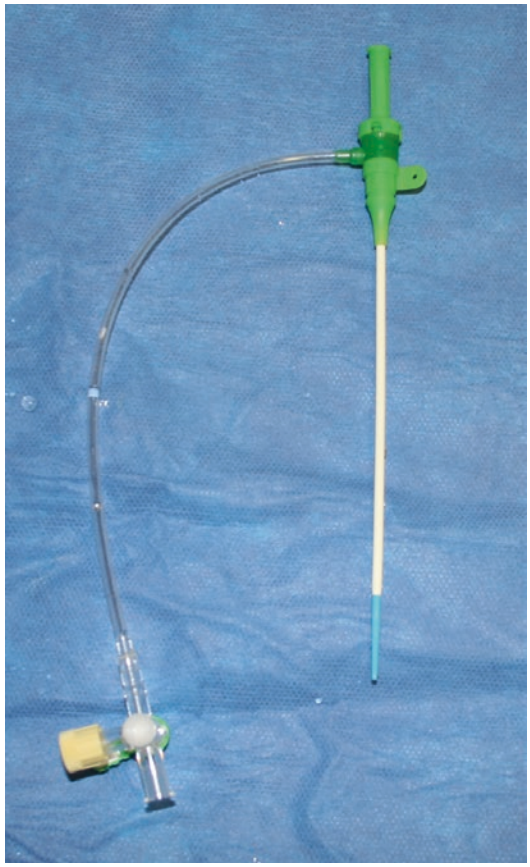

Fig. 1.1 6F femoral sheath

Radial Artery Sheath Types

Coronary catheterization and intervention has largely moved from the transfemoral approach to the transradial approach [4]. This approach is associated with reduced risk of major access site bleeding, vascular injury causing limb ischemia, and is generally preferred by patients as it does not require lengthy periods lying flat. It is also preferred for its efficiency on a systems level as patients can be discharged to home more quickly after elective procedures. Adoption within the neurointervention community has been more gradual, but is gathering momentum [5].

Transradial access platforms have been developed by multiple neuroendovascular vendors. These sheaths allow access to the radial artery over a microwire rather than an 0.035-inch wire. They are designed to minimize the outer diameter while maximizing the inner diameter. This is achieved by thinner wall construction which may be associated with greater fragility and less support. Despite these limitations, the transradial approach is now being used for an expanding number of therapeutic procedures and has largely supplanted the transfemoral approach to diagnostic angiography in many centers [6].

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% [7].

Typically, a 5-French standard catheter is used for cerebral angiography (4 French in children). Catheters should have good torque control, be soft and nontraumatic, 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 such as Simmons II shaped, Headhunter, or Mikaelsson can be used [8].

Guide Catheters, Intermediate Catheters, 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

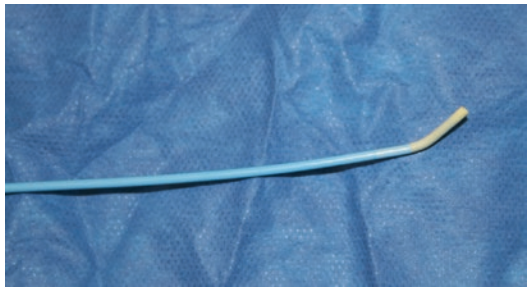

Fig. 1.2 6F Envoy guide catheter. (Credit: DePuy Companies, used with permission)

guidance over a micro-guidewire into the aneurysm. Subsequently, coils are advanced and detached inside the aneurysm [9]. 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.

A new catheter category came into vogue in the mid-2010s: the intermediate catheter [10]. These catheters are placed telescopically through a guide sheath or guide catheter. They have a large enough inner lumen to accommodate commonly used microcatheters, but are flexible/atraumatic enough to be navigated intracranially into the proximal branches of the circle of Willis. These devices have the advantage of providing greater support in the delivery of large and stiffer devices such as flow disruptors or for very distal catheterization as in tortuous arteriovenous malformation pedicles. The current crop of suction thrombectomy catheters (see below) also are of a similar size and construction and may be considered members of this family.

Microcatheters can be hydrophilic or nonhydrophilic, but only hydrophilic microcatheters are recommended since they are proven to be less thrombogenic [11]. 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.; hence, 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 [12]. 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.

Coils can be "filling," "framing," or "finishing." They have different diameters, stiffness pro-

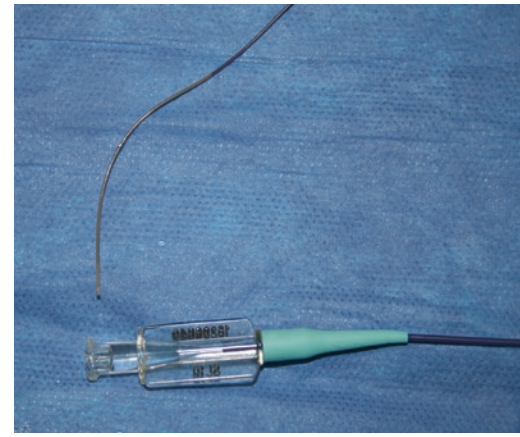

Fig. 1.3 Excelsior® SL-10® microcatheter. (Credit: Stryker, used with permission)

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

file, and geometry that influence their stability within the aneurysm [13].

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 [14]. 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 bare platinum coils with adjunctive polymers polyglycolic acid (PGA), polyglycolic/polylactic acid (PGLA), or hydrogel that have the properties of affecting thrombosis, inflammation, and healing processes within the aneurysm [15]. Theoretically, bioactive coils were expected to produce a more prominent healing response within the aneurysm that resulted in less recanalization. While trial results have been mixed, hydrogel coils have been associated with lower recanalization rates in several well-designed randomized studies [16].

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). 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 [17]. 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 [17]. 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 [18]. 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 tumor embolization. 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 hypervascularized 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 remains controversial [19]. 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 [20]. They provide more stability to the coil mass by holding it in place, and theoretically, they reduce the possibility of recanalization [20]. Early complications include thromboembolism, and, in a late setting, stent stenosis and occlusion of the parent vessel can rarely occur [21] (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.

Intracranial stents for atherosclerotic stenosis (ICAD) are rarely used at present due to the superior results seen with aggressive medical management in the SAMMPRIS trial [22]. The device utilized in this trial, the *Wingspan Stent* (Boston Scientific, Boston MA), remains the only FDA-approved device for the treatment of ICAD refractory to aggressive medical management. It is based on the Neuroform platform and is also of a self-expanding nitinol construction. The device has since been studied in the WEAVE prospective registry which showed low complication rates when used on-label, but conversely high complications when used off-label [23]. The use of coronary stents and aneurysm scaffolding stents for ICAD has also been described, but the lack of rigorous randomized studies makes efficacy unproven.

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 [21, 24]. 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 [21]. The potential complications reported have been embolic events, stent thrombosis, delayed aneurysm rupture, and in-stent stenosis [21, 25].

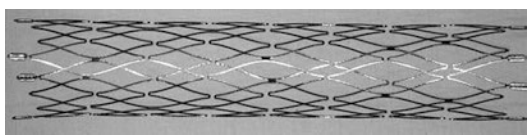

Fig. 1.5 Neuroform Atlas® stent system. (Credit: Stryker, used with permission)

Endosaccular flow disruptors are part of a new family of devices designed to be deployed within the aneurysm sac rather than the parent vessel. Like flow diverters, they are constructed of a woven wire mesh but they are basket-like devices rather than being cylindrical. They are particularly effective in bifurcation aneurysms where coil recanalization is a common problem. The first device to market in the USA is the Woven EndoBridge (WEB; Microvention) [26]. At present, these devices, while effective, are delivered through relatively large and stiff microcatheters. They will undoubtedly become more easily delivered over time, and their applications will likely expand to other aneurysm types.

Cervical carotid stenting is a 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 advanced past the stenotic area and then deployed. This is followed by an over the wire 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 can be followed by a second angioplasty procedure to fully expand the stent if needed [1]. Carotid stents are also commonly constructed of nitinol and often taper, with the proximal end conforming to the larger common carotid diameter, while the distal end is smaller to better match the diameter of the internal carotid artery.

Mechanical Clot Retrievers

Mechanical clot retrievers and aspiration catheters are used as an alternative or in combination with pharmacological thrombolytic agents in the setting of acute ischemic stroke. This is an established treatment for large-vessel occlusion strokes. There are currently multiple devices available commercially, and they can be categorized according to their mode of action into two main groups, aspiration or 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 a large bore catheter which is attached to a power aspiration pump. A major advantage of these devices is that they work at the proximal edge of the clot, and therefore, there is no need to pass through the thrombus. They are effective with soft or intermediate clots but could have more difficulty with firm fibrinous clots.

Retrieval devices, on the other hand, consist of a microcatheter containing a stent retrieval device which is passed distal to the thrombus. The microcatheter is then retracted, and the stent retrieval device is unsheathed. The stent device traps the clot within its struts and when pulled out removes it from the vessel [27]. The use of a balloon guide catheter in association with this technique can reduce the risk of clot embolization during retrieval to otherwise unaffected vessels. These devices can be used independently or in combination to achieve clot retrieval.

Trevo (Stryker, Kalamazoo, Michigan) and Solitaire (Medtronic, Irvine, California) are examples of available stent retrievers in the USA. Trevo is a stent-like device designed to integrate the clot into its structure, allowing it to retract both the device and clot from the blood vessel. The Solitaire is also a self-expanding nondetachable stent that acts in a similar way, incorporating the clot and allowing to completely retrieve it [28]. In 2012, Mendonca et al. published their results comparing both devices, and their study showed no significant differences between them [28].

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

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].

For radial access procedures no endovascular closure devices are available. However, hemostasis can generally be effectively achieved through the application of external pressure over the arteriotomy using a bracelet-like device with an inflatable bladder. After initial application, the bladder is slowly deflated over time until the device can be removed.

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Neurovascular Anatomy

2

Weston R. Gordon and Randall C. Edgell

Arterial Supply of the Head and Neck

Aortic Arch

The three main branches of the aortic arch are the brachiocephalic artery (sometimes referred to as the innominate artery), the left common carotid artery (CCA), and the left subclavian artery (SCA). The best angiographic visualization of the origins of the great vessels is obtained from a left anterior oblique (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 left CCA seen in about one-fourth of patients. Another variant includes the left CCA arising directly from the brachiocephalic artery in about 7% of patients. More rare variants include the left CCA and left SCA sharing a common trunk and the left vertebral artery (VA) originating directly from the arch. There are also several anomalies of the aortic arch. Anomalies refer to the persistence, migration, or interruption of one or more of the embryonic arches at an abnormal location and are most commonly errors of laterality or level of interruption. The most common among these is an aberrant right SCA arising directly from the left aortic arch instead of as a continuation of the brachiocephalic trunk. Some of these anomalies, such as the bitruncus arch, may cause symptoms by forming a compressive vascular ring [2] around the trachea and can be associated with cyanotic congenital heart disease.

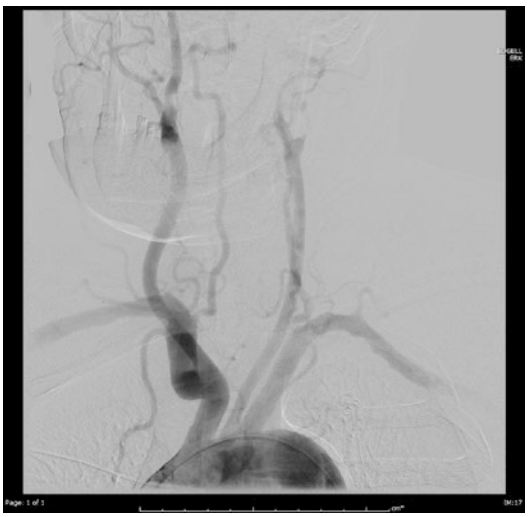

Fig. 2.1 Left anterior oblique projection of the standard aortic arch configuration

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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, terminating at the level of the parotid gland by dividing into its two main distal branches. Multiple angiographic projections may be required to view the ECA and its branches well.

The ECA has eight branches (Fig. 2.4):

1. Superior Thyroid Artery (STA)—typically is the first ECA branch, although occasionally it can arise directly from the carotid bifurcation. It supplies the larynx and superior aspect of the thyroid gland.

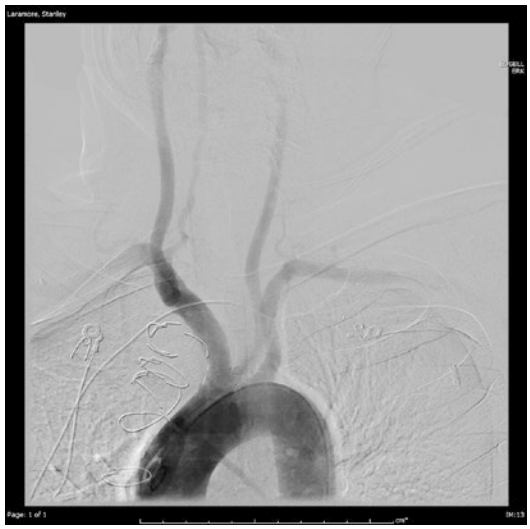

Fig. 2.2 Left anterior oblique projection of the bovine aortic arch variant

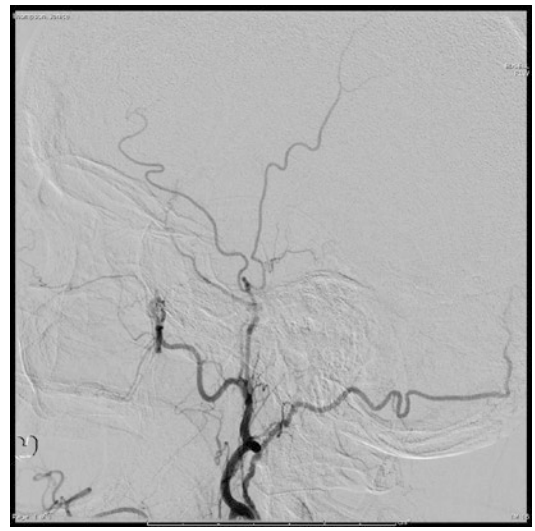

Fig. 2.4 Lateral projection images of the external carotid artery branches

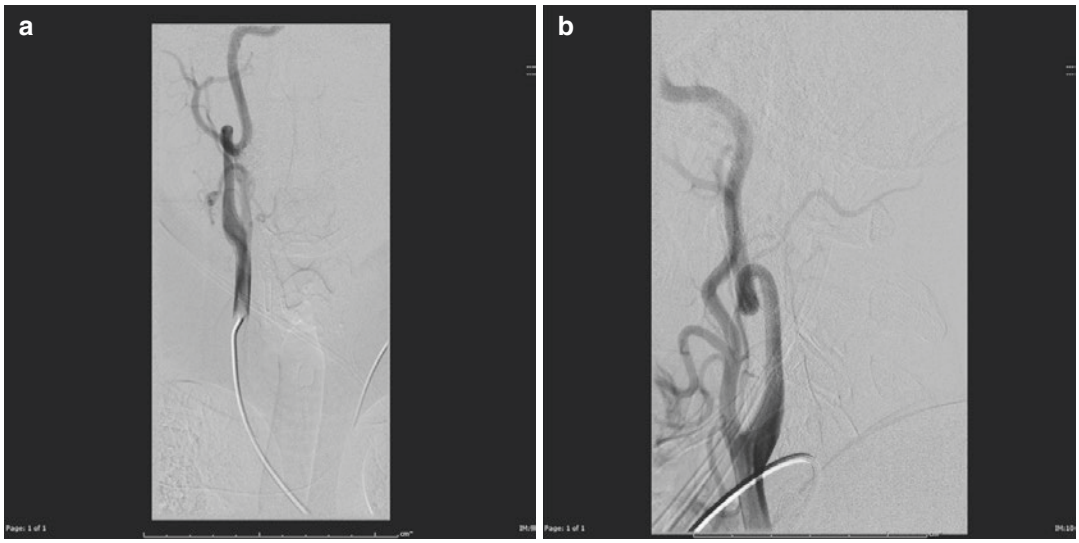

Fig. 2.3 External carotid artery in the anteroposterior (**a**) and lateral (**b**) projections

2. Ascending Pharyngeal Artery (APA) [3]—it is the first posterior branch and supplies the pharynx and middle ear. Similar to the STA, it occasionally originates from the carotid bifurcation. The neuromeningeal branch is an important branch supplying the dura and lower cranial nerves.
3. Lingual Artery (LA)—supplies the tongue and the oral cavity and anastomoses with other ECA branches. It has a distinctive U-shaped appearance.
4. Facial Artery (FA)—courses superolaterally supplying the face and terminates near the medial canthus of the eye, where it becomes the angular artery. At this point the FA *anastomoses with the orbital branches of the ICA*.
5. Occipital Artery—courses posterosuperiorly to supply the scalp and posterior aspect of the neck. There are numerous muscular and segmental branches that *anastomose with branches of the VA* and on occasion may arise directly from the VA.
6. Posterior Auricular Artery (PAA)—small branch that supplies the scalp, pinna, and external auditory canal. The chorda tympani is supplied by an important branch, the stylomastoid artery.
7. Internal Maxillary Artery (IMA)—the larger of the two terminal ECA branches and supplies the nose. It can further be subdivided into three segments. The mandibular (proximal) segment is where the largest branch of the IMA, the middle meningeal artery (MMA), originates. The pterygoid (middle) segment gives rise to the deep temporal arteries. The pterygopalatine (distal) segment terminates as the sphenopalatine arteries and supplies the nose. It also gives rise to the infraorbital artery that supplies the lower eyelid and parts of the cheek and nose. The greater palatine artery arises from this segment and supplies the soft palate and tonsils [4, 5].
8. Superficial Temporal Artery (STA)—the smaller of the two terminal ECA branches and supplies the anterior two-thirds of the scalp, part of the ear, and parotid gland. It often serves as the origin for the transverse facial artery, an important anastomosis with the FA and IMA.

External Carotid: Internal Carotid Anastomoses

1. The APA anastomoses with the ICA through the inferolateral trunk, the Vidian artery, and the caroticotympanic artery.
2. The FA anastomoses with the ICA via the ophthalmic artery through branches of the angular artery near the medial canthus (Fig. 2.5). This anastomosis serves as part of an important hemodynamic balance along with the ipsilateral IMA, transverse facial, ophthalmic, and LA.
3. The stylomastoid branch of the PAA anastomoses with the caroticotympanic branch of the ICA as well as with branches from the MMA.
4. The IMA 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 channels can lead to complications during head and neck embolization procedures. The MMA may anastomose with branches from the cavernous segment of the ICA and can be an important source of collateral flow in carotid bulb atherosclerosis.

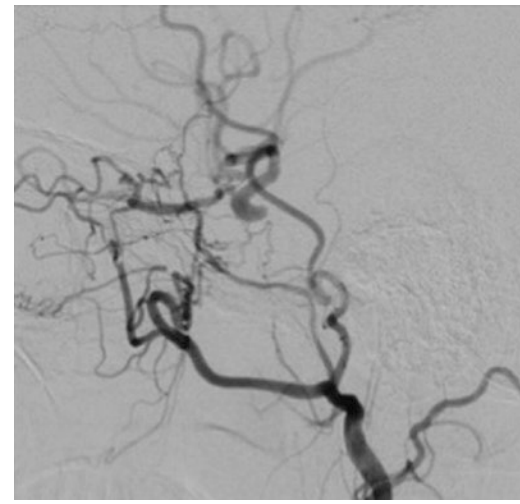

Fig. 2.5 Lateral projection images demonstrating the anastomotic connection between the angular branch of the facial artery and the ophthalmic artery

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

Internal Carotid Artery

There are various classification systems of the segments of the ICA. A widely adopted system proposed by Bouthillier [8] divides the ICA into the following seven segments:

Cervical (C1)

The ICA usually originates from the CCA at C3–C4 level. This segment has two distinct parts:

- The carotid bulb—a dilated segment with a complex flow dynamic and is a frequent site for the development of atherosclerotic disease.
- The ascending cervical segment—from the bulb it courses upward within the carotid space. At this point blood flow has returned to a more typical laminar pattern. 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 from an acquired occlusion of a normally developed vessel [9]. Fetal anastomoses can fail to obliterate following development of the posterior communicating artery. Two of these can connect the cervical ICA to the vertebrobasilar system: the persistent hypoglossal artery, which may connect to the basilar artery, and the proatlantal intersegmental artery, which may anastomose with the vertebral artery.

Petrous (C2)

The petrous ICA enters the temporal bone just anterior to the internal jugular vein and 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) and is an important anastomotic connection between the ICA and the IMA. 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 when significant bleeding during middle ear surgery is encountered. 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].

Lacerum (C3)

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.

Cavernous (C4)

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 CN III, IV, V1, and V2 run lateral to it within the dural wall, whereas CN VI runs inferolaterally and lies free in the cavernous sinus. 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.

The posterior genu gives off the posterior trunk, or the meningohypophyseal artery, and is often seen angiographically. 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. 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, supplies CN III, IV, and VI as well as the dura of the cavernous sinus. It anastomoses with the IMA through the artery of the foramen rotundum. 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 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 (PTA), which is the most common carotid–basilar anastomotic anomaly [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 fistula formation [13].

Clinoid (C5)

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.

Ophthalmic (C6)

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. The 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]. Lastly, the 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 segment are the superior hypophyseal arteries. The C6 segment completes the S-shaped carotid siphon by curving upward and backward and is best visualized on lateral views on angiography [16].

Communicating (C7)

The C7 segment is the terminal ICA segment and begins proximal to the posterior communicating artery (PComm) and ends at the ICA bifurcation into the anterior and middle cerebral arteries. The first major branch from this segment is the PComm that arises from the posterior aspect of the ICA, runs above CN III, and gives off several of the more anterior thalamoperforating arteries. An important anatomical variant occurs when the PComm supplies the entire ipsilateral PCA territory in the absence of a P1 segment, a so-called fetal PCA (Fig. 2.6). Another frequently encountered variant is a dilatation at the origin of the PComm 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 parts of the lateral geniculate body, 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 the AChA arises proximally to the PComm.

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 typically include the internal carotid arteries, anterior cerebral

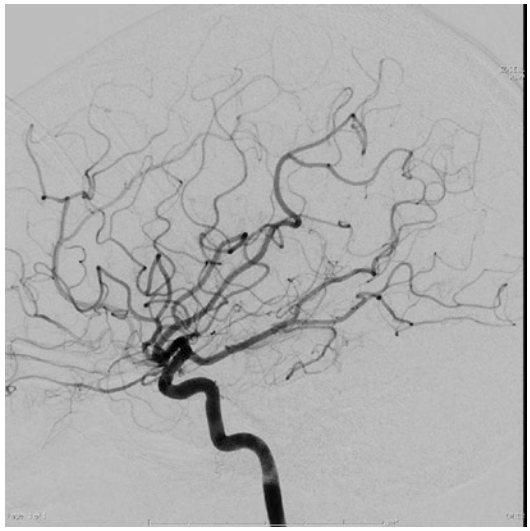

Fig. 2.6 Lateral projection images of a fetal posterior cerebral artery anatomical variant

arteries (A1 segments), anterior communicating artery (AComm), PComm, posterior cerebral arteries (P1 segments), and the basilar artery (BA). A complete COW is present in less than 50% of all cases, and anatomic variants are common [17].

The A1 segment may be hypoplastic (10%) or absent (1–2%). There may be duplicated or fenestrated anterior communicating arteries. A plexiform AComm is one in which multiple channels are 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 of the COW. The ACA gives rise to the recurrent artery of Heubner and the medial lenticulostriate arteries. The AComm itself gives rise to small perforating branches that supply the optic chiasm and parts of the corpus callosum. The PComm gives rise to numerous anterior thalamoperforators, which supply the thalamus and the optic tracts. The posterior thalamoperforators arise from the distal BA and P1 segments, which supply the midbrain and thalamus.

Anterior Cerebral Artery

The A1, or 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 it extends from the ACA origin to its junction with the AComm. The A2, or postcommunicating 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 numerous 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 AComm.

The distal ACA and cortical branches 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. The main ACA trunk is represented distally as the pericallosal artery and curves around the corpus callosum. It gives off the callosomarginal artery, and then the most distal group of branches are the parietal branches. 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, or horizontal segment, originates at the ICA bifurcation and then

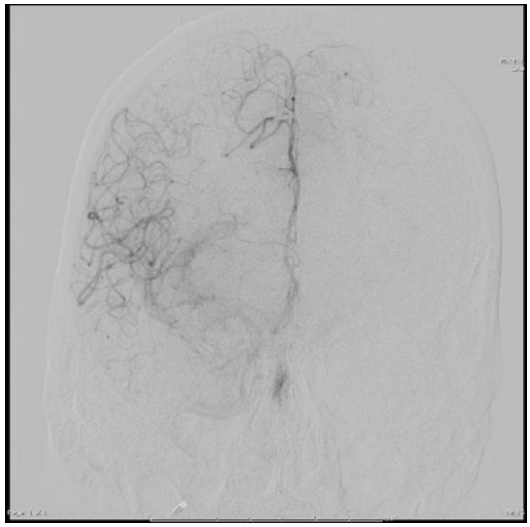

Fig. 2.7 Anteroposterior projection images of the pericallosal and callosomarginal branches of the anterior cerebral artery

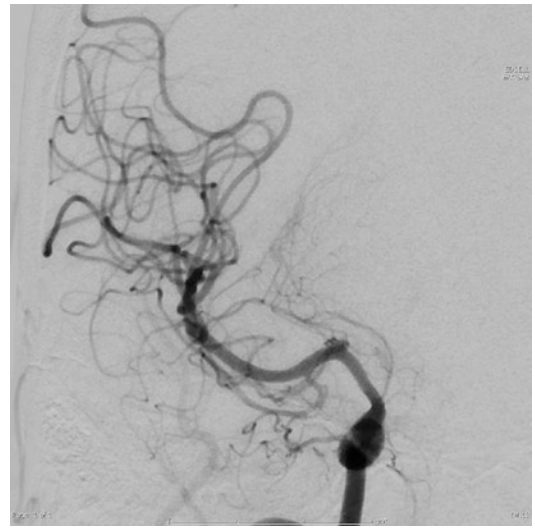

Fig. 2.8 Anteroposterior projection images of the middle cerebral artery

courses laterally till the limen insulae where the MCA branches begin to turn upward. Proximal to the MCA genu, the M1 segment gives off two groups of penetrating branches, the medial and lateral lenticulostriate arteries. The M2, or insular segments, start as the MCA turns posterosuperiorly at the genu. They are comprised of six to eight branches that lie over the insula. The M3, or opercular segments, course laterally within the Sylvian fissure. The M4, or cortical segments, begin as they surface from the Sylvian fissure and then take varying courses to the cortical areas they supply [20].

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 temporo-occipital 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 neurointerventional procedures as its relatively straight course allows for better distal wire access during thrombectomies of the middle cerebral artery. These cortical branches terminate as small pial anastomoses with the distal branches of the anterior and posterior cerebral arteries at the so-called "watershed" vascular zones.

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 at the basilar artery bifurcation (Fig. 2.9a) in the interpeduncular cistern and is divided into four segments [22]. The P1, or pre-

communicating segment, starts at the basilar bifurcation and extends to its junction with the PComm. From this point, the P2, or 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, or quadrigeminal segment, extends from the quadrigeminal plate to the calcarine fissure. The P4, or calcarine segment, is the terminal segment within the calcarine fissure and includes the cortical branches of the PCA.

Several perforating branches, the thalamoperforators and thalamogeniculates, arise from the P1 and P2 segments, respectively. Two main choroidal arteries, the medial posterior choroidal artery and the lateral posterior choroidal artery, arise from the P2 segment and are well visualized on the lateral projection. The lateral posterior choroidal arteries *anastomose with the medial posterior choroidal artery as well as the anterior choroidal artery*, a branch of the ICA. The first cortical branches arise from the P2 segment and are the anterior and posterior temporal arteries. The P3 segment 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 parieto-occipital artery that supplies the brain adjacent to the parieto-occipital 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 course posterosuperiorly to enter the C6 transverse foramen. The vertebral artery ostium is frequently affected by atherosclerotic disease in posterior circulation strokes [24]. The origin of vertebral arteries may be variable, though most often they arise from the superior aspect of the subclavian. The subclavian

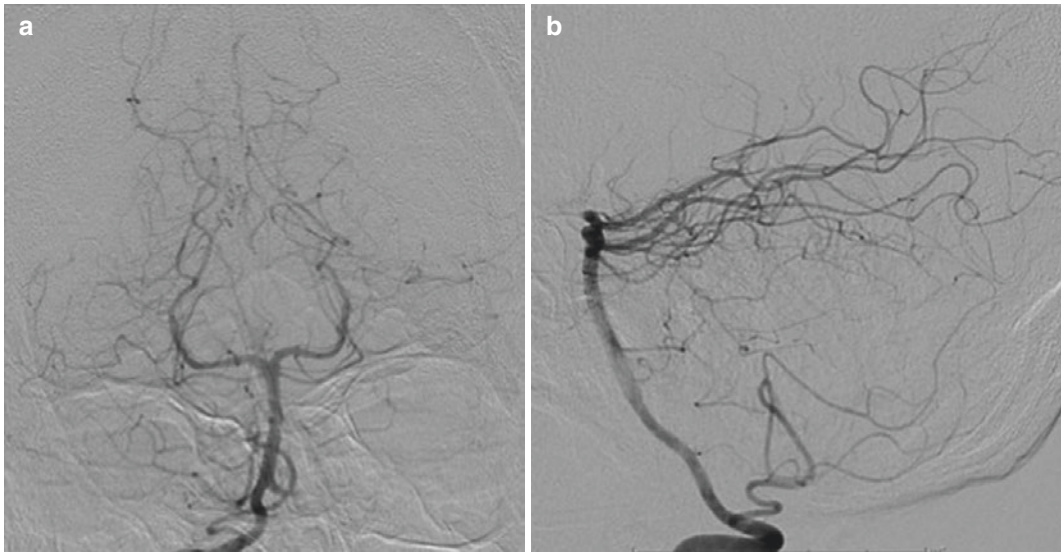

Fig. 2.9 Anteroposterior (**a**) and lateral projection (**b**) images of the posterior cerebral arteries

artery may overlap with the vertebral artery origin on a straight AP projection due to variability at the origin and may be difficult to visualize angiographically. The V2 (foraminal) segment then ascends cephalad from the C6 to the C2 transverse foramina and turns laterally as it exits from C1. As the segment ascends it gives off multiple muscular branches that supply the cervical musculature. The anterior meningeal artery is a branch that arises from the distal V2 segment and supplies part of 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 posterior meningeal artery branches off just below the foramen magnum and supplies the falx cerebelli and additional parts of the dura. 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].

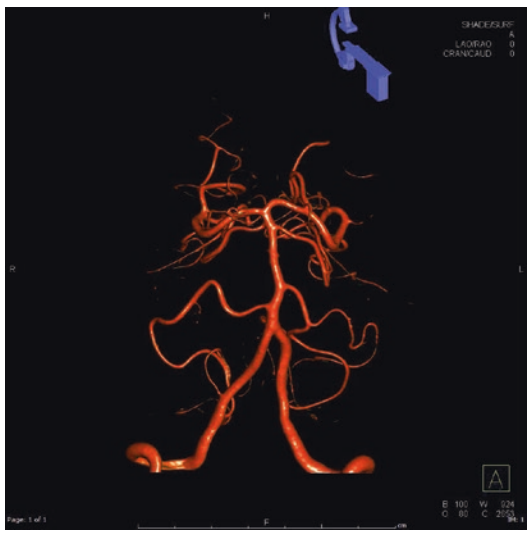

Fig. 2.10 3D angiogram of the vertebrobasilar system

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 with spinal radicular arteries that continues inferiorly along the spinal cord. The anterior spinal artery (ASA) also arises from the distal VA. It gives off a small number of perforators that supply the anterior medulla before uniting with its contralateral counterpart and then runs caudad, supplying the anterior two-thirds of the spinal cord.

The largest 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 and characteristically loops caudally just lateral to the medulla. 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 an extradural origin of the PICA, which is of important consideration during posterior fossa surgeries. More rare variants include a duplicated PICA and a VA 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 within the prepontine cistern 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. 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. The AICA supplies the anterolateral surface of the cerebellum. It is also an important source of labyrinthine branches, and an AICA stroke may present with unilateral sensorineural hearing loss [26]. 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 fenestration of the vessel. Persistent embryonic connections, such as a primitive trigeminal, persistent otic, persistent hypoglossal, or proatlantal intersegmental artery, may result in carotid–basilar anastomotic channels.

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 and connects with the pterygoid venous plexus. The pterygoid plexus anastomoses with the cavernous sinus and deeper pharyngeal venous plexus eventually draining into the internal jugular vein (IJV). The IJV drains blood from the skull and brain and subsequently forms the brachiocephalic vein in combination with the subclavian vein [28], whereas the external jugular vein drains the scalp, pinna, and deep face veins.

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 and collect blood from the cerebral veins, meninges, and calvarium.

The superior sagittal sinus (SSS) (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 torcular Herophili, or confluence of sinuses, 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 (ISS) 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 (SS) [30] (Fig. 2.11) which then courses posteroinferiorly and receives tributaries draining the vermis. The SS also terminates in the torcular Herophili, which is formed by the confluence of the SS and SSS, and is well visualized on the AP projection. The transverse sinuses (TS) receive blood from SS and SSS as well as tributaries from the cerebellum and temporal and occipital lobes. It also

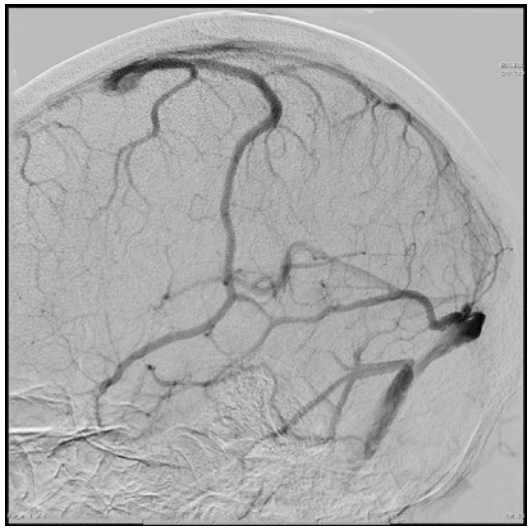

Fig. 2.11 Lateral projection images of the dural sinuses, cortical veins, and deep cerebral veins

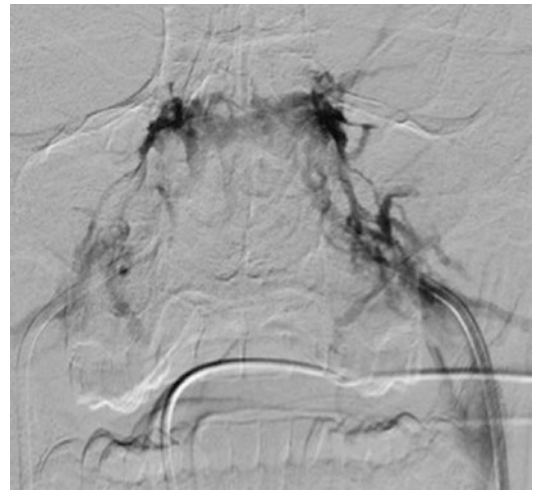

Fig. 2.12 Anteroposterior images of the cavernous and circular sinuses

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 (CS) (Fig. 2.12) 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 receives the superior and inferior ophthalmic veins and communicates with the pterygoid plexus inferiorly. The CS drains into the superior and inferior petrosal sinuses which eventually terminate by draining into the jugular bulb.

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 torcular 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.

The Cerebral Veins

The cerebral veins are further subdivided into the following:

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 outward like spokes of a wheel. There are three prominent veins which are named:
   (a) The superficial middle cerebral vein (SMCV)—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 Labbé—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 the following [33]:
   (a) Medullary veins—small deep veins which course along the walls of the lateral ventricles and drain into subependymal veins. 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 (ICV). 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 terminate by joining with each other as well as the basal veins to form the great cerebral vein of Galen that curves just underneath the splenium. The basal veins of Rosenthal (BVR) are deep veins that are formed by the coming together of anterior and deep middle cerebral veins. The ICVs and BVRs form the vein of Galen that terminates by joining the ISS to form the SS.
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.

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3 Intensive Care of the Neurointerventional Patient

Joanna I. Ramiro

Introduction

The fields of neurointervention and neurocritical care have both grown exponentially over the last few decades. 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 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.

Pre-procedural Care

Fasting

Pre-procedural fasting (NPO or *nulla* per os) reduces the risk of gastric regurgitation, which can lead to vomiting and aspiration. 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 for at least 2 h prior to elective procedures and at least 6 h for meals [1]. These recommendations are meant for healthy individuals only, and modifications must be made 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

Fluids should be administered for patients with adequate renal and cardiac function at a rate of 30 ml/kg/day. 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

Contrast media mediates renal toxicity via direct cytotoxicity to the renal endothelial and tubular cells, which leads to oxidative stress, hypoxia, and further tubular damage [3]. The risk of

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Table 3.1 Summary of 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 3–5 days after contrast exposure	If ≥2 risk factors for contrast nephropathy, NAC 600–1200 mg PO Q12 h × four doses pre-procedure and/or 1–1.5 ml/kg/h isotonic solution 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. Unstable vital signs. 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 and vital sign 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 Vascular surgery consult
Stroke thrombectomy Intracranial hemorrhage (ICH) Herniation or ICP crisis	Frequent neurological examination BP management 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), lower TICI scores Sustained ICP >22 mmHg with neuro worsening Anisocoria	CT scan with or without CT angiogram if exam changes Complete recanalization—SBP range 120–140 mmHg Partial/failed recanalization—BP range more liberal Prompt reversal of anticoagulation; consider checking fibrinogen levels with FFP ± platelet transfusion Head elevation to 30° Consider prophylactic hypernatremia using hypertonic saline Mannitol (average 1 g/kg) Q6 h. monitor osmolar gap and renal function Neurosurgery consultation for potential decompression or EVD placement For acute herniation: Hyperventilate to maintain PaCO2 ~ 30 mmHg; bolus mannitol 1–1.5 g/kg or 23.4% NaCl
Subarachnoid hemorrhage Vasospasm Increased ICP management	Frequent neurological examination Commonly seen 3–21 days post-aSAH Neurological deterioration Sustained ICP >22 mmHg with neuro worsening	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 Seizure prophylaxis Diagnostic angiogram or CT/MR angiography Induce hypertension using boluses with or without vasopressor For sustained vasospasm, use intra-arterial vasodilator and/or angioplasty ICP management as above

Table 3.1 (continued)

Condition	Synopsis of clinical condition and monitoring	Synopsis of management
Carotid artery stenting 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 Periprocedural MI high ~1.3% Periprocedural stroke risk ~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 0.5 IV 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 to rule out ICH CT angiography or conventional angiography to investigate in-stent thrombosis versus intraluminal occlusion Consider emergent intra-arterial tPA or mechanical thrombectomy Maintain normotension Symptomatic headache therapy Symptomatic seizure therapy
Intracranial embolization procedures Hemorrhagic complications Ischemic complications Seizure	Frequent neurological examination Neurological deterioration Iatrogenic secondary to catheter-induced emboli Common occurrence ~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 antiepileptics

NAC n-acetylcysteine, *ICP* intracranial pressure, *AVF* arteriovenous fistula, *SBP* systolic blood pressure

contrast-induced nephropathy (CIN) is higher in older patients and those with diabetes, chronic kidney disease, preexisting renal insufficiency, congestive heart failure, acute MI, and cardiogenic shock. CIN is defined as a rise in absolute serum creatinine of 0.5 mg/dl or an increase of 25% from baseline value. This is typically seen 2–5 days after contrast exposure and may persist for 2 weeks or longer. This can be a serious event, resulting in significant morbidity and mortality. The treatment for CIN consists of supportive measures [4], and prevention is the best strategy. The risk of CIN is less with a smaller amount of contrast and using iso-osmolar, dimeric, nonionic contrast [5]. Hydration with 1 ml/kg/h of intravenous normal saline for 6–12 h before and after the procedure is also recommended. 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 [6]. *N*-Acetylcysteine (NAC) 600–1200 mg orally for four doses periprocedurally could also be considered.

Post-procedural Care

Vascular Access Site Complications

Vascular access site (VAS) care is important in post-procedural care. The rate of percutaneous VAS complications in neurointervention procedures is reported to be as low as 1.4% and as high as 11.65% [7]. Improved closure devices have contributed to decreased morbidity and mortality in recent years [8]. A detailed hand-off communication helps in early detection and prompt management [9, 10]. Although trans-radial arterial approach has been gaining popularity over the past few years, catheter-based angiography and other neurointerventional procedures are usually performed via transfemoral approach due to the

length and size of endovascular equipment. Complications of femoral punctures will be discussed below:

Hematoma

Localized hematomas remain as the most common complication in endovascular procedures. They range from mild local bruising to life-threatening extension into the retroperitoneal space, which can lead to hemorrhagic shock and death if left untreated. High femoral punctures above the inguinal ligament increase the risk of retroperitoneal hemorrhage. Local superficial hematomas can cause pain, swelling, and bruising, while retroperitoneal hematomas may result in flank/abdominal pain, a painful/cold limb, loss of peripheral pulses, acute anemia, hemodynamic instability, and hemorrhagic shock in extreme cases. Management involves keeping the patient supine for 2–6 hours, local manual compression, serial groin/flank checks marking hematoma growth, and frequent follow-up of hemoglobin. A CT of the abdomen and pelvis should be obtained promptly if there is a clinical suspicion of retroperitoneal hematoma. 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.

Pseudoaneurysm

In cases of low puncture, there is a higher risk of pseudoaneurysm formation (1%) [11]. These lesions create turbulent flow between the vessel and soft tissue space, which usually manifest with a pulsatile bruit and groin site pain and swelling. 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") [12]. 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 AVFs are rare vascular access site complications. Arteriovenous fistula (AVF) is an anomalous direct communication between an artery and a vein that results in shunting of blood between the two. This bypasses the high-resistance capillary vasculature, producing a low-resistance, high-flow situation with pulsatile blood flow in the veins that denies local tissue perfusion [13]. Most cases resolve spontaneously, but more severe cases should be pursued using USGC or endovascular or open surgical repair.

Infection

Infection is an infrequent complication in percutaneous interventions and prophylactic antibiotics are not warranted [14].

Stroke Thrombectomy (See Chap. 7)

Complications after endovascular treatment can be divided into issues that are a result of the stroke itself as well as issues commonly encountered in all critically ill patients [11]. It can also be related to the procedure (hemorrhagic conversion and malignant edema) or direct complications (volume overload, arteriotomy site complications, vessel perforation, vasospasm, device retention, and vessel reocclusion) of the procedure [11]. Medical management of such patients in the neurocritical care unit remains an important task for the neurointensivist.

Blood Pressure Management

Hemodynamic parameters in the patient with acute ischemic stroke are complex and dynamic. The optimal BP post-thrombectomy remains an area of uncertainty. Large fluctuations in the post-thrombectomy BP from the mean are predictive of worse outcomes. Hence, frequent BP monitoring and avoiding extremes in blood pressure readings are recommended.

Experts suggest different titration strategies based on the extent of recanalization. In patients with complete or nearly complete reperfusion, a stricter SBP upper limit of 120–140 mm Hg may be considered to reduce the risk of hemorrhagic conversion or reperfusion injury. Those receiving mechanical thrombectomy alone with only partial recanalization may benefit from a higher BP target—up to 180/105 mmHg [11, 15, 16].

Intracranial Hemorrhage

Small volume intracranial hemorrhage (ICH) after thrombolysis is frequently seen on follow-up imaging studies (Fig. 3.1). Despite the treatment success of endovascular therapy, ICH remains a major complication [17, 18]. Hemorrhagic transformation (HT) can be associated with a higher morbidity and mortality in case of intracranial hematoma with space-occupying effect (parenchymal hematoma [PH]) [17].

There are patient-related (age, high NIHSS, history of DM, CHF, HTN, longer treatment delays, collaterals), imaging-related (extent of infarction on imaging, low ASPECTS score), as well as procedure-related factors (general anesthesia, longer onset-to-reperfusion times, and equipment used) that increase the risk of parenchymal hematoma after thrombectomy [17–19].

Guidelines regarding management of sICH following thrombolysis/thrombectomy are currently lacking, and empirical treatment is done based on the clinician's judgment. Some strategies involve use of plasma and/or plasma-derived blood products. 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 [20]. 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 [21]. Hemicraniectomy provides definitive treatment for malignant brain edema while medical management is at best temporizing in such situations.

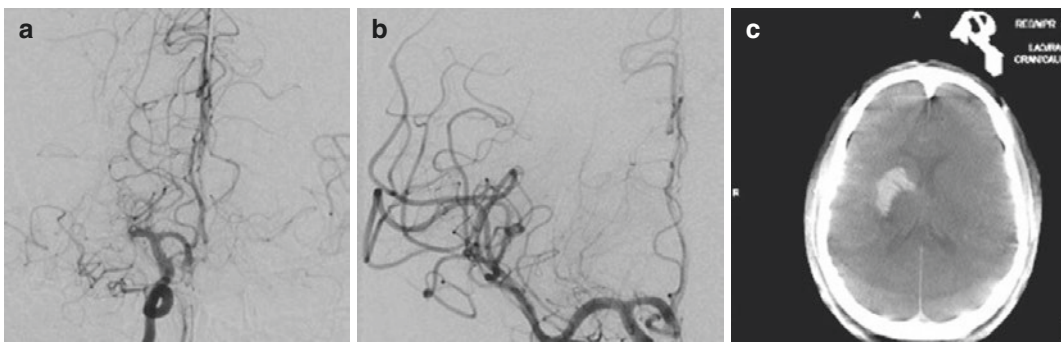

Fig. 3.1 Reperfusion hemorrhage following successful treatment of MCA occlusion. Cerebral angiogram shows a MCA-M1 occlusion (**a**), which was successfully recanalized (**b**). Post-thrombectomy computed tomography (CT) shows intracerebral hemorrhage (**c**)

Medical

Prior to utilizing more specific measures of ICP control, the first priority in ICP management is ensuring adequate airway, breathing, and circulation. It is important to note that these medical interventions are merely temporizing and when used alone confers >70% mortality in this patient population. Medical management of ICP includes elevation of bed to 30°, avoiding training and coughing, use of mannitol (average 1 g/kg) every 6 h while maintaining euvolemia, monitoring osmolar gap and renal function, hypertonic saline (HTS) with frequent sodium checks, and intubation with hyperventilation. While the use of a continuous infusion of HTS titrated to sodium goals is a common practice in neurocritical care, there is currently insufficient evidence to advocate its use [22, 23].

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. These trials included patients with MCA strokes on either side. A reduction in mortality was seen in patients up to 60 years of age (number needed to treat = 2) [24]. Similar benefits may be seen in patients up to 70 years of age based on the findings from the recently completed DESTINY II trial [25]. 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 [26].

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 [27]. 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.

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. Typically, the decision to will be under the discretion of the proceduralist.

Subarachnoid Hemorrhage

(See Chap. 11)

SAH management at a high nontraumatic SAH volume facility (35 cases/year) is associated with reduced inpatient mortality compared to management at a low-volume facility due to the complex nature of the disease and its complications [29, 30]. Various organ systems may be affected, and 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

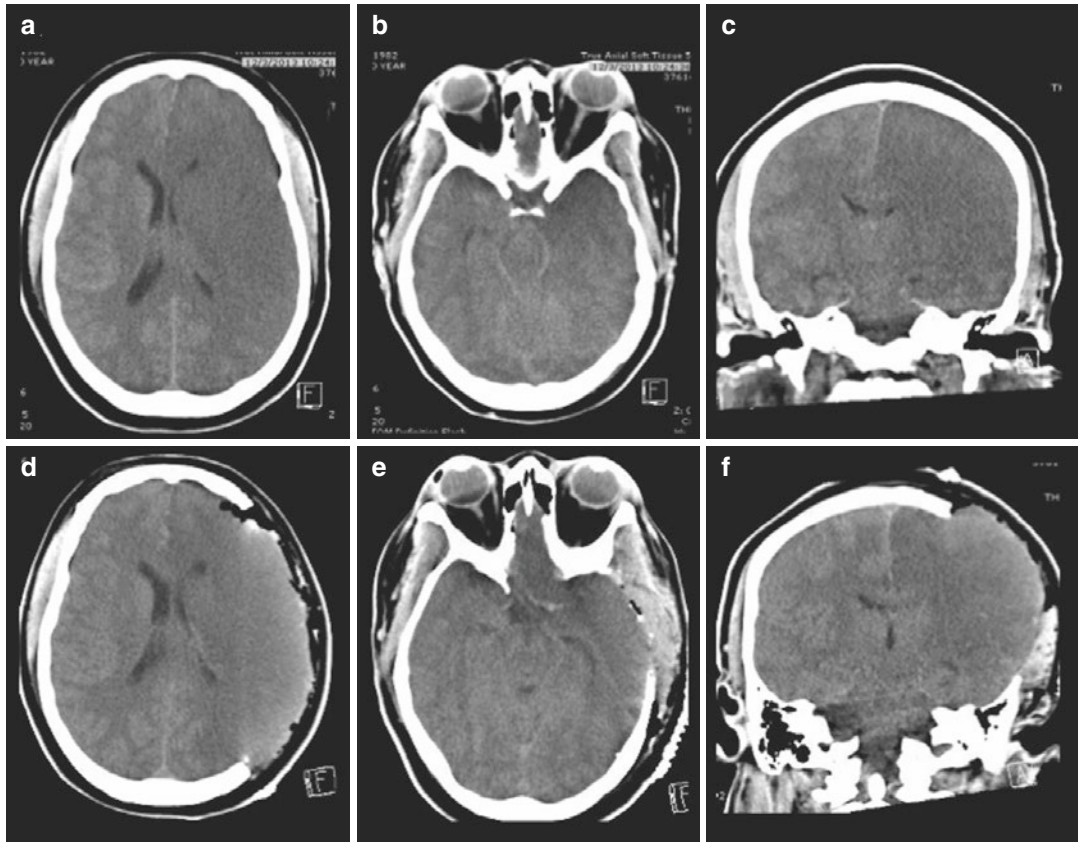

Fig. 3.2 Malignant MCA infarction requiring decompressive craniectomy. Computed tomography (CT) shows malignant right middle cerebral artery (MCA) infarction with extension into the temporal lobe (**a**–**c**). Post-surgical resolution of subfalcine herniation with overlying scalp expanded to accommodate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

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. After the aneurysm is secured, BP control can be liberalized to allow for cerebral perfusion. Strict BP control may mask the early warning signs of vasospasm during which BP typically increases.

Short-acting BP medications (e.g., labetalol or hydralazine) may be used intermittently or continuously (e.g., nicardipine) to ensure constant blood pressure control.

Vasospasm

Arterial narrowing or vasospasm as evidenced on angiography is typically seen between 3 and 21 days post-aneurysmal rupture peaking at 7–10 days post ictus. 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 [31]. 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.

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 may be 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 uptitrate 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

SAH is a systemic disease, and patients commonly experience additional medical complications. Anticipation of these complications leads to rapid recognition and treatment [30]. The SAH patient requires comprehensive medical management as various physiologic derangements can result in worsened outcomes.

Cardiopulmonary Complications

Cardiopulmonary function can be affected by a catecholamine surge-induced dysfunction leading to cardiac arrhythmias, "stunned" myocardium, and hypoxemia due to pulmonary edema.

Minor ECG changes, such as T-wave inversions and prolonged QTc intervals, are common and lead to arrhythmias such as bradycardia, atrial fibrillation, and ventricular fibrillation. Left ventricular dysfunction, troponin elevations, and wall motion abnormalities are also usual. Loss of myocardial compliance leads to a characteristic shape of the heart on chest radiographs, known as *takotsubo* (fishing pot). Pulmonary edema is common and is either a result of acute LV dysfunction or sympathetic surge causing pulmonary capillary leakage [29].

These complications are typically transient and resolve within a few days to weeks. Supportive care is important to ensure appropriate cerebral perfusion, avoiding hypoxia and hypotension. 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 [31].

Fever

Fever is common after SAH, specially in those with high-grade SAH and poor neurologic status. Fever has been associated with delayed cerebral ischemia and worse clinical outcomes. It is recommended to rule out infectious etiologies and suppress fevers and shivering that should be managed through non-pharmacologic (surface warming) as well as pharmacologic (antipyretics, NSAIDs, buspirone, etc.) means [30, 32, 33].

Anemia

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 [34]. 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.

Hyponatremia

Hyponatremia is the most common electrolyte disorder in SAH and can occur in up to 30% of patients. It is presumed to be due to hypothalamic dysfunction which results in cerebral salt wasting secondary to increased natriuretic peptide. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) could be considered but is generally uncommon in SAH [30]. Fluid restriction should be avoided in this patient population. Euvolemia with hypertonic fluids should be the goal in the vasospasm period [35].

Carotid Stenting (CAS) (See Chap. 4)

Carotid artery stenting (CAS) is emerging as an alternative to carotid endarterectomy (CEA) to treat symptomatic carotid artery stenosis. There are nontrivial risks associated with carotid revascularization, but most patients accept these risks due to the high incidence of recurrent stroke [36, 37].

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 frequently seen in CAS patients due to compression of the carotid body during balloon dilatation and stent expansion [38, 39]. Although hypotension is welcome because it reduces the risk of hyperperfusion, cerebral perfusion should be maintained, as prolonged hypotension can result in expansion of ipsilateral stroke or new ischemic stroke [40]. Hypotension unresponsive to gentle fluid boluses should be treated with vasopressors as required.

