Endovascular Surgery of Cerebral Aneurysms

Xianli Lv
Editor

Springer

Endovascular Surgery of Cerebral Aneurysms

Xianli Lv
Editor

Endovascular Surgery of Cerebral Aneurysms

Springer

Editor
Xianli Lv
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital
School of Clinical Medicine, Tsinghua University
Beijing, China

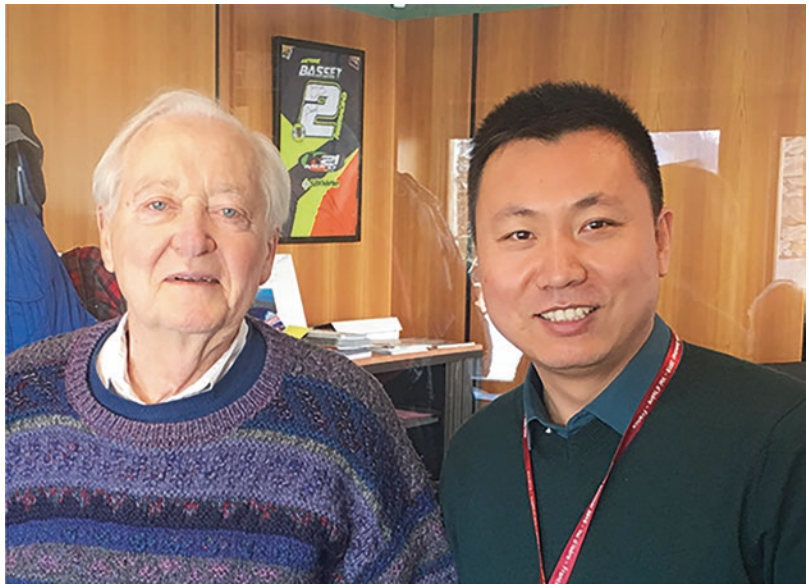
ISBN 978-981-16-7101-2 ISBN 978-981-16-7102-9 (eBook)
https://doi.org/10.1007/978-981-16-7102-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd. The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

In memory of Academician Zhongcheng Wang.

Prof. Zhongcheng Wang (December 20, 1925, to September 30, 2012), Academician of Chinese Academy of Engineering

In memory of Prof. Luc Picard

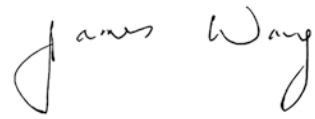


Professor Luc Picard (1937–2021), a pioneer of Interventional Neuroradiology, Professor of Neuroradiology of the Faculty of Medicine in Nancy, France

Foreword

Neurosurgeons have a long history of treating cerebral aneurysms. Understanding the vascular anatomy and physiology of the nervous system and management of patients with abnormalities of these vascular structures are vitally important aspects of neurosurgery resident training. Over the past few decades, the treatment of cerebral aneurysms has been evolving toward endovascular strategies for many patients. Interventional neuroradiologists play an important role in developing this area of therapy, but the number of neurosurgical trainees in neuroendovascular treatment is increasing. Other specialties, including neurology and vascular surgery, are now entering the field of neuroendovascular treatment, the neurosurgeons are better trained and provide safe treatment options. We have compiled and edited this book to report current neuroendovascular techniques and their impact on the treatment of cerebral aneurysms. Readers will benefit from the perspicacity among some of our most experienced practitioners on the treatment strategies for cerebral aneurysms. Even today, the number of neurosurgeons who had formal training in both endovascular and surgical treatment of cerebrospinal vascular diseases remains limited; the complexity of these difficult problems clearly calls for more neurosurgeons who can be efficient and knowledgeable

in both treatment modalities. This book will be very helpful for both practitioners and trainees alike pursuing the practice of excellence in neurovascular surgery.



James Wang
Department of Neurosurgery
Beijing Tsinghua Changgung Hospital
School of Clinical Medicine
Tsinghua University
Beijing, China

Department of Neurosurgery
University of Washington
Seattle, WA, USA
March 6, 2020

Preface

Endovascular neurosurgery provides effective and minimally invasive treatment of a broad spectrum of diseases. This area of expertise has continued to gain both wider application and greater depth as new and better techniques are developed and as landmark clinical studies are performed to guide their use. The treatment of cerebral aneurysms has evolved substantially, increasing the number of aneurysms that can be treated successfully with minimally invasive therapy. The book aims to report current neuroendovascular techniques and the efficacy and safety of procedures used for cerebral aneurysms and to summarize key aspects of best practice. Attendees, fellows, residents, medical students, or anyone interested in sharpening their diagnostic and therapeutic skill set will benefit from reading this text. Finally, I must thank all the authors who have contributed so much of their time, wisdom, and experience in creating the final product you hold in your hands. On behalf of everyone associated with this work, I sincerely hope you enjoy learning and implementing your new skills as much as I have enjoyed organizing the material.

Beijing, China
March 6, 2020

Xianli Lv

This work was supported by the Beijing Municipal Administration of Hospitals Incubating Program (PX2020039), Beijing, China, and Tsinghua Precision Medicine Foundation (20219990008), Tsinghua University, Beijing, China.

Acknowledgment

Thanks Prof. Zhongxue Wu(left), my great teacher, who is a human being of immense qualities, a man of incredible energy, and an extraordinary individual whom we will always love and admire.

Contents

About the Editor

Xianli Lv, M.D., is an associate professor of Endovascular Neurosurgery, Neurosurgery Department, at Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, in Beijing (China). His research focuses on endovascular neurosurgery of intracranial aneurysm, cerebral AVM, intracranial dural arteriovenous fistula, spinal AVM, and pediatric cerebrospinal AVMs. He has authored 195 peer-reviewed scientific articles indexed in international databases. He is an editorial member of the journals: *Interventional Neuroradiology*, *Stroke and Vascular Neurology*, *Journal of Neuroradiology*, and *the Neuroradiology Journal*. He is also a deputy editor of *Neuroscience Informatics*. Dr. Lv is a member of the World Federation of Interventional Therapeutic Neuroradiology (WFITN).

Pathophysiology of Cerebral Aneurysms

1

Zaid Aljuboori, Samer S. Hoz, Zahraa Al-Sharshahi, and Mohammed A. Alrawi

Abstract

Understanding the pathophysiology of the formation and growth of cerebral aneurysms is crucial for early detection, risk assessment, and therapeutic monitoring of intracranial aneurysms. A multifactorial model can be applied to study the formation and growth of cerebral aneurysms. This model is mainly based on patient and aneurysm-specific characteristics. Potential patient-specific factors include smoking status, hypertension, inflammatory disease, bone mineral loss, and sex hormone exposure. Aneurysm-specific factors include aneurysm size, bifurcation site, multiplicity, presence of a daughter sac, higher dome-to-neck ratio, multi-lobularity, and adjacent arterial geometry. Other factors that can affect the development and growth of aneurysms include female sex, short stature, bone fragility, malnutrition, and the existence of genetic disorders, and a range of aortic pathologies, including bicuspid aortic valve, dilated aortic root, aortic aneurysm, and arterial dissection. The goal of this chapter is to summarize the existing evidence and potential prospects for cerebral aneurysm pathophysiological studies.

Keywords

Intracranial aneurysms · Pathophysiology
Formation · Growth · Risk factors

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
CA	Cerebral aneurysms
IL-1β	Interleukin 1B
MMPs	Matrix metalloproteinases
SAH	Subarachnoid hemorrhage
SNPs	Single nucleotide polymorphisms
TNF	Tumor necrosis factor
UIA	Unruptured intracranial aneurysm

1.1 Introduction

Cerebral aneurysms (CAs) represent areas of focal dilatations of the vascular lumen caused by weakness of the vessel wall, most commonly located around the bifurcation sites of the circle of Willis. It is estimated that 5% of the population have cerebral aneurysms, with 20–30% of this cohort harboring multiple aneurysms [1].

Z. Aljuboori (✉)
Department of Neurosurgery, University of Washington, Seattle, WA, USA
e-mail: zaidsa@uw.edu

S. S. Hoz · Z. Al-Sharshahi · M. A. Alrawi
Department of Neurosurgery, Neurosurgery Teaching Hospital, Baghdad, Iraq
e-mail: zahraaalsharshahi@rcsi.ie

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_1

Furthermore, 20% of patients with unruptured CAs have a positive family history for a CA. Aneurysmal subarachnoid hemorrhage (SAH) accounts for approximately only 5% of all strokes, and the consequences are devastating due to high mortality and morbidity rates [2].

Unruptured cerebral aneurysms are primarily asymptomatic and are most commonly detected incidentally or by screening those at high risk. Cerebral aneurysms are mostly acquired lesions resulting from a defective vascular wall response to local hemodynamic stress forces. The structural deterioration of the arterial wall involves inflammation and tissue degeneration with degradation of the extracellular matrix and smooth muscle cell apoptosis [3]. Three-fourth of all cerebral aneurysms occur at one of three locations—the middle cerebral artery, the posterior and the anterior communicating arteries, at the bifurcation, the internal carotid artery junction and the anterior cerebral artery junction, respectively. Less than 5% of patients with unruptured intracranial aneurysms (UIAs) are children. There are substantial differences in the risk factors and mechanisms of UIAs formation between children and adults. In children, 50–70% of UIAs cases are due to infection, trauma, or dissections, only 20–30% have a cystic shape, and the majority have clinical symptoms [4].

CAs can be divided into "True" and "False" aneurysms. True aneurysms are abnormal focal dilatations of the vascular lumen due to areas of vessel wall weakness, while false or pseudoaneurysms represent sites of contained perivascular hematoma that do not possess the same histological layers of the parent vessel. False aneurysms are primarily caused by penetrating trauma but may also result from periadventitial infections, or rarely, an infiltrating malignancy.

Morphologically, CAs can be saccular or fusiform. Saccular ("berry") aneurysms are rounded outpouchings from the vessel wall, characterized by the presence of a neck and dome. Saccular aneurysms can be subdivided into seven categories based on their etiology: Developmental aneurysms develop secondary to congenital weakness in the arterial wall. Hemodynamically induced aneurysms are the result of high shear forces at the bifurcation sites, mostly presenting at the apex of the bifurcation where these forces are most pronounced. High-flow aneurysms develop in the vicinity of arteriovenous malformations, especially where its feeder vessels are located. Other subtypes include traumatic and oncotic aneurysms as well as those related to vasculitis, connective tissue disease, and medication side effects.

Fusiform (dolichoectatic) aneurysms have no identifiable neck and include atherosclerotic, mycotic (infectious), and dissecting aneurysms. Atherosclerotic aneurysms form when an unusual form of atherosclerosis damages the media leading to arterial stretching and elongation that could extend over a considerable length, leading to a serpentine, giant, and bizarre aneurysm shape. Such aneurysms tend to predominate in the older age group, affect proximal arteries (the vertebrobasilar system is commonly affected), have perforating branches over the entirety of its length, harbor intraluminal clots leading to ischemic symptoms, and present with mass effect (bleeding is rare). Mycotic (infectious) aneurysm is the term used when an infectious process destroys the vessel wall. Examples of such infection sources include septic emboli secondary to intravenous drug use of infective endocarditis, and meningitis. Dissecting aneurysms result when an intramural hematoma extends into the subadventitial plane and are most commonly located at the extracranial segments of the internal carotid and the vertebral arteries.

1.2 Structure of the Cerebral Arteries

The cerebral arteries are similar to other systemic arteries in that their wall is composed of the tunica intima, tunica media, and the adventitia. The internal elastic lamina partitions the tunica intima and tunica media. The internal elastic lamina partitions the tunica intima and tunica media, while the external elastic lamina marks out the adventitia from the tunica media.

Cerebral arteries can be further classified as "muscular" or "elastic" with respect to the com-

position of their tunica media. For example, the common carotid artery is an elastic artery, while the internal carotid and intracranial arteries are muscular. The intra- and extradural segments of the intracranial arteries vary in their histopathology; the adventitia is thinner in the intradural portion than in the extradural portion, and the collagen part of adventitia plays an important role in decreasing the risk of rupture in the event of a sudden blood pressure change [5]. The intradural segments also lack the external elastic lamina, which could explain the higher propensity of these vessels to develop aneurysms with higher risk of rupture.

Location is an important risk factor for aneurysm formation. For example, vasculature remodeling capability is higher in the posterior as opposed to the anterior circulation. Also, arterial bifurcation sites are preferred locations for aneurysm formation, given the higher level of hemodynamic stress created by the blood flow-associated deflection and oscillation forces. Aneurysmal changes usually involve multiple vessels with a shared embryonic origin, a phenomenon attributed to neural crest malposition and/or malfunction. Epidemiological observations revealed that patients with thoracic aortic aneurysms have a ninefold increased risk of cerebral aneurysms, as compared to the general population [6].

Recently, it has been found that ascending aortic aneurysms occur more frequently in association with anterior and middle cerebral artery aneurysms, while abdominal aortic aneurysms tend to co-occur with internal carotid artery aneurysms. Anecdotal studies have shown that cerebral aneurysms can be considered as a typical pathological phenomenon of neurocristopathy, such as congenital heart disease, bicuspid aortic valve, type 1 neurofibromatosis, and fibromuscular dysplasia. In line with this concept, patients with multiple, larger, and ruptured aneurysms tend to have a dilated aortic root. Clinically, multiple defects of the extracellular matrix have been detected in patients with connective tissue diseases linked to aneurysms, including osteogenesis imperfecta, vascular Ehlers-Danlos syndrome, and Marfan's syndrome [7–9].

Clinically, several abnormalities of the extracellular matrix have been detected in patients with connective tissue disorders such as osteogenesis imperfecta, vascular Ehlers-Danlos syndrome, and Marfan syndrome, which are generally associated with cerebral aneurysms [7–9].

1.3 Formation of Intracranial Aneurysms

Aneurysm formation is a gradual process that entails the combination of hemodynamic, vascular genetic, molecular, and hormonal variables [10].

1.3.1 Hemodynamic Factors and Associated Structural Changes

The walls of cerebral arteries have a sparse tunica adventitia and a lower proportion of elastic fibers. Moreover, cerebral arteries are immersed in the cerebrospinal fluid of the subarachnoid space rather than in connective tissue. These structural factors are thought to make cerebral arteries susceptible to aneurysm formation [10].

In the wall of a healthy cerebral artery, the internal lamina maintains the elasticity and structural integrity of the vessel wall at the bifurcation sites. Degeneration or disruption of the internal elastic lamina at a bifurcation is a key event in the formation of an intracranial aneurysm. The definite cause of the degeneration and why it only occurs in certain individuals, however, remains unclear. Anatomical variations such as bifurcations comprising hypoplastic branching arteries or bifurcations with particularly sharp angles are considered to be a crucial factor in intracranial aneurysm formation [11].

Common sites for aneurysm formation include the anterior and posterior communicating arteries, middle cerebral artery, and basilar artery bifurcation sites, where local shear stress forces on the vessel wall are most pronounced. Blood flow at the arterial junctions, bifurcation sites with wide

angles, or locations with abrupt changes in vascular angulation create an environment of turbulent blood flow with higher levels of shear stress. This wall induces a cascade of changes, including endothelial cell damage, smooth muscle degeneration, and media layer thinning. Smoking, on the other hand, is linked with both higher prevalence of cerebral aneurysms and higher risk of rupture. The mechanisms by which smoking can cause cerebral aneurysm formation and rupture are suggested to be elevated wall shear stress due to increased blood volume and viscosity and nicotine-induced vasoconstriction [12].

1.3.2 Genetic Factors

Although evidence suggests that individuals with a family history of intracranial aneurysms or SAH are at increased risk of an intracranial aneurysm formation, no specific genes have yet been identified. One meta-analysis which included (32,887) sporadic aneurysms and (83,683) controls has identified three single nucleotide polymorphisms (SNPs) that were associated with the presence of sporadic intracranial aneurysms. The SNPs were located on chromosome 9 within the CDKN2B-AS1 gene, on chromosome 8 near the SOX17 transcription regulator gene, and on chromosome 4 near the endothelin receptor gene [13].

The strongest confirmation for the linkage was with a locus on 7q11 near the gene that encodes elastin, which is a protein that is involved in the preservation of integrity of the vessel wall [4]. Some heritable connective tissue diseases are also associated with an increased risk of cerebral aneurysms and SAH. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorders associated with SAH. Ehlers-Danlos type IV (caused by mutation of collagen type III), fibromuscular dysplasia, and possibly Marfan syndrome (mutation of fibrillin-1 gene) are other inherited disorders associated with the CAs and SAH [14].

1.3.3 Molecular Changes

In addition to the disruption of the internal elastic lamina and the resulting mechanical overload and tensile force shift, the vascular smooth muscle cells, and fibroblasts synthesize type I and V collagens, which are the main molecular constituents of intracranial aneurysms. As the molecular mechanisms fail to compensate for the mechanical overload of the vessel wall and the myointimal injury, the cellular and humoral inflammatory responses serve as the key drivers of aneurysm development. These responses, which are mediated by inflammatory cytokines such as tumor necrosis factor (TNF), IL-1β and matrix metalloproteinases (MMPs), facilitate the flow of macrophages and continuous degradation of collagen and elastin fibers [15].

1.3.4 Hormonal Changes Related to Aneurysm Formation and Rupture

There is evidence to support the difference in incidence and rate of cerebral aneurysm formation and rupture between men and women, and between pre- and postmenopausal women, indicating that aneurysm formation may be affected by hormonal changes. Estrogen and its interactions with estrogen receptors have been shown to be associated with regulation of arterial cell wall matrix, mediation of inflammation, and regulation of proteolytic and apoptotic pathways. Estrogen's effect on the regulation of the cerebrovascular system and its association with various vascular diseases, including stroke, trauma, and dementia, has been demonstrated and thought to be related to the reduction of inflammation and preservation of vessel wall integrity. Early menopause is associated with the development of cerebral aneurysms, whereas the use of hormone replacement therapy is protective against the formation of aneurysms [16].

1.4 Risk Factors Associated with Formation and Rupture of Cerebral Aneurysms

1.4.1 Conventional Risk Factors

Many risk factors have been linked to the formation of aneurysms, including cigarette smoking, heavy alcohol consumption, cocaine usage, familial history, ethnicity, gender, age, and most importantly, hypertension. From the above risk factors, some are thought to cause aneurysm formation via mechanisms that increase blood pressure and hemodynamic stresses. For example, heavy alcohol consumption has been shown to be an independent risk factor for spontaneous aneurysmal SAH, potentially through its effects on blood pressure and hemodynamic factors. Cocaine and its metabolites increase the risk and severity of aneurysms and SAH through its vasoconstrictor properties, which act via nervous stimulation of the vascular smooth muscle, causing profound hypertension.

As far as race is concerned, the risk of aneurysm tends to be comparable in whites, blacks, and Hispanics. It is well known that women are at higher risk of aneurysm formation, but the female preponderance is apparent only in the perimenopausal and postmenopausal periods. Finally, regular physical exercise may decrease the risk of aneurysm formation [14, 17].

Currently, screening for cerebral aneurysms is recommended for patients with a positive family history. Experts suggest screening of all individuals with two affected first-degree relatives due to the high incidence of CAs in this population. It may also be advisable to screen patients who have one affected first-degree relative if they have other risk factors for developing CAs such as female sex, older age, heavy smoking, hypertension, having an affected sibling, or having an affected relative with multiple aneurysms manifesting at an early age [14, 18].

1.4.2 Innate Risk Factors

Genetic disorders with a number of phenotypes have been identified with cerebral aneurysms. ADPKD is associated with defects in one of two genes; PKD1 and PKD2. Approximately, 20–40% of ADPKD cases have cerebral aneurysms, and 10–30% have multiple aneurysms. The prevalence of cerebral aneurysms in fibromuscular dysplasia is estimated to be 13 percent, which is around six times higher than that of the general population.

Cerebral aneurysms are also common in patients with aortic coarctation and bicuspid aortic valve. Cardiac outflow tracts and cerebral arteries share the origin of neural crest cells and pathological changes. Hence, the combination of these congenital heart diseases and the development of cerebral aneurysms are called neurocristopathic phenotypes. It has also been found that dilated aortic roots with no apparent heart disease are associated with nonconventional aneurysm features, such as multiple lesions, larger sizes, or early rupture [19].

1.4.3 Acquired Risk Factors

Acquired inflammatory conditions such as trauma, atherosclerosis, and infection can damage the arterial wall, leading to the formation of CAs. The development of CAs at relatively older ages is connected to age-related risk factors as well as the accumulation of atherosclerosis during the aging process.

There are other acquired risk factors to be recognized as aneurysm-inducing factors. Smoking induces the inflammatory response in the cerebral vessel and weakens the wall. Sex hormones may contribute to the acquired arterial wall weakness. Women are more susceptible to having a CA and occurrences of multiple aneurysms, as they experience a variety of reproductive and hormonal phases in menarche, menopause, oophorectomy, and hormone replacement ther-

apy over their life. As a consequence, a shift in the degree of exposure to estrogen can cause women to have different vulnerabilities to cerebral aneurysms. Gender-related differences may also support the link between sex hormones and extracellular matrix degeneration. Osteoporosis shows a female predominance, and bone mineral density reflects a cumulative estrogen exposure. Recent studies have shown that reduced bone mineral density is associated with cerebral aneurysms, large aneurysms, and multiple aneurysms [20, 21].

1.5 Common Risk Factors for Cerebral Aneurysm Rupture

Risk factors for CA rupture include both aneurysmal and patient factors. Aneurysmal factors include size, location (specifically in the posterior circulation and aneurysms arising from the posterior and anterior communicating arteries), and morphology (aneurysms with a daughter sac have higher rates of rupture). Patient factors include aging, female gender, current smoking, alcohol consumption, hypertension, history of SAH, and positive family history. Aneurysms larger than 10 mm have a 1% risk of rupture per year. Aneurysms of the anterior communicating artery rupture more easily in smaller sizes than those in other locations. Although larger aneurysms usually have a higher risk of rupture, ruptured aneurysms are generally small. If the size surges or morphological changes take place within a brief time period, the probability of rupture increases.

Multiple aneurysms are predominately found in the pediatric age group and younger adults and they pose a higher risk of recurrence. Morphological changes suggestive of an increased risk of rupture include the presence of a daughter sac, a high dome-to-neck ratio, and multilobular appearance. Recently, the PHASES study found that geographical location, e.g., Finnish or Japanese origin, was also a strong risk factor for aneurysmal rupture, possibly supporting a genetic influence on rupture risk [22, 23].

Cigarette smoking has been reliably documented as an important risk factor for SAH. Even those undergoing embolization, cigarette smoking is a risk factor for aneurysm recurrence, and patients should also be advised to quit smoking [24].

High blood pressure has been shown to predispose to SAH in prospective cohort studies. Blood pressure management is therefore yet another simple intervention to minimize the risk of aneurysm rupture [25].

While heavy alcohol consumption has been shown to increase the risk of SAH, it does not predispose to aneurysm development. The increased risk of SAH with alcohol use is possibly due to a fleeting rise in blood pressure [14]. Some factors have been identified as immediate triggers for aneurysm rupture, including coffee and Cola consumption, anger, startling, straining for defecation, sexual intercourse, nose blowing, and vigorous physical exercise [26].

Generally, aneurysms ≥7 mm in diameter should be treated as a result of their tendency to rupture, except in older patients and those with severe medical comorbidities and short life expectancy. Factors that permit strong consideration for treatment regardless of the aneurysm's size include young age, change in the size or configuration of the aneurysm, and the presence of many, daughter sac, or symptomatic aneurysms. Factors that can give priority to intervention over observation are active smoking, hypertension, posterior circulation aneurysm, anterior/posterior-anterior communicating artery aneurysms, previous SAH, history of familial SAH, and high aspect ratio [27].

A multitude of CA geometric indices have been studied as potential determinants of the probability of rupture. The aspect ratio is identified as cerebral aneurysm height divided by the diameter of the neck, it is the most studied and perhaps the most useful shape parameter. Studies have shown that 80% of ruptured aneurysms have an aspect ratio of >1.6, while 90% of unruptured aneurysms have an aspect ratio of <1.6. Another simple and useful geometric index, particularly suitable for small aneurysms, is the aneurysm-to-vessel size ratio, more commonly referred to as

the size ratio. In clinical practice, this means that a 3-mm aneurysm arising from the anterior communication artery has a higher risk of rupture than a 3-mm aneurysm of the paraclinoid internal carotid artery [27]. The growth of a CA is a strong risk factor for future rupture. As such, several experts recommend treating any aneurysm that has increased in size during the follow-up period. The annual risk of rupture was found to be 2.4% in aneurysms with growth compared with just 0.2% in those without growth (i.e., 12-fold increase in risk of rupture) [28].

References

1. De Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid hemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78:1365–72.
2. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke. 2002;33:1321–6.
3. Bourcier R, Chatel S, Bourcereau E, Jouan S, Marec HL, Daumas-Duport B, Sevin-Allouet M, Guillon B, Roualdes V, Riem T, Isidor B. Understanding the pathophysiology of intracranial aneurysm: the ICAN project. Neurosurgery. 2017 Apr 1;80(4):621–6.
4. Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture and preventive management. Nat Rev Neurol. 2016 Dec;12(12):699.
5. Cherng TW, Jackson-Weaver O, Kanagy NL. Introduction to cardiovascular physiology. In: McQueen C, editor. Comprehensive toxicology. 3rd ed. Oxford: Elsevier; 2018. p. 29–45.
6. Zhang XJ, Gao BL, Hao WL, Wu SS, Zhang DH. Presence of anterior communicating artery aneurysm is associated with age, bifurcation angle, and vessel diameter. Stroke. 2018;49:341–7.
7. Schievink WI, Raissi SS, Maya MM, Velebir A. Screening for intracranial aneurysms in patients with bicuspid aortic valve. Neurology. 2010;74:1430–3.
8. Schievink WI, Riedinger M, Maya MM. Frequency of incidental intracranial aneurysms in neurofibromatosis type 1. Am J Med Genet A. 2005;134A:45–8.
9. Southerland AM, Meschia JF, Worrall BB. Shared associations of nonatherosclerotic, large-vessel, cerebrovascular arteriopathies: considering intracranial aneurysms, cervical artery dissection, moyamoya disease and fibromuscular dysplasia. Curr Opin Neurol. 2013;26:13–28.
10. Shin YW, Jung KH, Kim JM, Cho YD, Lee ST, Chu K, et al. Echocardiographic evidence of innate aortopathy in the human intracranial aneurysm. PLoS One. 2014;9:e100569.
11. Sadasivan C, Fiorella DJ, Woo HH, Lieber BB. Physical factors effecting cerebral aneurysm pathophysiology. Ann Biomed Eng. 2013 Jul 1;41(7):1347–65.
12. Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, Dligach D, et al. Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. Neurology. 2017;89:1408–15.
13. Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. Neurology. 2013;80:2154–65.
14. Chalouhi N, Chitale R, Jabbour P, Tjoumakaris S, Dumont AS, Rosenwasser R, et al. The case for family screening for intracranial aneurysms. Neurosurg Focus. 2011;31:E8.
15. Kilic T, et al. Expression of structural proteins and angiogenic factors in normal arterial and unruptured and ruptured aneurysm walls. Neurosurgery. 2005;57:997–1007.
16. Ding C, Toll V, Ouyang B, Chen M. Younger age of menopause in women with cerebral aneurysms. J Neurointerv Surg. 2013;5:327–31.
17. Vlak MH, Rinkel GJ, Greebe P, Algra A. Independent risk factors for intracranial aneurysms and their joint effect: a case-control study. Stroke. 2013;44:984–7.
18. Rinkel GJ. Intracranial aneurysm screening: indications and advice for practice. Lancet Neurol. 2005;4:122–8.
19. Nurmonen HJ, Huttunen T, Huttunen J, Kurki MI, Helin K, Koivisto T, et al. Polycystic kidney disease among 4,436 intracranial aneurysm patients from a defined population. Neurology. 2017;89:1852–9.
20. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, et al. Estrogens and androgens in skeletal physiology and pathophysiology. Physiol Rev. 2017;97:135–87.
21. Shin YW, Park KI, Moon J, Lee ST, Chu K, Lee SK, et al. Association of bone mineral density with the risk of intracranial aneurysm. JAMA Neurol. 2018;75:179–86.
22. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362:103–10.
23. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol. 2014;13:59–66.
24. Chalouhi N, Ali MS, Starke RM, Jabbour PM, Tjoumakaris SI, Gonzalez LF, et al. Cigarette smoke and inflammation: role in cerebral aneurysm formation and rupture. Mediat Inflamm. 2012;2012:271582.
25. Sandvei MS, Romundstad PR, Müller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid

hemorrhage in a prospective population study: the HUNT study in Norway. Stroke. 2009;40:1958–62.
26. Vlak MH, Rinkel GJ, Greebe P, van der Bom JG, Algra A. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. Stroke. 2011;42:1878–82.
27. Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. Stroke. 2013 Dec;44(12):3613–22.
28. Villablanca JP, Duckwiler GR, Jahan R, Tateshima S, Martin NA, Frazee J, et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. Radiology. 2013;269:258–65.

2 Aneurysmal SAH Induced Vasospasm: Pathogenesis and Management

Ashis Pathak

Abstract

Introduction: Vasospasm remains a major cause of poor outcome after subarachnoid hemorrhage (SAH) following rupture of intracranial aneurysms. The pathogenesis still remains misty due to its complexity even though a lot of progress has been made in understanding various causative mechanisms through intense clinical and experimental research.

Method: Study carried out by a review of English literature on topics related to pathogenesis and management of post SAH induced vasospasm.

Result: Evidence-based information available points toward multifactorial biochemical phenomena instigated by Ferrous Hemoglobin which revolve around:

(a) Concept of early brain injury and evidence of cortical spreading depression
(b) Effect of ischemia in pre-vasospasm period and blood–brain barrier disruption.
(c) Role of Nitric oxide (NO), Endothelin-1 levels, and oxidative stress on smooth muscle cells.
(d) Changes induced by free radical production, lipid peroxidation, and alteration of ionic channels.
(e) Differential upregulation of genes.

Conclusion: To date the understanding of pathophysiology of delayed vasospasm has made significant stride for which the role of research using animal models cannot be overemphasized. The treatment of this complex condition still remains vague.

Keywords

Delayed vasospasm · SAH · Aneurysm
Cerebral ischemia

2.1 Introduction

Vasospasm remains a major cause of poor outcome after subarachnoid hemorrhage (SAH) following rupture of intracranial aneurysms. The pathogenesis still remains misty due to its complexity even though a lot of progress has been made in understanding various underlying mechanisms through intense clinical and experimental research. Though statistically 3.4% of population harbor incidental aneurysm [1] yet, depending on the risk factors, their rate of rupture varies from 0% to 100% with an annual rupture rate of 0–6.5% [2]. The risk factors vary from size of aneurysm, age of patient, history of smoking, and

A. Pathak (✉)
Department of Neurosurgery, Fortis Hospital Mohali, Mohali, Punjab, India

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_2

hypertension to pathophysiology of aneurysm formation. In familial aneurysms, however, the risk of rupture is threefolds the normal [3]. Despite lot of progress in understanding of the molecular changes culminating into delayed vasospasm, the exact interplay of various pathophysiological substrates remains an enigma. Interestingly, aneurysmal SAH was recognized since the time of Hippocrates and the outcome remains quite grim even to date [4].

2.2 Delayed Cerebral Vasospasm

Though management of aneurysmal SAH remains a major neurocritical care issue delayed cerebral vasospasm, which occurs usually between 3 and 14 days of SAH, remains the most elusive challenge [5]. Based on the belief that vasospasm is the main culprit for deterioration in SAH patients several trials antagonizing the suspected precursors of vasospasm were conducted, however, they failed to achieve a good functional outcome [6, 7]. Hence the role of vasospasm as the sole prognostic factor in clinical outcome after SAH remains questionable. On the contrary, it now seems evident that the pathological events starting at the very onset of SAH, which culminates into various biochemical changes, need to be understood better. Vasospasm and DCI may be the extreme manifestation of the same pathophysiological process rather than isolated phenomena. This has led to the concept of "Early Brain Injury."

Most of the management regimes for treatment of vasospasm has been directed toward the end result of pathophysiological phenomenon rather than treating the causative mechanism. Based on it, till now, the main treatment modalities include partial Triple H therapy (Hypervolemia, Hemodilution, and Hypertension), calcium channel antagonists, chemical or mechanical vasodilation. As a result, it still remains to be proven whether any of these treatment modalities have an evidence-based prognostic benefit in a patient with refractory vasospasm [8]. The diversity of opinion is reflected on the deliberations in 15 international conferences dedicated to vasospasm and SAH till the year 2019.

The process of vasospasm is far from the mere feature of spasm of blood vessels [9] and its ischemic consequences [10]. Clinical observation and experimental evidence point to the evolution of vasospasm as a complex multifactorial phenomenon that may remain subclinical or may progress to clinically manifested vasospasm with its devastating consequences [11–15]. There are various other pathophysiological mechanisms implicated in the clinical manifestations after SAH apart from vasospasm namely microcirculatory dysfunction, ionic disbalance, cortical spreading depolarization, micro-thrombosis, and inflammation at neuronal cell level [16].

2.3 The Pathophysiological Changes After SAH

2.3.1 Understanding Early Brain Injury

The event of SAH initiates a process of transient global ischemia which has a consequential bearing on the further pathophysiological events that follow. These may be in the form of brief microcirculatory arrest, blood–brain barrier disruption, microvascular constriction, brain edema [17]. The impact of these phenomena weighs heavily on the further events which progress in complex chain manifesting in the form of cerebral inflammation, dysregulation of blood flow, cortical spreading depolarization, microthrombi formation, and apoptosis [18]. These changes may be self-limiting with minimal or no clinical consequence or may progress into severe form leading to clinical deterioration with poor prognosis or fatal outcome.

2.4 What Leads to Vaso Constriction?

To date, a wide-ranging biochemical and molecular mechanisms have been implicated in vasospasm. These processes include mopping up of

nitric oxide (NO), high levels of endothelin 1 (ET-1) activity [19], alteration of ionic channels [20], lipid peroxidation, and free radical production [21]. These contribute to smooth muscle changes through oxidative stress [15] and apoptosis of endothelial cells [22]. There is now clear identification of upregulation of genes, which can point to individual susceptibility [23, 24]. Needless to say, the root cause of all these phenomena is triggered off by the release of ferrous components from the disintegrated hemoglobin released by the ruptured aneurysm in the subarachnoid space.

The role of oxidative stress [25]seems to have taken a center stage through its mechanism of direct activation of calcium channels and also through production of vasoactive molecules. The action of reactive oxygen species leads to vasoconstriction by its action on arachidonic acid which in turn leads to release of vasoactive lipids. Though the role of bilirubin oxidative products, formed as a result of hemoglobin break down, has been also considered but its role is not convincing [26] (Fig. 2.1).

2.4.1 Endothelin 1 (The Physiological Vasoconstrictor)

There are several substrates that contribute to the progression of vasospasm. ET-1 is a potent vasoconstrictor released in vascular wall whose levels are detected to be high in CSF following SAH. The exact levels, which can induce vasoconstriction, are still not determined because experimental studies need much higher levels than what is normally witnessed clinically after SAH. This raises the question of whether ET-1 needs potentiation by other factors [27, 28]. There is also evidence of enhanced ET-1 receptor expression and function in experimental animals suggesting its activation after SAH [29]. The role of Ca^{+} in the smooth muscle contraction is evident in acute phase of SAH as influx of Ca^{+} in the cells leads to phosphorylation of myosin light chain by stimulation of myosin light chain kinase [30]. The sustained contraction of the smooth muscles is regulated by the postulated mechanism of RhoA kinase activity which is stimulated by ET-1. Rho kinase is formed by ET-1 activation of Rho A. This initiates a cascade of chemical changes whereby Rho kinase inhibits myosin phosphatase subunit (MYPT1) of myosin light chain phosphatase (MLCP) augmenting phosphorylation of myosin light chain (MLC) [31]. Thus, once triggered the prolonged contraction of vascular smooth muscle is sustained by the enhanced phosphorylated MLC independent of intracellular Ca^{+} levels [32]. Further studies endorsed these postulates whereby the expression of Rho-associated protein kinase (ROCK), MYPT1 subunits, Protein kinase C (PKC), and upregulation of ET-1 receptor are demonstrated after SAH [33].

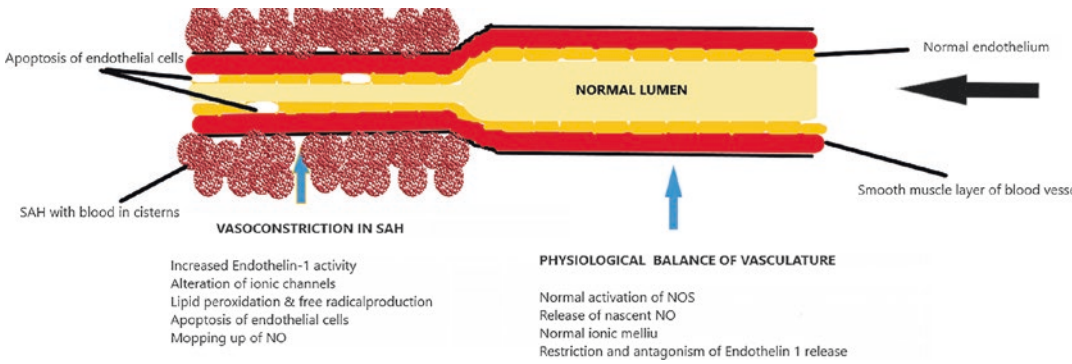


Fig. 2.1 Factors contributing to vasospasm

2.4.2 Nitric Oxide (The Physiological Vasodilator)

Endothelial nitric oxide is a potent physiological vasodilator that maintains a balancing act with ET-1 to maintain a steady patency of vessel lumen. It is produced by activation of endothelial nitric oxide synthase (eNOS). It produces cyclical guanine monophosphate (cGMP) through its stimulation effect of guanyl cyclase. The end result, which is vascular smooth muscle relaxation, is achieved by dephosphorylation of MLC through activation of cGMP-dependent protein kinases [34]. Following SAH the nascent NO liberated by the endothelium is mopped by hemoglobin to which it has a very strong affinity leading to reduction of local NO concentration tilting the balance for other substrates to induce vasospasm in an unchallenged situation. Furthermore, various molecular cascades of events lead to endothelial cell apoptosis reducing the NO secreting cell population [35]. There is also activation of protein kinase C after SAH which has an inhibitory regulation on NOS resulting in lower levels of NO [36]. Hence, it is derived that in normal situation a steady balance between NO and Endothelin-1 plays a vital role in maintaining the lumen of cerebral blood vessels.

2.4.3 Inflammatory Changes Leading to Apoptosis

Investigations of cerebral arteries of patients who died after SAH and vasospasm revealed apoptotic changes of vascular endothelial cells [36]. The endothelial loss further reduces NO production exposing the bare vascular smooth muscles to spasmogenic substances like ET-1 to act directly. This apoptotic change is in response to a molecular cascade of events which is demonstrated in experimental studies and takes place through inflammatory mediators, e.g., tumor necrosis factor alfa and interleukin-1beta [37] and activated caspase-3 [35, 38].

In addition, release of inflammatory substances as a reaction to blood in the subarachnoid space potentiates spasmogenic effect and brain ischemia. Potent among them are thromboxane A2, serotonin released from platelets [39, 40], and ET-1 released from leucocytes [41]. Elevated ICAM-1 (intracellular adhesion molecule 1), TNF alfa, CD18 suggests interplay of various inflammatory mediators in response to SAH [42–44]. Studies suggest that there is c-Jun N-terminal kinase (JNK) pathway activation after SAH which is one of the signalling cassettes of mitogen-activated protein kinase (MAPK) pathways [45]. JNK is known to play an important role in cytokine production, inflammatory changes, and also apoptosis.

2.4.4 The Ischemic Insult

The very critical event after SAH is a sudden rise in the ICP which is dependent on the amount and duration of blood released in the subarachnoid space. Decreased perfusion of the brain contributes to global ischemia which has a serious consequence if it does not reverse early. An immediate impact on the cerebral blood flow is reflected in reduction of brain parenchymal oxygen pressure [46]. Though many patients may not survive the immediate impact of raised ICP, severe ischemic secondary insult in the surviving patients leads to blood–brain barrier (BBB) disruption [47] contributing to further brain damage, progressive cerebral edema [48] and delayed apoptosis of cerebral and vascular cells [22]. Any ischemia in the brain lasting for more than a few minutes will trigger a cascading chain reaction at the molecular level due to release of various biochemical substrates, which propagates BBB disruption. One of the inducible factors is HIF-1 which, when excessively activated, overexpresses its target gene VEGF (vascular endothelial growth factor) which increases BBB permeability. It also overexpresses BNIP3 and Nip3-like proteins, which are known mediators of apoptosis [49, 50]. Experimental studies using HIF-alpha inhibitors show attenuated expression of HIF-alpha with a reduction in vasospasm [51]. In addition to apoptosis triggered by activated HIF-1alpha and BNIP3 [50], elevated levels of pro-apoptotic p53

proteins in vasospastic cerebral arteries seem to play a role in the phenomenon of induction of vasospasm [52–54].

2.4.5 Free Oxygen Radicals

Autoxidation of hemoglobin leads to liberation of reactive oxygen species (ROS), which play a role in arterial narrowing. The use of antioxidants demonstrated reversal of its effect on experimental vasospasm [55, 56]. The effect of ROX on bilirubin leads to oxidation products of bilirubin which has an inhibiting effect on endothelial nitric oxide synthase (NOS) leading to dampening of physiological vasodilation because of reduced production of NO [57]. The role of ROS in vasoconstriction is also postulated because of its stimulation effect on production of vasoconstrictor metabolites of arachidonic acid which have shown to decrease cerebral blood flow by blocking calcium-activated potassium channels in experimental animals [58]. The superoxide radicals (SOR) produced after SAH from NADPH oxidase have an indirect vasoconstrictive effect as these SOR combine with NO to produce peroxynitrite which in turn inhibits eNOS [59]. This mechanism is corroborated by reversal of vasospasm using NADPH inhibitors experimentally [60].

2.4.6 Is Vasospasm All About Cerebral Vasculature?

Until recent past, cerebral vasospasm was related to constriction changes in cerebral vasculature as a result of reactive changes secondary to effect of blood and its products released in the subarachnoid space after SAH. However, the mechanism seems to be related to the phenomenon of spreading depression set off by glial cell dysfunction (Cortical Spreading Depolarization) which is heavily dependent upon the changes secondary to pathophysiology of SAH [61–64]. Following the event of SAH there is a marked change in the milieu of ions in the neuroglial cells resulting in a significant increase of extracellular potassium with simultaneous decrease of extracellular sodium, chloride, and calcium ions due to their influx in the cell along with water. This results in a state of EEG silence [65–67].

Normally increase in functional activity of brain is directly proportional to increase blood flow and oxygen uptake, which enhances metabolism and glucose uptake [68, 69]. This coupling of flow and metabolism is regulated by interaction between astrocytes, neurons, and endothelial cells, which is mediated by electrical and chemical changes in milieu contributed by agents like nitric oxide (NO), carbon dioxide, endothelin 1, alteration of ionic channels**,** adenosine**,** lipid peroxidation, and free radical production. The role of astrocytes in maintaining the local extracellular potassium concentration is important as they are described as perfect potassium electrodes [70], acting as a spatial buffer in local change of potassium [71].

Extracellular acidosis and hypercapnia have a linear correlation with cerebral vasodilation with maximum dilation achievable up to pH 7. This acidosis-induced dilation due to high extraluminal H^+ concentration is mediated through activated K_{ATP} & $K_{Ca'}$. Even though there is contribution of NO in moderate increase in extraluminal proton concentration however its role becomes ineffective at a lower pH of 7 [72–75]. The aggravation of cerebral ischemia is augmented by periodic waves of Cortical Spreading Depolarization (CSD), which develop as a complex biochemical change secondary to oxyhemoglobin, ET-1, and K^+ ions [76]. The major trigger for CSD is changed in ionic milieu which happens due to inactivation of Na^+/K^+-ATPase activity at synaptic membrane level after SAH [77]. CSD thus contributes to spasm in distal small vessels and cellular necrosis (Fig. 2.2).

2.5 Diagnosis of Vasospasm

The diagnosis of vasospasm is best performed with a modality that can demonstrate the cerebral blood vessels and their caliber. Hence, CT angiogram (CTA), MR angiogram (MRA), or Digital Subtraction Angiography (DSA) are the options

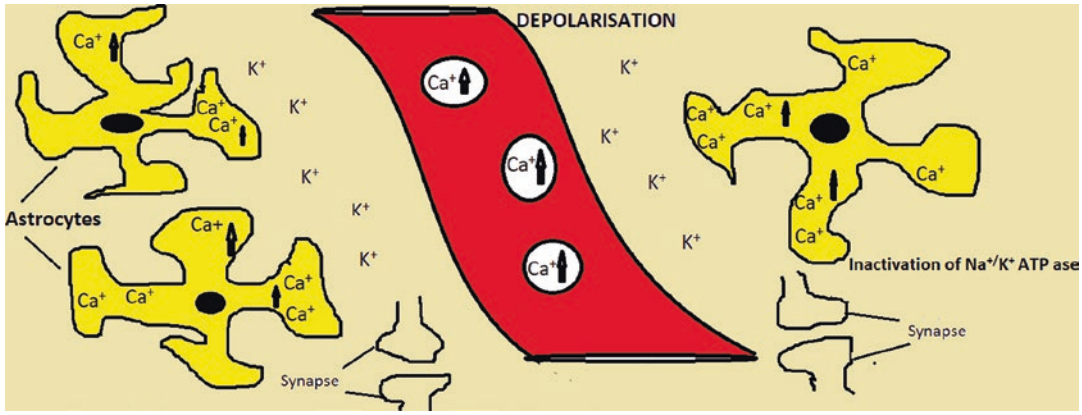


Fig. 2.2 Cortical Spreading depolarization

to study the vascular territory involved in vasospasm. However, all these modalities are appropriate to diagnose spasm in large and medium-size intracranial vessels but their utility in diagnosis of small vessels vasospasm is very limited. Though the diagnostic ability of these modalities is good for moderate-to-severe vasospasm but the logistic feasibility of repeating these studies precludes them for use in daily monitoring of status of vasospasm. DSA provides a more detailed picture of the status of vessels and the cross circulation but the intraluminal maneuvering of catheters and use of contrast medium can aggravate vasospasm in a spastic vessel [78]. CT perfusion studies are a useful substitute and can be helpful in diagnosing the imminent ischemia as well as the status of perfusion but the exact degree and distribution of spasm in the vasculature would not be apparent through this investigation.

Transcranial Doppler Ultrasound (TCD) is now being extensively used as a handy modality to assess the degree and extent of vasospasm. It has the logistic advantage of being noninvasive, easy to repeat, available at the bedside, and user friendly. The assessment through TCD is not only operator dependent but it has bearing on the anatomy of cerebral vasculature, exact site of vasospasm, the thickness of temporal bony window, viscosity of blood, ICP status, fluctuation of CO_2, and systemic blood pressure levels. Though it does not fulfil all the needed criteria for a detailed diagnosis, it gives a fair reading of velocity of blood flow in all the major vessels, thus alerts the observer on the magnitude of impending or existing vasospasm. TCD diagnosis of vasospasm in the MCA has a sensitivity of 39–94% and specificity of 85–100% [79]. There are different windows of access to mainly three intracranial vessels namely, the most commonly used middle cerebral artery (MCA) and anterior cerebral artery (ACA) both through the thin temporal squama, the basilar artery (BI) through the foramen magnum, and the transorbital window for the anterior cerebral vessels. TCD monitoring should ideally be done on a daily basis and the mean velocity of MCA would normally be between 80 and 100 cm/s. The respective values for mild, moderate, and severe vasospasm of MCA are 100–120, 120–200, and >200 cm/s, respectively [80].

The Lindegaard ratio of flow velocity between MCA and extracranial Internal Carotid Artery (ICA), which has got an almost 90% accuracy of detecting angiographic vasospasm, is a useful method for diagnosis of vasospasm whereby vasospasm is established if the ratio of MCA/ICA is more than 3 and a value of 6 or more indicates very severe vasospasm [81, 82]. A similar ratio of flow between BA and extracranial vertebral artery (EVA) has been advocated to establish vasospasm of BA [83].

2.6 Management Options for Vasospasm

2.6.1 Trials on Targeted Substrates

2.6.1.1 Lipid Peroxidation Inhibitors

Since lipid peroxidation induced by free radicals has a potent role in inducing vasospasm hence its inhibition by a nonglucocorticoid 21-aminosteroid (Tirilazad mesylate) was tried by virtue of its radical scavenging action and membrane stabilizing properties. Tirilazad mesylate underwent a global multi-centric randomized, double-blind trial with an aim to look for improvement in vasospasm and outcome at 3 months follow up. Though there was a significant reduction of vasospasm using 6 mg/kg/day, the benefits failed to reach a statistical significance even though it showed better efficacy in males in contrast to female patients [84].

2.6.2 Role of Endothelin-1 Antagonist

Endothelin-1 an endogenous potent vasoconstrictor which maintains a balancing act with nascent NO, is a potent vasodilator, released by the endothelium of cerebral arteries. CSF studies after SAH demonstrate an increase in ET-1 levels. There are two types of Endothelin-1 receptors, Endothelin A (ETA) receptor and Endothelin B (ETB) receptor [85]. ETA is directly responsible for smooth muscle contraction and hence a random placebo-controlled trial (CONSCIOUS 1) with Endothelin 1A antagonist (Clazosentan) was carried out to look for relief from ischemia and infarction of the brain [6]. Though the trial demonstrated significant benefit in terms of angiographic vasospasm, it did not show any impact on DCI [7]. Subsequently, CONSCIOUS-2 and CONSCIOUS-3, Phase III trials were conducted, respectively, for clipped and coiled patients with no significant advantage on either mortality, morbidity, or long-term functional outcome [86].

2.6.3 Is There Any Role of Statins?

Due to the unique combination of anti-inflammatory properties, dampening effect on reactive oxygen production, upregulating effect on NO synthase, and reduction of excitotoxicity the statins were also tried to look for amelioration of vasospasm and DCI. Limited studies endorse some beneficial effects of statins but there was asymptomatic alteration in liver function noted as a side effect [87]. However, the STASH trial (Simvastatin in Aneurysmal Subarachnoid Hemorrhage Trial) could not establish the use of statins in acute phase of treatment of SAH [88].

2.6.4 Augmenting NO Activity

2.6.5 Sildenafil Citrate

Sildenafil citrate is a phosphodiesterase inhibitor which along with NO is known to relax the smooth muscles by preventing hydrolysis of cyclic guanosine monophosphate (cGMP) and inducing smooth muscle relaxation. Its role is already established in vertebrobasilar insufficiency, angina, and erectile dysfunction. Experimental studies suggested a beneficial effect of intrathecal sildenafil apart from its smooth muscle relaxation to produce changes in cognitive function [89]. To avoid the logistic implication of intrathecal sildenafil therapy, treatment through enteral route was tried on a series of patients in a pilot study which claims to show benefit in limited number of patients with refractory vasospasm. However, there were considerable side effects of the drug and no controlled study has been undertaken to prove its efficacy [90].

2.6.5.1 Nascent NO Donors

The mopping up of nascent NO released from the vascular endothelium by oxyhemoglobin is an important biochemical phenomenon that has a major implication in the pathophysiology of

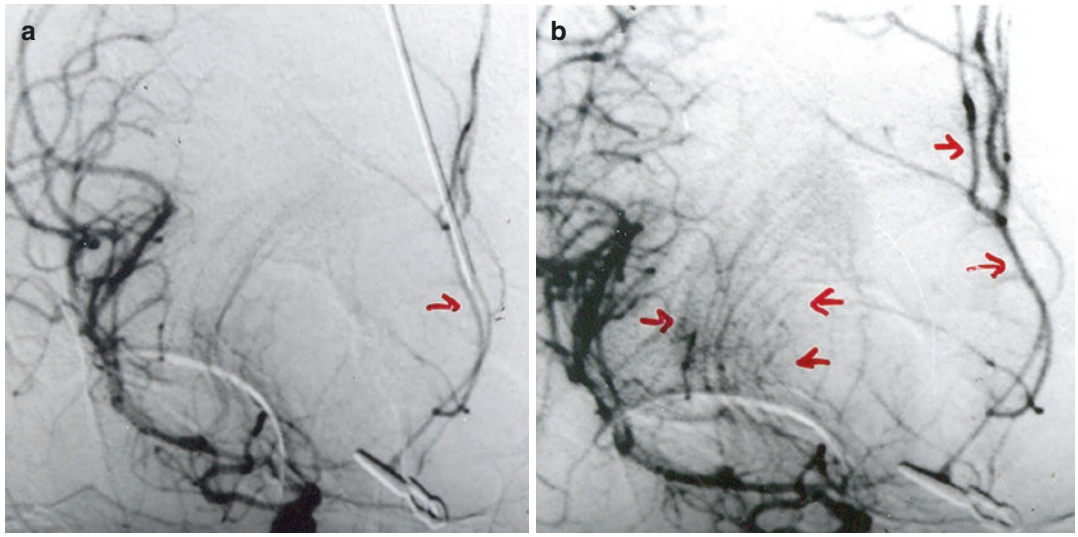


Fig. 2.3 (**a**, **b**) Treatment of vasospasm using NO donor. (**a**) Pre-treatment and (**b**) Post-treatment. Reversal of vasospasm in a clipped patient with TCD value of 300 cm/s using intrathecal NO donor (sodium Nitroprusside) instillation. Note may be made on the effect of therapy on perforators

vasospasm. Hence, any therapy to augment the availability of NO would be a logical and efficacious way to prevent or reverse vasospasm [91]. The main hurdle is the ultra-short life of NO which remains active for a very brief period. Accordingly, intrathecal instillation of sodium nitroprusside as a potent NO donor was carried out in a study with very good angiographic evidence of reversal of vasospasm (Fig. 2.3). Though the study showed reversal of early vasospasm with its prevention in imminent cases, however, its role in refractory vasospasm was not established [92]. Other nitric oxide donors like $NaNO_2$ were reported to be useful in animal models [93], but its efficacy in humans is yet to be established.

2.6.5.2 Magnesium Sulfate

Magnesium is long known to be an important cation, which has a role in various metabolic processes. Its role resembling a physiological calcium antagonist [94] was intensely studied with considerable improvement in DCI and vasospasm in animal studies [95, 96]. Magnesium Sulfate ($MgSO_4$) was therefore put through Phase I and Phase II trials with potentially encouraging results. A subsequent Phase II trial IMASH (Intravenous Magnesium Sulfate for Aneurysmal Subarachnoid Hemorrhage) was undertaken which, however, failed to show any significant good outcome at 6 months [97]. A further MASH-II (Magnesium in Aneurysmal Subarachnoid Hemorrhage II Study) using Mg therapy for 20 days after SAH failed to demonstrate any beneficial effect [98]. The lower CSF penetration and the side effects of Mg therapy were considered as important reasons for the suboptimal response.

2.7 Treatment Regime for SAH/Vasospasm

2.7.1 Optimizing Physiological Disruption

2.7.1.1 Catecholamine Surge and Increased Sympathetic Activity

SAH is associated with increased catecholamine surge, which has a bearing on the prognosis [99, 100]. This in turn enhances sympathetic activity manifested in the form of cardiovascular changes recorded in ECG and also neurogenic pulmonary

edema in severe cases [101]. Hence, close monitoring of cardiac and pulmonary function is of utmost importance specifically in patients manifesting with extracranial sympathetic manifestations and appropriate remedial measures are to be instituted, e.g., positive pressure ventilation for neurogenic pulmonary edema.

2.7.1.2 Controlling Body Temperature

Fever is a recognized entity in SAH which is common in patients with poor grade SAH or intraventricular hematomas [102]. For every degree Celsius change in body temperature, the glucose utilization demand in different areas of brain increases by 5 to 10%. Poor outcome has been documented with patients of SAH associated with fever [103]. Contrarily hypothermia has a protective effect on brain by reducing the rate of metabolism and free radical production, maintaining integrity of blood–brain barrier and aerobic metabolism and also lowering excitatory neurotransmitters release [104, 105]. The role of targeted temperature control therapy, therefore, is claimed in several studies to have a significantly beneficial role in restoring the alteration in brain metabolism secondary to SAH [106–108].

2.7.1.3 Electrolyte Management

Fluctuation in serum sodium levels is well known in SAH with observation of initial rise followed by significant fall in the second week [109]. The reason for hyponatremia is related to various factors which include cerebral salt wasting syndrome, SIADH, glucocorticoid deficiency. Despite hyponatremia being a known cause of reduced cerebral function and infarction of the brain, its contribution to poor outcomes is not clear [110].

Hypernatremia is commonly a manifestation of hypothalamic insult and may be associated with diabetes insipidus. It has been shown to have a poor outcome as per studies available [111, 112]. Based on the above observations serum sodium level within the normal physiological range is ideal even though the exact relationship of sodium imbalance with outcome is not fully established.

2.7.1.4 Maintaining Cerebral Perfusion

To counter the effects of decreased perfusion and poor blood flow secondary to vasospasm and DCI the triple H therapy (Hypervolemia, Hypertension, and Hemodilution) was in vogue with the aim to improve circulatory blood volume, cerebral perfusion pressure, and reduce the viscosity of blood. Low molecular weight dextran, mannitol, and albumin were used for volume expansion as a routine measure in the past. However, there was mounting evidence that hypervolemia and hemodilution were not be of much benefit [113, 114] with convincing evidence to suggest harmful effects of hemodilution [115, 116]. Hence induced hypertension, to maintain a high mean arterial pressure (MAP), remains one of the efficacious components of the regime, which is followed routinely in most of the centers [115]. Maintaining a high level of hemoglobin has also been seen to have contributed to better outcomes [116]. Since cerebral perfusion is guided by a balance between the intracranial pressure and the MAP there remains a role of anti-edema measures through pharmacological means as well as ventilation. Mannitol, which is a commonly used drug to reduce ICP, was also popular because of its volume expansion effect. However, there remains a concern in long-term use of mannitol due to its effect on blood rheology through serum osmolality changes, electrolyte imbalance, and rebound rise in ICP after its withdrawal. ICP reduction, in order to improve cerebral perfusion, is therefore better managed through controlled ventilation.

2.7.1.5 Calcium Channel Antagonists

Calcium channel blockers are known to act on the “slow calcium” channels and hence have a relaxing effect on vascular smooth muscles and cardiac muscles without any effect on skeletal muscle. Apart from their action on smooth muscle vasculature they are known to play a significant role in blood rheology, calcium entry in ischemic cells, dilation of collateral leptomeningeal vessels, and platelet aggregation [117–119].

2.7.1.6 Nimodipine

Dihydropyridine calcium antagonists are known to reduce spasm of vascular smooth muscles and amongst them nimodipine has been proved to have class I evidence to be efficacious in significant number of cases, more so, if it is prophylactically started on the day of SAH [78, 95, 113, 120, 121]. Nimodipine has been shown to also improve outcomes in DCI as it demonstrates a neuroprotective effect through a reduction in the degree of apoptosis by decreasing Ca influx and antiplatelet aggregation properties and also by improving collateral channels and blood rheology. Results of the British aneurysm nimodipine trial substantiate these facts with a significant reduction in incidence infarction and improvement in outcome [122, 123]. The treatment with nimodipine has shown to be cost-effective also with nominal side effects [124].

Nimodipine is administered by oral or intravenous route, ideally in an ICU setting, and the recommended dose is 60 mg every 4 hourly. In case this dose interferes with maintenance of desired MAP, required for sustained cerebral perfusion, a revised dose of 30 mg every 2 to 4 hourly may be administered under strict monitoring.

2.7.2 Strategies to Reduce Blood Load in Subarachnoid Space

2.7.2.1 Lumbar Drain

Since free blood remains the main spasmogenic source in the subarachnoid space (SAS) studies were conducted to reduce the blood load around the vessels in order to attenuate the harmful effect of blood or its products. The EARLY DRAIN Trial (Early Lumbar Cerebrospinal Fluid Drainage in Aneurysmal Subarachnoid Haemorrhage Trial) [125] and the LUMAS trial (Lumbar Drainage in Subarachnoid Haemorrhage Trial) [126] were instituted to look for decrease in the incidence of DCI and improved early clinical outcome. Both the studies were found to be safe and showed a reduction in the incidence of DCI with improvement in early clinical outcomes. However, the long-term clinical outcome did not reveal any significant improvement. Even then, the use of lumbar drain and removal of blood load in the basal cisterns during open surgery is still practiced by many clinicians with disputed claims of achieving lower incidence of ischemia and vasospasm [78]. However, one needs to be cautious as too much drainage of CSF is found to be associated with shunt dependency [126].

2.7.2.2 Cisternal Lavage and Local Thrombolytics

Studies conducted to look for efficacy of cisternal and ventricular lavage, mechanical agitation (kinetic therapy), and use of local thrombolytics were analyzed to see for reduction in DCI and improvement in outcome. The studies definitely suggest improvement in early outcome and reduced incidence of vasospasm in the group who are subjected to cisternal and/or ventricular lavage with added kinetic therapy. However, there are limitations of these procedures as it involves potential risk of infection and is a subject of logistic debate in patients who are treated purely be radiological intervention.

2.7.3 Intrathecal Treatment Options

2.7.3.1 Intrathecal Thrombolysis

Early and quick resolution of blood in subarachnoid space seems to be an attractive alternative to clear the blood from the thecal space. Several studies were undertaken using intracisternal thrombolysis using urokinase or tissue plasminogen activator to lyse the clot from the cisternal/intraventricular space. Recent meta-analysis suggests a clear advantage of intrathecal fibrinolysis showing improved functional outcome with lower mortality risk and lesser incidence of hydrocephalus [127, 128]. Despite claims of efficacy in this management, issues related to inconsistency of technical aspects cast a doubt on safety and side effects, infection and hemorrhage being of serious concern. A prospective randomized control trial on intraventricular thrombolysis is already underway to answer these important issues [129].

2.7.3.2 Intrathecal Nicardipine

Nicardipine, a calcium channel blocker which is used to treat hypertension and chronic angina, has been tried to treat vasospasm after SAH [130, 131]. The drug was used as a slow-release loaded polymer for local release which demonstrated promising results. However, the problems of logistics in delivery and its efficacy in the distant vascular tree, especially with thick load of blood clot in subarachnoid space around the vessel precluded it from coming into regular use.

2.7.4 Endovascular Intervention for Vasospasm

Endovascular treatment options for vasospasm are considered when the other options do not yield encouraging response to the clinician, even though they are not bereft of side effects and complications. The options include the use of intra-arterial drug infusions and balloon angioplasty [132, 133].

2.7.5 Role of Intra-arterial Pharmacotherapy

2.7.5.1 Intra-arterial Nimodipine

Since nimodipine is considered to be of proven efficacy as a calcium channel blocker its role in preventing and reversing vasospasm has been very much tried in various studies with reasonable success in controlling and reversing vasospasm specifically when it is in mild or moderate form. However, its efficacy in severe vasospasm with advanced DCI is not very well established. In a single-center study conducted in the recent past using intra-arterial nimodipine for vasospasm the outcome was good in 73.8% of patients [134].

2.7.5.2 Papaverine

Papaverine (a nonspecific phosphodiesterase inhibitor) which is a potent vasodilator was initially considered a useful agent for intra-arterial use. Though good vasodilation was achieved, the effect of the drug was short-lasting [135]. Moreover, intra-arterial papaverine did not last the test of time because of issues of unpredictable complications, e.g., systemic hypotension, brainstem function depression, seizures [136]. A comparison of intra-arterial papaverine and nimodipine was studied to see for the efficacy of each agent. Though papaverine has a diffuse effect on all the vessels in comparison to nimodipine (83%), there was no demonstrable difference in perfusion at the capillary level [137].

2.7.5.3 Milrinone

Milrinone, a phosphodiesterase III inhibitor, is widely used to treat patients with acute cardiac failure having a dual role of vasodilation and inotropic effect. This therapy has shown significant improvement in the patients of vasospasm including refractory vasospasm in patients of poor grade SAH [138]. Safety and efficacy of milrinone are being assessed in MilriSpasm Trial (Safety of Intravenous Milrinone for the Treatment of Subarachnoid Hemorrhage-induced Vasospasm) is due to complete in early 2021. The drug seems to hold a promise in reversing vasospasm through chemical angioplasty.

2.7.5.4 Balloon Angioplasty

Balloon angioplasty remains an important option for refractory vasospasm when pharmacotherapy fails. Though it gives relief from focal vasospasm it may not be very useful in diffuse vasospasm particularly if it involves distal vessels. More so, this therapy is ideally to be implemented in centers which are equipped with the facility and expertise. The procedure is not without any risk or failures and hence may need to be repeated several times during the phase of acute vasospasm. The controversy remains in the timing of mechanical balloon dilation where studies have shown the procedure to be effective if performed within the first 2 h of onset of vasospasm in contrast to that performed within 24 h [132, 139].

If normal or supranormal diameter of the vessel is achieved at initial angioplasty then subsequent need for angioplasty can be obviated in contrast to a subnormal dilatation where repeat dilations may be necessary [140]. The main limitation of mechanical angioplasty is in its effec-

tiveness mainly in short segment vasospasm and it remains technically difficult to exploit its role in vasospasm involving long arterial segments or distal vessels. Hence, a combination of intra-arterial mechanical dilation and infusion using nimodipine was found to be more effective than isolated use of individual modalities and the effect was most pronounced on ICA and BA [141]. However, the procedure of mechanical angioplasty needs to be done with caution as there are reported complications which include perforation and rupture of vessels, occlusion, stroke, dissection, displacement of aneurysm clips. [144.] Attempts for prophylactic dilation of major vessels to prevent vasospasm did not yield the desired outcome of preventing delayed ischemia of the brain [132].

The Invasive Diagnostic and Therapeutic Management of Cerebral Vasospasm After Aneurysmal Subarachnoid Haemorrhage trial (IMCVS) to sort out the optimal treatment modality has not been able to provide a defined guideline for treatment in individual cases [142]. However, endovascular treatment for vasospasm remains an effective alternative in situations of refractory vasospasm with comparatively better functional outcome [143].

2.8 Conclusion

Vasospasm, which is an important cause of morbidity and mortality, remains a major challenge in patients of SAH. Over the decades there is a definite improvement in outcome because of better perioperative management using aggressive treatment and prevention protocols. Understanding of the pathophysiological changes after SAH and identification of various substrates involved in its genesis has helped in formulating management guidelines yielding better outcome. The identity of primary trigger spasmogenic molecules remains illusive, and the cascading events initiated by activation of various biochemical pathways starting from release of oxyhemoglobin to oxygen free radicals and their consequences are yet to be precisely understood. In comparison to the past, the molecular changes and their impact are now better revealed but there has been no breakthrough in countering their impact on the brain. As various trials to date have failed to come out with a panacea the age-old concept of augmentation of cerebral perfusion, creation of an optimal milieu for the brain parenchyma still remains an important strategy for ICU management. Nimodipine is the only drug with proven efficacy but it fails to ameliorate all stages of vasospasm especially the refractory group. Hence, the emerging concept of "Early Brain Injury" and its prevention remains a major target for timely institution of treatment strategies in such patients.

References

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis the Lancet. Neurology. 2011 Jul;10(7):626–36. https://doi.org/10.1016/S1474-4422(11)70109-0.
2. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish Cohort Study. Stroke. 2014;45:1958–63. https://doi.org/10.1161/STROKEAHA.114.005318.
3. Mensing LA, Greving JP, Verhoeff TA, Rinkel GJE, Ruigrok YM. Comparison of rupture risk of intracranial aneurysms between familial and sporadic patients. Stroke. 2019;50:1380–3. https://doi.org/10.1161/STROKEAHA.118.023783.
4. Karenberg A, Moog FP. Die Apoplexieimmedizinischen Schrifttum der Antike. Apoplexy in Ancient Medical Writings. Fortschritte der Neurologie-Psychiatrie. 1997;65(11):489–503. https://doi.org/10.1055/s-2007-996355.
5. Lawton MT, Vates GE. Subarachnoid hemorrhage. New Engl J Med. 2017;377:257–66. https://doi.org/10.1056/NEJMcp1605827.
6. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke. 2008 Nov;39(11):3015–21. https://doi.org/10.1161/STROKEAHA.108.519942.
7. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, et al. Clazosentan, an

endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011 Jul;10(7):618–25. https://doi.org/10.1016/S1474-4422(11)70108-9.
8. Dorsch N. Therapeutic approaches to vasospasm in subarachnoid hemorrhage. Curr Opin Crit Care. 2002 Apr;8(2):128–33. https://doi.org/10.1097/00075198-200204000-00007.
9. Ecker A, Rimenschneider P. Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysms. J Neurosurg. 1951 Nov;8(6):660–7. https://doi.org/10.3171/jns.1951.8.6.0660.
10. Weir B, Grace M, Hansen J, et al. Time course of vasospasm in man. J Neurosurg. 1978 Feb;48(2):173–8. https://doi.org/10.3171/jns.1978.48.2.0173.
11. Nornes H. The role of intracranial pressure in the arrest of hemorrhage in patients with ruptured intracranial aneurysms. J Neurosurg. 1973;39:226–34. https://doi.org/10.3171/jns.1973.39.2.0226.
12. Trojanowski T. Blood Elsevier brain barrier changes after experimental subarachnoid hemorrhage. Acta Neurochirurgica (Wien). 1982;60(1–2):45–54. https://doi.org/10.1007/BF01401749.
13. Baldwin ME, Loch Macdonald R, Huo D, Novakovia RL, Goldenberg FD, Frank JI, Rosengart AJ. Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. Stroke. 2004 Nov;35(11):2506–11. https://doi.org/10.1161/01.STR.0000144654.79393.cf.
14. Dreier JP, Ebert N, Priller J, Megow D, Lindauer U, Klee R, Reuter U, Imai Y, Einhäupl KM, Victorov I, Dirnagl U. Products of hemolysis in the subarachnoid space inducing spreading ischemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? J Neurosurg. 2000 Oct;93(4):658–66. https://doi.org/10.3171/jns.2000.93.4.0658.
15. Ostrowski RP, Colohan AR, Zhang JH. Molecular mechanisms of early brain injury after subarachnoid hemorrhage. Neurol Res. 2006 Jun;28(4):399–414. https://doi.org/10.1179/016164106X115008.
16. Geraghty JR, Testai FD. Delayed cerebral ischemia after subarachnoid hemorrhage: beyond vasospasm and towards a multifactorial pathophysiology. Curr Atheroscler Rep. 2017 Oct 23;19(12):50. https://doi.org/10.1007/s11883-017-0690-x.
17. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet. 2017;389:655–66.
18. Fujii M, Yan J, Rolland WB, Soejima Y, Caner B, Zhang JH. Early brain injury, an evolving frontier in subarachnoid hemorrhage research. Transl Stroke Res. 2013 Aug;4(4):432–46. https://doi.org/10.1007/s12975-013-0257-2.
19. Seifert V, Löffler B-M, Zimmermann M, Roux S, Stolke D. Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage: correlation with cerebral vasospasm, delayed ischemic neurological deficits and volume of hematoma. J Neurosurg. 1995 Jan;82(1):55–62. https://doi.org/10.3171/jns.1995.82.1.0055.
20. Zuccarello M, Bonasso C, Lewis A, Sperelakis N, Rapoport RM. Relaxation of subarchnoid hemorrhage-induced spasm of rabbit basilar artery by the K^+ channel activator cromakalim. Stroke. 1996 Feb;27(2):311–6. https://doi.org/10.1161/01.str.27.2.311.
21. Sehba F, Bederson J. Mechanisms of acute brain injury after subarachnoid hemorrhage. Neurol Res. 2006 Jun;28(4):381–98. https://doi.org/10.1179/016164106X114991.
22. Cahill WJ, Calvert JH, Zhang JH. Mechanisms of early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2006 Nov;26(11):1341–53. https://doi.org/10.1038/sj.jcbfm.9600283.
23. Turner C, Bergeron M, Matz P, et al. Heme oxygenase-1 is induced in glia throughout brain by subarachnoid hemoglobin. J Cereb Blood Flow Metab. 1998 Mar;18(3):257–73. https://doi.org/10.1097/00004647-199803000-00004.
24. Vikman P, Beg S, Khurana T, Hansen-Schwartz J, Edvinsson L. Gene expression and molecular changes in cerebral arteries following subarachnoid hemorrhage in the rat. J Neurosurg. 2006 Sep;105(3):438–44. https://doi.org/10.3171/jns.2006.105.3.438.
25. Dietrich H, Dacey R. Molecular keys to the problems of cerebral vasospasm. Neurosurgery. 2000 Mar;46(3):517–30. https://doi.org/10.1097/00006123-200003000-00001.
26. Clark JF, Sharp FR. Bilirubin oxidation products (BOXes) and their role in cerebral vasospasm after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2006 Oct;26(10):1223–33. https://doi.org/10.1038/sj.jcbfm.9600280.
27. Sharkey J, Butcher SP, Kelly JS. Endothelin-1 induced middle cerebral artery occlusion: pathological consequences and neuroprotective effects of MK801. J Auton Nerv Syst. 1994 Sep;49(Suppl):S177–85. https://doi.org/10.1016/0165-1838(94)90109-.
28. Gaetani P, Rodriguez y Baena R, Grignani G, Spanu G, Pacchiarini L and Paoletti P. Endothelin and aneurysmal subarachnoid haemorrhage: a study of subarachnoid cisternal cerebrospinal fluid. J Neurol Neurosurg Psychiatry. 1994;57:66–72.
29. Hansen-Schwartz J, Hoel NL, Zhou M, Xu CB, Svendgaard NA, Edvinsson L. Subarachnoid hemorrhage enhances endothelin receptor expression and function in rat cerebral arteries. Neurosurgery. 2003 May;52(5):1188–94.
30. Rothoerl RD, Ringel F. Molecular mechanisms of cerebral vasospasm following aneurysmal SAH. Neurol Res. 2007 Oct;29(7):636–42. https://doi.org/10.1179/016164107X240224.

31. Grassie ME, Moffat LD, Walsh MP, MacDonald JA. The myosin phosphatase targeting protein (MYPT) family: a regulated mechanism for achieving substrate specificity of the catalytic subunit of protein phosphatase type 1delta. Arch Biochem Biophys. 2011 Jun 15;510(2):147–59.
32. Miao L, Dai Y, Zhang J. Mechanism of RhoA/Rho kinase activation in endothelin-1-induced contraction in rabbit basilar artery. Am J Physiol Heart Circ Physiol. 2002 Sep;283(3):H983–9. https://doi.org/10.1152/ajpheart.00141.2002.
33. Kikkawa Y, Matsuo S, Kameda K, Hirano M, Nakamizo A, Sasaki T, Hirano K. Mechanisms underlying potentiation of endothelin-1-induced myofilament Ca(2+) sensitization after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2012 Feb;32(2):341–52. https://doi.org/10.1038/jcbfm.2011.132.
34. Nakamura K, Koga Y, Sakai H, Homma K, Ikebe M. cGMP-dependent relaxation of smooth muscle is coupled with the change in the phosphorylation of myosin phosphatase. Circ Res. 2 Aug 2007;(101):712–22. https://doi.org/10.1161/CIRCRESAHA.107.153981.
35. Zhou C, Yamaguchi M, Kusaka G, Schonholz C, Nanda A, Zhang JH. Caspase inhibitors prevent endothelial apoptosis and cerebral vasospasm in dog model of experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2004 Apr;24(4):419–31. https://doi.org/10.1097/00004647-200404000-00007.
36. Zubkov AY, Ogihara K, Bernanke DH, Parent AD, Zhang J. Apoptosis of endothelial cells in vessels affected by cerebral vasospasm. Surg Neurol. 2000 Mar;53(3):260–6. https://doi.org/10.1016/s0090-3019(99)00187-1.
37. Kimura H, Gules I, Meguro T, Zhang JH. Cytotoxicity of cytokines in cerebral microvascular endothelial cell. Brain Res. 2003 Nov 14;990(1–2):148–56. https://doi.org/10.1016/s0006-8993(03)03450-4.
38. Iseda K, Ono S, Onoda K, Satoh M, Manabe H, Nishiguchi M, Takahashi K, Tokunaga K, Sugiu K, Date I. Antivasospastic and antiinflammatory effects of caspase inhibitor in experimental subarachnoid hemorrhage. J Neurosurg. 2007 Jul;107(1):128–35. https://doi.org/10.3171/JNS-07/07/0128.
39. Satoh S, Suzuki Y, Harada T, Ikegaki I, Asano T, Shibuya M, Sugita K, Saito A. The role of platelets in the development of cerebral vasospasm. Brain Res Bull. 1991 Nov;27(5):663–8. https://doi.org/10.1016/0361-9230(91)90042-i.
40. Takeuchi H, Tanabe M, Okamoto H, Yamazaki M. Effects of thromboxane synthetase inhibitor (RS-5186) on experimentally-induced cerebral vasospasm. Neurol Res. 1999 Jul;21(5):513–6.
41. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, Fritzinger M, Horn P, Vajkoczy P, Wendel-Wellner M, Ragoschke A, Kuehl S, Brunner J, Schurer L, Schmiedeck P, Hennerici M. Endothelin-1 in subarachnoid hemorrhage: an acute-phase reactant produced by cerebrospinal fluid leukocytes. Stroke. 2000 Dec;31(12):2971–5. https://doi.org/10.1161/01.str.31.12.2971.
42. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, Lee KS. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. J Neurosurg. 1998 Oct;89(4):559–67. https://doi.org/10.3171/jns.1998.89.4.0559.
43. Bavbek M, Polin R, Kwan AL, Arthur AS, Kassell NF, Lee KS. Monoclonal antibodies against ICAM-1 and CD18 attenuate cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. Stroke. 1998 Sep;29(9):1930–5. https://doi.org/10.1161/01.str.29.9.1930.
44. Prunell GF, Svendgaard NA, Alkass K, Mathiesen T. Inflammation in the brain after experimental subarachnoid hemorrhage. Neurosurgery. 2005 May;56(5):1082–92.
45. Allen BG, Walsh MP. The biochemical basis of the regulation of smooth-muscle contraction. Trends Biochem Sci. 1994 Sep;19(9):362–8. https://doi.org/10.1016/0968-0004(94)90112-0.
46. Hoffman WE, Wheeler P, Edelman G, Charbel FT, Torres NJ, Ausman JI. Hypoxic brain tissue following subarachnoid hemorrhage. Anesthesiology. 2000 Feb;92(2):442–6. https://doi.org/10.1097/00000542-200002000-00026.
47. Park S, Yamaguchi M, Zhou C, Calvert JW, Tang J, Zhang JH. Neurovascular protection reduces early brain injury after subarachnoid hemorrhage. Stroke. 2004;35(2412–2417) https://doi.org/10.1161/01.STR.0000141162.29864.e9.
48. Jan Claassen J, Carhuapoma R, Kreiter KT, Du EY, Sander Connolly E, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke. 2002;33:1225–32. https://doi.org/10.1161/01.STR.0000015624.29071.1F.
49. Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda, MD). 2009 Apr;24:97–106. https://doi.org/10.1152/physiol.00045.2008.
50. Schmidt-Kastner R, Aguirre-Chen C, Kietzmann T, Saul I, Busto R, Ginsberg MD. Nuclear localization of the hypoxia-regulated pro-apoptotic protein BNIP3 after global brain ischemia in the rat hippocampus. Brain Res. 2004 Mar 19;1001(1–2):133–42. https://doi.org/10.1016/j.brainres.2003.11.065.
51. Yan J, Chen C, Lei J, Yang L, Wang K, Liu J, Zhou C. 2-methoxyestradiol reduces cerebral vasospasm after 48 hours of experimental subarachnoid hemorrhage in rats. Exp Neurol. 2006;202(2):348–56.
52. Cahill J, Calvert JW, Solaroglu I, Zhang JH. Vasospasm and p53-induced apoptosis in an experimental model of subarachnoid hemorrhage. Stroke. 2006 Jul;37(7):1868–74. https://doi.org/10.1161/01.STR.0000226995.27230.96.

53. Cahill J, Calvert JW, Marcantonio S, Zhang JH. p53 may play an orchestrating role in apoptotic cell death after experimental subarachnoid hemorrhage. Neurosurgery. 2007 Mar;60(3):531–45. https://doi.org/10.1227/01.NEU.0000249287.99878.9B.
54. Pearl JD, Macdonald RL. Vasospasm after aneurysmal subarachnoid hemorrhage: need for further study. Acta Neurochir Suppl. 2008;105:207–10.
55. Guney O, Erdi F, Esen H, Kiyici A, Kocaogullar Y. N-acetylcysteine prevents vasospasm after subarachnoid hemorrhage. World Neurosurg. 2010 Jan;73(1):42–9. https://doi.org/10.1016/j.surneu.2009.06.003.
56. Munakata A, Ohkuma H, Shimamura N. Effect of a free radical scavenger, edaravone, on free radical reactions: related signal transduction and cerebral vasospasm in the rabbit subarachnoid hemorrhage model. Acta Neurochir Suppl. 2011;110(Pt 2):17–22. https://doi.org/10.1007/978-3-7091-0356-2_4.17-22.
57. Hofmann F. The biology of cyclic GMP-dependent protein kinases. J Biol Chem. 2005 Jan;280(1):1–4. https://doi.org/10.1074/jbc.R400035200.
58. Kehl F, Cambj-Sapunar L, Maier KG, Miyata N, Kametani S, Okamoto H, Hudetz AG, Schulte ML, Zagorac D, Harder DR, Roman RJ. 20-HETE contributes to the acute fall in cerebral blood flow after subarachnoid hemorrhage in the rat. Am J Physiol Heart Circ Physiol. 2002 Apr;282(4):H1556–65. https://doi.org/10.1152/ajpheart.00924.200.
59. Kim DE, Suh YS, Lee MS, Kim KY, Lee JH, Lee HS, Hong KW, Kim CD. Vascular NAD(P)H oxidase triggers delayed cerebral vasospasm after subarachnoid hemorrhage in rats. Stroke. 2002 Nov;33(11):2687–91. https://doi.org/10.1161/01.str.0000033071.99143.9e.
60. Zheng JS, Zhan RY, Zheng SS, Zhou YQ, Tong Y, Wan S. Inhibition of NADPH oxidase attenuates vasospasm after experimental subarachnoid hemorrhage in rats. Stroke. 2005 May;36(5):1059–64. https://doi.org/10.1161/01.STR.0000163102.49888.b7.
61. Pyne-Geithman GJ, Caudell DN, Prakash P, Clark JF. Glutathione peroxidase and subarachnoid hemorrhage: implications for the role of oxidative stress in cerebral vasospasm. Neurol Res. 2009 Mar;31(2):195–9. https://doi.org/10.1179/174313209X393906.
62. Pluta RM, Hansen-Schwartz J, Dreier J, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol Res. 2009 Mar;31(2):151–8. https://doi.org/10.1179/174313209X393564.
63. Andresen J, Shafi NI, Bryan RM Jr. Endothelial influences on cerebrovascular tone. J Appl Physiol. 2006 Jan;100(1):318–27. https://doi.org/10.1152/japplphysiol.00937.2005.
64. Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. J Neurosci Res. 2009 Jan;87(1):1–11. https://doi.org/10.1002/jnr.21823.
65. Leao AA. Spreading depression of activity in the cerebral cortex. J Neurophysiol. 1944;7:359–90.
66. Leao AA. Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol. 1947 Nov;10(6):409–14. https://doi.org/10.1152/jn.1947.10.6.409.
67. Dreier JP, Woitzik J, Fabricius M, Bhatia R, Major S, Drenckhahn C, Lehmann T-N, Sarrafzadeh A, Willumsen L, Hartings JA, Sakowitz OW, Seemann JH, Thieme A, Lauritzen M, Strong AJ. Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain. 2006 Dec;129(Pt 12):3224–37. https://doi.org/10.1093/brain/awl297.
68. Sotero RC, Trujillo-Barreto NJ. Biophysical model for integrating neuronal activity, EEG, fMRI and metabolism. Neuroimage. https://doi.org/10.1016/j.neuroimage.2007.08.001.
69. Filosa JA. Vascular tone and neurovascular coupling: considerations toward an improved in vitro model. Front Neuroenergetics. 2010;2:16. https://doi.org/10.3389/fnene.2010.00016.
70. Gardner-Medwin AR. Analysis of potassium dynamics in mammalian brain tissue. J Physiol. 1983 Feb;335:393–426. https://doi.org/10.1113/jphysiol.1983.sp014541.
71. Orellana JA, Sáez PJ, Shoji KF, Schalper KA, Palacios-Prado N, Velarde V, Giaume C, Bennett MVL, Sáez JC. Modulation of brain hemichannels and gap junction channels by pro-inflammatory agents and their possible role in neurodegeneration. Antioxid Redox Signal. 2009;11:369–99.
72. Lindauer U, Kunz A, Schuh-Hofer S, Vogt J, Dreier JP, Dirnagl U. Nitric oxide from perivascular nerves modulates cerebral arterial pH reactivity. Am J Physiol Heart Circ Physiol. 2001 Sep;281(3):H1353–63. https://doi.org/10.1152/ajpheart.2001.281.3.H1353.
73. Horiuchi T, Dietrich HH, Hongo K, Goto T, Dacey RG Jr. Role of endothelial nitric oxide and smooth muscle potassium channels in cerebral arteriolar dilation in response to acidosis. Stroke. 2002;33:844–9. https://doi.org/10.1161/hs0302.104112.
74. Lindauer U, Vogt J, Schuh-Hofer S, Dreier JP, Dirnagl U. Cerebrovascular vasodilation to extraluminal acidosis occurs via combined activation of ATP-sensitive and Ca^{2+}-activated potassium channels. J Cereb Blood Flow Metab. 2003;23:1227–38.
75. Celotto AC, Capellini VK, Baldo CF, Dalio MB, Rodrigues AJ, Evora PRB. Effects of acid-base imbalance on vascular reactivity. Braz J Med Biol Res. 2008 Jun;41(6):439–45. https://doi.org/10.1590/s0100-879x2008005000026.
76. Kleeberg J, Petzold GC, Major S, Dirnagl U, Dreier JP. ET-1 induces cortical spreading depression via

activation of the ETA receptor/phospholipase C pathway in vivo. Am J Physiol Heart Circ Physiol. 2004;286:H1339–46.
77. Yufu K, Itoh T, Edamatsu R, Mori A, Hirakawa M. Effect of hyperbaric oxygenation on the Na+, K(+)-ATPase and membrane fluidity of cerebrocortical membranes after experimental subarachnoid hemorrhage. Neurochem Res. 1993;18:1033–9.
78. Mortimer AM, Steinfort B, Faulder K, Bradford C, Finfer S, Assaad N, Harrington T. The detrimental clinical impact of severe angiographic vasospasm may be diminished by maximal medical therapy and intensive endovascular treatment. J Neurointerv Surg. 2015 Dec;7(12):881–7. https://doi.org/10.1136/neurintsurg-2014-011403.
79. Chugh C, Agarwal H. Cerebral vasospasm and delayed cerebral ischemia: Review of literature and the management approach. Neurol India. 2019;67(1):185–200. https://doi.org/10.4103/0028-3886.253627.
80. Treggiari MM. Hemodynamic management of subarachnoid hemorrhage. Neurocrit Care. 2011 Sep;15(2):329–35. https://doi.org/10.1007/s12028-011-9589-5.
81. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm after subarachnoid hemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir Suppl (Wien). 1988;42:81–4. https://doi.org/10.1007/978-3-7091-8975-7_16.
82. Meyer R, Deem S, Yanez ND, Souter M, Lam A, Treggiari MM. Current practices of triple-H prophylaxis and therapy in patients with subarachnoid hemorrhage. Neurocrit Care. 2011 Feb;14(1):24–36. https://doi.org/10.1007/s12028-010-9437-z.
83. Soustiel JF, Shik V, Shreiber R, Tavor Y, Goldsher D. Basilar vasospasm diagnosis. Stroke. 2002;33:72–8.
84. Kassell NF, Haley EC Jr, Apperson-Hansen C, Alves WM. Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. J Neurosurg. 1996 Feb;84(2):221–8. https://doi.org/10.3171/jns.1996.84.2.0221.
85. Pollock DM, Keith TL, Highsmith RF. Endothelin receptors and calcium signaling. FASEB J. 1995 Sep;9(12):1196–204. https://doi.org/10.1096/fasebj.9.12.7672512.
86. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, Vajkoczy P, Wanke I, Frey A, Marr A, Roux S, Kassell NF. Preventing vasospasm improves outcome after aneurysmal subarachnoid hemorrhage: rationale and design of CONSCIOUS-2 and CONSCIOUS-3 trials. Neurocrit Care. 2010 Dec;13(3):416–24. https://doi.org/10.1007/s12028-010.
87. Tseng MY. Summary of evidence on immediate statins therapy following aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011 Sep;15(2):298–301. https://doi.org/10.1007/s12028-011-9596-6.
88. Kirkpatrick PJ, Turner CL, Christopher Smith PJ, Hutchinson PG, Murray D. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet. 2014;13:666–75.
89. Kruuse C, Gupta S, Nilsson E, Kruse L, Edvinsson L. Differential vasoactive effects of sildenafil and tadalafil on cerebral arteries. Eur J Pharmacol. 2012 Jan 15;674(2–3):345–51. https://doi.org/10.1016/j.ejphar.2011.10.037.
90. Mukherjee KK, Singh SK, Khosla VK, Mohindra S, Salunke P. Safety and efficacy of sildenafil citrate in reversal of cerebral vasospasm: a feasibility study. Surg Neurol Int. 2012;3:3. https://doi.org/10.4103/2152-7806.92164.
91. Fathi AR, Bakhtian KD, Pluta RM. The role of nitric oxide donors in treating cerebral vasospasm after subarachnoid hemorrhage. Acta Neurochir Suppl. 2011;110(Pt 1):93–7. https://doi.org/10.1007/978-3-7091-0353-1_17.
92. Pathak A, Mathuriya SN, Khandelwal N, Verma K. Intermittent low dose intrathecal sodium nitroprusside therapy for treatment of symptomatic aneurysmal SAH-induced vasospasm. Br J Neurosurg. 2003 Aug;17(4):306–10. https://doi.org/10.1080/02688690310001601180.
93. Fathi AR, Pluta RM, Bakhtian KD, Qi M, Lonser RR. Reversal of cerebral vasospasm via intravenous sodium nitrite after subarachnoid hemorrhage in primates. J Neurosurg. 2011 Dec;115(6):1213–20. https://doi.org/10.3171/2011.7.JNS11390.
94. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984;108:188–93.
95. Castanares-Zapatero D, Hantson P. Pharmacological treatment of delayed cerebral ischemia and vasospasm in subarachnoid hemorrhage. Ann Intens Care. 2011;1:12. https://doi.org/10.1186/2110-5820-1-12.
96. Suarez JI. Magnesium sulfate administration in subarachnoid hemorrhage. Neurocrit Care. 2011 Sep;15(2):302–7. https://doi.org/10.1007/s12028-011-9603-y.
97. Wong GK, Poon WS, Chan MT, Boet R, Gin T, Ng SC, Zee BC. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. Stroke. 2010 May;41(5):921–6. https://doi.org/10.1161/STROKEAHA.109.571125.
98. Vergouwen MD. Magnesium sulfate for aneurysmal subarachnoid hemorrhage: the end of the road or more trials? Crit Care (London, Engl). 2011;15(2):140. https://doi.org/10.1186/cc10055.
99. Benedict CR, Loach AB. Sympathetic nervous system activity in patients with subarachnoid hemorrhage. Stroke. 1978;9(3):237–44. https://doi.org/10.1161/01.str.9.3.237.

100. Ogura T, Satoh A, Ooigawa H, Sugiyama T, Takeda R, Fushihara G, et al. Characteristics and prognostic value of acute catecholamine surge in patients with aneurysmal subarachnoid hemorrhage. Neurol Res. 2012 Jun;34(5):484–90. https://doi.org/10.1179/1743132812Y.0000000033.
101. Hall A, O'Kane R. The extracranial consequences of subarachnoid hemorrhage. World Neurosurg. 2018 Jan;109:381–92. https://doi.org/10.1016/j.wneu.2017.10.016.
102. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, Kreiter KT, Ostapkovich ND, Kowalski RG, Parra A, Sander Connolly E, Mayer SA. Fever after subarachnoid hemorrhage: risk factors and impact on outcome. Neurology. 2007 Mar 27;68(13):1013–9. https://doi.org/10.1212/01.wnl.0000258543.45879.f5.
103. Kramer CL, Pegoli M, Mandrekar J, Lanzino G, Rabinstein AA. Refining the association of fever with functional outcome in aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2017 Feb;26(1):41–7. https://doi.org/10.1007/s12028-016-0281-7.
104. Schubert GA, Poli S, Schilling L, Heiland S, Thomé C. Hypothermia reduces cytotoxic edema and metabolic alterations during the acute phase of massive SAH: a diffusion-weighted imaging and spectroscopy study in rats. J Neurotrauma. 2008;25:841–52.
105. Török E, Klopotowski M, Trabold R, Thal SC, Plesnila N, Schöller K. Mild hypothermia (33 °C) reduces intracranial hypertension and improves functional outcome after subarachnoid hemorrhage in rats. Neurosurgery. 2009;65:352–9.
106. Badjatia N, Fernandez L, Schmidt JM, Lee K, Claassen J, Connolly ES, Mayer SA. Impact of induced normothermia on outcome after subarachnoid hemorrhage: a case-control study. Neurosurgery. 2010;66(4):696–700. https://doi.org/10.1227/01.NEU.0000367618.42794.AA.
107. Kuramatsu JB, Kollmar R, Gerner ST, Madzar D, Pisarcikova A, Staykov D, et al. Is hypothermia helpful in severe subarachnoid hemorrhage? An exploratory study on macro vascular spasm, delayed cerebral infarction and functional outcome after prolonged hypothermia. Cerebrovasc Dis (Basel, Switzerland). 2015;40(5–6):228–35. https://doi.org/10.1159/000439178.
108. Choi W, Kwon SC, Lee WJ, CheolWeon Y, Choi B, Lee H, Park ES, Ahn R. Feasibility and safety of mild therapeutic hypothermia in poor-grade subarachnoid hemorrhage: prospective pilot study. J Kor Med Sci. 2017 Aug;32(8):1337–44. https://doi.org/10.3346/jkms.2017.32.8.1337.
109. Okazaki T, Hifumi T, Kawakita K, Shishido H, Ogawa D, Okauchi M. Atsushi Shindo, Masahiko Kawanishi, Takashi Tamiya, Yasuhiro Kuroda. Target serum sodium levels during intensive care unit management of aneurysmal subarachnoid hemorrhage. Shock. 2017 Nov;48(5):558–63. https://doi.org/10.1097/SHK.0000000000000897.
110. Shah K, Turgeon RD, Gooderham PA, Ensom MHH. Prevention and treatment of hyponatremia in patients with subarachnoid hemorrhage: a systematic review. World Neurosur. 2018;109:222–9.
111. Beseoglu K, Etminan N, Steiger HJ, Hanggi D. The relation of early hypernatremia with clinical outcome in patients suffering from aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg. 2014 Aug;123:164–8. https://doi.org/10.1016/j.clineuro.2014.05.022.
112. Spatenkova V, Bradac O, de Lacy P, Skrabalek P, Suchomel P. Dysnatremia as a poor prognostic indicator in patients with acute subarachnoid hemorrhage. J Neurosurg Sci. 2017 Aug;61(4):371–9. https://doi.org/10.23736/S0390-5616.16.03411-1.
113. Rabinstein AA, Lanzino G, Wijdicks EF. Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage. Lancet Neurol. 2010 May;9(5):504–19. https://doi.org/10.1016/S1474-4422(10)70087-9.
114. Wolf S. Routine management of volume status after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011 Jul;10(7):626–36. https://doi.org/10.1016/S1474-4422(11)70109-0.
115. Diringer MN, Bleck TP, Claude Hemphill J, Menon D, Shutter L, Vespa P, Bruder N, Connolly ES Jr, Citerio G, Gress D, Hanggi D, Hoh BL, Lanzino G, Le Roux P, Rabinstein A, Schmutzhard E, Stocchetti N, Suarez JI, Treggiari M, Tseng MY, Vergouwen MD, Wolf S, Zipfel G. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15:211–40.
116. Chittiboina P, Conrad S, McCarthy P, Nanda A, Guthikonda B. The evolving role of hemodilution in treatment of cerebral vasospasm: a historical perspective. World Neurosurg. 2011;75(5–6):660–4. https://doi.org/10.1016/j.wneu.2011.02.019.
117. Schanne FA, Kane AB, Young EE, Farber JL. Calcium dependence of toxic cell death: a final common pathway. Science (New York, NY). 1979 Nov 9;206(4419):700–2. https://doi.org/10.1126/science.386513.
118. Auer LM. Pial arterial vasodilation by intravenous nimodipine in cats. Arzneimittelforschung. 1981;31(9):1423–5.
119. Dale J, Landmark KH, Myhre E. The effects of nifedipine, a calcium antagonist, on platelet function. Am Heart J. 1983 Jan;105(1):103–5. https://doi.org/10.1016/0002-8703(83)90285-5.
120. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC. Cerebral arterial spasm: A controlled trial of nimodipine in patients with subarachnoid hemorrhage. New Engl J Med. 1983 Mar 17;308(11):619–24. https://doi.org/10.1056/NEJM198303173081103.

121. Mees SMD, Rinkel GJE, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007 Jul 18;2007(3):CD000277. https://doi.org/10.1002/14651858.CD000277.
122. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989 Mar 11;298(6674):636–42. https://doi.org/10.1136/bmj.298.6674.636.
123. Murray GD. Surgical bleeding and calcium antagonists. British aneurysm nimodipine trial reported improved clinical outcome with nimodipine. Br Med J. 1995; https://doi.org/10.1136/bmj.311.7001.388c.
124. Karinen P, Koivukangas P, Ohinmaa A, Koivukangas J, Ohman J. Cost-effectiveness analysis of nimodipine treatment after aneurysmal subarachnoid hemorrhage and surgery. J Neurosurg. 1988 Nov;69(5):683–6. https://doi.org/10.3171/jns.1988.69.5.0683.
125. Bardutzky J, Witsch J, Juttler E, Schwab S, Vajkoczy P, Wolf S. EARLYDRAIN- outcome after early lumbar CSF-drainage in aneurysmal subarachnoid hemorrhage: study protocol for a randomized controlled trial. Randomized Controlled Trials. 2011;12:203.
126. Al-Tamimi YZ, Bhargava D, Feltbower RG, Hall G, Goddard AJ, Quinn AC. Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial (LUMAS). Stroke. 2012 Mar;43(3):677–82. https://doi.org/10.1161/STROKEAHA.111.625731.
127. Yamamoto T, Esaki T, Nakao Y, Mori K. Efficacy of low-dose tissue-plasminogen activator intracisternal administration for the prevention of cerebral vasospasm after subarachnoid hemorrhage. World Neurosurg. 2010;73:675–82. https://doi.org/10.1016/j.wneu.2010.04.002.
128. Lu X, ChengyuanJi JW, You W, Wang W, Wang Z, Chen G. Intrathecal fibrinolysis for aneurysmal subarachnoid hemorrhage: evidence from randomized controlled trials and Cohort studies. Front Neurol. 2019;10:885. https://doi.org/10.3389/fneur.2019.00885.
129. Gaberel T. Intraventricular Fibrinolysis for Aneurysmal Subarachnoid Hemorrhage (FIVHeMA). Available online https://clinicaltrials.gov/ct2/show/NCT03187405. Accessed 01 February 2019.
130. Kasuya H, Onda H, MikihikoTakeshita YO, Hori T. Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans. Stroke. 2002 Apr;33(4):1011–105. https://doi.org/10.1161/01.str.0000014563.75483.22.
131. Kasuya H, Onda H, Sasahara A. Application of nicardipine prolonged-release implants: analysis of 97 consecutive patients with acute subarachnoid hemorrhage. Neurosurgery. 2005 May;56(5):895–902.
132. Rosenwasser RH, Armonda RA, Thomas JE, Benitez RP, Gannon PM, Harrop J. Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options. Neurosurgery. 1999;44:975–9.
133. Zwienenberg-Lee M, Hartman J, Rudisill N, Madden LK, Smith K, Eskridge J. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial. Stroke. 2008;39:1759–65.
134. Narayan V, Pendharkar H, Devi BI, Bhat DI, Shukla DP. Aggressive management of vasospasm with direct intra-arterial nimodipine therapy. Neurol India. 2018;66(2):416–22.
135. Vajkoczy P, Horn P, Bauhuf C, Munch E, Hubner U, Ing D, Thome C, Poeckler-Schoeninger C, Roth H, Schmiedek P. Effect of intra-arterial papaverine on regional cerebral blood flow in hemodynamically relevant cerebral vasospasm. Stroke. 2001;32:498–50. https://doi.org/10.1161/01.STR.32.2.498.
136. Firlik KS, Kaufmann AM, Firlik AD, Jungreis CA, Yonas H. Intra-arterial papaverine for the treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Surg Neurol. 1999 Jan;51(1):66–74. https://doi.org/10.1016/s0090-3019(97)00370-4.
137. Kerz T, Boor S, Beyer C, Welschehold S, Schuessler A, Oertel J. Effect of intraarterial papaverine or nimodipine on vessel diameter in patients with cerebral vasospasm after subarachnoid hemorrhage. Br J Neurosurg. 2012 Aug;26(4):517–24. https://doi.org/10.3109/02688697.2011.6507373.
138. Abulhasan YB, Jimenez JO, Teitelbaum J, Simoneau G, Angle MR. Milrinone for refractory cerebral vasospasm with delayed cerebral ischemia. J Neurosurg. 134(3):971–82.
139. Bejjani GK, Bank WO, Olan WJ, Sekhar LN. The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery. 1998;42:979–86.
140. Miley JT, Tariq N, Souslian FG, Qureshi N, Suri MF, Tummala RP. Comparison between angioplasty using compliant and noncompliant balloons for treatment of cerebral vasospasm associated with subarachnoid hemorrhage. Neurosurgery. 2011 Dec;69(2 Suppl):ons161-8. https://doi.org/10.1227/NEU.0b013e31822a8976.
141. Kerz T, Boor S, Ulrich A, Beyer C, Hechtner M, Mueller-Forell W. Endovascular therapy for vasospasm after aneurysmatic subarachnoid hemorrhage.

Br J Neurosurg. 2016 Oct;30(5):549–53. https://doi.org/10.3109/02688697.2016.1173193.

142. The invasive diagnostic and therapeutic management of cerebral vasospasm after aneurysmal subarachnoid haemorrhage trial (IMCVS) as cited by Chandril Chugh, Himanshu Agarwal in Cerebral vasospasm and delayed cerebral ischemia: Review of literature and the management approach. Neurol India. 2019; 67(1):185–200.

143. Sokolowski JD, Chen C-J, Ding D, Buell TJ, Raper DM, Ironside N, Taylor DG, Starke RM, Liu K. Endovascular treatment for cerebral vasospasm following aneurysmal subarachnoid hemorrhage: predictors of outcome and retreatment. J Interv Surg. 2018;10(4):367–74. https://doi.org/10.1136/neurintsurg-2017-013363.

History of Endovascular Surgery of Cerebral Aneurysms

3

Osama Mahmoud Ahmed Ramadan and Xianli Lv

Abstract

Brain aneurysms are the most frequent cause of intracranial hemorrhage in young people. In the last 40 years the treatment of brain aneurysm has been revolutionized by the advent and the growth of endovascular techniques. Treatment of aneurysms with the aid of various foreign bodies such as needle and wire insertion with or without electrical current has been reported since the first half of the nineteenth century. In 1832 Phillips induced clot formation in the femoral and carotid arteries of dogs by leaving needles in the arteries for variable lengths of time. Simultaneously, in France, Velpeau had proposed using "l'acupuncture des arteres dans le traitement des anevrismes." The introduction of detachable balloons by Serbinenko in the mid-1970s to occlude ruptured or symptomatic aneurysms was the first step of the neurovascular progress that goes on today. Then, endovascular therapies emerged in the 1990s with the advent of the Guglielmi detachable coil system. This chapter concisely describes the history of endovascular intracranial navigation and the history of the endovascular endosaccular treatment of brain aneurysms, from detachable balloons to detachable coils.

Keywords

Aneurysm · Endovascular · Detachable balloons · Detachable coils

3.1 Introduction

Studies of Egyptian mummies have revealed that atherosclerosis and arterial calcification were relatively common 3500 years ago [1]. The Ebers Papyrus is among the earliest medical writings and is thought to have been prepared around 2000 BC. The writer clearly identified arterial aneurysms, probably peripheral aneurysms, and recommended the following treatment: Treat it with a knife and burn it with a fire so that it bleeds not too much [2].

In 117 BC, Flaenius Rufus (Fig. 3.1), an Ephesian physician trained in Alexandria, Egypt, provided the first insight into the underlying causes of this class of vascular lesions by suggesting that their origins might lie in trauma [3]. Progress in treatments for the disease and coining of the term—aneurysm did not occur until Galen described the entity in AD 200 [4].

O. M. A. Ramadan (✉)
Department of Neurosurgery, Faculty of Medicine, Assiut University, Assiut, Egypt
e-mail: oramadan@aun.edu.eg

X. Lv
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_3

Fig. 3.1 Rufus of Ephesus (Flaenius Rufus, 80–150 AD, above)

Antyllus, a Greek surgeon of the second century AD, has left the earliest record of attempted therapy of aneurysms. Although his writings have been destroyed, his ideas are recorded in the works of Oribasius, who lived in the fourth century AD. According to Oribasius, Antyllus said,—We decline exceptionally big aneurysms, but we will operate as follows on aneurysms in the extremities, the limbs and the head [5].

3.2 Middle Ages

During the 1600s and 1700s, forensic studies conducted on patients whose death was sudden and unexpected led to the proposal that the cerebral aneurysm could be the cause of death.

In 18, Dinis P. (1643–1718) described the cases of the Duke of Aurelia and the Prince of Espinoza, who died suddenly. Autopsies revealed that the cerebral ventricles were distended with sanguineous extravasation of blood in both cases [6].

Giovanni Battista Morgagni (1682–1771) was an Italian anatomist, described the dilatation of posterior branches of the carotid arteries, which may have been aneurysms in his book—"De Sedibus et causis morborum per anatomem indagatis" in 1761 (Fig. 3.2) [7].

Aneurysm surgery entered an era with the advent of the proximal artery ligation technique. Arterial ligation was popularized in the 1800s by John Hunter (1728–1793), who demonstrated a technique of arterial ligation—Hunterian ligation, named in his honor, which is a safe reproducible means of. Lighting certain peripheral arteries [8].

Fig. 3.2 Giovanni Battista Morgagni (1682–1771)

Fig. 3.3 Ambrose Paré uses ligature during amputation

John Hunter described a case of false popliteal aneurysm whose rupture after a first attempt of classical proximal ligation at its neck was the motive for an ipsilateral femoral artery ligation [9]. However, the first reports of peripheral artery ligation belong to Ambrose Paré (1510–1590). In 1552 Ambroise Paré performed the first surgical control of a cervical vascular injury (Fig. 3.3) [10].

In 1760 Jean-Louis Petit revealed his discovery that there is no significant effect on the brain even if one of the carotid arteries is thrombosed. He stated that his patient had an aneurysm at the bifurcation of the right common carotid artery. 7 years later, an autopsy was done on that patient showed complete occlusion of the lumen by organized thrombus [11]. This opened the way towards elective carotid artery ligation for conditions other than injury. Hebenstreit of Germany in 1793 reported a case of carotid ligation for hemorrhage, and the patient is said to have lived, and this case may be considered the first elective carotid artery ligation [12]. John Abernethy, in London in 1798, ligated the carotid artery for trauma, but the patient died of cerebral causes [13]. The first authentic, successful ligation of the carotid artery on record was performed by David Fleming, a young British naval surgeon on October 17, 1803, on a servant who tried to commit suicide by cutting his throat. The patient survived [14].

The first case of ligature of the carotid artery in the United States was that of Mason F. Cogswell of Hartford, Conn, performed November 4, 1803; the report was published in October of 1824. The patient, a 38-year-old woman, had an extensive tumor of the left side of her neck that completely enveloped the carotid artery. During the course of its removal, the carotid artery had to be ligated and divided. The patient did well at first, but on the 20th day, she died as a result of a hemorrhage from the wound. Cogswell stated the circumstances attending this case were such as entirely to establish the practicability and safety of dividing the carotid artery on the living subject [15].

The first successful ligation of the carotid artery in the United States was performed by Dr. Amos Twitchell of Keene, NH, on October 18, 1807 [16]. Sir Ashley Cooper (1768–1841) made history in 1808 when he performed at Guy‘s Hospital in London, the first successful treatment of a carotid aneurysm (Fig. 3.4). The operation consisted of ligation of the common carotid artery, and the patient, a 50-year-old man, left the hospital after a 3-month period of recovery (because of smoldering wound infection) [17]. On May 23, 1809, Benjamin Travers, Cooper’s pupil, performed ligation of the common carotid artery in a 28-year-old female with unilateral pulsating exophthalmos; this became the first documented surgical treatment of CCF [18].

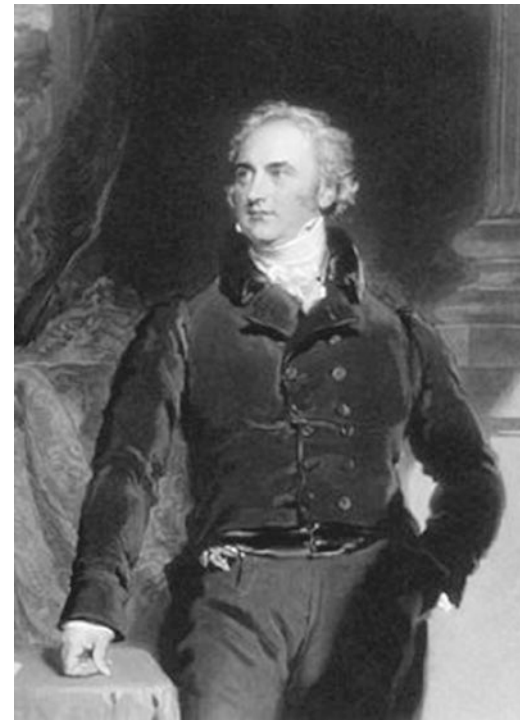


Fig. 3.4 Sir Ashley Cooper (1768–1841)

3.3 Twentieth Century Era

By the begging of the twentieth century, many efforts were carried out to modify ligation techniques to minimize complications and increase efficacy and safety. It was started by Halsted in 1905, who tried to use aluminum strips that would enable radial occlusion of the ligated arteries [19]. In such a similar way, Mata R. Published his work in 1911 of testing the efficacy of collateral circulation using slowly tightening removable aluminum bands before complete occlusion [20, 21]. Hamby and Gardner were the first to succeed in surgically treating carotid-cavernous fistula by carotid ligation in two cases in 1933 [22]. In 1951 Poppen J. Published his experience with 143 surgically treated patients with intracranial aneurysms and illustrated his plication tech-

nique of the carotid artery, which considerably reduced intimal damage [23].

The outcomes of proximal artery ligation for aneurysm treatment also frustrated many surgeons, including Norman Dott of Edinburgh, who decided to take the risk of tackling an aneurysm directly. In 1931, with no angiographic assistance, he performed a frontal craniotomy in a 53-year-old patient, discovering a 3-mm aneurysm of the ICA, at which point he wrapped it with muscle from the patient's leg. The next day his patient was awake. Until his death, 11 years after, the patient did not have any hemorrhagic events [24].

Few years later, Walter E. Dandy (1886–1946), who is well known for his studies on hydrocephalus, published his results on the treatment of carotid-cavernous fistula using a trapping technique by ligation of the cervical carotid artery and clipping of the intracranial ICA aiming to induce thrombosis and in somewhere of the vascular system participating in the fistula.

Many neurosurgeons nowadays consider Dandy the father of modern vascular neurosurgery as he was the first, who planned to direct clipping procedure for intracranial aneurysm in March 1937 using a Cushing silver clip used previously in hemostatic purposes during brain tumors surgery (Fig. 3.5) [25]. Clip technology and manufacture continue to improve and update till the present day. In 1949 Duane changed the shape of Cushing's V clip to U shaped clip, increasing its efficacy (Fig. 3.6) [26].

One-year late, Schwartz devolved a temporary clip for arterial occlusion called cross action alpha clip which was modified 20 years later by Mayfield to obtain better handling of the applicator allowing trial and error in clip placement [27]. Then Sundt (1930–1992) designed what is so-called encircling clip graft which was devolved to repair defects in the vessel wall [28]. Edgar M. Housepian, a pioneer in the development of stereotactic surgery, designed the Housepian clip in 1976, which is safer and controllable (Fig. 3.7) [29].

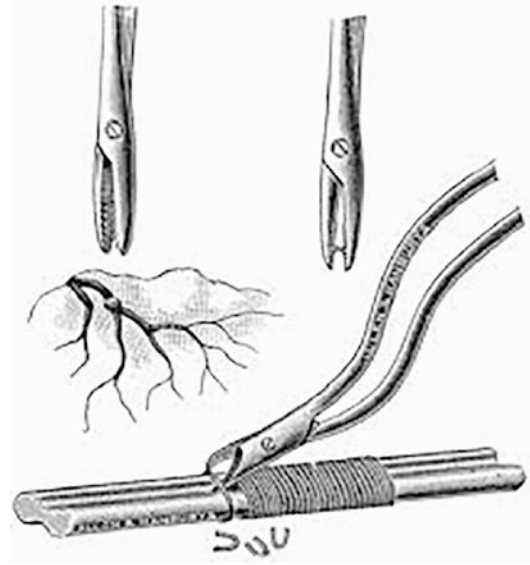


Fig. 3.5 Cushing's clips showing the silver wire sutures for the meningeal artery. The set consists of a rod for making the sutures, and forceps for cutting and applying them

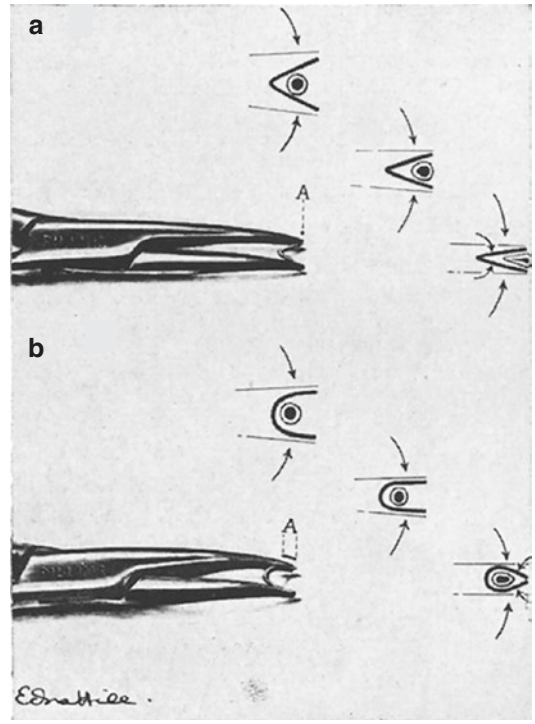


Fig. 3.6 A modification of the McKenzie silver clip (**a**) to U shaped clip (**b**)

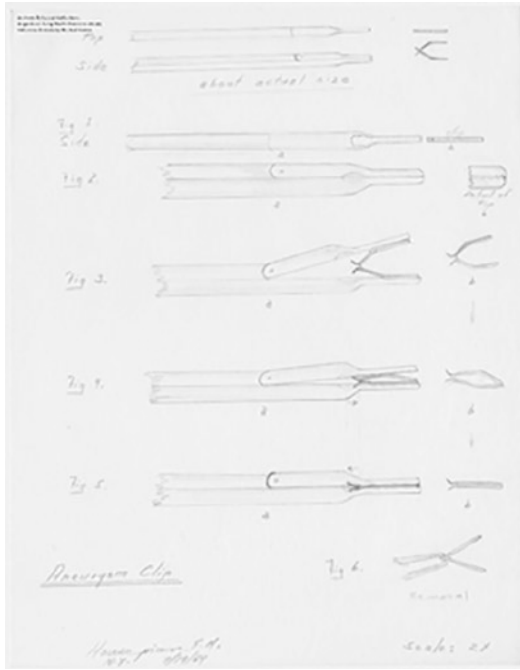


Fig. 3.7 Housepian clip design

In the same way with the evolution of extravascular approaches to cerebral aneurysms, many attempts, from pioneering ones to hazardous ones, were done to build up the era of the endovascular route to cerebral aneurysms. In 1824, Scudamore observed that blood thrombosed at a positive but not a negative electrode [30]. Velpeau and Philips described the blockage of arterial vessels by temporary puncture with a pin [31]. In 1847, Ciniselli described the use of direct current applied through pins in an aneurysm to induce thrombosis [32]. Dawbarn was the first to report on the embolization of head and neck tumors in 1904. He invented the Starvation operation to treat malignant tumors by embolizing them at the region of the external carotid artery [33].

At this time, it was not possible to take radiographic images of the brain in a living human except by pneumoventriculography, a method devolved by Dandy by introducing air into the ventricles. This method provided faint images of the cerebral ventricles, but it had many hazards to the patients [34].

Egan Moniz (1874–1955), a Nobel prize awarded, described in his book the several steps leading to the discovery of cerebral angiography. A very difficult procedure was given the possibility to take only three films in sequence after injecting a contrast agent directly into the carotid. In 1937, he originally described internal carotid occlusion as documented by angiography. His observations and comments on the clinical, pathogenic, and therapeutic aspects of internal carotid thrombosis are reviewed [35].

Norman Dott dramatically improved methods of diagnosis with the introduction of angiography. Equipment capable of performing angiography was installed in Edinburgh soon after the original description of the technique by Moniz. Dott quickly utilized. The new method to identify an arteriovenous malformation (AVM)—the earliest attempts at cerebral arterial radiography were made in 1927 when we used Sodium Iodide as the opaque medium. On March 24, 1933, Dott performed the first angiogram demonstrating an intracranial aneurysm [36]. Fourteen years later, Stig Radner published the first vertebral angiography (Fig. 3.8) [37].

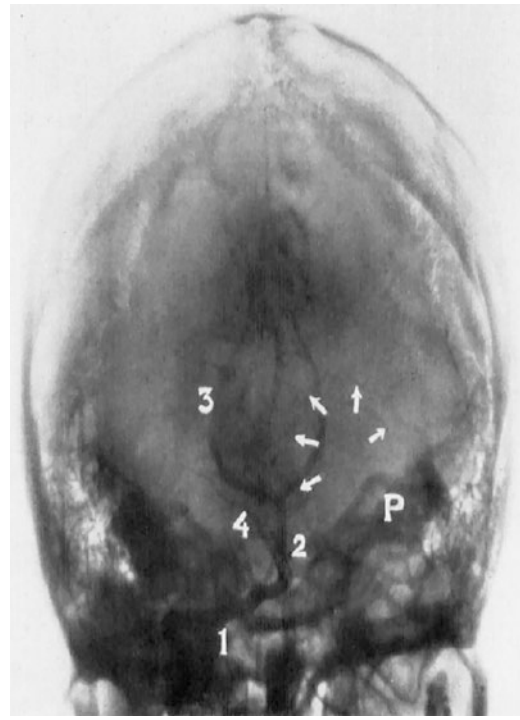


Fig. 3.8 First vertebral angiogram done by Stig Rander

The first attempt carried out to an endovascular embolization of carotid-cavernous sinus fistula was in 1930 by Barney Brooks. He used a free piece of muscle through the internal carotid artery (ICA) [38]. It was hoped that the embolus would be carried out by the blood flow to the fistulous opening.

In 1964, Speakman was the first to describe the internal occlusion of carotid-cavernous sinus fistula. The case was of 27 years old patients who had post-traumatic CCF and was treated with an extravascular approach by staged trapping procedures consisting of gradual occlusion of the left cervical common carotid artery with Selverstone clip then replaced by ligature to decrease the risk of complications. Later, a left frontal craniotomy allowed the left ICA and ophthalmic arteries. To be clipped. Unfortunately, 2 months later, the patient‘s symptoms recurred. Speakman pushed a catheter inside the ICA, and marked pieces of gelfoam were released in the blood flow under radiographic guidance to stick to the point of the fistula [39]. Three years later, Ishimori published his success in treating two patients of CCF by gel foam embolization marked with thin films of gold [40]. In 1970, Fabian Isamat reported his deal with a patient of 86 who developed a carotid-cavernous fistula. Artificial embolization alone was considered the safest treatment for this patient and proved to be adequate. Post-operative preservation of the patency of the ICA was demonstrated by angiography [41].

In this era, it was common to see neurosurgeons deal with cerebrovascular diseases with combined extravascular and intravascular routes. However, the strategy changed, and all the efforts and thinking shifted towards how to change the route of filling aneurysmal sac from transfundal route to endovascular route. Werner and Blackmore credited the first successful trial for electrothrombosis of giant ICA aneurysm of 15 years old girl eroding the orbital roof. This large aneurysm was difficult to treat in the usual way. He introduced 9 m of silver enameled wire after a trans-orbital puncture of the aneurysmal sac. The heat was applied for 40 s at 80 °C [42].

Another huge steps were made by the pioneers Luessenhop and Spence in 1960 by their trial of artificial embolization of cerebral arteries to treat a case of cerebral AVM Using silastic beads in a surgically exposed common carotid artery. A predetermined size and configuration of the embolus are introduced even far proximal to the malformation, and it will find its way to it. By its size, the embolus will be excluded from passage to smaller branches [43]. In 1976, Sanyo K. treated 205 cases of cerebral AVM, 192 of them were followed to 24 years using different material like polymerizing silicone [44].

The first case of cerebral aneurysm treated by pilojection was reported by Gallagher in 1964. Using shafts of hog hair delivered under high velocity into the wall of the sac, a large aneurysm of the anterior cerebral artery was closed by thrombosis [45]. Despite all the previous efforts, the morbidity and mortality of ruptured cerebral aneurysms remain high. This made the surgeons worked hard to develop improved methods of therapy. In 1965, Mullan devolved a method that achieve aneurysm thrombosis without open surgery by craniotomy. The technique is composed of an insertion of a steel electrode with a sharp end through burr hole into the aneurysm sac. Once the aneurysm is punctured, an electric current is applied that would not only trigger electrothrombosis of the aneurysm but also erode the tip of the electrode to permit safe removal [46]. Mullan concluded that the passage of a direct current through a needle was the most effective. Unfortunately, the thrombi were not permanent.

Alksne devolved another technique to overcome the problem of guiding the embolization agent in a safe manner without the need for craniotomy. He used iron microspheres guided with a magnet produced on the dome of the aneurysm. He introduced a magnetic probe through a burr hole and directed towards the dome under radiographic guidance. He used a carbonyl iron powder suspended in human serum albumin, but rapidly he shifted towards injecting the embolization material directly inside the aneurysm with a needle due to the encouraging results he obtained [47]. Later in 1977, he modified the embolization agent by reducing the solidification times to minimize the risk of distal embolization dissemination [48].

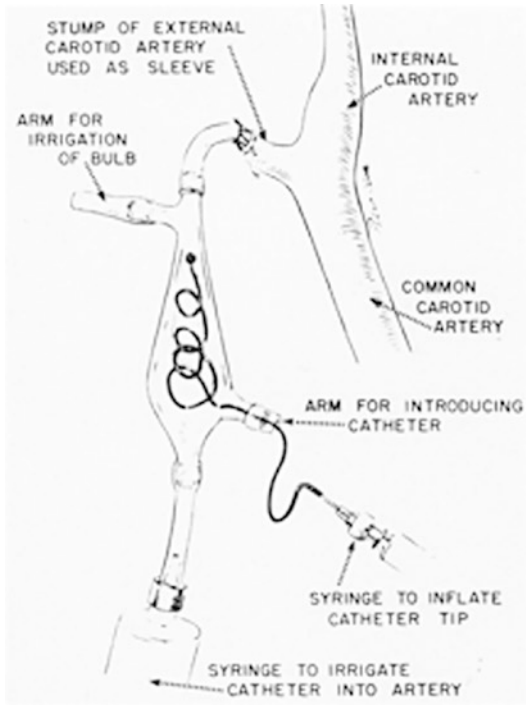


Fig. 3.9 Schematic illustration showing the report on the first catheterization of intracranial arteries. Luessenhop AJ, Velasquez AC: Observations on the tolerance of the intracranial arteries to catheterization. J Neurosurg 21:85–91, 1964

At the beginning of the second half of twentieth century, experiments were carried out to test the tolerance of cerebral vessels to catheterization by flexible tubes. The credit went to Luessenhop and Velasquez. Tests on cadavers and animals were done before choosing silastic tubing for that purpose. They used their material in three patients only (Fig. 3.9) [49]. It was pointed out that once inside the endovascular space, few means are available to negotiate arterial bifurcation.

Frei in 1966 came with a possible solution with the development of POD or para operational device. This catheter was designed for superselective catheterization with a minimum of vessel trauma. The proximal portion was made of polyethylene, and the distal portion of soft silicone rubber. The distal section measured only 1.3 mm in outer diameter and was 7 cm in length. Embedded in the tip of the silicone tubing was a micromagnet which measured 1 mm in diameter [50]. A slight modification was done on POD by Yoder by introducing a detachable platinum-cobalt magnet tip [51]. Another modification made by Hilal in 1974 and reported the use of a modified POD microcatheter in 120 patients [52].

In 1975, Debrun invented a coaxial microcatheter with a detachable latex balloon at the tip. Unfortunately, this microcatheter could only reach the cavernous part of ICA due to its relatively stiffness [53]. All that happened before 1974 is considered the pre-balloon era. In 1974, the society of neuroendovasular specialist was shocked by the report of Serbinenko who reported the endovascular treatment over 300 patients using detachable and non-detachable balloons in the period from 1969 to 1972 [54]. It is considered the first report about the ability of temporary balloon occlusion of cerebral arteries, endovascular occlusion of direct carotid-cavernous fistula with preservation of the parent artery. This study has a unique influence on most of endovascular neurosurgeons all over the world. Later on, many caters were established and adopted the technique of Serbinenko (Fig. 3.10).

In 1978, Debrun reported the use of balloon occlusion on five patients with intracavernous aneurysms with preservation of the parent artery [55]. He suggested the addition of latex strings to avoid contrast leakage. Balloon-based procedures continue to spread around the world rapidly (Fig. 3.11). In 1982 Romodanov published a series of 120 patients treated with detachable, silicon-filled latex balloons. In 73% of cases, preservation of the parent vessel was observed [56]. However, the problem they faced was that the balloons did not adopt the shape of the aneurysm. Therefore, in 1990, Higashida published an 84 patient series of inoperable aneurysms treated by balloon embolization by the use of 2-hydroxyethyl methacrylate (HEMA), a solidifying agent to prevent balloon deflation. The series showed 18% mortality and 11% morbidity [57]. These higher results of morbidity and mortality discouraged most neurosurgeons from carrying out this technique. Due to the failures of the detachable balloon, the world was put in another challenge, and new pioneers appeared on the field with a brilliant solution.

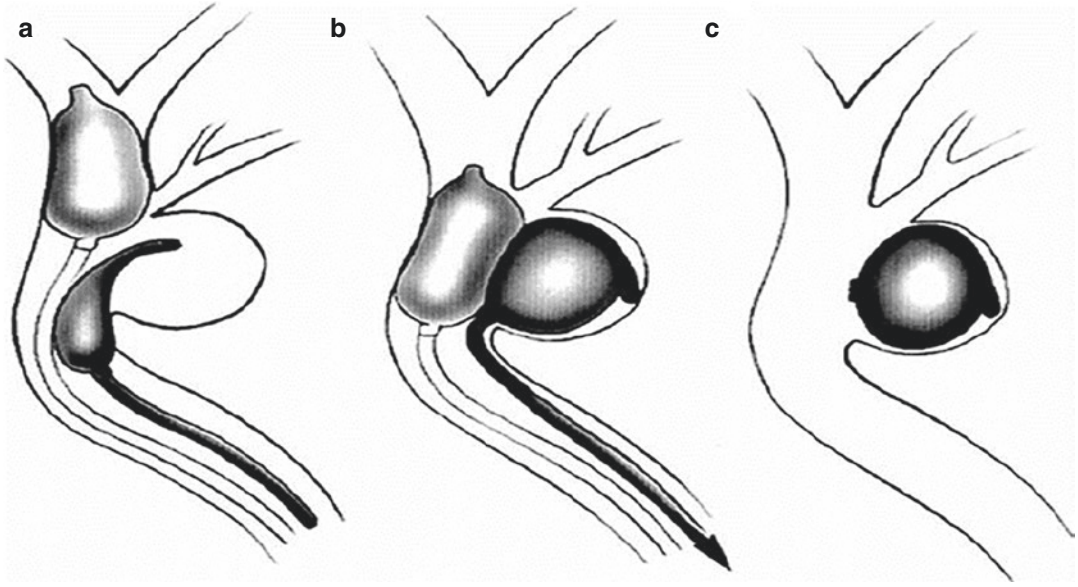


Fig. 3.10 Early illustration of the balloon embolization technique. (**a**) The non-detachable balloon catheter guides the detachable balloon into the aneurysm sac. (**b**) The detachable balloon is placed into the aneurysm sac with help from the non-detachable balloon. (**c**) The detachable balloon is deployed to occlude the aneurysm

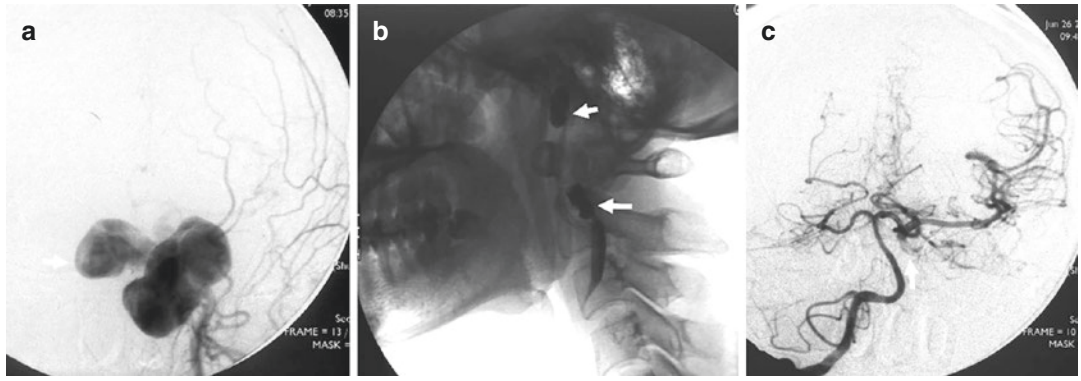


Fig. 3.11 A 43-year-old man presented with headaches. (**a**) Frontal view of the right carotid artery injection showing a giant aneurysm of the cavernous segment of the internal carotid artery (arrow). (**b**) Unsubtracted image, lateral projection, showing the left internal carotid artery was occluded using two detachable balloons (arrows). (**c**) Frontal view of the right vertebral artery injection showing the left middle cerebral artery was filled through the posterior communicating artery (arrow)

The first trial of using short pushable coils for endovascular packing intracranial aneurysms made by Hilal in 1988. However, due to the stiffness of the coil packing could not be achieved [58].

The year 1989 was the year of the second shake for the neuroendovascular world. Gugliemi and his team announced that they devised very soft retrievable detachable platinum coils for more safety and efficacy in the treatment of brain

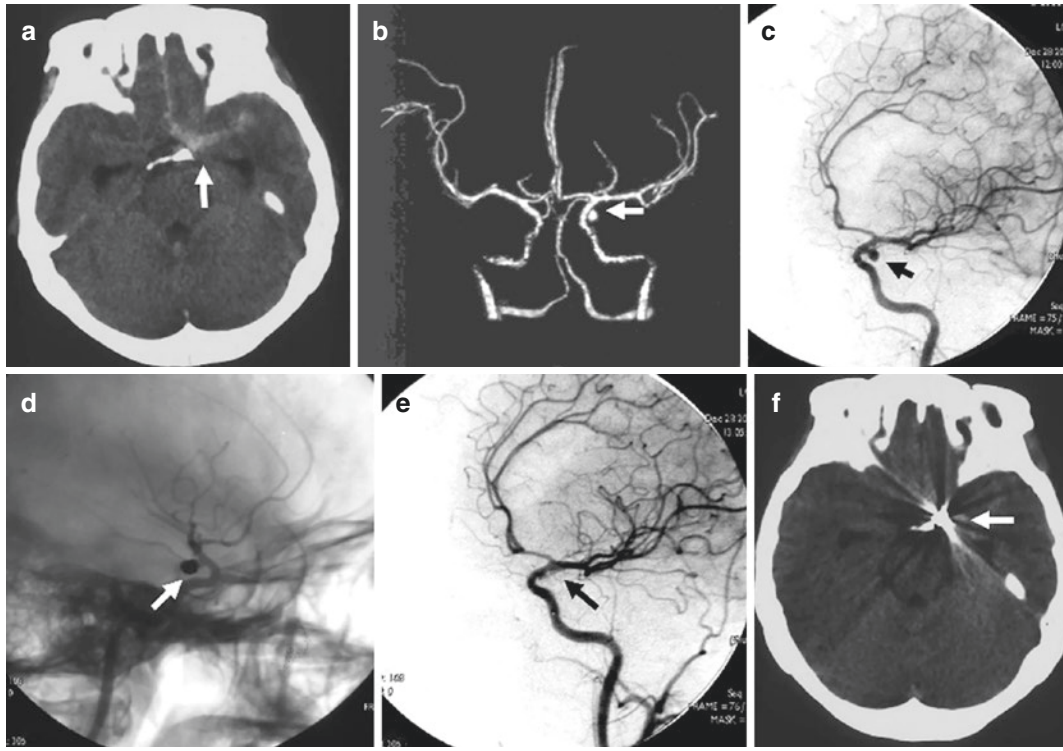


Fig. 3.12 A 38-year-old woman with a ruptured posterior communicating artery aneurysm was coiled. (**a**) Cranial CT scanning showing subarachnoid hemorrhage of the suprasellar cistern (arrow). (**b**) CT angiography. (**c**) Oblique view of the left internal carotid artery injection. Showing the aneurysm of the left posterior communicating artery (arrows). (**d**) Lateral view of the unsubtracted image showing the coil mass in the aneurysm sac (arrow). (**e**) Oblique view of the left internal carotid artery injection after aneurysm coil embolization showing the aneurysm was completely occluded (arrow). (**f**) Control cranial CT scanning showing the artifact of the coil mass without additional bleeding and infarction

aneurysm. Vinuela (interventional neuropathologist), Sepetka and Engelson (engineer at Target therapeutic) had an undeniable role in the production of the new detachable coils [46]. This technique was successfully developed to overcome the disadvantages of balloon embolization.

Now the aneurysm could be treated in the acute phase of hemorrhage and in the presence of vasospasm (Fig. 3.12). The embolic material is a soft, controllable, detachable, platinum coil, 1 to 50 centimeters in length, soldered to a stainless steel delivery wire (Fig. 3.13). The tip of an "over the wire" microcatheter (vide supra) is positioned in the aneurysm. The detachable coil is then advanced through the microcatheter and deposited in the aneurysm. A positive direct electrical current is then applied to the proximal end of the delivery wire. The current electrolytically dissolves the delivery wire just proximal to the platinum coil, detaching the coil within the aneurysm (Fig. 3.14) [59].

This quick journey through the history and the early beginnings of the endovascular treatment of cerebral aneurysms has reached an end. We owe respect and thank all their pioneers who lighten our way to where we are now.