CAS is utilized in patients at high risk for carotid endarterectomy (CEA). 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 [41]. 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 [42, 43]. Dual antiplatelet therapy must be started prior to the procedure in all patients [44]. Optimization of electrolytes is recommended to prevent arrhythmia that may lead to PMI.

Ischemic Complications

Periprocedural ischemic stroke risk is ~3.7%, but higher rates have been reported in older age groups. They typically occur during or within the first 7 days of carotid stenting [45]. About two-thirds of periprocedural strokes are due to thromboembolism; other causes include arterial spasm and intraluminal thrombosis or occlusion [46]. A CT of head is obtained in sudden neurologic deterioration. Once hyperperfusion injury or ICH has been excluded, CT angiography (CTA) or standard angiography is 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). The decision to perform stroke intervention is challenging as the patient may have a subacute preexisting stroke that creates a high risk of reperfusion hemorrhage.

Cerebral Hyperperfusion Syndrome (CHS) and Intracerebral Hemorrhage

Cerebral hyperperfusion syndrome (CHS) is a well-known condition after carotid revascularization, which most likely occurs in the very early post-procedural period. Overall procedural CHS risk of 3.5% has been reported although the CHS rate varies substantially across studies [47]. Reperfusion of the brain may lead to significant complications including cerebral hyperperfusion syndrome, intracerebral hemorrhage (ICH), and contrast encephalopathy. Cerebral autoregulation involves an intimally mediated physiological response of smooth muscles in the large vessels. Ischemic insult 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 vasogenic edema, SAH, or hemorrhagic transformation (Fig. 3.4) [36].

The following criteria have been proposed to define CHS: symptom onset within 30 days post vascularization; clinical features such as new-onset headache, seizure, hemiparesis, or radiological features including cerebral edema or intracerebral hemorrhage (ICH); evidence of hyperperfusion on imaging studies (TCD,

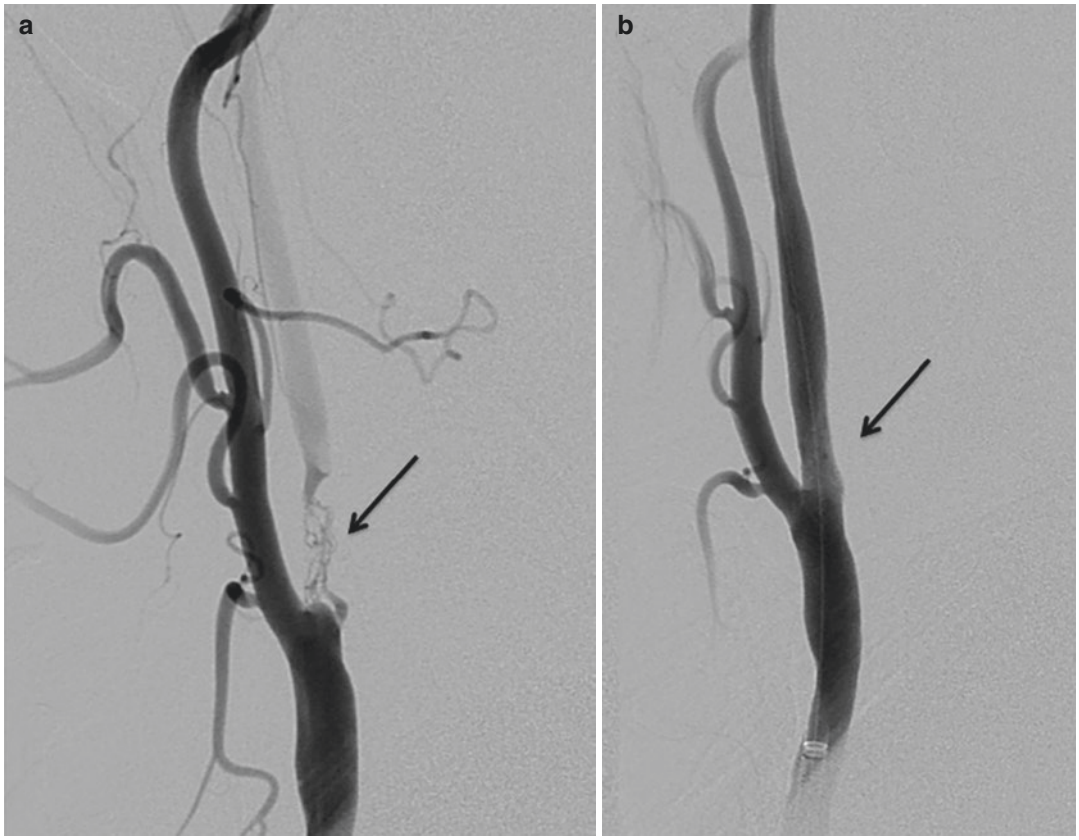

Fig. 3.3 Right common carotid stenosis; pre-stenting showing significant stenosis (**a**). Post-stenting flow void representing acute in-stent thrombosis (**b**)

SPECT, MR perfusion) or systolic blood pressure > 180 mmHg; and no evidence of new cerebral ischemia, postoperative carotid occlusion, and metabolic or pharmacologic cause [47].

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.

ICH is the most disastrous event secondary to hyperperfusion [48]. The incidence of ICH post-CAS is 0.36–4.5% [49]. The risk of hemorrhagic transformation is greater with larger preexisting infarct volumes [50]. 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.

Contrast Encephalopathy

This is a rare, reversible neurotoxic phenomenon caused by contrast agents used during percutaneous carotid interventions. The patient can develop minor or profound neurological deficits related to the involved hemisphere and can present with motor and sensory disturbances, aphasia, vision disturbance, seizures, and transient cortical blindness (the most commonly reported symptom) [51]. A CT of the brain will show cortical enhancement, edema, and rarely subarachnoid hemorrhage [52,

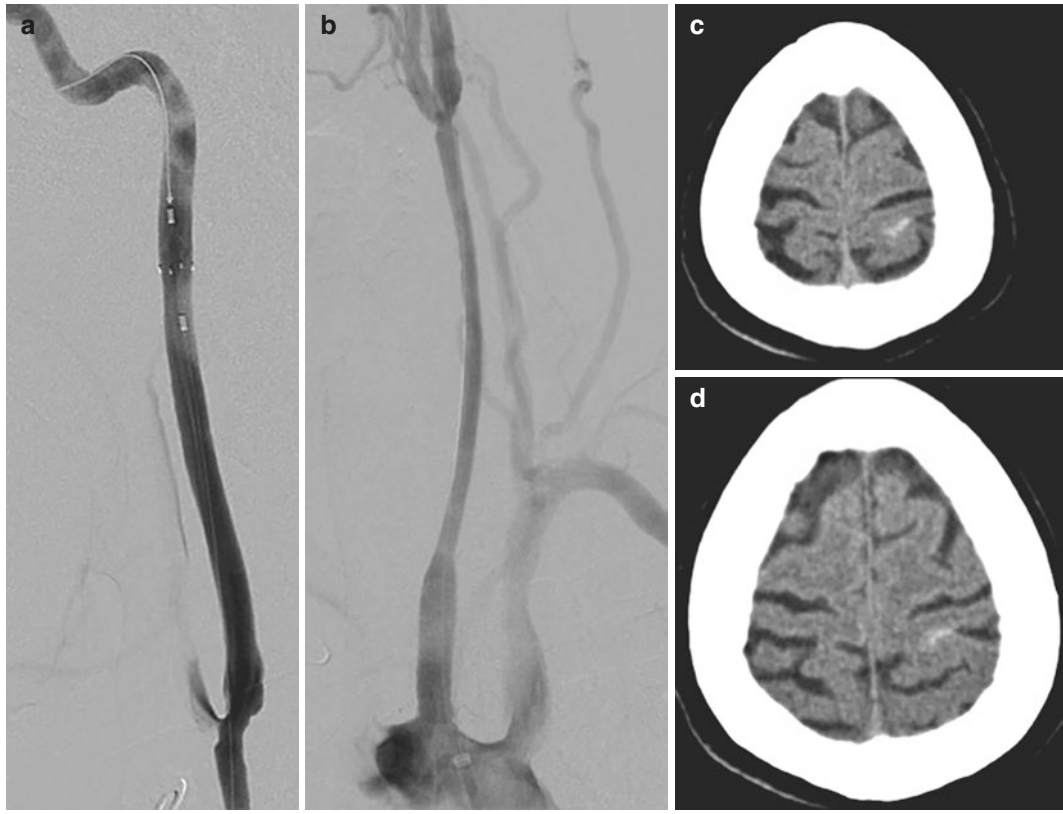

Fig. 3.4 Right common carotid stenosis (**a**) post-stenting (**b**). CT scan showing subarachnoid hemorrhage (SAH) secondary to reperfusion injury post-stenting in ipsilateral cerebral hemisphere (**c**, **d**)

53]. Usually, no angiographic vascular abnormalities are detected by angiography.

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 stand-alone 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 [54, 55]. Patients should be kept normotensive and euvolemic [56]. 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 [57].

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4 Endovascular Treatment of Extracranial Disease

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Cervical Carotid Artery Disease

Internal carotid artery arteriosclerosis at its origin is the most important cause of transient ischemic attack (TIA) and stroke of arterial origin. Carotid endarterectomy (CEA) is effective in secondary stroke prevention in patients with symptomatic stenosis measuring >50% in severity. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [1], CEA was superior to medical therapy in patients with >70% stenosis, reducing the ipsilateral stroke rate from 26% to 9% at 2 years. Patients with 50–69% luminal narrowing benefited less from surgery with a decrease in 5-year ipsilateral stroke rates from 22.2% to 15.7% but fared better than those treated medically. This then is the gold standard therapy against which newer therapies must be measured. CEA has limitations, and the margins for benefit in NASCET were dependent on a low 30-day perioperative stroke and death rate of 5.8%. Higher surgical complication rates can reduce the benefit from this surgery. 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 3, 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]), patients age 80 and older, 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 was a 7.6% incidence of cranial neuropathy and an 8.9% incidence of surgical wound hematoma or infection [1].

Carotid angioplasty and stenting (CAS) 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 they are 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 and neck irradiation, as well as

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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. Additional experience has shown that carotid artery stenting (CAS) is best performed with an emboli prevention device. Many non-randomized but large series studies (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) [2]. A consensus statement of the world experts in CAS states that the use of emboli prevention devices should be standard practice.

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

High-Surgical-Risk Patients

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 of an embolism prevention device) had not been validated outside of registries [3–6]. Several small trials were initiated [7, 8], but to date the only large randomized trial of protected CAS vs. CEA in high-surgical-risk patients was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study [9]. 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 combined 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,

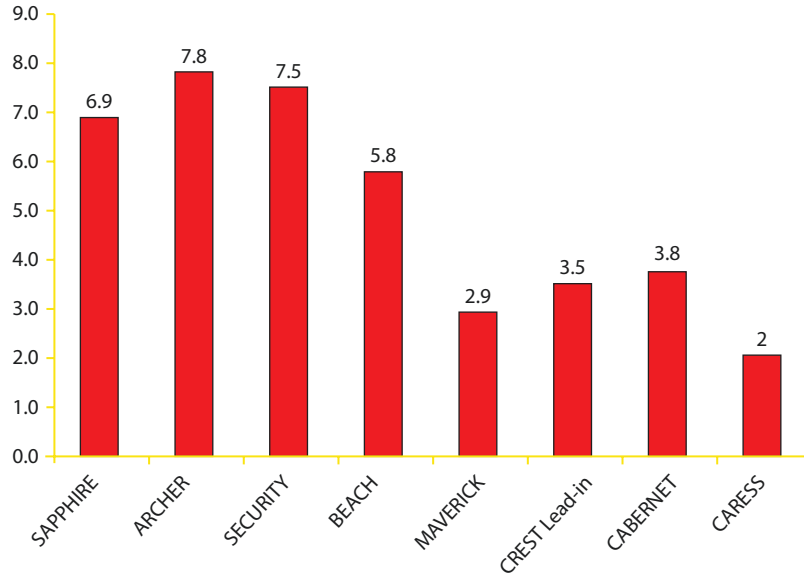

Fig. 4.1 Graph showing 30-day events in studies of CAS

$p = 0.05$ 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%). 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 two large post-marketing studies, CAPTURE [10] and CASES-PMS [11], show continued good outcomes with CAS in high-surgical-risk patients. These registries both consisted of real-world experience with commercially available stent and emboli prevention systems as well as independent neurological adjudication of neurological outcomes and events.

The CAPTURE registry enrolled more than 6000 high-risk patients from 280 sites and 672 operators and the data on the first 6300 patients have been published [12]. Most of the patients were asymptomatic (86.9%), and all received independent pre- and post-procedure neurological evaluation by neurologists. The 30-day results were 0.9% death, 3.1% all stroke, and 0.3% MI. However when the NASCET endpoint was used, the overall 30-day event rate was 3.6%. For symptomatic patients the 30-day event rate was 5.3% (95% CI, 3.6–7.4%) with a major stroke rate of 1.4%. For asymptomatic patients, the 30-day event rate was 2.9% (95% CI, 2.4–3.4%) with a major stroke rate of 0.6%. This trial was one of the first to show that age was associated with a major increase in complications, and in the >80yo symptomatic patients the complication rate was 10.5% (95% CI, 6.3–16.0%) and in asymptomatic >80yo it was 4.4% (95% CI, 3.3–5.7%).

The CASES-PMS registry enrolled more than 4000 patients with the data on the first 1480 high-risk patients published in 2007 [11]. In that cohort the 30-day death/stroke/MI rate was 5% in all patients and 4.7% in the asymptomatic patients. If NASCET/ACAS outcome definitions are used, then the 30-day death/stroke rate was 4% in asymptomatic patients. The much larger follow-up registry of the same device, the SAPPHIRE Worldwide Registry, has enrolled more than 15,000 patients since October 2006 [13]. The peri-procedural results were presented at the TCT conference in October 23, 2012, on the first 15,003 patients, 4569 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 now that in the high-risk patient who has a symptomatic ICA stenosis, CAS with a filter device is the procedure of choice.

The SAPPHIRE study results clearly showed that CEA carries a markedly elevated risk to asymptomatic high-risk patients, and it should not be offered to them. 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 whom medical therapy may be the best treat-

ment. Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is currently enrolling to help answer this question. In CREST-2 the patient will be randomized to medical therapy vs. revascularization with CAS or CEA. The patient who is randomized to revascularization therapy will be evaluated to determine which procedure is best for him/her depending on factors mentioned previously in this chapter [14].

Low-Surgical-Risk Patients

Four subsequent studies have greatly clouded the issue of CEA vs. CAS in low-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 [15]. The SPACE trial was a randomized comparison of CEA vs. CAS in 1183 symptomatic patients. Not surprisingly, since less than 30% of patients were treated with emboli 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 emboli prevention devices is not safe [16]. The most problematic study was the EVA-3S study of 527 randomized patients with symptomatic stenosis. This study was conducted with poor standardization of CAS technique including 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 [17]. 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. 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 ten 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 ($p = 0.004$) [18].

The most important trial of CAS, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), was actually started in 2000 but took 10 years to complete [9, 10]. 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. CREST was sponsored by both the National Institutes of Health (NIH) and Guidant (now Abbott Vascular). It was designed as a 2500-patient superiority trial with equal randomization between CEA and protected CAS using the Accunet™ emboli 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 tomographic angiography or magnetic resonance angiography were enrolled. Asymptomatic patients were enrolled with a stenosis ≥60% by angiography, ≥70% on ultrasonography, or ≥80% on computed tomographic 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 interventionalists with a lead-in/credentialing phase of approximately 20 patients per interventionist [19, 20]. In fact only 225 (52%) of 429 interventionists were approved for randomization [21]. 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's 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 [22]. Patients underwent independent neurological evaluations.

A total of 2522 patients were enrolled (1271 CAS and 1251 CEA) with a median follow-up of 2.5 years [13]. Approximately 5.4% of the CAS patients and 8.8% of the CEA patients were lost to follow-up or withdrawn 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 (96.1%) and most had predilation before stenting (67.7%). There was 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 stroke/MI/death within 30 days (CAS 5.2 ± 0.6 vs. CEA 4.5 ± 0.6, hazard ratio [HR] 1.18 [0.82–1.68], $p = 0.38$) or up to 4 years (CAS 7.2 ± 0.8 vs. CEA 6.8 ± 0.8, HR 1.11 [0.81–1.51], $p = 0.51$). 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 [1.14–2.82], $p = 0.01$) or MI (CAS 1.1 ± 0.3 vs. CEA 2.3 ± 0.4, HR 0.50 [0.26–0.94], $p = 0.03$). 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 [0.55–1.86]). 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 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 low-surgical-risk symptomatic and asymptomatic patients, has shown that both procedures are relatively 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 [23].

The results of CREST were reinforced in the Asymptomatic Carotid Trial (ACT I) published in 2016. This trial included 1453 subjects 79 years or younger with asymptomatic severe carotid stenosis who were considered not a high surgical risk. Subjects were randomized at a 3:1 ratio to CAS with emboli protection vs. CEA. The primary endpoint was a composite of death, stroke, or MI within 30 days after the procedure or ipsilateral stroke within 1 year. CAS was non-inferior to CEA with regard to the primary composite endpoint (event rate, 3.8% and 3.4%, respectively: $p = 0.01$ *for non-inferiority*). The risk of perioperative stroke was slightly higher in the endovascular group (2.9% vs. 1.7%; $p = 0.33$). Most of these strokes were minor, similar to the results from CREST. The rate of freedom from non-procedure-related ipsilateral stroke through 5 years was 97.8% in the stenting group and 97.3% in the endarterectomy group ($p = 0.51$) [24].

These results contradict the results of the three randomized European trials discussed earlier [16–18]. The EVA-3S, ICSS, and SPACE trial results have greatly reduced the enthusiasm for CAS and initially 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 must be reconciled with those of the CREST trial, ACT I trial, and the registries. As with the early trials of CEA, the differences in outcomes have to do with patient and operator selection as well as procedural techniques. Several authorities have highlighted the limitations of these trials, and Table 4.2 highlights the differences and possible explanations for the differing results between trials. Chief among the limitations was the inexperience of the operators performing the stenting and the lack of consistent EPD use. In an observational study of 24,701 Medicare beneficiaries from 2005 to 2007 who underwent CAS by 2339 operators, the median case volume was 3/year [25]. When outcomes were analyzed based on high experience (≥24 cases/year), medium (12–23 cases/year), low (6–11 cases/year), and very low (<6 cases/year), mortality was associated with decreasing experience: adjusted OR 1 in high-experience group (reference), 1.2 (95% CI 0.8–1.7) in medium-experience group, 1.4 (95% CI 1.0–2.0) in low-experience group, and 1.9 (95% CI 1.4–2.7) in the very-low-experience group. Interestingly as a further marker of technical skill the OR for not using an EPD were also greatly increased with decreasing experience: adjusted OR 1 (reference, high experience), 1.6 (95% CI 0.8–3.2, medium experience), 2.9 (95% CI 1.5–5.6, low experience), and 8.1 (95% CI 4.4–14.9). Gray et al. [10] also reviewed the large CAPTURE data set and found a linear relationship between increasing experience and decreased complications. Smout et al. [26] conducted a literature review and meta-analysis and also found a consistent association between experience and outcomes. These outcomes would seem to be self-evident, yet the aforementioned randomized

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"

trials seemed to ignore the obvious. To summarize then, the EVA-3S, SPACE, and ICSS trials have confirmed that CAS performed poorly by inexperienced operators is inferior to properly performed CEA.

A meta-analysis of all the trials that had exclusive use of emboli protection devices comparing CAS to CEA was published by Sardar et al. [27]. There was no significant difference in the composite outcome of periprocedural death, stroke, myocardial infarction (MI), or non-periprocedural ipsilateral stroke between CAS and CEA (OR 1.22; 95% CI 0.94–1.59). The risk of any ipsilateral stroke was higher with CAS (OR 1.50; 95% CI 1.22–1.84). This increased stroke risk with CAS was mostly attributed to periprocedural minor stroke (OR 2.43; 95% CI 1.71–3.46). Significantly lower risk of periprocedural MI (OR 0.45; 95% CI 0.27–0.75), cranial nerve palsy (OR 0.07; 95% CI 0.04–0.14), and the composite outcome of death, stroke, MI, or cranial nerve palsy during the periprocedural period (OR 0.75; 95% CI 0.60–0.93) was seen in association with CAS.

Long-term follow-up from CREST over 10 years showed no significant difference between patients who underwent CAS vs. CEA. Post-procedural ipsilateral stroke over the 10 years was 6.9% (95% CI, 4.4–9.7) for CAS group and 5.6% (95% CI, 3.7–7.6) for CEA group [22].

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 [1]. 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 (CREST, CAPTURE). In the CREST trial [22, 28] lead-in phase (N = 1246) 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.

There are several issues that have not yet been addressed by the published results, such as the long-term patency of each procedure has yet to be determined, and given that newer emboli prevention devices and stents are available, might one or several of them be associated with lower stroke rates?

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

Other Considerations

There have been debates about the type of stent used with some suggesting that closed cell stents are associated with lower periprocedural stroke [29]. Proximal occlusion EPDs have also been touted to be 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 1300 patients treated with proximal occlusion, the 30-day stroke/death rate was 1.38% with independent neurological assessment at 24 h and 30 days [30]. In a meta-analysis of 2397 patients from six independent databases, Bersin et al. found that the composite of stroke/MI/death occurred in 2.25% of cases [31]. While these data are tantalizing,

there are no definitive randomized trial data that show one type of EPD device is superior to another. Retrospective analysis of 13,786 CAS procedures using different stent-EPD combinations such as Xact-Emboshield (n = 2438, 17.6%), Precise-Angioguard (n = 1480, 10.7%), Acculink-Accunet (n = 829, 6.01%), and Acculink-Emboshield (n = 660, 4.8%) showed no statistically significant difference in rates of periprocedural stroke/TIA across device combination [32]. Clinicians should, in the author's opinion, become familiar with one or two devices/approaches and use them exclusively until there is definitive data on superiority of one approach or device over another.

Predictors of Complications

A study pooled data on 2104 patients from four Cordis Endovascular Inc.-sponsored registries [33]. 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 declines with increasing time between incident event and CAS [34]. 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 [35]. The fear of reperfusion/hyperperfusion intracerebral hemorrhage (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 [36], and early CAS can also be performed safely in selected patients [37].

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 usually performed under minimal sedation in order to avoid mental status impairment. This procedure usually involves five stages: 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.

Procedural Considerations

- *Antiplatelet therapy*:
  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 for 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 [22]. More

recently eptifibatide, a highly selective platelet glycoprotein IIb–IIIa receptor inhibitor, emerged as safe adjunct to CAS [38]. Eptifibatide has a rapid antiplatelet effect and is rapidly reversible with a half-life of 10–15 min. Its IV route of administration made it popular especially in emergent CAS.

- *Sedation:* Overall, 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.
- *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) was noted 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 peri-procedural major adverse clinical event (OR 3.05 [range 1.35–5.23], $p < 0.02$) or stroke (OR 3.34 [95% CI 1.13–9.90], $p < 0.03$) [39]. Close monitoring of blood pressure and heart rate is recommended during and after CAS, and 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. Peri-procedural 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 of 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. Secure 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, and their technique involved temporary occlusion of the cervical ICA distal to the lesion by a nondetachable latex balloon [40].

Many EPDs have been introduced since then, and 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 procedural-related deaths was 5.29% in the 6753 cases done without protection and 2.23% in the 4221 cases with cerebral protection [41]. Embolic protection can be achieved by distal balloon occlusion, distal filter devices, or proximal balloon occlusion with or without flow reversal.

- 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 depends on filter wall opposition and the size of pores. Table 4.4

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	1400	MAVERIC III	No

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, dislodging emboli from the filter during filter retrieval, and letting micreoemboli pass through the device due to poor wall opposition or through the pores of the device.

- 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 a static blood column at the carotid bifurcation. At the end of procedure, aspiration with at least three 20 cc syringes is performed before deflating the balloons.

  The Parodi Anti-Emboli System (W.L. Gore & Associates, Flagstaff, AZ) requires an 11-French 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. Oversize 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 Wallstents, 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 [42].

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 prevent 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% [43, 44]. This can be treated with intra-arterial administration of abciximab or recombinant tissue plasminogen activator (r-tPA). This 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 can be treated with in-stent balloon inflation or implantation of a second stent.

Emboli: Cerebral emboli can occur despite meticulous CAS technique, and a rapid neurological evaluation should be performed if this complication is suspected. Symptomatic large emboli should be treated with mechanical thrombectomy 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 glycoprotein IIb/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 [45]. This is usually self-limited but can be treated with intra-arterial spasmolytic administration if it persisted or thought to be symptomatic. Filter occlusion was seen in 4.9% of patients in one series; it is usually due to entrapment of a large load of embolic material in the basket and does not seem to correlate to the type of the filter used. As long as it is 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 must 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. with a mild-shape catheter can also be used to retrieve the EPD.

Hyperperfusion Syndrome: This was first described by Sundt as a combination of increased arterial blood pressure with the clinical triad of ipsilateral migraine-like headache, seizure, and transient focal neurological deficits in the absence of cerebral ischemia after a successful CEA in 1981 [46].

Cerebral hyperperfusion is defined as cerebral blood flow that exceeds the metabolic requirements of brain tissue and/or an increase in cerebral perfusion of more than 100% compared to pretreatment values. This syndrome usually occurs in the first week after carotid revascularization and typically results in headache, seizures, and focal neurological deficits. Intracerebral or subarachnoid hemorrhage commonly occurs in those patients and can result in a high rate of mortality. The following risk factors have been identified as predictors of hyperperfusion syndrome after carotid revascularization: DM, chronic hypertension, increased age, recent contralateral carotid revascularization, high-grade stenosis with poor collateral flow, incomplete circle of Willis, and post-procedural hypertension. Post-procedural intensive treatment of hypertension seems to decrease the risk of this syndrome in patients who underwent CAS [40].

Contrast Encephalopathy: This usually occurs in the first 24 h after CAS and can be attributed to contrast toxicity to the brain. Patients usually present with symptoms that mimic a stroke with transient visual loss or obscuration being the most common symptom. This benign and self-limited complication has to be differentiated from thromboembolic events to avoid additional invasive therapies.

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. Transend 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).

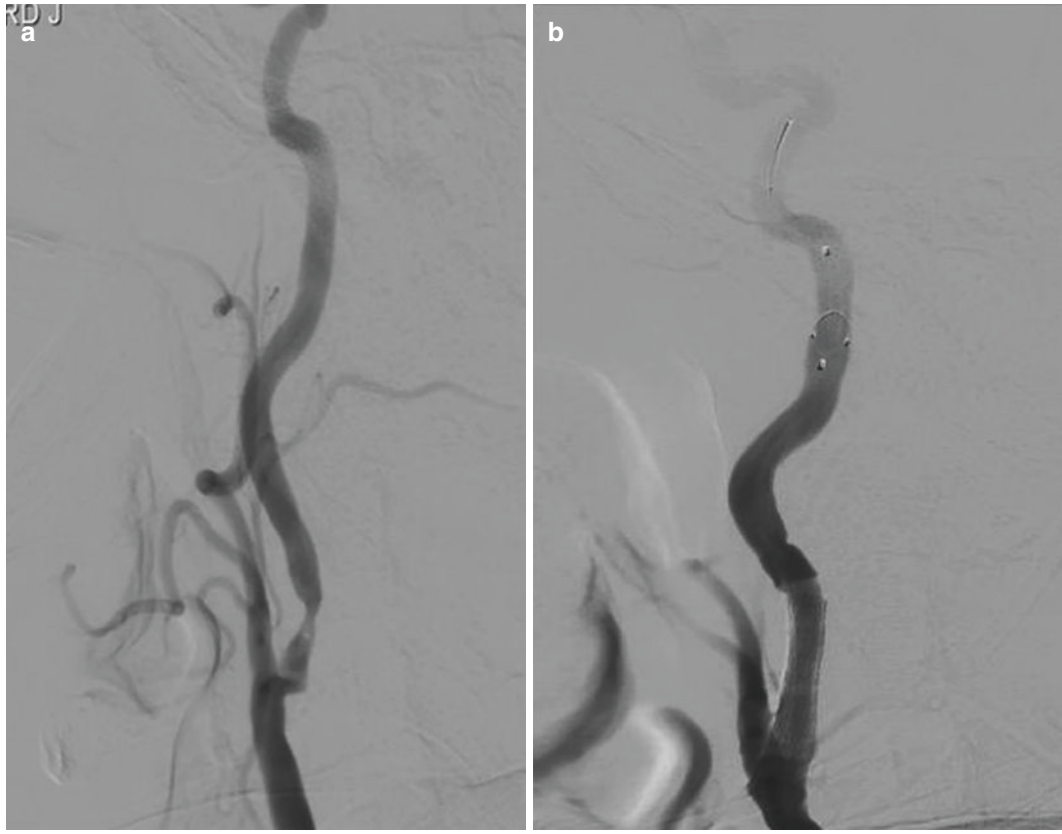

Fig. 4.2 Lateral projection angiogram showing high-grade carotid bulb stenosis (**a**) and resolution post-stenting with EPD (**b**)

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 [47]. 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 [48, 49]. 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. Transend 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.

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.

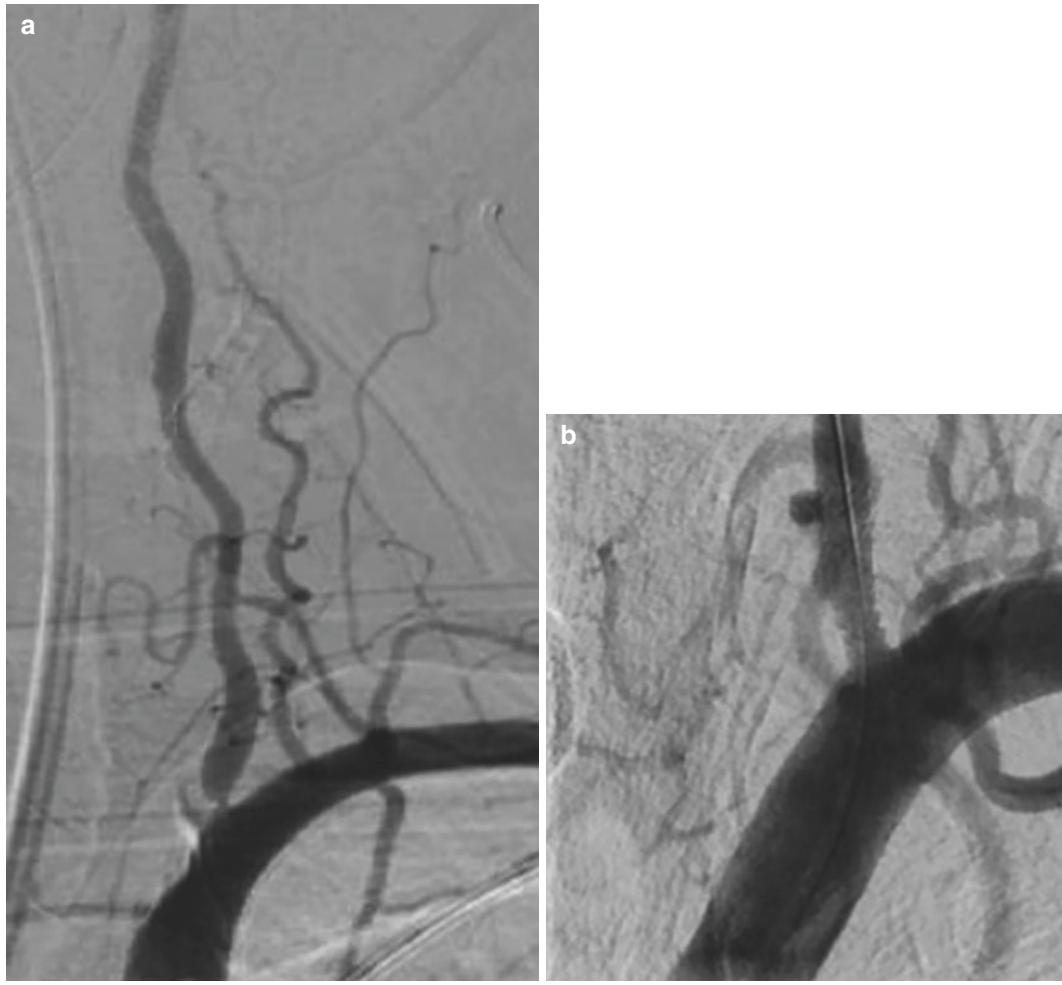

Fig. 4.3 Left anterior oblique angiogram showing high-grade vertebral artery origin stenosis (**a**) with resolution post-stenting (**b**)

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.
- *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

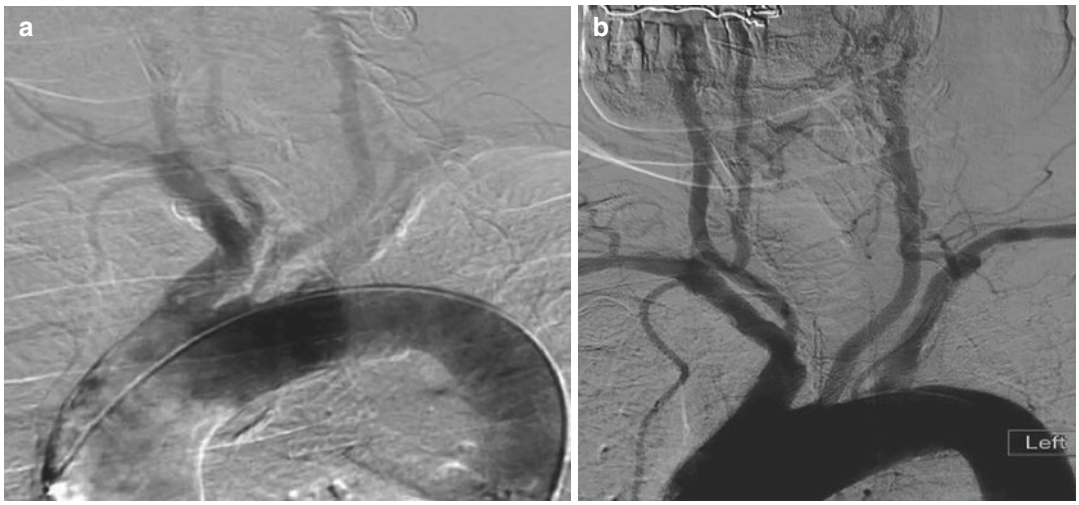

Fig. 4.4 Left anterior oblique angiogram showing severe proximal left common carotid artery stenosis (**a**) with resolution post-stenting (**b**)

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.

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5 Endovascular Treatment of Intracranial Atherosclerosis

Saif Bushnaq, Nicholas Liaw, 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 still remains overall high at 1- and 2-year follow-up. Certain high-risk ICAD patients may 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

ICAD is a common cause of stroke worldwide, afflicting the Black, Asian, and Hispanic populations at a higher rate than Whites [1, 2]. ICAD is found in an estimated 10% of stroke patients in the USA, while in Asia, it accounts for approximately 30–50% [3, 4]. Age, hypertension, smoking, diabetes mellitus, hypercholesterolemia, and metabolic syndrome are all risk factors for ICAD [5, 6]. Although the high rate of uncontrolled risk factors partially accounts for the increased incidence of ICAD in some populations [7–10], this does not appear to be the case in others [11–13]. It stands to reason that management of risk factors alone may not be sufficient in controlling the disease.

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]. Even with optimal medical therapy and lifestyle modification including blood pressure reduction, smoking cessation, weight loss, cholesterol reduction, and dual antiplatelet therapy, the risk of stroke in ICAD patients remains at a high 12.2–15% [16, 20].

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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].

Differential Diagnosis

Anatomic arterial narrowing detected on imaging studies may be due to a variety of pathologies, and determining the cause of narrowing can be challenging. Mimics include partially recanalized thrombus, intracranial dissection, vasculitis, vasculopathy, and vasospasm. 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 will usually resolve on repeat imaging [5, 31, 32]. The presence of a severe headache and diffuse intracranial narrowing suggests reversible vasoconstrictive syndrome. Limited data exists, but studies of extracranial vessel imaging with pathologic correlation have shown inflammatory processes such as vasculitis are associated with concentric, circumferential wall thickening and enhancement, while ICAD is associated with eccentric wall thickening [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]. 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 one study over 80% of ICAD strokes showed combination of multiple mechanisms [16, 37]. The mechanism of the current stroke is predictive of the risk and mechanism of recurrent strokes. 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].

Stenosis Characterization

Imaging including CTA, MRA, and digital subtraction angiography (DSA) can be used to detect intracranial stenosis. With this, one can ascertain the degree and length of stenosis, differentiate the atherosclerotic stenosis from mimics, and assess the state of collateral circulation.

DSA is considered the standard for the evaluation of intracranial stenosis. As standardized by the methods described in the WASID study, 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 (Fig. 5.1) [23, 38].

For noninvasive modalities of evaluating large vessel ICAD, transcranial Doppler (TCD) and MRA compared with DSA were shown to have good negative predictive values of 86–91% but low positive predictive values of 36–59% [15, 26]. CTA was shown to have a higher sensitivity, specificity, and positive predictive value compared to MRA [29, 39]. The higher sensitivity and specificity of CTA have been observed for stenosis 50% or higher [30]. For ICAD in small intracranial arteries, a study showed that multidetector CT angiography depicted ≥90% of all examined small intracranial arteries compared

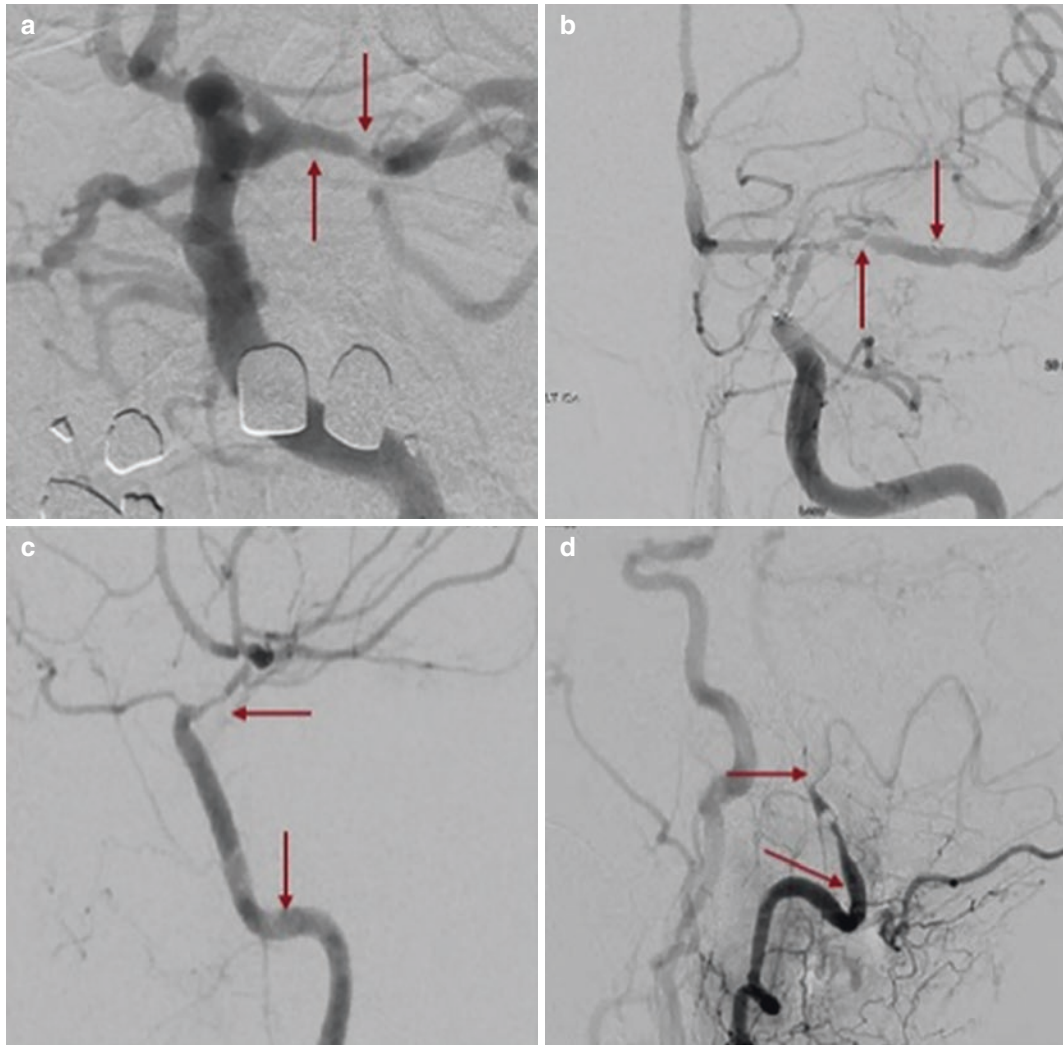

Fig. 5.1 Measurement of intracranial stenosis using the WASID method. (**a**) The diameter of the proximal part of the artery at its widest, non-tortuous, normal segment is chosen (first choice). (**b**) If the proximal artery is diseased, the diameter of the distal portion of the artery at its widest, parallel, non-tortuous normal segment is substituted (second choice). (**c**) For the internal carotid artery disease involving the pre-cavernous, cavernous, and post-cavernous 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)

to DSA, and the smallest arterial size reliably detected with CTA was 0.7 mm versus 0.4 mm for DSA.

Stenoses can be further characterized by the vessel tissue surrounding the luminal stenosis. Vessel wall imaging can be achieved with high-resolution MRI, intravascular ultrasound, and fat-suppressed T1-weighted MRI. High-resolution MRI can identify the thickness and pattern of protrusion [31, 32]. Identification of recent intraplaque hemorrhage and inflammation can be made with fat-suppressed T1-weighted MRI [34, 35, 40, 41]. Black-blood MRI with or without contrast allows for visualization of the heterogeneity of the thickened vessel wall due to various plaque components, lipid core,

Table 5.1 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

fibrous cap, intraplaque hemorrhage, calcifications, and enhancement. Intravascular ultrasound can be used for distinguishing calcium and lipid deposits but is limited in its use due to its invasive nature [33].

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. As with above, DSA remains the gold standard for assessing collaterals. CTA and MRA modalities offer less detailed but noninvasive alternatives. The ASITN collateral score (Table 5.1) is the most commonly used grading system [36, 43].

Surgical Treatment of Intracranial Stenosis

Surgical treatments have been used for decades to treat ICAD. In general, the current evidence does not favor surgical intervention. The EC/IC (extracranial to intracranial) bypass study showed no benefit of surgical bypass versus medical therapy for the reduction of overall ipsilateral major strokes or death in patients with intracranial or extracranial stenotic and occlusive diseases [38, 44].. The Carotid Occlusion Surgery Study (COSS) evaluated patients with ipsilateral ischemic events within 120 days in the setting of cervical carotid occlusion and increased oxygen extraction fraction. Patients were randomized to medical treatment versus EC/IC 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% vs. 23%) [37, 43, 45, 46].

Medical Treatment of Intracranial Atherosclerotic Stenosis

Medical treatment has evolved over the years and is currently the first line of treatment for ICAD. The WASID trial compared aspirin versus warfarin in patients with ICAD. The primary endpoint of ischemic stroke, brain hemorrhage, or vascular death was similar in the aspirin (22.1%) and warfarin (21.8%) groups. However, the warfarin cohort had significantly more non-vascular death, major hemorrhage, and myocardial infarction or sudden death [15, 47]. The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial compared maximal medical therapy to stenting in ICAD patients. At 1 year, the event rate was 17.6% in the stenting arm and 12.2% in the medical management arm [2, 6, 48]. The medical arm of SAMMPRIS is now considered the standard of care for first-time symptomatic ICAD patients: 325 mg aspirin and Plavix 75 mg daily for 3 months, followed by aspirin only. Additionally, patients were treated with a statin and 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

The results of the SAMMPRIS trial demonstrating medical management superiority compared to stenting have relegated endovascular treatment to a more secondary role, but new studies employing modern techniques and stricter selection of

Table 5.2 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 scale score of ≤3 prior to intervention [49, 50]

patients show promising results. Endovascular treatment of intracranial stenosis aims to reduce luminal stenosis to improve downstream perfusion. This can be divided into three possible treatments: stand-alone balloon angioplasty, balloon-mounted stent (BMS), and self-expanding stent (SES) placement. Devices can also be drug-eluting, such as with drug-eluting stents (DES). Indications for each procedure (Table 5.2), outcomes from literature, and example case presentations are provided in the chapter.

Intracranial Balloon Angioplasty Without Stenting

Initially described with percutaneous transluminal angioplasty of the coronary arteries, the first reported cases of stand-alone balloon angioplasty in the 1980s saw high rates of dissections, emboli, and rupture [44, 51]. A small rupture or dissection not significant in the coronary circulation would result in devastating subarachnoid or parenchymal hemorrhage [47, 52–54]. In modern times improvement with technique and balloon selection have seen improved complication rates. Slow inflation over minutes as opposed to seconds and undersized balloons have decreased complication rates to as low as 5% [41, 55–57] (see Fig. 5.2). 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, 50, 51, 55, 56, 58–60].

Stand-alone intracranial balloon angioplasty has been advocated by some over stenting based on case series with low periprocedural complication rates [40, 41, 61]. Some studies have suggested that restenosis and outcomes in balloon angioplasty without stenting versus stenting are similar [49, 51].

There are several intracranial balloons used for 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 also been used off-label to treat ICAD [48, 56]. Coronary balloons have been used with excellent technical success, and promising outcomes include Maverick balloon, NC Quantum Apex balloon, and drug-coated balloons [62–65].

Balloon-Mounted Stents

Balloon-mounted stents (BMS) have also been used in ICAD with some success. Most of the reported literature has used coronary BMS. NeuroLink, a dedicated intracranial BMS system, has been reported in the SYLLVIA trial. Results showed a 35% restenosis rate although 61% of these were asymptomatic [66]. The difficulty with the current BMS systems is that they are stiff and, therefore, harder to track in the tortuous intracranial circulation.

Self-Expanding Stents

Self-expanding nitinol stents have been the mainstay of intracranial stenting ever since the FDA approval of the Wingspan Stent (Stryker, Kalamazoo, Michigan, USA) (Fig. 5.3). They have had a high technical success rate: 98.8 and

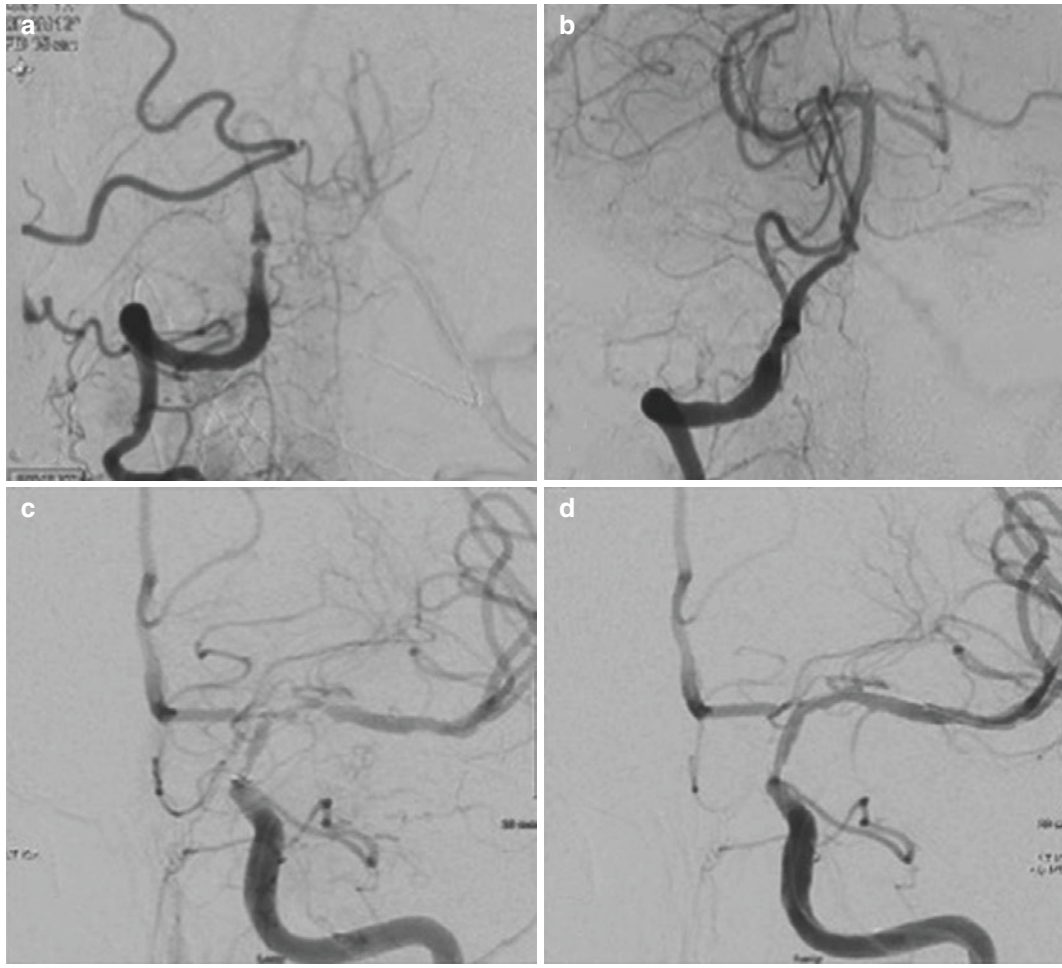

Fig. 5.2 (**a**, **b**) Patient with vertebral artery stenosis with recurrent strokes on optimal medical therapy before and after balloon angioplasty cerebral angiogram in AP projections, (**c**, **d**) patient with in-stent intimal hyperplasia before and after balloon angioplasty cerebral angiogram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

96.7% in the two large registries and 94.6% in the SAMMPRIS trial [3, 50, 51, 60]. Its small outward radial force (<0.1 atm) theoretically decreases chances of vessel rupture or dissection. It also does not need a balloon and can be delivered through a microcatheter, making it more trackable. Despite these advantages, the SAMMPRIS trial revealed better outcomes in the rate of stroke and death in the medically treated group compared to stenting [3, 20, 59]. Following criticism of the study that the stenting was not performed on-label by interventionalists of sufficient training, the WEAVE trial (Wingspan Stent System Post Market Surveillance) was conducted. The trial enrolled 152 patients, which was the largest on-label trial performed in the USA to date, and excellent results were seen. The periprocedural complication rate of 2.6% was also the lowest complication rate obtained compared to prior trials and registries. The trial inclusion protocol was stricter (criteria included age 22 to 80 years, symptomatic intracranial atherosclerotic stenosis of 70% to 99%, baseline modified Rankin Scale score ≤3, ≥2 strokes in the vascular territory of the stenotic lesion with at least one stroke while on medical therapy, and stenting of the lesion ≥8 days after the last stroke) [50, 60, 67, 68].

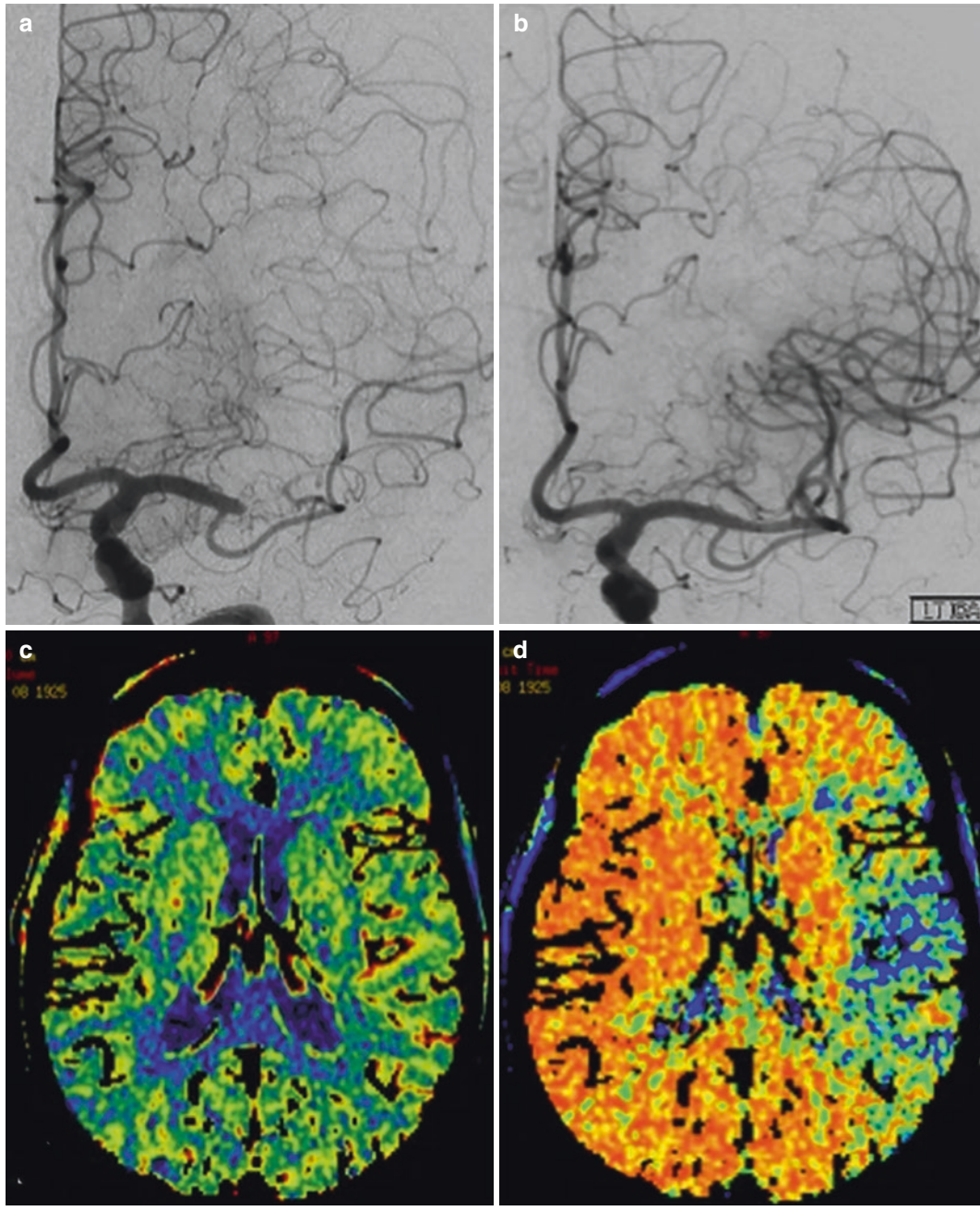

Fig. 5.3 Patient with near occlusion of M1 MCA who is symptomatic when her blood pressure is dropped. (**a**) Cerebral angiogram demonstrating the M1 MCA near occlusion before angioplasty and stenting, (**b**) cerebral angiogram after treatment with improved stenosis, (**c**) CBV (cerebral blood volume)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

Drug-Eluting Stents

Extracranial drug-eluting stents (DES) have been used off-label in the intracranial circulation. The devices are coated with antiproliferation drugs such as everolimus, sirolimus, and paclitaxel, which are designed to decrease intimal hyperplasia and restenosis of the stent. DES

have been used in both the anterior and posterior circulation with periprocedural complication rates ranging from 0% to 25% [3, 52–54]. Most DES 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 [69, 70]. There is some literature on newer DES that points to a lower incidence of delayed thrombotic events, but research is still ongoing [55, 71]. The lack of long-term follow-up in patients treated with DES has limited their acceptance. A small case series ($n = 11$) with a mean follow-up period of 67 months has shown no patients with greater than 50% restenosis [57, 72].

Procedural Considerations

Patient Selection

It is important to remember that endovascular treatment of ICAD is a high-risk procedure, and care must be taken for patient selection and procedural preparation. Patients with recurrent symptoms in the setting of high-grade intracranial stenosis (≥70%) despite 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. Endovascular treatment of non-perforator-rich locations (intracranial internal carotid and vertebral arteries) is lower risk than perforator-rich locations (basilar and proximal middle cerebral arteries). Patients with hypoperfusion-related events are theoretically more likely to benefit from treatment.

Pre-procedure

It is important to perform a DSA for presurgical planning. A three-dimensional image is helpful to further characterize the lesion and to identify the optimal angle to utilize during endovascular surgery. It also allows for risk stratification by characterizing the extracranial and 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 genua of the cavernous carotid is a key determinant of success. Highly angulated genua may prohibit the navigation of a stent distally. The strategy must be tailored to the patient and his/her individual anatomy.

Dual antiplatelet agents (aspirin and clopidogrel) and high-dose statin therapy should 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.

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 peri- and post-procedure blood pressure monitoring.

Sheaths

A 6F or larger sheath is needed to perform these procedures. A long sheath (35 cm or greater) that bypasses the iliac 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

Intermediate or distal access catheter (DAC) can be 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 shapeable 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. The Gateway balloon (Stryker, Kalamazoo, MI) is FDA approved for ICAD treatment. It is an over-the-wire, low-profile, and highly navigable balloon. Coronary angioplasty balloons have also been used off-label (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 sized 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 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 may lead to vessel perforation. A J- or C-shaped wire tip will reduce the tendency of the wire to enter small branch vessels. If the wire migrated proximally, trans-lesion access may be lost, or insufficient distal access may make balloon/stent navigation impossible. These exchanges generally require two operators. 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, and 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 intracranial hemorrhage. 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

Despite having many options for treatment of ICAD with endovascular techniques, none has been established as primary treatment. Table 5.3 outlines some of the major literature on these approaches.

Table 5.3 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
WEAVE trial [a] [68] VISSIT [a] [73] Miao [b] [48]	None BES plus medical therapy vs medical therapy alone medical	SES (Wingspan) ICA, MCA, VA, BA, and PCA Balloon-expandable stent PTA, stent *MCA*	83 → 28 NR 84 → NR	NR 26.5% NR	2.6% 24.1% 8.3%	2.6% stent 36.2% 19.4% stent 17.6% med
SAMMPRIS [b] (2011) [3]	Aggressive medical	SES *A and P circulation*	80 → NR	NR	19.2%	14.7% stent 5.8% med
Yu et al. [70]	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. [55]	None	PTA *I, M, and ACA, B and VA*	79 → 34%	NR	5	8.5%
INTRASTENT [72]	None	Stenting (NR) *ICA, MCA, BA, VA*	NR	NR	NR	12.4%
Siddiq et al. (2008) [51]	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. [59]	None	PTA, DES, BMS *ICA, MCA, BA, VA*	85 → 0%	16%	NR	10.1%
Zaidat et al. [50]	None	SES *ICA, MCA, BA, VA*	82 → 20%	25%	6.2%	14%
Fiorella et al. [60]	None	SES *ICA, MCA, BA, VA*	75 → 27%	NR	15.3%	6.1%
Marks et al. [41]	None	PTA, stent (NR) *I, M, and PCA, B and VA*	82 → 36%	NR	NR	5.8%
SSLYVIA [66]	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 randomized control trials to indicate its use as primary treatment of symptomatic patients with ICAD. The SAMMPRIS trial argues that it is likely harmful as first-line treatment [3, 8, 10]. VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) randomized controlled trial showed increased 30-day risk of any stroke or TIA with stenting [73]. Despite this many experts still believe endovascular treatment of ICAD can play a role [12, 49].

Analysis of SAMMPRIS periprocedural strokes revealed that avoidance of perforator-rich areas, close monitoring of hemorrhages from wire perforation, Plavix loading, and close adherence to target activated clotting time could help produce better results from endovascular treatment [15, 74, 75]. Subsequent studies revealed lower complication rates and lower long-term stroke risk in well-selected patients undergoing angioplasty or stenting in ICAD (e.g., patients with poor collaterals, severe stenosis 70–99%, treated by an experienced operator at a high-volume center) [64, 76, 77]. Most recently, the WEAVE trial (Wingspan Stent System Post Market Surveillance) assessed the periprocedural safety profile of Wingspan Stent System to treat ICAD. This evaluated a strict on-label application of Wingspan Stent in 152 patients. On-label criteria included age 22 to 80 years, symptomatic ICAD stenosis of 70% to 99%, baseline modified Rankin Scale score ≤3, ≥2 strokes in the vascular territory of the stenotic lesion with at least 1 stroke while on medical therapy, and stenting of the lesion ≥8 days after the last stroke. A lower than expected periprocedural stroke, bleed, and death rate was achieved at 2.6% (4/152 patients) [68]. Currently patients should be evaluated on a case-by-case basis to determine if they would benefit from 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 first-line maximal medical therapy has a 1-year 12% stroke rate and increased rate of stroke at follow-up [3, 20]. There is continued interest in endovascular ICAD treatment among experts [22, 49]. Imaging developments to assess intracranial arteries and identify high-risk plaque features are promising. Carefully selected patients with poor collaterals, hemodynamic symptoms, and recurrence despite medical therapy can potentially benefit from endovascular treatment. Future studies should focus on stricter selection of patients, which may utilize biomarkers from emerging imaging criteria or techniques. The endovascular technology also continues to evolve, with more devices tailored specifically for the intracranial vasculature rather than co-opted from cardiac applications.

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Triage of Stroke Patients for Urgent Intervention

6

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Introduction

The neurointerventional treatment of acute ischemic stroke (AIS) continues to evolve at a rapid pace [1, 2]. Advances in devices and operational strategies have been closely paralleled by improved diagnostic algorithms that, when applied using appropriate workflows, greatly assist to achieve the ultimate goal of triage: to identify the ideal patient for urgent intervention: the one most likely to benefit and least likely to suffer an unplanned reperfusion injury [3]. Profiling such an ideal patient, whom we have chosen to label the *High Value Target* (HVT), requires the integration of clinical and imaging diagnostic information [3–6]. In the following pages, we will review the fundamental principles that underscore an optimal workflow for triaging AIS patients who may benefit from urgent intervention, as well as the tools available to convert theory into practice.

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Cerebral Ischemia and Infarction

The cornerstone of the current approach to selecting AIS patients for urgent intervention is an understanding of how the ischemic process affects brain cells, from the moment of onset until the arterial territory compromised becomes permanently damaged (i.e., undergoes infarction). In this context, three important attributes are used to describe the ischemic process (Fig. 6.1): (a) depth of ischemia (i.e., degree of tissue perfusion compromise), (b) distribution of ischemia (i.e., volume of ischemic tissue), and (c) duration of ischemia (i.e., interval of time elapsed since onset). In the past, the relationship between these attributes was thought to follow a simple and linear pattern, giving rise to the premise that the success of AIS reperfusion treatment was *exclusively* time dependent (i.e., "Time is Brain!") [7, 8]. However, more recent experimental and clinical data have demonstrated that the ischemic process follows a more heterogeneous, nonlinear, and less predictable course [3, 6, 9–15]. Thus, although time remains a critical variable in our triage and management of AIS, some patients can successfully undergo reperfusion many hours after the onset of ischemia, provided their profile matches that of a HVT [16–22]. This realization has fueled an expansion of the availability of urgent intervention to this subset of stroke patients, with a consequential improvement in neurologic outcomes [1, 2]. In this con-

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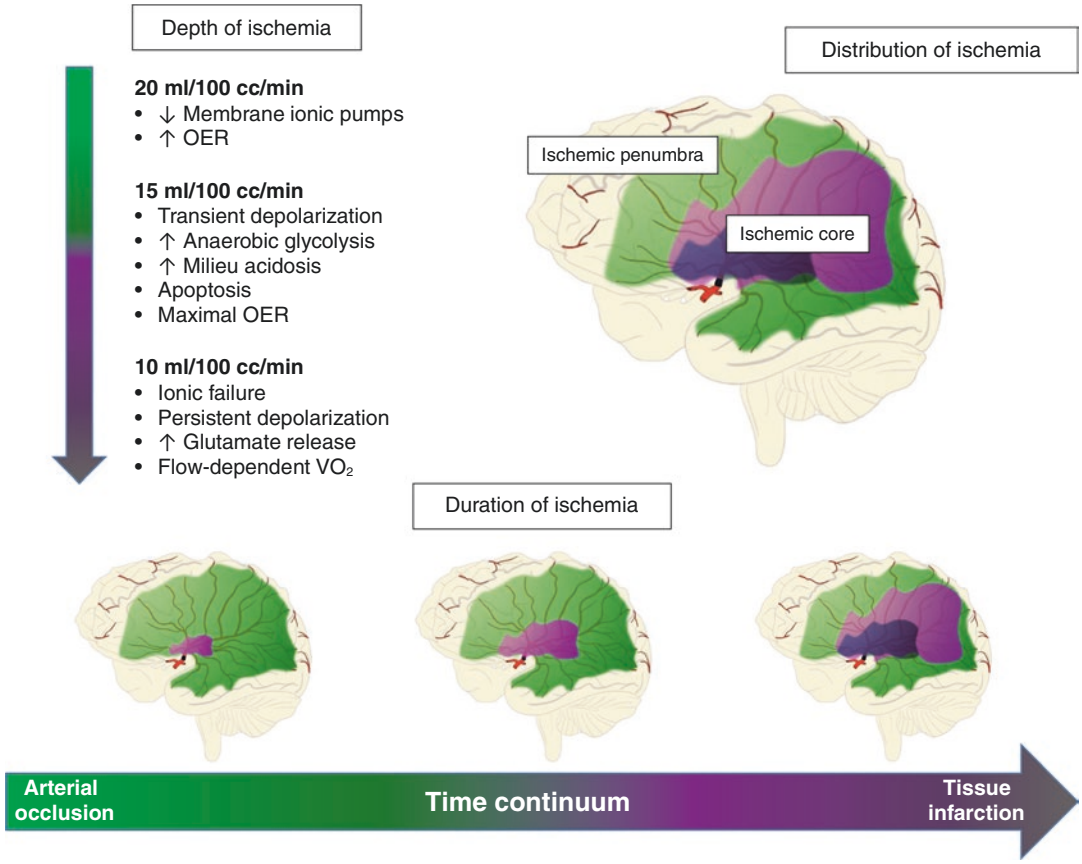

Fig. 6.1 Attributes of the ischemic process
The three important aspects that describe cerebral ischemia are illustrated, including its depth (i.e., severity) with its consequences, distribution (i.e., relation between the ischemic core and the penumbra), and duration (i.e., centrifugal growth of ischemic core and failure of the penumbra along the time continuum)

text, each of the descriptors of cerebral ischemia must be individually understood and incorporated into a diagnostic workflow.

Depth of Ischemia

Under normal circumstances, cerebral blood flow (CBF) is kept relatively constant at approximately 60 ml/100 cc/min by the rapid adaptation of precapillary vasomotor arterioles, whose diameter (< 400 μm) changes in response to a variety of stimuli (e.g., cerebral perfusion pressure, cerebral metabolic demands, serum CO_2, and pH) [23–25]. This steady-state CBF is necessary because brain tissue depends almost exclusively on oxidative phosphorylation for energy production, a process that can only be sustained through the high consumption of oxygen and glucose [23–25]. Acute arterial occlusion results in rapid reduction of tissue perfusion and decreased delivery of substrates, leading to predictable physiologic consequences that have been mapped to the degree of ischemia (Fig. 6.1) [23–25]: (a) Reduction below a threshold of approximately 20 ml/100 cc/min impairs functioning of energy-dependent cell membrane processes that maintain ionic gradients, and this is accompanied by partially compensatory mechanisms such as enhanced oxygen extraction rate (OER); (b)

below 15 ml/100 cc/min there is transient partial cellular depolarization, progressive shift to anaerobic glycolysis, acidosis of the cellular milieu, apoptosis, and maximization of the OER, and (c) a fall under 10 ml/100 cc/min results in ionic failure, persistent cellular depolarization, reduced glucose utilization, excessive glutamate release (i.e., excitotoxicity), and inability to further increase the OER leading to flow-dependent oxygen uptake (VO_2). Unfortunately, from the clinical point of view, it is impossible to know what degree of CBF reduction is producing the patient's symptoms. Moreover, as we will discuss below, the reversibility of the physiologic derangements described is also time-dependent, following an inversely proportional pattern (i.e., lesser levels of ischemia remain viable for longer periods of time) [25, 26].

Distribution of Ischemia

Acute cerebral arterial occlusion results in ischemia that affects the brain steadily, creating the physiologic derangements described above and morphologically appearing as concentric volumes (Fig. 6.1) [27–31]. As such, the most centrally located component (i.e., the "ischemic core") corresponds to the severest blood flow reduction (e.g., ≤ 10 ml/100 cc/min), has been conventionally thought to represent irreversibly damaged brain tissue, and seems to be typically surrounded by an area of lesser flow reduction (e.g., 10–20 ml/100 cc/min) considered potentially viable (i.e., the "ischemic penumbra"). The latter is further surrounded by a third concentric volume with only mild reduction (e.g., ≥ 20 ml/100 cc/min) in blood flow, previously designated as "benign oligemia," whose viability does not seem to be threatened, at least in the early stages of the process. The difference in volumes between the ischemic core and the overall area of reduced tissue perfusion generally corresponds to the surrounding ischemic penumbra, is known as "ischemic mismatch," and is directly proportional to the opportunity for intervention and good clinical outcome [27–31].

Duration of Ischemia

Following acute arterial occlusion, as time elapses, the viability of the ischemic penumbra progressively fails at a certain rate and is replaced by centrifugal expansion of the ischemic core (Fig. 6.1), whose volume is inversely proportional to a good clinical outcome since it is predictive of the final volume of infarcted tissue (i.e., irreversible damaged) [3, 8, 12, 15, 23–26, 32–35]. The most recent evidence suggests that this infarct growth rate (a) is subject to a considerable degree of variability [14, 15, 36], (b) is largely dependent on the functional performance of the collateral circulation [11, 13, 15, 37, 38], and (c) significantly slows down over time, remaining stable for prolonged intervals that can last many hours [10, 35]. In fact, several models have confirmed that infarct growth rate is nonlinear, decreasing over time as infarct volume increases, eventually leveling off along an exponential decay (increasing form) asymptotic curve [3, 10, 11, 13, 34, 35]. Therefore, although the time interval elapsed since the onset of ischemia (i.e., the moment of actual arterial occlusion) must always be considered one of the criteria for identifying HVT patients for urgent intervention, additional metrics are necessary for optimally triaging these individuals [3–7, 9, 12, 20, 26–30, 38–44].

The Ideal Therapeutic Profile: High Value Target

Urgent endovascular intervention is shown to improve outcome of AIS patients with acute large arterial occlusion (LAO) [16–19, 21, 22, 45]. The practical reasons for such a focused application include the following: (a) The occurrence of a LAO typically results in very severe neurologic deficits (i.e., high scores in the National Institutes of Health Stroke Scale (NIHSS)); and in stroke syndromes that are easily recognizable [46], (b) the occluded large artery is of sufficient caliber to allow procedural completion using currently available devices; and (c) the occlusive clot bur-

den is so large that, even in cases when AIS patients present within short intervals after the estimated time of onset (ETO), exclusive treatment with intravenous tissue plasminogen activator (IV-tPA) has historically proved to be wholly ineffective and possibly risky when followed by urgent intervention [22, 47–51]. Presently, however, the emergent triage of AIS patients for urgent intervention demands factoring additional metrics, in order to properly identify HVT patients, especially in cases presenting at prolonged intervals after the ETO [3, 4, 6, 9, 10, 12, 14, 16, 17, 19, 21, 26, 30, 34, 37, 38, 42, 43, 49, 52–56]. Along these lines, estimating the likelihood of the success of urgent intervention at any one point along the time continuum requires having information about the difference between the volume of already infarcted tissue (i.e., beyond recovery) and the volume of tissue remaining at risk to progress to infarction (i.e., salvageable). This dichotomy is of particular importance since the former has consistently been shown to directly correlate with mortality, poor outcome, and therapeutic complications (e.g., hemorrhagic transformation) [3, 33, 41, 54, 57]. Based on these considerations, we frame our profiling of HVT patients for urgent intervention using the following criteria: (a) clinical presentation (i.e., stroke syndrome and its evolution), (b) volume difference between tissue likely to be infarcted and that remaining at risk (i.e., degree of ischemic mismatch), and (c) documentation of an identifiable LAO suitable for intervention.

Clinical Syndrome

The two principal syndromes to consider are those resulting from occlusion of (a) the internal carotid (ICA) and/or the middle cerebral (MCA) arteries and (b) the basilar BA and/or "isolated" dominant vertebral (VA) arteries. As noted above, these are easily recognizable [46], their natural histories are characterized by high morbidity and mortality, and their treatment with IV-tPA is largely ineffective in restoring adequate tissue perfusion or leading to good outcomes in a substantial proportion of patients. The syndromes associated with occlusion of the ICA and MCA can be virtually indistinguishable, depending upon a variety of collateral patterns, and often differing in a matter of magnitude. They are characterized by major cerebral hemispheric dysfunction, contralateral gaze paresis, hemianopia, and a motor deficit that affects the face and upper limb to a greater degree. Similarly, LAO in the vertebrobasilar system results in syndromes with catastrophic implications [46]. Proximal or mid-BA occlusion compromises the entire brainstem and cerebellum, as it also does occlusion of an "isolated" dominant VA (i.e., no contralateral vertebral artery collateral flow). This is manifested by a severely depressed level of consciousness, hemi- or quadriparesis, bilateral gaze palsy, and a variety of other brainstem dysfunction signs. Occlusion of the top of the BA characteristically leads to a combination of (a) altered sensorium, (b) visual and ocular motor abnormalities, and (c) long tract dysfunction (i.e., the "Top of the Basilar" syndrome) [46]. A partial form of this syndrome accompanies unilateral occlusion of the posterior cerebral artery (PCA) origin and is characterized by highly congruous visual field defects, with concurrent disorders of eye movement control and/or behavioral abnormalities [46]. Finally, in the carotid system, occasionally a patient presents with occlusion of the origin of an anterior cerebral artery (ACA) in the context of lacking an anterior communicating artery (AComA). The resulting syndrome includes contralateral hemiparesis, selectively affecting the lower limb and, at times, abulia [46].

In addition, more recent advances in technology and procedural experience have allowed the application of interventional techniques to the treatment of patients whose stroke syndrome stems from acute closure of a major branch of one of the large brain arteries described [58]. These patients deserve separate consideration, since their neurologic deficits are of lesser severity (i.e., lower NIHSS scores), they have smaller clot burdens [51] and a somewhat higher response rate to IV-tPA, and their benefit/risk ratio is lower. We have chosen to label this subset as *Not-so-Large Arterial Occlusion* (NSLAO), a group that primarily includes acute closure of an MCA divi-

sion (i.e., M2). These patients display partial forms of the full MCA syndrome, largely motor dysfunction for the anterosuperior division, and sensory/perceptual deficits for the posteroinferior division [46].

The evolution of the stroke syndrome over time is just as important as its clinical appearance and encompasses both its ETO and its progression pattern along the time continuum. In order to assess all other variables required to identify HVT patients and qualify them for urgent intervention, it is imperative that the ETO is determined with as much precision as possible [59]. This is frequently difficult since these patients present with NIHSS scores that are extremely elevated, making it difficult for them to provide the necessary historical details. Ideally, the moment of acute LAO that results in the neurologic deficit is *witnessed*, and, therefore, the witnesses can provide a fairly accurate ETO. However, in those patients whose AIS onset is *unwitnessed*, there is an implicit component of uncertainty within their ischemic time continuum: the interval between the moment of onset and the time they were found! Historically, the conservative approach to dealing with this uncertainty has been to assign the time they were "last known well" (LKW) (i.e., at their baseline and without acute symptoms) as a surrogate for the actual ETO, thereby reducing the risk of urgent intervention. Nevertheless, as we will review, the incorporation of additional criteria in the workflow to identify HVT patients allows the ability to qualitatively narrow the uncertainty component of the ischemic interval, reducing the importance of the LKW time [60, 61].

Ischemic Penumbra Mismatch

As noted above, the difference in volumes between the likely infarcted tissue and the overall area of reduced tissue perfusion corresponds to the potentially salvageable tissue (i.e., the "at-risk" tissue, or ischemic penumbra) and is directly proportional to the opportunity for successful urgent intervention and good clinical outcomes. It is generally agreed that smaller infarct volumes are associated with better outcomes, and a lesser risk of complications, following intervention. Therefore, the wider the gap in volume between these two variables (i.e., the larger the mismatch), the greater the likelihood that the patient can be qualified as a HVT for urgent intervention [10, 20, 21, 30, 43, 44, 54].

In practice, any estimation of these two parameters results in one of four types of perfusion maps (Figs. 6.2 and 6.3), based on a contingency grid of the dichotomous assessment of the ischemic core and the ischemic mismatch (i.e., either "small" or "large") using operational definitions akin to those in published series (Table 6.1) [3]. Such a scheme allows identification of two extreme types (I and IV) with the clearest clinical implications, particularly as the therapeutic window becomes increasingly prolonged. Patients displaying type I perfusion maps (e.g., Patient #1; Fig. 6.4) represent the ideal HVT for urgent intervention, almost irrespective of their time of presentation relative to their ETO. In fact, it is precisely this type of patient the one consistently selected for participation in the most important prospective series (Table 6.1), representing a major driving force for their unmistakable success [16–19, 21, 22]. Conversely, the identification of a type IV perfusion map (e.g., Patient #2; Fig. 6.5) should be of great concern, particularly as time elapses, since it represents the coexistence of a large volume of a likely injured tissue, concurrent with a small volume of salvageable brain [3, 17, 44, 57]. In fact, patients with type IV perfusion maps were consistently excluded from randomization into the major prospective studies (Table 6.1) [16–19, 21, 22].

The remaining two types of perfusion maps (i.e., II and III) have a less predictable fate and, therefore, represent a greater clinical challenge. Patients with type II perfusion maps (Figs. 6.2 and 6.3) usually present with minimal clinical symptomatology (i.e., low NIHSS score) and yet an evident LAO. These patients typically have what has been termed an "exuberant" collateral circulation, resulting in an exceedingly small volume of ischemic penumbra and a neurologic deficit characterized by a surprisingly low NIHSS [62–64]. This scenario invariably leads to a pre-

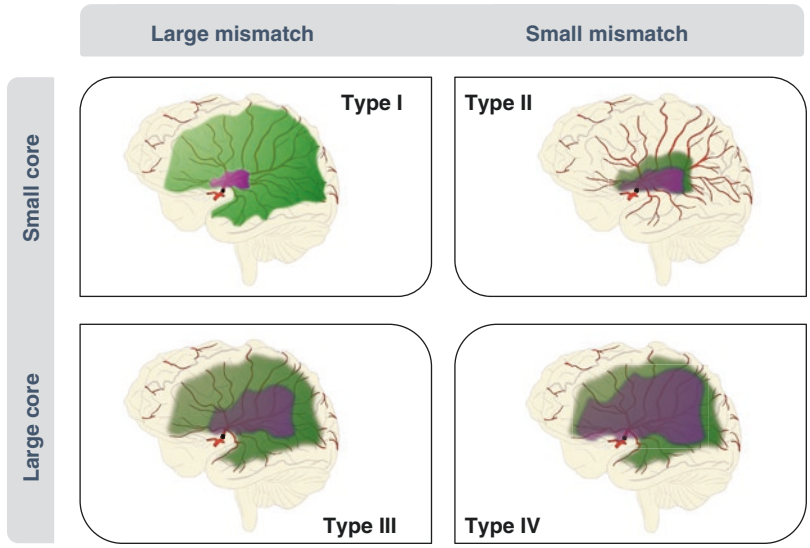

Fig. 6.2 Types of cerebral perfusion maps for stroke triage
Contingency grid based on a dichotomous assessment of the volume of ischemic core and penumbra mismatch, showing the four possible types of cerebral perfusion maps. Types I and IV represent the two extremes, the former being ideal for profiling a patient as a HVT for urgent intervention, while the latter represents the poorest set of attributes for such treatment (i.e., little to gain and a lot to lose). Types II and III, however, have less predictable fates, and yet the literature seems to favor interventional treatment (see text for additional information)

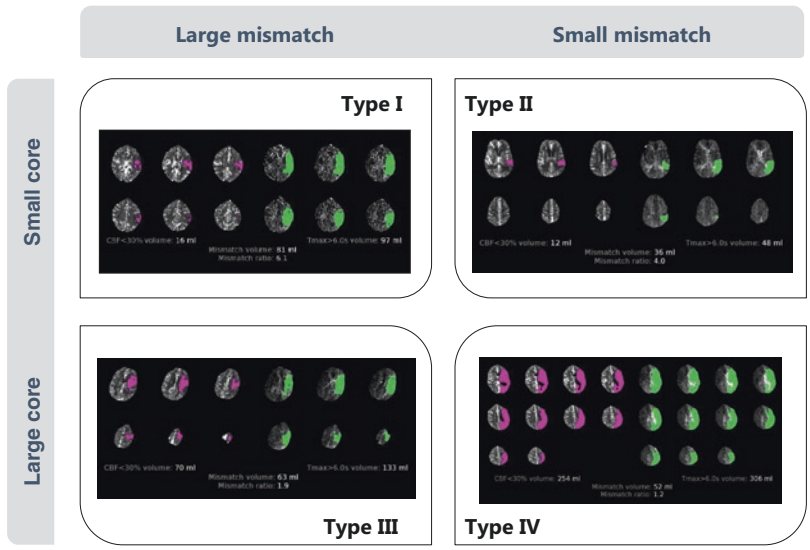

Fig. 6.3 Practical examples of perfusion map types based on CTP studies
Using current dedicated software (RapidAI™ from iSchemaView, Inc., San Mateo, CA in these cases), it is possible to expedite a more accurate assessment of the ischemic penumbra mismatch during triage. Note that the software provides numerical volume information about the ischemic brain tissue (i.e., Tmax; green volume), the ischemic core (i.e., CBF; pink volume), and the difference between these two (i.e., ischemic mismatch). The latter is expressed both as an absolute volumetric subtraction and a ratio

Table 6.1 Cerebral perfusion criteria incorporated for inclusion and/or exclusion into some of the prospective clinical studies

Study (type of criteria)	Ischemic core	Ischemic penumbra
EXTEND-IA (inclusion) [17]	Volume < 70 cc	Mismatch volume > 10 cc AND Mismatch ratio > 1.2
ESCAPE (exclusion) [18]	Low CBV AND Very low CBF in >1/3 OR ASPECTS < 6	Not specified
SWIFT PRIME (exclusion) [22]	DWI volume > 20–50 cc[a] OR Low CBV volume > 15–40 cc[a]	Tmax > 10 s Volume > 100 cc OR Volume ≥ 15 cc PLUS Mismatch ratio > 1.8
REVASCAT (exclusion) [19]	Low CBV for ASPECTS <7 OR Abnormal DWI for ASPECTS <6	Not specified
DAWN (inclusion) [21]	Volume ≤ 20–50[a]	Not specified
DEFUSE 3 (inclusion) [16]	Volume < 70 cc	Mismatch volume > 15 cc AND Mismatch ratio > 1.8

[a]Age-dependent criteria applied to subpopulations

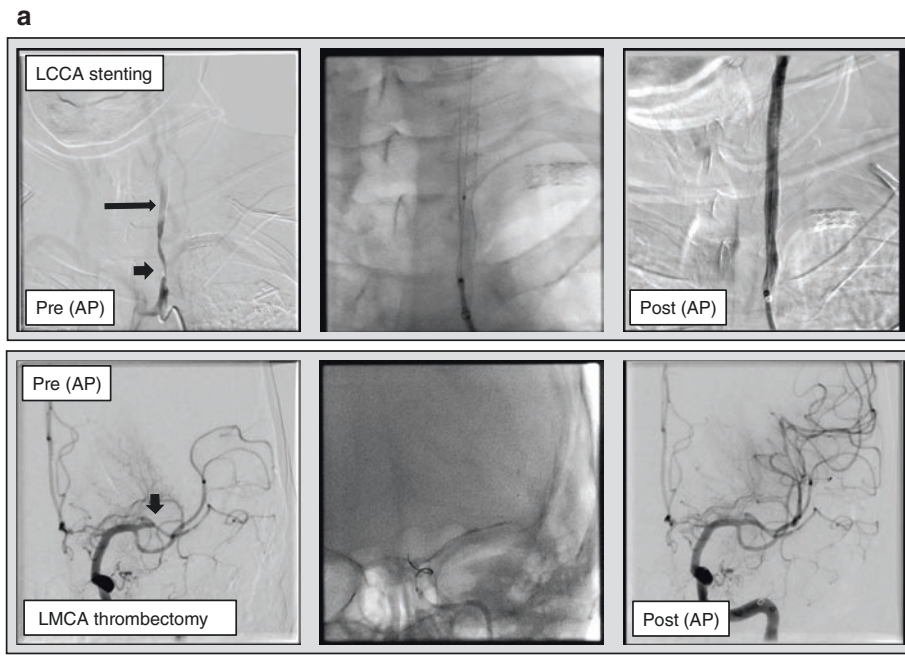

Fig. 6.4 Patient example #1
A 75-year-old woman presented with a sudden syndrome consistent with left hemisphere ischemia. (**a**) Her triage resulted in treatment by means of a *thrombectomy PLUS* procedure that encompassed angioplasty and stenting of a severe left common carotid artery (LCCA) intrathoracic stenosis (upper panel), followed by thrombectomy of the left middle cerebral artery (LMCA). The underlying stenoocclusive pathology (upper panel; short arrow) was associated with downstream intraluminal thrombus (upper panel: long arrow). The occluded LMCA is indicated in the lower panel by the short arrow. (**b**) The decision to proceed with urgent intervention was based on a triage process that rendered a perfusion map type I (left panel). The procedure was successful in restoring perfusion to the bulk of the left hemisphere (middle panel). Only the left angular artery had a residual perfusion defect (middle panel; white arrows), which resulted in the final volume of ischemic injury

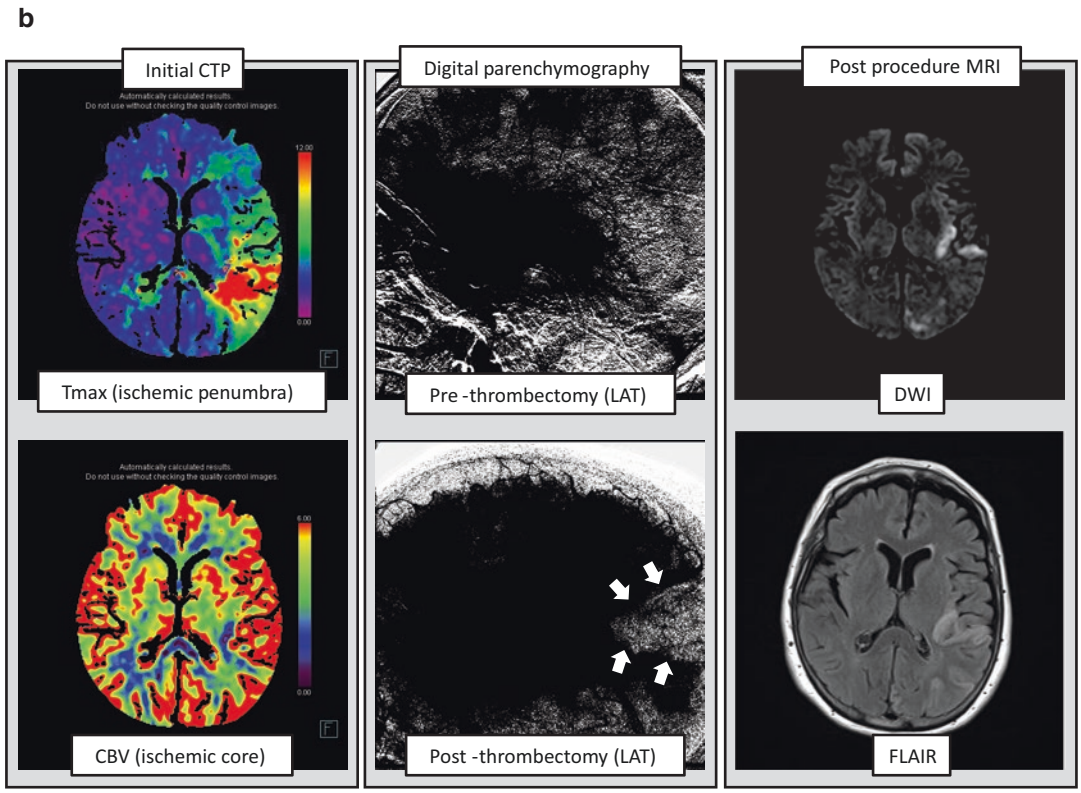

Fig. 6.4 (continued)

dictable clinical conundrum: Should the patient undergo thrombectomy, with its inherent small yet potentially serious procedural risk, or be managed conservatively, risking the possibility of delayed neurologic worsening should the collaterals become incapable of maintaining flow over time? The most recent literature favors proceeding with urgent intervention rather than offering the more conservative approach of inpatient observation, although prospective randomized data may be necessary in order to definitely qualify these patients as HVT for urgent intervention [65–70].

Finally, type III perfusion maps (e.g., Patient # 3; Fig. 6.6) probably represent a transitional stage between type I and type IV. As such, they lack the predictability of either of these two extremes, making them an optimal topic for additional research efforts, particularly in relation to (a) the significance of the ischemic core during the early hours of ischemia, a topic of considerable controversy [71–73], and (b) the factors that relate the volume of ischemic core and the risk of symptomatic hemorrhagic complications [57]. Furthermore, since these patients are likely to show moderate neurologic deficits, and considering the distinct possibility that the volume of ischemic core is irreversibly injured, they also illustrate the ethical dilemma of what is an acceptable neurologic deficit. Still, the most recent literature suggests that offering urgent intervention is reasonable, particularly within early therapeutic windows, and that the conventional ischemic core volume thresholds may be mistakenly lower than clinically tolerated [44, 73–75].

Large Arterial Occlusion

The third attribute that comprises the HVT profile of patients likely to benefit from urgent

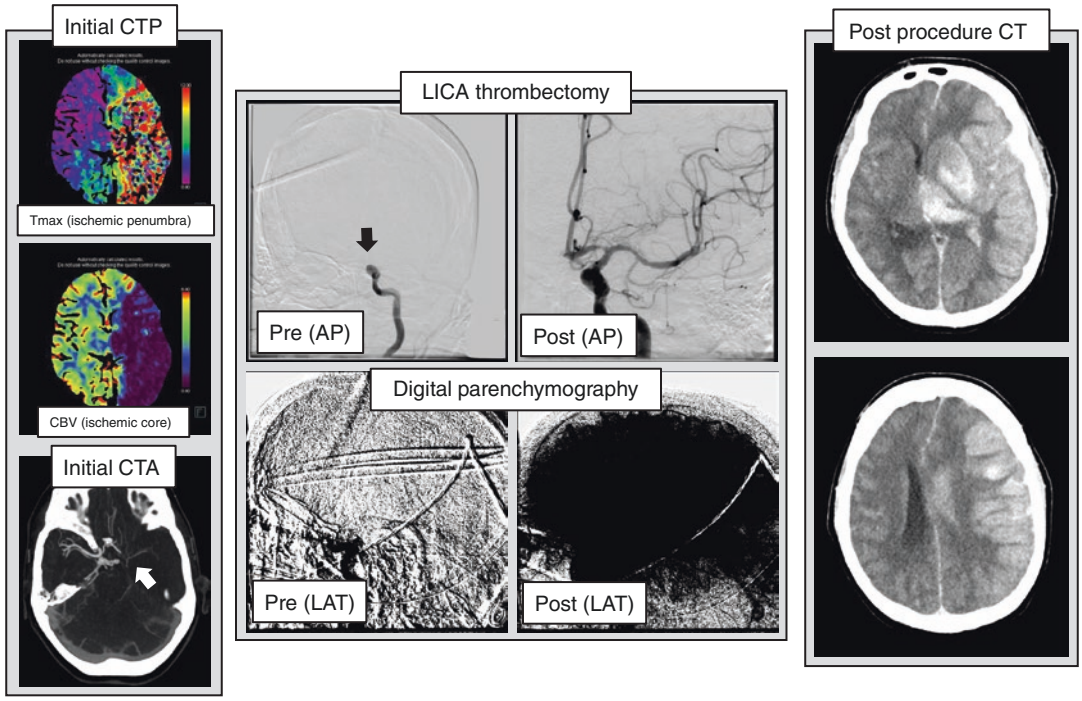

Fig. 6.5 Patient example #2
A 64-year-old woman presented within 3 h following the sudden onset of a syndrome consistent with left hemisphere ischemia, despite taking apixaban (Eliquis™, Bristol Myers Squibb, Inc., New York, NY) for atrial fibrillation. Her triage process rendered a perfusion map type IV (left panel), as well as evidence of a left internal carotid artery (LICA) occlusion (left panel; white arrow). Note the severity of the perfusion defect of the ischemic core, despite a relatively early presentation. Although the *simple thrombectomy* procedure was successful in restoring perfusion to the bulk of the left hemisphere approximately 4 h after onset (middle panel), the patient deteriorated within a few additional hours, eventually succumbing from a reperfusion hemorrhage (right panel)

stroke intervention is an obvious one: the presence of an identifiable LAO that would allow the interventional procedure to be both feasible and reasonable. Qualifying any particular LAO occlusion based on these procedural requirements depends on its location (i.e., target arterial segment) [58, 65, 67, 70, 76–80], extent (i.e., clot burden) [49, 51], and associated cerebrovascular pathology (i.e., underlying or tandem steno-occlusive lesions) [79, 81, 82]. Using these three criteria, it is possible to categorize the type of urgent intervention, matching each to somewhat different HVT patients (Table 6.2). The overwhelming amount of the existing literature directly derives from urgent treatment of acute embolic occlusion of the MCA [16–19, 21, 22] and, to a lesser degree, of the BA [76, 83–86]. These two scenarios typically represent ideal situations for treatment via *simple thrombectomy*, whereby the occluding particle is directly removed using stent retrievers, catheter aspiration, or their combination. Generally, other than requiring more than one attempt (i.e., "pass") [87, 88], the operational complexity is minimal and the procedural blueprint is straightforward (e.g., Patients #2 and 3; Figs. 6.5 and 6.6). Such an approach can be extended to treatment of acute "isolated" ACA [89–92] or PCA [78, 80, 93] origin occlusions, although they are less common and may display a slightly lower benefit/risk ratio. Similarly, embolic occlusion of a second-level arterial branch only requires a slightly more careful *NSLAO thrombectomy*, which can generally be accomplished with comparable success, although a marginally lower benefit/risk

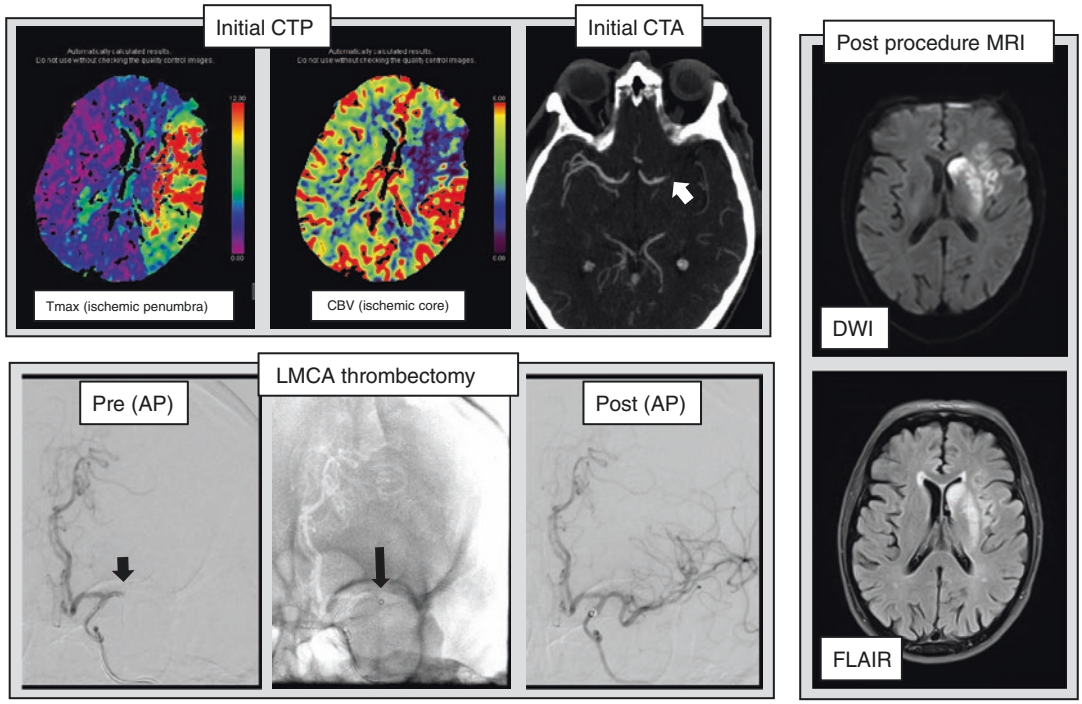

Fig. 6.6 Patient example #3
A 79-year-old man presented with a sudden syndrome consistent with left hemisphere ischemia. His triage process rendered a perfusion map type III (upper panel), as well as evidence of a left middle cerebral artery (LMCA) occlusion (upper panel; white arrow). This was confirmed by angiography (lower panel; short arrow), and a *simple thrombectomy* by direct catheter aspiration (lower panel; long arrow) was successful in restoring perfusion to the bulk of the left hemisphere. Only volume comparable to the original ischemic core was later found to be infarcted (right panel), and the patient underwent major neurologic improvement prior to discharge

ratio [58, 77, 94–98]. Finally, however, some patients present with a LAO that requires more than just clot removal, by virtue of the presence of concurrent steno-occlusive pathology. These *thrombectomy PLUS* cases must be carefully assessed since the operational requirements are more complex and the procedural interval is always prolonged (e.g., Patient #1; Fig. 6.4). Two different attributes must be considered when assessing these patients: (a) location (e.g., upstream vs. in situ) and (b) type (e.g., atherosclerosis vs. dissection) of the steno-occlusive pathology. In these cases, the operator must preemptively assess the likely need for more extensive thrombectomy (i.e., large clot burden), balloon angioplasty, or even stenting of the causative arterial lesion [81, 82, 99–101].

Tools Review

Clinical Assessment

The triage of patients in search for HVT profiles that are likely to benefit from urgent intervention begins with acquiring information about the ETO or its surrogate the LKW time, followed by an account of how the symptoms have and are continuing to evolve over time. As noted above, this is much easier in cases when the AIS onset is *witnessed*, and additional information about the health and neurologic status of the patient prior to the onset also has paramount importance. Ideally, this information is gathered by the emergency medical personnel and conveyed to the stroke and interventional teams *en route* to the ED [102–

104]. The second component is the assessment of the neurologic deficit. In the ED, the ideal tool for this purpose continues to be the NIHSS, since it has been shown time and again to be reproducible, comparable, and predictive. It is also ideal to have information about stroke severity prior to arrival to the ED, and, to this end, several different stroke scales have been created for the purpose of being used on the field [105]. Although not one of them is particularly better than the others, the point is to incorporate within the workflow some measure to alert the receiving stroke team that there is a *high probability* of the transported AIS patient requiring urgent intervention [105].

Estimation of Ischemic Mismatch: Perfusion Imaging

Because of its significant correlation with outcomes, the importance of infarcted volume in the ischemic mismatch paradigm cannot be overstated. In practice, infarct volume estimation can be carried out using one of several diagnostic methodologies that generally depend on surrogate markers to ascertain tissue viability [3, 10, 20, 30, 43, 44, 54]. Although given sufficient time, it is feasible to accurately measure the volume of infarcted brain tissue using CT or MRI, such luxury cannot be afforded during the urgent management of patients with AIS [106–109]. On the contrary, in order for such assessment to be clinically meaningful, it must be reliably carried out even during the very early stages of the ischemic process. However, it is well known that there is an inherent delay in the demonstration of infarcted tissue by CT, generally leading to underestimation of the infarct volume [106–109]. Nevertheless, different paradigms have been used to gauge the presence of infarcted tissue in the initial CT study, notably the Alberta Stroke Program Early CT Score (ASPECTS), which has recently been incorporated into some of the existing dedicated software for imaging analysis, including artificial intelligence (AI) algorithms (RapidAI™, iSchemaView, Inc., San Mateo, CA) [106–110]. Using standard CT perfusion (CTP) protocols, both the measured CBF and cerebral blood volume (CBV) have independently been noted to correspond with the ischemic core and to predict final infarct volume [111–113]. Conversely, MRI measurements need to be carefully chosen, considering the tendency to overestimate volumes when using T2-weighted images [9, 114–116]. In general, the fluid attenuated inversion recovery (FLAIR) sequence seems to correlate well with infarcted tissue [9, 114–116].

The reciprocal parameter to the volume of infarcted brain tissue is the "at-risk" volume of tissue that is potentially salvageable by means of reperfusion strategies. It is generally agreed that this parameter corresponds to the ischemic penumbra, and its estimation using various imaging techniques has also required the use of surrogate markers. Diffusion-weighted imaging (DWI) MRI allows very early detection of ischemic brain tissue, making it very attractive for early estimation measurements [29, 32, 34, 43, 52]. Advances in functional MRI during the decade of the 1990s led several groups to postulate that the volume difference between DWI and PWI abnormalities constituted the ischemic penumbra [29, 32, 34, 43, 52]. More recently, this paradigm has been challenged, not only on the basis of the demonstrated reversibility of some of the early DWI abnormal findings [117, 118] but also due to the fact that the PWI abnormality leads to overestimation of the penumbra due to its inclusion of the adjacent areas of "benign oligemia" mentioned above [30]. CTP provides an alternative method for estimating the volume of tissue at risk of subsequent infarction while allowing the acquisition of relevant data with considerable ease and speed during the urgent evaluation of AIS patients, effectively bypassing some of the limitations of MRI techniques [12, 40, 41, 56, 112, 119]. However, critics also point out its low signal-to-noise ratio as an inherent weakness of the technique, one that may lead to measurement errors in individual patients [71].

Both PWI and CTP rely on several surrogate markers for the evaluation of perfusion defects, the most effective being those that measure delay and dispersion of flow through collateral path-

ways. This group includes (a) the mean transit time (MTT) of the contrast through the tissue, (b) the time to peak (TTP) or raw concentration-time curve, and (c) the time to peak of the deconvoluted tissue residue function (Tmax) [53, 56]. Thresholds and limits for the use of these measurements for patient selection have also been incorporated among the inclusion and exclusion criteria of various studies (Table 6.1). It is generally agreed that Tmax delays greater than 6 s provide the best criterion for identifying tissue at risk to progress to infarction unless reperfusion occurs, spontaneously or therapeutically. Additionally, the identification of the ischemic penumbra has also been based on calculating the ratio between the volume of hypoperfused tissue and that of the ischemic core. All of this taken into consideration, irrespective of which imaging modality is used and which surrogate marker is chosen, the principles of the dynamic and reciprocal relation between the core and the penumbra volumes are the same, and, for the purposes of urgent AIS evaluation and HVT patient profiling, it should be possible to estimate both of them at the bedside and in real time. Presently, most institutions utilize computerized algorithms via dedicated software to expedite these calculations and assessments, notably RapidAI™ (iSchemaView, Inc., San Mateo, CA) and Viz.AI™ (Viz.AI, Inc., San Francisco, CA), both of which incorporate AI into their algorithms (Fig. 6.3). The expectation is that such an approach facilitates the identification of HVT patients [120], although, in our opinion, these technologic advances cannot replace the ability of expert interventional operators to integrate clinical and imaging information in order to identify HVT patients and the best approach to their endovascular treatment.

Documentation of the Occlusive Process: MR and CT Angiography

Our ability to identify in real time the LAO requires rapid and reliable vascular imaging. On the practical side, CTA has proved to be the most useful tool, since it can be applied readily as part of an efficient imaging strategy within an optimal workflow for urgent care. Generally speaking, the CTA should include not only the intracranial but also the extracranial segments of the cerebral vasculature, in order to parse patients according to their procedural needs (Table 6.2). Multiplanar reconstruction is necessary in order to more precisely define the occlusive process

Table 6.2 Attributes of the various types of HVT stroke patients according to the types of intervention necessary

	High value target (HVT) attributes		
Procedural complexity	Clinical syndrome	Ischemic mismatch	Large arterial occlusion
Category 1 Simple thrombectomy	NIHSS ↑↑↑ (i.e., >15)	CTP types I or II (III?!)	MCA, ICA(t), ACA(i), BA, VA(i)
	COMMENTS: Minimal operational complexity and straightforward procedural blueprint. Enerally a quick procedure, with small risk, supported by the bulk of the literature		
Category 2 NSLAO thrombectomy	NIHSS ↑ or ↑↑ (i.e., 6–14)	CTP type I (penumbra ≥ 70 ml)	MCA(d)
	COMMENTS: Somewhat lower benefit/risk ratio since target vessel is smaller. Operational completion can be quick. The supporting literature is limited		
Category 3 Thrombectomy PLUS	NIHSS ↑↑↑ (i.e., >15)	CTP types I or II (III?!)	Underlying or tandem stenosis
	COMMENTS: Operational complexity can be considerable, and completion is typically prolonged by the need to address the concurrent pathology. The supporting literature is limited yet favorable		

and to better plan for the most appropriate type of neurointerventional procedure. The sensitivity and specificity of CTA for detecting LAO are a factor of the amount of clot burden [49], the duration of the occlusive process, and the size of the occluded artery, both progressively decreasing as these parameters become smaller in magnitude. Although we favor incorporating CTA into urgent AIS evaluation workflows, MRA can also be useful in the identification of LAO, particularly when ischemic mismatch assessment is also based on MRI techniques, allowing seamless evaluation, or in scenarios in which radiation or iodinated contrast administration is of concern (e.g., pediatric AIS). In addition, CTA is also helpful in assessing the degree of collateral support for the occluded arterial territory, a measure that has been found to have a helpful and predictive value [62–64].

Optimal Triage Workflow

Ideally the different tasks involved in triaging AIS patients in search of those who qualify as HVTs for urgent intervention should be carried out following a predetermined workflow that assures consistency and expediency. A sample of such a workflow, the one we favor because of its proved usefulness in our various clinical practices, is illustrated in Fig. 6.7 and is displayed as a cross-functional flowchart that assigns each diagnostic step its optimal location in the sequence of events while matching it with the necessary resources (both human and physical) for its completion. Although by no means perfect or inclusive of all possible scenarios, such a workflow provides the framework for specialized multidisciplinary management of these patients while allowing longitudinal monitoring, operational scrutiny, outcome analysis, and quality improvement processes.

The process begins with the assessment of all patients brought to the ED with suspected AIS. This is typically carried out by the vascular neurology team, following their activation as part of a Code Stroke Alert by the ED staff [121]. Should the preponderance of information point to an alternative diagnosis (which historically happens on an average of 25–50% of the cases) [122–124], the alert can be cancelled, the team can stand down, and the patient's care can be shifted to different management processes (Fig. 6.7). Otherwise, since such a neurologic evaluation is carried out while the patient is *en route* to the CT scanner, the decision-making process is expedited, including qualifying patients for appropriate treatment with IV-tPA, barring the discovery of imaging evidence of a contraindication for such an approach in the upcoming CT study. Next, while IV-tPA is administered in the CT scanner to those patients who qualify for such treatment, additional imaging studies geared are defining the degree of ischemic mismatch, and identifying the LAO can be completed as a parallel process (Fig. 6.7). Once all the clinical and imaging information is available, if the patient is profiled as a HVT for urgent intervention, the entire interventional team (including anesthesiology support staff) can be alerted in unison (i.e., via a group paging system), as the patient is transferred to the angiography suite for procedural completion (Fig. 6.7). Once the procedure is completed, all of these patients are transported to the neurointensive care unit for continued care.