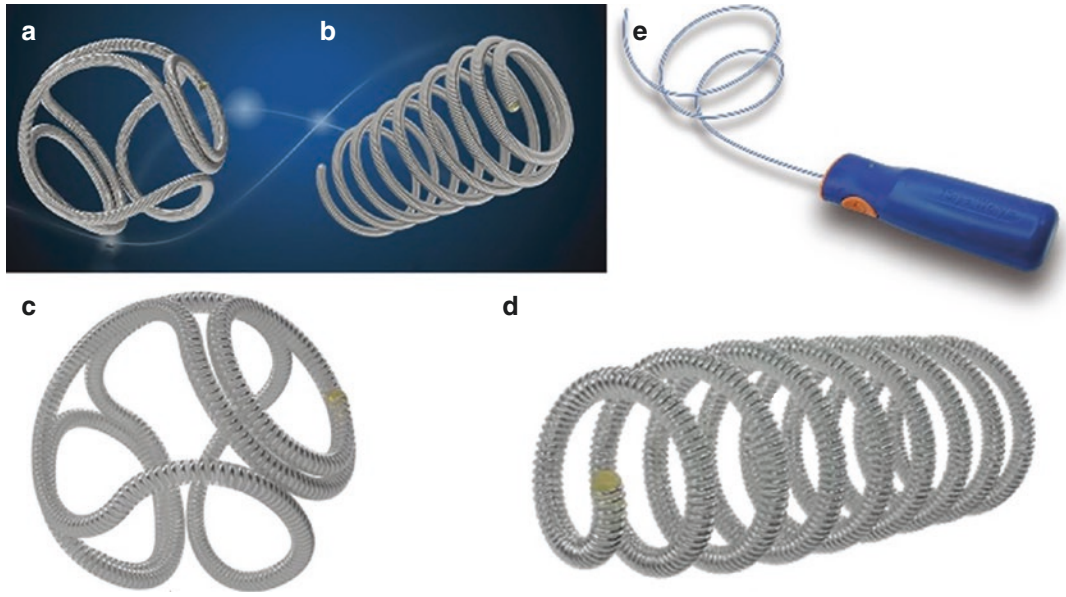


Fig. 3.13 Perdenser detachable coils (TJWY Medical Company, Beijing, China) come in two different shapes. (**a**) 3-D coil. (**b**) Helical coil. (**c**) 3-D hydrogel coil. (**d**) helical hydrogel coil. (**e**) detachment system

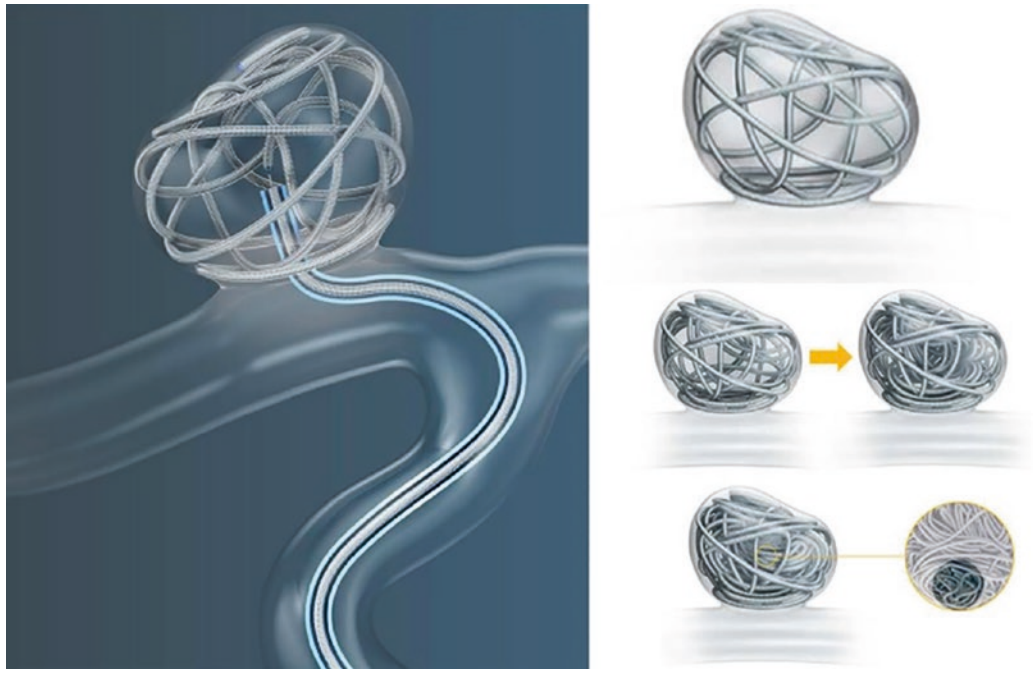


Fig. 3.14 Left, advance and deploy. Right, from frame to finish

References

1. Slaney G. A history of aneurysm surgery. In: Greenhalgh RM, Mannick JA, Powell JT, editors. The cause and management of aneurysms. London: W.B. Saunders; 1990. p. 1–18.
2. Barker WF. Clio: the arteries. Austin, TX: RG Landers; 1992. p. 2–502.
3. De Moulin D. Aneurysms in antiquity. Arch Chir Neerl. 1961;13:49–63.
4. Magnus V. Aneurysm of the internal carotid artery. JAMA. 1927;88:1712–3.
5. Crowe SJ. Halsted of Johns Hopkins: the man and his men. Springfield: Charles C. Thomas; 1957. p. 210–8.
6. Dinis P. Dissertation sur la mort subtitle et sur la cataleptic: Alec la relation de plusieurs personnes qui en ont tee attaques. Ld Houry, Paris. [quoted by Walton, 1956].
7. Morgagni JB. De Sedibus et causes Morborum per Anatomen Indagastis. Venetia, ex typog. Remondiniana, vol. 1. New York: Hefner; 1960.
8. Cooper BB. Lectures on the principles and practice of surgery. 2nd ed. Philadelphia: Blanchard & Lee; 1852.
9. Robicsek F, Roush TS, Cook JW, Reames MK. From Hippocrates to Palmaz-Schatz, the history of carotid surgery. Eur J Vasc Endovasc Surg. 2004 Apr 1;27(4):389–97.
10. Pare A. The workes of that famous Chirurgion Ambrose Parey. (Translated from Latin and compared with French by T. Johnson. From the first English edition, London, 1634. Reprinted, New York: Milford House, 1968).
11. Thompson JE. The evolution of surgery for the treatment and prevention of stroke. Stroke. 1996;27:1427–34.
12. Hebenstreit EBG. Zusatze zu Benj. Leipzig, Germany: Bell's Abhandlung yon den Geschwuren und deren Behandlung; 1793.
13. Abernethy J. Surgical observations, vol. 2. London: Surgical Works; 1804. p. 193–209.
14. Coley RW. Case of rupture of the carotid artery, and wounds of several of its branches, successfully treated by tying the common trunk of the carotid itself. Med Chir J Rev. 1817;3(13):1–4.
15. Cogswell MF. Account of an operation for the extirpation of a tumour, in which a ligature was applied to the carotid artery. N Engl J Med Surg. 1824;13:357–60.
16. Twitchell A. Gun-shot wound of the face and neck: ligature of the carotid artery. N Engl Quart J Med Surg. 1842;1:188–93.
17. Hertzer NR. Extracranial carotid aneurysms: a new look at an old problem. J Vasc Surg. 2000 Apr 1;31(4):823–5.
18. Travers B. A case of aneurism by anastomosis in the orbit, cured by the ligature of the common carotid artery. Med Chir Trans. 1811;2:1.
19. Halsted WS. The partial occlusion of blood vessels especially of the abdominal aorta. Bull Johns Hopkins Hosp. 1905;14:345.
20. Matas RI. Testing the efficiency of the collateral circulation as a preliminary to the occlusion of the great surgical arteries. Ann Surg. 1911 Jan;53(1):1.
21. Matas R, Allen CW. Occlusion of large surgical arteries with removable metallic bands to test the efficiency of the collateral circulation: experimental and clinical observations. J Am Med Assoc. 1911 Jan 28;56(4):233–9.
22. Hamby WB, Gardner WJ. Treatment of pulsating exophthalmos: with report of two cases. Arch Surg. 1933 Oct 1;27(4):676–85.
23. Poppen JL. Specific treatment of intracranial aneurysms: experiences with 143 surgically treated patients. J Neurosurg. 1951 Jan 1;8(1):75–102.
24. Dott NM. Intracranial aneurysmal formations. Clin Neurosurg. 1969;16:1–16.
25. Louw DF, Kaibara T, Sutherland GR. Aneurysm clips. J Neurosurg. 2003 Mar 1;98(3):638–41.
26. Duane W. A modification of the McKenzie silver clip. J Neurosurg. 1950 Jan 1;7(1):92–3.
27. Mayfield FH, Kees G. A brief history of the development of the Mayfield clip. J Neurosurg. 1971 Jul 1;35(1):97–100.
28. Park PJ, Meyer FB. The Sundt clip graft. Oper Neurosurg. 2010 Jun 1;66(Suppl 2):300.
29. Fox JL. Vascular clips for the microsurgical treatment of stroke. Stroke. 1976 Sep;7(5):489–500.
30. Scudamore C. Essay on the blood. London: Longmans, Hurst, Rees, Orme, Brown, & Green; 1824.
31. Velpeau AA. Memoir on stinging or acupuncture of the arteries in the treatment of aneurysms. Gaz Med Paris. 1831;2:1–4.
32. Ciniselli L. Sulla elettro-puntura nella cura degli aneurismi. Gazz Med Ital Lomb. 1847;6:9–14.
33. Dawbarn RH. The starvation operation for malignancy in the external carotid area. Its failures and successes. J Am Med Assoc. 1904 Sep 17;43(12):792–5.
34. Tondreau RL. Ventriculography and pneumoencephalography: contributions of Dr. Walter E. Dandy. Radiographics. 1985 Jul;5(4):553–5.
35. Ferro JM. Egas Moniz and internal carotid occlusion. Arch Neurol. 1988 May 1;45(5):563–4.
36. Todd NV, Howie JE, Miller JD. Norman Dott's contribution to aneurysm surgery. J Neurol Neurosurg Psychiatry. 1990 Jun 1;53(6):455–8.
37. Radner S. Intracranial angiography via the vertebral artery: preliminary report of a new technique. Acta Radiol. 1947 Sep;28(5–6):838–42.
38. Brooks B. The treatment of traumatic arteriovenous fistula. J South Med. 1930;23:100–6.
39. Speakman TJ. Internal occlusion of a carotid-cavernous fistula. J Neurosurg. 1964 Apr 1;21(4):303–5.
40. Ishimori S, Hattori M, Shibata Y, Shizawa H, Fujinaga R. Treatment of carotid-cavernous fistula by gelfoam embolization. J Neurosurg. 1967 Oct 1;27(4):315–9.

41. Isamat F, et al. Artificial embolization of carotid-cavernous fistula with post-operative patency of internal carotid artery. J Neurol Neurosurg Psychiatry. 1970;33(5):674–8. https://doi.org/10.1136/jnnp.33.5.674.
42. Werner SC, Blakemore AH, King BG. Aneurysm of the internal carotid artery within the skull: wiring and electrothermic coagulation. J Am Med Assoc. 1941 Feb 15;116(7):578–82.
43. Luessenhop AJ, Spence WT. Artificial embolization of cerebral arteries: report of use in a case of arteriovenous malformation. J Am Med Assoc. 1960 Mar 12;172(11):1153–5.
44. Sano K, Jimbo M, Saito I, Basugi N. Artificial embolization of inoperable angioma with polymerizing substance. In: Cerebral angiomas. Berlin: Springer; 1975. p. 222–9.
45. Gallagher JP. Pilojection for intracranial aneurysms: report of progress. J Neurosurg. 1964 Feb 1;21(2):129–34.
46. Guglielmi G, Viñuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach: part 1: electrochemical basis, technique, and experimental results. J Neurosurg. 1991 Jul 1;75(1):1–7.
47. Alksne JF, Fingerhut AG, Rand RW. Magnetically controlled focal intravascular thrombosis in dogs. J Neurosurg. 1966 Nov 1;25(5):516–25.
48. Alksne JF, Smith RW. Iron-acrylic compound for stereotaxic aneurysm thrombosis. J Neurosurg. 1977 Aug 1;47(2):137–41.
49. Luessenhop AJ, Velasquez AC. Observations on the tolerance of the intracranial arteries to catheterization. J Neurosurg. 1964 Feb 1;21(2):85–91.
50. Frei EH. The POD and its applications. Med Res Eng. 1966;5:11–8.
51. Yodh SB, Pierce NT, Weggel RJ, Montgomery DB. A new magnet system for _intravascular navigation. Med Biol Eng. 1968 Mar 1;6(2):143–7.
52. Hilal SK, WJ M. Magnetically guided devices for vascular exploration and treatment. Radiology. 1974;113:529–40.
53. Debrun G, Lacour P, Caron JP, Hurth M, Comoy J, Keravel Y. Inflatable and released balloon technique experimentation in dog—application in man. Neuroradiology. 1975 Sep 1;9(5):267–71.
54. Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg. 1974 Aug 1;41(2):125–45.
55. Debrun G, Lacour P, Caron JP, Hurth M, Comoy J, Keravel Y. Detachable balloon and calibrated-leak balloon techniques in the treatment of cerebral vascular lesions. J Neurosurg. 1978 Nov 1;49(5):635–49.
56. Romodanov AP, Shcheglov VI. Intravascular occlusion of saccular aneurysms of the cerebral arteries by means of a detachable balloon catheter. In: Krayenbühl H, editor. Advances and technical standards in neurosurgery. New York: Springer.
57. Higashida RT, Halbach VV, Barnwell SL, Dowd C, Dormandy B, Bell J, Hieshima GB. Treatment of intracranial aneurysms with preservation of the parent vessel: results of percutaneous balloon embolization in 84 patients. Am J Neuroradiol. 1990 Jul 1;11(4):633–40.
58. Hilal SK, Khandji A, Solomon RW, Chi L. Obliteration of intracranial aneurysms with pre-shaped highly thrombogenic coils. Radiology. 1989;173(1):250–7.
59. Guglielmi G. History of endovascular endosaccular occlusion of brain aneurysms: 1965–1990. Interv Neuroradiol. 2007 Sep;13(3):217–24.

4 Drugs in Neurovascular Intervention

Vikram Karmarkar, Rakesh Singh, Neeraj Singh, and C. Deopujari

Abstract

Neuroendovascular procedures are associated with a risk of immediate or delayed thromboembolic and ischemic complications. Anticoagulants and antiplatelet agents are widely used to lower the risk of perioperative thromboembolic events in neuroendovascular surgery. Immature embolization of the aneurysmal sac, protrusion of coils, balloon remodeling, or stenting maneuvers may lead to acute thrombus formation by platelet activation. Antiplatelet therapy prior to procedures has significantly lowered the risk of thromboembolic complications in stent-assisted coil embolization of cerebral aneurysms. Although several antithrombotic therapeutic options are available, optimized antithrombotic management in neuroendovascular surgery is not well defined. Appropriate antiplatelet agents, anticoagulants, dosing, and duration of treatment have not been adequately determined. The present chapter provides our experiences of available antithrombotic agents, focusing on practical aspects of their use in different clinical settings.

Keywords

Antiplatelet drug · P2Y12 inhibitors · GPI IIb/IIIa · heparin · Antithrombotic drug

4.1 Introduction

The field of neurovascular intervention is expanding rapidly. Newer instruments and better techniques optimized by the use of drugs have resulted in better outcomes. More number of neurologists, neurosurgeons, and radiologists are undertaking this field as their career choice [1]. Multiple ongoing trials are presenting new evidence in management [2, 3]. Hence, updated knowledge about drugs used in neurovascular intervention techniques is important. This chapter deals with drugs used in intervention procedures.

4.2 Fibrinolytic Agents

Sudden occlusion due to thrombus formation results in acute ischemic stroke. Early intervention with fibrinolytic agents in carefully selected patients results in re-establishing blood flow. Figure 4.1 shows the mechanism of fibrinolytic

V. Karmarkar (✉) · N. Singh · C. Deopujari
Department of Neurosurgery, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

R. Singh
Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_4

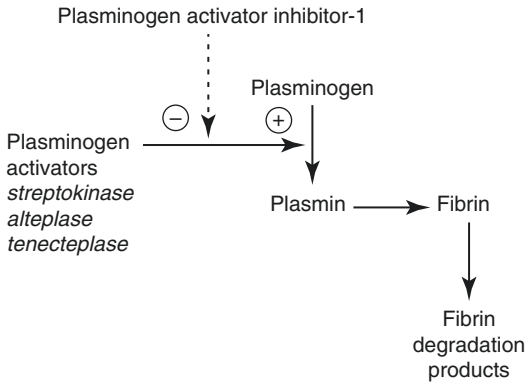


Fig. 4.1 Mechanism of fibrinolytic drugs

agents. Fibrinolytic drugs activate plasminogen to plasmin, thus degrading insoluble fibrin to fibrin degradation products causing lysis of clot. Currently, Alteplase and Tenecteplase are approved for use in acute ischemic stroke [4]. Compared to first-generation streptokinase, these agents generally do not cause antigenic reactions [5].

4.2.1 Alteplase

Recombinant tissue-type plasminogen activator (rtPA or alteplase) is more fibrin specific than streptokinase [6]. It has a short half-life (3–4 min), so need to be given as a continuous intravenous infusion. Patient needs to be admitted to intensive care or stroke unit for monitoring. Prior CT scan of brain should be done to rule out intracranial hemorrhage. Alteplase is given as 0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of the dose given as bolus over 1 min. Initially approved for use during 3 h of ischemic stroke, it is also recommended for select patients within 3 and 4.5 h of ischemic stroke after ECASS III trial [7]. BP monitoring and neurological assessment should be done every 15 min during infusion. During infusion or within 24 h after infusion, if the patient develops a severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, infusion should be discontinued (if IV alteplase is being administered) and emergency head CT scan should be done to rule out intracranial hemorrhage. AHA/ASA 2019 guidelines on acute ischemic stroke management describe detailed indications and contraindications for use of alteplase [8]. Important eligibility recommendations for use of alteplase are window period within 3 h, window period between 3 and 4.5 h in carefully selected patients, age group above 18 years, blood pressure < 185/110 mmHg, and blood sugar level above 50 mg/dL. In patients with blood pressure > 185/110 mmHg, careful lowering of BP can be done using Labetalol (10 mg IV followed by continuous IV infusion 2–8 mg/min), Nicardipine (5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h), or Clevidipine (1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached, maximum 21 mg/h). Potential contraindications for use are previous ischemic stroke, severe head trauma, and intracranial/intraspinal surgery within 3 months. Alteplase should not be given to patients who have received treatment doses of low molecular weight heparin within last 24 h. Patients who are taking thrombin/factor Xa inhibitors should not be given alteplase till laboratory tests such as aPTT, INR, platelet count, eccrine clotting time, thrombin time, and factor X assay are normal. It is important to note that patients who taking antiplatelet monotherapy prior to stroke should be given alteplase as benefits outweigh the risk of bleeding. In case the patient develops orolingual angioedema during alteplase infusion, discontinue infusion, maintain airway, administer IV methylprednisolone (125 mg), IV diphenhydramine (50 mg), IV ranitidine (50 mg), or famotidine (20 mg). If there is a further increase in angioedema, give epinephrine (0.1%; 0.3 mL subcutaneously). Management of symptomatic intracranial bleeding secondary to alteplase requires more intensive approach. Alteplase infusion must be stopped, emergency CT scan of Brain should be done to confirm hemorrhage [9]. Such patients should be given Cryoprecipitate (10 U infused over 10–30 min), Tranexamic acid (1000 mg IV infused over 10 min), or e-aminocaproic acid (4–5 g over 1 h, followed by 1 g IV) until bleeding is controlled.

4.2.2 Tenecteplase

(TNK-t-PA) It is derived from alteplase, differing in its fibrin binding specificity, plasma half-life (20 min), and resistance to Plasminogen Activator Inhibitor-1 [10]. Tenecteplase has higher fibrinolytic potency on platelet-rich clots than its parent molecule. It is given in a dose of 0.4 mg/kg as single bolus administration. Extend IA TNK trial showed Tenecteplase (0.25 mg/kg, max 25 mg) was non-inferior to alteplase in restoring perfusion large vessel occlusion of intracranial cerebral artery (internal carotid artery, basilar artery, and middle cerebral artery) [11]. Overall functional outcome was better with tenecteplase. There was no significant difference in the incidence of cerebral hemorrhage.

4.3 Antiplatelet Agents

Platelets play a central role in achieving hemostasis. Platelet activation, followed by aggregation and adhesion to vascular endothelium lead to formation of a clot which is subsequently stabilized by coagulation cascade. Collagen, vWF (Von-Willibrand factor), and other platelet activators like ADP (Adenosine diphosphate) mediate this process. ADP acts on adenosine-specific receptor, P2Y12, present on platelet plasma membrane and activates G protein-coupled expression of GP IIb-IIIa receptors on platelet surface which cause platelet aggregation [12]. Neurointervention procedures like intraluminal stenting, coiling of aneurysms, and flow diversions have potential for thromboembolic events during or after the procedure. Platelet inhibitors prevent platelet activation, aggregation, or adhesion, thereby preventing clot formation and propagation. Pre-procedure antiplatelet drugs are administered to prevent thrombosis in stenting and flow diverters [13]. Other treatment options for preventing or treating thromboembolic events include intravenous unfractionated heparin and thrombolytics. Various classes of antiplatelet agents have different targets as shown in Fig. 4.2.

4.3.1 Aspirin

Prostaglandin pathway involving cyclooxygenase enzyme leads to formation of thromboxane

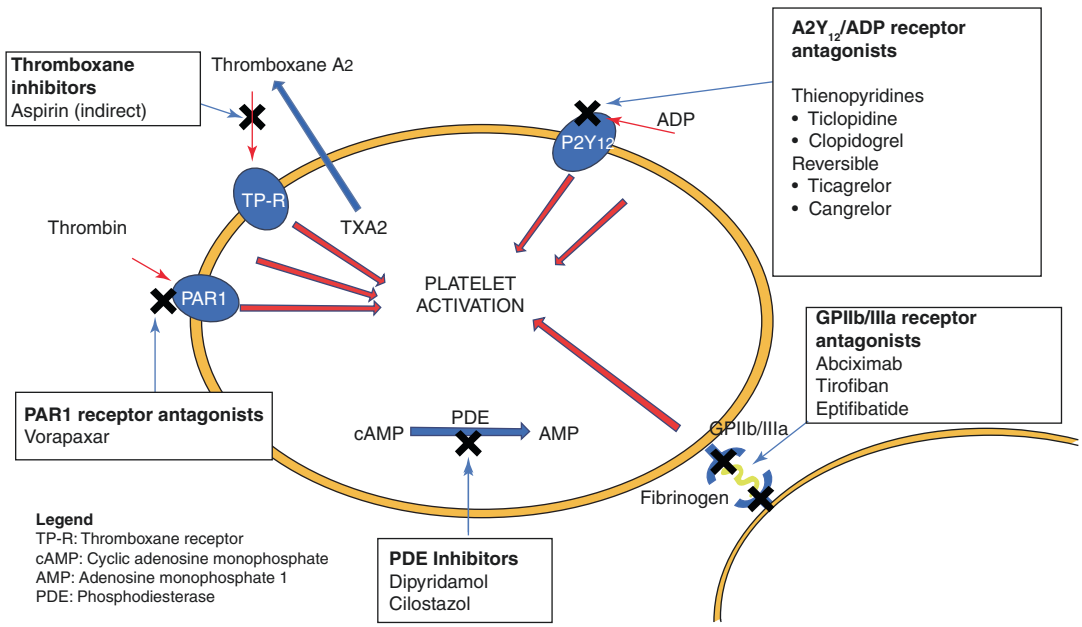


Fig. 4.2 Mechanism of action of antiplatelet agents

A2, which is a potent platelet aggregator. Aspirin is irreversible, non-selective cyclooxygenase inhibitor. It has more specificity for COX 1 receptors than COX 2 receptors. It is most widely available, frequently used, and extensively backed by clinical trials for its use in intervention and stroke treatment. It has onset of action within 15–30 min and its effect on platelets lasts for 8–10 days due to irreversible inhibition [14]. Doses used during neurointervention typically range from 81 to 325 mg daily (Table 4.1). Most neurovascular interventionists start Aspirin 3–5 days before stenting procedure, but some consider it before 14–21 days. In case of hemorrhage, platelet transfusion may be considered to reverse the effects of aspirin. Common side effects include gastritis and ulceration.

4.3.2 ADP Antagonists/P2Y12 Inhibitors

ADP acts on P2Y1 and P2Y12 receptors concomitantly to activate platelets and cause aggregation. Thienopyridines (Clopidogrel, Ticlopidine, and Prasugrel) cause irreversible and competitive inhibition of P2Y12 receptors [15]. These are prodrugs that gets metabolized in vivo to form active form of drug, thus delaying onset of action. Loading dose is required to hasten to onset of action. Cytochrome P450 polymorphism, specially CYP2C19 polymorphism found in Asian population, causes different metabolism and clopidogrel resistance or hypo-responders [16]. Yet, this polymorphism is not consistently associated with increased thromboembolic events so routine testing of polymorphism by genetic testing is not required.

Clopidogrel is most commonly used with aspirin in dual antiplatelet therapy as it is most tolerated thienopyridine, with lesser side effects than ticlopidine and prasugrel [15]. It has a half-life of 7–8 h and onset of action is 2–4 h. It is given as 75 mg daily dose with 300–600 mg loading dose at onset of therapy. It causes lesser gastrointestinal bleeding than aspirin, but causes diarrhea, nausea, and vomiting. Ticlopidine is not a commonly used drug clinically due to its side effects profile, which includes marrow suppression, rarely thrombotic thrombocytopenic purpura (TTP), cholestatic jaundice, and colitis.

Prasugrel has a faster onset of action and more potent inhibition of platelet activation [17]. It causes more bleeding related complications than clopidogrel offsetting its benefits clinically. It can be used in those patients with clopidogrel resistance or in those unable to tolerate clopidogrel as a first-line agent. Usual dose regimens for intervention use are 5–10 mg daily with a 20–60 mg loading dose.

Ticagrelor is a noncompetitive antagonist of P2Y12 receptor [18]. It is not influenced by CYP polymorphisms. Ticagrelor has a median onset of action of 1.3–2 h. Commonly, it is used in patients who have thromboembolic complications in carotid stents or flow diverters. It is used as dual antiplatelet therapy with aspirin in suspected clopidogrel resistance. It is started with loading dose of 180 mg with daily maintenance of 90 mg twice a day. Commonest side effect requiring discontinuation of drug is respiratory discomfort.

4.3.3 GP IIb/IIIa Inhibitors

GP (glycoprotein) IIb-IIIa receptors are present on platelet plasma membrane which on activation bring about conformational change exposing binding sites for fibrinogen, vWF, and adhesion molecules [19]. GP IIb-IIIa inhibitors are highly potent, fast-acting antiplatelet agents. These are mostly used as rescue therapies in the treatment of acute thrombosis during or immediately after procedure.

Abciximab is a monoclonal antibody directed at the GPIIb-IIIa receptor [19]. It is administered intravenously (IV) or intra-arterially (IA). A bolus of 250 μg/kg inhibits platelet aggregation by 80% at 15 min post-administration. Platelet function reverses 50% in 48 h after stopping infusion. The effect of abciximab is reversed by platelet transfusion in case of life-threatening bleeding. The drug is cleared by reticuloendothelial system, so no dose adjustment is required in case of renal failure. Profound thrombocytopenia

Table 4.1 Drugs and doses commonly used in neuroendovascular surgery

No.	Drugs	Doses	Remarks
1	Aspirin (irreversible inhibitor cyclooxygenases 1 & 2)	Loading dose 325 mg PO maintenance doses ranging from 81 to 325 mg daily	• Onset 7–60 min. • At least 3–5 days prior to carotid or intracranial stenting • Many practitioners may start therapy as long as 14–21 days prior to a procedure • In emergency neuroendovascular interventions in which pre-procedure aspirin therapy is not possible, loading doses have varied from 200 to 650 mg
2	Clopidogrel (Plavix) (irreversible inhibitor P2Y12 ADP receptor)	Loading dose: 300 or 600 mg, followed by 75 mg daily	• Onset 2 h • Duration of action 3–7 days
3	Ticagrelor (Brilinta) (reversible inhibitor P2Y12 ADP receptor)	Loading dose: 180 mg, followed by 90 mg bid	• Onset 30 min • Duration of action 12–24 h • Dose should not be missed. • No problem of drug resistance compared to clopidogrel
4	Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)		
	(A) Abciximab (irreversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 0.25 mg/kg IV rapid bolus followed by 125 μg kg/min infusion (to a maximum of 10 mg/min) for 12 h.	• Onset 2 h • Duration of action 48 h • Can be reversed, if needed, with platelet transfusion • Drug is a monoclonal antibody
	(B) Eptifibatide (Integrilin) (reversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 180 μg/kg IV bolus Then a second 180 μg/kg IV bolus 10 min After the first bolus, followed by 2 μg/kg infusion for 12 h	• Onset immediate • Plasma half-life 2.5 h • Duration of action 2–4 h • Cannot be reversed with platelet transfusions
	(C) Tirofiban (reversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 25 μg/kg IV bolus. Then 0.15 μg/kg infusion for 12–24 h	• Onset 5 min • Half-life 2-h • Duration of action 3–8 h • Cannot be reversed with platelet transfusions
5	Prasugrel (irreversible inhibition of ADP receptor P2Y12)	Loading dose: 60 mg, followed by 10 mg QD	• Have better platelet inhibition than clopidogrel but higher bleeding rate

(continued)

Table 4.1 (continued)

No.	Drugs	Doses	Remarks
6	Heparin	Flush and irrigation—adult—10000 unit/L Pediatric (age < 6 years)—2000 unit/L. The initial bolus dose for an adult is about 60–80 μ/kg followed by 20–40 μ/kg every hour for long procedures. Pediatric loading dose is 50 unit/L	• Half-life: 90 min • Monitoring: ACT of 250–350 s, monitored every hour during procedure; APTT monitored every 6 h • Reversal: Protamine sulfate, 1 mg for 100 units (not to exceed 50 mg total)
7	Atropine	0.5–1 mg or 0.04 mg/kg IV q5min, Max. 3 mg	• Half-life: 2–3 h (>2 years and adults); 7 hr. (<2 years); 10 h (65–75 years) • Onset: Rapid (IV/IM)
8	Fentanyl	1–2 μg/kg IV bolus or 25–100 μg/dose PRN or 1–2 μg/kg/h by continuous IV infusion or 25–200 μg/h	• For analgesia and sedation. • Use undiluted or diluted in 250 mL of D5W
9	Nitroglycerin (NTG)	100 to 200 μg is commonly given intra-arterially to prevent artery spasm	• Treatment of catheter-induced vasospasm • It has an immediate effect and has a short duration of action of 3 to 5 min
10	Protamine	1 mg for 100 units	• Not to exceed 50 mg
11	Acetylcysteine	Tab 600 mg B.D	• Treatment of patients with renal insufficiency
12	Flumazenil		• Reversal of benzodiazepines
13	Furosemide		• Management of elevated intracranial pressure
14	Glucagon	To inhibit motility of stomach and small bowel: 0.2–0.5 mg IV over 1 min or 1 mg IM To inhibit motility of colon: 0.5–0.75 mg IV over 1 min or 1–2 mg IM	• Control of gastric motility during spinal angiography
15	Mannitol	20%;0.5 to 1.5 g/kg IV infused over 30–60 min; may repeat q6-8hr	• Management of elevated intracranial pressure
16	Milrinone	Loading 0.1 mg/kg IV Followed by continuous IV infusion of 0.75 μg/kg/min for 7 to 10 days	• Used for vasospasm in SAH
17	Ondansetron	4 to 16 mg	• Antiemetic • IV, IM, oral
18	Alteplase (tPA)	0.9 mg/kg IV; not to exceed 90 mg total dose; administer 10% of the total dose as an initial IV bolus over 1 min and the remainder infused over 60 min	• Rule out contraindication for tPA • Powder for injection (reconstitute before use) Dosage forms: 50 mg, 100 mg

caused by the drug needs monitoring during treatment.

Eptifibatide is a cyclic heptapeptide derived from rattlesnake venom [20]. It binds reversibly to GPIIb-IIIa receptor. A bolus dose of 180 μg/kg intravenously achieves over 80% inhibition of platelet function in 15 min. Platelet function recovers by 50% in 4 h after stopping the infusion. Eptifibatide has renal clearance, so dose adjustment is needed in case of renal failure.

Tirofiban binds reversibly to the GPIIb-IIIa receptor [21]. It has a faster onset of action. A bolus dose of 0.4 μg/kg causes 90% inhibition of platelet aggregation after 10-40 min. Platelet function returns to near baseline within 4–8 h of stopping of the infusion. Tirofiban is also renally cleared, so dose must be adjusted in patients with renal failure.

4.3.4 Phosphodiesterase Inhibitors

Cilastazol and dipyridamole act as phosphodiesterase (PDE) inhibitors [22]. PDE inhibitors, through cAMP and cGMP mediated metabolism inhibition decreases platelet activation. It has secondary effect of vasodilation. Cilastazol is in cardiac setting along with aspirin and clopidogrel but it can cause tachycardia and arrhythmia [23]. It is contraindicated in cardiac failure.

Antiplatelet therapy remains cornerstone in periprocedural management in intracranial, extracranial stenting, flow diverter placement, and placing Woven EndoBridge (WEB) Device™ [13]. In patients who are undergoing extracranial angioplasty and stenting, dual antiplatelets; aspirin, and clopidogrel are started 5 days before the planned procedure [24]. Appropriate antihypertensive medications are given to control blood pressure to prevent procedure-related complications like bleeding and cerebral hyperperfusion syndrome. During the procedure, Atropine 0.5 mg IV is given prior to dilation angioplasty to prevent baroreceptor-induced bradycardia and hypotension [25]. If a patient develops bradycardia (HR < 60 bpm), Atropine is administered 0.75 mg IV bolus dose. Post procedure, patients should receive dual antiplatelets aspirin (150 mg once a day) and clopidogrel (75 mg once a day) with high dose statin for 30 days, followed by continuation of aspirin (150 mg once a day). Other treatment options post procedure includes aspirin 325 mg once a day, or a combination of aspirin 81 mg once a day and ticagrelor 90 mg twice a day for 30 days followed by continuing aspirin thereafter.

In patients who are undergoing intracranial angioplasty-stenting and flow diverter placement, dual antiplatelets; aspirin (150 mg once a day) with clopidogrel (75 mg once a day) are given 5 days prior to procedure. Strict medical management to maintain blood pressure below 140 mmHg systolic (<130 mmHg in diabetic patients), low-density lipoprotein (LDL) below 70 mg/dl is an important part of management in patients with intracranial atherosclerotic diseases.

Prior to placing WEB device, patients can be administered single antiplatelet; aspirin 150 mg once a day 5 days prior or loading dose of aspirin 300 mg on the day of procedure [13]. In post-procedure management, dual antiplatelet therapy is not universally employed when using the WEB. Some interventionists consider aspirin 75–100 mg daily and clopidogrel 75 mg daily for 3 months, especially when an adjunctive stent or endoluminal flow diverter is used.

4.4 Anticoagulating Agents

Coagulation factors along with platelets form stable clot. Exposure to tissue factor or denuded endothelial surface activates coagulation cascade, forming activated factor X (Xa). This factor converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. Insoluble fibrin forms clot, which further propagates to achieve hemostasis. Figure 4.3 demonstrates coagulation cascade and site of anticoagulation drugs. This topic limits discussion to heparin which is most commonly used in intervention procedure.

Heparin inhibits thrombosis by preventing Factor X activation [26]. The overall risk of thromboembolic complications during neurointerventional procedures is significant.

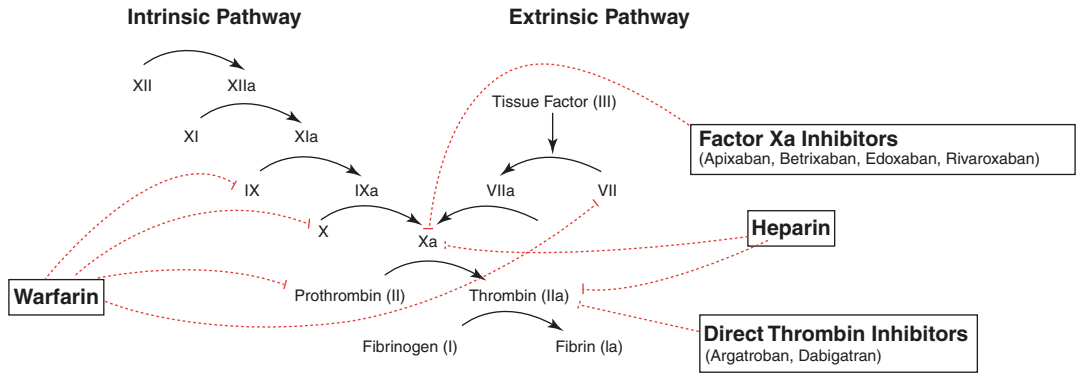


Fig. 4.3 Coagulation cascade and site of anticoagulation drugs

Anticoagulation with unfractionated heparin is standard for most procedures. Anticoagulation during diagnostic cerebral angiograms is usually done, but with a lower dose. The only exception to the use of heparin is in subarachnoid hemorrhage where anticoagulation is deferred until one or two coils are deployed to secure the aneurysm. All the catheters and sheaths should be continuously flushed with heparinized saline (3000–5000 Units in 1 L normal saline) to prevent clot formation. Dosing for flush and irrigation during procedure in adults is 10,000 units/L and in pediatric (age < 6 years) is 2000 units/L. The initial bolus dose for adult is about 60–80 μ/kg followed by 20–40 μ/kg every hour for long procedures. Pediatric loading dose is 50 units/L. Half-life of heparin is 90 min. Monitoring of heparin therapy is done by measuring activated clotting time (ACT), which is kept between 250 and 350 s. It is monitored every hour during a prolonged procedure. During diagnostic digital subtraction angiography (DSA), heparin is given at the dose of 20 mg/kg IV [26]. Bleeding is the commonest side effect. Heparin effects are reversed by Protamine sulfate (1 mg for 100 units of heparin, not to exceed 50 mg total). Partial thromboplastin time should be monitored at 5–15 min after dose, followed by 2–8 h afterward. Protamine sulfate has an independent weaker anticoagulant tendency in higher doses. Heparin is contraindicated in patients with a known allergic tendency to this drug and in patients with a history of heparin-induced thrombocytopenia.

Alternatives to heparin include Argotraban, Bivalirudin, lepirudin, and danaparoid [27]. They are used in patients with heparin-induced thrombocytopenia requiring anticoagulation.

4.5 Treatment of Vasospasm: (Chemical Angioplasty)

Following class of drugs are used to treat vasospasm in subarachnoid hemorrhage.

(A) Calcium Channel Blocker: Nimodipin, Nicardipin, Verapamil
(B) Phosphodiesterase inhibitors: Papavarin, Milrinone
(C) Nitroglycerin (NTG)

Calcium channel blockers are commonly used as intra-arterial vasodilators. No single agent has been shown to be more efficacious than others. Intra-arterial infusion of these agents can be used to treat vessels that cannot be dealt with, or are difficult to treat with balloon angioplasty, such as distal branches and the A1 segment.

Nicardipine (dose 0.5 to 40 mg) is diluted in 0.9% NaCl (without heparin) to a concentration of 0.1 mg/mL [28]. It is injected 1 mL through the micro Catheter to a maximal dose of 5 mg per

vessel. Nicardipine precipitates in heparinized saline, so the system should be flushed with saline without heparin before and after injecting nicardipine. Angiographic improvement is demonstrable in almost all arteries, neurologic improvement occurs in around 42% of patients. Nicardipine causes transient intracranial pressure (ICP) elevation.

Nimodipine (dose 0.8 to 3.2 mg) is a preferred drug for intra-arterial injection [29]. Nimodipine is diluted in saline to 25% concentration. Slow infusion at the rate of 2 mL/min is done, with each vessel infused for 10–30 min. Total dose is per vessel is 1–3 mg and total dose per patient is 5 mg. Clinical improvement is observed in about 76% of patients. Blood pressure needs to be monitored as hypotension is a major side effect. Nimodipine is also be used for irrigation during procedures through guiding catheter to prevent artery to go into spasm (10–15 mL in 1 L pressure bag).

Verapamil (dose 2 to 120 mg) is diluted as 5 mg vial with normal saline to a concentration of 1 mg/mL [30]. It is injected as 10–20 mg per vessel for a maximum of 20 mg per carotid. Transient hypotension and bradycardia are side effects. Neurological improvement is seen in 29% of patients.

Papavarin (dose 200–400 mg), once a popular intraarterial drug, now has fallen out of favor because of short-lived effect and dramatic rise of intracranial pressure, decreased brain oxygenation, and incidences of ischemic infarctions of infused territories [31]. It is administered as 300 mg at a rate of 3 mL/min.

Nitroglycerine (dose 30 microgram in individual artery) is used intra-arterially, but can cause raised intracranial pressure and hypotension [32].

Milrinone (dose 2.5–24 mg), acts by inhibiting phosphodiesterase 3 causing vasodilation and also has inotropic properties (inodilator) [33]. It is used as a loading dose of 0.1 mg/kg Iv followed by infusion of 0.75 μg/kg/min for 7–10 days. It can cause hypotension and hypokalemia.

4.6 Radial Artery Cocktail

It is used to prevent spasm of artery during radial access. It contains 10 mL of saline with Heparin (5000 IU), Verapamil (2.5 mg), Lidocaine (2%, 1 mL), and Nitroglycerine (0.1 mg) [34].

Contrast Agents and Treatment of Contrast-Induced Nephropathy and Allergic Reactions Nonionic contrast agents are safer and less allergenic than ionic preparations [35]. Most commonly used contrast agent in cerebral angiography is Iohexol (Omnipaque®, GE Healthcare, Princeton, NJ). It is a low osmolality, nonionic contrast agent, and is relatively inexpensive. It is used as 300 mg I/mL in diagnostic angiograms and 240 mg I/mL in neurointerventional procedures. Patients with normal renal function can tolerate as much as 400–800 mL of Omnipaque®.

Maximum tolerable volume of 300 mg I/mL nonionic contrast agent is calculated by formula—Weight in kg × 5 (adults) or 4 (children)/serum creatinine (mg/dl).

Contrast-induced nephropathy (CIN) remains most worrisome issue clinically [36]. Clinically significant contrast-induced nephropathy is considered if serum creatinine rises by 0.5 mg/dl or 25% above baseline during 48–72 h following contrast injection. In severe cases, serum creatinine continues to rise for 5–10 days, sometimes requiring dialysis. Incidence of CIN increases with serum creatinine level, 0% at <1.5 mg/dl, 50–75% at 1.6–4.5 mg/dl, to 90–100% at >4.5 mg/dl. Risk factors for CIN include age above 60 years, serum creatinine level above1.5 mg/dl, diabetes mellitus, dehydration, hypertension, hyperuricemia, cardiovascular disease and use of diuretics, and in patients having paraproteinemias.

Methods to reduce risk of CIN include reduction in use of contrast, use of Visipaque™ (270 mL I/mL) instead of Omnipaque™, oral hydration (water, 500 mL prior to the procedure and 2000 mL after the procedure), intravenous

hydration (0.9% NaCl), intravenous hydration with sodium bicarbonate. Acetylcysteine (600 mg orally twice a day, one the day before and on the day of the procedure) is an antioxidant functioning as a free radical scavenger. It also stimulate intrarenal vasodilation. Acetylcysteine has been shown to reduce serum creatinine elevation in patients undergoing radiological procedures using nonionic, low-osmolality contrast material. Prophylactic administration of acetylcysteine (600 mg PO twice a day) and 0.45% saline IV, before and after administration of the contrast agent, has been shown to decrease serum creatinine compared to patients receiving saline only. Sodium bicarbonate infusion has also been shown to reduce rates of CIN. Sodium bicarbonate (150 mEq) in 1 L of 5% dextrose is infused at 3 mL/kg/h for 1 h prior to procedure, at 1 mL/kg/h through procedure, and for 6 h after procedure. Incidence of CIN can be decreased by hydration with 0.45% saline or 0.9% saline beginning 12 h before and continuing 12 h after angiography.

Contrast allergy is one of the commonest side effects noted [37]. Prednisolone 50 mg orally (or hydrocortisone 200 mg IV) is given 13, 7, and 1 h prior to contrast injection. Diphenhydramine (50 mg IV, IM, or PO 1 h prior to contrast injection) is also used. Steroids should be given at least 6 h prior to the procedure [38]. Administration less than 3 h prior to the procedure does not reduce the risk of an adverse reaction.

4.7 Statins (Hypolipidemic Therapy)

Atherosclerotic diseases manifestation including transient ischemic attack and stroke need high-dose statin therapy use to reduce further risk. Atorvastatin 80 mg daily or Rosuvastatin 20 mg daily have been advised [38].

References

1. Lv X, Li W, Li Y. Training residents and fellows in the procedure of diagnostic cervicocerebral angiography: techniques to avoid complications. Neurol India. 2018;66(3):652–6.
2. Soize S, Foussier C, Manceau PF, Litré CF, Backchine S, Gawlitza M, Pierot L. Comparison of two preventive dual antiplatelet regimens for unruptured intracranial aneurysm embolization with flow diverter/disrupter: a matched-cohort study comparing clopidogrel with ticagrelor. J Neuroradiol. 2019;46:378–83.
3. Enomoto Y, Yoshimura S, Sakai N, Egashira Y, Japanese Registry of Neuroendovascular Therapy Investigators. Current perioperative management of anticoagulant and antiplatelet use in neuroendovascular therapy: analysis of JR-NET1 and 2. Neurol Med Chir (Tokyo). 2014;54(1):9–16.
4. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021 Mar;6(1):I–LXII. https://doi.org/10.1177/2396987321989865.
5. Semba CP, Sugimoto K. Razavi MK; Society of Cardiovascular and Interventional Radiology (SCVIR). Alteplase and tenecteplase: applications in the peripheral circulation. Tech Vasc Interv Radiol. 2001 Jun;4(2):99–106. https://doi.org/10.1016/s1089-2516(01)90003-4.
6. Moussaddy A, Demchuk AM, Hill MD. Thrombolytic therapies for ischemic stroke: triumphs and future challenges. Neuropharmacology. 2018 May 15;134(Pt B):272–9.
7. Zheng H, Yang Y, Chen H, Li C, Chen Y, Shi FD, Yang L, Cui X, Lu Z, Liang Y, Cui S, Xu A, Wu Y, Sun Y, Wang Y. Thrombolysis with alteplase 3-4.5 hours after acute ischaemic stroke: the first multicentre, phase III trial in China. Stroke Vasc Neurol. 2020 Sep;5(3):285–90.
8. Niforatos JD, Pescatore RM. Financial relationships with industry among guideline authors for the management of acute ischemic stroke. Am J Emerg Med. 2019 May;37(5):921–3.
9. Safouris A, Kargiotis O, Magoufis G, Katsanos AH, Stamboulis E, Tsivgoulis G. Early neurological deterioration during Alteplase infusion for acute ischemic stroke: an uncommon complication of intravenous thrombolysis. Neurologist. 2017 May;22(3):90–1.
10. Warach SJ, Dula AN, Milling TJ Jr. Tenecteplase thrombolysis for acute ischemic stroke. Stroke. 2020 Nov;51(11):3440–51.
11. Oliveira M, Fidalgo M, Fontão L, Antão J, Marques S, Afreixo V, Gregório T. Tenecteplase for thrombolysis in stroke patients: systematic review with meta-analysis. Am J Emerg Med. 2021 Apr;42:31–7.
12. Nishi H, Nakahara I, Matsumoto S, et al. Platelet reactivity and hemorrhage risk in neurointerventional procedures under dual antiplatelet therapy. J Neurointerv Surg. 2016;8(9):949–53.
13. Adeeb N, Griessenauer CJ, Moore JM, et al. Ischemic stroke after treatment of intraprocedural thrombosis during stent-assisted coiling and flow diversion. Stroke. 2017;48(4):1098–100.
14. Hwang G, Jung C, Park SQ, et al. Thromboembolic complications of elective coil embolization of

unruptured aneurysms: the effect of oral antiplatelet preparation on periprocedural thromboembolic complication. Neurosurgery. 2010;67(3):743–8.
15. Ge H, Lv X, Ren H, Jin H, Jiang Y, He H, Liu P, Li Y. Influence of CYP2C19 genetic polymorphisms on clinical outcomes of intracranial aneurysms treated with stent-assisted coiling. J Neurointerv Surg. 2017;9(10):958–62.
16. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360(4):354–62.
17. Leslie-Mazwi TM, Chandra RV, Oh DC, et al. Novel use of prasugrel for intracranial stent thrombosis. J Neurointerv Surg. 2011;3(4):358–60.
18. Atallah E, Saad H, Bekelis K, El-Chalouhi N, Tjoumakaris S, Hasan D, Eller G, Stidd D, Rosenwasser RH, Jabbour P. The use of prasugrel and ticagrelor in pipeline flow diversion. JHN J. 2018;13:5. https://doi.org/10.29046/JHNJ.013.2.005.
19. Qureshi AI, Suri MF, Ali Z, et al. Carotid angioplasty and stent placement: a prospective analysis of perioperative complications and impact of intravenously administered abciximab. Neurosurgery. 2002;50(3):466–75.
20. Qureshi AI, Siddiqui AM, Hanel RA, et al. Safety of high-dose intravenous eptifibatide as an adjunct to internal carotid artery angioplasty and stent placement: a prospective registry. Neurosurgery. 2004;54(2):307–17.
21. Onal Y, Acunas B, Samanci C, Ugurlucan M, Umutlu MR, Oztas DM, Alpagut U. Preliminary results of stent-assisted coiling of wide-necked visceral artery aneurysms via self-expandable neurointerventional stents. J Vasc Interv Radiol. 2019 Jan;30(1):49–53.
22. Moncada S, Korbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet. 1978 Jun 17;1(8077):1286–9.
23. Barta J, Sanganalmath SK, Kumamoto H, Takeda N, Edes I, Dhalla NS. Antiplatelet agents sarpogrelate and cilostazol affect experimentally-induced ventricular arrhythmias and mortality. Cardiovasc Toxicol. 2008 Fall;8(3):127–35.
24. Hassan AE, Zacharatos H, Vazquez G, Rodriguez GJ, Suri MF, Tummala RP, Taylor RA, Qureshi AI. Low risk of intracranial and systemic hemorrhages in patients on dual antiplatelet treatment beyond 1 month following neuroendovascular angioplasty and/or stent placement. J Neuroimaging. 2012 Jan;22(1):67–73.
25. Lin PH, Zhou W, Kougias P, El Sayed HF, Barshes NR, Huynh TT. Factors associated with hypotension and bradycardia after carotid angioplasty and stenting. J Vasc Surg. 2007 Nov;46(5):846–54.
26. Zenteno M, Moscote-Salazar LR, Alvis-Miranda H, Lee A. Use of heparin in neurointervention: a review of the literature. Rom Neurosurg. 2013;20:369–74.
27. Hassan AE, Memon MZ, Georgiadis AL, Vazquez G, Suri MF, Qureshi AI. Safety and tolerability of high-intensity anticoagulation with bivalirudin during neuroendovascular procedures. Neurocrit Care. 2011;15(1):96–100.
28. Badjatia N, Topcuoglu MA, Pryor JC, et al. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. AJNR Am J Neuroradiol. 2004;25:819–26.
29. Biondi A, Ricciardi GK, Puybasset L, et al. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. AJNR Am J Neuroradiol. 2004;25:1067–76.
30. Feng L, Fitzsimmons B-F, Young WL, et al. Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: safety and 2-year experience. AJNR Am J Neuroradiol. 2002;23:1284–90.
31. Vajkoczy P, Horn P, Bauhuf C, et al. Effect of intra-arterial papaverine on regional cerebral blood flow in hemodynamically relevant cerebral vasospasm. Stroke. 2001;32:498–505.
32. Ghani GA, Sung YF, Weinstein MS, Tindall GT, Fleischer AS. Effects of intravenous nitroglycerin on the intracranial pressure and volume pressure response. J Neurosurg. 1983;58:562–5.
33. Dorigo P, Fraccarollo D, Gaion RM, Santostasi G, Borea PA, Floreani M, Mosti L, Maragno I. New inotropic agents: milrinone analogs. Gen Pharmacol. 1997 May;28(5):781–8.
34. Pate G, Broderick B. Variations in the usage and composition of a radial cocktail during radial access coronary angiography procedures. Ir Med J. 2011 Oct;104(9):280–1.
35. Barrett BJ, Parfrey PS, Vavasour HM, O'Dea F, Kent G, Stone E. A comparison of nonionic, low-osmolality radiocontrast agents with ionic, high-osmolality agents during cardiac catheterization. N Engl J Med. 1992;326:431–6.
36. Katholi RE, Taylor GJ, Woods WT, et al. Nephrotoxicity of nonionic low-osmolality versus ionic high-osmolality contrast media: a prospective double-blind randomized comparison in human beings. Radiology. 1993;186:183–7.
37. Aykan AÇ, Altıntaş Aykan D, Katırcıbaşı MT, Özgül S. Management of radio-contrast allergy in radiocontrast allergic patients undergoing coronary angiography and intervention. Kardiologiia. 2020 Nov 12;60(10):62–5.
38. Raggi P, Gadiyaram V, Zhang C, Chen Z, Lopaschuk G, Stillman AE. Statins reduce Epicardial adipose tissue attenuation independent of lipid lowering: a potential pleiotropic effect. J Am Heart Assoc. 2019 Jun 18;8(12):e013104.

Current Devices and Uses

5

Marios Lampros, Xianli Lv, and George A. Alexiou

Abstract

The prevalence of saccular intracranial aneurysms is about 1–3% in the general population. The introduction of the Guglielmi detachable coil system, three decades ago, provided a new approach for treating aneurysms without the need for a craniotomy. In the new era of technological advancements, several devices have been developed to aid endovascular treatment such as flow diverters, flow disrupters, and stent- or balloon-assisted coil embolization. Herewith, we provide a summary of the latest innovations in the endovascular treatment of cerebral aneurysms.

Keywords

Cerebral aneurysm · Endovascular surgery
Coil · Stent · Embolization · Device

M. Lampros · G. A. Alexiou (✉)
Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece
e-mail: galexiou@uoi.gr

X. Lv
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

5.1 Introduction

The prevalence of saccular intracranial aneurysms (IA) in the general population is approximately 1–3%, with most being asymptomatic until the moment of rupture. Rupture of an aneurysm and the following subarachnoid hemorrhage (SAH) is an emergency event that is linked with a high mortality rate (25–45%) as well as with possible significant permanent neurological impairment. The quality of life is dramatically reduced in patients with ruptured IA. Numerous risk factors for IA development have been suggested, such as Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease (ADPKD), neurofibromatosis, and positive family history of IA. The risk of IA rupture is higher in women, with the sex ratio being 1,5 [1–3].

Clipping of the aneurysm neck with craniotomy was the optimal treatment of IA. All that changed 30 years ago with the introduction of endovascular approaches for the treatment of IA and especially the Guglielmi detachable coil system's entry. Dr. Fedor Serbinenko is considered the father of endovascular neurosurgery, as it was him who in 1974 first proposed the use of a detachable balloon for the management of intracranial aneurysms and vascular lesions. Early technical difficulties, such as the device's cumbrousness, were the main reason for this method

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_5

being discontinued, but the era of endovascular neurosurgery had just begun [2–4].

The initial dilemma of "clip vs. coil" after the widespread use of the Guglielmi device led to the conduction of two large studies, the International Subarachnoid Aneurysm Trial (ISAT) and the International Study of Unruptured Intracranial Aneurysms (ISUIA). Ultimately, these studies' results supported the use of coil over clip in terms of overall morbidity and mortality (ISAT: 30% vs. 23%, ISUIA: 13% vs. 10%). Open approaches are still utilized in selected cases of IA (e.g., in the presence of complex or giant aneurysms, aneurysms of the posterior circulation, or failure of endovascular approaches) [2, 3, 5, 6].

Currently, novel devices have been developed for IA's endovascular treatment, such as balloon-assisted coiling system (BAC), stent-assisted coiling system (SAC), Flow Diverters, Flow Disrupters, and Medina embolization system (Table 5.1). All these devices were designed to treat IA, which cannot be feasibly treated with the standard coil method and otherwise would require an open approach [2, 3]. Herewith, we provide a summary of the latest innovations in the endovascular treatment of cerebral aneurysms. The indications, efficacy, and complications associated with the use of each device will be discussed.

5.1.1 The Guglielmi Detachable Coil System (GDC)

The filling of the aneurysmal cavity for IA treatment had been initially described by Werner et al. back in 1940 when via an extravascular approach they attempted to puncture the aneurysmal cavity and introduce a wire into the aneurysm [7]. During the next 50 years, several other authors described various extravascular and intravascular (including Serbinenko) approaches to occlude the aneurysmal cavity. The success rates of those methods varied, with many technical difficulties. These issues, together with the widespread use of aneurysmal clipping, were the main reason these methods did not find widespread implementation. Nevertheless, endovascular treatment's previous efforts resulted in the innovation of new delivery systems such as microcatheters of variable stiffness ("Trackers"), which can pass through the arterial bifurcations. The development of trackers was a step forward, but two significant problems persisted, namely the lack of appropriate occluding embolization materials and a mechanism for material detachment from the catheter. Finally, in 1990, Guglielmi gave a solution to the aforementioned problems, with the development of appropriate coil materials and a detachment mechanism based on electrolysis. To date, GDC has been systematically used

Table 5.1 Devices that have been developed for intracranial aneurysms endovascular treatment

Technique/ device	Mechanism	Main indication	Complications
GDC	Embolization	Berry aneurysms	TE, IOR, RC, RB
BAC	Embolization	Wide neck (over 4 mm), dome/neck ratio < 1,5)	TE, IOR, RC, RB
SAC	Embolization, flow diversion	Wide neck (over 4 mm), dome/neck ratio < 1,5), Unruptured aneurysms	TE, IOR, stent stenosis and migration
Flow diverters	Flow diversion	Large/giant aneurysms, or very small aneurysms, Unruptured aneurysms	TE, rupture in the latent phase, cerebral hemorrhage
Flow disrupters	Flow disruption	Large/giant aneurysms, no need for antiplatelet regimen	TE, IOR, rupture in the latent phase
Medina	Hybrid (embolization and flow diversion)	Wide neck aneurysms	Stroke in 6 months, IOR

TE thromboembolism; *IOR* intraoperative rupture; *RC* recanalization; *RB* rebleeding

worldwide and is considered the "gold-standard" for the management of brain aneurysms [8, 9].

The entirety of GDC embolization procedure is accomplished under fluoroscopic guidance while the patient is under general anesthesia, or if possible, sedation. The next step is to confirm access to the femoral artery with a femoral French (F) sheath. The delivery system is promoted via the sheath. The sheath size is usually 6F or 7F, with 7F sheaths preferred when there is a possibility to use a stent or a balloon [10]. The Seldinger technique is utilized to access the femoral artery [11]. When access to the femoral artery has been ensured, a guide catheter is navigated toward the aneurysm's parental artery with the help of a guidewire. The latter is followed by the insertion of a microcatheter via the initial catheter. When the microcatheter is at the level of the aneurysmal cavity a microwire is placed inside the microcatheter, and the microcatheter–microwire complex is guided into the aneurysmal cavity. Confirmation of microcatheter appropriate location (close to the aneurysm dome) is followed by guidewire removal and coils' introduction into the aneurysm. Three types of coils are currently used, the classic platinum-based GDC coil, the Matrix coil, which is a coil similar to GDC but with a polymer coverage (with the ability to induce thrombosis), and hydrogel coated coils. Initially, a 3-D "basket" coil is placed into the aneurysmal cavity to prevent the migration or bulging of the next placed coils in the parent vessel. After the initial 3-D coil placement, the procedure continues with the placement of additional softer coils until the cavity is occluded. The success of the method is confirmed with angiography (with no inflow into the aneurysm). Finally, by electrolysis, there is a detachment of the coil from the microcatheter [8–10, 12, 13] (Fig. 5.1).

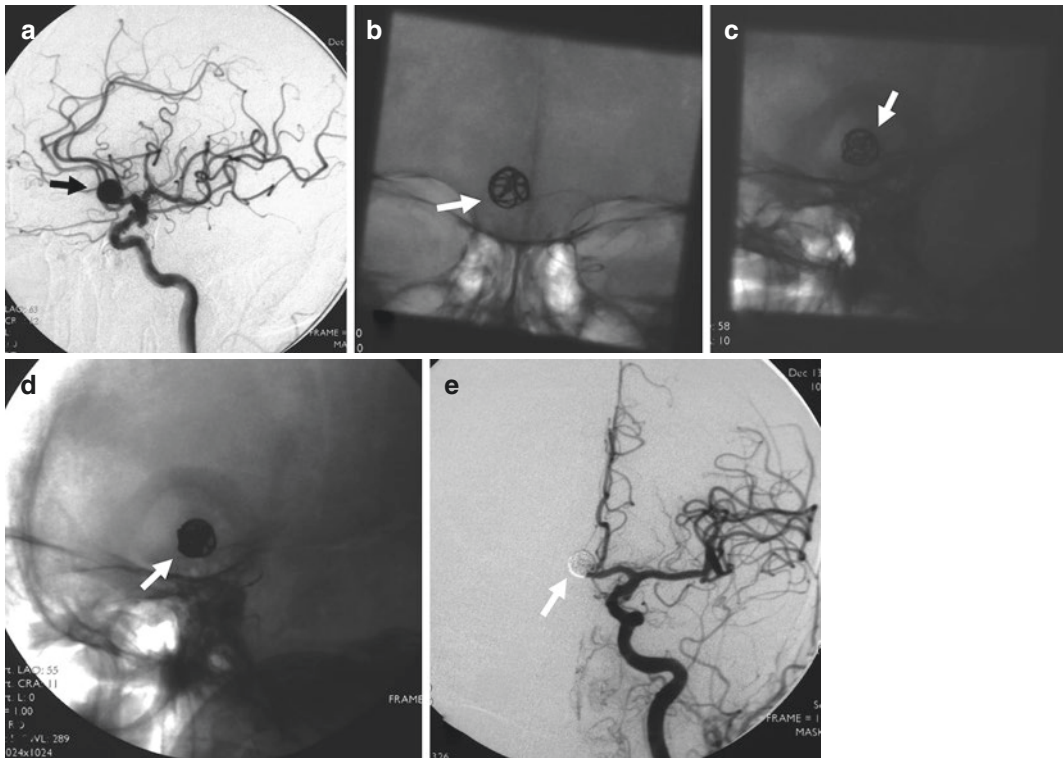


Fig. 5.1 A 76-year-old woman with an anterior communicating artery aneurysm was coiled. (**a**) Lateral view of the left internal carotid artery injection showing the aneurysm of the anterior communicating artery (arrow). (**b**) Frontal view of the unsubtracted image showing the first 3-D coil. (**c**, **d**) Lateral view of the unsubtracted images showing subsequent coils were inserted (arrows). (**e**) Frontal view of the left internal carotid artery injection after aneurysm coiling showing complete occlusion of the aneurysm (arrow)

The two major and life-threatening complications of coil embolization are thromboembolic events and intraoperative rupture. The frequency of thromboembolic events during coil embolization is approximately 5–30%, with the higher frequencies observed in embolization of ruptured aneurysms, wide-neck aneurysms, or in the case of large-giant aneurysms (Fig. 5.2). Nevertheless,

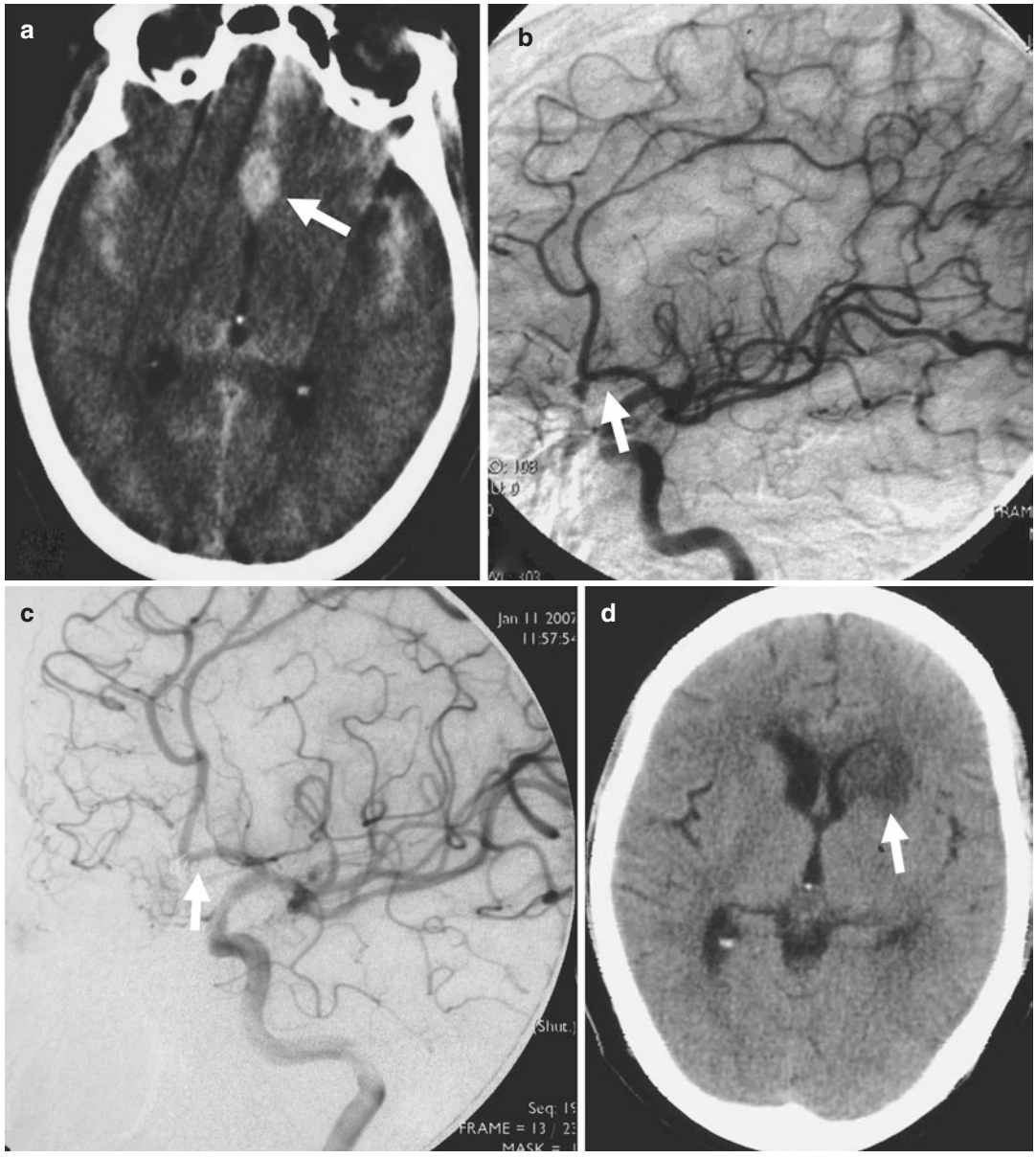


Fig. 5.2 A 44-year-old woman. (**a**) Cranial CT scanning showing subarachnoid hemorrhage from an anterior communicating artery complex aneurysm. (**b**) Oblique view of the left internal carotid artery angiogram showing a left dominant filling of the anterior communicating artery complex and aneurysm. Noting the Heubner's artery arising from the aneurysm neck (arrow). (**c**) Working angle view of the left internal carotid artery angiogram after aneurysm occlusion showing the disappearance of the Heubner's artery due to the retrograde thrombosis (arrow). (**d**) Cranial CT on day 4 after treatment showing the infarction of the head of the caudate nucleus on the left side (arrow)

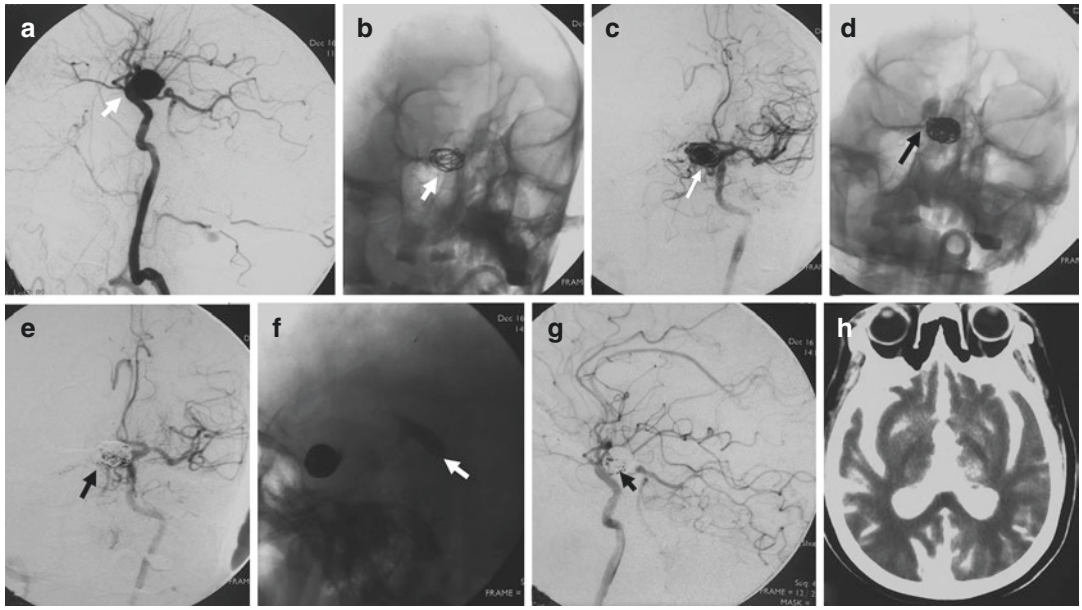


Fig. 5.3 A 68-year-old woman with an incidental paraclinoid aneurysm of the left internal carotid artery. (**a**) Lateral view of the left internal carotid artery injection showing a large paraclinoid aneurysm (arrow). (**b**) Oblique projection of the unsubtraction image showing the first 3-D coil in the aneurysm sac. (**c**) Intraoperative angiogram of the left internal carotid artery. (**d**) Intraoperative unsubtraction image showing the coil mass in the aneurysm sac and contrast extravasation (arrow). (**e**) Frontal projection of the final angiogram image showing no contrast extravasation and incomplete occlusion of the aneurysm (arrow). (**f**) Lateral projection of the unsubtraction image showing the coil mass in the aneurysm sac and contrast extravasation (arrow). (**g**) Lateral projection of the final angiogram image showing no contrast extravasation and incomplete occlusion of the aneurysm (arrow). (**h**) Postprocedural CT image showing diffuse contrast medium extravasation and an enlarged ventricle

some authors propose that the real rate of thromboembolism could be as high as 50–70%, but only a small percentage of them will occur with neurological deficits and will lead to fatal events. The introduction of Diffusion-Weighted Images (DWI)/MRI gave the ability to highlight "small" silent strokes early after the procedure. Thromboembolism is a well-known complication, and a dual-antiplatelet regimen (in unruptured aneurysms) and low molecular weight heparin is administered in the patients before the operation to prevent this complication. Typically, an arterial blood flow obstruction is seen in angiography. Treatment of thromboembolism includes intra-arterial use of antiplatelet, anticoagulant, or other thrombolytic agents such as urokinase with an aim of artery recanalization. Another common treatment option during operation includes mechanical thrombectomy with a stent [2, 10, 14–16].

Intraoperative rupture is the second most common (2–4%) and deadliest complication of IA coil embolization (Fig. 5.3). The mortality rate of intraoperative rupture is approximately 15%. As in thromboembolism, the intraoperative rupture rate is higher in previously ruptured aneurysms. The extravasation of contrast medium suggests aneurysm rupture. The first step after the rupture diagnosis is the injection of protamine to reverse the anticoagulative effect of heparin. Administration of mannitol is required to reduce the raised intracranial pressure. The coil that caused the perforation should remain in the site as it may tamponade the perforation. Instead of removing it, a second microcatheter should be inserted in the aneurysmal cavity to place more coils until the extravasation stops. In the case of an early rupture, the inflation of a non-detachable balloon in the aneurysm's parental artery may limit the extent of bleeding [10, 16, 17].

Aneurysm recanalization (or regrowth) is another well-known complication of coil embolization and may occur in approximately 2–10% of patients at some point after the operation. Despite that, the recanalization would not be significant and not require treatment in half of the patients with this complication. The wide neck (over 4 mm) of the aneurysm is considered a major risk factor for aneurysm regrowth and may lead to recurrence in 85% of the patients treated with the GDC system. The latter is one of the main reasons novel endovascular devices were developed to treat such aneurysms (Fig. 5.4). Rebleeding of the aneurysm is another complication after IA embolization and occurs in approximately 1% of the patients [16, 18].

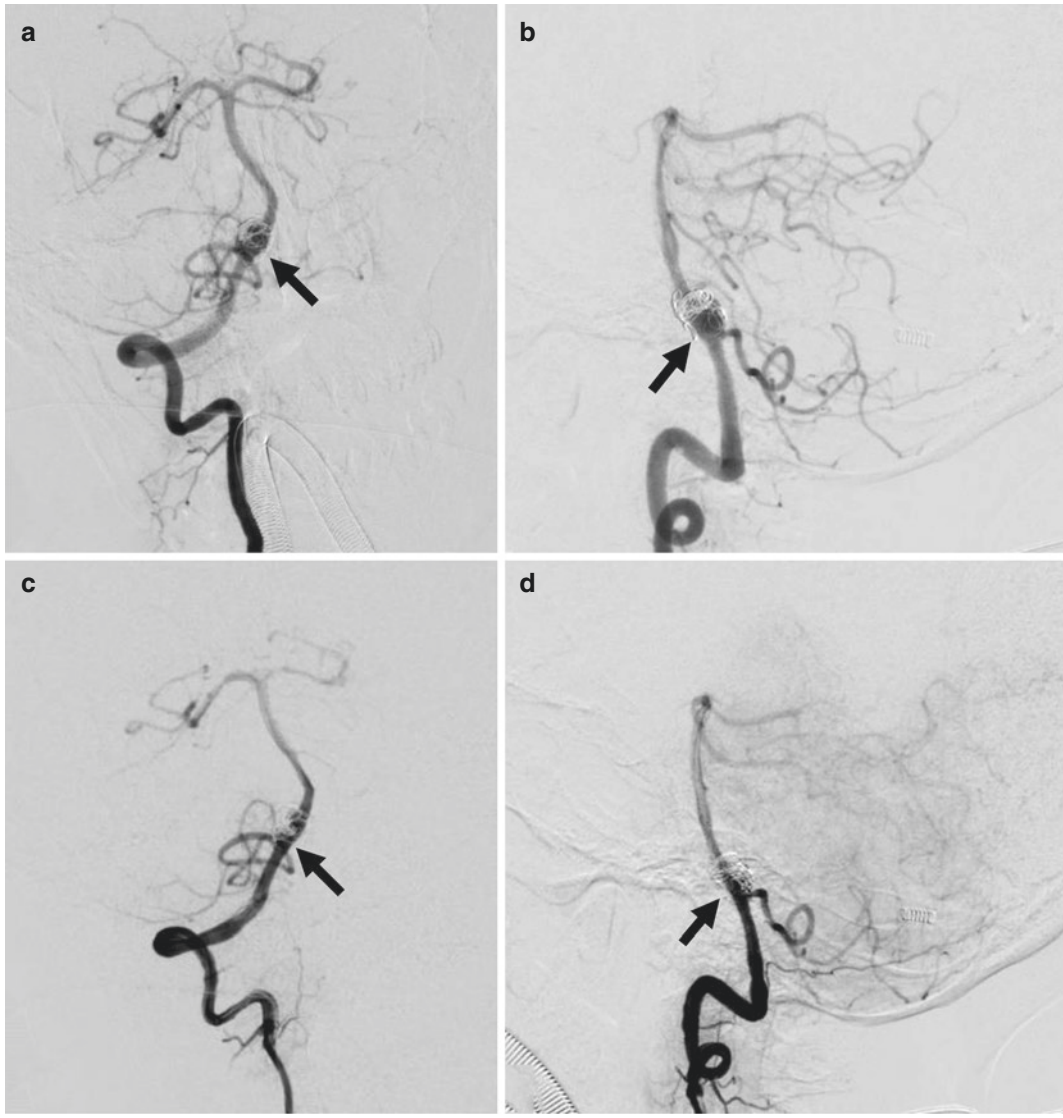


Fig. 5.4 A 50-year-old woman presented with a recurrent vertebral artery-posterior inferior cerebellar artery dissecting aneurysm. Frontal view (**a**) and lateral view (**b**) of the right vertebral artery injection showing a recurrent dissecting aneurysm after LVIS stent-assisted coiling (arrows). Frontal view (**c**) and lateral view (**d**) of the right vertebral artery injection showing the aneurysm was retreated with 3.5 mm × 35 mm Tubridge flow diversion (Microtherapeutic, Shanghai, China) and coils (arrows)

5.1.2 Balloon Assisted Coiling (BAC)

The GDC system for the treatment of berry aneurysms soon became the procedure of choice, but results were poor for aneurysms with a wide neck or giant aneurysms. The main reasons for failure were the aneurysm recanalization and coil herniation. Soon it was visible that a coil stabilization mechanism was necessary for the treatment of wide-neck aneurysms [18, 19]. Moret et al. in 1997 described a method of stabilization with the use of a non-detachable balloon, the so-called "Remodeling technique" (or "Balloon assisted coiling"). They placed a non-detachable balloon next to the aneurysm before the coils' insertion, intending to stabilize the coils and keep them inside the aneurysmal cavity. The initially deflated balloon is directed in the parental artery of the aneurysm. Then, the balloon is inflated to cover the aneurysm neck. After balloon inflation, coil insertion may begin. After each coil placement, the balloon is deflated and coil stability and aneurysm occlusion are evaluated with angiography. The circle of inflation-coil placement-deflation continues until the aneurysm is occluded, and the coils are stabilized (Fig. 5.5) [19].

The main indication for BAC is the treatment of wide-neck aneurysms (over 4 mm), but today it is clear that the dome/neck ratio rather than the absolute value of neck diameter can better predict the success rate of GDC. A dome/neck ratio lower than 1.5 is considered a good indication for BAC (Fig. 5.6). Today BAC is additionally utilized in the classic GDC procedure in cases of intraoperative rupture as previously discussed. The total or subtotal occlusion rate after BAC was over 90% in Moret et al. series and other series [19, 20].

The complication rates and comparison with the standard GDC procedure have been analyzed in two multicenter trials, the "CLARITY" and "ATENA" conducted by Pierot et al., and concern ruptured and unruptured aneurysms, respectively. The results from both of these studies found similar or slightly higher complication rates (thromboembolism and intraoperative rupture) compared to the standard GDC procedure [2, 21, 22].

5.1.3 Stent-Assisted Coiling (SAC)

Another technique used in the treatment of "complex" or "wide" neck aneurysms involves using a stent. The idea behind the use of stents in the SAC procedure is similar to that of a balloon in BAC. In both techniques, a wall-like structure prevents the herniation or migration of coils in the parental artery. Additionally, in the SAC technique, the stent remains in the parental artery after the operation and offers long-term prevention of coil herniation. Theoretically, the stent limits the blood inflow into the aneurysm and thus the aneurysm's regrowth. Currently, the stents applied in the treatment of IA are specialized for delivery and placement in the intracranial vessels, contrary to the previously used coronary stents. "Open" and "Closed" types of stents are used in the SAC technique, with the open type being more flexible and preferred in bifurcated aneurysms. "Neuroform" and "Enterprise" stents are the most frequently used stents for SAC (Fig. 5.7) [2, 23]. Accero is a novel, very promising braided self-expandable stent, which can easily be directed through the intracranial vessels and may overcome some challenges observed with the laser-cut stents [24]. In order to prevent stent thrombosis, a dual antiplatelet regimen is required in patients following. Consequently, the SAC technique was initially limited to unruptured aneurysms, but today is also utilized in ruptured aneurysms in some institutions [2, 23, 25].

In the standard SAC procedure, the stent is implanted in the parental artery before the microcatheter placement. This method's main disadvantage is that sometimes the microcatheter cannot pass through the tiny stent struts. For this reason, an alternative method has been developed, the so-called "Jailing-technique." In jailing technique, the coil microcatheter is placed into the aneurysmal cavity before stent delivery. When the stent is well placed and deployed, the

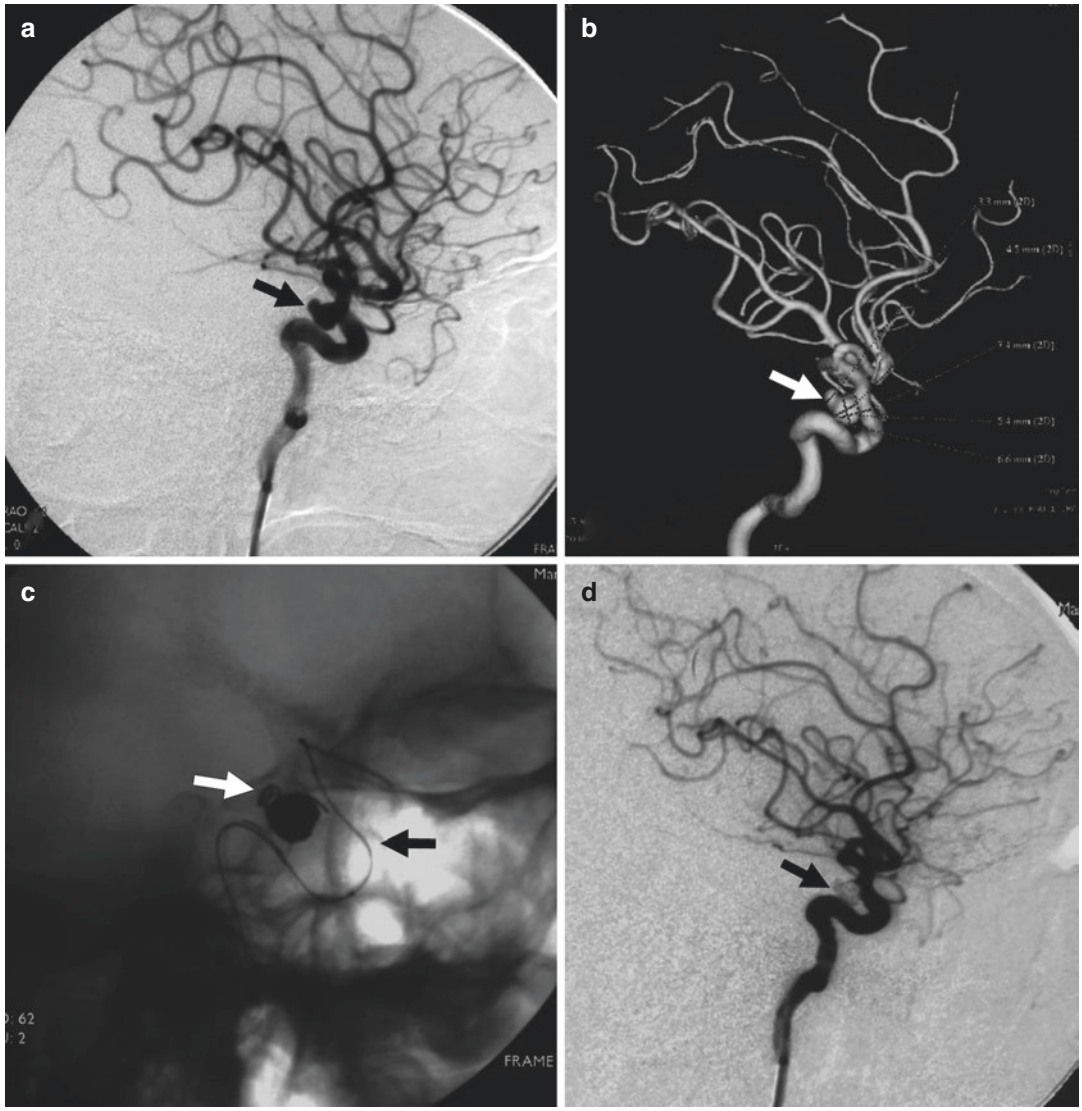


Fig. 5.5 A 54-year-old man presented with a ruptured posterior communicating artery aneurysm. (**a**) Oblique view of the left internal carotid artery injection. (**b**) 3-D reconstruction of the left internal carotid artery injection. Showing a 5 mm × 6 mm aneurysm of posterior communicating artery segment (arrows). (**c**) Unsubtracted image showing the aneurysm was coiled (white arrow) with the assistance of a 4 mm × 20 mm Hyperglide balloon catheter (Medtronic ev3, USA) (black arrow). (**d**) Lateral view of the left internal carotid artery injection showing the aneurysm was completely occluded (arrow)

coil introduction via the microcatheter can begin. The disadvantage of this method is the limitation of microcatheter maneuvers after stent deployment. The "Y-technique" is another method used for aneurysms of the basilar tip (or other bifurcated aneurysms) and includes the use of two stents (stent inside stent). The first stent is placed into the main artery and one of the two branches, while the other stent is placed inside the first stent up to the level of bifurcation and then continues to the other branch. Finally, the neck of the aneurysm is fully covered, and the insertion of the coils follows. Lately, another method combining BAC and SAC procedures has been

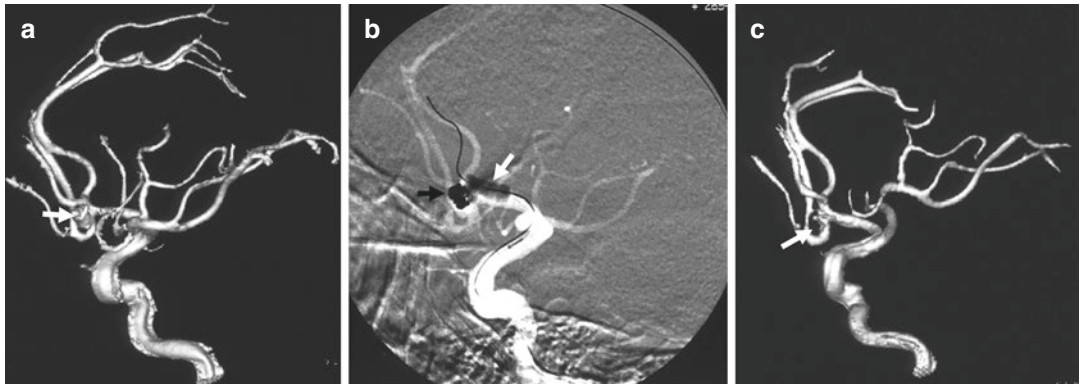


Fig. 5.6 A 48-year-old woman presented with an anterior communicating artery aneurysm. (**a**) 3-D reconstruction of the left internal carotid artery injection showing an anterior communicating artery aneurysm (arrow). (**b**) Roadmap image showing the aneurysm was coiled (black arrow) with the assistance of a 4 mm × 7 mm Hyperform balloon catheter (Medtronic ev3, USA) (white arrow). (**c**) 3-D reconstruction of the left internal carotid artery injection after embolization showing disappearance of the aneurysm (arrow)

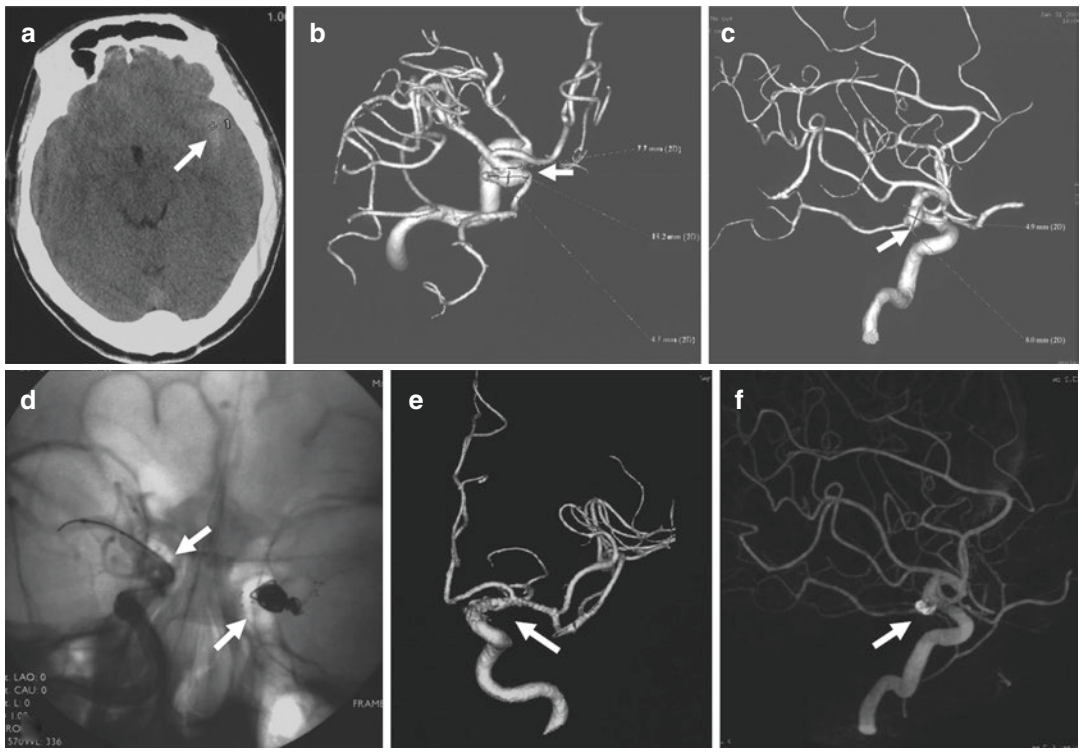


Fig. 5.7 A 62-year-old man presented with a ruptured posterior communicating artery aneurysm. (**a**) CT scanning showing subarachnoid hemorrhage of the left Sylvian fissure. (**b**) 3-D reconstruction of the left internal carotid artery injection showing a 13 mm × 5 mm posterior communicating artery aneurysm (arrow). (**c**) 3-D reconstruction of the right internal carotid artery injection showing a 5 mm × 8 mm posterior communicating artery aneurysm (arrow). (**d**) Frontal view of the unsubtracted image showing bilateral aneurysms were all treated with Neuroform stent-assisted coiling (arrows). (**e**) 3-D reconstruction of the left internal carotid artery injection after treatment showing the disappearance of the aneurysm (arrow). (**f**) 3-D reconstruction of the right internal carotid artery injection after treatment showing the coil mass in the aneurysm (arrow)

developed. Initially, a typical BAC procedure is performed, and then a stent is placed in the neck of the aneurysm. The stent stabilizes the coil mass and blocks the blood inflow into the aneurysmal cavity, while there is no limitation in the microcatheter maneuvers because the stent is implanted after the placement of coils [2, 23]. The theoretical advantage of the last method has been supported by the results of the Spiotta et al. study [26].

The total occlusion rate in SAC is approximately 75% in wide-neck aneurysms. The rate of thromboembolic events is approximately 10%, significantly higher compared to the standard GDC procedure. Recanalization rate is approximately 5–6%, while stent stenosis is observed in 1% of the patients. Up to date, it is unclear whether the SAC procedure is superior to BAC or vice versa. Park et al. performed a study to compare these techniques but did not find significant differences in efficacy, complications, and mortality rates [2, 27, 28].

5.1.4 Flow Diverters

The observation that the stents induce a reduction in blood inflow into the aneurysmal cavity led to the creation of stents specially made for this purpose. However, the high porosity of the stents limited the efficacy in terms of restricting the blood inflow. The development of new devices of low porosity gave the solution to this problem. These devices are called "flow-diverters"(Fig. 5.8). Flow diverters are "stent-like" devices with low porosity and high pore density, which divert blood flow away from the aneurysm leading to blood stasis and clot formation inside the aneurysm similar to a coil. The endothelization observed in the device surface further obstructs blood flow. Some of the devices used as flow diverters are the "Pipeline," "Silk," "Stryker," and "FRED." Currently, Pipeline (Medtronic-ev3, USA) and Surpass (Stryker, USA) are the only devices with US (United States)/FDA (Food and Drug Association) approval. Another advantage of the flow diverters over other devices is the absence of perioperative maneuvers within the aneurysm, ultimately leading to a reduction of intraoperative rupture (Fig. 5.9). The risk of rupture is increased in giant aneurysms whose wall is very vulnerable (Fig. 5.10) [2, 28].

For this reason, flow diverters are predominantly utilized in the treatment of such large-giant aneurysms. Wide neck or tiny aneurysms may also be treated with flow diverters. As with stents, a dual antiplatelet regimen is necessary. Thus, the use of flow-diverters in ruptured aneurysms is controversial. Unlike the standard method of coil embolization, thrombus induction within the aneurysm may not be achieved immediately. It is estimated that only 10–20% of the

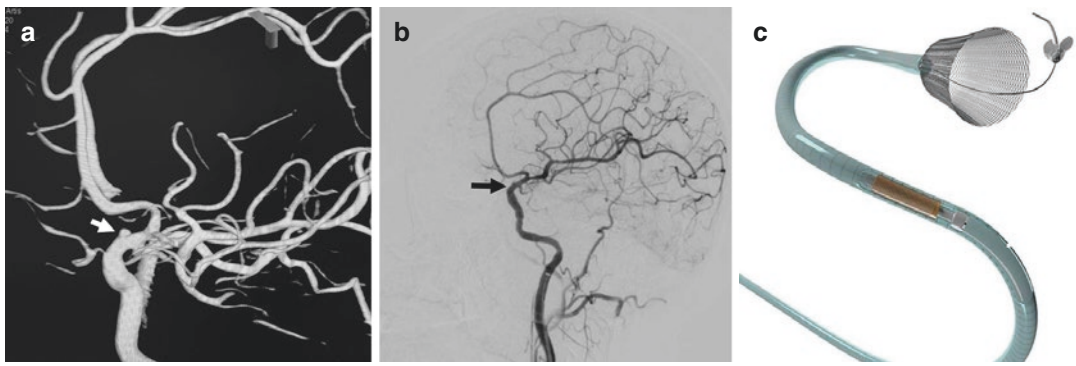


Fig. 5.8 A 50-year-old woman presented with Hunt–Hess grade 1 subarachnoid hemorrhage. (**a**) 3-D reconstruction of the left internal carotid artery injection showing a 1.5 mm × 1.5 mm blood-blister like aneurysm (arrow) of the supraclinoid internal carotid artery. (**b**) Oblique view of the internal carotid artery injection showing the aneurysm was treated with 3.5 mm × 20 mm Pipeline flow diversion and a 1.5 mm × 2 cm coil (Nano, Stryker, USA) (arrow). (**c**) Picture showing the Pipeline flow diversion system (Medtronic, USA)

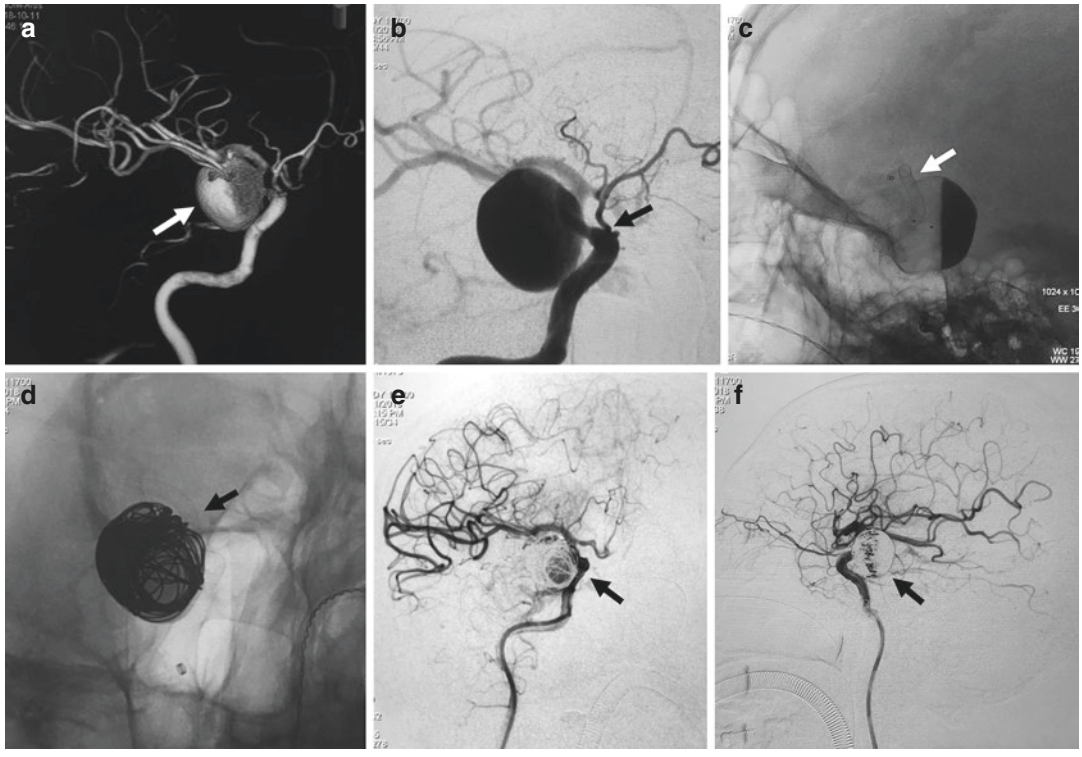


Fig. 5.9 A 42-year-old man presented with an incidental giant aneurysm of the internal carotid artery. (**a**) 3-D reconstruction of the right internal carotid artery injection showing a giant aneurysm of the posterior communicating artery segment of the internal carotid artery (arrow). (**b**) Oblique view of the right internal carotid artery injection showing the giant aneurysm (arrow). (**c**) Unsubtracted image showing the Pipeline flow diversion (arrow). (**d**) Unsubtracted image showing additional coils were placed (arrow). (**e**) Oblique angiography showing the patent internal carotid artery (arrow). (**f**) Lateral view of the angiography showing the aneurysm was partially occluded

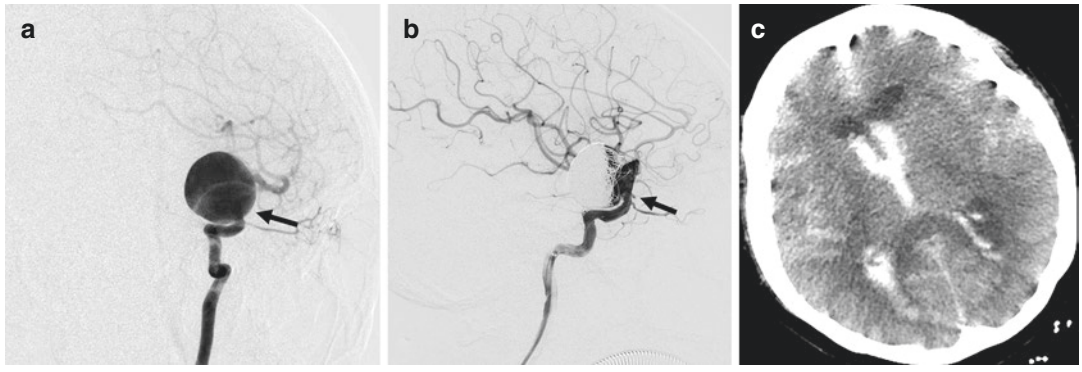


Fig. 5.10 A 39-year-old woman presented with a blurred vision of the left eye. (**a**) Oblique view of the left carotid artery injection showing a giant aneurysm of the supraclinoid segment of the internal carotid artery (arrow). (**b**) Oblique view of the left internal carotid artery injection showing the aneurysm was partially thrombosed after flow diversion and additional coils treatment. (**c**) CT scanning showing aneurysm rupture 20 h after treatment and the patient died

aneurysms will be occluded entirely after applying these devices. In total, it can take up to a year to achieve complete occlusion and shrinkage of the aneurysm. However, it should be mentioned that giant aneurysms have a very high risk of intraoperative rupture compared to other aneurysms. Therefore, the optimal treatment should be assessed case-by-case by weighing the risk of rupture in the latent phase (flow-diverters) with the risk for intraoperative rupture (other endovascular approaches and surgical clipping) [2, 28–30].

Thromboembolic events and device migration are not unusual after flow diverter implantation. The risk of intraoperative rupture still exists despite the lack of maneuvering inside the aneurysm. Obstruction of the parental artery's perforators is another complication of this technique. The obstruction usually concerns the paraclinoid carotid artery and ophthalmic artery branches, although it seems that a significant degree of coverage is required to cause ischemia in the perforator territory [28].

Early and late (after 1–2 months) ruptures may occur, with early ruptures being more common. The pathophysiological mechanism of late rupture is still unclear, but the aneurysm wall's inflammatory response to elements secreted from the clot is considered a possible cause. The overall rupture frequency is about 2–4%. Prognosis post aneurysm rupture is poor, but this is probably related to the nature of the aneurysms (large/giant aneurysms) treated with this technique. Late intraparenchymal cerebral hemorrhage (not related to aneurysm rupture) is another paradoxical event after the treatment with flow-diverters with a frequency of 3–4%. The majority of intraparenchymal hemorrhages are located in the ipsilateral parenchyma in which the device is implanted. Thus, the correlation of the device with this event is unavoidable. Other authors suggest that the hemorrhagic transformation of small ischemic lesions in the brain-territory (caused by the device) of the parental artery is a possible pathophysiological mechanism, while others suggest that hemodynamic alterations are the primary mechanism. Antiplatelets' role in this event is unclear, but the occurrence of the hemorrhage predominantly in ipsilateral parenchyma discredits them as a cause [28–31].

5.1.5 Flow Disrupters

Although flow diverters provided several advantages, their intraluminal location generates a high risk of thromboembolic events and a necessity for a prophylactic antiplatelet regimen. Flow disrupters are devices whose mechanism is similar to flow diverters, with the difference that they possess an intrasaccular location instead of intraluminal. Thus, they overcome the need for an antiplatelet regimen and the restriction of application only in unruptured aneurysms. The "WEB" (Woven Endo Bridge) is a nitinol-based flow disrupter, available in a spherical or cylindrical shape. One or two layers of wire are available, with the efficacy being similar in both versions. The feasibility is very high (95–100%), with the device being preferred in wide-neck bifurcated aneurysms such as basilary tip aneurysms or aneurysms located in anterior and middle cerebral arteries. "Artisse" is another oval-shaped disrupter like WEB and is mainly used for the management of small aneurysms. These devices have yet to be certified by US-FDA and are currently used in European countries. Despite their intrasaccular location, thromboembolic events may occur in 10% of the patients and the risk of rupture in the latent period still remains [32, 33].

5.1.6 Hybrids and Other Novel Devices

Currently, many variations of the devices mentioned above have been developed for the endovascular treatment of IA. Medina embolization device (MED) is a woven cage that combines an embolization device and a flow disrupter. It is essentially a coil with the ability to transform into a 3D structure when fully deployed inside the aneurysmal cavity. The barrel stent is another device used in bifurcated aneurysms with an expanded middle part to fully cover the neck cir-

cumference. The "eCLIPS" and "PulseRider" are also endovascular devices used in bifurcated aneurysms. eCLIPS has an anchor segment to stabilize the structure into the main vessel and a leaflet segment used for the placement of coils into the aneurysm. This is another hybrid device because the leaflet segment blocks the blood inflow into the aneurysm. The Pulserider is a "Y" or "T" shaped structure that helps the coiling of bifurcated aneurysms with concurrent protection of artery branches. Finally, many other experimental devices are being developed and are expected to be used for IA's endovascular treatment in the coming years [3, 25].

5.2 Conclusion

Endovascular treatment of IA is an effective and relatively safe method that has replaced, to a great extent, classic surgical clipping. The development of novel techniques and devices such as BAC, SAC, and flow diverters/disrupters for the treatment of wide-neck or giant/large aneurysm has expanded the use of endovascular approaches beyond the exclusive treatment of berry aneurysms. Finally, other hybrid devices are being developed to treat challenging aneurysms such as basilary tip aneurysms and are expected to be used in the upcoming years.

References

1. Keedy A. An overview of intracranial aneurysms. Mcgill J Med. 2006;9(2):141–6.
2. Pierot L, Wakhloo A. Endovascular treatment of intracranial aneurysms: current status. Stroke. 2013;44(7):2046–54. https://doi.org/10.1161/strokeaha.113.000733.
3. Jia Z, Shi H, Miyachi S, Hwang S, Sheen J, Song Y, et al. Development of new endovascular devices for aneurysm treatment. J Stroke. 2018;20(1):46–56. https://doi.org/10.5853/jos.2017.02229.
4. Teitelbaum G, Larsen D, Zelman V, Lysachev A, Likhterman L. A tribute to Dr. Fedor A. Serbinenko, founder of endovascular neurosurgery. Neurosurgery. 2000 Feb;46(2):462–9. https://doi.org/10.1097/00006123-200002000-00037.
5. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366:809–17.
6. Wiebers D, Whisnant JP, Huston J, Meissner I, Brown RD, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362:103–10.
7. Werner SC, Blakemore AH, King BG. Aneurysm of the internal carotid artery within the skull. Wiring and electrothermic coagulation. JAMA. 1941;116:578–82.
8. Guglielmi G. History of the genesis of detachable coils. J Neurosurg. 2009;111(1):1–8. https://doi.org/10.3171/2009.2.jns081039.
9. Guglielmi G. History of endovascular endosaccular occlusion of brain aneurysms: 1965–1990. Interv Neuroradiol. 2007;13:217–24.
10. Bendok B, Hanel R, Hopkins L. Coil embolization of intracranial aneurysms. Neurosurgery. 2003;52(5):1125–30. https://doi.org/10.1227/01.neu.0000057833.50219.25.
11. Seldinger S. Catheter replacement of the needle in percutaneous arteriography. Acta Radiol. 1952;39:368–76.
12. Nestor G, Yuichi M, Yih Lin N, Neil M, John F, Gary D, et al. Treatment of unruptured aneurysms with GDCs: clinical experience with 247 aneurysms. Am J Neuroradiol. Apr 2004;25(4):577–83.
13. Katsaridis V, Papagiannaki C, Violaris C. Guglielmi detachable coils versus matrix coils: a comparison of the immediate posttreatment results of the embolization of 364 cerebral aneurysms in 307 patients: a single-center, single-surgeon experience. AJNR Am J Neuroradiol. 2006 Oct;27(9):1841–8.
14. Hong-Ki K, Sung-Kyun H, Sung-Hak K. Types of thromboembolic complications in coil embolization for intracerebral aneurysms and management. J Korean Neurosurg Soc. 2009;46:226–31. https://doi.org/10.3340/jkns.2009.46.3.226.
15. Nomura M, Mori K, Tamase A, Kamide T, Seki S, Iida Y. Thromboembolic complications during endovascular treatment of ruptured cerebral aneurysms. Interv Neuroradiol. 2017;24(1):29–39. https://doi.org/10.1177/1591019917739448.
16. Ross I, Dhillon G. Complications of endovascular treatment of cerebral aneurysms. Surg Neurol. 2005;64(1):12–8. https://doi.org/10.1016/j.surneu.2004.09.045.
17. Gupta V. Aneurysm rupture during coiling: key actions. 100 interesting case studies in neurointervention. Tips Tricks. 2019;2019:169–72. https://doi.org/10.1007/978-981-13-1346-2_41.
18. Fernandez Zubillaga A, Guglielmi G, Viñuela F, Duckwiler GR. Endovascular occlusion of intracranial aneurysms with electrically detachable coils: correlation of aneurysm neck size and treatment results. AJNR Am J Neuroradiol. 1994 May;15(5):815–20.

19. Moret J, Cognard C, Weill A, Castaings L, Rey A. The "Remodelling technique" in the treatment of wide neck intracranial aneurysms. Angiographic results and clinical follow-up in 56 cases. Interv Neuroradiol. 1997 Mar 30;3(1):21–35. https://doi.org/10.1177/159101999700300103.
20. Cottier JP, Pasco A, Gallas S, Gabrillargues J, Cognard C, Drouineau J, et al. Utility of balloon-assisted Guglielmi detachable coiling in the treatment of 49 cerebral aneurysms: a retrospective, multicenter study. AJNR Am J Neuroradiol. 2001 Feb;22(2):345–51.
21. Pierot L, Spelle L, Leclerc X, Cognard C, Bonafé A, Moret J. Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils. Radiology. 2009;251:846–55.
22. Pierot L, Cognard C, Anxionnat R, Ricolfi F, for the CLARITY Group. The remodelling technique for endovascular treatment of ruptured intracranial aneurysms is more efficacious than standard coiling with a similar safety. Radiology. 2011;258:546–53.
23. Stephan M, Demetrius L, Crowley RW. Stent-assisted coil embolization. In: Spiotta AM, et al., editors. Management of cerebrovascular disorders. Cham: Springer Nature; 2019. p. 187–203. https://doi.org/10.1007/978-3-319-99016-3_12.
24. Beuing O, Lenz A, Donitza A, Becker M, Serowy S, et al. Stent-assisted coiling of broad-necked intracranial aneurysms with a new braided microstent (Accero): procedural results and long-term follow-up. Sci Rep. 2020;10(1):412. https://doi.org/10.1038/s41598-019-57102-6.
25. Zuckerman S, Eli I, Morone P, Dewan M, Mocco J. Novel technologies in the treatment of intracranial aneurysms. Neurol Res. 2014;36(4):368–82. https://doi.org/10.1179/1743132814y.0000000318.
26. Spiotta A, Wheeler A, Smithason S, Hui F, Moskowitz S. Comparison of techniques for stent assisted coil embolization of aneurysms. J Neurointerv Surg. 2011;4(5):339–44. https://doi.org/10.1136/neurintsurg-2011-010055.
27. Aguilar-Salinas P, Brasiliense LB, Santos R, et al. Safety and efficacy of stent-assisted coiling in the treatment of unruptured wide-necked intracranial aneurysms: a single-center experience. Cureus. 2019;11(6):e4847. https://doi.org/10.7759/cureus.4847.
28. Park K, Jang C, Lee J, Kim D, Kim B, Chung J. Preliminary experience of stent-assisted coiling of wide-necked intracranial aneurysms with a single microcatheter. BMC Neurol. 2019;19(1):245. https://doi.org/10.1186/s12883-019-1470-8.
29. D'Urso P, Lanzino G, Cloft H, Kallmes D. Flow diversion for intracranial aneurysms: a review. Stroke. 2011;42(8):2363–8. https://doi.org/10.1161/strokeaha.111.620328.
30. Burrows AMH, Kallmes DF, et al. Neurointerv Surg. https://doi.org/10.1136/neurintsurg-2014-011184.
31. Rouchaud A, Brinjikji W, Lanzino G, Cloft H, Kadirvel R, Kallmes D. Delayed hemorrhagic complications after flow diversion for intracranial aneurysms: a literature overview. Neuroradiology. 2015;58(2):171–7. https://doi.org/10.1007/s00234-015-1615-4.
32. Dmytriw A, Salem M, Yang V, Krings T, Pereira VM, Moore JM, Thomas AJ. Endosaccular flow disruption: a new frontier in endovascular aneurysm management. Neurosurgery. 2020 Feb 1;86(2):170–81. https://doi.org/10.1093/neuros/nyz017.
33. Papagiannaki C, Spelle L, Januel A, Benaissa A, Gauvrit J, Costalat V, et al. WEB intrasaccular flow disruptor—prospective, multicenter experience in 83 patients with 85 aneurysms. Am J Neuroradiol. 2014;35(11):2106–11. https://doi.org/10.3174/ajnr.a4028.

6 Neuroendovascular Management of Wide-Neck Bifurcation Aneurysms

Xianli Lv

Abstract

This chapter is to give an overview of the endovascular treatment of intracranial bifurcation aneurysms. These aneurysm locations were the internal carotid artery bifurcation, anterior communicating artery complex, middle cerebral artery bifurcation, and basilar artery bifurcation. Development in neuroendovascular devices and techniques, such as stent-assisted coiling, balloon-assisted coiling, low-profile stent system (LEO Baby, LVIS Jr., and Atlas) and flow diversion techniques has treated more challenging aneurysms, such as wide-necked or complex bifurcation aneurysms. We will describe these available neuroendovascular devices and techniques in this chapter. We hope this would help to encourage advancements in managing the bifurcation aneurysms and assist real-time decision-making in clinical practices.

Keywords

Bifurcation aneurysm · Stent · Endovascular therapy · Complete occlusion

6.1 Background

Neuroendovascular therapy of wide-neck, complex, bifurcation aneurysms is a challenging issue [1]. Coil embolization has become a standard treatment for ruptured and unruptured cerebral aneurysms [2]. Subsequent development in neuroendovascular devices and techniques, such as self-expanding stents, has greatly improved the ability to treat intracranial aneurysms [3]. Stent-assisted coiling of cerebral aneurysms has been performed initially using coronary stents in the 1990s (Fig. 6.1) [4]. Until 2002 and 2003, the first neurostent, the self-expanding Neuroform (Stryker, Kalamazoo, MI, USA) (Fig. 6.2) and the self-expanding Leo stent (Balt, Montmorency, France), were designed as open-cell and braided neurostents deliverable through a 0.027-inch microcatheter [5–7]. They were followed by the closed-cell Solitaire AB (Covidien, Irvine, CA, USA) (Fig. 6.3), Enterprise (Codman, Raynham, MA, USA) (Fig. 6.4), and braided LVIS (Low-Profile Visualized Intraluminal Support, Microvention, USA) stents [8–10]. Recently, ministents deliverable through 0.0165-inch microcatheters have become possible, such as Leo Baby (Balt, France) (Fig. 6.5), LVIS Jr. (Microvention, USA) (Fig. 6.6) and the open-cell Atlas (Stryker, Kalamazoo, MI, USA) (Fig. 6.7) stents [11, 12]. The use of ministents has become a good option for complex bifurcation aneurysms. These low-profile neurostents can be

X. Lv (✉)
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_6

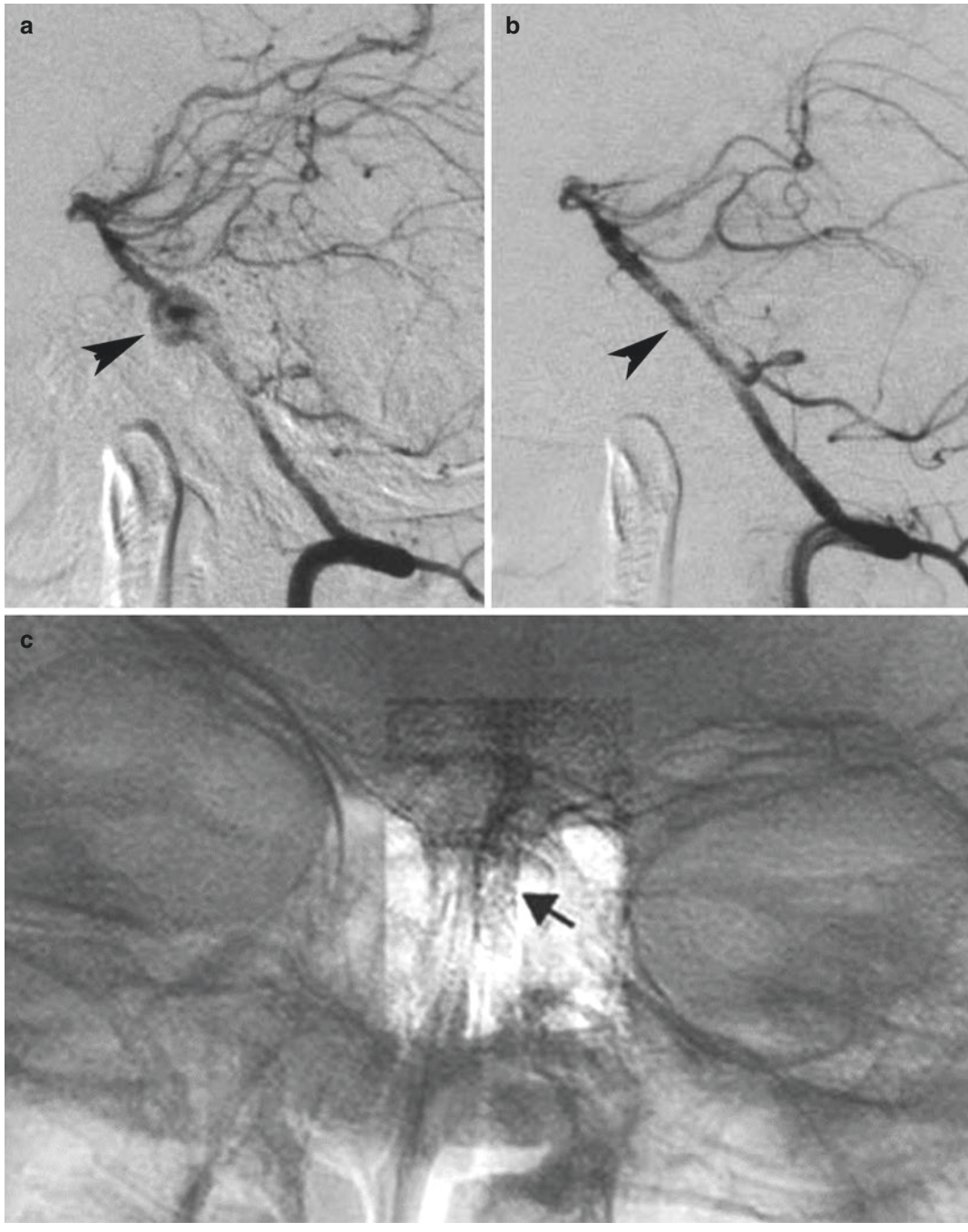


Fig. 6.1 Stenting of a mid-basilar artery aneurysm using coronary stent in the 1990s. (**a**) Lateral angiogram of the left vertebral artery showing a large mid-basilar artery aneurysm (arrowhead). (**b**) Lateral angiogram of the left vertebral artery after implant of a 3.5 mm × 18 mm Bx Velocity stent (Cordis, USA) showing disappearance of the aneurysm (arrowhead). (**c**) Frontal view of the unsubtracted image showing the stent (arrow)

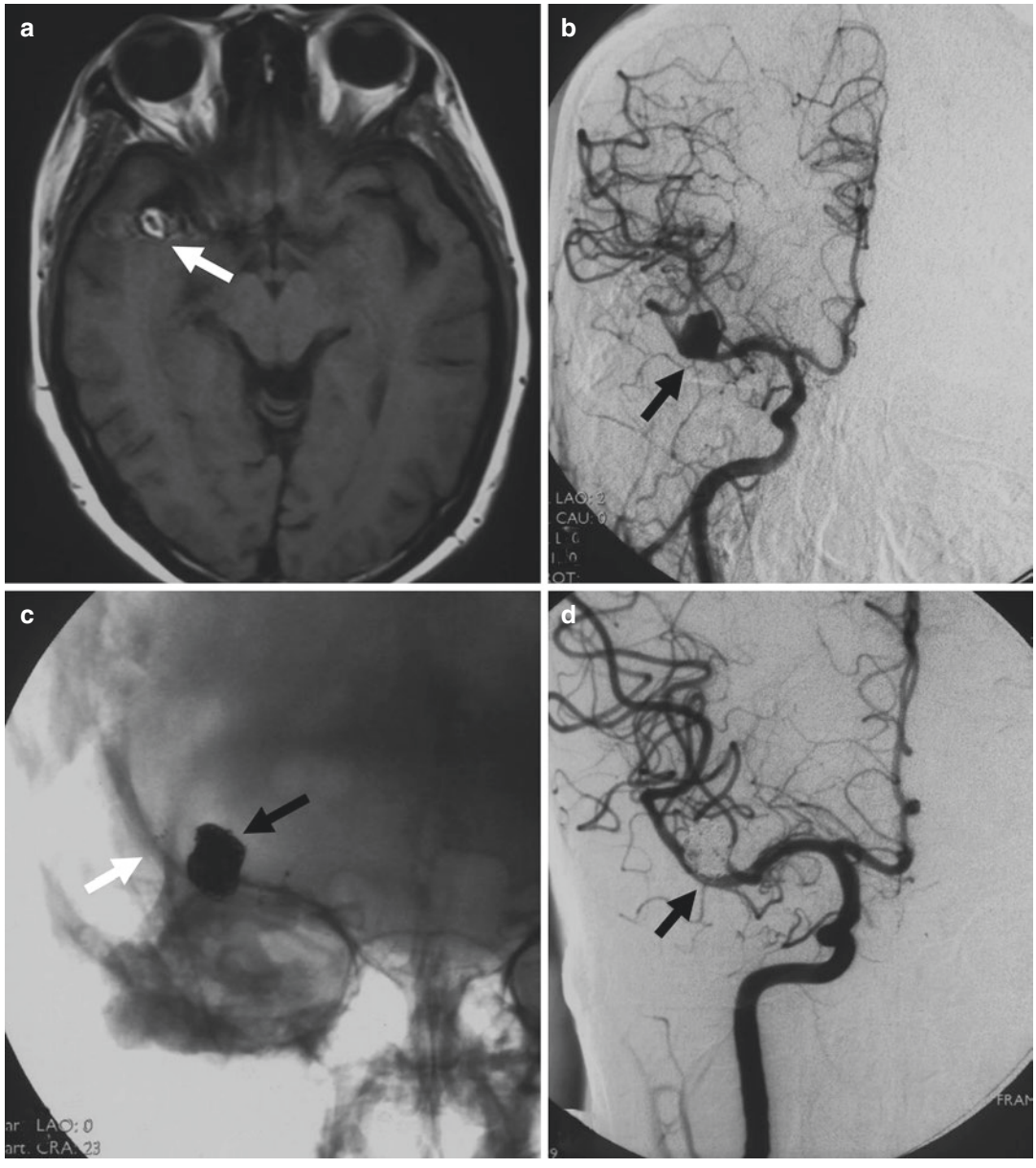


Fig. 6.2 A 55-year-old woman presented with an unruptured middle cerebral artery aneurysm. (**a**) T1-weighted MR imaging showing a hypertensity in the right Sylvian fissure(arrow). (**b**) Frontal view of the right carotid artery injection showing a 7 mm × 8 mm aneurysm of the middle cerebral artery (arrow). (**c**) Frontal view of the unsubtracted image showing the 3.0 mm × 20 mm Neuroform stent (Boston Scientific, USA) (white arrow) and coil mass (black arrow) after treatment. (**d**) Frontal view of the right carotid artery injection showing the aneurysm was completely occluded after treatment

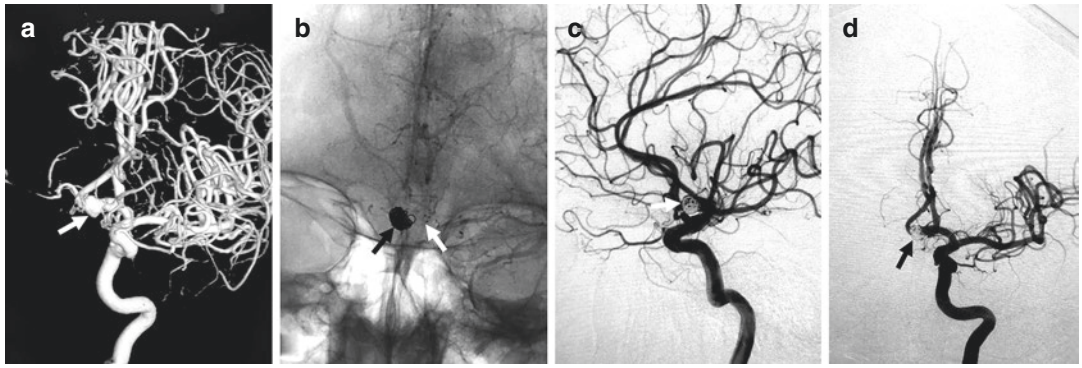


Fig. 6.3 A patient presented with subarachnoid hemorrhage. (**a**) 3-D reconstruction of the left internal carotid artery injection showing the 4 mm × 5 mm anterior communicating artery aneurysm (arrow), which was treated with 4.0 mm × 15 mm Solitaire AB stent and coils. (**b**) The unsubtracted image showing the Solitaire AB stent (white arrow) and the coil mass (black arrow). Lateral view (**c**) and frontal view (**d**) of the left internal carotid artery injection after coiling showing the aneurysm was occluded completely (arrows)

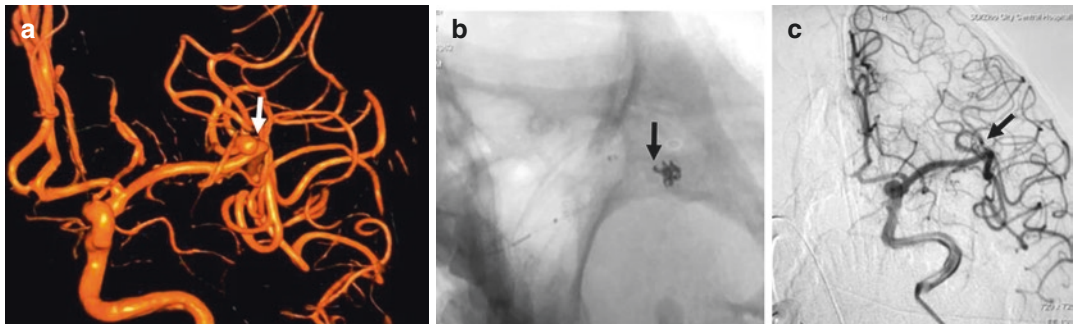


Fig. 6.4 A 58-year-old woman presented with an unruptured middle cerebral artery bifurcation aneurysm. (**a**) frontal view of the left carotid artery injection showing a 3 mm × 4 mm aneurysm of the middle cerebral artery bifurcation (arrow). (**b**) Working angle of the unsubtracted image showing the 4.5 mm × 15 mm Enterprise stent (Cordman, USA) and coil mass (arrow) during treatment. (**c**) Working angle of the left carotid artery injection showing the aneurysm was completely occluded after treatment (arrow)

introduced into distal arteries with diameters between 1.5 and 3.0 mm through 0.0165-inch microcatheters allowing easier navigation. In addition to stent-assisted coiling, intrasaccular techniques such as the Woven EndoBridge Device (WEB) and pCONus (Phenox GmbH, Bochum, Germany) are used to prevent parent artery occlusion [13–15]. The pCONus (Phenox GmbH, Bochum, Germany) protrudes into the aneurysmal lumen and thus protects against accidental closure of the lateral branches [16]. To protect the lumen, either 2 stents can be inserted side by side or inside each other in both outgoing vessel branches. In this chapter, we will provide young practitioners, particularly those in endovascular training, with an overview of the different types of bifurcation aneurysms and various treatment strategies available.

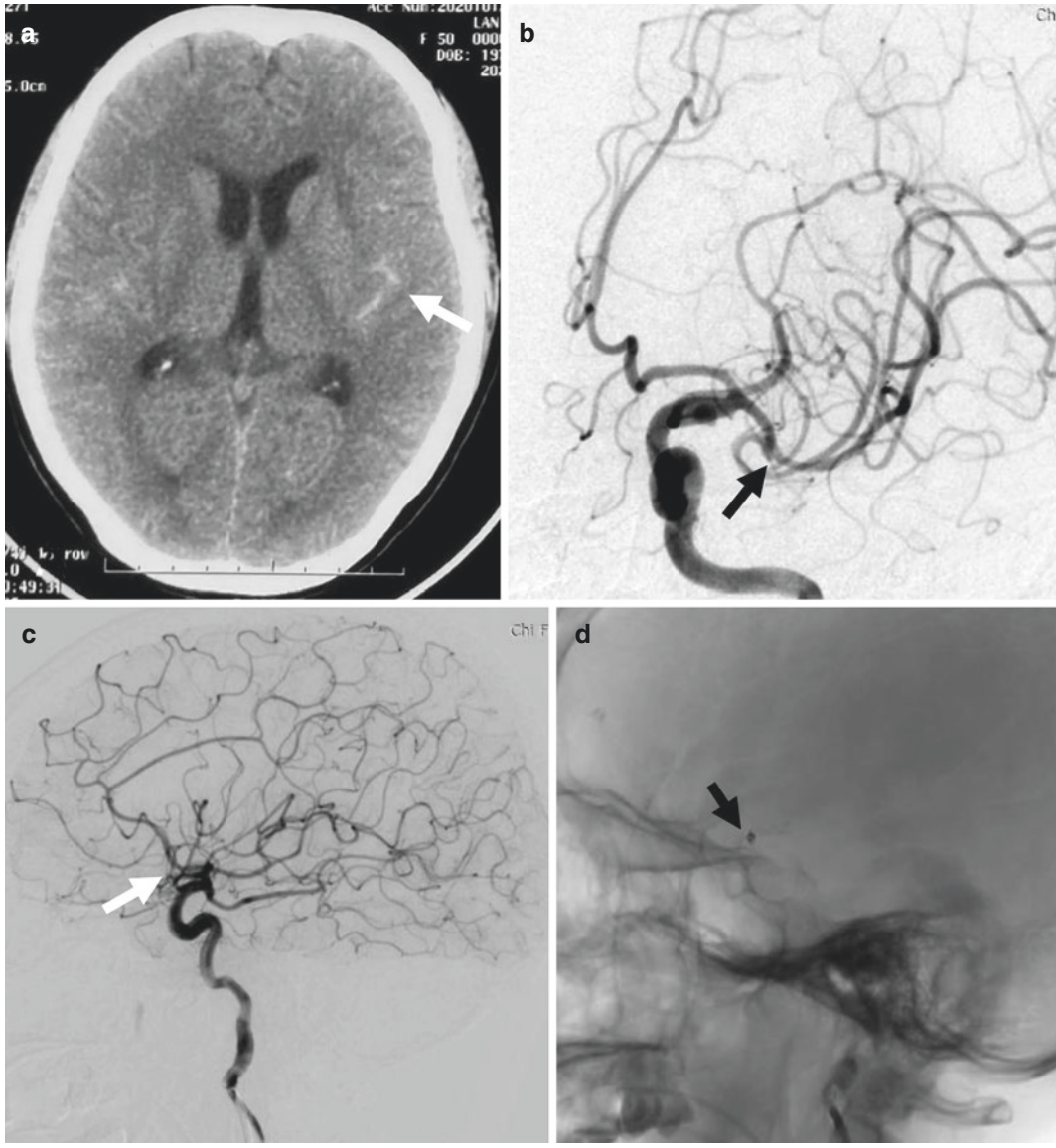


Fig. 6.5 A 50-year-old female presented with Hunt–Hess grade1 subarachnoid hemorrhage. (**a**) CT scanning showing a hypertensity in the left Sylvian fissure (arrow). (**b**) Frontal view of the left internal carotid artery injection showing the 1.5 mm × 1.5 mm bifurcation aneurysm of the middle cerebral artery (arrow), which was treated with 2.5 mm × 18 mm Leo baby stent and coil. (**c**) Lateral view of the left internal carotid artery injection after coiling showing the aneurysm was occluded completely (arrow). (**d**) Lateral view of the unsubtracted image showing the Leo baby stent and the coil mass (arrow)

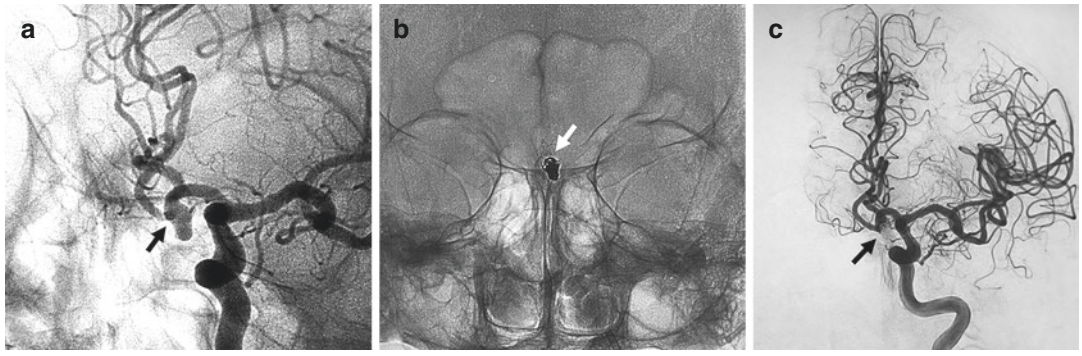


Fig. 6.6 A patient presented with subarachnoid hemorrhage. (**a**) Frontal view of the left internal carotid artery injection showing the 3 mm × 4 mm anterior communicating artery aneurysm (arrow), which was treated with 2.5 mm × 17 mm LVIS Jr. stent and coils. (**b**) The unsubtracted image showing the LVIS Jr. stent and the coil mass (arrow). (**c**) Frontal view of the left internal carotid artery injection after coiling showing the aneurysm was occluded completely (arrow)

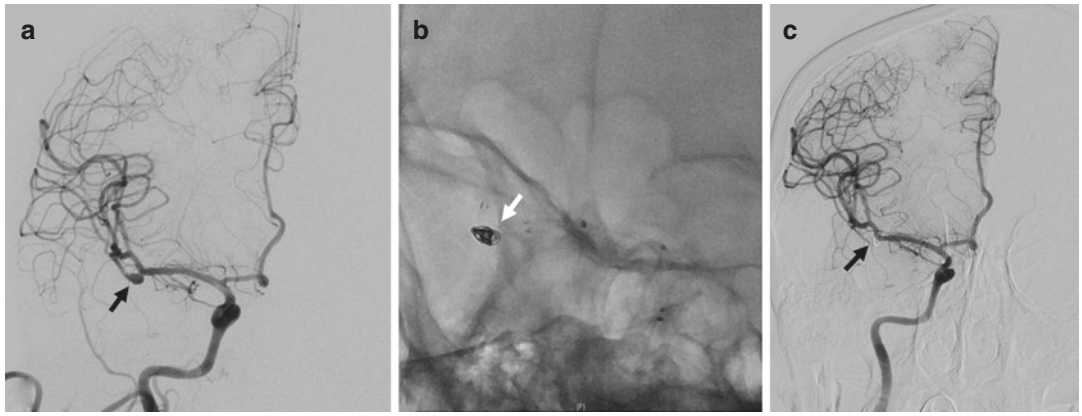


Fig. 6.7 A 46-year-old female presented with Hunt–Hess grade3 subarachnoid hemorrhage. (**a**) Frontal view of the right internal carotid artery injection showing the 3 mm × 3 mm bifurcation aneurysm of the middle cerebral artery (arrow), which was treated with 3.0 mm × 15 mm Neuroform Atlas stent and coils. (**b**) Working angle of the unsubtracted image showing the Atlas stent and the coil mass (arrow). (**c**) Frontal view of the right internal carotid artery injection after coiling showing the aneurysm was occluded completely (arrow)

6.2 Three Types of Bifurcation Aneurysms

6.2.1 Saccular Aneurysms

Saccular aneurysms are the most common type of bifurcations [17]. They are a round outpouching with well-defined aneurysmal domes and necks connecting to the parenting vessel. They favor bifurcation locations of the internal carotid artery, the middle cerebral artery (MCA) and the basilar artery (BA), and the anterior communicating artery (Acoma). Saccular aneurysms can be classified into microaneurysms (<2 mm in diameter), small aneurysms (2–10 mm in diameter) large aneurysm (10–25 mm in diameter) and

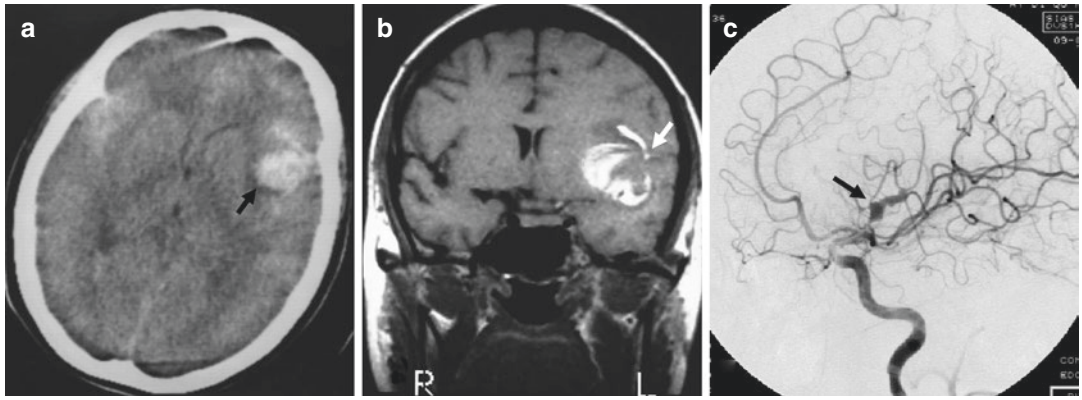


Fig. 6.8 A 36-year-old female presented with a giant serpentine aneurysm. (**a**) CT scanning showing a giant hypertensive mass in the left Sylvian fissure (arrow). (**b**) Coronial view of the T1-weighted MR imaging showing a giant hypertensive mass in the left Sylvian fissure (arrow). (**c**) Oblique view of the left internal carotid artery injection showing the dissecting aneurysm of the middle cerebral artery (arrow)

giant aneurysm (>25 mm in diameter) [18]. Untreated giant aneurysms have over 50% risk in rupturing and 88% to 100% in mortality at 2-year follow-up [19].