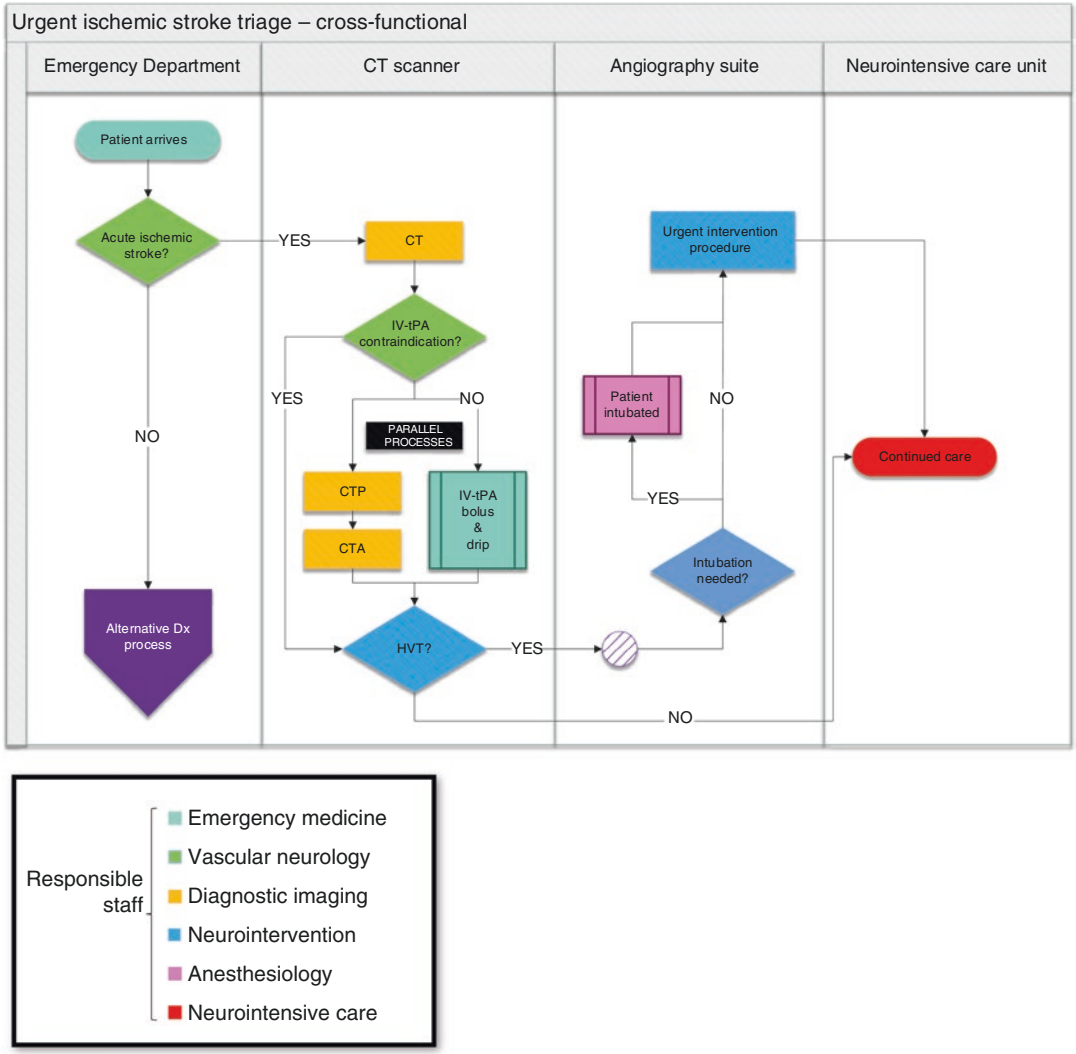

Fig. 6.7 Cross-functional flowchart of an urgent ischemic stroke triage process. Striped circle = neurointerventional team group page activation

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7 Endovascular Reperfusion of Acute Large Vessel Occlusion Stroke

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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. These reports signaled a meaningful benefit with IA therapies and paved the way for further endovascular studies of not only thrombolytics but also mechanical devices. Several mechanical thrombectomy (MT) devices have been approved by the US Food and Drug Administration for the treatment of acute large vessel occlusion (LVO) stroke as the sole therapy or in combination with intravenous thrombolysis (IVT) [3]. These devices include the Merci retrieval and Penumbra aspiration systems, as well as the second-generation Solitaire-FR and Trevo stentrievers. Additionally, stentrievers and aspiration systems are frequently used in combination to optimize MT times and recanalization rates. Five randomized controlled trials were published in 2015 that demonstrated significant clinical benefits of MT for LVO within 6 h from last known well (LKW). Meta-analysis of these trials demonstrated a number needed to treat of 2.6 to improve neurological outcome at 90 days [4]. In 2018, two additional landmark LVO trials, DAWN and DEFUSE 3, established the benefit of MT in the extended time window up to 24 h LKW in select patients with favorable perfusion imaging [5, 6]. Most recently in 2020, the DIRECT-MT trial randomized thrombolysis-eligible LVO patients to IVT with MT versus MT alone and concluded that the two strategies were noninferior [7]. The SKIP study shared a similar randomized design but did not show noninferiority of direct MT compared to combined IVT and MT with respect to favorable outcomes [8]. The ASTER trial demonstrated that combined IVT and MT resulted in improved functional outcome with higher recanalization and lower mortality when compared to MT alone [9]. Additional study of direct to MT for IVT eligible LVO is needed to understand this treatment approach that parallels cardiac systems of care for myocardial infarction.

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Endovascular Recanalization Techniques

Intra-Arterial Thrombolysis

The use of IAT as a stand-alone therapy or adjunct to mechanical clot removal has become

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rare. It involves infusion of a thrombolytic agent through a guide catheter in the cervical internal carotid artery or a microcatheter advanced intracranially into or immediately proximal to the occlusive thrombus. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial demonstrated improved outcomes in patients with acute middle cerebral artery (MCA) occlusions treated with IA infusion of prourokinase compared to controls when treated within 6 h of onset, despite an increased incidence of symptomatic intracranial hemorrhage (ICH) [10]. Prourokinase did not receive FDA approval, but numerous other thrombolytic agents including urokinase, reteplase, recombinant tissue plasminogen activator (tPA), and tenecteplase have subsequently been used. Although IAT appears safe after the administration of IV tPA [11–14], there is no dose equivalence among various thrombolytic agents in terms of safety or efficacy [15, 16]. Prior to approval of MT devices, mechanical clot disruption with a J-shaped microwire or an ultrasound microcatheter was shown to be safe and potentially enhance the IA fibrinolytic process [17, 18].

Mechanical Thrombectomy Devices

Merci Retriever

The Merci retriever (Stryker, Kalamazoo, MI) became the first FDA thrombectomy device in 2004 [19]. While no longer widely used, it is of historical interest. 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 large bore 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 retriever [20] showed further improved recanalization rates; however, favorable clinical outcomes (modified Rankin Scale 0–2) only occurred in 36%, and symptomatic intracerebral hemorrhage was 9.8%. The Merci retriever had certain limitations: Tortuous arterial segments and thrombus extending into distal arterial branches negatively impacted recanalization rates [21] as did fibrin-rich clots [22]. Investigators also demonstrated that up to three passes with the Merci retriever were optimal and that additional passes were not only unlikely to achieve recanalization but also potentially increase complication risks [23].

Direct Aspiration Systems

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 LVO [24]. Unlike the Merci retrieval device, the Penumbra aspiration system was designed for direct clot aspiration which minimizes risk of thrombus fragmentation with distal emboli or emboli to new vascular territory [25]. The Penumbra system showed better recanalization rates [26, 27] than those reported in the MERCI trials, and recent randomized studies of first-line therapy with a direct aspiration first-pass technique (ADAPT) have shown noninferiority when compared to stentrievers [28, 29]. Additional aspiration systems include Medtronic Riptide (Covidien, Irvine, CA) and Imperative Care Zoom (Campbell, CA) that received FDA approval in 2018 and 2019, respectively.

Retrievable Stents (Stentrievers)

Stentrievers are widely used, second-generation, MT devices and have demonstrated significant improvement in recanalization rates and time to recanalization, when compared to prior devices [30]. The two most commonly used, FDA-approved stentrievers are Solitaire X (Covidien, Irvine, CA) and Trevo XP (Stryker, Kalamazoo, MI). Meta-analysis of multiple randomized controlled trials demonstrated that early MT with a stentriever was associated with high rates of functional independence and successful recanalization [31].

Combined Aspiration and Stentriever

Today, aspiration catheters and stentrievers are not only used individually as first-line therapy but often combined to optimize recanalization times and rates. The combination of large bore aspiration catheter with a stentriever has been called "Solumbra" and provides several potential synergistic effects. Localized aspiration at the site of the thrombus may promote entrapment of the clot within the stent. It can also reduce the incidence of thrombus fragmentation and distal embolization. Studies of the combined techniques have shown good recanalization rate and favorable mRS outcomes at 90 days [32].

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- to 8-French sheath is generally adequate, but depending on the guide catheter size, a larger sheath may be needed to allow for 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*: A 6-French guiding catheter with a distal segment designed to be positioned within the distal cervical to cavernous segment is currently the norm. These catheters combine a stable proximal end with a flexible, atraumatic, distal tip. 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.
- *Intermediate/Suction Thrombectomy Catheters*: See discussion above.
- *Microcatheter*: A 0.014-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. Additionally, larger microwires including the Fathom-16 (Boston Scientific, Marlborough, MA) and Asahi Chikai-18 (Asahi Intecc, Irvine, CA) may be used for additional intracranial support when advancing microcathers and thrombectomy systems.
- *Thrombolytic/Antiplatelet Agents*: In rare cases, IA t-PA can be used 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. Glycoprotein IIb/IIIa agents are infrequently administered in an acute stroke; the exception being when emergent cervical or intracranial stenting for refractory atherosclerosis is necessary.

Mechanical Devices

- *Sheath*: Although short sheaths are still used in conjunction with balloon guides and larger aspiration systems, a 6-Fr or wider, 90-cm-

long sheath is most often used for MT procedures.
  - *Neuron MAX or BMX* (Penumbra, Inc., Alameda, CA): Long sheaths designed for distal cervical carotid access. The Neuron MAX 088 delivery catheter is braid/coil reinforced and has a 6F OD with 0.088″ ID. The Benchmark BMX96 delivery catheter is reinforced with a laser-cut stainless steel hypotube and has a 6F OD with 0.096″ ID. Although often used in conjunction with the Penumbra aspiration system (see below), these long sheaths are the workhorses for acute stroke interventions.
  - *TracStar LDP* (Imperative Care, Campbell, CA): Large distal platform is a 0.088″ ID intracranial access catheter designed to reach the distal cavernous ICA with enhanced stability and control. It requires placement of an 8-Fr or larger short sheath in the femoral artery.
- *Balloon guide catheter:* These specially designed guiding catheters come in 8F 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 achieve flow reversal. Products on the market include the Stryker balloon guide (Stryker, Kalamazoo, MI) and the Cello balloon guide (Covidien, Irvine, CA).
- *Access wire*: A standard hydrophilic 0.035″ wire 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 or long sheath. This is especially true when using the balloon guide catheters. Alternatively, the Neuron MAX or BMX long sheaths come with select catheters that are used in a co-axial fashion with an 0.035″ wire to selectively catheterize and advance long sheaths into the carotid or vertebral arteries.
- *Microwire*: As described above, there are a variety of microwire sizes ranging from 0.014″ to 0.016″ that may be used to access and cross the target clot.
- *Devices:*
  - *Direct aspiration systems:* The Penumbra (Penumbra, Inc., Alameda, CA), Riptide (Covidien, Irvine, CA), and Zoom (Imperative Care, Campbell, CA) aspiration systems are intended for mechanical clot revascularization and include a family of reperfusion catheters. The Penumbra JET 7, Riptide React 71, and Zoom 88 are the largest aspiration catheters of each lineup. These reperfusion catheters are often delivered to the clot through the use of a triaxial setup including long groin sheath, reperfusion catheter, and microcatheter. Once the clot is crossed with the microwire, the micro and reperfusion catheters are either advanced through or positioned at the proximal clot face. The microwire and microcatheter are removed, and continuous clot aspiration is applied via the reperfusion catheter. The clot may be successfully aspirated or "corked" in the distal tip of the aspiration catheter, after which it is removed from the body.
  - *Stent retrievers*: The two most commonly used stentrievers are Solitaire X (Covidien Medical) and Trevo XP (Stryker Neurovascular) which consist of a nitinol, slotted tube stent attached to a microwire. The Solitaire device comes in 4-mm and 6-mm diameters and 20-mm to 40-mm lengths. It has the unique feature of a longitudinal gap that allows the stent to fold upon itself, potentially creating greater clot engagement. The Trevo XP device varies in size from 3 to 6 mm in diameter and 20–30 mm in length. It has full-length radiopacity within the struts that allows greater visualization and 360 degrees of large cells that potentially allows greater clot engagement. Both stentrievers are deployed through microcatheters with inner diameters ranging from 0.021″ to 0.027″. The delivery microcatheter is positioned across the clot, and the microwire is removed. Next, the stentriever 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 recommended period of 5 min is allowed to pass, permitting the stent to become fully enmeshed in the clot. The stentriever is then pulled out of the arterial system. A proximal balloon guide may be used in conjunction with these devices to achieve flow reversal as previously described.

– *Solumbra technique*: The combination technique involves advancing a 0.021–0.027″ microcatheter with a 0.014–0.018″ microwire across the clot, removing the microwire, and deploying the stentriever. The stentriever then serves as an anchor by which the large bore aspiration catheter may easily advance to the proximal face of the thrombus. If possible, the delivery microcatheter is removed over the stentriever wire to maximize aspiration. The stentriever is pulled back under continuous aspiration, and ideally, the clot is removed within the stentriever or corked in the aspiration catheter tip. However, in the event that the stentriever is unsuccessful, continued direct aspiration may be performed after stentriever removal. The aspiration catheter should then be removed and flushed on the table before an additional pass is performed.

Acute Middle Cerebral Artery Occlusion

Occlusions of the MCA account for the majority of acute intracranial large artery distribution ischemic strokes. Proximal M1 occlusions have reported recanalization rates of 30% within 2 h of IV t-PA [33].

Illustrative Case 1 (MCA Occlusion)

A 52-year-old woman with COVID-19 was transferred from an outside hospital after acutely developing aphasia and right-sided weakness. She required intubation, and advanced neuroimaging demonstrated a left MCA occlusion with favorable mismatch profile. Cerebral angiogram revealed a tortuous cervical left ICA and an ipsilateral left MCA occlusion. A 90-cm Neuron MAX was placed in the cervical left ICA proximal to the tortuosity. A JET 7 aspiration catheter was then advanced distally with the aid of a Velocity microcatheter and Synchro 14 microguidewire. The microcatheter was advanced through the M1 thrombus, and superselective angiography confirmed placement distal to the thrombus in an M2 branch. Mechanical thrombectomy was then performed with a Solitaire stentriever 6 mm × 40 mm and JET 7 aspiration catheter that advanced to the M1 origin following stentriever deployment. Final DSA examination demonstrated complete recanalization of the left MCA distribution (Fig. 7.1).

Acute Vertebrobasilar Occlusion

Vertebrobasilar occlusions account for about 3% of all acute intracranial large artery strokes [33] with high mortality rates ranging 40–80% in some studies as well as a high likelihood of poor functional outcome among survivors [34, 35]. Achieving recanalization results in significant reduction in mortality [36, 37]. 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 [38]. Little is known about thrombectomy treatment of vertebrobasilar artery branch occlusion (VEBABO), including posterior and anterior inferior cerebellar artery and superior cerebellar artery, in acute ischemic stroke. One multicenter study shows that MT for VEBABO is rare but appears to be feasible and effective; however, there is a comparatively high rate of procedure-related hemorrhage [39].

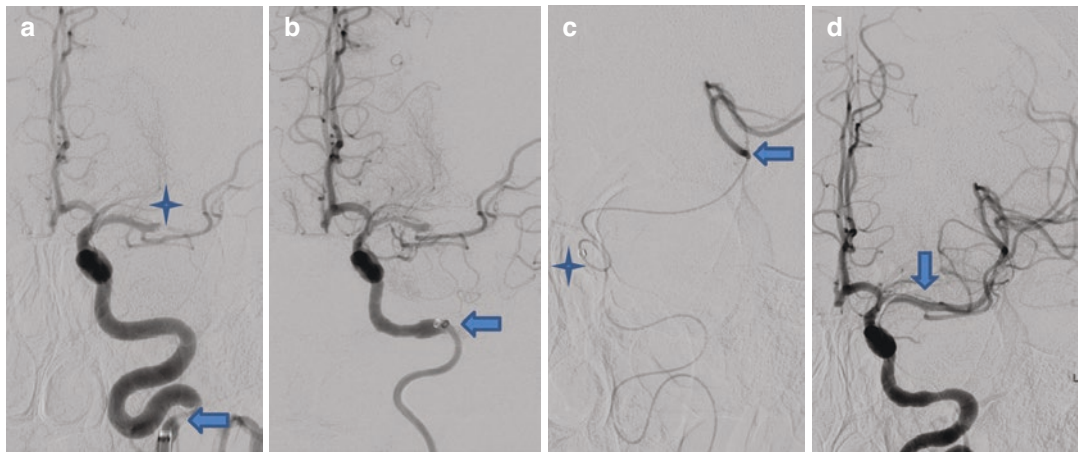

Fig. 7.1 Left MCA thrombectomy. (**a**) Tortuous, cervical left ICA shows vasospasm just distal to the Neuron MAX (*arrow*). The left MCA is occluded at the M1 segment (*star*). (**b**) The JET 7 aspiration catheter is advanced beyond the cervical ICA tortuosity (*arrow*). (**c**) Superselective microcatheter injection demonstrates placement of the microcatheter tip (*arrow*) distal to the clot burden and in a M2 branch. The JET 7 aspiration catheter is further advanced intracranially (*star*). (**d**) The left MCA (*arrow*) remains patent after mechanical thrombectomy with stentriever and aspiration

Illustrative Case 2 (Basilar Occlusion)

A 61-year-old man developed ataxia and difficulty walking for 1 week. His symptoms acutely worsened with right-sided weakness, left gaze deviation, and lethargy. The patient required intubation. Advanced neuroimaging demonstrated bilateral intracranial vertebral artery occlusions with basilar thrombosis which was confirmed with diagnostic cerebral angiography. A Neuron MAX was placed in the left subclavian artery, and a JET D aspiration catheter was advanced with the aid of a Velocity microcatheter and Synchro 14 microguidewire into the distal cervical left vertebral artery. Due to occlusion at the level of C1-C2, the microcatheter could not be advanced intracranially. Therefore, the Neuron MAX was selectively advanced into the right subclavian artery, and the reperfusion system was advanced into the distal cervical right vertebral artery. Under roadmap imaging, a Velocity microcatheter with the aid of the microguidewire was successfully advanced through the occlusion. Superselective angiography confirmed basilar thrombosis, and the microcatheter was further advanced into the proximal left PCA. A mechanical thrombectomy was then performed with a 6-mm × 40-mm Solitaire stentriever and continuous JET D aspiration which was advanced to the V3 segment. Final DSA examination demonstrated complete recanalization of the basilar artery with residual high-grade stenosis of the right vertebral artery V4 segment. TICI 2b reperfusion was achieved due to persistent right PCA occlusion (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 [40, 41]. Updated MT studies with stentrievers and aspiration catheters report significant improvement in recanalization rates in patients with ICA-T occlusions without any additional increase in symptomatic intracranial hemorrhage [42].

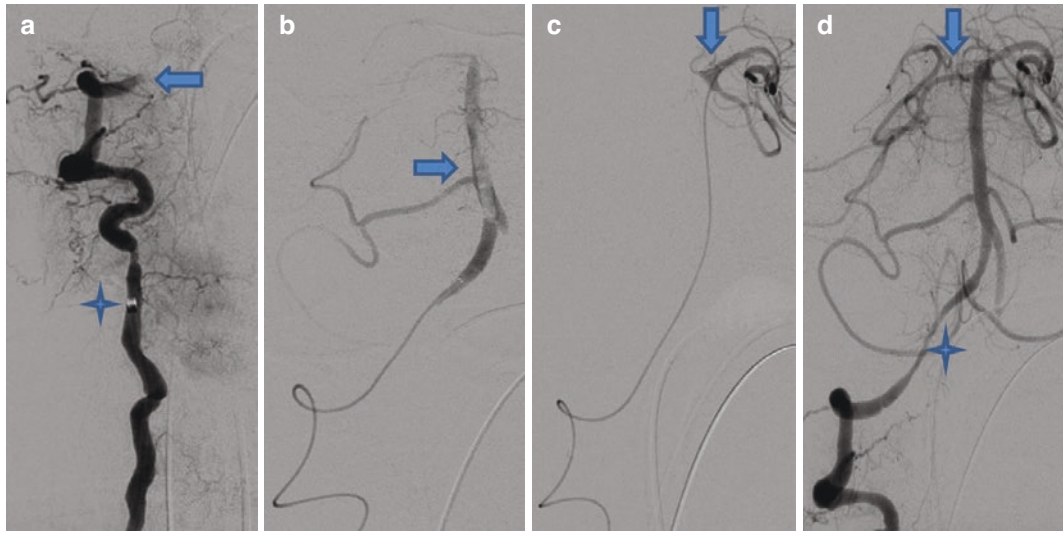

Fig. 7.2 Basilar artery thrombectomy. (**a**) JET 7 aspiration catheter (*star*) is placed in cervical right vertebral artery, and complete occlusion of the V4 segment is seen (*arrow*). (**b**) Superselective microcatheter injection demonstrates basilar artery thrombus (*arrow*). (**c**) Superselective microcatheter injection demonstrates placement of the microcatheter tip (*arrow*) distal to the clot burden in proximal left PCA. (**d**) Final DSA examination demonstrates recanalization of the basilar artery with persistent high-grade V4 segment stenosis (*star*) and right PCA occlusion (*arrow*)

Illustrative Case 3 (Carotid-T Occlusion)

A 32-year-old man with no remarkable past medical history awoke with aphasia, left gaze deviation, and right-sided weakness. He was given IV thrombolysis, and advanced neuroimaging was favorable for MT. Cerebral angiogram was performed with conscious sedation and demonstrated complete occlusion of the left terminus ICA. A 90-cm Neuron MAX long sheath was then placed in the left cervical ICA. Under roadmap imaging, a JET 7 aspiration catheter was advanced with the aid of a Velocity microcatheter and Synchro 14 microguidewire. JET 7 direct aspiration was performed twice resulting in recanalization of the ICA terminus left MCA M1 segment. Persistent distal occlusion was noted in the left MCA M2 inferior branch. The velocity microcatheter was then advanced through the left M2 branch occlusion, and superselective angiography demonstrated catheter tip position distal to the thrombus. A third pass was then successfully performed with a 6-mm × 40-mm Solitaire stentriever. Final DSA demonstrated complete recanalization of the left MCA with TICI 3 reperfusion (Fig. 7.3).

Tandem ICA/MCA Occlusions

Occlusions of cervical ICA and ipsilateral MCA comprise about 7% of all acute intracranial large artery ischemic strokes [33]. Tandem ICA/MCA occlusions are associated with poor outcomes after IVT [43]. Revascularization of the proximal ICA with angioplasty and stent placement 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 [44–46]. The American Heart Association/American Stroke Association (AHA/ASA) 2018 guidelines report that treatment of both extracranial and intracranial occlusions when performing thrombectomy may be reasonable. This technique has also been reported to be safe and feasible in tandem ICA/MCA occlusions in the setting of acute ICA dissection [47, 48].

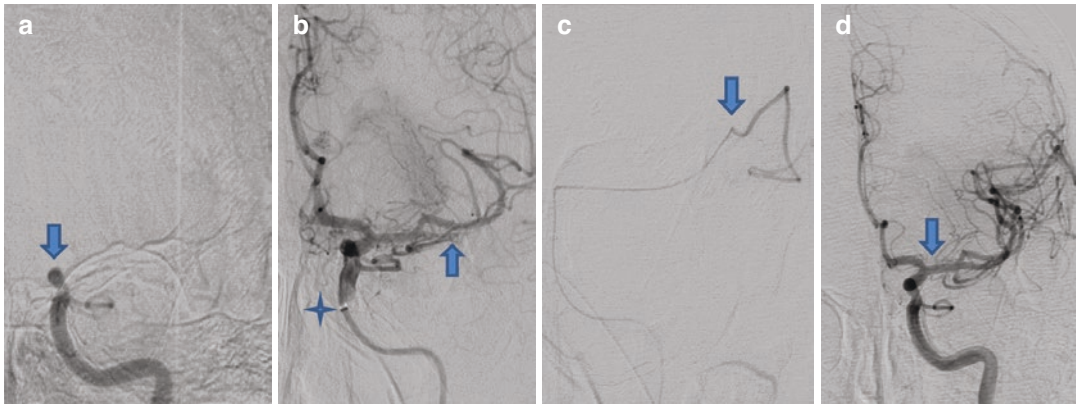

Fig. 7.3 Carotid terminus thrombectomy. (**a**) Complete occlusion of the left ICA terminus is seen at the level of the posterior communicating artery segment (*arrow*). (**b**) The left ICA terminus and proximal MCA are recanalized with JET 7 aspiration catheter (*star*). Residual distal MCA M2 inferior branch occlusion is noted (*arrow*). (**c**) The Velocity microcatheter (*arrow*) is advanced into the occluded left MCA M2, and superselective angiography confirms positioning distal to the thrombus. A mechanical thrombectomy with Solitaire stentriever was then performed. (**d**) Final DSA examination demonstrates complete recanalization of left ICA terminus and MCA occlusions (*arrow*)

Illustrative Case 4 (Tandem ICA/MCA Occlusion)

A 63-year-old man with extensive smoking history was found down unable to speak with profound right-sided weakness. He was determined to be a wake-up stroke, and advanced neuroimaging showed a favorable mismatch profile. Cerebral angiogram was performed under conscious sedation and demonstrated a string sign of the left ICA at the bifurcation with intracranial left M1 occlusion. A 80-cm Neuron MAX long sheath was then placed in the left CCA. The patient was bolused with heparin 4000 units and weight-based Integrilin followed by infusion. A 4-mm × 7-mm embolic protection device was advanced through the stenosis and deployed in the distal cervical ICA. A Viatrac 14 balloon 4 mm × 20 mm was advanced across the stenosis and angioplasty was performed. A Xact carotid stent 6 mm × 8 mm × 40 mm was then successfully deployed across the stenosis. Follow-up angiography showed a patent stent with slow distal flow in the cervical ICA. Under roadmap imaging, a JET 7 aspiration catheter was advanced to the M1 occlusion with the aid of a Velocity microcatheter and Synchro 14 microguidewire. A single-pass JET 7 direct aspiration was performed, and TICI 3 reperfusion was achieved (Fig. 7.4).

Acute Large Artery Occlusion in Anticoagulated Patients

Patients with acute ischemic stroke receiving coumadin (with INR > 1.7) or novel oral anticoagulants are considered ineligible for IVT due to risk of ICH. However, case series have reported safety and feasibility of IAT in patients receiving therapeutic doses of anticoagulants [49, 50]. The American Heart Association/American Stroke Association (AHA/ASA) guidelines promote endovascular therapies as a reasonable approach to treat patients with acute LVO in whom IVT is contraindicated [51].

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

Certain complications such as arterial dissections and perforations, contrast-induced renal dysfunction, and groin hematomas can occur in any endovascular procedure. Additionally, hem-

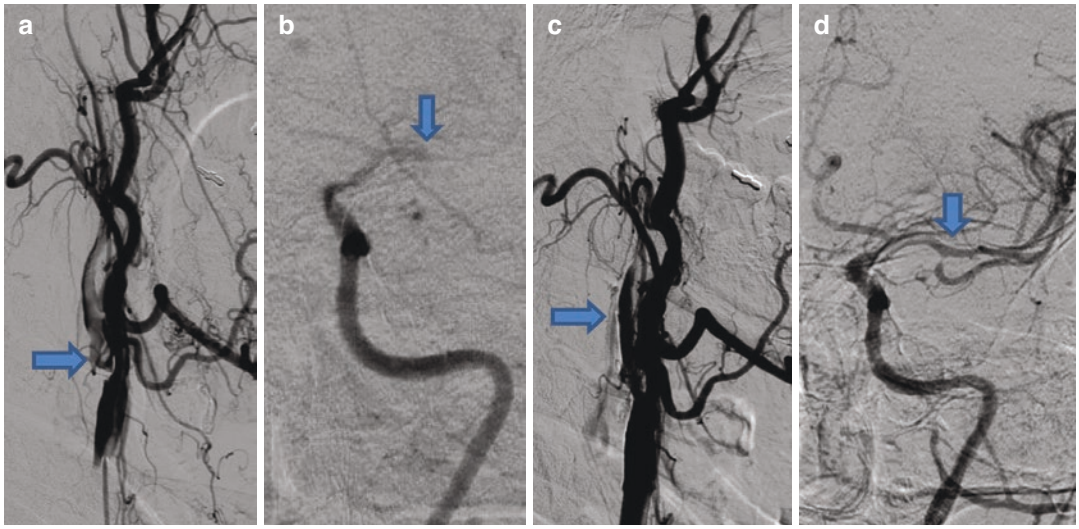

Fig. 7.4 Endovascular treatment for tandem occlusion—carotid artery stenting followed by MCA thrombectomy. (**a**) The cervical right ICA demonstrates a string sign (*arrow*) consistent with a high-grade stenosis. (**b**) Cerebral angiogram distal to the carotid stenosis demonstrates occlusion of the left MCA (*arrow*). (**c**) Successful deployment of a carotid stent across the stenosis results in patent right ICA with slow distal cervical ICA filling (*arrow*). (**d**) Successful mechanical thrombectomy with direct aspiration results in left MCA recanalization (*arrow*)

orrhagic transformation (HT) is a well-known complication of reperfusion injury after MT which can be associated with higher morbidity and mortality. A recent multicenter study reported HT of any degree in 44.5% and parenchymal hematoma in 11.6% of patients at 24 h after MT (accessed according to the European Collaborative Acute Stroke Study Classification). However, the majority of these patients (43%) had an asymptomatic ICH that was considered a marker of reperfusion and did not adversely affect outcomes. The DAWN and DEFUSE 3 trials reported rates of symptomatic HT in the range of 6–7% indicating that MT can be performed safely [5, 6]. To date, studies suggest that predictors of symptomatic HT include higher initial National Institutes of Health Stroke Scale (>18), Alberta Stroke Program Early CT Score of <7, history of prior congestive heart failure, older age, high initial blood pressure and glucose level, very low cerebral blood volume lesions, longer onset to treatment, extended procedure times, general anesthesia, poor collaterals, and embolization to new territory during procedure [52, 53]. Multiple studies have confirmed that MT procedure time is an important predictor of patient outcomes using both older-generation and contemporary devices and techniques [54]. Data suggests that a time window beyond 35 min increases the risk of HT and worsening outcomes [55].

Periprocedural Management (See Chap. 3)

The role of general anesthesia (GA) and intubation pre-procedure is controversial. Meta-analyses suggest poorer neurologic outcomes and higher mortality in patients receiving GA when compared to conscious sedation (CS) or local [56, 57]. However, randomized clinical trials have not found an outcome difference between GA and CS [58]. 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. On the other hand, CS is often associated with patient motion and may delay treatment due to angiographic quality degradation. Operator experience and comfort level with motion artifact are important considerations. Regardless of anesthesia type, patients should be observed closely in an

intensive care unit that follows protocols with attention to neurologic exam and hemodynamic monitoring. Current guidelines recommend BP goal <180/105 in the first 24 h post-reperfusion therapies in ischemic stroke. However, higher post-thrombectomy BP within this goal has been associated with worse outcomes [59]. Whether aggressive post-thrombectomy BP control, particularly in patients with favorable recanalization (TICI 2B or 3), optimizes outcome remains a consideration and is being investigated [60].

Conclusion

Technology continues to improve with larger direct aspiration platforms and stentriever enhancements. These devices may be used independently, together, or in conjunction with IVT to more effectively achieve recanalization. MT continues to be optimized by identifying stroke subgroups (see Chap. 6), enhancing stroke systems of care, and incorporating new devices into the acute LVO triage.

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8 Endovascular Treatment of Cerebral Sinus Thrombosis

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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 it 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].

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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 pres-

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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
Hepatitis
Herpes simplex
Varicella zoster
Cytomegalovirus for
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 for
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 for
Dysgerminoma
Ewing's sarcoma
Allogenic transplant for acute lymphoblastic leukemia
Paraneoplastic syndrome
Meningioma
Rheumatologic disease
Behcet's disease
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 for
Lumbar puncture
Endocrine disorders: diabetes, thyroid disease
Renal allograft
Dehydration
Anemia
Prolonged airline flights

sure (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].

Clinical Presentation

Clinical Features

Consistent with the variations in the underlying pathophysiology, clinical presentations also vary significantly, depending on 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 it 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].

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 they are less sensitive for cortical vein and deep vein thrombosis. The sensitivity may be increased with catheter angiography, but it 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).

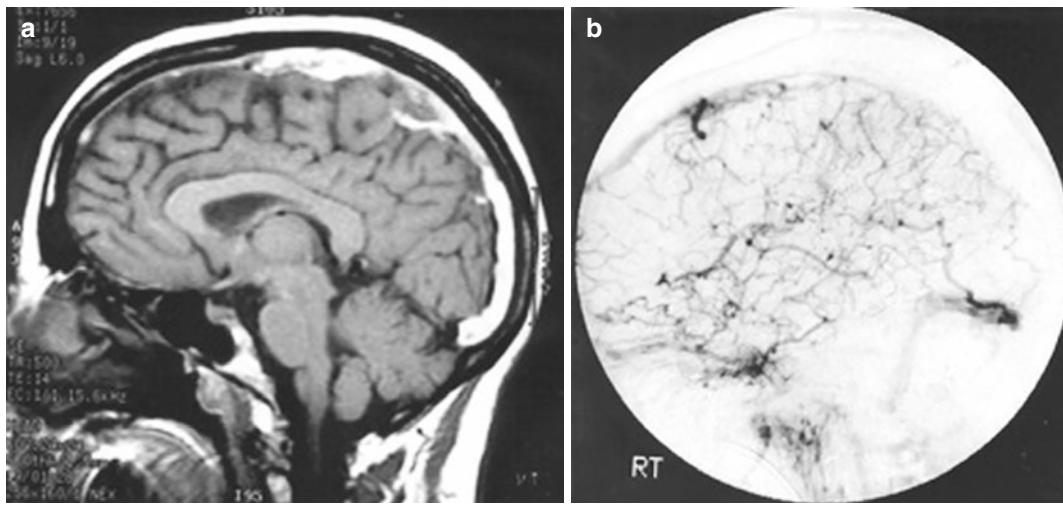

Fig. 8.1 (**a**) Gadolinium-enhanced sagittal MRI showing thrombus within the superior sagittal sinus (SSS). (**b**) Lateral projection cerebral angiogram confirming SSS thrombosis and demonstrating the collateral venous drainage patterns

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 it 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 lifesaving 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 the following:

- 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 irrevers-

ible 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. A large inner diameter (0.071″ or larger) reperfusion catheter 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 reperfusion catheter). Once the clot is crossed with the microwire, the reperfusion 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 reperfusion catheter and 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 devices have also been used with some success to disrupt large volume thrombi and allow suction thrombectomy or potentiate thrombolytics.
- *Suction thrombectomy*: 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 0.071-in. inner diameter, highly flexible, suction catheters, there is great potential for improved speed and safety through the use of direct thrombus aspiration. Either manual or mechanical suction can be applied. The clot is either ingested into the catheter or "corked" at the tip. If corking occurs, both the reperfusion catheter and clot are removed as a unit [31].

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 a headache of 1 week's duration. An abdominal CT scan showed superior mesenteric vein thrombo-

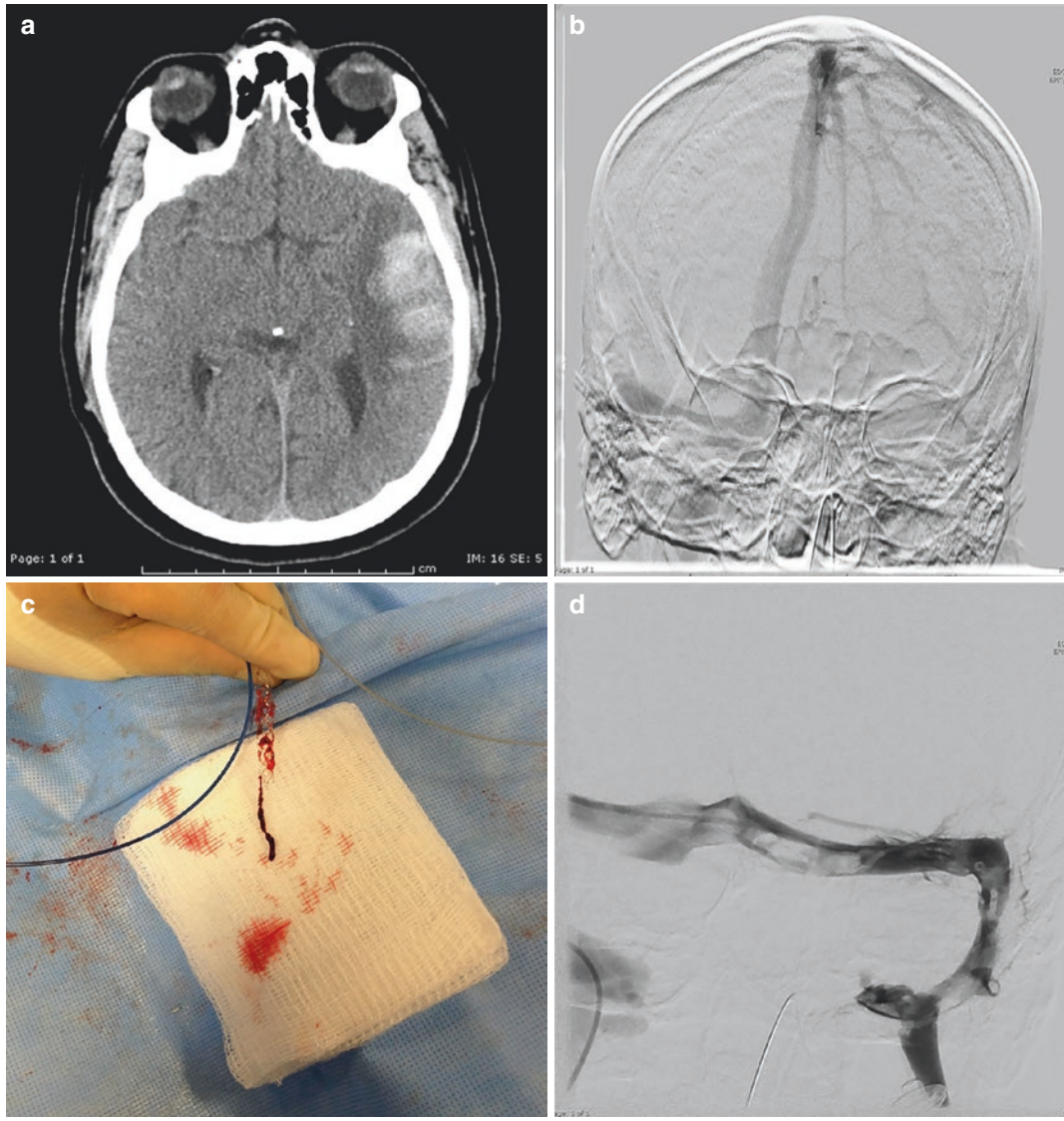

Fig. 8.2 (**a**) Axial, non-contrast head CT shows a left temporal venous infarct with hemorrhagic transformation. (**b**) Anterior–posterior projection angiogram showing occlusion of the left transverse sinus (TS) and sigmoid sinus (SS). (**c**) Extensive clot extracted with the aid of the Solitaire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

sis, 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.

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9 Rare but Interesting: Wada Testing and Inferior Petrosal Sinus Sampling

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Wada Testing

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]. It developed as a tool to evaluate the lateralization of speech dominance and memory [2]. Such information is important prior to resection for medically refractory epilepsy or tumors and can be complementary to grid mapping and fMRI in assessing the resectability of potentially eloquent cortex.

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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.

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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 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 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.

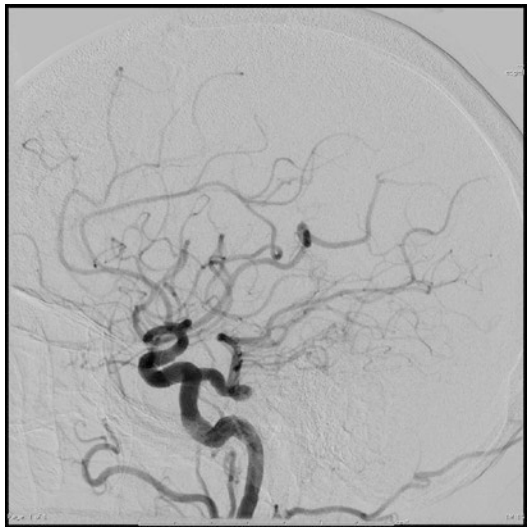

Fig. 9.1 Lateral projection image of a persistent trigeminal artery. These fetal remnants may allow intra-arterial injections to affect the brainstem and thalami, potentially leading to impairment of consciousness and respiratory depression

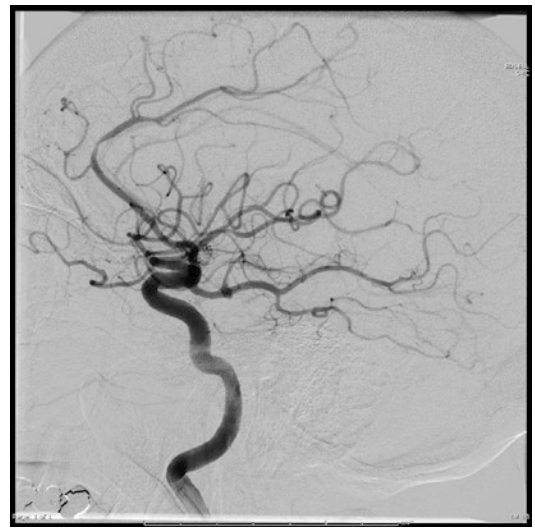

Fig. 9.2 Lateral projection image of a fetal posterior cerebral artery. This common anatomical variant does not preclude carotid injection, but care must be taken to administer the agent gradually in order to avoid filling of the posterior circulation

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 disinhibition 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 [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% dex-

trose, 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 0.018–0.021″ 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 is 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 0.018–0.021″ 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 one to two 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 the Wada test was performed by a neurologist and neuropsychologist. The Brevital was redosed at 1-min 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.

Inferior Petrosal Sinus Sampling

Introduction

The technique of inferior petrosal sinus (IPS) sampling for Cushing's syndrome (CS) 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) [21]. Using this selective catheterization technique, it was possible to sample adrenocorticotropic hormone (ACTH) output centrally and peripherally and later even lateralize ACTH production [22]. This chapter will explain IPSS including its applications, limitations, complications, and cost-effectiveness.

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-

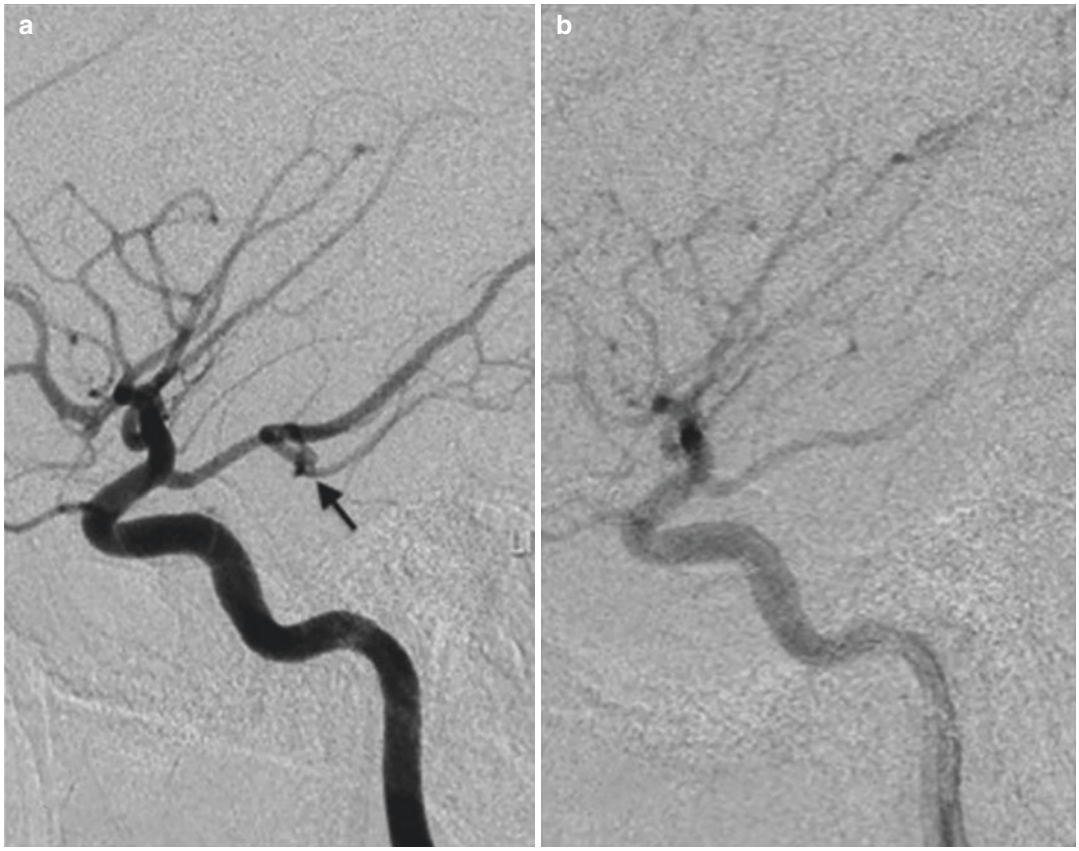

Fig. 9.3 (**a**) Cerebral run from the left ICA at standard injection rate shows filling of the top of the basilar artery (*arrow*). (**b**) Injecting at a slower rate prevents reflux into the basilar artery suggesting that slow injection of the barbiturate will not likely result in significant brainstem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

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 9.1): CS is a serious disease which if untreated has a 50% 5-year mortality [23]. 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. The diagnosis is confirmed if at least two of the tests in Table 9.1 are clearly abnormal. A referral to an endocrinologist for additional diagnostic testing is preferred to reaffirm the diagnosis [24].

2. *CS etiology and differential diagnostic testing* (Fig. 9.4): Appropriate therapy for CS requires an etiologic diagnosis between adrenal, pituitary, and an ectopic ACTH-producing tumor (EAS) [25]. Understanding the tests used to establish the etiology requires knowledge of the hypothalamic–pituitary–adrenal (HPA) axis (see Fig. 9.4) [26]. 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 ectopic ACTH syndrome (EAS) (see Table 9.2) [27].

(a) *ACTH-independent CS* (see Table 9.2): 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 [28]. Adrenal CS can be easily diagnosed by the combination of low ACTH levels and finding adrenal nodule(s) by CT or MRI.

Table 9.1 Establishing the diagnosis of Cushing's syndrome

Clinical suspicion for Cushing's syndrome
↓
Urinary free cortisol (two-three 24 h collections)
Low-dose (1 mg) overnight dexamethasone suppression
Late-night salivary cortisol level (two-three tests)

(b) *ACTH-dependent CS* (see Tables 9.2 and 9.3): The vast majority of CS is ACTH dependent—largely from two causes: CD (~80%) and EAS (~10%) [29]. Many different tumor types both benign and malignant can produce EAS, and many produce other ectopic biomarkers (see Table 9.3) [22]. Historically, differentiating CD from EAS had been difficult but that changed when IPSS was introduced [21]. Since then, it has achieved a high level of diagnostic accuracy. This has improved with modifications including bilateral sampling [30], 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:

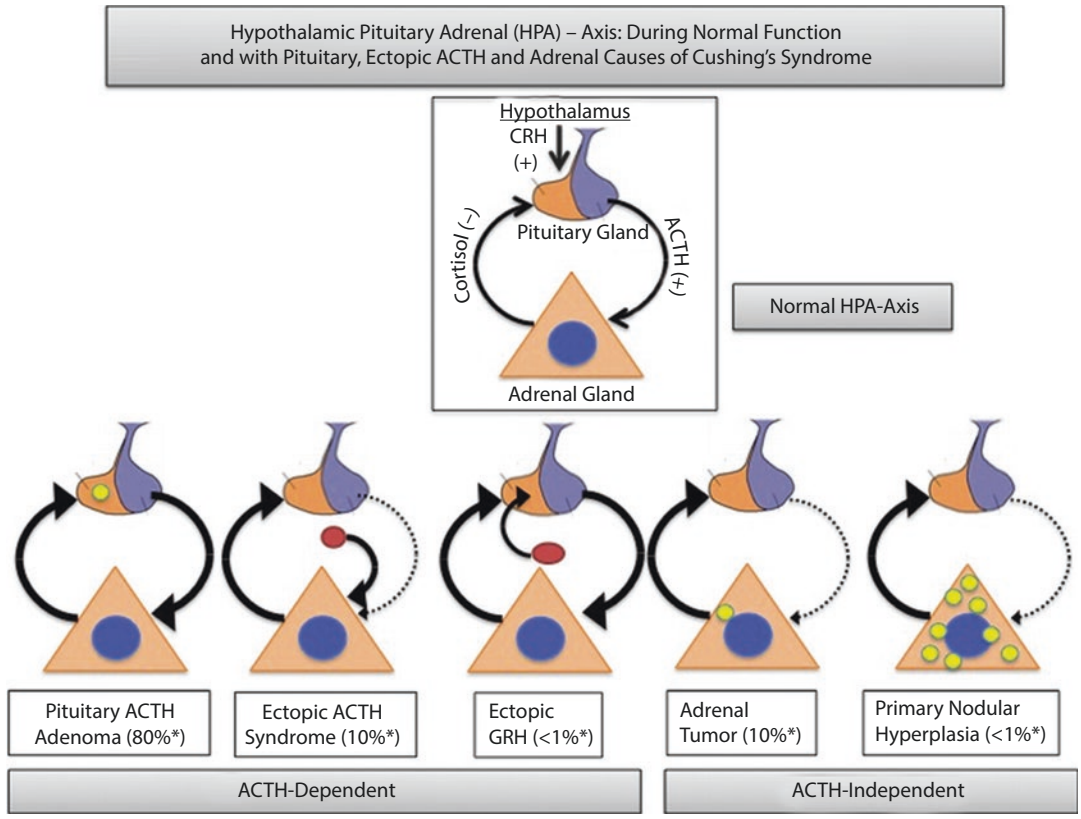

Fig. 9.4 Hypothalamic–pituitary–adrenal axis: during normal function and with various etiologies of Cushing's syndrome

Table 9.2 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 9.3 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

(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. 9.5 and 9.6). 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 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 9.4). Loss of the normal glucocorticoid feedback inhibition was found by dexamethasone suppression testing (DST). ACTH independence was

Fig. 9.5 A 24-year-old woman with Cushing's syndrome taken during first hospitalization for diagnostic testing

Fig. 9.6 (**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

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. 9.7). 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. 9.8a, b). Increased ACTH production was localized to the pituitary gland confirming the diagnosis of CD (Tables 9.5 and 9.6). ACTH production within the pituitary body lateralized to the left side consistent with the MRI findings (Table 9.5).

(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-sup-

Table 9.4 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	<1.8 μg/dl	7–63 pg/ml	0–50 μg/day	<0.112 μg/dl	<7.5 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

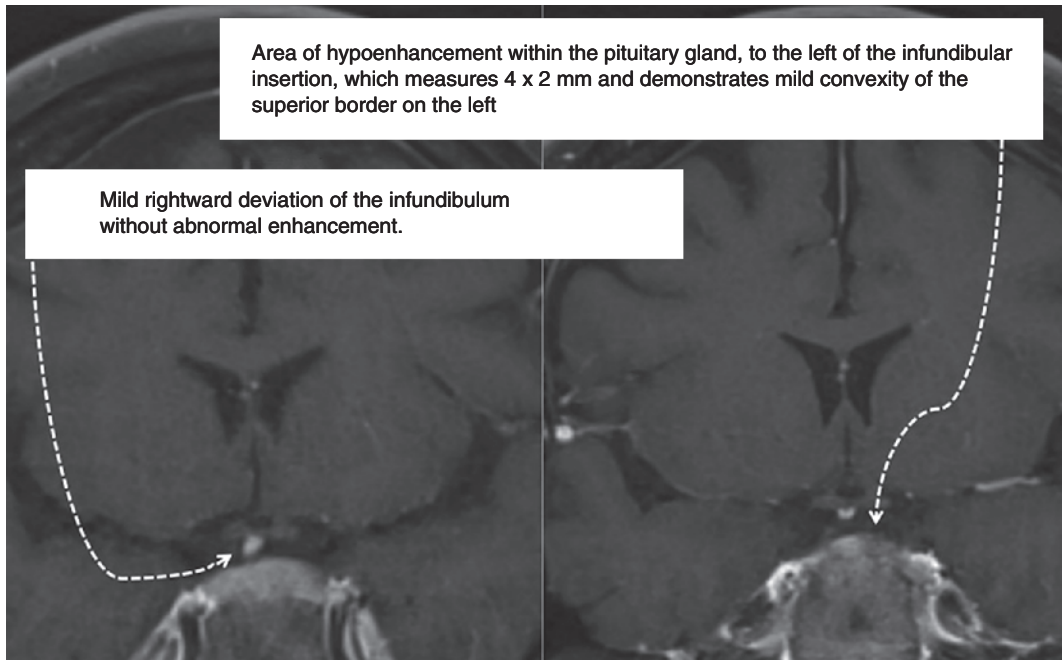

Fig. 9.7 Pituitary MRI findings in a 24-year-old woman with CS

pressed plasma ACTH levels and normal adrenal gland imaging. On transsphenoidal 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 9.2). Given the frequent small size of pituitary tumors and occasional occurrence of occult EAS tumors, differentiating CD and EAS can be difficult [31]. 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% [32]. These tests are discussed below (see Table 9.2).