6.2.2 Dissecting Aneurysms

Dissecting aneurysms, or arterial dissections, start with a minor tear on the inner wall, and then layers are further separated by the shearing force of blood flow which results in pseudoaneurysm formation [20]. Spontaneous dissections can occur anterior cerebral artery, middle cerebral artery, and internal carotid artery and involve their bifurcations caused by increased shear force. Supraclinoid segment of internal carotid artery navigates its path through ligaments with little mobility, and it breaks free from these bonds as it enters the dura adding to the risk of tearing.

6.2.3 Giant Serpentine Aneurysms

Giant serpentine aneurysm (GSA) is a subtype of dissecting aneurysms [21]. They were often described as partially thrombosed aneurysms. The blood flow through GSAs is slow, leading to repeated episodes of intramural clot formation. The clots build up and eventually become a giant mass, leaving only a tortuous channel, which appears to be serpent-like under digital subtract angiograph (DSA) (Fig. 6.8). Due to their chronic nature, the thrombus inside is highly fibrosed, giving them stiff and rubber-like textures.

6.3 Neuroendovascular Strategies for Bifurcation Aneurysms

Coil embolization is insufficient when dealing with complex bifurcation aneurysms. Neuroendovascular techniques have been innovated over the past years to handle these complex lesions (Tables 6.1 and 6.2).

6.4 Coiling

Since detachable coils were invented by Guglielmi in the 1990s [22], coil embolization has become a standard therapy for cerebral aneurysms (Fig. 6.9). Simple coiling is transluminal navigation of a 0.0165-inch or 0.0170-inch microcatheter into the aneurysm sac with the help of 0.014-inch microguidewires and the

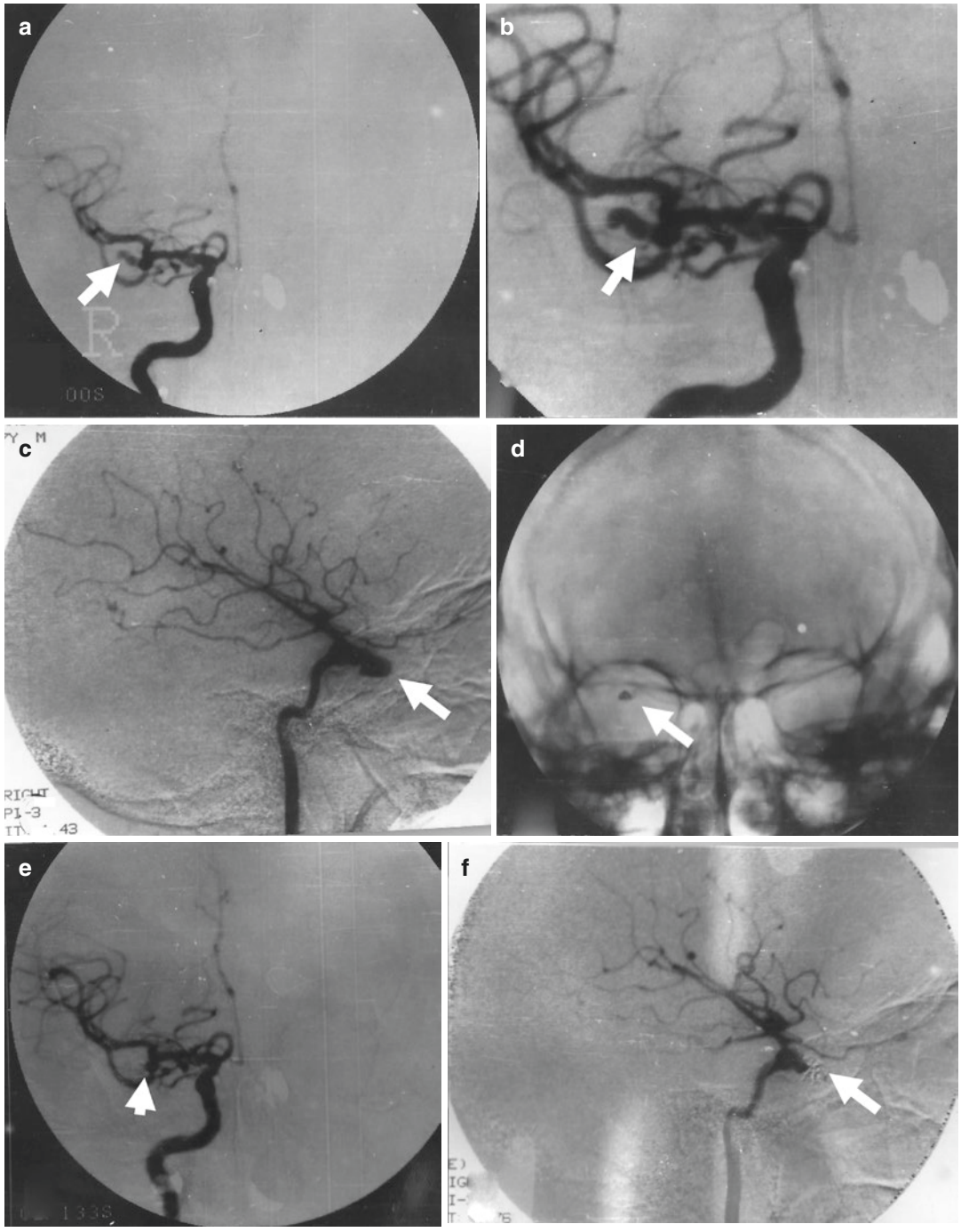


Fig. 6.9 A 27-year-old man with a ruptured right middle cerebral artery bifurcation aneurysm was coiled with Guglielmi detachable coils (GDC, Boston Scientific, USA) in 1998. (**a**, **b**) Frontal view of the right internal carotid artery injection showing the aneurysm of the middle cerebral artery bifurcation (arrows). (**c**) Lateral view of the internal carotid artery injection showing the aneurysm(arrow). (**d**) Frontal view of the fluoroscopic image after aneurysm coiling showing the coil mass (arrow). (**e**) Frontal view of the right internal carotid artery injection after aneurysm coil embolization. (**f**) Lateral view of the right internal carotid artery injection after aneurysm coil embolization. Showing the aneurysm was completely occluded (arrows)

Table 6.1 Types of bifurcation aneurysms and their neuroendovascular techniques

	Neuroendovascular techniques		
Neuroendovascular techniques	Saccular	Dissecting	Serpentine
Coiling	Yes	No	Yes
Balloon-assisted coiling	Yes	No	No
Stent-assisted coiling	Yes	Yes	No
Intra-luminal flow diversion	Large or giant	Yes	Yes
Intra-saccular flow diversion	Yes	No	No

Table 6.2 Devices in neuroendovascular techniques

Techniques	Devices
Balloon-assisted coiling	Single/dual lumen
Stent-assisted coiling	Solitaire AB, Enterprise, LVIS, LVIS Jr., Leo+, Leo baby, Neuroform EZ, Neuroform atlas
Intra-luminal flow diversion	Silk, FRED, pipeline, surpass
Intra-saccular flow diversion	WEB
Device selection	Efficacy, safety, access option, bail out strategy
Limiting factors	Aspirin/Plavix, durability, ease of use/convenience, experience

delivery and packing of detachable coils within the aneurysmal sac. The goal of coil embolization is to achieve dense packing and induce rapid blood clot formation within the aneurysmal sac, hence preventing it from bleeding for all aneurysms with desirable dome-to-neck ratios (>2.0).

6.5 Double Catheter Technique

Double catheter technique is for saccular aneurysms with a slightly unfavorable dome-to-neck ratio (2.0, >1.5). The 2 microcatheters are positioned in the proximal and distal aspects of the aneurysm sac before coil embolization. The first 3-D coil is introduced through the proximal catheter to make a supporting frame, and then the filling coils are inserted via the distal microcatheter. The framing coil is not detached until satisfactory packing is obtained. This technique is safe and effective for the aneurysms at MCA bifurcation and Acoma complex (Fig. 6.10).

6.6 Balloon-Assisted Coiling

Balloon-assisted coiling was initially described as "remodeling technique" in treating aneurysms with a wide neck [23]. It is described as using 1 or 2 nondetachable temporarily inflated balloons to block the aneurysmal neck during coil placement (Fig. 6.11). For difficult situations or complex cases, double-balloon technique is used. Besides double-balloon technique, special balloons are also being developed, such as hypercompliant, round-shaped, and double-lumen balloons.

6.7 Stent-Assisted Coiling

Stent-assisted coiling can overcome the disadvantages of wide-necked bifurcation aneurysms [24]. Similar to balloon-assisted coiling, a stent is deployed to block the aneurysmal neck before coil packing, which is defined as stent-assisted coiling. The aneurysms with an extremely unfavorable dome-to-neck ratio (1.0) require stent-assisted coiling generally due to the need of permanent support to prevent coil prolapse and migration. There are 4 major stent-assisted coiling techniques: mesh technique, stent jail technique, semi-jailing technique, stent jack technique, and Y-stenting technique. Stent jail technique is safe and effective, and it is one of the most used stent-assisting techniques nowadays [25]. In mesh technique, it would be difficult to navigate a microcatheter into the aneurysmal sac via the mesh of the stent. However, in stent jail technique, the microcatheter is positioned before the stent bridging over the aneurysmal neck and

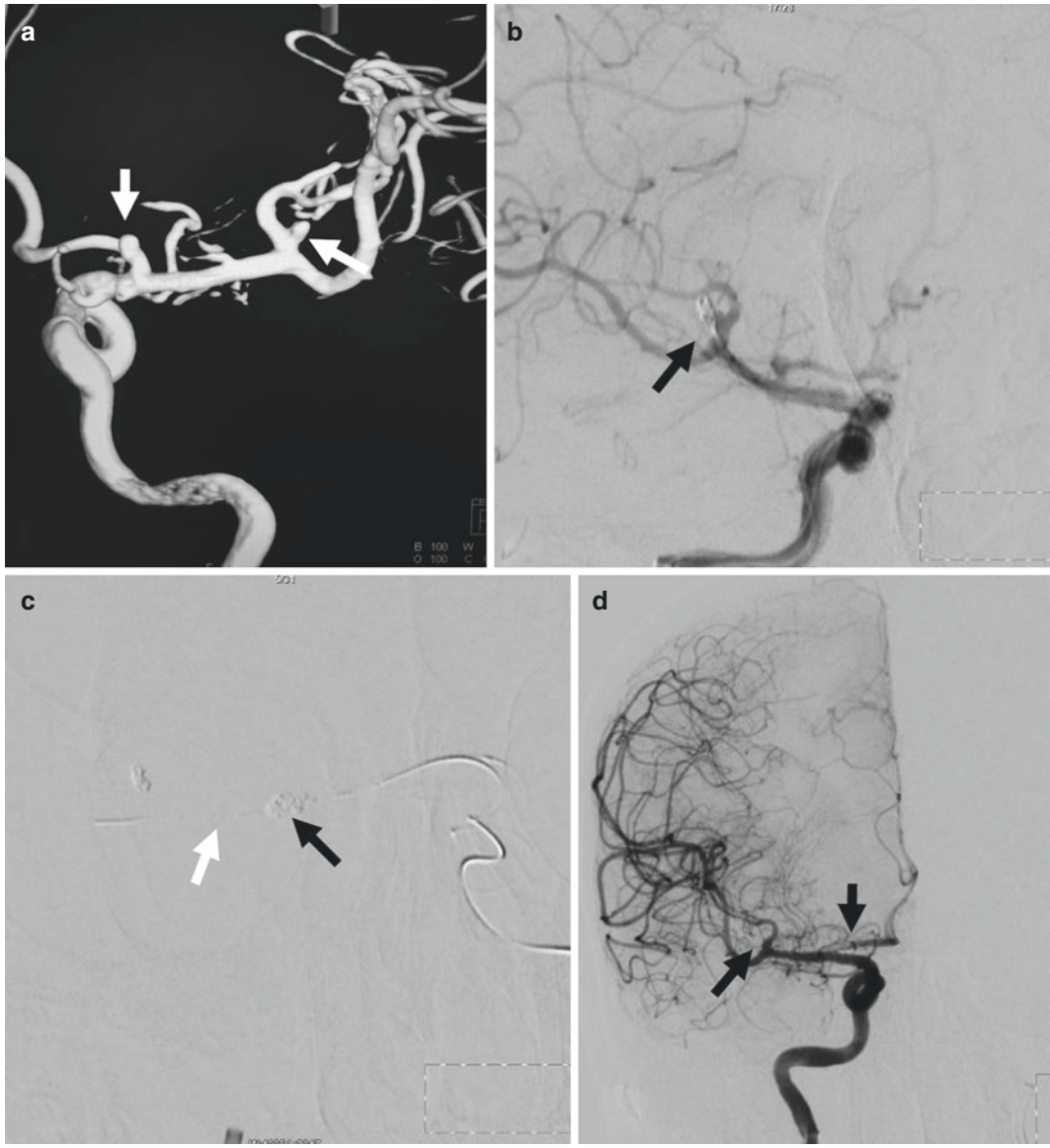


Fig. 6.10 A 52-year-old woman presented with Hunt–Hess grade 1 subarachnoid hemorrhage. (**a**) 3-D reconstruction of the right internal carotid artery injection showing a middle cerebral artery bifurcation aneurysm and an A1 origin aneurysm of the right anterior cerebral artery (arrows). (**b**) Oblique review of the right internal carotid artery injection showing the middle cerebral bifurcation aneurysm was coiling. (**c**) The void roadmap image showing the A1 aneurysm was treated via the transcirculation approach because of the microwire cannot be passed through the ipsilateral approach. White arrow, the 4.5 mm × 22 mm Enterprise stent; black arrow, coils. (**d**) Frontal view of the right internal carotid artery injection showing the 2 aneurysms were occluded completely (arrows)

there is no difficulty in holding the microcatheter's position during coil packing as it is trapped by the stent. In the stent jack technique, the stent delivery system and the microcatheter are both in place as the first step, and the stent is deployed after the deployment of the first coil in the aneurysmal sac. It allows the first coil to form a larger loop which is then pushed back into the sac,

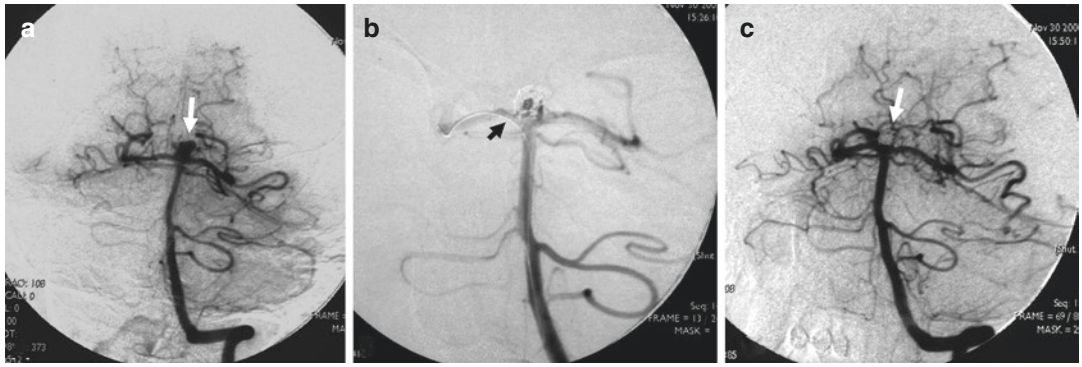


Fig. 6.11 A 38-year-old man presented with subarachnoid hemorrhage. (**a**) Frontal view of the left vertebral artery injection showing a basilar tip aneurysm (arrow). (**b**) Frontal view of the left vertebral artery injection showing the aneurysm was coiled with the assistance of a 4 mm × 7 mm Hyperform balloon catheter (Medtronic ev3, USA) (arrow). (**c**) The left vertebral artery injection showing the aneurysm was completely occluded (arrow)

resulting in better coil wall positioning. However, it is not recommended for the increased risks of rupture and the possibility of compromising the stent's integrity and stability.

6.8 Y-stenting Technique

Y-stenting technique is developed for treating bifurcation aneurysms, where 1 or more microcatheter are in place with 2 stents blocking the aneurysmal neck [26]. The Y-stenting was initially carried out and described by Chow and colleagues when treating a basilar apex aneurysm [27]. In classic Y-stenting, 2 stents are applied, the first being initially in one of the branches and the second is finally inserted through the meshes of the first stent into the second branch [26]. Another method is the so-called kissing stent technique. Here, the two stents are unfolded parallel in the main carrier vessel [28]. A meta-analysis that included 27 studies and 750 aneurysms treated with Y-stent placement has been published in 2019 [29]. In this study, the long-term complete/near-complete occlusion rate was 95.4%, and the treatment-related complication rate was 8.9%. Morbidity and mortality after treatment were 2.4% and 1.1%, respectively. Crossing Y-stent placement was associated with a slightly lower complication rate compared with the kissing configuration. Occlusion rates were quite comparable among Enterprise, Neuroform, and LVIS stents, whereas the Enterprise stent was associated with lower rates of complications (6.5%) compared with the others (14%). Another possibility is intrasaccular procedures such as the web device, in which, for example, a nitinol basket is inserted into the aneurysmal lumen [13]. A wide aneurysm neck can also be covered with a pConus system [30].

6.9 Intrasaccular Flow Disruptions

Intrasaccular flow disruption devices have been developed, among which is the Woven EndoBridge Embolization Device (Sequent Medical, Aliso Viejo, California) [31]. It is to be deployed inside the aneurysmal sac to induce fast thrombosis. It is suitable for most saccular bifurcation aneurysms and even ruptured bifurcation aneurysms, as it facilitates acute aneurysmal occlusion. Some authors point out its limitation in treating irregular dome-shaped intracranial aneurysms as good wall apposition is impossible. Lv et al. have performed a meta-analysis before June 2017, identifying and including 19 uncontrolled case-series studies (935 patients) [13]. Most aneurysms were wide-neck bifurcation aneurysms of the middle cerebral artery (43%) and the anterior communicating artery (23%). The technical success rate was 97%. There were 10% of peri-procedural complications. After a

mid-term clinical follow-up, mortality was 2% and adequate occlusion was 81%. Lv et al. concluded that although the WEB showed high rates of adequate aneurysm occlusion at midterm, there is no comparison of currently available treatment options, such as stent-assisted coiling. The intrasaccular WEB device is a good alternative, with closure rates of over 85% and permanent morbidity and mortality rates of 4 and 1.3%, respectively.

6.10 Intralumenal Flow Diversion

Another competing vascular treatment method for bifurcation aneurysms is flow diversion with so-called flow diverters (Fig. 6.12). Flow-diverting stents (FDSs) are a new generation of stents designed to treat aneurysms by isolating the aneurysmal lumen from the circulation via recanalization. They are braided mesh stents, such as the Silk Flow Diverter (Balt Extrusion, Montmorency, France), the Pipeline Embolisation Device (ev3, Irvine, California) [32]. The FDSs are suitable for both wide-necked and fusiform aneurysms. A systematic review showed a complete occlusion rate in over 81% of cases with a morbidity and mortality rate of 6.9% [33]. The main concern with FDSs is the risk of perforator and side branch blockage which makes them less desirable in treating bifurcation wide-neck aneurysms. However, the outcomes were satisfactory with preserved perforators and side branches [34].

6.11 The pCONus Bifurcation Aneurysm Implant

The pCONus Bifurcation Aneurysm Implant (Phenox GmbH, Bochum, Germany) is a stent-like endoluminal device for the treatment of wide-necked bifurcation aneurysms [30]. In a meta-analysis published in 2019 concerning the pCONus device for the treatment of aneurysms [35], 203 intracranial aneurysms were treated with per-procedural morbidity, and mortality rates were 7% and 0%, respectively. The long-

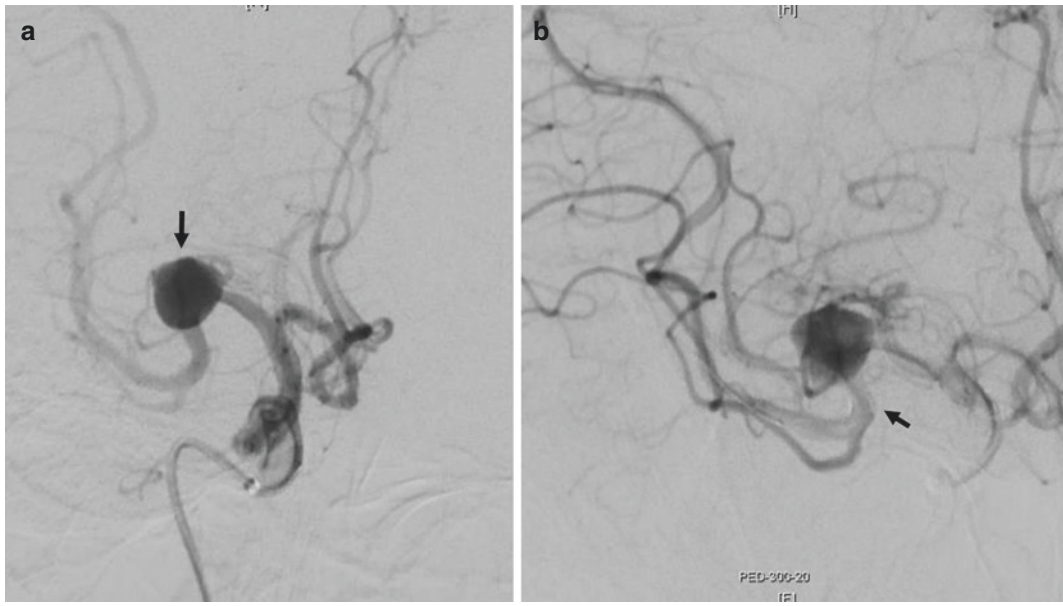


Fig. 6.12 A 54-year-old woman presented with an unruptured middle cerebral artery bifurcation aneurysm. (**a**) Frontal view of the right carotid artery injection showing a 8 mm × 8 mm aneurysm of the middle cerebral artery bifurcation (arrow). (**b**) Frontal view of the right carotid artery injection showing the aneurysm was treated using Pipeline flex flow diverter (arrow)

term complete occlusion rate was 60% and the retreatment rate was 14%. According to the authors, the pCONus devices are an additional tool for the treatment of wide-necked bifurcation aneurysms with high rates of technical success and sufficiently low rates of morbidity and mortality. Henkes et al. published a biocompatibility patient study on a new version of the pCONus device, called the pCONus HPC, which is coated with a novel glycan-based multilayer polymer coating, in an attempt to inhibit platelet adhesion [36]. The pCANvas Neck Bridging Device is a third-generation device [37]. The major upgrade as compared to pCONus is the biocompatible membrane on the distal end of the device, in order to redirect the flow away from the aneurismal sac.

6.12 Salvation Techniques

Salvation techniques are for dealing with thrombosis, ruptured aneurysms, or vascular trauma during interventional procedures [38]. The principle of salvation technique is to restore the integrity of vessel and stop the bleeding. The most commonly used one is to deploy small coils to block the perforation, to scaffold the protruding coils by stent placement. In extreme scenarios, a balloon is used to occlude the entire parent artery as a life-saving procedure to stop bleeding.

6.13 Observation for Bifurcation Aneurysms

Current evidence in the literature does not conclusively support a standard treatment strategy regarding asymptomatic unruptured intracranial aneurysms, especially for small-sized asymptomatic unruptured aneurysms in patients without a previous subarachnoid hemorrhage [39]. Management decisions require an accurate assessment of the risks of various treatment options compared with the natural history of asymptomatic aneurysms. In 1998, the International Study of Unruptured Intracranial Aneurysms (ISUIA) investigators reported the results of a large retrospective multicenter study on the natural course of asymptomatic unruptured aneurysms [40]. In this study, the natural course of 1937 asymptomatic unruptured aneurysms in 1449 patients was retrospectively assessed. The findings obtained suggested that annual hemorrhage rates of aneurysms <10 mm, 10–25 mm, and >25 mm in diameter in patients with no history of SAH were 0.05%, approximately1%, and 6%, respectively. Moreover, this study suggested that small unptured aneurysms have a benign natural course and a very low risk of bleeding when left untreated [40]. After this seminal publication, many cerebrovascular centers moved away from treating small incidentally discovered aneurysms, particularly in older patients (Fig. 6.13).

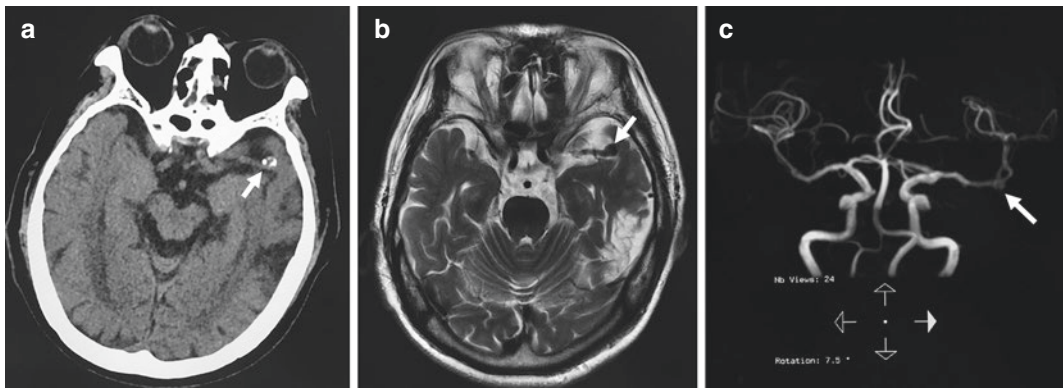


Fig. 6.13 An 84-year-old woman presented with an incidental middle cerebral artery bifurcation aneurysm. (**a**) CT scanning showing a hypertensive mass in the left Sylvian fissure, which suggested a calcification (arrow). (**b**) Axial view of the T2-weighted MR imaging showing flow void signal in the left Sylvian fissure (arrow). (**c**) MR angiography showing an aneurysm of the middle cerebral artery bifurcation (arrow). The aneurysm was not treated since old age and the aneurysmal calcification

6.14 Conclusion

Intracranial aneurysms most commonly occur at bifurcation sites. In the case of dealing with broad-based aneurysms, the risk of accidental vessel occlusion during embolization should not be underestimated. Therefore, several devices are available, e.g., WEB device and low-profile stents. Besides that, Y-stenting technique using double closed cell stent-assisted coiling is also feasible and safe for selected patients in the management of complex wide-necked bifurcations.

References

1. Akgul E, Balli T, Aksungur EH. Hybrid, Y-configured, dual stent-assisted coil embolization in the treatment of wide-necked bifurcation aneurysms. Interv Neuroradiol. 2015 Feb;21(1):29–39.
2. Bae IS, Yi HJ, Ko Y, Kim YS, Chun HJ, Choi KS. Practical incidence of complications and degree of patient satisfaction after endovascular coil embolization for unruptured intracranial saccular aneurysm based on patients' surveys. World Neurosurg. 2019 Jul;127:e76–85.
3. Lanzino G, Wakhloo AK, Fessler RD, Hartney ML, Guterman LR, Hopkins LN. Efficacy and current limitations of intravascular stents for intracranial internal carotid, vertebral, and basilar artery aneurysms. J Neurosurg. 1999 Oct;91(4):538–46.
4. Higashida RT, Smith W, Gress D, Urwin R, Dowd CF, Balousek PA, Halbach VV. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery. Case report and review of the literature. J Neurosurg. 1997 Dec;87(6):944–9.
5. Alfke K, Straube T, Dörner L, Mehdorn HM, Jansen O. Treatment of intracranial broad-neck aneurysms with a new self-expanding stent and coil embolization. AJNR Am J Neuroradiol. 2004 Apr;25(4):584–91.
6. Lv X, Li Y, Jiang C, Yang X, Wu Z. Potential advantages and limitations of the Leo stent in endovascular treatment of complex cerebral aneurysms. Eur J Radiol. 2011;79:317–22.
7. Luo J, Lv X, Jiang C, Wu Z. Preliminary use of Leo stent in endovascular treatment of wide-necked cerebral aneurysms. World Neurosurg. 2010;73:379–84.
8. Zhang J, Lv X, Yang J, Wu Z. Stent-assisted coil embolization of intracranial aneurysms using solitaire stent. Neurol India. 2012;60:278–82.
9. Lv X, Li Y, Xinjian Y, Jiang C, Wu Z. Results of endovascular treatment for intracranial wide-necked saccular and dissecting aneurysms using the Enterprise stent: a single center experience. Eur J Radiol. 2012;81:1179–83.
10. Lv X, Jiang C, Liang S. Small ruptured and unruptured complex cerebral aneurysms: single center experience of low-profile visualized intraluminal support stent. J Neurorestoratol. 2019;7(4):235–41.
11. Negrotto M, Crosa R, Casagrande W. Assisted coiling using LEO baby or LVIS Jr stents: report of six cases. Interv Neuroradiol. 2015 Oct;21(5):566–74.
12. Kwon O, Chung J. Outcomes of stent-assisted coiling using the neuroform atlas stent in unruptured wide-necked intracranial aneurysms. J Korean Neurosurg Soc. 2020 Aug 7; https://doi.org/10.3340/jkns.2020.0054.
13. Lv X, Zhang Y, Jiang W. Systematic review of woven EndoBridge for wide-necked bifurcation aneurysms: complications, adequate occlusion rate, morbidity, and mortality. World Neurosurg. 2018 Feb;110:20–5.
14. Fujimoto M, Lylyk I, Bleise C, Albiña P, Chudyk J, Lylyk P. Long-term outcomes of the WEB device for treatment of wide-neck bifurcation aneurysms. AJNR Am J Neuroradiol. 2020 Jun;41(6):1031–6.
15. Labeyrie PE, Gory B, Aguilar-Perez M, Pomero E, Biondi A, Riva R, Turjman F, Henkes H. The pCONus device for treatment of complex wide-neck anterior communicating artery aneurysms. World Neurosurg. 2017 May;101:498–505.
16. Ulfert C, Pfaff J, Schönenberger S, Bösel J, Herweh C, Pham M, Bendszus M, Möhlenbruch M. The pCONus device in treatment of wide-necked aneurysms: technical and midterm clinical and angiographic results. Clin Neuroradiol. 2018 Mar;28(1):47–54.
17. Kaspera W, Ćmiel-Smorzyk K, Wolański W, Kawlewska E, Hebda A, Gzik M, Ładziński P. Morphological and hemodynamic risk factors for middle cerebral artery aneurysm: a case-control study of 190 patients. Sci Rep. 2020 Feb 6;10(1):2016.
18. Mortimer AM, Bradley MD, Mews P, Molyneux AJ, Renowden SA. Endovascular treatment of 300 consecutive middle cerebral artery aneurysms: clinical and radiologic outcomes. AJNR Am J Neuroradiol. 2014 Apr;35(4):706–14.
19. Medical Advisory Secretariat. Coil embolization for intracranial aneurysms: an evidence-based analysis. Ont Health Technol Assess Ser. 2006;6(1):1–114.
20. Lv X, Yu J, Zhang W, Zhao X, Zhang H. Acute hemorrhagic cerebral artery dissection: characteristics and endovascular treatment. Neuroradiol J. 2020;33(2):112–7.
21. Lv X, Li Y, Liu A, Jiang P, Lv M, Wu Z. Endovascular treatment of intracranial giant serpentine aneurysms. Neuroradiol J. 2007;20(2):237–41.
22. Eskridge JM, Song JK. Endovascular embolization of 150 basilar tip aneurysms with Guglielmi detachable coils: results of the Food and Drug Administration multicenter clinical trial. J Neurosurg. 1998 Jul;89(1):81–6.
23. Aletich VA, Debrun GM, Misra M, Charbel F, Ausman JI. The remodeling technique of balloon-assisted

Guglielmi detachable coil placement in wide-necked aneurysms: experience at the University of Illinois at Chicago. J Neurosurg. 2000 Sep;93(3):388–96.
24. Ge H, Lv X, Yang X, He H, Jin H, Li Y. LVIS stent versus enterprise stent for the treatment of unruptured intracranial aneurysms. World Neurosurg. 2016 Jul;91:365–70.
25. Lv X, Wu Z, Qu RB, Jin H. Endovascular treatment of cerebral aneurysms during acute (<72 hours) subarachnoid hemorrhage. J Neurol Sci [Turkish]. 2012;29:535–41.
26. Castaño C, Terceño M, Remollo S, García-Sort MR, Domínguez C. Endovascular treatment of wide-neck intracranial bifurcation aneurysms with 'Y'-configuration, double Neuroform® stents-assisted coiling technique: experience in a single center. Interv Neuroradiol. 2017 Aug;23(4):362–70.
27. Chow MM, Woo HH, Masaryk TJ, Rasmussen PA. A novel endovascular treatment of a wide-necked basilar apex aneurysm by using a Y-configuration, double-stent technique. AJNR Am J Neuroradiol. 2004 Mar;25(3):509–12.
28. Brassel F, Melber K, Schlunz-Hendann M, Meila D. Kissing-Y stenting for endovascular treatment of complex wide necked bifurcation aneurysms using Acandis Acclino stents: results and literature review. J Neurointerv Surg. 2016 Apr;8(4):386–95.
29. Cagnazzo F, Limbucci N, Nappini S, Renieri L, Rosi A, Laiso A, Tiziano di Carlo D, Perrini P, Mangiafico S. Y-stent-assisted coiling of wide-neck bifurcation intracranial aneurysms: a meta-analysis. AJNR Am J Neuroradiol. 2019 Jan;40(1):122–8.
30. Gory B, Aguilar-Pérez M, Pomero E, Turjman F, Weber W, Fischer S, Henkes H, Biondi A. One-year angiographic results after pCONus stent-assisted coiling of 40 wide-neck middle cerebral artery aneurysms. Neurosurgery. 2017 Jun 1;80(6):925–33.
31. Arthur AS, Molyneux A, Coon AL, Saatci I, Szikora I, Baltacioglu F, Sultan A, Hoit D, Delgado Almandoz JE, Elijovich L, Cekirge S, Byrne JV, Fiorella D, WEB-IT Study investigators. The safety and effectiveness of the Woven EndoBridge (WEB) system for the treatment of wide-necked bifurcation aneurysms: final 12-month results of the pivotal WEB Intrasaccular Therapy (WEB-IT) Study. J Neurointerv Surg. 2019 Sep;11(9):924–30.
32. Lv X, Yang H, Liu P, Li Y. Flow-diverter devices in treatment of intracranial aneurysms: a meta-analysis and systematic review. Neuroradiol J. 2016;29(1):66–71.
33. Briganti F, Leone G, Marseglia M, Mariniello G, Caranci F, Brunetti A, Maiuri F. Endovascular treatment of cerebral aneurysms using flow-diverter devices: a systematic review. Neuroradiol J. 2015 Aug;28(4):365–75.
34. Michelozzi C, Darcourt J, Guenego A, Januel AC, Tall P, Gawlitza M, Bonneville F, Cognard C. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: complications, aneurysm sac occlusion, reabsorption, recurrence, and jailed branch modification at follow-up. J Neurosurg. 2018 Dec 21;131(6):1751–62.
35. Sorenson TJ, Iacobucci M, Murad MH, Spelle L, Moret J, Lanzino G. The pCONUS bifurcation aneurysm implants for endovascular treatment of adults with intracranial aneurysms: a systematic review and meta-analysis. Surg Neurol Int. 2019 Feb 28;10:24.
36. Henkes H, Bhogal P, Aguilar Pérez M, Lenz-Habijan T, Bannewitz C, Peters M, Sengstock C, Ganslandt O, Lylyk P, Monstadt H. Anti-thrombogenic coatings for devices in neurointerventional surgery: case report and review of the literature. Interv Neuroradiol. 2019 Dec;25(6):619–27.
37. Sirakov S, Panayotova A, Sirakov A, Penkov M, Minkin K, Hristov H. Using the pCANvas neck-bridging device in treating a wide-necked aneurysm of the basilar tip. Neuroradiol J. 2019 Jun;32(3):193–9.
38. Mahmoud M. Rescue stenting in endovascular treatment of acutely ruptured cerebral aneurysms. Interv Neuroradiol. 2013 Mar;19(1):21–6.
39. Rinkel GJ, Djibuti M, Algra A, et al. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29:251–6.
40. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: risk of rupture and risks of surgical intervention. N Engl J Med. 1998;339:1725–33.

Dual Lumen Balloon-Assisted Coil Embolization

7

Zaid Aljuboori, Abigail McCallum, Dale Ding, and Robert James

Abstract

Intracranial aneurysm is an abnormal dilation of a vessel wall. A multitude of factors have been linked to the development of and risk for rupture of these malformations. The consequences of these vascular abnormalities depend predominantly on whether the aneurysm ruptures. Aneurysmal subarachnoid hemorrhage (aSAH) is a serious condition that is a result of aneurysm rupture. It is associated with a high case fatality rate (45%) and severe disability in afflicted patients. The incidence rates are between 2 and 32 per 100,000 person-years. There are multiple treatment modalities available for the treatment of both ruptured and unruptured intracranial aneurysms. In this chapter, we will focus on the double-lumen balloon-assisted coiling technique for the treatment of intracranial aneurysms.

Z. Aljuboori (✉) · A. McCallum · D. Ding
Department of Neurological Surgery, University of Louisville School of Medicine, Louisville, KY, USA
e-mail: zaidsa@uw.edu

R. James
Department of Neurological Surgery, Indianna University School of Medicine, Indianapolis, IN, USA

Keywords

Intracranial aneurysm · Wide neck · Balloon assisted · Double lumen · Coil embolization

7.1 Rationale for the Use of Double-Lumen Balloon

Anatomic variability can make endovascular treatment technically challenging. Especially, when the aneurysm has a wide neck (>4 mm) or unfavorable dome/neck ratio. Under these circumstances, stand-alone aneurysm coiling can lead to suboptimal results [1]. Some studies have reported that the stand-alone coiling technique can result in a complete occlusion rate of 15% for wide-neck aneurysms in comparison to an occlusion rate of 85% for small-neck aneurysms [1]. The argument for these unsatisfactory results was that a wide-neck aneurysm prevented dense packing of the fundus because of the risk of coil prolapse. This is especially important in the case of ruptured aneurysms where a complete occlusion is of uttermost importance to prevent rehemorrhage [1–3]. A balloon remodeling technique (BRT) was described to circumvent this technical limitation with wide-neck aneurysms. The concept behind the BRT is to temporarily inflate a

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_7

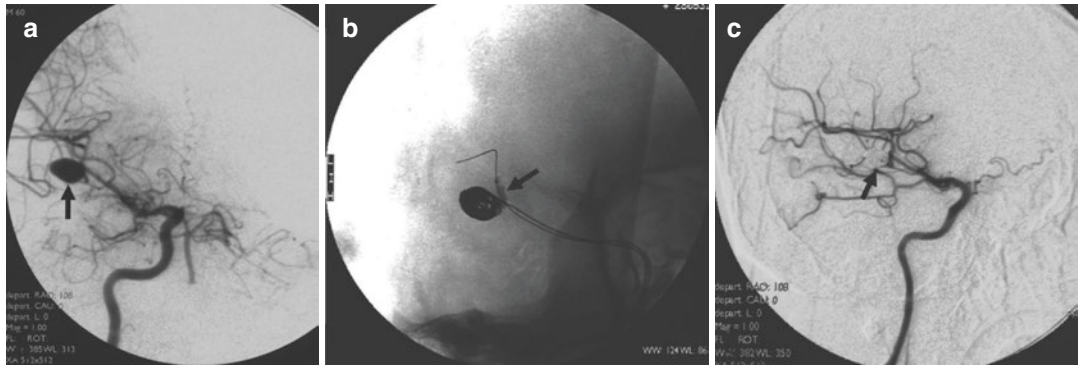


Fig. 7.1 A 60-year-old man presented with a large middle cerebral artery aneurysm. (**a**) Frontal view of the right internal carotid artery injection showing a large middle cerebral artery aneurysm (arrow). (**b**) Oblique view of the unsubtracted image showing the aneurysm was coiled with the assistance of a 4 mm × 7 mm Hyperform balloon catheter (Medtronic ev3, USA) (arrow). (**c**) Oblique view of the right internal carotid artery injection showing the aneurysm was completely occluded (arrow)

non-detachable balloon in the parent vessel spanning the neck of the aneurysm during coils deployment, and then the balloon is removed at the end of the procedure [1–10] (Fig. 7.1).

The use of BRT has shown good results for aneurysm occlusion after initial treatment and during follow-up. A recent review article reported a complete occlusion rate of 73% after initial treatment of wide-neck aneurysms in the BRT group versus 49% in the stand-alone coiling group. The subtotal occlusion and the incomplete occlusion rates were 22% and 5% in the BRT group vs 39% and 13% in the stand-alone coiling group [2, 8]. At follow-up, the results were similar; the complete occlusion rate was 72% in the BRT group versus 54% in the stand-alone coiling group, and the subtotal and the incomplete occlusion rates were 17% and 10% in the BRT group vs 34% and 11% in the stand-alone coiling group [2, 8].

In the Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms (ATENA) study, the investigators reported similar initial anatomic results for both the stand-alone coiling and the BRT groups (complete occlusion rate was 59.8% of aneurysms in the stand-alone coiling group and 59.8% of aneurysms in the BRT group) [11]. In the Remodeling Technique for Endovascular Treatment of Ruptured Intracranial Aneurysms study**,** the initial anatomic results were different between the BRT and the stand-alone coil embolization groups. The rate of satisfactory aneurysm occlusion rate was significantly higher in the BRT group (94.9%) than in the stand-alone coil embolization group (88.7%) [12]. Finally, Shapiro et al. published a meta-analysis that elucidated the superiority of BRT over stand-alone coiling for both immediate (BRT 73% vs stand-alone coiling 49%) and follow-up (BRT 72% vs stand-alone coiling 54%) angiographic occlusion rates [2].

7.2 Advantages

7.2.1 General Advantages of Balloons

(a) BRT does not usually necessitate antiplatelet therapy, which increases the risk of rebleeding in case of a ruptured aneurysm or the presence of external ventricular drain [1, 7, 8].

(b) BRT balloon conformity clearly delineates the neck of the aneurysm and adjacent vessels. Therefore, vessels originating from the aneurysm neck are safe during coiling [1, 7, 8].

(c) BRT can be used to stop blood flow in the parent vessel in case of intraprocedural rupture [1, 7, 8].

7.2.2 Advantages Specific to Double-Lumen Balloons

(a) Double-lumen balloons have a better navigability compared to single lumen balloons due to their ability to pass a thicker guide wire 0.014-inch vs 0.010-inch [9].
(b) Dual-lumen balloons catheters are denser (2 lumens) with a larger Profile and rely on occlusion of vent holes by contrast to create seal. The hydrophilic coating on the balloon and catheter shaft assists in the trackability.
(c) Double-lumen balloons can be used to deploy coils through the inner lumen, which permits the use of a single catheter technique. This is not applicable to single lumen balloons [9].
(d) Double-lumen balloons can be used to deploy low-profile stents through the inner lumen of the coaxial system. This feature can be used as a salvage option in cases where stenting was not planned but is deemed to be necessary to terminate aneurysm coiling with the deployment of the stent in order to keep the parent vessel open [13].

7.3 Potential Complications

(a) Thromboembolic complications: it occurs in 8% of patients, but only 4.4% are symptomatic [1, 8].
(b) Aneurysm rupture: the rate of aneurysm rupture due to balloon use is 1.7% in ruptured aneurysms, and 1.8% in unruptured aneurysms treated with BRT [1, 8].
(c) Parent vessel rupture: there is a 1% risk of parent vessel rupture due to balloon inflation [1, 8].
(d) Ischemia due to balloon inflation: a longer maximum inflation time correlates significantly with increased watershed infarcts. There are no clear-cut guidelines that delineate what is acceptable for balloon inflation time limits, because patient-related factors such as status of collateral circulation and presence of atherosclerosis do affect the patient tolerance to maximum balloon inflation time [1, 8].

7.4 Specific Indications

(a) Coiling of wide-neck aneurysms (>4 mm) [1, 3, 7, 8].
(b) Coiling of aneurysms with an unfavorable dome-to-neck ratio (<½) [1, 3, 7, 8].
(c) Coiling of aneurysms in patients whom a stand-alone coiling is expected to yield suboptimal results due to complex anatomy and are unable to receive antiplatelet therapy (e.g., acutely ruptured aneurysm) which precludes the use of stent-assisted coiling or flow diverting stent [1, 3, 7, 8].
(d) Coiling of aneurysms with a vessel or vessels originating from the aneurysm neck [1, 3, 7, 8].

7.5 Available Options for Double-Lumen Balloons

Balloons are made from a thermoplastic elastomer that is mounted on a nitinol slotted hypotube with hundreds of micromachined ports for contrast infusion. Two types of intracranial compliant balloons and coaxial dual-lumen systems are available. The Ascent (Codman Neuro, Pennsylvania, USA) and the Scepter (Microvention/Terumo, California, USA). Both have an inner lumen that permits the passage of a 0.014-inch guidewire and the deployment of 0.010- and 0.018-inch-diameter coils. The inner lumen is surrounded by a parallel outer noncommunicating lumen for contrast injection to inflate the balloon. Double-lumen balloon preparation is time-consuming and is less flexible compared to single lumen balloons.

The Ascent balloon is available in two forms, a semi-compliant form (4 mm × 10 mm, 4 mm × 15 mm) and a super-compliant form

(6 mm × 9 mm, 4 mm × 7 mm). The Scepter balloon is available in two forms as well: The Scepter-C (compliant, 4-mm x 10, 15, and 20 mm) and the Scepter-XC (extracompliant, 4 × 11 mm). Both balloons can also be used for embolization of intracranial vascular malformations as they are compatible with dimethyl sulfoxide (DMSO) [1, 3, 7, 8]. The Ascent semi-compliant and Scepter-C are less compliant versions that offer longitudinal coverage and minimal slipping for the treatment of sidewall aneurysms, while the more compliant version (Ascent super-compliant and Scepter-XC) conforms to vascular bifurcations and is more useful for bifurcation aneurysms [1, 3, 7, 8]. Both balloons have comparable results when used with the balloon remodeling technique for aneurysm coiling [3, 9, 14].

7.6 Technique for Device Preparation (Manufacturer Recommendations)

7.6.1 Ascent Balloon Preparation

1. Follow hospital procedures for removing the balloon catheter from packaging.
2. Attach a 3-way stopcock and a 20 cc syringe filled with 3 cc of contrast solution to the inflation port of the hub. Point the syringe down then pull vacuum and close the stopcock to the inflation lumen.
3. Point syringe up and purge air out.
4. Point syringe down, open stopcock, and pull a second vacuum, then slowly lower the plunger to let contrast to flow into the inflation lumen.
5. Hold the balloon in a vertical position, inject contrast with the 20 cc syringe to replace air with contrast in the balloon.
6. Once all air is out you should notice contrast exiting the tip of the catheter, confirm no air bubbles visible in the balloon.
7. Deflate the balloon while the catheter tip is in contrast solution.
8. Balloon inflation lumen prime volume is 0.45 cc.
9. Check manufacturer recommendations for using different contrast viscosity and associated balloon deflation time, also check inflation volumes for each balloon size.

7.6.2 Scepter Balloon Preparation

1. Follow hospital procedures for removing the balloon catheter from packaging.
2. Attach a 3-way stopcock and a 20 cc syringe filled with contrast/saline solution to the inflation port of the hub.
3. With the distal tip of the balloon catheter submerged in saline, slowly inflate and allow all the air to escape from the distal purge hole.
4. After purging all the air out, the balloon starts inflating with contrast/saline solution.
5. Balloon inflation lumen prime volume is 0.44 cc.
6. Check manufacturer recommendations for using different contrast viscosity and associated balloon deflation time, also check inflation volumes for each balloon size.

7.7 Device Uses

1. Sidewall aneurysms: place the balloon in the parent vessel covering the aneurysm neck [1, 3, 7, 8].
2. Bifurcation aneurysms, it is not as straightforward as sidewall aneurysms because of anatomical complexity and the increased likelihood of coil prolapse, the best option is decided based on a case-by-case basis depending on the anatomy of the parent vessel, the circle of Willis, and the aneurysm [1, 3, 7, 8]. Available options:
   (a) Place one balloon starting in the parent vessel and extend into one of the branches. Inflate the balloon sufficiently to completely cover the neck especially if the balloon is compliant enough to assume a pear shape (Figs. 7.2 and 7.3).
   (b) Place a balloon parallel to the neck of the aneurysm through a trans-circulation approach. For example, for a basilar aneurysm, the balloon can be navigated through one posterior communicating artery into the posterior cerebral artery

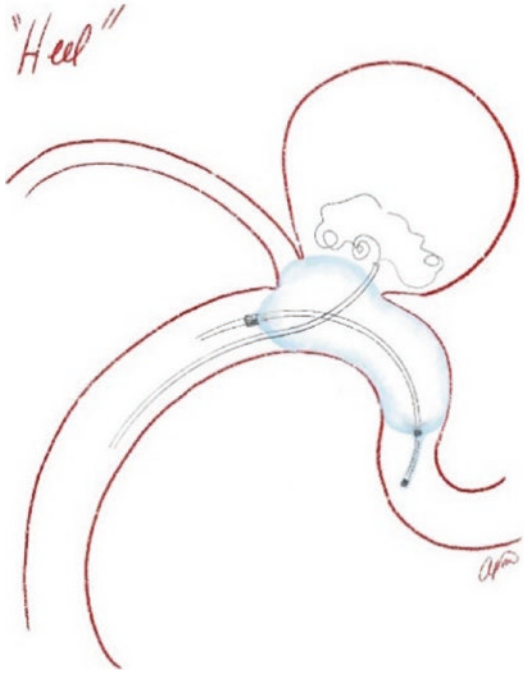


Fig. 7.2 An art sketch depicts the balloon remodeling technique where the balloon inflated into the parent vessel and covers the aneurysm neck assuming a pear shape

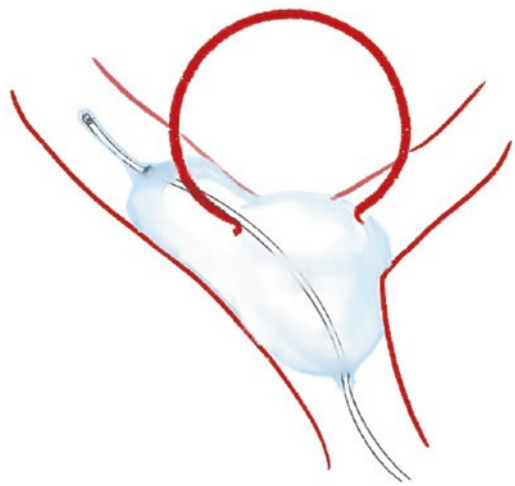


Fig. 7.3 An art sketch depicts the balloon remodeling technique where the balloon inflated into the parent vessel to cover the aneurysm neck and ostium of the adjacent branch for protection

crossing the aneurysm neck into the contralateral posterior cerebral artery. This approach requires a large circle of Willis anastomoses (Fig. 7.4).

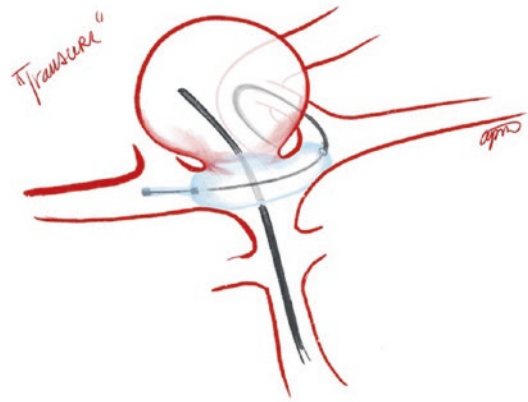


Fig. 7.4 An art sketch depicts the balloon remodeling technique where the balloon is parallel and covering the neck of the aneurysm through a trans-circulation approach

(c) Use a double-lumen balloon for both BRT and coil deployment. In this case, the balloon is positioned to cover the aneurysm neck, and the coils passed through the inner lumen of the coaxial system. There are some limitations to this technique as it can only be used in aneurysms that are large enough to accommodate the microcatheter tip (Fig. 7.5).

(d) Two balloons technique, position two balloons in front of the aneurysm neck starting in a single parent vessel with each extending into one of the bifurcation vessels (e.g., basilar tip aneurysm). Another scenario is the placement of two balloons in front of the aneurysm neck in two parent vessels starting proximal to the aneurysm and extending distal to it (e.g., bilateral A1 and A2 segments of the anterior cerebral artery in the case of anterior communicating artery aneurysm) (Figs. 7.6 and 7.7).

7.8 Alternative Options

(a) Stent assisted coiling: this technique works by deploying a stent across the aneurysm neck, followed by coiling of the aneurysm through a separate microcatheter passed outside the stent or through the stent into the aneurysm. This approach has been widely

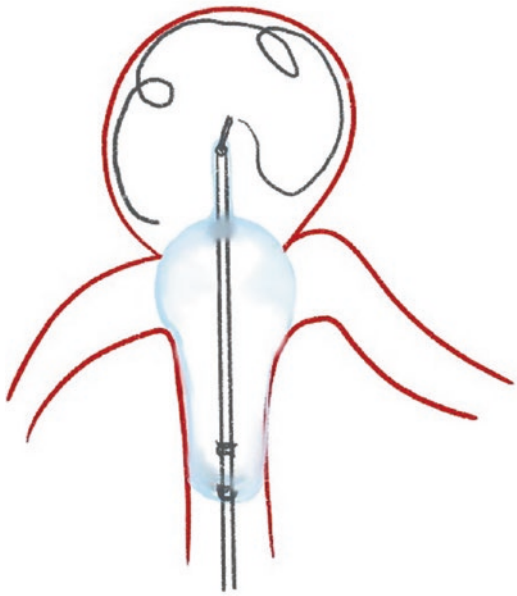


Fig. 7.5 An art sketch depicts the use of the double-lumen balloon for covering the neck as well as coil deployment. In this case, the balloon positioned to cover the aneurysm neck, and the coils passed through the inner lumen of the coaxial system

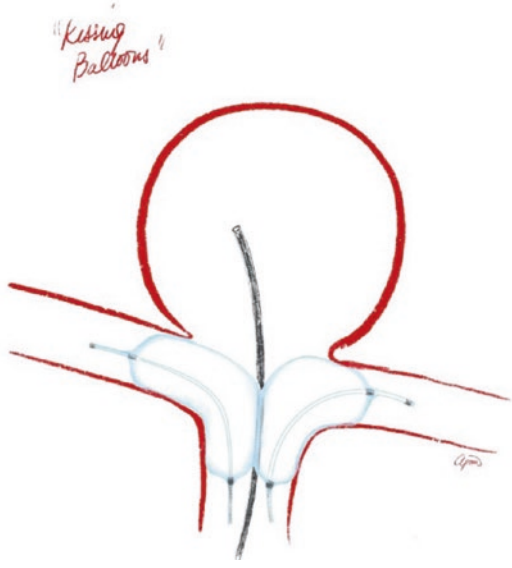


Fig. 7.6 An art sketch depicts the two-balloon technique for ACoA aneurysm where two balloons are positioned in front of the aneurysm neck starting in the A1 on each side and extending into each of the A2 vessels

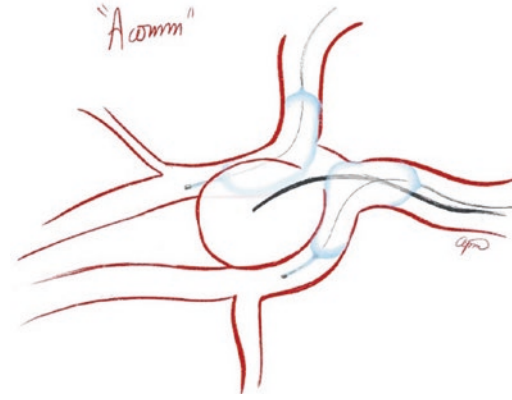


Fig. 7.7 An art sketch depicts the two-balloon technique for basilar tip aneurysm where two balloons are positioned in front of the aneurysm neck starting in the basilar trunk and extending into each of the posterior cerebral vessels

adopted, especially for wide-neck complex aneurysms. Conceptually, the stent provides stability to the coil mass inside the aneurysm and prevents coil prolapse into the parent vessel. Major limitations of this technique include the need for dual antiplatelet therapy which renders it inapplicable in the case of ruptured aneurysm treatment. Another limitation is the parent vessel diameter relative to the stent diameter. A minor limitation of this technique is the potential for delayed in-stent stenosis and parent vessel occlusion. The reported thromboembolic and hemorrhagic complications are 5.6% and 0.8%. Procedure-related mortality is 0.8% [1, 8, 15].

(b) Endosacular flow disrupter: this device was designed to be placed completely within the aneurysm sac and span the ostium, where it causes flow disruption. It obviates the need for antiplatelet therapy. Studies have shown an occlusion rate of approximately 60% with low morbidity and mortality. An example of this technology is the (Woven endobridge [WEB] device, Microvention, California, USA), this device has a globular shape and is predominantly made of braided nitinol wire [16].

(c) Flow diverting stents: these stents work through reconstruction of the parent artery. They have a high metal surface area coverage (30–35%) with full deployment into a size-matched vessel. The stent brings forth an endovascular scaffold on which a de novo artery can be reconstructed across the diseased segment. Eventually, the neointima and endothelium grow across the stent and become contiguous with the normal endoluminal surfaces of the distal and proximal parent artery, thereby excluding the abnormal segment. The reconstruction process starts immediately after the stent deployment and continues to evolve over a period of weeks to months. In terms of flow dynamics, these changes translate into an initial flow disruption that progresses to complete angiographic occlusion of the aneurysm and ultimately to curative anatomical restoration of the diseased vessel segment. An example of this technology is the Pipeline Embolization Device (PED; Medtronic, Dublin, Ireland). The FDA approved the PED for the endovascular treatment of adults with large or giant wide-neck intracranial aneurysms of the internal carotid artery. Off-label uses of the PED for the treatment of different aneurysm sizes and locations showed a good safety profile and high angiographic occlusion rates [8, 17–19].

(d) Surgical clipping: although the role of surgical clipping in the treatment of intracranial aneurysms has declined over time, still is considered a viable option in certain situations where endovascular techniques are of limited use.

References

1. Alaraj A, Wallace A, Dashti R, Patel P, Aletich V. Balloons in endovascular neurosurgery: history and current applications. Neurosurgery. 2014;74(Suppl 1):S163–90.
2. Shapiro M, Babb J, Becske T, Nelson PK. Safety and efficacy of adjunctive balloon remodeling during endovascular treatment of intracranial aneurysms: a literature review. AJNR Am J Neuroradiol. 2008;29(9):1777–81.
3. Spiotta AM, Miranpuri A, Hawk H, Chaudry MI, Turk AS, Turner RD. Balloon remodeling for aneurysm coil embolization with the coaxial lumen scepter C balloon catheter: initial experience at a high volume center. J Neurointerv Surg. 2013;5(6):582–5.
4. Das JP, Asadi H, Kok HK, Phelan E, O'Hare A, Lee MJ. Balloon-assisted coil embolization (BACE) of a wide-necked renal artery aneurysm using the intracranial scepter C compliant occlusion balloon catheter. CVIR Endovasc. 2018;1(1):12.
5. Mehta S, Hussain SI, Edgell RC. Coil embolization of wide-neck bifurcation aneurysms using a single-balloon microcatheter. Interv Neurol. 2015;3(3–4):135–41.
6. Nelson PK, Levy DI. Balloon-assisted coil embolization of wide-necked aneurysms of the internal carotid artery: medium-term angiographic and clinical follow-up in 22 patients. AJNR Am J Neuroradiol. 2001;22(1):19–26.
7. Pierot L, Cognard C, Spelle L, Moret J. Safety and efficacy of balloon remodeling technique during endovascular treatment of intracranial aneurysms: critical review of the literature. AJNR Am J Neuroradiol. 2012;33(1):12–5.
8. Piotin M, Blanc R. Balloons and stents in the endovascular treatment of cerebral aneurysms: vascular anatomy remodeled. Front Neurol. 2014;5:41.
9. Pukenas B, Albuquerque FC, Weigele JB, Hurst RW, Stiefel MF. Use of a new double-lumen balloon catheter for single-catheter balloon-assisted coil embolization of intracranial aneurysms: technical note. Neurosurgery. 2011;69(1 Suppl Operative):ons8-12.
10. Rho MH, Kim BM, Suh SH, Kim DJ, Kim DI. Initial experience with the new double-lumen scepter balloon catheter for treatment of wide-necked aneurysms. Korean J Radiol. 2013;14(5):832–40.
11. Pierot L, Spelle L, Leclerc X, Cognard C, Bonafe A, Moret J. Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils. Radiology. 2009;251(3):846–55.
12. Pierot L, Cognard C, Anxionnat R, Ricolfi F, Investigators C. Remodeling technique for endovascular treatment of ruptured intracranial aneurysms had a higher rate of adequate postoperative occlusion than did conventional coil embolization with comparable safety. Radiology. 2011;258(2):546–53.
13. Spiotta AM, Miranpuri A, Chaudry MI, Turner RDt, Turk AS. Combined balloon stent technique with the Scepter C balloon and low-profile visualized intraluminal stent for the treatment of intracranial aneurysms. J Neurointerv Surg. 2013;5(Suppl 3):iii79–82.
14. Lazzaro MA, Darkhabani Z, Zaidat OO, Fitzsimmons BF. Initial experience with the coaxial dual-lumen ascent balloon catheter for wide-neck aneurysm coil embolization. Front Neurol. 2011;2:52.

15. Geyik S, Yavuz K, Yurttutan N, Saatci I, Cekirge HS. Stent-assisted coiling in endovascular treatment of 500 consecutive cerebral aneurysms with long-term follow-up. AJNR Am J Neuroradiol. 2013;34(11):2157–62.
16. Dmytriw AA, Salem MM, Yang VXD, et al. Endosaccular flow disruption: a new frontier in endovascular aneurysm management. Neurosurgery. 2019;86(2):170–81.
17. Brasiliense LBC, Aguilar-Salinas P, Lopes DK, et al. Multicenter study of pipeline flex for intracranial aneurysms. Neurosurgery. 2019;84(6):E402–9.
18. Fiorella D, Lylyk P, Szikora I, et al. Curative cerebrovascular reconstruction with the pipeline embolization device: the emergence of definitive endovascular therapy for intracranial aneurysms. J Neurointerv Surg. 2009;1(1):56–65.
19. Malhotra A, Wu X, Brinjikji W, et al. Pipeline endovascular device vs stent-assisted coiling in small unruptured aneurysms: a cost-effectiveness analysis. Neurosurgery. 2019;85(6):E1010–9.
20. Figueredo LF, Camila Pedraza-Ciro M, Sebastian Lopez-McCormick J, Javier Rueda-Esteban R, Armando M-CJ. Aneurysmal subarachnoid hemorrhage associated with small aneurysms in smokers and women: a retrospective analysis. World Neurosurg X. 2019;4:100038.
21. Worthington JM, Goumas C, Jalaludin B, Gattellari M. Decreasing risk of fatal subarachnoid hemorrhage and other epidemiological trends in the era of coiling implementation in Australia. Front Neurol. 2017;8:424.
22. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000;31(5):1054–61.
23. Pai AM, Kameda-Smith M, van Adel B. A review of recent advances in endovascular therapy for intracranial aneurysms. Crit Rev Biomed Eng. 2018;46(4):369–97.

8 Blood Blister-Like Aneurysms: Pathogenesis and Endovascular Treatment

Xianli Lv

Abstract

The exact pathogenesis of BBA is still uncertain. Despite variant treatment modalities, the outcomes have been unsatisfactory, because many treatments did not target the BBA pathology. Based on angiograms, pathologic change of vessels adjacent to BBA means the pathogenesis of BBA is acute vascular dissection. Open-cell and braided stents assisted coiling may be the appropriate treatment of BBAs for their good wall apposition. Adjunctive use of coiling facilitates immediate complete occlusion of BBAs. Flow diversion (FD) is also suggested for BBAs. Multistent reconstruction and stent-in-stent technique were reported for treating BBAs before the FD era. Despite the lack of data of BBAs treated with FD from large series of clinical studies, a few recent small clinical studies or case reports suggested FD to be a safe and feasible alternative for BBAs. The use of antiplatelet therapy after FD treatment for BBAs still remained controversial.

Keywords

Blood blister-like aneurysm · Pathogenesis Treatment · Endovascular

X. Lv (✉)
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

Abbreviations

BBA	Blood blister-like aneurysms
CT	Computed tomography
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
ICA	Internal carotid artery
mRS	Modified Rankin Scale;
SAH	Subarachnoid hemorrhage

8.1 Introduction

Blood blister-like aneurysms (BBAs) are defined as small aneurysms originating from nonbranching sites of the terminal internal carotid artery (ICA) with a broad base, which are assumed to be dissecting in nature (Fig. 8.1) [1, 2]. Despite its definition, they can also be found in other locations of the cerebral circulation [3]. Several studies reported BBA in the circle of Willis, even the middle cerebral artery, anterior communicating artery, and vertebrobasilar circulation could be found (Fig. 8.2) [3]. The BBAs are rare, accounting for 0.9–6.5% of all intracranial aneurysms. They have extremely fragile walls and are highly prone to spontaneous rupture. Little is known about their pathogenesis at present, but they are hypothesized to arise from dissections [4, 5]. BBA can also increase in size and change its configuration into a saccular shape when the aneurysm points toward the optic nerve [6].

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_8

Fig. 8.1 A lateral projection of internal carotid artery angiogram showing a small bulge of the dorsal wall of the supraclinoid segment of the internal carotid artery, which is called blood blister-like aneurysm (arrow)

According to a systematic review, female gender, hypertension, younger age, and right-sided ICA origins are associated factors of BBA [3]. The overall mortality following various treatment modalities was 19%. Therefore, the natural history of BBAs is still dismal. The optimal management of ruptured BBAs still remains unclear because the pathogenesis of BBAs is still uncertain [7]. In a recent review, neither surgical nor endovascular treatments have an effect on clinical outcome, aneurismal regrowth, rebleeding, or complication rate [7]. This study has diminished the value of the combining application of stents and coils. The number of BBAs treated by endovascular technique is increasing along with the sprouting of new intracranial stents (Fig. 8.3). Consolidate understanding of BBA pathogenesis will facilitate us to manage and prevent rebleeding and regrowth of BBA maximizing patient outcomes. In this chapter, we reviewed experiences of reconstruction treatment and previous literatures, focusing on the pathogenesis of BBA that led us to choose the optimal management modality.

8.1.1 Pathogenesis of BBA

Our concept of BBA treatment is ICA reconstruction and in our experience, the ICA reconstruction of BBA is often successful and not too difficult to be done [8–10]. Although there have been reports of BBAs located at other vessels of the cerebral circulation, the initial and most classic location of a BBA is restricted to the ICA [7]. They are typically diagnosed after a bleed on the CTA and DSA. However, the critical point is not only the difficulty in BBAs diagnosis but also the complexity of their treatment, which is always challenging no matter the therapeutic modality chosen [7].

In recent studies, the pathomechanism underlying the development of BBAs has been explored [11–13]. Pathological examination usually demonstrates subintimal dissection involving the supraclinoid ICA and extending a variable distance to the middle cerebral artery (Fig. 8.4). Yanaka et al. found an intraoperative arterial tear at the base of a BBA [11]. Guo et al. reported a case of BBA, in which the laceration of the arterial wall was repaired (Fig. 8.5) [12]. In a case of ruptured BBA, intramural hematoma had been detected with MRI in the subacute stage, which suggested BBA was a focal dissection of the ICA [13]. These findings supported the hypothesis that focal dissection causes the formation of BBAs. This precise definition will facilitate BBA treatment.

Hemodynamic stress may play an important role in the formation of BBAs because the anterior wall of the ICA is curved and the shear forces impinge between the mobile supraclinoid and fixed intracavernous segments [14]. The spiral extension and weakening of the vessel wall of the superaclinoid ICA facilitate a focal dissection dilation at the site of the initial dissection (Fig. 8.6). According to Laplace's law, the wall tension is directly proportional to the radius of a vessel [15]. The general relation of Laplace's law, expressing that the product of the vessel radius (r) and blood pressure (P) is equal to vessel wall tension (T) (i.e., $r \times P = T$) (Fig. 8.7). The supraclinoid ICA wall is asymmetrically flatter than the cavernous ICA will experience a greater wall tension.

Cerebral ischemia was a presenting feature reported in 73% of patients with anterior circulation dissections, the incidence of SAH due to ICA dissection reported between 12% and 20%

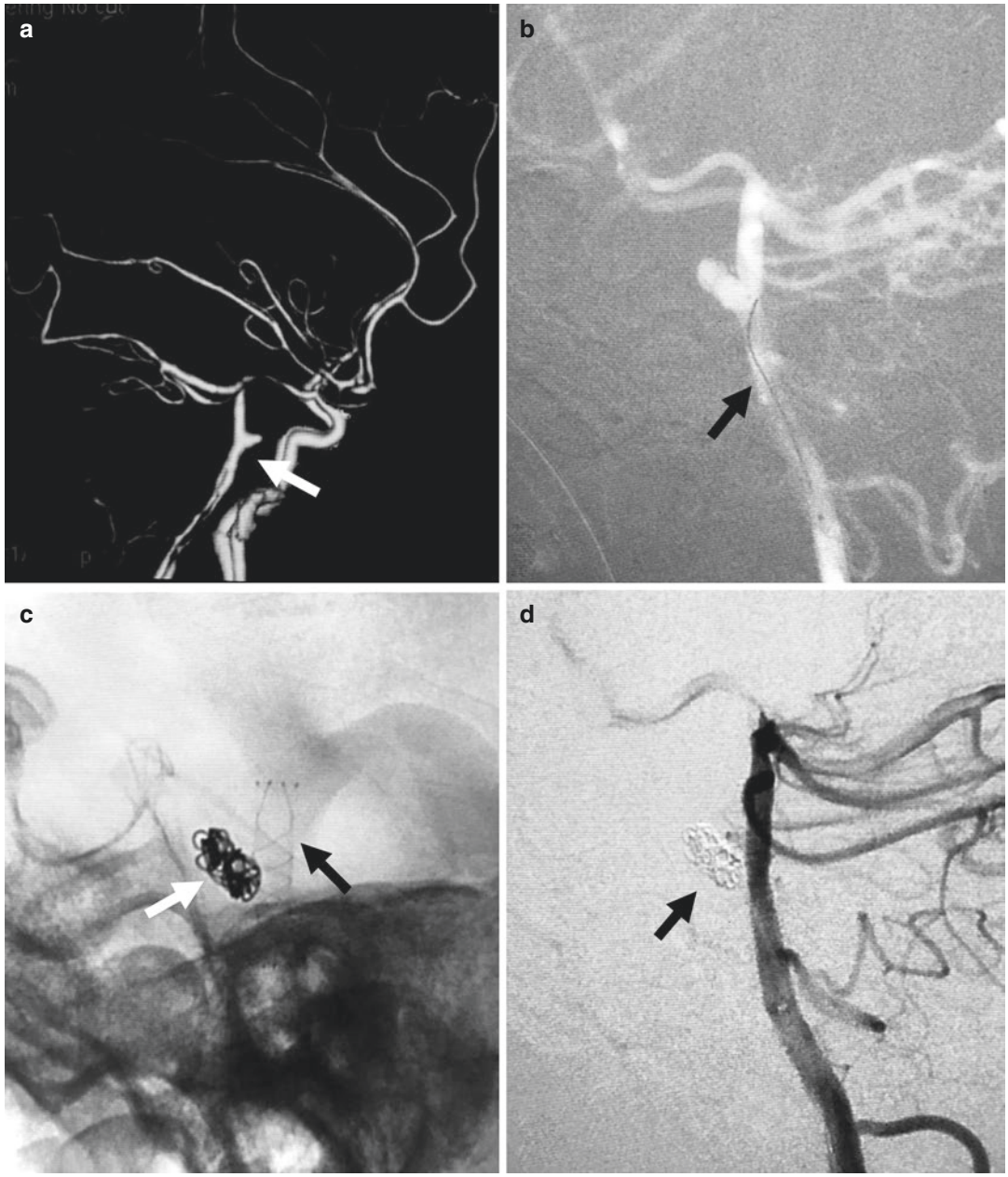


Fig. 8.2 A BBA of the basilar artery treated with LVIS stent-assisted coiling. (**a**) CT angiography showing a broad-based bulge arising from the non-branch site of the basilar artery. (**b**) Under roadmap image, a microcatheter was navigated over a micro-guidewire. (**c**) Lateral projection of the unsubtraction image showing the 3.5 mm × 15 mm LVIS stent (Microvention, USA) (black arrow) and coil mass (white arrow). (**d**) Lateral projection of the post-embolization angiogram showing the BBA was completely occluded (arrow)

[16]. But the SAH is reported up to 99% in BBA cases. Chronic dissection is a "string sign" or "pearl and string sign" on DSA and the dissection usually occurs in the plane between the internal elastic lamina and the media [17, 18]. In ischemic cases, an Enterprise stenting and coiling is indicated in my patients to prevent further formation of thrombus and subsequent thrombus emboliza-

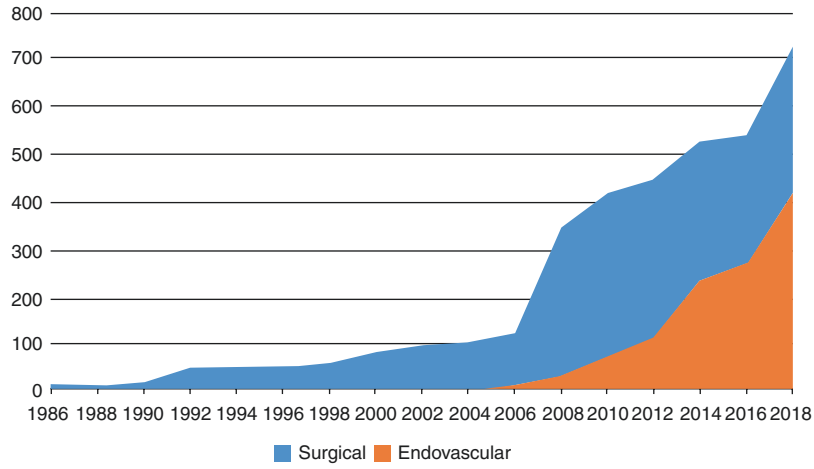


Fig. 8.3 Cumulative number of BBAs treated endovascular is increasing and close to the surgical treatment. Surgical (blue line) and endovascular (orange line). The endovascular techniques were initiated in BBAs in 2000 until now. The systematic reviews of ruptured BBAs were conducted in recent years

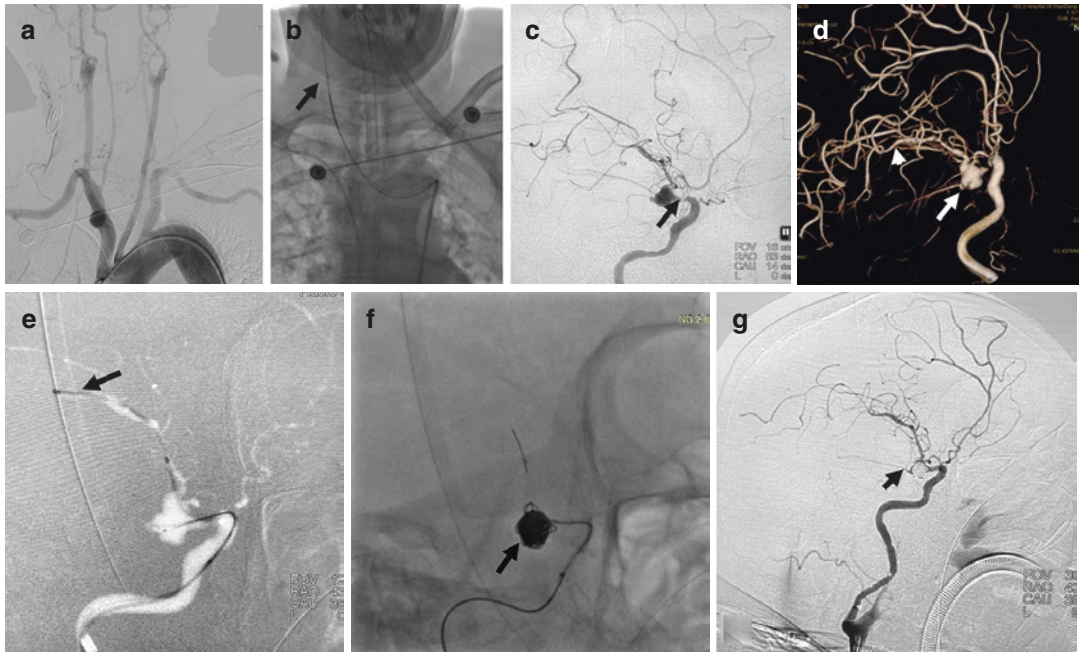


Fig. 8.4 Showing a supraclinoid ICA dissection extended to the distal MCA caused Hunt–Hess grade 3 SAH in a 67-year-old female patient. (**a**) Frontal view of the aortic angiogram. (**b**) Unsubtraction image showing a 6-F intermediate catheter was advanced into the right carotid artery (arrow). (**c**) Oblique view of the right internal carotid artery angiogram. (**d**) 3D reconstruction of the right internal carotid artery injection. Showing the supraclinoid ICA dissection (arrows) extended to the distal MCA (arrowhead). (**e**) Roadmap image showing a prowler plus catheter was navigated to the distal MCA (arrow) and a microcatheter was inserted into the aneurysm sac. (**f**) Unsubtraction image showing the aneurysm was coiled with the assistance of a 4.5 mm × 28 Enterprise (Codman, USA). (**g**) Post-treatment angiogram showing the aneurysm was completely occluded

tion [18, 19]. Enterprise stenting is useful for its higher radial force when a patient has tight luminal narrowing. Little attention has been given to acute intracranial arterial dissection as a cause of SAH [5], though the clinical and radiological features of chronic intracranial arterial dissection have been described in detail. The cleavage plane will be extended transmurally from the lumen through intima, elastic lamina, and media to the adventitia when SAH is the primary presentation

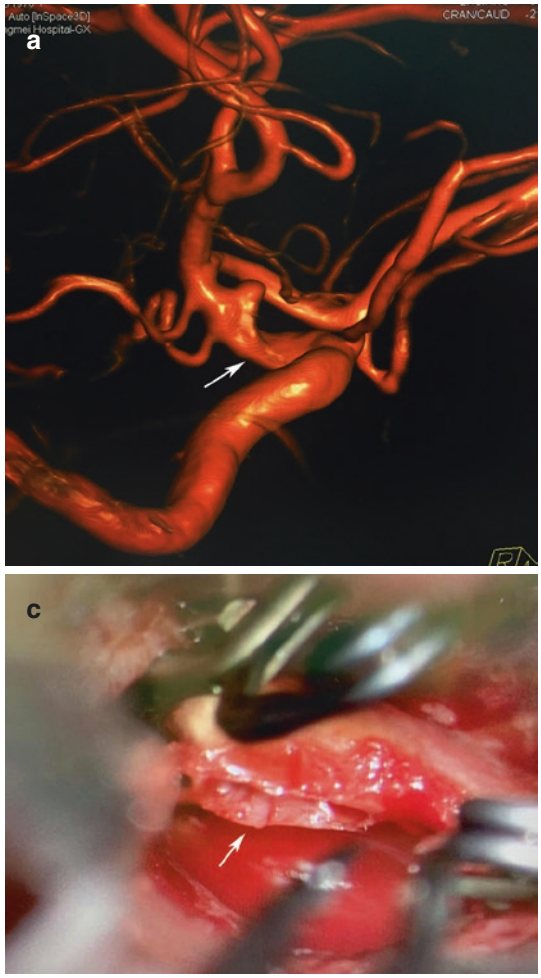


Fig. 8.5 (**a**) 3-D reconstruction of ICA injection of a BBA showing a spiral extension of a focal dissection of the vessel wall associated with a BBA. (**b**) Frontal view of the right carotid artery injection showing a BBA of the ICA. (**c**) intraoperative view showing a 5-mm laceration of the right ICA after removing the clot

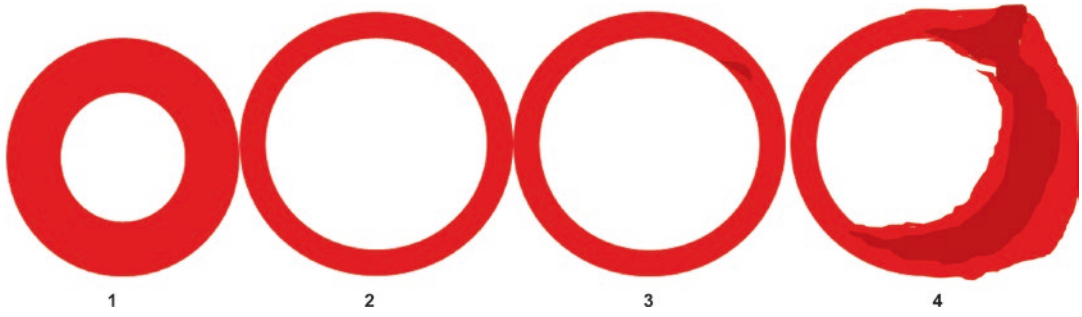


Fig. 8.6 Illustrations showing a spectrum of hemodynamic forces injury acting upon the ICA wall. Panel 1 shows the normal situation of the ICA. Panel 2 shows ICA dilatation as the initial event. Panel 3 shows a tear in the inner ICA wall secondary to laceration. Panel 4 shows ICA wall laceration gradually merges to form a complete dissection and rupture

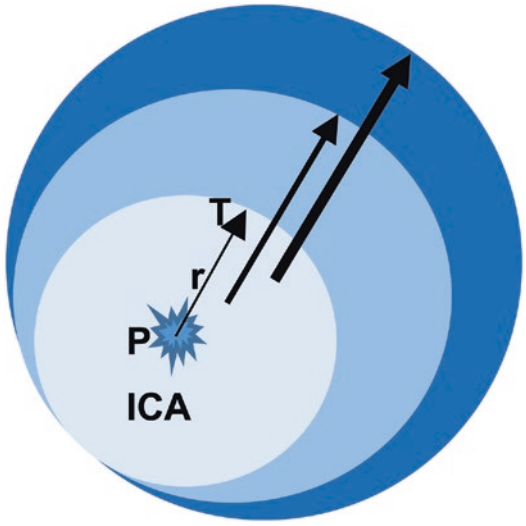


Fig. 8.7 Illustration of Laplace's law. P indicates intra-arterial pressure. The irregular asterisk indicates a constantly fluctuating value of pressure, r indicates the artery radius and T indicates arterial wall tension. T will increase with the increasing dilatation of the ICA. This will initiate a vicious cycle of events that may lead to further arterial pathologic changes

of an intracranial dissection [5]. The subsequent course of the dissection is determined by several factors which may include systolic blood pressure, vessel location, vessel curvature, and side branches [5].

8.1.2 Neuroendovascular Strategies

Given the proposed pathogenesis of BBA, endovascular reconstruction is potentially useful and should be considered as a treatment option [5]. Acute surgery for BBAs resulted in intraoperative bleeding in 43.2% of all patients with unfavorable patient outcomes [20]. Anastomosis to proximal MCA is difficult with a swollen brain in patients with high-grade SAH [21, 22]. Endosaccular coil embolization is reported to fail to prevent rebleeding or regrowth of BBAs (Fig. 8.8) [23]. Endovascular ICA trapping has been suggested, but it is unsuitable while PcomA or AchoA originates too close to BBA [21, 22].

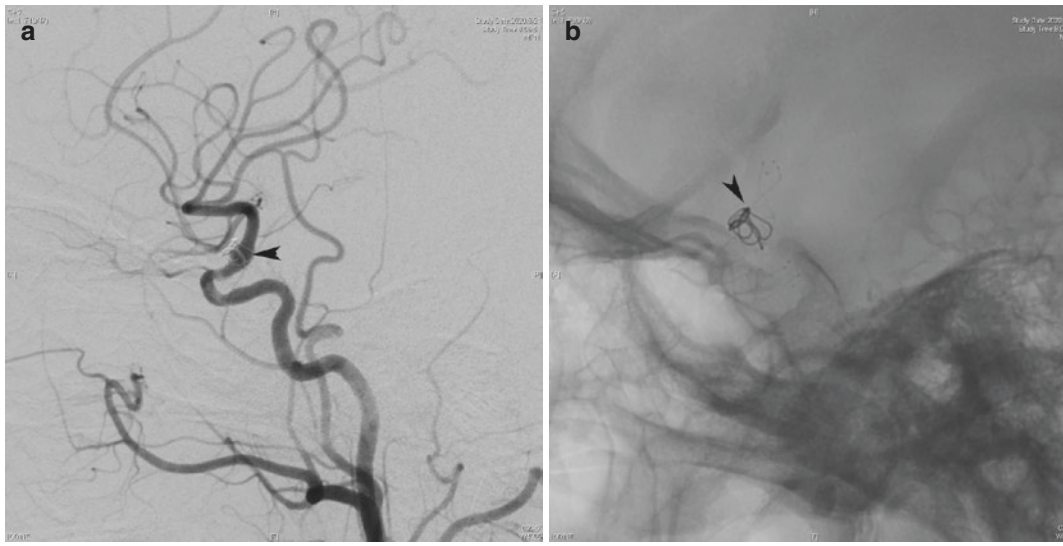


Fig. 8.8 One-year follow-up angiogram showing regrowth of a BBA in a 31-year-old female patient. (**a**) Lateral projection of the carotid artery angiogram showing the regrowth of the BBA (arrowhead). (**b**) Unsubtraction image showing the BBA was treated with stent-jail technique using 3.5 mm × 20 mm LVIS stent and a coil 1 year before

And the sacrifice of the ICA within 48 hours following an SAH will lead to a poor outcome even in patients with adequate collateral circulation demonstrated by preoperative DSA (good cross-filling of the MCA and ACA, good-sized AComA, and good-sized PComAs), probably because of vasospasm and high intracranial pressure compromise the cerebral collaterals [24]. Although an EC–IC bypass and endovascular trapping also constitute one treatment option, the risk of thromboembolic or hemorrhagic complications must be considered in this complex therapy [21]. The ICA preserving usually resulted in a benign clinical course. In a systematic review of 334 patients, the surgical morbidity for BBAs is estimated to be 20%, with a 10.7% mortality [25]. For endovascular outcomes, the morbidity is 7.0% and a 9.0% mortality for BBAs. The endovascular outcomes differ according to the endovascular techniques used, the highest percentages of a good outcome are among those treated with stents (86.4%), stent-assisted coiling (85.2%), and flow-diverting stents (82.2%); the lowest rate of good outcomes (mRS 0–2) is treated with coiling (52.9%). In a systematic review from 2005 to 2015, 36 papers including 256 patients with BBAs treated endovascularly (122 procedures) or surgically (139 procedures) are analyzed to therapeutic efficacy and safety [26]. In surgical group, immediate and late (mean 20.9 months) aneurysm occlusion rates are 88.9% and 88.4%, respectively. In endovascular group, immediate and late aneurysm obliteration rates are 63.9% and 75.9%, respectively. However, procedure-related complications and overall poor neurological outcomes are slightly greater in the surgical cases than those in the endovascularly cases (27.8% [95% CI 19.6%–37.8%] vs 26.2% [95% CI 18.4%–35.8%]), indicating that endovascular therapy may provide better outcomes.

The use of various stents, stent-assisted coiling, or stent-within-a-stent has been described in treating these lesions. Fiorella et al. have obtained good outcomes by using open-cell stents to reconstruct the ICA (Fig. 8.9) [27]. Other authors have tried close-cell stents, 2 patients suffered

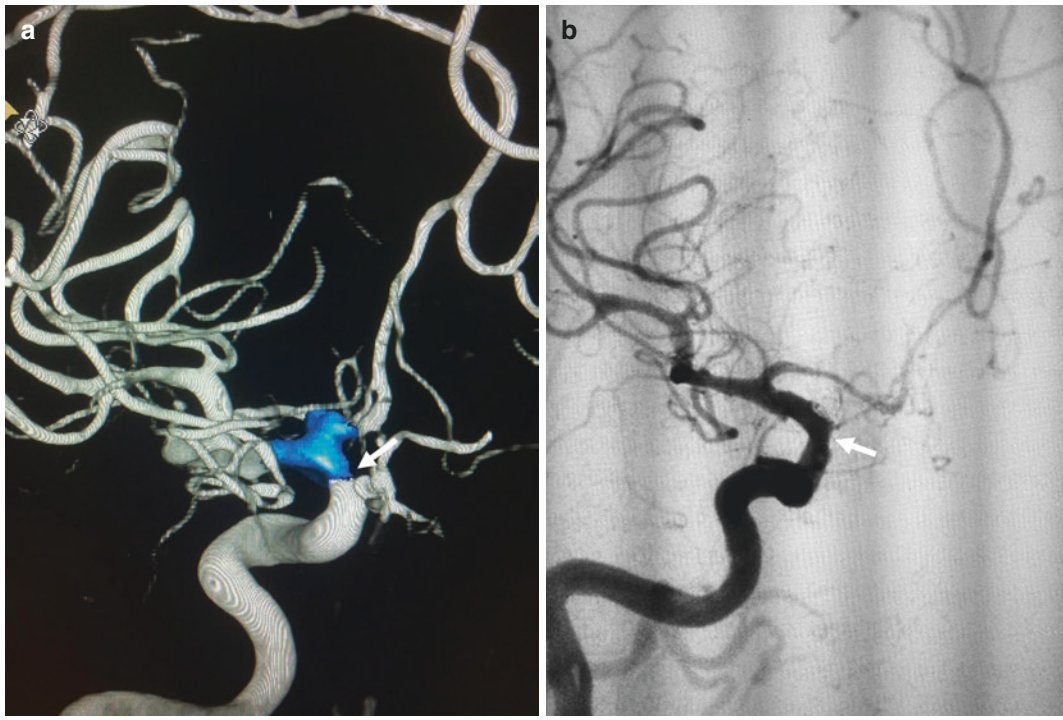


Fig. 8.9 (**a**) 3-D reconstruction of left ICA injection showing a BBA. (**b**) Left ICA injection after 3.5 mm × 20 mm Neuroform stent-assisted coiling showing the BBA was embolized completely

regrowth and rebleeding after overlapping technique in 7 patients [28]. Among Lv et al. cases, one patient with BBA treated with close-cell stent-assisted coiling had undergone an aneurysm rebleeding [19]. Close-cell stent seems to have a potential risk of rebleeding in immediate postoperative periods for its incomplete wall apposition. For many years at our institution, stenting plus coiling is the standard endovascular treatment. Recently, new braided stents with a dense porosity, known as LVIS and Pipeline flow-diverting stents, have been used [8–10]. Previous studies demonstrated the safe management of BBA with a standard endovascular approach using LVIS stenting (Fig. 8.9) and coiling or, more recently, flow-diverting stents (Figs. 8.10 and 8.11). The possibility of performing a parent vessel reconstruction appears to be a more physiological method to avoid ICA sacrifice. A recent review by Szmuda et al. from 2010 to 2016, only ruptured BBAs of a supraclinoid ICA treated with flow-diverting stents were included [7]. From a total of 17 studies, 56 patients which fitted the criteria were obtained. Twenty-three patients (41.1%) were treated in the acute stage of SAH. Thirty-four patients (60.7%)

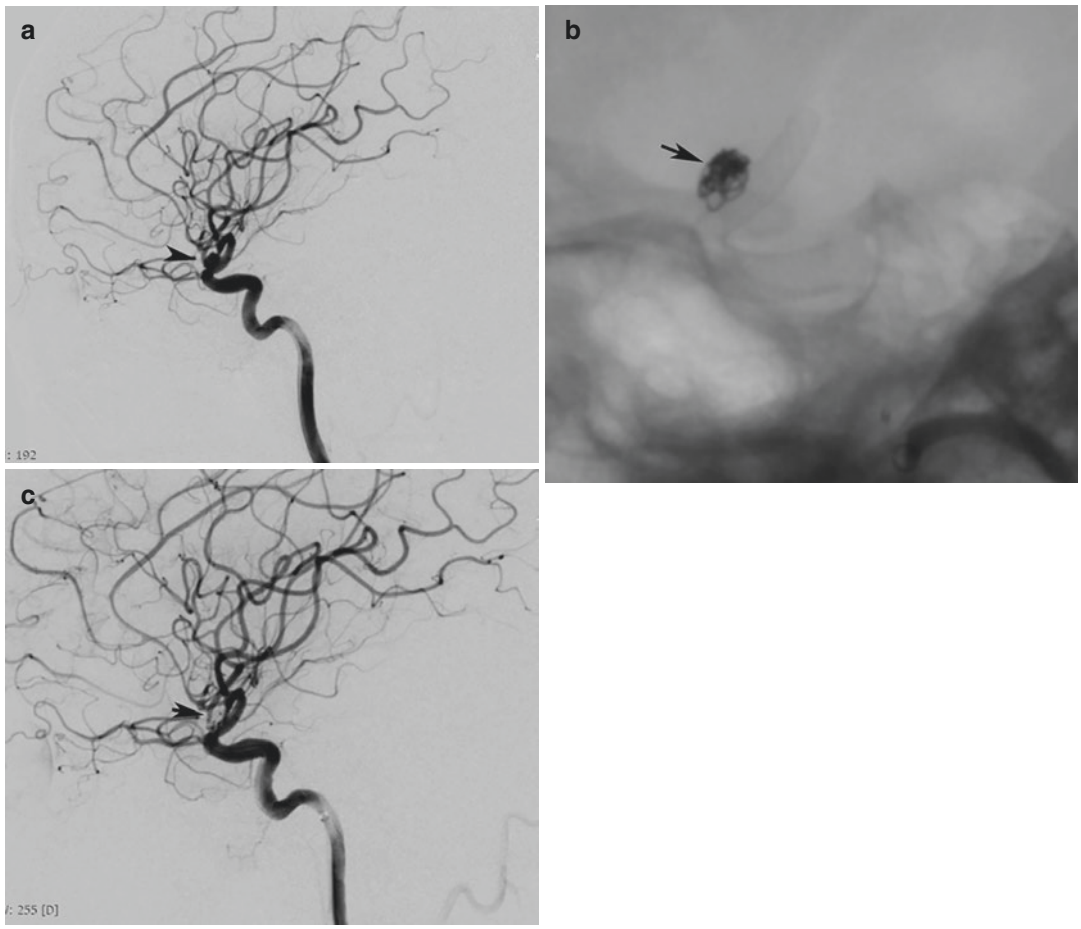


Fig. 8.10 A BBA was treated with FD-assisted coiling in a 56-year-old female patient with Hunt–Hess grade 3 SAH. (**a**) Lateral projection of the left internal carotid artery injection showing a BBA (arrowhead). (**b**) Unsubtraction image showing the BBA was treated with coils and a 3.5 mm × 25 mm Pipeline Flex FD (Medtronic, USA) (arrow). (**c**) Lateral projection of the left internal carotid artery injection showing complete occlusion of the BBA after treatment (arrowhead)

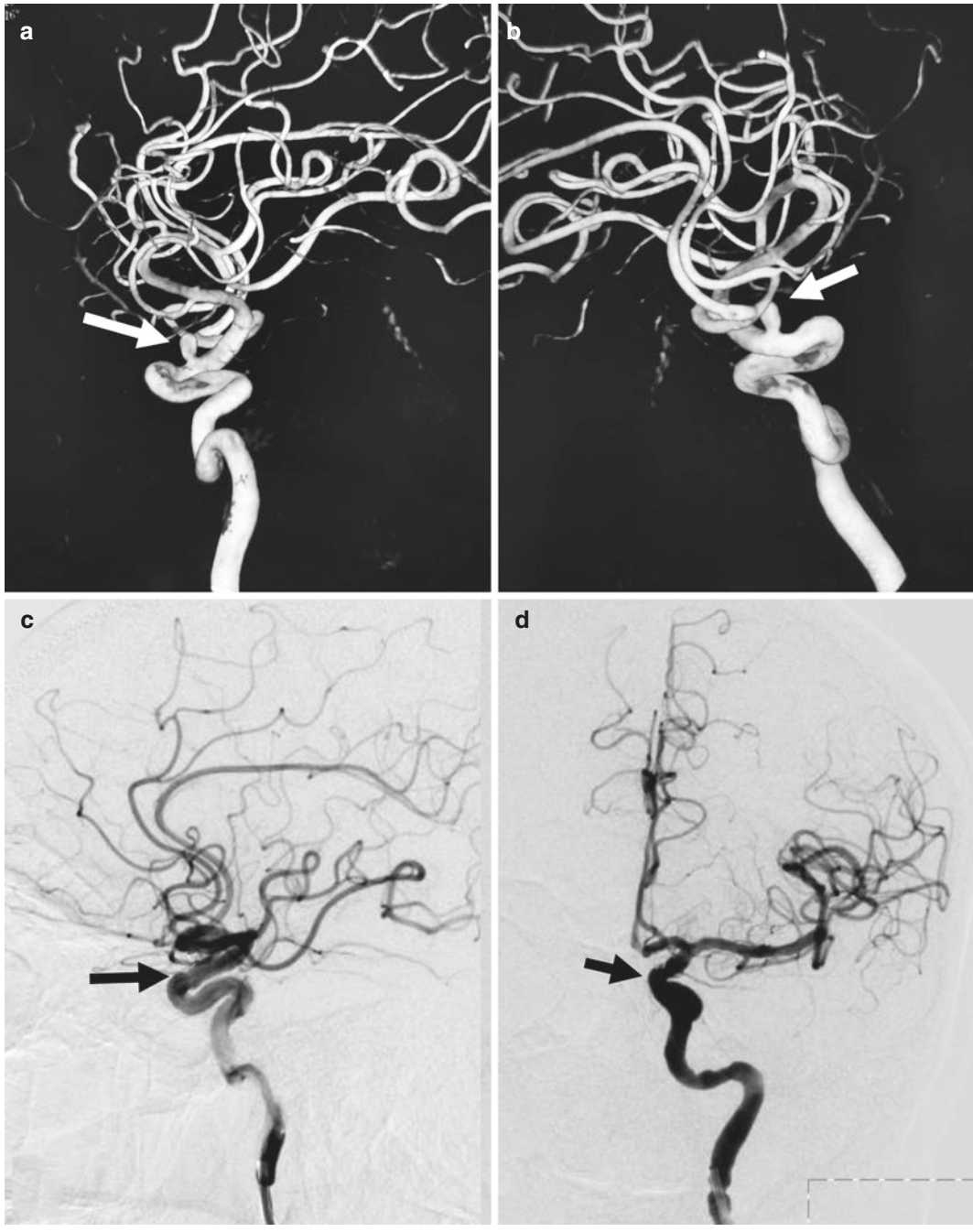


Fig. 8.11 A BBA was treated with FD-assisted coiling in a 54-year-old female patient with Hunt–Hess grade 1 SAH. (**a**, **b**) 3-D reconstruction of the left ICA injection showing a BBA. The BBA was treated with Pipeline flow-diverting stent-assisted coiling. After treatment, lateral projection (**c**) and frontal projection (**d**) of the left ICA injection showing the BBA was completely embolized

were initially treated with a single flow-diverting stent, 19 patients (33.9%) with 2 flow-diverting stents, and 3 (5.4%) were treated with a combination of flow-diverting stent and coils. Immediate occlusion rates of single flow-diverting stent, telescoping flow-diverting stents, and flow-diverting stent+coils were 27.3% (6/22 patients), 18.8% (3/16), and 100% (1/1), respectively. Further endovascular treatment of additional flow-diverting stents was needed in 5 patients, of whom 3 died. In the clinical follow-up period, an overall good outcome (mRS 0–2) was obtained for 83.3% (45/54) of patients. Concerns are highlighted in case examples of persistent aneurysm flow/growth despite flow-diverting stent placement and leading to re-rupture and death. Therefore, we propose concomitant coiling to promote earlier aneurysm complete occlusion. This has been shown by other authors to be a potentially successful and durable technique for BBAs. None of our patients had rebleed following treatment and results were overall positive.

The major disadvantage is the need for double antiplatelet therapy. In some cases of hydrocephalus, the external ventricular drain may be necessitated for the treatment [3]. A systematic review by Bodily et al. showed clinically significant external ventricular drainage-related bleeding complication rates to be between 3% and 10% in patients on antiplatelets who had undergone stent-assisted coiling in acutely ruptured aneurysms [29]. In our institution, lumbar puncture and drainage is routine practice if required. All patients did not suffer any related symptomatic hemorrhage. However, for patients who have already commenced dual antiplatelets needing additional external ventricular drainage, a very careful balance of the antiplatelet medication must be thought about.

8.2 Conclusions

This review focused on stent-assisted coiling and FD as the treatment of choice for BBA. Open-cell, braided, or FD stent-assisted coiling may be the ideal treatment for BBAs. It is a definitive and immediate cure for a potentially devastating pathology.

References

1. Meling TR, Sorteberg A, Bakke SJ, Sletteb H, Hernesniemi J, Sorteberg W. Blood blister-like aneurysms of the internal carotid artery trunk causing subarachnoid hemorrhage: treatment and outcome. J Neurosurg. 2008 Apr;108(4):662–71.
2. Sim SY, Shin YS, Cho KG, Kim SY, Kim SH, Ahn YH, Yoon SH, Cho KH. Blood blister-like aneurysms at nonbranching sites of the internal carotid artery. J Neurosurg. 2006 Sep;105(3):400–5.
3. Gonzalez AM, Narata AP, Yilmaz H, et al. Blood blister-like aneurysms: single center experience and systematic literature review. Eur J Radiol. Jan 2014;83(1):197–205.
4. Sim SY, Chung J, Shin YS. Are blood blister-like aneurysms a specific type of dissection? A comparative study of blood blister-like aneurysms and ruptured mizutani type 4 vertebral artery dissections. J Korean Neurosurg Soc. 2014 Nov;56(5):395–9.
5. Lv X, Yu J, Zhang W, Zhao X, Zhang H. Acute hemorrhagic cerebral artery dissection: characteristics and endovascular treatment. Neuroradiol J. 2020;33(2):112–7.
6. Nishikawa H, Shimizu S, Nakajima H, Kitano Y, Sano T, Mouri G, Miya F, Suzuki H. Characteristics of blood blister-like aneurysms with a saccular-shape appearance. World Neurosurg. 2017 Dec;108:595–602.
7. Szmuda T, Sloniewski P, Waszak PM, Springer J, Szmuda M. Towards a new treatment paradigm for ruptured blood blister-like aneurysms of the internal carotid artery? A rapid systematic review. J Neurointerv Surg. 2016 May;8(5):488–94.
8. Lv X, Jiang C, Wu Z, Jiang W, Wang G. Complex cerebral aneurysms: intra-luminal reconstruction using pipeline flow-diverting stent and the obliteration mechanism. Neuroradiol J. 2020;33(2):91–7.
9. Lv X, Jiang C. Advanced flow diversion embolization strategies for cerebral aneurysms. Endovasc Tod. 2020;19(2):95–8.
10. Lv X, Jiang C, Liang S. Small ruptured and unruptured complex cerebral aneurysms: single center experience of low-profile visualized intraluminal support stent. J Neurorestoratol. 2019;7(4):235–41.
11. Yanaka K, Meguro K, Nose T. Repair of a tear at the base of a blister-like aneurysm with suturing and an encircling clip: technical note. Neurosurgery. 2002 Jan;50(1):218–21.
12. Guo Y, Zhang J, Chen H, Xu K, Yu J. Suturing and Dural wrapping for a blood blister-like aneurysm on the supraclinoid segment of the internal carotid artery due to dissection. World Neurosurg. 2018 Jan;109:165–70.
13. Horie N, Morikawa M, Fukuda S, Hayashi K, Suyama K, Nagata I. Detection of blood blister-like aneurysm and intramural hematoma with high-resolution magnetic resonance imaging. J Neurosurg. 2011 Dec;115(6):1206–9.

14. Kim BC, Kwon OK, Oh CW, Bang JS, Hwang G, Jin SC, Park H. Endovascular internal carotid artery trapping for ruptured blood blister-like aneurysms: long-term results from a single centre. Neuroradiology. 2014 Mar;56(3):211–7.
15. Hademenos GJ, Massoud T, Valentino DJ, Duckwiler G, Viñuela F. A nonlinear mathematical model for the development and rupture of intracranial saccular aneurysms. Neurol Res. 1994 Oct;16(5):376–84.
16. Balik V, Yamada Y, Talari S, Kei Y, Sano H, Sulla I, Suyama D, Kawase T, Takagi K, Takizawa K, Kato Y. State-of-art surgical treatment of dissecting anterior circulation intracranial aneurysms. J Neurol Surg A Cent Eur Neurosurg. 2017 Jan;78(1):67–77.
17. Kim BM, Shin YS, Kim SH, et al. Incidence and risk factors of recurrence after endovascular treatment of intracranial vertebrobasilar dissecting aneurysms. Stroke. 2011;42(9):2425–30.
18. Lv X, Lv M, Li Y, Yang X, Jiang C, Wu Z. Endovascular treatment of ruptured and unruptured vertebral artery aneurysms. Neuroradiol J. 2011;1(17):797–806.
19. Lv X, Li Y, Xinjian Y, Jiang C, Wu Z. Results of endovascular treatment for intracranial wide-necked saccular and dissecting aneurysms using the Enterprise stent: a single center experience. Eur J Radiol. 2012;81:1179–83.
20. McLaughlin N, Laroche M, Bojanowski MW. Surgical management of blood blister-like aneurysms of the internal carotid artery. World Neurosurg. 2010 Oct-Nov;74(4–5):483–93.
21. Kawashima A, Okada Y, Kawamata T, Onda H, Kubo O, Hori T. Successful treatment of a blood blister-like aneurysm of the internal carotid artery by trapping with a high-flow bypass. J Clin Neurosci. 2008 Jul;15(7):797–800.
22. Ishikawa T, Mutoh T, Nakayama N, Yasuda H, Nomura M, Kazumata K, Moroi J, Yasui N. Universal external carotid artery to proximal middle cerebral artery bypass with interposed radial artery graft prior to approaching ruptured blood blister-like aneurysm of the internal carotid artery. Neurol Med Chir (Tokyo). 2009;49(11):553–8.
23. Matsubara N, Miyachi S, Tsukamoto N, Izumi T, Naito T, Haraguchi K, Wakabayashi T. Endovascular coil embolization for saccular-shaped blood blister-like aneurysms of the internal carotid artery. Acta Neurochir. 2011 Feb;153(2):287–94.
24. Lv X, Li W, Ge H, Jin H, He H, Jiang C, Li Y. Parent artery sacrifice for ruptured aneurysms in acute and chronic phases: a systematic review. Neurol India. 2018 May–Jun;66(3):695–9.
25. Peschillo S, Cannizzaro D, Caporlingua A, Missori P. A systematic review and meta-analysis of treatment and outcome of blister-like aneurysms. AJNR Am J Neuroradiol. 2016 May;37(5):856–61.
26. Shah SS, Gersey ZC, Nuh M, Ghonim HT, Elhammady MS, Peterson EC. Microsurgical versus endovascular interventions for blood-blister aneurysms of the internal carotid artery: systematic review of literature and meta-analysis on safety and efficacy. J Neurosurg. 2017 Dec;127(6):1361–73.
27. Fiorella D, Albuquerque FC, Deshmukh VR, McDougall CG. Usefulness of the neuroform stent for the treatment of cerebral aneurysms: results at initial (3-6-mo) follow-up. Neurosurgery. 2005 Jun;56(6):1191–201.
28. Ihn YK, Kim SH, Sung JH, Kim TG. The efficacy of endovascular treatment of ruptured blood blister-like aneurysms using stent-assisted coil embolization. Interv Neuroradiol. 2012 Dec;18(4):432–41.
29. Bodily KD. Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature. AJNR Am J Neuroradiol. 2011 Aug;32(7):1232–6.

Flow Diverter Stents

9

Julien Ognard, Mohamed Abdelrady, and Jean-Christophe Gentric

Abstract

Flow Diversion is one of the relevant technical improvements of the past decade in the endovascular treatment of cerebral aneurysms. When the efficacy and safety of a recent tool allow treating challenging aneurysms, this adoption in daily practice is fast even if the benefit of use is incompletely shown. We will review studies of these stents called "Flow Diverters" (FD) in animal models and in clinical use, mainly to discuss the technical characteristics inherent to its endovascular prostheses, which determine the choice and the manner in which this medical device can be used. During the chapter we will come back to this choice depending on the type of intracranial aneurysm to be treated, supported by the literature and illustrations of a series of personal cases, also resuming the management of complications in the presence of these devices, antiplatelet treatments as well as retreatment possibilities.

Keywords

Flow diverter · Flow diversion · Stent
Intracranial aneurysm · Stent-assisted coiling
Endovascular

9.1 Introduction

Endovascular treatment of cerebral aneurysms is the treatment of choice for ruptured intracranial aneurysms [1]. The invention of detachable coils in the early 1990s is largely responsible for the success of endovascular treatment and its adoption by the majority of neuroendovascular operators [2]. However, large, fusiform, or wide-necked aneurysms are more difficult to treat with simple coiling and required, when possible, recourse to a "de-constructive" approach with occlusion of the parent vessel [3]. The more advanced techniques of stent-assisted coiling or balloon remodeling were until recently alternative approaches to simple coiling in the management of some of these aneurysms [4]. However, numerous studies have shown the limitations of coiling approaches, with or without stenting, particularly in large and wide-necked aneurysms, with significant recanalization rates [5].

Flow diversion is a unique, innovative endovascular approach. It consists of treating the aneurysm-parent artery, rather than packing the aneurysmal sac with embolization materials.

J. Ognard (✉) · M. Abdelrady · J.-C. Gentric
Interventional Neuroradiology, University Hospital of Brest, Western Brittany, Brest, France
e-mail: julien.ognard@chu-brest.fr

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_9

Flow diversion has been used for about 15 years. Initially designed for large side-wall aneurysms, its use by operators has been widely diversified without high-grade recommendations linked to robust scientific evidence on the scope of Flow Diverter (FD) indications. The flow diverter technique (Fig. 9.1) can be used alone or in combination with other endovascular tools such as coils and stents.

The Flow Diverter, because of its low porosity, creates intra-aneurysmal hemodynamic changes, with blood stagnation and occlusion of the aneurysm, while most often keeping the arteries whose origins are covered by the FD permeable [6]. At the level of the aneurysm, blood stagnation is followed by thrombosis, inflammation, and thrombus organization, whereas at the level of the treated artery, the FD is covered by a neointimal formation that will eventually lead to healing [7].

Proposing such a tool for aneurysm treatment can only be done responsibly by exploring the chances of success and the expected or potential risks in a variety of preclinical studies; studies of the properties of the tool, flow studies, animal studies, etc., that will lead to a better discernment of this technique: its functioning, its limits, its potential complications, and therefore its indications.

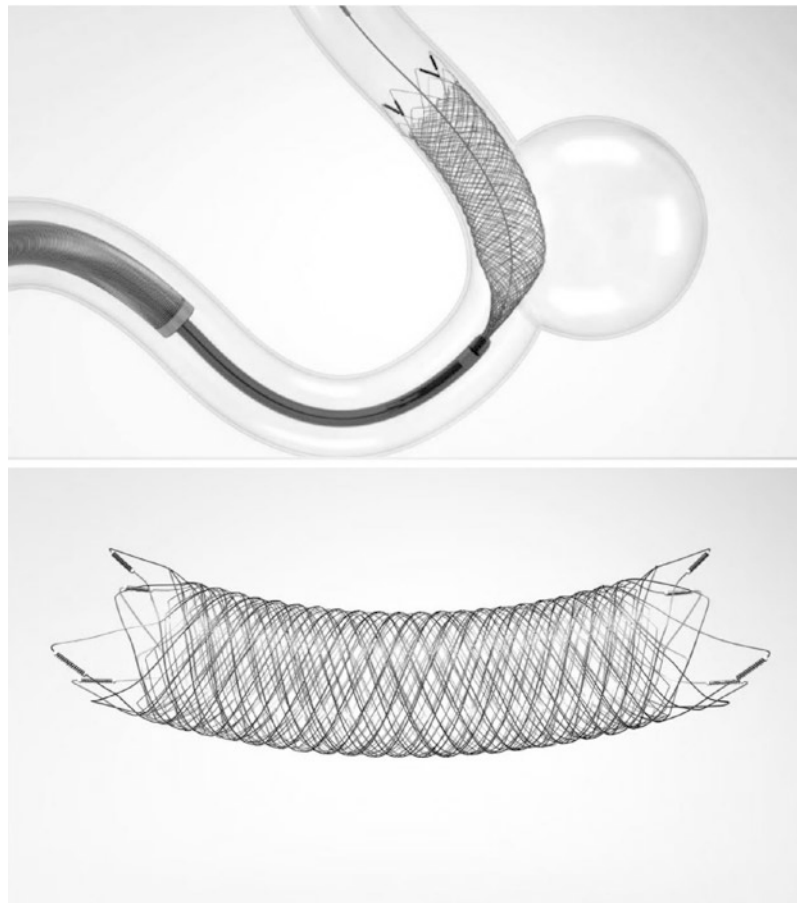


Fig. 9.1 The FRED and FRED Jr. flow diversion devices (MicroVention, Aliso Viejo, California, USA) feature a unique dual-layer construction designed to achieve excellent vessel wall apposition, which fosters neointimal growth and long-term aneurysm occlusion. The FRED Jr. device is the first flow diverter that can be delivered using a 0.021″ microcatheter for safe delivery in distal locations. Both devices may be used with or without embolic coils

9.2 Study of the FD Characteristics

9.2.1 Flow Diverters: Braided and Low Porosity Stents

FDs differ from previously used stents in their design. Conventional stents were most often constructed by laser cutting a hollow metal tube (hypo tube). FDs are formed by braiding so-called "super elastic" woven wires together, forming a mesh.

The wires forming the FD can slide over each other (Fig. 9.2), which gives it a high conformability, i.e., adaptation to the geometry of the vessel [8]. This braided construction constrains the implant and allows it to pass through the microcatheter before expanding upon exit (Fig. 9.1).

There are a growing number of different FDs. Some are approved by the Food and Drugs Administration in the USA (PED, SURPASS). Others have obtained the CE mark (SILK, FRED, P64, DERIVO), and others are used in Asia (TUBRIDGE, FLOW WISE). All these products are grouped under the term "Flow diverters" but they have a large number of technical differences.

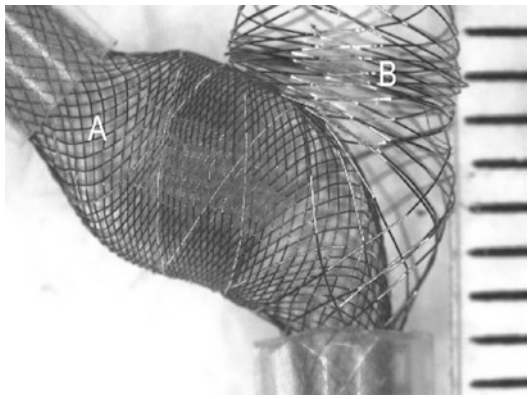


Fig. 9.2 Porosity, FD, and non-FD stents. Stent A is an FD, its porosity is lower. Stent B is also a braided stent but is not an FD. A braided stent is able to deform and open a unit cell in a very important way. Here the FD enters through a unit cell of the non-FD stent without being constrained. Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

In addition to design differences, FDs differ from conventional stents in their porosity. Not all braided stents are considered FDs (LVIS stents and LEO stents are porous braided stents, but have little flow diversion capacity). There is no quantifiable definition that differentiates a braided stent from an FD. However, it is accepted that an FD is a low-porosity stent, unlike non-FD braided stents. For example, it is almost impossible to pass a microcatheter through the mesh of an FD, whereas this strategy is possible (and conventional) when using other stents. The surface area of a unit cell is approximately 1–1.5 mm^2 for non-FD braided stents such as LVIS and LEO, whereas this surface area is 0.05 mm^2 for FDs.

9.2.2 Porosity

Porosity is calculated by the below Formula (9.1), developed to understand the different technical characteristics influencing the porosity (9.2 and 9.3) with N = Number of wires, d = Wire diameter (section), B = Wire length to make a complete turn (no braiding), α = Angle between the wires in the long axis of the stent.

$$\text{Porosity} = 1 - \text{Metal Coverage}\left(\text{MC}\right) \tag{9.1}$$

$$\text{MC} = \text{Pore Density}\left(\text{PD}\right) \cdot d^2 \tag{9.2}$$

$$\text{PD} = N^2 / \left(B \cdot \sin\alpha\right) \tag{9.3}$$

The porosity value of an implanted FD is different from non-implanted unconstrained ones. Its porosity changes according to the external constraints imposed by the local hemodynamic environment (curvatures of the artery, length of the aneurysmal neck, etc.).

The nominal porosity of stents is partly existent in the literature, but most of the time it is mentioned by the manufacturers without details of the measurement conditions [9]. It varies according to the devices between 45% and 85%; this porosity corresponds to the non-metallic proportion of the surface of the FD deployed at its nominal diameter.

The compaction imposed or not by the operator during deployment, the choice of FD diameter and its relationship with the diameter of the recipient arterial segment are all factors that also modify the porosity of the implant in place.

Pore size (unit cell) is also not a clearly detailed data by the manufacturers. Some give the surface of the unit cell at the nominal diameter. For example, it is 0.02–0.05 mm^2 for PED and 0.04–0.05 mm^2 for TUBRIDGE.19,20 Others give the major axis of the unit cell, which would be between 110 and 250 μm for SILK or 300–350 μm for DERIVO.17,21 To give an element of comparison, the size of the cells of LEO BABY is 1 mm of major axis and those of LVIS JR is 1.5 mm. Moreover, the data from the literature and those from the industry are not always comparable. There is a perpetual advance in technology in the FD industry. Dandapat et al. recently reviewed current flow diversion technology and clinical use [10].

To understand the adaptation of the FD to its container, an experiment consists in placing an FD in several transparent tubes of increasing size. A change in the shape and orientation of the unit cells is then observed. If the FD is oversized, the unit cell takes on the shape of a rhombus that has its largest diagonal in the axis of the vessel. The unit cell changes its shape to a square when the FD is less oversized relative to its container. Then, when the FD is undersized relative to its container, the unit cell takes the shape of a rhombus with its long axis perpendicular to the long axis of the vessel. The porosity is weaker, the closer the shape of the unit cell is to a square. The more rhombic the unit cell, the greater the porosity, regardless of the direction of the rhombus (Fig. 9.3). The alpha angle is the angle of the unit cell in the axis of the FD. Thus, the closer the alpha angle is to 90°, the lower the porosity, which can reach a minimum of 20%. When the alpha angle is less than 30° (as when the FD is compressed in the microcatheter) or greater than 150°; porosity increases significantly [11–13].

The porosity of an FD will always be less at the concavity of the curve than at the convexity (Fig. 9.4). On the other hand, it is relatively constant at the lateral faces [14]. It should be noted that oversizing the FD increases its porosity at the constrained segment but not at the unconstrained segment (aneurysm neck), where it naturally regains its size. This phenomenon gives the appearance of spindle-shaped dilation of the middle portion of the FD [15].

Porosity has been individualized as a parameter influencing flow reduction within the aneurysm [16]. In vitro work comparing the effect on flow reduction of high-porosity stents and DFs unequivocally concludes that there is a stronger effect of the FD, when compared with multiple telescopically nested non-FD stents [17].

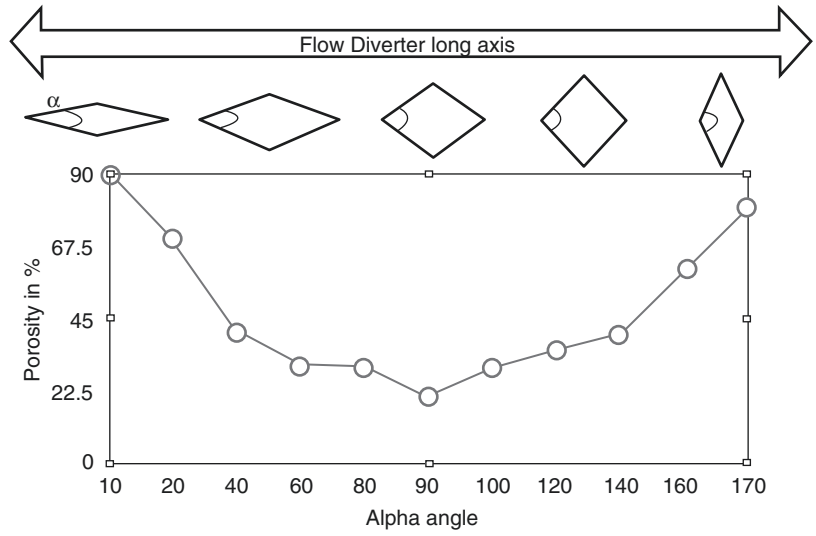


Fig. 9.3 Schematic representing the variation of porosity as a function of unit cell shape and alpha angle

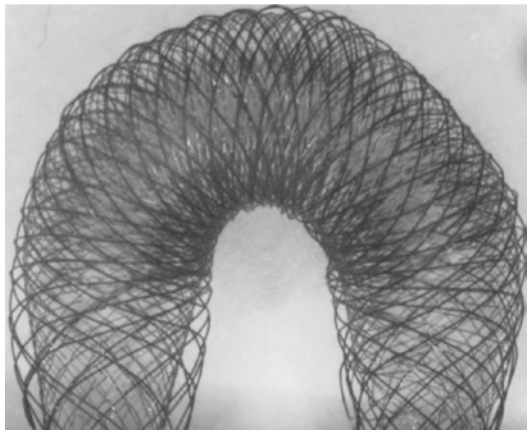


Fig. 9.4 Photograph of an FD prototype (stent-in-stent construction), it can be seen that the porosity is lower at the concavity of the curve than at the convexity. Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

Implantation of multiple FDs is sometimes proposed in certain clinical indications in case of ineffectiveness of a first implanted FD (Fig. 9.5). This strategy is also used to treat an aneurysm in cases where anatomic constraints require it. For example, if there is a significant difference in caliber between the distal and proximal anchor zones, different sized FDs can be implanted [18]. However, the porosity resulting from multiple FD assemblies is more difficult to anticipate. For example, a 3.75-mm diameter PED placed in a 3.5-mm tube has an estimated porosity of 78%, but the placement of a second PED of the same size does not necessarily increase porosity significantly [19]. Indeed, layering can be done in a variable manner, thus affecting porosity.

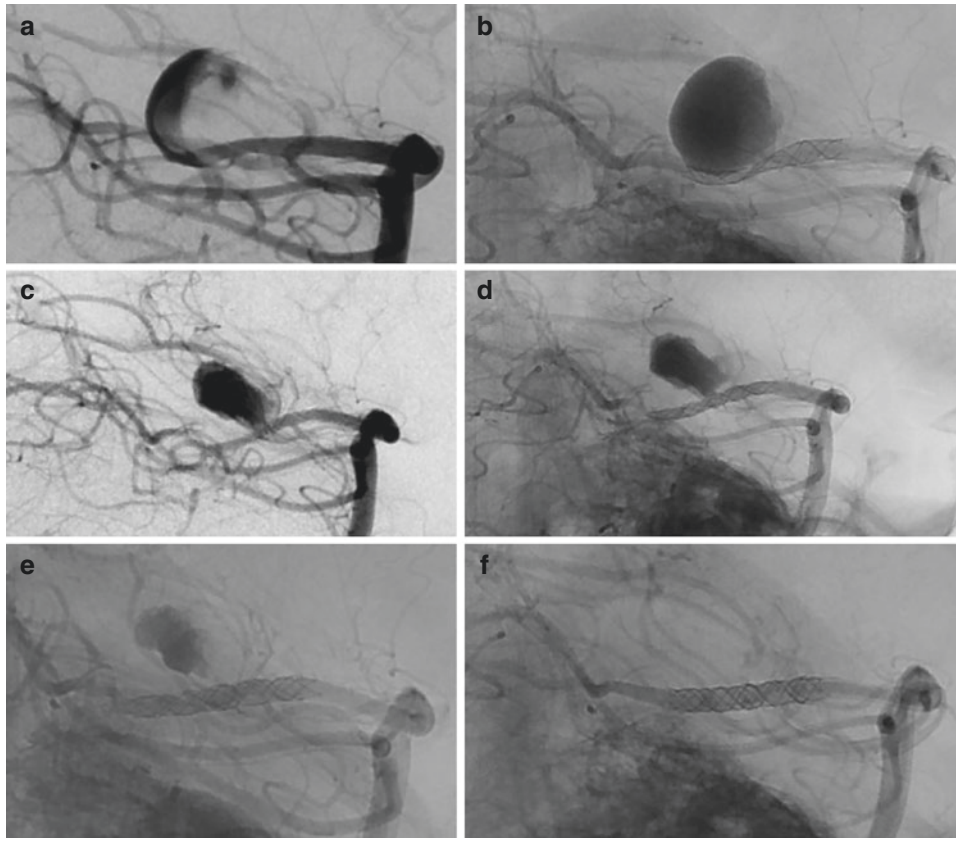


Fig. 9.5 Case of a 50 years-old patient with right P2-P3 junction unruptured aneurysm (**a**). First treatment was done with a single PED (**b**). Control angiogram (**c**) denoted a persistent patency of the aneurysm at 6 months. Second treatment was done with a same-sized PED at 9 months (results in **d**). Successive control angiograms at 15 months (**e**) and 21 months (**f**) showed the progressive interruption of flux within the aneurysm, it also permits to appreciate the stent-in-stent construction

In the case of a stent-in stent, the wires can be placed exactly the same way or they can be placed in the free metal gaps. This arrangement is random, thus the porosity values obtained have wide confidence intervals. As a result, Shapiro et al. advise oversizing the second implanted FD. For example, they suggest placing a second 4.25 mm FD within a first 3.25 mm diameter FD to achieve 60–65% porosity more consistently.

9.2.3 Pore Density

Pore density is a different entity from porosity. It represents the number of pores (unit cells) per unit area (Fig. 9.5). Sadasivan et al. state that pore density is the most important parameter for judging the effectiveness of FDs [20]. Pore density (PD) is calculated by the formula previously shown in [3].

Thus, the greater the number of wires and the shorter the length of wire needed to go around the FD, the greater the pore density. The pore density varies between 12 and 32 pores per mm^2. The pore densities of some FDs are as follows; SURPASS 21–32 pores/mm^2, SILK 12 pores/mm^2, and PED 15–22 pores/mm^2. For comparison, a WALL STENT used in the stenting of atheromatous carotid stenosis has a pore density of 0.2 pores/mm^2 [21].

9.2.4 Composition

As previously said, considering a perpetual evolution of the FD stents technology, the following details are only given as examples, to image characteristics that can vary and be considered when implanting FD.

The PED is composed of 48 wires with the same gauge for all strands (30 μm) [18]. The SILK has 44 strands of 25 μm gauge and 4 radiopaque wires of 40 μm gauge [14]. The p64 is composed of 64 strands and the TUBRIDGE of 62 strands. The DERIVO has wires of different calibers ranging from 35 ($n = 44$) to 85 μm ($n = 4$) [22]. Regarding the SURPASS and TUBRIDGE, the number of wires increases with the diameter of the implant, reaching 96 wires for a 5-mm-diameter implant for the SURPASS and 62 wires if the diameter of the FD is >3.5 mm for the TUBRIDGE. The FRED is a stent-in-stent system with 16 wires on the outer stent and 48 wires on the inner stent [23].

The diameter of the wires and the number of strands influence: friction within the microcatheter, radial force within the artery, and coverage of the perforating arteries. Indeed, the diameter of the ostium of the latter oscillates between 100 μm and 1 mm [20].

The wires used to braid FDs can be made of Nitinol (i.e., SILK, FRED, TUBRIDGE, p64, DERIVO) or cobalt-chromium (PED, SURPASS). Nitinol (Nickel-Titanium) has less radial strength but is easy to handle and has the advantage of excellent shape memory. It is also less radiopaque than cobalt chrome and requires the addition of markers or platinum 'coils' for better visibility. Dandapat et al. recall that Cobalt/chromium adds stiffness and radial force while nitinol brings flexibility and easy navigation and deployment, and that Cobalt/chromium implants allow a better answer to ballooning when an incomplete wall apposition is observed [10].

The value of the radial force is difficult to find in the literature but would be more than 1.5 times higher in the case of PED compared to SILK [24]. These data, although rarely reported, may make sense in clinical practice. Indeed, too low a radial force could be the cause of poor opening of the FD in cases where there is an external constraint, such as a pre-aneurysmal stenosis or spasm of the artery.

Alternatively, decreasing porosity by maintaining or increasing pore density increases the amount of metal in the implant. The more metal an FD contains, the more flexible it becomes and the more difficult it is to navigate. The more support the FD needs, the more friction it experiences when navigating the microcatheter, which requires larger diameter microcatheters.

The choice of the FD might govern the microcatheter (diameter) needed for implantation. The latter will obviously define the navigability of the set, and sometimes the feasibility of the procedure (Figs. 9.6 and 9.7).

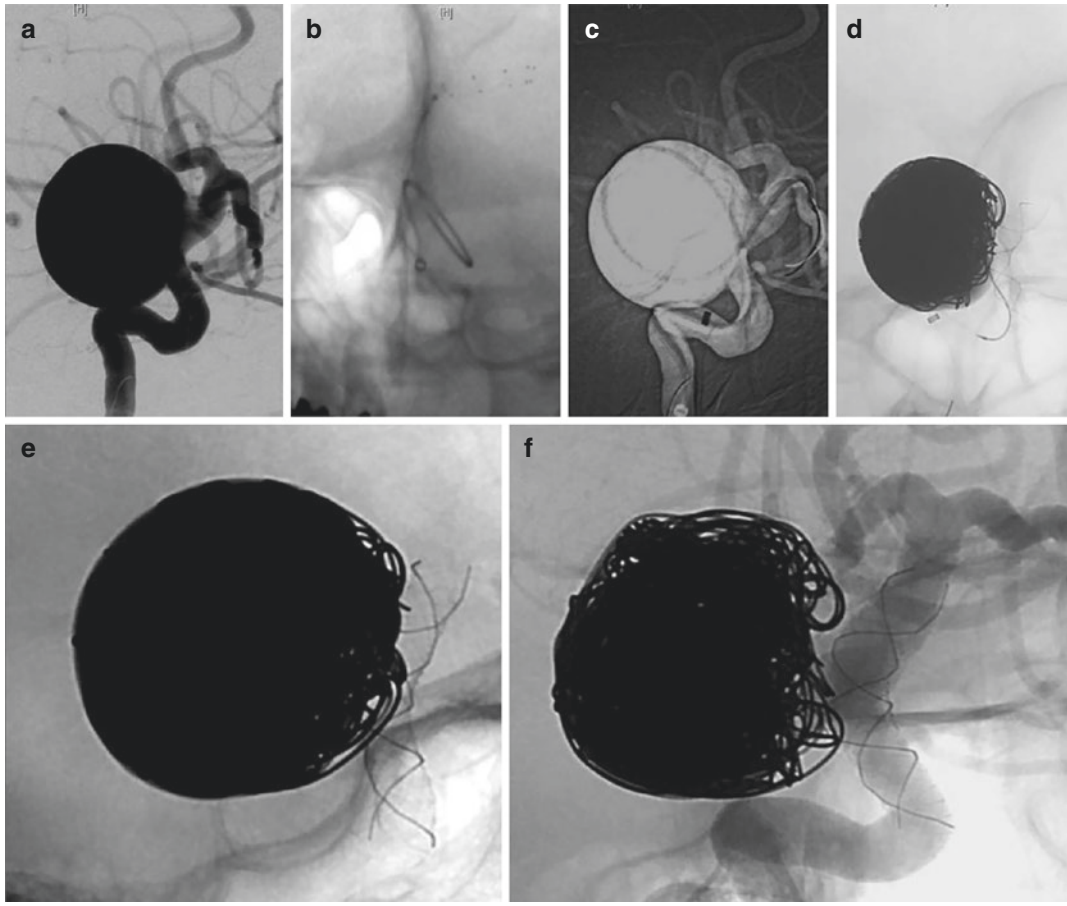


Fig. 9.6 Patient of 60 years old with a giant unruptured aneurysm of the left carotid siphon (**a**). Anchoring technic was used to pass through the distal neck of the aneurysm, which was impossible to navigate directly or using two microwires, because of the angioarchitecture and the misfit between the wire and the microcatheter diameters (**b**, **c**). A tutor-stent was initially placed (Leo) (**d**) to perform coiling with jailing technic. A PED was finally placed in the first stent (**e**). Control angiogram at 6 months showed good results (**f**)

These catheters can nowadays have a diameter of 0.017″ (Silk Vista Baby, 48 wires Nitinol stent with platinum DFT technology), 0.021″ (SILK, p48, Fred Jr), 0.027″ (PED, Survpass Evolve, Fred, p64, Derivo 2nd generation), and 0.025″ to 0.040″ (Silk+, Turbridge, Surpass streamline).

Friction problems also increase with stent length but can be improved by surface treatments. An FD that is too rigid can be difficult to navigate, requiring more seating downstream of the aneurysm, and thus taking more risks in the distal delivery area in particular. 48-wire nitinol FDs have the advantage of easy distal placement (e.g., SILK and in particular Silk vista baby, FRED).

The "stent-in-stent" construction of FRED allows for fewer contact points between the FD and the inner wall of the microcatheter, similar to the wooden logs that were used to roll the limestone blocks during the construction of the pyramids.

FDs are self-expanding stents, and their apposition to the vessel walls is done slowly and sequentially by the operator [25]. However, these stents are not all braided in the same way, and the varying braiding "pitch" characterized by different Alpha and Beta angles. The Alpha angle represents the angle of wire crossing in the long axis of the stent, and the Beta angle represents the

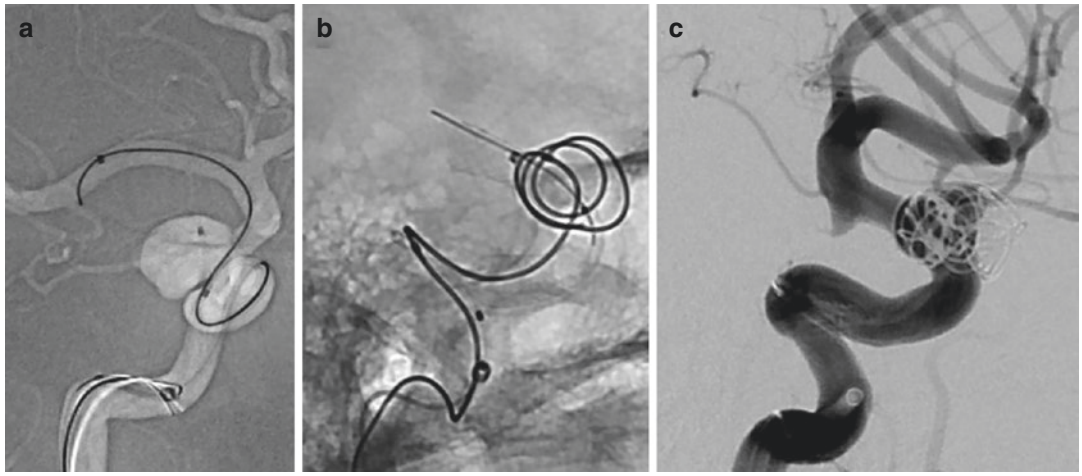


Fig. 9.7 Flow diverter stent-assisted coiling. The microcatheter is jailed during the deployment of the FD (**a**–**c**) and the coiling is done after a partial or total placement. The required set-up to perform this kind of procedure is obviously linked to the microcatheter (the one which will deploy the FD) diameter

angle of wire crossing in the short axis of the stent. These angles change depending on the curve made by the FD, as well as its degree of compaction (Fig. 9.6) [14].

Between the constrained zone affixed to the walls of the portal artery and the "free" stent (Free Segment of Stent = FSS) located in front of the aneurysm neck exist two transitional zones (TZ) [26]. These transitional zones, reported in the literature, are described as two incompressible zones, where porosity is higher than at the level of the compaction (central) zone (Fig. 9.8) [27]. Knowledge of these transitional zones is important for the clinician when using an FD to treat a wide-neck aneurysm [28]. The transition zone will be more porous the larger the size of the FD compared with the diameter of the artery [27]. Thus, the tendency is to recommend the use of an FD that is slightly larger than the diameter of the artery in order to ensure the stability of the FD and to decrease the risk of migration.

Some precautions can be considered in order to minimize the importance of transition zones. The first is to avoid oversizing the FD. Another strategy is to first place a non-FD stent at the neck of the aneurysm, and to deploy the DF within this first stent, which then acts as a stent, and allows to avoid fusiform dilation of the FD placed within

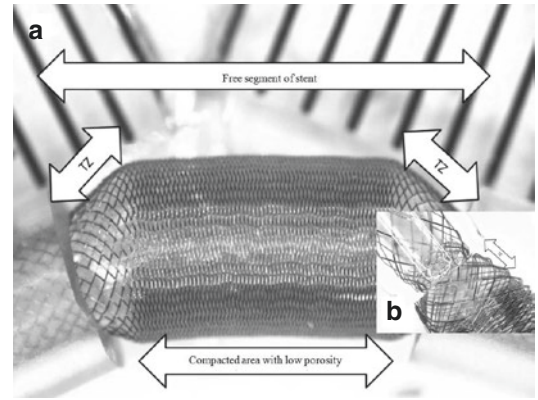


Fig. 9.8 (**a**) Photograph of a PED inserted in two hollow tubes. We individualize the free segment of the stent which is the portion of the FD without constraint composed of a compaction area and two transition zones (TZ). (**b**) Photograph of an FD inserted in a glass tube to emphasize TZ. Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

it (Figs. 9.5 and 9.9). This strategy is sometimes useful in the presence of very large collars or fusiform aneurysms. It should be noted that the FRED device is a stent-in-stent, with a 16-wire braided outer stent and a 48-wire inner stent. Despite this, fusiform dilatation of the entire device remains possible as observed in some works [15]. Other authors, mainly PED users, advise the placement of several FDs to avoid this

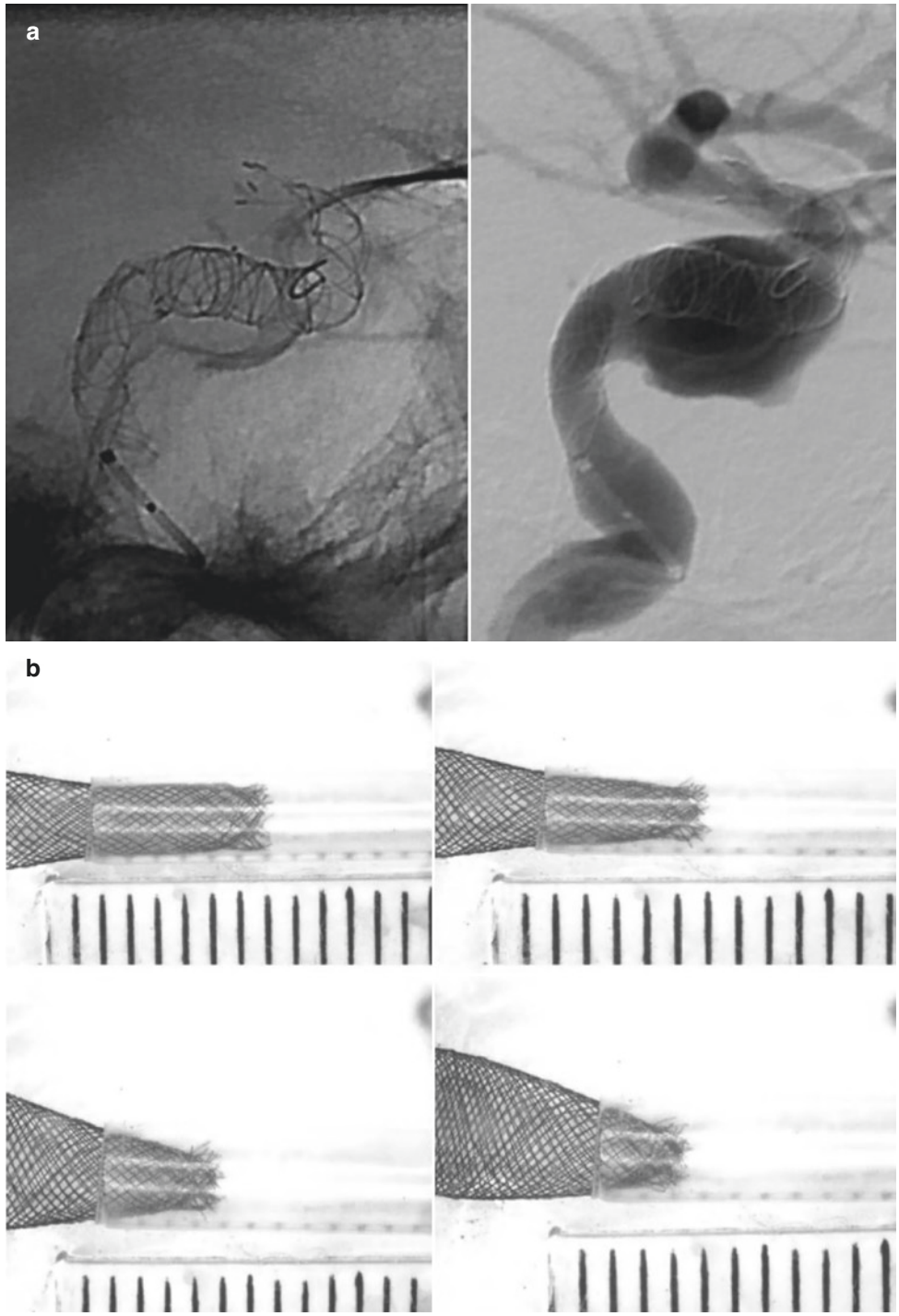


Fig. 9.9 (**a**). Clinical case illustrating the deployment of a non-FD stent prior to the implantation of 2 FD (SILKS). Courtesy of J. Raymond (Montréal). (**b**) Photographs showing the importance of a 6–7 mm anchoring zone to avoid stenosis of the FD tip. Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

phenomenon. A first FD, with a smaller diameter, is placed downstream, and then a larger diameter FD is inserted within it and deployed to the proximal anchoring zone [19].

9.2.5 Choice

Particle velocimetry data show that the closer the nominal diameter of the DF is to that of the artery, the greater the effectiveness [17]. However, the choice of DF diameter depends on multiple factors, including mainly habits, the operator's deployment technique, and measurements made during the procedure, which are aimed at choosing the right FD to be placed in the right place. The choice of the diameter is an important step in the implantation process and different techniques exist depending on the operator. The most common is to take into account only the proximal diameter (most often the largest), but some operators sum the distal and proximal diameters to make an average. It should be noted that the risk of migration is greater, the smaller the FD compared to the diameter of the artery. Some authors have described cases of migration following the shortening of SILK and PED [29, 30]. For some FDs, the unconstrained diameter (when deployed in the open) is greater than the diameter under which they are labeled (e.g., +0.25 mm for PED, and +0.3 mm for p64) [31].

Proximal misapposition of the FD causes significant changes in flow within the aneurysm after implantation. Indeed, the work of Rayepalli et al. shows that poor proximal apposition leads to a reversal of the direction of flow in the aneurysm, which then enters preferentially through the proximal collar in a direct manner and then exits through the FD [32]. Incomplete apposition may also be a source of thromboembolic events, as shown for some stents [33].

The PED is 2–3 times longer when constrained in the microcatheter compared to its nominal diameter length. This translates into a percentage shortening of 50–66% during deployment. Knowledge of this fact is particularly important in fusiform aneurysms, in which the DF takes on its nominal size because it is not constrained, thus responsible for a significant shortening, which is potentially difficult to predict [24].

9.2.6 Implantation

All of these FDs are available in a wide range of diameters and lengths, and are implanted via microcatheters with internal lumens ranging from 0.017 to 0.040″. The newer FDs can be recaptured after partial implantation [34]. The ability to recapture is a definite addition to the safety of these procedures, as the operator can attempt to avoid unwanted branch coverings, but can also use multiple attempts to anchor the FD, both anteriorly and posteriorly, in order to avoid its tilting in the aneurysm.

Operators use the "Pull and Push" technique to alternately apply pressure to the microcatheter to allow the implant to open and then relax the system to affix the FD in the bends [25]. However, all situations require adaptation. For example, in the case of cavernous aneurysms, because of the absence of major functional arterial branches, maximum compaction is sought. On the other hand, if a functional arterial branch needs to be covered during placement of a DF, the surgeon may decide to increase the porosity of the FD in front of it by decreasing the compaction and/or by oversizing the diameter of the implant used [18] (Fig. 9.10).

9.2.7 Surface Treatment

Because of the many links between coagulation pathways, inflammatory reactions, and cell proliferation in the vessel wall, high biocompatibility of FDs is necessary to avoid intra-stent thrombosis [4, 35, 36]. Teams have evaluated the thrombogenicity of Nitinol stents. They have compared bare Nitinol stents with stents that are coated with heparin or albumin and showed that coating these stents with albumin or heparin reduced their thrombogenicity [37]. Most FDs undergo polishing. Others offer a surface treatment that may reduce friction (DERIVO) or increase the biocompatibility of the implant. The developers of the PED FLEX have developed a

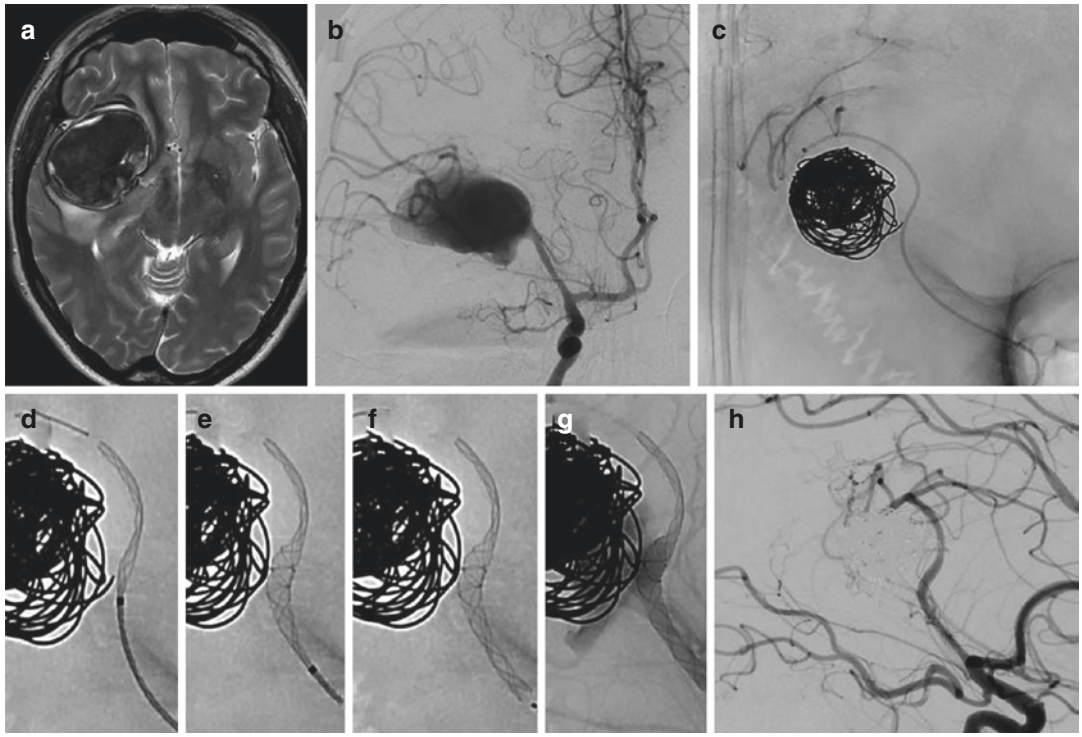


Fig. 9.10 65 years old female that presented with chronic headaches and asthenia revealing a giant unruptured partially thrombosed right Sylvian aneurysm (**a**, **b**). After a coiling session (**c**), a PED FD was placed covering the Sylvian bifurcation. From (**d**–**g**) the placement of the FD with a low push at the neck. Control angiogram at 6 months showed a full occlusion (**h**), note the occlusion of the inferior Sylvian branch covered by the stent, the patient was asymptomatic

new surface modification with the "SHIELD" technology. This technology is based on phosphorylated choline (PC), abundant on the surface of red blood cells. This technique, known for more than 10 years, allows the PED FLEX SHIELD to be coated with a layer of less than 3 nm, which mimics the cell membrane. Platelet activation and thrombosis phenomena are decreased by PC-coated stents in animal peripheral arteries [38–40]. Girdhar et al. showed that SHIELD FLEX PED was less thrombogenic (in vitro experiment with quantification of thrombin formation) than other FDs [41]. They also show that its "degree of thrombogenicity" was more similar to a SOLITAIRE AB stent, which has only 5–8% metal coverage. Manning et al. reported the use of a simple antiplatelet therapy in settings of hemorrhagic presentations [42]. Even if further prospective investigation is needed, this knowledge may be important in case of hemorrhagic presentations (Fig. 9.11) or following hemorrhagic complications.

9.2.8 Extremities

Flares are modifications of the distal ends of stents (Fig. 9.12). The flared ends can be related to real Flares of significant size. In these cases, markers (e.g., FRED) are added to these Nitinol arms. The flared ends can be less marked and only represent a continuity of the FD mesh (ex: SILK, DERIVO). Their main role is to facilitate the anchoring of the stent ends. However, true Flares raise concerns about thrombogenicity and distal opening, with a tendency to distal stenosis when placed in smaller caliber arteries, sometimes amplifying the "fish-mouth" phenomenon. These Flares can also complicate secondary catheterization of FDs during retreatment or during

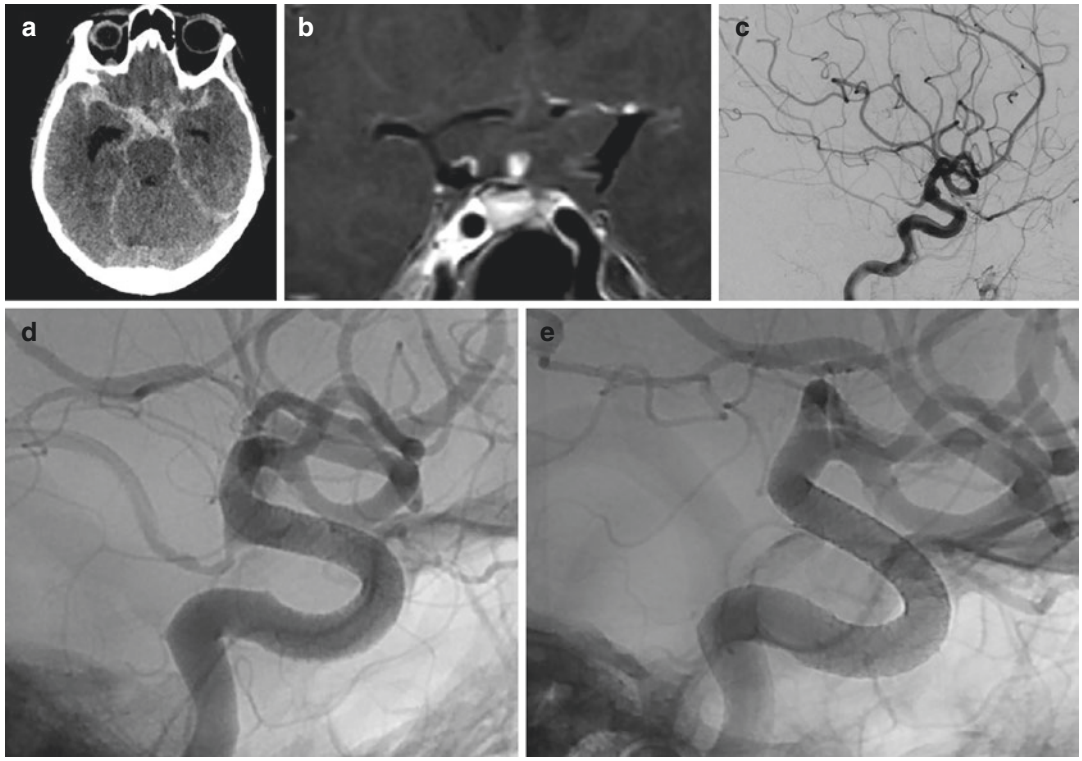


Fig. 9.11 A 43 years old patient presented with mFisher IV SAH (**a**), CTA was considered normal and contrast-enhanced MRI showed a gadolinium uptake within an addition image of the dorsal wall of the right internal carotid artery (**b**). Angiogram confirmed the presence of a highly suspected blood blister-like aneurysm (**c**). 2 PED-Shield were placed in a stent-in-stent fashion, to cover the latter abnormality (**d**). Control angiogram at 6 months showed no more parietal aneurysm (**e**)

placement of a second FD inside the first. The concern then is to ensure that the FD never exits the lumen of the FD during catheterization, to avoid deployment of the second FD between the artery wall and the first [43].

9.2.9 In Vitro Studies

Preclinical in vitro studies are also making progress in the attempt to understand the mechanisms leading to ischemic and hemorrhagic complications. Thus, intra-aneurysmal pressure following FD placement has been studied. To explain delayed ruptures, hypotheses of increased intra-aneurysmal pressure or surface pressure have been put forward. Experiments have shown that the placement of an FD opposite to the aneurysm neck did not modify the pressure in a durable way. In fact, the pressure simply decreased transiently during the placement of the FD to regain a normal pressure shortly afterward. These data initially obtained on bench work were later confirmed by computer-assisted flow studies, but also by data collected on humans [17, 44, 45]. Another concern of the operator is the occlusion of functional arterial branches covered by the FD. Roszelle et al. showed by particle velocimetry study that flow could be decreased by 32.7–46.5% in such a branch covered by a single PED [46].

9.2.10 Computational Fluid Dynamic Studies

It is difficult to talk about flow diversion without mentioning flow studies. In fluid mechanics, the Navier–Stokes equations are nonlinear partial dif-

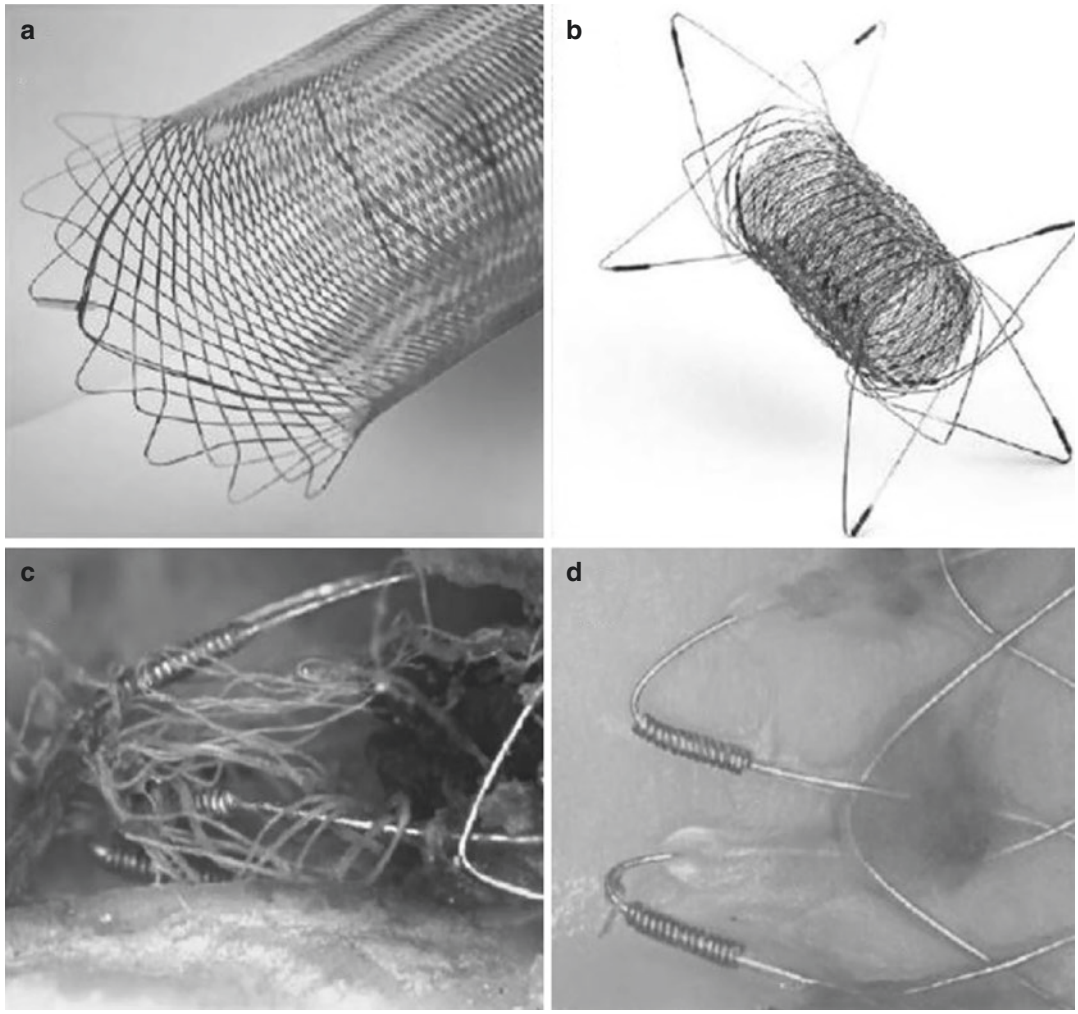


Fig. 9.12 Photographs showing the difference between a flared tip and true Flares (**a** versus **b**, respectively). (**c**, **d**) Showing clots and neointima bridges on flares (animal experiments). Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

ferential equations that are supposed to describe the motion of "Newtonian" fluids (ordinary viscous liquids and gases) in the continuous media approximation. Blood is treated as a Newtonian fluid, with a specified density and viscosity. The blood is assumed to be laminar at the inlet and outlet, with constant and incompressible flow. This flow is calculated from a Doppler or MRI phase-contrast examination, under static and pulsatile conditions, with synchronization to the heart rate. The fluid/structure interaction is thus simulated. These simulations are then generated by a software. Classically, the model generates an inflow and an outflow separated by a helical flow called a vortex [47]. It is worth noting that all the assumptions below have many limitations [48].

Authors have characterized intra-aneurysmal flows using, in particular, the complexity and stability of the flows during the cardiac cycle. The concentration of the inflow and the size of the area receiving the inflow (− or +50% of the area) have also been studied. Cebral et al. showed that in ruptured aneurysms, there was more likely to be angulation of the inflow and numerous recir-

culation zones [47, 49, 50]. They also reported that complex recirculation flow, concentrated inflow, and a small inflow landing area were risk factors for rupture.

These simulations allow for the quantification of variables of interest; Wall Shear Stress (WSS), pressure, relative residence time (RRT), inflow velocity, inflow volume, oscillatory shear index OSI… The RRT being a reflection of the time of blood contact with the inner surface of the aneurysm. Unfortunately, although flow studies generate a large amount of data, the indexes or variables produced are still subject to speculation.

Therefore, we will focus on the concepts that are most commonly recognized and in particular the WSS. WSS is a shear force that can be described as a tangential friction force between the aneurysm wall and the blood, related to the viscosity of the blood [51]. It can be expressed in terms of maximum or average stress. It is known to play a role in wall remodeling and aneurysm progression [52]. WSS is transformed into biological signals via mechanical receptors on endothelial cells. Thus, a WSS that is too low to maintain endothelial functions may facilitate degeneration of the aneurysmal wall and be responsible for AIC growth and rupture [53, 54]. Abnormal WSS are known to induce inflammatory responses mediated by: endothelial cells, activation of MMP metalloproteases, cell death, degradation of the extracellular matrix, and vascular remodeling [55–58]. However, and despite the fact that this parameter is cited as the most important, conclusions about its role vary widely [59]. Finally, the authors seem to agree on the role of too high WSS in the initiation phases, and they propose two pathways that can lead to rupture. The first is related to thrombus formation and the inflammatory reaction in the case of low WSS. The second, more direct, is related to matrix degradation secondary to destructive remodeling in the case of high WSS [57].

Two different parameters such as WSS and velocity decrease during FD placement at the aneurysm neck and the appearance of the flow lines changes before and after FD implantation. For example, placement of a NEUROFORM stent decreases the mean inflow velocity by 15%, whereas a PED reduces mean inflow by more than 80% [60]. This link between porosity and inflow reduction has been known since the use of non-DF stents. It is even more important when porosity is low, raising the suspicion that changes in these two variables play an important role in thrombus formation within the aneurysm [61]. A greater relative reduction in WSS and velocity is observed in small or fusiform aneurysms after DF implantation and some authors report that a one-third decrease in velocity is predictive of occlusion at 12 months [62, 63].

9.2.11 Cellular and Tissular Level

If the relationship between the stent and the wall has been extensively studied in cardiology, the particularity of the animal studies that focus on flow diverters is that it is the free segment of the stent (FSS) located at the level of the neck of the aneurysm (where there is no contact between the stent and the wall) that is the major zone of interest.

Indeed, the FSS must undergo biological changes in order to allow the occlusion of the aneurysm. In the first days (D1–3), there is a denudation of the endothelial cells of the artery where the DF is implanted. There are also islands of inflammatory cells at the wire intersections at the level of the FSS. Neonintimal formation at the artery is quite rapid compared with the more delayed formation at the FSS (Fig. 9.13).

There are two potential sources of neointimal and neoendothelial cells to overlay the FSS: cells from the adjacent arterial wall (near-to-near migration) and circulating stem cells. For some authors, the neointima spreads over the FSS wires from the artery [13]. In this sense, it is possible that the most perfect possible apposition of the FD is important to allow this layer to form. On the other hand, poor FD apposition could lead to an increase in thrombotic risks. It could also lead to failure to heal because of channels

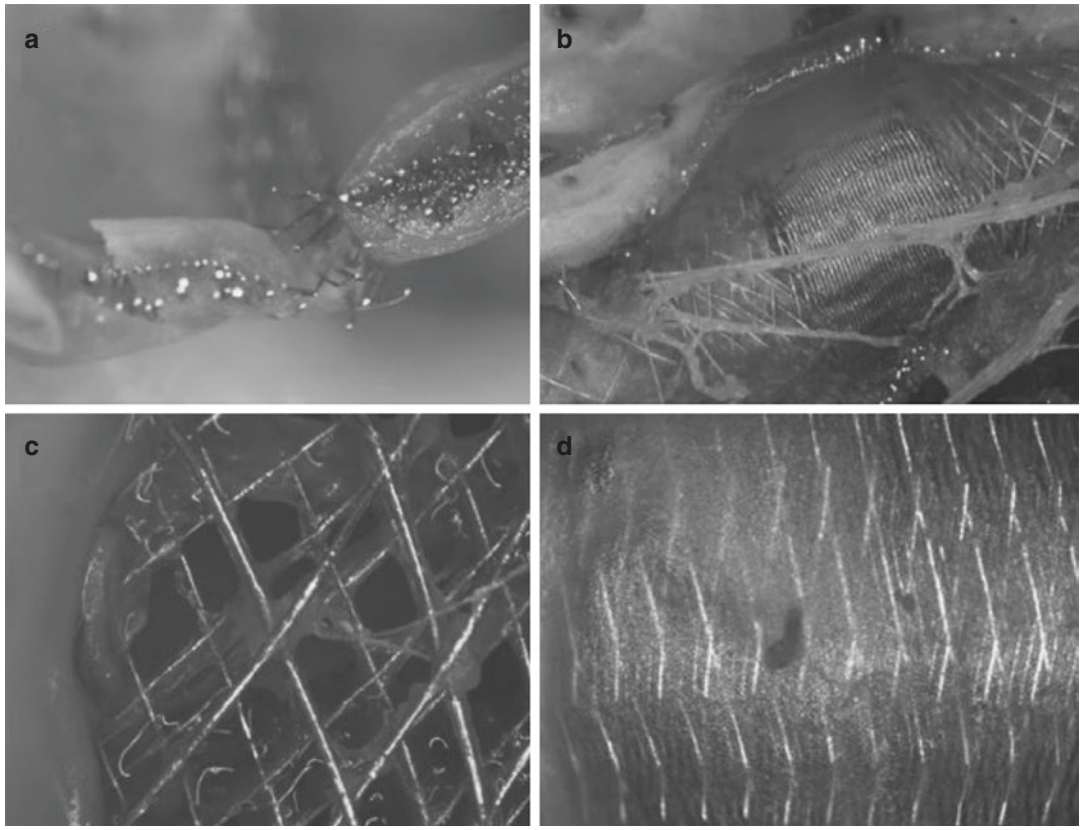


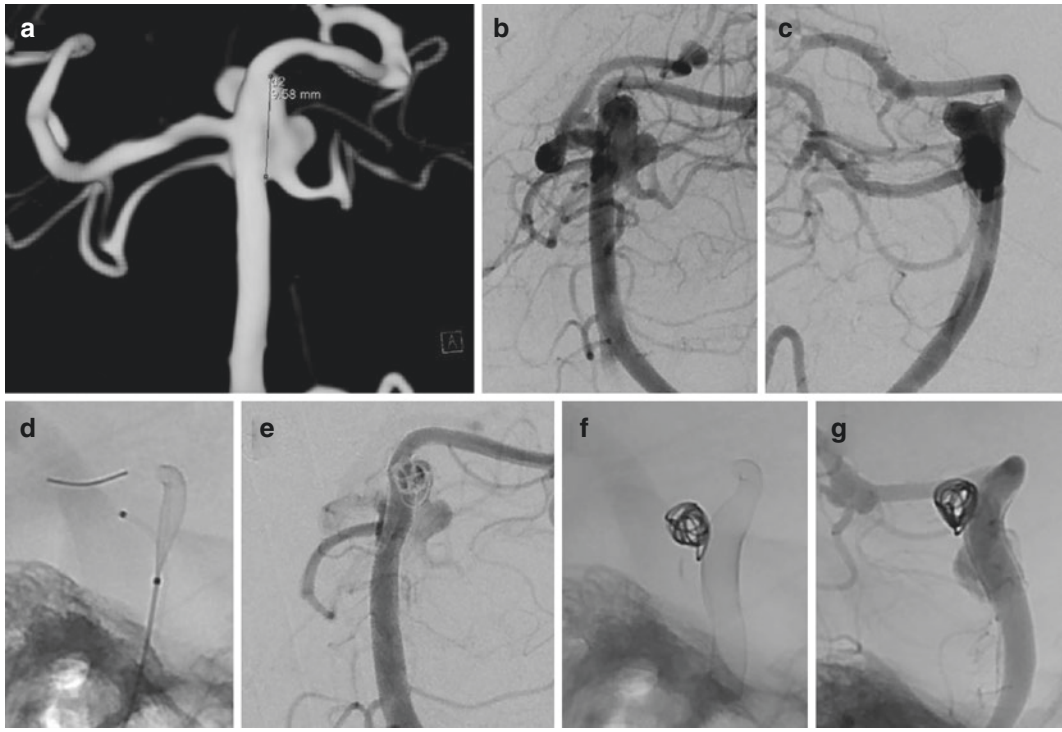
Fig. 9.13 (**a**) Section of the free segment of the FD after extraction which finds a thick neointima. (**b**) Neointima "bridges" are sometimes found on the luminal side that did not follow the "rule" of a close progression. (**c**) Photograph of the FSS of an FD 3 months after implantation in a canine model. This image shows the neointimal progression, which starts from the artery and propagates over the FD guides, predominating at the crossings, and proceeding in the direction of flow. (**d**) Shows the luminal aspect of the FSS of an angiographically occluded aneurysm at 3 months and finds a continuous neointimal layer on the surface of the FD. Courtesy of J. Raymond – I. Salazkin – A. Makoyeva (Montréal)

between the DF and the artery that prevent migrating progenitor cells from "sliding" from the artery to the FD [64–66]. A complexification of these explanations would be to propose a multifactorial healing process starting from a flow modulation inducing thrombosis notably at the dome, with the concomitant neointimal formation of the FD starting at the portal artery. There may be a link between thrombus formation and endothelialization of the FD that is intertwined in the healing process.

9.2.12 Factors Related to Aneurysm Characteristics

9.2.12.1 The Importance of Aneurysm Size and Volume

It is likely that the size and total aneurysmal volume have an impact on the efficacy of FDs. In a review of the literature, experiments in large animals that resulted in aneurysms with larger volumes had lower efficacy rates than experiments involving smaller aneurysms [67].



9.2.12.2 The Importance of a Curve at the FSS or Covered Branch

FD has been shown to be more effective in lateral aneurysms in straight arteries than in curved arteries, regardless of whether one or more FDs are used [68]. The angle between the FSS and the direction of flow is important as studied by CFD [69]. The more parallel the flow is to the FSS, the better the conditions seem to be for providing support to the neointima. In the case of a curved FSS, which concerns a major part of the clinical situations, the porosity of the implant is of course more important at the convexity of the curve (Fig. 9.14).

9.2.12.3 Lateral or Bifurcation Aneurysms and Fusiform Aneurysms

Some authors have studied the efficacy of the FD in bifurcation aneurysm situations and report a low rate of efficacy [70]. Flow diversion in the treatment of bifurcation aneurysms may be less effective because of the presence of a branch covered by the DF. Thus, in some experiments, the presence of a branch from the aneurysmal neck or fundus has been identified as a factor for failure [71]. Some anatomic configurations (lateral aneurysms) facilitate complete ap-positioning of the FSS at the aneurysm neck allowing continuous neointimal coverage along the DF wires (Fig. 9.15). This is more commonly encountered in lateral aneurysms and is not possible in bifurcation aneurysms in which the SSF only partially covers the neck. The size of the neck is also a factor influencing the outcome.

9.2.12.4 The Covered or "Jailed" Branch

The presence of a covered, or "jailed" branch arising from the neck or aneurysm is often cited as a cause of ineffective FDs. An FSS can cover both the neck of the aneurysm and a branch. It is desired that this branch remains open, with no or minimal occlusive tissue formation at its ostium. Darsaut et al., in a canine model of a lateral aneurysm with a branch, demonstrated the ability of

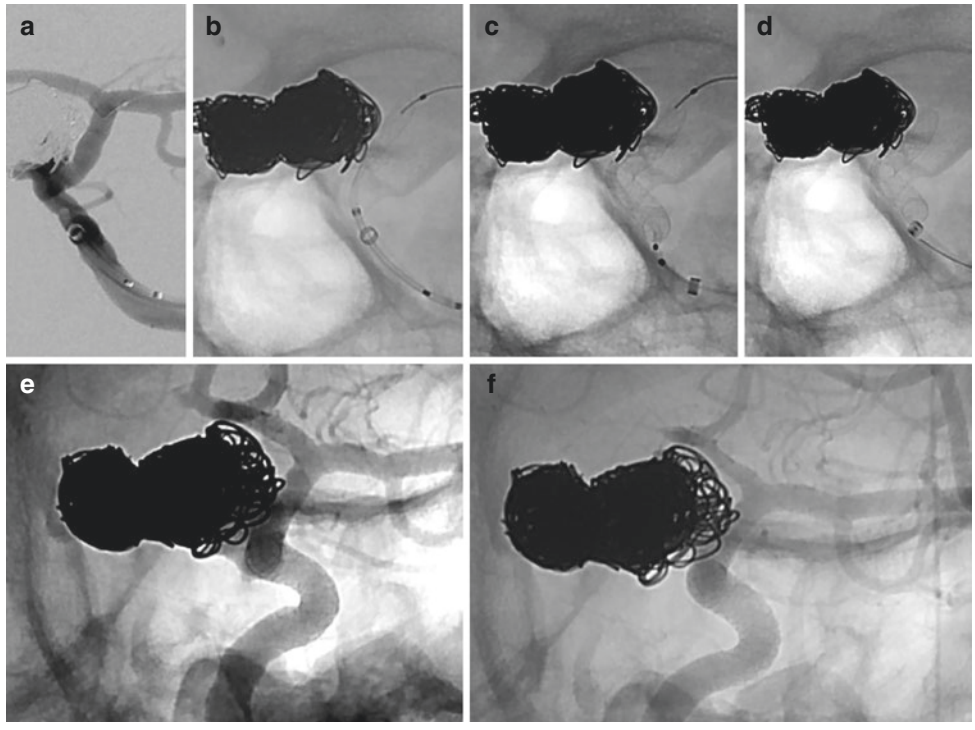


Fig. 9.14 (**a**–**d**) placement of an FD (PED) for the recanalization of a left carotid-cave unruptured aneurysm. The angioarchitecture permits here to have the FSS in front of a lateral aneurysm, in a quite straight segment, and the stent was placed with push providing a good compaction at the neck (**e**). Control angiogram at 6 months showed a total occlusion (**f**)

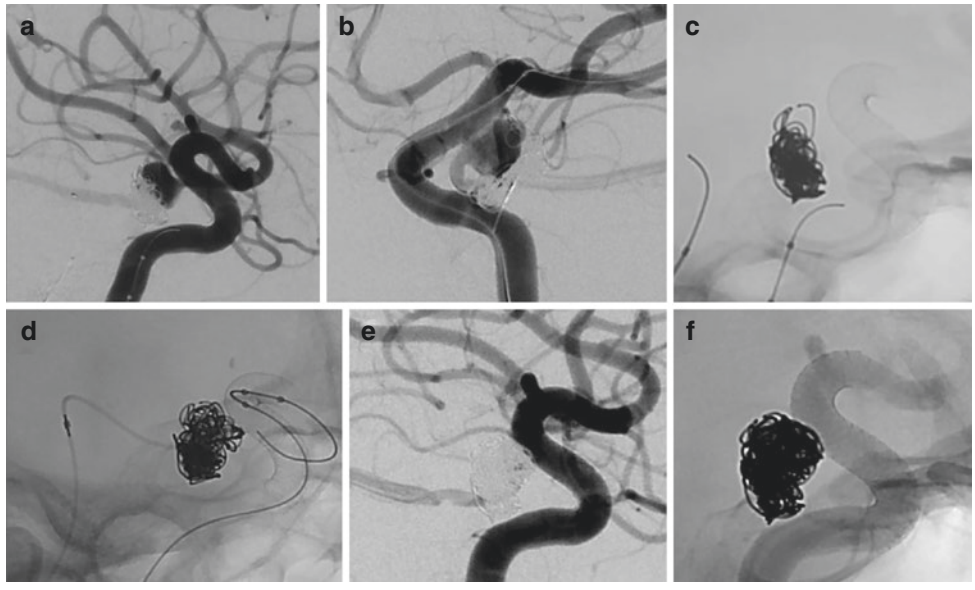


Fig. 9.15 Recurrent aneurysm of previously ruptured Posterior Communicating artery was treated with FD (**a**). Persistence of a flux within the sac was noted for 12 months after the treatment by FD (**b**, **c**) and retreatment was performed using direct access of the sac through the Posterior Communicating artery and simple coiling with the concomitant use of a balloon inside the FD (**d**, **e**). Control angiogram at 6 months of the retreatment showed a total occlusion of the aneurysm (**f**)

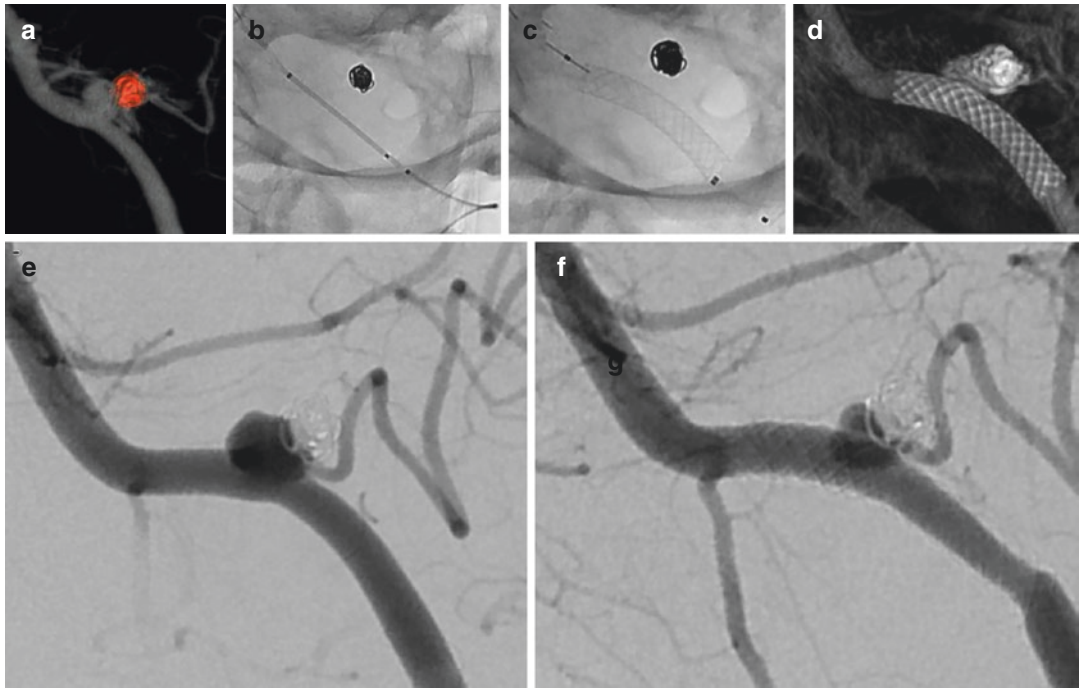


Fig. 9.16 Recanalization of a previously ruptured left posteroinferior cerebellar artery initially treated by coils (**a**). Stenting with an FD in the vertebral artery, covering both aneurysm neck and PICA ostium (**b**–**e**). The control angiogram at 6 months showed a preserved patency of the PICA. The aneurysm is still circulating but partially collapsed (**f**)

the FD to occlude the aneurysm while leaving the branch open [72] (Fig. 9.16). To date, in animal models of large bifurcation aneurysms, the FD has failed to occlude these aneurysms, which corroborates some clinical papers that have, for example, shown the ineffectiveness of FDs in bifurcation aneurysms with a jail branch considered hemodynamically significant [68, 73].

9.2.12.5 Factors Related to the Choice of the FD

The effects of the FSS on flow are influenced by the porosity and pore density, which are themselves related to the thickness of the unitary wires and the distance between them [74]. The final porosity of the FSS differs significantly from the nominal porosity, which should be a characteristic given by the manufacturer. The more oversized a DF is in relation to the artery; the longer and more porous its transition zone is, and the greater its deformation is. Conceptually, a high pore density decreases the physiological distance between unitary wires facilitating neointimal coverage from proximal to proximal. Sadisvan et al. showed that pore density was a more important parameter than porosity in terms of effectiveness [20]. It is likely that increasing the number of wires, thus affecting the two cardinal parameters of porosity and pore density, will increase the effectiveness of the implant. Hong et al. showed that the amount of neointima formed was proportional to the amount of metal coverage (MC) of the implant [75]. In clinical practice, the diameter of FD is usually chosen in relation to the proximal diameter (proximal delivery zone), with a degree of oversizing always present to avoid the risk of migration. This oversizing is often greater at the distal anchor zone because of the progressive decrease in vessel caliber. The degrees of expansion are variable and the stent will expand where space is available, either at the aneurysmal neck or in covered branches of significant caliber. This deformation will be even more important if the FD is oversized. The TZs between the areas

compressed by the vascular tree and the uncompressed areas are areas of lower porosity.

Compaction of the Flow Diverter by the Operator

Compaction of the device during deployment will decrease the porosity of the implant to increase its potential to reduce aneurysmal flow and provide better support for neointimal formation. Unfortunately, the transition zones are not accessible to compaction by the operator and their porosity is even more important when the implant is oversized in diameter. Their responsibility in post-FD failures is likely, especially since these zones are often located in the flow entry zones [68, 69].

9.3 Clinical Studies

9.3.1 Efficacy

Numerous series report the efficacy rates (in terms of angiographic occlusion) as well as the morbidity and mortality rates of the use of the flow diversion technique. The differences within these series are numerous and are related to: the characteristics of the treated aneurysms, such as their nonproximal location, or at a bifurcation [76–79]; the context of their use, ruptured aneurysms [80–82], blister dissections [83, 84], surgical wounds [85, 86], aneurysmal recurrences [87]; the FD type [87, 88].

The FDA approval followed the PUFS study, a prospective uncontrolled study that obtained 73.6% complete occlusion at 6 months and a morbidity rate of 5.6% in 107 patients [89]. Similar efficacy and morbidity figures have been found in many prospective registries, such as InterPED [90].

In the meta-analysis of Arrese et al. [91], 15 studies were analyzed for a total of 897 patients with 1018 aneurysms. The mean duration of patient follow-up was 8.5 months. The early mortality rate (1 month) was 2.8% (1.7% hemorrhage and 0.9% ischemia). The early neurological morbidity rate was 7.3%. At more than 1 month, the most frequent complication was ischemia (3.6%), followed by mass effect (1.1%), and rupture (0.9%). The delayed mortality rate was 1.3% (total 4.1%) and the delayed neurological morbidity rate was 2.6%. This represents a total of 14% of morbidity and mortality over the average follow-up period (8.5 months. With regard to the occlusion rate, the average rate was 76.2%. The authors mention that in light of their work the results with FDs are worse than in reported series of coiling, or even clipping [92, 93]. The bias here is obvious, and the conclusion severe if FDs were used after ruling out other treatments (Figs. 9.17 and 9.18). However, the high rate of occlusion at 9 months questions whether this population is predominantly composed of complex aneurysms.

The meta-analysis of Brinjikji et al. [94] included a total of 1451 patients and 1654 aneurysms. The 6-month complete occlusion rate was 76%. Procedure-related morbidity was 5% and mortality was 4%. The postprocedure subarachnoid hemorrhage rate was 3%. The rate of intracerebral hemorrhage was also 3%. The rate of infarction was also 3%, significantly lower in the anterior circulation than in the posterior circulation. The same is true for the rate of ischemic events, which was 6%, and significantly lower in the anterior circulation than in the posterior circulation. This meta-analysis shows that FD treatment is safer in small aneurysms with a lower rate of ischemic events and subarachnoid hemorrhage. These complication rates are in agreement with a systematic review by Briganti et al. who found a mean neurological morbidity of 3.5% and a mean mortality of 3.4% [95]. And also with Lv et al. that analyzed 29 studies or 1524 patients between 2009 and 2014 and reported a morbidity of 14% and a mortality of 6.6%. In this latter study, fusiform, dissecting, circumferentially implanted, posteriorly located, and distal aneurysms were the selected risk factors [96].

Considering flow diversion among MCA, anterior communicating artery, and distal anterior cerebral artery aneurysms, the recent meta-analysis of Cagnazzo et al. [97] included 27 studies (484 aneurysms). The long-term adequate occlusion rate (O'Kelly–Marotta scale, C–D)

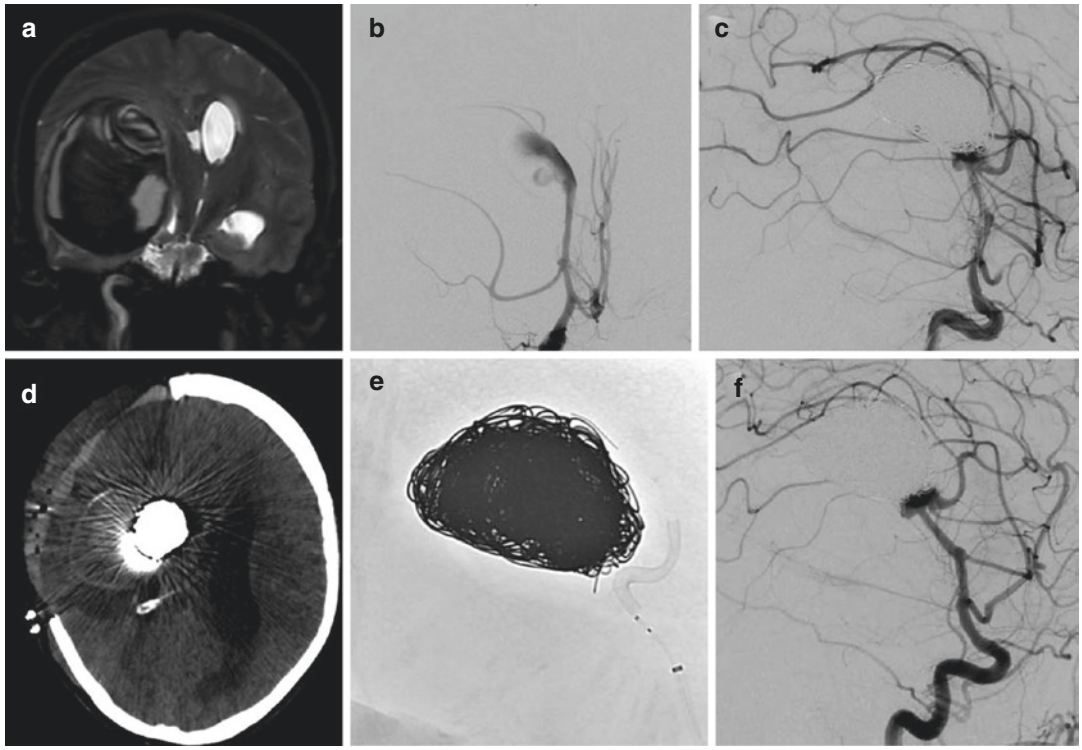


Fig. 9.17 Illustrative case for the use of FDs in complex cases. Case of a 53 years old female that presented with rapidly progressive intracranial hypertension symptoms. MRI revealed a giant partially thrombosed right Sylvian aneurysm (**a**). Treatment was performed by coiling and flow diverter (Silk Vista Baby) after a craniectomy (**b**–**e**). Follow-up images performed at 12 months showed the near-complete occlusion of the aneurysm sac and a significant reduction of the mass effect that permitted to replace the bone flap (**f**)

was 82.7%. Treatment-related complications were 12.5%, with 5.4% morbidity. MCA location was an independent factor associated with lower occlusion (OR = 0.5, $P = 0.03$) and higher complication rates (OR = 1.8, $P = 0.02$), compared with anterior communicating artery and distal anterior cerebral artery aneurysms. Large/giant aneurysms were associated with higher odds of complications (OR = 2.2, $P = 0.03$). The rates of occlusion and narrowing of arteries covered by flow-diverter stents were 6.3% and 23.8%, respectively. Symptoms related to occlusion and narrowing of the jailed arteries were 3.5% and 3%, respectively.

Regarding the posterior circulation, data from previous reviews are in agreement with a meta-analysis that was published in Neuroradiology in 2016, including 14 studies for a total of 225 posterior circulation aneurysms in 220 patients. The procedure-related mortality rate was 15%, with an occlusion rate of 84%. The rate of ischemic events was 11% (7% related to perforators). The post-procedure subarachnoid hemorrhage rate was 3%. The rate of intracerebral hemorrhage was 4% [98].

9.3.2 Classifications

To evaluate our interventions, we have no choice but to reduce the variety and heterogeneity of clinical outcomes [99, 100]. It is best to judge the outcomes of these interventions in a reduced number of categories. The names of these categories must then be determined in order to differentiate successes from failures. Angiographic

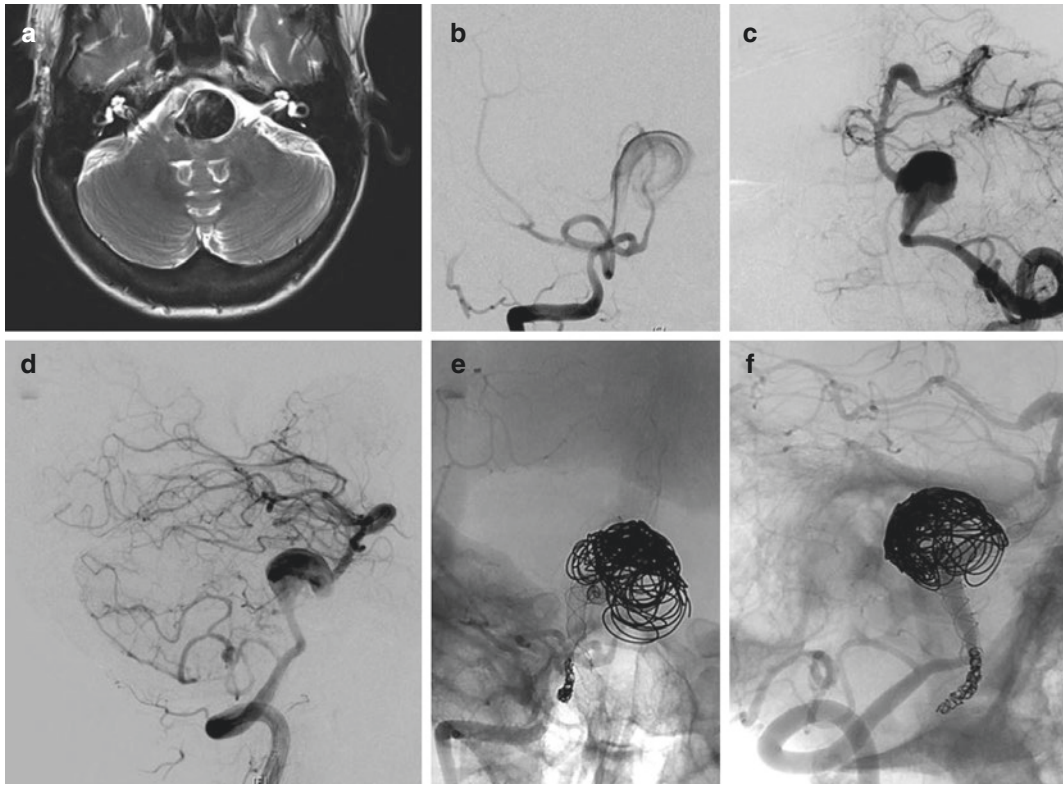


Fig. 9.18 Illustrative case for the use of FDs in complex cases. Patient of 25 years old presenting with diplopia. MRI found and fusiform aneurysm with parietal hemorrhagic and thrombotic changes responsible for a brainstem focal ischemia (**a**–**d**). After a preventive posterior fossa craniectomy, an occlusion of the post-PICA segment of the right vertebral artery was performed, and 2 FD were placed after the implantation of a tutor stent (Leo) and coiling (control angiogram at 3 months: **e**, **f**)

judgments after coiling of cerebral aneurysms are generally reported using the Roy/Raymond classification which judges occlusion in three categories of aneurysm occlusion (complete occlusion, residual neck, or residual aneurysm). While this scale is easy to use for judging coiled aneurysms, there are limitations in the reproducibility of assigning an angiographic result to a coiled patient by different observers [101]. Similar results have been obtained in magnetic resonance [102]. The same classification has been used to evaluate post-FD results, but its appropriateness is questionable. Indeed, residual aneurysms are common findings after FD placement, and occlusion results have the potential to improve with time. The situation is different with the coiling of cerebral aneurysms where it is desired that the end result persists. A residual neck is often an acceptable outcome in the follow-up of a coiled aneurysm. This may also be the case with FD treatment, but not always, because even slow opacification of an FD-treated aneurysm may be sufficient to sustain a mass effect, aneurysm progression, and in some cases rupture. Several classifications dedicated to post-flow diversion angiographic findings have been proposed. The main are listed below.

9.3.2.1 O'Kelly–Marotta (OKM) Classification [103]

In this classification, a grade is assigned to each aneurysm based on the degree of initial opacifica-

tion (ABCD) and the degree of stasis [1–3] observed during the degree of initial opacification (ABCD) and the degree of stasis [1–3] observed during different angiographic phases (arterial = 1, capillary = 2, and venous = 3).

- A: Total opacification
- B: Subtotal opacification
- C: Residual collar
- D: Complete occlusion

9.3.2.2 Kamran–Byrne (KB) Classification [104]

This classification is proposed for saccular and fusiform aneurysms. For both types of aneurysms, it documents two items: the degree of aneurysmal occlusion using a 5-grade classification for aneurysmal occlusion and a three-point classification for the artery.

Item 1: Degree of occlusion for saccular aneurysms (an equivalent exists for fusiform aneurysms)

- Grade 0, No change in intra-aneurysmal flow
- Grade 1, Opacification of more than 50% of initial aneurysm volume
- Grade 2, Opacification of less than 50% of initial aneurysm volume
- Grade 3, Opacification limited to the region of the aneurysmal neck
- Grade 4, Complete occlusion

Item 2: Assessment of the artery.

- "a": No change in caliber of the artery
- "b": Stenosis of the artery
- "c": occlusion of the artery

9.3.2.3 Grunwald Classification (SMART) [105]

This classification includes 5 grades from 0 to 4. This classification is the same for saccular aneurysms and fusiform aneurysms. The SMART classification takes into account the appearance of the inflow, the stasis (a, b, or c), and the location of residual opacification within the aneurysm as well as the degree of stenosis of the artery.

Assessment of the occlusion

- Grade 0 (arterial time): Early in-jet is found
- Grade 1 (venous time): The aneurysm is circulating
- Grade 2 (venous time): The walls and the dome are judged to be unsafe
- Grade 3 (venous time): The walls and the dome are judged secure
- Grade 4 (venous time): Complete occlusion

Hemodynamic evaluation

- "a": no significant stasis
- "b": stasis is visible in the capillary phase
- "c": stasis is visible in the venous phase

Carrier axis, intra-stent stenosis (ISS):

- Grade 0: No stenosis
- Grade 1: Mild stenosis
- Grade 2: Moderate stenosis
- Grade 3: Severe stenosis (>70%)
- Grade 4: Occlusion

9.4 Complications

They can be neurological or systemic. When they are neurological, they are of two main types, ischemic or hemorrhagic. They may or may not be symptomatic; simply revealed by follow-up examinations. The main difficulty is their definition, because it is obvious that the reported rates will differ according to the definition. In the case of the flow diverter, the implant puts the artery at risk permanently and complications may occur in a delayed fashion. This is important because case series often have a short average follow-up time, which may not reveal these complications at a distance.

9.4.1 Ischemic

Endovascular treatment that requires intra-arterial implantation of a metallic prosthesis raises concerns prosthesis, raises fears of throm-

boembolic complications (TE) similar to thromboembolic (TE) complications similar to the subacute thrombosis encountered during angioplasty-stenting of stenosing coronary or peripheral arteries [106]. They are largely related to uncontrolled platelet aggregation on the surface of the foreign body that has not yet been incorporated into the wall via neointimal formation. Flow diversion, therefore, requires a priori dual antiplatelet therapy, which will be discussed in the last paragraph.

TE complications can be immediate or delayed, symptomatic or not. They can occur at the level of the stent (Fig. 9.19), but also downstream or at the level of a branch covered by the FD. They represent a wide spectrum of complications: FD thrombosis, FD stenosis, downstream thrombus, ischemia of perforators or covered branches, etc. The heterogeneity of their causes and presentations also makes their report in clinical series very heterogeneous. However, the rate of TE complications is reported to be higher in the posterior circulation, but also in large aneurysms [94, 107]. However, these published data are limited by the short duration of patient follow-up. Skukalek et al. recently published a literature review and meta-analysis of post-FD complications, including TE complications. Nineteen studies were analyzed for a total of 1110 patients [108]. Their results were as fol-

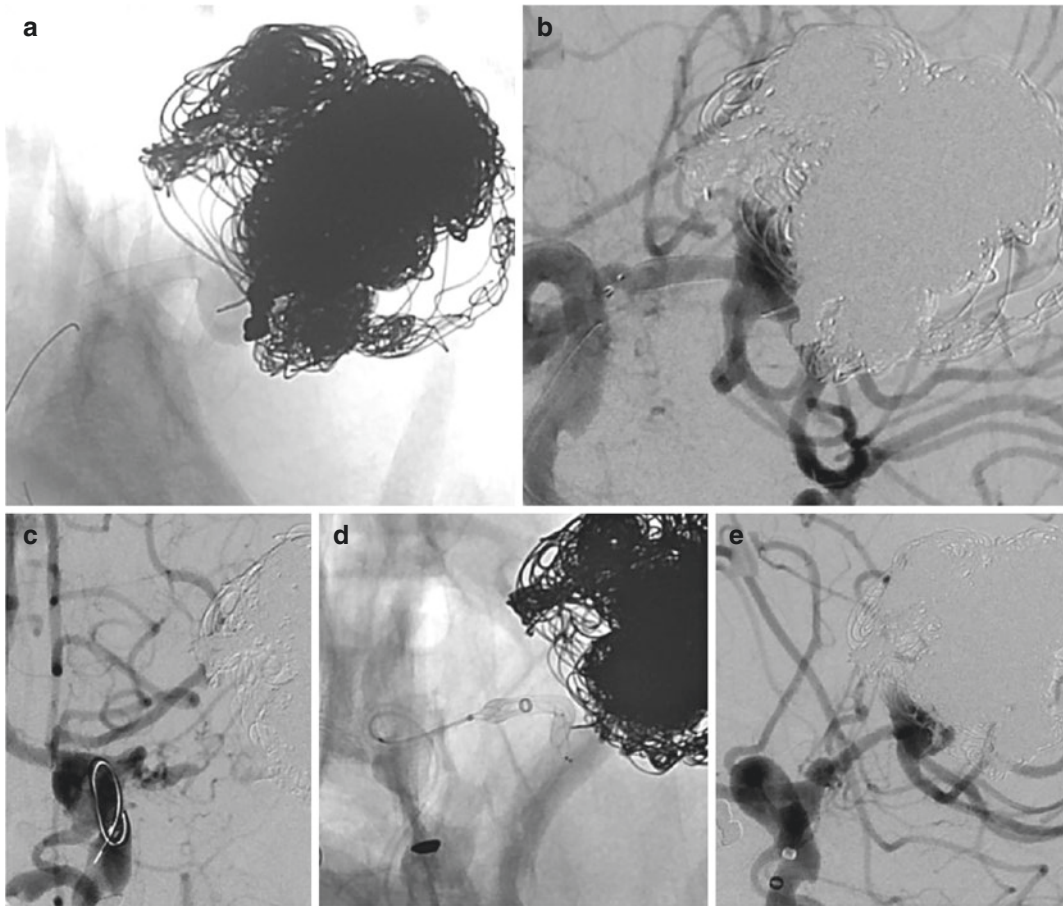


Fig. 9.19 Illustrative case of a left Sylvian bifurcation aneurysm, previously ruptured and with multiple sessions of treatment by coils treated by FD (**a**, **b**) under dual antiplatelets therapy. Intra-stent thrombosis at hour 3, presented with severe aphasia and right hemiplegia (**c**). Rescue manoeuvers of mechanical thrombectomy intra-stent with anti-GpIIbIIa infusion (**d**) yielded to quick reperfusion (**e**), but a frontal area of necrosis and aphasia persisted

lows: Symptomatic and transient TE: 3.67%. Permanent symptomatic TE and mortality: 1.35%. Asymptomatic TE: 1.93%.

Early or delayed FD thrombosis is always reported in a series of about 100 patients, with an occurrence rate of less than 5% [109]. It is important to keep in mind that the indications in which the first FDs were firstly implanted (proximal carotid aneurysm) were previously treated by occlusion of the (carotid) vessel. In these patients, for whom occlusion was possible, the impact of complete thrombosis of an FD is assumed to be low (unless the DF overlaps the bypass of the polygon of Willis). In this sense Labeyrie et al. report in January 2015 a series of large or fusiform aneurysms treated by occlusion of the supporting axis. The permanent neurological morbidity in this series was also 5% [110]. Thus, evaluation of the polygon or usual or unusual anastomotic support is important to assess before placement of an FD. In other words, if an FD is implanted in a patient tolerant of occlusion, it is important to know this before implant placement.

Another complication associated with the use of FD is delayed stenosis of the bearing artery. Chalouhi et al. report an observation rate of 15.8% of these stenoses, all asymptomatic, in an angiographic study of 139 patients; 73% of these stenoses were detected at 6 months [111].

Finally, as shown in the literature on non-DF intracranial stents, an eventual period of discontinuation of anti P2Y12 is a delicate moment. One of the causes, always raised by the authors, is the role of antiplatelets in ischemic and hemorrhagic complications. Some very late thrombosis (defined in the cardiology literature as occurring more than 1 year after implantation) has been reported [36, 112, 113]. In a series of 86 patients including aneurysms of the anterior or posterior circulation, Guédon et al. report a 3.5% rate of late ischemic complications. The other reported delayed cases are fusiform aneurysms of the basilar trunk treated with multiple PEDs in a telescopic fashion. Certainly, neointimal formation on fusiform aneurysms treated with multiple PEDs takes longer to achieve. It may also never be achieved, and the addition of new FDs as suggested by some may not be the answer. The longer the aneurysm segment, the greater the thrombotic potential of these FDs seems to be. In such cases, the authors advise maintaining double antiplatelets for a longer duration (more than 1 year). These particular cases are difficult in practice, because faced with patients who are clinically worsening, the difficulty is to do nothing.

Ischemic complications related to perforator occlusions after flow diversion are well known and described. Their overall rate is estimated by meta-analyses to be about 6%. The branch covered by the FD may be an artery whose vascularization is terminal, of the perforating artery type, or it may be a branch whose vascularization regime has or may have suppletions (communicating arteries, pial arteries, ophthalmic artery, etc.) (Fig. 9.20). With respect to posterior fossa aneurysms, the number of perforators potentially

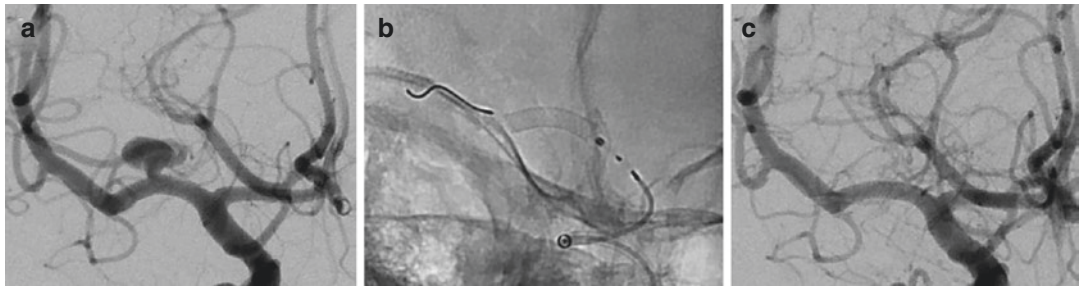


Fig. 9.20 Illustrative case of an aneurysm of the right Sylvian artery with a recurrent branch (**a**) covered by a flow diverter (**b**), yielding to the occlusion of this branch (depicted on the control angiogram at 6 months, **c**), without symptomatic events

covered by the FD is very large. The greater number of complications in the treatment of basilar aneurysms could be explained by the delicate and terminal perfusion of the functional structures of the brain stem, and their limited possibility of collateralization. With regard to the anterior circulation, Gawlitza et al. report on 18 aneurysms, 17.6% of symptomatic lacunar lesions rapidly regressed and 29.4% of asymptomatic lacunar lesions [79, 114–117].

In this context, coverage of the anterior choroidal artery (AchoA) with FDs has been the subject of several publications [116, 118]. Most authors report the absence of clinical complications. However, they report rare cases of asymptomatic occlusions. The AchoA territory can be supplemented by other contributions. Takahashi et al. describe 7 cases of retrograde filling of the AchoA in case of occlusion of the clinoid ICA occlusion. The normal AchoA presents anastomoses with the posterior communicating artery and the PCA. These anastomoses are located at the level of the choroid plexuses, the lateral geniculate body, or at the level of the geniculate body, or at the proximal portion of the PCA [119].

Another artery often covered is the ophthalmic artery. Some authors have reported a 25% occlusion rate of this artery during FD placement [114, 120]. Rouchaud et al. performed ophthalmologic examinations of 28 patients treated with FD for carotid ophthalmic aneurysms; 31% of patients complained of the onset or progression of visual symptoms. In 39.3% of cases, abnormalities were found on ophthalmologic examination, including retinal emboli and optic nerve atrophy [114]. Collateral branches to the ophthalmic artery are numerous, and while proximal occlusion does not appear to be dangerous, it is the emboli to the retina that appear to be of greater concern.

Regarding the coverage of arteries with obvious bypasses (arteries communicating arteries, A1 segment with an effective anterior communicator), these may decrease in caliber or become occluded depending on the hemodynamic regimes, and this without neurological deficit in the vast majority of cases [121] (Fig. 9.21). Another important factor is the actual porosity of the FD located in front of these branches, which is influenced by the placement technique (compression of the implant) and by the choice of its size [122].

9.4.2 Hemorrhagic

When a flow diverter is used to treat an aneurysm, the rate of hemorrhagic complications is estimated at about 5%, but the figures vary from 0% to 10% depending on the series [80, 123–125]. The complications described are subarachnoid and intraparenchymal hemorrhages. These may be near or distant from the aneurysm corresponding to aneurysmal rupture or parenchymal hemorrhage. Hemorrhagic complications have a poor prognosis including major morbidity and mortality. The management of these patients under dual antiplatelets therapy is delicate and the transfusion of platelets, the possible recourse to surgery, and the risk of DF thrombosis create clinical situations that are often complicated [108].

Ruptures following the placement of flow diverters have been widely reported [126–128] (Fig. 9.22). Their time of occurrence is not limited to the perioperative period according to reported clinical cases. Rouchaud et al. review the literature and reported that 3/4 of delayed ruptures occurred within the first month, that in 50% of cases, these were giant aneurysms, and that in 20% of cases, these ruptures occurred despite prior coiling. The prognosis of these ruptures is very poor in 80% of cases [129]. There are many hypotheses to explain these ruptures: Related to the thrombus that could cause transient destabilization of the aneurysmal wall [126]. Biological origin related to mural hypoxia, inflammation, and enzymatic degradation. This biological reaction may cause inflammatory secretions in the aneurysm wall via proteases in particular [130]. Hemodynamic origin, such as

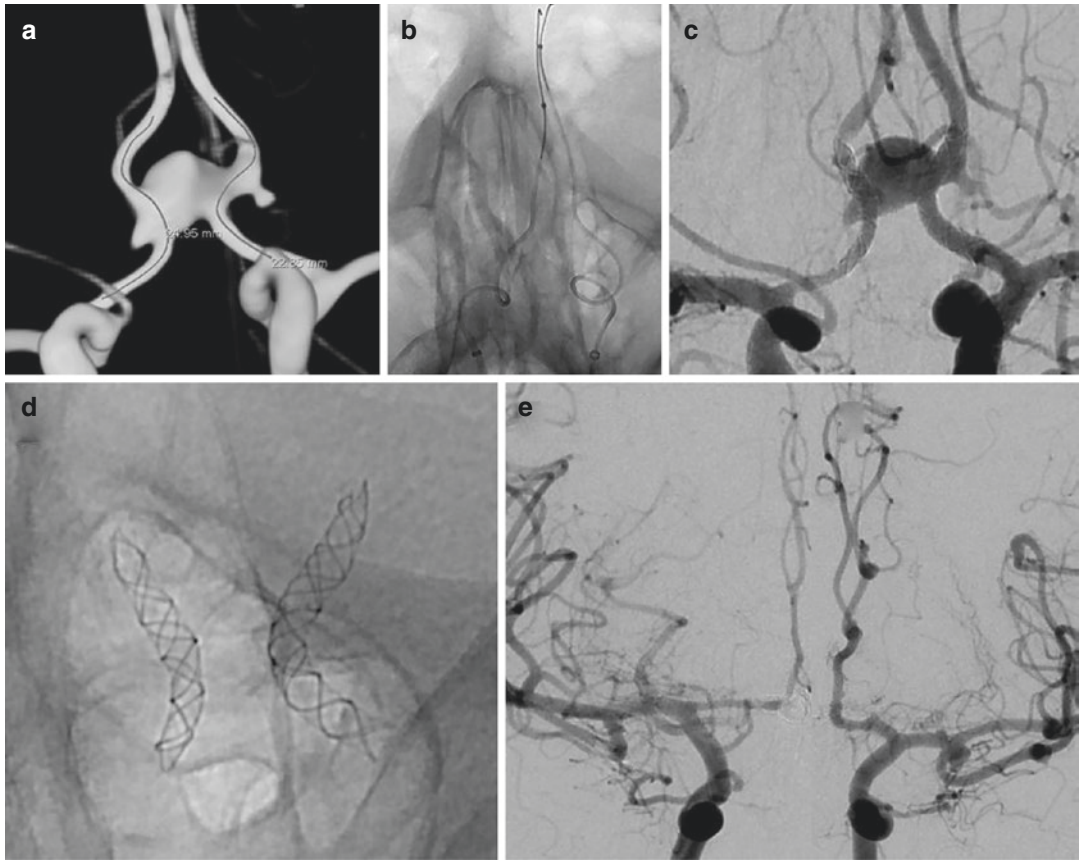


Fig. 9.21 Case of a 37 years old female with an Anterior communicating unruptured "fusiform" aneurysm (**a**). Treatment consisted of the placement of an FD in each A1–A2 segment (Silk Vista Baby) (**b**–**d**). Control angiogram showed the exclusion of the aneurysm, and note the modification of flux and caliber within both cerebral anterior circulations (**e**)

the presence of residual flow at the inflow zone [131] or the rapid creation of an intra-aneurysmal thrombus that creates an internal force responsible for tearing the aneurysm sac [132].

Some authors recommend the use of coils associated with the FD implantation. However, these coils do not provide perfect protection, with Siddiqui et al. reporting two cases of rupture after coiling and FD, and Fischer et al. reported one [133, 134]. Staged techniques, with initial coiling of the aneurysm fundus followed by FD implantation, have been reported in cases of ruptured aneurysms. The goal is twofold: to avoid early aneurysmal rupture and to maximize aneurysmal occlusion. However, there is a lack of strong scientific data to support this strategy except [81, 135].

Intraparenchymal hemorrhages vary in severity depending on the situation and the size of the hematoma. There is no consensus for the management of these hemorrhages, and attitudes obviously depend on the clinical presentation. Depending on the clinical presentation, several options are possible: modification, or not, of the antiplatelet regimen, recourse to surgery [124, 136].

The most common explanation is the hemorrhagic transformation of a silent ischemic lesion, aggravated by double antiplatelet aggregation. However, it is interesting to note that no prior

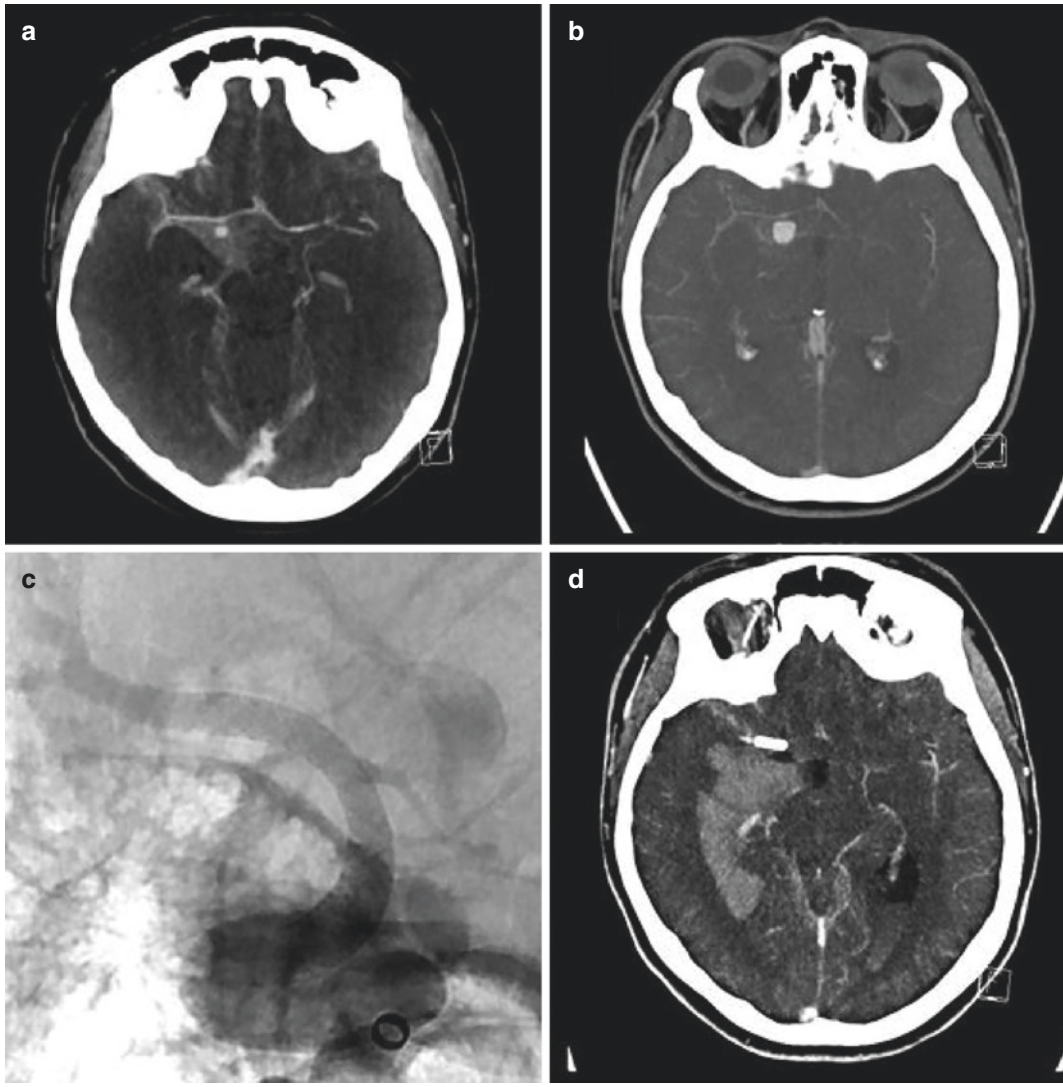


Fig. 9.22 Patient of 53 years old presented with a SAH (mFisher 4) WFNS 1 (**a**). Cerebral angiography did not depict a saccular aneurysm, but a late-filling and stagnating millimetric area rising from the right retro-carotidian segment. Conservative management was primarily decided, and control angiography at day 7 showed a slight rebleeding and growth of the aneurysm (**b**). FD placement under dual antiplatelet therapy was decided and done on day 7 (**c**). Early control CTA at day 8 was performed following a clinical deterioration, and showed a re*bleeding* (**d**), note the absence of opacification of the aneurysm and the patency of the FD

ischemic lesion was observed in the reported cases of hematoma. Yet, these patients frequently have postprocedural control imaging, but MRI series have shown that silent ischemic lesions are common [137]. One could always imagine a hemorrhagic transformation of a small lesion, or of an ischemic lesion that took place remotely from the procedure. Other authors have suggested microscopic embolisms of foreign bodies (PVP, polyvinylpyrrolidone), composed of the internal linings of catheters, which have been found in the brain parenchyma of patients who died of post-FD hemorrhagic complications [138].

Another original explanation is the modification by the flow diverter of the compliance of the

vessel in which it is placed. This implantation would change the pressure regime transmitted to the distal vasculature and would result in a hemorrhagic complication [124, 139].

9.5 Antiplatelets Regimen

Antiplatelets are used more and more frequently in daily practice. They are used pre-procedure, intra-procedure, and post-procedure, sometimes for several years following treatment. However, there are actually no recommendations based on strong scientific evidence, and the management of antiplatelets both before and after the procedure remains debated.

The classic preparation, which uses two complementary molecules, Aspirin and Clopidogrel, has its limitations. The variability of response to Clopidogrel has been demonstrated, and its link to ischemic and hemorrhagic complications is strongly suspected [140]. In this context, some learned societies such as SNIS concluded in 2014 that there is insufficient evidence to recommend the routine use of platelet function tests [141]. The life span of platelets is 7–10 days. Approximately 10–15% of the platelet supply is replaced daily. Tests to assess the degree of platelet inhibition are numerous, and the gold standard is LTA (Light Transmission Aggregometry). In the field of INR, the most studied test is the "Verify Now" test, which is the subject of author recommendations [142]. This test estimates the ability of a drug to block the P2Y12 receptor and thus makes it possible to identify hypo- and hyperresponders. Indeed, general and specific reasons make each person's sensitivity to antiplatelets such as clopidogrel unique (obesity, drug interactions, genetic mutations, procoagulant states, smoking, etc.) [102, 143]. The results are reported in P2Y12 reactive units (PRU). If the PRU is high: many platelets are reactive, the risk is thrombotic, If the PRU is low: few platelets are reactive, the risk is hemorrhagic. Delgado et al. proposed acceptable values between 60 and 240 for endovascular stent/DF treatment of cerebral aneurysms [144]. However, other authors such as Tan et al. place the threshold at 208 [140]. In his meta-analysis, Skukalek et al. report the following: a high dose of Aspirin administered for more than 6 months is associated with fewer TE or bleeding events. Less than 6 months of Clopidogrel administration is associated with more TE events. Loading doses of Aspirin and Clopidogrel are associated with fewer bleeding events. Platelet inhibition test results did not correlate with complications [108]. The data from this meta-analysis appear to support the use of high-dose Aspirin and Clopidogrel for at least 6 months in combination with a pre-procedure loading dose.

Aspirin is a COX-1 inhibitor and prevents the synthesis of TXA2, which inhibits platelet function throughout its life. Aspirin is rapidly effective, with maximum activity measurable as early as 30–60 min after administration [145]. Small doses, less than 100 mg, are sufficient to completely block TXA2 synthesis. However, if a period of 4–7 days is required for full normalization of platelet activity, normalization of TS is observed between 48 and 72 h after cessation. Reversal of the therapeutic effect can be achieved by platelet transfusion. Resistance to aspirin is controversial, with reported rates of resistance ranging from 5% to 40%, and resistance can be overcome by increasing the dose [146].

Clopidogrel is a hepatically metabolized prodrug that induces irreversible ADP blockade at the P2Y12 surface receptor. Clopidogrel has no immediate effect at a maintenance dose of 75 mg but requires 3–7 days to achieve the desired inhibition [147]. A loading dose of Clopidogrel 600 mg achieves platelet inhibition in 2–4 h [148]. The definition of resistance varies between trials and influences the proportion of resistant patients. The rate of resistance to Clopidogrel varies between studies and tests used, reaching over 50% in some series [149]. The most commonly reported interaction is with proton pump inhibitors. This interaction was the subject of an FDA warning in 2009, and one study suggested that the combination of Clopidogrel and pantoprazole should be preferred when these drugs are used together.

Prasugrel and Ticagrelor have already been adopted by many teams despite the lack of evi-

dence of superiority [150] and randomized studies are needed on this topic. While Prasugrel is a pro-drug that requires hepatic hydrolysis and oxidation before binding to the P2Y12 receptor, Ticagrelor does not undergo a transformation in vivo. Prasugrel, for example, shows less interpatient variability than Clopidogrel. The largest published series is that of Akbari et al., who reported in a non-randomized study a bleeding complication rate of 19.4% in the Aspirin/Prasugrel arm compared with a rate of 3.6% in the Aspirin/Clopidogrel arm [151]. The authors also recommend lowering the daily dose of Prasugrel to 5 mg.

Ticagrelor is not all good. It requires twice-daily dosing, which decreases compliance, and it is difficult to antagonize, with little theoretical efficacy of platelet transfusions in case of bleeding complications. It also has adverse effects such as dyspnea. It is necessary to be wary of its drug interactions; thus, it is recommended to keep the dose of aspirin below 100 mg per day and to avoid doses above 40 mg of the following statins: Simvastatin and Lovastatin.

Anti-GpIIbIIa (Abciximab, Eptifibatide, Tirofiban) molecules cause more rapid platelet inhibition than Clopidogrel. They can be injected intra-arterially or intravenously. They can be used preventively or in the context of clinical or angiographic thromboembolic complications. They can be used during coiling, stenting, or FD implantation [152–154]. A bolus type protocol per IV or IA procedure could allow a rapid and constant platelet inhibition, thus avoiding prior preparations and tests. However, the modalities of relaying the treatment which will be continued orally by the patient raise questions. Indeed, the interest of a preparation tested before the procedure is the probable obtaining of a stable regime and a predefined post-procedure treatment. If a per-procedure bolus approach were to be applied, the post-procedure therapy should not suffer from resistance and/or an excessive rate of bleeding complications. In these cases, molecules such as Prasugrel and Ticagrelor may be interesting because of their efficacy, but may also raise concerns about an increase in the bleeding complications described in the cardiology literature [155].

Similar in action mechanism to Ticagrelor, Cangrelor allows intravenous administration and offers the benefit of a very short duration of action (2 min) with a half-life of 3 to 6 min after stopping the infusion. Cangrelor may be a feasible alternative for patients requiring immediate intervention with the use of FD. It allows the possibility for a secure transition to long-term ticagrelor and progression to surgery in the setting of unexpected complications, but the recent introduction of an intravenous P2Y12 inhibitor further adds to the multitude of modalities and contexts in which changes in therapy can occur [156–158].

References

1. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 26 Oct 2002;360(9342):1267–74.
2. Guglielmi G, Viñuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. J Neurosurg. 1991;75(1):1–7.
3. Mascitelli JR, Oermann EK, De Leacy RA, Moyle H, Mocco J, Patel AB. Predictors of treatment failure following coil embolization of intracranial aneurysms. J Clin Neurosci. 2015;22(8):1275–81.
4. Spelle L, Piotin M, Blanc R, Moret J. Remodeling technique in the treatment of intracranial aneurysms: indications, limits and non-indications. Interv Neuroradiol. 2008;14(Suppl 1):52–9.
5. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke. 2003;34(6):1398–403.
6. Augsburger L, Farhat M, Reymond P, Fonck E, Kulcsar Z, Stergiopulos N, et al. Effect of flow diverter porosity on intraaneurysmal blood flow. Klin Neuroradiol. 2009;19(3):204–14.
7. Kadirvel R, Ding Y-H, Dai D, Rezek I, Lewis DA, Kallmes DF. Cellular mechanisms of aneurysm occlusion after treatment with a flow diverter. Radiology. 2014;270(2):394–9.
8. Valdivia y Alvarado M, Ebrahimi N, Benndorf G. Study of conformability of the new leo plus stent to a curved vascular model using flat-panel detector computed tomography (DynaCT). Neurosurgery. 2009;64(3 Suppl):ons130-134.

9. Simgen A, Ley D, Roth C, Yilmaz U, Körner H, Mühl-Benninghaus R, et al. Evaluation of a newly designed flow diverter for the treatment of intracranial aneurysms in an elastase-induced aneurysm model, in New Zealand white rabbits. Neuroradiology. https://doi.org/10.1007/s00234-013-1296-9.
10. Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, Macho J, Derakhshani S, Foa Torres G, et al. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg. 2021;13(1):54–62.
11. Wang K, Yuan S. Actual metal coverage at the neck is critical for flow-diverting stents in treating intracranial aneurysms. AJNR Am J Neuroradiol. 2013;34(3):E31–2.
12. Cantón G, Levy DI, Lasheras JC. Hemodynamic changes due to stent placement in bifurcating intracranial aneurysms. J Neurosurg. 2005;103(1):146–55.
13. Hong B, Wang K, Huang Q, Xu Y, Fang X, Li Z, et al. Effects of metal coverage rate of flow diversion device on neointimal growth at side branch ostium and stented artery: an animal experiment in rabbit abdominal aorta. Neuroradiology. 2012;54(8):849–55.
14. Aurboonyawat T, Blanc R, Schmidt P, Piotin M, Spelle L, Nakib A, et al. An in vitro study of silk stent morphology. Neuroradiology. 2011;53(9):659–67.
15. Bing F, Darsaut TE, Salazkin I, Makoyeva A, Gevry G, Raymond J. Stents and flow diverters in the treatment of aneurysms: device deformation in vivo may alter porosity and impact efficacy. Neuroradiology. 2013;55(1):85–92.
16. Baráth K, Cassot F, Fasel JHD, Ohta M, Rüfenacht DA. Influence of stent properties on the alteration of cerebral intra-aneurysmal haemodynamics: flow quantification in elastic sidewall aneurysm models. Neurol Res. 2005;27(Suppl 1):S120–8.
17. Dennis KD, Rossman TL, Kallmes DF, Dragomir-Daescu D. Intra-aneurysmal flow rates are reduced by two flow diverters: an experiment using tomographic particle image velocimetry in an aneurysm model. J Neurointerv Surg. 2015;7(12):937–42.
18. Shapiro M, Raz E, Becske T, Nelson PK. Variable porosity of the pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy. AJNR Am J Neuroradiol. 2014;35(4):727–33.
19. Shapiro M, Raz E, Becske T, Nelson PK. Building multidevice pipeline constructs of favorable metal coverage: a practical guide. AJNR Am J Neuroradiol. 2014;35(8):1556–61.
20. Sadasivan C, Cesar L, Seong J, Rakian A, Hao Q, Tio FO, et al. An original flow diversion device for the treatment of intracranial aneurysms: evaluation in the rabbit elastase-induced model. Stroke. 2009;40(3):952–8.
21. Ma D, Dargush GF, Natarajan SK, Levy EI, Siddiqui AH, Meng H. Computer modeling of deployment and mechanical expansion of neurovascular flow diverter in patient-specific intracranial aneurysms. J Biomech. 2012;45(13):2256–63.
22. Ley D, Mühl-Benninghaus R, Yilmaz U, Körner H, Cattaneo GFM, Mailänder W, et al. The Derivo embolization device, a second-generation flow diverter for the treatment of intracranial aneurysms, evaluated in an elastase-induced aneurysm model. Clin Neuroradiol. 2017 Sept;27(3):335–43.
23. Kocer N, Islak C, Kizilkilic O, Kocak B, Saglam M, Tureci E. Flow re-direction endoluminal device in treatment of cerebral aneurysms: initial experience with short-term follow-up results. J Neurosurg. 2014;120(5):1158–71.
24. Kim BM, Kim DJ, Kim DI. A new flow-diverter (the FloWise): in-vivo evaluation in an elastase-induced rabbit aneurysm model. Korean J Radiol. 2016;17(1):151–8.
25. Ma D, Xiang J, Choi H, Dumont TM, Natarajan SK, Siddiqui AH, et al. Enhanced aneurysmal flow diversion using a dynamic push-pull technique: an experimental and modeling study. AJNR Am J Neuroradiol. 2014;35(9):1779–85.
26. Darsaut TE, Bing F, Makoyeva A, Gevry G, Salazkin I, Raymond J. Flow diversion to treat aneurysms: the free segment of stent. J Neurointerv Surg. 1 Sep 2013;5(5):452–7.
27. Makoyeva A, Bing F, Darsaut TE, Salazkin I, Raymond J. The varying porosity of braided self-expanding stents and flow diverters: an experimental study. AJNR Am J Neuroradiol. 2013;34(3):596–602.
28. Darsaut TE, Bing F, Salazkin I, Gevry G, Raymond J. Testing flow diverters in giant fusiform aneurysms: a new experimental model can show leaks responsible for failures. AJNR Am J Neuroradiol. 2011;32(11):2175–9.
29. Cohen JE, Gomori JM, Moscovici S, Leker RR, Itshayek E. Delayed complications after flow-diverter stenting: reactive in-stent stenosis and creeping stents. J Clin Neurosci. 2014;21(7):1116–22.
30. Chalouhi N, Tjoumakaris SI, Gonzalez LF, Hasan D, Pema PJ, Gould G, et al. Spontaneous delayed migration/shortening of the pipeline embolization device: report of 5 cases. AJNR Am J Neuroradiol. 2013;34(12):2326–30.
31. Fischer S, Aguilar-Pérez M, Henkes E, Kurre W, Ganslandt O, Bäzner H, et al. Initial experience with p64: a novel mechanically detachable flow diverter for the treatment of intracranial saccular sidewall aneurysms. AJNR Am J Neuroradiol. 2015;36(11):2082–9.
32. Rayepalli S, Gupta R, Lum C, Majid A, Koochesfahani M. The impact of stent strut porosity on reducing flow in cerebral aneurysms. J Neuroimaging. 2013;23(4):495–501.
33. Heller R, Calnan DR, Lanfranchi M, Madan N, Malek AM. Incomplete stent apposition in Enterprise stent-mediated coiling of aneurysms: persistence over time and risk of delayed ischemic events. J Neurosurg. 2013;118(5):1014–22.

34. Pereira VM, Kelly M, Vega P, Murias E, Yilmaz H, Erceg G, et al. New pipeline Flex device: initial experience and technical nuances. J Neurointerv Surg. 2015;7(12):920–5.
35. Tulamo R, Frösen J, Hernesniemi J, Niemelä M. Inflammatory changes in the aneurysm wall: a review. J Neurointerv Surg. 2010;2(2):120–30.
36. Fiorella D, Hsu D, Woo HH, Tarr RW, Nelson PK. Very late thrombosis of a pipeline embolization device construct: case report. Neurosurgery. 2010;67(3 Suppl):onsE313-314.
37. Krajewski S, Neumann B, Kurz J, Perle N, Avci-Adali M, Cattaneo G, et al. Preclinical evaluation of the thrombogenicity and endothelialization of bare metal and surface-coated neurovascular stents. AJNR Am J Neuroradiol. 2015;36(1):133–9.
38. Kuiper KK, Robinson KA, Chronos NA, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J. 1998;32(5):261–8.
39. Lewis AL, Stratford PW. A review on phosphorylcholine-coated stents. J Long-Term Eff Med Implants. 2017;27(2–4):233–52.
40. Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart. 2000;83(3):338–45.
41. Girdhar G, Li J, Kostousov L, Wainwright J, Chandler WL. In-vitro thrombogenicity assessment of flow diversion and aneurysm bridging devices. J Thromb Thrombolysis. 2015;40(4):437–43.
42. Manning NW, Cheung A, Phillips TJ, Wenderoth JD. Pipeline shield with single antiplatelet therapy in aneurysmal subarachnoid haemorrhage: multicentre experience. J Neurointerv Surg. 2019;11(7):694–8.
43. Gentric J-C, Fahed R, Darsaut TE, Salazkin I, Roy D, Raymond J. Fatal arterial rupture during angioplasty of a flow diverter in a recurrent, previously Y-stented giant MCA bifurcation aneurysm. Interv Neuroradiol. 2016;22(3):278–86.
44. Schneiders JJ, VanBavel E, Majoie CB, Ferns SP, van den Berg R. A flow-diverting stent is not a pressure-diverting stent. AJNR Am J Neuroradiol. 2013;34(1):E1–4.
45. Cebral JR, Mut F, Raschi M, Scrivano E, Ceratto R, Lylyk P, et al. Aneurysm rupture following treatment with flow-diverting stents: computational hemodynamics analysis of treatment. AJNR Am J Neuroradiol. 2011;32(1):27–33.
46. Roszelle BN, Gonzalez LF, Babiker MH, Ryan J, Albuquerque FC, Frakes DH. Flow diverter effect on cerebral aneurysm hemodynamics: an in vitro comparison of telescoping stents and the pipeline. Neuroradiology. 2013;55(6):751–8.
47. Cebral JR, Mut F, Raschi M, Ding Y-H, Kadirvel R, Kallmes D. Strategy for analysis of flow diverting devices based on multi-modality image-based modeling. Int J Numer Method Biomed Eng. 2014;30(10):951–68.
48. Xiang J, Tutino VM, Snyder KV, Meng H. CFD: computational fluid dynamics or confounding factor dissemination? The role of hemodynamics in intracranial aneurysm rupture risk assessment. AJNR Am J Neuroradiol. 2014;35(10):1849–57.
49. Cebral JR, Castro MA, Burgess JE, Pergolizzi RS, Sheridan MJ, Putman CM. Characterization of cerebral aneurysms for assessing risk of rupture by using patient-specific computational hemodynamics models. AJNR Am J Neuroradiol. 2005;26(10):2550–9.
50. Cebral JR, Mut F, Weir J, Putman CM. Association of hemodynamic characteristics and cerebral aneurysm rupture. AJNR Am J Neuroradiol. 2011;32(2):264–70.
51. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. JAMA. 1 Dec 1999;282(21):2035–42.
52. Shojima M, Oshima M, Takagi K, Torii R, Hayakawa M, Katada K, et al. Magnitude and role of wall shear stress on cerebral aneurysm: computational fluid dynamic study of 20 middle cerebral artery aneurysms. Stroke. 2004;35(11):2500–5.
53. Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. N Engl J Med. 1994;330(20):1431–8.
54. Omodaka S, Sugiyama S-I, Inoue T, Funamoto K, Fujimura M, Shimizu H, et al. Local hemodynamics at the rupture point of cerebral aneurysms determined by computational fluid dynamics analysis. Cerebrovasc Dis. 2012;34(2):121–9.
55. Kang H, Duran CL, Abbey CA, Kaunas RR, Bayless KJ. Fluid shear stress promotes proprotein convertase-dependent activation of MT1-MMP. Biochem Biophys Res Commun. 2015;460(3):596–602.
56. Kolega J, Gao L, Mandelbaum M, Mocco J, Siddiqui AH, Natarajan SK, et al. Cellular and molecular responses of the basilar terminus to hemodynamics during intracranial aneurysm initiation in a rabbit model. J Vasc Res. 2011;48(5):429–42.
57. Meng H, Tutino VM, Xiang J, Siddiqui A. High WSS or low WSS? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis. AJNR Am J Neuroradiol. 2014;35(7):1254–62.
58. Xiang J, Natarajan SK, Tremmel M, Ma D, Mocco J, Hopkins LN, et al. Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. Stroke. 2011;42(1):144–52.
59. Castro MA, Putman CM, Sheridan MJ, Cebral JR. Hemodynamic patterns of anterior communicating artery aneurysms: a possible association with rupture. AJNR Am J Neuroradiol. 2009;30(2):297–302.
60. Shobayashi Y, Tateshima S, Kakizaki R, Sudo R, Tanishita K, Viñuela F. Intra-aneurysmal hemody-

namic alterations by a self-expandable intracranial stent and flow diversion stent: high intra-aneurysmal pressure remains regardless of flow velocity reduction. J Neurointerv Surg. 2013;5(Suppl 3):iii38–42.
61. Liou T-M, Li Y-C. Effects of stent porosity on hemodynamics in a sidewall aneurysm model. J Biomech. 2008;41(6):1174–83.
62. Kulcsár Z, Augsburger L, Reymond P, Pereira VM, Hirsch S, Mallik AS, et al. Flow diversion treatment: intra-aneurismal blood flow velocity and WSS reduction are parameters to predict aneurysm thrombosis. Acta Neurochir (Wien). 2012;154(10):1827–34.
63. Ribeiro de Sousa D, Vallecilla C, Chodzynski K, Corredor Jerez R, Malaspinas O, Eker OF, et al. Determination of a shear rate threshold for thrombus formation in intracranial aneurysms. J Neurointerv Surg. 2016;8(8):853–8.
64. Chiu AHY, Marotta TR. Pipeline embolization device thrombosis induced peri-construct collateral channels. J Neurointerv Surg. 2016;8(11):e47.
65. Bavinzski G, Talazoglu V, Killer M, Richling B, Gruber A, Gross CE, et al. Gross and microscopic histopathological findings in aneurysms of the human brain treated with Guglielmi detachable coils. J Neurosurg. 1999;91(2):284–93.
66. Ozawa T, Tamatani S, Koike T, Abe H, Ito Y, Soga Y, et al. Histological evaluation of endothelial reactions after endovascular coil embolization for intracranial aneurysm. Clinical and experimental studies and review of the literature. Interv Neuroradiol. 2003;9(Suppl 1):69–82.
67. Fahed R, Raymond J, Ducroux C, Gentric J-C, Salazkin I, Ziegler D, et al. Testing flow diversion in animal models: a systematic review. Neuroradiology. 2016;58(4):375–82.
68. Darsaut TE, Bing F, Salazkin I, Gevry G, Raymond J. Flow diverters failing to occlude experimental bifurcation or curved sidewall aneurysms: an in vivo study in canines. J Neurosurg. 2012;117(1):37–44.
69. Darsaut TE, Bing F, Makoyeva A, Gevry G, Salazkin I, Raymond J. Flow diversion of giant curved sidewall and bifurcation experimental aneurysms with very-low-porosity devices. World Neurosurg. 2014;82(6):1120–6.
70. Raymond J, Darsaut TE, Makoyeva A, Bing F, Salazkin I. Endovascular treatment with flow diverters may fail to occlude experimental bifurcation aneurysms. Neuroradiology. 2013;55(11):1355–63.
71. Gentric JC, Darsaut TE, Makoyeva A, Salazkin I, Raymond J. The success of flow diversion in large and giant sidewall aneurysms may depend on the size of the defect in the parent artery. AJNR Am J Neuroradiol. 2014;35(11):2119–24.
72. Darsaut TE, Bing F, Salazkin I, Gevry G, Raymond J. Flow diverters can occlude aneurysms and preserve arterial branches: a new experimental model. AJNR Am J Neuroradiol. 2012;33(10):2004–9.
73. Tsang ACO, Fung AMY, Tsang FCP, Leung GKK, Lee R, Lui WM. Failure of flow diverter treatment of intracranial aneurysms related to the fetal-type posterior communicating artery. Neurointervention. 2015;10(2):60–6.
74. Kim M, Taulbee DB, Tremmel M, Meng H. Comparison of two stents in modifying cerebral aneurysm hemodynamics. Ann Biomed Eng. 2008;36(5):726–41.
75. Wang K, Huang Q, Hong B, Li Z, Fang X, Liu J. Correlation of aneurysm occlusion with actual metal coverage at neck after implantation of flow-diverting stent in rabbit models. Neuroradiology. 2012;54(6):607–13.
76. Briganti F, Delehaye L, Leone G, Sicignano C, Buono G, Marseglia M, et al. Flow diverter device for the treatment of small middle cerebral artery aneurysms. J Neurointerv Surg. 2016;8(3):287–94.
77. Caroff J, Neki H, Mihalea C, D'Argento F, Abdel Khalek H, Ikka L, et al. Flow-diverter stents for the treatment of saccular middle cerebral artery bifurcation aneurysms. AJNR Am J Neuroradiol. 2016;37(2):279–84.
78. Chalouhi N, Tjoumakaris S, Dumont AS, Gonzalez LF, Randazzo C, Starke RM, et al. Treatment of posterior circulation aneurysms with the pipeline embolization device. Neurosurgery. 2013;72(6):883–9.
79. Gawlitza M, Januel A-C, Tall P, Bonneville F, Cognard C. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: a single-center series with special emphasis on covered cortical branches and perforating arteries. J Neurointerv Surg. 2016;8(5):481–7.
80. McAuliffe W, Wycoco V, Rice H, Phatouros C, Singh TJ, Wenderoth J. Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. AJNR Am J Neuroradiol. 2012;33(1):164–70.
81. Brinjikji W, Piano M, Fang S, Pero G, Kallmes DF, Quilici L, et al. Treatment of ruptured complex and large/giant ruptured cerebral aneurysms by acute coiling followed by staged flow diversion. J Neurosurg. 2016;125(1):120–7.
82. Lin N, Brouillard AM, Keigher KM, Lopes DK, Binning MJ, Liebman KM, et al. Utilization of pipeline embolization device for treatment of ruptured intracranial aneurysms: US multicenter experience. J Neurointerv Surg. 2015;7(11):808–15.
83. Chalouhi N, Zanaty M, Tjoumakaris S, Gonzalez LF, Hasan D, Kung D, et al. Treatment of blister-like aneurysms with the pipeline embolization device. Neurosurgery. 2014;74(5):527–32.
84. Kalani MYS, Albuquerque FC, Levitt M, Nakaji P, Spetzler RF, McDougall C. Pipeline embolization for definitive endoluminal reconstruction of blister-type carotid aneurysms after clip wrapping. J Neurointerv Surg. 2016;8(5):495–500.
85. Iancu D, Lum C, Ahmed ME, Glikstein R, Dos Santos MP, Lesiuk H, et al. Flow diversion in the treatment of carotid injury and carotid-cavernous fistula after transsphenoidal surgery. Interv Neuroradiol. 2015;21(3):346–50.

86. Nerva JD, Morton RP, Levitt MR, Osbun JW, Ferreira MJ, Ghodke BV, et al. Pipeline embolization device as primary treatment for blister aneurysms and iatrogenic pseudoaneurysms of the internal carotid artery. J Neurointerv Surg. 2015;7(3):210–6.
87. Chalouhi N, Chitale R, Starke RM, Jabbour P, Tjoumakaris S, Dumont AS, et al. Treatment of recurrent intracranial aneurysms with the pipeline embolization device. J Neurointerv Surg. 2014;6(1):19–23.
88. Berge J, Biondi A, Machi P, Brunel H, Pierot L, Gabrillargues J, et al. Flow-diverter silk stent for the treatment of intracranial aneurysms: 1-year follow-up in a multicenter study. AJNR Am J Neuroradiol. 2012;33(6):1150–5.
89. Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858–68.
90. Kallmes DF, Hanel R, Lopes D, Boccardi E, Bonafé A, Cekirge S, et al. International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. AJNR Am J Neuroradiol. 2015;36(1):108–15.
91. Arrese I, Sarabia R, Pintado R, Delgado-Rodriguez M. Flow-diverter devices for intracranial aneurysms: systematic review and meta-analysis. Neurosurgery. 2013;73(2):193–9.
92. Naggara ON, White PM, Guilbert F, Roy D, Weill A, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. Radiology. 2010;256(3):887–97.
93. Ogilvy CS, Cheung AC, Mitha AP, Hoh BL, Carter BS. Outcomes for surgical and endovascular management of intracranial aneurysms using a comprehensive grading system. Neurosurgery. 2006;59(5):1037–42.
94. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44(2):442–7.
95. Briganti F, Napoli M, Leone G, Marseglia M, Mariniello G, Caranci F, et al. Treatment of intracranial aneurysms by flow diverter devices: long-term results from a single center. Eur J Radiol. 2014;83(9):1683–90.
96. Lv X, Yang H, Liu P, Li Y. Flow-diverter devices in the treatment of intracranial aneurysms: a meta-analysis and systematic review. Neuroradiol J. 2016;29(1):66–71.
97. Cagnazzo F, Perrini P, Dargazanli C, Lefevre P-H, Gascou G, Morganti R, et al. Treatment of unruptured distal anterior circulation aneurysms with flow-diverter stents: a meta-analysis. AJNR Am J Neuroradiol. 2019;40(4):687–93.
98. Wang C-B, Shi W-W, Zhang G-X, Lu H-C, Ma J. Flow diverter treatment of posterior circulation aneurysms. A meta-analysis. Neuroradiology. 2016;58(4):391–400.
99. Suh SH, Cloft HJ, Lanzino G, Woodward K, Kallmes DF. Interobserver agreement after pipeline embolization device implantation. AJNR Am J Neuroradiol. 2013;34(6):1215–8.
100. Gaha M, Roy C, Estrade L, Gevry G, Weill A, Roy D, et al. Inter- and intraobserver agreement in scoring angiographic results of intra-arterial stroke therapy. AJNR Am J Neuroradiol. 2014;35(6):1163–9.
101. Tollard É, Darsaut TE, Bing F, Guilbert F, Gevry G, Raymond J. Outcomes of endovascular treatments of aneurysms: observer variability and implications for interpreting case series and planning randomized trials. AJNR Am J Neuroradiol. 2012;33(4):626–31.
102. Nakagawa I, Park HS, Yokoyama S, Wada T, Hironaka Y, Motoyama Y, et al. Influence of diabetes mellitus and cigarette smoking on variability of the Clopidogrel-induced antiplatelet effect and efficacy of active management of the target P2Y12 reaction unit range in patients undergoing neurointerventional procedures. J Stroke Cerebrovasc Dis. 2016;25(1):163–71.
103. O'kelly CJ, Krings T, Fiorella D, Marotta TR. A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. Interv Neuroradiol. 2010;16(2):133–7.
104. Kamran M, Yarnold J, Grunwald IQ, Byrne JV. Assessment of angiographic outcomes after flow diversion treatment of intracranial aneurysms: a new grading schema. Neuroradiology. 2011;53(7):501–8.
105. Grunwald IQ, Kamran M, Corkill RA, Kühn AL, Choi IS, Turnbull S, et al. Simple measurement of aneurysm residual after treatment: the SMART scale for evaluation of intracranial aneurysms treated with flow diverters. Acta Neurochir (Wien). 2012;154(1):21–6.
106. Saleh A, Hammoudeh A, Tabbalat R, Al-Haddad I, Al-Mousa E, Jarrah M, et al. Incidence and prognosis of stent thrombosis following percutaneous coronary intervention in middle eastern patients: the first Jordanian Percutaneous Coronary Intervention registry (JoPCR1). Ann Saudi Med. 2016;36(1):17–22.
107. Wong GKC, Kwan MCL, Ng RYT, Yu SCH, Poon WS. Flow diverters for treatment of intracranial aneurysms: current status and ongoing clinical trials. J Clin Neurosci. 2011;18(6):737–40.
108. Skukalek SL, Winkler AM, Kang J, Dion JE, Cawley CM, Webb A, et al. Effect of antiplatelet therapy and platelet function testing on hemorrhagic and thrombotic complications in patients with cerebral aneurysms treated with the pipeline embolization device: a review and meta-analysis. J Neurointerv Surg. 2016;8(1):58–65.
109. Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR Am J Neuroradiol. 2010;31(6):1139–47.
110. Labeyrie M-A, Lenck S, Bresson D, Desilles J-P, Bisdorff A, Saint-Maurice J-P, et al. Parent artery

occlusion in large, giant, or fusiform aneurysms of the carotid siphon: clinical and imaging results. AJNR Am J Neuroradiol. 2015;36(1):140–5.
111. Chalouhi N, Polifka A, Daou B, Kung D, Barros G, Tjoumakaris S, et al. In-pipeline stenosis: incidence, predictors, and clinical outcomes. Neurosurgery. 2015;77(6):875–9.
112. Guédon A, Clarençon F, Di Maria F, Rosso C, Biondi A, Gabrieli J, et al. Very late ischemic complications in flow-diverter stents: a retrospective analysis of a single-center series. J Neurosurg. 2016;125(4):929–35.
113. Klisch J, Turk A, Turner R, Woo HH, Fiorella D. Very late thrombosis of flow-diverting constructs after the treatment of large fusiform posterior circulation aneurysms. AJNR Am J Neuroradiol. 2011;32(4):627–32.
114. Rouchaud A, Leclerc O, Benayoun Y, Saleme S, Camilleri Y, D'Argento F, et al. Visual outcomes with flow-diverter stents covering the ophthalmic artery for treatment of internal carotid artery aneurysms. AJNR Am J Neuroradiol. 2015;36(2):330–6.
115. Kulcsár Z, Ernemann U, Wetzel SG, Bock A, Goericke S, Panagiotopoulos V, et al. High-profile flow diverter (silk) implantation in the basilar artery: efficacy in the treatment of aneurysms and the role of the perforators. Stroke. 2010;41(8):1690–6.
116. Brinjikji W, Kallmes DF, Cloft HJ, Lanzino G. Patency of the anterior choroidal artery after flow-diversion treatment of internal carotid artery aneurysms. AJNR Am J Neuroradiol. 2015;36(3):537–41.
117. van Rooij WJ, Sluzewski M. Perforator infarction after placement of a pipeline flow-diverting stent for an unruptured A1 aneurysm. AJNR Am J Neuroradiol. 2010;31(4):E43–4.
118. Raz E, Shapiro M, Becske T, Zumofen DW, Tanweer O, Potts MB, et al. Anterior choroidal artery patency and clinical follow-up after coverage with the pipeline embolization device. AJNR Am J Neuroradiol. 2015;36(5):937–42.
119. Takahashi S, Suga T, Kawata Y, Sakamoto K. Anterior choroidal artery: angiographic analysis of variations and anomalies. AJNR Am J Neuroradiol. 1990;11(4):719–29.
120. Puffer RC, Kallmes DF, Cloft HJ, Lanzino G. Patency of the ophthalmic artery after flow diversion treatment of paraclinoid aneurysms. J Neurosurg. 2012;116(4):892–6.
121. Brinjikji W, Lanzino G, Cloft HJ, Kallmes DF. Patency of the posterior communicating artery after flow diversion treatment of internal carotid artery aneurysms. Clin Neurol Neurosurg. 2014;120:84–8.
122. Berg P, Iosif C, Ponsonnard S, Yardin C, Janiga G, Mounayer C. Endothelialization of over- and undersized flow-diverter stents at covered vessel side branches: An in vivo and in silico study. J Biomech. 2016;49(1):4–12.
123. Byrne JV, Beltechi R, Yarnold JA, Birks J, Kamran M. Early experience in the treatment of intracranial aneurysms by endovascular flow diversion: a multicentre prospective study. PLoS One. 2 Sep 2010;5(9):e12492.
124. Cruz JP, Chow M, O'Kelly C, Marotta B, Spears J, Montanera W, et al. Delayed ipsilateral parenchymal hemorrhage following flow diversion for the treatment of anterior circulation aneurysms. AJNR Am J Neuroradiol. 2012;33(4):603–8.
125. Leung GKK, Tsang ACO, Lui WM. Pipeline embolization device for intracranial aneurysm: a systematic review. Clin Neuroradiol. 2012;22(4):295–303.
126. Chow M, McDougall C, O'Kelly C, Ashforth R, Johnson E, Fiorella D. Delayed spontaneous rupture of a posterior inferior cerebellar artery aneurysm following treatment with flow diversion: a clinicopathologic study. AJNR Am J Neuroradiol. 2012;33(4):E46–51.
127. Hampton T, Walsh D, Tolias C, Fiorella D. Mural destabilization after aneurysm treatment with a flow-diverting device: a report of two cases. J Neurointerv Surg. 2011;3(2):167–71.
128. Kacar E, Fatih Nas O, Erdogan C, Hakyemez B. Intracranial aneurysm rupture during flow diverter stent placement: successful treatment with stent-in-stent combination. Diagn Interv Imaging. 2015;96(4):411–3.
129. Rouchaud A, Brinjikji W, Lanzino G, Cloft HJ, Kadirvel R, Kallmes DF. Delayed hemorrhagic complications after flow diversion for intracranial aneurysms: a literature overview. Neuroradiology. 2016;58(2):171–7.
130. Hasan DM, Chalouhi N, Jabbour P, Magnotta VA, Kung DK, Young WL. Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: preliminary results. J Neuroradiol. 2013;40(3):187–91.
131. Ikeda H, Ishii A, Kikuchi T, Ando M, Chihara H, Arai D, et al. Delayed aneurysm rupture due to residual blood flow at the inflow zone of the intracranial paraclinoid internal carotid aneurysm treated with the pipeline embolization device: histopathological investigation. Interv Neuroradiol. 2015;21(6):674–83.
132. Fox B, Humphries WE, Doss VT, Hoit D, Elijovich L, Arthur AS. Rupture of giant vertebrobasilar aneurysm following flow diversion: mechanical stretch as a potential mechanism for early aneurysm rupture. J Neurointerv Surg. 2015;7(11):e37.
133. Fischer S, Vajda Z, Aguilar Perez M, Schmid E, Hopf N, Bäzner H, et al. Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. Neuroradiology. 2012;54(4):369–82.

134. Siddiqui AH, Kan P, Abla AA, Hopkins LN, Levy EI. Complications after treatment with pipeline embolization for giant distal intracranial aneurysms with or without coil embolization. Neurosurgery. 2012;71(2):E509–13.
135. Princiotta C, Dall'olio M, Cirillo L, Leonardi M. Staged treatment of a blood blister-like aneurysm with stent-assisted coiling followed by flow diverter in-stent insertion. A case report. Interv Neuroradiol. Sep 2011;17(3):365–70.
136. Clarençon F, Di Maria F, Biondi A, Chiras J, Sourour N-A. Distant and delayed (>7 days) hemorrhage after treatment by flow-diverter stents in intracranial aneurysms: a rare but potentially serious complication. AJNR Am J Neuroradiol. 2013;34(7):E81–2.
137. Grunwald IQ, Papanagiotou P, Politi M, Struffert T, Roth C, Reith W. Endovascular treatment of unruptured intracranial aneurysms: occurrence of thromboembolic events. Neurosurgery. 2006;58(4):612–8.
138. Hu YC, Deshmukh VR, Albuquerque FC, Fiorella D, Nixon RR, Heck DV, et al. Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the pipeline embolization device. J Neurosurg. 2014;120(2):365–74.
139. Mitha AP, Mynard JP, Storwick JA, Shivji ZI, Wong JH, Morrish W. Can the Windkessel hypothesis explain delayed Intraparenchymal Haemorrhage after flow diversion? A case report and model-based analysis of possible mechanisms. Heart Lung Circ. 2015;24(8):824–30.
140. Tan LA, Keigher KM, Munich SA, Moftakhar R, Lopes DK. Thromboembolic complications with pipeline embolization device placement: impact of procedure time, number of stents and pre-procedure P2Y12 reaction unit (PRU) value. J Neurointerv Surg. 2015;7(3):217–21.
141. Gandhi CD, Bulsara KR, Fifi J, Kass-Hout T, Grant RA, Delgado Almandoz JE, et al. Platelet function inhibitors and platelet function testing in neurointerventional procedures. J Neurointerv Surg. 2014;6(8):567–77.
142. Delgado Almandoz JE, Kadkhodayan Y, Crandall BM, Scholz JM, Fease JL, Tubman DE. Variability in initial response to standard clopidogrel therapy, delayed conversion to clopidogrel hyper-response, and associated thromboembolic and hemorrhagic complications in patients undergoing endovascular treatment of unruptured cerebral aneurysms. J Neurointerv Surg. 2014;6(10):767–73.
143. Luinstra M, Naunton M, Peterson GM, Bereznicki L. PPI use in patients commenced on clopidogrel: a retrospective cross-sectional evaluation. J Clin Pharm Ther. 2010;35(2):213–7.
144. Delgado Almandoz JE, Crandall BM, Scholz JM, Fease JL, Anderson RE, Kadkhodayan Y, et al. Pre-procedure P2Y12 reaction units value predicts perioperative thromboembolic and hemorrhagic complications in patients with cerebral aneurysms treated with the pipeline embolization device. J Neurointerv Surg. Nov 2013;5(Suppl 3):iii3–iii10.
145. Dabaghi SF, Kamat SG, Payne J, Marks GF, Roberts R, Schafer AI, et al. Effects of low-dose aspirin on in vitro platelet aggregation in the early minutes after ingestion in normal subjects. Am J Cardiol. 1 Oct 1994;74(7):720–3.
146. McKee SA, Sane DC, Deliargyris EN. Aspirin resistance in cardiovascular disease: a review of prevalence, mechanisms, and clinical significance. Thromb Haemost. 2002;88(5):711–5.
147. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost. 1999;25(Suppl 2):15–9.
148. Steinhubl SR, Berger PB, Mann JT, Fry ETA, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 20 Nov 2002;288(19):2411–20.
149. Guo LZ, Kim MH, Jin CD, Lee JY, Yi SJ, Park MK, et al. Comparison of pharmacodynamics between low dose ticagrelor and clopidogrel after loading and maintenance doses in healthy Korean subjects. Platelets. 2015;26(6):563–9.
150. Jones GM, Twilla JD, Hoit DA, Arthur AS. Prevention of stent thrombosis with reduced dose of prasugrel in two patients undergoing treatment of cerebral aneurysms with pipeline embolisation devices. J Neurointerv Surg. 1 Sep 2013;5(5):e38.
151. Akbari SH, Reynolds MR, Kadkhodayan Y, Cross DT, Moran CJ. Hemorrhagic complications after prasugrel (Effient) therapy for vascular neurointerventional procedures. J Neurointerv Surg. 2013;5(4):337–43.
152. Gentric J-C, Brisson J, Batista AL, Ghostine J, Raymond J, Roy D, et al. Safety of Abciximab injection during endovascular treatment of ruptured aneurysms. Interv Neuroradiol. 2015;21(3):332–6.
153. Sedat J, Chau Y, Gaudard J, Suissa L, Lachaud S, Lonjon M. Administration of eptifibatide during endovascular treatment of ruptured cerebral aneurysms reduces the rate of thromboembolic events. Neuroradiology. 2015;57(2):197–203.
154. Chalouhi N, Jabbour P, Daou B, Starke RM, Shields B, Hasan DM. A new protocol for anticoagulation with Tirofiban during flow diversion. Neurosurgery. 2016;78(5):670–4.
155. Valgimigli M, Tebaldi M, Campo G, Gambetti S, Bristot L, Monti M, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given

at loading dOse) trial. JACC Cardiovasc Interv. 2012;5(3):268–77.
156. Linfante I, Ravipati K, Starosciak AK, Reyes D, Dabus G. Intravenous cangrelor and oral ticagrelor as an alternative to clopidogrel in acute intervention. J Neurointerv Surg. 2021;13(1):30–2.
157. Aguilar-Salinas P, Agnoletto GJ, Brasiliense LBC, Santos R, Granja MF, Gonsales D, et al. Safety and efficacy of cangrelor in acute stenting for the treatment of cerebrovascular pathology: preliminary experience in a single-center pilot study. J Neurointerv Surg. 2019;11(4):347–51.
158. Cortez GM, Monteiro A, Sourour N, Clarençon F, Elhorany M, Grigoryan M, et al. The use of cangrelor in neurovascular interventions: a multicenter experience. Neuroradiology. 2020;63(6):925–34.

The Off-Label Use of Flow Diverter

10

Ting Liao, Ukam Wong, Yiu Wah Fan, and Xianli Lv

Abstract

The Pipeline embolization device (PED) is the most widely used flow diverter in endovascular treatment of cerebral aneurysms. In 2011, the device received FDA of USA approval for the treatment of large and giant aneurysms in the internal carotid artery (ICA) extending from the petrous to the superior hypophyseal segments. As popularity of the device grew and neurosurgeons gained more experience, its indications were extended to complex wide-necked aneurysms located in the ICA with parent vessels between 2.0 and 5.0 mm in diameter approved by FDA in 2019. However,there are many types of aneurysms ouside this range are considered challenging to treat using the standard surgical and endovascular methods. The PED may be a promising alternative for these otherwise challenging lesions. The off-label uses of flow diverters include blister-like aneurysms, distal circulation aneurysms, posterior circulation aneurysms, previously treated aneurysms, acutely ruptured aneurysms, dissecting aneurysms, and pseudoaneurysms. We will discuss the safety and efficacy of the PED in these off-label uses in this chapter. The off-label use of PED has a reasonable risk-to-benefit profile for appropriately selected aneurysms.

Keywords

Flow diversion · Pipeline embolization device
Off-label uses · Cerebral aneurysms

The treatment of intracranial aneurysms has undergone a few very significant paradigm shifts in its history. Surgical clipping served as the initial basis for successful treatment of these lesions. And then the endovascular therapy arose from the desire to reduce the invasiveness of therapy. The Guglielmi detachable coil (GDC) was developed in the 1990s. This represented a significant paradigm change, aneurysms were occluded not by the clip preventing ingress of arterial blood, but by coils invoking thrombosis by the action of Virchow's triad. The International Subarachnoid Aneurysm Trial (ISAT) began in 1994 found better results with endovascular coiling compared to surgical clipping [1]. The risk of death at 5 years was significantly lower in the coiled group than it was in the clipped group (11% vs. 14%). There was an increased risk of recurrent bleeding from

T. Liao (✉) · Y. W. Fan
Department of Neurosurgery, Kiang Wu Hospital, Macau, China

U. Wong
Department of Neurology, Kiang Wu Hospital, Macau, China

X. Lv
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_10

a coiled aneurysm compared with a clipped aneurysm, but the risks were small [2]. However, post-treatment aneurysm recanalization remains a major challenge. In one prospective, consecutive, multicenter European study consisting of 404 intracranial aneurysms in 390 patients treated with Nexus detachable coils (ev3-Covidien, Irvine, CA), complete occlusion was seen in 48% of aneurysms with a neck remnant in 22% and an aneurysmal remnant in 30% [3]. Much like in the context of surgical clipping, the morphology of an aneurysm and its proximity to other branches and perforators can pose unique challenges while planning for endovascular coiling. Aneurysms that are large (>10 mm diameter) and/or giant (>25 mm diameter), wide-necked (aneurysms with a dome-to-neck ratio of <2), and fusiform (aneurysms with no distinct neck, consisting of diffuse enlargement of a diseased vessel segment) are difficult to treat either by the endovascular or microsurgical treatment. The next significant paradigm shift after GDC is the remodelling technique by balloon and stent assistance. This technique facilitates improved packing density of the coils, reduces the risk of coil protrusion into the parent vessel, and stent-assisted coil embolization has empowered interventionists to tackle wide-necked/giant aneurysms. Initially, stent-assisted coiling was employed to prevent coil herniation into the parent vessel and allow denser packing of the aneurysm, which is known to correlate with a decreased rate of aneurysm recurrence and better long-term outcomes [4]. Computational fluid dynamics analyses suggested that placement of the stent in the parent vessel itself may alter flow within the aneurysm, potentially accelerating the rate of aneurysm thrombosis [5]. Thus, the idea of flow diversion was established, it was hypothesized that the stent disrupted blood flow from the parent artery into the aneurysm, and the stent provided a scaffold on which endothelial cells could grow, therefore isolating the aneurysm from the parent artery. Flow diverter (FD) needs to have greater metal coverage and decreased porosity, while maintaining pore density. A porosity of 70% is reported to be the ideal porosity for aneurysm occlusion [6]. It changed the pathophysiological understanding that many aneurysms do not in fact need to be completely occluded at the time of treatment. When reducing flow into and within the aneurysm, the aneurysm itself can either thrombose spontaneously or remodel. Advantage of flow diversions compared to traditional microsurgical or endovascular therapies is that aneurysms with no neck can be treated efficaciously, and the aneurysm itself, the most fragile part of the vasculature, does not need to be manipulated directly. As the paradigm of flow disruption, or hemodynamic decoupling, between "normal" vessel and "aneurysmal lumen," FD stents are now accepted as an integral option in the management of cerebral aneurysms.

In the 2010s, a single flow diversion stent was approved by the Food & Drug Administration (FDA) for use in the United States, the Pipeline Embolization Device (PED; ev3-Covidien, Irvine, CA). At the same time, Silk flow diverter (Balt Extrusion, Montmorency, France), Flow-Redirection Endoluminal Device (FRED; MicroVention, Inc., Tustin, CA), Surpass (Stryker Corp., Kalamazoo, MI), and p64R Flow Modulation Device (Phenox, Bochum, Germany) are commercially available in Europe, Asia, and South America. A new flow diverter of Nuva™ (TJWY Medical Company, Beijing, China) in a clinical trial will be launched soon in China (Fig. 10.1).

The PED is the first-generation flow diversion stent to achieve the optimum degree of stent porosity in a single device while being deliverable for the more tortuous intracranial vasculature. The PED has been supported by clinical trials, the Pipeline for Intracranial Treatment of Aneurysms

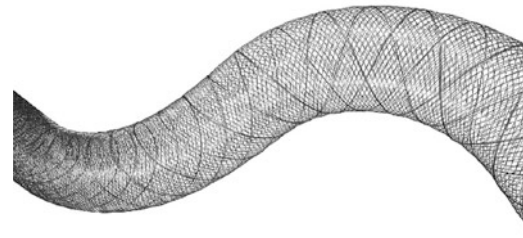


Fig. 10.1 Picture showing the Nuva™ flow diverter (TJWY Medical Company, Beijing, China)

Trial (PITA) [7] and the Pipeline for Uncoilable or Failed Aneurysms Trial (PUFS) [8] both demonstrated high complete aneurysmal occlusion rates (93.3% at 180 days and 86.8% at 1 year, respectively, increasing to 95.2% at 5 years for PUFS) as well as safety profile (6.4% major ipsilateral stroke in PITA and 5.6% major ipsilateral stroke or death in PUFS). In 2011, the FDA approved the PED for endovascular treatment in adults with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segment. After initial experience proved encouraging, it has been documented to have precipitated a significant change in practice pattern, confirming it as a disruptive technological advance [9]. As the popularity of the device grew and neurosurgeons gained more experience, its indications were extended. In 2019, FDA approved PED indications to complex wide-necked aneurysms located in the ICA attached to parent vessels between 2.0 and 5.0 mm in diameter.

PEDs implanted in ICA have been shown a low occlusion rate for the involved branches and the occlusion of side branches were clinically silent [10]. Supraclinoid internal carotid usage in unruptured aneurysms is the most accepted and is probably the least complication prone, due to the lower number of small eloquent branches with potential for occlusion. The flow diverter (FD) has become a separate entity from the stent, with a different purpose and set of indications. Nowadays, FD is being more broadly applied to blister-like aneurysm, distal circulation aneurysm, posterior circulation aneurysm, previously treated aneurysm, acutely ruptured aneurysm, dissecting aneurysm, and pseudoaneurysm.

10.1 Blister-Like Aneurysm

Blister aneurysms are a rare but well-recognized form of cerebral vascular lesions. Comprising less than 2% of all intracranial aneurysms [11], they are typically found on the dorsal or dorsomedial wall of the internal carotid artery (ICA). With a characteristic thorn-like appearance on angiography, blister aneurysms have the fragile wall, which not only reflects the unique pathology of these lesions but also predetermines their high rupture risk, aggressive clinical course, and tendency for rapid growth and progression. In the most common scenario, a blister aneurysm will be diagnosed after an episode of subarachnoid hemorrhage. Being initially small, it will substantially enlarge within days of presentation, reaching finally a shape much similar to that of its saccular counterparts [12]. Commonly, the end result is a rerupture with potentially catastrophic consequences for the patient.

Although most authors agree that blister aneurysms are either dissecting or false lesions, their optimal management remains unknown. The alternative treatment modalities for blister aneurysms are:

1. Reconstructive Techniques
   Surgery: Primary clipping (including encircling clips), wrapping, clip-wrapping, wrap-clipping, and direct suturing.
   Endovascular therapy: Primary coiling, stent-assisted coiling, telescopic stenting (stent-in-stent technique), and flow diverters.
2. Deconstructive Techniques
   Parent artery occlusion (PAO): Surgical or endovascular means with or without bypass surgery.

Management of blister aneurysms is associated with a high overall rate of mortality and morbidity [13]. The main causes for this include the small size and broad neck morphology along with the prominent fragility of such lesions, features that often lead to intra-procedural rupture when traditional surgical or endovascular techniques such as clipping or primary coiling are to be applied [13, 14]. Even if an initial intervention proves successful, subsequent regrowth requiring further treatment has been commonly reported [15]. Other factors contributing to the grim prognosis of blister aneurysms include a commonly grave clinical presentation as well as delays in an appropriate diagnosis.

Traditionally, surgery has been advocated as the first-line treatment. Primary clipping, wrap-

ping, wrap-clipping, or even carotid artery sacrifice (with or without a bypass) have all been tried. However, results have always been far from satisfying, often making neurosurgeons reluctant to operate on such cases. Ogawa et al. described an operative aneurysmal rerupture risk of 38% with direct aneurysm clipping, aneurysmal segment trapping, or aneurysm wrapping. Of this operative rerupture cohort, only 13% had good clinical outcomes, and 53% died as a result of surgery [12]. Other single-center series of open surgical management of ruptured blister aneurysms reported 55% and 41% operative rerupture rates, respectively [14, 16].

A meta-analysis including endovascular deconstructive parent-vessel occlusion treatment of ruptured blister aneurysms found a significantly higher procedural ischemic infarct complication of 29%, versus only 5% for endovascular reconstructive approaches with FD or for other endovascular methods, including stent-assisted coil occlusion, balloon-assisted coil occlusion, or overlapping placement of traditional intracranial stents, with similar rates of perioperative morbidity, and long-term good outcomes [17].

Initial attempts at endovascular reconstructive treatment with primary coiling of blister aneurysms have been disappointed also [18]. A high risk of intra-procedural rupture and coil protrusion or migration were problems commonly encountered due to the small size, their fragile nature, and difficult catheterization access to the sac without perforation [13]. Additionally, the lack of a true wall often allowed for posttreatment progression and rerupture [19]. As a consequence, most authors advocated that blister aneurysms are unsuitable for endovascular treatment and should therefore be left to surgery.

Stent-assisted coiling became the new trend in the field. The procedure is carried out either by first placing the stent and then introducing coils through its struts (trans-stent coiling) or by catheterizing the aneurysm sac and deploying the stent over the microcatheter prior to coiling (jailing technique). Facilitating stable intrasaccular coil deployment while at the same time reinforcing the underlying diseased arterial wall, stent-assisted coiling promised to provide a safe and reliable therapeutic alternative [20]. However, it was soon realized that results, even though better than those of surgery, were far from optimal. Intraoperative complications, mainly bleeding, were encountered in up to 17% of cases, while the risk for recurrence of the lesion, need for further treatment and postoperative repeat hemorrhage were reported at 65, 50, and 13%, respectively [13]. Most authors now use stent-assisted coiling as a preliminary means to achieve a certain degree of protection until definite treatments, in the form of some other techniques, can be instituted.

As blister aneurysms are regarded by many as pseudoaneurysms, FD is the only endovascular technique capable of actually reconstructing the vessel wall and sealing off any underlying defect [21]. This results in thrombosis of the lesion and effect augmented by endothelial proliferation along the length of the implanted stents. However, the off-label use of FD to treat ruptured blister aneurysms is associated with high rates of complete occlusion and good long-term neurological outcomes in most patients. Linfante et al. treated 10 patients with ruptured blister aneurysms of the supraclinoid ICA using a PED, which resulted in the immediate occlusion or near occlusion in 90%, and the follow-up DSA showed the 100% complete occlusion [22]. Of 62 ruptured blister aneurysms treated with FD in a recent meta-analysis, 86% achieved good clinical outcomes, and 17% suffered procedural complications including an almost 8% risk of procedural ICH [17].

Major concerns with the use of FD for the treatment of blister lesions include an even more prominent need for antiplatelets as well as the fact that such an approach does not guarantee protection from postoperative progression and rerupture. Regarding the latter, and despite reports of a marked decrease in intra-aneurysmal flow on the intraoperative already angiogram, hemodynamic stress upon the lesion theoretically remains at least for a few days [19]. The most serious problem that occurs after the placement of FD is the continued existence or growth of blister aneurysms. For example, in the 2016 report by Linfante et al., a blister aneurysm of the

supraclinoid ICA remained patent and tended to grow, despite the placement of three FDs in two procedures, but rerupture did not occur in this patient. However, the patient died of severe vasospasms, despite the administration of a dual antiplatelet regimen and growth of the lesion [22]. A valid alternative possibly addressing the whole issue is the combination of FD with coiling, which is my preference in practice. Figure 10.2 shows an acute ruptured blister aneurysm treated with PED recently. The initial plan was one PED with coiling in the sac. Two PEDs was deployed as the alternative to unstable cathetering in the aneurysm sac during the deployment of PED. Only one antiplatelet drug was used after the procedure since the bleeding existed after two PEDs telescopic stenting which was stopped by reversion of anticoagulation. Kim et al. have

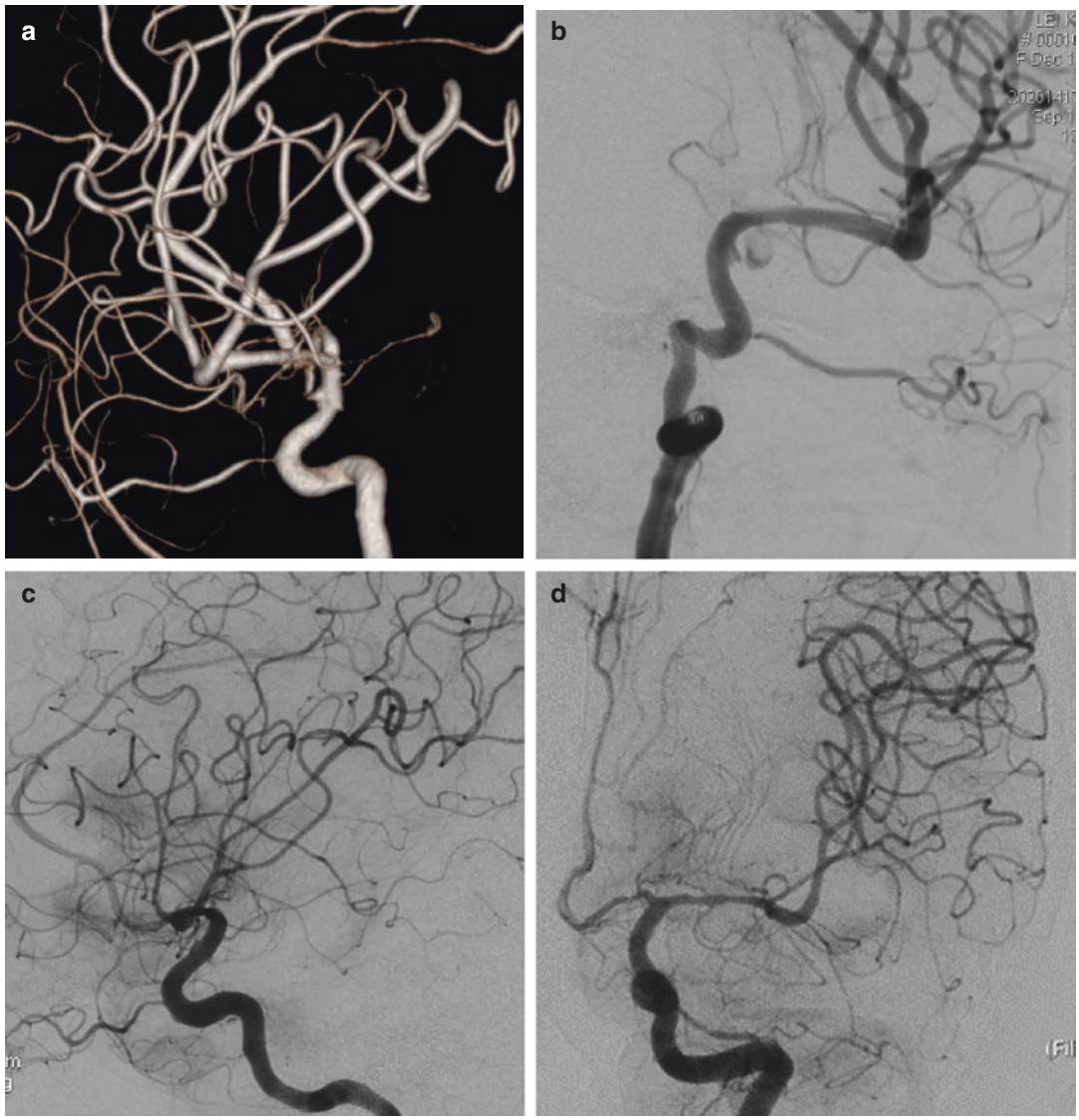


Fig. 10.2 A 27-year-old patient with ICA blister aneurysm ruptured (**a**) in poor grade SAH showed bleeding during treatment with 2 PED shield (**b**) and was stopped after reversion of heparin. Follow-up angiogram 6 days later showed aneurysm occlusion without in-stent thrombosis or occlusion of branch (**c**, **d**), even only a single antiplatelet with ASA was used without inhibitors of IIb/IIIa glycoproteins

reported favorable results with stent-assisted coiling as a primary treatment augmented by deployment of a second flow diverting stent if needed (i.e., postoperative progression of the lesion) [23]. In cases with extremely small lesions where coil deployment is perceived as carrying a significant risk, the reverse route can also be followed: telescopic stenting and subsequent transstent coiling should the lesion further grow to allow that [19].