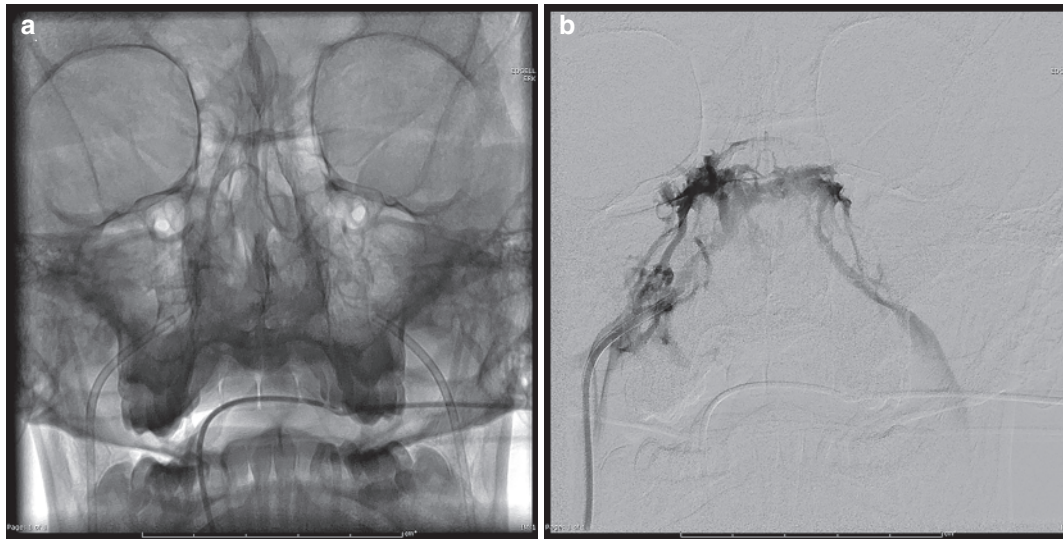

Fig. 9.8 (**a**) Fluoroscopic visualization of catheter placement in bilateral inferior petrosal sinuses. (**b**) Venogram of cavernous sinuses obtained from catheter in right inferior petrosal sinus

Table 9.5 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	1137	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 9.6 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

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 [33]. The primary use of IPSS is to localize the source of ACTH (see Table 9.7). 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 [34] and young children [35]. The diagnostic IPSS criteria to localize and lateralize the source of ACTH are seen in Table 9.8. Despite its successes IPSS still has inaccuracies in otherwise difficult cases [36]. Furthermore, because IPSS requires a high degree of technical 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 [37]. 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 [38]. 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 [39]. Difficulty procuring CRH has led to the interest in alternatives such as naloxone, metyrapone, and vasopressin [40–42]. A synthetic version of vasopressin and desmopressin (DDAVP; Ferring Pharmaceuticals) compared to CRH produces less ACTH stimulation [43]. Nevertheless, desmopressin stimulation improves diagnostic accuracy over 90% and is comparable to CRH [44]. The desmopressin technique is similar to CRH and 10 mg of desmopressin is used in place of the CRH.

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 (Table 9.9). 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 [45]. 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 [46].

Table 9.7 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 9.8 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—confirms or exclude pituitary is source of ACTH
Catheter placement—validates 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—lateralizes side of pituitary venous effluent
Corrected ACTH lateralization—corrects IPS ACTH for laterality of pituitary venous effluent

Table 9.9 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

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 [47]. It is surrounded by two venous compartments known as the cavernous sinuses. 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 (IJV) 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 IJV.

A schematic diagram of pituitary venous drainage, fluoroscopic image of placement of the IPSS catheters, and an IPSS venogram are seen in Figs. 9.8 and 9.9.

- *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 prelabeled 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 [48]. 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

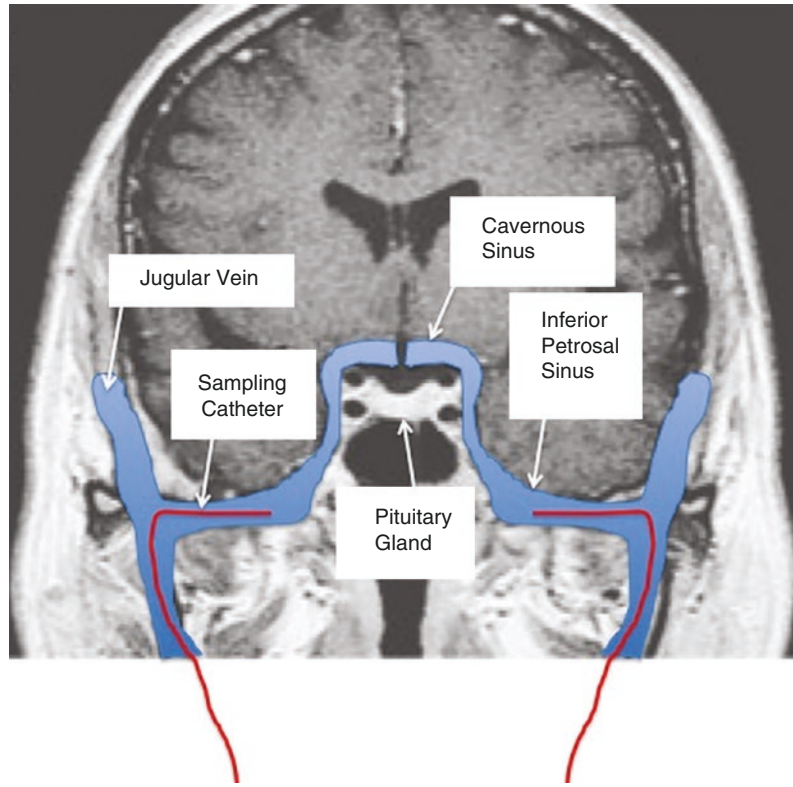

Fig. 9.9 Schematic diagram of pituitary venous drainage and placement of the inferior petrosal sinus sampling catheter

the anatomy of the IPS. Shiu et al. described four distinct patterns of drainage of the IPS [49], 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 Headhunter 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 [50] 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) was the commercially available synthetic form of CRH that is administered in a dose of 1 μg/kg intravenously [38]. It is now difficult to source.
- *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 one to two 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 9.10. 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.

Table 9.10 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
3–5000 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
xPost-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)

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, sampling 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 [51].

(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 [52].

Table 9.11 Reported complications of IPSS

0.2% per year[a]
Groin hemorrhage (3%)
Thromboembolism
Transient brainstem symptoms
Brainstem 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

7. Complications: The incidence of serious complications, such as ischemic stroke, is 0.2% when the procedure is performed by an experienced neurointerventionalist [53, 54]. A list of reported IPSS complications is in Table 9.11. These include transient cranial nerve palsy, hemiparesis and gaze palsy, Raymond's syndrome, pulmonary embolism, and deep venous thrombosis. 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 [55].

8. 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.

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Unruptured Intracranial Aneurysms

10

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Introduction

Unruptured intracranial aneurysms (UIAs) are increasingly encountered in cerebrovascular practices around the world. This is due to increased utilization of noninvasive cerebral imaging as well as a significant improvement in the quality of these imaging modalities. By definition, UIAs are those aneurysms in which there has been no breach in the aneurysm wall. While these breaches are often clinically obvious through aneurysmal rupture into the subarachnoid or ventricular spaces, clinicians should be aware of more subtle presentation such as headaches suggestive of sentinel bleeds or even MRI findings suggestive of prior rupture and thrombosis. In addition to being incidentally found, UIA can also present with aneurysm-related mass effect such as third nerve palsy secondary to a posterior communicating artery aneurysm.

Management of UIAs can be complex. In general it falls into three categories: observation, endovascular treatment, or open surgical repair. The treatment approach might get more complicated for recurrent aneurysms. Open surgery can be used to treat previously coiled aneurysms and vice versa. Redo surgery or endovascular interventions are also an option. To advise the patient about the optimal approach for their specific aneurysm, it is important for the treating physician to understand the natural history, risk factors for rupture, and risks of treatment.

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Natural History

Our current understanding of the natural history of UIAs comes from a number of retrospective and prospective cohort studies. In the absence of randomization, included aneurysms that get followed longitudinally with no treatment are more likely those that are thought to be "low risk." Further, in the absence of a control arm, the degree of certainty that comes out of these studies remains low. However, despite the inherent limitations of these studies, several factors have emerged and represent our best understanding of the natural history of UIAs. We will discuss these factors below:

Size

Size has been identified as a predictor of rupture risk across several studies. In the International

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Study of Unruptured Intracranial Aneurysms (ISUIA), one of the most cited studies of the natural history of UIAs, 4060 patients were included in the prospective cohort. Of those 1692 patients were not treated. The patients were divided into a group with no previous SAH and a group with previous SAH from another aneurysm. The average follow-up was 4.1 years. The authors 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 also showed higher rates of rupture justifying treatment [1].

The ISUIA was criticized for showing data that diverged from other clinical studies in which the average diameter of ruptured aneurysms was in the range of 7 mm. Hypotheses to explain these discrepancies included a selection bias, as well as the possibility that ruptured aneurysms shrink in size [2].

In the Unruptured Cerebral Aneurysm Study (UCAS) of Japan, 6697 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 [3].

Cerebral aneurysms measuring more than 25 mm in diameter are considered giant intracranial aneurysms (GIAs) [4]. These remain some of the hardest aneurysms to treat 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.

While aneurysm size is clearly an important factor, it cannot be used in isolation to determine whether an UIA should be treated.

Location

The location of an aneurysm is also related to the risk of rupture. The prospective ISUIA cohort identified a relative risk of rupture of 2.3, 2.1, and 0.15 for aneurysms of the basilar apex, posterior communicating artery, and cavernous carotid, respectively, when compared to anterior circulation aneurysms [1]. However, the ISUIA was criticized for classifying posterior communicating artery aneurysms as posterior circulation aneurysms.

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 [3].

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].

Morphology

The shape 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 [3]. 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]. More recently, the ISUIA investigators, upon investigating 12 morphological metrics in 198 patients, showed that perpendicular height and size ratio, defined as the ratio of the maximum diameter of the aneurysm to that parent vessel diameter, were the only predictors of aneurysm rupture in univariate analysis. In this recent study, aspect ratio, daughter sacs, multiple lobes, aneurysm angle, neck diameter, parent vessel diameter, and the calculated aneurysm volume were not statistically significant predictors of rupture [10].

Presenting Symptoms and Comorbidities

The clinical presentation of patients with UIA is also associated with rupture risk [5, 11]. 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. However, this difference was not noted in larger aneurysms [1, 12]. Patient age, sex (females are more likely to have a ruptured aneurysm), smoking, and hypertension can potentially increase the risk of rupture [11, 13].

Of all the modifiable risk factors, smoking has been found to have the greatest association with multiple aneurysms, growth of UIAs, and to independently increased risk of rupture [14–16]. In the meta-analysis by Wermer et al., both Japanese and Finnish descent increased the risk of rupture [5].

Future Advances

Advances in aneurysm imaging promise to enhance our understanding of which aneurysms are at risk of rupture. Dynamic MRI aneurysm imaging could detect the aneurysm wall permeability to gadolinium which could be a surrogate for an aneurysm risk of hemorrhage [17–19]. Further, biomarkers are being investigated and could help dictate aneurysm management in the future [20]. Such biomarkers include blood and CSF levels of selectins, the elastase-to-alpha-1-antitrypsin ratio, and others.

Noninvasive Management

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 $1-(\text{annual chance of not bleeding})\times\text{expected}$ 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 or "conservative" management is often equated with doing nothing. However, patient education, modification of risk factors such as smoking and hypertension, and routine screening can improve the outcomes in patients with UIAs. Patient education, immediate steps to modify lifestyle, and general medical health are imperative to reducing the risk of rupture and new aneurysm formation.

Because of decreased perioperative morbidity for both surgical and endovascular techniques, conservative management is usually only offered to patients with a low lifetime risk of rupture. Typically, these are patients with small aneurysms and a relatively short life expectancy. However, patients might opt for conservative management even when they have high-risk aneurysms.

When patients opt for conservative management, aneurysms need to be monitored on a regular basis. A change in aneurysm morphology or

interval growth may imply a risk of impending rupture. New onset of headaches is more worrisome in the setting of known UIA. 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 first ever surgical clipping of an intracranial aneurysm was performed at Johns Hopkins Hospital by Dr. Walter Dandy in 1937. Since then, the surgical strategy and techniques have significantly evolved. The goal of surgery is to exclude the treated aneurysm from the circulation, thus making its risk of rupture virtually zero. The options for surgery include direct clip ligation, aneurysm trapping and bypass, and rarely wrapping of a dysplastic vessel or aneurysm.

Classically, after primary clipping of an aneurysm, the risk of residual aneurysm had been quoted at 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 one aneurysm rebled [24]. In a series by David et al., late angiographic follow-up was performed in 160 aneurysms. They found two 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]. These numbers have recently improved with the introduction of intraoperative standard angiography or indocyanine green angiography [27, 28].

Based on the ISUIA prospective cohort of 1917 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. The Cleveland Clinic looked at their series of 449 UIAs treated by ten 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-year experience prior to the onset of the study achieved better outcomes. Increasing patient age and aneurysm size were predictors of worsened functional outcome [29].

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. Specifically, clip ligation, parent vessel occlusion, aneurysm trapping, and extracranial-intracranial bypasses are some of the techniques that have been described.

Endovascular Management

Endovascular surgery is an increasingly utilized option for the treatment of UIAs. At a large majority 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, stent-assisted coiling, and flow diversion has enabled the extension of endovascular techniques to treat less favorable aneurysms such as wide-neck aneurysms or GIAs.

Equipment Review

- *Sheath*: A 6-F sheath is the minimum size required for UIA coiling. A 35-cm or longer sheath is recommended to bypass tortuous iliac 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 preshaped 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* (Fig. 10.1):
  - *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 helical or complex 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 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*: Several such stents are currently available. Most commonly these are constructed from a nickel-titanium (nitinol), laser-slotted tube. However, there are braided stents on the market as well.
- Neuroform Atlas Stent (Stryker, Fermont, California) is a new-generation stent. Early

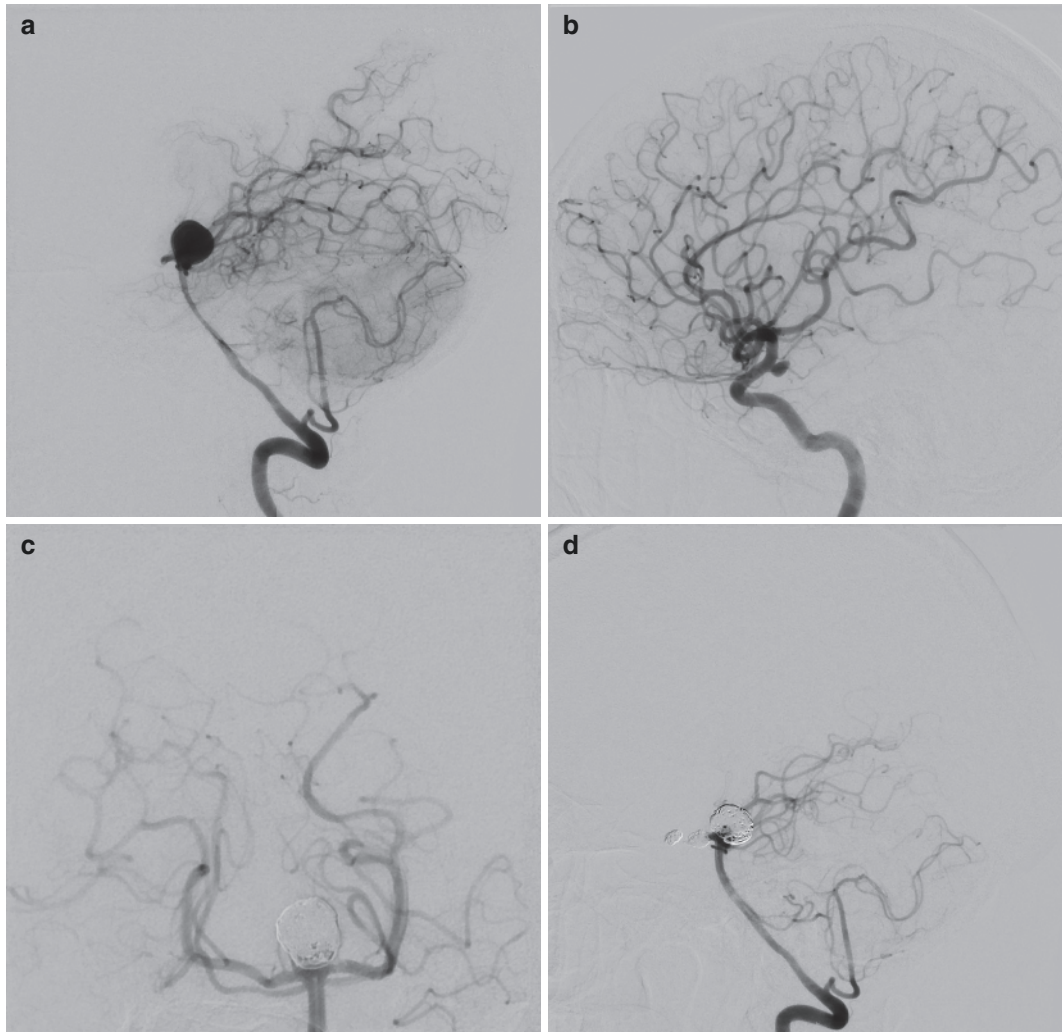

Fig. 10.1 Patient with basilar tip aneurysm and bilateral posterior communicating artery aneurysm. (**a**) Shows a left vertebral artery injection showing the basilar tip aneurysm. (**b**) shows a left carotid injection showing the left P com aneurysm. (**c**, **d**) show post coiling images

data has shown safety, feasibility, and high obliteration rate [30]. It received FDA approval in May 2019. The Neuroform Atlas Stent has an open-cell distal end, a closed-cell distal end, and eight cell structural elements for support, along with 12 cell structural elements for flexibility (Fig. 10.1). It can be delivered through a 0.0165 or 0.017 catheter [31]. The open-cell design augments its conformability and enhances the deployment accuracy; acquiring a higher number of connectors gives it a better scaffolding edge [32]. Several retrospective studies reported immediate obliteration rates ranging from 88% to 52%, with follow-up obliteration rates ranging from 82% to 63% [31–34]. Caragliano et al. in their series have reported 6.2% of intra-procedural complications and less than 3% of mortality related to subarachnoid hemorrhage [31].

- The low-profile visualized intraluminal support junior stent (LVIS Jr. MicroVention-Terumo, Tustin, CA, USA) is also commonly used in current practice. LVIS Jr. stent is a

self-expanding, closed-cell nitinol microstent with a braided construction designed to improve conformability to the vessel's shape. It has three radiopaque and distal markers plus three helical radiopaque threads throughout the stent body, permitting improved visualization. The device is compatible with the 0.017-inch microcatheter [35, 36]. The stent has shown high immediate and long-term total occlusion rates with very acceptable morbidity and mortality rates [37]. Cagnazzo et al., in their systematic review and meta-analysis, have reported a technical success rate of about 96%, with complete or near-complete occlusion in 86% of the cases, morbidity was near 7%, mostly thromboembolic related, and no mortality was reported in their investigational study [38].

- *Flow diverters* (Fig. 10.2):

  Five types of FDDs are currently available for the treatment of intracranial aneurysms. Some are only available in Europe at this time: the Pipeline Flex Embolization Device (PED) (Covidien, Mansfield, MA, USA), the Silk (Balt Extrusion, Montmorency, France), the FRED (Microvention, Tustin, CA, USA), the p64 Flow Modulation Device (Phenox), and the Surpass (Surpass; Stryker Neurovascular, Fremont, CA, USA).

  The Pipeline Embolization Device (PED; Covidien, Irvine, CA) is the first FDD to receive FDA approval. Ultimately, neointimal growth across the aneurysm neck results in arterial wall reconstruction and aneurysm sac occlusion [39]. The flow-diverting properties of the PED come from its design which includes 48 individual cobalt, chromium, and platinum strands providing 30–35% metal surface area coverage when fully deployed [40]. These strands are in stark contrast to the 6–9.5% wall coverage with conventional bare metal stents such as Neuroform EZ (Stryker, Kalamazoo, MI) and Enterprise (Codman Neurovascular, Raynham, MA) [41]. 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 pre-mounted 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 [42].

  The Flow Redirection Endoluminal Device (FRED) is a double-layer flow diverter with a stent-like outer layer and a flow diverter inside the stent. That architecture enhances the device's navigation, particularly in tortuous vasculature. The FRED has several radiopaque markers; it is delivered through a 0.027 microcatheter [43, 44]. FRED has shown high feasibility and efficacy in terms of aneurysmal occlusion and technical success. In a European retrospective multicentric study led by Killer-Oberpfalzer et al., the reported aneurysm occlusion was up to 95.3% in the first year, which is similar to the rates of the Italian FRED Registry, a multicentric study in more than 30 Italian centers, which included 196 aneurysms managed; they reported 94% occlusion rate in the first year, which increased to 96% at 12–24 months [44, 45].

  The SAFE study is a multicenter French study. It is the first prospective study to evaluate the safety of the FRED for aneurysmal management, their analysis confirms the high safety of the device with 1-year morbidity of 2.9% and mortality of 1.9%, and they have also reported low retreatment rates at the first year (2.2%) .

  Other flow diverter devices that are less commonly used include the Silk (Balt Extrusion, Montmorency, France), the p64 Flow Modulation Device (Phenox), and the Surpass (Surpass; Stryker Neurovascular, Fremont, CA, USA); several retrospective studies have investigated the morbidity, procedural complications, and mortality of the Surpass and the Silk devices; permanent morbidity in Surpass and Silk was 6% and 9.6%, respectively, and the mortality rates were 2.7% and 3.2%, respectively, in both devices [46, 47].
- Intrasaccular Flow Disrupters

  The Woven EndoBridge (WEB) aneurysm embolization system is a self-expanding mesh

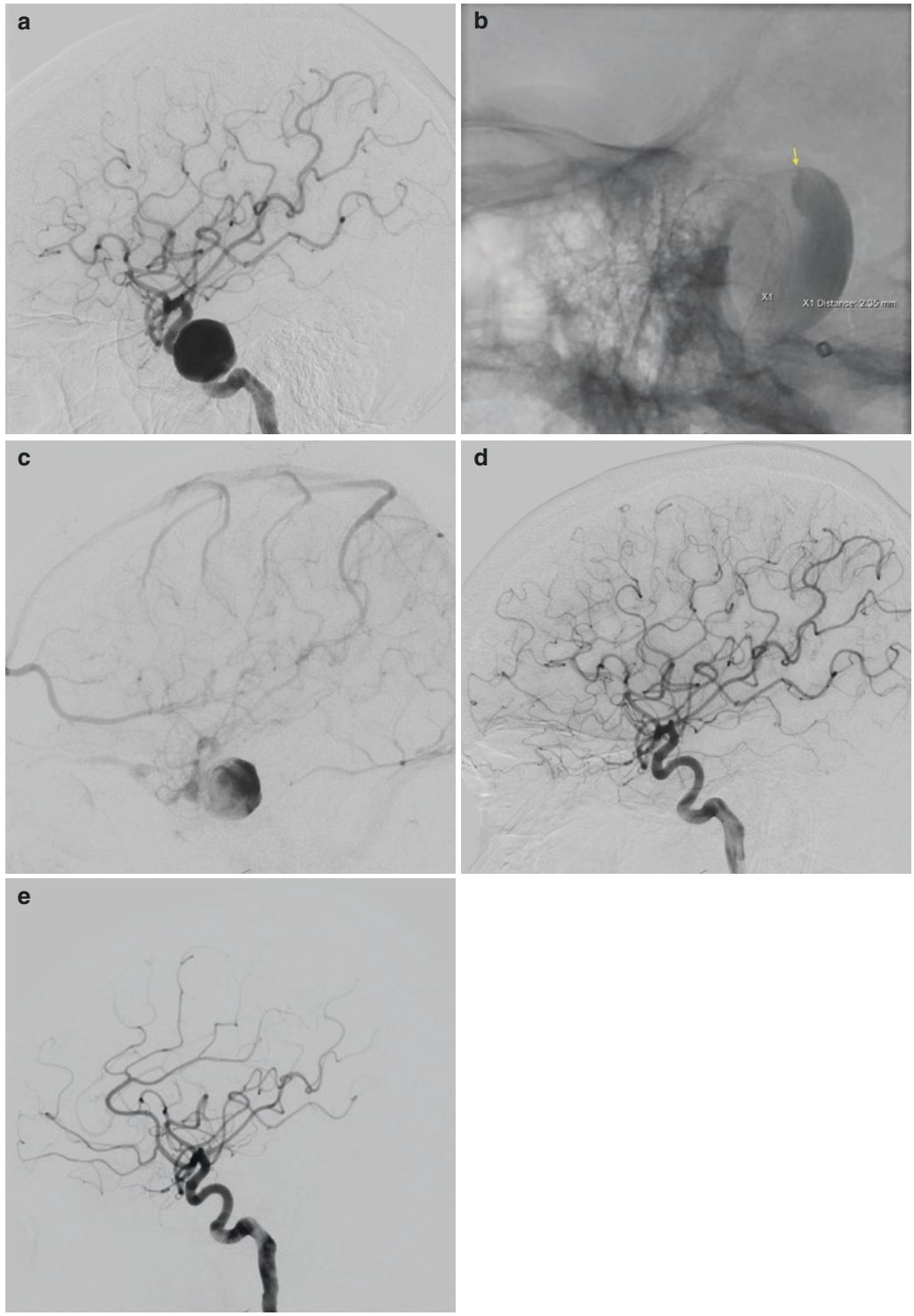

Fig. 10.2 Patient with a 22.5 mm × 18.8 mm fusiform left internal carotid artery cavernous segment aneurysm. (**a**) shows a left carotid injection demonstrating the aneurysm. (**b**) shows deployment of the flow diverter, immediate flow turbulence can be noted in the aneurysm at the yellow arrow. (**c**) Flow turbulence in the aneurysm after deployment of the flow diverter. (**d**) Six months follow up shows almost complete resolution of the aneurysm. (**e**) one year follow up shows complete resolution of the aneurysm

basket implant that was specifically designed for wide-neck intracranial bifurcation aneurysms. However, applications of WEB devices have been extended due to their efficacy [48]. Numerous studies have looked at factors that determine aneurysm occlusion after embolization with WEB devices. Kabbasch et al. found that initial aneurysm thrombosis, recurrent aneurysms, aneurysm size, and simultaneous treatment by WEB and coils were associated with residual aneurysms and aneurysm recurrence [49]. Other studies attempted to evaluate the risk factors of procedural complications related to WEB embolization and found that increased width to height ratio and a lower aspect ratio could predict periprocedural complications [50]. Due to the results of early clinical trials and real-world results, the use of the WEB device is likely to increase in the next few years; however better data is needed to understand their long-term efficacy [51].

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% [52]. 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 because the observed risk of thromboembolic complications outweighs the risk of intraprocedural rupture. Some groups use aspirin alone, while others use a combination of aspirin and clopidogrel [53]. The latter facilitates the safe use of balloon assistance or stent assistance if the need arises during the case.
- *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 [54]. In addition to a similar safety profile, balloon remodeling has a better immediate and follow-up anatomical result than coiling alone.
- *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 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.

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 pre-existing thrombus. In the past GIAs frequently required retreatment, sometimes multiple times. Even the use of BAC and SAC did not adequately addressed these high rates of recanalization [55, 56] (Fig. 10.3).

- *Liquid embolics*

  This technique is largely of historical interest [57].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. These risks, along with concerns about long-term durability, have limited the use of liquid embolic agent use to treat GIAs.

- *Parent vessel occlusion*

  Again, rarely needed in the modern era, 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. PVO can be performed by several techniques including coil embolization and/or Onyx embolization. In most patients with unruptured aneurysms presenting with mass effect on the cranial nerves, symptoms are improved soon after therapy [58]. Complications from endovascular PVO

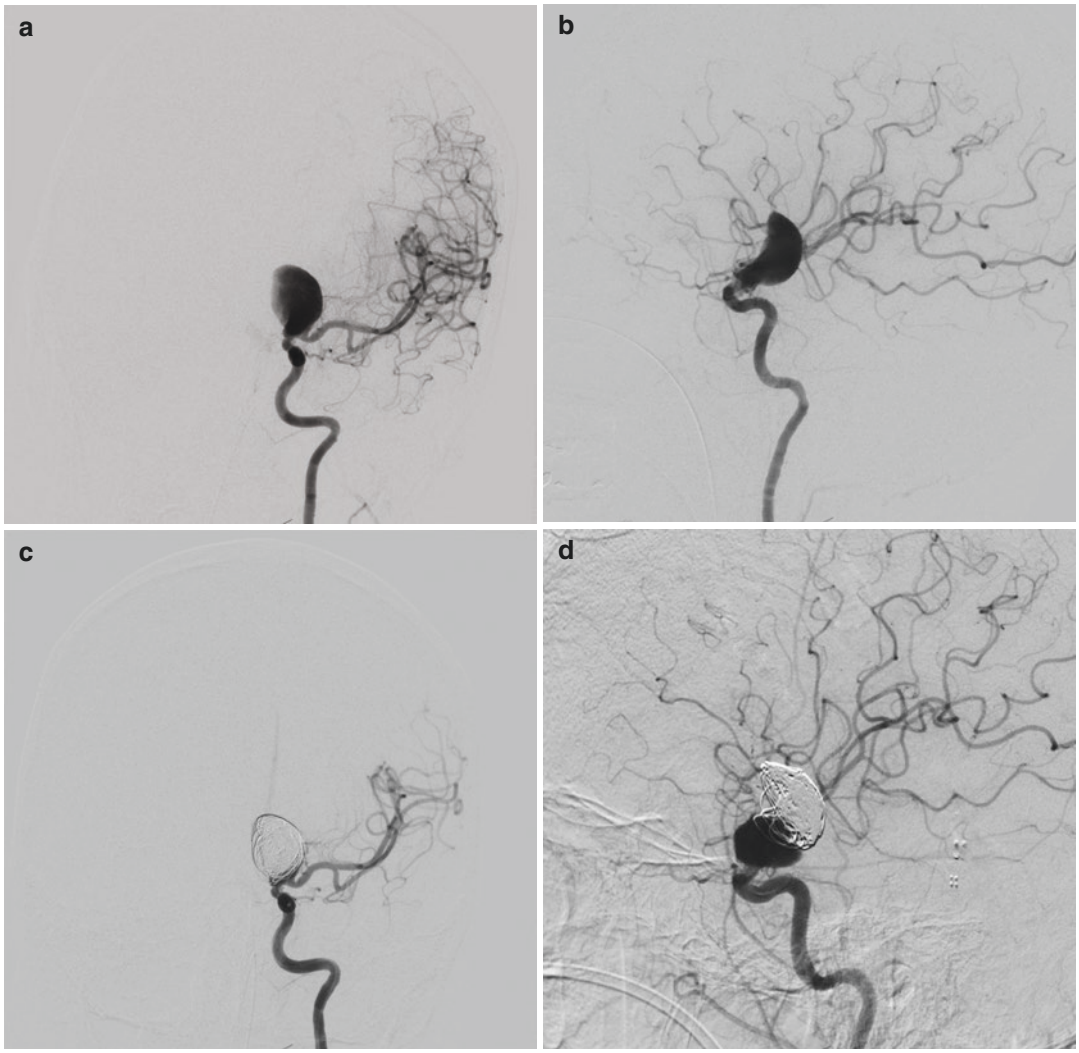

Fig. 10.3 Patient with left ICA terminus aneurysm measuring 20 mm × 10 mm. The patient failed pipeline embolization due to the MCA take-off being in proximity to the aneurysm, patient eventually taken for a craniotomy for extracranial-intracranial bypass with right radial artery graft and obliteration of right internal carotid artery. (**a**, **b**) show a left carotid injection demonstrating the aneurysm. (**c**, **d**) Initial embolization demonstrates a large coil mass. (**e**) Demonstrates recanalization of the aneurysm. (**f**, **g**) demonstrate a patent radial artery graft ensuring good blood flow to the left MCA territory

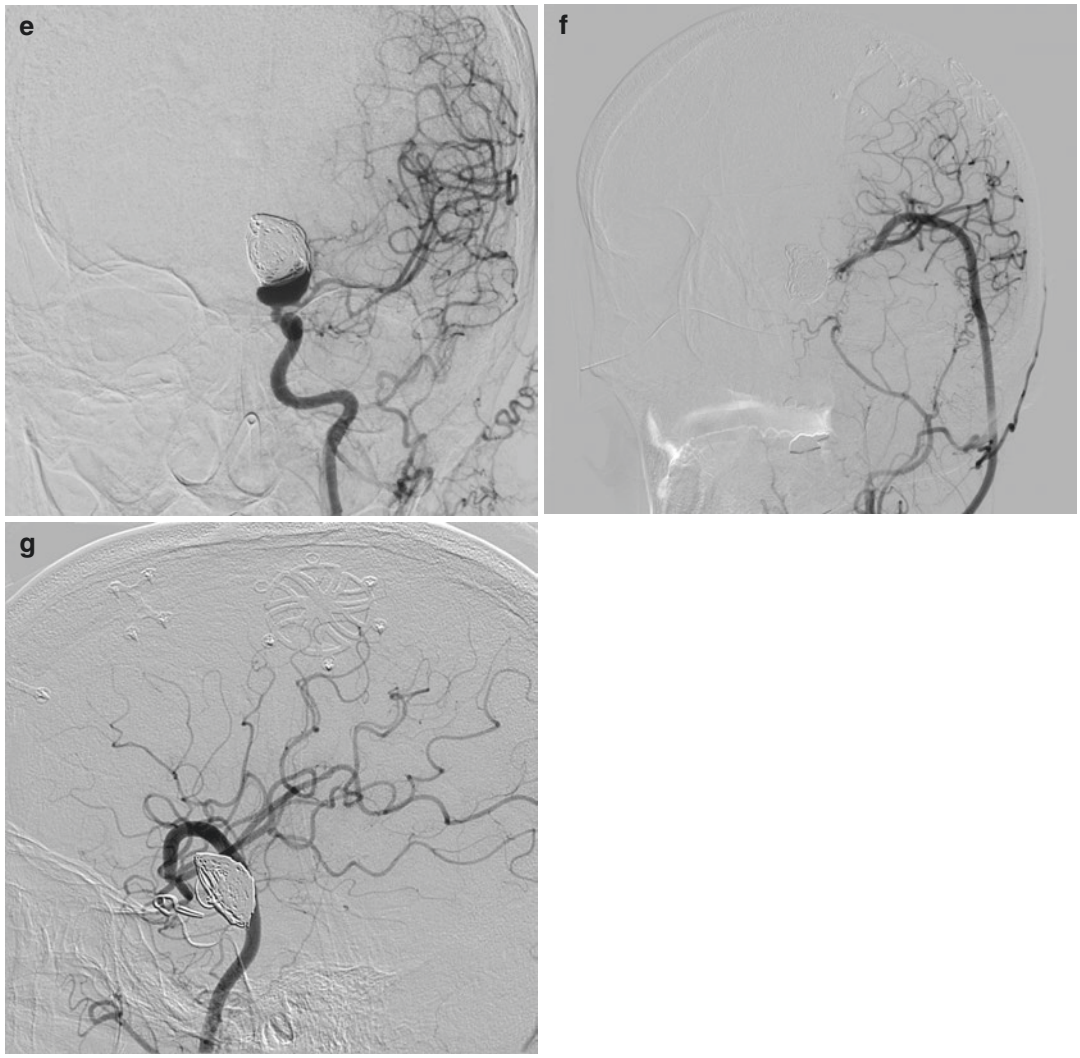

Fig. 10.3 (continued)

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 [59].

- *Flow diversion*

  Flow diversion is effective in treating the majority of GIA. The technology 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. However, over time the aneurysm occlusion rates were

higher than conventional treatments with complete occlusion ranging from 69% at 6 months to >90% at 1 year, even with large and giant aneurysms [60, 61]. The PITA trial (Pipeline for the Intracranial Treatment of Aneurysms) included 31 aneurysms, nine were large and two were GIAs. Follow-up complete aneurysm occlusion was observed in 28 of 30 (93.3%) patients, and residual aneurysm filling was noted in two (6.7%). 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. Lubicz et al. advocate 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 [60]. 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. Complications of the PED include in-stent thrombosis (6%), in-stent stenosis (1%), intracranial hemorrhage (3.8%), and perforator vessel occlusion [62]. 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 [61, 63]. In PITA, two patients had periprocedural stroke, and no other neurologic deterioration was observed in any of the patients at discharge [64].

Siddiqui et al. [65] 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, while 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.

Conclusion

The treatment of unruptured intracranial aneurysms requires a holistic approach to the patient. A good understanding of the natural history of the disease as well as a careful consideration of all management options is required to ensure good patient outcomes. Novel endovascular options promise to further advance the way we treat aneurysms by providing safer and more efficient treatment options.

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Ruptured Cerebral Aneurysms

11

Guillermo Linares

Introduction

Subarachnoid hemorrhage (SAH) has a worldwide incidence of 10:100,000 [1, 2]. 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 50 are more likely than their counterparts to suffer an aSAH [5]. This effect diminishes as women approach menopause; the risk of aSAH is higher in women than men by the age of 60 [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 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 stems 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

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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 break down 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 of aSAH [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 higher than in patients with no history of previous aneurysm rupture [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]. It is speculated that this is because the posterior circulation has less robust autoregulation and is less able to adapt to elevated blood pressures resulting in more significant hemodynamic stress (Table 11.1).

Table 11.1 Risk of aneurysm rupture by size and location

	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. More recent thinking postulates 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]. 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). Non-motor 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]. 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, arterial 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 angiograms 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 illus-

trating its limitations. Anderson et al. [61] reported that preoperative CTA provided sufficient information to directly proceed to surgery in only 48% of aneurysms—predominantly those coming off the middle cerebral artery. While the anatomic details including size, shape, neck characteristics, and orientation were sufficient in these cases, bony artifacts limited visualization of the posterior circulation. Anderson's study also demonstrated CTA's poor sensitivity to detect small (<4 mm) aneurysms as 24 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 important pieces of 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 the 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.

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

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.

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 eight 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 theoretical concern has not been observed in most 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 delayed cerebral ischemia (DCI). 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 cerebral ischemia (DCI). 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 vasospasm. 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].

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		

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 DCI 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 DCI 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 been stable 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 were 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 largely supplanted open surgical clipping of aneurysms over the last 20 years. 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 superiority to clipping, this minimally invasive technique has gained widespread adoption [93]. Techniques for aneurysm treatment such as the use of balloon remodeling have increased the safety and efficacy of endovascular coiling. New devices such as flow diverters, neck remodeling stents, and intrasaccular flow disruption among many others are available for aneurysm treatment [109, 110]. However, the obligate use of dual antiplatelet therapy limits their applicability in the treatment of ruptured aneurysms. In rare cases such as ruptured blister aneurysms, these new devices represent a less than optional but life-saving treatment intervention. In the future, drug-coated devices and reabsorbable materials might expand the number of tools available for the treatment of ruptured aneurysms.

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.

Illustrative Case 1

A 75-year-old woman 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).

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" in section "Stabilization"), select patients with a high likelihood of decline are taken to the angiography suite for further treatment.

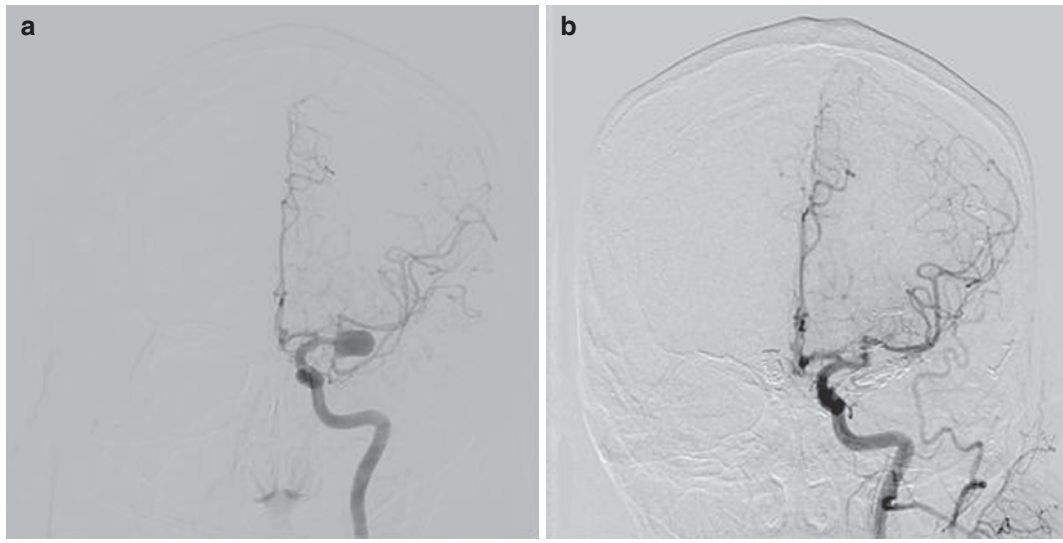

Fig. 11.1 (**a**) Left middle cerebral artery (MCA) aneurysm. (**b**) Same patient after surgical clipping of the left MCA aneurysm

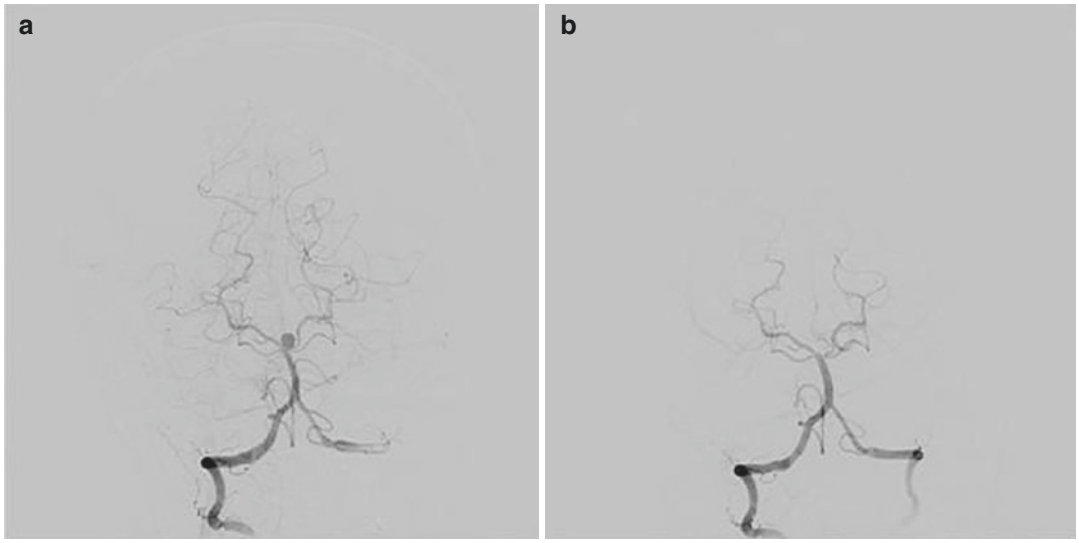

Fig. 11.2 (**a**) Tip of the basilar artery (BA) aneurysm. (**b**) Same patient after endovascular coiling of the BA aneurysm

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

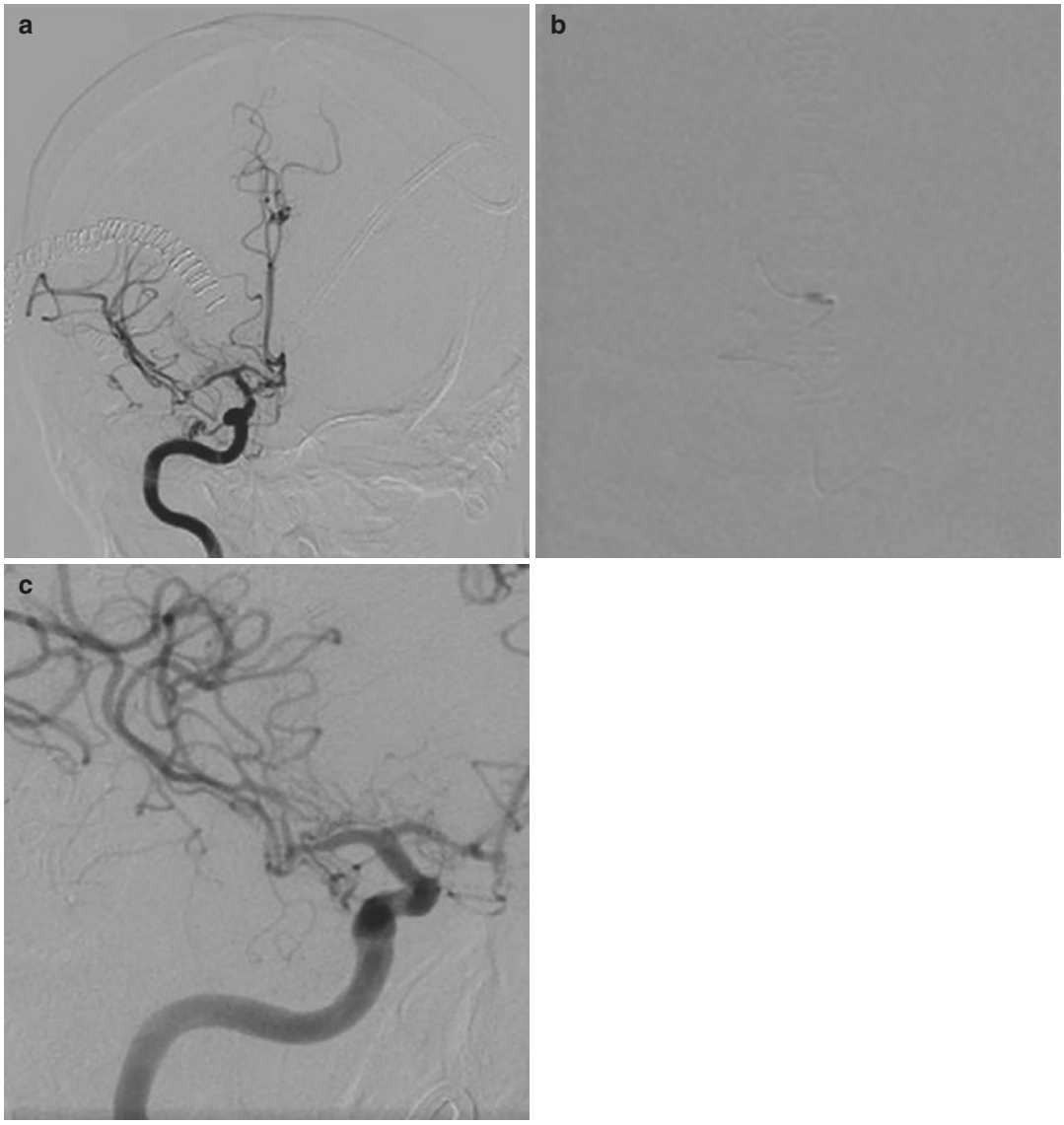

Fig. 11.3 (**a**) Right middle cerebral artery (MCA) with evidence of vasospasm involving the distal right M1 segment of the MCA. (**b**) A Hyperglide balloon is inflated within the right MCA (magnified view) within the stenotic segment. Contrast is seen filling the lumen of the balloon. (**c**) A magnified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

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.

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).

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Arteriovenous Malformations of the Brain

12

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Introduction

Brain arteriovenous malformations (AVMs) are relatively uncommon lesions. Their etiology remains unclear despite considerable progress investigating their origin [1, 2]. It is commonly accepted that AVMs are congenital lesions related to a 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 [1, 5–9]. However, while the congenital hypothesis is plausible, there have been reports of de novo AVM formation [10–12]. These reports noted the occurrence of new AVMs in patients with other known vascular lesions, or the de novo occurrence of an AVM following a complete prior resection of a prior lesion.

AVMs have been shown to be dynamic lesions with a variety of morphologies. This dynamic nature has two direct implications: First, it means that AVMs are not constant over time. For example, they might recruit additional feeding vessels, flow-related aneurysms might develop, and venous varices might develop [13]. Second, it also means that an AVM's response to treatment cannot be fully predicted [13]. In an attempt to understand the nature of these lesions, Niazi et al. distinguished three AVM morphologies [4]: 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 grow, develop, and even recur after therapy due to flow characteristics, growth factors, and remodeling secondary to small hemorrhages, as evidenced by hemosiderin deposition, and pressure differentials [1, 4, 5, 14, 15].

Epidemiology

AVMs are relatively uncommon lesions. Based on hospital autopsy data, it has been estimated that their prevalence is up to 500–600 per

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100,000 people [16–18]. However, the accuracy of these autopsy series had been questioned [17, 19–22]. A more modern survey of imaging studies suggests the true prevalence is closer to 0.82–1.42 per 100,000 person-years [16, 17, 19–25].

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, 19, 20, 22, 24–30].

The vast majority of AVMs are sporadic, but up to 5% of AVMs are associated with genetic syndromes such as 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, 27].

More recent genetic studies have suggested that even sporadic AVMs could have an underlying genetic predisposition. For example, a single nucleotide polymorphism (SNP) in activin receptor-like kinase-1 (ALK1) was found to be associated with sporadic AVM susceptibility [13]. Other hypotheses about the origin of sporadic AVMs have also emerged. In 2016, Thomas et al. proposed that AVMs result from epigenetic changes in endothelial cells. More specifically, they noted that AVMs could result from changes in DNA methylation and histone modifications in genes related to vascular development [31].

Natural History

The overall rate of hemorrhage from an AVM has been reported to range from 2% to 4% per year [1, 7, 16, 25, 27, 29, 32–36]. AVMs are responsible for 1–2% of strokes [24]. The lifetime risk of hemorrhage can be estimated by $1 - (1 - \text{risk of hemorrhage})^n$, where n is the number of expected years of life remaining [1, 27]. 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 as we will discuss below [1, 27, 32].

Multiple factors have been associated with predicting AVM rupture: previous hemorrhage, size, location, pattern of venous drainage, the presence of associated aneurysms, and genetics. Ethnicity seems to play a role, with Hispanic patients at significantly higher risk for hemorrhage (~3.1-fold) [29]. 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, 28]. 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. However, in the absence of these risk factors, the lifetime risk of rupture in these AVMs is lower.

Since these variables have been mostly studied in longitudinal retrospective series, it is important to acknowledge the inherent biases of these studies. There is probably a large proportion of AVMs that is not included in many natural history studies and as such makes the data limited. As more sporadic AVMs are incidentally discovered, prospective series and registries are likely to improve our understanding of the natural history of AVMs over time.

In most series, previous hemorrhage is the most consistent predictor of subsequent hemorrhage [1, 6, 7, 16, 25, 27, 29, 30, 32–37]. The risk of recurrent hemorrhage seems to be the highest in the first year and ranges from 6% to 17% [7, 27, 32]. Some evidence supports even higher risk, up to 25%, after a second hemor-

rhage. 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, 32].

The impact of AVM size has been controversial, with some studies supporting increased risk with small size [1, 25, 27, 38], while others saw higher rates of hemorrhage in larger AVMs [33, 34]. Others have shown no association with AVM size [18]. 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, 38]. 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, 33].

Location has been shown to impact the risk of hemorrhage risk. Both deep and infratentorial lesions have higher hemorrhage rates [1, 7, 18, 21, 25, 27, 33, 39, 40]. For example, Fleetwood et al. demonstrated an annualized hemorrhage risk of 9.8% per patient-year in basal ganglia and thalamic AVMs [40]. 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, 33].

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, 15, 18, 27, 32, 33, 38].

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, 18, 41]. 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 [41].

From a genetic standpoint, SNPs in interleukin-6 (IL6), tumor necrosis factor alpha (TNF-a), and apolipoprotein-E (APOE) were associated with an increased risk of AVM rupture [13].

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, 16, 32, 40]. Risk of mortality is higher for patients with hemorrhage in the infratentorial compartment (~66%) [39, 42]. 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, 16, 32–34, 42]. 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, 16, 32, 39, 40, 43].