During the past few years, clinicians' interest in blister aneurysm has been renewed with the introduction of endovascular modalities in everyday practice. Among all the different available approaches, FD seems lately to be gaining ground, showing promising results. Of course, until consensus has been reached, blister aneurysms are still to be treated on a case-by-case basis.

10.2 Distal Circulation Aneurysm

Distal cerebral circulation aneurysms may be defined as those located beyond the circle of Willis. They may be either saccular (at the level of bifurcations mainly), fusiform, or dissecting aneurysms. They are rare, representing approximately 1–9% of all intracranial aneurysms. Ruptured distal anterior cerebral aneurysms (DACA) cause intracerebral hemorrhage (in addition to SAH) in more than one-half of cases and are associated with worse outcome after rupture when compared with aneurysms in other locations [24]. Both microsurgical clipping and endovascular coiling of aneurysms of the distal cerebral circulation can be associated with high morbidity. Lahaska treated 258 ruptured DACA by clipping with 15% morbidity and 84 unruptured DACA clipping with 12% morbidity [24]. Meanwhile, complications associated with endovascular treatment of these aneurysms are not rare and probably related to a higher level of technical difficulty because of distal location, morphology (with frequent partial incorporation of the parent artery in the neck), and higher association with anatomic variations. These challenges may explain the relatively higher procedure-related complication rates compared with aneurysms in more common locations. Sturiale et al. reviewed 16 studies with 279 distal cerebral circulation aneurysms (185 ruptured) treated by coiling, procedure-related morbidity rate was 8% and mortality rate was 9% [25]. Thus, making FD a potentially attractive alternative. However, off-label use of FD in vessels smaller than 2.5 mm may be technically challenging, as these systems are stiffer and have a higher profile than conventional stents, and require larger caliber microcatheters, which can cause proximal spasm and inability to deliver the devices to the required distal location. The other potential concerns are vessel injury, acute stent thrombosis, delayed branch vessels occlusion, and in-stent stenosis.

Successful delivery of FD needs more robust and versatile catheter support systems. From this arose a newer generation of catheters, the distal intracranial catheters (DICs) or intermediate catheters (ICs), which are designed with the flexibility to safely travel further into the cranial circulation. Initial versions of these catheters, including Neuron (Penumbra, San Leandro, California, USA), helped move support systems from the proximal cervical circulation to the distal cervical vessels and proximal intracranial vessels [26]. The Navien (Medtronic, Minneapolis, MN, USA), with additional advances in catheter technology, allowed for the placement of 5-Fr and 6-Fr support catheters distal into the intracranial anterior and posterior circulations [27]. Further improvements in catheter technology have focused on atraumatic distal tracking, stability in distal position, and resistance to catheter deformation. The AXS Catalyst 5 distal access catheter (Cat5; Stryker, Freemont, CA, USA) is a novel multi-durometer intracranial support catheter [28]. And Syphontrak (Codman Neuro, Raynham, MA, USA) is the newest. Colby et al. have a series reports of their institutional experience with the DICs. Compared to earlier experiences with the Navien, both the Catalyst 5 and the Syphontrak cases utilized statistically significantly less fluoroscopy time, despite similar

numbers and sizes of PED. The last 2 DICs were routinely positioned in the distal cavernous ICA and even tracked the catheter to the supraclinoid ICA and M1 without evidence of vessel injury or significant flow-limiting vasospasm. In addition to serving as a support system, the DIC can also be used as an instrument or advanced technique for augmenting PED Flex deployment with the ability of tracking and pushing. DICs can be tracked over the 0.027″ microcatheter with ease to bump and foreshorten the proximal end of the PED Flex in order to improve vessel wall apposition if needed. The DIC also can be tracked over the microcatheter into the PED Flex for endoluminal access in cases needing multi-device deployments or balloon angioplasty. The use of verapamil was their institutional practice patterns to utilize IA vasodilation prophylactically rather than as a reactive measure to vasospasm [29]. And they used the Via (Sequent Medical/MicroVention; Terumo, Tustin, California, USA) microcatheter with its increased column strength and stiffness facilitated bringing the PED through regions of vessel tortuosity and deploying it predictably without the accordion effect of the Marksman in distal locations [30]. After successful delivery, PED can be deployed by more unsheathing rather than pushing to minimize the force buildup during deployment and mitigate the possibility of translating push force into wire perforation [31]. Another choice to improve delivery and deployment is low-profile FD, dedicated to small vessels, which have been lately developed. The first has been the small-sized version of the dual-layer Flow Direction Endoluminal Device (FRED) (MicroVention, Aliso Viejo, California), called FRED Jr. More recently, the P48MW Flow Modulation Device (Phenox GmbH, Bochum, Germany) has been launched. Both FRED Jr. and P48MW are delivered through a 0.021-inch microcatheter. Very recently, the Silk Baby Vista (Balt Extrusion, Montmorency, France) has been launched in Europe; this is the only FD delivered through a 0.017-inch microcatheter. During PED deployment, extreme attention has to be paid not to perforate small, distal branches with the inner wire as it is pushed forward while unsheathing the stent. FRED Jr. delivery wire is shorter and it remains inside the stent during its deployment, thus minimizing the risk of perforation; however, the drawback of this system probably is the inferior stability. Interestingly, the P48 inner wire can be moved independently from the implant, potentially improving safety and stability during deployment.

Heightened concern for acute stent thrombosis associated with PED deployments in small caliber vessels is justified. In the series of 67 PEDs deployed in 57 patients, Bender et al. found 5 cases (7.5%) of intra-procedural thrombosis in the stent, higher than in their overall experience with anterior circulation PED (4%), and treated successfully with escalating doses of intra-arterial abciximab [31]. The other institutions prefer alternative glycoprotein IIb/IIIa inhibitors such as eptifibatide or tirofiban because of their shorter half-lives [32]. The experience of Bender also suggests that platelet plugging may be more difficult to reverse in small caliber vessels. In their overall PED series of 30 patients treated with intra-arterial abciximab, only 4 (13%) went on to experience symptomatic ischemic infarcts. In the distal series, 2 of 5 patients (40%) had major strokes [31]. In Ravindran series, 5 patients (10%) experienced a transient parent artery occlusion immediately after FD deployment, resolved with intra-arterial glycoprotein IIb/IIIa inhibitor, with no clinical deficits experienced [33].

Heightened concern for symptomatic delayed stent thrombosis in distal small vessels is not justified. Several studies reveal asymptomatic in-stent stenosis with mild associated flow limitation in small vessels aneurysms treated with PED [31, 33, 34]. Significant reduction in parent vessel caliber at the proximal end of the stent but not the distal end of the stent was found in Bender series. They believed that there was a tendency for the device to adopt a similar diameter across its length in small vessels, and was restricted by the smaller (typically distal) vessel diameter and results in a greater reduction in the larger (typically proximal) diameter [31].

However, the risk of perforator stroke secondary to FD coverage of perforator-rich arterial seg-

ments, particularly the A1 and M1, has thus largely dissuaded the use of FD for aneurysms at these locations. In Ravindran series [33], 76.1% aneurysms had associated perforator vessel coverage by the FD, and 88.9% bifurcation aneurysms with side branch coverage. Despite this situation, there were only 3 complications related to perforator or side branch coverage, and all neurologic deficits were transient. These results suggest that it is safe to cross side branches with the FD. In MCA bifurcation aneurysms treated with FD, the risk of cortical infarction secondary to bifurcation branch coverage seems to be subclinical. In Iosif et al.'s study of MCA bifurcation aneurysms, although angiographic narrowing or occlusion of covered branches was observed in 29 of 63 patients at 6-month follow-up, only 2 cases of branch occlusion were symptomatic. Furthermore, at 12-month follow-up, only 10 cases of branch narrowing were observed, all of which were asymptomatic [35]. In my practice on distal aneurysm treated with PED, only one case was found late occlusion of the covered branch (Fig. 10.3) but no symptom.

With the 4.5% major stroke and 1.5% mortality, complete occlusion was observed in 42 (89%) cases of Bender's study at on average 10 months after embolization [31]. Occlusion outcomes of other studies from 77.8% to 100%, are similar to the aforementioned small-caliber vessel series [33, 36, 37].

Antiplatelet therapy decisions to balance thromboembolic and hemorrhagic risk are always challenging, perhaps more so when treating aneurysms arising from small vessels. In our institute, P2Y12 test is performed routinely for all patients undergoing PED and adjust antiplatelet regimens based on its results. Meanwhile, some authors do not test P2Y12 routinely. Bender et al. reported the largest series of clopidogrel hyporesponders (P2Y12 > 200) to undergo PED, in which rates of ischemic complications are on a par with the overall PED literature (2/52 cases, 4%) [38]. However, given the increased risks of acute stent thrombosis, this population may be appropriate for clopidogrel alternatives, such as prasugrel and ticagrelor, with more predicable pharmacodynamics.

FD for distal circulation cerebral aneurysms represents a safe and effective application of flow diversion technology. The small-vessel PED delivery and deployment technique differs from its on-label use in ICA. Improvements in robust polyaxial catheter access platforms have facilitated the use of FD in the distal location of cerebral artery. Heightened vigilance for the prevention and management of acute stent and vessel thrombosis is warranted in these cases. Despite the distal location, issues related to vessel trauma and delayed occlusion are uncommon and should not limit use of this technique.

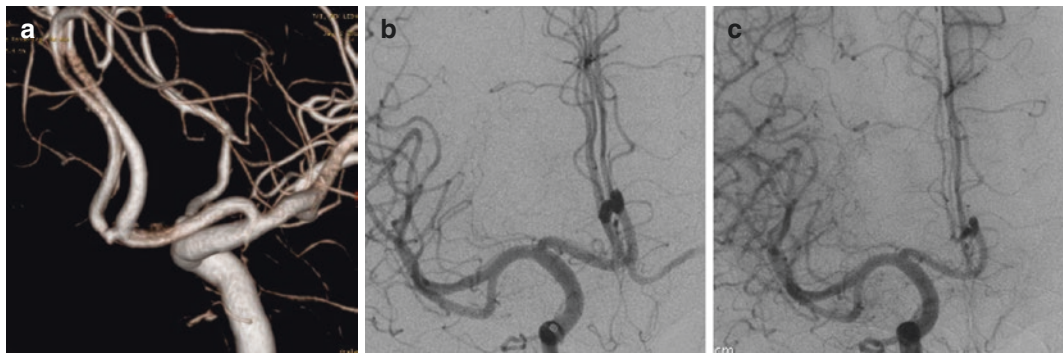


Fig. 10.3 A 66-year-old patient presented with SAH and the first angiogram negative, follow-up angiogram 2 weeks later revealed anterior communicating artery blister aneurysm (**a**), which was treated with PED deployed from right A1 to left A2. Aneurysm was occluded immediately with distal ACA patent (**b**). A follow-up angiogram 27 months later revealed the asymptomatic occlusion of right A2 (**c**)

10.3 Previously Treated Aneurysms

Conventional therapies for intracranial aneurysms are microsurgical clipping and endovascular coiling. Two randomized, controlled trials have evaluated these 2 methods and looked at recurrence and retreatment rates. In the International Subarachnoid Hemorrhage Trial (ISAT), 9.0% of patients treated with coiling and 0.85% of patients treated with microsurgical clipping had to be retreated due to recurrence [39]. In the Barrow Ruptured Aneurysm Trial (BRAT), the retreatment rates at the 3-year follow-up were 13% and 5% for coiling and clipping, respectively [40]. To reduce the recurrence associated with conventional treatments, several investigators have studied the safety and efficacy of the FD as a treatment for recurrent aneurysms after previous coiling, stenting, or clipping. Dornbos III et al. reviewed a total of 13 cases in which patients underwent secondary placement of a PED for aneurysm recurrence following prior treatment with another modality. The PEDs were used to treat aneurysm recurrence or residual following endovascular coiling in 7 cases, FD in 2, and microsurgical clipping in 4. The rate of complete occlusion was 80% at 6 months and 100% at 12 months in these patients who underwent PED placement following failed endovascular coiling; there were no adverse clinical sequelae at a mean follow-up of 26.1 months [41].

Daou et al. looked at subsets of patients with recurrent aneurysms that were previously coiled and previously stented [42, 43]. One study followed 32 patients with single lesions who had a recurrence of previously coiled aneurysms, and found a total rate of complete and near-complete occlusion of 86.7%, a complication rate of 3%, and no mortalities [42]. In a series of 21 previously stented aneurysms, the complete occlusion rate after PED placement was found to be 55.6% and the complication rate was 14.3% [43]. In this second study, the authors compared these results with a group of patients who underwent PED placement for aneurysms not previously stented. They concluded that the PED was less effective in managing previously stented aneurysms compared with non-stented aneurysms, and can also be associated with a higher complication rate in the previously treated aneurysms. Similar result was found in a series of 20 patients with recurrent aneurysms successfully treated with PED in the presence of preexisting stents, both FD and reconstructive stent. Cases with in-dwelling stents present additional technical challenges, as evident from the greater number of devices used, longer procedural time, higher radiation exposure, and balloon angioplasty rate. Salvage FD offers a good chance of occlusion (56% complete occlusion at on average 13-month follow-up angiography) with acceptable complication rates (10%), including 1 mortality (5%) [44].

In our institute, FD placement is the first choice for recurrent aneurysms not previously stented (e.g., the case in Fig. 10.4), but re-coiling is a preference to aneurysm treated with stent-assisted coiling previously since technical challenge of a salvage FD case revolves around the indwelling stent. In Fig. 10.5, the recurrent case after 3 times coiling performed the flow diversion and achieved complete occlusion finally.

The indwelling stent poses an obstacle both to delivery and deployment. Given the large cell size and the proximal tines at the parent vessel wall, it can be difficult to stay in the true lumen while navigating across an indwelling stent. A FD deployed through a cell in an indwelling stent will initially appear to have a restricted opening. In addition to hypervigilance for any catching of the wire while crossing the indwelling stent, techniques that can be used to ensure deployment within the lumen of the parent vessel include: crossing with a J-tip wire, compliant balloon inflation following crossing, and visualization on DynaCT after crossing. Crossing an indwelling stent is more difficult when the proximal end/stent tines are located in a vessel bend, such as the anterior genu. The indwelling stent also creates challenges during FD deployment, given the risk of catching on the distal end of the indwelling device and anchoring the device to be implanted, leading to stretching and incomplete opening of the device. It should be deployed directly in its final location and rely more on balloon angioplasty for device opening instead of the drag and drop tech-

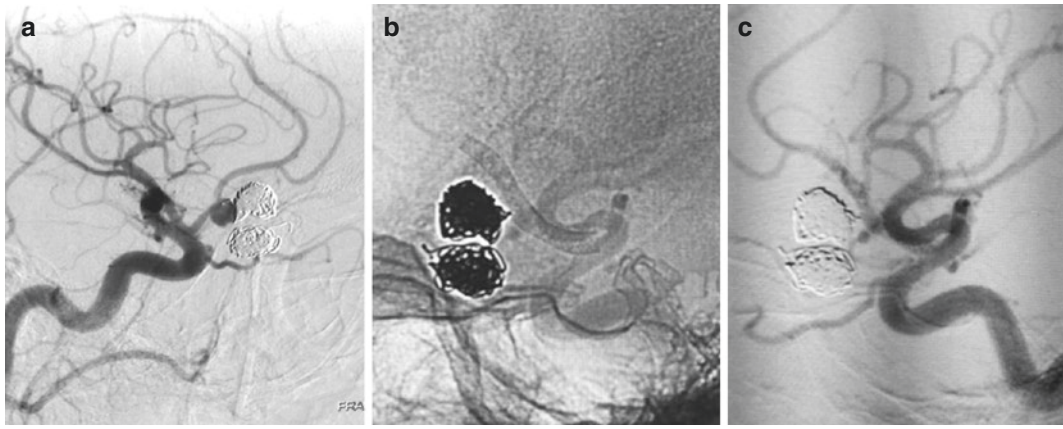


Fig. 10.4 A 40-year-old patient presented with recurrent A1 aneurysm after coiling (**a**), retreated with 1 PED (**b**). Follow-up angiogram showed complete occlusion 6 months later (**c**)

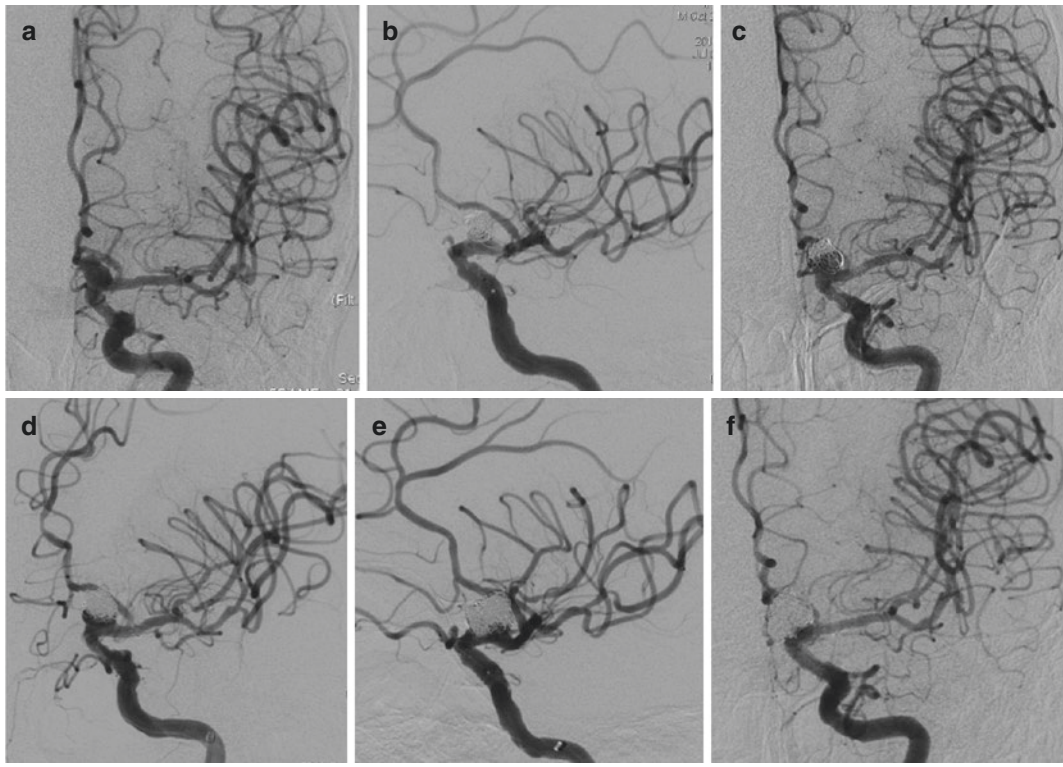


Fig. 10.5 A 73-year-old patient with left ICA asymtomative wide neck aneurysm (**a**), performed stent-assisted coiling first (**b**). Angiogram 9 months later revealed the enlargement of aneurysm, retreatment was performed with coiling (**c**). Follow-up angiogram another 6 months later showed the enlargement again and third coiling performed (**d**). Retreatment with flow diversion 6 months after the third coiling with neck residue (**e**). Final angiogram 27 months from the first treatment showed the complete occlusion (**f**)

nique. The rate of balloon angioplasty in salvage cases was 40% as compared with 13% in all anterior circulation PED cases [44].

A common mechanism of aneurysm persistence after FD is malapposition between the stent and vessel wall, which allows blood flow to insin-

uate between the stent and vessel, continuing to fill the aneurysm, a so-called "endoleak" [45]. The risk of endoleak is greater in salvage FD cases given how a poorly endothelialized preexisting stent may prevent contact between the newly placed FD and vessel endothelium. So the new FD should be deployed to cover the preexisting stent both proximally and distally in salvage cases. Following successful deployment of salvage PED, heightened thrombogenicity of the multi-stent construct is a concern at every follow-up time point. Fischer et al. observed that placing one stent inside another will always delay the endothelialization process and that extended or lifetime DAPT should be considered for these patients [46].

In another more difficult series, PED retreatments were performed for 6 anterior communicating artery region recurrent aneurysms after surgical clipping. Occlusion rate was 83% without complication [47]. Promising results were found in a series of 24 patients who underwent PED placement for previously clipped and coiled aneurysms. The complete or near-complete occlusion rates of previously treated ruptured and unruptured aneurysms were 94.4% at 6 months and 93.3% at 12 months. These investigators also did not observe any severe procedure-related complications [48].

Safety and effectiveness of FD as a salvage treatment following failed coiling or clipping was confirmed in these limited series. Positive results suggest that ruptured complex aneurysms might be deliberately treated 2 times: immediate subtotal coiling (with or without balloon assistance) and planned flow diversion after the acute phase. This strategy will be discussed in detail in the following chapter "Ruptured Aneurysm." FD treatment results for recurrence of previously stented aneurysms are not encouraging, the presence of a stent raises technical challenges. Retreatment is reserved for recanalized stent-coiled aneurysms with a history of prior rupture or progressive symptoms, typically from mass effect. By contrast, retreatment of previously FD treated aneurysms is commonly for persistence or failure to occlude and occasionally for device foreshortening. Continued patency of aneurysm following coverage by FD is dependent on several factors, including the degree of metal coverage, device-to-wall apposition, thrombogenic disposition of the patient, degree of individual intimal reactivity. Given the perceived ease of re-FD some authors have a low threshold for retreatment [45]. Since occlusion outcomes continue to accrue for up to 5 years after PED placement, some authors wait to complete DPAT tapering and have performed re-FD cases at an average of 18 months after the first procedure [44]. There is a need for larger studies to assess the safety and efficacy of the FD in treating such cases.

10.4 Posterior Circulation Aneurysms

Posterior circulation aneurysms are a heterogeneous disease group including sidewall, bifurcation, dissecting, saccular, and fusiform aneurysms. The natural history of the different aneurysm types is not well known. As compared with anterior circulation aneurysms, there is a higher proportion of non-saccular morphologies, which commonly present with a variety of different symptoms ranging from asymptomatic and incidental findings on routine imaging, posterior circulation ischemic strokes, brainstem compression, cranial nerve palsies (most commonly V–VIII), obstructive hydrocephalus, and hemorrhage [49]. The natural history of these lesions is fateful with a review by Shapiro et al. suggesting that mortality could be even higher at 43% [50]. If left untreated they carry significant morbidity with growth of these aneurysms seen in 46% of patients over a median interval period of 8.5 years [49]. Saccular aneurysms of the posterior circulation are at higher risk of rupture than their anterior circulation counterparts and, when ruptured, present in worse clinical grade. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), the rupture rate for posterior circulation aneurysms >7 mm was 3–10% a year [51]. This creates an impetus toward elective treatment, but existing treatments are limited by morbidity and efficacy. Surgery for these lesions—because of the deep exposure and proximity of cranial nerves

and perforating arteries—carries high morbidity [52, 53]. Endovascular coiling has lower morbidity but comparatively inferior occlusion outcomes [54]. Residual posterior circulation aneurysms remain at significant rupture risk and retreatment of these lesions is technically challenging.

The off-label use of FD may be an alternative for these challenging lesions that avoids high morbidity of open surgery while sufficiently excluding the aneurysm. However, overall poor outcome or death was seen in 40% of patients treated for fusiform posterior circulation aneurysms in a large series [55]. A similar trend has been described in a meta-analysis of intracranial FD, which included 29 reports, 1451 patients and 1654 aneurysms. Ischemic strokes and perforator infarctions were significantly higher in the posterior circulation, although there were no difference in subarachnoid hemorrhage and intracranial hemorrhage rates [56].

The main risk factor of the FD treatment in the posterior circulation is due to the unique characteristics of the cerebral vasculature and aneurysms arising in this location. Specifically, numerous unforgiving perforator vessels arise in this area and supply brainstem structures; the occlusion of these perforators can lead to significant disabilities. It is generally believed that covered branch arteries will remain patent provided that flow is maintained through the FD. One theory is that demand phenomena continue to draw blood into the covered branch. Phillips et al. assessed the safety of PED placement in 32 patients with posterior circulation aneurysms. The aneurysm occlusion rate achieved 96% of patients followed up more than 1 year. But perforator infarctions rate was 14% of the 21 patients who had basilar artery aneurysms. Clinical perforator infarction rates may be higher when the PED is placed within the basilar artery compared with the ICA [57]. More recent studies have demonstrated good outcomes with FD. Munich et al. present good outcomes in 12 patients with vertebrobasilar fusiform aneurysms treated with the PED. The complete aneurysm occlusion rate was 90% without thromboembolic complications [58]. None of the patients in Marcus series developed flow restriction of a covered PICA with one PED positioned proximal to the vertebrobasilar junction in 10 of 11 patients. Only 1 patient experienced a PICA occlusion during PED placement and developed an associated region of diffusion restriction on postoperative MRI [59].

The patient shown in Fig. 10.6 presented with right cerebellum infarction, angiogram 1 month later revealed the fusiform aneurysm involved PICA. Flow diversion was achieved with PICA patency at the angiogram after 1 PED was deployed to cover the PICA origin. Dual antiplatelet treatment was stopped 1 year later when angiogram showed complete occlusion of aneurysm with PICA patency. The patient had been follow-up for 3 years without any thromboembolic complications. Strict adherence to adequate platelet inhibition to avoid thromboembolic complications and also vigilant monitoring of patients receiving antiplatelet therapy to avoid hemorrhagic complications.

The other risk factors are multiple overlapped PEDs inserted, clopidogrel resistance, poor apposition of the PED to the aneurysm wall, aneurysm morphology, size, and clinical presentation. Natarajan et al. used an average of 1.7 devices to treat 12 posterior circulation aneurysms with an average size of 13 mm and encountered 1 major complication, a pontomedullary infarct attributed to occlusion of a distal vertebral perforating artery [60]. In contrast, poor result was found in their previous report on 6 patients who underwent PED treatment: 4 (66%) were basilar fusiform aneurysms and 3 had pretreatment strokes as demonstrated by MRI. An average of 5.3 ± 2.9 PEDs without adjunctive coiling were used resulted 83.3% brainstem ischemic events and 33% aneurysms reruptured. During the follow-up period, 4 patients (67%) died, 1 was disabled with mRS score 5, only 1 recovered to mRS score 0 [61]. The author attributed these improved results to the following factors. First, basilar fusiform aneurysms and pretreatment ischemic infarction patient was excluded; second, critical attention to the antiplatelet regimen; third, the number of PED was limited; final, adjunctive

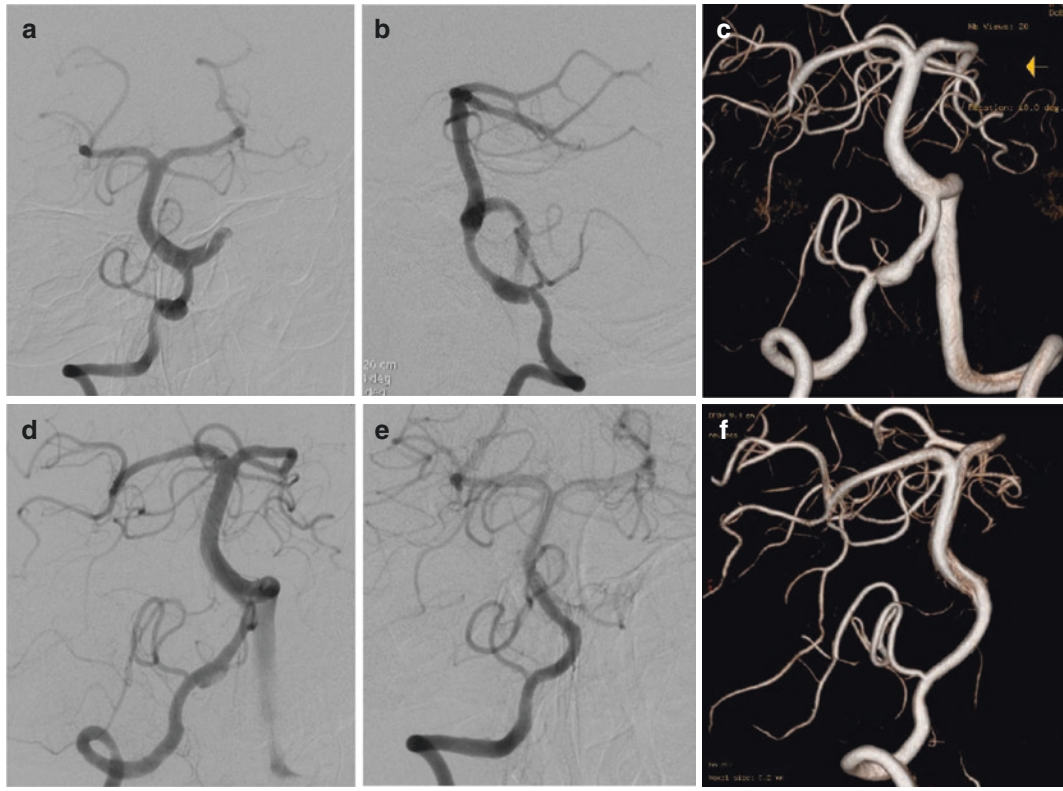


Fig. 10.6 A 43-year-old patient presented with right cerebellum infarction, angiogram 1 month later revealed the fusiform aneurysm involved PICA (**a**–**c**). Flow diversion was achieved with PICA patency at the angiogram after 1 PED was deployed to cover the PICA origin (**d**). Follow-up angiogram 1 year later showed complete occlusion of aneurysm with PICA patency (**e**, **f**)

coiling with FD in the most saccular component of the aneurysm, served as a scaffold to organize thrombi [60]. Bender et al. present the large single-center experience about 59 embolization procedures performed on 55 patients. Morphology was saccular (45%), fusiform (29%), or dissecting/pseudo-aneurysms (25%). Most of the aneurysms (62%) arose along the vertebral artery. 1 PED was placed in 85%; and coiling was performed in 17% of cases. Complete occlusion rate was 78% at 12 months with 8% complications (all stroke). Fusiform or dissecting morphology and large or giant aneurysm size were predictors of aneurysm persistence on multivariate logistic regression. The resolutions of reduced ischemic risk were as follow: first, in the distal basilar artery, the degree of metal coverage was titrated by using devices with relatively short length and oversized diameter to reduce perforator infarction; second, maintain systemically heparinized for 24 h post-embolization and on dual antiplatelet treatment for life (Prasugrel was used rather than Clopidogrel for basilar apex-region aneurysms); Third, single device was used whenever possible, choosing longer and large diameter devices in the fusiform segment, and adjunctive coiling to expedite occlusion rather than telescoping multiple devices [62].

The most difficult and risky morphology in posterior circulation aneurysms with FD treatment is nonsaccular aneurysms. Occlusion rates were lower (57% at last follow-up) in a large single center series focused on the nonsaccular aneurysms [63]. The aneurysms were classified as either dolichoectatic, fusiform, or transitional according to the classification of Flemming et al., with the definition of each subtype based on the following imaging appearance [49]:

1. Fusiform: Dilation >1.5 times normal involving a part of the vertebral or basilar artery, without any discernible neck and with any degree of tortuosity (Fig. 10.7).
2. Dolichoectatic: Uniform dilation >1.5 times normal involving the entire basilar artery, vertebral artery, or both with any degree of tortuosity (Fig. 10.8).
3. Transitional: Uniform dilation of an entire arterial segment >1.5 times normal involving the vertebral artery, basilar artery, or both with a superimposed dilation of a portion of the involved arterial segment (Fig. 10.9).

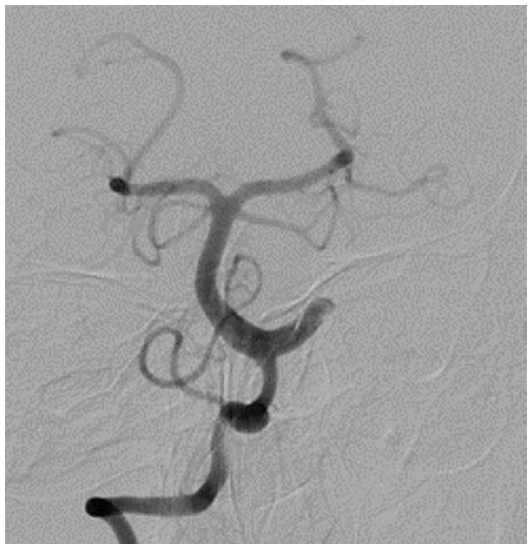


Fig. 10.7 A patient with fusiform aneurysm of the right vertebral artery presented with ischemia attack

In this cohort, the transitional and fusiform types were more likely to be symptomatic and dolichoectatic aneurysms appeared more benign in clinical course. The annual risk of rupture for fusiform and transitional aneurysms was 2.3% while that of dolichoectatic aneurysms was 0.4%. Compressive symptoms were seen in 22% of patients and importantly, 7.5% who did not initially have compressive symptoms developed them. Aneurysm growth was associated with the development of compressive symptoms, which was statistically associated with the transitional and fusiform subtypes, and also affects mortality, with a 5 year 56.6% mortality of enlarging aneurysms compared with 3.7% of stable aneurysms [64]. Given the prognosis, it is no wonder then that management options have been aggressively sought. The author believed that early management prior to infarction or compressive symptoms was extremely important to achieve a good clinical outcome. Strict antiplatelet regimen was also important to avoid in-stent thrombosis or thromboemboli. And direct oral anticoagulants (2 × 100 mg dabigatran daily) were added for patients with large fusiform or transitional type aneurysms involving the basilar trunk. Adjunctive

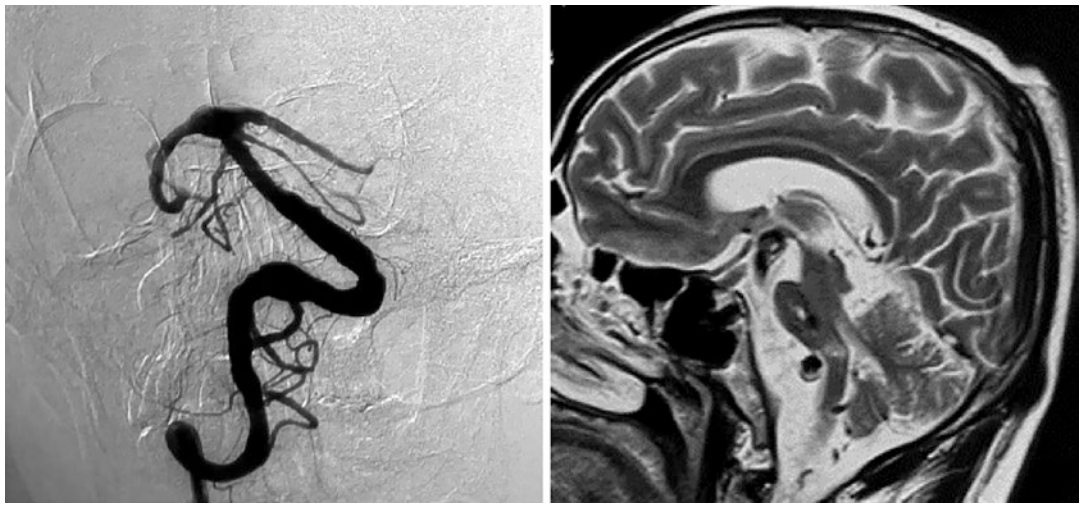


Fig. 10.8 A patient with dolichoectasia of the vertebrobasilar artery presented with symptoms of compression of brain stem. MRI revealed the compression of brain stem without mass

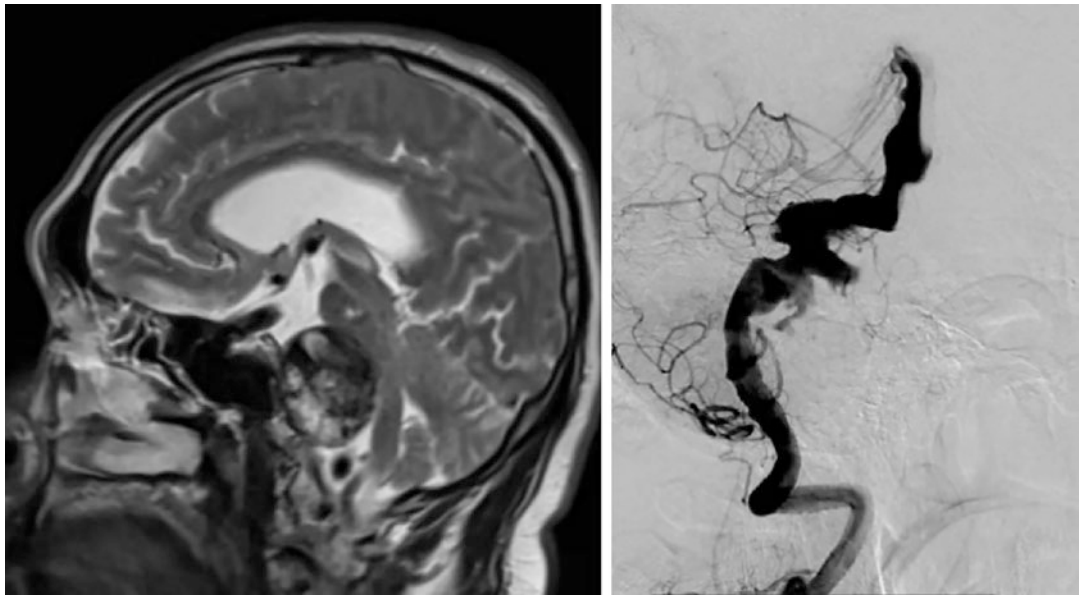


Fig. 10.9 A patient presented with symptoms of mass effect from vertebrobasilar transitional aneurysm. MRI revealed the partially thrombosed and superimposed dilation portion of basilar artery with compression of brain stem

coiling may be useful but did not appear to be necessary and needed to be based on individual anatomy. The number of FD required was based on the longitudinal extent of the disease. Because endothelialization commences from the site of contact with the parent artery, it was important to land the FD in a portion of the vessel that demonstrates a normal appearance, both at the proximal and at the distal end. And longer diseased segments will require a much longer time to endothelialize. This means that a tailored approach is required with some patients likely to require lifelong dual antiplatelet therapy (DAPT). The author prefers telescoping from proximal to distal with about 30% overlap of the implanted FD. The diameter of the most proximal stent should be slightly larger than the diameter of the landing zone. Subsequent FD should have the same or larger but never smaller diameters, since smaller diameters will result in FD displacement. Since the PED for less and p64 for more coverage, a combination of PED and p64, devices with nonmatching braiding patterns, will result in more coverage than telescoping of devices of the same kind. The procedure is usually stopped as soon as a hemodynamic effect becomes visible through repeated catheter angiography. The patient returns for repeat angiography and MRI after approximately 6–12 weeks to observe for flow changes and changes in size of the aneurysm. If no significant flow redirection has occurred compared with the pretreatment angiography, then more FDs are placed inside the construct. Gradual vessel reconstruction obviously allows for the development of collateral brain stem circulation, eventually with no opacification of pontine basilar artery branches but without signs of brain stem ischemia, neither clinically nor MRI. In conclusion, gradual adaption of the local circulation through staged FD implantation, confirmed DPAT, and mild oral anticoagulation is key. Disease of the basilar trunk and disease that crosses the vertebrobasilar junction can be the most difficult to treat. In addition to the FD, coil occlusion of the contralateral vertebral artery is required to prevent a persistent endoleak around the FD. The author proposes early treatment prior to the development of symptoms and when the maximum diameter and length of the diseased segment is minimized. Both transitional and fusiform aneurysmal subtypes should be managed aggressively given their poor prognosis; however, a "watch and wait" strategy could be used for dolichoectatic disease with treatment commenced as soon as enlargement is seen.

As mention above, there is significant variability in mortality, permanent new morbidity, and occlusion rates of posterior circulation aneurysms treated with FD. These studies have several limitations. Interpretation of the results is difficult owing to heterogeneity of the patients and aneurysms, relatively short follow-up, retrospective analysis, and relatively small total numbers. One of the important observations from the overall outcomes is that mortality and morbidity appear to be higher with symptomatic aneurysms. This poses a difficult clinical dilemma, because, reasonably, physicians feel obliged to offer treatment when symptoms are present to prevent further decline. Unfortunately, it is not known what percentage of the incidentally discovered asymptomatic aneurysms would go on to become symptomatic over time. The challenging question is whether it is worth considering treating asymptomatic posterior circulation aneurysms earlier when they may be a lower treatment risk, or waiting to treat until they become symptomatic, less stable, and the risk of intervention is greater. The other finding is in line with prior opinions that fusiform basilar aneurysms have the highest treatment risks, probably owing to extensive involvement of perforators. These aneurysms have unfavorable characteristics for any treatment, including FD. The fate of small perforator arteries is difficult to predict. There is no good understanding of the dynamics of aneurysm thrombosis around FD stent in a large and elongated fusiform vessel segment. In particular, increased distance from the device wall to the perforator vessel origin seems to be very important. The other risk factor is higher number of stents, probably owing to overlapping coverage of the small perforators, more metal and foreign body presence, increased risk of ischemic events, and longer procedure times. An important component of preventing perforator infarcts or other ischemic complications is the strict adherence to the obligatory DAPT. Noncompliance is a rare, but dreaded problem in patients with intravascular stents. Life-threatening consequences should be explicitly discussed with the patient and family before proceeding with FD treatment. The use of antiplatelet inhibition testing appears important and provides guidance about the effect of treatment; however, significant thrombotic or hemorrhagic events may still occur despite adequate testing. Extended follow-up of previously treated patients will be valuable to better understand the long-term risks and benefits of FD.

There is usually a significant dilemma about treatment indications for these challenging aneurysms, which clearly have an unfavorable natural history, and also, an increased risk of treatment. In most large tertiary care centers, intervention is usually considered necessary if new symptoms develop, and/or there is evidence of change in morphology over time, prior hemorrhage, expansion, or progressive posterior circulation mass effect.

Newer-generation devices and computational flow dynamic models may help in tailoring treatment to individual patients in the future. Further prospective data are necessary to assess the role of FD in the posterior circulation.

10.5 Acute Ruptured Aneurysms

Endovascular management of ruptured intracranial aneurysms is well established. However, broad necked or giant saccular, fusiform, or blister aneurysms pose specific challenges for conventional endovascular treatments. These aneurysms may also pose challenges for microsurgical clipping. Few options are available for the safe and effective treatment of this subpopulation of ruptured intracranial aneurysms. In these aneurysms, the use of stent-assisted coiling or FD may be a viable treatment strategy. However, there is understandable resistance to the use of intravascular stents for aneurysmal subarachnoid hemorrhage (aSAH), owing to the risks of thromboembolic and hemorrhagic complications. DAPT reduces the risk of the former at the cost of increasing the risk of the latter. When treating aSAH, multiple additional intracranial procedures may be required, such as external ventricular drain (EVD) placement, ventriculoperitoneal (VP) shunt insertion, or decompressive craniotomy for hematoma evacuation. These subsequent surgeries can be complicated by DAPT that is required in conjunction with FD placement. In addition, placement of FDs like the

PED results in gradual rather than immediate thrombosis of the aneurysm, which may increase the risk of aneurysm rerupture in the acute phase of aSAH.

As mentioned previously in the treatment of ruptured blister aneurysm, flow diverse technique resulted in the immediate occlusion or near occlusion in 90%, and the follow-up DSA showed the 100% complete occlusion [22]. Of 62 ruptured blister aneurysms treated with FD in meta-analysis, 86% achieved good clinical outcomes, and 17% suffered procedural complications including an almost 8% risk of procedural ICH [17]. A recent meta-analysis of 20 studies including 233 patients treated with FDs for acutely ruptured aneurysms reported an almost 90% rate of total or subtotal occlusion at a mean of 9.6 months and although the immediate occlusion rate was only 32%, the rerupture rate was nonetheless low at 4% suggesting that aneurysmal rerupture is not a significant concern with the use of FDs despite the persistent filling. The overall complication rate was 18% with 7% treatment-related morbidities and comparable rates of hemorrhagic and thromboembolic complications [65]. The results suggest an excellent efficacy but higher complication of FD for the management of acutely ruptured aneurysms. VP shunt-related ICH rates of up to 71% have been reported in patients concomitantly treated with dual antiplatelet agents after stent-assisted aneurysm coiling [66]. A matched cohort pilot study by Paisan also found that significantly longer time interval between presentation with aSAH and shunt placement in the DAPT cohort, which reflect the reluctance of practitioners to perform surgical procedures on this subset of patients [67]. However, the same study revealed that patients receiving DAPT after the stent-assisted coiling of acutely ruptured aneurysms did not have an increased risk of shunt-related complications or unfavorable long-term functional outcomes compared to endovascular treatment without DAPT. Another series including 80 aSAH cases with VP shunt found in patients who performed stent-assisted coiling or FD treatment, there was an elevated risk (22% vs 2%) for VP shunt-associated radiographic hemorrhage, but the risk of clinically significant hemorrhage was low (3%) [66].

Given the Iatrogenic hemorrhage complication relative to DAPT, there is considerable debate on the ideal timing of FD placement. Some experts recommend early flow diversion (less than 2 days from SAH ictus) [68, 69], while others advocate for delayed treatment (2–14 days from SAH ictus) [70, 71]. However, the meta-analysis of 13 studies with 142 patients did not show a difference in overall complication rate (primary outcome) between early vs. delayed FD for ruptured aneurysms [72]. Early treatment for blister or dissecting/fusiform aneurysms was associated with a low complication rate in comparison to saccular aneurysms. Given the high risk of rerupture and subsequent mortality from primary FD for large, saccular ruptured aneurysms, acute coiling followed by staged flow diversion, median time of 16 weeks between the coiling and flow diversion, appears to be a safer endovascular option for these ruptured aneurysms. In Brinjikji series, 27 patients with aSAH from large/giant ruptured aneurysms, 18 patients had complete or near-complete aneurysm occlusion, and 25 patients had good performance status [73].

Natarajan et al. present their series [74], despite 18.2% mortality, the patients in the remaining 9 of 11 cases (81.8%) achieved good functional recovery and 100% obliteration of the aneurysm without rebleeding. At their protocol, an EVD was placed before angiogram if needed, followed by primarily dome protection and obliteration of rupture points in aneurysms by coiling or clipping. If the aneurysm morphology was complex (blister or fusiform aneurysms) and/or if the patient was not a good candidate for surgical clipping (elderly patients and/or those with poor Hunt and Hess grades), FD or stent assistance was attempted to achieve aneurysm occlusion.

Despite the importance of antiplatelet therapy on the success of FD-based interventions, there is wide variability in antiplatelet management surrounding the off-label use of FDs in aSAH. Some authors reported performing invasive procedures (EVD or central line placement) 12 h before FD placement or DAPT, administering a loading dose of DPAT before FD placement and continuing DAPT for at least 3 months [68]. Other authors avoided pre-procedural anti-

platelet therapy altogether, instead administering DAPT, and a glycoprotein IIb/IIIa inhibitor during FD placement, followed by a 12-hour maintenance infusion of a glycoprotein IIb/IIIa inhibitor and post-procedural DAPT for 6 months [75]. The inhibitors of IIb/IIIa glycoproteins have a very potent inhibitory effect on platelets, and rapid onset of action, can be used just for short periods of time [76]. The protocol with tirofiban or eptifibatide infusion, drugs with reversible binding to platelets, may be easier to handle than irreversible antagonists (abciximab), was proposed starting immediately after the stent deployment and continuing for 12 h after the procedure, making coagulation better controllable and allowing restoration of coagulation in case of bleeding. The authors reported 17% complications and 2.8% aneurysm rebleeding [75]. One meta-analysis [65] found 4 main groups of antiplatelet therapy administration. There were no statistically significant differences among the analyzed subgroups of antiplatelet therapy, with an overall complication rate ranging from 17% to 23%. The most common drugs were clopidogrel plus ASA, administered intraoperatively and maintained after treatment (19.5% complications and 3% rebleeding). Ticagrelor has an advantage compared with ASA, clopidogrel, and prasugrel in that it binds reversible to platelets and therefore partial platelet activity returns after 12 h and is used for clopidogrel nonresponders.

A promising recent advancement has been surface modification to reduce the inherent thrombogenicity of FD. The PED with Shield Technology (PED Shield, Medtronic) is a phosphorylcholine surface modification of the PED that has shown a reduction in material thrombogenicity in vitro [77]. Manning et al. used the PED with shield technology (with adjunctive coiling in 83%) under single antiplatelet therapy in treating 14 patients with ruptured intracranial aneurysms and reported no hemorrhagic or thromboembolic complications in the subgroup that did not receive post-interventional heparin infusion (heparin infusion postoperatively was associated with all complications combined) [78]. However, PED with shield is not the universal key in the real world. After PED with Shield deployment for the acute ruptured ICA aneurysm, parent artery kept patency in the case of Fig. 10.2 but occlusion in Fig. 10.10 case. Even glycoprotein IIb/IIIa inhibitor (Eptifibatide) was injected immediately with the parent artery reopened, the patient still had minor weakness in the acute phase. Until establishing the efficacy and safety of such coatings in a large clinical trial, the use of FD will remain limited by the need for DAPT.

Flow diversion is not the primary treatment of choice after aSAH, but is a reasonable last option if other, safer options are not available to treat the aneurysm. Careful patient selection, selective use of coiling, timing of flow diversion after dome protection, and timing of heparin and antiplatelet therapy in the periprocedural period improve the safety of flow diversion as a strategy to achieve permanent aneurysm occlusion in the rupture setting. Further development of surface modification technology may allow flow diversion with a single antiplatelet agent, and thus may broaden the use of FD in this setting.

10.6 Intracranial Dissecting Aneurysms

There are relatively few studies of intracranial dissecting aneurysm in the literature, but they seem to have a predilection for young adults and arteries of the posterior circulation [79]. There are numerous mechanisms in the formation of dissections, and each has a different clinical presentation and imaging findings (saccular, fusiform, or pseudoaneurysm). Patients most often present with a nonspecific headache followed by ischemic stroke or SAH. The heterogeneity of this rare condition precludes standardized diagnostic criteria and evidence-based treatment guidelines.

In adults, involvement of the posterior circulation is at least three times more common than the anterior circulation and V4 is the most frequently implicated [79, 80].

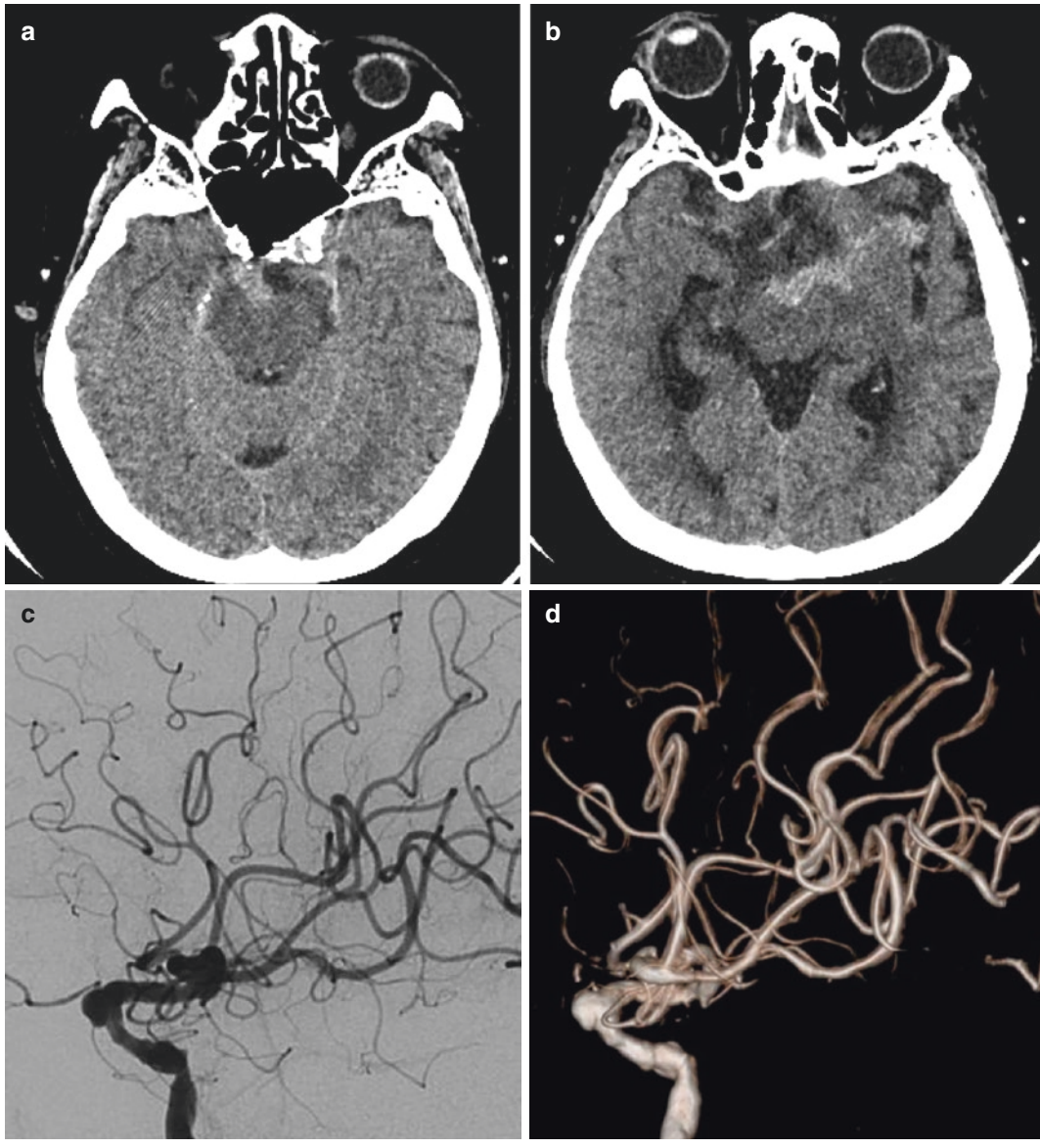


Fig. 10.10 A 76-year-old patient presented with acute headache and vomit, brain CT showed SAH (**a**, **b**), angiogram revealed multiple aneurysms involving both anterior and posterior circulation (**c**–**f**). It was difficult to confirm which one was responsible, so all the aneurysms were treated in one procedure. After loading dose dual antiplatelet drugs was given, the tandem wide-neck aneurysms in left ICA were treated with Pipeline shield stent and coiling at first (**g**) and followed by coiling of the aneurysm in basilar artery (**h**). However, acute thrombosis was found in the flow diverter (**i**). Glycoprotein IIb/IIIa inhibitor (Eptifibatide) was injected immediately and continue to 12 h. Left ICA was reopened at the end (**j**). The patient presented with weakness of right upper limb after the procedure and small infarction was confirmed in day 1 MRI (**k**), limb power recovered well in one week

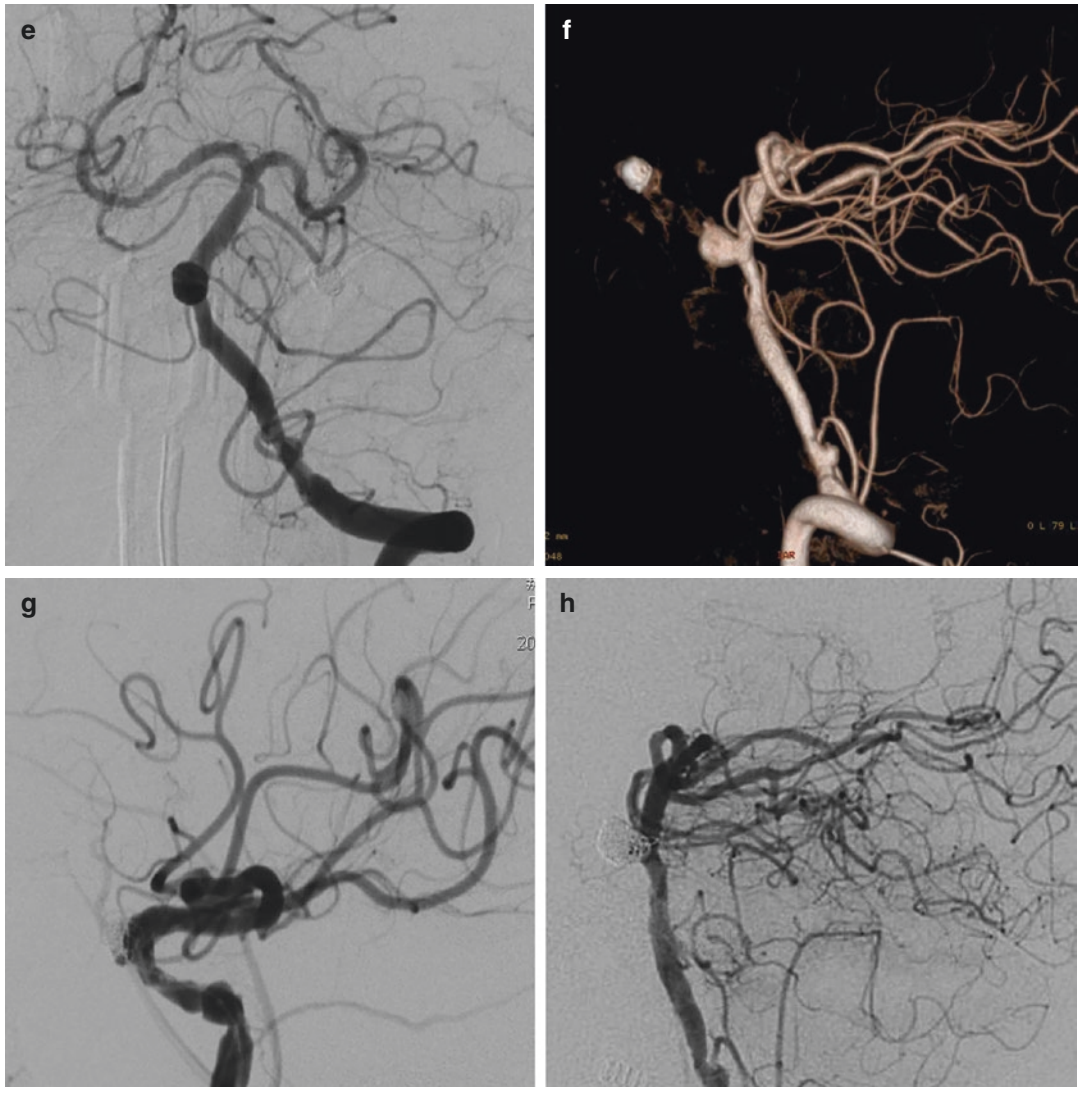


Fig. 10.10 (continued)

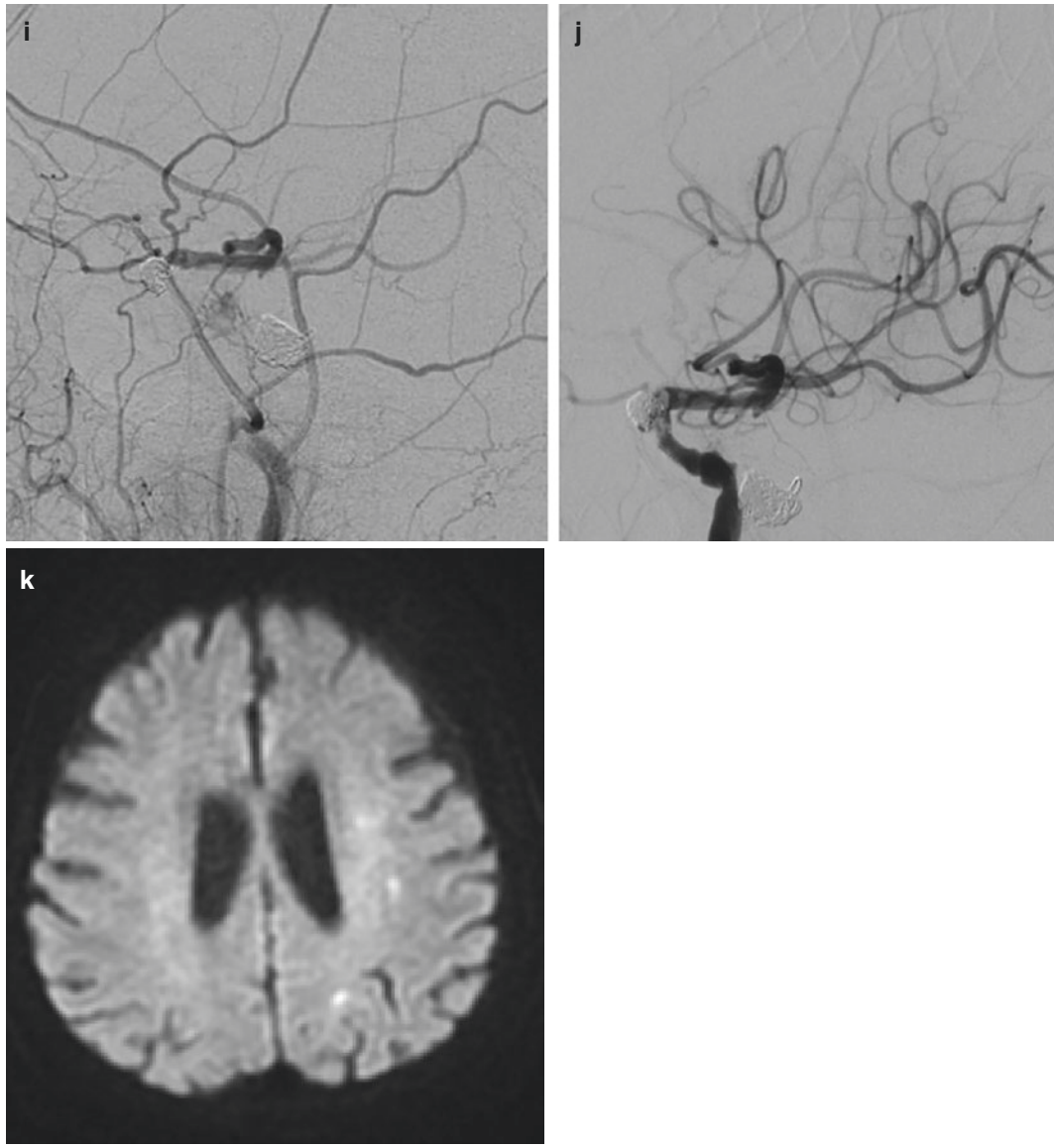


Fig. 10.10 (continued)

The most common location in the anterior circulation of dissection is the supraclinoid internal carotid artery [79].

Approximately 80% of patients with intracranial dissection have a prodromal headache preceding SAH or symptoms of cerebral ischemia, whether it be a stroke or transient ischemic attack [81]. An estimated 50–60% of intracranial dissecting aneurysm patients develop SAH, and 30–78% of patients have ischemic events. Other uncommon presentations include isolated headache or mass effect from brain stem and/or cranial nerve compression [79]. Patients who present with ischemic stroke are at high risk of subsequent ischemic stroke and low risk of SAH while those who present with hemorrhage are at high risk of subsequent hemorrhage but low risk of subsequent ischemic stroke [79]. Mortality is reported to be 19–83% in patients with SAH and 0–3% without SAH [79]. Up to 40% of patients

who present with SAH experience rebleeding, most commonly within the first week. For patients who present with ischemia, recurrent ischemic events have been reported at a rate of 2–38% in numerous studies with widely variable follow-up lengths [82, 83].

When the patient presents with Ischemic, medical management includes antithrombotic or antiplatelet therapy for the prevention of thromboembolic stroke. In patients present with large vessel occlusion, urgent endovascular recanalization should be performed when SAH can be ruled out. In patients with recurrent strokes despite medical therapy, stent reconstruction is reasonable to perform.

In patients present with SAH, there is a significant risk of rebleeding after initial stabilization [83]. As such, surgical or endovascular treatment is often pursued in this population. Various surgical and endovascular treatment methods have been proposed for intracranial dissecting aneurysms. All treatment methods aim to reduce blood flow in the dissected region. Deconstructive techniques sacrifice the parent artery, whereas reconstructive techniques aim to maintain a parent artery. Deconstructive techniques are associated with higher rates of both short-term (90% versus 50%) and long-term complete occlusion (90% versus 80%) [82]. However, there is a trend towards better clinical outcomes in patients treated with reconstructive techniques, likely due to the lower risk of stroke and hypoperfusion due to preservation of the parent artery. Reconstructive techniques are alternative options for patients who are not suitable candidates for parent vessel occlusion [84, 85]. FD and stenting, with or without coiling, selectively occlude the dissection while maintaining patency of the parent vessel. Patients often require treatment with dual antiplatelet therapy after device implantation. There is a risk of rebleeding following reconstructive treatment due to the fact that FD still allows for some blood flow to the aneurysm which is not immediately "protected" against rerupture until vessel wall remodeling and endothelialization of the stent construct. There are also issues surrounding the risks of placing CSF diversion devices while patients are on dual antiplatelet therapy. The timing and technique about additional surgical procedures and antiplatelet treatment have been discussed in the section *Acute ruptured Aneurysms*. Nonetheless, it appears as though reconstructive techniques, especially flow diversion, have become the preferred option for treatment of ruptured intracranial dissections.

The most important consideration in treating unruptured dissecting aneurysms is weighing the risks of treatment with the risks of the natural history of these lesions, especially located in the posterior circulation. It has been discussed in the section *Posterior Circulation Aneurysms*. The Tubridge flow diverter (MicroPort Medical Company, Shanghai, China) was used in Fig. 10.11 case. In Fig. 10.12 case, the small saccular aneurysms maintained patency in portion stented while stenosis improved in portion without stenting after 17 months of antiplatelet treatment. Flow in the false lumen existing with the non-cover proximal portion of dissecting may be the reason.

As expected, treatment with deconstructive techniques (i.e., parent vessel sacrifice) is associated with high rates of complete occlusion in the immediate and postoperative setting (90–100%) while reconstructive techniques including FD require some time to achieve complete occlusion. FD is generally the preferred means of treatment of these lesions due to its high rate of treatment efficacy, high long-term occlusion rates and ability to preserve the parent vessel.

Flow diversion is a new paradigm shift in the treatment of intracranial aneurysms, but, not a universal key. As popularity of the device grew and neurosurgeons gained more experience, its indications were extended. In recent years, off-label use of flow diversion in treatment of intracranial aneurysms has become more and more

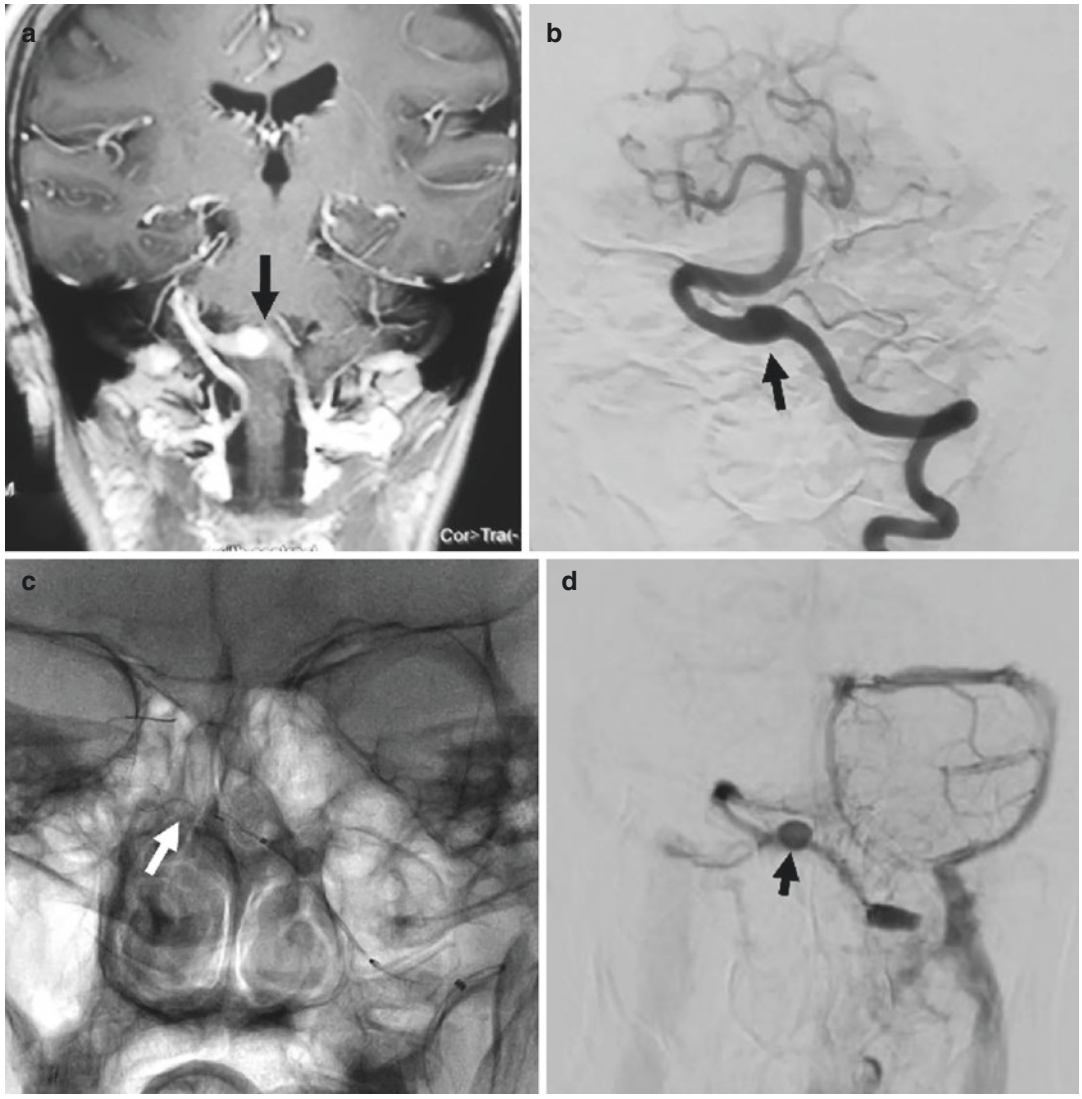


Fig. 10.11 A 58-year-old woman presented with an incidental vertebral artery aneurysm. (**a**) Coronal view of the enhanced MR image showing a fusiform aneurysm of the left vertebral artery (arrow). (**b**) Frontal view of the left vertebral artery injection showing a fusiform aneurysm (arrow). (**c**) Frontal view of unsubtracted image showing the releasing of a 4.0 mm × 50 mm Tubridge flow diversion (Microtherapeutic, Shanghai, China) (arrow). (**d**) Frontal view of the venous phase of the left vertebral artery injection showing intra-aneurysm contrast stagnation (arrow)

popular. It has proven to be a safe and efficacious treatment option for many of these off-label uses, whereas others may still require larger, more extensive studies to draw conclusions. Nevertheless, the FD may be a promising treatment alternative and should be considered when we face the challenge of complex aneurysms that may be deemed difficult to treat by using conventional surgical and endovascular techniques in the real world.

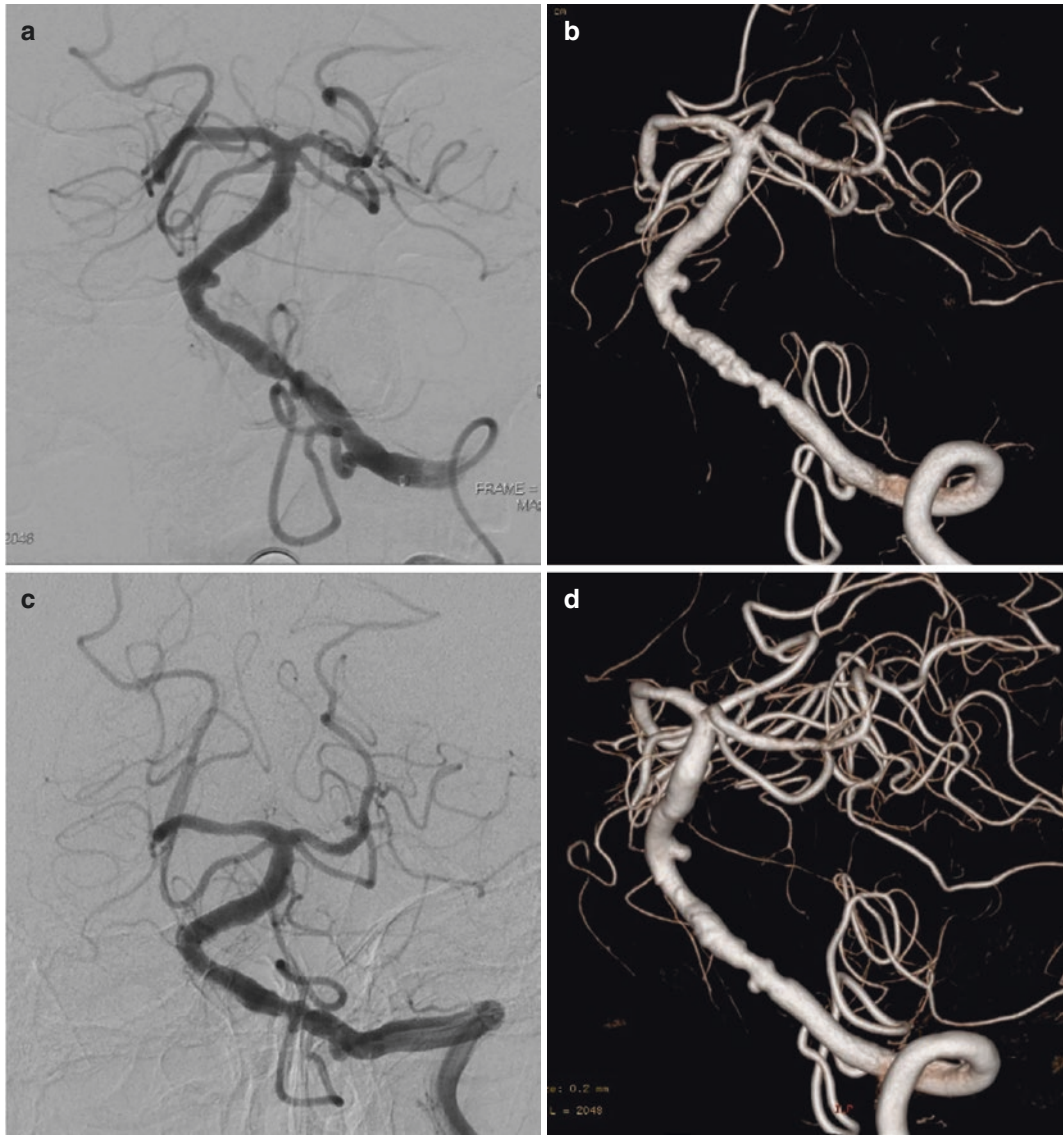


Fig. 10.12 A 63-year-old patient presented with headache was treated left VA dissection (**a**, **b**) with 1 PED covered the saccular portion of vertebrobasilar junction, and kept the focal stenosis and dilation ("string and pearl sign") portion intact. After 17 months of antiplatelet therapy, a follow-up angiogram showed the saccular patency maintained in portion stented while stenosis improved in portion without stenting (**c**, **d**)

References

1. Molyneux AJ, Kerr RSC, Yu L-M, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809–17.
2. Molyneux AJ, Kerr RSC, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol. 2009;8(5):427–33.
3. Gory B, Turjman F. Endovascular treatment of 404 intracranial aneurysms treated with nexus detachable coils: short-term and mid-term results from a prospective, consecutive, European Multicenter study. Acta Neurochir. 2014;156(5):831–7.

4. Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, et al. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. Stroke. 2010;41(1):110–5.
5. Hoi Y, Ionita CN, Tranquebar RV, Hoffmann KR, Woodward SH, Taulbee DB, et al. Flow modification in canine intracranial aneurysm model by an asymmetric stent: studies using digital subtraction angiography (DSA) and image-based computational fluid dynamics (CFD) analyses. Proc Soc Photo Opt Instrum Eng. 2006 Mar 13;6143:61430J.
6. Sadasivan C, Cesar L, Seong J, Rakian A, Hao Q, Tio FO, et al. An original flow diversion device for the treatment of intracranial aneurysms: evaluation in the rabbit elastase induced model. Stroke. 2009;40:952–8.
7. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. AJNR Am J Neuroradiol. 2011;32(1):34–40.
8. Becske T, Kallmes DF, Saatci I, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858–68.
9. Crobeddu E, Lanzino G, Kallmes DF, Cloft HJ. Marked decrease in coil and stent utilization following introduction of flow diversion technology. J NeuroIntervent Surg. 2013;5(4):351–3.
10. Wu X, Tian Z, Li W, Liu J, Zhang Y, Zhang Y, Zhou Y, Yang X, Mu S. Patency of branch vessels after pipeline embolization: comparison of various branches. Front Neurol. 2019;10:838.
11. Lee BH, Kim BM, Park MS, Park SI, Chung EC, Suh SH, et al. Reconstructive endovascular treatment of ruptured blood blister-like aneurysms of the internal carotid artery. J Neurosurg. 2009;110:431–6.
12. Ogawa A, Suzuki M, Ogasawara K. Aneurysms at nonbranching sites in the surpaclinoid portion of the internal carotid artery: internal carotid artery trunk aneurysms. Neurosurgery. 2000;47:578–86.
13. Meckel S, Singh TP, Undrén P, et al. Endovascular treatment using predominantly stent-assisted coil embolization and antiplatelet and anticoagulation management of ruptured blood blister-like aneurysms. AJNR Am J Neuroradiol. 2011;32:764–71.
14. Meling TR, Sorteberg A, Bakke SJ, Slettebø H, Hernesniemi J, Sorteberg W. Blood blister-like aneurysms of the internal carotid artery trunk causing subarachnoid hemorrhage: treatment and outcome. J Neurosurg. 2008;108:662–71.
15. Gonzalez AM, Narata AP, Yilmaz H, et al. Blood blister-like aneurysms: single center experience and systematic literature review. Eur J Radiol. 2014;83:197–205.
16. Owen CM, Montemurro N, Lawton MT. Blister aneurysms of the internal carotid artery: microsurgical results and management strategy. Neurosurgery. 2017;80(2):235–47.
17. Rouchaud A, Brinjikji W, Cloft HJ, Kallmes DF. Endovascular treatment of ruptured blister-like aneurysms: a systematic review and meta-analysis with focus on deconstructive versus reconstructive and flow-diverter treatments. AJNR Am J Neuroradiol. 2015;36:2331–9.
18. McNeely PD, Clarke DB, Baxter B, et al. Endovascular treatment of a "blister-like" aneurysm of the internal carotid artery. Can J Neurol Sci. 2000;27:247–50.
19. Gaughen JR, Hasan D, Dumont AS, et al. The efficacy of endovascular stenting in the treatment of supraclinoid internal carotid artery blister aneurysms using a stent-in-stent technique. *AJNR*. Am J Neuroradiol. 2010;31:1132–8.
20. Ahn JY, Cho JH, Jung JY, et al. Blister-like aneurysms of the supraclinoid internal carotid artery: challenging endovascular treatment with stent-assisted coiling. J Clin Neurosci. 2008;15:1058–61.
21. Kulcsár Z, Wetzel SG, Augsburger L, et al. Effect of flow diversion treatment on very small ruptured aneurysms. Neurosurgery. 2010;67:789–93.
22. Linfante I, Mayich M, Sonig A, Fujimoto J, Siddiqui A, Dabus G. Flow diversion with pipeline embolic device as treatment of subarachnoid hemorrhage secondary to blister aneurysms: dual-center experience and review of the literature. J Neurointerv Surg. 2017 Jan;9(1):29–33.
23. Kim BM, Chung EC, Il PS, et al. Treatment of blood blister-like aneurysm of the internal carotid artery with stent-assisted coil embolization followed by stent-within-a-stent technique. Case report. J Neurosurg. 2007;107:1211–3.
24. Lahaska M, Lehto H, Niemelä M, Juvela S, Dashti R, Koivisto T, et al. Distal anterior cerebral artery aneurysms: treatment and outcome analysis of 501 patients. Neurosurgery. 2008;62:590–601.
25. Sturiale CL, Brinjikji W, Murad MH, Cloft HJ, Kallmes DF, Lanzino G. Endovascular treatment of distal anterior cerebral artery aneurysms: single-center experience and a systematic review. AJNR Am J Neuroradiol. 2013;34:2317–20.
26. Chaudhary N, Pandey AS, Thompson BG, Gandhi D, Ansari SA, Gemmete JJ. Utilization of the Neuron 6 French 0.053 inch inner luminal diameter guide catheter for treatment of cerebral vascular pathology: continued experience with ultra-distal access into the cerebral vasculature. J Neurointerv Surg. 2012;4(4):301–6.
27. Colby GP, Lin LM, Huang J, et al. Utilization of the Navien distal intracranial catheter in 78 cases of anterior circulation aneurysm treatment with the Pipeline embolization device. J Neurointerv Surg. 2013;5(suppl 3):iii16–21.
28. Colby GP, Lin LM, Xu R, Beaty N, Bender MT, Jiang B, Huang J, Tamargo RJ, Coon AL. Utilization of a novel, multi-durometer intracranial distal access catheter: nuances and experience in 110 consecutive cases of aneurysm flow diversion. Interv Neurol. 2017;6:90–104.
29. Lin LM, Jiang B, Bender MT, Westbroek EM, Campos JK, Tamargo RJ, Huang J, Coon AL, Colby GP. 47 consecutive cases of pipeline flex flow diversion utilizing a novel large-bore intracranial intermediate catheter: nuances and institutional

experience with the Syphontrak. Interv Neurol. 2018;7(3–4):153–63.
30. Lin L-M, Colby GP, Bender MT, et al. Use of the 0.027-inch VIA microcatheter for delivery of pipeline flex: a technical note. J Neurointerv Surg. 2017;9:689–93.
31. Bender MT, Zarrin DA, Campos JK, Lin L-M, Huang J, et al. Tiny pipes: 67 cases of flow diversion for aneurysms in distal vessels measuring less than 2.0 mm. World Neurosurg. 2019;127:193–201.
32. Dornbos D, Katz JS, Youssef P, Powers CJ, Nimjee SM. Glycoprotein IIb/IIIa inhibitors in prevention and rescue treatment of thromboembolic complications during endovascular embolization of intracranial aneurysms. Neurosurgery. 2017;82:268–77.
33. Ravindran K, Alejandro EM, Kan PT, et al. Use of flow diversion for the treatment of distal circulation aneurysms: a multicohort study. World Neurosurg. 2018;118:825–33.
34. Mazaris P, Mehta T, Hussain M, et al. Endovascular treatment of complex distal posterior cerebral artery aneurysms with the pipeline embolization device. World Neurosurg. 2017;107:1–5.
35. Iosif C, Mounayer C, Yavuz K, Saleme S, Geyik S, Cekirge HS, et al. Middle cerebral artery bifurcation aneurysms treated by extrasaccular flow diverters: midterm angiographic evolution and clinical outcome. AJNR Am J Neuroradiol. 2017;38:310–6.
36. Lin N, Lanzino G, Lopes DK, Arthur AS, Ogilvy CS, Ecker RD, et al. Treatment of distal anterior circulation aneurysms with the pipeline embolization device: a US multicenter experience. Neurosurgery. 2016;79:14–22.
37. Puri AS, Massari F, Asai T, et al. Safety, efficacy, and short-term follow-up of the use of pipeline embolization device in small (<2.5 mm) cerebral vessels for aneurysm treatment: single institution experience. Neuroradiology. 2015;58:267–75.
38. Bender MT, Lin L-M, Colby GP, et al. P2Y12 hyporesponse (PRU>200) is not associated with increased thromboembolic complications in anterior circulation pipeline. J Neurointerv Surg. 2017;9:978–81.
39. Campi A, Ramzi N, Molyneux AJ, Summers PE, Kerr RS, Sneade M, et al. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). Stroke. 2007;38:1538–44.
40. Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, et al. The Barrow ruptured aneurysm trial: 3-year results. J Neurosurg. 2013;119:146–57.
41. Dornbos D III, Karras CL, Wenger N, et al. Pipeline embolization device for recurrence of previously treated aneurysms. Neurosurg Focus. 2017;42(6):8.
42. Daou B, Starke RM, Chalouhi N, Tjoumakaris S, Hasan D, Khoury J, et al. Pipeline embolization device in the treatment of recurrent previously stented cerebral aneurysms. AJNR Am J Neuroradiol. 2016;37:849–55.
43. Daou B, Starke RM, Chalouhi N, Tjoumakaris S, Khoury J, Hasan D, et al. The use of the pipeline embolization device in the management of recurrent previously coiled cerebral aneurysms. Neurosurgery. 2015;77:692–7.
44. Bender MT, Chau DV, Jiang B, Campos JK, et al. Pipeline embolization for salvage treatment of previously stented residual and recurrent cerebral aneurysms. Intervent Neurol. 2018;7:359–69.
45. Shapiro M, Becske T, Nelson PK. Learning from failure: persistence of aneurysms following pipeline embolization. J Neurosurg. 2016;126:578–85.
46. Fischer S, Vajda Z, Aguilar Perez M, Schmid E, Hopf N, Bäzner H, et al. Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. Neuroradiology. 2011;54:369–82.
47. Lin LM, Iyer RR, Bender MT, Monarch T, Colby GP, et al. Rescue treatment with pipeline embolization for postsurgical clipping recurrences of anterior communicating artery region aneurysms. Intervent Neurol. 2017;6:135–46.
48. Kühn AL, Rodrigues MK, Lozano JD, Rex DE, Massari F, Tamura T, et al. Use of the pipeline embolization device for recurrent and residual cerebral aneurysms: a safety and efficacy analysis with short-term follow-up. J Neurointerv Surg. 2017;9(12):1208–13.
49. Flemming KD, Wiebers DO, Brown RD Jr, et al. The natural history of radiographically defined vertebrobasilar nonsaccular intracranial aneurysms. Cerebrovasc Dis. 2005;20:270–9.
50. Shapiro M, Becske T, Riina HA, et al. Non-saccular vertebrobasilar aneurysms and dolichoectasia: a systematic literature review. J Neurointerv Surg. 2014;6:389–93.
51. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. N Engl J Med. 1998;339:1725–33.
52. Steinberg GK, Drake CG, Peerless SJ. Deliberate basilar or vertebral artery occlusion in the treatment of intracranial aneurysms. J Neurosurg. 1993;79(2):161–73.
53. Lawton MT. Basilar apex aneurysms: surgical results and perspectives from an initial experience. Neurosurgery. 2002;50(1):1–8.
54. Fargen KM, Mocco J, Neal D, et al. A multicenter study of stent-assisted coiling of cerebral aneurysms with a Y configuration. Neurosurgery. 2013;73(3):466–72.
55. Coert BA, Chang SD, Do HM, et al. Surgical and endovascular management of symptomatic posterior circulation fusiform aneurysms. J Neurosurg. 2007;106:855–65.
56. Brinjikji W, Murad MH, Lanzino G, et al. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44:442–7.
57. Phillips TJ, Wenderoth JD, Phatouros CC, Rice H, Singh TP, Devilliers L, et al. Safety of the pipeline embolization device in treatment of posterior

circulation aneurysms. AJNR Am J Neuroradiol. 2012;33:1225–31.
58. Munich SA, Tan LA, Keigher KM, Chen M, Moftakhar R, Lopes DK. The pipeline embolization device for the treatment of posterior circulation fusiform aneurysms: lessons learned at a single institution. J Neurosurg. 2014;121:1077–84.
59. Mazur MD, Kilburg C, Wang V, Taussky P. Pipeline embolization device for the treatment of vertebral artery aneurysms: the fate of covered branch vessels. J Neurointerv Surg. 2016;8:1041–7.
60. Natarajan SK, Lin N, Sonig A, et al. The safety of pipeline flow diversion in fusiform vertebrobasilar aneurysms: a consecutive case series with longer-term follow-up from a single US center. J Neurosurg. 2016;125(1):111–9.
61. Siddiqui AH, Abla AA, Kan P, Dumont TM, Jahshan S, Britz GW, et al. Panacea or problem: flow diverters in the treatment of symptomatic large or giant fusiform vertebrobasilar aneurysms. J Neurosurg. 2012;116:1258–66.
62. Bender MT, Colby GP, Jiang B, Lin LM, Campos JK, et al. Flow diversion of posterior circulation cerebral aneurysms: a single-institution series of 59 cases. Neurosurgery. 2019;84:206–16.
63. Bhogal P, Pérez MA, Ganslandt O, Bäzner H, Henkes H, Fischer S. Treatment of posterior circulation non-saccular aneurysms with flow diverters: a single-center experience and review of 56 patients. J Neurointerv Surg. 2017;9(5):471–81.
64. Mangrum WI, Huston J, Link MJ, et al. Enlarging vertebrobasilar nonsaccular intracranial aneurysms: frequency, predictors, and clinical outcome of growth. J Neurosurg. 2005;102:72–9.
65. Cagnazzo F, di Carlo DT, Cappucci M, Lefevre P-H, Costalat V, Perrini P. Acutely ruptured intracranial aneurysms treated with flow-diverter stents: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2018;39:1669–75.
66. Hudson JS, Nagahama Y, Nakagawa D, et al. Hemorrhage associated with ventriculoperitoneal shunt placement in aneurysmal subarachnoid hemorrhage patients on a regimen of dual antiplatelet therapy: a retrospective analysis. J Neurosurg. 2018;129:916–21.
67. Paisan GM, Ding DL, Xu ZY, Liu KC. Effect of dual antiplatelet therapy on shunt outcomes in patients with aneurysmal subarachnoid hemorrhage: a matched cohort pilot study. Cureus. 2018;10(3):2383.
68. Lin N, Brouillard AM, Keigher KM, et al. Utilization of pipeline embolization device for treatment of ruptured intracranial aneurysms: US multicenter experience. J Neurointerv Surg. 2015;7:808–15.
69. Maus V, Mpotsaris A, Dorn F, et al. The use of flow diverter in ruptured, dissecting intracranial aneurysms of the posterior circulation. World Neurosurg. 2018;111:424–33.
70. Aydin K, Arat A, Sencer S, et al. Treatment of ruptured blood blister-like aneurysms with flow diverter SILK stents. J Neurointerv Surg. 2015;7:202–9.
71. Duman E, Coven I, Yildirim E, Yilmaz C, Pinar HU. Endovascular treatment of wide necked ruptured saccular aneurysms with flow-diverter stent. Turk Neurosurg. 2017;27:362–7.
72. Dossani RH, Patra DP, Kosty J, Jumah F, Kuybu O, Mohammed N, Waqas M, Riaz M, Cuellar H. Early versus delayed flow diversion for ruptured intracranial aneurysms: a meta-analysis. World Neurosurg. 2019;126:41–52.
73. Brinjikji W, Piano M, Fang S, et al. Treatment of ruptured complex and large/giant ruptured cerebral aneurysms by acute coiling followed by staged flow diversion. J Neurosurg. 2016;125:120–7.
74. Natarajan SK, Shallwani H, Fennell VS, Beecher JS, Shakir HJ, Davies JM, Snyder KV, Siddiqui AH, Levy EI. Flow diversion after aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am. 2017;28:375–88.
75. Chalouhi N, Zanaty M, Whiting A, et al. Treatment of ruptured intracranial aneurysms with the pipeline embolization device. Neurosurgery. 2015;76:165–72.
76. Altenburg A, Haage P. Antiplatelet and anticoagulant drugs in interventional radiology. Cardiovasc Intervent Radiol. 2012;35:30–42.
77. Girdhar G, Andersen A, Pangerl E, Jahanbekam R, Ubl S, Nguyen K, Wainwright J, Wolf MF. Thrombogenicity assessment of pipeline flex, pipeline shield, and FRED flow diverters in an in vitro human blood physiological flow loop model. J Biomed Mater Res 2018; 106A:3195–3202.
78. Manning NW, Cheung A, Phillips TJ, Wenderoth JD. Pipeline shield with single antiplatelet therapy in aneurysmal subarachnoid haemorrhage: multicentre experience. J Neurointerv Surg. 2019;11:694–8.
79. Debette S, Compter A, Labeyrie MA, et al. Epidemiology, pathophysiology, diagnosis, and management of intracranial artery dissection. Lancet Neurol. 2015;14(6):640–54.
80. Huang YC, Chen YF, Wang YH, Tu YK, Jeng JS, Liu HM. Cervicocranial arterial dissection: experience of 73 patients in a single center. Surg Neurol. 2009;72(Suppl 2):S20–7.
81. Mizutani T. Natural course of intracranial arterial dissections. J Neurosurg. 2011;114(4):1037–44.
82. Nakajima S, Tsukahara T, Minematsu K. A study of vertebrobasilar artery dissection with subarachnoid hemorrhage. Acta Neurochir Suppl. 2010;107:45–9.
83. Ono H, Nakatomi H, Tsutsumi K, Inoue T, Teraoka A, Yoshimoto Y, et al. Symptomatic recurrence of intracranial arterial dissections: follow-up study of 143 consecutive cases and pathological investigation. Stroke. 2013;44(1):126–31.
84. Park SI, Kim BM, Kim DI, et al. Clinical and angiographic follow-up of stent-only therapy for acute intracranial vertebrobasilar dissecting aneurysms. AJNR Am J Neuroradiol. 2009;30(7):1351–6.
85. Narata AP, Yilmaz H, Schaller K, Lovblad KO, Pereira VM. Flow-diverting stent for ruptured intracranial dissecting aneurysm of vertebral artery. Neurosurgery. 2012;70(4):982–8.

11 Complications of Aneurysm Embolization and Their Management: Basic and Practical Considerations

Fumitaka Yamane, Takeshi Uno, Michiyuki Miyamoto, Akihiro Ito, Yuta Oyama, Ichiro Nakasato, Akira Matsuno, Shinya Kohyama, and Tomofumi Iboshi

Abstract

This chapter discusses the periprocedural complications of coil embolization for cerebral aneurysms and their management. Moreover, an explanation on delayed leukoencephalopathy after coil embolization has been included. The most important complications are hemorrhagic and ischemic events. The associated factors include type of aneurysm (ruptured or unruptured); aneurysm location, size, and morphology; and its relationship with the parent vessels. Five hundred and seventy ruptured cerebral aneurysms embolizations were performed, in total, 29 (5.1%) patients presented with perioperative hemorrhagic complications. Moreover, 1178 patients with unruptured cerebral aneurysms underwent embolization. Among them, 22 (1.9%) presented with perioperative hemorrhagic complications. The risk factors for perioperative bleeding include aneurysms with an anterior communicating artery, small-size aneurysms, and ruptured aneurysms. By contrast, local thrombus formation is a periprocedural ischemic complication and is correlated to aneurysm neck size, use of stents (particularly for ruptured aneurysms), aneurysm angle relative to the parent artery, and duration of the procedure. The endovascular outcomes of aneurysm embolization were presented and systematically compared with those of previous reports. Moreover, the pathophysiology and management of complications and methods associated with a decreased risk of catastrophic events were discussed. In all cases, the initial treatment is important, and a multidisciplinary team who can respond to emergency situations should be established.

Keywords

Intracranial aneurysm · Complications · Coil embolization

F. Yamane (✉)
Department of Neurosurgery, International University of Health and Welfare Narita Hospital, Narita, Chiba, Japan
e-mail: fyamane@iuhw.ac.jp

T. Uno · M. Miyamoto · A. Ito · Y. Oyama
Department of Neurosurgery, Teikyo University School of Medicine, Tokyo, Japan

I. Nakasato · A. Matsuno
Department of Neurosurgery, International University of Health and Welfare Narita Hospital, Narita, Chiba, Japan

S. Kohyama · T. Iboshi
Department of Endovascular Neurosurgery, Saitama Medical University, International Medical Center, Hidaka, Saitama, Japan

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_11

11.1 Introduction

This chapter discusses the complications of coil embolization for cerebral aneurysms and their management. In 1991, Guglielmi et al. first reported the use of coil embolization for cerebral aneurysms [1]. Compared with clipping, which is the standard treatment for cerebral aneurysms, the technique is minimally invasive. Hence, it was considered a breakthrough in the history of cerebral aneurysm therapy. In particular, the indications for aneurysms located at the vertebral basilar artery system, which are challenging to manage with clipping, were expanded to facilitate safer interventions. The International Subarachnoid Hemorrhage Trial [2] and the Barrow Ruptured Aneurysm Trial [3] have a significant impact, particularly in the treatment of ruptured aneurysms, to communities in this field worldwide. Endovascular coiling involves the replacement of surgical clipping, and it is the preferred option for treating not only ruptured but unruptured aneurysms in the USA [4]. A previous research has compared the complication rates between coiling and clipping [5]. Intraoperative bleeding (IOB) is common among patients undergoing surgical clipping for ruptured aneurysms. Moreover, some studies showed that the incidence rate of IOB with new disability was similar between the endovascular and surgical treatment groups [2, 3, 5].

The important complications of coiling are hemorrhagic and ischemic events [6–12]. Three general perspectives should be considered when discussing complications. First, the concept of "risk factors," including the demographic patient's data and aneurysmal morphology was used if the risk of developing complications is significantly high. Whether postoperative complications can be predicted or prevented remains to be elucidated. This can be addressed by acknowledging the existence of risk factors first. Second, technical issues as well as problems and pre-cautionary measures in handling devices, such as micro-guidewire, microcatheter, microballoon, and coil, must be examined. Third, treatment measures for complications should be planned. That is, simulation is useful in ensuring that all members of a team can take appropriate and prompt actions when managing crisis [13]. Moreover, one wrong procedure can worsen the situation, resulting in devastating consequences.

Delayed leukoencephalopathy, a complication of unruptured aneurysmal embolization, is also explained in this study. Delayed encephalopathy, which occurs several months after treatment, has been attributed to contrast-induced encephalopathy [14], nickel allergy [15], and plugging due to the use of hydrophilic catheter coated with polyvinylpyrrolidone (PVP) [16]. PVP is a coating material widely used on catheters and guidewires, and it has been considered a causative agent [17, 18]. Although this complication is rare and not observed perioperatively, it should be considered by all neurointerventionists because it is unique in endovascular management [17].

Some of our results are presented in this chapter. Factors associated with complications, including incidence, mechanism, and prognosis, have been discussed. However, each case is unique, and there is no general principle that can be used because the situations are multifactorial, unpredictable, and specific [5, 7–9]. In this chapter, complications from the perspective of what should be the focus in performing coil embolization for cerebral aneurysm were discussed.

11.2 Hemorrhagic Complications

11.2.1 Incidence, Risk Factors, and Mechanisms of IOB

This section aimed to present the incidence, mechanism, management, and outcome of hemorrhagic complications in endovascular coil embolization for cerebral aneurysms. Hemorrhagic complications are among the most serious complications [6–8], and they affect prognosis. We addressed some complications based on risk factors and technical problems. Hemorrhagic complications in endovascular coiling include procedural aneurysmal perforations caused by the use of devices such as microcatheter, micro-guidewire, microballoon, and coil. IOB is defined as the first radiographic sign of a

perforation caused by a breach of any device out of the aneurysmal boundary on a road-map image [13]. This breach is followed by an increase in blood pressure and pulse rate. Contrast material that does not wash out in the venous phase indicates blood in the extravascular space. Decreasing the risk of mortality and permanent neurologic disability caused by IOB is dependent on immediate and appropriate treatment measures after a perforation occurs. Hence, IOB should be immediately recognized.

The complication rate was first described in a multicenter study. Results showed that the aneurysm perforation rate was 2.7% among patients (n = 403) admitted in eight centers [6]. Doerfler et al. [19] reported that the rupture rate was 3% in a series of 164 patients with acute rupture of aneurysm. In the study of Ricolfi [20], Cognard et al. [21], and Raymond et al. [22], the iatrogenic rupture rates were 4.4%, 4%, and 5.8%, respectively. The IOB rates vary from 1% to 5%. Regardless of whether the procedure is performed for ruptured or unruptured aneurysms, the prognosis of IOB is generally poor, with a mortality rate of up to 40% [8, 23, 24]. However, the severity of IOB may vary, ranging from a slight leakage of contrast material into the subarachnoid space to a massive hemorrhage with severe intracranial hypertension.

Several studies have assessed the risk factors of IOB. A meta-analysis showed that the risk of aneurysm perforation in coil embolization was significantly higher in patients with previous ruptured aneurysms than in those with unruptured ones [8]. Ruptured differ from unruptured aneurysms due to the presence of a rupture point and bleb. Moreover, a history of SAH may stimulate blood vessel walls and aneurysms with blood filling the subarachnoid space, resulting in an increased susceptibility to aneurysm rupture [8]. Although IOB is less common in unruptured than in ruptured aneurysms [25, 26], it is associated with increased morbidity and mortality rates [11, 27–29]. The other risk factors of IOB are small-size aneurysms and those with an anterior communicating artery (Acom) aneurysm [25]. A high risk of rupture in small-size aneurysms is attributed to the increased restriction of microcatheter movement within the aneurysm, resulting in greater stress within the aneurysm sac, particularly in cases of Acom aneurysms [30]. The risk factors of IBO may include unfavorable dome-neck ratio, acute angle between the internal carotid artery and the anterior cerebral artery, and morphological complexities of Acom [31]. Coronary artery disease, hyperlipidemia, race, chronic obstructive pulmonary disease (COPD), and low Hunt and Hess grade were associated with a greater risk of IOB, thereby indicating differences in vessel fragility requiring further confirmation [5]. For patients undergoing coiling, the independent predictors of IOB were Asian and black race, COPD, and lower initial Hunt and Hess grade [5]. Since the complication rate is low, the identification of these risk factors becomes challenging.

Regarding procedural issues, the balloon-assisted technique is similar to the use of temporary clips for the treatment of aneurysms. However, some studies showed that the use of balloons is a risk factor for IOB [32]. However, others have contrasting results [33–35]. In a retrospective study on subarachnoid hemorrhage (SAH), the incidence rate of IOB was significantly higher in patients who received local anesthesia than in those who received general anesthesia [36]. The high incidence rate of IOBs is attributed to unexpected movements, which can displace micro-instruments, during local anesthesia administration. The hemorrhagic complications of endovascular coiling include procedural aneurysmal perforations caused by devices including microcatheter, micro-guidewire, microballoon, or coil. Although these complications can occur, they are unexpected, complex and can have devastating outcomes [9]. Cloft et al. reported that the morbidity and mortality rates of perforations caused by coils (39%) and microcatheters (33%) were similar, and the morbidity and mortality rates of IOBs caused by micro-guidewires were considerably lower than those caused by coils or microcatheters [8]. Kawabata et al. showed that the clinical outcomes depend on the cause of IOB, and patients who experience aneurysmal rupture caused by microcatheter present with worst outcomes. Moreover,

the rates of good clinical outcomes associated with the use of coils, micro-guidewires, and microcatheters were 90%, 100%, and 57%, respectively [37]. Over-packing of the aneurysm, oversized coils, and use of stiff three-dimensional coils and inappropriate devices are associated with IOBs [33].

Decreasing the risk of mortality and permanent neurologic disability caused by IOB is dependent on immediate and proper treatment after a perforation occurs [8]. The immediate identification of IOB is extremely important. The first radiographic sign of a perforation is breakage caused by any tool used beyond the anatomic boundary on a road-map image. This is followed by increased blood pressure and pulse rate. Occasionally, false breaching can appear due to a patient's feeble movement, partially thrombosed aneurysm, or superimposed parent artery [9, 13]. Moreover, blood pressure quickly increases without an IOB when manipulation of devices stimulates the endothelium of a cerebral artery or in the event of diminished anesthesia [13].

11.2.2 Comparison Between the Outcomes of Coiling and Clipping

The incidence rates of IOB caused by coiling range from 1% to 2% for unruptured aneurysms and from 4% to 5% for ruptured aneurysms. The rate has been discussed and compared with that of IOB caused by clipping, which is the standard treatment for cerebral aneurysms. Several retrospective case series conducted in single institutions showed that the incidence rates of IOB vary from 2% to 4.5% for coiling and from 7.6% to 34.9% for clipping [3, 19, 26, 38–43]. CARAT is an ambidirectional cohort study of 1010 unselected patients with ruptured intracranial aneurysms who were treated by coil embolization or surgical clipping at 9 high volume centers in the United States from 1996 to 1998 and who were followed-up for more than 5 years. Moreover, it is an important prospective study as it revealed the complication rates between clipping versus coiling [5]. According to the study, IOB occurred in 148 (14.6%) patients, and ruptures during coiling (5%) or clipping (19%) increased the risk of periprocedural mortality/disability by four- and two-fold, respectively. The complications, risks, and morbidity and mortality of ruptured cerebral aneurysms are significantly low in coil embolization. Moreover, race and lower initial Hunt and Hess grade were associated with IOB based on a univariate analysis. The relationship between lower Hunt and Hess grade and a higher risk of IOB is perplexing probably because data were not collected prospectively and patients were not randomized to treatment type. The risk of IOB with COPD may be lower with clipping because vessels are not approached intraluminally or simply because the risk is predicted based on other unidentified factors that obscure an association with COPD.

However, the technical challenges between clipping and coil embolization are challenging to compare in terms of SAH severity and location of the targeted aneurysm because both are completely different treatment modalities. In the BRAT study [3], a policy of intent to treat favoring coil embolization, rather than clip occlusion, resulted in a low incidence of poor outcomes. Hence, a substantial number of treatments were switched from endovascular coiling to surgical clipping. Therefore, high-quality surgical clipping should be used as an alternative treatment modality. In summary, whether coiling is superior to clipping has not been validated in real-world settings, and performing either coiling or clipping should be based on the protocols of each institution.

11.2.3 Results

Data on IOB are described in this section. This retrospective study aimed to investigate the prevalence, risk factors, and management of complications among patients admitted to our institutions.

11.2.3.1 Material and Methods

Between April 2007 and October 2020, 570 ruptured cerebral aneurysm embolization procedures

Table 11.1 Total number of coiling procedures for ruptured and unruptured aneurysms and incidence of intraoperative bleeding (IOB) and mortality. The overall incidence rate of IOB was 2.9%, and the incidence of IOB and mortality was high in ruptured aneurysms

	Total number of interventions	Proportion of patients with IOB	%	No. of deaths	Mortality rate
Ruptured	570	29	5.1%	8	1.4%
Unruptured	1178	22	1.9%	3	0.3%
Total	1748	51	2.9%	11	0.6%

were performed at our institution and affiliated hospitals. Then, 29 (5.1%) patients presented with perioperative hemorrhagic complications, and 1178 patients with unruptured cerebral aneurysms underwent embolization. Moreover, 22 (1.9%) had perioperative hemorrhagic complications (Table 11.1). Next, we examined the location, shape, size, and severity of aneurysms and SAH in patients with intraoperative hemorrhage.

Our interventions have been reported in a previous study [44]. In brief, patients with unruptured aneurysms received two types of antiplatelet treatment (ticlopidine and aspirin or clopidogrel and aspirin) 1 week before surgery. Those treated with antiplatelet drugs received oral aspirin 100 mg daily and ticlopidine 100 mg twice a day. Heparin was administered intravenously (50 IU/kg) after the placement of a vascular sheath in the common femoral artery. In patients with ruptured aneurysms, treatment with systemic heparin was delayed until the guiding catheter was successfully placed. Anticoagulation therapy aimed to maintain the activating clotting time (ACT) at 1.5–2 times above the control level. The guiding catheters were continuously flushed with saline, and the sheaths were not continuously flushed. In all cases, systemic heparin was not reversed, and the patient was transferred to the stroke intensive care unit.

11.2.3.2 Results

Ruptured aneurysm: In total, 29 (5.1%) patients presented with perioperative hemorrhagic complications. Acom is the affected site in 16 (9.7%) of 165 patients. Intraoperative rupture was fatal in eight (50%) patients. Intraoperative hemorrhagic and other cases are presented below, followed by middle cerebral artery aneurysms in 2 (6.3%) of 32 patients and paraclinoid aneurysms of the internal carotid artery in 1 [5.0%] of 20 patients. IC-posterior communicating artery (Pcom) aneurysms (3 [1.9%] of 156) and basilar top aneurysms (0/48) were less common (Table 11.2). The total aneurysm size was smaller in the IOB group than in the non-IOB group (5.1 vs 6.3 mm), and the VER was higher in the IOB group than in the non-IOB group (44.4% and 33.1%, respectively) (Table 11.3). Intraoperative hemorrhage was characterized by neck outpouching (NOP) in four (26.7%) patients with Acom aneurysms.

Table 11.2 Proportion of patients with and location and incidence rate of IOB in embolization for ruptured aneurysms

Location	No.	IOB	%
Acom	165	16	9.7
ICPC	159	3	1.9
BA-top	48	0	0
ICaca	36	2	5.6
MCA	32	2	6.3
BASCA	23	0	0
ICpara	20	1	5.0
VAPICA	17	2	7.1
BA trunk	12	0	0

Acom is the most common site of IOB. By contrast, there is no IOB on BA-top. In addition, the incidence rate of IOB in MCs is high. However, the number of cases is small. *Acom* anterior communicating artery; *ICPC* internal carotid–posterior communicating artery; *ICaca* internal carotid–anterior choroidal artery; *MCA* middle cerebral artery; *BASCA* basilar artery–superior cerebellar artery aneurysms; *ICpara* paraclinoid aneurysms of the internal carotid artery; *VAPICA* vertebral–posterior inferior cerebellar artery aneurysms

Unruptured aneurysms: Perioperative hemorrhagic complications occurred in 22 (1.9%) of 1178 patients, of which three (0.3%) resulted in death (Table 11.1) and residual disability with a

modified Rankin scale (mRS) score 4 or greater in 2 (0.1%) patients. Then, 15 patients were discharged from the hospital with an mRS score 0 or 1 without any disability. Four (0.3%) patients underwent clipping. In 5 (4.6%) of 107 patients, the middle cerebral aneurysm (MCA) was the site of intraoperative hemorrhage. Intraoperative hemorrhage and other cases are presented below, followed by IC–Pcom aneurysms in 6 (3.7%) of 163 cases and Acom aneurysms in 4 (2.8%) of 140 cases. IC–paraclinoid aneurysms (4 [1.0%] of 402) and basilar top aneurysms (0/64) were less common (Table 11.4). IOB was most common in MCA aneurysms in unruptured aneurysms than in ruptured aneurysms. The total aneurysm size was smaller in the IOB group (5.7 mm) than in the non-IOB group (6.4 mm), and the VER was high in the hemorrhagic group (44.1% and 35.4%, respectively) (Table 11.5).

Intraoperative rupture caused by different devices was observed (Table 11.6). Intraoperative rupture during filling is common in ruptured cerebral aneurysms. However, poor prognosis is somewhat less common. Patients with intraoperative rupture with microcatheters and framing coils had a poor prognosis. There were no complications with the use of micro-guidewires or microballoons in ruptured cerebral aneurysms. Two patients with unruptured cerebral aneurysms presented with microballoon-induced vessel cracking, which is a fatal complication. In several intraoperative rupture cases, the cause was unknown. Thus, disease onset is difficult to predict.

Table 11.3 Size of the neck, long axis, and volume of embolization (VER) for ruptured aneurysms between the IOB and non-IOB groups. In the IOB group, endovascular obliterated aneurysms have a small neck and long axis size, and the volume embolization rate was high

	IOB group (n = 29)	Non-IOB group (n = 541)	Total number of patients (n = 570)
Age	66.5	64.7	64.8
Neck (mm)	3.1	3.8	3.8
Long axis (mm)	5.1	6.3	6.3
VER (%)	44.4%	33.1%	33.8%

11.2.3.3 Case Presentations

Case 1 (Fig. 11.1). A 69-year-old woman was unconscious and admitted to our institution. The preoperative WFNS grade was 4. The patient was diagnosed with ruptured aneurysm at Acom. Thus, coil embolization was performed. In particular, the angle from A1 to the axis of the mass was acute. Thus, the approach used was challenging. Moreover, there was neck outpouching (NOP). When the fifth coil was embolized, extravascular leakage of the contrast agent was observed. Two coils were subsequently embolized and hemostasis was achieved. However, the patient died due to severe SAH.

Table 11.4 Location of unruptured aneurysm, number of interventions, and proportion of patients with IOB. In unruptured aneurysms, IOB is more common in MCA and ICPC and is less common in BA-top and ICpara

Location	No. of interventions	Proportion of patients with IOB	%
ICpara	402	4	1.0
ICPC	163	6	3.7
Acom	140	4	2.8
MCA	107	5	4.6
BA-top	64	0	0
ICaca	46	0	0
BASCA	40	1	2.5
AC distal	27	0	0
IC others	26	0	0

Acom anterior communicating artery; *ICPC* internal carotid–posterior communicating artery; *ICaca* internal carotid–anterior choroidal artery; *MCA* middle cerebral artery; *BASCA* basilar artery–superior cerebellar artery aneurysms; *ICpara* paraclinoid aneurysms of the internal carotid artery; *VAPICA* vertebral–posterior inferior cerebellar artery aneurysms

Case 2 (Fig. 11.2). A 66-year-old man presented with grade 3 SAH. The patient was diagnosed with ruptured aneurysm in Acom. Moreover, NOP was observed. Axelguide 6F (Medikit), Fubuki 4.2F (Asahi Intec.), Neurodeo 10 (Medicos Hirata), Chikai14 (Asahi Intec.), first coil: Galaxy 3.5 mm 9 cm (J&J), one loop of the first coil was applied to the NOP, and the framing was good. After deploying the second coil, the loop deviated outside the coil mass at a slightly distant site from NOP, thereby indicating intraoperative rupture. Further embolization of the coils was performed to achieve hemostasis.

Case 3 (Fig. 11.3). A 67-year-old woman was admitted to the hospital for the endovascular treatment of right ICPC aneurysm without neurological deficits. Coil embolization was performed, and blood vessel cracking was observed during the third coil insertion. The aneurysm neck size was 4.0 mm; depth, 4.4 mm; width, 4.2 mm; and thickness, 3.8 mm. Axelguide 5F (Medikit), Hyperform 7 mm:7 mm (Medtronics), Neurodeo10 (Medicos Hirata), Chikai14 (Asahi Intec.), first coil: Galaxy 3.5 mm 5 cm (J&J), second coil: Target 360 nano 2 mm 4 cm (Striker), third coil: Target 360 nano 2 mm 4 cm. Balloon-assisted coil embolization was performed. The Hyperform 7*7 mm balloon caused cracks in the internal carotid artery, resulting in fatal vascular injury. The recommended infusion volume for Hyperform 7*7 mm is 0.27 mL. Visibility was not an issue in the use of this balloon, and the recommended infusion volume was maintained.

Table 11.5 Aneurysm neck and size and volume of embolization (VER) for unruptured aneurysms. The characteristics were similar to those of ruptured lesions (long axis size and high volume embolization rate)

	IOB group (n = 22)	Non-IOB group (n = 1156)	Total number of patients (n = 1178)
Age	60.8	61.4	61.4
Neck size (mm)	3.9	4.0	4.0
Long axis (mm)	5.7	6.4	6.4
VER (%)	44.1	35.4	35.6

11.2.3.4 Discussion

In this study, the incidence of IOB was similar to that of previous reports: 5.1% and 1.9% for ruptured and unruptured aneurysms, respectively. Compared with unruptured aneurysms, ruptured ones are associated with a higher incidence of IOB, and risk factors such as aneurysmal rupture, small-size aneurysms, and location in Acom have been reported previously. Moreover, a significantly high proportion of patients with IOB presented with neurologic deterioration at discharge and last follow-up. However, the proportion of functionally independent patients with an mRS score of 0–2 did not differ between the two cohorts. This result indicated that the degree of disability caused by IOB among patients with

Table 11.6 Devices that could cause intraoperative bleeding. Patients with intraoperative rupture caused by microballoon, framing coil, or microcatheter had a poor prognosis, whereas those with intraoperative rupture caused by filling coil had a better prognosis

	Number of ruptured cases	Mortality in ruptured cases	Number of unruptured cases	Mortality in unruptured cases
Microcatheter	1	1	1	0
Micro-guidewire	0	0	1	0
Microballoon	0	0	2	2
Coil				
Framing	2	2	1	0
Filling	10	1	6	0
Finishing	1	0	5	0
Increase in hematoma size	3	3	(−)	(−)
Unknown	10	2	6	1

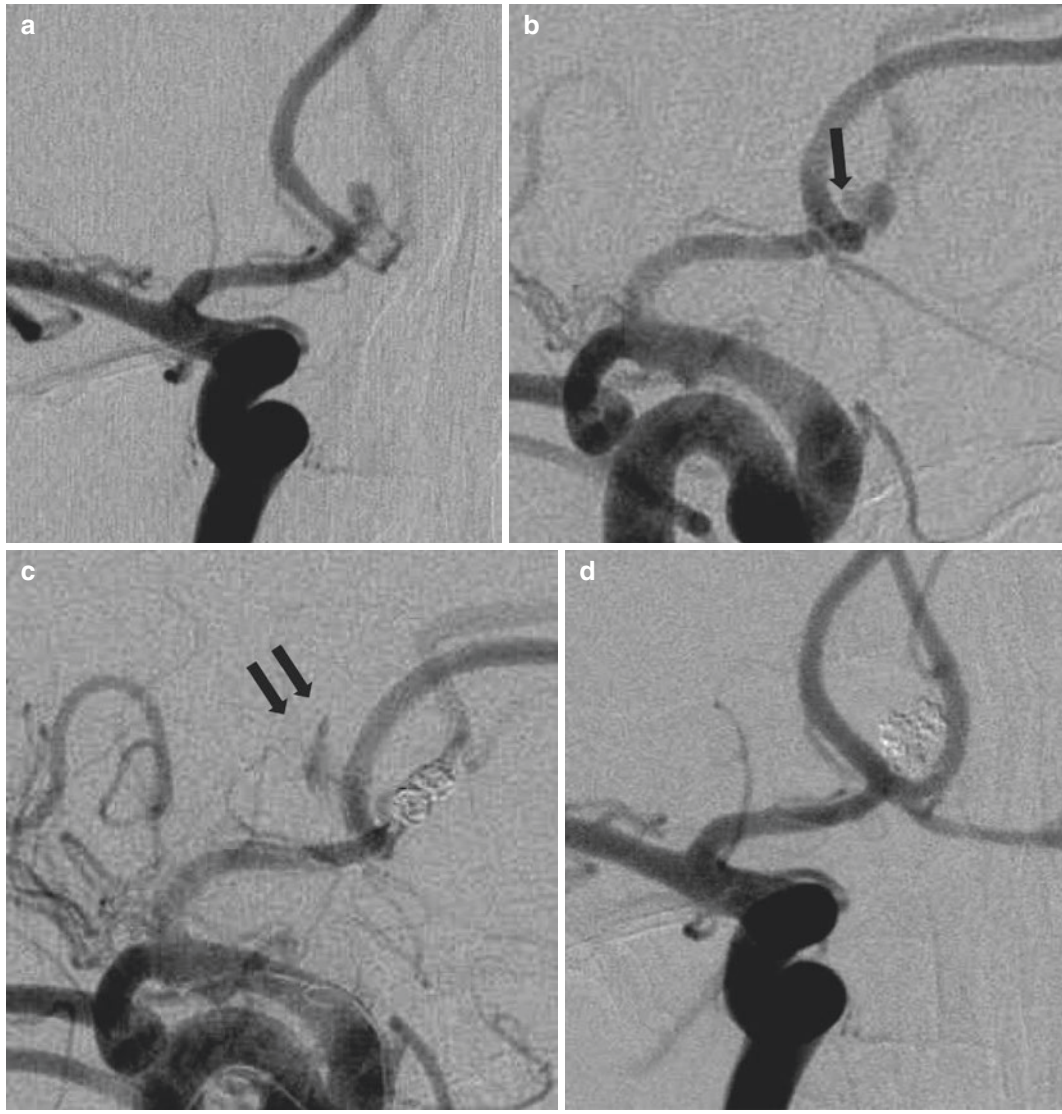


Fig. 11.1 Case 1. See text for full details. (**a**) Preoperative left carotid artery angiogram, neck view. (**b**) Other view on left carotid angiogram. A small basal neck outpouching was observed (arrow). (**c**) After five coils were embolized, extravasation of the contrast material was noted (double arrow). (**d**) Two coils were embolized and intraoperative bleeding was controlled

unruptured aneurysms was not severe. Notably, none of the patients in the IOB cohort with an aneurysm in Acom, which was the most common location of IOB in the ruptured aneurysms group, experienced neurological deterioration. By contrast, the IOB cohort with BA aneurysm had a high risk of neurological deterioration (two [66.7%] of three cases) [45]. There is a high incidence of IOB in Acom in our institution. However, no cases of intraoperative rupture of basilar artery aneurysms, which vary per institution, were observed.

Most cases of aneurysm intraoperative breach during filling were caused by microcatheter perforation and vascular damage caused by a microballoon in unruptured aneurysm treatment. There are only few reports on complications caused by microballoon as the Case 3. This complication is

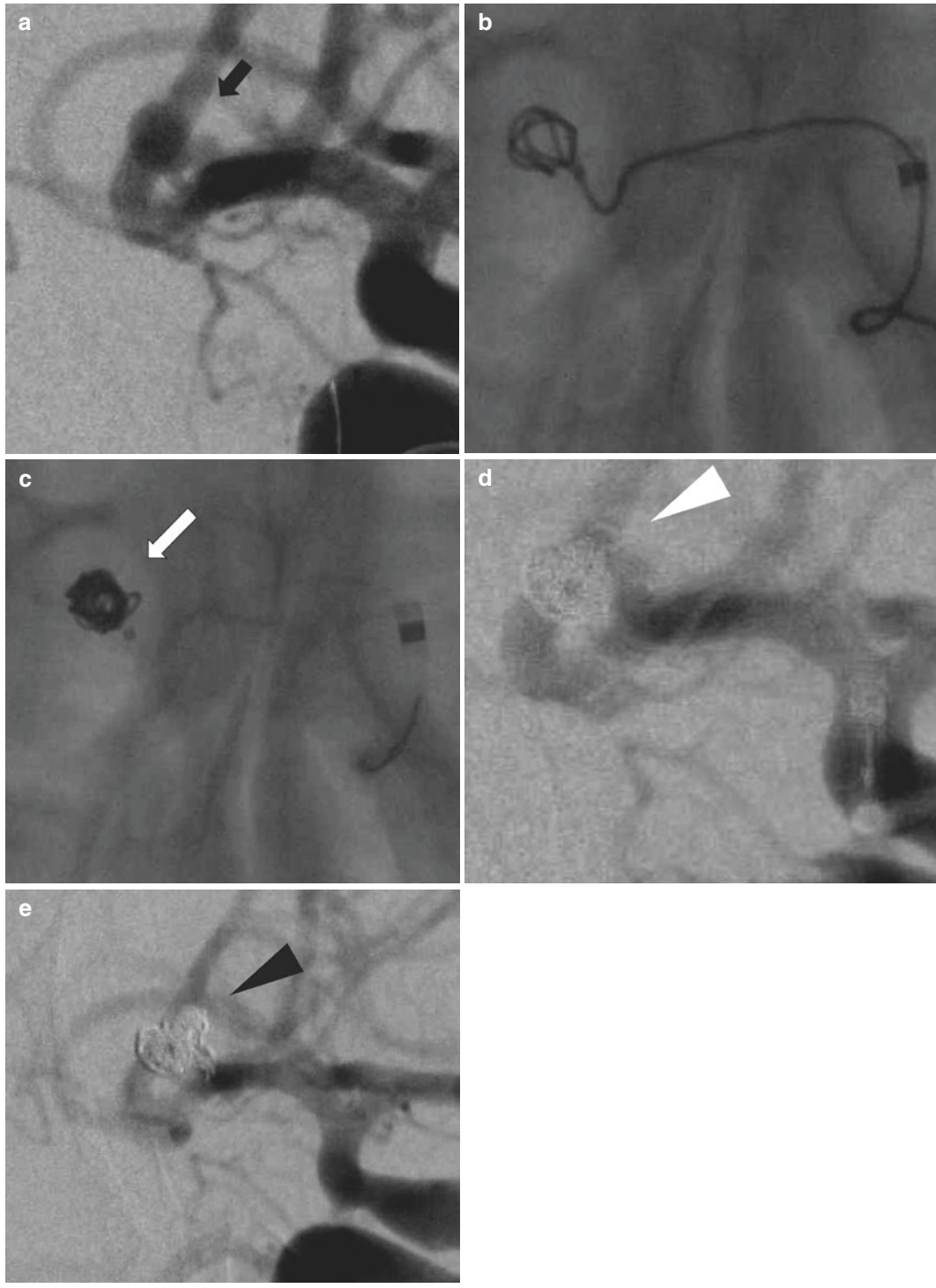


Fig. 11.2 Case 2. See text for full details. A 68-year-old man with grade 3 SAH. See text for full detail. A diagnosis of ruptured Acom was made. (**a**) There was a basal neck outpouching (NOP: black arrow). (**b**) Framing was in progress. (**c**) A coil loop was placed on the NOP and a good frame was made. (**d**) Coil protrusion outside the aneurysm during the second coil embolization. The loop was observed at site slightly distant to NOP (white arrowhead), resulting in an intraoperative rupture. (**e**) Hemostasis is complete and extravascular leakage has stopped (black arrowhead)

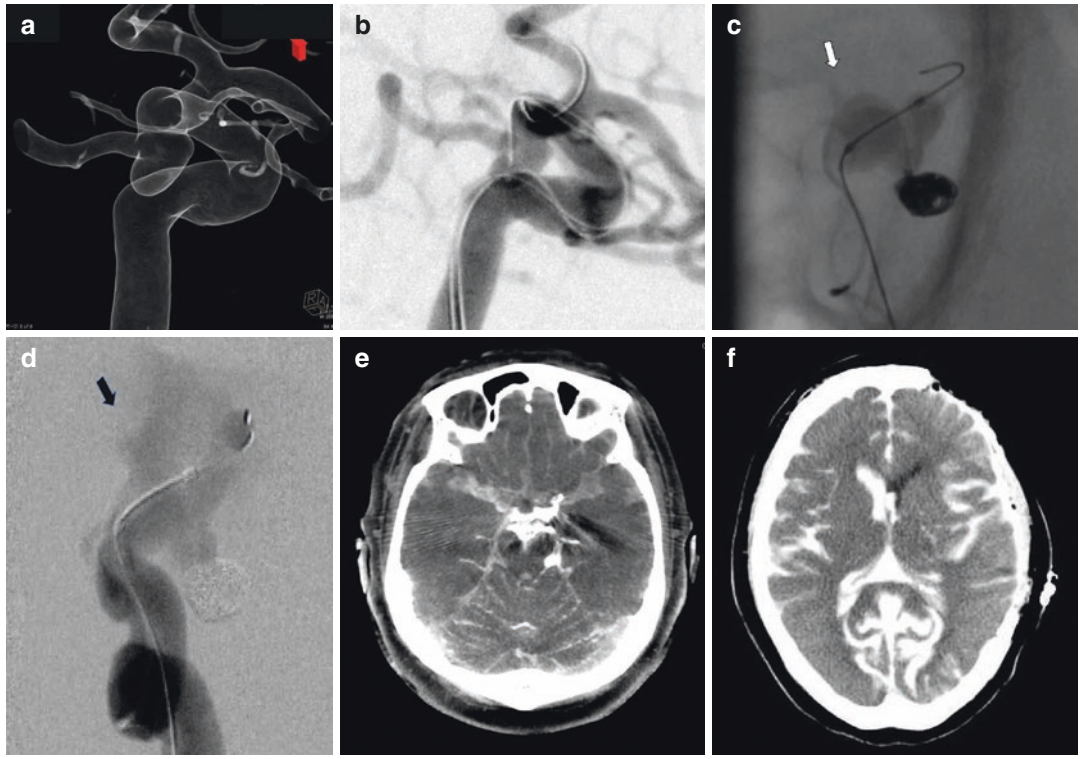


Fig. 11.3 Case 3. Fatal rupture with the use of microballoon. See text for full detail. Size of the neck 4.0 mm, aneurysmal dome size 4.4 mm. Broad neck and relatively small-size aneurysm. In placing the third coil the vessel laceration occurred. (**a**, **b**) ICPC aneurysm was observed on three-dimensional angiogram. Pcom branched from the neck. Although the dome-to-neck ratio was low, balloon-assisted coil embolization could be feasible. (**c**) The Hyperform balloon 7*7 mm was tearing the vessel wall. (**d**) Intraoperative rupture occurred. Balloon bursting was suspected. Local hemostasis was unsuccessful, and the patient died after external decompression. (**e**, **f**) The procedures were performed at the interventional room combined with multidetector computed tomography (CT). (**e**) Hemorrhagic complication was found in plain CT scan immediately after the rupture. (**f**) The patient underwent immediate decompressive craniotomy, the CT scan revealed diffuse swelling of the whole brain parenchyma and the cortico-medullary boundary was obscured

often fatal. Local hemostasis with balloons is no longer feasible, and parent vessel occlusion may be performed, or, alternatively, a liquid embolic material can be used. Middle cerebral and small-size aneurysms were associated with IOB in unruptured cases in the series. Most patients had a good prognosis due to rapid response to microballoons. Preoperative planning was considered important, and this management should consider the structure of the blebs and masses as well as microcatheter movement and coil embolization.

The presence of NOP, as shown in Figs. 11.1 and 11.2, is another issue. Although intracranial saccular aneurysms invariably rupture in the dome area, the wall of the aneurysm base can be the point of rupture. This finding has been reported for quite some time. In terms of incidence [44], the rate was 2% according to an autopsy study by Crompton [46]. Nonetheless, the recognition of such a basal rupture on angiographic evaluation is crucial for optimal treatment [47]. In a patient with an aneurysmal subarachnoid hemorrhage, the basal outpouching may be the point of rupture. These so-called basal ruptures are often accompanied by an angiographically identified blister at the neck region of the aneurysm [48]. In this series, the rupture site is the basal outpouching observed along with

Table 11.7 Risk factors of intraoperative bleeding in coiling based on previous studies

History of aneurysmal rupture [8, 25, 26]
Location (e.g., Acom [25, 30, 31] & BA-top [45])
Neck basal outpouching [47–49]
Small size [5, 8, 25]
History of chronic obstructive pulmonary disease [5]
Race (Asian, black [5])

ruptured aneurysms in approximately 33% of patients with surgically explored aneurysms with this pathoanatomic feature [49]. This finding was correlated with coil perforation of the ruptured basal outpouching or coil compaction into the dome, which exposes the basal rupture site. Hence, NOP is important and can be considered a risk factor.

Table 11.7 summarizes the risk factors for IOB in conjunction with the related previous reports. These include factors for which consensus has not yet been established. However, there is a consensus that at least ruptured aneurysms, small aneurysms, Acom, and the presence of NOP should be treated with full awareness.

11.2.4 Management of Hemorrhagic Complications

Angiogram can be performed to confirm the presence of IOB. Contrast material staying in the venous phase indicates blood in the subarachnoid space. Cone-beam computed tomography (CT) can be conducted to assess for this condition. If aneurysmal perforations are detected during the procedure, prompt treatments are critical. That is, blood pressure should be controlled, and anticoagulants must be immediately reversed. However, in some cases, we do not recommend protamine administration if rapid mechanical hemostasis can be achieved. Antiplatelet medications such as aspirin and clopidogrel can also be reversed [50].

Perforation caused by micro-guidewire may be minimal, and embolization can be continuously performed. However, caution should be taken. When perforation caused by devices such as coil and microcatheter is observed, the instrument should not be removed to prevent further injury to the structures. Laceration caused by a coil can be mitigated by leaving the perforating coil in place. Hence, the part of the coil outside of the aneurysm should be deployed, and the microcatheter tip must be withdrawn from the proximity of the aneurysm wall. Upon positioning the microcatheter tip, the rest of the coil should be delivered into the aneurysm. With the use of a second microcatheter, the aneurysm must be packed with coils, thereby temporarily leaving the first microcatheter in place. This multiple microcatheter technique is more advantageous than a single microcatheter technique for the immediate and accurate management of IOB [51]. In addition, hemorrhage can be immediately and effectively controlled with the application of a balloon, which is considered as temporary clipping, across the aneurysmal neck at the time of rupture. However, caution must be taken when using balloons because it may increase the risk of secondary procedural complications. In such circumstances, n-butyl cyanoacrylate can be considered in the closure of aneurysmal ruptures [52]. McDougall et al. reported that uncontrolled advancement of microcatheters can be a factor for IOB. The incidence of microcatheter perforation can be decreased by ensuring that no forward pressure is exerted on the microcatheter before the micro-guidewire is removed and by withdrawing the micro-guidewire very slowly while under fluoroscopy [39].

All endovascular devices placed into the aneurysm lumen can cause perforation. Moreover, neurointerventionists should be aware that microcatheters have a radiolucent distal segment with a length of approximately 0.5–1 mm between the distal marker visible on fluoroscopy and the actual microcatheter tip [53]. However, the incidence of wire perforations is underreported. The size of the perforation was correlated with the device size. Because of the small number of perforations in unruptured aneurysms, performing a statistical comparison is not practical.

11.3 Ischemic Complications

11.3.1 General Considerations

A thromboembolic event is defined as any event with complete or partial occlusion of arteries at the site of the parent vessel and aneurysm distal to the vascular territory where the endovascular procedure was performed and/or in other vascular territories. The mechanisms and management of thromboembolic complications are described in this section. Ischemic complications are important factors influencing prognosis after endovascular therapy for intracranial aneurysms. The incidence rates of symptomatic ischemic complications among individuals receiving this therapy range from 2% to 3% [54–56]. Furthermore, about 10%–60% of patients present with small high-intensity signals on diffusion-weighted images [57, 58]. Thromboembolic complications may begin with the emergence of a small thrombus in a vessel. First, a small thrombus develops in a vessel [9]. This can lead to vascular occlusion due to thrombosis. In addition, a thrombus may develop in the catheter when DAC is used, and the thrombus may somehow flow distally, causing an infarction. Although thromboembolic complications are more common and are associated with higher morbidity rates than intraprocedural ruptures, identifying a thromboembolism is more challenging than confirming the presence of aneurysmal perforations [9]. Appropriate response is still essential at an early stage. Heparinization and preoperative coagulation therapy can prevent complications. Oral clopidogrel and/or aspirin decreased the symptomatic thromboembolic complication rate of elective coil embolization for unruptured aneurysms [58]. This result indicates that the treatment of unruptured cerebral aneurysms begins with preoperative preparation.

Thromboembolic complications start with the formation of microthrombus in the local vessels. First, the pathogenesis of microthrombus was discussed. This condition might be attributed to the administration of antiplatelet therapy preoperatively. GP inhibitors [59, 60] might be more effective than fibrinolysis because acute thrombi are rich in platelets (white clot). Although it is used for the treatment of thromboembolic complication during procedures, there might be a higher risk of complication at the vascular access site, hemorrhage if emergency surgery is needed, thrombocytopenia, and intracranial hemorrhage, and the effects are not easily reversed. We administered aspirin 200 mg via a stomach tube, and systemic hypertension was controlled. In case of flow disturbance, tPA and GP1 inhibitors combined with fibrinolysis using urokinase were recommended. In recent years, the usefulness of prasugrel has been reported and it is being widely used in clinical practice [61]. In any opinion, thrombus formation in the parent vessels initially occurs in thromboembolic complications. Therefore, knowledge on the mild effects of contrast agents is important.