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 (Fig. 12.1a). The second most common presentation is seizure (15–35%). Mechanisms for this include cortical irritation from mass effect, steal syndrome resulting in ischemia and gliosis of surrounding tissues, and hemosiderin irritation from prior microhemorrhages. Less common presentations include a headache (5–15%) that mimics migraine, neurologic deficit not related to new hemorrhage (up to 10%, including focal

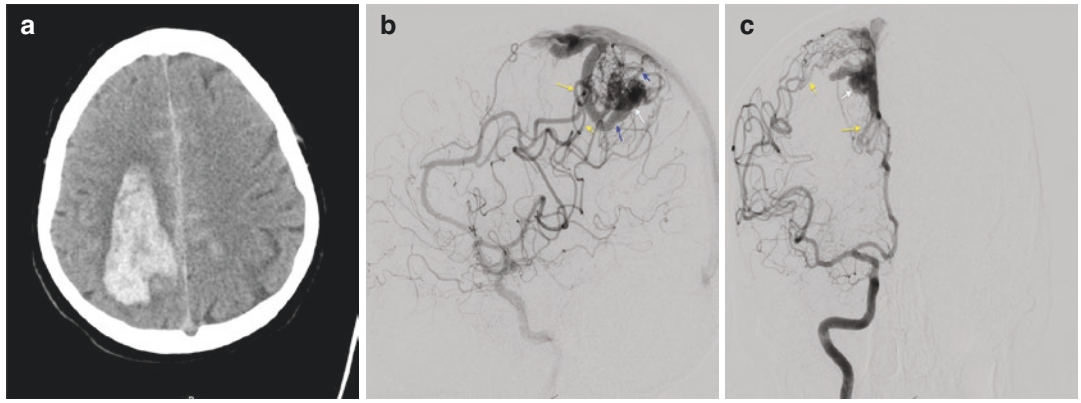

Fig. 12.1 (**a**) CT scan showing and AVM presenting with intraparenchymal hemorrhage and subarachnoid hemorrhage. (**b**, **c**) Conventional DSA demonstrating the AVM angioarchitecture. (Feeding arteries-yellow arrows, nidus-white arrow, draining veins-blue arrows)

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, 16, 18, 32].

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 (Fig. 12.1b, c).

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, focal neurologic deficits, or even headaches [32, 44]. Non-contrast CT scans are usually the initial testing of choice for evaluation of hemorrhage. 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 [45]. An advantage of MRI over other imaging modalities is its unique 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. Diffusion tensor imaging (DTI) and functional MRI (fMRI) can further define the relationship of an AVM to critical cortical and white matter structures [46, 47]. MRI also plays an important role in pre-radiosurgery planning and posttreatment follow-up [45, 48].

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 (Fig. 12.2a, b). However, they remain 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 [32, 45]. The flow dynamics of an AVM can be significantly

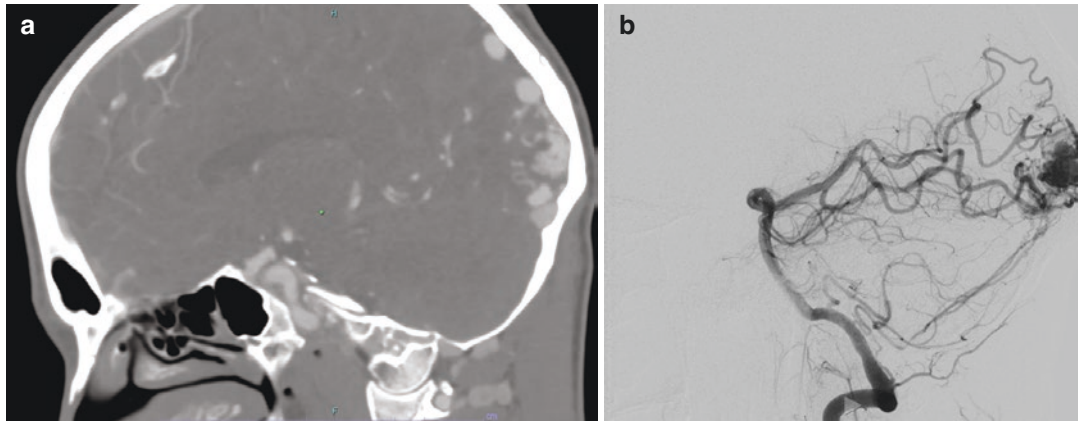

Fig. 12.2 (**a**) CT angiogram demonstrating an occipital AVM. (**b**) Conventional DSA showing the same occipital AVM

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 [20, 49].

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. 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 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 [50, 51]. Although invasive in nature, modern DSA has been shown to be extremely safe with a very low risk of complications and long-term sequelae [52].

Therapeutic Decision-Making

Multiple variables must be considered when choosing the best course of treatment. At our institution, we advocate a holistic approach to the patient that takes into account the patient's overall health and clinical history as well as the AVM's characteristics. A multidisciplinary approach is better suited to achieve the most favorable outcome. An AVM can be observed, resected, embolized, and radiated. Any combination of these options is also a possibility. This is why it is essential that AVMs be reviewed by a team capable of doing all the above so the technique bias is put aside and the patient's health is prioritized.

At this stage, there is no clear data to suggest that one treatment is superior to another. We will review the advantages and disadvantages of the different therapeutic modalities below. Experts generally agree that previously ruptured AVMs and AVMs at high risk of rupture such as those with associated flow-related aneurysms should be treated. However, there is no consensus on the best course of action for unruptured AVMs. The ARUBA trial concluded that observation is supe-

rior to any intervention when it comes to the management of unruptured AVMs [43]. However, despite being one of few prospective randomized clinical trials in vascular neurosurgery, it is also one of the most heavily criticized trials in the field. ARUBA was heavily criticized for including AVMs that are typically deemed inoperable in the treatment arm. The study also combined all treatment modalities in a way that does not reflect the true clinical approach to AVMs [53]. In a way ARUBA failed to acknowledge the presence of the classification systems that are used to guide management decisions for AVM patients.

Classification

The most widely used AVM grading 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 [54].

Evaluation of this grading system has been correlated with patient outcomes [1, 55–61]. 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 [55]. Comparable results were noted 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 [61]. 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 [56]. 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 [57]. The overall trend does point to correlation with Spetzler–Martin grading; however, variations in the literature between each group have led to proposed modifications in the system, ranging from expanding the classification to identify differences within groups [62] 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 [63, 64]. However, none of these modifications are currently widely used.

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 and Martin [54]

Microsurgery

Microsurgery is generally recommended for low-grade AVMs due to its curative nature and the low risk of associated morbidity and mortality. 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 when strategically implemented as a step in the multimodal approach to the AVM [65]. The ultimate goal of surgery is the prevention of hemorrhage by completely resecting the AVM. Secondary goals are alleviation of seizures and neurological deficits; however, the efficacy

of surgery with these indications is less clear since both can be complications of surgery as well [1, 65].

Surgery for AVMs is typically performed in an elective manner. While there are some reports of acute resection of AVMs after hemorrhage [1, 66, 67], 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 is more likely to produce favorable outcomes. An ideal compromise can usually be accomplished with the presence of liquefied hematoma surrounding the AVM and the 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.

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, 66, 67].

Approach and positioning of the patient depend on the location of the AVM. 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. Deep-seated AVMs are best approached with the assistance of neuronavigation, 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 [68].

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 toward the nidus, where they are coagulated and divided, or clips can be applied. Care should be taken to identify en-passant 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, 65].

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. 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 the 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, 65] (Fig. 12.3).

Throughout the surgery, 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, 65].

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. The 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

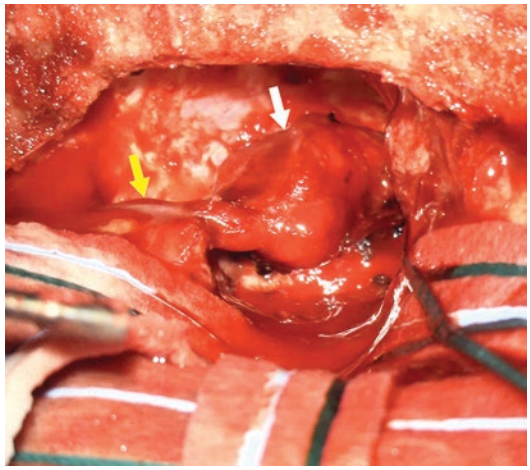

Fig. 12.3 Intraoperative image showing the AVM nidus (white arrow) after it has been fully dissected of the surrounding parenchyma. The last point of connection is the draining vein (yellow arrow) which at this stage of surgery appears deflated

nidus and differentiating normal from residual AVM vessels and are useful tools for assessment of total resection [1, 65, 69].

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. 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 [70–72] (Fig. 12.4).

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.

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 [73, 74].

- *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 [75–77]. The purpose of adjunctive embolization is to supplement 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 [78–80]. As an adjunct to microsurgical resection, endovascular embolization

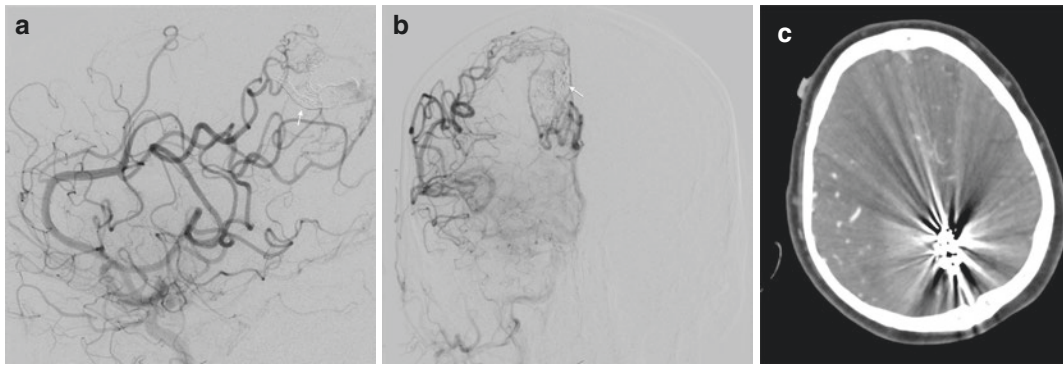

Fig. 12.4 (**a**, **b**) Conventional DSA showing the same AVM shown in Fig. 12.1 has been embolized using Onyx (white arrow). (**c**) CT scan showing embolization of the same AVM

has proven very helpful in cases of AVMs with a large nidus, deep-feeding vessels, and high-flow shunts. 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 [70, 81, 82].

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 [83].

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 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 [84–87]. In some instances, the embolic agents could shield the AVM from radiation. Many researchers have advocated radiating first them embolizing the AVM to allow the full radiation dose to be delivered to the lesion [88]. In some cases, endovascular embolization is used post-radiosurgery in a delayed fashion, in AVMs that fail to obliterate after radiosurgery [79, 87].

- *Curative*

  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 super selectively catheterizing and obliterating all of the small feeders that most AVMs have. In a 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 [70, 85, 89]. 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%

[71, 90]. 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 [72, 89]. 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 [91].

- *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 [92, 93]. 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 [32, 93] and with some studies suggesting it may actually increase the risk of intracerebral hemorrhage [91, 94].

Tools Review: Embolic Agents

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) [95, 96]. 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 [97, 98].

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 [99, 100].

  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 [74]. 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 [101].

- *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 [102].

  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 [103, 104]. 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 Versus 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 [105]. 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 [106]. This however comes at the expense of a prolonged endovascular procedure time and increased radiation exposure with Onyx [107]. Finally, some evidence suggests that Onyx may be associated with AVM recanalization due to its lower inflammatory-induced angiofibrosis [108].

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 the AVM population varies widely and ranges from 3% to 58% [109–112]. The presence of AVM-related aneurysms significantly increases the risk of hemorrhagic presentations [7, 41, 113].

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 [109, 114, 115]. Multiple aneurysms are frequently found as well; however, these are not associated with additional risk versus single aneurysms [109, 111]. 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 [109, 111, 115]. 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 [110, 114]. 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 [109].

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 [83, 116]. 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 [50, 51, 117].

Hemorrhagic complications can occur either intraoperatively or postoperatively and are related to changes in flow dynamics induced by occlu-

sive 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) [73]. Hemorrhage can also result from inadvertent embolization of draining veins leading to venous congestion with subsequent hemorrhage [118]. 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 [74, 82, 116].

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 [74, 116]. 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 [74, 116, 119, 120].

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 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 (DAC) can act as intermediate catheters and help navigate the intracranial circulation. They can help provide support to help direct

flow-guided microcatheters toward 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 Apollo (Metronic) 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, detachable tip Apollo catheter is preferable. These detachable tip microcatheters allow greater safety in catheter extraction as they are designed to leave a 1.5 cm or 3 cm portion of the catheter tip behind if it cannot be extracted from the Onyx cast with minimal force.
- 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.
- *Embolic agents*: As described earlier in this chapter, the mainstays of liquid embolic agents are n-BCA and EVOH. Coils 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. 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 044 DAC intermediate catheter to help advance our microcatheter toward the AVM in a coaxial fashion. The DAC is also useful to perform a focused roadmap of the territory of concern. The chosen microcatheter is advanced 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 a 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.

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.

Additional Neuro-endovascular Modalities

Transvenous Approach

TVE (transvenous embolization) is a tool that can be considered for select AVMs. It can when other arterial approaches are high risk [142–145]. Navigation through the TVE approach is technically challenging due to the venous system's tortuosity and might pose some risk, especially for less experienced neurointerventionalists [148]. Reduction or cessation of venous flow through a temporary balloon inflation or partial venous coiling can improve transvenous nidal embolic penetration. Such techniques reduce the reflux of embolic material from the arterial side and diminish the risk of AVM rupture [142, 147].

Onyx is considered a safe option with TVE due to its gradual polymerization rate and cohesive nature. NCBA, on the other hand, is not suitable for TVE, as it might cause rapid occlusion of the draining vein because of its instant polymerization [146, 148]. Mendez et al. reported their experience managing 41 AVMs through the TVE approach and noted a 3% complication rate [149].

Pressure Cooker Technique

As previously discussed, reflux of the embolic agent is a limiting factor in AVM embolization. Chaopt et al. described the pressure cooker technique as a method to generate an anti-reflux effect by trapping the detachable part of the microcatheter with coils and glue, thus producing controlled Onyx embolization. The addition of coils to the plug, besides blocking reflux, enhances the ability of the endovascular surgeon to push more Onyx through the arterial feeder, thus helping faster and more comprehensive nidal penetration [150, 151]. The same group also reported the safety of NBCA along with coils as a plug for preventing reflux of Onyx.

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

Stereotactic radiosurgery (SRS) is a nonsurgical procedure in which a precise beam of high-energy 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 [121]. 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 [122]. The process of lesion obliteration is gradual and prolonged, taking months to years before the desired effect is achieved [123–125] (Fig. 12.5).

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 [126–128]. SRS is generally considered a less invasive approach to AVMs treatment.

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 [129, 130]. 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) [127, 131].

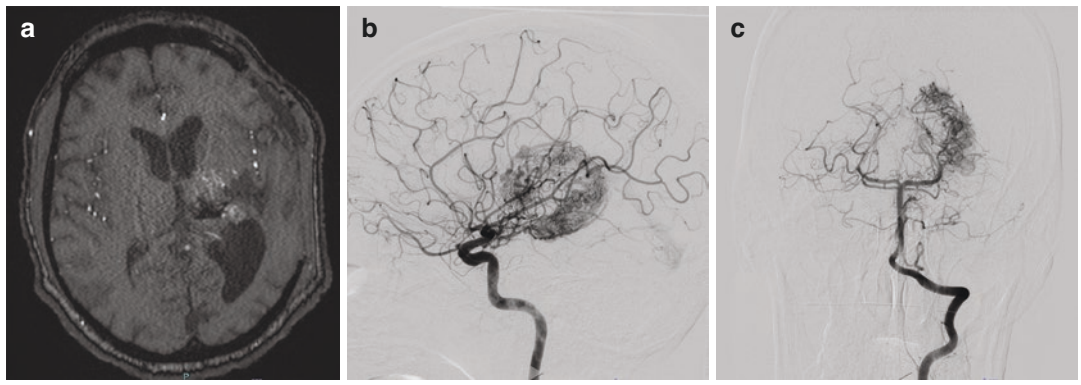

Fig. 12.5 (**a**) MRI showing a basal ganglia AVM with diffuse nidus, likely a good radiosurgery candidate. (**b**, **c**) Conventional angiogram demonstrating the deep-seated AVM

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 [127, 132–134]. Other factors found to favor SRS success were younger patients, hemispheric AVM location, and smaller number of draining veins [133]. 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 [134, 135].

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 [45, 136, 137]. 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 [137].

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 [134, 138, 139]. Transient abnormal signal in the peri-AVM region on brain MRI following treatment is also seen [140].

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% [124, 130]. Finally, rare recanalization or reappearance of the AVM several years after conclusion of SRS therapy and declared obliteration has also been reported [141].

Conclusion

Management of AVMs has significantly evolved to include numerous treatment modalities. Microsurgical, endovascular, and radiosurgical options should all be considered as part of a multidisciplinary approach to AVMs. Future studies promise to improve our understanding of the natural history of these lesions and the way they respond to treatment.

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13 Intracranial Dural Arteriovenous Fistula

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Introduction

Intracranial dural arteriovenous fistulae (dAVFs) are frequently underdiagnosed lesions with natural histories that range from benign and incidental to fatal. The first description in the literature appeared in 1873 when the Italian surgeon Francesco Rizzoli described the case of a young girl with seizures and occipital swelling, who on postmortem examination as found to have direct anastomosis of the occipital artery to the transverse sinus [1]. The first angiographic visualizations were performed in the 1930s by Sachs and/or Bergstrom [2]. Following these initial descriptions, the lesions were initially thought to be congenital in nature. But in the 1970s, Castaigne and Djindjian proposed that dAVF could result from enlargement of preexisting microscopic arteriovenous shunts within the dura as a result of a variety of venous pathologies [3]. This concept, that dAVFs are acquired lesions that develop as a result of venous hypertension or thrombosis, remains the prevailing etiological explanation today.

Though varied in presentation and structure, the underlying pathology of these lesions is constant and consists of an abnormal connection between the arteries and veins in the dura. The risk of hemorrhage associated with dAVFs is closely tied to the degree of venous disease and reliance on the cortical venous system for drainage. For dAVFs that warrant treatment, multiple options are available including transvenous or transarterial endovascular embolization, open surgery, or radiosurgery. The goal of all these treatments, however, is the same, which is disconnection of the anastomoses between the meningeal arterial inputs to the dural sinus or cortical vein. In this chapter, we will cover the epidemiology, pathophysiology, and treatment options in the context of clinical care, focusing on lesions in the adult population. Illustrative cases are provided to highlight the teaching points.

Epidemiology

dAVFs are widely quoted to account for approximately 10–15% of all intracranial vascular malformations. The exact incidence and prevalence are unknown as some dAVFs are clinically silent and go undiscovered [4]. Several population-based studies have been performed, which reported detection rates of 0.15 per 100,000/year in an American cohort, 0.29 per 100,000/year in a Japanese cohort, and 1.1 per 100,000/year in a Scottish cohort [5]. The age range for dAVFs is quite wide, with the mean age of presentation being between 50 and 60 years of age [4]. They

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occur less commonly in children. There does not appear to be any correlation between incidence of dAVFs with race or sex, though males are more likely than females to present with intracranial hemorrhage (ICH). Roughly one quarter to one-third of patients diagnosed with dAVFs present with hemorrhage [6].

Pathophysiology of Formation

dAVFs can be differentiated from other arteriovenous shunts of the brain in that they lack a nidus (compared to arteriovenous malformations) and that the arterial supply is from dural vessels (compared to pial fistulae). The exact etiology of dAVF remains controversial, but there is increased acceptance that they result from venous hypertension or thrombosis resulting in enlargement of existing microscopic connections in the dural leaflets between the meningeal arteries and dural veins. In the majority of patients, no inciting event can be identified, but for a subset, injuries such as trauma, prior cranial surgery, compressive tumors, infection, or dural venous sinus thrombosis precede the diagnosis [7, 8]. In addition, there has been increasing evidence that there may be an association with inherited causes of thrombophilia and formation of dAVF, though these inherited causes (e.g., factor V Leiden, MTHFR, prothrombin G20210A) on their own are unlikely to cause dAVF [7].

dAVFs are typically located near a venous sinus with roughly half of them involving the transverse and sigmoid sinuses, 15% involve the cavernous sinus, 10% tentorial sinus, and 8% superior sagittal. A few DAVFs can occur at the vein of Galen, though these typically present earlier and are thought to be congenital in nature [8].

These lesions are dynamic in nature. They can recruit additional arterial inputs over time, increasing the degree of shunting and resultant venous hypertension, with potential to develop reliance on cortical venous reflux (CVR) as well. These changes, besides increasing the risk for intracerebral hemorrhage from venous rupture due to arterialization fragile parenchymal veins, can also result in parenchymal ischemia, as the increased venous pressures resist the delivery of arterial supply [8]. As a result, nonhemorrhagic neurological deficits (NHND) have been described to be progressive and can include dementia, epilepsy, aphasia, paresis, ataxia, and parkinsonism. Of note, dAVFs can also recede, with spontaneous occlusion of the anastomotic connections and resolution of the fistula described in some cases [9].

Clinical Presentation

Clinical presentations of dAVFs vary depending on the location, arterial supply, venous drainage pattern, and the presence of CVR [5, 9–13]. dAVFs without CVR may present incidentally or with benign symptoms related to the increased dural sinus blood flow. These symptoms depend on the location of the drainage (Table 13.1).

dAVFs located in anterior fossa may receive arterial supply from ethmoidal branches from ophthalmic arteries in addition to meningeal vessels and drain into the cavernous sinus or orbital veins [9, 10]. These lesions typically present with ocular symptoms because of its proximity to orbit. The symptoms and signs include proptosis, chemosis, ophthalmoplegia, exophthalmos, glaucoma, and vision impairment [10, 12]. Cavernous sinus dAVFs present in a similar way of anterior cranial fossa dAVF, including symptoms of cavernous sinus syndrome such as conjunctival injection, ophthalmoplegia, exophthalmos, and visual impairment [13] as well as cranial nerve deficits [9, 13]. Middle cranial fossa lesions drain into the transverse or sigmoid sinus. Their close proximity to the auditory apparatus can frequently lead to symptoms of pulsatile tinnitus [9, 10, 13]. dAVFs draining into the superior sagittal sinus or deep venous systems present with symptoms and signs of global venous congestion and elevated intracranial pressure such as headache, hydrocephalus, seizure, or dementia. Although less common, brainstem dVAFs can present with myelopathy, cranial neuropathy, or ICH.

Table 13.1 Most common locations of DAVF [9, 12, 14–19]

Location (sinus)	Typical feeding arteries	Venous outlet	Typical symptoms
Transverse/sigmoid sinus (39–50%)	OA, PAA, APA, MMA, VA	Transverse/sigmoid sinus	Pulsatile tinnitus, bruit, headaches, ICH
Cavernous sinus (10–29%)	MMA, AMA, AFR, APA	Cavernous sinus, ophthalmic vein, inferior petrosal sinus	Chemosis, proptosis, bruit, vision loss, headache
Tentorial incisura (4–14%)	MHT, MMA	Straight sinus, deep cerebral veins	ICH, tinnitus, headache
Convexity (SSS) (8–13%)	OphA, MMA, PMA	Superior sagittal sinus	Headache, dementia, seizures
Anterior cranial fossa (5%)	OphA, IMA, MMA, STA	Olfactory vein, frontal veins, cavernous sinus	ICH, headache
Foramen magnum (2–5%)	MMA APA, OA, VA	Anterior/posterior spinal vein, medullary vein, basilar plexus	Myelopathy, ICH, tinnitus

OA occipital artery, *PAA* posterior auricular artery, *APA* ascending pharyngeal artery, *MMA* middle meningeal artery, *VA* vertebral artery, *AMA* accessory meningeal artery, *AFR* artery of foramen rotundum, *ICA* internal carotid artery, *OphA* ophthalmic artery, *PMA* posterior meningeal artery, *MHT* meningohypophyseal trunk, *IMA* internal maxillary artery, *STA* superior temporal artery

Differential Diagnosis

The presenting symptoms of dAVF may be nonspecific, and given their relative rarity, other etiologies should be investigated.

Headache Headache is a nonspecific symptom, and there are no characteristic headache patterns of dAVF. One observational study found that the most common presentation of dAVF was headache without correlation with the location. Migraine-like headache was the most common description of the headache in the study [20]. Because headache sometimes can be an initial symptom [21, 22], keeping the dAVF in differential is important. See discussion below on noninvasive imaging modality evaluations that may suggest dAVF as etiology.

ICH The approach to ICH should be systematic, as the etiology of ICH varies with presenting features as well as location. Nontraumatic intraparenchymal hemorrhage can be from hypertension, amyloid angiopathy, hemorrhagic transformation of ischemic stroke, vascular malformation including arteriovenous malformation, dAVF, and cavernoma, neoplasm, vasculopathy, or venous infarct. Extra-axial hemorrhage etiology includes aneurysmal/non-aneurysmal subarachnoid hemorrhage, vascular malformation, vasculopathy, or traumatic hemorrhage [23, 24]. dAVF-related ICH is usually lobar intraparenchymal, most often located near the fistula site [25]. However, it can be associated with intraventricular, subarachnoid, or subdural hemorrhage.

Pulsatile Tinnitus Pulsatile tinnitus is subjective or objective perception of repetitive sounds synchronous to the heartbeat. The causes of pulsatile tinnitus include vascular etiologies such as dAVF, arteriovenous malformation, or carotid artery dissection, or nonvascular etiologies including glomus tumor, idiopathic intracranial hypertension, or anemia [26]. dAVF is a relatively uncommon cause of tinnitus, and a workup with noninvasive imaging as well as expert ENT evaluation is usually warranted prior to further exploration with catheter angiography.

Cavernous Sinus Syndrome dAVF can present with various degrees of cavernous sinus syndrome including chemosis, ophthalmoplegia, proptosis, vision impairment, or double vision. When it presents with only mild symptoms such as chemosis, it can be hard to suspect the underlying DAVF. Therefore, additional signs and symptoms need to be explored for the differential diagnosis. The differential diagnosis of cavernous sinus syndrome/ocular presentations includes tumors such as pituitary tumor, meningioma, schwannoma or metastatic disease, vas-

cular pathologies such as aneurysms or cavernous sinus thrombosis, infections, or inflammation like Sarcoidosis or Tolosa-Hunt syndrome [27, 28].

Imaging Evaluations

Non-contrast Computed Tomography

As with most vascular lesions, dAVFs are not typically visible by non-contrasted computed tomography (CT). The following features might be noted:

- The presence of intracranial hemorrhage, most commonly intraparenchymal hemorrhage which usually lobar. Subarachnoid hemorrhage and subdural hematoma are also possible. Intraventricular hemorrhage can be seen when intraparenchymal hemorrhage extends to the ventricles. However, the pattern of ICH is not specific.
- Ventriculomegaly secondary to communicating hydrocephalus.
- Hyperdensity of a dural sinus suggesting thrombosis.

CT Angiography

Due to the high-flow nature of dAVF and the fact that they are commonly located near the 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 the following:

- Venous varices.
- Dilation and/or occlusion of a venous sinus.
- Dilation of the ophthalmic vein.
- Abnormally enlarged subpial or external carotid vessels.

Magnetic Resonance Imaging

dAVFs are typically not definitively diagnosed on magnetic resonance imaging (MRI). However, the following findings can be seen and suggest the presence of dAVF:

- Dilated cortical veins as flow voids within the cortical sulci on T2-weighted imaging.
- Parenchymal or leptomeningeal enhancement in post-gadolinium T1-weighted imaging.
- Venous congestion with vasogenic edema on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences.
- Venous sinus thrombosis can also be seen on gadolinium-enhanced sequences.

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.

Four-Dimensional (Time-Resolved) CT Angiography and MR Angiography

Recent advances in imaging technology allow hemodynamic evaluations of DAVF using 4D CT angiography or MR angiography. These four-dimensional (4D) techniques have been evaluated for its use as alternatives of DSA as their less invasive, less time consuming, and less exposure to contrast and radiation. 4D-CTA can provide flow dynamics with the first-pass contrast bolus. It is less invasive, as well as it has less exposure to radiation. Multiple studies have shown high sensitivity and specificities detecting DAVF when it is compared with DSA [29–32]. Contrast-enhanced time-resolved MR angiography (CE TR-MRA) showed highly sensitive detection of DAVFs and good evaluation of venous drainage and sinus involvement. In addition, with high accuracy in identification of residual fistula and retrograde venous drainage, CE TR-MRA can be a good follow-up modality for DAVF monitoring. However, its limitation exists in detecting feeding arteries [33–35]. Non-contrast-enhanced four-dimensional MRA (NCE 4D-MRA) uses arterial spin labeling. This technique uses arterial blood magnetization which acts as a tracer without

injecting a contrast agent. NCE 4D-MRA shows good detection of arterial feeders, addressing a limitation of CE 4D-MRA, and it allows vessel-specific evaluation by vessel-selective labeling [36–38]. At present, the availability and utilization of these techniques remain limited.

Digital Subtraction Angiography

Even with the recent advances of the imaging studies, digital subtraction angiography (DSA) remains the gold standard for the diagnosis, staging, and treatment planning of the 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 as well as venous access routes. The typical angioarchitecture of dAVF consists of a network of arterial feeders that converge on to a singular fistulous region of a recipient vein. The goals of DSA include the following:

- Identify arterial feeders.
- Identify the fistulous portion of the involved recipient vein.
- Look for evidence of cortical venous reflux and ectasia.
- Evaluate venous drainage pathways.
- Assess for arterial and venous pathways to the fistulous site.

Natural History

The natural history of dAVF is influenced heavily by the pattern of venous drainage as well as presentation symptoms and other angiographic features. Over a dozen classification schemes for dAVFs have been proposed over time [39]. At present, the two most commonly used classifications are those of Borden and Cognard. In both systems, the primary differentiator between benign and aggressive or high-risk lesions is the presence of CVR, the reliance on cortical veins to drain the shunted blood flow. This finding, which typically requires catheter angiography to visualize, demonstrates the pathophysiological basis of ICH resulting from dAVF. Thin-walled cortical veins exposed to substantially greater arterial pressures will over time undergo arterialization and are at risk of rupture. The Cognard classification includes additional categories for the presence or absence of venous ectasia, which can result from chronic venous hypertension, and anterograde vs. retrograde flow in the venous sinus. However, the primary predictor of mortality and annual hemorrhagic risk remains CVR.

In a series with long-term follow-up in 68 patients with dAVF without CVR, 98.5% did well with conservative management, with a 2% conversion rate to developing CVR [40]. In another series with 133 patient-years of follow-up, most patients' symptoms improved with time [41]. The rate of ICH, neurological deficit, or death was low (<2%) in both treated and untreated patients. As such, the most common management strategy for patients with low-grade dAVF without CVR is conservative. However, in some patients, the benign symptoms including ocular changes and pulsatile tinnitus can be debilitating, and elective treatment is warranted in such patients. In addition, because of the possibility of development of CVR, monitoring for worsening symptoms is important in all patients with dAVF (Fig. 13.1).

In patients with dAVF that present with CVR on the other hand, significant morbidity and mortality have been reported. Van Dijk et al. investigated the long-term adverse events of dAVFs with CVR in patients who declined recommended treatment or had persistent CVR despite treatment attempts. During the 89.9 patient-years follow-up, 45% of patients died, with an annual mortality rate of 10.4%; 35% suffered a hemorrhage, with a combined annual risk of ICH and NHND of 15.0%. Moreover, those presenting with acute ICH were reported to have a high rebleeding risk [6]. In a series of 20 patients presenting with acute intracerebral hemorrhage due to high-grade dAVFs, the risk of rebleeding was found to be 35% within 2 weeks from the initial presentation [6]. Early treatment is strongly recommended for such lesions.

Cortical venous ectasia, which is included in the Cognard classification as discussed above, has

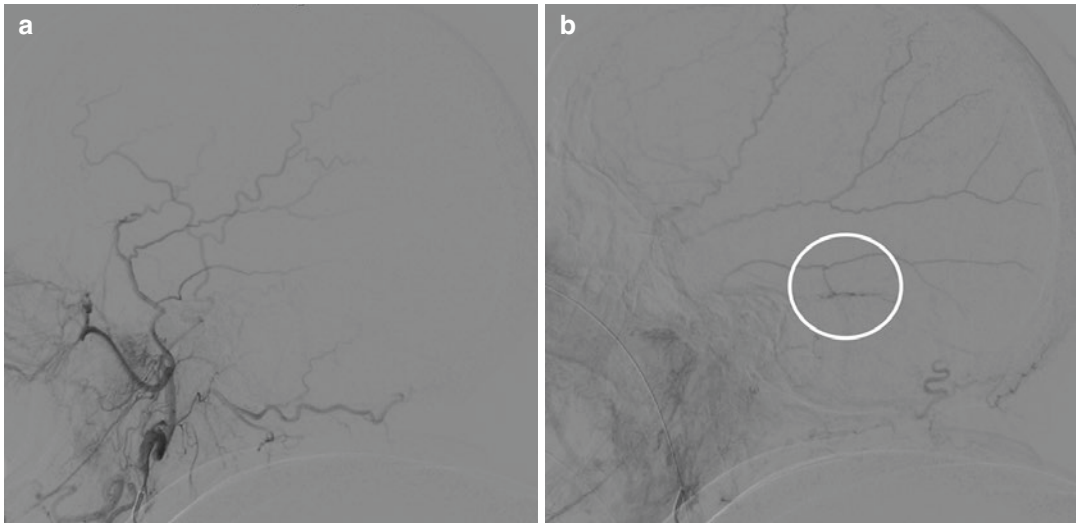

Fig. 13.1 Low-grade dAVF. 62F with diagnostic cerebral angiogram performed in the workup of ischemic infarction. Lateral projection right external carotid artery angiograms in the early (**a**) and later (**b**) phases. A low-flow, low-grade dAVF of the right transverse/sigmoid sinus with arterial input from the middle meningeal artery can be seen (circle). No further angiographic follow-up is required for this lesion

also been shown as a risk factor for hemorrhage. In a series of 75 dAVF with CVR, the absence of venous ectasia was associated with a significantly lower rate of risk of annual hemorrhage, 3.5%. In contrast, the presence of venous ectasia carried an annual risk of hemorrhage of 27%.

Treatment Strategies for DAVF

The treatment strategies for dAVF include transarterial embolization, transvenous embolization, open surgical techniques, and stereotactic radiosurgery (SRS). Regardless of treatment modality, the goal of therapy is to create an effective and durable occlusion of the fistulous connection. Obliteration of arterial inputs is generally insufficient as additional dural connections will be recruited without disconnection of the fistula. Conversely, overaggressive occlusion of venous outlets can worsen venous hypertension and result in infarction or intracerebral hemorrhage.

Endovascular Treatment

Endovascular treatment is the first-line therapy for most dAVFs. Both transarterial and transvenous approaches are routinely performed.

Transarterial Approach

Transarterial embolization is a frequently used technique, and when performed in middle meningeal branches distal to key anastomoses to the orbit and by the skull base, can be accomplished with a very good safety profile [42]. This approach is particularly appealing if a good arterial route to the fistulous site can be identified [43]. In addition, as shown in Illustrative case 2, complete embolization with occlusion of many non-catheterized arterial inputs can be embolized with injection of a single arterial input [44] (Fig. 13.2).

The development of dual-lumen balloon microcatheters that are capable of delivering liquid embolic material has improved the ability to perform trans-arterial dAVF embolization. By inflating the balloon and conferring flow arrest, embolization agents such as Onyx (Medtronic) or Phil (Microvention) can be delivered without concern for reflex, and without having to spend time creating a proximal plug. As a result, the embolic agent travels forward reliably. This technique has shown high occlusion rates, with less volume of liquid embolic agent and reduced procedure time [45, 46] (Fig. 13.3).

Another technique that has been described is combined transarterial balloon-assisted endovascular embolization and concomitant transvenous

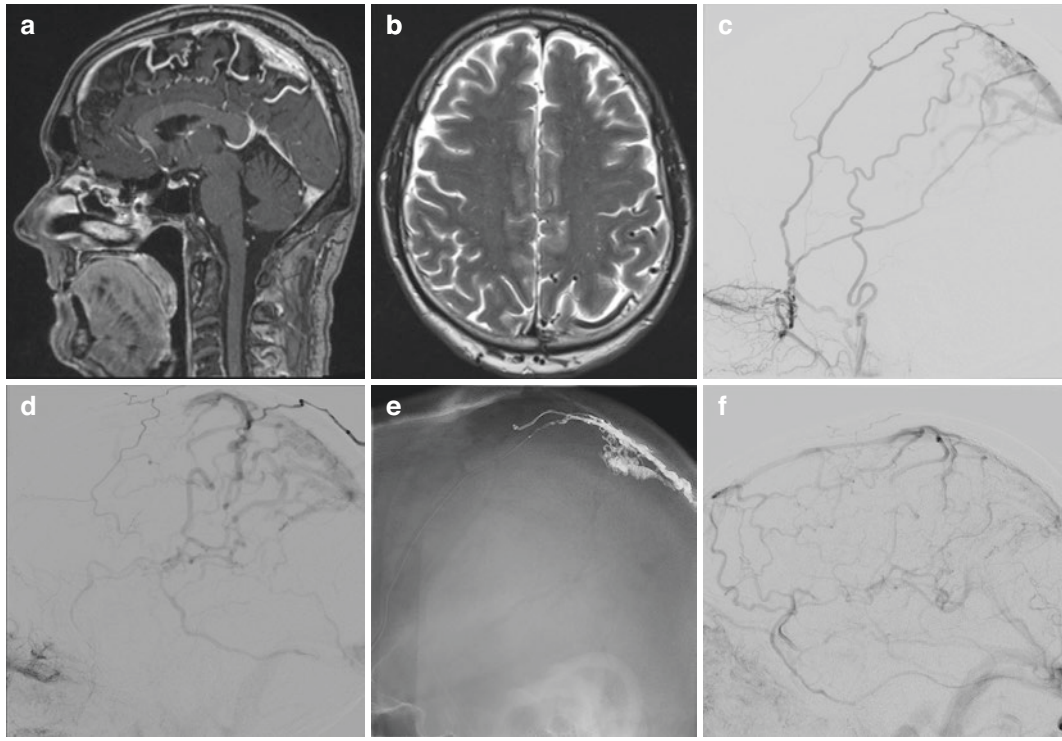

Fig. 13.2 High-grade dAVF. 57 M with a history of renal carcinoma with MRI performed for evaluation of cerebral metastases. (**a**) T1 post-contrast imaging was concerning for prominent tortuous vessels along the surface of the left posterior parietal lobe as well as prominent draining veins. (**b**) T2 imaging showed large flow voids in the same region. Lateral projection left external carotid artery angiography in the arterial phase (**c**) confirmed the presence of a superior sagittal sinus dAVF with arterial supply from middle meningeal artery branches. Later venous phase images (**d**) confirmed the presence of cortical venous reflux. Embolization was performed with injection of Onyx into a single middle meningeal artery feeder, which resulted in occlusion of multiple arterial inputs (**e**), and successful obliteration of the fistulous connection to the recipient vein with preservation of the superior sagittal sinus (**f**)

balloon protection. This technique has been associated with a reduction in inadvertent occlusion a functioning sinus, preservation of venous patency, facilitation of occlusion of abnormal arteriovenous connections within the sinus wall and separate venous channels, and increased penetration of embolic material by retrograde reflux into other dural feeders of the fistula network [46].

Transvenous Approach

Transvenous approaches offer several advantages relative to transarterial approaches including the potential for direct catheterization of the fistulous portion of the recipient vein, for targeted embolization. In many cases of transverse or cavernous sinus dAVF, venous access to the fistulous site can be attained in a relatively straightforward fashion. In addition, for particular lesions such as anterior cranial fossa dAVF, transvenous approaches may be safer than transarterial approaches, which can require catheterization and embolization within the ophthalmic artery. In a series of 23 patients with anterior cranial fossa dAVFs treated with endovascular approach, transvenous embolization using nonadhesive liquid embolic agents (Onyx and Phil), coils, or combination of coils and Onyx, resulted in immediate angiographic cure in 89.5% after a single transvenous treatment session compared to a failure rate (persistent opacification of the draining vein at the end of the procedure) of 77.8% for transarterial embolization. At a mean angiographic follow-up of 25 months, dAFV was completely cured in 95% of the cases [47].

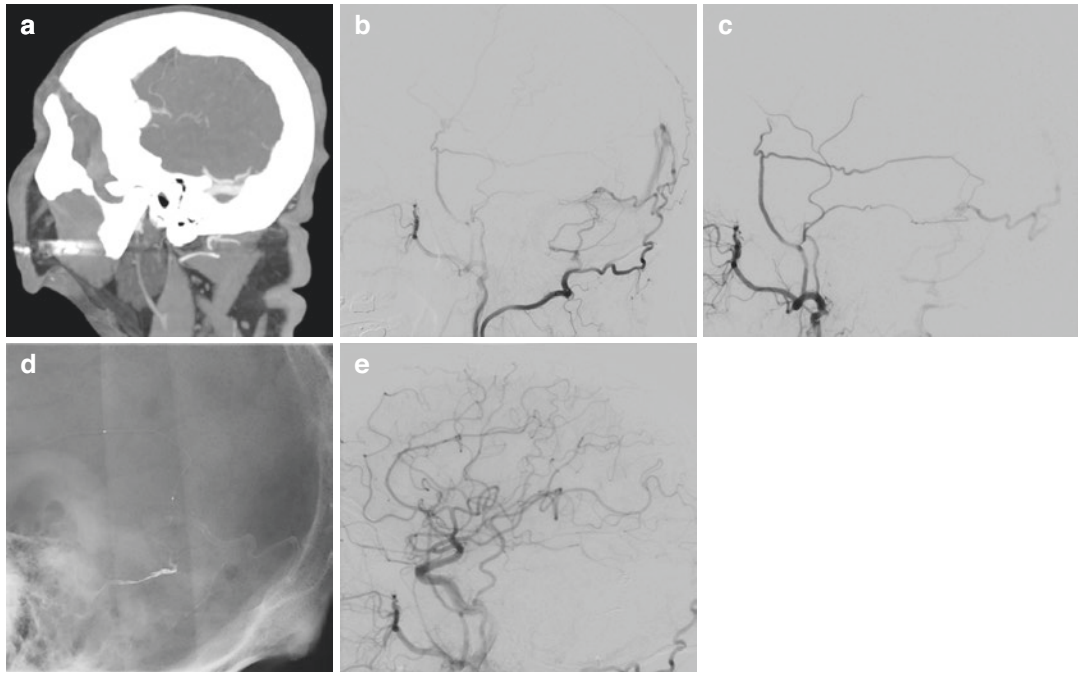

Fig. 13.3 High-grade dAVF. 57 M presented after mechanical fall with facial injury. MRI (not shown) and (**a**) CTA were largely unremarkable. Catheter angiogram was performed to evaluate for possible vertebral artery injury. (**b**) Lateral projection left external carotid artery angiogram revealed dural arteriovenous fistula located in the dural wall of the sigmoid/transverse sinus, with drainage via a dysplastic cortical vein into the superior sagittal sinus, without connection to the transverse/sigmoid sinus. The transverse/sigmoid sinus was patent (not shown). Embolization of the occipital artery feeders was performed using dual-lumen balloon microcatheter (**c**, **d**) followed by embolization and successful obliteration of the fistula via the middle meningeal artery. (**e**) Completion angiography confirmed fistula obliteration

Open Surgical Treatments

As discussed above, the goal of surgical treatment is obliteration of the fistulous connection. This task can be accomplished with electrocautery of the connection, or surgical clipping of the draining vein adjacent to the fistula. Combined open surgical and endovascular approaches have also been described, with surgical exposure of the target vessels followed by direct puncture and embolization with coils and/or liquid embolic agents [48].

Stereotactic Radiosurgery (SRS)

SRS is considered an adjunctive treatment mainly for endovascular embolization to achieve higher rates of complete and durable obliteration. SRS has been utilized as a first-line treatment in patients with mild symptoms, no CVD, poor vascular access, and underlying morbidities. In a recent series in which SRS was the only or adjunctive treatment to embolization, Yang et al. suggested embolization to be performed immediately before or after SRS to achieve best obliteration [49].

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Preoperative Tumor Embolization

14

Elvira Lekka, 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].

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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 into particulate or liquid agents 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

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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]. Liquid 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 micro-

catheter [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 results 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 [33], angiographic control runs [34], transcranial Doppler [35], xenon 133 imaging [36], xenon CT [37], CT perfusion [38], PET [39], SPECT [40], and MR perfusion [41].

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 the 150–250 μm range. Liquid embolic agents (e.g., NBCA or EVOH) are preferred by some practitioners, 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 the 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 [42]. Capillary hemangiomas proliferate during the first 9–12 months of life and subsequently involute at a variable course over many years [43]. 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 [44].

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 [45]. 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 [46].

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 [47, 48].

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 tumors 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 meningiomas commonly receive 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 [49].

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 [50]. 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 [51].

Arterial supply for JNA arises initially from the pterygopalatine portion of the internal maxil-

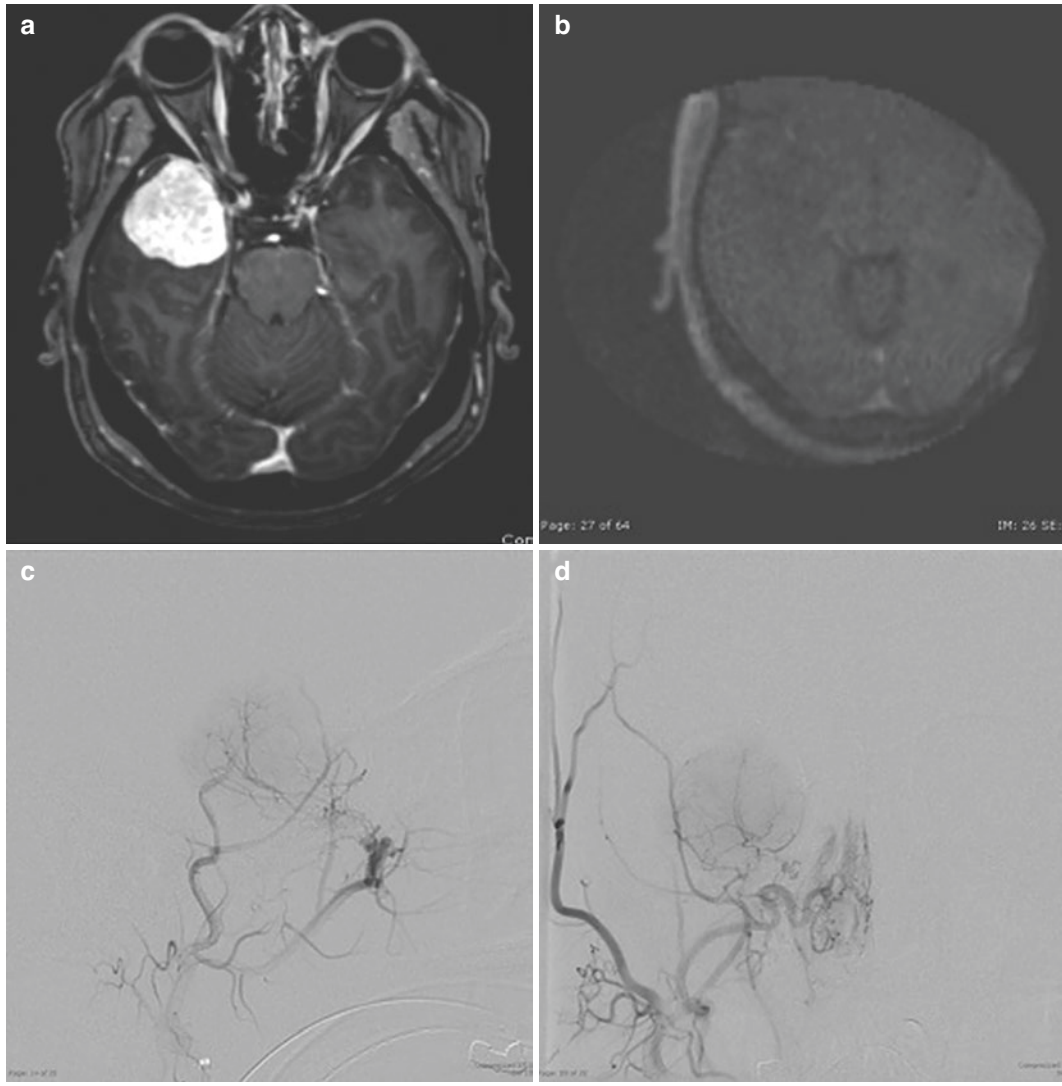

Fig. 14.1 Gadolinium-enhanced axial image showing avid enhancement of a right middle fossa meningioma (**a**). Catheter angiography demonstrates a significant tumor blush with microcatheter injection of the internal maxillary artery on anterior–posterior (**b**) and lateral (**c**) projections. No residual enhancement is seen on intraoperative gadolinium-enhanced MRI (**d**)

lary artery including the sphenopalatine, infraorbital, and descending palatine branches. Recruitment of adjacent vessels including the accessory meningeal, 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 [52]. Bilateral blood supply is not uncommon, and when present, both branches should be embolized to prevent excessive hemorrhage at the time of resection [53].

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 [54].

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 concern when embolization is attempted for tumors involving the skull base [54]. Endoscopic assistance has been used for direct transnasal tumor puncture and intratumoral embolization using the liquid embolic agent Onyx [55].

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.

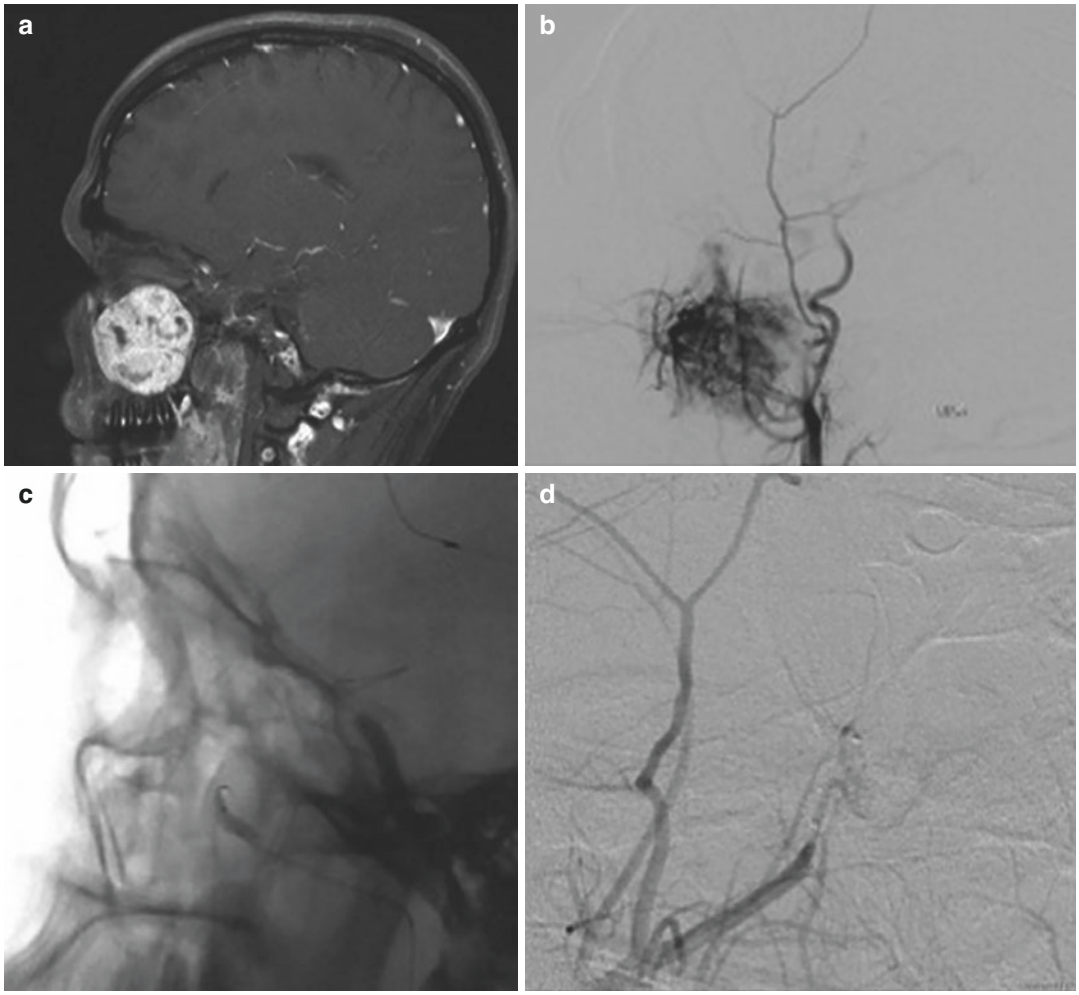

Fig. 14.2 Gadolinium-enhanced sagittal MRI showing avid enhancement of a maxillary sinus juvenile nasal angiofibroma (**a**). Microcatheter injection of the internal maxillary artery demonstrates significant tumor blush (**b**) that was treated with particle embolization (**c**), resulting in elimination of the previously seen blush (**d**)

Glomus Tumors

Paragangliomas, also known as glomus tumors, are rare hypervascular neoplasms that arise from chemoreceptor organs derived from the neural crest [56]. 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 are 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 [57].

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 structures. 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 [58].

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 [59]. 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 [60]. 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 the 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 paragangliomas inferior to the skull base [61].

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 [62]. 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 also been reported [63].

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 [64].

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 [65].

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 [66]. 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 endolymphatic duct that in turn joins the utricular and saccular ducts. It is believed to be involved in the regulation of endolymphatic fluid volume [67].

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 of a component of hemorrhage, cyst, residual bone, and cholesterol granuloma. Flow voids may be present suggesting high vascular flow [68].