11.3.2 Local Thrombus Formation: Angiographic Classifications of Appearance and Management

Intraprocedural thrombus that forms at the boundary between the parent vessel and the aneurysm neck during coil embolization can be successfully treated if detected at an early stage [62–65]. The sources of these emboli vary, thereby indicating a potential risk of frequent thrombus formation during coil placement. In this procedure, particularly at the late stage, a minute thrombus appears around the parent vessel at the aneurysm neck with coil mass [65]. Intraprocedural thrombus that forms at the boundary between the parent vessel and the aneurysm neck during coil embolization can be successfully treated if detected at an early stage [63–65]. The following are some points regarding angiographic findings.

The coil–parent artery interface is the surface of the coil mass that interacts with the inflow and/or outflow of blood stream and is located at the parent artery and coil mass. Moreover, it includes areas in the parent artery where turbulence or stasis of flow might occur during procedures. Fresh thrombus was defined as the presence of a small

volume of contrast material at the coil–parent artery interface zone in coil embolization. A grading system that was modified based on the TICI grading systems [66–68] was used:

- Grade 1: microthrombus formation with normal flow, no distal occlusion
- Grade 2: distal artery occlusion without normal filling in the distal branch with near-normal appearance
- Grade 3: thrombus formation with significant flow reduction, poor filling of the parent
- Grade 4: no flow, parent vessel occlusion (Fig. 11.4)

Therapy for microthrombi was started based on the physician's discretion. Aspirin 200 mg was administered via a stomach tube. Moderate perfusion was achieved immediately after control angiography. Patients with grade 2 thrombus on angiography received fibrinolytic therapy. Intra-arterial urokinase infusion was started via continuous manual injection. The infusion rate was about 5000 IU/min, and the infusion lasted for 15–30 min. Angiography was performed repeatedly. Even if perfusion was not achieved, treatment was discontinued at a maximum dose of 100,000 IU. ACT was conducted in all patients before starting fibrinolysis therapy. Cronqvist et al. reported the outcomes of super-selective intra-arterial fibrinolytic therapy for thromboembolic events occurring during endovascular aneurysm treatment in 19 patients. Results showed complete recanalization in 10 and partial recanalization in 9 patients, and 14 eventually presented with good outcomes [59]. However, three of six patients with ruptured aneurysms had intracranial bleeding. Hence, compared with rescue therapy

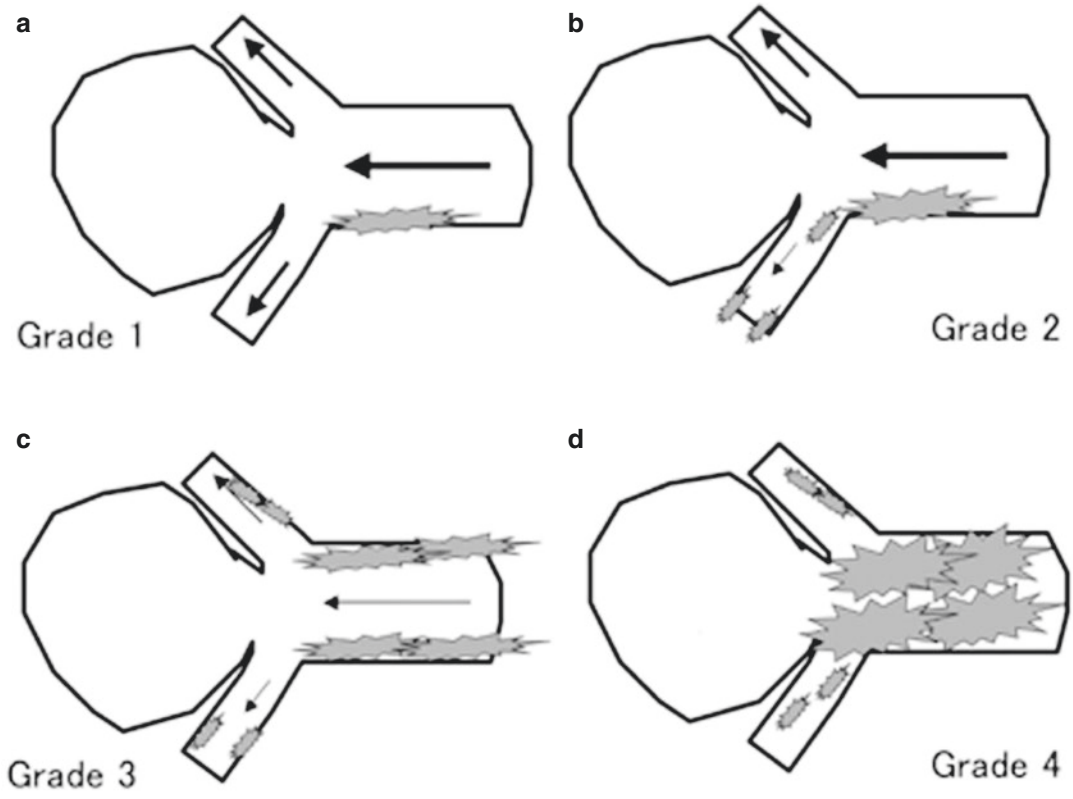


Fig. 11.4 Schematic representation of thrombus formation at the parent vessels. (**a**) Grade 1: Microthrombus formation with normal flow. (**b**) Grade 2: distal artery occlusion without normal filling in the distal branch. (**c**) Grade 3: thrombus formation with a significant flow reduction. (**d**) Grade 4: no flow, occlusion of the parent artery

with glycoprotein IIb/IIIa inhibitors, that with fibrinolytic agents for intraprocedural thromboembolic events is associated with significantly higher morbidity and mortality [69]. Therefore, urokinase and tPAs are no longer considered as the primary treatment for thrombi during coiling of aneurysms.

11.3.2.1 Case Presentation

Case 5 (Fig. 11.5)**. Grade 1: Microthrombus Formation**

A 67-year-old-woman underwent coil embolization for a ruptured Acom cerebral aneurysm (H&K grade 4, WFNS grade 4, and Fisher score of 3). The procedure was performed on day 0. The patient underwent elective coiling of the aneurysm. Embolization of the aneurysm was performed with a single catheter technique. A microthrombus appeared in the left A2 after the final stage of coil embolization. Aspirin 200 mg was administered immediately via a stomach tube. Serial angiography revealed diminished thrombus, and no distal artery emboli were observed. The thrombus soon disappeared.

Case 6 (Fig. 11.6)**. Grade 3: Thrombus Formation with Significant Decrease in Blood Flow**

A 63-year-old woman was admitted to our hospital due to altered mental status. CT scan revealed SAH (H&K grade 4, WFNS grade 4, and Fisher score of 3). The patient was diagnosed with ruptured cerebral aneurysm in Acom. Coil embolization was performed on day 0, with a simple catheter technique. A short time after catheter removal, a microthrombus was observed in the right A2. Then, there was a tendency for microthrombi to infiltrate toward the neck with significant decrease in blood flow in the parent artery. Aspirin 200 mg was administered immediately via a stomach tube, and serial angiography revealed diminished thrombus. No distal artery emboli were observed, and the microthrombus was resolved.

Case 7 (Fig. 11.7)**. Grade 1: Microthrombus Formation**

An unruptured basilar top aneurysm was detected on magnetic resonance imaging (MRI) in a 69-year-old female patient. She underwent elective coiling of the aneurysm. The longest aneurysms measured 8.84 mm, and the neck size was 6.20 mm. After the vascular sheath was placed, heparin 5000 IU was administered. Coil embolization of the aneurysm was performed using the balloon-assisted techniques. Coil treatment of the aneurysm was continued until a tight coil mass was achieved. The total coil length used was 133 cm, and the volume embolization ratio was 26.4%. When the last coil was placed and the balloon was removed, control angiography revealed

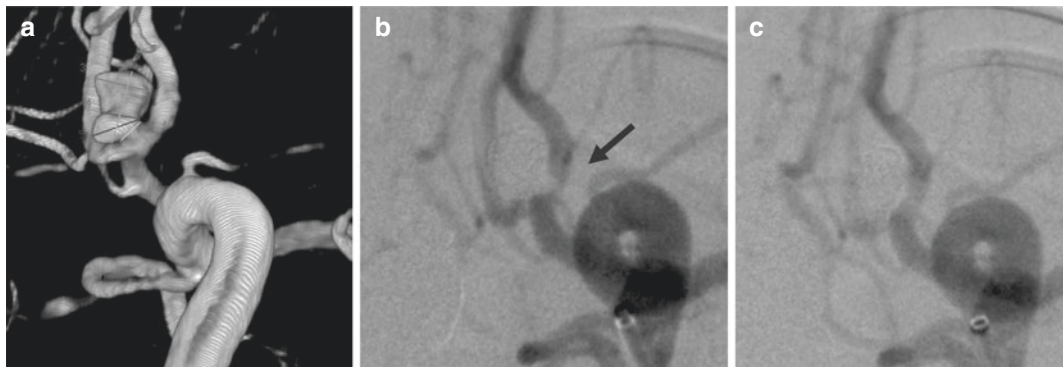


Fig. 11.5 Case 5. Grade 1 thrombus formation. (**a**) Ruptured aneurysm in Acom was observed on left internal carotid artery three-dimensional angiogram. (**b**) Left internal carotid artery angiogram revealed a small embolus at the left A2. (**c**) Complete recanalization of the vessel was achieved after the administration of aspirin 200 mg via a stomach tube

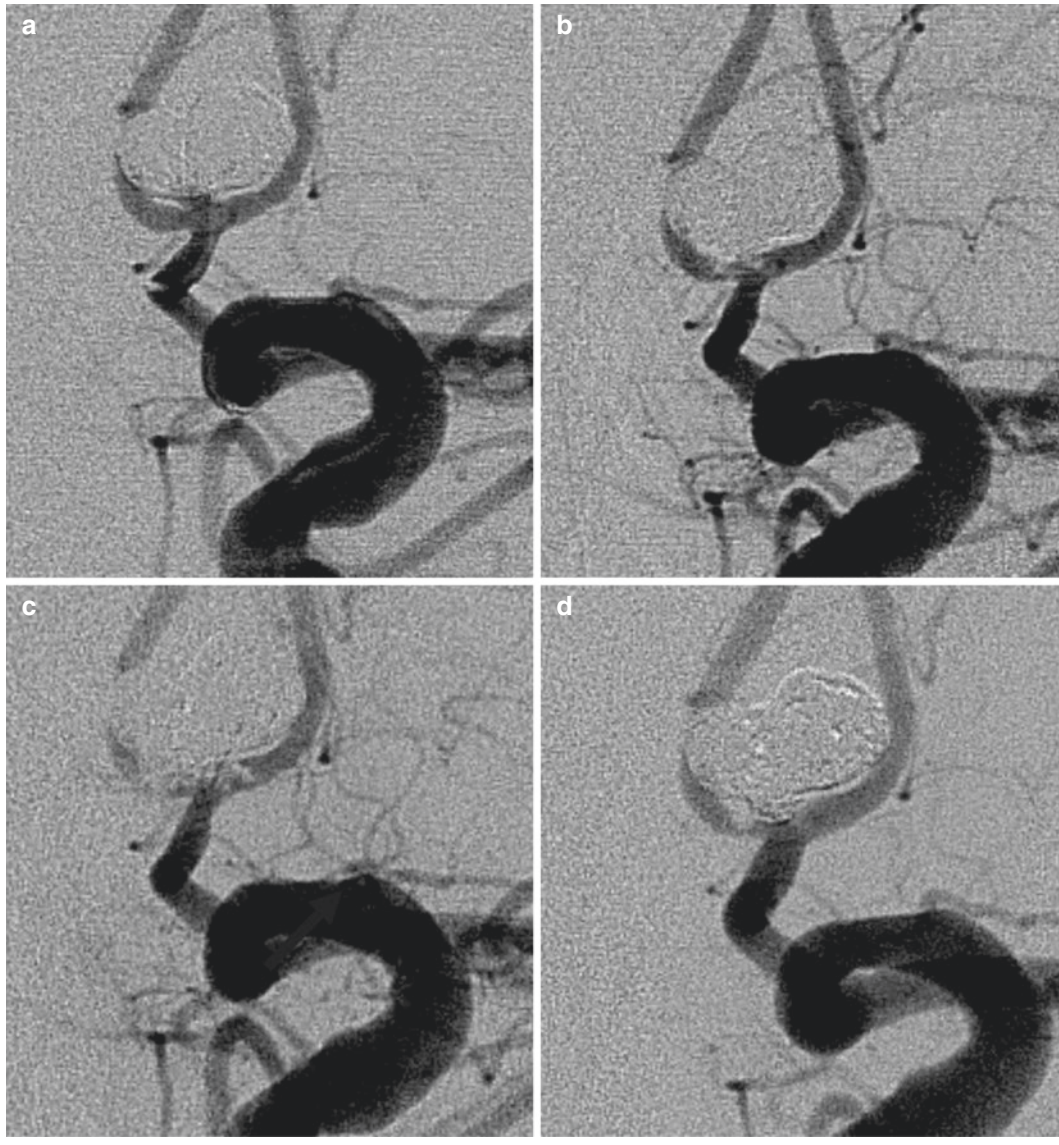


Fig. 11.6 Case 6. See text for full details. Grade 3 thrombus formation with significant reduction in blood flow. Left internal carotid angiogram revealed the following: aneurysm size, 9 mm; depth, 6.3 mm; and neck size, 2.9 mm. A simple technique of coil embolization. (**a**) Before microcatheter removal, complete embolization was achieved. (**b**) Twenty coils were used, one coil was added, and the microcatheter was removed at a VER of 26.9%. (**c**) After 10 min of waiting, there was further microthrombotic enhancement. (**d**) The microthrombus was stabilized by the drug (arrow), and the right A2 was well delineated, thereby completing the procedure

a small thrombus at the coil–parent artery interface. Aspirin 200 mg was administered immediately via a stomach tube, and serial angiography revealed diminished thrombus. No distal artery emboli were observed. After recovery from anesthesia, overnight heparinization and oral aspirin were started and continued for 3 months. The patient had no other morbidities.

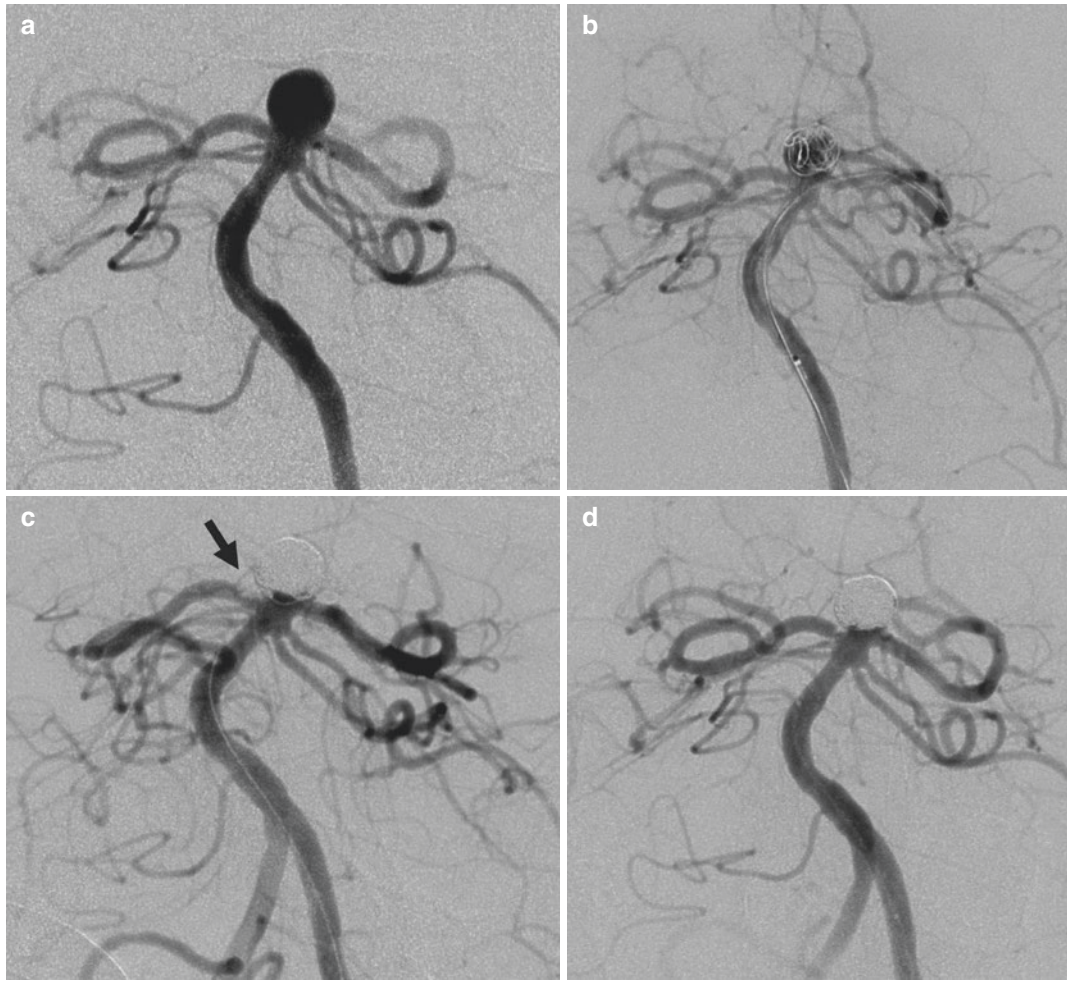


Fig. 11.7 Case 7. See text for full details. Acute thrombus formation: Grade 1. Microthrombus appeared at the right P1 of the coil–vessel border zone. (**a**) Left vertebral angiogram (frontal projection) before embolization. (**b**) Left vertebral angiogram revealed that the coil loop protruded into the parent artery, thereby maintaining normal flow in the vessel. (**c**) After balloon removal, the control angiogram showed a small volume of contrast material at the coil–parent artery interface, indicating grade 1 thrombus formation (arrow). (**d**) Angiogram after treatment. After the administration of aspirin 200 mg via a stomach tube, an almost complete resolution of thrombus at the coil surface line was observed

11.3.3 Risk Factors and Considerations

Thromboembolic complications may be caused by clot formation in the guiding catheter, on the coil mashes, or in parent vessels caused by induced vasospasm or coil mispositioning [70]. Prolapsed coil loops are the sites of platelet aggregation, leading to local thrombosis or distal thromboembolism [71]. Several reports have shown that embolic sources include air embolism, atheroma dislodgement during catheterization, thrombus formation from the device used during the procedure, and hydrophilic coating from catheters and wires [72, 73]. There are two types of factors for ischemic complications: procedure-related factors (procedure time and methods, number of coils inserted, extent of procedure manipulations, operator experience, etc.) and non-modifiable factors (patient age, aneu-

rysm size and location, presence of SAH, smoking, etc.). Regardless of the technique used, thromboembolic complications are more common in patients with a ruptured aneurysm than in those with an unruptured aneurysm [74]. A previous research showed that the other risk factor is a large aneurysm. In some studies, multivariate logistic analysis revealed that presence of SAH and procedure time were independent predictors of ischemic events during endovascular coiling of intracranial aneurysms [65, 75].

Recent advancements in vascular reconstruction devices and coils have facilitated the application of coil embolization even for aneurysms with a relatively wide neck. Despite tight coil packing, protrusion of coil segments out of the aneurysm and into the parent artery still occurs. Coil protrusions were sub-grouped according to form, degree of protrusion into the parent vessel, and position in the vessel. Coil protrusions did not increase the incidence of high-intensity lesions (infarcts) on diffusion-weighted MRI (33.3% vs 29% in cases without coil protrusion) [75]. A longer operative time increased the risk of infarct, and lesions were more commonly observed in the cortical area than in the perforating area [70, 75]. Coil protrusion was more likely to occur in cases of wide-neck aneurysms with loose neck framing. Moderate and less coil protrusion carries no additional thromboembolic risk if blood flow is maintained, which can be facilitated by additional postoperative antiplatelet therapy. Whether coil protrusion into the parent artery increases the risk of thromboembolic events is still a cause of debate. However, coil retrieval [76, 77] or parent artery stent deployment is commonly recommended for severe protrusion.

Some reports showed that stent-assisted coiling (SAC) was associated with a higher rate of thromboembolic complications than non-SAC [78]. However, if antiplatelets and anticoagulants are used appropriately, SAC is not likely associated with an increased risk of thromboembolic events, which are more common in coiling for acutely ruptured aneurysms [79, 80]. In the case of ischemic complications, there are many reports of risk factors, but no consensus has been reached by authors. This may be due to variation in treatment protocols, i.e. use of antithrombotic agents, timing and volume of their administrations in each institution. For ischemic complications, it may be difficult to compile a list similar to that for hemorrhagic complications.

11.4 Delayed Encephalopathy

11.4.1 General Considerations

Delayed leukoencephalopathy is a rare complication of coil embolization for unruptured cerebral aneurysms, and it occurs several months after treatment [17, 81]. Histologically, foreign body embolization is caused by catheter hydrophilic polymers resulting in distal embolization [16]. The cause can be hydrophilic polymer reactions, which may present as various lesions, including those in encephalopathy, chemical meningitis, and hydrocephalus. Because of insufficient data regarding this disease, a multicenter study should be conducted to elucidate its pathogenesis and prevention. Lesion biopsy suggests that device-associated PVP can cause distal embolization and granulomatous response [18]. Moreover, hydrophilic coating inside the catheter may detach during the insertion and removal of coils, which then leads to the formation of a distal embolus, resulting in granuloma at that site. In general, this condition has been reported in numerous cases of large cerebral aneurysms in which multiple coils have been used. However, in some case reports, it occurs after the implantation of flow diverters [73].

The characteristic imaging findings of multiple dots on gadolinium-enhanced T1-weighted images are granulomatous changes. These conditions are highly responsive to steroid treatment. The imaging findings are highly distinctive and have diagnostic significance. Thus, symptoms of relatively sudden neurologic deteriorations appeared several months after aneurysm coil embolization or pipeline implantation for unruptured aneurysm, in such a case, this is the first step to suspect this disease. Diagnosis is rela-

tively easy by MRI findings and is based on the following three points.

1. Multiple lesions with small patchy enhancement consistent with the access route of a cerebral aneurysm to appear after a few months later of the operation.
2. Only a slight change was observed on diffusion-weighted image in the white matter in the same area on fluid-attenuated inversion recovery with a wide range of high-signal area.
3. A low signal on magnetic susceptibility-weighted image.

It was associated with marked edema in the white matter, which might be caused by headache. The protein levels in the CSF fluid were elevated. However, no other findings were noted. Corticosteroid improved both symptoms and imaging findings and, in some cases, therapeutic diagnosis. Moreover, it has been used for treatment and found to improve both symptoms and imaging findings. Treatment with corticosteroids significantly improved both symptoms based on MRI findings.

11.4.2 Case Presentation

Case 8 (Fig. 11.8). A 62-year-old woman underwent stent-assisted coil embolization for a large unruptured left basilar artery–superior cerebellar artery aneurysm. 20.7 mm 16 mm 14.9 mm. Envoy 6F (J&J) placed at RT VA, two SL-10 (Stryker) jailed, LT VA: dominant, FUBUKI 6F (Asahi Intec), Headway17 (TERUMO), LVIS Jr. 2.5 mm 17 mm (TERUMO), 32 coils deployed, 762 cm; 819.9 mm^3, VER: 32.3%. The patient was discharged without new postoperative complications. She often complained of severe headaches. One month after coil embolization, the

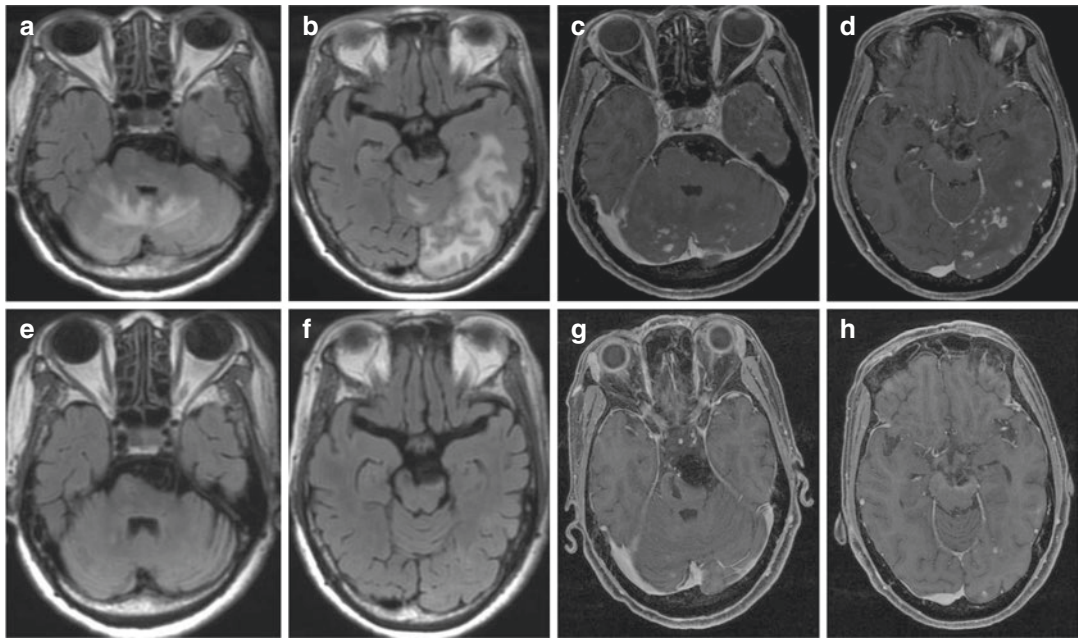


Fig. 11.8 Delayed encephalopathy. (**a**–**d**) Magnetic resonance imaging (MRI) at admission to our hospital about 1 month after coil embolization. (**a**, **b**) Fluid-attenuated inversion recovery (FLAIR) images. (**c**, **d**) Contrast-enhanced T1-weighted images. (**e**–**h**) MRI conducted 6 weeks after steroid pulse therapy. (**e**, **f**) FLAIR images, (**g**, **h**) Contrast-enhanced T1-weighted images. In the FLAIR image, there were high-signal areas in the bilateral cerebellum, left thalamus, and left temporal to the occipital lobes. On contrast-enhanced T1-weighted images, the same area had multiple punctate lesions. Six weeks after steroid pulse therapy, the high-signal range of the FLAIR images and the structures that should be assessed with contrast enhancement disappeared

patient was admitted to the hospital due to disorientation, behavioral abnormality, slurred speech, and aphasia. Fluid-attenuated inversion recovery magnetic resonance imaging revealed a high-signal intensity in the interventional perfusion areas. Multiple lesions were observed on contrast-enhanced imaging. The patient's symptoms improved with steroid pulse therapy after 6 weeks, and abnormal imaging findings disappeared.

11.5 Conclusion

The development of complications is challenging to predict and investigate using statistical methods because of their low incidence. The risk factors of IOB include ruptured, Acom, and small-size aneurysms and anatomical, morphological difficulties including NOP. Thus, these should be considered by neurointerventionists. The life-threatening factors associated with thromboembolism include large-size aneurysms, wide neck, long procedure time, and use of stent. However, this finding is controversial. To prevent thromboembolic complications, the early detection of a thrombus is important. While these risk factors are controversial, those are well known. Therefore, they should be cautiously considered in preoperative planning. When complications occur, a prompt response is important to reduce damage.

Disclosure None of the authors declared any conflict of interest.

References

1. Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach, II: preliminary clinical experience. J Neurol Surg. 1991;75:8–14.
2. Molyneux A, Kerr R. International subarachnoid hemorrhage Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysm: a randomized trial. Lancet. 2012;11:304–14.
3. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, Albuquerque FC. The Barrow ruptured aneurysm trial. J Neurol Surg. 2012;116:135–44.
4. Lin N, Cahill KS, Frerichs KU, Friedlander RM, Claus EB. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg. 2018;10:69–76.
5. Elijovich L, Higashida RT, Lawton MT, Duckwiler G, Giannotta S, Johnston SC, Cerebral Aneurysm Rerupture After Treatment (CARAT) Investigators. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: the CARAT study. Stroke. 2008;39:1501–6.
6. Viñuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute Intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. J Neurol Surg. 1997;86:475–82.
7. Murayama Y, Viñuela F, Duckwiler GR, Gobin YP, Guglielmi G. Embolization of incidental cerebral aneurysms by using the Guglielmi detachable coil system. J Neurol Surg. 1999;90:207–14.
8. Cloft HJ, Kallmes DF. Cerebral aneurysm perforations complicating therapy with Guglielmi detachable coils: a meta-analysis. AJNR Am J Neuroradiol. 2002;23:1706–9.
9. Ihn YK, Shin SH, Baik SK, Choi IS. Complications of endovascular treatment for intracranial aneurysms: management and prevention. Interv Neurorad. 2018;24:237–45.
10. Stapleton CJ, Walcott BP, Butler WE, Butler WE, Ogilvy CS. Neurological outcomes following intraprocedural rupture during coil embolization of ruptured intracranial aneurysms. J Neurol Surg. 2015;122:128–35.
11. Fan L, Lin B, Xu T, Xia N, Shao X, Tan X, Zhong M, Yang Y, Zhao B. Predicting intraprocedural rupture and thrombus formation during coiling of ruptured anterior communicating artery aneurysms. J Neurointerv Surg. 2017;9:370–5.
12. Algra AM, Lindgren A, Vergouwen MDI, Greving JP, van der Schaaf IC, van Doormaal TPC, Rinkel GJE. Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. JAMA Neurol. 2019;76:282–93.
13. Chen M. A checklist for cerebral aneurysm embolization complications. J Neurointerv Surg. 2013;5:20–7.
14. Nagamine Y, Hayashi T, Kakehi Y, Yamane F, Ishihara S, Uchino A, Tanahashi N. Contrast-induced encephalopathy after coil embolization of an unruptured internal carotid artery aneurysm. Intern Med. 2014;53:2133–8.
15. Park HS, Nakagawa I, Yokoyama S, Wajima D, Wada T, Motoyama Y, Kichikawa K, Nakase H. Nickel-associated delayed multiple white matter lesions after stent-assisted coil embolization of intracranial unruptured aneurysm. J Neurointervent Surg. 2018;10:e1.
16. Mehta RI, Mehta RI. Polymer-induced central nervous system complications following vascular procedures: spectrum of iatrogenic injuries and review of outcomes. Hum Pathol. 2016;53:178–90.

17. Shapiro M, Ollenschleger MD, Baccin C, Spiegel GR, Wang Y, Song X, Raz E, Zumofen D, Potts MB, Nelson PK. Foreign body emboli following cerebrovascular interventions: clinical, radiographic, and histopathologic features. AJNR Am J Neuroradiol. 2015;36:2121–6.
18. Oh SW, Shin NY, Lee HJ, Kim BM, Kim DJ. Delayed enhancing lesions after coil embolization of aneurysms: clinical experience and benchtop analysis. J Neurointerv Surg. 2017;9:1243–7.
19. Doerfler A, Wanke I, Egelhof T, Dietrich U, Asgari S, Stolke D, Forsting M. Aneurysmal rupture during embolization with Guglielmi detachable coils: causes, management, and outcome. AJNR Am J Neuroradiol. 2001;22:1825–32.
20. Ricolfi F, Le Guerinel C, Blustajn J, Combes C, Brugieres P, Melon E, Gaston A. Rupture during treatment of recently ruptured aneurysms with Guglielmi electrodetachable coils. AJNR Am J Neuroradiol. 1998;19:1653–8.
21. Cognard C, Weill A, Castaings L, Rey A, Moret J. Intracranial berry aneurysms: angiographic and clinical results after endovascular treatment. Radiology. 1998;206:499–510.
22. Raymond J, Roy D. Safety and efficacy of endovascular treatment of acutely ruptured aneurysms. Neurosurgery. 1997;41:1235–45.
23. Brisman JL, Niimi Y, Song JK, Berenstein A. Aneurysmal rupture during coiling: low incidence and good outcomes at a single large volume center. Neurosurgery. 2005;57:1103–9.
24. Pierot L, Spelle L, Vitry F, Investigators ATENA. Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study. Stroke. 2008;39:2497–504.
25. Schuette AJ, Hui FK, Spiotta AM, Obuchowski NA, Gupta R, Moskowitz SI, Tong FC, Dion JE, Cawley CM. Endovascular therapy of very small aneurysms of the anterior communicating artery: five-fold increased incidence of rupture. Neurosurgery. 2011;68:731–7.
26. Tummala RP, Chu RM, Madison MT, Myers M, Tubman D, Nussbaum ES. Outcomes after aneurysm rupture during endovascular coil embolization. Neurosurgery. 2001;49:1059–66.
27. Levy E, Koebbe CJ, Horowitz MB, Jungreis CA, Pride GL, Dutton K, Kassam A, Purdy PD. Rupture of intracranial aneurysms during endovascular coiling: management and outcomes. Neurosurgery. 2001;49:807–11.
28. Santillan A, Gobin YP, Greenberg ED, Leng LZ, Riina HA, Stieg PE, Patsalides A. Intraprocedural aneurysmal rupture during coil embolization of brain aneurysms: role of balloon assisted coiling. AJNR Am J Neuroradiol. 2012;33:2017–21.
29. Sluzewski M, Bosch JA, van Rooij WJ, Nijssen PC, Wijnalda D. Rupture of intracranial aneurysms during treatment with Guglielmi detachable coils: incidence, outcome, and risk factors. J Neurol Surg. 2001;94:238–40.
30. Oishi H, Yamamoto M, Shimizu T, Yoshida K, Arai H. Endovascular therapy of 500 small asymptomatic unruptured intracranial aneurysms. AJNR Am J Neuroradiol. 2012;33:958–64.
31. Gonzalez N, Sedrak M, Martin N, Vinuela F. Impact of anatomic features in the endovascular embolization of 181 anterior communicating artery aneurysms. Stroke. 2008;39:2776–82.
32. van Rooij WJ, Sluzewski M, Beute GN, Nijssen PC. Procedural complications of coiling of ruptured intracranial aneurysms: incidence and risk factors in a consecutive series of 681 patients. AJNR Am J Neuroradiol. 2006;27:1498–501.
33. Santillan A, Gobin YP, Mazura JC, et al. Balloon assisted coil embolization of intracranial aneurysms is not associated with increased periprocedural complications. J Neurointerv Surg. 2013;5:1156–61.
34. Lubicz B, Lefranc F, Bruneau M, Balériaux D, De Witte O. Balloon-assisted coiling of intracranial aneurysms is not associated with a higher complication rate. Neuroradiology. 2008;50:769–76.
35. Shapiro M, Babb J, Becske T, Nelson PK. Safety and efficacy of adjunctive balloon remodeling during endovascular treatment of intracranial aneurysms: A literature review. AJNR Am J Neuroradiol. 2008;29:1777–81.
36. Park SD, Kim JH, Chang CH, Jung YJ. Procedure-related complication rate for the endovascular treatment of aneurysmal subarachnoid hemorrhage under local anesthesia. J Cerebrovasc Endovasc Neurosurg. 2016;18:215–22.
37. Kawabata S, Imamura H, Adachi H, Tani S, Tokunaga S, Funatsu T, Suzuki K, Sakai N. Risk factors for and outcomes of intraprocedural rupture during endovascular treatment of unruptured intracranial aneurysms. J Neurointerv Surg. 2018;10:362–6.
38. Li MH, Gao BL, Fang C, Cheng YS, Li YD, Wang J, Xu GP. Prevention and management of intraprocedural rupture of intracranial aneurysm with detachable coils during embolization. Neuroradiology. 2006;48:907–15.
39. McDougall CG, Halbach VV, Dowd CF, Higashida RT, Larsen DW, Hieshima GB. Causes and management of aneurysmal hemorrhage occurring during embolization with Guglielmi detachable coils. J Neurol Surg. 1998;89:87–92.
40. Sandalcioglu IE, Schoch B, Regel JP, Wanke I, Gasser T, Forsting M, Stolke D, Wiedemayer H. Does intraoperative aneurysm rupture influence outcome? Analysis of 169 patients. Clin Neurol Neurosurg. 2004;106:88–92.
41. Leipzig TJ, Morgan J, Horner TG, Payner T, Redelman K, Johnson CS. Analysis of intraoperative rupture in the surgical treatment of 1694 saccular aneurysms. Neurosurgery. 2005;56:455–68.

42. Schramm J, Cedzich C. Outcome and management of intraoperative aneurysm rupture. Surg Neurol. 1993;40:26–30.
43. Phuenpathom N, Ratanalert S, Saeheng S, Sripairojkul B. Intraoperative intracranial aneurysm rupture. J Med Assoc Thai. 1999;82:332–5.
44. Fisher CM, Ojemann RG. Basal rupture of saccular aneurysm. A pathological case report. J Neurol Surg. 1978;48:642–4.
45. Yamagami K, Hatano T, Nakahara I, et al. Long-term outcomes after intraprocedural aneurysm rupture during coil embolization of unruptured intracranial aneurysms. World Neurosurg. 2020;134:e289–97.
46. Crompton MR. Mechanism of growth and rupture in cerebral berry aneurysms. Br Med J. 1966;1:1138–42.
47. Frerichs KU, Stieg PE, Friedlander RM. Prediction of aneurysm rupture site by an angiographically identified bleb at the aneurysm neck. J Neurol Surg. 2000;93:517.
48. Park J. Saccular aneurysm with basal rupture angiographically depicted as an aneurysm with stalk-like narrow neck. J Neurol Surg. 2011;114:1065–8.
49. Park J, Woo H, Kang DH, Kim Y, Baik SK. Ruptured intracranial aneurysms with small basal outpouching: incidence of basal rupture and results of surgical and endovascular treatments. Neurosurgery. 2012;71:994–1001.
50. Powner DJ, Hartwell EA, Hoots WK. Counteracting the effects of anticoagulants and antiplatelet agents during neurosurgical emergencies. Neurosurgery. 2005;57:823–31.
51. Willinsky R, terBrugge K. Use of a second microcatheter in the management of a perforation during endovascular treatment of a cerebral aneurysm. AJNR Am J Neuroradiol. 2000;21:1537–9.
52. Patsalides A, Smith M, Gobin YP. Intra-procedural aneurysm rupture treated with n-butyl cyanoacrylate embolization: technical note. J Neurointerv Surg. 2010;2:145–6.
53. Lim YC, Kim BM, Shin YS, Kim SY, Chung J. Structural limitations of currently available microcatheters and coils for endovascular coiling of very small aneurysms. Neuroradiology. 2008;50:423–7.
54. Pelz DM, Lownie SP, Fox AJ. Thromboembolic events associated with the treatment of cerebral aneurysms with Guglielmi detachable coils. AJNR Am J Neuroradiol. 1998;19:1541–7.
55. Albayram S, Selcuk H, Kara B, Bozdag E, Uzma O, Kocer N, Islak C. Thromboembolic events associated with balloon-assisted coil embolization: evaluation with diffusion-weighted MR imaging. AJNR Am J Neuroradiol. 2004;25:1768–77.
56. Rordorf G, Bellon RJ, Budzik RE Jr, Farkas J, Reinking GF, Pergolizzi RS, Ezzeddine M, Norbash AM, Gonalez RG, Putman CM. Silent thromboembolic events associated with the treatment of unruptured cerebral aneurysms by use of Guglielmi detachable coils: prospective study applying diffusion-weighted imaging. AJNR Am J Neuroradiol. 2001;22:5–10.
57. Soeda A, Sakai N, Murao K, Sakai H, Ihara K, Yamada N, Imakita S, Nagata I. Thromboembolic events associated with Guglielmi detachable coil embolization with use of diffusion-weighted MR imaging. Part II. Detection of the microemboli proximal to cerebral aneurysm. AJNR Am J Neuroradiol. 2003;24:2035–8.
58. Yamada NK, Cross DT, Pilgram TK, Moran CJ, Derdeyn CP, Dacey RG Jr. Effect of antiplatelet therapy on thromboembolic complications of elective coil embolization of cerebral aneurysms. AJNR Am J Neuroradiol. 2007;28:1778–82.
59. Cronqvist M, Pierot L, Boulin A, Cognard C, Castaings L, Moret J. Local intraarterial fibrinolysis of thromboemboli occurring during endovascular treatment of intracerebral aneurysm: a comparison of anatomic results and clinical outcome. AJNR Am J Neuroradiol. 1998;19:157–65.
60. Song JK, Niimi Y, Fernandez PM, Brisman JL, Buciuc R, Kupersmith MJ, Berenstein A. Thrombus formation during intracranial aneurysm coil placement: treatment with intra-arterial abciximab. AJNR Am J Neuroradiol. 2004;25:1147–53.
61. Niimi J, Takahashi Y, Ueda K, Tasaka K, Tsuruoka A, Nemoto F, Moriwaki T, Hatayama K, Otake M, Naito H. The usefulness of prasugrel as rescue medication in neuroendovascular therapy. J Neuroendvascular Therapy. 2020;14:90–5.
62. Layton KF, Cloft HJ, Gray LA, Lewis DA, Kallmes DF. Balloon-assisted coiling of intracranial aneurysms: evaluation of local thrombus formation and symptomatic thromboembolic complications. AJNR Am J Neuroradiol. 2007;28:1172–5.
63. Workman MJ, Cloft HJ, Tong FC, Dion JE, Jensen ME, Marx WF, Kallmes DF. Thrombus formation at the neck of cerebral aneurysms during treatment with Guglielmi detachable coils. AJNR Am J Neuroradiol. 2002;23:1568–76.
64. Yamane F, Ishihara S, Kohyama S, Kanazawa R, Ishihara H, Suzuki M, Araki R, Suzuki H, Satoh A. Local thrombus formation at the coil-parent artery interface during endovascular coil embolization of cerebral aneurysms. J Neurol Surg A. 2012;73:358–68.
65. Kocur D, Paździora P, Przybyłkol N, Kukier W, Baron J, Rudnik A. Thromboembolism during coiling of intracranial aneurysms: predictors and clinical outcome. Wideochir Inne Tech Maloinwazyjne. 2020;15:319–28.
66. The Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and The Society of Interventional Radiology. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. J Vasc Interv Radiol. 2003;14:S493–4.
67. Higashida RT, Furlan AJ, for the Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology. Trial design and reporting standards for intra-arterial cere-

bral thrombolysis for acute ischemic stroke. Stroke. 2003;34:e109–37.
68. Klötzsch C, Nahser HC, Henkes H, Kühne D, Berlit P. Detection of microemboli distal to cerebral aneurysms before and after therapeutic embolization. AJNR Am J Neuroradiol. 1998;19:1315–8.
69. Brinjikji W, McDonald JS, Kallmes DF, Cloft HJ. Rescue treatment of thromboembolic complications during endovascular treatment of cerebral aneurysms. Stroke. 2013;44:1343–7.
70. Tokunaga K, Hatano T, Nakahara I, et al. Factors associated with postprocedural diffusion-weighted imaging-positive lesions in endovascular treatment for unruptured cerebral aneurysms. World Neurosurg. 2019;130:e457–62.
71. Derdeyn CP, Cross DT, Moran CJ, Brown GW, Pilgram TK, Diringer MN, Grubb RJ Jr, Rich KM, Chicoine MR, Dacey RG Jr. Postprocedure ischemic events after treatment of intracranial aneurysms with Guglielmi detachable coils. J Neurol Surg. 2002;96:837–43.
72. Kim DY, Park JC, Kim JK, Sung YS, Park ES, Kwak JH, Choi C-G, Lee DH. Microembolism after endovascular treatment of unruptured cerebral aneurysms: reduction of its incidence by microcatheter lumen aspiration. Neurointervention. 2015;10:67–73.
73. Hu YC, Deshmukh VR, Albuquerque FC, Fiorella D, Nixon RR, Heck DV, Barnwell SL, McDougall CG. Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the pipeline embolization device. J Neurosurg. 2014;120:365–74.
74. Altay T, Kang HI, Woo HH, et al. Thromboembolic events associated with endovascular treatment of cerebral aneurysms. J Neurointerv Surg. 2011;3:147–50.
75. Ishihara H, Ishihara S, Niimi J, Neki H, Kakehi Y, Uemiya N, Kohyama S, Yamane F. Risk factors for coil protrusion into the parent artery and associated thrombo-embolic events following unruptured cerebral aneurysm embolization. Interv Neuroradiol. 2015;21:178–83.
76. Yonaha H, Hyodo A, Inaji T, Kushi S, Tsuchida K, Saito A, Sugimoto K, Yoshii Y. Thromboembolic events associated with coil protrusion into parent arteries after GDC treatment. Interv Neuroradiol. 2006;12:105–11.
77. Yang H, Sun Y, Jiang Y, Lv X, Zhao Y, Li Y, Liu A. Comparison of stent-assisted coiling vs coiling alone in 563 intracranial aneurysms: safety and efficacy at a high-volume center. Neurosurgery. 2015;77:241–7.
78. Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, Moret J. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. Stroke. 2010;41:110–5.
79. Bodily KD, Cloft HJ, Lanzino G, Fiorella DJ, White PM, Kallmes DF. Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature. AJNR Am J Neuroradiol. 2011;32:1232–6.
80. Yamao Y, Satow T, Murao K, Miyamoto S, Iihara K. Research of postoperative complications after coil protrusions in embolization of unruptured cerebral aneurysms. No Shinkei Geka. 2012;40:23–9.
81. Cruz JP, Marotta T, O'Kelly C, Holtmannspötter M, Saliou G, Willinsky R, Krings T, Agid R. Enhancing brain lesions after endovascular treatment of aneurysms. AJNR Am J Neuroradiol. 2014;35:1954–8.

Clipping in Uncoilable Aneurysms

12

Suchanda Bhattacharjee and Manas Panigrahi

Abstract

Aneurysms are common disease in a neurosurgical setup with an incidence of 2 to 16 per one lakh persons. Not all aneurysms are easy to treat. With increasing endovascular management of aneurysms, clipping has taken a backstage in certain types. But for uncoilable cases, microneurosurgery is still the best option. Aneurysms that are good in appearance in terms of size, shape, or contour and ready to visit hospitals for regular follow-ups or where there is absence of thrombus or mass effect are good candidate for coiling as well as clipping. Aneurysms that are tiny, large, or giant, irregular in size, shape or contour, not ready for multiple visits or not ready for dual antiplatelets are best managed with clipping. In this chapter, the modalities of treating an uncoilable aneurysm have been addressed.

Keywords

Aneurysm · Clipping · Coiling

S. Bhattacharjee (✉)
Department of Neurosurgery, Nizam's Institute of Medical Sciences, Hyderabad, India

M. Panigrahi
Department of Neurosurgery, Krishna Institute of Medical Sciences, Hyderabad, India

12.1 Introduction

This chapter reflects those situations which a clinician faces in decision-making for the management of a cerebral aneurysm that cannot be coiled. Ruptured brain aneurysms resulting in subarachnoid hemorrhage occur with an incidence ranging from 2 to 16 per 100,000 persons [1]. Even though there is a gross decline in historical microsurgical clipping techniques for the treatment of unruptured intracranial aneurysms (UIAs) over the past 20 years, yet the procedure shall never die as there are many situations where clipping of aneurysm is the best solution. The literature has all the evidence of what is best for the patient. Endovascular options are more favored in the current time, and the surgical skills on handling clipping of aneurysms are dwindling in the younger generations [2].

The paradox remains that failed coiling of aneurysms does come at infrequent intervals, and the new budding neurosurgeon does not have the necessary expertise to deal with such difficult cases due to the lack of experience in clipping of aneurysms. Endovascular expertise is also available in only a few centers. The number of neuro interventionists is just a few handfull globally. The huge investment required for its setup is a disadvantage to providing neuro intervention services in resource-constrained places. This limits the use of endovascular procedures in complex cases where expertise is required.

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_12

All treatment decisions are patient specific, but there are situations where certain aneurysms cannot be coiled. In such situations, the clipping of aneurysm does pitch in as the most reliable as well as an economic option. However, those aneurysms which cannot be coiled can still be managed these days with newer endovascular techniques like flow diverters, stent, or balloon assistance. These techniques also come with their share of difficulties and complications. Aneurysms have a very high propensity to re-rupture, requiring treatment to repair the aneurysm in the acute phase, which is in many situations is better for clipping rather than the newer endovascular techniques.

Clipping also remains the mainstay of treating a cerebral aneurysm in many parts of the developing world for economic reasons. The huge costs of endovascular treatment still are not affordable in many parts of the world, and so clipping still is quiet in vogue in those parts of the world. Besides, it has also been seen that in spite of the best treatment by either clipping or coiling, the level of headaches after surgical aneurysm clipping decreases significantly faster compared to endovascular coiled patients. It has been shown in a study by Petridis et al.; that post clipping, the headaches almost disappeared after 24 h and did not reappear during the follow-up period of 3 months, whereas after coil embolization, headaches were still present in the first 3 weeks and disappeared after 3 months [3]. The available treatments for a ruptured aneurysm in the current time is given in the table below (Table 12.1).

In this chapter, we will discuss the treatment of aneurysms in three different groups.

- Group 1: Uncoilable aneurysms
- Group 2: Unclippable aneurysms
- Group 3: Both uncoilable and unclippable aneurysms

12.2 Factors for Decision-Making in Coiling or Clipping

According to the European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage [5]:

Table 12.1 Major therapies available for ruptured brain aneurysms

Method	Common indication	Need for antiplatelet therapy	Class of evidency[a]
Clipping	Most aneurysms	–	1
Coiling	Most aneurysms	–	1
Flow diversion	Large proximal internal carotid artery aneurysms, blister aneurysms	+	4
Flow diversion with adjunctive coiling	Large and giant aneurysms with wide necks	+	4
Intrasaccular flow diversion	Bifurcation aneurysms with neck C4 mm	–	4
Coiling with assistive stenting	Wide-neck aneurysms and aneurysms with branch vessels near/incorporating aneurysm neck	–	3
Parent vessel sacrifice or branch vessel sacrifice with bypass	Dissecting aneurysms, giant aneurysms with branch vessels incorporating aneurysm neck	+	4
Parent vessel sacrifice without bypass	Distal posterior inferior cerebellar artery aneurysms, distal posterior cerebral artery aneurysms, distal mycotic aneurysms	–	4

[a]Modified from the Oxford Center for Evidence-Based Medicine for ratings of individual studies: 1—Properly powered and conducted randomized clinical trial, systematic review with meta-analysis; 2—Well-designed controlled trial without randomization, prospective comparative cohort trial; 3—Case-control studies, retrospective cohort study; 4—Case series with or without intervention, cross-sectional study; 5—Opinion of respected authorities, case reports [4]

Factors in favor of the endovascular intervention(coiling) are:

1. Age above 70 years [class II, level B]
2. Space occupying ICH not present [class II, level B]
3. Aneurysm specific factors such as:
   Posterior location
   Small aneurysm neck
   Unilobar shape [class III, level B]

Factors in favor of clipping are:

1. Younger age
2. Space occupying ICH [class II, level B]
3. Aneurysm specific factors:
   Location: MCA aneurysm, Pericallosal aneurysm [class III, level B]
   Wide-neck aneurysms [class III, level B]
   Branches arising out of sack [class III, level B]
   Unfavorable vascular and aneurysmal configuration for coiling [class IV, level C]

12.3 What does the Landmark Trials Say?

Endovascular coiling practically became popular after the ISAT trial, but there were strong criticisms of the trial as well.

International Subarachnoid Aneurysm Trial [ISAT] [6]

The results were published in 2005 and the 10 years outcome in 2015.

In patients with ruptured intracranial aneurysms suitable for both treatments, endovascular coiling is more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continues for at least 7 years. The risk of late rebleeding is low but is more common after endovascular coiling than after neurosurgical clipping.

However, at 10 years of follow-up rebleeding was more likely after endovascular coiling than after neurosurgical clipping [7]. The outcome assessment scale, biases regarding patient selection and center participation criteria were issues of criticism in this trial [8].

The Barrow Ruptured Aneurysm Trial [BRAT]: Six-Year Results: Randomized Controlled Trial [9]

The results were published in 2015 and 2019

Although BRAT was statistically underpowered to detect small differences, these results suggest *little difference* in outcome between the two treatments for anterior circulation aneurysms. This was not the case for the *posterior circulation aneurysms*, where coil embolization appeared to provide a sustained advantage over clipping. However, retreatment was higher in coiling.

At 10 years, there was no significant difference in clinical outcomes between the two assigned treatment groups as measured by mRS outcomes or deaths. Clinical outcomes in the patients with posterior circulation aneurysms were better in the coiling group at 1 year, but after 1 year, this difference was no longer statistically significant. Rates of complete aneurysm obliteration and rates of retreatment favored patients who actually underwent clipping compared with those who underwent coiling [10].

J-ASPECT Trial

The results were published in 2018

In this study, the effect of treatment modality on in-hospital outcomes in patients with subarachnoid hemorrhage on a nationwide basis was done. They concluded that despite the increasing use of coiling, clipping remains the mainstay treatment for SAH. Clipping was associated with reduced in-hospital mortality, similar unfavorable functional outcomes and medical costs, and a longer hospital stay as compared with coiling in 2012 in Japan [11].

The Cerebral Aneurysm Re-rupture After Treatment (CARAT) Study

The results were published in 2008

This study reported a re-rupture rate of 3.4% for coiled aneurysms during a mean time of

3 days postoperatively. Among 1001 patients during a mean of 4.0 years follow-up, there were 19 postprocedural re-ruptures; median time to re-rupture was 3 days, and 58% led to death. The degree of aneurysm occlusion after treatment was strongly associated with risk of re-rupture (overall risk: 1.1% for complete occlusion, 2.9% for 91% to 99% occlusion, 5.9% for 70% to 90%, 17.6% for <70%; $P < 0.0001$ in univariate and multivariable analysis). Overall risk of re-rupture tended to be greater after coil embolization compared with surgical clipping (3.4% versus 1.3%; $P = 0.092$), but the difference did not persist after adjustment ($P = 0.83$). They concluded that the degree of aneurysm occlusion after the initial treatment is a strong predictor of the risk of subsequent rupture in patients presenting with subarachnoid hemorrhage, which justifies attempts to occlude aneurysms [12] completely.

12.4 Group I: Uncoilable Aneurysms

Aneurysms where you cannot think of coiling at all. The factors which are unfavorable are:

- Tiny aneurysm
- Blood blister-like aneurysm
- Dome: Neck ratio < 2
- Neck width > 4mm
- Bad contour of aneurysm like multilobulation
- Incorporation of parent or branch arteries
- Unstable thrombus in giant aneurysms
- Poor Access
- Complex anatomy.
- Experience of the endovascular surgeon.

12.4.1 Tiny Aneurysm Are Difficult to Coil (Fig. 12.1a, b)

They have suboptimal microcatheter access, increased risk of rupture and size of coil sometimes is a problem. The smallest coil available is 2 mm with a wire thickness of 0.010 inch.

12.4.2 Blood Blister-Like Aneurysm

Blood Blister Aneurysm (Fig. 12.2) are small, fragile walled. They are typically described as small, sessile aneurysms that occur at non-branch

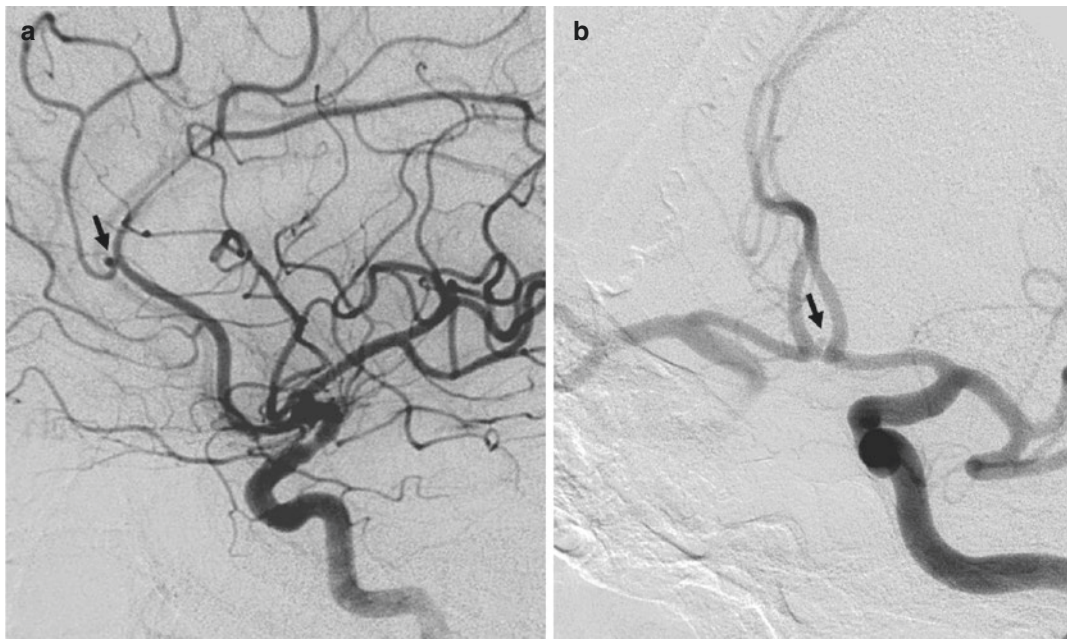


Fig. 12.1 (**a**, **b**) Tiny aneurysms (arrows)

points along the artery wall [13, 14]. Anatomically, they represent a deficiency in the parent vessel (usually dorsal internal carotid artery) rather than the typical dome-neck configuration of a saccular aneurysm, and primary surgical clipping is difficult. Ruptured blister aneurysms also have a high tendency for intraoperative hemorrhage, with the potential for catastrophe [15]. Those which are located at non-branching sites on dorsomedial ICA are not good for coiling. People have tried stent-assisted coiling/stent-in-stent with some success. They are known to have high re-rupture rates. Clipping is also not a viable option in such cases. Surgical alternatives to primary clipping include aneurysm wrapping or trapping with cerebrovascular bypass.

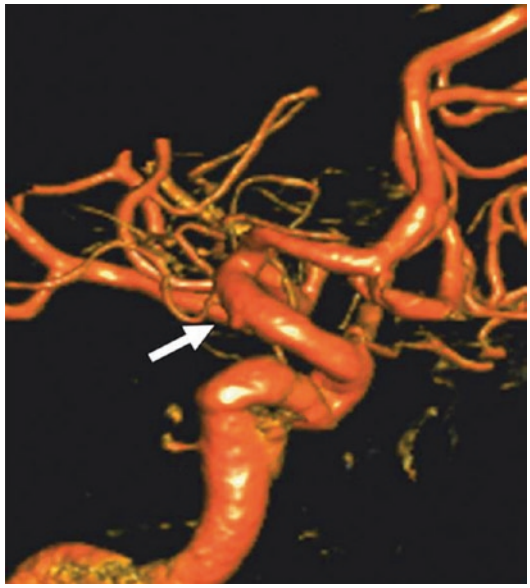


Fig. 12.2 Blood Blister Aneurysm (arrow)

12.4.3 Wide-Necked Aneurysm (Fig. 12.3a, b)

12.4.4 Bad Contour (Fig. 12.4a, b)

12.4.5 Incorporation of Parent or Branch Arteries (Fig. 12.5a, b)

12.4.6 Large and Giant Aneurysms (Fig. 12.6a–e)

They are difficult to coil. Coil increases the mass effect due to the huge number of coils required to take control of the aneurysm. Flow diverters are used in certain cases but again have its inherent risks. In ruptured cases, immediacy of treatment effect has limited the use of these flow diverting

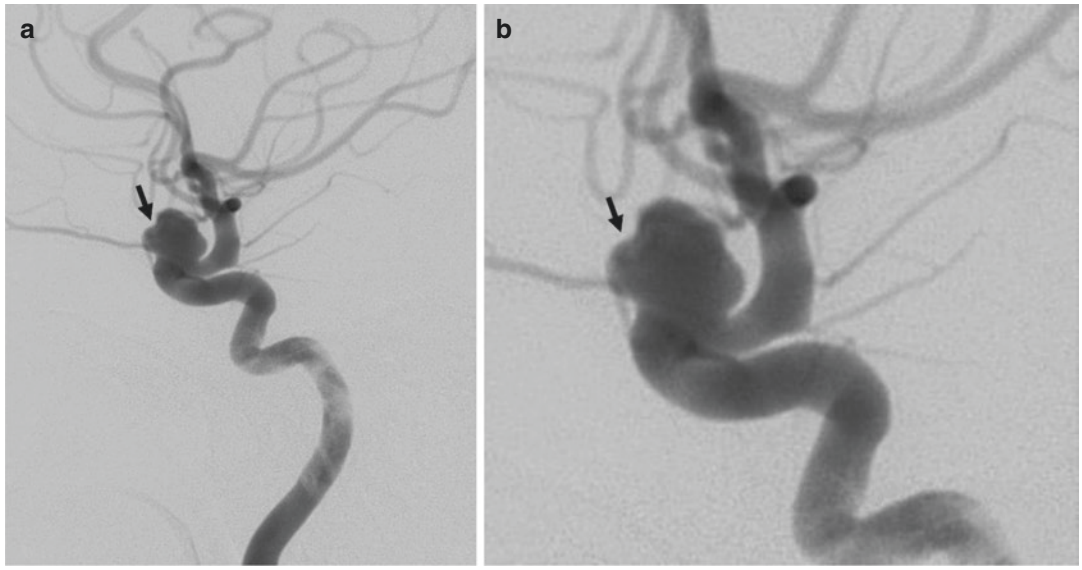


Fig. 12.3 (**a**, **b**) wide-neck aneurysms [Neck >4 mm. Dome: Neck ratio < 2] (arrow)

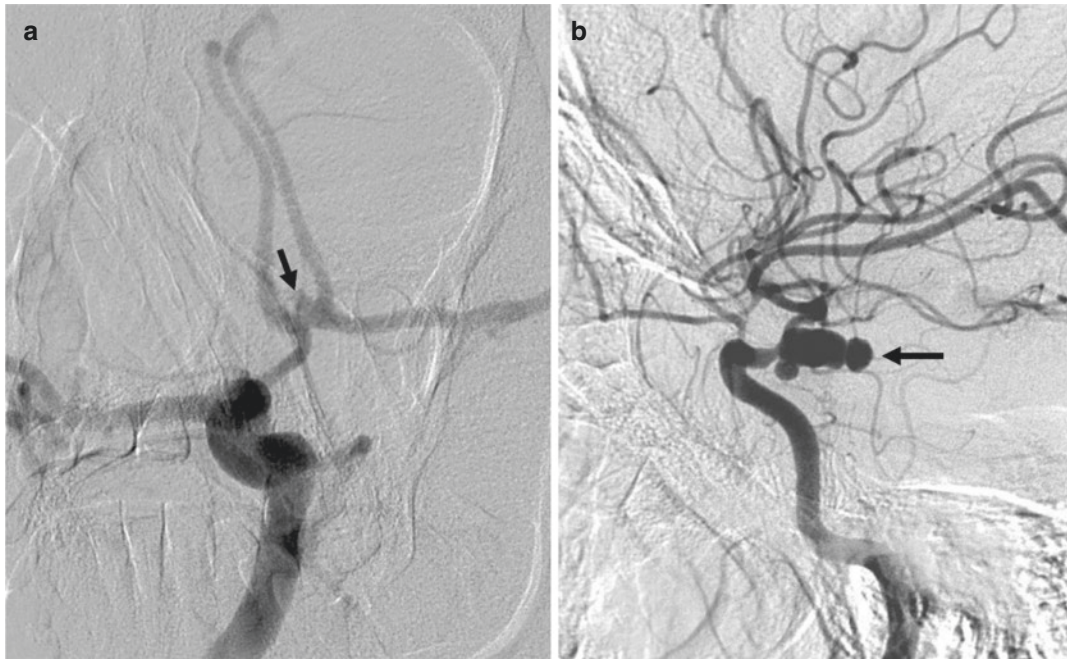


Fig. 12.4 (**a**) Pyramidal shape of aneurysm (arrow). (**b**) lobulated aneurysm

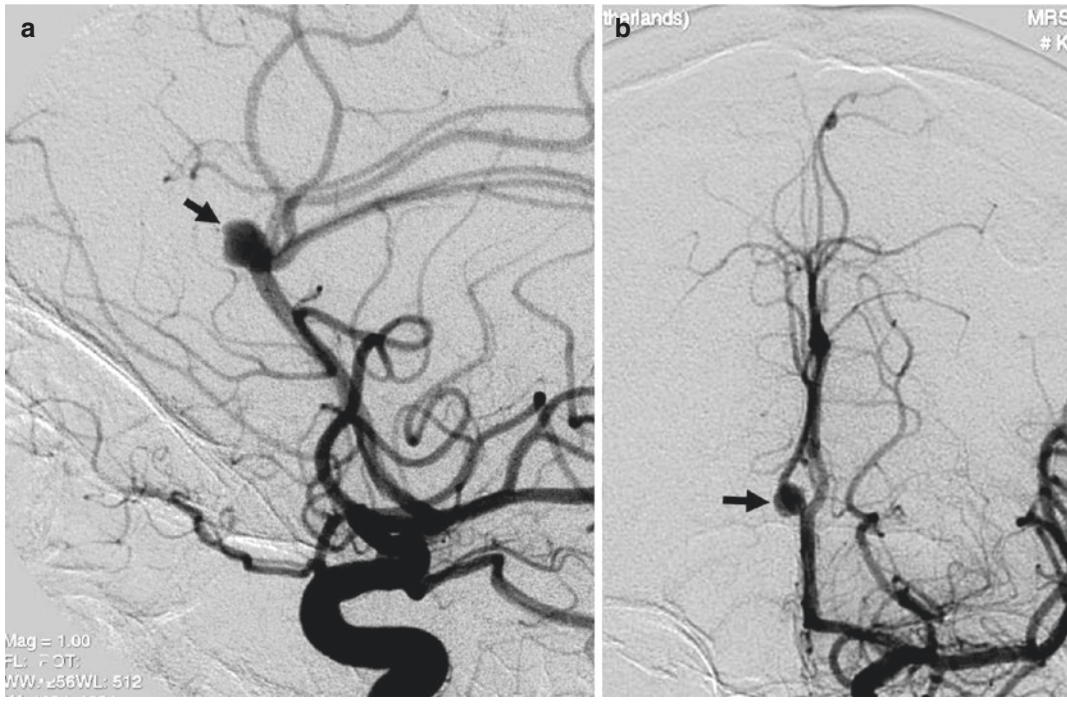


Fig. 12.5 (**a**, **b**) Incorporation of vessel in a DACA aneurysm

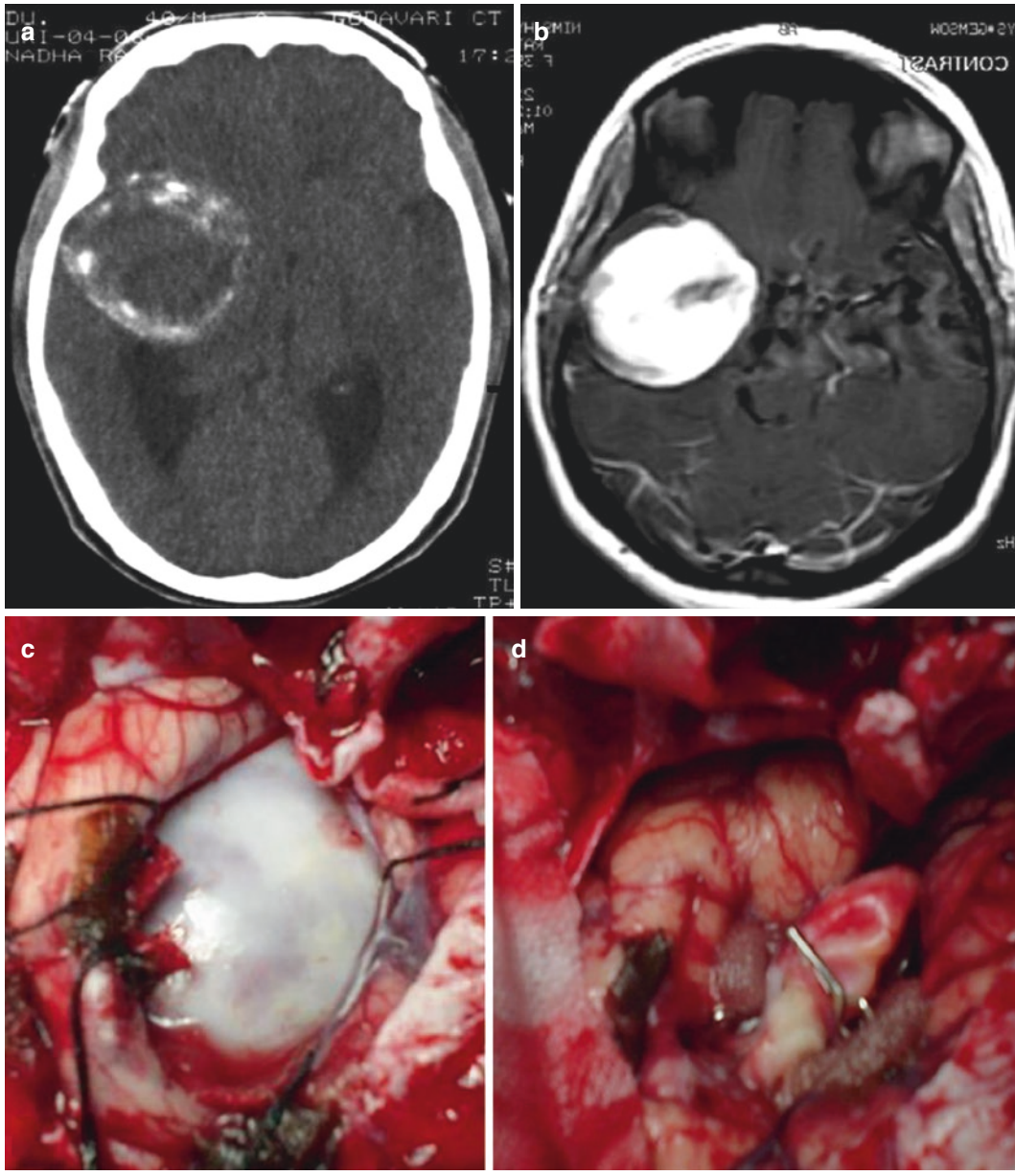


Fig. 12.6 (**a**–**e**) Aneurysms with mass effect: (**a**, **b**) Giant aneurysm with mass effect as seen in the CT scan axial section. (**c**) operative pic of a giant aneurysm. (**d**) Giant aneurysm after decompression and clipping. (**e**) Thrombus being removed from a giant aneurysm

devices in cases of subarachnoid hemorrhage. Early bleeding events from the aneurysm have been reported, even with the treatment of unruptured aneurysms [16, 17]. The best way is clipping and excising the sac and removing the thrombus. Clipping may not be possible all the time as the neck is not under vision because the sac occludes the vision. The better option remains bypass and trapping. It usually requires a high-flow bypass in complex cases. In cases when the aneurysm is feasible for clipping, a low flow superficial temporal artery to middle cerebral

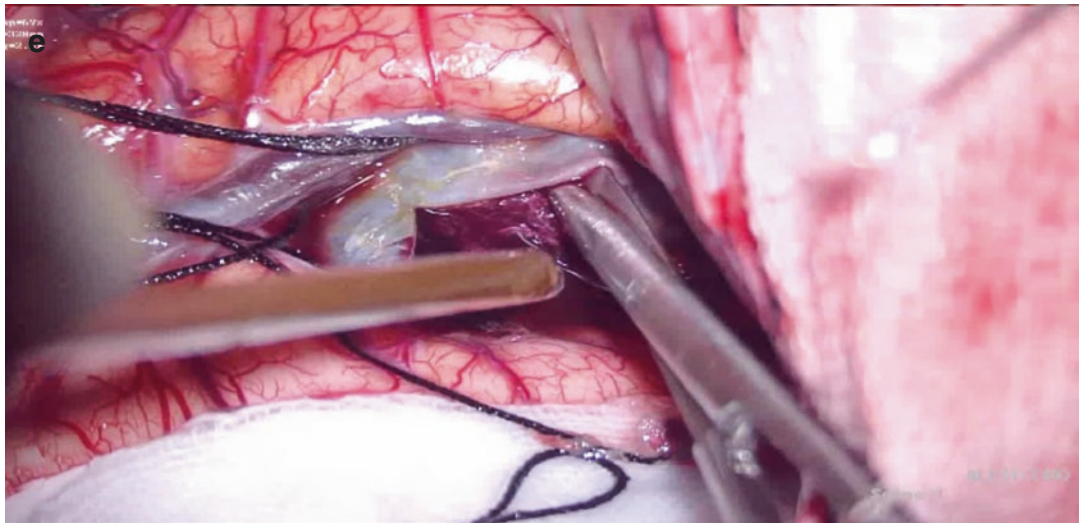


Fig. 12.6 (continued)

artery bypass also suffices. This facilitates the increased duration for the neck of aneurysm manipulation under temporary clipping.

In a meta-analysis of 900 patients where a comparison of endovascular techniques (reconstructive surgery) and parent artery occlusion (deconstructive surgery) for very large and giant aneurysms was done, it has been shown that in unruptured aneurysms, deconstructive treatments allowed higher rates of occlusion (93% versus 71%) and lower rates of complications (16% versus 30%), compared with reconstructive techniques. The rate of good neurologic outcome was approximately 80% and 60% for unruptured and ruptured treated aneurysms with endovascular treatments, whereas overall, long-term occlusion was achieved in about 90% of patients, with low recanalization and retreatment rates among unruptured lesions (5% and 4%, respectively), a low risk of rupture after treatment, and a high rate of good neurologic outcome [18].

12.4.7 Poor Access (Figs. 12.7a–c and 12.8a, b)

12.4.8 Complex Anatomy (Fig. 12.9 a–d)

12.4.9 Resistant Vasospasm (Fig. 12.10)

Vasospasm is treated by IA Nimodipine or by Papaverine. Sufficient access for coiling is usually achieved with infusion; however, at times may be resistant.

12.4.10 Pseudoaneurysms (Fig. 12.11)

12.4.11 Clipping as an Option to Newer Endovascular Techniques When Coiling Is Not Feasible?

Newer endovascular techniques like flow diverters, stents, stent-assisted coils, balloon-assisted coils are increasingly being used when simple coiling is not possible. However, they have their limitations, and in such cases also clipping is a reasonably good option.

Flow Diverters Flow diverters have a must requirement for dual antiplatelet therapy (DAPT) like the stent. It also has the additional drawback of occluding aneurysms only after some time,

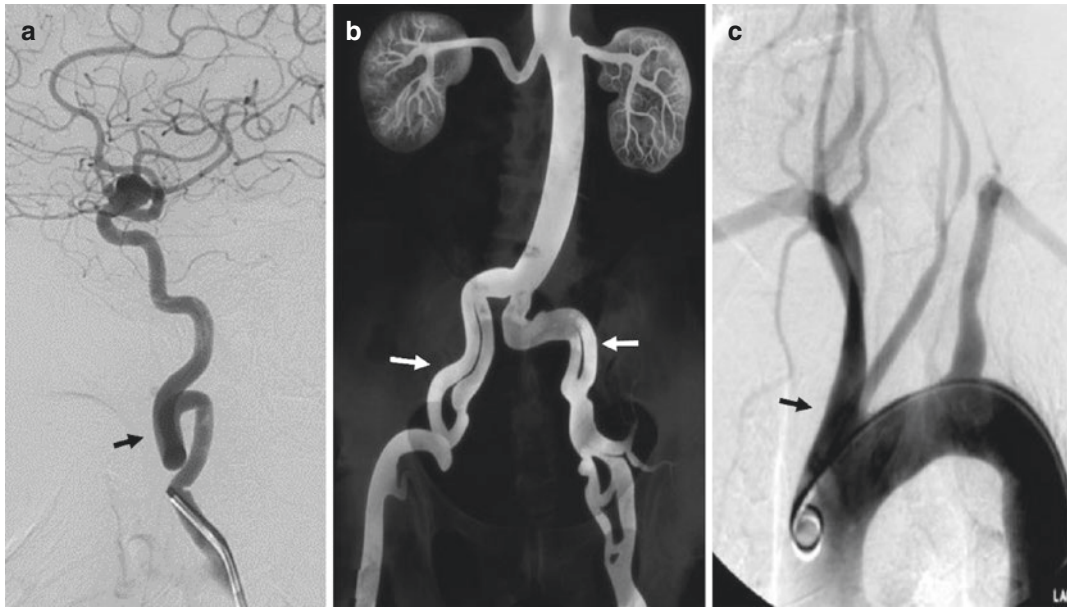


Fig. 12.7 (**a**) Neck vessel tortuosity (arrow). (**b**) iliac artery tortuosity (arrow). (**c**) Elongated arch with unfolded origins of great vessels (arrow)

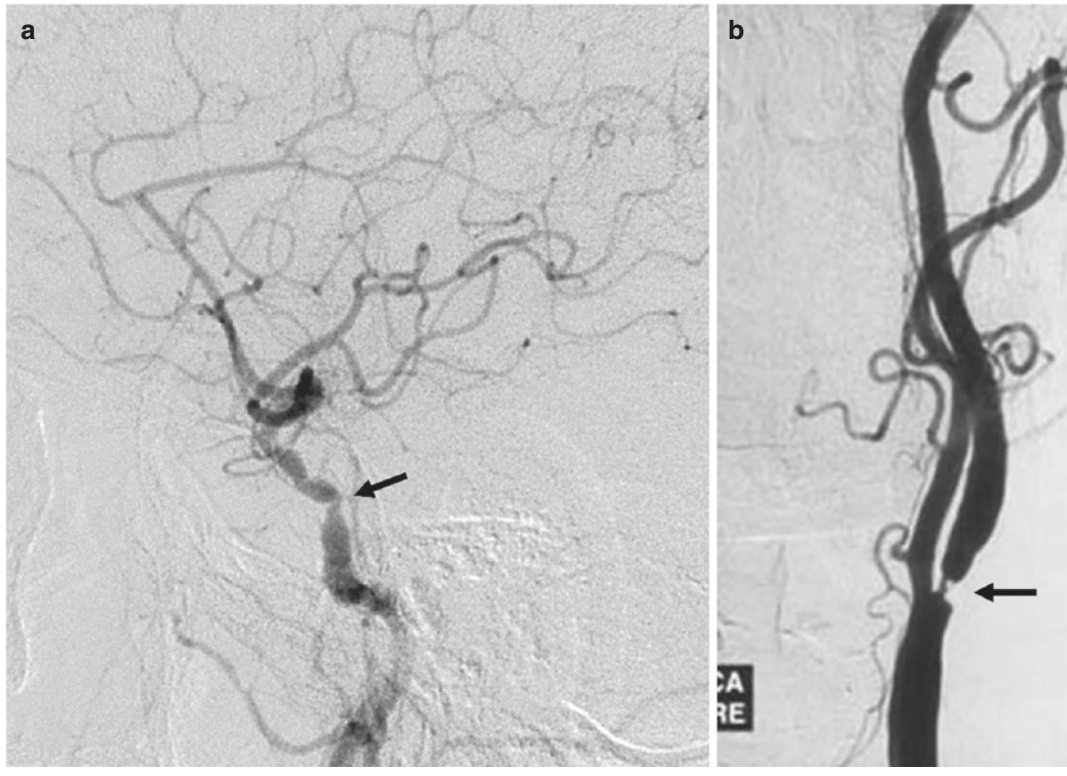


Fig. 12.8 (**a**, **b**) Severe atherosclerotic stenoses (arrow)

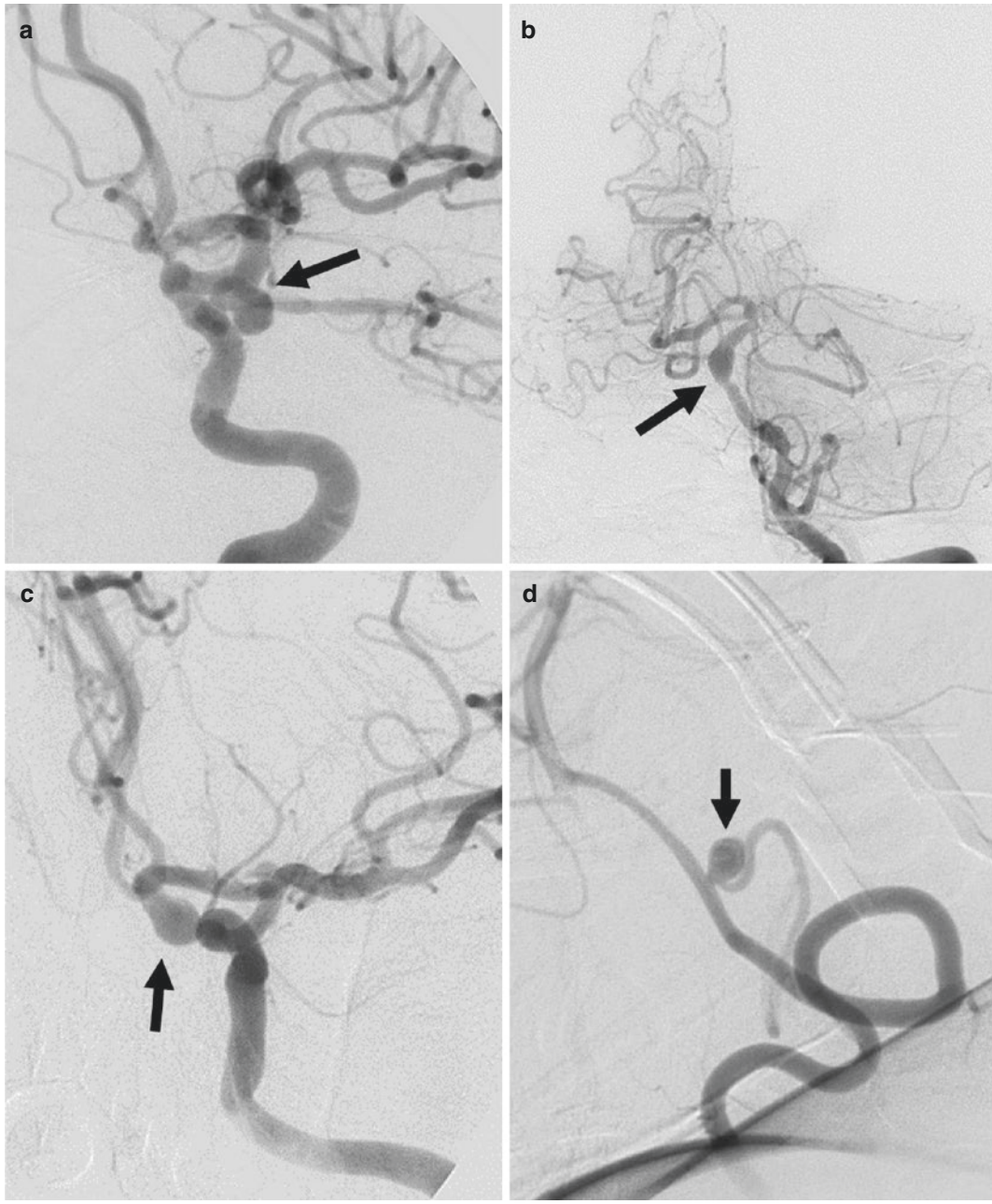


Fig. 12.9 (**a**, **b**) Complex anatomy in the presence of vital arteries. (**c**, **d**) Reverse origin of aneurysm/artery

which may be undesirable for ruptured aneurysms because of the risk of re-rupture and the need for immediate aneurysm protection in the event that induced hypertension becomes necessary for the treatment of vasospasm. Flow diverters are known to cause delayed aneurysm rupture. Even with the use of antiplatelet agents, endoluminal flow diverting stents can result in silent ischemia detected by surveillance magnetic resonance imaging in up to 62% of patients [19]. In a prospective randomized multicenter study by Kiselev et al.; the rate of complete occlusion at

12 months was 65% in the flow diverter group and 97.5% in the surgical group where parent artery occlusion was done after bypass [20].

Balloon-Assisted Coils Balloon devices require complete occlusion of blood flow through the parent vessel during aneurysm coiling, and the balloons themselves may lead to intraprocedural ischemic complications, especially if the patient is not anticoagulated. Balloon catheters also may be difficult to navigate through tortuous anatomy, to distal aneurysm locations, or through small vessels or vessels with acute takeoff angles relative to their parent artery, as shown in the examples above. Balloon-assisted coiling of unruptured aneurysms, the intraprocedural complication rate was 9%, with permanent deficits in 2% [21].

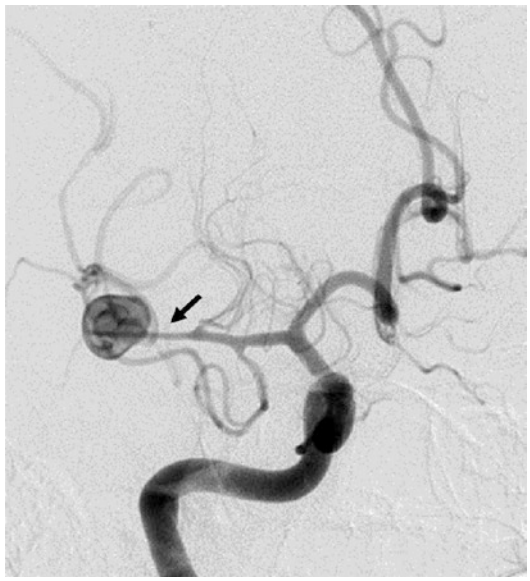


Fig. 12.10 Resistant vasospasm

Stent-Assisted Coils The use of stent-assisted coil embolization of ruptured wide-necked aneurysm is still a major concern for neurointerventional doctors because of the high rate of thromboembolic events due to inadequate antiplatelet drug preparation [22]. The perioperative thrombotic events of stent-assisted coil treatment of wide-necked aneurysm are about 30%. In a study by Zhengzhe Feng et al., procedure-related complications of stent-assisted coil treatment for the selected acutely ruptured wide-necked intracranial aneurysms occurred in 14.2% of patients, 56.7%of which were ischemic events. Inadequate antiplatelet therapy is thought to play an important role [23]. It is also established that Stent-induced hemodynamic changes, promotion of endothelialization of the aneurysm neck, and morphologic changes of parent artery after stent-

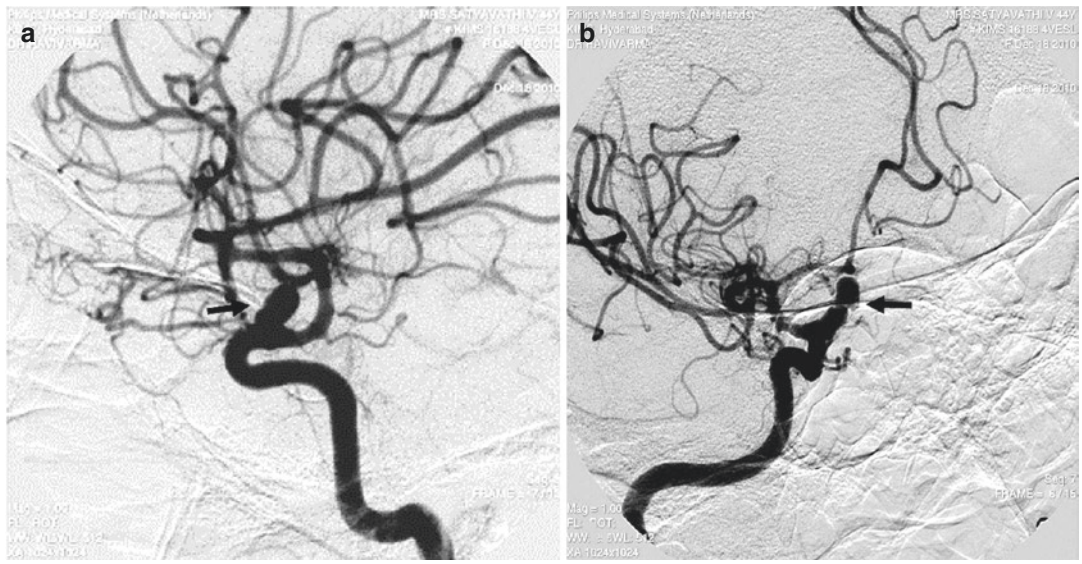


Fig. 12.11 (**a**, **b**) Pseudoaneurysms (arrow)

ing. A double antiplatelet is mandatory, and also follow-up imaging of patients treated with endovascular therapy is recommended due to concerns for its long-term durability and increased recurrence rates coupled with the greater need for retreatment compared with microsurgical clipping [24–26].

12.4.12 Coiling Risks Which Can Be Handled Well by Clipping

Coiling complications can be divided into the following categories:

(a) Complications in the intracranial artery,
(b) Complications in the extracranial artery,
(c) Complications related to the placing of the guiding catheter,
(d) Complications related to the puncture site.

The two most common types of complications which occur during coiling in the intracranial artery are intraprocedural aneurysm ruptures (IARs) and thromboembolic complications.

Even though the risk of aneurysmal rupture is higher with clipping, but in the reported 5% incidence of intraaneurysmal rupture during coiling, the mortality is as high as 40%. In open surgery, the rupture can be easily controlled most of the time as you have direct access to the site. Cloft et al.; reported that the morbidity and mortality rates of perforations caused by coil (39%) and microcatheter (33%) were similar [27]. Rupture in case of coiling happens due to overpacking of coils, stiffness, or oversized coils. Since they cannot be addressed as in clipping of aneurysm, the role of immediate external ventricular drainage (EVD) or a craniectomy for the urgent management of severe SAH and intracranial hypertension after the coiling procedure is of paramount importance. The causes for thromboembolic complications are due to clot formation in the guiding catheter, on the coil mashes, or in parent vessels caused by the induced vasospasm or malposition of coils. Prolapsed coil loops serve as a site for platelet aggregation, leading to local thrombosis or distal thromboembolism [28]. The embolic sources are air embolisms, atheroma dislodged during catheterization, thrombus formation from the device used over the course of the procedure, and hydrophilic coating from catheters and wires [29, 30]. It is also seen that larger aneurysms are more likely to have residual flow within the coil mass than small aneurysms, and the greater volume of thrombus in a larger aneurysm could yield an increased risk of propagation or distal embolization [31]. Clipping should be considered for all ruptured aneurysms and should not be overlooked when deciding on how to treat the lesion in question best. When there is no safe option to completely occlude a ruptured aneurysm with the use of an endoluminal device, strong consideration should be given to surgical clipping or other open techniques [32].

12.4.13 Why Clipping Is Better in Specific Cases?

As mentioned earlier, during an untoward event of intraoperative rupture during clipping, both preoperative and intraoperative subarachnoid blood can be removed, whereas during coiling blood cannot be cleared either ictal or intraprocedural. In cases of P.com segment aneurysm, either ruptured or unruptured, where the presentation is ptosis, clipping has an advantage. The ptosis is due to the mass effect of the aneurysm. The pressure is either due to the size of the aneurysm or the thrombotic component of the aneurysm on the adjacent third nerve. During clipping the contents of the sac or the whole sac can be removed or excised, which gives an immediate noticeable recovery of the ptosis. This advantage does not lie with coiling, even though the aneurysm may be favorable for coiling [33, 34]. In cases of high-grade aneurysmal subarachnoid hemorrhages, the outcome with coiling is not superior to clipping. Also, coiling has a greater risk of mortality [35].

12.5 Group II: Unclippable Aneurysms

Unclippable aneurysms are hard to define. They include giant, fusiform, serpentine aneurysms or those which has incorporated branches arising from them. Many MCA and Basilar top aneurysms remain unclippable due to the incorporation of branches and perforators. Microsurgical techniques like trapping of aneurysms at any location with a rescue or augmentative bypass, however, fill in the gap for the unclippable aneurysms, which in the majority of cases are also not endovascular friendly. Parent artery occlusion is a very viable solution in case of good cross collateral circulation. For example, in the case of a giant aneurysm of the ICA, if a good cross circulation exists, an augmentative low flow STA-MCA bypass suffices to provide the additional time required for temporary clipping during manipulation of the aneurysm. The same holds true for an MCA complex giant aneurysm.

For a complex A.com giant or distal anterior cerebral artery giant aneurysm A2-A2 bypass and trapping of aneurysm can be done.

For giant PICA aneurysm, occipital vertebral artery anastomosis can be done, and aneurysm trapped or clipped and excised.

For giant unclippable basilar aneurysm without any fetal p.com support, a middle meningeal artery to PCA anastomosis is advocated on both sides and then the aneurysm is trapped at the basilar and both PCA.

We need to know that the basilar parent artery may not be seen at all. In such case, a suction decompression technique can be done, the aneurysm deflated or thrombus addressed, and the trapping done.

In other words, it will not be wrong to say that no aneurysm exists, which is not amenable to microvascular surgery until and unless the medical condition of the particular patient does not allow one to take up for surgery.

12.6 Group III: Both Unclippable and Uncoilable Aneurysms

There is a subset of aneurysms that are highly complex, and their natural history is also poor. They can neither be coiled or clipped due to the complexity. This category includes large or giant aneurysms with wide neck and branches or perforating arteries incorporated at the neck or the dome, atherosclerotic or calcified walls, and a partially thrombosed lumen. Certain fusiform aneurysms and serpentine aneurysms also fall in this category. Fusiform aneurysms do not have a neck at all, and the entire wall of the involved arterial segment is pathologically dilated, and the lumen may be partially thrombosed. These lesions are not amenable to conventional surgical treatments or coiling. Endovascular treatments in combination with extracranial-intracranial bypass surgery in such complex aneurysms as mentioned above, results in durable, and often definitive, protection against hemorrhage and further aneurysmal growth. The mortality rate and clinical outcomes were superior to those associated with the natural history of these treatment-resistant aneurysms in studies carried out with the small number of patients. In a very recent study by Kenichi Sato et al.; from Japan, they managed such cases with a combined approach which they described in three categories in their series:

- Type A: Endovascular parent artery occlusion with bypass surgery to restore cerebral blood flow
- Type B: Endovascular trapping with bypass surgery to isolate branches incorporated into the aneurysm
- Type C: Intraaneurysmal coil embolization with bypass surgery to isolate branches incorporated into the aneurysm. The type of bypass surgery used was (single, double, or high-flow bypass using the saphenous vein) [36].

These combined procedures are done at a short interval. Endovascular procedures are long time dependant on anticoagulants, whereas bypass procedures needless anticoagulant temporary support only. So doing at same sitting looks a little difficult but bypass followed shortly by the endovascular procedure is well tolerated and gives good results.

12.7 Cost of Hospitalization

Clipping always has a distinct advantage of being less costly than coiling. Despite a shorter length of hospitalization in patients with unruptured aneurysms, coiling was associated with higher hospital costs in both patients with unruptured and ruptured aneurysms. This is likely attributable to the higher device cost of coils than clips [37].

12.8 Conclusions

Clipping still remains the viable, economic, and long durable option for the majority of aneurysms. Coiling or clipping decisions should be customized to the particular patient depending on

- Clinical signs and symptoms
- Presence of hematoma on CT scan
- Angiographic anatomy of aneurysm
- Management of intraprocedural complications
- Cost-effectiveness

The simple guideline to decide for coiling or clipping suggested her is to remember as "A for coiling" and "B for clipping as given below in Table 12.2.

To summarize, cases that are good candidates for coiling are also good candidates for clipping. Candidates who are not good candidates for coiling are in most cases clip friendly. The choice depends on the geographical availability, economic stability and the aneurysm features to decide the best modality of treatment.

Table 12.2 Guidelines for coiling and clipping decision

A for coiling	B for clipping
Affordable	Below 2 mm
Afford to come for multiple follow-up angiograms	Beyond 20 mm in MCA, supraclinoid aneurysm
Appearance, size, shape, contour	Bad appearance
Apprehensive for surgery	Below 40 years of age
Absence for thrombus or mass effect	Bad neurological condition due to mass effect
Above 40 years	Bad branches from fundus
	Bad infrastructure
	Bad finance
	Bad coiling
	Bypass necessary
	Ballon assisted or stent assisted

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
2. Lin N, Cahill KS, Frerichs KU, Friedlander RM, Claus EB. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg. 2018 Jul;10(Suppl 1):i69–76. https://doi.org/10.1136/jnis.2011.004978.rep.
3. Petridis AK, Cornelius JF, Kamp MA, Falahati S, Fischer I, Steiger HJ. Level of headaches after surgical aneurysm clipping decreases significantly faster compared to endovascular coiled patients. Clin Pract. 2017;7:56–9. https://doi.org/10.4081/cp.2017.936.
4. Walcott BP, Koch MJ, Stapleton CJ, Patel AB. Blood flow diversion as a primary treatment method for ruptured brain aneurysms-concerns, controversy, and future directions. Neurocrit Care. 2017 Jun;26(3):465–73. https://doi.org/10.1007/s12028-016-0318-y.
5. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G, European Stroke Organization. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35(2):93–112. https://doi.org/10.1159/000346087. Epub 2013 Feb 7
6. Molyneux AJ, Kerr RSC, Yu L-M, Clarke M, Sneade M, Yarnold JA, Sandercock P, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on

survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366:809–17.
7. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet. 2015 Feb 21;385(9969):691–7.
8. Sade B, Mohr G. Critical appraisal of the international subarachnoid aneurysm trial (ISAT). Neurol India. 2004 Mar;52(1):32–5.
9. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Russin JJ, Partovi S, Nakaji P, Wallace RC. The Barrow ruptured aneurysm trial: 6-year results. J Neurosurg. 2015 Sep;123(3):609–17. https://doi.org/10.3171/2014.9.JNS141749.
10. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Nakaji P, Karis JP, Wallace RC. Ten-year analysis of saccular aneurysms in the Barrow ruptured aneurysm trial. J Neurosurg. 2019 Mar 8;132(3):771–6. https://doi.org/10.3171/2018.8.JNS181846.
11. Kurogi R, Kada A, Nishimura K, Kamitani S, Nishimura A, Sayama T, Nakagawara J, Toyoda K, Ogasawara K, Ono J, Shiokawa Y, Aruga T, Miyachi S, Nagata I, Matsuda S, Yoshimura S, Okuchi K, Suzuki A, Nakamura F, Onozuka D, Hagihara A, Iihara K. J-ASPECT Study Collaborators. Effect of treatment modality on in-hospital outcome in patients with subarachnoid hemorrhage: a nationwide study in Japan (J-ASPECT Study). J Neurosurg. 2018 May;128(5):1318–26. https://doi.org/10.3171/2016.12.JNS161039.
12. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR, CARAT Investigators. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. Stroke. 2008 Jan;39(1):120–5. https://doi.org/10.1161/STROKEAHA.107.495747.
13. Sundt TM Jr, Murphey F. Clip-grafts for aneurysm and small vessel surgery. 3. Clinical experience in intracranial internal carotid artery aneurysms. J Neurosurg. 1969 Jul;31(1):59–71. https://doi.org/10.3171/jns.1969.31.1.0059.
14. Nakagawa F, Kobayashi S, Takemae T, Sugita K. Aneurysms protruding from the dorsal wall of the internal carotid artery. J Neurosurg. 1986 Sep;65(3):303–8. https://doi.org/10.3171/jns.1986.65.3.0303.
15. Russin JJ, Kramer DR, Thomas D, Hasson D, Liu CY, Amar AP, Mack WJ, Giannotta SL. The importance of preoperative diagnosis of blister aneurysms. J Clin Neurosci. 2015 Sep;22(9):1408–12. https://doi.org/10.1016/j.jocn.2015.03.010.
16. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013 Feb;44(2):442–7. https://doi.org/10.1161/STROKEAHA.112.678151.
17. Kallmes DF, Hanel R, Lopes D, Boccardi E, Bonafé A, Cekirge S, Fiorella D, Jabbour P, Levy E, McDougall C, Siddiqui A, Szikora I, Woo H, Albuquerque F, Bozorgchami H, Dashti SR, Delgado Almandoz JE, Kelly ME, Turner R 4th, Woodward BK, Brinjikji W, Lanzino G, Lylyk P. International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. AJNR Am J Neuroradiol. 2015 Jan;36(1):108–15. https://doi.org/10.3174/ajnr.A4111.
18. Cagnazzo F, Mantilla D, Rouchaud A, Brinjikji W, Lefevre PH, Dargazanli C, Gascou G, Riquelme C, Perrini P, di Carlo D, Bonafe A, Costalat V. Endovascular treatment of very large and giant intracranial aneurysms: comparison between reconstructive and deconstructive techniques: a meta-analysis. AJNR Am J Neuroradiol. 2018 May;39(5):852–8. https://doi.org/10.3174/ajnr.A5591.
19. Brasiliense, Leonardo B C; Stanley, Morgan A; Grewal, Sanjeet S; Cloft, Harry J; Sauvageau, Eric; Lanzino, Giuseppe; Miller, David; Kallmes, David F; Hanel R. Silent ischemic events after pipeline embolization device: a prospective evaluation with MR diffusion-weighted imaging. J Neurointerv Surg. 2016. https://doi.org/10.1136/neurintsurg-2015-012091.
20. Kiselev R, Orlov K, Dubovoy A, Berestov V, Gorbatykh A, Kislitsin D, Shayakhmetov T, Tasenko A, Seleznev P, Strelnikov N, Ovsyannikov K, Gladkikh V, Moskalev A. Flow diversion versus parent artery occlusion with bypass in the treatment of complex intracranial aneurysms: immediate and short-term outcomes of the randomized trial. Clin Neurol Neurosurg. 2018 Sep;172:183–9. https://doi.org/10.1016/j.clineuro.2018.06.042.
21. Velasco González A, Stracke P, Nordmeyer H, Heddier M, Saleme S, Sauerland C, Berkemeyer S, Buerke B, Heindel W, Chapot R. Low rates of recanalization for wide-necked aneurysms treated with stenting after balloon-assisted coiling: combination of techniques delivers stable and improved results during follow-up. Neuroradiology. 2018 Nov;60(11):1223–30. https://doi.org/10.1007/s00234-018-2088-z.
22. Ryu CW, Park S, Shin HS, Koh JS. Complications in stent-assisted endovascular therapy of ruptured intracranial aneurysms and relevance to antiplatelet administration: a systematic review. AJNR Am J Neuroradiol. 2015 Sep;36(9):1682–8. https://doi.org/10.3174/ajnr.A4365.
23. Feng Z, Zuo Q, Yang P, Li Q, Zhao R, Hong B, Xu Y, Huang Q, Liu J. Staged stenting with or without additional coils after conventional initial coiling of acute ruptured wide-neck intracranial aneurysms. World Neurosurg. 2017 Dec;108:506–12. https://doi.org/10.1016/j.wneu.2017.09.040.
24. Byrne JV, Sohn MJ, Molyneux AJ, Chir B. Five-year experience in using coil embolization for ruptured intracranial aneurysms: outcomes and incidence of

late rebleeding. J Neurosurg. 1999 Apr;90(4):656–63. https://doi.org/10.3171/jns.1999.90.4.0656.
25. Campi A, Ramzi N, Molyneux AJ, Summers PE, Kerr RS, Sneade M, Yarnold JA, Rischmiller J, Byrne JV. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). Stroke. 2007 May;38(5):1538–44. https://doi.org/10.1161/STROKEAHA.106.466987.
26. Plowman RS, Clarke A, Clarke M, Byrne JV. Sixteen-year single-surgeon experience with coil embolization for ruptured intracranial aneurysms: recurrence rates and incidence of late rebleeding. Clinical article. J Neurosurg. 2011 Mar;114(3):863–74. https://doi.org/10.3171/2010.6.JNS091058.
27. Cloft HJ, Kallmes DF. Cerebral aneurysm perforations complicating therapy with Guglielmi detachable coils: a meta-analysis. AJNR Am J Neuroradiol. 2002 Nov-Dec;23(10):1706–9.
28. Derdeyn CP, Cross DT 3rd, Moran CJ, Brown GW, Pilgram TK, Diringer MN, Grubb RL Jr, Rich KM, Chicoine MR, Dacey RG Jr. Postprocedure ischemic events after treatment of intracranial aneurysms with Guglielmi detachable coils. J Neurosurg. 2002 May;96(5):837–43. https://doi.org/10.3171/jns.2002.96.5.0837.
29. Kim DY, Park JC, Kim JK, Sung YS, Park ES, Kwak JH, Choi CG, Lee DH. Microembolism after endovascular treatment of unruptured cerebral aneurysms: reduction of its incidence by microcatheter lumen aspiration. Neurointervention. 2015 Sep;10(2):67–73. https://doi.org/10.5469/neuroint.2015.10.2.67.
30. Hu YC, Deshmukh VR, Albuquerque FC, Fiorella D, Nixon RR, Heck DV, Barnwell SL, McDougall CG. Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the pipeline embolization device. J Neurosurg. 2014 Feb;120(2):365–74. https://doi.org/10.3171/2013.11.JNS131599.
31. Ihn YK, Shin SH, Baik SK, Choi IS. Complications of endovascular treatment for intracranial aneurysms: Management and prevention. Interv Neuroradiol. 2018 Jun;24(3):237–45. https://doi.org/10.1177/1591019918758493.
32. Corliss BM, Barkley KF, Polifka AJ, Hoh BL, Fox WC. Single-center case series of temporary stent assistance for coiling of acutely ruptured aneurysms. World Neurosurg. 2019 Mar;123:e766–72. https://doi.org/10.1016/j.wneu.2018.12.029.
33. Gaberel T, Borha A, di Palma C, Emery E. Clipping versus coiling in the management of posterior communicating artery aneurysms with third nerve palsy: a systematic review and meta-analysis. World Neurosurg. 2016 Mar;87:498–506.e4. https://doi.org/10.1016/j.wneu.2015.09.026.
34. Zheng F, Dong Y, Xia P, Mpotsaris A, Stavrinou P, Brinker G, Goldbrunner R, Krischek B. Is clipping better than coiling in the treatment of patients with oculomotor nerve palsies induced by posterior communicating artery aneurysms? A systematic review and meta-analysis. Clin Neurol Neurosurg. 2017 Feb;153:20–6. https://doi.org/10.1016/j.clineuro.2016.11.022.
35. Xia ZW, Liu XM, Wang JY, Cao H, Chen FH, Huang J, Li QZ, Fan SS, Jiang B, Chen ZG, Cheng Q. Coiling is not superior to clipping in patients with high-grade aneurysmal subarachnoid hemorrhage: systematic review and meta-analysis. World Neurosurg. 2017 Feb;98:411–20. https://doi.org/10.1016/j.wneu.2016.11.032.
36. Sato K, Endo H, Fujimura M, Endo T, Matsumoto Y, Shimizu H, Tominaga T. Endovascular treatments in combination with extracranial-intracranial bypass for complex intracranial aneurysms. World Neurosurg. 2018 May;113:e747–60. https://doi.org/10.1016/j.wneu.2018.02.143.
37. Hoh BL, Chi YY, Dermott MA, Lipori PJ, Lewis SB. The effect of coiling versus clipping of ruptured and unruptured cerebral aneurysms on length of stay, hospital cost, hospital reimbursement, and surgeon reimbursement at the University of Florida. Neurosurgery. 2009 Apr;64(4):614–9. https://doi.org/10.1227/01.NEU.0000340784.75352.A4.

13 Open Treatment of Cerebral Aneurysms in the Endovascular Age

Roland Jabre, Brenna McElenney, and Peter Nakaji

Abstract

With the advent of new endovascular devices, open surgery is becoming less popular for the treatment of intracranial aneurysms. However, in many situations it maintains material advantages and should therefore be considered among the tenable treatment options. This chapter discusses the specific indications for considering surgery as an option due to evidence that surgery yields a better outcome or because equipoise remains regarding the best treatment strategy. The different clinical situations presented include morphological aneurysm characteristics (wide-neck, giant size, fusiform shape, thrombotic, small size and blister aneurysms), the presence of multiple aneurysms, aneurysms causing neural compression or epilepsy, patient's age, aneurysm location (middle cerebral and anterior communicating aneurysms), and aneurysm recurrence after endovascular treatment.

Keywords

Intracranial aneurysm · Clipping · Bypass · Flow diverter · Coiling · Stenting · Woven EndoBridge device

13.1 Introduction

Following the publication of the International Subarachnoid Aneurysm Trial (ISAT) results [1–6] in 2002, a shift toward endovascular treatment of both unruptured and ruptured intracranial aneurysms began [7–9]. This trend has persisted during the last decade [10–12]. As the number of endovascular treatment strategies continues to grow, open surgery increasingly has begun to appear as a less desirable option. However, open surgical treatment may offer significant advantages in many specific cases. Herein, we discuss the indications in which an open surgical approach may be the preferred choice in the treatment of intracranial aneurysms.

13.2 General Advantages of Open Surgical Treatment of Aneurysms

While endovascular approaches offer a scarless approach among other benefits, open surgery has its own advantages: instant aneurysm occlusion

R. Jabre · P. Nakaji (✉)
Department of Neurosurgery, Banner University Medical Center – Phoenix, Phoenix, AZ, USA

Department of Neurosurgery, University of Arizona College of Medicine, Phoenix, AZ, USA
e-mail: nakaji@arizona.edu

B. McElenney
University of Arizona College of Medicine, Phoenix, AZ, USA

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_13

after the surgery, higher rates of complete occlusion [13], lower rates of retreatment and rebleeding [14], approaches to all types of aneurysms, decompression of neural structures, and the absence of required antiplatelet therapy. Furthermore, there are specific anatomical configurations and clinical situations where external exclusion, remodeling, or the ability to add flow through bypass makes open surgery a preferred therapeutic option for intracranial aneurysms.

13.3 Wide-Neck Aneurysms

Wide-neck aneurysms most commonly refer to a neck diameter of ≥ 4mm or a dome-to-neck ratio of < 2 (Fig. 13.1) [15]. Being wide-neck is often cited as a factor favoring surgical clipping. For example, a post hoc analysis conducted on a cohort of wide-neck aneurysms included in the Barrow Rupture Aneurysm Trial (BRAT) showed that even though clinical outcomes were similar between clipping and coiling (mRS > 2 of 49.5% and 40.0% respectively, $P = 0.33$), the aneurysm obliteration rate was higher (91.8% vs 35.7%, $P < 0.001$) and the retreatment rate was lower (0% vs 28.8%, $P < 0.001$) in the patients actually treated by clipping [16]. Subsequently, several endovascular techniques and devices have been developed in order to increase the occlusion rate and decrease the recurrence rate of this specific type of aneurysm, including balloon-assisted coiling, stent-assisted coiling, flow diverters, the WEB device, and others. Although there are two ongoing trials on the subject [17, 18], no published studies have effectively compared these techniques with surgical treatment yet. Since the complete occlusion rate is high using microneurosurgery (>90%) [16, 19], this modality remains the gold standard treatment for wide-neck aneurysms. Of note, these lesions might need more than simple clipping (e.g., complex clip reconstruction or bypasses); however, these interventions do not necessarily lessen efficacy or raise risk.

13.4 Giant Aneurysms

Giant aneurysms are defined as having a diameter of ≥2.5 cm. They pose a challenge for both endovascular and open surgery. These lesions can engulf branches, compress neural structures, and can be thrombosed, which makes their treatment more complex and riskier than that of regular aneurysms. Although flow diverters seem promising in the management of such lesions, this strategy has yet to be proven more effective and less morbid than open surgery. In the meantime, the literature suggests that surgery remains the

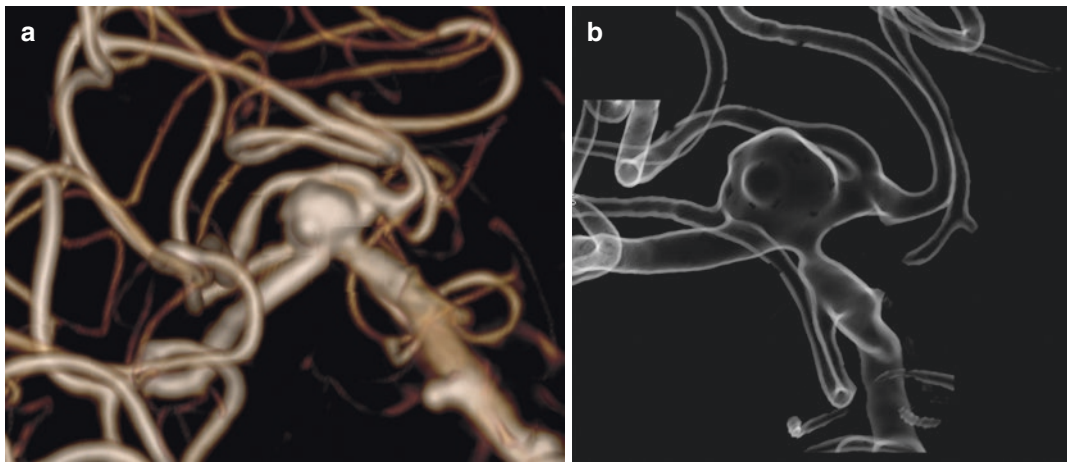


Fig. 13.1 Wide-neck aneurysm of the middle cerebral artery seen in (**a**) solid and (**b**) transparent 3D angiographic reconstruction

gold standard treatment with an occlusion rate of ≥84% [20, 21] and a mortality rate of ≤15.5% [20] (Table 13.1). Surgery also offers reconstructive possibilities such as better ability to avoid the sacrifice of a vessel branch and has the advantage that it immediately decompresses neural structures when necessary. In some cases, direct clipping or a clip-reconstruction technique may be possible, while in other cases revascularization is needed. Skull base approaches, cardiac standstill (or use of adenosine or induced hypotension through transvenous pacing) and intrasaccular thrombectomy are adjuncts that often prove useful when clipping giant aneurysms. Sometimes even these procedures fail to treat such aneurysms. In these circumstances, revascularization is available, and may be a better treatment modality. Additionally, multiple different revascularization techniques are available: bypass plus flow reversal using either proximal or distal occlusion, bypass plus aneurysm trapping, and aneurysm excision plus direct bypass (provided enough vessel redundancy).

13.5 Neural Compression

Although still debated in the literature, surgery is intuitively more effective than endovascular techniques as a method to decompress neural structures. However, in the case of oculomotor neuropathy, coiling can result in oculomotor function recovery, because in addition to direct compression of the nerve, the pulsatile effect of the aneurysm also might explain the neurological deficit. While some studies concluded that embolization leads to equivalent clinical outcome regarding oculomotor neuropathy [6, 58–62], others seem to point toward a better outcome with surgery [2, 4, 6, 63–69] (Table 13.2). Microneurosurgical treatment seems to lead to a higher rate of complete recovery of oculomotor neuropathy than embolization and less recurrence [58–79, 83, 86, 103–105]. Although the current literature is not definitive as to whether surgery is equivalent or better than endovascular treatment for treating aneurysm-related oculomotor neuropathy, it is clearly an effective modality which makes it the preferred approach in many institutions that can offer both modalities.

Aneurysm-related optic neuropathy however seems to be more effectively treated with surgery compared to coiling (Table 13.3) [106, 111, 121, 122, 127, 139, 142, 146, 154]. Although data regarding the results of flow diverters for this indication seem promising (Table 13.3) [19, 106, 108, 154–156], they have yet to prove their long-term efficacy and safety. In the meantime, surgery offers a rapid and safe option of treatment for this pathology.

Although flow diverters promise to be effective in treating aneurysm-related cranial neuropathies [154, 156], this has yet to be proven in a randomized controlled trial.

13.6 Epilepsy

Patients with aneurysms causing seizures are considered to be epileptic according to the latest definition of the International League Against Epilepsy [157] since they have “a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.” Surgical treatment has proven effective according to case reports and case series in treating the epilepsy of such patients (Table 13.4) [159–165, 167–171, 174–178, 180–182, 184–186, 189–191]. While surgery has not clearly proven more effective than medical treatment for these patients’ seizures, surgery has more data regarding its effectiveness compared to endovascular treatment [158, 166, 192]. It also seems more logical that surgical reduction of mass effect secondary to an aneurysm will better treat epilepsy than packing the same aneurysm and not alleviating the compression of the brain. However, aneurysm shrinkage seen after flow diverter placement may lead to a similar result, although the current literature does not have enough data either to confirm or invalidate this hypothesis. In the meantime, surgery (compared to endovascular therapy) remains the best approach in the case of aneurysm-related

Table 13.1 Published studies on the treatment of giant intracranial aneurysms

Study	Year	Technique	Patients treated	Aneurysms treated	Complete occlusion (at treatment)		Good clinical outcome		Mortality		Recurrence		Retreatment		Postoperative hemorrhage	
			n	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Endovascular																
Derrey et al. [22]	2015	–	34	34	15	44.1	N/A	–	N/A	–	N/A	–	N/A	–	N/A	–
Gao et al. [23]	2012	Coiling ± balloon or stent assistance	31	31	11	35.5	N/A	–	N/A	–	13	41.9	N/A	–	N/A	–
Gobin et al. [24]	1996	Coiling	9	9	6	66.7	9	100.0	0	0.0	2	22.2	1	11.1	0	0.0
Gruber et al. [25]	1999	Coiling	12	12	5	41.7	6	50.0	4	33.3	2	16.7	5	41.7	1	8.3
Ha and Jang [26]	2012	Coiling ± stenting	9	9	0	0.0	6	66.7	1	11.1	2	22.2	2	22.2	0	0.0
Hallacq et al. [27]	2002	Coiling ± balloon assistance or histoacryl embolization or parent artery occlusion	9	9	9	100.0	9	100.0	0	0.0	0	0.0	0	0.0	0	0.0
Hauck et al. [28]	2009	Coiling ± stenting	11	11	3	27.3	9	81.8	0	0.0	N/A	–	9	81.8	N/A	–
Hayakawa et al. [29]	2000	Coiling	10	10	0	0.0	N/A	–	N/A	–	9	90.0	N/A	–	N/A	–
Huh et al. [30]	2018	Coiling ± parent artery occlusion	13	13	3	23.1	6	46.2	4	30.8	2	15.4	1	7.7	N/A	–
Jahromi et al. [31]	2008	Coiling ± stenting or proximal occlusion or balloon embolization	38	39	14	35.9	15	39.5	11	28.9	N/A	–	21	53.8	3	7.9
Li et al. [32]	2007	Coiling ± stenting or parent artery occlusion	20	20	11	55.0	11	55.0	1	5.0	4	20.0	4	20.0	1	5.0
Lylyk et al. [33]	2009	Flow diverter	8	8	0	0.0	N/A	–	0	0.0	N/A	–	N/A	–	N/A	–
Murayama et al. [34]	2003	Coiling	73	73	19	26.0	N/A	–	N/A	–	43	58.9	N/A	–	N/A	–
Shi et al. [35]	2009	Coiling	3	3	0	0.0	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0
Sluzewski et al. [36]	2003	Coiling	16	17	5	29.4	5	31.3	2	12.5	N/A	–	11	64.7	N/A	–

Tateshima et al. [37]	2000	Coiling	10	10	0	0.0	N/A	–	N/A	–	4	40.0	N/A	–	1	10.0
Vinuela et al. [38]	1997	Coiling	18	18	9	50.0	N/A	–	N/A	–	N/A	–	N/A	–	N/A	–
Wang et al. [39]	2015	Coiling ± stenting or parent artery occlusion	39	39	18	46.2	N/A	–	N/A	–	N/A	–	N/A	–	N/A	–
Darsault et al. [40]	2011	Coiling ± stenting or parent artery occlusion	60	60	19	31.7	36	60.0	5	8.3	N/A	–	17	28.3	N/A	–
Endovascular total			**423**	**425**	**147**	**34.6**	**114**	**57.0**	**29**	**13.9**	**81**	**40.7**	**71**	**35.1**	**6**	**5.5**
Surgery																
Ausman et al. [41]	1990	–	62	62	N/A	–	41	66.1	3	4.8	N/A	–	N/A	–	N/A	–
Cantore et al. [42]	2008	–	99	99	N/A	–	N/A	–	8	8.1	N/A	–	N/A	–	N/A	–
Chalouhi et al. [43]	2014	–	11	11	11	100.0	N/A	–	N/A	–	N/A	–	N/A	–	N/A	–
Derrey et al. [22]	2015	–	29	29	15	51.7	N/A	–	N/A	–	N/A	–	N/A	–	N/A	–
Drake [44]	1979	–	174	174	N/A	–	78	44.8	25	14.4	N/A	–	N/A	–	N/A	–
Inci et al. [45]	2020	–	70	70	52	74.3	49	70.0	5	7.1	0	0.0	0	0.0	2	2.9
Jafar et al. [46]	2002	–	29	29	N/A	–	N/A	–	1	3.4	0	0.0	N/A	–	0	0.0
Kodama and Suzuki [47]	1982	–	49	49	N/A	–	30	61.2	11	22.4	N/A	–	N/A	–	N/A	–
Lawton and Spetzler [48]	1998	–	262	262	N/A	–	175	66.8	18	6.9	N/A	–	N/A	–	N/A	–
Li et al. [49]	2019	–	21	21	N/A	–	N/A	–	1	4.8	N/A	–	N/A	–	N/A	–
Lozier et al. [50]	2004	–	19	19	6	31.6	7	36.8	6	31.6	N/A	–	N/A	–	N/A	–
Luzzi et al. [20]	2020	–	82	82	78	95.1	62	75.6	9	11.0	4	4.9	3	3.7	1	1.2
Nanda et al. [51]	2012	–	59	59	N/A	–	41	69.5	6	10.2	N/A	–	N/A	–	N/A	–
Osawa et al. [52]	2001	–	12	12	N/A	–	1	8.3	4	33.3	N/A	–	N/A	–	N/A	–

(continued)

Table 13.1 (continued)

Study	Year	Technique	Patients treated	Aneurysms treated	Complete occlusion (at treatment)		Good clinical outcome		Mortality		Recurrence		Retreatment		Postoperative hemorrhage	
			n	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Sekhar et al. [53]	2001	–	8	8	8	100.0	5	62.5	1	12.5	0	0.0	0	0.0	0	0.0
Sharma et al. [54]	2008	–	177	181	106	58.6	131	74.0	16	9.0	N/A	–	N/A	–	N/A	–
Sughrue et al. [21]	2011	–	140	141	118	83.7	93	66.4	18	12.9	3	2.1	5	3.5	1	0.7
Tamaki et al. [55]	1991	–	3	3	N/A	–	3	100.0	0	0.0	N/A	–	N/A	–	0	0.0
Darsault et al. [40]	2011	–	114	114	80	70.2	82	71.9	14	12.3	N/A	–	7	6.1	N/A	–
Surgery total			**1420**	**1425**	**474**	**72.4**	**798**	**64.8**	**146**	**10.6**	**7**	**2.1**	**15**	**3.6**	**4**	**1.2**
Combined																
Darsault et al. [40]	2011	Bypass + endovascular parent artery occlusion	9	9	6	66.7	6	66.7	2	22.2	N/A	–	0	0.0	N/A	–
Arnautovic et al. [56]	1998	Clipping with balloon-assisted proximal control	8	8	N/A	–	8	100.0	0	0.0	N/A	–	N/A	–	N/A	–
Hacein Bey et al. [57]	1998	–	3	3	N/A	–	3	100.0	0	0.0	N/A	–	N/A	–	0	0.0
Shi et al. [35]	2009	Bypass + parent artery occlusion or aneurysm coiling	6	6	4	66.7	3	50.0	0	0.0	0	0.0	0	0.0	0	0.0
Combined total			**26**	**26**	**10**	**66.7**	**20**	**76.9**	**2**	**7.7**	**0**	**0**	**0**	**0**	**0**	**0**
All techniques			**1869**	**1876**	**631**	**57.6**	**932**	**64.0**	**177**	**11.0**	**88**	**16.4**	**86**	**13.6**	**10**	**2.2**

Table 13.2 Published studies on the treatment of aneurysm-related compressive CN III neuropathy

Study	Year	Patients with oculomotor impairment	Improved	
		n	*n*	%
Endovascular				
Signorelli et al. [70]	2020	31	19	61.3
Tian et al. [4]	2020	39	39	100.0
Zhong et al. [6]	2019	63	61	96.8
Su et al. [71]	2019	39	32	82.1
Gao et al. [64]	2017	29	25	86.2
Hall et al. [66]	2017	15	15	100.0
Zu et al. [72]	2017	34	29	85.3
Mino et al. [61]	2015	8	8	100.0
Sheehan et al. [73]	2015	20	20	100.0
Tan et al. [2]	2015	44	30	68.2
Brigui et al. [58]	2014	14	11	78.6
Patel et al. [62]	2014	9	9	100.0
Khan et al. [69]	2013	9	8	88.9
Chalouhi et al. [74]	2013	37	33	89.2
Güresir et al. [65]	2011	7	7	100.0
Ko and Kim [75]	2011	10	8	80.0
Panagiotopoulos et al. [76]	2011	10	9	90.0
Nam et al. [60]	2010	6	5	83.3
Kassis et al. [77]	2010	20	19	95.0
Santillan et al. [78]	2010	11	9	81.8
Zhang et al. [79]	2010	13	13	100.0
Hanse et al. [80]	2008	21	19	90.5
Mansour et al. [81]	2007	7	6	85.7
Chen et al. [68]	2006	6	6	100.0
Ahn et al. [59]	2006	10	10	100.0
Kim et al. [82]	2003	3	3	100.0
Stiebel-Kalish et al. [83]	2003	11	11	100.0
Yanaka et al. [84]	2003	1	0	0.0
Mavilio et al. [85]	2000	6	6	100.0
Birchall et al. [86]	1999	3	3	100.0
Endovascular total		**536**	**473**	**88.2**
Surgery				
Signorelli et al. [70]	2020	24	21	87.5
Tian et al. [4]	2020	31	31	100.0
Zhong et al. [6]	2019	39	39	100.0
Gao et al. [64]	2017	23	23	100.0
Mino et al. [61]	2015	9	9	100.0
Tan et al. [2]	2015	132	130	98.5
Brigui et al. [58]	2014	7	7	100.0
Patel et al. [62]	2014	9	9	100.0
Khan et al. [69]	2013	8	8	100.0
Motoyama et al. [87]	2012	1	1	100.0
Park et al. [88]	2011	13	13	100.0
Javalkar et al. [89]	2010	26	20	76.9
Nam et al. [60]	2010	8	7	87.5
Yeramneni et al. [90]	2010	13	13	100.0
Grunwald et al. [91]	2008	1	1	100.0

(continued)

Table 13.2 (continued)

Study	Year	Patients with oculomotor impairment	Improved	
		n	*n*	%
Saito et al. [92]	2008	3	3	100.0
Ahn et al. [59]	2006	7	7	100.0
Bhatti et al. [93]	2006	1	1	100.0
Chen et al. [68]	2006	7	7	100.0
Dimopoulos et al. [94]	2005	5	5	100.0
Kraus et al. [95]	2004	1	1	100.0
Arle et al. [96]	2002	1	1	100.0
Yanaka et al. [84]	2003	14	13	92.9
Park-Matsumoto and Tazawo [97]	1997	1	1	100.0
Fujiwara et al. [98]	1989	26	22	84.6
Kyriakides et al. [99]	1989	22	22	100.0
Bartleson et al. [100]	1986	12	11	91.7
Román-Campos and Edwards [101]	1979	1	1	100.0
Kasoff and Kelly [102]	1975	1	1	100.0
Surgery total		**446**	**428**	**96.0**
All techniques		**995**	**914**	**91.9**

epilepsy especially considering the possibility of simultaneous invasive monitoring and resection of the seizure-onset zone if necessary.

13.7 Small Aneurysms

Small aneurysms (usually defined as having a diameter of ≤ 4mm) may be challenging to treat (Table 13.5). Although one can argue on the indication of treating a small unruptured aneurysm since it is believed that its rupture rate is low [219], many ruptured aneurysms are small [220] and their treatment is important to prevent further rebleeding. Moreover, some consider unruptured and ruptured small aneurysms as arising from different pathological processes; the latter could result from a process of rapid formation of the aneurysm, explaining its fragility and propensity to rupture early [221, 222]. While open surgical treatment of these aneurysms is straightforward, endovascular strategies can result in serious complications such as aneurysm perforation (which is more frequent in small ruptured aneurysms [210]), coil migration, and thrombus formation. And because these aneurysms are often treated when they are ruptured, the use of stents and flow diverters is disadvantaged by the requirement of dual antiplatelet therapy and the hemorrhagic risks it entails acutely after an aneurysm rupture and in the frequent clinical setting of the requirement for external ventricular drainage. Although a comparative study has shown similar disability outcomes between endovascular treatment and surgery (with increased periprocedural complications), these results have to be analyzed cautiously since this study is not randomized [218]. Given all this information, many small aneurysms should be considered for surgical treatment (Fig. 13.2). Although there is not definitive prospective data, there is solid rationale for the notion that the smaller the aneurysm, the greater the preference for open surgery.

13.8 Blister Aneurysms

Blister aneurysms are usually defined as arising at nonbranching sites of the dorsal wall of the supraclinoid portion of the internal carotid artery [223–232], although they may arise on other vessels as well [233]. Their size makes them challenging to diagnose. This characteristic along with their friability render these aneurysms even harder to treat; aneurysm coiling may result in intraprocedural rupture, trapping may lead to brain ischemia even with a negative balloon test occlusion [234] and the use of stents or flow

Table 13.3 Published studies on the treatment of aneurysm-related compressive CN II neuropathy

Study	Year	Technique	Patients with visual impairment	Improved	
			n	*n*	%
Endovascular					
Hirata et al. [106]	2019	Flow diverter	6	3	50.0
Hirata et al. [106]	2019	Coiling	12	5	41.7
Silva et al. [19]	2018	Flow diverter	15	14	93.3
Silva et al. [19]	2018	Coiling	3	0	0.0
Park et al. [107]	2015	Coiling	10	2	20.0
Sahlein et al. [108]	2015	Flow diverter	17	9	52.9
Shimizu et al. [109]	2015	Coiling	6	4	66.7
Zanaty et al. [110]	2015	Flow diverter	12	9	75.0
Durst et al. [111]	2014	Coiling	22	15	68.2
Heller et al. [112]	2014	Coiling	32	11	34.4
Tanweer et al. [113]	2014	Flow diverter	19	16	84.2
Drazin et al. [114]	2013	Coiling	15	8	53.3
O'Kelly et al. [115]	2013	Flow diverter	10	5	50.0
Szikora et al. [116]	2013	Flow diverter	6	5	83.3
Wang et al. [117]	2013	Coiling	13	4	30.8
Schuss et al. [118]	2011	Coiling	8	3	37.5
Sun et al. [119]	2011	Coiling	7	3	42.9
Yadla et al. [120]	2011	Coiling	13	4	30.8
Heran et al. [121]	2007	Coiling	16	8	50.0
Schmidt et al. [122]	2007	Coiling	7	5	71.4
Park et al. [123]	2003	Coiling	5	1	20.0
Hoh et al. [124]	2001	Coiling	4	3	75.0
Malisch et al. [125]	1998	Coiling	6	2	33.3
Halbach et al. [126]	1994	Coiling	7	6	46.2
Coiling total			**186**	**84**	**45.2**
Flow diverter total			**85**	**61**	**71.8**
Endovascular total			**271**	**145**	**53.5**
Surgery					
Silva et al. [19]	2018	–	3	1	33.3
Kamide et al. [127]	2018	–	17	9	52.9
Matano et al. [128]	2016	–	2	1	50.0
Matsukawa et al. [129]	2016	–	2	2	100.0
Pasqualin et al. [130]	2016	–	20	3	15.0
Shimizu et al. [109]	2015	–	12	5	41.7
Aboukaïs et al. [131]	2015	–	5	1	20.0
Lai and Morgan [132]	2013	–	28	16	57.1
Mattingly et al. [133]	2013	–	14	11	78.6
Dehdashti et al. [134]	2012	–	12	9	75.0
Kanagalingam et al. [135]	2012	–	6	0	0.0
Nanda and Javalkar [136]	2011	–	15	10	66.7
Schuss et al. [118]	2011	–	12	9	75.0
Xu et al. [137]	2010	–	17	12	70.6
Park et al. [138]	2009	–	10	8	80.0
de Oliveira [139]	2009	–	14	14	100.0
Raco et al. [140]	2008	–	26	13	50.0
Iihara et al. [141]	2008	–	7	3	42.9
Nonaka et al. [142]	2007	–	16	9	56.3

(continued)

Table 13.3 (continued)

Study	Year	Technique	Patients with visual impairment	Improved	
			n	*n*	%
Zhao et al. [143]	2006	–	25	21	84.0
Barami et al. [144]	2003	–	5	0	0.0
Hoh et al. [124]	2001	–	12	8	66.7
Meyer et al. [145]	2001	–	13	2	15.4
Date et al. [146]	1998	–	6	3	50.0
Kattner et al. [147]	1998	–	10	5	50.0
Arnautović et al. [56]	1998	–	6	2	33.3
Fries et al. [148]	1997	–	19	15	79.0
Day [149]	1990	–	23	17	73.9
Diaz et al. [150]	1989	–	6	3	50.0
Norwood et al. [151]	1986	–	8	5	62.5
Heros et al. [152]	1983	–	16	10	62.5
Ferguson and Drake [153]	1981	–	21	12	57.1
Surgery total			**408**	**239**	**58.6**
All techniques			**679**	**384**	**56.6**

diverters plus dual antiplatelet therapy can lead to dramatic rebleeding [235]. Although a meta-analysis comparing open surgery to endovascular therapy has shown lower morbidity and mortality rates with endovascular therapy and a higher rate of complete occlusion with surgery, this conclusion is limited by the fact that the included studies were all case reports and case series [233]. Notably, the same meta-analysis showed better aneurysm occlusion rates with surgery than with endovascular approaches (96.4% vs 44.5%, respectively, in the early posttreatment period) [233]. Thus, while the approach should be individualized for any given patient, open surgery is still a valuable treatment option for the treatment of blister aneurysms (Table 13.6).

13.9 Thrombotic Aneurysms

Thrombotic aneurysms have been less often studied as a separate entity. Their treatment is aimed toward obliteration, decompression, and prevention of ischemic events. Surgery is a logical management strategy in this setting since thrombectomy and aneurysm exclusion can be done simultaneously within the same intervention with immediate effect. This approach results in high exclusion rates (97%), good clinical outcomes (87% improved or unchanged compared to preoperative state) while having a low mortality rate (6%) and low chances of permanent neurologic deficit (7%) [279]. A meta-analysis comparing surgery to endovascular treatment showed no significant difference in the clinical outcome of both cohorts. However, the two cohorts were not very similar; 80% of patients in the endovascular group had an unruptured aneurysm, while 72.6% of the patients in the surgical group presented with a ruptured aneurysm ($P = 0.0001$) [280]. Given the fact that the treatment of unruptured aneurysm has generally a better clinical outcome than for ruptured aneurysms, these results raise some concerns regarding the presumed safety of the endovascular treatment of ruptured thrombotic aneurysms. Since all patients in the endovascular group were treated by coiling, stenting, stent-assisted coiling, or trapping techniques, new endovascular technology may still prove safe and effective in future studies. In the meantime, a surgery-first policy may be safer when treating a thrombosed aneurysm.