The vascular nature of the neoplasm has led to the recommendations for preoperative embolization to aid in surgical resection [69].

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15 Neurointervention in Ophthalmologic Disorders

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Cerebral Aneurysm

Introduction

Cerebral aneurysms are localized abnormal dilatation of the cerebral artery resulting from weakening of the vascular wall. Cerebral aneurysms most commonly involve the branch points of the major arteries at the circle of Willis [1]. The overall prevalence of intracranial aneurysms varies from 1% to 5% [1–3]. The majority of small cerebral aneurysms (less than 7 mm in diameter) remain unruptured, with an average annual rate of rupture of approximately 0.95%; patient age, smoking, and size of aneurysm are important risk factors for rupture [4, 5]. The annual rate of rupture increases to 3–8% for aneurysms greater than 7 mm in diameter [6].

Clinical Manifestations

The ocular manifestations of cerebral aneurysms take three forms: [1] visual loss as a result of retinal/vitreous 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 [7–9]. Other rare ocular manifestations have been reported, as a result of either the cerebral aneurysm or its related intervention, such as retinal arterial emboli [10], orbital compartment syndrome and blindness [11], and internuclear ophthalmoplegia [12].

Terson syndrome manifests as multilayer bleeding in the subretinal space, in the retina, between retina and vitreous, and in the vitreous and occurs in more than 30% of patients who survive subarachnoid hemorrhage [13]. The mechanism of intraocular bleeding is postulated to be rupture of the fine optic nerve head 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, the presence of Terson syndrome may predict poorer neurologic outcome from subarachnoid hemorrhage [14].

The intimate relationship between the anterior visual pathways and the circle of Willis makes visual loss a not infrequent presenting symptom of cerebral aneurysms. Cerebral aneurysms aris-

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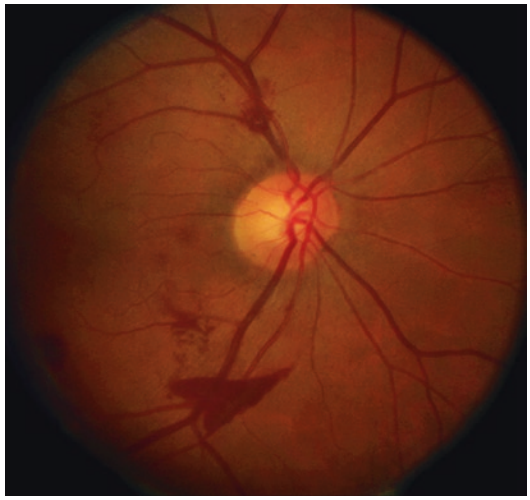

Fig. 15.1 Retinal and subhyaloid (between vitreous face and retina) hemorrhage in a patient with Terson syndrome as result of a ruptured middle cerebral artery aneurysm. Note typical appearance of triangular-shaped or boat-shaped subhyaloid hemorrhage in inferior retina

ing 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 [8]. 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 [5, 15]. 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 [16].

Diplopia and ocular motility abnormalities are commonly associated with aneurysms arising from cavernous carotid segment, posterior communicating, and basilar arteries [17]. Posterior communicating artery aneurysm is a frequent cause of third nerve palsy, which presents with a symptom complex of ptosis, fixed and dilated pupil, and the so-called down and out eye [18]. 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 the cavernous sinus; the ocular motor abnormalities are sometimes associated with decreased sensation or pain along the V1 and V2 distributions of the trigeminal nerve [9]. Cavernous segment carotid aneurysms 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 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 [17].

The radiographic features and endovascular intervention for cerebral aneurysm are described in Chaps. 10 and 11.

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

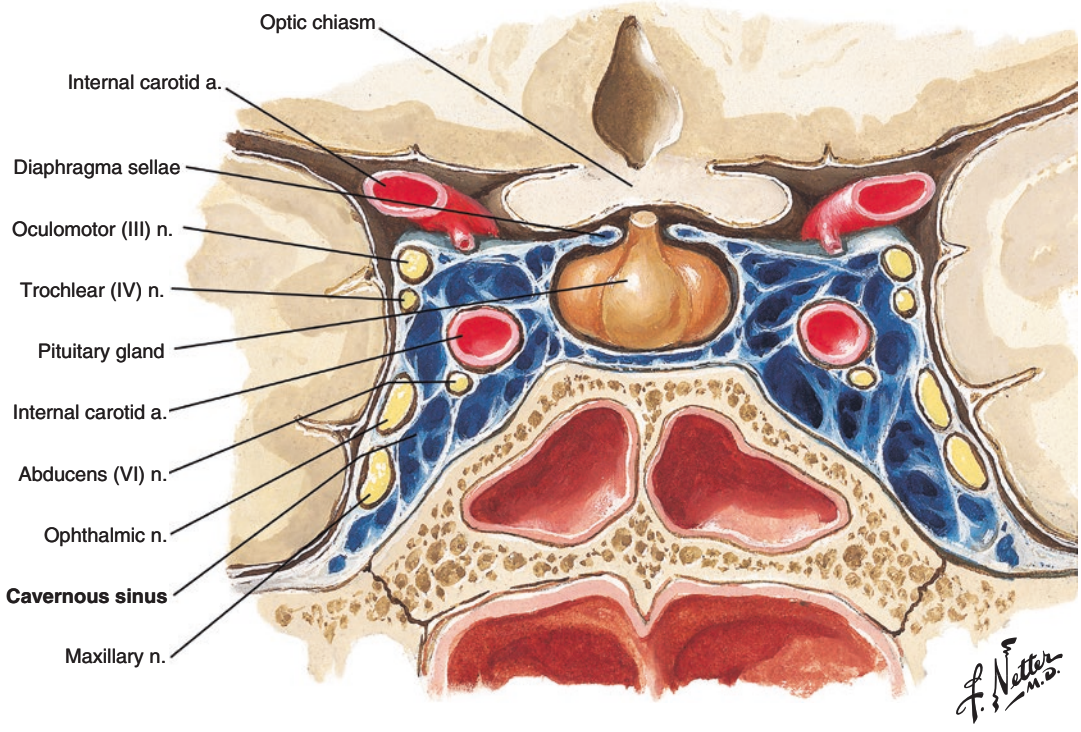

Fig. 15.2 Coronal view of the cavernous sinus demonstrating the passage of the third, fourth, fifth, and sixth cranial nerves and internal carotid artery inside the cavernous sinuses. (Permission from Netter's production)

veins and then drains posteriorly to the internal jugular vein through the superior and inferior petrosal sinuses and the transverse sinus [19]. 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 venous 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 [20]. 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. Barrow et al. [21] defined four types (Types A–D) of CCFs. Type A CCFs are direct, high-flow lesions connecting the ICA directly to the cavernous sinus. Type A CCFs often result from a single tear in the carotid artery wall, caused either by trauma or aneurysm rupture. Type B, C, and D CCFs are all indirect, low-flow lesions that arise from meningeal branches of either the ICA or ECA. Another angiography-based classification system is proposed for dural AV fistulas – the Cognard classification based on the direction of dural sinus drainage (antegrade or retrograde), the presence or absence of cortical venous drainage, and venous outflow architecture [22].

Clinical Manifestation

A direct CCF is caused by a tear in the intracavernous segment of the internal carotid artery, usually in the setting of trauma, although in a small proportion of patients, it may occur spontaneously [23]. The classic triad of proptosis, conjunctival chemosis, and orbital bruit is a consequence of significantly elevated venous pressure in the superior ophthalmic vein and cavernous sinus system [24]. Typical ocular findings are prominent pulsatile proptosis, chemosis, hyperemia, and periorbital pain or headache [25, 26]. 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. 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 [27–29].

In contrast to direct CCF, indirect CCFs usually have a spontaneous onset and are slowly progressive [30]. 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.

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 stasis retinopathy [28, 30, 31]. 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 [32–34].

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 [35]. 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 [36].

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. These are best observed on thin section MRI [37].

CT angiogram and MR angiogram can add additional information [38, 39]. Orbital ultrasonography may also provide sensitive and reliable measurement by demonstrating dilatation and arterialization of flow of the superior ophthalmic vein but cannot give any information on posterior cortical venous drainage [40, 41].

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 and/or magnetic resonance imaging should be 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 are sometimes recognized only on catheter angiography.

Management of CCF

Spontaneous resolution of indirect CCFs due to venous thrombosis either unprovoked or after angiography has been reported in 20–60% of indirect CCFs, some in the literature [42, 43]. Spontaneous resolution of direct CCF has also been reported but is rarer [44, 45]. 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 [42, 46, 47]. 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. 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) [35]. Indications for treatment include persistently elevated intraocular pressure, visual deterioration due to retina or optic nerve ischemia, severe proptosis, symptomatic ocular deviation with diplopia, exposure keratopathy, severe pain, and/or intolerable bruit.

A conservative approach is not likely to succeed in cases of direct carotid-cavernous fistulas. Resolution without recurrence has been described in only 17% of attempted cases [47].

Endovascular Treatment

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 [48–50]. Compared to carotid artery surgery (trapping or ligation), endovascular intervention has significant lower risk of complications especially of cerebral ischemia. 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 direct fistulas, trans-arterial approach via the ipsilateral femoral artery then up through the internal carotid artery into the fistula ending into the cavernous sinus is often used. Different embolic materials are then injected into the cavernous sinus through the microcatheter; these may include detachable coils, *n*-butyl cyanoacrylate (acrylic glue), or ethylene vinyl alcohol copolymer [51]. The material of choice may be influenced by the size of the fistula. In case of a large tear, flow diverting stent assistance may be used [52, 53]. The stents require the use of antiplatelet therapy postoperatively.

Transvenous embolization of direct fistulas may be performed; however, it is not preferred due to the risks of migration of embolic material

into the ICA. For direct CCFs, overall endovascular occlusion rates have been reported to be between 55% and 99% with low <1% mortality [54–57], and the morbidity was described to be as high as 10–40%. 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. Recent literature on endovascular approach promises high success rates of over 90%, with low complication rates ranging between 2.3% and 5% [50, 58]. The cavernous sinus is most commonly accessed through the inferior petrosal sinus; however, there are multiple other endovenous approaches including catheterization of the superior petrosal sinus or the facial vein takeoff from the internal jugular vein or the arterialized dilated superior ophthalmic vein can be directly accessed via an eyelid crease incision [59, 60].

Regardless of the access route, 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 but tends to be transient [61]. Coil overpacking or direct liquid embolic local effects on nerves may generate posttreatment cranial nerve deficits (which commonly improve) [62].

Successful angiographic closure was achieved in 93% of direct and 92% of indirect fistulas. Multiple treatments were required in 33% of direct and 16% of indirect fistulas [63]. When an endovascular approach is not feasible or has been unsuccessful, stereotactic radiosurgery (SRS) may be considered for treatment of a dural CCF. Radiosurgery has been demonstrated in case series to be effective with 90% success at 1–2 years [64, 65]; however, the latency period for the obliteration of the fistula and symptom improvement is typically of several months; hence, it is not appropriate if there is risk of acute visual or neurologic worsening. It may have an important role for incompletely treated indirect fistulas. Using a therapeutic radiation dose of about 20 Gy, SRS induces an injury of the targeted vessel, thus obliterating the vessel lumen.

Illustrative Case 1

A 57-year-old woman presented with diplopia and evidence of lateral rectus paresis. Subsequently she developed chemosis, prominent episcleral vessels, and increased intraocular pressures involving the left eye (Fig. 15.3a). A MRI orbit with contrast showed prominent cavernous sinus and enlarged superior ophthalmic vein in left orbit (Fig. 15.3b) which showed arterialization of flow on MRA (Fig. 15.3c). Conventional angiography confirmed a Barrow Type C indirect fistula which means it only had filling from a deep branch of the internal maxillary artery ultimately fed by the external carotid artery. There was no filling from the internal carotid. Early arterial phase filling of the cavernous sinus and the arterialized superior ophthalmic veins were clearly demonstrated (Fig. 15.3d, e). The microcatheter was advanced through the femoral vein into the left jugular vein, then into the enlarged left facial vein, and ultimately through the superior ophthalmic vein into the cavernous sinus. This approach was used to coil embolize the fistula. She did well post intervention and showed resolution of episcleral congestion and normalization of her extraocular motility (Fig. 15.3f).

Idiopathic Intracranial Hypertension

Introduction

Idiopathic intracranial hypertension (IIH), also called pseudotumor cerebri or benign intracranial hypertension, refers to a condition of elevated

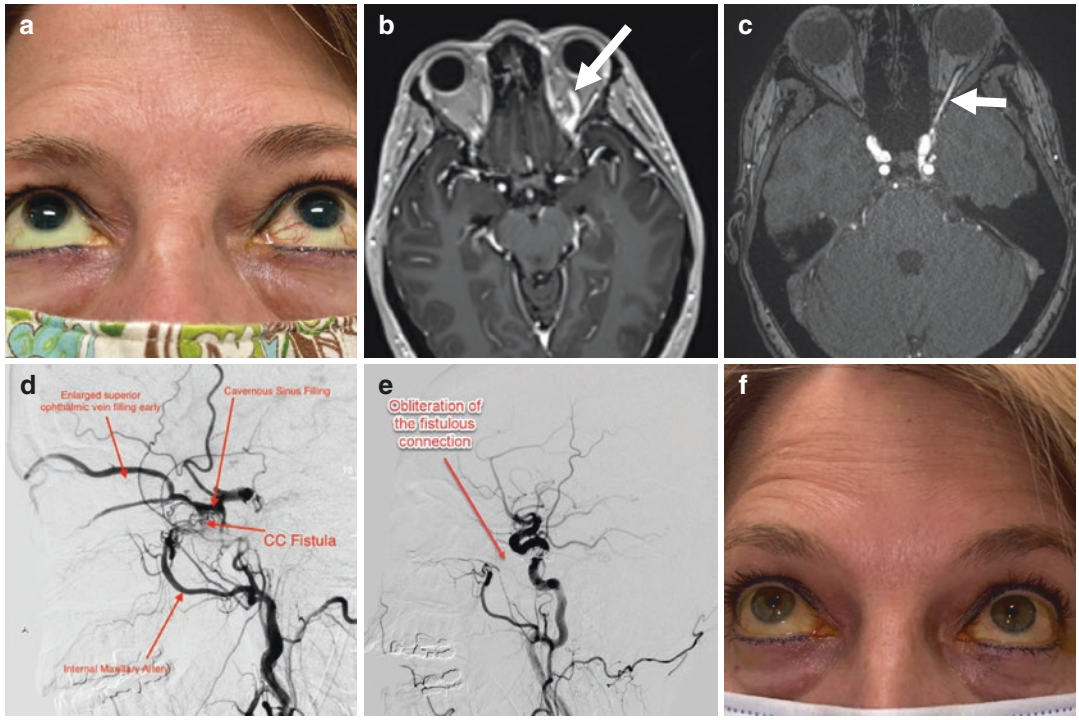

Fig. 15.3 (**a**) Clinical photo demonstrating prominent episcleral vessels of the left eye compared to normal appearance of right conjunctiva and sclera. (**b**) MRI orbit with contrast demonstrating enlarged superior ophthalmic vein in left orbit *(white arrowhead).* (**c**) MRA of the head with contrast demonstrating arterialization of the superior ophthalmic vein (*white arrowhead*). (**d**) Lateral angiogram projections that show the caroticocavernous (CC) fistula with early cavernous sinus filling from a deep branch of the internal maxillary artery and early filling of enlarged superior ophthalmic vein. (**e**) Post coil embolization angiogram showing obliteration of the fistulous connection as shown by lack of early arterial phase filling of the cavernous sinus. (**f**) Clinical photo after coil embolization that shows resolution of episcleral congestion left eye. (Panel **d** and **e** angiogram images are courtesy of Dr. Rano Chatterjee, Washington University School of Medicine, Department of Neuroradiology)

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 [66–69]. 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 [70], and cyclosporine. Obstructive sleep apnea and recent weight gain may also contribute to an elevated intracranial pressure [71].

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. Still to be explored is the role of the newly named "glymphatic system" in the pathogenesis of IIH [72, 73]. 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 is a common radiographic finding in IIH [74], 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 prestenotic vs. poststenotic pressure gradient [75–86].

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 [87]. Prior studies suggested headaches associated with IIH most often presented as pain in a nerve root distribution or as retro-ocular pain with eye movement [88, 89]. More recently, the understanding has changed, and migraine is recognized as the predominant phenotype [90]. Pulse-synchronous tinnitus, described as a "whooshing" sound synchronized with the heartbeat, 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 [89]. A small proportion of patients (2–3%) with IIH present with fulminant visual loss over days [91], necessitating aggressive intervention to salvage vision.

Investigation and Diagnosis

The diagnostic criteria of IIH were created by Dandy in 1937 and were formulated by Friedman in 2002 [92]. In 2013, Friedman et al. proposed a revision to the diagnostic criteria that separated patients into two groups: those with papilledema and those without papilledema [93]. In both groups, the revised diagnostic criteria emphasize a normal neurological exam with the exception of cranial nerve abnormalities, 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. The diagnosis is confirmed in patients who also demonstrate cerebrospinal opening pressure greater than 250 mm H2O and normal CSF analysis and papilledema. In the absence of papilledema, the diagnosis may be confirmed by the presence of a unilateral or bilateral abducens nerve palsy or at least three of the characteristic neuroimaging findings associated with IIH [93]. 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 [92, 94]. 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, empty sella, and transverse venous sinus stenosis [95]. One study using a specially designed MRV protocol found stenosis in the transverse and sigmoid sinuses to be both sensitive and specific for IIH [74].

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 punc-

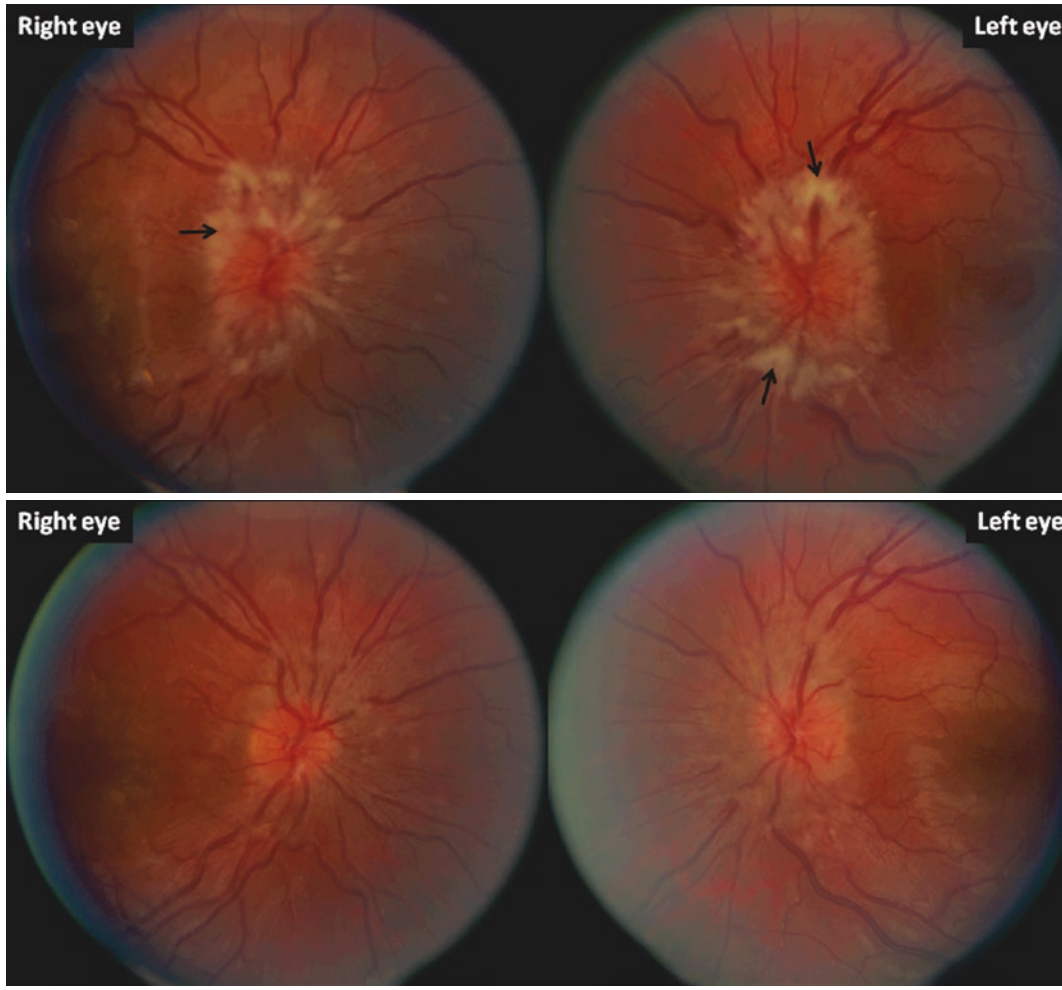

Fig. 15.4 Bilateral papilledema in a 26-year-old lady with concurrent right sixth nerve palsy. Note the elevation of the optic disc, engorgement of the central retinal veins, and obscuration of the retina vessels both on the disc and as the vessels exit the disc margin (*top*). There are disc hemorrhages 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*)

ture serves as one of the mainstays of diagnosis [96]. While sometimes resulting in relief of headaches, repeated lumbar punctures are not recommended as a treatment methodology.

Weight loss serves as an important step in the management of IIH, and successful reduction of body weight of 5–10% may have a significant impact on the evolution of both headache and papilledema [97, 98]. Pharmacologic treatment commonly includes carbonic anhydrase inhibitor and topiramate, or methazolamide or furosemide can be used when acetazolamide is poorly tolerated [99]. Prospective data from the Idiopathic Intracranial Hypertension Treatment Trial (IIHT) showed that treatment with acetazolamide in conjunction with weight loss resulted in statistically significant improvement in visual field function in patients with IIH and mild visual loss

compared to placebo and weight loss [100]. 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. The current surgical options for treatment of IIH are optic nerve sheath fenestration, CSF diversion (lumboperitoneal or ventriculoperitoneal shunt), or venous sinus stenting. Currently, there are no evidence-based guidelines regarding choosing a surgical procedure to treat severe IIH, so the therapy used is based on local availability and expertise. 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 [101]. Optic nerve sheath fenestration is generally regarded as a low-risk procedure, although serious complications 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. Image-guided shunt placement may result in improved shunt placement accuracy but does not affect long-term shunt survival [102, 103]. This allows treatment of headache and leads to stabilization or improvement of visual acuity and visual fields. Shunting may also decrease average retinal nerve fiber layer thickness and improve Frisen papilledema grade [104]. However, revision surgery is frequently necessary, and other complications (as low-pressure headache, infection, arachnoiditis of nerve roots) might develop [105, 106]. Complication rates and shunt removal rates do not differ between lumboperitoneal and ventriculoperitoneal shunts [107, 108]. Venous sinus stenting is another emerging treatment modality that addresses the transverse-sigmoid sinus stenosis and resulting transvenous pressure gradient commonly seen in patients with IIH. This is discussed below.

Endovascular Treatment

Venous sinus stenting is a more recent endovascular treatment option for IIH that has been used since the early 2000s [108].

Venous sinus stenosis appears to result from increased intracranial pressure, thus decreasing CSF resorption into the venous system and causing worsening intracranial pressure. However, there is still some discussion as to whether venous sinus stenosis is the cause or result of elevated intracranial pressure, and the exact mechanism has not yet been definitively elucidated [109]. Patients with IIH were found to have substantial bilateral sinovenous stenosis in 27 of 29 (93%) patients with IIH versus 4 of 59 (6%) in control patients by MR gadolinium-enhanced venography [74].

Venous sinus stenting may be considered in patients who demonstrate a pressure gradient across the respective stenotic sinus. The overall rate of an elevated cerebral venous pressure gradient in patients with IIH is 35% which is determined on catheter venography after lumbar puncture [110]. Current evidence suggests a promising role of venous sinus stenting with significant improvements in papilledema, headache, and pulsatile tinnitus and improved or stabilized vision with few 1-year or even late failures [77, 106, 111]. However, though complications are relatively rare, they can be severe [80, 111, 112].

A meta-analysis from 2019 included 474 patients with IIH that were treated with venous sinus stenting. The overall rate of improvement of headaches was reported to be 79.6%. Papilledema was reported to be improved in 93.7%, and pulsatile tinnitus improved in 90.3% of patients. The rate of major complications was 1.9% [111].

A systematic review published in 2020 included 47 studies that represented 825 patients in total with follow-up ranging from 0 to 136 months. Resolution or improvement was observed in 87.1% of the cases with papilledema and 72.1% of the cases with headaches. Major complications occurred in 19 patients (2.3%) and

included subdural hematoma, intracerebral hematoma, subarachnoid hemorrhage, and obstructive hydrocephalus. Symptom relapse occurred in 25 patients (3.4%) and required restenting or supplemental intervention [111].

A review from 2018 of 32 studies that included 186 patients found that higher mean pressure gradients (22.8 ± 11.5 mm Hg vs. 17.4 ± 8.0 mm Hg, $p = 0.033$) and higher changes in pressure gradients (19.4 ± 10.0 mm Hg vs. 12.0 ± 6.0 mm Hg, $p = 0.006$) after stent placement were associated with improved clinical outcomes. After controlling for age, sex, body mass index, CSF opening pressure, pre- and post-stent pressure gradient, the change in pressure gradient was found to be an independent predictor of favorable outcomes ($p = 0.028$) [109].

Periprocedural Steps

The first step in endovascular treatment involves angiographic confirmation of dural sinus stenosis and measurement of the trans-stenotic pressure gradient (typically ≥8 or 10 mmHg is considered clinically significant [77, 113]. Guide catheter navigation and venous sinus stenting can be painful, and general anesthesia is generally used. However, several recent studies have demonstrated that general anesthesia results in significant differences in venous sinus pressure measurements [114, 115]. Based on these findings, conscious sedation may be preferred to general anesthesia when pressure measurement is being conducted, with conversion to general anesthesia if the determination to stent is made [115]. Patients must be pretreated with aspirin and clopidogrel (3–5 days of 75 mg nightly or a 300 mg loading dose 24 h prior to stenting). Intraprocedurally, therapeutic heparin anticoagulation (ACT > 250 s) 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 is showing a promising role.

Illustrative Case 2

A 37-year-old woman with a 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 H_2O. Headache was refractory to acetazolamide and repeated therapeutic lumbar punctures. Her vision worsened, and she was referred for 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 presence 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.

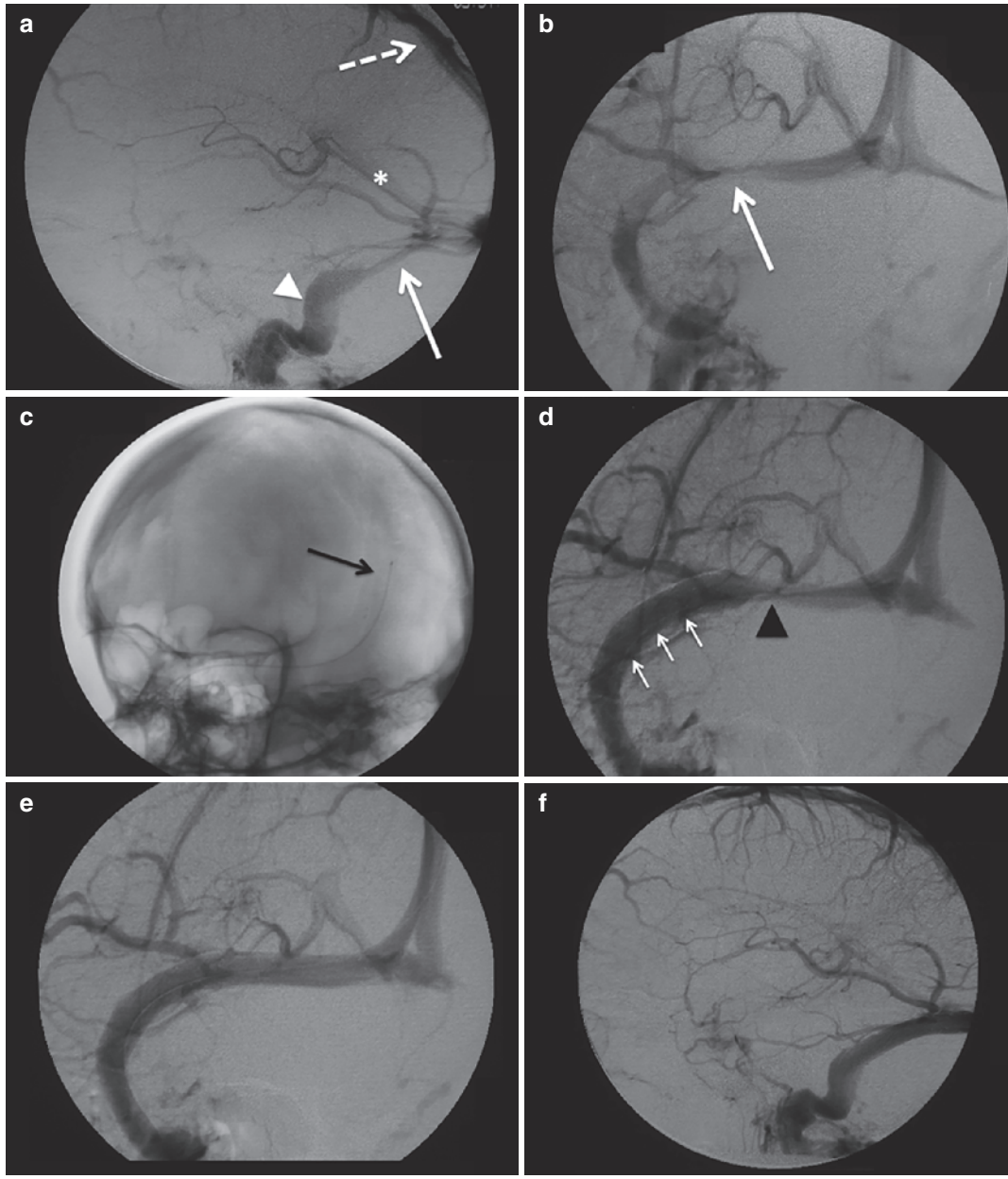

Fig. 15.5 (**a**) Lateral venous phase of arterial angiogram revealing stenosis of the transverse-sigmoid junction (*white arrow*). The sigmoid sinus is normal (*white arrowhead*), and the superior sagittal (*dashed arrow*) and straight sinuses are observed (*asterisk*). (**b**) An anterior–posterior 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

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16 Neurointervention and the Otolaryngologist: Head and Neck Surgeon

Randall C. Edgell and Jastin Antisdel

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 also increased. Preoperative tumor embolization is now widely applied. Endovascular treatment of epistaxis lessened the need for open vascular ligation [4] and is now used alongside endoscopic vessel ligation to treat refractory cases. 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.

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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.

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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, while increasingly rare, 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 section "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 the 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 nondetachable 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 manner 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 possibility.

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 neck dissection (dissection with the goal of preserving the IJV, the sternocleidomastoid muscle, or the spinal accessory nerve). 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, the 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 the airway with a cuffed tracheostomy tube and cross-matching 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 for 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 post-irradiated 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 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 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 the use of stents without antiplatelet agents carry 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 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 edema, 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 in the internal or common carotid artery, vertical sutures are preferred instead of horizontal sutures 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 resect the carotid artery. Reconstruction of the artery with interpositional grafts with Gore-Tex or saphenous vein may be undertaken. Reconstruction is avoided in the presence of infected or 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 several 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 nondetachable 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. 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 tracheostomy, nose, and mouth. He was found to have a recurrent mass with erosion into the esopha-

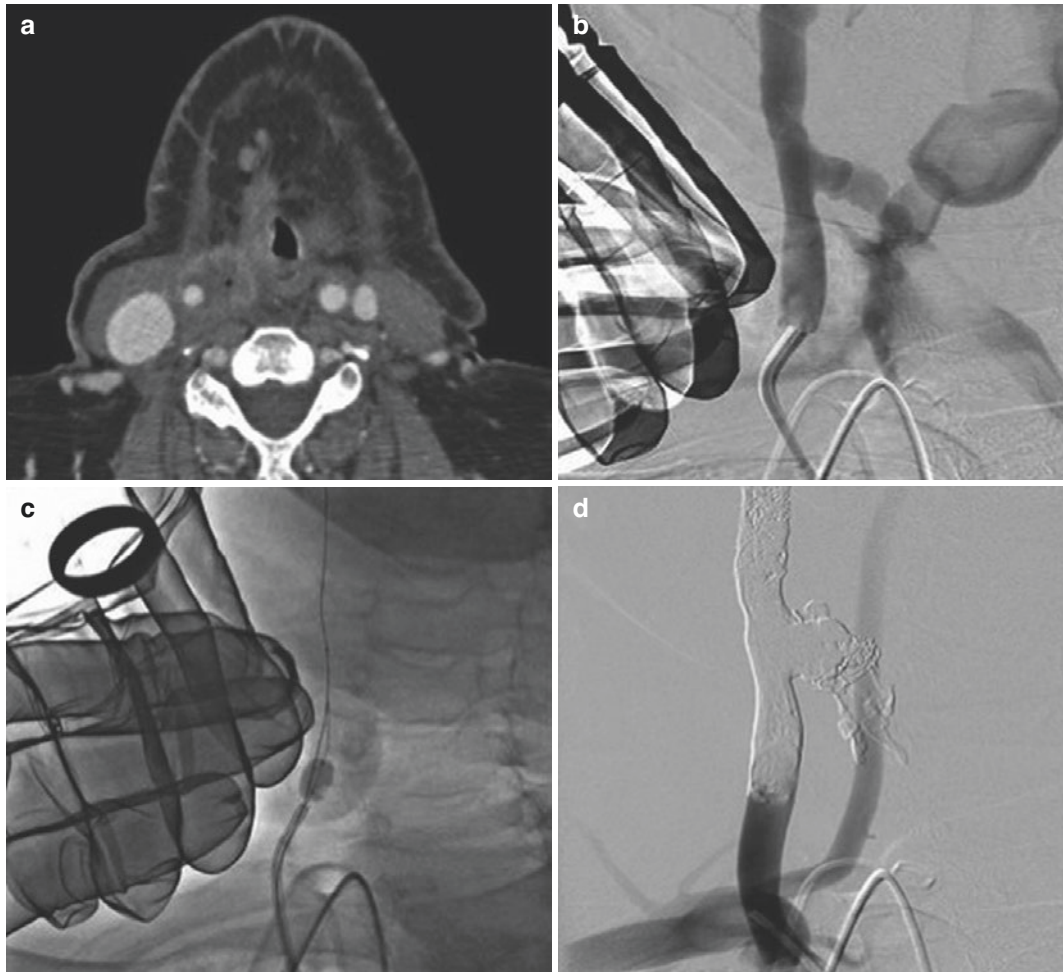

Fig. 16.1 Carotid blowout. (**a**) Contrast cervical axial CT scan showing recurrent laryngeal cancer encasing the right carotid artery (*arrow*). (**b**) Pretreatment angiogram showing a carotid-esophageal fistula with manual compression being applied. (**c**) Inflation of a balloon in the common carotid 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

gus 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].

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): 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. Endoscopic 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/Endoscopic 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 epi-

staxis 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 at it 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 the greater palatine canal (optionally) 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 or radial 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 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. They are also rarely associated with skin "tattooing" when cutaneous branches are inadvertently embolized.

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 of cranial nerves, skin, and mucosa. When large tumors are treated, perioperative

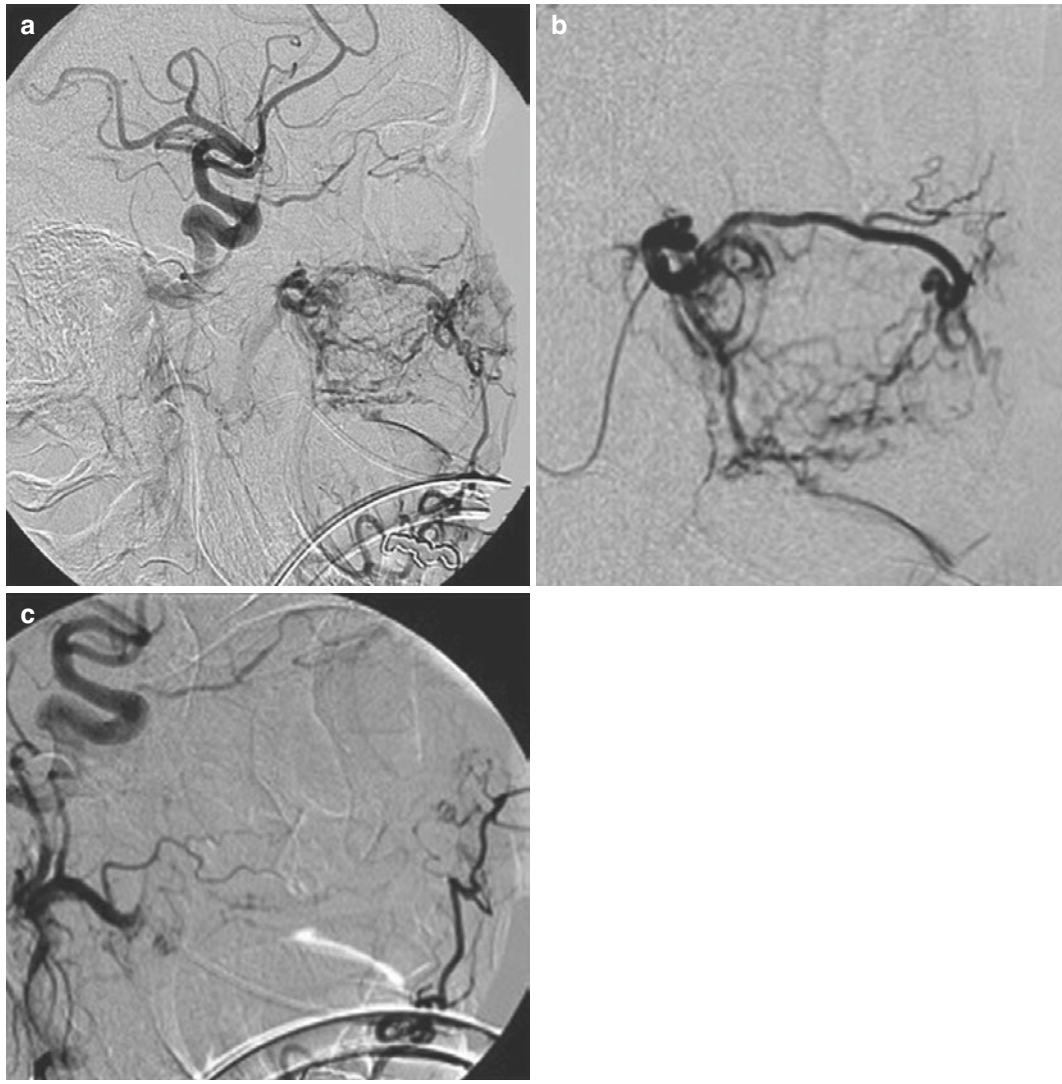

Fig. 16.2 Epistaxis. (**a**) Guide catheter angiogram showing vascular supply to the nasal cavity (sphenopalatine arteries, *bracket*; inferior orbital, *open arrow*; superior labial, *small arrow*). (**b**) Microcatheter angiogram of the distal internal maxillary artery (IMAX). (**c**) Post-PVA embolization showing occlusion of the distal IMAX

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.
  - Carotid body tumor.
  - 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 post radiation 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

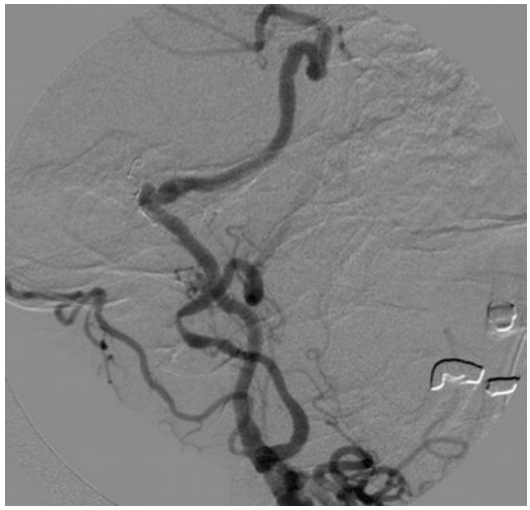

Fig. 16.3 Persistent stapedial artery

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.

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.

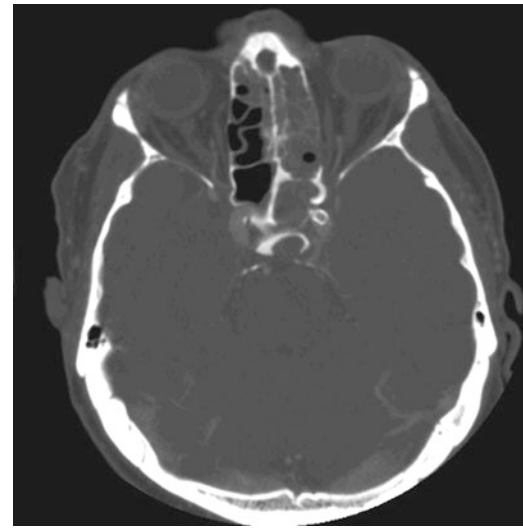

Fig. 16.4 Iatrogenic laceration of the left internal carotid artery. *Large arrow* shows damage to lateral wall of the sphenoid sinus. *Small arrow* shows covered stent deployment in the cavernous ICA

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).

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17 The Role of Neurointervention in Traumatic Vascular Injury and Vascular Surgery

Justin D'Addario, Matthew R. Smeds, Ahmed Abdelsalam, and Randall C. Edgell

Introduction

The evolution of the treatment of vascular injury and disease toward endovascular approaches has brought the trauma surgeon, vascular surgeon, and neurointerventionalist into contact with great potential synergies between the fields. In this chapter, we explore some of the more common areas in which these specialists collaborate.

Screening for Vascular Injury

Neurovascular injury associated with blunt trauma is too often recognized late in the clinical course of the trauma patient. During the acute phase of assessment and stabilization, the focus on airway protection and need for emergent surgery may lead to intubation without a preceding detailed neurologic assessment. If neurovascular injury is not considered in this early phase, the diagnosis may not be made until days later when the patient is noted to have neurological deficits in the intensive care unit. At this point, the neurological injury is often complete [1]. These injuries are associated with mortality as high as 23% and morbidity of 48%, adding to the urgency of early diagnosis [2].

The need to more rapidly diagnose neurovascular injury has led to the development of institutional and societal guidelines for screening (see Table 17.1).

CT angiography (CTA) has emerged as the preferred screening test for carotid or vertebral artery traumatic injury [3–6]. It has the advantage of rapid availability in most hospitals and short acquisition times. The latter factor is vital in the trauma population given the potential of hemodynamic instability and/or patient movement during the examination. CTA has nearly 100% sensitivity for carotid and 96% sensitivity for vertebral injuries when reviewed by experienced radiologists [4].

While highly sensitive, there is up to a 43% false-positive rate seen with CTA used for traumatic neurovascular injury screening [7]. Catheter-based angiography, thus, continues to have an important role as the definitive diagnostic

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Table 17.1 Clinical and radiological criteria to screen for neurovascular injury*

Clinical criteria	Radiological criteria
Penetrating head injury with a GCS < 13	Cervical spine fracture involving the foramen transversarium, occipital condyle, or C1-3
Closed head injuries (CHI) consistent with DAI and GCS < 6	CT or MR evidence of cerebral infarction
Arterial hemorrhage from neck, mouth, nose, ears	Displaced midface fracture (LeFort II or III)
Large expanding cervical hematoma	Skull base fracture involving the carotid canal
Cervical bruit in a patient younger than 50	30% or greater subluxation of a vertebral body at or above C5-6
Focal or lateralizing neurologic deficit	
Transient ischemic attack	
Horner's syndrome	
Oculosympathetic paresis	
Vertebrobasilar insufficiency	
Neurologic deficit that is incongruous with CT or MRI findings	
Near hanging with anoxia	
Clothesline type injury or seat belt abrasion with significant swelling, pain, or altered MS	

Adapted from Biffl et al. [3]
Kansagra et al. [8]

tool when CTA shows possible neurovascular injury and should be strongly considered when CTA findings are equivocal.

Traumatic vascular injuries of the head and neck can be dynamic for several days after injury. Dissecting injuries may improve or worsen spontaneously, with initially mild luminal narrowing progressing to vessel occlusion in some cases, and in others with injuries becoming less apparent on subsequent imaging. In addition, vessel injuries are at times associated with delayed thrombus formation which could lead to a switch from antiplatelet agents to anticoagulation. For these reasons, follow-up imaging 5–7 days after injury is initially diagnosed is generally recommended [3] (Table 17.2).

Table 17.2 Denver grading scale for blunt cerebrovascular injuries [9, 10]

Grade	Description
I	Irregular vessel wall or dissection/intramural hematoma with <25% luminal stenosis
II	Intraluminal thrombus or raised intimal flap, or dissection/intramural hematoma with 25% luminal stenosis
III	Pseudoaneurysm
IV	Vessel occlusion
V	Vessel transection

Penetrating Injuries

Penetrating injuries of the neurovasculature are most commonly due to gunshot wounds (GSW) and stab wounds (SW). The locations of injury have been divided into three zones: Zone 1, which extends from the clavicle to the cricoid cartilage; Zone 2, from cricoid cartilage to mandible; and Zone 3, superior to the angle of the mandible. Zone 2 is the most common and the most surgically accessible location of injury. In patients with hemodynamic instability from active extravasation/bleeding or airway compromise due to a large hematoma, open surgical exploration is indicated for injuries in this location. If the patient is hemodynamically stable without hard signs of vascular trauma, further testing and medical management is recommended. In Zone 1 and 3 injuries, endovascular surgery may be preferable given the complexity of open exploration. Such interventions may include placement of covered stents or coils in the setting of ongoing hemorrhage and hemodynamic compromise or stent repair in the setting of carotid or vertebral injury with resultant stenotic lesions and hemodynamic stability. These procedures obviate the need for antiplatelet medications and intraoperative anticoagulation, which should be considered when planning intervention in trauma patients with other injuries [11].

Occasionally, facial fractures or bullet fragments lead to transection of branches of the external carotid artery. Such injuries are well addressed endovascularly with particulate embolic materials or liquid embolics.

Blunt Injuries

Carotid Artery Dissection

Internal carotid artery (ICA) dissection has been increasingly recognized as a primary cause of stroke in young patients, accounting for 20% of strokes in patients younger than 45 years of age. However, carotid dissection is an infrequent cause of stroke in the general population, accounting for only 0.4 to 2.5 percent of all strokes [12, 13]. The cervical segment of the ICA is frequently affected. While classic mechanisms of injury are described as being associated with posterior oropharyngeal injuries, such as falls while holding objects orally; there is great heterogeneity in traumatic etiology. Traumatic dissection can be caused by blunt trauma to the neck directly or in association with trauma subjecting the neck to excessive flexion, extension, or rotation. A common mechanism involves compression of the internal carotid artery against the lateral process of cervical vertebra [14]. This inciting trauma results in an intimal tear or intramural hematoma allowing for intima-media separation. Cerebral ischemia results from direct luminal narrowing by the dissection flap, subsequent thrombosis at the site of dissection, or distal embolization of micro emboli created from turbulent flow and a now thrombogenic vessel wall.

Headache and ipsilateral neck pain are the commonest clinical findings present in 75% of patients, and a minority will present with Horner syndrome. Though uncommon, the findings of pupillary constriction, ptosis, and anhidrosis in combination with trauma, minor or otherwise, should prompt investigation into a possible dissection [15–17].

Angiography, usually initially obtained via computed tomography, is the diagnostic gold standard, which shows differing radiologic patterns depending on severity of injury. Small intimal defects may be evident by a small vessel wall irregularity or minor filling defect due to associated thrombus. Larger dissections tend to create a linear filling defect that may or may not be flow limiting. Though identification of an intimal flap is specific for carotid dissection, it is only seen in 10% of patients with dissection. The most common angiographic finding being irregular narrowing with a smooth luminal taper can be seen in 65% of patients [18].

Medical treatment is the mainstay of management of flow limiting carotid dissection. There is some disagreement in the literature over the first-line antithrombotic medication. The trauma surgery literature often advocates for intravenous heparin as a first-line treatment, while neurological studies have generally shown no advantage of anticoagulation over antiplatelet agents [19, 20]. The use of either class is complicated by the patient with polytrauma, particularly in those with bleeding risk and in the absence of neurologic findings. If symptoms worsen despite medical therapy, surgical management may be offered to select patients. Surgical intervention is usually reserved for patients in extremis, either from active hemorrhage or a focal thrombosis in the context of new-onset neurologic deficits, and consists of either bypass or rarely ligation [21]. Endovascular management has generally been shown to be low risk in the stable patient who can be appropriately pre-treated with dual antiplatelet therapy and who have anatomy suitable for these intervention. Self-expanding, Nitinol, stents are typically used and sized to the diameter of the carotid segment in question [22, 23]. Adjunctive angioplasty is generally not needed but can be used if luminal narrowing persists after stent deployment [24]. Indications for treatment include impaired cerebral perfusion, infarction despite appropriate antithrombotic use, or acute, ongoing stroke [25].

A carotid artery “pseudoaneurysm” occurs when the dissection tract is between the media and adventitia and the adventitia bows outward. Arterial flow permits continued perfusion of the newly formed sac [26]. Etiologies of traumatic carotid pseudoaneurysm include blunt and penetrating mechanisms of injury as well as post-procedural (i.e., inadvertent line placement, post-endarterectomy). Traumatic pseudoaneurysms are associated with dissection in 13% to 49% of cases [27]. On conventional angiography, a pseudoaneurysm is demonstrated by contained extravasation of blood from the arterial lumen.

Symptoms common include headache and at times tinnitus when the lesion is near the skull base. At other times, they can present with neck swelling to local mass effects. Carotid pseudoaneurysms can compress adjacent nerves and local musculoskeletal structures, commonly affecting cranial nerves IX, X, and XI. Horner syndrome may also be observed from stretching of the cervical sympathetic chain [28]. Once again, observation is the mainstay of pseudoaneurysm treatment. Rupture of traumatic pseudoaneurysms is rare, and spontaneous regression at 12 months is common if the lesion is small [27]. At times, however, the lesion persists and can cause disabling head and/or tinnitus. In these instances, endovascular treatment with stenting, stent-assisted coiling, or flow-diverting devices can be considered [29, 30]. In cases with anatomy not suitable for endovascular repair, open surgical repair with interposition bypass grafting is an option.

Case Study

A 22-year-old man suffered extensive polytrauma after involvement in a head on motor vehicle collision. He was intubated by emergency medical services at the scene and upon arrival at the hospital was found to have C3 and C4 spinal fractures. He was taken emergently for operative repair of bladder and kidney lacerations. While undergoing a routine neurological check in the intensive care unit postoperatively, he was noted to have decreased movement on the left side of the body. CT angiography showed bilateral carotid dissection, and MR showed left hemisphere, low volume, watershed distribution infarcts. The risk for further bleeding was assessed to be low, and the patient was loaded with aspirin and clopidogrel. He underwent overlapping stent insertion to treat a left internal carotid artery dissection with associate narrowing of the distal cervical internal carotid artery and pseudoaneurysm of the mid-cervical internal carotid artery (Fig. 17.1a). A 6 F cook shuttle sheath was placed within the distal left carotid artery and a 5F Spider Rx filter was deployed distal to the site of stenosis. Over the filter wire, a 6 × 40 mm Xact stent was deployed with the distal end across the stenosis and the proximal end covering the entry zone of the cervical pseudoaneurysm. A second 6–8 × 30 mm Xact stent was deployed across the entry zone to "double cover" and promote flow diversion (Fig. 17.1b).

Carotid Cavernous Fistula (See Chap. 15)

Head trauma may rarely lead to traumatic injury to the intracranial carotid artery as it passes through the cavernous sinus. This dural sinus is the main venous drainage pathway for the eye. The carotid injury can lead to a high-flow/direct fistula through which arterial blood enters the cavernous sinus, leading to arterialized pressure and poor orbital drainage. The fistulous connection in such cases is most commonly located in the inferior aspect of the horizontal limb of the cavernous segment of the internal correct artery. Clinically, patients will rapidly develop ipsilateral or bilateral orbital chemosis, proptosis, and scleral edema. Ocular motility is frequently impaired. Intraocular pressure is elevated due to impaired venous drainage of the globe. If left untreated, permanent vision loss may occur. This makes the early recognition of high-flow carotid fistulas important for the trauma surgeon. Such lesions are amenable to endovascular treatment via both a transvenous and transarterial approach. See Chap. 15 for a more detailed description of these approaches [31].

Vertebral Artery Dissection

While less emphasized in the literature, vertebral artery dissection is also seen in the setting of blunt trauma to the head and neck [32, 33]. When these dissections occur, they are sometimes associated with cervical spine injuries, especially subluxations and fractures of the foramen transversarium. When not in the setting of boney injury, vertebral dissections most commonly occur at the skull base as the vertebral artery enters the dura.

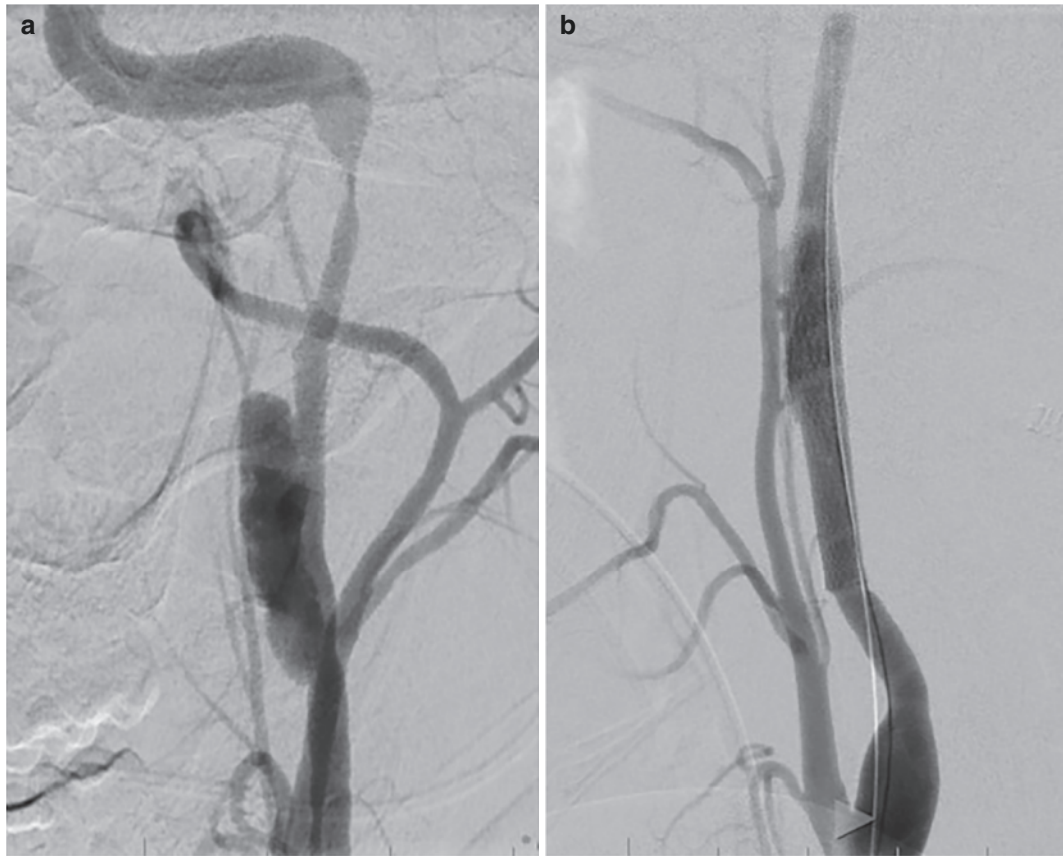

Fig. 17.1 Carotid dissection and psuedoaneurysm

Presenting symptoms often include neck pain that radiates to the skull base. Symptoms and signs of posterior circulation ischemia such as vertigo, nausea, diplopia, hemibody anesthesia or weakness, limb ataxia, dysarthria, and/or hemianopsia should also prompt consideration of this diagnosis [34].

Unlike carotid dissection, vertebral artery dissection that extends intracranially can also be associated with vessel rupture and subarachnoid hemorrhage, a potentially lethal complication.

Management of patients without signs of symptoms of TIA or stroke usually focuses on antiplatelet use and anticoagulation if there is associated thrombus. However, in patients with brainstem flow compromise and stroke symptoms, stenting or open surgical repair can be considered. In those with subarachnoid hemorrhage, vessel preserving techniques such as stent-assisted coiling or flow-diverting device insertion can be considered. As a last resort, vessel sacrifice may be needed [35].

Postoperative Large Vessel Stroke (See Chaps. 6 and 7)

While rare, artery-to-artery embolism occasionally occurs post-carotid stent insertion, carotid endarterectomy, or transcarotid artery revascularization. If the volume of embolic material is large, major stroke can result [36]. Mechanical thrombectomy may be a viable treatment modality in this setting, even following open carotid revascularization. If the initial procedure was done in a hybrid operating room and identified by intraoperative assessment via post repair angiogram done to assess the repair, subsequent neuro-

interventions may be expeditiously done in that same setting. Mechanical thrombectomy has been well studied and shows great potency in large vessel occlusive stroke with one in three patients treated returning to a nondisabled state [37]. Undergoing MT requires immediate recognition of the stroke syndrome followed by activation of the stroke team and CT angiography of the head and neck to identify the site of occlusion. If an occlusion of the intracranial carotid or middle cerebral artery is seen, mechanical clot retrieval via a suction thrombectomy catheter or retrievable stent is recommended. See Chap. 7 for procedural details.

Incidental Intracranial Abnormalities

Vascular disease is rarely confined to a single vascular bed. Therefore, it is common for vascular specialists to encounter "incidental" disease of the cervical and intracranial vessels in their patient populations.

Atherosclerotic Stenosis (See Chaps. 4 and 5)

The most common underlying form of vascular pathology throughout the body is atherosclerosis. Frequently, patients with atherosclerotic stenosis of the iliofemoral arteries, coronary arteries, or other systemic vascular beds will also have cervical or intracranial stenosis [38].

Extracranial carotid revascularization is of established utility in patients with symptomatic stenosis ≥50% in severity [39]. With evolving medical therapy, the treatment of asymptomatic severe disease has been brought into question but is still performed. Please refer to Chap. 4 for a more detailed discussion of these revascularization modalities.

A less commonly recognized site of extracranial atherosclerosis is the vertebral artery. These lesions most often affect the ostium of the vertebral artery but can also involve the more distal vertebral artery [40]. While there are few randomized clinical trials (RTC) of vertebral artery surgery, several small European studies have been published [41, 42]. Both studies showed excellent safety for extracranial vertebral artery stenting, with one (VAST) showing a potential efficacy signal for stenting despite its small size and premature termination.

Intracranial atherosclerosis (ICAD), unlike extracranial disease, is primarily managed with medication [43]. This is based on the results of the SAMMPRIS trial of stenting with the Wingspan intracranial stent system (Stryker Neurovascular) plus best medical therapy (BMT) versus BMT alone. In this trial, BMT was superior to stenting primarily due to the perioperative stroke risk associated with the procedure. In the best medical arm, patients were treated with aspirin and clopidogrel for 90 days along with general risk factor modification. This protocol has largely been adopted as the first-line therapy for patients with ICAD. Patients who fail BMT can be considered for stent revascularization, based on the excellent outcomes seen in the nonrandomized WEAVE trial [44].

Aneurysms (See Chap. 10)

There is growing recognition that the vascular weakening underlying intracranial aneurysms is related in some if not most cases to the risk factors that underlie atherosclerotic disease [45]. *When* encountered, such lesions warrant careful risk stratification based on aneurysm size and morphology along with patient age and comorbid conditions. Given the importance of morphological details, cerebral catheter angiography should be considered when the findings may sway decision-making and/or choice of surgical modality. Generally, intracranial aneurysms of the anterior circulation greater than or equal to 7 mm in size and those 5 mm or larger in the posterior circulation should be considered for surgery [46]. The majority of unruptured aneurysms in the United States and Europe are currently treated endovascularly with catheter-based platforms

such as detachable coils and flow-diverting devices. Occasionally, morphological features may make open surgical clipping the best option. See Chap. 10 for details of endovascular aneurysm repair.

Dural Arteriovenous Fistula (See Chaps. 13 and 15)

Arteriovenous fistulas (AVFs) are rare vascular malformations. Their basic angioarchitecture involves arteries directly filling a vein without an intervening capillary bed. The most common form of AVF is the dural AVF (dAVF), in which arteries normally supply the dura mater, instead directly empty into one of the dural sinuses. These lesions are of interest to the trauma surgeon because one speculated etiology is as sequelae of traumatic injury. Thus, dAVFs are sometimes discovered in the follow-up of the traumatic brain injury patient. Presenting symptoms include tinnitus, bruit, dizziness, headache, and progressive cognitive decline. Diagnosis starts with noninvasive vascular imaging such as MR angiography, but if the clinical suspicion is high, the workup is not complete without a catheter angiogram. The small caliber of the involved arteries means that the higher resolution of an invasive angiogram is often required [47]. See Chap. 13 for a complete discussion of the endovascular management of this disorder.

Role of Transcarotid Artery Revascularization (TCAR) with Flow Reversal (See Chap. 4)

Transcarotid artery revascularization is a minimally invasive surgical modality for treating carotid stenosis. It involves open exposure of the common carotid artery via supraclavicular incision along with the use of the ENROUTE transcarotid neuroprotection system (Silk Road Medical, Sunnyvale, CA, USA) [48]. This relatively new procedure may be of interest to neurointerventionalists and vascular surgeons faced with patients with high-risk features for both stenting and carotid endarterectomy.

See Chap. 4 for a discussion of high-risk features for carotid endarterectomy. Features that make transfemoral or transradial stenting high risk include severe aortic arch angulation, excessive redundancy and tortuosity of the common carotid artery, and/or internal carotid artery and heavily calcified composition of the stenotic lesion [49]. Although carotid endarterectomy and carotid stenting are the most frequently used procedures for carotid revascularization, TCAR has shown excellent early results in nonrandomized prospective cohort studies, particularly in high-risk patients [50].

Several multicenter studies compared TCAR to CEA and found that both modalities had a comparable pre-procedural stroke and all-cause mortality rates immediately following the procedure and 1 year later. However, TCAR was associated with a lower risk of cranial nerve injury. According to a recent meta-analysis, the risk of CN injury was less than 0.4 percent [48]; therefore, TCAR may be a viable option for patients at high risk for open surgery, including those with surgically inaccessible lesions, prior neck surgery, neck irradiation, laryngeal nerve palsy, and tandem lesions [51]. The TCAR procedure has a favorable safety profile in nonrandomized prospective registries, with a reported periprocedural stroke rate of 1.4 percent and a 1-year follow-up stroke rate of less than 0.6 [51]. However, randomized controlled trials comparing TCAR with CEA and/or CAS have not been published to date.

A significant constraint on the use of TCAR is the technical challenges it presents: it is a hybrid procedure requiring both open surgical and interventional management. The infrastructure and operator skill set are not available in all centers [52]. Additionally, to be eligible for TCAR, patients must have amenable anatomy. Patients must have an ICA > 4 mm, CCA free of plaque and >6 mm and a distance from the clavicle to carotid bifurcation of at least 5 cm [53].

Procedural Steps

TCAR can be performed under general or local anesthesia with intra-procedural heparin. A small supraclavicular incision is made to allow for dissection of the proximal common carotid artery. A micropuncture kit is used to cannulate the arterial wall followed by the advancement of a guidewire and arterial sheath without crossing the lesion. Venous access is then obtained by percutaneous puncture of the contralateral common femoral vein. Both the arterial and venous sheaths are connected to a "flow controller" to form a flow circuit that includes an embolic protection filter. The common carotid artery is occluded proximal to the arterial puncture site with a vascular clamp which initiates flow reversal is initiated. The goal of flow reversal is to pull all potential embolic debris away from the intracranial circulation and toward the filter before blood is returned to the venous system. A guidewire is used to cross the stenotic carotid segment under fluoroscopy. This is followed by stent deployment and balloon angioplasty in a similar sequence to traditional carotid stenting [48, 51].

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18 Future of Aneurysm Surgery: Flow Disruption

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Aneurysm Characteristics

Cerebral Aneurysm Types and Morphology

Several factors contribute to the pathogenesis of aneurysm formation, some of which are circulatory and anatomic and others related to vessel wall changes. Saccular or berry aneurysms are the most common type encountered in clinical practice followed by the fusiform aneurysms (Fig. 18.1A–C) and microaneurysms (including mycotic types). Saccular aneurysms account for 90% of the total aneurysm morphology, and their rupture is the most common cause of subarachnoid hemorrhage (SAH) [1]. Dissecting aneurysms of the cerebral circulation are less frequent pathologic entities compared to the extracranial vessels, and most of those are due to traumatic events. Atraumatic dissecting aneurysm in the cerebral circulation may occur in conjunction with other pathologies such as moyamoya disease [2]. Multiple studies evaluated the relationship between aneurysm morphology and the risk of rupture. Excessive aneurysm lobulation and development of a daughter sac predict future rupture [3, 4] (Fig. 18.1D). The Unruptured Cerebral Aneurysm Study (UCAS) of Japan is the only prospective study to identify a daughter sac as a factor that increases the relative risk of rupture with a hazard ratio of 1.63 [5]. In addition, it is suggested 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 [5]. The aspect ratio (Fig. 18.2) has been shown to be significantly higher in ruptured compared to unruptured aneurysms in several studies [6, 7], while Esharkway et al. found only a height to width ratio >1, an irregular wall, and location at the main middle cerebral artery bifurcation predicted rupture in middle cerebral artery aneurysms [8].

Aneurysm Size and Location

Two large prospective studies have reported on the natural history of unruptured intracranial aneurysms, the International Study of Unruptured Intracranial Aneurysms (ISUIA), which prospectively assessed 1692 patients with 2686 unruptured, untreated aneurysms (6544 patient-years) in the United States, Canada, and Europe [9] and the Unruptured Cerebral Aneurysms Study (UCAS), a Japanese cohort that followed 6697 aneurysms in 5720 patients [5]. Both of these studies noted that aneurysm size and location

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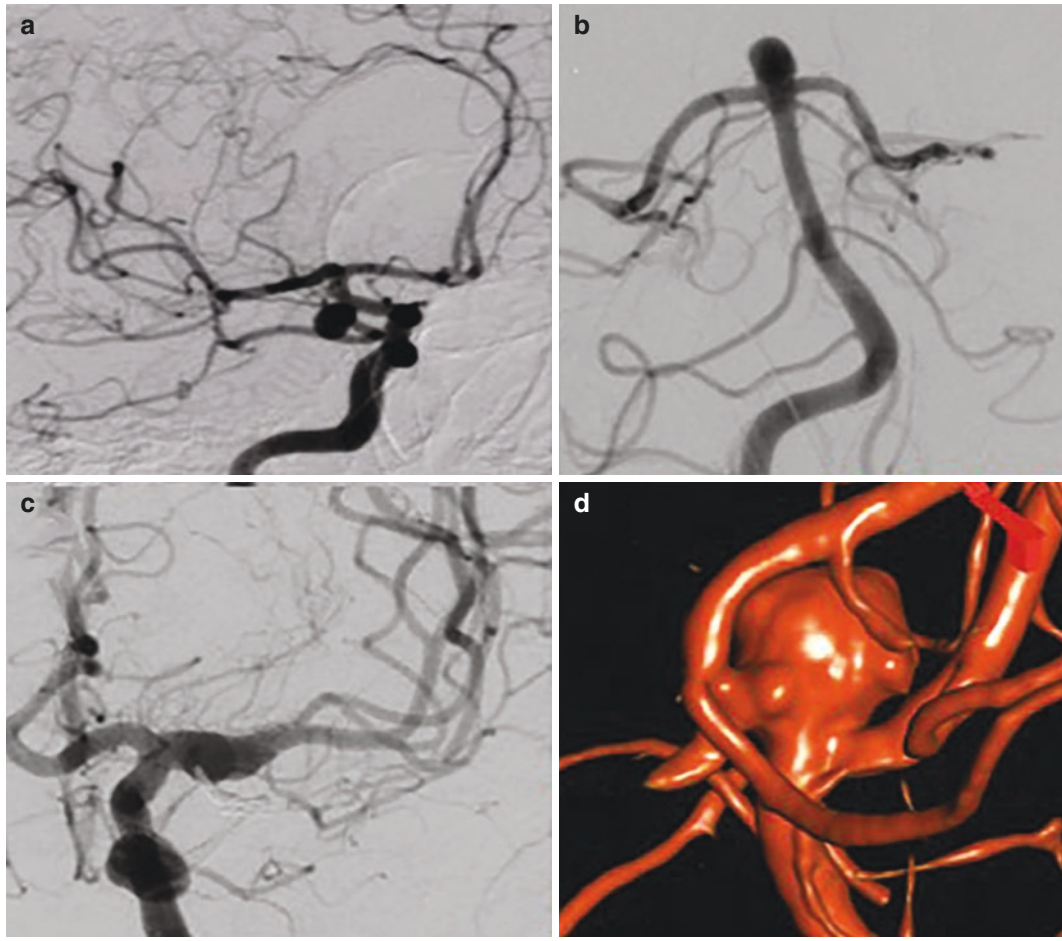

Fig. 18.1 (**a**) Saccular narrow neck aneurysm in the posterior communicating artery; (**b**) saccular wide neck aneurysm at the basilar summit; (**c**) fusiform aneurysm in the M1 segment of the left middle cerebral artery; (**d**) bifurcation complex aneurysm with multiple daughter aneurysms

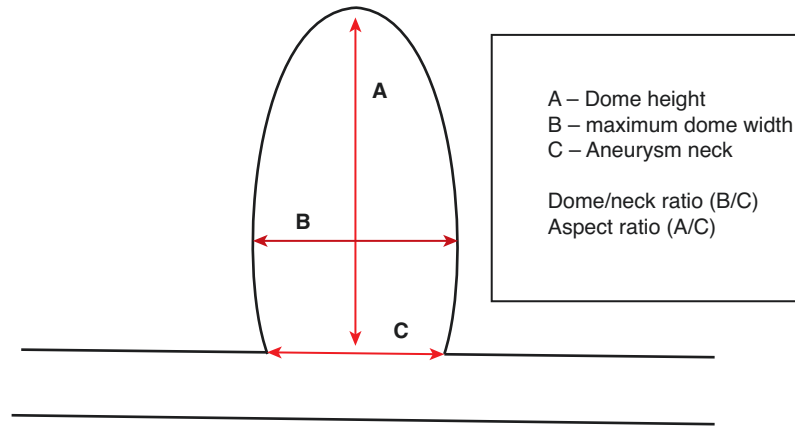

Fig. 18.2 Aneurysm height (**a**), dome width (**b**), and aneurysm neck (**c**) determine the dome to neck and aspect ratios

were associated with the risk of rupture. Large aneurysm size predicted the risk of rupture in the ISUIA [9]. This study consisted of a retrospective and prospective cohort; the prospective cohort included 4060 patients, of which 1692 patients were not treated. The patients were divided into group 1 (no previous SAH) and group 2 (previous SAH from another aneurysm). With an average follow-up of 4.1 years, authors found a progressive increase in the risk of rupture with increasing aneurysm size. 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 identified in the setting of prior SAH (group 2) also had higher rates of rupture justifying treatment. Using the 3–4-mm aneurysm size as a reference in the UCAS of Japan, 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 [5]. While aneurysm size is clearly an important factor, it cannot be used in isolation to determine whether unruptured aneurysms should be treated, for instance, the observed annual risk of rupture of 0.05% rupture risk of small aneurysms less 7 mm [9]. However, in a study of almost 1000 patients presenting with ruptured aneurysms, Weir and colleagues showed that 70% of ruptured aneurysms were less than 10 mm in size [10]. This controversial observation suggested other important factors to predict rupture. Very small and blister aneurysms are controversial even when they are ruptured; these account for less than 2% of all cerebral aneurysms [11].

Cerebral aneurysms are found throughout the circle of Willis, higher incidence in the anterior than posterior circulation. Certain locations predict a higher risk of rupture as demonstrated by the ISUIA. Using the intradural internal carotid artery aneurysms as a reference, the ISUIA identified a relative risk of rupture of 2.3, 2.1, and 0.15 for aneurysms at the basilar apex, posterior communicating artery, and cavernous carotid artery, respectively [9]. UCAS of Japan identified the anterior communicating artery to be the location with highest rupture risk followed by the posterior communicating artery and basilar apex. They also found the risk of rupture in posterior circulation is higher even in small aneurysm size less than 7 mm [5].

Aneurysm Physiology and Flow Dynamics

All components of the cerebral vessels (including elastic laminas and medial and adventitial collagen fibers) have specific functions, of which resistance to mechanical stretch and maintenance of structural integrity [12]. Collagen fibers are relatively indistensible compared to the elastic fibers, and the growth of an aneurysm (sometimes up to a size multiple times the original diameter of the parent artery) requires remodeling of the collagen fibers in the aneurysm wall. Under standardized laboratory conditions, the wall of ruptured cerebral aneurysm is weaker than unruptured one [13]. The remodeled collagen fibers in the aneurysm wall are oriented according to flow and the wall shear stress sensed by the endothelial cell layer [14]. Wall shear stress is a blood flow induced force per unit area tangential to the direction of the flow and dependent on the rate of flow.

Bifurcation Aneurysms The largest increase in wall shear stress is generally seen at outer walls of curved vessel segments, highly constricted regions of arteries, and the apex regions of bifurcations (Fig. 18.3). The ability to model cerebral blood flow based on 3D blood vessel morphology (computational fluid dynamics) as well as to perform quantitative in vivo measurements via phase contrast magnetic resonance imaging (MRI) (4D Flow MRI) has become an important clinical tool to stratify procedural risk prior to considering treatment options [15]. Slowing of the endoluminal blood flow by stent implants in the parent vessel has been observed in multiple studies; a notion led to flow diversion treatment of complex aneurysms and wide neck aneurysms.

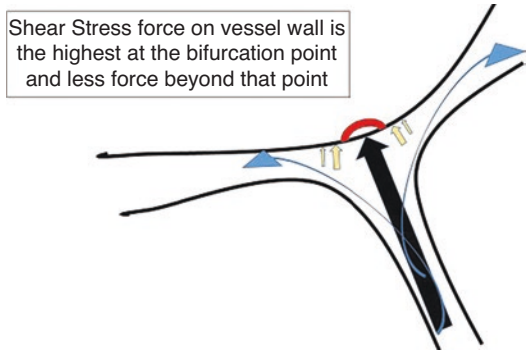

Fig. 18.3 Wall shear stress at the bifurcation is frictional force on the wall, which is a function of dynamic viscosity, flow velocity, and distance from vessel centerline

Treatment of Wide Neck and Bifurcation Aneurysm

The history of aneurysm treatment was discussed in-depth elsewhere in Chaps. 10 and 11 of this book. Briefly, the utilization of microsurgical clipping for treatment of cerebral aneurysms has declined with the innovation of endovascular approaches. The introduction of the Guglielmi detachable coils in the late 1980s [16] was the first step of endoluminal flow obliteration, which later proved an efficacious and safe treatment option compared to microsurgical clipping [17]. Subsequently, several endovascular treatment strategies have been developed over the past decade; these can be classified into (1) intrasaccular obliteration or disruption, (2) extrasaccular or endoluminal flow diversion or support, and (3) the combination of the above two strategies. Despite these options, wide neck and bifurcation aneurysms remain a challenge for endovascular therapy; hence, surgical clipping remained a viable option especially for aneurysms at the middle cerebral artery bifurcation with operative risk of 3.5% [18]. Endoluminal flow diversion and intrasaccular disruption have been developed to tackle some of these aneurysms. The tenet of aneurysm closure in both of these strategies is essentially similar. It is documented that intrasaccular flow decreases with placement of endoluminal flow diverter stent; these diverters provide a scaffold for endothelial growth across the aneurysm neck leading to aneurysm closure [19]. Flow diverters are optimal in wide neck simple or complex side wall aneurysms, though they are not so applicable for bifurcation aneurysms. It is important to highlight that endoluminal devices activate platelets aggregation, and thus, platelet inhibition is central in utilizing these devices. Woven intrasaccular implants provide similar decrease in the saccular flow and similar neointimal endothelial growth across the neck of the aneurysm [19]. These implants provide a few advantages over endoluminal flow diverters. First, they can be used for bifurcation wide neck aneurysms, locations where flow diversion may lead to branch occlusion. Second, treatment with antiplatelets is not essential with intrasaccular disruption compared to endoluminal flow diversion. The latter observation is especially important in ruptured aneurysms. Because a single intrasaccular device can be used to occlude a saccular aneurysm, it is presumed to have the following advantages over coil embolization: less manipulation of equipment, less procedural times, less radiation exposure, and eliminates the need for antiplatelet therapy. Intrasaccular flow disruptors are approved for four locations in the cerebral circulation including the anterior communicating artery, middle cerebral artery bifurcation, carotid terminus, and basilar summit aneurysms (Fig. 18.4).

Intrasaccular Flow Disruptors

Saccular flow disruptors are self-expanding devices with a high metal density that are inserted within the aneurysm sac. The first human use of flow disruptor was reported by Klisch et al. in 2011 [20]. Since then, several saccular disruption devices have been introduced and currently under various stages of research and development. These include the Woven EndoBridge or WEB (Microvention), Medina Embolic Device or MED (Medtronic), Artisse (Medtronic), Contour Neurovascular System, Cerus Intrasaccular Stent (Cerus Endovascular), and SEAL GT (Galaxy Therapeutics). The WEB is the only approved

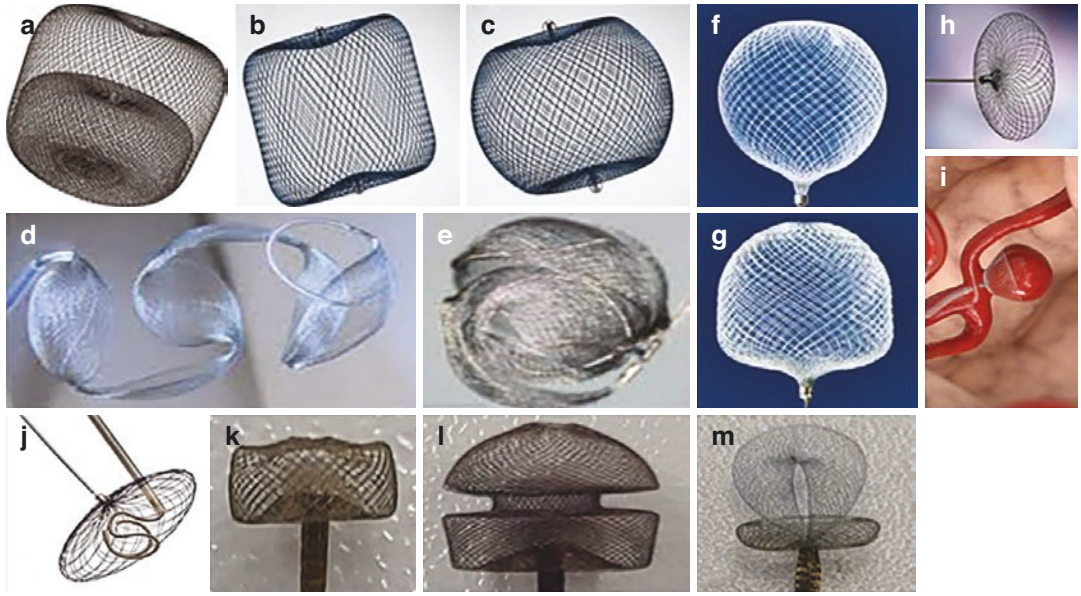

Fig. 18.4 Woven EndoBridge (WEB), (**a**) double layer, (**b**) single layer, (**c**) single-layer spherical. Medina embolic device (MED) (**d**) petals and (**e**) fully deployed. Artisse device, (**f**) spheroid, and (**g**) flared. (**h**) Contour self-anchoring flat disc (**i**) situated at the neck of the aneurysm. (**j**) Cerus device also called Neqstent to cover the neck of the aneurysm through which coiling can be performed. SEAL GT device, (**k**) Base SEAL, (**l**) Polar SEAL, and (**m**) Arch SEAL

intrasaccular disruptor in the United States; other devices are being investigated in preclinical and clinical studies.

Woven EndoBridge (Microvention, Aliso Viejo, California)

The Woven EndoBridge (WEB) is a self-expanding nitinol mesh ball that is constructed with a special micro braid. It was the first saccular flow disruptor to gain FDA approval in December 2018. It was approved for the treatment of saccular, wide neck, bifurcation cerebral aneurysm with dome diameters from 3 mm to 10 mm, neck size ≥4 mm, or a dome to neck ratio of <2. Off-label use in non-bifurcating cerebral aneurysms with good outcomes has been reported [21]. The WEB has distal and proximal radiopaque markers to enhance visibility. It is a resheathable device and can be deployed using electrothermal detachment. Once the WEB is inside the aneurysm sac, it reshapes according to the morphology of the aneurysm. The device's low porosity and metal mesh helps to reconstruct the interface between the parent artery and the aneurysm neck and then provides lattice for neoendothelial growth. The WEB can be delivered with VIA 17, 21, 27, or 33 microcatheters depending on the needed size of the WEB device. It was first introduced as a double layer (WEB DL) and then reconstructed as single layer (WEB SL) and was further configured in spherical shape (WEB SLS).

Clinical Data The WEB is the most studied saccular flow disruptor with favorable morbidity and mortality outcomes. Three prospective studies (WEBCAST, WEBCAST-2, and the French Observatory Study) with a total of 168 patients showed a 78% neointimal coverage grade A and B (according to the WEB Occlusion Scale) [22] at 1-year follow-up [16]. At 1 month postoperatively, there was 2.3% morbidity and 0 mortali-

ties. In the WEBCAST study, 56% achieved complete saccular occlusion at 6 months follow-up; most of the aneurysms studied in the WEBCAST were predominantly unruptured, wide neck, and bifurcation aneurysms. Even though the WEB implant has limited contact with blood, thromboembolism seems to be an occasional observation. In the WEBCAST study, the use of antiplatelet therapy did not prevent the thromboembolic complications even if dual antiplatelet agents were to be employed [23]. Among 51 patients treated in the WEBCAST, 9 thromboembolic events were encountered, but only 1 patient had a permanent deficit with modified Rankin Scale of 1 (2%). A meta-analysis by Lv et al. (2017) that analyzed 19 studies with 935 patients found a lower thromboembolic complication rate of 8% [24]. At 3-year follow-up from the WEBCAST and WEBCAST 2 trials, the rates of complete and neck remnant occlusion rate were 83.6% with retreatment rate of 11.4% [25]. Long-term outcomes are being evaluated by the WEB Intrasaccular Therapy (WEB-IT) study in the United States; preliminary data suggest good safety and procedural success [26]. Most of the WEB trials included patients with unruptured aneurysms; however, a retrospective single-center study by van Rooij et al. that included 2018 patients with ruptured aneurysms (nearly half of the population) showed a complete occlusion rate of 72% [27]. The CLARYS (Clinical Assessment of WEB Device in Ruptured AneurYSms) trial is an ongoing prospective study designed to evaluate the safety and efficacy of the WEB device in the treatment of ruptured aneurysms.

Case study 1: Conventional Indication. A 66-year-old man with incidental 5 millimeter aneurysm in the anterior communicating artery. Angiographic evaluation of the aneurysm showed it to be 5 × 5 millimeter in the widest dimensions with 3 millimeter neck (Fig. 18.5A). Though this aneurysm shows a borderline dome to neck ratio (1.6), intrasaccular disruption felt to be a better treatment option compared to primary coiling. A 7 × 3 millimeter WEB SL device was selected and implanted using a VIA 21 catheter system. After ¾ of the device deployed within the aneurysm sac, the WEB started conforming (Fig. 18.5B). Complete conformation and lateral compression of the device within the sac were achieved with immediate complete closure of the aneurysm (Fig. 18.5C and D).

Case study 2: Unconventional Indication. A 68-year-old woman with a history of subarachnoid hemorrhage that occurred 6 years earlier due to a ruptured aneurysm in the anterior communicating artery that was successfully coiled with complete closure achieved then. She improved and returned to normal functions; though, she lately started complaining of increasing headaches. Angiographic evaluation in follow-up showed evidence of coil compaction and sac recanalization causing a 5-millimeter saccular growth (Fig. 18.6A). Initial plans for a flow diversion were halted due to the angulated anatomy of the right anterior cerebral artery. Though WEB device is not approved as add-on therapy, a decision was made to proceed with WEB implantation within the residual sac. A 6 × 3 millimeter WEB SL navigated and deployed using the VIA 21 catheter system led to complete saccular occlusion (Fig. 18.6B).

Medina Embolic Device (Medtronic, Dublin, Ireland)

The medina embolic device (or MED) is a three-dimensional self-expanding mesh of petals that lies on the axis of a single wire core (Fig. 18.4D and E). The mesh when fully deployed resembles flower petals that occlude the sac and act as a flow disruptor [26]. The MED is a resheathable device and can be redeployed like a standard coil. The smallest size is 5 mm; hence, it cannot be used to treat aneurysms smaller than 5. It can be used to treat large or giant aneurysms which are an advantage over the WEB device. The MED is best suited for the cavernous, paraophthalmic, and supraclinoid aneurysms, and similar to the WEB, the MED can be used for bifurcation aneurysms. It can be delivered with

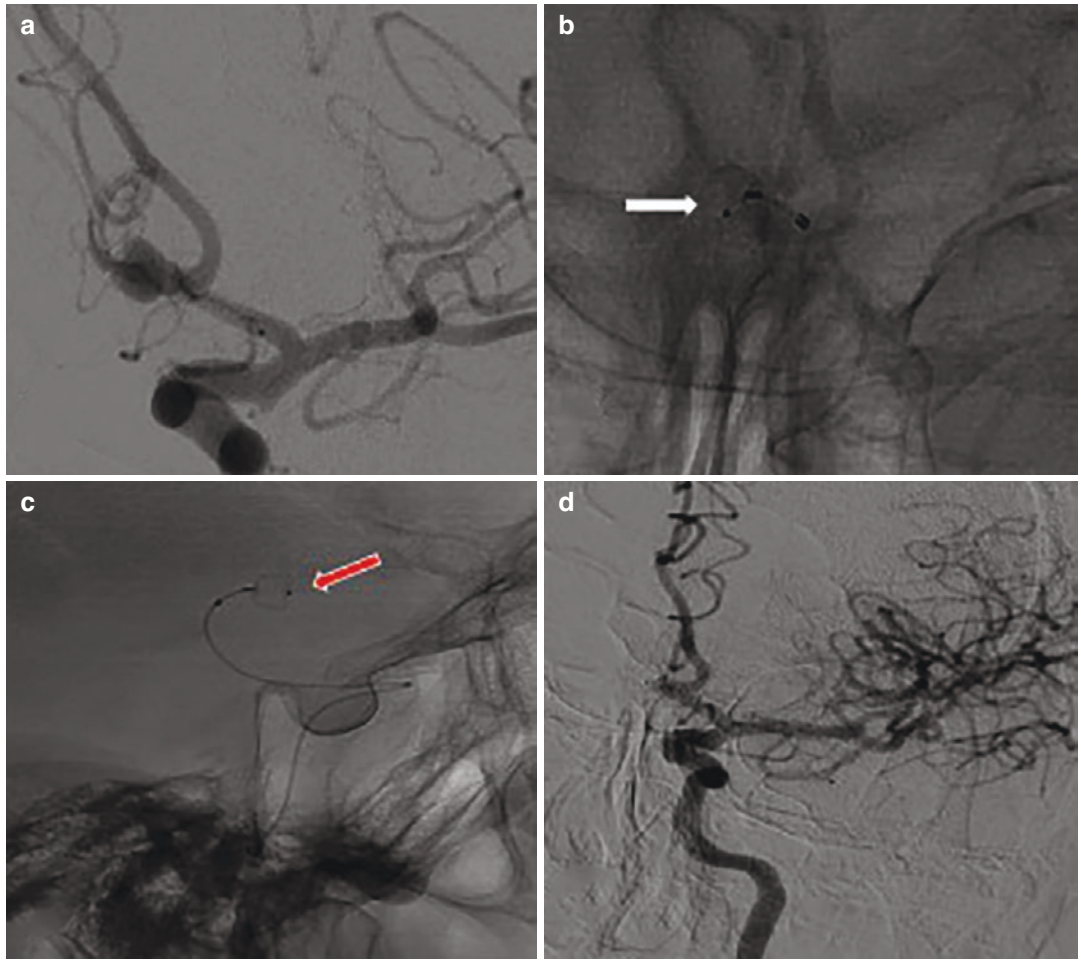

Fig. 18.5 Cerebral aneurysm at the anterior communicating artery, (**a**) pretreatment angiographic view; (**b**) WEB SL device ¾ deployed inside the aneurysm sac (white arrow); (**c**) lateral view of a fully deployed WEB SL device (red arrow); and (**d**) final angiogram immediately following the WEB detachment showing complete aneurysm occlusion

021-inch microcatheters and has a mechanical deployment system.

Clinical Data No large series are yet available; though, small studies with short follow-up showed mixed results. Bhogal et al. reported 75% aneurysm occlusion rate at 6-month follow-up after MED saccular implant [28]. A similar study by Sourer et al. showed 83% complete occlusion rate at 6 months; 85% of patients needed adjunctive therapy with standard coiling [29]. The MED received the CE mark in the European Union, not widely used and lacks long-term data. The combination of MED with intraluminal device has been tested on 25 patients, and angiographic follow-up on 19 patients showed 89% occlusion rate at 9 months [30].

Case study: Perez et al. reported a patient with increasing headache and large cavernous carotid aneurysm treated with multiple MEDs [30]. Angiographic evaluation performed 2 days later showed complete occlusion of the aneurysm with normal parent artery (Fig. 18.7).

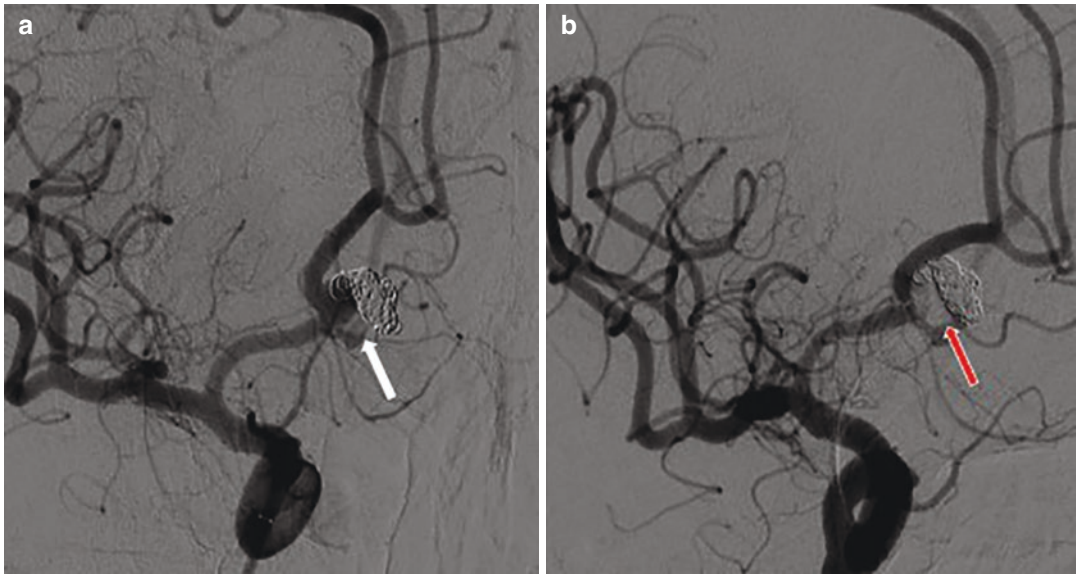

Fig. 18.6 (**a**) Angiographic view of a previously coiled aneurysm in the anterior communicating artery with evident coil compaction leaving 5 mm saccular filling (white arrow); (**b**) angiographic view after deploying a WEB SL device (red arrow)

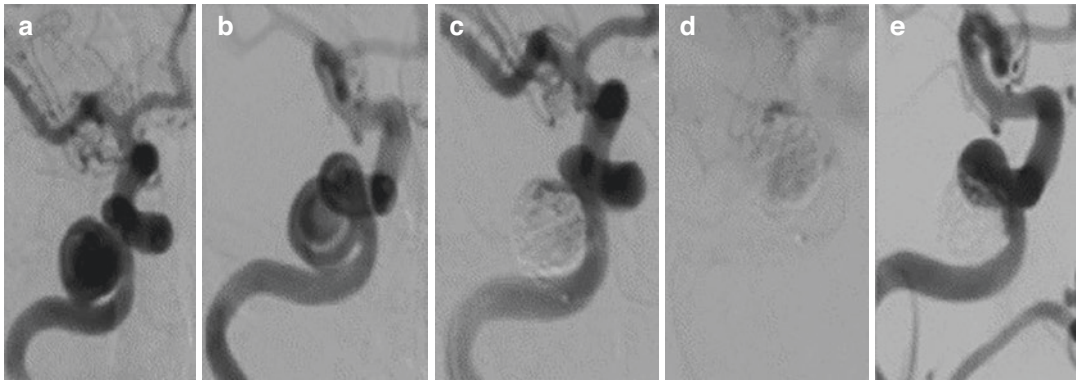

Fig. 18.7 (**a**) A right internal carotid artery angiogram shows a large cavernous aneurysm (**b**) with contrast swirling inside the aneurysmal dome. (**c**) Angiography at the end of the procedure shows minimal opacification along the superior edge of the aneurysm and (**d**) pronounced stagnation. (**e**) A follow-up angiogram 2 days after the intervention shows complete exclusion of the aneurysm from the circulation (Perez MA, JNS 2017), with permission

Artisse (Medtronic, Dublin, Ireland)

The Artisse device was formerly known as the Luna device. It is similar to the WEB in that it's braided, self-expanding, and made of nitinol (Fig. 18.4F–G). It has platinum markers that enhance visibility, and it's mechanically deployed via a standard 0.027-inch microcatheter. It is currently used in Europe but not in the United States. A few studies evaluated this device; the largest of which reported by Piotin et al. (2018) showed complete occlusion of 45.8% and ade-

quate occlusion (complete occlusion with residual neck) of 78% at 1-year follow-up, with a good safety profile [31].

Contour Neurovascular System (Cerus Endovascular, Fremont, California)

The Contour device is a self-anchoring flat disc-like mesh that covers the neck and lower half of the aneurysm (Fig. 18.4H, I). The main aim of this device is to cover the neck of the aneurysm, by which it provides flow diversion and disruption from within the aneurysm sac. The device is designed to treat both ruptured and unruptured aneurysms. Similar to the WEB, the device is resheathable, detached electrolytically, and delivered via 0.027-inch microcatheter. One mechanism proposed for its physiology is that hemodynamic flow and blood pressure at the intravascular side of the deployed device transmits into the intrasaccular part and leads to stability of the aneurysm around the neck which is abutted by an oversized Contour device seated at the aneurysm neck. Over time, thrombosis from within the aneurysm sac coupled with endothelial growth over the neck of the aneurysm effectively occludes the aneurysm sac. The Contour is not limited by the aneurysm size and not dependent on using antiplatelet agents. Currently, only unruptured aneurysms have been treated with the Contour system, and it is still undergoing clinical trials in Europe.

Neqstent (Cerus Endovascular, Fremont, California)

This is similar to the Contour device with fewer mesh wires that allow the passage of a coiling microcatheter. The Neqstent device is oversized to the aneurysm neck and used in conjunction with coils. It is resheathable and detached electrolytically. Neqstent is an intrasaccular device, and therefore, it can be used to treat both ruptured and unruptured aneurysms. The device is oversized to cover the neck of the aneurysm, and a coil mass is applied to fill up the aneurysm sac. The coil mass prevents the upward migration of the Neqstent device into the aneurysm. Similar to stent-assisted coiling of cerebral aneurysm, the Neqstent device acts as intrasaccular stent, not in the vessel lumen. Clinical studies are underway to evaluate the safety and efficacy.

Seal GT (Galaxy Therapeutics, Brookfield, WI)

Seal GT is a self-expanding detachable nitinol mesh designed to span and bridge the aneurysm neck. The device comes in different sizes, shapes, and configurations (Fig. 18.4K–M) and can be delivered through 0.021- to 0.033-inch microcatheters. Seal GT is designed to accommodate different aneurysm types and shapes. Thirteen elastase-induced aneurysms in animals were treated and followed at 4 and 12 weeks [32]. Results of the first Seal GT generation in animals showed 80% complete aneurysm occlusion among those treated with the Anchor Seal GT device, with 88% neointimal coverage grades A and B (according to the WEB Occlusion Scale) [22]. Further safety and efficacy studies in humans are underway.

Future of Intrasaccular Flow Disruptors

The field of intrasaccular flow disruption is evolving rapidly. The WEB device is the most widely used flow disruptor and the only approved device in the United States. In recent years, many other devices have surfaced, a few of which are in the trial phase. The WEB device's current limited scope of FDA indications, wide neck bifurcation aneurysms, leaves the field open for new applications to other lesions such as side wall aneurysms (narrow or wide neck types), small, and giant aneurysms. Smaller delivery systems, especially for small and ruptured cerebral aneurysms, will also improve ease of use and adoption. Combined strategies of saccular disruption and endoluminal

flow diversion may also be worth exploring. Finally, the safety and effectiveness of some of the disrupters may be enhanced by coatings with drug-eluting medications that could reduce the incidence of thromboembolism [33, 34] or hydrophilic gel to improve endothelialization and final aneurysm occlusion.

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19 On the Horizon: Innovative Techniques and Procedures

Guillermo Linares

Introduction

In 1927, Moniz was the first to use a radiopaque substance and X-rays to image the cerebral vasculature in living human subjects. A few decades later, in 1953, Ivar Seldinger was the first to describe a percutaneous approach to access and visualize peripheral arteries. Seldinger's technique brought on a revolution in angiography and avoided the need for surgical cutdown in order to access vessels. It remains a foundational technique for both vascular and nonvascular access to this day [1]. The remainder of the twentieth and first decades of the twenty-first centuries has been marked by steady advances in neuroendovascular techniques such as the introduction of the Guglielmi detachable coil in the 1990s. More recently, the tremendous effect size of mechanical thrombectomy in improving patient outcomes has revolutionized the way in which ischemic stroke patients are treated [2, 3]. The future is bright with new therapies emerging and promising to continue the revolutionary impact of the field on neurovascular diseases and the nervous system more broadly.

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Beyond Femoral Access

The neurointerventional community is increasingly turning to non-femoral access for diagnostic and interventional procedures. The radial approach has been gaining more widespread use and benefits from the growing cardiology literature showing safety and improved morbidity and mortality. Clinical trials such as RIVAL show that transradial access (TRA) is associated with reduced morbidity, mortality, length of hospital stay, and cost. There are limitations to TRA due to the size of the vessel and anatomical considerations which make its catheterization challenging in some cases. The left-sided supra-aortic vessels, specifically the left carotid, present a challenge through the transradial approach [4].

While not a novel technique, transcervical access of the intracranial circulation through direct carotid puncture has the potential to allow faster recanalization times and to offer therapy to those with complex anatomy of the aortic arch or its branches. This approach to access has become particularly attractive for mechanical thrombectomy (MT). The MT population is often older and has a high incidence of severe vessel angulation and redundancy. This can sometimes make transfemoral or transradial access of the intracranial clot difficult, time-consuming, and sometimes impossible. In these cases, direct carotid puncture has proven successful but is associated

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with its own challenges such as iatrogenic carotid injury and postoperative access site bleeding with hematoma formation [5]. The development of carotid access sheath and arteriotomy closure systems may overcome these challenges in the future. A second arena in which direct carotid access is gaining adoption is in transcarotid artery revascularization (TCAR) procedures. This approach to carotid revascularization combines direct carotid access, flow reversal as a means of emboli protection, and carotid stent insertion. Again, it is useful in populations with difficult transfemoral access, but head-to-head comparisons with transfemoral stenting and CEA are lacking [6].

Endovascular Treatment of Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) is an ophthalmologic emergency with an incidence of 1/10,000 but as high as 57/100,000 person-years in the age range of 80–84. Acute retinal infarction and vision loss is the result of CRAO. This carotid circulation ischemic syndrome should be considered as a nervous system condition but has not benefited from the therapeutic growth that has come with systemic and catheter-based therapies for stroke. Proof of efficacy for reperfusion therapies is still lacking. Recognition of CRAO as a neurological emergency makes delayed diagnosis frequent, but the American Academy of Ophthalmology (AAO)-endorsed preferred practices highlight that acute symptomatic CRAO should prompt an immediate referral to the nearest stroke referral center. Several case series and some small controlled trials have investigated the use of endovascular infusion of pharmacologic agents to improve outcomes, but a large randomized clinical trial is still needed making treatments of CRAO one of the future challenges for the neurointerventional field [7]. Multidisciplinary collaborations and standardization of protocols will be needed for this promising therapy to gain more widespread use and offer the potential to spare patients from blindness [8].

Middle Meningeal Artery Embolization for Chronic Subdural Hematomas

Chronic subdural hematomas (cSDH) are common with an increasing prevalence as the population ages. The population that should be considered for embolization can be defined as patients with an "extra-axial, crescentic, fluid collection, the majority of which (>50% volume) is either hypo- or isodense to the underlying brain on CT" and is associated with neurological decompensation [9]. There are an estimated 60,000 new cases per year expected by 2030 which represents double the number of ruptured aneurysms in the United States annually. Embolization of the middle meningeal artery (MMA) has quickly become part of management armamentarium for cSDH. It involves microcatheterization of the external carotid artery, the internal maxillary artery, and finally the middle meningeal artery itself. Embolization with a liquid embolic agent is the most widely used technique. Large case series have reported dramatic results when MMA embolization is used as a primary treatment or as an adjunct to surgical interventions [10]. However, controlled clinical trials are still needed. Standardization of treatment protocols and investigations into the advantages of liquid embolics or other forms of vessel embolization will further clarify the efficacy of this procedure [11].

Endovascular Treatment of Headache

Headache is a leading cause of pain and disability in adults. One in five adults in the United States suffers from severe headaches or chronic migraines. This tremendous disease burden is also associated with a large annual economic cost. Pharmacologic interventions are available for headache, but it continues to lead to almost 4% of all Emergency Room visits where a significant number of patients are treated with opiates. The MMA is the main arterial feeder of the dura and is dilated during migraines. A recent

study reported successful administration of intra-arterial lidocaine and steroids into the MMA for refractory migraine [12]. Much remains to be learned from controlled trials regarding the safety and efficacy of this intervention, but there is a great need to alleviate pain and diminish disability due to headache, and endovascular treatment offers hope for the future [13].

Endovascular Neuro-Oncology

Central nervous system tumors have an incidence of 24,000 new cases per year in the United States. The most common primary brain tumor is glioblastoma (GBM), which is also the deadliest. Many advances in the chemotherapeutic and immunotherapy fields have shown promise, but nervous system malignancies continue to be a therapeutic challenge. Their complex molecular biology and the relative protection offered by the blood-brain barrier are partly responsible for the lack of response of these tumors to current therapies. Endovascular selective intra-arterial (ESIA) approaches offer a way to disrupt the blood-brain barrier and to deliver targeted biologic therapies to brain tumors. There is an increased urgency and need to develop ESIA approaches in brain tumor therapy [14]. In contrast to the difficulty of finding a successful IA therapy for brain tumors, IA chemotherapy (IAC) has become increasingly used to treat retinoblastoma, the most common childhood intraocular malignancy [15].

Endovascular Treatment of Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is a disease process of abnormally increased intracranial pressure in the absence of a mass lesion. Medical management, optic nerve fenestration, and surgical shunting procedures are sometimes successful, but a significant population of treatment refractory patients remains. In an unknown percentage of cases, intracranial hypertension is not idiopathic but instead is caused by dural venous sinus obstruction which can be treated with dural venous sinus stenting. The goal of these surgeries is to prevent progressive vision loss and worsening papilledema caused by underlying increased intracranial pressure from venous outflow obstruction. Documenting a pressure gradient of at least 8 mmHg or greater across the stenosis is diagnostic. When patients are selected with care, it is reasonable to expect normalization of the intracranial pressure, and there is an increasing body of literature showing stabilization and improvement in vision [16]. Randomized controlled trials of this approach are still needed to validate its widespread use.

Endovascular Neuromodulation

Endovascular neuromodulation is an emerging technology that is still largely confined to animal models, but it holds great future promise. An example interface is the StentrodeTM, a stent-electrode array which can be implanted into the superior sagittal sinus. The Stentrode transmits signals through a transvenous lead to a receiver located subcutaneously in the chest. Transvenous leads have been successfully employed for decades in the setting of implantable cardiac pacemakers and defibrillators. Through this brain-computer interface, patients with severe paralysis can control digital devices and overcome severe disability. It has the potential to restore a patient's ability to perform activities of daily living [17].

Direct Intravascular Visualization

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are two techniques that allow direct intravascular visualization. IVUS uses ultrasound to provide cross-sectional images of the vessel and vessel wall. Its use has mainly been described in cervical atherosclerotic disease and stenting, but the availability of smaller profile devices promises to expand this into the intracranial circulation.

OCT uses a wire that emits near-infrared light. This technology has been used to image the cervical stents and flow diverters. Like IVUS, the use of OCT will expand as the devices become smaller and trackable into the intracranial circulation [18].

Robotic Neurointerventional Techniques

Robotic neurointervention is a promising emerging field. Endovascular robots enable proceduralists who are not physically present in the procedural suite to control wires, catheters, and other devices. This ability to perform procedures remotely holds the potential to dramatically expand access to care. Telestroke technology coupled with these robotic techniques could make highly subspecialized care available to underserved areas and overcome the devastating consequences of the delayed treatment of cerebrovascular emergencies. It also could reduce occupational hazards such as radiation exposure. Preliminary clinical research has been published describing the safety and feasibility of such robotic technology in diagnostic cerebral angiography as well as cervical and intracranial interventions. Larger prospective clinical trials are currently being planned [19].

Artificial Intelligence and Neurointervention

Artificial intelligence (AI) can improve disease detection, auxiliary diagnosis, and precision medicine. The accuracy of brain imaging diagnostics has been increased by the extraction of imaging features using artificial intelligence techniques such as machine learning. Rapid automated differentiation of ischemic and hemorrhagic cerebrovascular diseases, risk assessment of intracranial aneurysm rupture, and rapid assessment of large vessel occlusion and ischemic penumbra by computerized brain imaging analysis algorithms are now common [20].

Conclusion

The armamentarium of the neurointerventionist is growing at an accelerating pace. While these tools hold great promise, many new technologies remain in an early phase or are yet to be tested in randomized controlled studies. This burgeoning collection of investigational treatments will likely continue to expand the role of neurointervention in the medical specialties.

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