Table 13.4 Published studies on the treatment of aneurysm-related epilepsy

Study	Year	Patients with seizures	Improved	
		n	*n*	%
Endovascular				
Peera and LoCurto [158]	2009	1	N/A	–
Kuba et al. [159]	2004	1	1	100.0
Endovascular total		**2**	**1**	**100.0**
Surgery				
Yefet et al. [160]	2020	1	1	100.0
Akimoto et al. [161]	2017	1	1	100.0
Lin et al. [162]	2017	1	1	100.0
Patil et al. [163]	2013	3	3	100.0
Lad et al. [164]	2012	1	1	100.0
Hänggi et al. [165]	2010	6	6	100.0
Kamali et al. [166]	2004	3	2	66.7
Miele et al. [167]	2004	1	1	100.0
Sena et al. [168]	2003	1	1	100.0
Roberts et al. [169]	2001	1	1	100.0
Ellamushi et al. [170]	1999	2	2	100.0
Mizobuchi et al. [171]	1999	1	1	100.0
Aladro et al. [172]	1998	1	1	100.0
Huang et al [173].	1996	1	1	100.0
Provenzale et al. [174]	1996	1	1	100.0
Casey and Moore [175]	1994	1	1	100.0
Yacubian et al. [176]	1994	1	1	100.0
Miyagi et al. [177]	1991	1	1	100.0
Putty et al. [178]	1990	1	1	100.0
Merva et al. [179]	1985	1	1	100.0
Whittle et al. [180]	1985	4	2	50.0
McCulloch and Ashworth [181]	1982	1	1	100.0
Stewart et al. [182]	1980	2	2	100.0
Pasqualin et al. [183]	1979	1	1	100.0
Sengupta et al. [184]	1978	3	3	100.0
Morley and Barr [185]	1969	1	1	100.0
Kamrin [186]	1966	3	3	100.0
Höök and Norlen [187]	1958	1	1	100.0
Frankel and Alpers [188]	1955	1	0	0.0
Surgery total		**47**	**43**	**91.5**
Combined				
Hänggi et al. [165]	2010	2	2	100.0
Combined total		**2**	**2**	**100.0**
All techniques		**51**	**46**	**92.0**

13.10 Ruptured Aneurysms Presenting with Intracerebral Hemorrhage

Aneurysmal subarachnoid hemorrhage is sometimes complicated by intracerebral hematoma. Such hematomas can produce local mass effect and increased intracranial pressure, making evacuation mandatory (Fig. 13.3). While some groups still prefer to treat the aneurysm endovascularly, surgical treatment offers obvious advantages: securing the aneurysm, evacuating the hematoma, and relieving the pressure on the brain, all within the same procedure. Only retrospective studies have been published comparing surgical

Table 13.5 Published studies on the treatment of small intracranial aneurysms

Study	Year	Technique	Patients treated	Aneurysms treated	Complete occlusion (at treatment)		Good clinical outcome		Mortality	
			n	*n*	*n*	%	*n*	%	*n*	%
Endovascular										
Catapano et al. [193]	2020	N/A	15	15	N/A	–	11	73.3	N/A	–
Yu et al. [194]	2015	Coiling + stenting	35	35	13	37.1	N/A	–	N/A	–
Jindal et al. [195]	2015	Coiling	14	14	12	85.7	N/A	–	2	14.3
Dalfino et al. [196]	2014	Coiling ± stenting	20	20	13	65.0	19	95.0	1	5.0
Li et al. [197]	2014	Coiling + stenting	16	16	15	93.8	16	100.0	0	0.0
Chung et al. [198]	2013	Coiling	72	72	35	48.6	63	87.5	7	9.7
Mohammadian et al. [199]	2013	Coiling	21	21	20	95.2	21	100.0	0	0.0
Starke et al. [200]	2013	Coiling ± stenting ± onyx	82	82	69	84.1	25	30.5	7	8.5
Lu et al. [201]	2012	Coiling ± stenting	46	52	14	26.9	45	97.8	0	0.0
Iskandar and Nepper-Rasmussen [202]	2011	Coiling ± stenting	107	111	43	38.7	N/A	–	10	9.3
Hong et al. [203]	2011	Coiling ± stenting	51	51	28	54.9	44	86.3	1	2.0
Hwang et al. [204]	2011	Coiling ± stenting	38	43	16	37.2	31	81.6	1	2.6
Zang et al. [205]	2010	Coiling ± stenting	11	11	8	72.7	11	100.0	0	0.0
Fang et al. [206]	2010	Coiling ± stenting	19	20	5	25.0	19	100.0	0	0.0
Ioannidis et al. [207]	2010	Coiling	94	97	64	66.0	61	64.9	7	7.4
Chae et al. [208]	2010	Coiling ± stenting	30	31	25	80.6	30	100.0	0	0.0
Pierot et al. [209]	2010	Coiling ± stenting	51	51	33	64.7	49	96.1	1	2.0
Brinjikji et al. [210]	2010	Coiling ± stenting	71	71	62	87.3	N/A	–	N/A	–
Gupta et al. [211]	2009	Coiling	7	7	6	85.7	6	85.7	0	0.0
Yang et al. [212]	2009	Coiling	12	12	6	50.0	8	66.7	0	0.0
van Rooji et al. [213]	2009	Coiling	187	196	186	94.9	163	87.2	9	4.8
Chen et al. [214]	2008	Coiling ± stenting	11	11	10	90.9	N/A	–	1	9.1
Nguyen et al. [215]	2008	Coiling	60	60	N/A	–	N/A	–	N/A	–
Suzuki et al. [216]	2006	Coiling	21	21	21	100.0	15	71.4	0	0.0
Endovascular total			**1091**	**1120**	**704**	**67.4**	**637**	**80.3**	**47**	**5.2**
Surgery										
Catapano et al. [193]	2020	N/A	58	15	N/A	–	35	60.3	N/A	–
Bruneau et al. [217]	2016	Clipping or wrapping	183	228	221	96.9	178	97.3	0	0.0
Chung et al. [198]	2013	Clipping	28	28	N/A	–	26	92.9	2	7.1
Chalouhi et al. [218]	2012	Clipping	60	60	N/A	–	16	26.7	3	5.0
Surgery total			**329**	**331**	**221**	**96.9**	**255**	**77.5**	**5**	**1.8**
All techniques			**1420**	**1451**	**925**	**72.7**	**892**	**79.5**	**52**	**4.4**

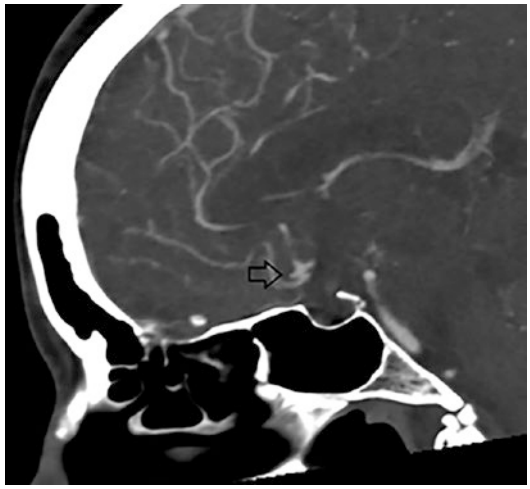


Fig. 13.2 Very small anterior communicating artery aneurysm (arrow) identified in the workup for subarachnoid hemorrhage, preferred for clipping

and endovascular approaches to obliterate the aneurysm when an ICH was present [281, 282]. These studies did not show a significant advantage of endovascular treatment although one would predict that their selection bias would have favored endovascular therapy over surgery. While a randomized control trial may help guide which treatment modality would be the best for treating stable patients, patients with increased intracranial pressure caused by the hematoma would probably be excluded from such a study and would be surgically treated. Until there is clear evidence of advantage of endovascular treatment in the literature, it is our opinion that patients with a significant intracerebral hemorrhage caused by an aneurysm rupture should be treated surgically (Table 13.7).

13.11 Young Population

As previously discussed, there is a shift toward endovascular treatment of intracranial aneurysms in general [7–9]. However, surgery leads to a more durable treatment (i.e., in terms of residual aneurysm, recurrence, and rebleeding) [14, 299]. This is the reason why surgical treatment is often cited as the appropriate management of aneurysms in the younger population, since this population has a longer life expectancy [300]. Since this patient population often has less comorbidities than older patients, they can more easily undergo surgery safely. Therefore, younger patients with aneurysms are usually more suitable for surgical treatment unless anatomical considerations strongly favor endovascular therapy. However, given the risks of de novo aneurysm formation and recurrence even with surgery, these patients should be followed with neurovascular imaging over a long period of time [301].

13.12 Fusiform Aneurysms

Fusiform aneurysms are difficult to treat both endovascularly and surgically. Their lack of neck makes simple coiling a high-risk treatment option because it can easily occlude the parent vessel. The advent of flow diverters was thought to revolutionize their treatment. However, perforator occlusion and aneurysm rupture secondary to ball-valve effect of telescopic flow diverters placement (extravasation and trapping of blood through the pores of the device into the extraluminal space) have been described after flow diverter placement [302–312]. Surgical options include clip reconstruction, clip-wrapping, aneurysm trapping, proximal or distal occlusion of the parent vessel with or without bypass and resection with reanastomosis [313–320]. Clip reconstruction can often be accomplished, although this modality can also be challenging when the parent vessel is calcified or severely atherosclerotic or when the aneurysmal segment contains perforating arteries [320]. In these cases, wrapping, trapping with bypass or aneurysm resection with reanastomosis may be preferred [320]. The morbidity and mortality of both endovascular and surgical treatment being high (Table 13.8), the treatment of fusiform aneurysms should be tailored to each case to make treatment as safe and effective as possible.

Table 13.6 Published studies on the treatment of blister intracranial aneurysms

Study	Year	Technique	Patients treated	Aneurysms treated	Good clinical outcome		Mortality	
			n	*n*	*n*	%	*n*	%
Endovascular								
Brown et al. [236]	2017	N/A	3	3	2	66.7	0	0.0
Kim et al. [237]	2014	ICA trapping	11	11	8	72.7	1	9.1
Meckel et al. [235]	2011	Stenting and/or coiling and/or parent artery occlusion	13	13	12	92.3	1	7.7
Yu-Tse et al. [238]	2012	Coiling ± stenting	2	2	1	50.0	0	0.0
Matsubara et al. [239]	2011	Coiling or trapping	9	9	6	66.7	2	22.2
Regelsberger et al. [240]	2011	Stenting	1	1	1	100.0	0	0.0
Gaughen et al. [241]	2010	Stenting ± coiling	6	6	5	83.3	0	0.0
Lee et al. [242]	2010	Coiling + ICA trapping	1	1	1	100.0	0	0.0
Lee et al. [243]	2009	Coiling + stenting	9	9	8	88.9	1	11.1
Ahn et al. [244]	2008	Coiling	1	1	1	100.0	0	0.0
Doorenbosch and Harding [245]	2008	Coiling + stenting	1	1	1	100.0	0	0.0
Korja et al. [246]	2008	Coiling + stenting	1	1	1	100.0	0	0.0
Meling et al. [247]	2008	Coiling or ICA trapping	3	3	2	66.7	1	33.3
Kim et al. [248]	2007	Coiling + stenting	1	1	1	100.0	0	0.0
Park et al. [249]	2007	Trapping or coiling ± stenting	5	5	3	60.0	0	0.0
Tanoue et al. [250]	2004	Coiling	1	1	0	0.0	0	0.0
McNeely et al. [251]	2000	Coiling	1	1	1	100.0	0	0.0
Endovascular total			**69**	**69**	**54**	**78.3**	**6**	**8.7**
Surgery								
Kim et al. [252]	2019	–	36	36	29	80.6	0	0.0
Brown et al. [236]	2017	–	10	10	6	60.0	0	0.0
Yu et al. [194]	2015	–	9	9	9	100.0	0	0.0
Kalani et al. [253]	2013	–	17	17	9	52.9	0	0.0
Park et al. [254]	2013	–	1	1	0	0.0	0	0.0
Murai et al. [255]	2012	–	5	5	4	80.0	0	0.0
Haji et al. [256]	2011	–	1	1	1	100.0	0	0.0
Horie et al. [257]	2011	–	1	1	1	100.0	0	0.0
Yu-Tse et al. [238]	2012	–	7	7	1	14.3	0	0.0
Horiuchi et al. [258]	2011	–	3	3	2	66.7	1	33.3
Lee et al. [242]	2010	–	1	1	0	0.0	1	100.0
McLaughlin et al. [259]	2010	–	7	7	7	100.0	0	0.0
Regelsberger et al. [240]	2011	–	2	2	1	50.0	1	50.0
Shimizu et al. [260]	2010	–	9	9	4	44.4	2	22.2
Chung et al. [261]	2009	–	1	1	1	100.0	0	0.0
Lee et al. [262]	2009	–	18	18	14	77.8	0	0.0
Otani et al. [263]	2009	–	6	6	3	50.0	0	0.0
Vashu et al. [264]	2009	–	1	1	1	100.0	0	0.0
Meling et al. [247]	2008	–	9	9	4	44.4	4	44.4
Tekkök and Bakkar [265]	2008	–	1	1	1	100.0	0	0.0

Table 13.6 (continued)

Study	Year	Technique	Patients treated	Aneurysms treated	Good clinical outcome		Mortality	
			n	*n*	*n*	%	*n*	%
Fiorella et al. [266]	2006	–	1	1	1	100.0	0	0.0
Joo et al. [267]	2006	–	2	2	2	100.0	0	0.0
Kim et al. [268]	2006	–	1	1	1	100.0	0	0.0
Kubo et al. [269]	2006	–	6	6	6	100.0	0	0.0
Sekula et al. [228]	2006	–	1	1	1	100.0	0	0.0
Sim et al. [229]	2006	–	10	10	8	80.0	1	10.0
Yanagisawa et al. [230]	2004	–	1	1	1	100.0	0	0.0
Yanaka et al. [231]	2002	–	1	1	1	100.0	0	0.0
Pelz et al. [270]	2003	–	2	2	2	100.0	0	0.0
Kurokawa et al. [271]	2001	–	1	1	1	100.0	0	0.0
Ogawa et al. [226]	2000	–	40	40	18	45.0	10	25.0
Wrobel and Taubman [272]	2000	–	1	1	1	100.0	0	0.0
Abe et al. [223]	1998	–	4	4	1	25.0	2	50.0
Ikeda et al. [273]	1998	–	1	1	1	100.0	0	0.0
Ishikawa et al. [224]	1997	–	1	1	0	0.0	1	0.0
Shigeta et al. [274]	1992	–	20	20	14	70.0	5	25.0
Nakagawa et al. [227]	1986	–	8	8	4	50.0	3	37.5
Sundt and Murphey [275]	1969	–	1	1	1	100.0	0	0.0
Surgery total			**247**	**247**	**162**	**65.6**	**31**	**12.6**
Combined								
Cho et al. [276]	2012	Stenting + clipping	1	1	1	100.0	0	0.0
Yu-Tse et al. [238]	2012	–	3	3	2	66.7	0	0.0
Lee et al. [242]	2010	Wrapping + bypass + ICA trapping	1	1	1	100.0	0	0.0
Baskaya et al. [277]	2008	Bypass ± coiling ± stenting ± trapping	4	4	3	75.0	1	25.0
Korja et al. [246]	2008	Coiling + stenting + clipping	1	1	0	0.0	1	100.0
Meling et al. [247]	2008	–	2	2	0	0.0	1	50.0
Park et al. [249]	2007	–	2	2	1	50.0	0	0.0
Fiorella et al. [266]	2006	Wrapping + stenting	1	1	1	100.0	0	0.0
Islam et al. [278]	2004	Embolization + ICA occlusion + EC-IC bypass	1	1	1	100.0	0	0.0
Abe et al. [223]	1998	Clipping + ICA occlusion	2	2	2	100.0	0	0.0
Combined total			**18**	**18**	**12**	**66.7**	**3**	**16.7**
All techniques			**334**	**334**	**228**	**68.3**	**40**	**12.0**

13.13 Multiple Aneurysms

Around 30% of patients with an intracranial aneurysm will be found to have multiple intracranial aneurysms [327, 328]. Since the presence of multiple aneurysms is a risk factor of aneurysm growth [329], this could justify the treatment of all aneurysms. While endovascular treatment offers the possibility of access to virtually every aneurysm location within the same approach, it

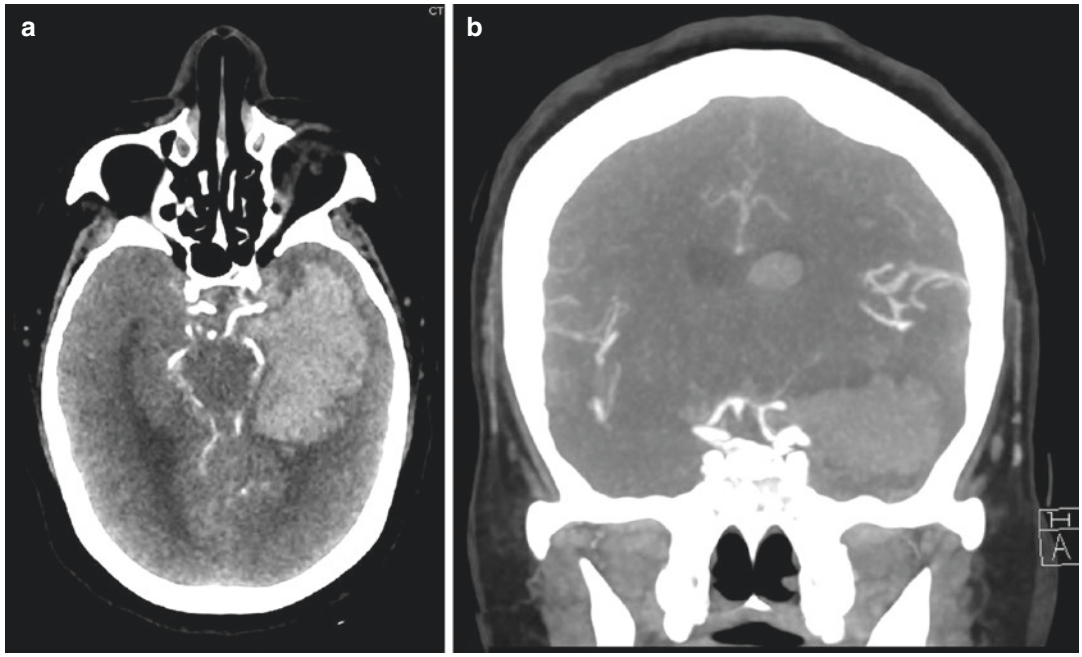


Fig. 13.3 Ruptured posterior communicating artery aneurysm causing uncal herniation secondary to temporal intracerebral hemorrhage and hydrocephalus secondary to intraventricular hemorrhage seen in (**a**) axial and (**b**) coronal CT angiographic views

may not be the best approach for multiple aneurysms, especially if the aneurysm suspected of rupture is not optimally treated by endovascular means. As previously described, some aneurysms are best treated surgically. In patients with such aneurysms, it may be more suitable to occlude the other aneurysms during the same surgery rather than to embolize them during another procedure. Since most aneurysms can be clipped using a single approach (usually a pterional craniotomy with or without an adjunct skull base technique) and since clipping can be performed from the contralateral side [330–335], surgery can be used to treat multiple aneurysms during the same procedure. Furthermore, unilateral minimally invasive approaches have also been described for the treatment of multiple intracranial aneurysms [336, 337]. Although in the setting of subarachnoid hemorrhage and multiple aneurysms a particular aneurysm is often suspected of being the ruptured one, endovascular treatment cannot confirm this the way clipping can. Considering that clipping offers confirmation that the ruptured aneurysm has been treated, a better rate of aneurysm obliteration, and a lower rate of recurrence in the treatment of multiple intracranial aneurysms [338], surgery should strongly be considered when all the aneurysms are accessible using a single craniotomy.

13.14 Middle Cerebral Artery Aneurysms

The middle cerebral artery (MCA) is one of the most common sites of intracranial aneurysm formation. These aneurysms often have a complex architecture including a wide neck which sometimes includes the ostium of an arterial branch. When ruptured, they often present with an intracerebral hemorrhage that may necessitate drainage. The former characteristic makes the endovascular approach more difficult without the use of a stent or a flow diverter which can result in the sacrifice of an arterial branch and necessitates the use of dual antiplatelet therapy. Furthermore, stent deployment and dual antiplatelet therapy increase the risk of re-rupture

Table 13.7 Published studies on the treatment of aneurysms presenting with intracerebral hemorrhage

Study	Year	Technique	Patients treated	Aneurysms treated	Complete occlusion (at treatment)		Good clinical outcome		Mortality	
			n	*n*	*n*	%	*n*	%	*n*	%
Endovascular										
Salaud et al. [281]	2016	Coiling	28	28	N/A	–	7	25.0	N/A	–
de los Reyes et al. [282]	2013	Coiling	10	10	N/A	–	0	0.0	3	30.0
Tawk et al. [283]	2010	Coiling	30	30	N/A	–	9	30.0	6	20.0
Chung et al. [284]	2009	Coiling	12	12	11	91.7	3	25.0	0	0.0
Kim et al. [285]	2008	Coiling	1	1	1	100.0	0	0.0	0	0.0
Jeong et al. [286]	2007	Coiling	9	9	N/A	–	4	44.4	0	0.0
Niemann et al. [287]	2003	Coiling	27	27	N/A	–	13	48.1	6	22.2
Endovascular total			**117**	**117**	**1**	**7.7**	**36**	**30.8**	**15**	**16.9**
Surgery										
Salaud et al. [281]	2015	–	16	16	N/A	–	4	25.0	N/A	–
Stapleton et al. [288]	2015	–	49	49	N/A	–	8	16.3	16	32.7
de los Reyes et al. [282]	2013	–	8	8	N/A	–	2	25.0	2	25.0
Prat and Galeano [289]	2007	–	12	12	N/A	–	2	16.7	4	33.3
Nakagawa et al. [290]	2005	–	129	129	N/A	–	54	41.9	N/A	–
Baskaya et al. [291]	2001	–	10	10	N/A	–	4	40.0	1	10.0
Hall et al. [292]	1999	–	6	6	6	100.0	5	83.3	0	0.0
Nowak et al. [293]	1998	–	43	43	N/A	–	7	16.3	8	18.6
Shimoda et al. [294]	1997	–	47	47	N/A	–	25	53.2	18	38.3
Tokuda et al. [295]	1995	–	98	95	N/A	–	22	22.4	46	46.9
Heiskanen et al. [296]	1988	–	15	15	15	100.0	2	13.3	4	26.7
Tapaninaho et al. [297]	1988	–	31	31	N/A	–	15	48.4	15	48.4
Pasqualin et al. [298]	1986	–	142	142	N/A	–	62	43.7	40	28.2
Surgery total			**606**	**603**	**21**	**100.0**	**212**	**35.0**	**154**	**33.4**
All techniques			**723**	**720**	**22**	**64.7**	**248**	**34.3**	**169**	**30.7**

Table 13.8 Published studies on the treatment of aneurysms fusiform intracranial aneurysms

Study	Year	Technique	Patients treated	Aneurysms treated	Complete occlusion (at treatment)		Good clinical outcome		Mortality	
			n	*n*	*n*	%	*n*	%	*n*	%
Endovascular										
Fang et al. [321]	2017	Flow diverter	6	6	5	83.3	6	100.0	0	0.0
Ertl et al. [304]	2014	Flow diverter	6	6	1	16.7	0	0.0	4	66.7
Fischer et al. [305]	2014	Flow diverter	69	65	33	50.8	46	66.7	2	2.9
Monteith et al. [308]	2014	Flow diverter	24	24	7	29.2	19	79.2	2	8.3
Munich et al. [309]	2014	Flow diverter	12	12	9	75.0	7	58.3	2	16.7
Toth et al. [312]	2015	Flow diverter	2	2	1	50.0	0	0.0	1	50.0
Meckel et al. [307]	2013	Flow diverter	10	10	5	50.0	6	60.0	4	40.0
van Oel et al. [302]	2013	Coil, stent, flow diverter	13	13	N/A	–	9	69.2	1	7.7
Siddiqui et al. [311]	2012	Flow diverter	7	7	2	28.6	2	28.6	4	57.1
Raphaeli et al. [310]	2011	Coil, parent artery occlusion, stent + coil, stent, flow diverter	31	31	18	58.1	21	67.7	6	19.4
Szikora et al. [322]	2010	Flow diverter	1	1	1	100.0	N/A	–	0	0.0
Lubicz et al. [306]	2010	Flow diverter	3	3	1	33.3	N/A	–	0	0.0
Fiorella et al. [323, 324]	2010	Flow diverter	1	1	1	100.0	1	100.0	0	0.0
Fiorella et al. [325]	2008, 2009	Flow diverter	1	1	1	100.0	0	0.0	1	100.0
Chiaradio et al. [326]	2002	Stent	1	1	N/A	–	N/A	–	0	0.0
Endovascular total			**187**	**183**	**85**	**50.3**	**117**	**64.3**	**27**	**14.4**
Surgery										
Safavi-Abbasi et al. [320]	2017	–	45	48	N/A	–	N/A	–	1	2.2
Lawton et al. [319]	2016	–	16	16	N/A	–	N/A	–	12	75.0
Kalani et al. [318]	2013	–	11	12	0	0.0	3	27.3	2	18.2
Drake et Peerless [316]	1997	–	120	120	N/A	–	83	69.2	16	13.3
Anson et al. [313]	1996	–	40	41	N/A	–	31	77.5	0	0.0
Surgery total			**232**	**237**	**0**	**0.0**	**117**	**68.4**	**31**	**13.4**
All techniques			**419**	**420**	**85**	**20.2**	**234**	**55.8**	**58**	**13.8**

and can result in hemorrhagic complications following ventricular drainage installation. In contrast, surgery does not necessitate the use for antiplatelet therapy and allows safe reconstruction of the MCA bifurcation while preserving arterial branches contained in the neck of the aneurysm. Additionally, most MCA aneurysms are quickly and easily exposed during surgery. Studies have compared the surgical and the endovascular treatment of MCA aneurysms, although none were randomized controlled trials. Most have concluded that even if the endovascular treatment was safe, the obliteration rate was higher and the recurrence rate was lower with surgery [339–345]. The high rate of crossover from coiling to clipping for MCA aneurysms in the BRAT study shows the preference of some clinicians toward clipping [346]. Notably, new endovascular devices have not been shown to have better occlusion rates than surgery [347]. Thus, an open surgical approach should be preferred for the treatment of MCA aneurysms.

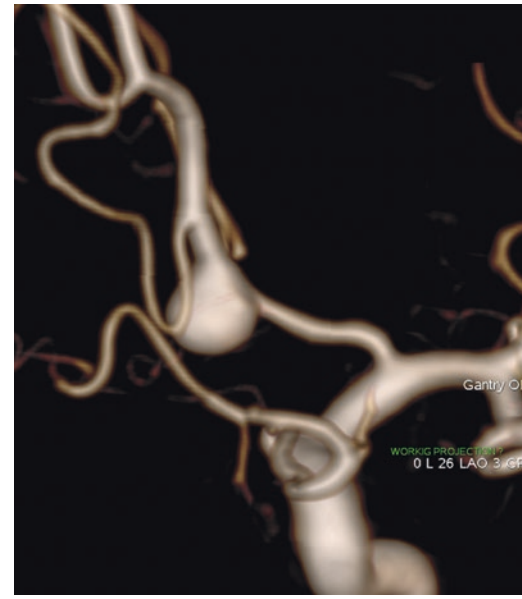


Fig. 13.4 Fusiform left anterior communicating artery aneurysm oriented inferiorly

13.15 Anterior Communicating Artery Aneurysms

Anterior communicating artery (ACoA) aneurysms are the most common ruptured intracranial aneurysms encountered (Fig. 13.4) [348]. While ISAT showed that patients with these aneurysms have better clinical outcomes when treated by endovascular means [1], this modality offers lower obliteration rate than surgery even when stent-assisted coiling or flow diversion techniques are used [349–359]. This might explain the high rate of crossover from coiling to clipping in the BRAT study for aneurysms in this location [360]. Nonetheless, new technological advances have permitted a wider proportion of ACoA aneurysms to be treated by endovascular techniques with similar outcomes as clipping [361]. Characteristics cited to favor surgical treatment of ACoA aneurysms are the presence of a wide neck, small aneurysm (too small or at the lower end of the size technically favorable for coiling), complex morphology, subarachnoid hemorrhage in the context of multiple aneurysms with uncertainty on which is the bleeding source, younger age, and the presence of a large intraparenchymal hemorrhage [360]. However, some characteristics carry a higher surgical risk such as a posteriorly oriented fundus [362]. In this case, an endovascular approach should probably be preferred. Some studies have also shown an advantage of endovascular treatment on cognitive outcome [363–368]. These differences should prompt both better surgical techniques such as minimally invasive approaches and preservation of the gyrus rectus and encouraging new technical advances in the endovascular realm to obtain better aneurysmal occlusion rates. In summary, ACoA aneurysms treatment should be discussed thoroughly in interdisciplinary meetings or be offered treatment by dually trained neurosurgeons in order to choose the best approach for a given patient.

13.16 Elderly Population

Given the constant increase in life expectancy, many patients present with intracranial aneurysms at an older age. Since elderly patients,

defined as being ≥65 years old or ≥70 years old depending on the study, have less years of life expectancy and more comorbidities than younger individuals, they may be more often advised to undergo a conservative management of their intracranial aneurysms when unruptured. However, in the setting of rupture, intervention is warranted even at this age [369]. Endovascular therapy may be riskier in this population since they tend to have tortuous and atherosclerotic vessels. However, surgery and endovascular treatment have both resulted in good clinical outcomes and should be considered [369–373]. Surgery results in better aneurysm obliteration rate [371, 374]; however, in this population, aneurysm rupture and retreatment rates might be more appropriate data to analyze given their lower life expectancy and the goals of preventing hemorrhage and retreatment rather than to aim for a perfect angiographic result. Given that there is no clinical evidence of a better outcome with surgery for these patients, a complete assessment should be done in order to choose the safest and most effective approach to treat aneurysms in the elderly population.

13.17 Recurrence After Endovascular Treatment

Following the shift toward endovascular treatment of intracranial aneurysms and because of the higher rate of recurrence associated with this approach [299], a new pathology has emerged: recurrent aneurysms following endovascular therapy (Fig. 13.5). Since approximately 20% of coiled aneurysms recur and 10% require another intervention [375], this entity is now very common. Young age, large aneurysm size, and incomplete occlusion have been demonstrated to be risk factors for retreatment after coiling [299]. When recoiling is attempted, up to 50% of aneurysms recurred [376] and their treatment often involved multiple coiling interventions which increases the risk of complications [377–379]. Considering that surgery has been demonstrated to result in better occlusion rates in aneurysms not previously treated compared to coiling, one could hypothesize that it may also be true for the treatment of recurrent aneurysms. Since the early ages of aneurysm coiling, studies have been published on surgical treatment of these lesions

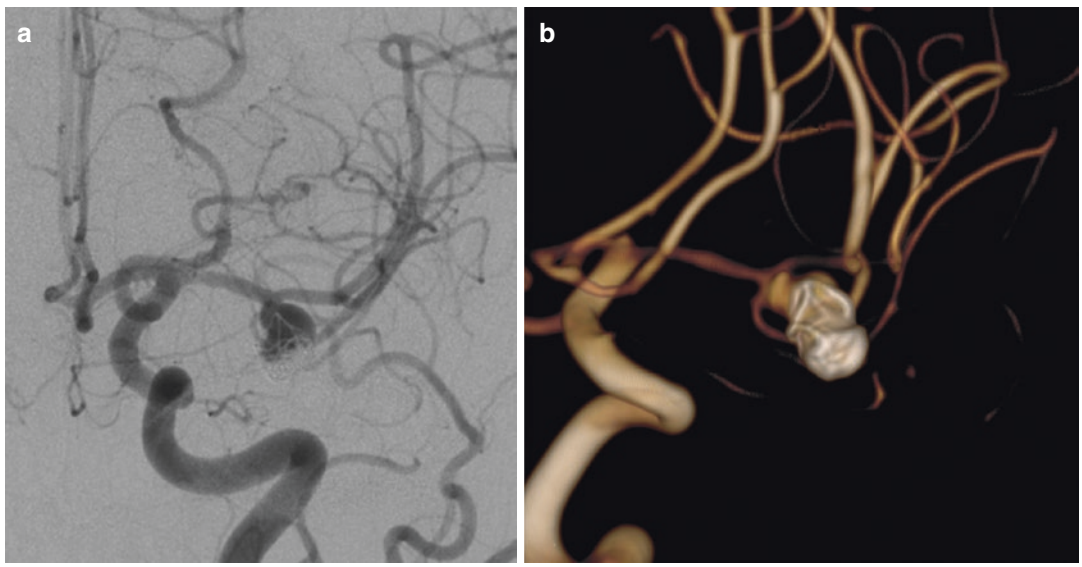


Fig. 13.5 Recurrent endovascularly treated middle cerebral artery aneurysm shown in (**a**) AP angiographic view and (**b**) reconstructed CT angiography

[380–382]. Notably, the number of studies published on the subject has multiplied within the last two decades [379, 383–417]. As hypothesized, these have demonstrated better occlusion rates with surgery than repeat endovascular treatment and good clinical outcomes. A sufficient residual neck is important in order to be able to clip these aneurysms [413]. The removal of coils in order to be able to occlude the aneurysm is much more technically complicated and might be dangerous [379, 408]. In response to this insight, a tandem clipping technique using a fenestrated clip has been described to avoid having to remove coils [389]. However, clipping is not always possible and a wrapping technique or a bypass with trapping of the aneurysm or proximal occlusion becomes necessary [379, 383, 405]. The constant evolution of technology in the endovascular realm could be thought to have had a positive effect on the obliteration rate. However, most studies on flow diverters and on the Woven EndoBridge (WEB) device have failed to show good obliteration rates [115, 418–431]. Presently, surgery still remains the most effective treatment option for aneurysms which have recurred after previous endovascular therapy.

13.18 Future of Open Aneurysm Surgery

The shift toward endovascular treatment has not only been beneficial for patients in terms of clinical outcomes after endovascular therapy, but it also forced open vascular neurosurgery to have better outcomes in order to continue to be part of our armamentarium. Meticulous microneurosurgical technique is probably the most important part of this evolution. In addition, minimally invasive techniques such as mini-pterional craniotomy, keyhole supraorbital craniotomy, endoscopy-assisted approaches, and even endoscopic endonasal approaches may help reducing the morbidity related to surgery. Indocyanine green video-angiography, intraoperative Doppler and intraoperative digital subtraction angiography are other examples of progress made to achieve better results for patients treated surgically.

13.19 Conclusion

Since the results of ISAT were released, endovascular therapy has increasingly become the preferred treatment modality for intracranial aneurysms rather than surgery [1]. However, as discussed above, endovascular therapy may not be the best approach for every aneurysm. Scant data comparing the two approaches are derived from randomized controlled trials. The results of ongoing trials might help us make more evidence-based decisions in specific cases [17, 18, 40, 432–435]. In the meantime, a thorough evaluation of each patient should be performed so as to offer the best possible treatment modality. Interdisciplinary meetings and/or the involvement of a dual-trained vascular neurosurgeon comfortable with the full range of techniques of both modalities are certainly beneficial in this decision-making process.

Although the endovascular field has seen several great technological advances, surgery remains a valid and critically important modality in the treatment of intracranial aneurysms. Therefore, these two techniques should be considered complementary rather than opposite approaches which should be thoughtfully deployed to achieve the safest and most effective result for individual patients.

References

1. Molyneux A. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267–74.
2. Tan H, et al. A retrospective comparison of the influence of surgical clipping and endovascular embolization on recovery of oculomotor nerve palsy in patients with posterior communicating artery aneurysms. Neurosurgery. 2015;76(6):687–94.

3. Taweesomboonyat C, et al. Outcome of ruptured posterior communicating artery aneurysm treatment comparing between clipping and coiling techniques. World Neurosurg. 2019;125:e183–8.
4. Tian LQ, Fu QX. Recovery of posterior communicating artery aneurysm induced oculomotor nerve palsy: a comparison between surgical clipping and endovascular embolization. BMC Neurol. 2020;20(1):351.
5. Zheng F, et al. Is clipping better than coiling in the treatment of patients with oculomotor nerve palsies induced by posterior communicating artery aneurysms? A systematic review and meta-analysis. Clin Neurol Neurosurg. 2017;153:20–6.
6. Zhong W, et al. Posterior communicating aneurysm with oculomotor nerve palsy: predictors of nerve recovery. J Clin Neurosci. 2019;59:62–7.
7. Andaluz N, Zuccarello M. Recent trends in the treatment of cerebral aneurysms: analysis of a nationwide inpatient database. J Neurosurg. 2008;108(6):1163–9.
8. Lin N, et al. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg. 2012;4(3):182–9.
9. Qureshi AI, et al. Impact of international subarachnoid aneurysm trial results on treatment of ruptured intracranial aneurysms in the United States. Clinical article. J Neurosurg. 2011;114(3):834–41.
10. Golnari P, et al. Volumes, outcomes, and complications after surgical versus endovascular treatment of aneurysms in the United States (1993-2015): continued evolution versus steady-state after more than 2 decades of practice. J Neurosurg. 2020;2020:1–14.
11. Luther E, et al. Treatment and diagnosis of cerebral aneurysms in the post-International Subarachnoid Aneurysm Trial (ISAT) era: trends and outcomes. J Neurointerv Surg. 2020;12(7):682–7.
12. Wang AS, et al. Cerebral aneurysm treatment trends in National Inpatient Sample 2007-2016: endovascular therapies favored over surgery. J Neurointerv Surg. 2020;12(10):957–63.
13. Spetzler RF, et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. J Neurosurg. 2019;2019:1–6.
14. McDougall CG, et al. The Barrow ruptured aneurysm trial. J Neurosurg. 2012;116(1):135–44.
15. Hendricks BK, et al. Wide-neck aneurysms: systematic review of the neurosurgical literature with a focus on definition and clinical implications. J Neurosurg. 2019;2019:1–7.
16. Mascitelli JR, et al. Analysis of wide-neck aneurysms in the Barrow ruptured aneurysm trial. Neurosurgery. 2019;85(5):622–31.
17. Raymond J, et al. The RISE trial: a randomized trial on intra-saccular endobridge devices. Interv Neuroradiol. 2020;26(1):61–7.
18. Raymond J, et al. Flow diversion in the treatment of aneurysms: a randomized care trial and registry. J Neurosurg. 2017;127(3):454–62.
19. Silva MA, et al. Comparison of flow diversion with clipping and coiling for the treatment of paraclinoid aneurysms in 115 patients. J Neurosurg. 2018;2018:1–8.
20. Luzzi S, et al. Surgical management of giant intracranial aneurysms: overall results of a large series. World Neurosurg. 2020;144:e119–37.
21. Sughrue ME, et al. Giant intracranial aneurysms: evolution of management in a contemporary surgical series. Neurosurgery. 2011;69(6):1261–70.
22. Derrey S, et al. French collaborative group series on giant intracranial aneurysms: current management. Neurochirurgie. 2015;61(6):371–7.
23. Gao X, et al. A single-centre experience and follow-up of patients with endovascular coiling of large and giant intracranial aneurysms with parent artery preservation. J Clin Neurosci. 2012;19(3):364–9.
24. Gobin YP, et al. Treatment of large and giant fusiform intracranial aneurysms with Guglielmi detachable coils. J Neurosurg. 1996;84(1):55–62.
25. Gruber A, et al. Clinical and angiographic results of endosaccular coiling treatment of giant and very large intracranial aneurysms: a 7-year, single-center experience. Neurosurgery. 1999;45(4):793–803.
26. Ha SW, Jang SJ. Clinical analysis of giant intracranial aneurysms with endovascular embolization. J Cerebrovasc Endovasc Neurosurg. 2012;14(1):22–8.
27. Hallacq P, Piotin M, Moret J. Endovascular occlusion of the posterior cerebral artery for the treatment of p2 segment aneurysms: retrospective review of a 10-year series. AJNR Am J Neuroradiol. 2002;23(7):1128–36.
28. Hauck EF, et al. Stent/coil treatment of very large and giant unruptured ophthalmic and cavernous aneurysms. Surg Neurol. 2009;71(1):19–24.
29. Hayakawa M, et al. Natural history of the neck remnant of a cerebral aneurysm treated with the Guglielmi detachable coil system. J Neurosurg. 2000;93(4):561–8.
30. Huh CW, et al. Endosaccular treatment of very large and giant intracranial aneurysms with parent artery preservation : single center experience with long term follow-up. J Korean Neurosurg Soc. 2018;61(4):450–7.
31. Jahromi BS, et al. Clinical and angiographic outcome after endovascular management of giant intracranial aneurysms. Neurosurgery. 2008;63(4):662–74.
32. Li MH, et al. Endovascular treatment of giant or very large intracranial aneurysms with different modalities: an analysis of 20 cases. Neuroradiology. 2007;49(10):819–28.
33. Lylyk P, et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. Neurosurgery. 2009;64(4):632–42.
34. Murayama Y, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg. 2003;98(5):959–66.

35. Shi ZS, et al. Management of giant middle cerebral artery aneurysms with incorporated branches: partial endovascular coiling or combined extracranial-intracranial bypass: a team approach. Neurosurgery. 2009;65(6 Suppl):121–9.
36. Sluzewski M, et al. Coiling of very large or giant cerebral aneurysms: Long-term clinical and serial angiographic results. Am J Neuroradiol. 2003;24(2):257–62.
37. Tateshima S, et al. Endovascular treatment of basilar tip aneurysms using Guglielmi detachable coils: anatomic and clinical outcomes in 73 patients from a single institution. Neurosurgery. 2000;47(6):1332–9.
38. Vinuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. J Neurosurg. 1997;86(3):475–82.
39. Wang B, et al. Endovascular embolization is applicable for large and giant intracranial aneurysms: experience in one center with long-term angiographic follow-up. Acta Radiol. 2015;56(1):105–13.
40. Darsaut TE, et al. Predictors of clinical and angiographic outcome after surgical or endovascular therapy of very large and giant intracranial aneurysms. Neurosurgery. 2011;68(4):903–15.
41. Ausman JI, et al. Giant intracranial aneurysm surgery: the role of microvascular reconstruction. Surg Neurol. 1990;34(1):8–15.
42. Cantore G, et al. Surgical treatment of giant intracranial aneurysms: current viewpoint. Neurosurgery. 2008;63(4 Suppl 2):279–89.
43. Chalouhi N, et al. Microsurgical clipping of large and giant cerebral aneurysms: a single-center contemporary experience. J Clin Neurosci. 2014;21(8):1424–7.
44. Drake CG. Giant intracranial aneurysms: experience with surgical treatment in 174 patients. Clin Neurosurg. 1979;26:12–95.
45. Inci S, Akbay A, Aslan T. The longest angiographic and clinical follow-up of microsurgically treated giant intracranial aneurysms: experience with 70 cases. World Neurosurg. 2020;134:e412–21.
46. Jafar JJ, Russell SM, Woo HH. Treatment of giant intracranial aneurysms with saphenous vein extracranial-to-intracranial bypass grafting: indications, operative technique, and results in 29 patients. Neurosurgery. 2002;51(1):138–44.
47. Kodama N, Suzuki J. Surgical treatment of giant aneurysms. Neurosurg Rev. 1982;5(4):155–60.
48. Lawton MT, Spetzler RF. Surgical strategies for giant intracranial aneurysms. Neurosurg Clin N Am. 1998;9(4):725–42.
49. Li M, et al. Microsurgical outcome of unruptured giant intracranial aneurysms: a single-center experience. J Clin Neurosci. 2019;70:132–5.
50. Lozier AP, et al. Microsurgical treatment of basilar apex aneurysms: perioperative and long-term clinical outcome. Neurosurgery. 2004;54(2):286–96.
51. Nanda A, et al. Microsurgical management of giant intracranial aneurysms: a single surgeon experience from Louisiana State University. Shreveport. World Neurosurg. 2014;81(5-6):752–64.
52. Osawa M, et al. Results of direct surgery for aneurysmal subarachnoid haemorrhage: outcome of 2055 patients who underwent direct aneurysm surgery and profile of ruptured intracranial aneurysms. Acta Neurochir (Wien). 2001;143(7):655–63.
53. Sekhar LN, et al. Cerebral revascularization using radial artery grafts for the treatment of complex intracranial aneurysms: techniques and outcomes for 17 patients. Neurosurgery. 2001;49(3):646–58.
54. Sharma BS, et al. Surgical management of giant intracranial aneurysms. Clin Neurol Neurosurg. 2008;110(7):674–81.
55. Tamaki N, et al. Giant carotid-ophthalmic artery aneurysms: direct clipping utilizing the "trapping-evacuation" technique. J Neurosurg. 1991;74(4):567–72.
56. Arnautovic KI, Al-Mefty O, Angtuaco E. A combined microsurgical skull-base and endovascular approach to giant and large paraclinoid aneurysms. Surg Neurol. 1998;50(6):504–18.
57. Hacein-Bey L, et al. Complex intracranial aneurysms: combined operative and endovascular approaches. Neurosurgery. 1998;43(6):1304–12.
58. Brigui M, et al. Recovery from oculomotor nerve palsy due to posterior communicating artery aneurysms: results after clipping versus coiling in a single-center series. Acta Neurochir (Wien). 2014;156(5):879–84.
59. Ahn JY, et al. Clipping vs coiling of posterior communicating artery aneurysms with third nerve palsy. Neurology. 2006;66(1):121–3.
60. Nam KH, et al. Unruptured intracranial aneurysms with oculomotor nerve palsy: clinical outcome between surgical clipping and coil embolization. J Korean Neurosurg Soc. 2010;48(2):109–14.
61. Mino M, et al. Outcomes of oculomotor nerve palsy caused by internal carotid artery aneurysm: comparison between microsurgical clipping and endovascular coiling. Neurol Med Chir (Tokyo). 2015;55(12):885–90.
62. Patel K, et al. Recovery of oculomotor nerve palsy secondary to posterior communicating artery aneurysms. Br J Neurosurg. 2014;28(4):483–7.
63. Gaberel T, et al. Clipping versus coiling in the management of posterior communicating artery aneurysms with third nerve palsy: a systematic review and meta-analysis. World Neurosurg. 2016;87:498–506.
64. Gao G, et al. Comparison of the efficacy of surgical clipping and embolization for oculomotor nerve palsy due to a posterior communicating artery aneurysm. Eur Rev Med Pharmacol Sci. 2017;21(2):292–6.
65. Guresir E, et al. Posterior communicating artery aneurysm-related oculomotor nerve palsy: influence of surgical and endovascular treatment on

recovery: single-center series and systematic review. Neurosurgery. 2011;68(6):1527–33.
66. Hall S, et al. The resolution of oculomotor nerve palsy caused by unruptured posterior communicating artery aneurysms: a Cohort study and narrative review. World Neurosurg. 2017;107:581–7.
67. McCracken DJ, et al. Resolution of oculomotor nerve palsy secondary to posterior communicating artery aneurysms: comparison of clipping and coiling. Neurosurgery. 2015;77(6):931–9.
68. Chen PR, et al. Outcome of oculomotor nerve palsy from posterior communicating artery aneurysms: comparison of clipping and coiling. Neurosurgery. 2006;58(6):1040–6.
69. Khan SA, et al. Effect of surgical clipping versus endovascular coiling on recovery from oculomotor nerve palsy in patients with posterior communicating artery aneurysms: a retrospective comparative study and meta-analysis. Asian J Neurosurg. 2013;8(3):117–24.
70. Signorelli F, et al. Endovascular versus surgical treatment for improvement of oculomotor nerve palsy caused by unruptured posterior communicating artery aneurysms. J Neurointerv Surg. 2020;12(10):964–7.
71. Su Z, et al. Efficacy of endovascular intervention in patients with unruptured posterior communicating artery aneurysm-related oculomotor nerve palsy. Neuro Endocrinol Lett. 2019;39(6):459–64.
72. Zu QQ, et al. Recovery of oculomotor nerve palsy after endovascular treatment of ruptured posterior communicating artery aneurysm. Neuroradiology. 2017;59(11):1165–70.
73. Sheehan MJ, et al. Endovascular repair of posterior communicating artery aneurysms, associated with oculomotor nerve palsy: a review of nerve recovery. Interv Neuroradiol. 2015;21(3):312–6.
74. Chalouhi N, et al. Endovascular treatment of posterior communicating artery aneurysms with oculomotor nerve palsy: clinical outcomes and predictors of nerve recovery. AJNR Am J Neuroradiol. 2013;34(4):828–32.
75. Ko JH, Kim YJ. Oculomotor nerve palsy caused by posterior communicating artery aneurysm: evaluation of symptoms after endovascular treatment. Interv Neuroradiol. 2011;17(4):415–9.
76. Panagiotopoulos V, et al. Recovery of ophthalmoplegia after endovascular treatment of intracranial aneurysms. AJNR Am J Neuroradiol. 2011;32(2):276–82.
77. Kassis SZ, et al. Recovery of third nerve palsy after endovascular treatment of posterior communicating artery aneurysms. World Neurosurg. 2010;73(1):11–6.
78. Santillan A, et al. Early endovascular management of oculomotor nerve palsy associated with posterior communicating artery aneurysms. Interv Neuroradiol. 2010;16(1):17–21.
79. Zhang SH, et al. Endovascular management and recovery from oculomotor nerve palsy associated with aneurysms of the posterior communicating artery. World Neurosurg. 2010;74(2-3):316–9.
80. Hanse MC, et al. Recovery of posterior communicating artery aneurysm-induced oculomotor palsy after coiling. AJNR Am J Neuroradiol. 2008;29(5):988–90.
81. Mansour N, et al. Resolution of cranial nerve paresis after endovascular management of cerebral aneurysms. Surg Neurol. 2007;68(5):500–4.
82. Kim DJ, et al. Unruptured aneurysms with cranial nerve symptoms: efficacy of endosaccular Guglielmi detachable coil treatment. Korean J Radiol. 2003;4(3):141–5.
83. Stiebel-Kalish H, et al. Evolution of oculomotor nerve paresis after endovascular coiling of posterior communicating artery aneurysms: a neuro-ophthalmological perspective. Neurosurgery. 2003;53(6):1268–73.
84. Yanaka K, et al. Small unruptured cerebral aneurysms presenting with oculomotor nerve palsy. Neurosurgery. 2003;52(3):553–7.
85. Mavilio N, et al. Recovery of third nerve palsy after endovascular packing of internal carotid-posterior communicating artery aneurysms. Interv Neuroradiol. 2000;6(3):203–9.
86. Birchall D, Khangure MS, McAuliffe W. Resolution of third nerve paresis after endovascular management of aneurysms of the posterior communicating artery. AJNR Am J Neuroradiol. 1999;20(3):411–3.
87. Motoyama Y, et al. Pupil-sparing oculomotor nerve palsy caused by upward compression of a large posterior communicating artery aneurysm. Case report. Neurol Med Chir (Tokyo). 2012;52(4):202–5.
88. Park J, Kang DH, Chun BY. Superciliary keyhole surgery for unruptured posterior communicating artery aneurysms with oculomotor nerve palsy: maximizing symptomatic resolution and minimizing surgical invasiveness. J Neurosurg. 2011;115(4):700–6.
89. Javalkar V, Cardenas R, Nanda A. Recovery of third nerve palsy following surgical clipping of posterior communicating artery aneurysms. World Neurosurg. 2010;73(4):353–6.
90. Yerramneni VK, et al. Recovery of oculomotor nerve palsy following surgical clipping of posterior communicating artery aneurysms. Neurol India. 2010;58(1):103–5.
91. Grunwald L, Sund NJ, Volpe NJ. Pupillary sparing and aberrant regeneration in chronic third nerve palsy secondary to a posterior communicating artery aneurysm. Br J Ophthalmol. 2008;92(5):715–6.
92. Saito R, et al. Pupil-sparing oculomotor nerve paresis as an early symptom of unruptured internal carotid-posterior communicating artery aneurysms. Neurol Med Chir. 2008;48(7):304–6.
93. Bhatti MT, et al. Superior divisional third cranial nerve paresis: clinical and anatomical observations of 2 unique cases. Arch Neurol. 2006;63(5):771–6.
94. Dimopoulos VG, et al. Literature review regarding the methodology of assessing third nerve

paresis associated with non-ruptured posterior communicating artery aneurysms. Neurosurg Rev. 2005;28(4):256–60.
95. Kraus RR, et al. Oculomotor palsy from an unruptured posterior communicating artery aneurysm presenting with cerebrospinal fluid pleocytosis and enhancement of the third cranial nerve. Case report. J Neurosurg. 2004;101(2):352–3.
96. Arle JE, et al. Pupil-sparing third nerve palsy with preoperative improvement from a posterior communicating artery aneurysm. Surg Neurol. 2002;57(6):423–6.
97. Park-Matsumoto YC, Tazawa T. Internal carotid-posterior communicating artery aneurysm manifesting as an unusual ocular motor paresis after minor head trauma: case report. Neurol Med Chir (Tokyo). 1997;37(2):181–3.
98. Fujiwara S, et al. Oculomotor nerve palsy in patients with cerebral aneurysms. Neurosurg Rev. 1989;12(2):123–32.
99. Kyriakides T, Aziz TZ, Torrens MJ. Postoperative recovery of third nerve palsy due to posterior communicating aneurysms. Br J Neurosurg. 1989;3(1):109–11.
100. Bartleson JD, Trautmann JC, Sundt TM Jr. Minimal oculomotor nerve paresis secondary to unruptured intracranial aneurysm. Arch Neurol. 1986;43(10):1015–20.
101. Roman-Campos G, Edwards KR. Painful ophthalmoplegia: oculomotor nerve palsy without mydriasis due to compression by aneurysm. Headache. 1979;19(1):43–6.
102. Kasoff I, Kelly DL Jr. Pupillary sparing in oculomotor palsy from internal carotid aneurysm. Case report. J Neurosurg. 1975;42(6):713–7.
103. Abdurahman E, et al. Recovery of oculomotor nerve palsy after endovascular management of posterior communicating artery aneurysms. SA J Radiol. 2020;24(1):1887.
104. Bulsara KR, Jackson D, Galvan GM. Rate of third nerve palsy recovery following endovascular management of cerebral aneurysms. Neurosurg Rev. 2007;30(4):307–10.
105. Chang SI, Tsai MD, Wei CP. Posterior communicating aneurysm with oculomotor nerve palsy: clinical outcome after aneurysm clipping. Turk Neurosurg. 2014;24(2):170–3.
106. Hirata K, et al. Treatment outcomes of cerebral aneurysms presenting with optic neuropathy: a retrospective case series. Asian J Neurosurg. 2019;14(2):499–505.
107. Park W, et al. Anterior optic pathway compression due to internal carotid artery aneurysms: neurosurgical management and outcomes. J Stroke. 2015;17(3):344–53.
108. Sahlein DH, et al. Neuroophthalmological outcomes associated with use of the pipeline embolization device: analysis of the PUFS trial results. J Neurosurg. 2015;123(4):897–905.
109. Shimizu T, et al. Visual outcomes of endovascular and microsurgical treatment for large or giant paraclinoid aneurysms. Acta Neurochir (Wien). 2015;157(1):13–20.
110. Zanaty M, et al. Flow-diversion for ophthalmic segment aneurysms. Neurosurgery. 2015;76(3):286–9.
111. Durst CR, et al. Vision outcomes and major complications after endovascular coil embolization of ophthalmic segment aneurysms. AJNR Am J Neuroradiol. 2014;35(11):2140–5.
112. Heller RS, et al. Neuro-ophthalmic effects of stenting across the ophthalmic artery origin in the treatment of intracranial aneurysms. J Neurosurg. 2014;121(1):18–23.
113. Tanweer O, et al. Cavernous carotid aneurysms in the era of flow diversion: a need to revisit treatment paradigms. AJNR Am J Neuroradiol. 2014;35(12):2334–40.
114. Drazin D, et al. Improvement in visual symptomatology after endovascular treatment of cavernous carotid aneurysms: a multicenter study. J Vasc Interv Neurol. 2013;6(1):15–21.
115. O'Kelly CJ, et al. Canadian experience with the pipeline embolization device for repair of unruptured intracranial aneurysms. AJNR Am J Neuroradiol. 2013;34(2):381–7.
116. Szikora I, et al. Resolution of mass effect and compression symptoms following endoluminal flow diversion for the treatment of intracranial aneurysms. AJNR Am J Neuroradiol. 2013;34(5):935–9.
117. Wang Y, et al. Endovascular treatment of paraclinoid aneurysms: 142 aneurysms in one centre. J Neurointerv Surg. 2013;5(6):552–6.
118. Schuss P, et al. Influence of surgical or endovascular treatment on visual symptoms caused by intracranial aneurysms: single-center series and systematic review. J Neurosurg. 2011;115(4):694–9.
119. Sun Y, Li Y, Li AM. Endovascular treatment of paraclinoid aneurysms. Interv Neuroradiol. 2011;17(4):425–30.
120. Yadla S, et al. Open and endovascular treatment of unruptured carotid-ophthalmic aneurysms: clinical and radiographic outcomes. Neurosurgery. 2011;68(5):1434–43.
121. Heran NS, et al. Large ophthalmic segment aneurysms with anterior optic pathway compression: assessment of anatomical and visual outcomes after endosaccular coil therapy. J Neurosurg. 2007;106(6):968–75.
122. Schmidt GW, et al. Isolated progressive visual loss after coiling of paraclinoid aneurysms. AJNR Am J Neuroradiol. 2007;28(10):1882–9.
123. Park HK, et al. Endovascular treatment of paraclinoid aneurysms: experience with 73 patients. Neurosurgery. 2003;53(1):14–23.
124. Hoh BL, et al. Results after surgical and endovascular treatment of paraclinoid aneurysms by a combined neurovascular team. Neurosurgery. 2001;48(1):78–89.

125. Malisch TW, et al. Unruptured aneurysms presenting with mass effect symptoms: response to endosaccular treatment with Guglielmi detachable coils. Part I. Symptoms of cranial nerve dysfunction. J Neurosurg. 1998;89(6):956–61.
126. Halbach VV, et al. The efficacy of endosaccular aneurysm occlusion in alleviating neurological deficits produced by mass effect. J Neurosurg. 1994;80(4):659–66.
127. Kamide T, et al. Microsurgical clipping of ophthalmic artery aneurysms: surgical results and visual outcomes with 208 aneurysms. J Neurosurg. 2018;129(6):1511–21.
128. Matano F, et al. Surgical treatment of 127 paraclinoid aneurysms with multifarious strategy: factors related with outcome. World Neurosurg. 2016;85:169–76.
129. Matsukawa H, et al. Risk factors for visual impairments in patients with unruptured intradural paraclinoid aneurysms treated by neck clipping without bypass surgery. World Neurosurg. 2016;91:183–9.
130. Pasqualin A, et al. Outcome after surgical treatment of paraclinoid carotid aneurysms. Acta Neurochir Suppl. 2016;123:33–9.
131. Aboukais R, et al. Pericallosal aneurysm: a difficult challenge for microsurgery and endovascular treatment. Neurochirurgie. 2015;61(4):244–9.
132. Lai LT, Morgan MK. Outcomes for unruptured ophthalmic segment aneurysm surgery. J Clin Neurosci. 2013;20(8):1127–33.
133. Mattingly T, et al. Visual outcomes for surgical treatment of large and giant carotid ophthalmic segment aneurysms: a case series utilizing retrograde suction decompression (the "Dallas technique"). J Neurosurg. 2013;118(5):937–46.
134. Dehdashti AR, et al. Long-term visual outcome and aneurysm obliteration rate for very large and giant ophthalmic segment aneurysms: assessment of surgical treatment. Acta Neurochir (Wien). 2012;154(1):43–52.
135. Kanagalingam S, et al. Visual sequelae after consensus-based treatment of ophthalmic artery segment aneurysms: the Johns Hopkins experience. J Neuroophthalmol. 2012;32(1):27–32.
136. Nanda A, Javalkar V. Microneurosurgical management of ophthalmic segment of the internal carotid artery aneurysms: single-surgeon operative experience from Louisiana State University, Shreveport. Neurosurgery. 2011;68(2):355–70.
137. Xu BN, et al. Microsurgical management of large and giant paraclinoid aneurysms. World Neurosurg. 2010;73(3):137–46.
138. Park JH, et al. Anterior communicating artery aneurysm related to visual symptoms. J Korean Neurosurg Soc. 2009;46(3):232–8.
139. de Oliveira JG, et al. Intracranial aneurysms presenting with mass effect over the anterior optic pathways: neurosurgical management and outcomes. Neurosurg Focus. 2009;26(5):E3.
140. Raco A, et al. Long-term surgical results with aneurysms involving the ophthalmic segment of the carotid artery. J Neurosurg. 2008;108(6):1200–10.
141. Iihara K, et al. Unruptured paraclinoid aneurysms: a management strategy. J Neurosurg. 2003;99(2):241–7.
142. Nonaka T, et al. Clinical manifestations and surgical results for paraclinoid cerebral aneurysms presenting with visual symptoms. Surg Neurol. 2007;67(6):612–9. discussion 619
143. Zhao J, et al. Microneurosurgical management of carotid-ophthalmic aneurysms. J Clin Neurosci. 2006;13(3):330–3.
144. Barami K, et al. Paraclinoid carotid aneurysms: surgical management, complications, and outcome based on a new classification scheme. Skull Base. 2003;13(1):31–41.
145. Meyer FB, et al. Surgical repair of clinoidal segment carotid artery aneurysms unsuitable for endovascular treatment. Neurosurgery. 2001;48(3):476–85.
146. Date I, Asari S, Ohmoto T. Cerebral aneurysms causing visual symptoms: their features and surgical outcome. Clin Neurol Neurosurg. 1998;100(4):259–67.
147. Kattner KA, Bailes J, Fukushima T. Direct surgical management of large bulbous and giant aneurysms involving the paraclinoid segment of the internal carotid artery: report of 29 cases. Surg Neurol. 1998;49(5):471–80.
148. Fries G, et al. Contralateral and ipsilateral microsurgical approaches to carotid-ophthalmic aneurysms. Neurosurgery. 1997;41(2):333–42.
149. Day AL. Aneurysms of the ophthalmic segment. A clinical and anatomical analysis. J Neurosurg. 1990;72(5):677–91.
150. Diaz FG, et al. Surgical alternatives in the treatment of cavernous sinus aneurysms. J Neurosurg. 1989;71(6):846–53.
151. Norwood EG, et al. Aneurysmal compression of the anterior visual pathways. Neurology. 1986;36(8):1035–41.
152. Heros RC, et al. Large and giant paraclinoid aneurysms: surgical techniques, complications, and results. Neurosurgery. 1983;12(2):153–63.
153. Ferguson GG, Drake CG. Carotid-ophthalmic aneurysms: visual abnormalities in 32 patients and the results of treatment. Surg Neurol. 1981;16(1):1–8.
154. Silva MA, et al. Vision outcomes in patients with paraclinoid aneurysms treated with clipping, coiling, or flow diversion: a systematic review and meta-analysis. Neurosurg Focus. 2017;42(6):E15.
155. Durst CR, et al. Endovascular treatment of ophthalmic artery aneurysms: ophthalmic artery patency following flow diversion versus coil embolization. J Neurointerv Surg. 2016;8(9):919–22.
156. Brown BL, et al. The fate of cranial neuropathy after flow diversion for carotid aneurysms. J Neurosurg. 2016;124(4):1107–13.

157. Fisher RS, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
158. Peera MA, LoCurto M. Temporal lobe seizures from a posterior cerebral artery aneurysm presenting as memory flashbacks. CJEM. 2009;11(4):389–92.
159. Kuba R, et al. Unruptured intracranial aneurysm as a cause of focal epilepsy: an excellent postoperative outcome after intra-arterial treatment. Epileptic Disord. 2004;6(1):41–4.
160. Yefet LS, et al. Unruptured posterior cerebral artery aneurysm presenting with temporal lobe epilepsy. Can J Neurol Sci. 2020;47(6):866–8.
161. Akimoto J, et al. A case of unruptured aneurysm of the internal carotid artery presenting as olfactory hallucinations. Surg Neurol Int. 2017;8:197.
162. Lin F, et al. Small unruptured intracranial aneurysm (≤5 mm) associated with epilepsy: report of 2 cases and literature review. World Neurosurg. 2017;98:878.e1–6.
163. Patil A, Menon GR, Nair S. Unruptured anterior communicating artery aneurysms presenting with seizure: report of three cases and review of literature. Asian J Neurosurg. 2013;8(3):164.
164. Lad SP, Shannon L, Byrne RW. Incidental aneurysms in temporal lobe epilepsy surgery: report of three cases and a review of the literature. Br J Neurosurg. 2012;26(1):69–74.
165. Hanggi D, Winkler PA, Steiger HJ. Primary epileptogenic unruptured intracranial aneurysms: incidence and effect of treatment on epilepsy. Neurosurgery. 2010;66(6):1161–5.
166. Kamali AW, Cockerell OC, Butlar P. Aneurysms and epilepsy: an increasingly recognised cause. Seizure. 2004;13(1):40–4.
167. Miele VJ, Bendok BR, Batjer HH. Unruptured aneurysm of the middle cerebral artery presenting with psychomotor seizures: case study and review of the literature. Epilepsy Behav. 2004;5(3):420–8.
168. Sena JC, Reynier Y, Alliez B. Unruptured intracranial aneurysm presenting with epileptic seizure. Arq Neuro-Psiquiatr. 2003;61(3a):663–7.
169. Roberts DL, et al. Musical hallucinations associated with seizures originating from an intracranial aneurysm. Mayo Clin Proc. 2001;76(4):423–6.
170. Ellamushi H, Thorne L, Kitchen N. Unruptured cerebral aneurysms causing seizure disorder (report of two cases). Seizure. 1999;8(5):310–2.
171. Mizobuchi M, et al. Unidirectional olfactory hallucination associated with ipsilateral unruptured intracranial aneurysm. Epilepsia. 1999;40(4):516–9.
172. Aladro Y, et al. Complex partial seizures as the only manifestation of aneurysm of the posterior communicating artery. Neurologia. 1998;13(9):442–3.
173. Huang LT, Shih TY, Lui CC. Posterior cerebral artery aneurysm in a two-year-old girl. J Formos Med Assoc. 1996;95(2):170–2.
174. Provenzale JM, Gorecki JP, Koen JL. Cerebral aneurysms associated with seizures but without clinical signs of rupture: seemingly distinctive MR imaging findings in two patients. AJR Am J Roentgenol. 1996;167(1):230–2.
175. Casey AT, Moore AJ. A traumatic giant posterior cerebral artery aneurysm mimicking a tentorial edge meningioma. Br J Neurosurg. 1994;8(1):97–9.
176. Yacubian EM, et al. Intractable complex partial seizures associated with posterior cerebral artery giant aneurysm: a case report. Epilepsia. 1994;35(6):1317–20.
177. Miyagi J. et al. [Giant aneurysm of the middle cerebral artery presenting with complex partial seizure. Case report]. Neurol Med Chir (Tokyo). 1991;31(13):953–956.
178. Putty TK, et al. Magnetic resonance imaging diagnosis of a cerebral aneurysm in an infant. Case report and review of the literature. Pediatr Neurosurg. 1990;16(1):48–51.
179. Merva W, Jamshidi S, Kurtzke JF. Posterior communicating artery giant aneurysm as a cause of seizures. Neurology. 1985;35(4):620–2.
180. Whittle IR, Allsop JL, Halmagyi GM. Focal seizures: an unusual presentation of giant intracranial aneurysms. A report of four cases with comments on the natural history and treatment. Surg Neurol. 1985;24(5):533–40.
181. McCulloch DK, Ashworth B. Cerebral aneurysm presenting with epilepsy. Postgrad Med J. 1982;58(676):94–7.
182. Stewart RM, et al. Unruptured cerebral aneurysms presenting as recurrent transient neurologic deficits. Neurology. 1980;30(1):47.
183. Pasqualin A, et al. Giant unruptured aneurysm of the middle cerebral artery manifesting with epilepsy: successful surgical treatment. J Neurosurg Sci. 1979;23(4):303–10.
184. Sengupta RP, Saunders M, Clarke PR. Unruptured intracranial aneurysms: an unusual source of epilepsy. Acta Neurochir (Wien). 1978;40(1-2):45–53.
185. Morley TP, Barr HW. Giant intracranial aneurysms: diagnosis, course, and management. Clin Neurosurg. 1969;16:73–94.
186. Kamrin RP. Temporal lobe epilepsy caused by unruptured middle cerebral artery aneurysms. Arch Neurol. 1966;14(4):421–7.
187. Höök O, Norlén G. Aneurysms of the middle cerebral artery: a report of 80 cases. Acta Chir Scand Suppl. 1958;235:1–39.
188. Frankel K, Alpers BJ. The clinical syndrome of aneurysm of the middle cerebral artery. AMA Arch Neurol Psychiatry. 1955;74(1):46–67.
189. Baeesa SS, et al. Unusual association of intractable temporal lobe seizures and intracranial aneurysms in an adolescent: is it a coincidence? Pediatr Neurosurg. 1998;28(4):198–203.
190. Cagavi F, et al. Giant unruptured anterior communicating artery aneurysm presenting with seizure. J Clin Neurosci. 2006;13(3):390–4.
191. Zambrelli E, et al. A possible case of unruptured middle cerebral artery aneurysm presenting as epileptic seizures. Neurol Sci. 2003;24(3):141–4.

192. Gnanalingham KK, Colquhoun I, van Dellen J. Temporal lobe seizures: unusual presentation of a giant unruptured posterior communicating artery aneurysm. Br J Neurosurg. 2003;17(4):370–1.
193. Catapano JS, et al. Small intracranial aneurysms in the Barrow Ruptured Aneurysm Trial (BRAT). Acta Neurochir (Wien). 2020;163(1):123–9.
194. Yu J, et al. Direct clipping of a blister-like aneurysm in the supraclinoid segment of the internal carotid artery: a clinical analysis of nine cases. Int J Clin Exp Med. 2015;8(11):21786–95.
195. Jindal G, et al. Ultra-small diameter coils for treatment of intracranial aneurysms. Interv Neuroradiol. 2015;21(1):50–4.
196. Dalfino J, et al. Strategies and outcomes for coiling very small aneurysms. World Neurosurg. 2014;81(5–6):765–72.
197. Li CH, et al. The stent-assisted coil-jailing technique facilitates efficient embolization of tiny cerebral aneurysms. Korean J Radiol. 2014;15(6):850–7.
198. Chung KH, et al. Rate and clinical impact of intraprocedural complications during coil embolisation of ruptured small (3 mm or less) cerebral aneurysms. Clin Neurol Neurosurg. 2013;115(8):1356–61.
199. Mohammadian R, et al. Endovascular treatment of very small and very large ruptured aneurysms of the anterior cerebral circulation: a single-center experience. Cerebrovasc Dis. 2013;35(3):235–40.
200. Starke RM, et al. Endovascular treatment of very small ruptured intracranial aneurysms: complications, occlusion rates and prediction of outcome. J Neurointerv Surg. 2013;5(Suppl 3):iii66.
201. Lu J, et al. Tiny intracranial aneurysms: endovascular treatment by coil embolisation or sole stent deployment. Eur J Radiol. 2012;81(6):1276–81.
202. Iskandar A, Nepper-Rasmussen J. Endovascular treatment of very small intracranial aneurysms. Interv Neuroradiol. 2011;17(3):299–305.
203. Hong B, et al. Endovascular treatment of ruptured tiny intracranial aneurysms. J Clin Neurosci. 2011;18(5):655–60.
204. Hwang JH, et al. Endovascular coil embolization of very small intracranial aneurysms. Neuroradiology. 2011;53(5):349–57.
205. Zang P, Liang C, Shi Q. Endovascular embolization of very small cerebral aneurysms. Neurol India. 2010;58(4):576–80.
206. Fang C, et al. The effectiveness and feasibility of endovascular coil embolization for very small cerebral aneurysms: mid- and long-term follow-up. Ann Vasc Surg. 2010;24(3):400–7.
207. Ioannidis I, et al. Endovascular treatment of very small intracranial aneurysms. J Neurosurg. 2010;112(3):551–6.
208. Chae KS, et al. Endovascular coil embolization of very small intracranial aneurysms. Korean J Radiol. 2010;11(5):536–41.
209. Pierot L, et al. Endovascular treatment of very small unruptured aneurysms: rate of procedural complications, clinical outcome, and anatomical results. Stroke. 2010;41(12):2855–9.
210. Brinjikji W, et al. Endovascular treatment of very small (3 mm or smaller) intracranial aneurysms: report of a consecutive series and a meta-analysis. Stroke. 2010;41(1):116–21.
211. Gupta V, et al. Coil embolization of very small (2 mm or smaller) berry aneurysms: feasibility and technical issues. AJNR Am J Neuroradiol. 2009;30(2):308–14.
212. Yang MS, et al. Alternative option in the treatment of very small ruptured intracranial aneurysms. Surg Neurol. 2009;72(Suppl 2):S41–6.
213. van Rooij WJ, et al. Clinical and angiographic results of coiling of 196 very small (< or = 3 mm) intracranial aneurysms. AJNR Am J Neuroradiol. 2009;30(4):835–9.
214. Chen Z, et al. Endovascular treatment of very small intracranial aneurysms. Surg Neurol. 2008;70(1):30–5.
215. Nguyen TN, et al. Association of endovascular therapy of very small ruptured aneurysms with higher rates of procedure-related rupture. J Neurosurg. 2008;108(6):1088–92.
216. Suzuki S, et al. Endovascular surgery for very small ruptured intracranial aneurysms. J Neurosurg. 2006;105(5):777–80.
217. Bruneau M, et al. Surgical clipping of very small unruptured intracranial aneurysms: a multicenter international study. Neurosurgery. 2016;78(1):47–52.
218. Chalouhi N, et al. Treatment of small ruptured intracranial aneurysms: comparison of surgical and endovascular options. J Am Heart Assoc. 2012;1(4):e002865.
219. Wiebers DO, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103–10.
220. Bijlenga P, et al. Risk of rupture of small anterior communicating artery aneurysms is similar to posterior circulation aneurysms. Stroke. 2013;44(11):3018–26.
221. Ikawa F, et al. Rupture risk of small unruptured cerebral aneurysms. J Neurosurg. 2019;2019:1–10.
222. Sonobe M, et al. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. Stroke. 2010;41(9):1969–77.
223. Abe M, et al. Blood blisterlike aneurysms of the internal carotid artery. J Neurosurg. 1998;89(3):419–24.
224. Ishikawa T, et al. Pathological consideration of a "blister-like" aneurysm at the superior wall of the internal carotid artery: case report. Neurosurgery. 1997;40(2):403–5.
225. McLaughlin N, Laroche M, Bojanowski MW. Blister-like aneurysms of the internal carotid artery - management considerations. Neurochirurgie. 2012;58(2–3):170–86.
226. Ogawa A, Suzuki M, Ogasawara K. Aneurysms at nonbranching sites in the surpaclinoid portion of the

internal carotid artery: internal carotid artery trunk aneurysms. Neurosurgery. 2000;47(3):578–83.
227. Nakagawa F, et al. Aneurysms protruding from the dorsal wall of the internal carotid artery. J Neurosurg. 1986;65(3):303–8.
228. Sekula RF Jr, et al. Primary treatment of a blister-like aneurysm with an encircling clip graft: technical case report. Neurosurgery. 2006;59(1 Suppl 1):ONSE168.
229. Sim SY, et al. Blood blister-like aneurysms at nonbranching sites of the internal carotid artery. J Neurosurg. 2006;105(3):400–5.
230. Yanagisawa T, et al. Direct repair of a blisterlike aneurysm on the internal carotid artery with vascular closure staple clips. Technical note. J Neurosurg. 2004;100(1):146–9.
231. Yanaka K, Meguro K, Nose T. Repair of a tear at the base of a blister-like aneurysm with suturing and an encircling clip: technical note. Neurosurgery. 2002;50(1):218–21.
232. Bojanowski MW, et al. Morphological aspects of blister aneurysms and nuances for surgical treatment. J Neurosurg. 2015;123(5):1156–65.
233. Peschillo S, et al. A systematic review and meta-analysis of treatment and outcome of blister-like aneurysms. AJNR Am J Neuroradiol. 2016;37(5):856–61.
234. Mathis JM, et al. Temporary balloon test occlusion of the internal carotid artery: experience in 500 cases. AJNR Am J Neuroradiol. 1995;16(4):749–54.
235. Meckel S, et al. Endovascular treatment using predominantly stent-assisted coil embolization and antiplatelet and anticoagulation management of ruptured blood blister-like aneurysms. AJNR Am J Neuroradiol. 2011;32(4):764–71.
236. Brown MA, et al. Long-term follow-up analysis of microsurgical clip ligation and endovascular coil embolization for dorsal wall blister aneurysms of the internal carotid artery. J Clin Neurosci. 2017;39:72–7.
237. Kim BC, et al. Endovascular internal carotid artery trapping for ruptured blood blister-like aneurysms: long-term results from a single centre. Neuroradiology. 2014;56(3):211–7.
238. Yu-Tse L, et al. Rupture of symptomatic blood blister-like aneurysm of the internal carotid artery: clinical experience and management outcome. Br J Neurosurg. 2012;26(3):378–82.
239. Matsubara N, et al. Endovascular coil embolization for saccular-shaped blood blister-like aneurysms of the internal carotid artery. Acta Neurochir (Wien). 2011;153(2):287–94.
240. Regelsberger J, et al. Blister-like aneurysms--a diagnostic and therapeutic challenge. Neurosurg Rev. 2011;34(4):409–16.
241. Gaughen JR Jr, et al. The efficacy of endovascular stenting in the treatment of supraclinoid internal carotid artery blister aneurysms using a stent-in-stent technique. AJNR Am J Neuroradiol. 2010;31(6):1132–8.
242. Lee CC, et al. Ruptured symptomatic internal carotid artery dorsal wall aneurysm with rapid configurational change. Clinical experience and management outcome: an original article. Eur J Neurol. 2010;17(10):1277–84.
243. Lee BH, et al. Reconstructive endovascular treatment of ruptured blood blister-like aneurysms of the internal carotid artery. J Neurosurg. 2009;110(3):431–6.
244. Ahn JY, et al. Blister-like aneurysms of the supraclinoid internal carotid artery: challenging endovascular treatment with stent-assisted coiling. J Clin Neurosci. 2008;15(9):1058–61.
245. Doorenbosch X, Harding M. Primary treatment of a blood-blister-like aneurysm of the internal carotid artery with Guglielmi detachable coil embolisation. J Clin Neurosci. 2008;15(11):1276–9.
246. Korja M, et al. Primary treatment of ruptured blood blister-like aneurysms with stent-assisted coil embolization: report of two cases. Acta Radiol. 2008;49(2):180–3.
247. Meling TR, et al. Blood blister-like aneurysms of the internal carotid artery trunk causing subarachnoid hemorrhage: treatment and outcome. J Neurosurg. 2008;108(4):662–71.
248. Kim BM, et al. Treatment of blood blister-like aneurysm of the internal carotid artery with stent-assisted coil embolization followed by stent-within-a-stent technique. Case report. J Neurosurg. 2007;107(6):1211–3.
249. Park JH, et al. Endovascular treatment of blood blister-like aneurysms of the internal carotid artery. J Neurosurg. 2007;106(5):812–9.
250. Tanoue S, et al. Ruptured "blisterlike" aneurysm with a pseudoaneurysm formation requiring delayed intervention with endovascular coil embolization. Case report. J Neurosurg. 2004;101(1):159–62.
251. McNeely PD, et al. Endovascular treatment of a "blister-like" aneurysm of the internal carotid artery. Can J Neurol Sci. 2000;27(3):247–50.
252. Kim YS, Joo SP, Kim TS. Microsurgical management of ruptured blood blister aneurysms of the internal carotid artery without bypass: a retrospective single-center study of 36 patients over 20 years. World Neurosurg. 2019;128:e956–65.
253. Kalani MY, et al. Long-term follow-up of blister aneurysms of the internal carotid artery. Neurosurgery. 2013;73(6):1026–33.
254. Park J. Maintenance of cerebral blood flow during microsuture repair of the superior wall of the intracranial internal carotid artery. World Neurosurg. 2013;80(3–4):436.e1.
255. Murai Y, et al. Ischemic complications after radial artery grafting and aneurysmal trapping for ruptured internal carotid artery anterior wall aneurysm. World Neurosurg. 2012;77(1):166–71.
256. Haji FA, Boulton MR, de Ribaupierre S. Blister-like supraclinoid internal carotid artery pseudoaneurysm in a 15-year-old male: case report and review of the literature. Pediatr Neurosurg. 2011;47(6):449–54.

257. Horie N, et al. Detection of blood blister-like aneurysm and intramural hematoma with high-resolution magnetic resonance imaging. J Neurosurg. 2011;115(6):1206–9.
258. Horiuchi T, et al. Ruptured anterior paraclinoid aneurysms. Neurosurg Rev. 2011;34(1):49–55.
259. McLaughlin N, Laroche M, Bojanowski MW. Surgical management of blood blister-like aneurysms of the internal carotid artery. World Neurosurg. 2010;74(4-5):483–93.
260. Shimizu H, Matsumoto Y, Tominaga T. Non-saccular aneurysms of the supraclinoid internal carotid artery trunk causing subarachnoid hemorrhage: acute surgical treatments and review of literatures. Neurosurg Rev. 2010;33(2):205–16.
261. Chung JH, et al. Ideal internal carotid artery trapping technique without bypass in a patient with insufficient collateral flow. J Korean Neurosurg Soc. 2009;45(4):260–3.
262. Lee JW, et al. Surgical strategies for ruptured blister-like aneurysms arising from the internal carotid artery: a clinical analysis of 18 consecutive patients. Acta Neurochir (Wien). 2009;151(2):125–30.
263. Otani N, et al. Clinical and radiological findings and surgical management of ruptured aneurysms at the non-branching sites of the internal carotid artery. J Clin Neurosci. 2009;16(8):1018–23.
264. Vashu R, Tan S, Wong AS. Microsuture repair of intra-operative ruptures of cerebral aneurysms of the internal carotid artery. J Clin Neurosci. 2009;16(7):960–2.
265. Tekkok IH, Bakar B. Ruptured blister-like aneurysm of distal internal carotid artery: a distinct entity. Turkish Neurosurg. 2008;18(4):439–45.
266. Fiorella D, et al. Endovascular reconstruction with the Neuroform stent as monotherapy for the treatment of uncoilable intradural pseudoaneurysms. Neurosurgery. 2006;59(2):291–300.
267. Joo SP, et al. Arterial suturing followed by clip reinforcement with circumferential wrapping for blister-like aneurysms of the internal carotid artery. Surg Neurol. 2006;66(4):424–8.
268. Kim JH, et al. Internal carotid artery dorsal wall aneurysm with configurational change: are they all false aneurysms? Surg Neurol. 2006;66(4):441–3.
269. Kubo Y, et al. Wrap-clipping with polytetrafluoroethylene for ruptured blisterlike aneurysms of the internal carotid artery. Technical note. J Neurosurg. 2006;105(5):785–7.
270. Pelz DM, et al. Combined endovascular/neurosurgical therapy of blister-like distal internal carotid aneurysms. Can J Neurol Sci. 2003;30(1):49–53.
271. Kurokawa Y, et al. New method for obliterative treatment of an anterior wall aneurysm in the internal carotid artery: encircling silicone sheet clip procedure—technical case report. Neurosurgery. 2001;49(2):469–72.
272. Wrobel CJ, Taubman K. Blood-blister-like aneurysms. J Neurosurg. 2000;92(6):1076–7.
273. Ikeda H, et al. Angiographic documentation of de novo aneurysm: case report. Neurol Med Chir (Tokyo). 1998;38(11):730–2.
274. Shigeta H, et al. Dorsal internal carotid artery aneurysms with special reference to angiographic presentation and surgical management. Acta Neurochir (Wien). 1992;119(1-4):42–8.
275. Sundt TM Jr, Murphey F. Clip-grafts for aneurysm and small vessel surgery. 3. Clinical experience in intracranial internal carotid artery aneurysms. J Neurosurg. 1969;31(1):59–71.
276. Cho TG, et al. Salvage surgical treatment for failed endovascular procedure of a blood blister-like aneurysm. J Cerebrovasc Endovasc Neurosurg. 2012;14(2):99–103.
277. Baskaya MK, et al. Surgical treatment of blood blister-like aneurysms of the supraclinoid internal carotid artery with extracranial-intracranial bypass and trapping. Neurosurg Focus. 2008;24(2):E13.
278. Islam MS, et al. Successful staged treatment for ruptured blister-like dissecting aneurysm of the intracranial internal carotid artery: acute GDC embolization for the blister-like aneurysm followed by proximal occlusion with extracranial-intracranial bypass in the chronic stage. Minim Invasive Neurosurg. 2004;47(3):165–8.
279. Lawton MT, et al. Thrombotic intracranial aneurysms: classification scheme and management strategies in 68 patients. Neurosurgery. 2005;56(3):441–54.
280. Scerrati A, et al. Treatment and outcome of thrombosed aneurysms of the middle cerebral artery: institutional experience and a systematic review. Neurosurg Rev. 2019;42(3):649–61.
281. Salaud C, et al. Management of aneurysmal subarachnoid haemorrhage with intracerebral hematoma: Is there an indication for coiling first? Study of 44 cases. Interv Neuroradiol. 2016;22(1):5–11.
282. de los Reyes K, et al. Management of subarachnoid hemorrhage with intracerebral hematoma: clipping and clot evacuation versus coil embolization followed by clot evacuation. J Neurointerv Surg. 2013;5(2):99–103.
283. Tawk R, et al. Coiling of ruptured aneurysms followed by evacuation of hematoma. World Neurosurg. 2010;74(6):626–31.
284. Chung J, et al. Treatment of ruptured anterior communicating artery aneurysm accompanying intracerebral hematomas: endovascular coiling followed by hematoma evacuation with burr hole trephination and catheterization. Acta Neurochir (Wien). 2009;151(8):917–23.
285. Kim SH, et al. Coil embolization of aneurysm followed by stereotactic aspiration of Hematoma in a patient with anterior communicating artery aneurysm presenting with SAH and ICH. J Korean Neurosurg Soc. 2008;43(1):41–4.
286. Jeong JH, Koh JS, Kim EJ. A less invasive approach for ruptured aneurysm with intracranial hematoma:

coil embolization followed by clot evacuation. Korean J Radiol. 2007;8(1):2–8.
287. Niemann DB, et al. Treatment of intracerebral hematomas caused by aneurysm rupture: coil placement followed by clot evacuation. J Neurosurg. 2003;99(5):843–7.
288. Stapleton CJ, et al. Surgical management of ruptured middle cerebral artery aneurysms with large intraparenchymal or sylvian fissure hematomas. Neurosurgery. 2015;76(3):258–64.
289. Prat R, Galeano I. Early surgical treatment of middle cerebral artery aneurysms associated with intracerebral haematoma. Clin Neurol Neurosurg. 2007;109(5):431–5.
290. Nakagawa T, et al. Predicting the overall management outcome in patients with a subarachnoid hemorrhage accompanied by a massive intracerebral or full-packed intraventricular hemorrhage: a 15-year retrospective study. Surg Neurol. 2005;63(4):329–34.
291. Başkaya MK, et al. Results of surgical treatment of intrasylvian hematomas due to ruptured intracranial aneurysms. Clin Neurol Neurosurg. 2001;103(1):23–8.
292. Hall CA, Kaufmann AM, Firlik A. Aneurysmal intracerebral hemorrhage: clinical outcome after emergent surgical treatment. J Stroke Cerebrovasc Dis. 1999;8(4):240–7.
293. Nowak G, et al. Intracerebral hematomas caused by aneurysm rupture. Experience with 67 cases. Neurosurg Rev. 1998;21(1):5–9.
294. Shimoda M, et al. Surgical indications in patients with an intracerebral hemorrhage due to ruptured middle cerebral artery aneurysm. J Neurosurg. 1997;87(2):170–5.
295. Tokuda Y, et al. Intracerebral hematoma in patients with ruptured cerebral aneurysms. Surg Neurol. 1995;43(3):272–7.
296. Heiskanen O, et al. Acute surgery for intracerebral haematomas caused by rupture of an intracranial arterial aneurysm. A prospective randomized study. Acta Neurochir (Wien). 1988;90(3-4):81–3.
297. Tapaninaho A, Hernesniemi J, Vapalahti M. Emergency treatment of cerebral aneurysms with large haematomas. Acta Neurochir (Wien). 1988;91(1-2):21–4.
298. Pasqualin A, et al. Intracranial hematomas following aneurysmal rupture: experience with 309 cases. Surg Neurol. 1986;25(1):6–17.
299. Campi A, et al. Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). Stroke. 2007;38(5):1538–44.
300. Mitchell P, et al. Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial? J Neurosurg. 2008;108(3):437–42.
301. Tsutsumi K, et al. Risk of aneurysm recurrence in patients with clipped cerebral aneurysms: results of long-term follow-up angiography. Stroke. 2001;32(5):1191–4.
302. van Oel LI, et al. Reconstructive endovascular treatment of fusiform and dissecting basilar trunk aneurysms with flow diverters, stents, and coils. AJNR Am J Neuroradiol. 2013;34(3):589–95.
303. Byrne JV, et al. Early experience in the treatment of intra-cranial aneurysms by endovascular flow diversion: a multicentre prospective study. PLoS One. 2010;5(9) https://doi.org/10.1371/journal.pone.0012492.
304. Ertl L, et al. Use of flow-diverting devices in fusiform vertebrobasilar giant aneurysms: a report on periprocedural course and long-term follow-up. AJNR Am J Neuroradiol. 2014;35(7):1346–52.
305. Fischer S, et al. Pipeline embolization device for the treatment of intra- and extracranial fusiform and dissecting aneurysms: initial experience and long-term follow-up. Neurosurgery. 2014;75(4):364–74.
306. Lubicz B, et al. Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke. 2010;41(10):2247–53.
307. Meckel S, et al. Endovascular treatment of complex aneurysms at the vertebrobasilar junction with flow-diverting stents: initial experience. Neurosurgery. 2013;73(3):386–94.
308. Monteith SJ, et al. Endovascular treatment of fusiform cerebral aneurysms with the Pipeline Embolization Device. J Neurosurg. 2014;120(4):945–54.
309. Munich SA, et al. The Pipeline Embolization Device for the treatment of posterior circulation fusiform aneurysms: lessons learned at a single institution. J Neurosurg. 2014;121(5):1077–84.
310. Raphaeli G, et al. Endovascular treatment of posterior circulation fusiform aneurysms: single-center experience in 31 patients. Neurosurgery. 2011;69(2):274–83.
311. Siddiqui AH, et al. Panacea or problem: flow diverters in the treatment of symptomatic large or giant fusiform vertebrobasilar aneurysms. J Neurosurg. 2012;116(6):1258–66.
312. Toth G, et al. Posterior circulation flow diversion: a single-center experience and literature review. J Neurointerv Surg. 2015;7(8):574–83.
313. Anson JA, Lawton MT, Spetzler RF. Characteristics and surgical treatment of dolichoectatic and fusiform aneurysms. J Neurosurg. 1996;84(2):185–93.
314. Chen PR, et al. Surgical techniques for unclippable fusiform A2-anterior cerebral artery aneurysms and description of a frontopolar-to-A2 bypass. World Neurosurg. 2014;81(2):441.e9.
315. Day AL, et al. Spontaneous fusiform middle cerebral artery aneurysms: characteristics and a proposed mechanism of formation. J Neurosurg. 2003;99(2):228–40.
316. Drake CG, Peerless SJ. Giant fusiform intracranial aneurysms: review of 120 patients treated surgically from 1965 to 1992. J Neurosurg. 1997;87(2):141–62.

317. Hanel RA, Spetzler RF. Surgical treatment of complex intracranial aneurysms. Neurosurgery. 2008;62(6 Suppl 3):1289–97.
318. Kalani MY, et al. Bypass and flow reduction for complex basilar and vertebrobasilar junction aneurysms. Neurosurgery. 2013;72(5):763–75. discussion 775-6
319. Lawton MT, et al. Bypass surgery for the treatment of dolichoectatic basilar trunk aneurysms: a work in progress. Neurosurgery. 2016;79(1):83–99.
320. Safavi-Abbasi S, et al. Techniques and outcomes of microsurgical management of ruptured and unruptured fusiform cerebral aneurysms. J Neurosurg. 2017;127(6):1353–60.
321. Fang YB, et al. Long-term outcome of tubridge flow diverter(s) in treating large vertebral artery dissecting aneurysms-a pilot study. Clin Neuroradiol. 2017;27(3):345–50.
322. Szikora I, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR Am J Neuroradiol. 2010;31(6):1139–47.
323. Fiorella D, et al. Very late thrombosis of a pipeline embolization device construct: case report. Oper Neurosurg. 2010;67(3):onsE313.
324. Fiorella D, et al. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. Neurosurgery. 2008;62(5):1115–21.
325. Fiorella D, et al. Curative reconstruction of a giant midbasilar trunk aneurysm with the pipeline embolization device. Neurosurgery. 2009;64(2):212–7.
326. Chiaradio JC, et al. Intravascular graft stent treatment of a ruptured fusiform dissecting aneurysm of the intracranial vertebral artery: technical case report. Neurosurgery. 2002;50(1):213–6.
327. Qureshi AI, et al. Risk factors for multiple intracranial aneurysms. Neurosurgery. 1998;43(1):22–6.
328. Post KD, et al. Ruptured intracranial aneurysms. Case morbidity and mortality. J Neurosurg. 1977;46(3):290–5.
329. Chien A, et al. Enlargement of small, asymptomatic, unruptured intracranial aneurysms in patients with no history of subarachnoid hemorrhage: the different factors related to the growth of single and multiple aneurysms. J Neurosurg. 2013;119(1):190–7.
330. Nakao S, Kikuchi H, Takahashi N. Successful clipping of carotid-ophthalmic aneurysms through a contralateral pterional approach - report of 2 cases. J Neurosurg. 1981;54(4):532–6.
331. Lynch J, Andrade R. Unilateral pterional approach to bilateral cerebral aneurysms. Surg Neurol. 1993;39(2):120–7.
332. Vajda J, et al. Contralateral approach to bilateral and ophthalmic aneurysms. Neurosurgery. 1988;22(4):662–8.
333. McMahon JH, Morgan MK, Dexter MA. The surgical management of contralateral anterior circulation intracranial aneurysms. J Clin Neurosci. 2001;8(4):319–24.
334. Clatterbuck RE, Tamargo RJ. Contralateral approaches to multiple cerebral aneurysms. Neurosurgery. 2005;57(1 Suppl):160–3.
335. de Sousa AA, et al. Unilateral pterional approach to bilateral aneurysms of the middle cerebral artery. Surg Neurol. 2005;63(Suppl 1):S1–7.
336. Hopf NJ, Stadie A, Reisch R. Surgical management of bilateral middle cerebral artery aneurysms via a unilateral supraorbital key-hole craniotomy. Minim Invasive Neurosurg. 2009;52(3):126–31.
337. Martellotta N, et al. Unilateral supraorbital keyhole approach in patients with middle cerebral artery (M1-M2 segment) symmetrical aneurysms. Minim Invasive Neurosurg. 2003;46(4):228–30.
338. Dong QL, et al. Comparison of surgical and endovascular approaches in the management of multiple intracranial aneurysms. Int J Surg. 2016;32:129–35.
339. Zhang L, et al. Effect analysis of microsurgical clipping and endovascular embolization for the treatment of middle cerebral artery aneurysms. World Neurosurg. 2019;125:e1074–81.
340. Smith TR, et al. Comparison of the efficacy and safety of endovascular coiling versus microsurgical clipping for unruptured middle cerebral artery aneurysms: a systematic review and meta-analysis. World Neurosurg. 2015;84(4):942–53.
341. Schwartz C, et al. Microsurgical clipping and endovascular treatment of middle cerebral artery aneurysms in an interdisciplinary treatment concept: comparison of long-term results. Interv Neuroradiol. 2018;24(6):608–14.
342. Suzuki S, et al. Endovascular treatment of middle cerebral artery aneurysms with detachable coils: angiographic and clinical outcomes in 115 consecutive patients. Neurosurgery. 2009;64(5):876–88.
343. Diaz OM, et al. Middle cerebral artery aneurysms: a single-center series comparing endovascular and surgical treatment. World Neurosurg. 2014;81(2):322–9.
344. Dammann P, et al. Outcome for unruptured middle cerebral artery aneurysm treatment: surgical and endovascular approach in a single center. Neurosurg Rev. 2014;37(4):643–51.
345. Choi JH, et al. Aneurysmal Neck Clipping as the Primary Treatment Option for Both Ruptured and Unruptured Middle Cerebral Artery Aneurysms. J Korean Neurosurg Soc. 2016;59(3):269–75.
346. Mooney MA, et al. Long-term results of middle cerebral artery aneurysm clipping in the Barrow Ruptured Aneurysm Trial. J Neurosurg. 2018;130(3):895–901.
347. Toccaceli G, et al. Microsurgical clipping compared with new and most advanced endovascular techniques in the treatment of unruptured middle cerebral artery aneurysms: a meta-analysis in the modern era. World Neurosurg. 2020;137:451–64.

348. Locksley HB. Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Based on 6368 cases in the cooperative study. J Neurosurg. 1966;25(2):219–39.
349. O'Neill AH, Chandra RV, Lai LT. Safety and effectiveness of microsurgical clipping, endovascular coiling, and stent assisted coiling for unruptured anterior communicating artery aneurysms: a systematic analysis of observational studies. J Neurointerv Surg. 2017;9(8):761–5.
350. Ki HJ, et al. Clinical and morphological risk factors for the recurrence of anterior communicating artery aneurysms after clipping or coiling. Acta Neurochir (Wien). 2020;162(9):2245–50.
351. Pagiola I, et al. Flow diversion treatment of aneurysms of the complex region of the anterior communicating artery: which stent placement strategy should 'I' use? A single center experience. J Neurointerv Surg. 2019;11(11):1118–22.
352. Johnson AK, et al. Stent assisted embolization of 64 anterior communicating artery aneurysms. J Neurointerv Surg. 2013;5(Suppl 3):iii62.
353. Jang CK, et al. Recurrence and retreatment of anterior communicating artery aneurysms after endovascular treatment: a retrospective study. BMC Neurol. 2020;20(1):287.
354. Fang S, et al. Endovascular treatment of anterior communicating artery aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2014;35(5):943–7.
355. Colby GP, et al. Endovascular flow diversion for treatment of anterior communicating artery region cerebral aneurysms: a single-center cohort of 50 cases. J Neurointerv Surg. 2017;9(7):679–85.
356. Choi HH, et al. Stent-assisted coil embolization of anterior communicating artery aneurysms: safety, effectiveness, and risk factors for procedural complications or recanalization. J Neurointerv Surg. 2019;11(1):49–56.
357. Cagnazzo F, et al. Flow-diversion treatment of unruptured saccular anterior communicating artery aneurysms: a systematic review and meta-analysis. AJNR Am J Neuroradiol. 2019;40(3):497–502.
358. Brzegowy P, et al. Angiographic and clinical results of anterior communicating artery aneurysm endovascular treatment. Wideochir Inne Tech Maloinwazyjne. 2019;14(3):451–60.
359. Brasiliense LB, et al. A reappraisal of anterior communicating artery aneurysms: a case for stent-assisted embolization. Neurosurgery. 2016;78(2):200–7.
360. Moon K, et al. Treatment of ruptured anterior communicating artery aneurysms: equipoise in the endovascular era? Neurosurgery. 2015;77(4):566–71.
361. Moon K, et al. Changing paradigms in the endovascular management of ruptured anterior communicating artery aneurysms. Neurosurgery. 2017;81(4):581–4.
362. Proust F, et al. Treatment of anterior communicating artery aneurysms: complementary aspects of microsurgical and endovascular procedures. J Neurosurg. 2003;99(1):3–14.
363. Pietrantonio A, Trungu S, Raco A. Clinical and neuropsychological outcome after microsurgical and endovascular treatment of ruptured and unruptured anterior communicating artery aneurysms: a single-enter experience. Acta Neurochir Suppl. 2017;124:173–7.
364. Beeckmans K, et al. Cognitive outcome after surgical clipping versus endovascular coiling in patients with subarachnoid hemorrhage due to ruptured anterior communicating artery aneurysm. Acta Neurol Belg. 2020;120(1):123–32.
365. Chan A, Ho S, Poon WS. Neuropsychological sequelae of patients treated with microsurgical clipping or endovascular embolization for anterior communicating artery aneurysm. Eur Neurol. 2002;47(1):37–44.
366. Escartin G, et al. Decision-making impairment on the Iowa gambling task after endovascular coiling or neurosurgical clipping for ruptured anterior communicating artery aneurysm. Neuropsychology. 2012;26(2):172–80.
367. Fontanella M, et al. Neuropsychological assessment after microsurgical clipping or endovascular treatment for anterior communicating artery aneurysm. Acta Neurochir (Wien). 2003;145(10):867–72.
368. Proust F, et al. Quality of life and brain damage after microsurgical clip occlusion or endovascular coil embolization for ruptured anterior communicating artery aneurysms: neuropsychological assessment. J Neurosurg. 2009;110(1):19–29.
369. Yang H, et al. Treatment strategy for unruptured intracranial aneurysm in elderly patients: coiling, clipping, or conservative? Cell Transplant. 2019;28(6):767–74.
370. Park JH, Kim YI, Lim YC. Clinical outcomes of treatment for intracranial aneurysm in elderly patients. J Cerebrovasc Endovasc Neurosurg. 2014;16(3):193–9.
371. Kwinta BM, et al. Elective management of unruptured intracranial aneurysms in elderly patients in a high-volume center. World Neurosurg. 2019;126:e1343–51.
372. Jang EW, et al. Benefits of surgical treatment for unruptured intracranial aneurysms in elderly patients. J Korean Neurosurg Soc. 2011;49(1):20–5.
373. Bekelis K, et al. Comparison of clipping and coiling in elderly patients with unruptured cerebral aneurysms. J Neurosurg. 2017;126(3):811–8.
374. Cho WC, et al. Treatment outcome after coiling or clipping for elderly patients with unruptured intracranial aneurysms. J Cerebrovasc Endovasc Neurosurg. 2020;22(2):78–84.
375. Ferns SP, et al. Coiling of intracranial aneurysms: a systematic review on initial occlusion and reopening and retreatment rates. Stroke. 2009;40(8):e523–9.
376. Raymond J, Darsaut TE. An approach to recurrent aneurysms following endovascular coiling. J Neurointerv Surg. 2011;3(4):314–8.
377. Slob MJ, et al. Additional coiling of previously coiled cerebral aneurysms: clinical and

angiographic results. AJNR Am J Neuroradiol. 2004;25(8):1373–6.
378. Ringer AJ, et al. Defining the risk of retreatment for aneurysm recurrence or residual after initial treatment by endovascular coiling: a multicenter study. Neurosurgery. 2009;65(2):311–5.
379. Daou B, et al. Clipping of previously coiled cerebral aneurysms: efficacy, safety, and predictors in a cohort of 111 patients. J Neurosurg. 2016;125(6):1337–43.
380. Civit T, et al. Aneurysm clipping after endovascular treatment with coils: a report of eight patients. Neurosurgery. 1996;38(5):955–60.
381. Gurian JH, et al. Neurosurgical management of cerebral aneurysms following unsuccessful or incomplete endovascular embolization. J Neurosurg. 1995;83(5):843–53.
382. Horowitz M, et al. Aneurysm retreatment after Guglielmi detachable coil and nondetachable coil embolization: report of nine cases and review of the literature. Neurosurgery. 1999;44(4):712–9.
383. Arnaout OM, et al. Microsurgical treatment of previously coiled intracranial aneurysms: systematic review of the literature. World Neurosurg. 2015;84(2):246–53.
384. Asgari S, et al. Complementary management of partially occluded aneurysms by using surgical or endovascular therapy. J Neurosurg. 2002;97(4):843–50.
385. Boet R, Poon WS, Yu SC. The management of residual and recurrent intracranial aneurysms after previous endovascular or surgical treatment: a report of eighteen cases. Acta Neurochir (Wien). 2001;143(11):1093–101.
386. Chung J, et al. Early and late microsurgical clipping for initially coiled intracranial aneurysms. Neuroradiology. 2010;52(12):1143–51.
387. Conrad MD, et al. Regrowth of residual ruptured aneurysms treated by Guglielmi's detachable coils which demanded further treatment by surgical clipping: report of 7 cases and review of the literature. Acta Neurochir (Wien). 2002;144(5):419–26.
388. Deinsberger W, et al. Surgical management of previously coiled intracranial aneurysms. Br J Neurosurg. 2003;17(2):149–54.
389. Izumo T, et al. Microsurgical clipping for recurrent aneurysms after initial endovascular coil embolization. World Neurosurg. 2015;83(2):211–8.
390. Kivelev J, et al. Open surgery for recurrent intracranial aneurysms: techniques and long-term outcomes. World Neurosurg. 2016;96:1–9.
391. Klein O, et al. Aneurysm clipping after endovascular treatment with coils: a report of 13 cases. Neurosurg Rev. 2008;31(4):403–10.
392. Konig RW, et al. Neurosurgical management of previously coiled recurrent intracranial aneurysms. Zentralbl Neurochir. 2007;68(1):8–13.
393. Kutty RK, et al. Management of recurrent aneurysms after endovascular coiling: a Fujita experience. Asian J Neurosurg. 2019;14(4):1151–6.
394. Lee C-H, Choi C-Y. Microsurgical clipping and coil removal of previously coiled regrowing cerebral aneurysms. Korean J Cerebrovasc Surg. 2011;13(4):303–9.
395. Lee J, et al. Microsurgical treatment for the recurrent cerebral aneurysm initially treated using coil embolization. J Cerebrovasc Endovasc Neurosurg. 2020;22(3):165–75.
396. Lejeune JP, et al. Neurosurgical treatment for aneurysm remnants or recurrences after coil occlusion. Neurosurgery. 2008;63(4):684–91.
397. Liu, J.J., et al., Surgical treatment of recurrent previously coiled and/or stent-coiled intracerebral aneurysms: a single-center experience in a series of 75 patients. World Neurosurg. 2019. https://doi.org/10.1016/j.wneu.2018.12.171.
398. Minh T, et al. Neurosurgical management of intracranial aneurysms following unsuccessful or incomplete endovascular therapy. Br J Neurosurg. 2006;20(5):306–11.
399. Nakamura M, et al. Microsurgical clipping of previously coiled intracranial aneurysms. Clin Neurol Neurosurg. 2013;115(8):1343–9.
400. Nisson PL, et al. Surgical clipping of previously ruptured, coiled aneurysms: outcome assessment in 53 patients. World Neurosurg. 2018;120:e203–11.
401. Nomura M, et al. Aneurysm clipping after partial endovascular embolization for ruptured cerebral aneurysms. Interv Neuroradiol. 2000;6(Suppl 1):49–58.
402. Pirayesh A, et al. Microsurgery of residual or recurrent complex intracranial aneurysms after coil embolization - a quest for the ultimate therapy. Neurosurg Rev. 2020;44(2):1031–51.
403. Raftopoulos C, et al. Neurosurgical management of inadequately embolized intracranial aneurysms: a series of 17 consecutive cases. Acta Neurochir (Wien). 2007;149(1):11–9.
404. Raper DMS, et al. Definitive treatment with microsurgical clipping after recurrence and rerupture of coiled anterior cerebral artery aneurysms. Oper Neurosurg (Hagerstown). 2020;19(4):393–402.
405. Romani R, et al. Microsurgery for previously coiled aneurysms: experience with 81 patients. Neurosurgery. 2011;68(1):140–53.
406. Roy AK, et al. Microsurgical treatment of cerebral aneurysms after previous endovascular therapy: single-center series and systematic review. World Neurosurg. 2019;123:e103–15.
407. Rubino PA, et al. Microsurgical clipping of previously coiled aneurysms. World Neurosurg. 2014;82(1–2):e203–8.
408. Shtaya A, et al. Outcomes of microsurgical clipping of recurrent aneurysms after endovascular coiling. World Neurosurg. 2018;112:e540–7.
409. Thornton J, et al. Surgery following endovascular coiling of intracranial aneurysms. Surg Neurol. 2000;54(5):352–60.

410. Tirakotai W, et al. Surgery of intracranial aneurysms previously treated endovascularly. Clin Neurol Neurosurg. 2007;109(9):744–52.
411. Toyota S, et al. Clipping of recurrent cerebral aneurysms after coil embolization. Acta Neurochir Suppl. 2018;129:53–9.
412. Veznedaroglu E, Benitez RP, Rosenwasser RH. Surgically treated aneurysms previously coiled: lessons learned. Neurosurgery. 2004;54(2):300–3.
413. Waldron JS, Halbach VV, Lawton MT. Microsurgical management of incompletely coiled and recurrent aneurysms: trends, techniques, and observations on coil extrusion. Neurosurgery. 2009;64(5 Suppl 2):301–15.
414. Wang HW, et al. Surgical management of recurrent aneurysms after coiling treatment. Br J Neurosurg. 2017;31(1):96–100.
415. Wu J, et al. Microsurgical ligation for incompletely coiled or recurrent intracranial aneurysms: a 17-year single-center experience. Chin Neurosurg J. 2019;5:7.
416. Zhang YJ, et al. Neurosurgical management of intracranial aneurysms previously treated with endovascular therapy. Neurosurgery. 2003;52(2):283–93.
417. Yu LB, et al. Management of residual and recurrent aneurysms after clipping or coiling: clinical characteristics, treatments, and follow-up outcomes. World Neurosurg. 2019;122:e838–46.
418. Benaissa A, et al. Endovascular treatment with flow diverters of recanalized and multitreated aneurysms initially treated by endovascular approach. J Neurointerv Surg. 2015;7(1):44–9.
419. Bender MT, et al. Pipeline embolization for salvage treatment of previously stented residual and recurrent cerebral aneurysms. Interv Neurol. 2018;7(6):359–69.
420. Chalouhi N, et al. Treatment of recurrent intracranial aneurysms with the pipeline embolization device. J Neurointerv Surg. 2014;6(1):19–23.
421. Daou B, et al. The use of the pipeline embolization device in the management of recurrent previously coiled cerebral aneurysms. Neurosurgery. 2015;77(5):692–7.
422. Daou B, et al. Pipeline embolization device in the treatment of recurrent previously stented cerebral aneurysms. AJNR Am J Neuroradiol. 2016;37(5):849–55.
423. Dornbos D 3rd, et al. Pipeline embolization device for recurrence of previously treated aneurysms. Neurosurg Focus. 2017;42(6):E8.
424. Heiferman DM, et al. Use of flow-diverting stents as salvage treatment following failed stent-assisted embolization of intracranial aneurysms. J Neurointerv Surg. 2016;8(7):692–5.
425. Kuhn AL, et al. Use of the pipeline embolization device for recurrent and residual cerebral aneurysms: a safety and efficacy analysis with short-term follow-up. J Neurointerv Surg. 2017;9(12):1208–13.
426. McAuliffe W, et al. Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. AJNR Am J Neuroradiol. 2012;33(1):164–70.
427. Park KY, et al. Efficacy and safety of flow-diverter therapy for recurrent aneurysms after stent-assisted coiling. AJNR Am J Neuroradiol. 2020;41(4):663–8.
428. Tahtinen OI, et al. Stent-assisted embolization of recurrent or residual intracranial aneurysms. Neuroradiology. 2013;55(10):1221–31.
429. Gawlitza M, et al. Treatment of recurrent aneurysms using the Woven EndoBridge (WEB): anatomical and clinical results. J Neurointerv Surg. 2018;10(7):629–33.
430. Kabbasch C, et al. treatment of recurrent and residual aneurysms with the woven EndoBridge Device: analysis of 11 patients and review of the literature. World Neurosurg. 2019;129:e677–85.
431. van Rooij S, et al. The Woven EndoBridge (WEB) for recurrent aneurysms: clinical and imaging results. Interv Neuroradiol. 2019;25(1):21–6.
432. Darsaut TE, et al. Surgical clipping or endovascular coiling for unruptured intracranial aneurysms: a pragmatic randomised trial. J Neurol Neurosurg Psychiatry. 2017;88(8):663–8.
433. Darsaut TE, et al. International Subarachnoid Aneurysm Trial - ISAT part II: study protocol for a randomized controlled trial. Trials. 2013;14:156.
434. Darsaut TE, et al. A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: Interim results from ISAT2. Neurochirurgie. 2019;65(6):370–6.
435. Raymond J, et al. Flow diversion in aneurysms trial: the design of the FIAT study. Interventional Neuroradiology. 2011;17(2):147–53.

Recent Advances in Cerebral Aneurysms

14

V. V. Ramesh Chandra, B. C. M. Prasad, T. Goutham, K. Venkat, D. Sasank, and Xianli Lv

Abstract

Cerebral aneurysms are relatively common, and if found incidentally (unruptured aneurysm), have a relatively benign clinical course with a low annual risk of rupture. Subarachnoid hemorrhage following aneurysmal bleed lead to significant morbidity and mortality, even with the best possible care. Our understanding of the pathogenesis, natural history, diagnostic imaging, treatment modalities and outcomes of cerebral aneurysms has significantly increased in recent years. Despite these advances, providing optimal management requires consideration of several factors and has to be tailored for each patient. This chapter will provide the caretakers involved in the management of cerebral aneurysms with an insight into the recent advances in cerebral aneurysms and review the recent advances made in various aspects of cerebral aneurysms from pathogenesis to management. The different functional pathways and their histological/molecular markers contributing to the development of cerebral aneurysms are reviewed. The advances made in imaging modalities like vessel wall imaging and computational flow dynamics are elaborated. This chapter provides an update on the debate between the two primary modalities of treatment, clipping, and coiling. The recent advances made in microneurosurgery for the cerebral aneurysm to make it more safe and acceptable are described. Endovascular interventions continue to evolve, and this chapter throws some light on the latest advances in next-generation endovascular techniques for treating cerebral aneurysms.

Keywords

Cerebral aneurysm · Subarachnoid haemorrhage · Pathogenesis · Natural history Diagnosis · Imaging · Treatment Development

14.1 Introduction

Several advances were made in all the aspects of cerebral aneurysms in the recent past. The pathophysiology and natural history of cerebral aneurysms were extensively studied with particular

V. V. Ramesh Chandra (✉) · B. C. M. Prasad · T. Goutham · K. Venkat
Department of Neurosurgery, SVIMS, Tirupati, Andhra Pradesh, India

D. Sasank
Department of Neurosurgery, GGH, Kurnool, Kurnool, Andhra Pradesh, India

X. Lv
Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_14

emphasis on identifying risk factors for rupture, enabling personalized aneurysm care to the patient. Advances in imaging have led to the development of promising diagnostic and prognostic tools. Advances in Microneurosurgery and Endovascular techniques have made the treatment of complex aneurysms more safe and effective. This chapter throws light on these recent advances made in the management of cerebral aneurysms.

14.2 Pathophysiology of Aneurysms-Advanced Concepts

A cerebral aneurysm is an outpouching of an arterial wall due to focal disruption of the internal elastic lamina with inflammation [1]. There are many factors (luminal and extraluminal) involved in the process of aneurysm formation, growth, and rupture (Fig. 14.1). These factors contribute to the three main precursors of aneurysm formation: Focal hemodynamic stress, weakened vessel wall (congenital/environmental), and inflammation [2]. Extensive research on the etiopathogenesis of cerebral aneurysms in recent times has elucidated the mechanism of formation, growth, and rupture of cerebral aneurysms [3]. The hemodynamic stress due to abnormal flow patterns of blood induces several changes in the vessel wall. The vascular endothelial cells transform into pro-inflammatory cells secreting a cocktail of inflammation mediators, which further recruit leukocytes (Macrophages, Lymphocytes) and cause phenotypic modification of the medial cells from a contractile phenotype to a pro-inflammatory phenotype. These modified pro-inflammatory cells along with the recruited leukocytes release a plethora of inflam-

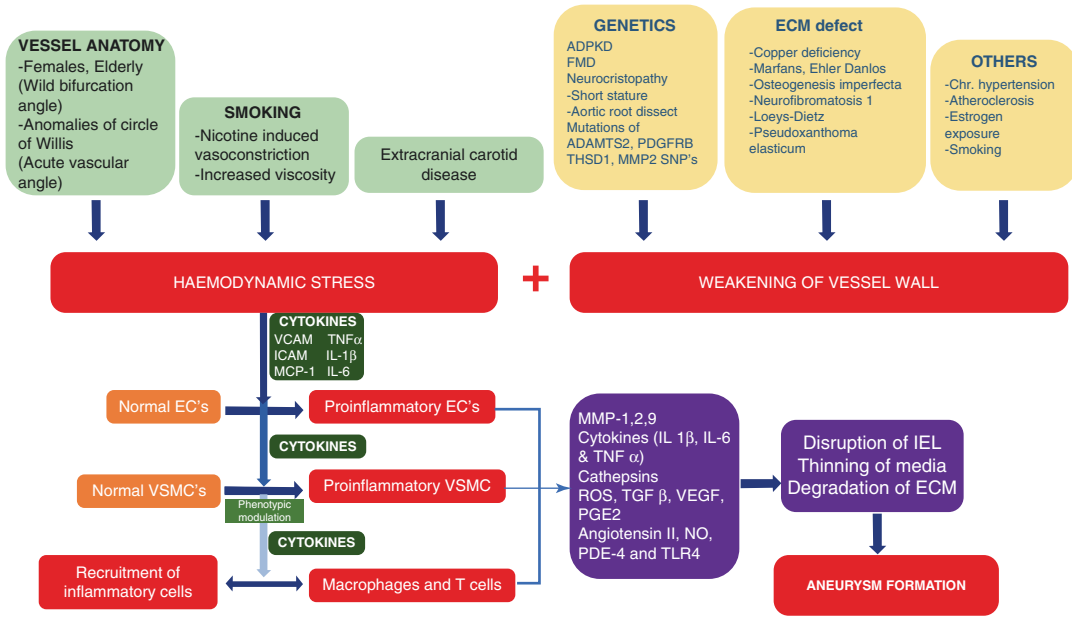


Fig. 14.1 Pathophysiology of intracranial aneurysms formation. *ADPKD* autosomal dominant polycystic kidney disease; *FMD* fibromuscular dysplasia; *ADAMTS2* A-disintegrin and metalloproteinase with thrombospondin motifs 2 genes; *PDGFRB* platelet-derived growth factor receptor β gene; *THSD1* thrombospondin type 1 domain-containing protein 1; *MMP2* matrix metalloproteinase 2 gene; *SNP's* single nucleotide polymorphisms; *VCAM* vascular cell adhesion molecule; *ICAM* intercellular adhesion molecule; *MCP-1* monocyte chemoattractant protein 1; *TNF α* tumor necrosis factor α; *IL-1β* Interleukin 1β; *IL-6* Interleukin 6; *EC's* endothelial cells; *VSMC's* vascular smooth muscle cells; *MMP* matrix metallo proteinase; *ROS* reactive oxygen species; *TGF β* transforming growth factor β; *VEGF* vascular endothelial growth factor; *PGE2* Prostaglandin E2; *NO* nitric oxide; *PDE-4* phosphodiesterase 4; *TLR4* Toll-like receptor 4; *IEL* Internal elastic lamina; *ECM* extracellular matrix

matory mediators, which bring about vascular remodeling (breakage of the internal elastic lamina, thinning of media, degradation of extracellular matrix), and aneurysm formation [4].

The most prominent hemodynamic factors responsible for aneurysm formation are Wall shear stress (WSS), Wall shear stress gradient (WSSG) and Oscillatory shear index (OSI) [5]. Although aneurysm formation has been linked to regions of high WSS, the hemodynamics causing the growth and rupture of aneurysms is more complex and controversial. Based on several Computational fluid dynamics (CFD) studies and animal experiments, two phenotypes of cerebral aneurysms are recognized, the thin, weak walled phenotype and the hyperplastic atherosclerotic phenotype [6]. Thin, weak walled aneurysms arise parallel to the flow of the artery, experience high WSS, high WSSG, low OSI, have faster-impinging flow and are caused due to endothelial injury and vessel wall degeneration. The thicker walled hyperplastic aneurysms arise perpendicular to the flow stream, experience low WSS, high OSI, have stagnant circulatory flow and are caused due to atherosclerosis, thrombosis, and inflammation [7]. With the advancements in imaging, small incidental unruptured aneurysms are being reported with increasing frequency. Still, the five-year risk of rupture (3%) is lower than the risk associated with prophylactic treatment [8]. Researchers have tried various parameters to stratify the risk of rupture and identify this small subset of unruptured aneurysms prone to rupture without convincing results [9]. The risk factors for rupture of an aneurysm can be classified into clinical, morphological, radiological, and hemodynamic aspects (Fig. 14.2). All these factors need to be considered before treating the aneurysm, and the treatment has to be individualized to give a personalized aneurysm treatment [10].

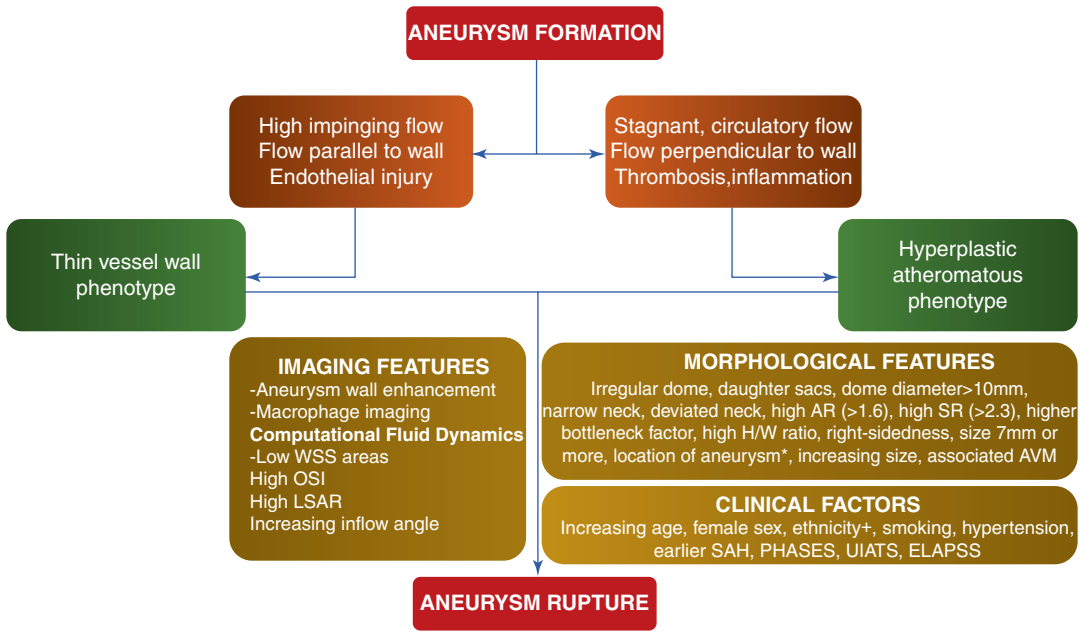


Fig. 14.2 Pathophysiology of intracranial aneurysm enlargement and rupture. *CFD* computational fluid dynamics; *WSS* wall shear stress; *OSI* oscillatory shear index; *LSAR* low wall shear stress area ratio; *AR* aspect ratio; *SR* size ratio; *H/W ratio* height-width ratio; *AVM* arteriovenous malformation; *PHASES* population, hypertension, age, size, earlier subarachnoid hemorrhage, site; *UIATS* unruptured intracranial aneurysm treatment score; *ELAPSS* earlier subarachnoid hemorrhage, location, age, population, size, shape. *basilar bifurcation, internal carotid-posterior communicating artery, anterior communicating artery †Finnish and Japanese

14.3 Advances in Imaging

Imaging of intracranial aneurysms has advanced substantially and plays a central role in the screening, diagnosis, management, and post-treatment surveillance of intracranial aneurysms. 2D-Digital subtraction angiography (DSA) with 3D rotational angiography is the investigation of choice in the imaging of intracranial aneurysms [11] gives the highest spatial and temporal resolution. Computed tomography angiography (CTA) is the investigation of choice for aneurysm detection in acute SAH [12]. The Magnetic Resonance Angiography (MRA) is the investigation of choice for non-emergent detection for screening intracranial aneurysms in high-risk populations and patients where contrast, ionizing radiation is contraindicated [13]. Technological advances like dual-energy CTA and three-dimensional time-of-flight (3D-TOF) MRA have significantly improved the spatial and temporal resolution of these modalities.

MR-vessel wall imaging (VWI) is a novel technique that suppresses the signals from the vessel lumen and CSF and highlights the structure of the vessel wall [14]. Wall enhancement in VWI helps in identifying aneurysms that are prone to rupture, helps in identifying the culprit aneurysm in a patient with multiple aneurysms and also helps in identifying the point of rupture in a multilobulated aneurysm [15].

Macrophage imaging is a diagnostic tool utilizing the phagocytic activity of macrophages. Macrophages play a pivotal role in the pathogenesis of aneurysms, and Ferumoxytol, a contrast agent used in MRI, is engulfed by the macrophages in the aneurysm wall. Enhancement of aneurysms with Ferumoxytol after 24 h of administration is associated with rupture of an aneurysm within 6 months of imaging [16].

Computational fluid dynamics (CFD) is a post-processing technique that utilizes images from CTA, MRA, and 3D Rotational angiography and replicates the hemodynamic conditions inside the aneurysm [17]. CFD analyses help in assessing the risk of rupture in the cerebral aneurysm and also predict the characteristics of the aneurysm wall. The hemodynamic parameters associated with increased risk of aneurysm rupture are elevated maximum WSS, low WSS with high OSI, high Pmax or maximum pressure, high OSI with high PD (pressure difference) [18].

14.4 Medical Management of Cerebral Aneurysms

A subset of patients with unruptured aneurysms who are categorized as aneurysms with a low risk of rupture by various criteria (PHASES, UIATS, ELAPSS) are managed conservatively and followed up with serial MRA imaging. The two most essential components of conservative management of unruptured aneurysms are blood-pressure reduction and Acetylsalicylic acid (ASA), which are being studied in a prospective, randomized, phase III trial titled PROTECT-U [19]. The incidence of Cerebral vasospasm (CVS) following aneurysmal SAH is high and has been associated with delayed cerebral ischemia leading to increased morbidity and mortality. Nimodipine is the only conventional drug to improve outcomes and decrease mortality prophylactically. Recent animal studies and clinical trials involving various emerging medical therapies (Cilostazol, Fasudil, Clazosentan, Rosiglitazone, Tenascin-C knockout, Sildenafil, Erythropoietin) have given contrasting results, and the search for an ideal drug to prevent/treat vasospasm is far from over [20].

14.5 Clipping Versus Coiling

The quest to choose the optimal treatment for aneurysmal SAH between Endovascular technique and microsurgical clipping is never ending. Ten years follow-up of International Subarachnoid Aneurysm Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT) gave contrasting results suggesting the need for a new perspective intent-to-treat trial to reach a conclusion [21, 22]. Recent metanalysis concluded that clipping is appropriate for ruptured aneurysms and coiling is superior for unruptured aneurysms [23]. Among

the endovascular options available for unruptured aneurysms patients treated with flow diverters fared better than those treated with coiling [24].

14.6 Advances in Microneurosurgery

The introduction of advanced microneurosurgery hardware and techniques has revolutionized the treatment of aneurysms. These advances in neurosurgical techniques have prompted neurosurgeons to innovate surgical tools and methods (Fig. 14.3) to make neurosurgery safer, cosmetically appealing, and less invasive [25].

Pterional craniotomy has been the main workhorse for clipping of anterior circulation aneurysms. The choice of craniotomies for these aneurysms has expanded with the addition of the minipterional craniotomy, lateral supraorbital craniotomy (LSO), Supraorbital keyhole approach (SOKHA) [26], f-SOKHA [27] and extradural minipterional approach [28]. These approaches are equally safe and effective as pterional craniotomy with shorter operative time and good cosmetic results.

Endoscopic-assisted microsurgery allows visualization of the blind spots to the microscope. Endoscopic ICG-VA combines the advantages of both ICG-VA and endoscope and enables the visualization of perforating arteries hidden in blind spots [29]. Purely Endoscopic approaches for clipping aneurysms are reported as small case series and need further studies to confirm the safety and efficacy before recommending broad application of these approaches [30].

Intraoperative ICG-VA is a complementary tool that increases the aneurysm occlusion rate.

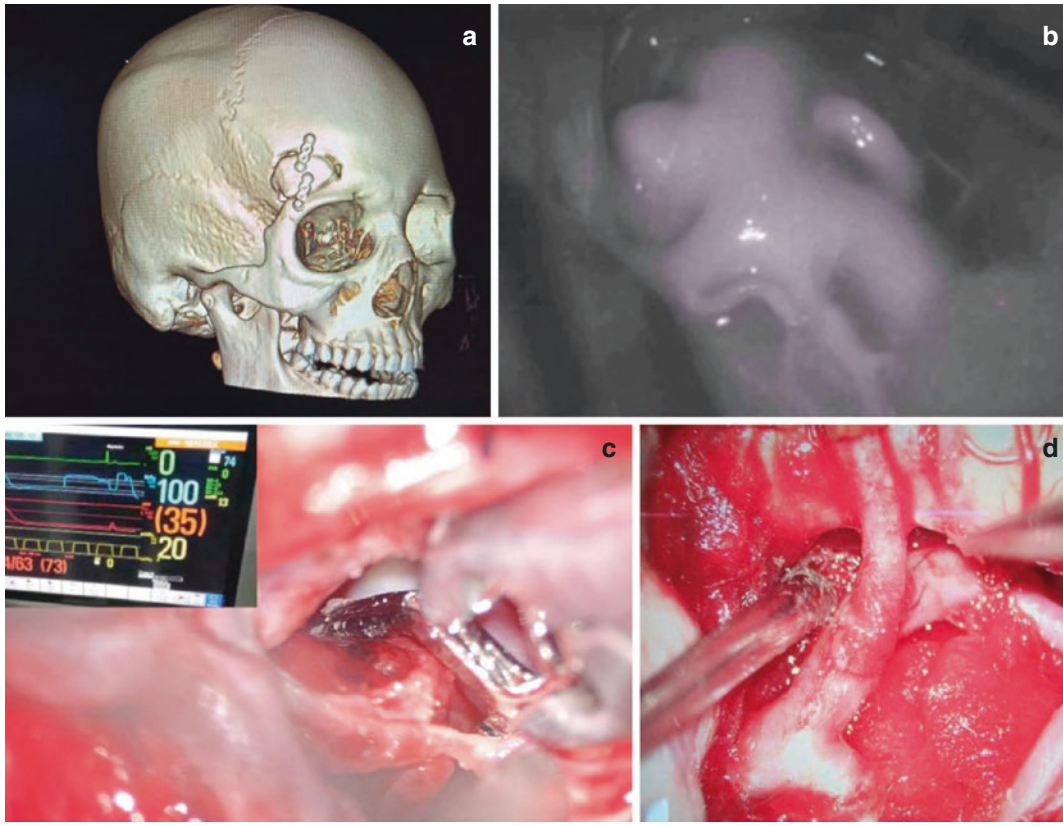


Fig. 14.3 Advances in Microneurosurgery of intracranial aneurysms. (**a**) Supraorbital craniotomy "keyhole" surgery, (**b**) Intraoperative Indocyanine Green vascular imaging, (**c**) Intraoperative transient cardiac standstill, (**d**) Superficial temporal artery—Middle cerebral artery bypass

The use of intraoperative ICG-VA revealed unexpected residual aneurysms in 9% and an intraoperative clip modification rate of 15% after an apparent complete occlusion under microscopic visualization [31]. Flow 800 is a microscope-integrated visualization tool that gives an objective analysis of ICG-VA rather than subjective assessment and gives a better idea of the vasculature, especially where ICG is ambiguous [32].

Ultrasonic transit-time flowmetry provides quantitative intraoperative measurements of arterial blood flow using a microflow probe. It is a valuable tool for clipping complex aneurysms and maintaining adequate flow (>50% of baseline), reducing the risk of postoperative ischemic events [33].

Intraoperative neurophysiological monitoring (IOM) (somatosensory-evoked potentials, motor-evoked potentials) reduces the incidence of ischemic complications and development of new motor deficit in monitored patients, more so in patients with the middle cerebral artery (MCA) aneurysms [34]. A small case series of 30 patients underwent clipping of aneurysm in awake condition and found three patients who developed neurological deficits without associated changes in neuromonitoring. This study revealed a potential advantage of awake aneurysm surgery, but additional studies are needed to establish the safety of this approach [35].

Transient cardiac standstill (Adenosine, Rapid ventricular pacing) softens the aneurysm sac, avoids intraoperative rupture, bleeding and facilitates permanent clip placement without the need for temporary clipping [36].

Cerebral revascularization is a crucial tool in the armamentarium of the cerebrovascular surgeon used to treat complex intracranial aneurysms that are difficult to manage with traditional surgical or endovascular methods. Apart from the primary EC-IC bypass, several creative and innovative bypasses ("the third generation" bypasses/in situ intracranial-intracranial bypasses, Reimplantation/Reanastomoses, and "the fourth generation" bypasses/double reimplantation using three end-to-side anastomoses) have been invented and used with good outcomes in patients with complex VA, PICA, MCA, and DACA aneurysms [37].

14.7 Advances in Endovascular Management of Aneurysms

Guglielmi introduced the detachable coil system in the 1990s, and this marked the development of a new field of Endovascular Neurosurgery [38]. The early results of coiling were not convincing. Still, significant technological advances were made to alter the coil properties and various devices were introduced to assist coil embolization (Fig. 14.4) and improve occlusion rates [39].

14.7.1 Advances in Coils

Many advances have been made in the design and deployment technique of coils to improve the outcomes of aneurysm coiling (Fig. 14.5). Soft Nano-type coils with increased conformability are used to fill out residual spaces post coiling and to treat small aneurysms. Longer coils with larger coil diameters are available to address larger aneurysms. Coils are coated with materials like polyglycolic/polylactic acid (PGLA) microfilament and hydrophilic acrylic copolymer to increase the thrombogenic effect (Bioactive coils) [40]. Another advancement in coils includes coils containing a hydrogel polymer (HES coils) that expands to fill the coil lumen once it makes contact with blood. Several trials (HELPS, PRET, GREAT, and HEAT) have demonstrated promising outcomes and lesser recurrences in patients managed with HES coils [41].

14.7.2 Balloon-Assisted Coiling

Balloon-assisted coiling involves the temporary inflation of a balloon catheter across the aneu-

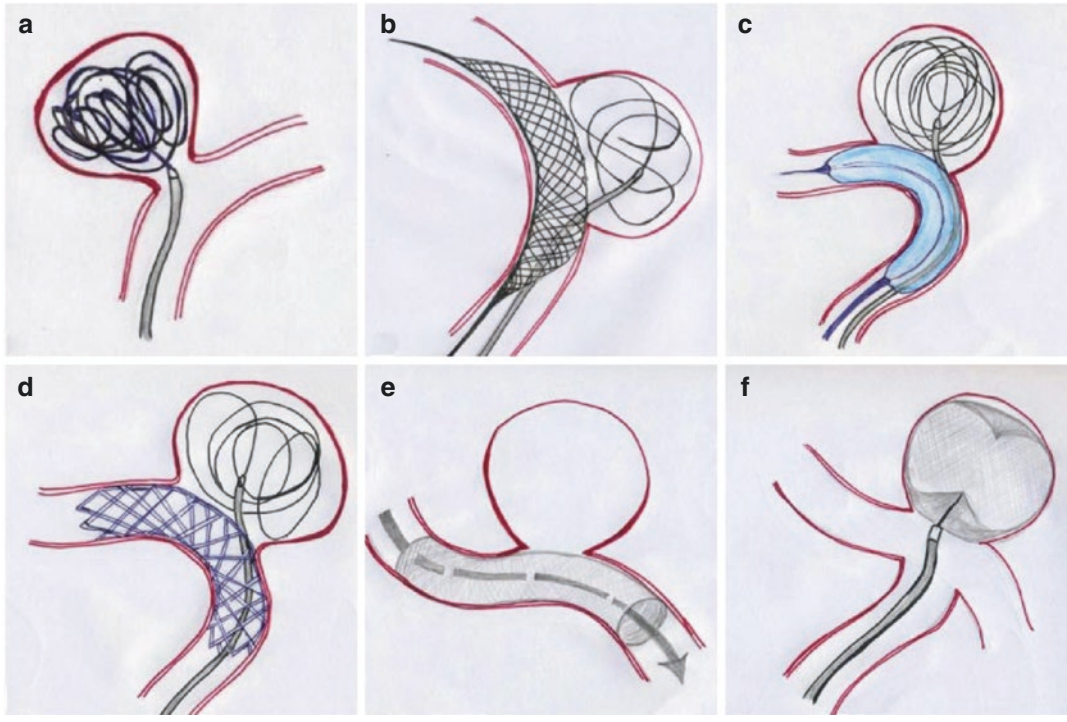


Fig. 14.4 Endovascular treatment of intracranial aneurysms. (**a**) Endovascular coiling, (**b**) Temporary bridging device assisted coiling, (**c**) Balloon-assisted coiling, (**d**) Stent-assisted coiling, (**e**) Intraluminal flow diverter, f-Intrasaccular flow diverter

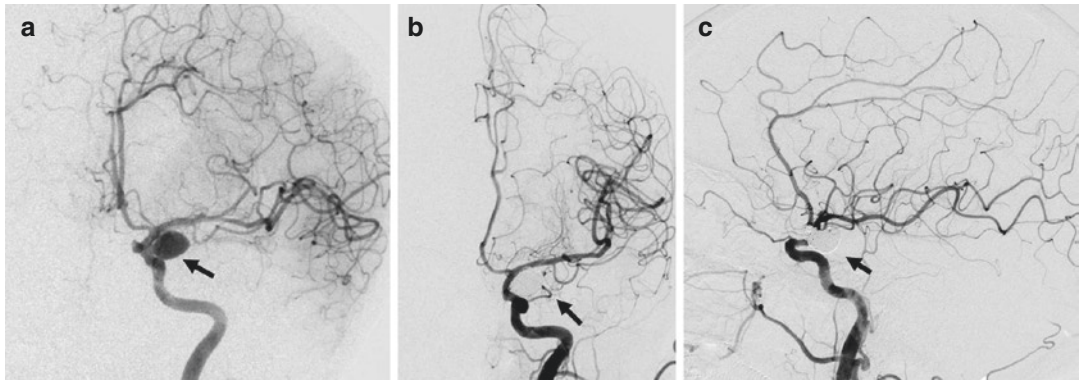


Fig. 14.5 A 42-year-old woman with a large aneurysm of the supraclinoid segment of the left internal carotid artery was coiled with Microplex coils (Microvention, USA). (**a**) oblique view of the left internal carotid artery injection showing the large aneurysm of the supraclinoid segment of the left internal carotid artery (arrows). (**b**) frontal view of the left internal carotid artery injection after aneurysm coil embolization. (**c**) lateral view of the left internal carotid artery injection after aneurysm coil embolization. Showing the aneurysm was completely occluded (arrows)

rysm neck to prevent herniation of coils back into the parent artery and acts as a rescue in case of aneurysm rupture. Advanced super compliant balloons (HyperForm, HyperGlide, TransForm, Scepter), double-lumen balloons (ECLIPSE 2L) have replaced low-compliance balloons. Balloon-assisted coiling simplified and made coiling safe by reducing the procedural time [42] (Fig. 14.6).

14.7.3 Stent-Assisted Coiling

Stent-assisted coiling (SAC) uses stents to stabilize coils inside the aneurysmal sac and prevent herniation back into the parent artery, maintaining the patency of the parent vessel. Unlike in balloon-assisted coiling, stents are left inside the vessels, require chronic antiplatelet therapy and carry the risk of delayed stenosis/occlusion. The stents used to depend on the type of SAC technique employed. In the Jailed coiling technique, a microcatheter is first inserted into the aneurysm sac, and then the stent is deployed to jail the microcatheter. Usually, resheathable closed-cell stents are used like LEO (Balt Extrusion, Montmorency, France), Enterprise stent (Codman Neurovascular, Raynham, MA, USA) and LVIS (MicroVention Inc., Aliso Viejo, CA, USA) (Figs. 14.7 and 14.8). Trans-cell coiling involves the stent deployment and advancement of the microcatheter into the aneurysm through the open cells. The trans-cell coiling technique is done with open-cell stents like Neuroform Atlas (Stryker Neurovascular, Fremont, CA, USA) [43].

Advances in stent-assisted coiling include Temporary Bridging Devices and Bifurcation support devices. Temporary bridging devices support coil packing without compromising blood flow aided by their compliant mesh design. They are retrieved once the coils are deployed and obviate the need for chronic antiplatelet therapy. The Comaneci device (Rapid Medical, Israel) and Cascade (Perflow Medical Ltd., Netanya, Israel) are examples of temporary bridging devices [44]. Bifurcation support devices offer support for coil mass as well as neck reconstruction in bifurcation aneurysms and have flow diversion properties. These are novel stent-like, self-expanding, nitinol devices with two components, a component each for the parent vessel and aneurysm sac. They need chronic antiplatelet therapy, and examples include pCANVAS (Phenox, Bochum, Germany), The PulseRider Device (Pulsar Vascular, Inc., Los Gatos, CA, USA), and eCLIPs (Evasc Medical Systems Corp, Vancouver, Canada) [45].

14.7.4 Flow Diverter Devices

Flow Diverter Devices (FDDs) are a novel breakthrough in the endovascular management

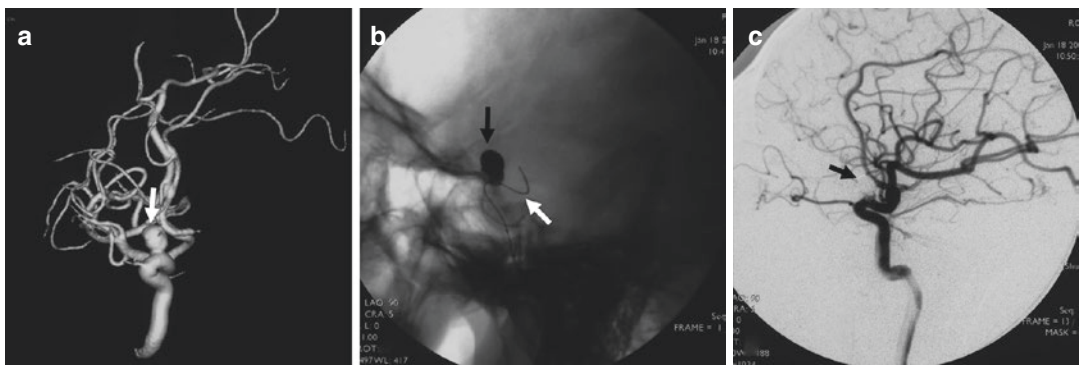


Fig. 14.6 A 41-year-old man presented with an unruptured ophthalmic aneurysm of the internal carotid artery. (**a**) 3-D reconstruction of the right internal carotid artery injection showing an aneurysm of the ophthalmic artery segment (arrow). (**b**) Unsubtracted image showing the aneurysm was coiled (black arrow) with the assistance of a 4 mm × 20 mm Hyperglide balloon catheter (Medtronic ev3, USA) (white arrow). (**c**) Lateral view of the right internal carotid artery injection showing the aneurysm was completely occluded (arrow)

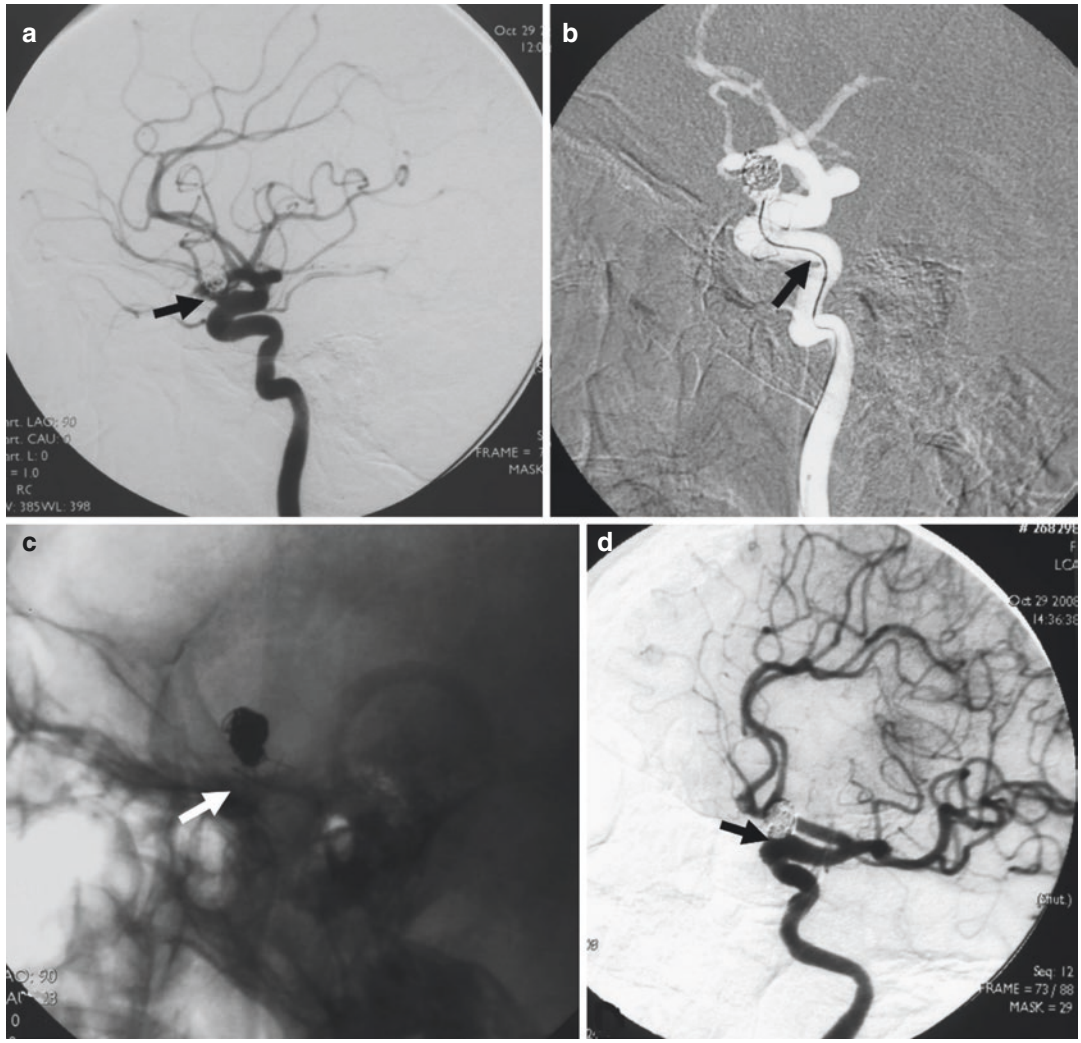


Fig. 14.7 A 62-year-old woman presented with a recurrent aneurysm after 2 years of coil embolization. (**a**) Lateral view of the left carotid artery injection showing recanalization of a supraclinoid aneurysm of the internal carotid artery (arrow). (**b**) Roadmap image of the left carotid artery injection showing coils was introduced (arrow) after the 4.5 mm × 25 mm Leo stent (Balt, France) placement. (**c**) Lateral view of the unsubtracted image showing the Leo stent (arrow) and coil mass. (**d**) Oblique view of the left carotid artery injection showing the aneurysm was completely occluded after treatment

of cerebral aneurysms and are rapidly evolving as the first-line of treatment modality for various complex aneurysms. The mesh of FDD creates an impedance that disrupts the blood flow into and out of the aneurysm. The substantial reduction in velocity of blood flow inside the aneurysm activates platelets to form a stable thrombus which over a few months to years transform into collagen, leading to complete occlusion of the aneurysm [46]. There are two types of flow diverters Intraluminal FDD and Intrasaccular FDD.

Intraluminal FDD involves the placement of a semipermeable stent in the parent artery, which redirects blood away from the aneurysm, causing flow stasis and thrombosis. The pipeline embolization device (PED; ev3/Covidien, Irvine, CA, USA) (Fig. 14.9), The Silk flow diverter device (Silk, Balt Extrusion, Montmorency, France) (Fig. 14.10), The Surpass flow diverter

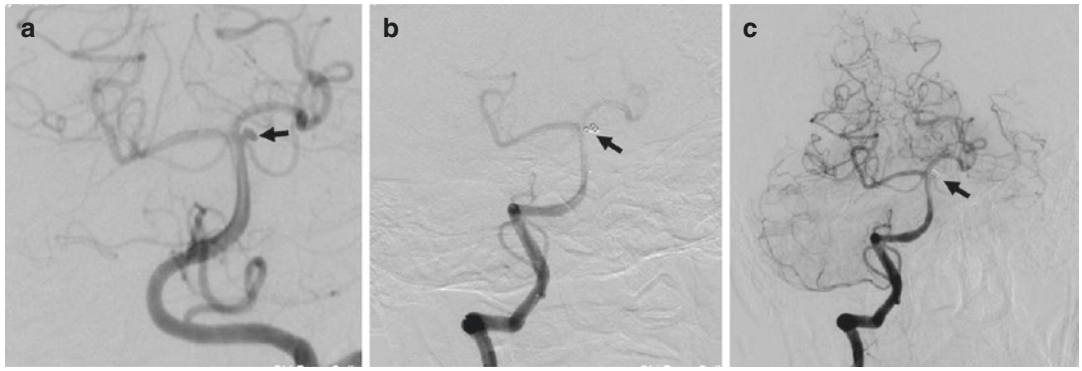


Fig. 14.8 A 54-year-old man presented with Hunt-Hess grade 1 subarachnoid hemorrhage. (**a**) Frontal view of the left vertebral artery injection showing a basilar artery aneurysm at the origin of the left superior cerebellar artery (arrow). (**b**) Frontal view of the right vertebral artery injection showing the aneurysm was treated with 2.5 mm × 23 mm LVIS-junior stent (Microvention, USA) and coils (black arrow). (**c**) Frontal view of the right vertebral artery injection showing the aneurysm was occluded completely (arrow)

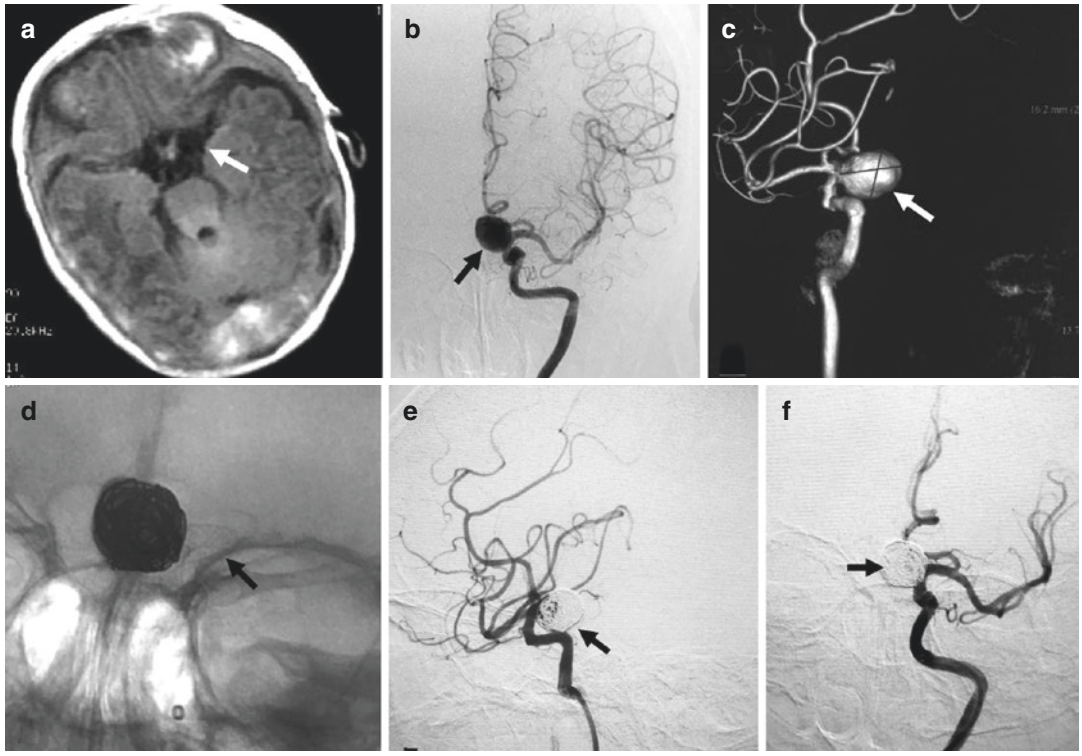


Fig. 14.9 A 53-year-old woman presented with a blurred vision of her left eye. (**a**) Axial MR imaging showing a round flow void signal near the left optic chiasm (arrow). (**b**) Frontal view of the left internal carotid artery injection showing a large aneurysm of the supraclinoid internal carotid artery (arrow). (**c**) 3-D reconstruction of the left internal carotid artery injection showing a 16 mm aneurysm of the supraclinoid internal carotid artery (arrow). (**d**) Frontal view of the unsubtracted image showing the aneurysm was treated with 4.0 mm × 20 mm Pipeline flow diversion and coils (Axium, Medtronic-ev3, USA) (arrow). (**e**) Lateral view of the left internal carotid artery injection after treatment. (**f**) frontal view of the left internal carotid artery injection after treatment

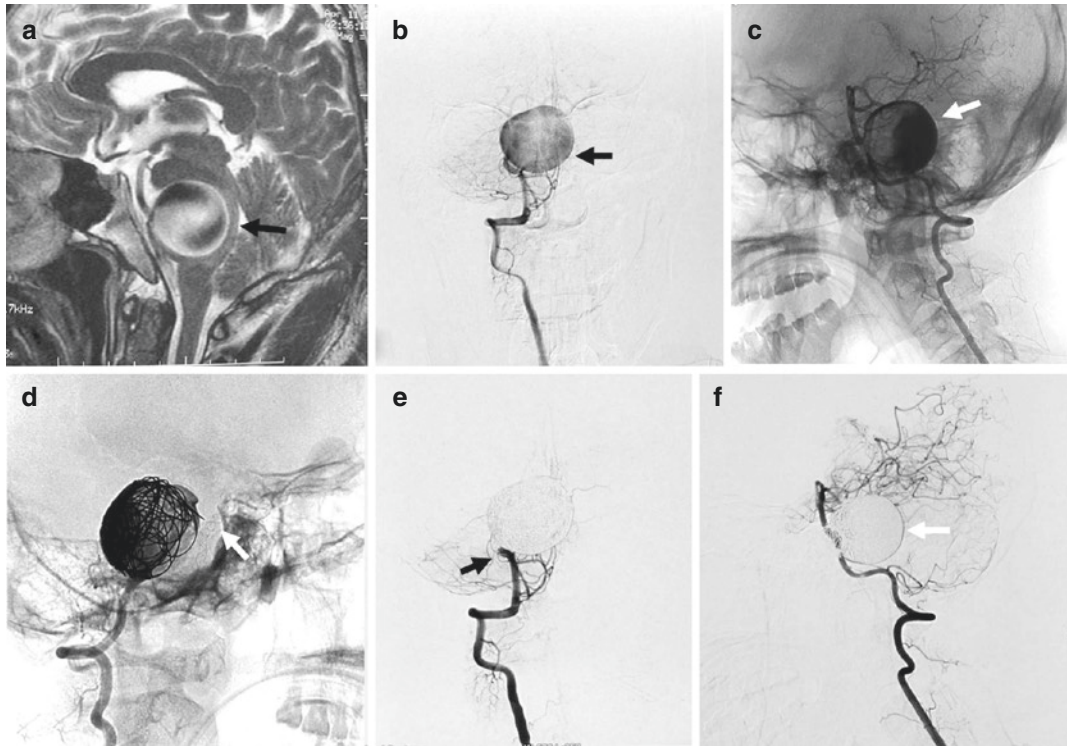


Fig. 14.10 A 37-year-old man suffered from swallowing difficulty and numbness of his left limbs. (**a**) Magnetic resonance imaging, sagittal view, T2-weighted, showing a giant saccular vascular lesion compressing the brain stem (arrow). (**b**) Frontal view of the right vertebral artery injection showing a giant aneurysm (arrow). (**c**) Lateral view of the left vertebral artery injection, unsubtraction image, showing a giant saccular aneurysm of the vertebrabasilar junction (arrow). (**d**) Unsubtraction image showing a 3.0 mm × 25 mm Silk flow diversion (Balt, France) was placed in the left vertebral artery (arrow), and the right vertebral artery was occluded using coils. (**e**) Frontal view of the right vertebral artery showing the right vertebral artery was occluded. (**f**) Lateral view of the left vertebral artery injection showing the aneurysm was completely thrombosed after flow diversion and additional coils treatment

device (Stryker Neurovascular, Fremont, CA, USA), The flow redirection endoluminal device system (FRED; MicroVention, Tustin, CA, USA) and The Tubridge flow diverter (MicroPort Medical Company Shanghai, China) are examples of intraluminal FDD [47] (Fig. 14.11). The role of flow diversion for aneurysm treatment has expanded, and various recent trials (PREMIER, SAFE, SCENT, PARAT) have proved their favorably low complication and high cure rates compared with alternative treatments [47].

Intrasaccular flow diverter/flow disrupters are deployed within the aneurysm and do not require the problematic catheterization of bifurcation branches nor the use of chronic antiplatelet therapy. Woven EndoBridge device (WEB, Sequent Medical, Aliso Viejo, California, USA), Luna aneurysm embolization device (AES; NFocus Neuromedical, Palo Alto, California), and Medina embolization device (MED, Medtronic, Irvine, California, USA) are examples of intrasaccular flow diverters. Several trials (WEBCAST 2, WEB-IT) have proven the

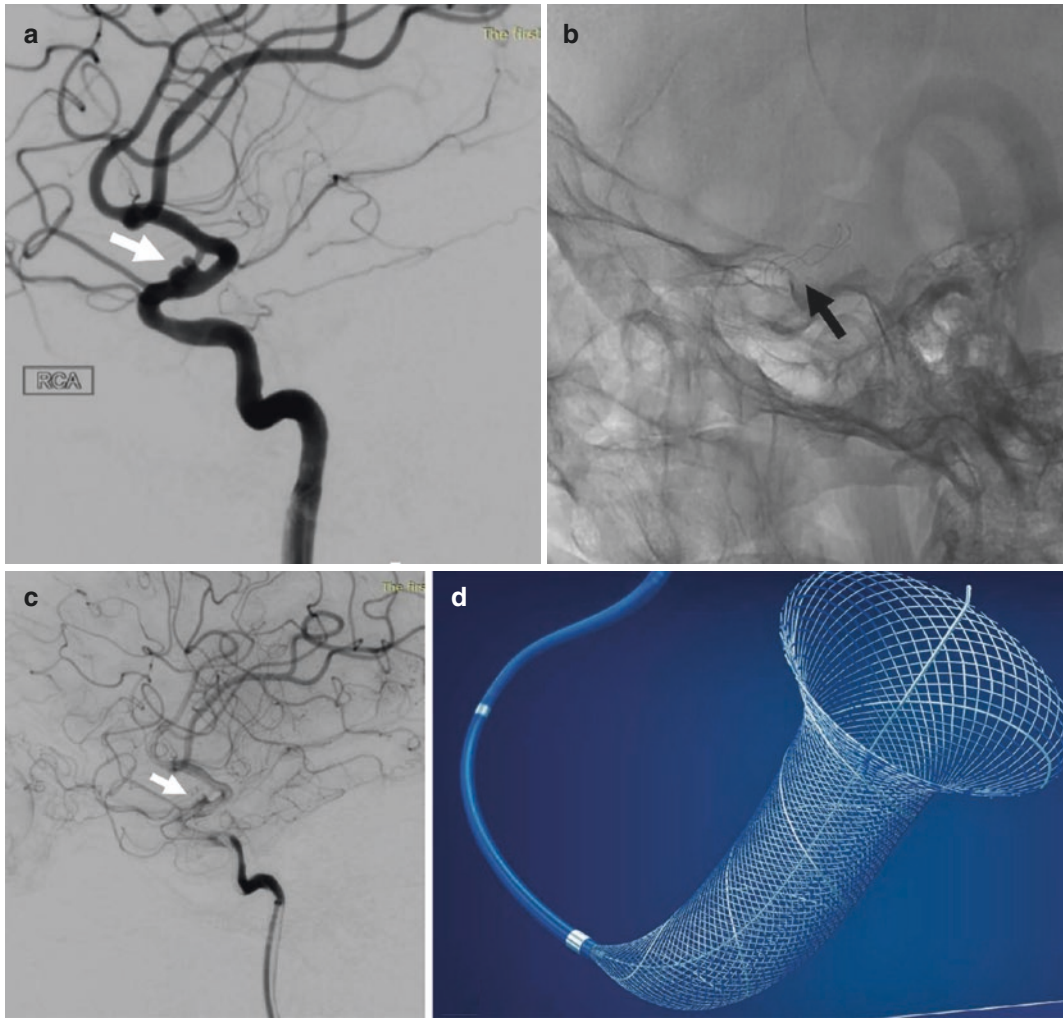


Fig. 14.11 A 72-year-old man presented with an incidental aneurysm of the supraclinoid internal carotid artery. (**a**) Lateral of the right internal carotid artery injection showing an aneurysm arising from the supraclinoid internal carotid artery (arrow), which was treated with Tubridge flow diversion (MicroPort Medical Company, Shanghai, China). (**b**) Lateral view of the unsubtracted image showing the 3.5 mm × 25 mm Tubridge flow diversion. (**c**) Lateral view of the right internal carotid artery injection after flow diversion treatment showing the intra-aneurysm contrast stagnation (arrow). (**d**) Picture showing the Tubridge flow diversion system

safety and have shown adequate occlusion rates of the aneurysm [48].

14.8 Conclusions

Significant advances were made in the last decade in various aspects of cerebral aneurysms. Future research should convincingly identify aneurysms at risk of rupture by using serum/genetic/imaging markers to give personalized aneurysm care. New Endovascular innovations to tackle complex aneurysms should be developed and extensively studied to confirm efficacy and safety. New training modules should be invented to give haptic feedback to beginners doing endovascular work to better the outcomes. The role of microneurosurgery in the management of cerebral aneurysms cannot be ignored. Microneurosurgery with innovative revascularisation techniques will continue

to be a significant treatment modality for complex aneurysms till time tested endovascular alternatives emerge.

References

1. Stehbens WE. Etiology of intracranial berry aneurysms. J Neurosurg. 1989 Jun;70(6):823–31.
2. Krings T, Mandell DM, Kiehl TR, Geibprasert S, Tymianski M, Alvarez H, et al. Intracranial aneurysms: from vessel wall pathology to therapeutic approach. Nat Rev Neurol. 2011 Sep 20;7(10):547–59.
3. Cebral J, Ollikainen E, Chung BJ, Mut F, Sippola V, Jahromi BR, et al. Flow conditions in the intracranial aneurysm lumen are associated with inflammation and degenerative changes of the aneurysm wall. AJNR Am J Neuroradiol. 2017 Jan;38(1):119–26.
4. Kim DH, Santiago-Sim T. Pathobiology of intracranial aneurysms. In: Richard Winn H, editor. Youmans and Winn neurological surgery. 7th ed. Philadelphia, PA: Elsevier; 2017. p. 3221–31.
5. Byrne G, Mut F, Cebral J. Quantifying the large-scale hemodynamics of intracranial aneurysms. AJNR Am J Neuroradiol. 2014 Feb;35(2):333–8.
6. Soldozy S, Norat P, Elsarrag M, Chatrath A, Costello JS, Sokolowski JD, et al. The biophysical role of hemodynamics in the pathogenesis of cerebral aneurysm formation and rupture. Neurosurg Focus. 2019 Jul 1;47(1):E11. https://doi.org/10.3171/2019.4.FOCUS19232.
7. Cebral JR, Detmer F, Chung BJ, Choque-Velasquez J, Rezai B, Lehto H, et al. Local hemodynamic conditions associated with focal changes in the intracranial aneurysm wall. AJNR Am J Neuroradiol. 2019 Mar;40(3):510–6.
8. Chen J, Liu J, Zhang Y, Tian Z, Wang K, Zhang Y, et al. China intracranial aneurysm project (CIAP): protocol for a registry study on a multidimensional prediction model for rupture risk of unruptured intracranial aneurysms. J Transl Med. 2018 Sep 26;16(1):263.
9. Feghali J, Gami A, Caplan JM, Tamargo RJ, McDougall CG, Huang J. Management of unruptured intracranial aneurysms: correlation of UIATS, ELAPSS, and PHASES with referral center practice. Neurosurg Rev. 2020. https://doi.org/10.1007/s10143-020-01356-6.
10. Darsaut TE, Desal H, Cognard C, Januel AC, Bourcier R, Boulouis G, et al. Comprehensive aneurysm management (CAM): an all-inclusive care trial for unruptured intracranial aneurysms. World Neurosurg. 2020 Sep;141:e770–7.
11. Brinjikji W, Gupta V, Vibhute P. Imaging of intracranial aneurysms. In: Ringer AJ, editor. Intracranial aneurysms. London: Academic Press An imprint of Elsevier; 2018. p. 59–83.
12. Pradilla G, Wicks RT, Hadelsberg U, Gailloud P, Coon AL, Huang J, et al. Accuracy of computed tomography angiography in the diagnosis of intracranial aneurysms. World Neurosurg. 2013 Dec;80(6):845–52.
13. Sailer AM, Wagemans BA, Nelemans PJ, de Graaf R, van Zwam WH. Diagnosing intracranial aneurysms with MR angiography: systematic review and meta-analysis. Stroke. 2014 Jan;45(1):119–26.
14. Mandell DM, Mossa-Basha M, Qiao Y, Hess CP, Hui F, Matouk C, et al. Intracranial vessel wall MRI: principles and expert consensus recommendations of the American society of neuroradiology. AJNR Am J Neuroradiol. 2017 Feb;38(2):218–29.
15. Texakalidis P, Hilditch CA, Lehman V, Lanzino G, Pereira VM, Brinjikji W. Vessel wall imaging of intracranial aneurysms: systematic review and meta-analysis. World Neurosurg. 2018;117:453–58.e1.
16. Shimizu K, Kushamae M, Aoki T. Macrophage imaging of intracranial aneurysms. Neurol Med Chir (Tokyo). 2019;59(7):257–63.
17. Can A, Du R. Association of hemodynamic factors with intracranial aneurysm formation and rupture: systematic review and meta-analysis. Neurosurgery. 2016 Apr;78(4):510–20.
18. Jirjees S, Htun ZM, Aldawudi I, Katwal PC, Khan S. Role of morphological and hemodynamic factors in predicting intracranial aneurysm rupture: a review. Cureus. 2020;12(7):e9178. https://doi.org/10.7759/cureus.9178.
19. Etminan N, Dörfler A, Steinmetz H. Unruptured intracranial aneurysms—pathogenesis and individualized management. Dtsch Arztebl Int. 2020 Apr 3;117(14):235–42.
20. Li K, Barras CD, Chandra RV, Kok HK, Maingard JT, Carter NS, et al. A review of the management of cerebral vasospasm after aneurysmal subarachnoid haemorrhage. World Neurosurg. 2019 Jun;126:513–27.
21. Hua X, Gray A, Wolstenholme J, Clarke P, Molyneux AJ, Kerr RSC, Clarke A, Sneade M, Rivero-Arias O. Survival, dependency, and health-related quality of life in patients with ruptured intracranial aneurysm: 10-year follow-up of the United Kingdom Cohort of the International Subarachnoid Aneurysm Trial. Neurosurgery. 2020 Oct 19. https://doi.org/10.1093/neuros/nyaa454
22. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Nakaji P, Karis JP, Wallace RC. Ten-year analysis of saccular aneurysms in the Barrow ruptured aneurysm trial. J Neurosurg. 2019 Mar;8:1–6.
23. Jiang Z, Chen Y, Zeng C, Feng J, Wan Y, Zhang X. Neurosurgical clipping versus endovascular coiling for patients with intracranial aneurysms: a systematic review and meta-analysis. World Neurosurg. 2020 Jun;138:e191–222.
24. Xin WQ, Xin QQ, Yuan Y, Chen S, Gao XL, Zhao Y, Zhang H, Li WK, Yang XY. Comparison of flow diversion and coiling for the treatment of unruptured intracranial aneurysms. World Neurosurg. 2019 Aug;128:464–72.
25. Kalani MYS, Wanebo JE, Martirosyan NL, Nakaji P, Zabramski JM, Spetzler RF. A raised bar for aneu-

rysm surgery in the endovascular era. J Neurosurg. 2017 May;126(5):1731–9.
26. Park J. Supraorbital keyhole approach for intracranial aneurysms: transitioning from concerns to confidence. J Korean Neurosurg Soc. 2020 Jan;63(1):4–13.
27. Chandra PS, Tej M, Sawarkar D, Agarwal M, Doddamani RS. Fronto-orbital variant of supraorbital keyhole approach for clipping ruptured anterior circulation aneurysms (f-Sokha). Neurol India. 2020 Sep-Oct;68(5):1019–27.
28. Martinez-Perez R, Joswig H, Tsimpas A, Poblete T, Albiña P, Perales I, et al. The extradural minipterional approach for the treatment of paraclinoid aneurysms: a stepwise cadaver dissection and clinical case series. Neurosurg Rev. 2020 Feb;43(1):361–70.
29. Catapano G, Sgulò F, Laleva L, Columbano L, Dallan I, de Notaris M. Multimodal use of indocyanine green endoscopy in neurosurgery: a single-centre experience and review of the literature. Neurosurg Rev. 2018 Oct;41(4):985–98.
30. Martinez-Perez R, Hardesty DA, Silveira-Bertazzo G, Albonette-Felicio T, Carrau RL, Prevedello DM. Safety and effectiveness of endoscopic endonasal intracranial aneurysm clipping: a systematic review. Neurosurg Rev. 2020. https://doi.org/10.1007/s10143-020-01316-0.
31. Riva M, Amin-Hanjani S, Giussani C, De Witte O, Bruneau M. Indocyanine green video angiography in aneurysm surgery: systematic review and meta-analysis. Neurosurgery. 2018 Aug 1;83(2):166–80.
32. Chavan VS, Yamada Y, Chandratej K, Gowtham D, Riccardo S, Firuz S, et al. Intraoperative use of microscope-integrated flow 800 - a valuable tool in the surgical management of anterior communicating artery aneurysm: our institutional experience. Asian J Neurosurg. 2020 Feb 25;15(1):26–30.
33. Van Lanen RHGJ, Jacobi-Postma LAA, Veersema TJ, Teernstra OPM, Dings JTA. Clinical and radiological outcomes of intracranial aneurysm clipping aided by transit-time flowmetry. World Neurosurg. 2020 Apr;136:e660–70.
34. Nasi D, Meletti S, Tramontano V, Pavesi G. Intraoperative neurophysiological monitoring in aneurysm clipping: does it make a difference? A systematic review and meta-analysis. Clin Neurol Neurosurg. 2020 Sep;196:105954. https://doi.org/10.1016/j.clineuro.2020.105954.
35. Abdulrauf SI, Vuong P, Patel R, Sampath R, Ashour AM, Germany LM, et al. "Awake" clipping of cerebral aneurysms: report of initial series. J Neurosurg. 2017 Aug;127(2):311–8.
36. Meling TR, Lavé A. What are the options for cardiac standstill during aneurysm surgery? A systematic review. Neurosurg Rev. 2019 Dec;42(4):843–52.
37. Raper DMS, Rutledge WC, Winkler EA, Meisel K, Callen AL, Cooke DL, et al. Controversies and advances in adult intracranial bypass surgery in 2020. Oper Neurosurg (Hagerstown). 2020. https://doi.org/10.1093/ons/opaa276.
38. Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. J Neurosurg. 1991 Jul;75(1):8–14.
39. Jiang B, Paff M, Colby GP, Coon AL, Lin LM. Cerebral aneurysm treatment: modern neurovascular techniques. Stroke Vasc Neurol. 2016 Oct 25;1(3):93–100.
40. Van Rooij WJ, de Gast AN, Sluzewski M. Results of 101 aneurysms treated with polyglycolic/polylactic acid microfilament nexus coils compared with historical controls treated with standard coils. AJNR Am J Neuroradiol. 2008 May;29(5):991–6.
41. Bendok BR, Abi-Aad KR, Ward JD, Kniss JF, Kwasny MJ, Rahme RJ, et al. The hydrogel endovascular aneurysm treatment trial (HEAT): a randomized controlled trial of the second-generation hydrogel coil. Neurosurgery. 2020 May 1;86(5):615–24.
42. Pop R, Harsan O, Martin I, Mihoc D, Richter JS, Manisor M, et al. Balloon-assisted coiling of intracranial aneurysms using the Eclipse 2L double-lumen balloon. Interv Neuroradiol. 2020 Jun;26(3):291–9.
43. Zhu Y, Zhang H, Zhang Y, Wu H, Wei L, Zhou G, et al. Endovascular metal devices for the treatment of cerebrovascular diseases. Adv Mater. 2019 Feb;31(8):e1805452. https://doi.org/10.1002/adma.201805452.
44. Sirakov S, Sirakov A, Minkin K, Karakostov V, Raychev R. Early clinical experience with Cascade: a novel temporary neck bridging device for embolization of intracranial aneurysms. J Neurointerv Surg. 2020 Mar;12(3):303–7.
45. Peach TW, Ricci D, Ventikos Y. A virtual comparison of the eCLIPs device and conventional flow-diverters as a treatment for cerebral bifurcation aneurysms. Cardiovasc Eng Technol. 2019 Sep;10(3):508–19.
46. Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, Macho J, Derakhshani S, Foa Torres G, et al. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg. 2020. https://doi.org/10.1136/neurintsurg-2020-015877.
47. Chancellor B, Raz E, Shapiro M, Tanweer O, Nossek E, Riina HA, et al. Flow diversion for intracranial aneurysm treatment: trials involving flow diverters and long-term outcomes. Neurosurgery. 2020 Jan 1;86(Suppl 1):36–45.
48. Kaya HE, Bakdık S, Keskin F, Erdi MF, Koç O. Endovascular treatment of intracranial aneurysms using the Woven EndoBridge (WEB) device: a retrospective analysis of a single-centre experience. Clin Imaging. 2020 Jan;59(1):25–9.

15 Microsurgery of Cerebral Aneurysms Not Amenable to Endovascular Therapy

Abhijit G. Warade and Basant K. Misra

Abstract

Over the last decade, there has been refinement in both microsurgical techniques as well as endovascular therapy (EVT) for the management of giant intracranial aneurysms (GIAs) and blood blister-like aneurysms (BBAs). Both of them come with their own set of problems in there management. GIAs are treacherous lesions with grave prognosis, and their management is problematic because of the wide atheromatous neck, involved branches, thrombus within, calcified wall, and complex anatomy resulting in a combined surgical morbidity and mortality that remains in the range of 20–30%. Posterior circulation aneurysms have a higher rupture risk (RR) over anterior circulation. While small saccular aneurysms are optimally excluded from circulation by EVT, there is a high failure rate after EVT of GIAs. Failures of EVT are often related to aneurysm morphology, a broad aneurysm neck (high neck: dome ratio), large and giant-size outflow arteries arising from the aneurysm base or walls, and fusiform/dolichoectatic morphology. An aneurysm with a broad neck can result in the herniation of coils into the parent artery lumen. Balloon- and stent-assisted coiling techniques are useful but are associated with the additional risk of parent artery ischemia, perforation, distal thromboembolism, and occlusion of adjacent perforators and branch arteries by the lattice of the stent. The rate of recurrence is also higher in broad neck aneurysms because the hemodynamics at the inflow zone is more complex. The other reasons for failure are incomplete initial obliteration, thrombus within the lumen, poor radiographic visualization of the aneurysm anatomy and its adjacent branches, and tortuosity of the feeding vessel, making catheterization difficult. Flow diverters are exciting, but it is still early days for prime time. Improvements in instrumentation and hardware, application of skull base surgical techniques, revascularization procedures, advances in anesthetic techniques like cerebral protection, adenosine-induced cardiac standstill, rapid ventricular pacing and hypothermic circulatory arrest, and intraoperative indocyanine green (ICG) angiography have made microsurgery a relatively safe and also a cost-effective option over EVT. Treatment of complex aneurysms like GIAs and BBAs is challenging. The modalities of treatment, microsurgery, EVT, or combined should be individualized taking into consideration the patient and pathological factors and available expertise. Although EVT is an attractive

A. G. Warade · B. K. Misra (✉)
Department of Neurosurgery & Gamma Knife Radiosurgery, P.D. Hinduja Hospital & MRC, Mahim, Mumbai, India
e-mail: dr_bmisra@hindujahospital.com

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_15

option, the high incidence of incomplete treatment, delayed complications, recurrence, and inadequate long-term follow-up data makes microsurgery relevant.

Keywords

Giant intracranial aneurysm · Blood blister aneurysm · Endovascular therapy Microsurgery

15.1 Introduction

Giant intracranial aneurysms (GIAs) have, by definition, a minimum diameter of 25 mm [1]. They represent <5% of all intracranial aneurysms, making them rare among all aneurysms [2]. GIAs are treacherous lesions with grave prognosis, and their management is problematic because of the wide atheromatous neck, involved branches, thrombus within, calcified wall, and complex anatomy resulting in a combined surgical morbidity and mortality that remains in the range of 20–30% [3]. Yet, the GIAs need treatment, as these often have a downhill course without treatment, with a mortality rate at 2 and 5 years after diagnosis being 68 and 85%, respectively [4]. Rupture risk (RR) of untreated, unruptured GIAs is 8–10% per year, with a mortality of 65–100% at 1–5 years follow-up [5, 6]. Posterior circulation aneurysms have a higher RR over anterior circulation [7]. Over the last few decades, there has been refinement in both microsurgical techniques and endovascular treatment (EVT). Continuous improvements in EVT offer promise in the management of GIAs. While small saccular aneurysms are optimally excluded from circulation by EVT, there is a high failure rate after EVT of GIAs. Failures of EVT are often related to aneurysm morphology, a broad aneurysm neck (high neck: dome ratio), large and giant-size outflow arteries arising from the aneurysm base or walls, and fusiform/dolichoectatic morphology [8]. An aneurysm with a broad neck can result in the herniation of coils into the parent artery lumen. Balloon- and stent-assisted coiling techniques are useful but are associated with the additional risk of parent artery ischemia, perforation, distal thromboembolism, and occlusion of adjacent perforators and branch arteries by the lattice of the stent [8]. The rate of recurrence is also higher in broad neck aneurysms because the hemodynamics at the inflow zone is more complex. The other reasons for failure are incomplete initial obliteration, thrombus within the lumen, poor radiographic visualization of the aneurysm anatomy and its adjacent branches, and tortuosity of the feeding vessel, making catheterization difficult [8]. Flow diverters are exciting, but it is still early days for prime time. Improvements in instrumentation and hardware, application of skull base surgical techniques, revascularization procedures, advances in anesthetic techniques like cerebral protection, adenosine-induced cardiac standstill, rapid ventricular pacing and hypothermic circulatory arrest, and intraoperative indocyanine green (ICG) angiography have made microsurgery a relatively safer and also a cost-effective option over EVT [9].

The natural history of giant intracranial aneurysms (GIAs) is characterized by progressive growth, thrombosis, and rupture [2], and the natural history of untreated giant cerebral aneurysms is significantly poor. In the International Study for Unruptured Intracranial Aneurysms (ISUIA), Wiebers et al. reported that the 5-year incidence of rupture was 40% for anterior and 50% for posterior circulation giant aneurysms or 8 to 10% per year [6]. Peerless et al. showed that the mortality rate of patients not presenting with hemorrhage was higher than 60% within 2 years, with the prognosis being worse for patients presenting with subarachnoid hemorrhage (SAH) [10]. This poor natural history is attributed to their mass effect on the surrounding brain tissue, higher risk for rupture, location, morphology (saccular versus fusiform), and the presence or absence of laminated thrombus and/or atherosclerotic plaque within the fundus and neck of the aneurysm [11, 12].

Management of Aneurysms not amenable to EVT can be broadly classified into:

1. Hemorrhagic presentation
2. Ischemic presentation
3. Mass effect as presentation

15.2 Operative Techniques

15.2.1 Choice of Operative Approach (Fig. 15.1)

The use of cranial base approaches to enhance exposure and to minimize damage to, and retraction of neural tissue is the golden rule of surgery. In fact, the authors currently utilize dedicated skull base approaches more often in aneurysm surgery than in surgery of skull base tumors. While tumors provide space to be tackled through conventional craniotomy, every millimeter of extra space gained through bone drilling helps significantly in aneurysm surgery. Aggressive drilling of bony structures at the skull base may consume time but ultimately provides a wide and safe corridor. Moreover, drilling is essential to expose the neck and provide proximal vessel control (anterior clinoidectomy for ICA, posterior clinoidectomy, and clivus drilling for BA). For lesions involving the anterior circulation, authors routinely use the frontotemporal (FT) craniotomy.

15.3 Anterior Circulation Aneurysms

15.3.1 Orbitozygomatic-Pterional Approach

The pterional transsylvian approach is the workhorse. It provides access to the entire circle of Willis and branches. Drilling the pterion can further increase basal exposure and bony ridges over the floor of the frontal fossa and OZ osteotomy [13, 14]. Intradural anterior clinoidectomy and carotid exposure in the neck are routinely performed in ophthalmic segment aneurysms. The OZ approach provides a lower trajectory along the skull base, which reduces the need for cerebral retraction. It also enhances access to upper clival lesions. The risks associated with this approach

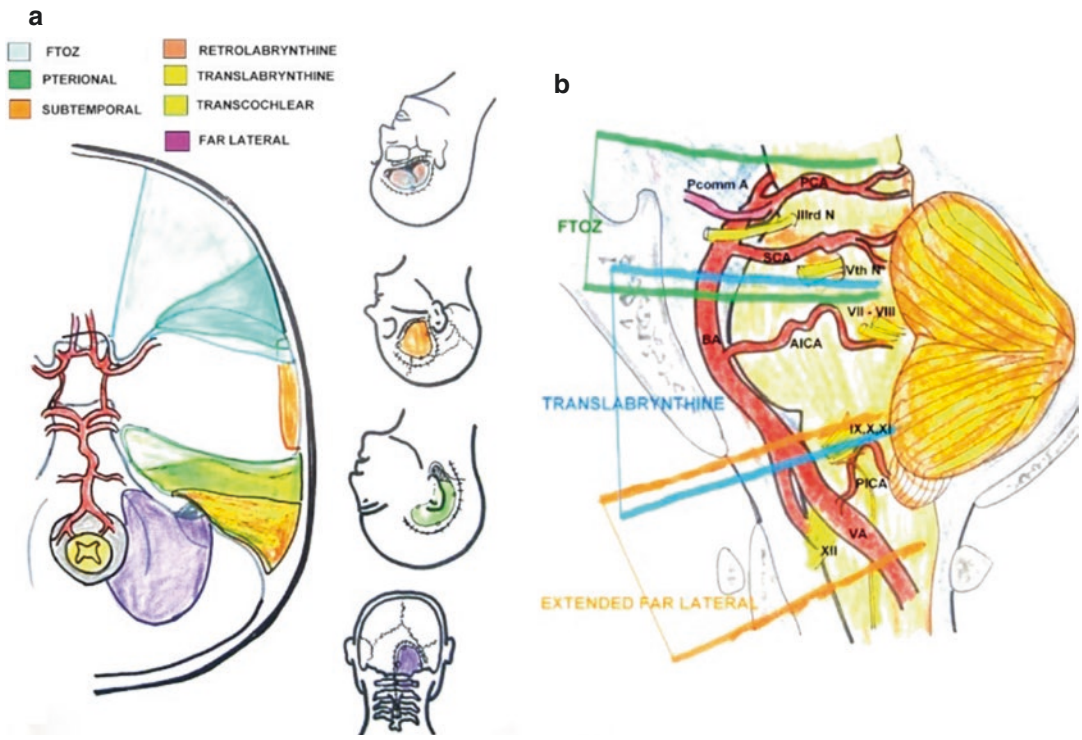


Fig. 15.1 Pictorial depiction of Individual & Combined Approaches to the Anterior and Posterior circulation aneurysms

are periorbital bruising, injury to the frontalis nerve, orbital entrapment, diplopia, and blindness. However, these are extremely rare [15, 16].

15.3.2 Interhemispheric Approach

This approach is traditionally used for DACA aneurysms.

15.4 Posterior Circulation Aneurysms

The OZ approach is optimal for lesions of the upper third, and the vertebrobasilar area is best accessed with the far-lateral approach. Lesions involving only the midbasilar zone may require transpetrosal or extended retrosigmoid approaches.

15.4.1 Orbitozygomatic Approach

Additional modification of drilling the anterior and posterior clinoid processes and the clivus itself allows visualization down towards the midbasilar zone [17]. The authors employ extradural anterior clinoidectomy and intradural posterior clinoidectomy for GIAs of the basilar top. It provides excellent exposure of the upper interpeduncular space without excessive frontal lobe traction for high-riding basilar top aneurysms. It also gives an overview of the adjacent vessels and perforators.

15.4.2 Transpetrosal Approaches

The transpetrosal approaches are divided into retrolabyrinthine, translabyrinthine, and transcochlear, depending on the degree of removal of the petrous ridge [18, 19]. This approach is reserved for complex lesions of the midbasilar zone.

15.4.3 Far-Lateral Approach

It provides an excellent exposure from the midbasilar zone down to the intradural vertebral artery, which includes giant aneurysms of the vertebrobasilar, vertebral, and proximal posterior inferior cerebellar arteries [20, 21].

15.4.4 Combined Approaches

If the situation demands, various conventional approaches can be combined to get wider access and control [22]. A combination of supratentorial and infratentorial approaches, for example, a subtemporal craniotomy with a transpetrosal approach, can be extended further inferiorly by the addition of a far-lateral approach to it [23].

For the management of complex aneurysms, including giants, the operating surgeon should have the following in his armamentarium.

15.5 Vascular Control

Proximal and distal vascular control is essential as it gives control during an event of intraoperative rupture of aneurysm. It softens the aneurysm, helps dissection and manipulation from the surrounding neural structures, and facilitates clipping. Proximal control can be easily obtained for GIAs of anterior circulation except if the lesion is more proximal at the level of clinoid and ophthalmic segment. Options available include exposure and control of the cervical carotid artery via a separate neck incision which is the most common, least risky and preferred by the authors. Other options include exposure of the petrous ICA through Glasscock's triangle, exposure of the clinoidal segment of the ICA after removal of the anterior clinoid process, and endovascular balloon occlusion of the cavernous segment of the ICA [24].

Vascular control of giant aneurysms of the posterior circulation is more difficult owing to the complex anatomy and its proximity to the skull base. There is a high risk of injury to the brainstem perforators if a temporary clip is placed along the middle portion of the basilar artery. Far-lateral exposure can give proximal control over the vertebral arteries, but distal control can be problematic. OZ exposure can give proximal control by access to the basilar trunk, but the contralateral superior cerebellar artery and posterior cerebral artery control are difficult.

Endovascular temporary balloon occlusion can be instrumental particularly in the proximal basilar and vertebral artery regions [25].

The ultimate vascular control is obtained with hypothermic circulatory arrest [26]. Hypothermic circulatory arrest was first applied in neurosurgery in 1938 [27, 28]. In the early 1960s, it was used to treat intracranial aneurysms in several studies; however, it soon lost favor because of its high complication rate due to intraoperative and postoperative coagulopathies. The patients who were earlier candidates for cardiac standstill are now being treated via alternative microsurgical techniques, endovascular therapy, or combined endovascular and microsurgical strategies [26].

Adenosine-induced cardiac asystole has been useful in the treatment of intracranial aneurysms. It gives brief periods (5–10 s) of cardiac arrest, thus facilitating clipping. It has largely obviated the need to use cardiac standstill in the treatment of GIAs [28–30].

15.6 Techniques for Clipping

For clipping to happen successfully, the ideal neck should be well defined and favorable to clip as what is commonly seen in a saccular aneurysm. However, the same does not happen if it is a GIA, especially fusiform or dolichoectatic GIAs. These have ill-defined neck and efferent vessels, and perforators may arise from the base or from the body.

The principle of clipping involves reconstruction of the lumen while preserving the branches/perforators and obliteration of the aneurysm. For this, the know-how of technicalities of the aneurysm clip is essential, e.g., the lowest closing force along the clip is located at its tip [31]. Hence instead of one long clip, multiple small clips placed in tandem can be better; they can also be stacked one above the other to prevent migration/slippage [17, 18]. Most frequently, GIAs are associated with atherosclerotic necks, which may prevent the blades of the clip to approximate; discretion is warranted while doing these procedures so as to avoid distal migration and emboli of the plaques in the vessel [32]. Hence preoperative angiographic evaluation can help to decide if a protective bypass is essential while clipping of these aneurysms.

Clipping should ensure that small perforators, especially those arising from the basilar top, ICA bifurcation, proximal MCA aneurysms, are preserved or else significant deficits can happen. Intraoperative ICG/angiography, microvascular Doppler can be used to ensure patency.

15.6.1 Aneurysm with Hemorrhagic Presentation

Illustration 1 (Fig. 15.2) Some GIAs are adherent to the dura of the skull base and do not collapse even with multiple clips unless the wall of the aneurysm is excised and released from the skull base. This is especially true for inferior wall ICA aneurysm and some vertebral aneurysms. Some MCA bifurcation aneurysms are multilobulated and wide neck and incorporate the branches. These need innovative clipping methods after excision of the aneurysmal sac to have a satisfactory outcome. This was the case in a 35-year-old woman who presented to us in a coma and left hemiplegia from WFNS Grade IV SAH. CTA revealed a partially thrombosed giant right MCA aneurysm with significant mass effect, the source of hemorrhage, as well as a

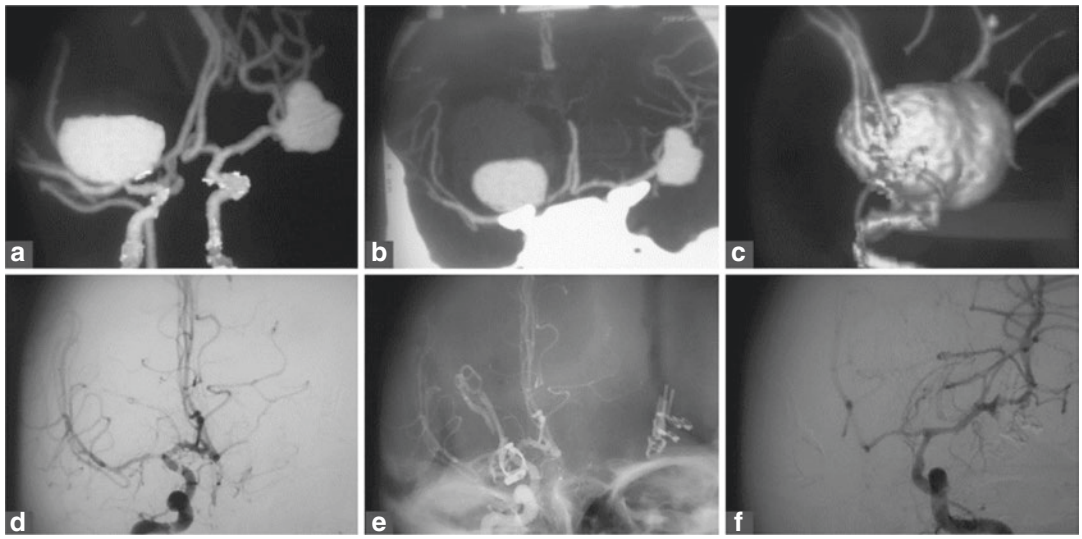


Fig. 15.2 (**a–c**) CTA showing a partially thrombosed giant right MCA bifurcation aneurysm with the branches incorporated in the aneurysm and a large left MCA bifurcation aneurysm. (**d**) Postoperative DSA after the right side aneurysm surgery shows complete exclusion of the aneurysm and preserved parent right MCA and its branches. (**e, f**) 1-year follow-up postoperative DSA after the second stage surgery demonstrating occlusion of both MCA aneurysm with preserved normal vessels

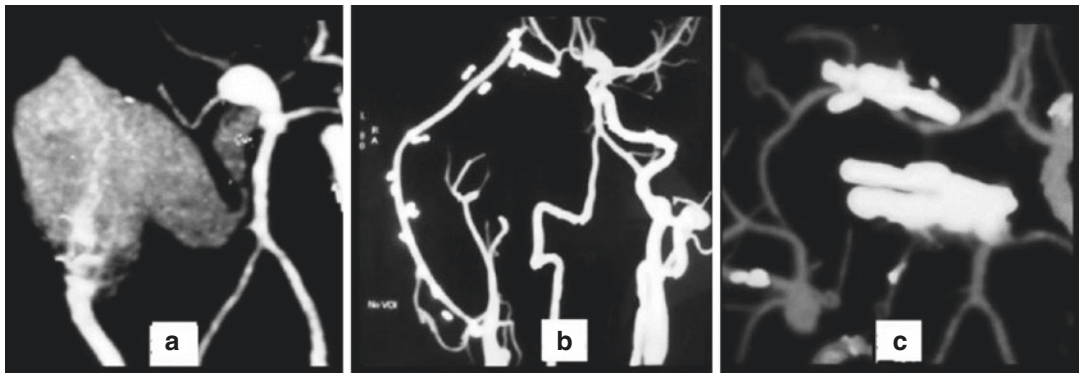


Fig. 15.3 (**a**) Shows "The Camel" a giant right petrous to supraclinoid segment ICA and a large basilar apex aneurysm on CT angiogram. (**b**) Shows postop CTA with clipped aneurysm and EC-IC bypass. (**c**) Shows postop CTA with both the aneurysms clipped

large left MCA bifurcation aneurysm. The patient was operated through a right FTOZ craniotomy. Hematoma evacuation, partial excision of the aneurysm wall, and occlusion of the aneurysm with preservation of the parent artery and branches were performed utilizing multiple clips. The patient had a prolonged hospitalization and gradually improved to become independent but was left with residual hemiparesis on the left side. Later at a second stage, the large left MCA bifurcation aneurysm was also successfully clipped without any complication.

Illustration 2 (Fig. 15.3) A 25-year-old man was admitted to another center in a comatose state with an acute subdural hematoma (SDH) from a giant ICA aneurysm; he had a decompressive craniectomy and gradually improved almost

completely. On evaluation, he was found to have a 77 mm partially thrombosed aneurysm involving the whole ICA from the petrous to the supraclinoid segment, the cause of his SDH. He also had a large, wide-necked basilar apex aneurysm. He was referred to us for definitive treatment. After further preoperative workup that included 3D CTA and 3D DSA, it was decided to perform in the first stage, ECA-M2 RAG bypass and trapping of ICA. While preparing to do the distal ECA-M2 anastomosis, it was observed that the length of the graft was not enough because of the large MCF mass caused by the aneurysm. Hence, initially, the ICA was trapped; the aneurysm was opened in the MCF and decompressed. Then interposing a RAG, an ECA-M2 anastomosis was successfully performed. The patient was subsequently referred to the neurointerventionist for taking care of the basilar top aneurysm. The configuration at the basilar top, the wide neck, the right posterior cerebral (PCA), inseparable from the aneurysm made the endovascular proposition unsafe, and the patient was referred back for a microsurgical option. Uneventful microsurgical clipping of the basilar apex aneurysm was thus performed at a second sitting 3 months after the first operation. The second operation was performed after inserting a lumbar drain and combining an OZ craniotomy to the previous FT craniotomy done at the first sitting. An extradural clinoidectomy and intradural posterior clinoidectomy completed the bone work. The aneurysm was completely obliterated with preservation of all perforators and the right PCA by using a combination of fenestrated and large Yasargil titanium clips and employing tandem clipping technique as advocated by Drake.

Illustration 3 (Fig. 15.4) A 34-year-old male presenting with CT angiogram showing a large distal right ICA aneurysm and WFNS Grade II SAH underwent a right frontotemporal approach

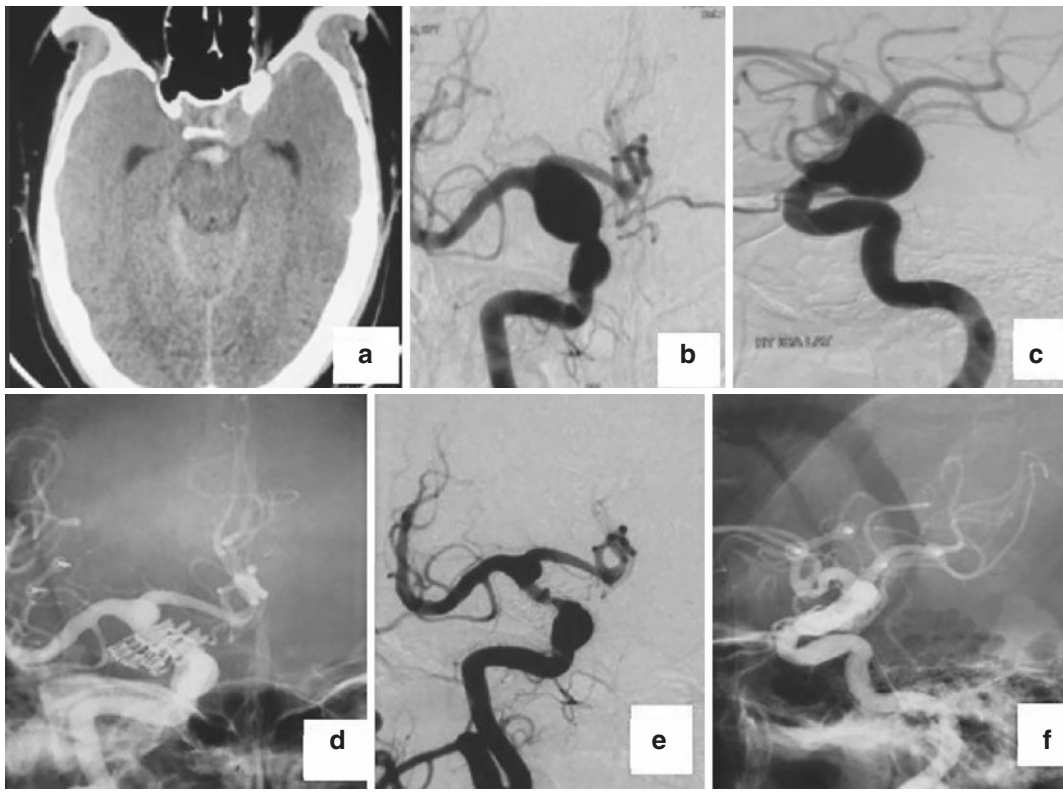


Fig. 15.4 (**a**) Shows CT brain plain shows WFNS grade II SAH. (**b**, **c**) Shows DSA with a large distal ICA aneurysm. (**d**, **e**) Showing postop angiogram and DSA with the clipped aneurysm. (**f**) Complete obliteration of the aneurysm

and clipping of the aneurysm. Vertical stacking of multiple clips was done in order to achieve obliteration of the aneurysm.

Illustration 4 (Fig. 15.5) A CT angiogram of a young male presenting with massive WFNS Grade 4 SAH showed a doubtful area of outpouching in the right supracliniod ICA, which was later confirmed to be a blood blister aneurysm on DSA. He underwent a right frontotemporal approach and clipping of the same using a Sundt Encircling clip.

Illustration 5 (Fig. 15.6) A 57-year-old gentleman presented with profuse right epistaxis, with a bling right eye and left hemiparesis. There was past history of road traffic accidents about a month back. CTA showed presence of a Right petrous ICA pseudoaneurysm. He underwent a right high flow (ECA-M2) bypass with radial

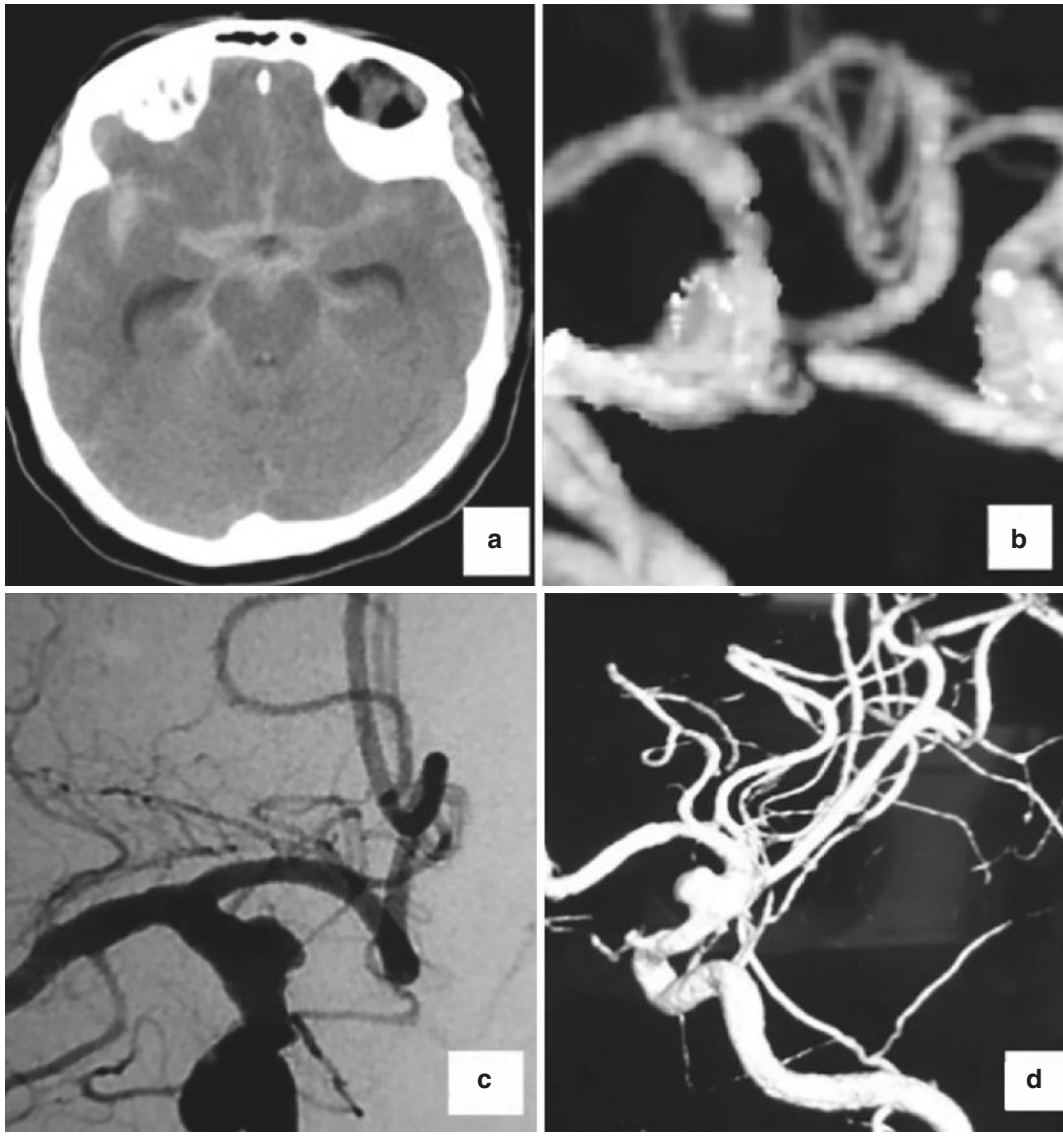


Fig. 15.5 (**a**) Shows CT brain plain shows WFNS grade IV SAH. (**b**) Shows CTA negative for aneurysm. (**c**, **d**) Showing angiogram with a blood blister aneurysm

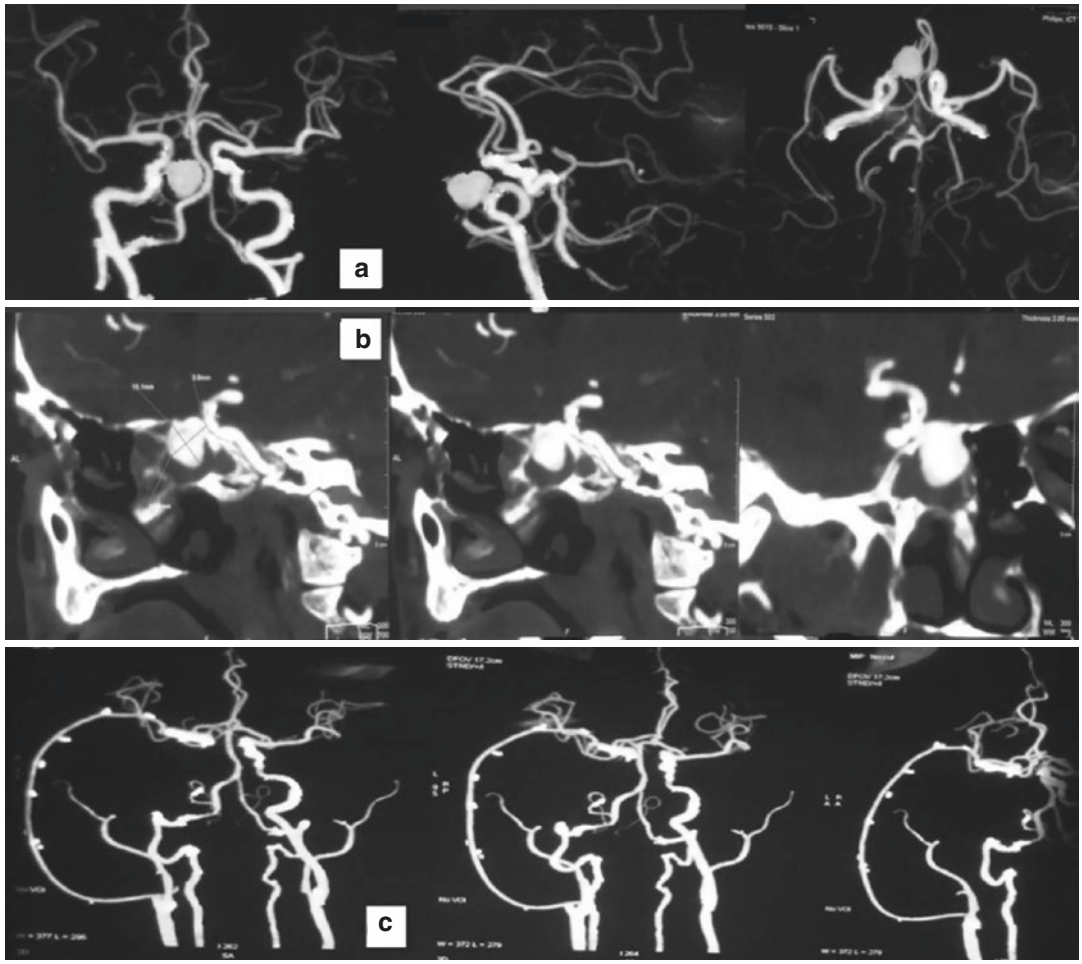


Fig. 15.6 (**a**, **b**) Shows CTA showing the right petrous ICA pseudoaneurysm. (**c**) Shows postop CTA showing a right high flow (ECA-M2) bypass with radial artery graft (RAG), and the clipped aneurysm

artery graft (RAG) followed by clipping of the aneurysm intradurally.

Illustration 6 (Fig. 15.7) Moyamoya disease presenting with hemorrhage, especially in young adults, can be treated with superficial temporal to middle cerebral artery bypass and clipping of any associated aneurysm at the same time.

15.6.2 Aneurysm with Ischemic Presentation (Fig. 15.8)

As seen in the figure, a left distal MCA thrombosed aneurysm presenting with ischemic changes as seen on diffusion-weighted sequences of the MRI necessitates the need for thrombectomy and clipping of the aneurysm for achieving the optimum outcome of the patient.

15.6.3 Aneurysm with Mass Effect as There Presentation

Illustration 1 (Fig. 15.9)**: Flow Diversion and Bypass** An elderly gentleman presented with a history of decreased vision in the right eye, MR angiogram showed the presence of pan-dolichocephalic vessels with fusiform dilatations of bilateral ICA, basilar and other vessels. He

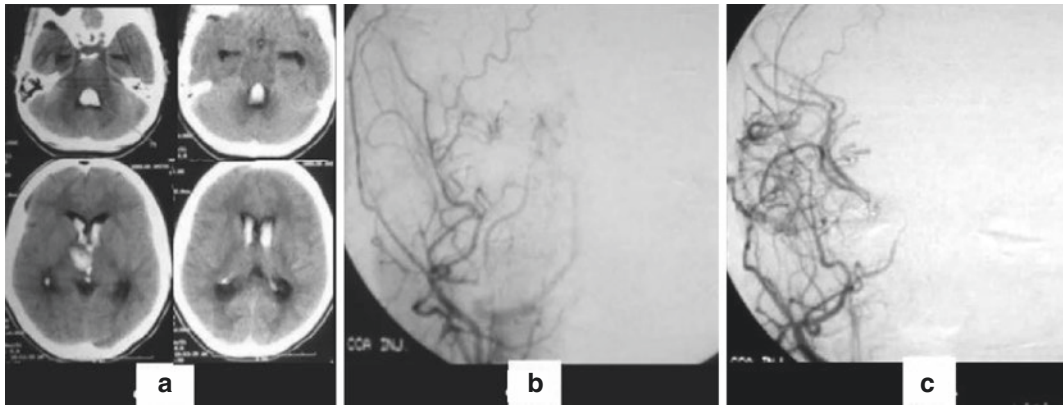


Fig. 15.7 (**a**) Shows CT Brain plain with intraventricular hemorrhage. (**b**) DSA with a puff of smoke appearance. (**c**) postop DSA with STMC anastomosis

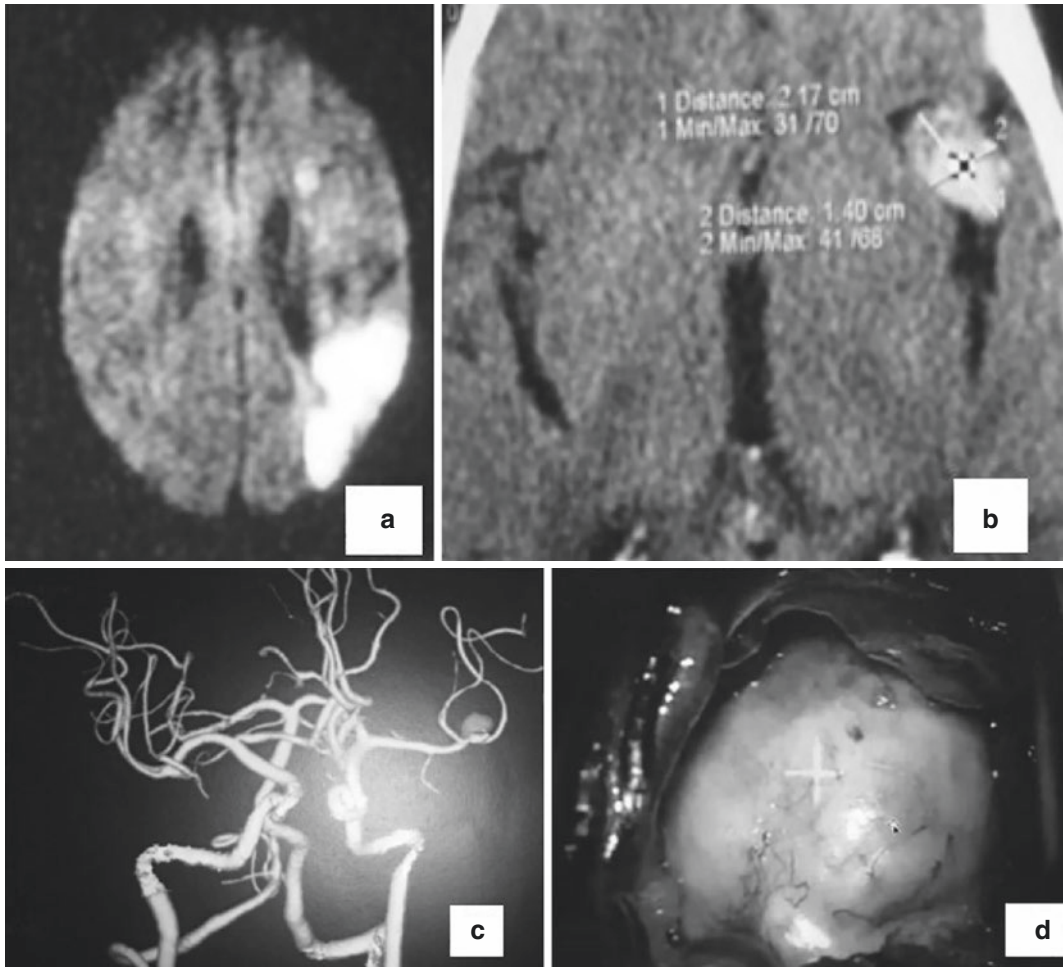


Fig. 15.8 (**a**) Shows MR Diffusion showing infarct. (**b**) shows CT brain showing the thrombosed aneurysm. (**c**) Shows CTA with a left distal MCA thrombosed aneurysm. (**d**) Shows the intraoperative picture of a thrombosed distal MCA aneurysm

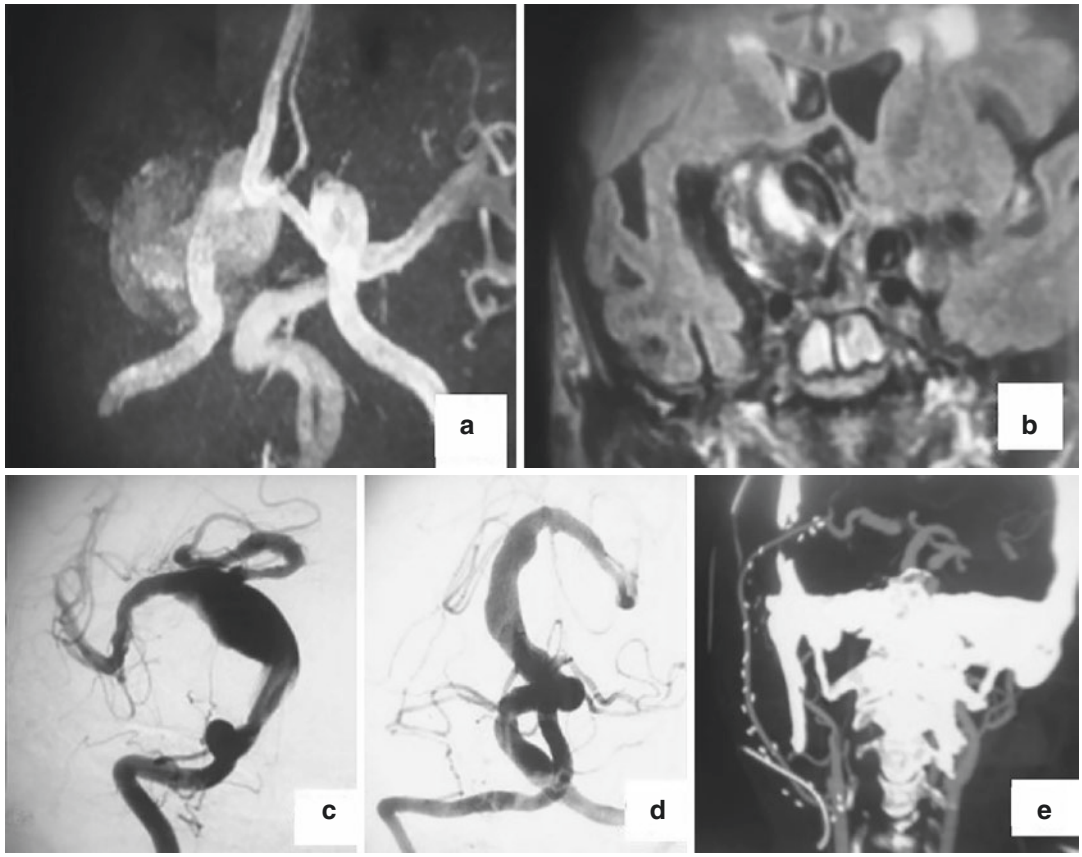


Fig. 15.9 (**a**, **b**) shows MRA with a giant right cavernous ICA aneurysm. (**c**, **d**) Shows the angiogram with pan-dolichocephalic vessels. (**e**) Shows complete obliteration following ECIC bypass with RAG & ligation of ICA in neck

underwent a high flow (ECA-M2) bypass with RAG followed by ligation of ICA in the neck.

Illustration 2 (Fig. 15.10)**: Flow Diversion and Bypass** An elderly lady presented with painful right ophthalmoplegia. CTA showed a giant cavernous ICA aneurysm for which she underwent EC-IC bypass with Radial artery graft (RAG) and ligation of ICA in the neck.

Illustration 3 (Fig. 15.11)**: Combined Approach (Microsurgery and EVT)** A young male presented with a Giant Supraclinoid aneurysm for which he underwent a Pterional approach, extradural anterior clinoidectomy and clipping of aneurysm. Postop angiogram showed residual filling of aneurysm, which was referred for EVT.

Illustration 4: Protective Bypass (Fig. 15.12) An elderly lady presenting with the progressive visual loss on evaluation was found to have a 4.1 × 3.8 cm Giant ICA Carotid-Ophthalmic segment aneurysm. Clipping of the aneurysm was carried out under protective STMC bypass to avoid ischemia during the prolonged period of temporary clipping of ICA

Illustration 5: Clipping After Failed Coiling (Fig. 15.13) Residual and recurrent aneurysms are more common after EVT than after microsurgical treatment. Moreover, even after total obliteration of the aneurysm, the patient worsens from the combined mass effect of the thrombosed aneurysm and the coils, as happened in the following case. A 2-year-young male child

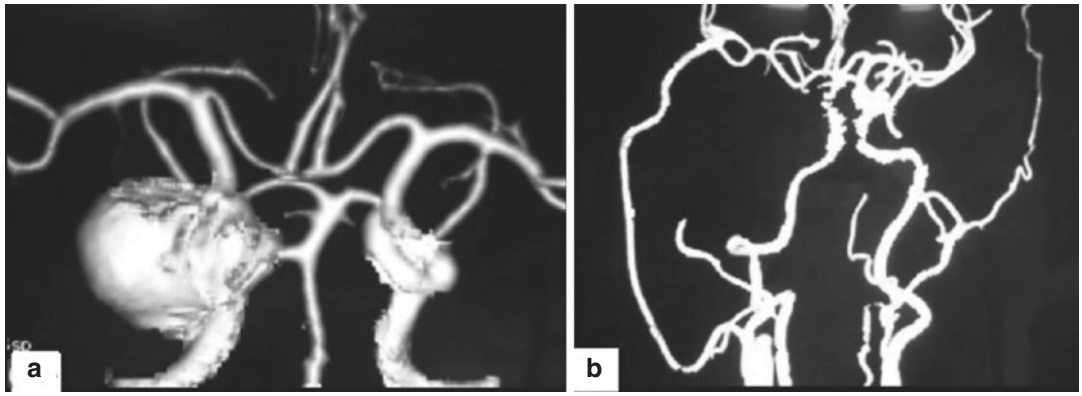


Fig. 15.10 (**a**) Shows CTA with a giant right cavernous ICA aneurysm. (**b**) Shows complete obliteration following ECIC bypass with RAG & ligation of ICA in neck

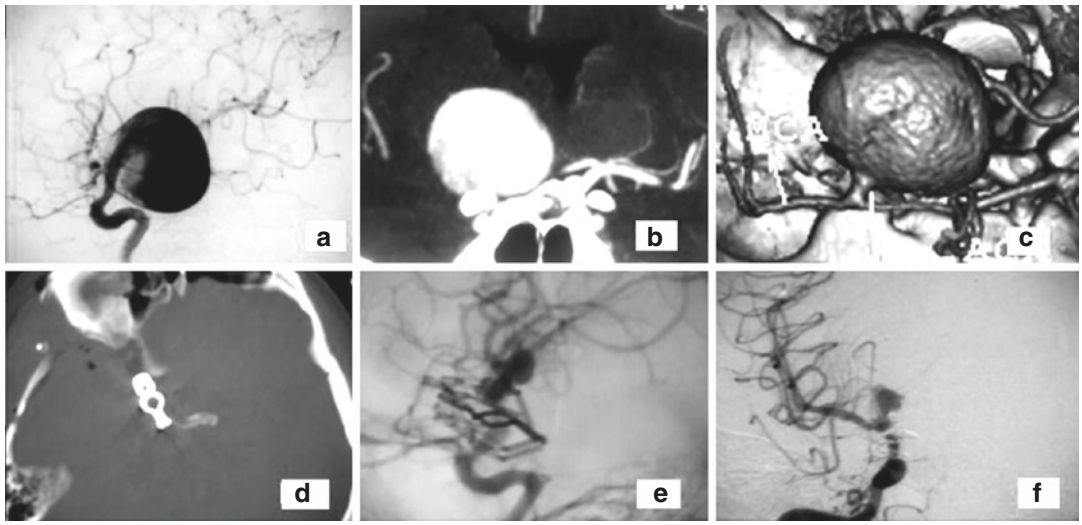


Fig. 15.11 (**a**–**c**) Show 3D reconstructed images of a giant right supraclinoid aneurysm. **D,** postop CT bone window with the clip. (**e**, **f**) Shows a small residue of the aneurysm post clipping

presented to the author in a drowsy state with a history of rapidly progressive quadriparesis, ataxia, and raised intracranial pressure. The evaluation revealed a 4.5 cm, heavily thrombosed, and calcified basilar top aneurysm with gross hydrocephalus. The child improved significantly following a right ventriculoperitoneal shunt. Our endovascular colleague suggested the coiling of the aneurysm. In view of the complex anatomy and morphology, the patient was treated by endovascular route with coils. The child remained stable for only 48 h before rapidly deteriorating in his sensorium to become comatose with extensor posturing and needed ventilator support. A repeat CT scan showed decompressed ventricles. The combined mass of the coils and the thrombosed giant aneurysm on the brain stem was thought to be the cause of the deterioration. The child was taken up for microsurgery in an attempt to decompress the aneurysm and relieve the mass effect. An FTOZ craniotomy, an extradural anterior clinoidectomy, and an intradural posterior clinoidectomy were performed. Through a transsylvian approach, the aneurysm was approached. The aneurysm was opened, partially decompressed, and with a short period of temporary

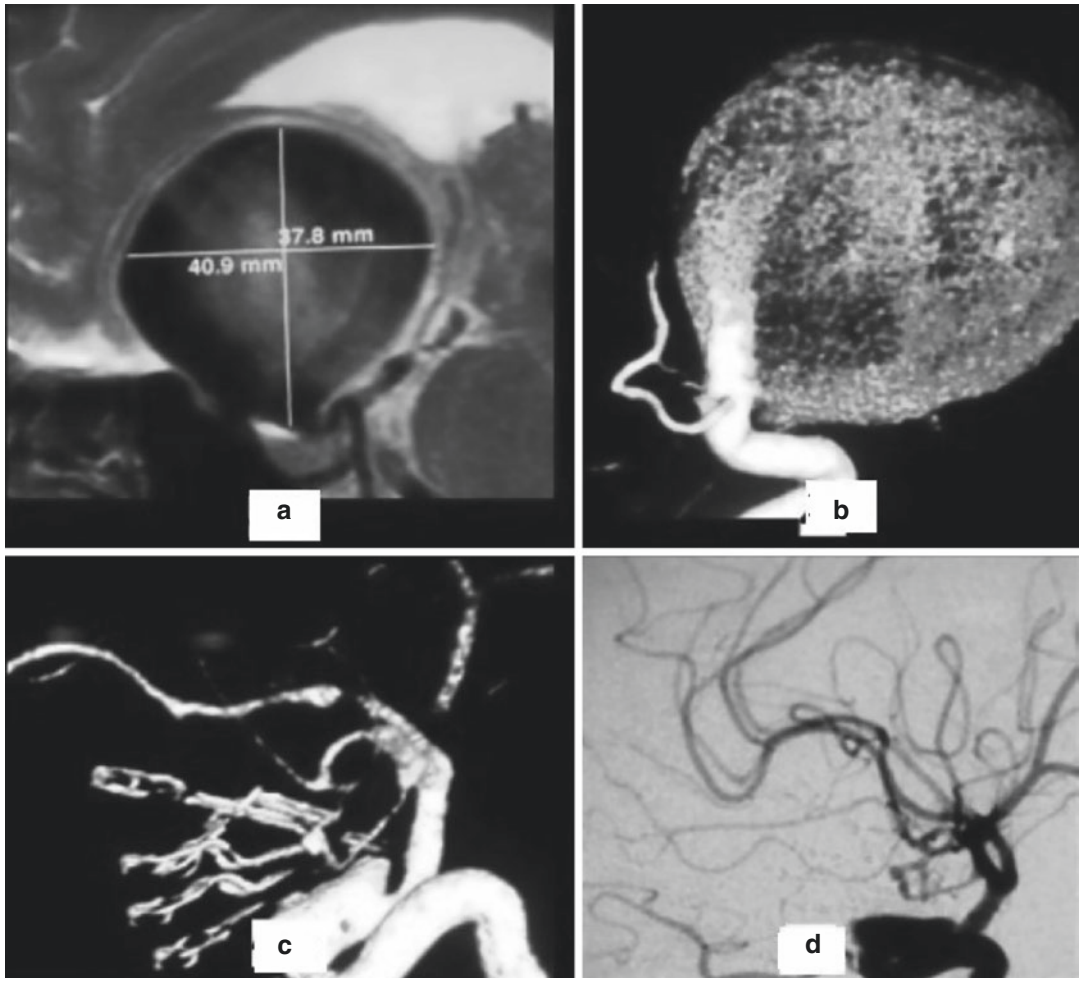


Fig. 15.12 (**a**) shows MRI brain with a giant left carotid-ophthalmic segment aneurysm. (**b**) Shows 3D reconstructed image of DSA. (**c**, **d**) Shows postoperative CTA and DSA respectively with obliteration of the aneurysm

clipping of the basilar trunk, the aneurysm neck was cleared off of thrombus and coils and clipped. All the branches and perforators were preserved. The patient had a prolonged ICU stay and hospitalization but slowly recovered remarkably. At the current follow-up, the child is going to school and has no disability or deficit other than minimal restriction of ocular motility

Illustration 6: Direct Clipping (Fig. 15.14) Obliteration of the aneurysm by direct microsurgical clipping, the preferred method of microsurgery in cerebral aneurysms, is often not possible in GIAs. However, it is essential to explore the possibility as some GIAs may be best treated by direct clipping, as was possible in the following patient. A 35-year-old man presented to us with history of recent worsening in instability of gait of 5 months' duration, inability to do fine movements of both hands of 3 months duration, and unprovoked, inappropriate, and uncontrolled spells of laughter of 3 months duration. On examination, he had left-sided deafness, bilateral cerebellar and pyramidal signs, and was unable to walk without support. MRI, DSA, and CTA revealed a partially thrombosed giant (3 cm) basilar top aneurysm with a significant mass effect on the brain stem and associated hydrocephalus. Patient was operated through a right fronto-temporo-orbito-zygomatic (FTOZ) crani-

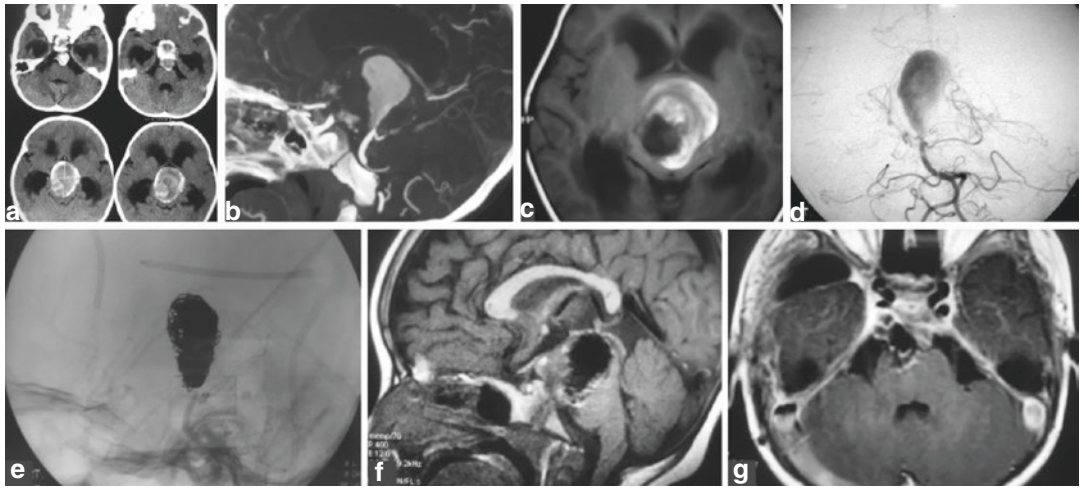


Fig. 15.13 (**a–d**) Plain CT, CTA, MRI, and DSA showing a 4.5 cm giant, calcified, partially thrombosed basilar top aneurysm. (**e**) Post-EVT DSA demonstrating successful complete occlusion of the aneurysm by coils. (**f, g**) 5-year follow-up post-microsurgery MRI confirming occluded aneurysm, decompressed brainstem without any ischemia infarct

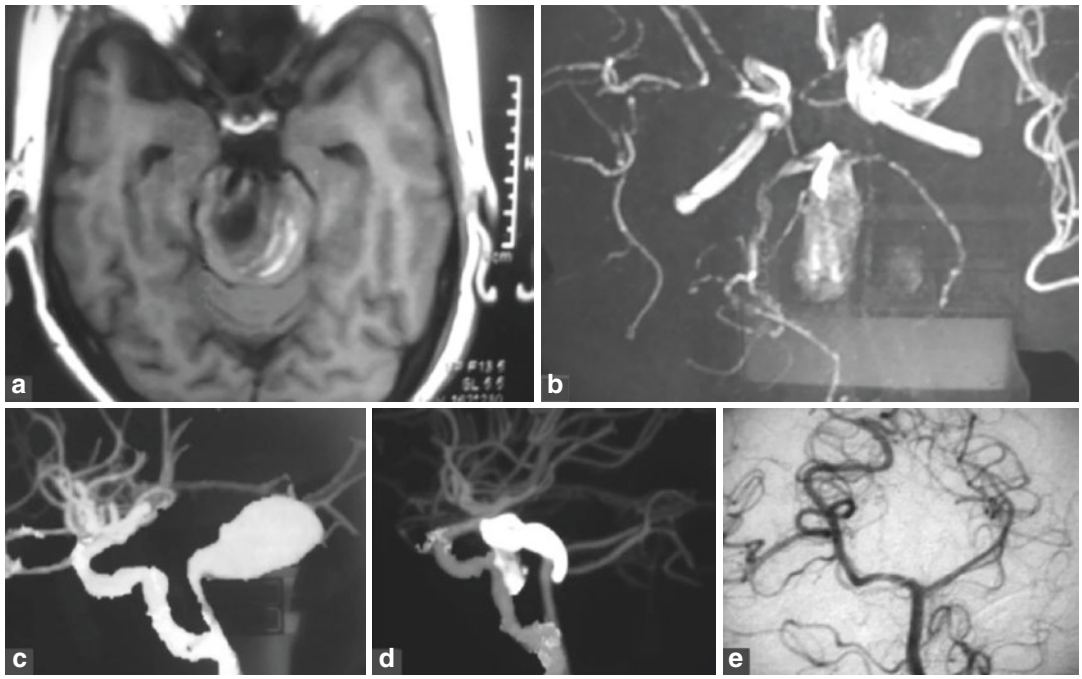


Fig. 15.14 (**a–c**) MRI brain and MRA demonstrating giant heavily thrombosed basilar top aneurysm. (**d, e**) Postoperative CTA and DSA showing complete occlusion of the aneurysm and preservation of all vessels

otomy with extradural anterior clinoidectomy and intradural drilling of dorsum sellae. A ventricular drain was inserted, and the aneurysm was exposed through a transsylvian route. After defining both the PCAs and dissecting away the perforators, two curved, large titanium clips secured the aneurysm neck. Preoperative ICG dye angiography showed satisfactory, complete occlusion of the aneurysm with a good filling of the basilar and all its branches. Patient made a slow recovery

and needed ventilator support and external ventricular drain in the postoperative period. At 3 weeks, the patient was fully conscious, ambulatory with support, and had a right third nerve paresis with mild left hemiparesis. At 3-month follow-up, the patient was independent with complete recovery of third nerve and hemiparesis. Postoperative DSA, CT, and CT angiography demonstrated complete occlusion of aneurysm and no evidence of infarct

Illustration 7 (Fig. 15.15**): Microsurgical Clipping Under Deep Hypothermic Circulatory Arrest** Deep hypothermic circulatory arrest technique has evolved but still results in significant mortality and morbidity in a third of the patients. Hence, its use is nowadays limited for giant and complex posterior circulation aneurysms, particularly the basilar apex that has failed or is inappropriate for EVT. It is very rarely employed in author's practice. The following case is an example of such an approach by us. A 12-year-old boy was referred to us in an altered sensorium after SAH. On admission, his GCS was E1M4V1. After initial resuscitation, endotracheal intubation and artificial ventilation, CT scan brain, CTA of cerebral vessels, and 3D cerebral DSA were performed. The investigations demonstrated bilateral frontal hypodensity, hydrocephalus, and Fisher grade 4 SAH from a giant multilobulated wide-necked basilar top aneurysm. The four-terminal branches of the basilar artery seemed to be arising from the aneurysm. CTA did not reveal the real complex nature of the aneurysm that could be correctly inferred from the 3D DSA. Hence, it was planned to attempt obliteration of the aneurysm under hypothermic circulatory arrest. After insertion of an external ventricular drain, an FTOZ craniotomy, extradural anterior clinoidectomy, and intradural posterior clinoidectomy were performed. After the majority of the dissection at the neck of the aneurysm, circulatory arrest was employed. The aneurysm was successfully obliterated with a combination of fenestrated and angled clips. The right PCA could not be saved. The patient had a

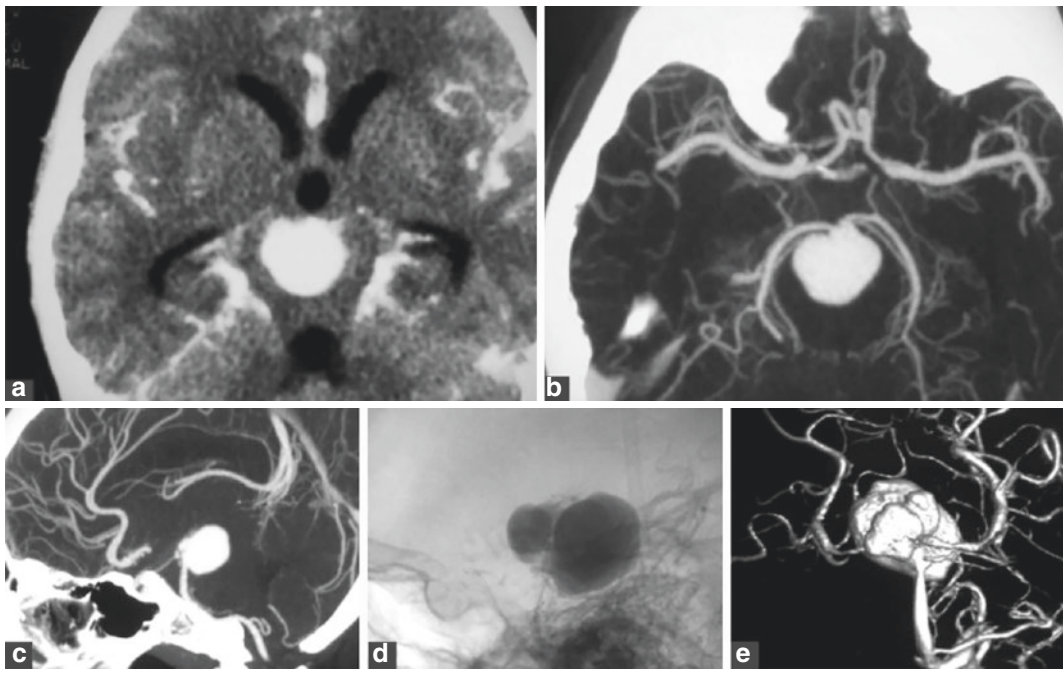


Fig. 15.15 (**a–c**) CTA showing a giant high basilar top aneurysm. The exact morphology of the multilobulated nature of the aneurysm and the branches incorporated in the aneurysm was only understood by DSA and 3D DSA and (**d, e**), not by CTA

prolonged stay in the ICU but finally successfully weaned off the ventilator. He was subsequently discharged to a chronic care hospital with percutaneous endoscopic gastrostomy feeding.

15.7 Literature Review

In microsurgical management of GIAs, Darsaut et al. reported a 69% rate of good clinical outcome. Their study also showed that patients younger than 50 years old had a better clinical outcome as compared with older patients (82% versus 65%), but the difference was not significant [33]. Ota et al., in their microsurgery series, reported a good outcome in 81.8% of patients, and complete occlusion rate in 86.8%. Poor outcomes were secondary to perforating artery infarctions and BA aneurysms, with the rate of perforating artery infarctions in BA aneurysms being 78.6% [34]. According to the ISUIA study, the 5-year rupture risk in patients harboring a very large or giant anterior circulation aneurysm is 15% and 40%, respectively [6]. Based on the ISUIA data, the risk of rupture of these aneurysms projected over a lifetime has been calculated to exceed 87% in a 30yearold patient and 71% in a 50yearold patient [35]. Compared with this grim natural history, the microsurgical intervention is justified. Good outcomes (mRS $\leq$ 3) were specifically seen in patients with $\leq$50 years of age. In a similar series by Hauck et al. 92% patients $\leq$50 years of age had a good outcome (GOS Score 4 or 5), resulting in 88% complete and 4% near complete aneurysm occlusions with an overall surgical morbidity and mortality rate at 8% [36]. In patients older than 70 years, the risk of surgery exceeded the lifetime risk of rupture [35]. A typical presentation of SAH showed a favorable outcome only in 50% of cases. A preoperative mRS score $\leq$ 1 was shown to have a good outcome in 86% of cases. Sughrue et al., in their series, proposed that indirect aneurysm occlusion (proximal occlusion, distal occlusion or trapping) with or without a bypass has become a more acceptable alternative than hypothermic cardiac arrest [3]. However, it is also associated with its unique complications like bypass graft occlusion and aneurysm thrombosis leading to thrombotic occlusion of perforators or branch arteries in 4 patients (7%) with flawless bypasses in their series. However, unlike non-giant aneurysms that can be trapped safely, giant aneurysm occlusion is often deliberately kept incomplete due to the presence of perforators or branches that would otherwise be trapped. Therefore, thrombosis initiated by bypass and aneurysm occlusion can potentially occlude these same arteries, too [3].

As with most types of technology-heavy fields, the specialty of endovascular neurosurgery has seen a tremendous refinement with the advent of detachable balloons and Guglielmi detachable coils (GDCs) and to the present use of flow diverters and pipeline embolization devices (PED) [37]. A brief literature review of the existing EVT articles is necessary to effectively compare EVT in aneurysms not amenable to EVT to the same being microsurgically clipped. Needless to say, a judicious approach is taken based on the merits of the case, as we have documented earlier in our illustrations. However, GIAs owing to their complexities and multiple anatomical, pathophysiological factors pose a challenge in the management of these lesions by EVT in terms of short-term and long-term results as well as its associated periprocedural morbidities and complications.

EVT management in wide-necked aneurysms, which are typically defined as lesions with necks of 4 mm or more wide or with dome/neck ratios of less than 2, involves stent-assisted coiling (SAC), Balloon-assisted coiling and flow-diverting stents (FDs) [38]. There are technical problems involved in achieving a complete angiographic occlusion after SAC, as a tight coil mass cannot be achieved due to difficulty in maneuvering the coiling microcatheter. In addition, the use of dual antiplatelet therapy often inhibits immediate aneurysmal thrombosis [39]. Overall complication rates of SAC are increased over those of primary coil embolization because of thromboembolic risks from stent placement and hemorrhagic risk from antiplatelet therapy. Shapiro et al., in their review, mentioned the overall incidence of complications to be 19% and mortality

rate to be 2.1% [40]. The main drawback of SAC is its heavy dependence on dual antiplatelet therapy, increased risk of hemorrhagic complications, and thromboembolic complications resulting from medication noncompliance or antiplatelet resistance [41–43]. Mocco and colleagues reported a procedural mortality rate of 12% with the use of SAC in ruptured aneurysms [44]. Complication rates of SAC are increased over those of primary coil embolization because of thromboembolic risk from stent placement and hemorrhagic risk from antiplatelet therapy [38]. In one review, the overall incidence of complications was reported to be 19% and the mortality rate to be 2.1% [40]. Thromboembolic complications were the primary contributor, responsible for approximately 10% of the overall complication rate and leading to death in 0.6% of cases. Hemorrhagic complications were responsible for 2.2% of overall complications and led to death in 0.9% of cases [38]. Fernandez et al. reported a series with 51 wide-necked aneurysms (necks > 4 mm) treated with coil embolization and achieved complete thrombosis in only 15% of cases [45]. Broad neck aneurysms, vessels arising from aneurysm base or walls, abnormal morphology etc., can result in herniation of coils into the parent artery lumen. BAC and SAC are associated with the additional risk of parent artery ischemia, perforation, distal thromboembolism, and occlusion of adjacent perforators and branch arteries by the lattice of the stent [8]. The rate of recurrence is also higher in broad neck aneurysms because the hemodynamics at the inflow zone is more complex. The other reasons for failure are incomplete initial obliteration, thrombus within the lumen, poor radiographic visualization of the aneurysm anatomy and its adjacent branches, and tortuosity of the feeding vessel, making catheterization difficult [8]. Flow diverters are exciting, but it is still early days for prime time.

The aneurysms most amenable to endovascular treatment are also those that are best treated by surgical techniques, namely, those with well defined, small, narrow necks [45, 46]. Most commonly, giant aneurysms have not been favorable lesions for endovascular therapy because they frequently widen the neck, distort the anatomy of parent and branch arteries at the base, and induce luminal thrombosis. Occlusion is incomplete in a considerable percentage of endovascular treatments leading to recurrent aneurysm, multiple retreatments, occasional re-hemorrhages, and neurological deterioration from progressive aneurysm enlargement. Further, follow-up studies have demonstrated refilling and recurrence of aneurysms thought to have been completely occluded [45–53]. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial (BRAT) showed no statistical significance difference in poor outcomes (mRS score > 2) or deaths between clipping and coiling on a 10 year follow-up. Of 178 clip-assigned patients with saccular aneurysms, 1 (<1%) was crossed over to coiling, and 64 (36%) of the 178 coil-assigned patients were crossed over to clipping. 2 of 241 (0.8%) clipped saccular aneurysms and 23 of 115 (20%) coiled saccular aneurysms required retreatment ($p < 0.001$). At the 10-year follow-up, 93% (50/54) of the clipped aneurysms were completely obliterated, compared with only 22% (5/23) of the coiled aneurysms ($p < 0.001$) [54]. Linfante et al. in their series of 45 GIA's managed by EVT had 7% mortality, 11.1% experienced ischemic strokes. Good clinical outcome (mRS score ≤ 2) was seen in 86% for anterior circulation cases and 55% for posterior circulation cases in their series (statistically significant, $n = 38$; $p < 0.05$) [2]. When GIAs are treated by microsurgical clipping, the mortality rates of both ruptured and unruptured GIAs were reported at 6–22% [5, 55]. Sluzewski et al. reported good clinical outcomes in 79% of very large and giant aneurysms at a median follow-up at 50 months, though 41% of aneurysms were still incompletely occluded even after repeated coiling [56]. A retrospective review that included large and GIAs treated with PED or PED + coils, and the authors found complete or near complete occlusion at the last follow-up in 77% of cases. Of the patients, 12% had symptomatic ischemic complications and 8% had symptomatic hemorrhagic complications, and the overall mortality was 6% [57]. Coiling alone as a treatment option

for GIAs has poor long-term outcomes because GIAs are often incompletely occluded and require repeated coiling [53]. Park et al. showed PED in combination with coiling had a higher neurological morbidity and required a longer procedural time versus PED alone [58]. Stent-assisted coiling and PED have shown to be equally effective, with no significant differences in complications and angiographic outcomes [59]. However, good results were seen in Bender et al. in their series of 445 PED procedures, with 85 large (19%) and 4 giant (1%) aneurysms, showed complete occlusion in 72%, 78% and 87% at 6, 12, and 24 months, respectively. Their overall rate of major complications was 3.5% and a 1.1% rate of mortality [60]. In a retrospective analysis by Liang et al. for giant posterior circulation aneurysms, 93.9% resulted in favorable clinical outcomes (mRS score, 0–2) with an overall mortality rate of 6.1% [61]. Darsaut et al. showed that EVT for very large and giant posterior circulation aneurysms was associated with poor clinical outcomes and a low complete obliteration rate [33]. This is also supported by a recent meta-analysis by Cagnazzo et al. that the incidence of treatment-related complications with endovascular treatment of very large and giant posterior circulation aneurysms was greater than that for anterior circulation aneurysms [62]. Siddiqui et al. advised judicious use of flow diversion procedures for large or giant vertebrobasilar aneurysms, owing to the high morbidity and mortality rates of 14.3% and 57.1%, respectively [63]. In a meta-analysis of flow diverter treatment for posterior circulation aneurysms, Wang et al. reported procedure-related mortality rate of 15% and significantly higher rates amongst patients with giant and basilar artery aneurysms [64]. Chalouhi et al. studied 334 large and giant aneurysms (80% anterior circulation) that were coiled at a single institution, 10% were giant aneurysms. Recanalization and retreatment rates were 39% and 33%, respectively [65]. Recanalization is highest in the setting of wide residual aneurysm necks, largely due to coil compaction, growing residual aneurysm neck, and refilling fundus [66–68].

Amongst all the above lesions, blood blister aneurysms (BBAs) deserve a special mention as the nuances of management of these treacherous lesions are challenging both microsurgically as well as by EVT. There is limited literature available currently on BBAs in regards to microsurgery versus EVT, without any current established consensus for the management of the same. BBAs are challenging small, bleb-like and ill-defined neck lesions at non-branching sites of the dorsal or anterior wall of the ICA, comprising 0.3–1.7% of all intracranial aneurysms and 6.6% of all ruptured aneurysms [69]. Owing to their fragile and difficult morphology, these lesions are a challenge to manage either surgically or endovascularly. A systematic review and meta-analysis by Zhu et al. of 15 noncomparative studies with a total of 165 target BBAs were studied. Complete occlusion rates were 72%, recurrence occurred in 13% and rebleed in 3% of patients. Procedure-related morbidity and mortality were 26% and 3%, respectively [70]. They concluded that FD was safe and effective, but treatment of BBA should be considered on a case-by-case basis to maximize patient benefits and limit the risk of perioperative complications. Shah et al. in their experience of microsurgery for BBAs observed that surgery provides a superior occlusion rate of up to 90% immediately postoperatively and superior sustained occlusion at follow-up than flow-diverting stents [71]. Kim et al. reported the rate of intraoperative rupture was 16.7%, higher than with FDs, however, 69.5% of patients had a good clinical outcome (mRS score of 0–2) at discharge, and a good long-term outcome in 80.1%, which is comparable to flow-diverting stents. Their study had a complete rate of aneurysm occlusion of 94.4%, and regrowth happened in only 1 case (0.28%) [72]. Thus concluding microsurgery for BBAs seem to have a slight edge over FDs and overlap FDs in term of superior occlusion rates and long-term control with a good postoperative mRS score and without the need for subjecting the patient to heavy antiplatelets which in itself is a reason for morbidity.

15.8 Conclusion

Treatment of complex aneurysms like GIAs and BBAs is challenging. The modalities of treatment, microsurgery, EVT, or combined should be individualized, taking into consideration the patient and pathological factors and available expertise. Although EVT is an attractive option, the high incidence of incomplete treatment, delayed complications, recurrence, and inadequate long-term follow-up data makes microsurgery preferable. The overall outcome of clinical and radiological results is a bit biased towards EVT as the more complex and difficult aneurysms are left for microsurgery. A judicious approach is hence recommended for a complex aneurysms based on their morphology, patient characteristics, departmental technical expertise in both microsurgery and EVT to give the patient the best outcome in terms of quality of life as well as cost affectivity, and the latter is extremely important in developing countries. Microsurgery thus remains an attractive treatment modality, in spite of the recent advances of endovascular techniques.

References

1. Bull J. Massive aneurysms at the base of the brain. Brain. 1969;92(3):535–70.
2. Linfante I, Andreone V, Ravelo N, Starosciak AK, Arif B, Shallwani H, et al. Endovascular treatment of giant intracranial aneurysms. Cureus. 2020;12(5):e8290.
3. Sughrue ME, Saloner D, Rayz VL, Lawton MT. Giant intracranial aneurysms: evolution of management in a contemporary surgical series. Neurosurgery. 2011;69(6):1261–70.
4. Vishteh AG, David CA, Spetzler RF. Giant aneurysms. In: Sekhar LN, Fessler R, editors. Atlas of neurosurgical techniques, vol. I. Stuttgart: Thieme; 2006. p. 212–21.
5. Hakma Z, Ramaswamy R, Loftus CM. Mortality rates for giant aneurysms. Acta Neurochir. 2011;153(8):1621–3.
6. Wiebers DO, Whisnant JP, Huston J, Meissner I, Brown RD Jr, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362:103–10. https://doi.org/10.1016/s0140-6736(03)13860-3.
7. Wermer MJ, Van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38:1404–10.
8. Quiñones-Hinojosa A, Du R, Lawton MT. Revascularization with saphenous vein bypasses for complex intracranial aneurysms. Skull Base. 2005;15(2):119–32.
9. Misra BK, Warade AG, Purandare HR. Giant intracranial aneurysms: microsurgery. In: Singh VP, Nair MD, editors. Progress in clinical neuroscience, vol. 29. Stuttgart: Thieme; 2015.
10. Peerless SJ, Wallace MD, Drake CG. Giant intracranial aneurysms. In: Yeoman's JR, editor. Neurological surgery: a comprehensive reference guide to the diagnosis and management of neurosurgical problems. 3rd ed. Philadelphia, PA: W.B. Saunders; 1990. p. 1742–63.
11. Barrow DL, Alleyne C. Natural history of giant intracranial aneurysms and indications for intervention. Clin Neurosurg. 1995;42:214–44.
12. Dannenbaum MJ, Rahimi SY, Schuette AJ. Natural history of giant intracranial aneurysms. In: Abdulrauf SI, editor. Cerebral revascularization: techniques in extracranial-to-intracranial bypass surgery. Philadelphia, PA: Elsevier; 2011. p. 225–30.
13. Lawton MT, Spetzler RF. Surgical strategies for giant intracranial aneurysms. Neurosurg Clin N Am. 1998;9(4):725–42.
14. Sano K, Asano T, Tamura A. Surgical technique. In: Sano K, Tamura A, editors. Acute aneurysm surgery: pathophysiology and management. New York: Springer; 1987. p. 194–246.
15. Zabramski JM, Kiriş T, Sankhla SK, Cabiol J, Spetzler RF. Orbitozygomatic craniotomy. Technical note. J Neurosurg. 1998;89(2):336–41.
16. Lawton MT, Spetzler RF. Surgical strategies for giant intracranial aneurysms. Acta Neurochir Suppl (Wien). 1999;72:141–56.
17. Drake CG. Giant intracranial aneurysms: experience with surgical treatment in 174 patients. Clin Neurosurg. 1979;26:12–95.
18. Drake CG. The treatment of aneurysms of the posterior circulation. Clin Neurosurg. 1979;26:96–144.
19. Malis L. Surgical resection of tumors of the skull base. In: Wilkins RH, Rengachary SS, editors. Neurosurgery. New York, NY: McGraw-Hill; 1885. p. 1011–21.
20. Hammon WM, Kempe LG. The posterior fossa approach to aneurysms of the vertebral and basilar arteries. J Neurosurg. 1972;37(3):339–47.
21. Sen CN, Sekhar LN. An extreme lateral approach to intradural lesions of the cervical spine and foramen magnum. Neurosurgery. 1990;27(2):197–204.
22. Lawton MT, Daspit CP, Spetzler RF. Technical aspects and recent trends in the management of large and giant midbasilar artery aneurysms. Neurosurgery. 1997;41(3):513–20.

23. Baldwin HZ, Miller CG, Van Loveren HR, Keller JT, Daspit CP, Spetzler RF. The far lateral/combined supra- and infratentorial approach. A human cadaveric prosection model for routes of access to the petroclival region and ventral brain stem. J Neurosurg. 1994;81(1):60–8.
24. Spetzler RF, Riina HA, Lemole GM Jr. Giant aneurysms. Neurosurgery. 2001;49(4):902–8.
25. Hacein-Bey L, Connolly ES Jr, Mayer SA, Young WL, Pile-Spellman J, Solomon RA. Complex intracranial aneurysms: combined operative and endovascular approaches. Neurosurgery. 1998;43(6):1304–12.
26. Ponce FA, Spetzler RF, Han PP, Wait SD, Killory BD, Nakaji P, et al. Cardiac standstill for cerebral aneurysms in 103 patients: an update on the experience at the Barrow Neurological Institute. Clinical article. J Neurosurg. 2011;114(3):877–84.
27. Rothoer RD, Brawanski A. The history and present status of deep hypothermia and circulatory arrest in cerebrovascular surgery. Neurosurg Focus. 2006;20(6):E5.
28. Groff MW, Adams DC, Kahn RA, Kumbar UM, Yang BY, Bederson JB. Adenosine-induced transient asystole for management of a basilar artery aneurysm. Case report. J Neurosurg. 1999;91(4):687–90.
29. Heppner PA, Ellegala DB, Robertson N, Nemergut E, Jaganathan J, Mee E. Basilar tip aneurysm – adenosine induced asystole for the treatment of a basilar tip aneurysm following failure of temporary clipping. Acta Neurochir. 2007;149(5):517–20.
30. Nussbaum ES, Sebring LA, Ostanny I, Nelson WB. Transient cardiac standstill induced by adenosine in the management of intraoperative aneurysmal rupture: technical case report. Neurosurgery. 2000;47(1):240–3.
31. Atkinson JLD, Piepgras DG. Giant aneurysms: supratentorial. In: Carter LP, Spetzler RF, editors. Neurovascular surgery. New York: McGraw-Hill; 1995. p. 815–28.
32. Symon L, Vajda J. Surgical experiences with giant intracranial aneurysms. J Neurosurg. 1984;61:100928.
33. Darsaut TE, Darsaut NM, Chang SD, Silverberg GD, Shuer LM, Tian L, et al. Predictors of clinical and angiographic outcome after surgical or endovascular therapy of very large and giant intracranial aneurysms. Neurosurgery. 2011;68:903–15.
34. Ota N, Matsukawa H, Noda K, Sato H, Hatano Y, Hashimoto A, et al. Evaluation of microsurgery for managing giant or complex cerebral aneurysms: a retrospective study. World Neurosurg. 2018;115:190–9.
35. Chang HS. Simulation of the natural history of cerebral aneurysms based on data from the international study of unruptured intracranial aneurysms. J Neurosurg. 2006;104:188–94.
36. Hauck EF, Wohlfeld B, Welch BG, White JA, Samson D. Clipping of very large or giant unruptured intracranial aneurysms in the anterior circulation: an outcome study. J Neurosurg. 2008;109(6):1012–8.
37. Park MS, Sanborn MR, McDougall CG, Albuquerque FC. Endovascular approaches to narrow-necked intracranial aneurysms. In: Winn HR, editor. Youman's & Winn neurological surgery. Philadelphia: Elsevier; 2017. p. 3362–71.
38. Moon K, Levitt MR, Albuquerque FC, McDougall CG. Endovascular approaches to wide-necked intracranial aneurysms. In: Winn HR, editor. Youman's & Winn neurological surgery. Philadelphia: Elsevier; 2017. p. 3372–5.
39. Piotin M, Blanc R. Balloons and stents in the endovascular treatment of cerebral aneurysms: vascular anatomy remodeled. Front Neurol. 2014;5:41.
40. Shapiro M, Becske T, Sahlein D, Babb J, Nelson PK. Stent-supported aneurysm coiling: a literature survey of treatment and follow-up. AJNR Am J Neuroradiol. 2012;33:159–63.
41. Goh C, Churilov L, Mitchell P, Dowling R, Yan B. Clopidogrel hyper-response and bleeding risk in neurointerventional procedures. AJNR Am J Neuroradiol. 2013;34:721–6.
42. Rossen JD, Chalouhi N, Wassef SN, Thomas J, Abel TJ, Jabbour PM, et al. Incidence of cerebral ischemic events after discontinuation of Clopidogrel in patients with intracranial aneurysms treated with stent-assisted techniques. J Neurosurg. 2012;117:929–33.
43. Fifi JT, Brockington C, Narang J, Leesch W, Ewing SL, Bennet H, et al. Clopidogrel resistance is associated with thromboembolic complications in patients undergoing neurovascular stenting. AJNR Am J Neuroradiol. 2013;34:716–20.
44. Mocco J, Snyder KV, Albuquerque FC, Bendok BR, Bolos AS, Carpenter JS, et al. Treatment of intracranial aneurysms with the Enterprise stent: a multicenter registry. J Neurosurg. 2009;110:35–9.
45. Zubillaga AF, Guglielmi G, Viñuela F, Duckwiler GR. Endovascular occlusion of intracranial aneurysms with electrically detachable coils: correlation of aneurysm neck size and treatment results. AJNR Am J Neuroradiol. 1994;15:815–20.
46. Standard SC, Guterman LR, Chavis TD, Fronckowiak MD, Gibbons KJ, Hopkins LN, et al. Endovascular management of giant intracranial aneurysms. Clin Neurosurg. 1995;42:26793.
47. Gobin YP, Vinuela F, Gurian JH, Guglielmi G, Duckwiler GR, Massoud TF, et al. Treatment of large and giant fusiform intracranial aneurysms with Guglielmi detachable coils. J Neurosurg. 1996;84:5562.
48. Gruber A, Killer M, Bavinzski G, Bernd R. Clinical and angiographic results of endosaccular coiling treatment of giant and very large intracranial aneurysms: a 7year, single center experience. Neurosurgery. 1999;45:793803.
49. Henkes H, Fischer S, Weber W, Miloslavski E, Felber S, Brew S, et al. Endovascular coil occlusion of 1811 intracranial aneurysms: early angiographic and clinical results. Neurosurgery. 2004;54:26880.

50. Jahromi BS, Mocco J, Bang JA, Gologorsky Y, Siddiqui AH, Horowitz MB, et al. Clinical and angiographic outcome after endovascular management of giant intracranial aneurysms. Neurosurgery. 2008;63:66274.
51. Klein GE, Szolar DH, Leber KA, Karaic R, Hausegger KA. Basilar tip aneurysm: endovascular treatment with Guglielmi detachable coils—midterm results. Radiology. 1997;205:1916.
52. Murayama Y, Viñuela F, Ishii A, Nien YL, Yuki I, Duckwiler G, et al. Initial clinical experience with matrix detachable coils for the treatment of intracranial aneurysms. J Neurosurg. 2006;105:1929.
53. Sluzewski M, Menovsky T, van Rooij WJ, Wijnalda D. Coiling of very large or giant cerebral aneurysms: long-term clinical and serial angiographic results. AJNR Am J Neuroradiol. 2003;24:25762.
54. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Nakaji P, et al. Ten-year analysis of saccular aneurysms in the Barrow ruptured aneurysm trial. J Neurosurg. 2019;132(3):771–6.
55. Wehman JC, Hanel RA, Levy EI, Hopkins LN. Giant cerebral aneurysms: endovascular challenges. Neurosurgery. 2006;59:125–38.
56. Sluzewski M, van Rooij WJ, Rinkel GJ, Wijnalda D. Endovascular treatment of ruptured intracranial aneurysms with detachable coils: long-term clinical and serial angiographic results. Radiology. 2003;227:720–4.
57. Adeeb N, Griessenauer CJ, Shallwani H, Shakir H, Foreman PM, Moore JM, et al. Pipeline embolization device in treatment of 50 unruptured large and giant aneurysms. World Neurosurg. 2017;105:232–7.
58. Park MS, Kilburg C, Taussky P, Albuquerque FC, Kallmes DF, Levy DI, et al. Pipeline embolization device with or without adjunctive coil embolization: analysis of complications from the IntrePED registry. AJNR Am J Neuroradiol. 2016;37:1127–31.
59. Adeeb N, Griessenauer CJ, Foreman PM, Moore JM, Motei-Langroudi R, Chua MH, et al. Comparison of stent-assisted coil embolization and the pipeline embolization device for endovascular treatment of ophthalmic segment aneurysms: a multicenter cohort study. World Neurosurg. 2017;105:206–12.
60. Bender MT, Colby GP, Lin L-M, Jiang B, Westbroek EM, Xu R, et al. Predictors of cerebral aneurysm persistence and occlusion after flow diversion: a single-institution series of 445 cases with angiographic follow-up. J Neurosurg. 2018;130:259–67.
61. Liang F, Zhang Y, Yan P, Ma C, Liang S, Jiang P, et al. Predictors of periprocedural complications and angiographic outcomes of endovascular therapy for large and giant intracranial posterior circulation aneurysms. World Neurosurg. 2019;125:378–84.
62. Cagnazzo F, Mantilla D, Rouchaud A, Brinjikji W, Lefvre PH, Dargazanli C, et al. Endovascular treatment of very large and giant intracranial aneurysms: comparison between reconstructive and deconstructive techniques—a meta-analysis. AJNR Am J Neuroradiol. 2018;39:852–8.
63. Siddiqui AH, Abla AA, Kan P, Dumont TM, Jahshan S, Britz GW, et al. Panacea or problem: flow diverters in the treatment of symptomatic large or giant fusiform vertebrobasilar aneurysms. J Neurosurg. 2012;116:1258–66.
64. Wang CB, Shi WW, Zhang GX, Lu HC, Ma J. Flow diverter treatment of posterior circulation aneurysms. A meta-analysis. Neuroradiology. 2016;58(4):391–400.
65. Chalouhi N, Tjoumakaris S, Gonzalez LF, Dumont AS, Starke RM, Hasan D, et al. Coiling of large and giant aneurysms: complications and long-term results of 334 cases. AJNR Am J Neuroradiol. 2014;35:546–52.
66. Katayama Y, Tsubokawa T, Miyazaki S, Furuichi M, Hirayama T, Himi K, et al. Growth of totally thrombosed giant aneurysm within the posterior cranial fossa. Diagnostic and therapeutic considerations. Neuroradiology. 1991;33:168–70.
67. Horowitz M, Purdy P, Kopitnik T, Dutton K, Samson D. Aneurysm retreatment after Guglielmi detachable coil and nondetachable coil embolization: report of nine cases and review of the literature. Neurosurgery. 1999;44:712–9.
68. Hasan DM, Nadareyshvili AI, Hoppe AL, Mahaney KB, Kung DK, Raghavan ML. Cerebral aneurysm sac growth as the etiology of recurrence after successful coil embolization. Stroke. 2012;43:866–8.
69. Peitz GW, Sy CA, Grandhi R. Endovascular treatment of blister aneurysms. Neurosurg Focus. 2017;42(6):E12.
70. Zhu D, Yan Y, Zhao P, Duan G, Zhao R, Liu J, et al. Safety and efficacy of flow diverter treatment for blood blister like aneurysm: a systematic review and meta-analysis. World Neurosurg. 2018;118:79–86.
71. Shah SS, Gersey ZC, Nuh M, Ghonim HT, Elhammady MS, Peterson EC. Microsurgical versus endovascular interventions for blood blister aneurysms of the internal carotid artery: systematic review of literature and meta-analysis on safety and efficacy. J Neurosurg. 2017;127:1361–73.
72. Kim YS, Joo SP, Kim TS. Microsurgical management of ruptured blood blister aneurysms of the internal carotid artery without bypass: a retrospective single-center study of 36 patients over 20 years. World Neurosurg. 2019;128:956–65.

Giant Intracranial Aneurysm: Flow Alteration vs Flow Diversion

16

Manas Panigrahi, Chirag Patel,
Y. B. V. K. Chandrasekhar, and Sudhindra Vooturi

Abstract

Giant intracranial aneurysms (GIA) are aneurysms >2.5 cm in any size and constitute nearly five percent of all aneurysms, with 35% of these aneurysms observed in posterior circulation. Surgical management of giant intracranial aneurysms aims to prevent rupture, thromboembolic complications and mass effect; thereby are the most difficult cerebrovascular lesions to operate. The surgeon could use a surgical approach, endovascular route or a combination of both to manage these aneurysms. Among various surgical options, clipping and coiling have been preferred option and have been extensively studied through meta-analysis and reviews providing level 1 evidence. However, recent nuances in the management of these aneurysms include endovascular flow diverter, stent-assisted coiling and surgical bypass with or without parent vessel ligation (level 4 evidence). In this chapter, the authors share their institutional experience and provide an insight into role of surgical bypass and endovascular management of complex GIAs.

M. Panigrahi (✉) · C. Patel ·
Y. B. V. K. Chandrasekhar
Department of Neurosurgery, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India

S. Vooturi
Department of Neurology, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India

Keywords

Giant intracranial aneurysms · Flow diversion
Bypass · Coiling · Clipping

16.1 Introduction

The sixties and seventies saw an unprecedented advent of surgical management of Giant Intracranial Aneurysms (GIA), where numerous techniques including usage of techniques like temporary bypass, hypothermia, bipolar coagulation, operating microscope and pharmacological neuroprotection formed a formidable support system, resulting in significant reduction in mortality due to GIAs. However, the giant leap in the surgical management of GIAs was with the introduction of Guglielmi Detachable Coils (GDC) in 1991, which revolutionized neuro-surgical management of aneurysms especially GIAs. However, complete occlusion with only GDC remains insufficient in treatment of GIAs with particularly broad necks, thus balloon-assisted GDC placement or stent intervention was introduced as a remedy. Over the last decade, microsurgical occlusion of GIAs is constantly being replaced by current endovascular techniques, widely regarded as having a lower risk for the patient. It is quite unusual in Evidence Based Medicine that despite rapid development in endovascular techniques, these techniques have only recently

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_16

become the standard for securing GIAs. This is evident by the fact that clipping and coiling have been extensively studied through meta-analysis and reviews providing level 1 evidence. However, recent nuances in the management of these aneurysms include endovascular flow diverter, stent-assisted coiling and surgical bypass with or without parent vessel ligation only have level 4 evidence [1] (Table 16.1), probably because fewer studies have been done.

Nevertheless, GIAs are the most challenging lesions for both experienced neurosurgeons and neuroradiologists. Constantly developing endovascular techniques are regarded as having lower risks for patients than open surgery and still seem to be unsatisfactory in terms of durability in aneurysm occlusion. The balloon-assisted remodelling and stent-assisted techniques partially solved the problem of neck remnants. After introducing the pipeline stent in 2011, there was reduction in number of patients treated with bypass in GIAs. However, complications revealed on long-term follow-up of patients treated with flow diverter resulted in increased adoption of a combination of both microsurgical and endovascular methods and leading to reduced mortality and improved functional outcomes, especially in patients treated with surgical clipping and those undergoing endovascular coiling. For example, a recent data from the US Nationwide Inpatient Sample reported that inpatient mortality decreased from 32.2% in 2002 to 22.2% in 2010, while discharge to home increased from 28.5% to 40.8% [2]. Similar trends have been observed in several other countries as well. The reasons for improved clinical and functional outcomes are likely multifactorial: protocol-driven treatment, the availability of advanced invasive monitoring and complex procedures to treat SAH-associated vasospasm (e.g. angioplasty), experienced vascular and endovascular surgeons and specialized nursing early identification and aggressive management of potential complications.

Table 16.1 Level of evidence in treatment of giant intracranial aneurysm (GIA)

Level of evidence	Treatment modality used for giant intracranial aneurysm
Level 1 evidence	Clipping Coiling
Level 3 evidence	Stent-assisted coiling
Level 4 evidence	Flow diversion Flow diversion with adjunctive coiling Intrasaccular flow diversion Parent vessel sacrifice with surgical bypass Parent vessel sacrifice without surgical bypass

16.2 Comparison for Outcome: Endovascular Treatment vs. Surgical Bypass

16.2.1 Occlusion, Recurrence and Re-bleeding

In Unruptured Aneurysms (meta-analysis) [3], the rate of long-term complete/near-complete occlusion was 71% and 93% after reconstructive (coiling/BAC, SAC, flow diversion alone, and flow diversion plus coiling) and deconstructive treatments (parent artery occlusion), respectively. The rate of recanalization was higher after reconstructive treatment (40%) compared with the deconstructive technique (5%). Similarly, the rate of retreatment was significantly higher among the reconstructive group (32% versus 4%). Early and late aneurysm ruptures after reconstructive techniques were 5% and 3%, respectively. No cases of rupture were described after PAO, Table 16.2.

In Ruptured Aneurysms, there were comparable rates of complete/near-complete occlusion (72% versus 80% after reconstructive and deconstructive treatments, respectively). Aneurysm recanalization was 47% after reconstructive and 22% after deconstructive techniques. There was a significantly higher rate of retreatment after reconstructive compared with deconstructive treatments. The rate of early aneurysm rupture after coiling was 8%, whereas no cases were described after deconstructive treatment, Table 16.2.

Coil embolization for large and giant wide-necked aneurysms is associated with high rates of

Table 16.2 Outcome comparison between surgical bypass and endovascular treatment [3–7]

		Complete occlusion (%)	Rehaemorrhage (%)	Retreatment (%)	Mortality (%)	Morbidity (%)
Surgical bypass	Lawton et al. (2002) Jafar et al. (2002) Sharma et al. (2008) Sughrue (2010) **Average**	100% 100% 90% 90% (90–100%)	0% 0% 0% 1% (0–5%)	0% 0% 0% 1% (0–3%)	14% 3% 9% 13% (3–15%)	11% 10% 12% 10% (10–12%)
Reconstructive endovascular treatment[a]	**Ruptured GIA**	72%	8%	48%		
	Unruptured GIA	71%	5%	32%		
					11–22%	15%
Destructive endovascular treatment[b]	**Ruptured GIA**	80%	0%	22%		
	Unruptured GIA	93%	0%	4%	6–9%	
						9%

[a]Reconstructive endovascular treatment—(coiling/BAC, SAC, flow diversion alone and flow diversion plus coiling)
[b]Destructive endovascular treatment—Parent artery occlusion

recurrence (40%–60%) and rebleeding (1.9%/year) [8]. Jahromi et al. reported a complete occlusion rate of 36%, stent-assistance in 66%, and an average of 2 sessions to treat each aneurysm. Surgical treatment with bypass (Kaplan–Meier analysis) demonstrated better control rate at 30 months of 96%, 93% and 84% for completely occluded, minimally residual and incompletely occluded giant aneurysms, respectively [9], Table 16.2.

16.2.2 Flow Diverter Stent in Posterior Circulation Giant Aneurysm

The rates of morbidity and mortality after flow-diversion treatment were higher among posterior circulation (16.5%) compared with anterior circulation (5%–9%) GIAs [10]. In fact, numerous studies have consistently associated flow diversion in the posterior circulation with ischaemic complications related to perforator infarcts. Occlusion rates for posterior circulation aneurysms have been reported separately at approximately 80%, similar to those reported for anterior circulation aneurysms [11]. Infarction may result from direct coverage of the perforator ostia by the tines of the device, by migration of acute thrombus or by neo-intimal growth across the ostia [12]. Clinical deterioration of patients with brainstem compression from giant, partially thrombosed posterior circulation aneurysms treated using flow diversion has also been reported.

16.2.3 Pressure Symptoms due to Cranial Nerve Compression

The coil mass could exert pressure on the cranial nerves and exacerbate neurological symptoms. Meta-analysis comparing clipping with coiling in terms of recovery from oculomotor palsy found a benefit to clipping for ruptured aneurysms specifically (88% vs 56%, respectively) [13].

16.2.4 Morbidity and Mortality

Among the endovascular experiences reported in 39 GIAs, cumulative treatment morbidity occurred in 12 patients (32%), and treatment mortality occurred in six patients (16%) [9]. Sughrue et al. reported a mortality rate of 13%,

morbidity in 9%, and favourable outcome in 81% [14] of the 140 patients with 141 GIAs. Similarly, Sharma et al. reported a mortality rate of 9%, and a morbidity rate of 12% for GIAs treated surgically, with favourable outcomes in 86% of patients [6].

16.3 Concepts of Flow Diversion and Flow Alteration

Flow Diversion Endovascular flow diverter changes the dynamics of intra-aneurysm flow followed by aneurysm thrombosis and exclusion from circulation. The term "flow diverter" is arguably a misnomer because it is endothelialization that eventually sequestrates the aneurysm [15].

Surgical Flow Alteration Flow alteration technique defined as incomplete parent artery occlusion which eventually causes reduction of intra-aneurysmal flow promotes intraluminal thrombosis and aneurysm occlusion [16]. Flow alteration could be made by a one-sided (proximal or distal) occlusion of the parent artery with or without bypass. Among several different methods for flow alteration, proximal occlusion with bypass is relatively well-established [17]. Flow alterations were performed when direct clipping, endovascular embolization or trapping were not possible.

Surgical treatment of GIAs consists of clipping, surgical bypass with ligation and trapping with bypass. The most common indications for surgical management include: Wide-necked aneurysms located at branch points of major vessels, large saccular aneurysms with multiple efferent arteries, dolichoectatic aneurysms, large aneurysms with mass effect, when there are technical complications with endovascular treatment. Moreover, in patients who cannot tolerate or have contraindications to antiplatelet therapy or in the setting of a subarachnoid haemorrhage endovascular treatment may not be appropriate [18].

16.4 Surgical Management for GIAs

1. *Clipping with reconstruction of vessel wall*
2. *Surgical Bypass with proximal ligation*
3. *Trapping of aneurysm with surgical bypass*

16.4.1 Clipping with Reconstruction of Vessel Wall

If critical artery does not origin from fundus of aneurysm, then clipping with multiple clips is one of the viable options. Giant thrombosed aneurysms are usually treated with exploration of aneurysm and direct clipping with vessel wall reconstruction. Maintaining the adequate diameter of artery is critical and most important point. Giant ICA and MCA aneurysms are commonest aneurysms to be attempted by this approach. Illustrated cases 1 and 2 show multiple clips with reconstruction of vessel wall (Figs. 16.1 and 16.2).

16.4.2 Surgical Bypass

Indications of Surgical bypass in GIAs include:

- Giant complex aneurysm
- Absence of a neck (fusiform or saccular-fusiform aneurysms)
- Severe atherosclerosis or calcification in the neck
- Extensive thrombosis
- Critical branch origin from neck or sac (MCA and ACA)
- Symptomatic dissecting aneurysm
- Blister aneurysm (failed endovascular option)
- People with antiplatelet resistance
- Recurrent aneurysm following endovascular treatment

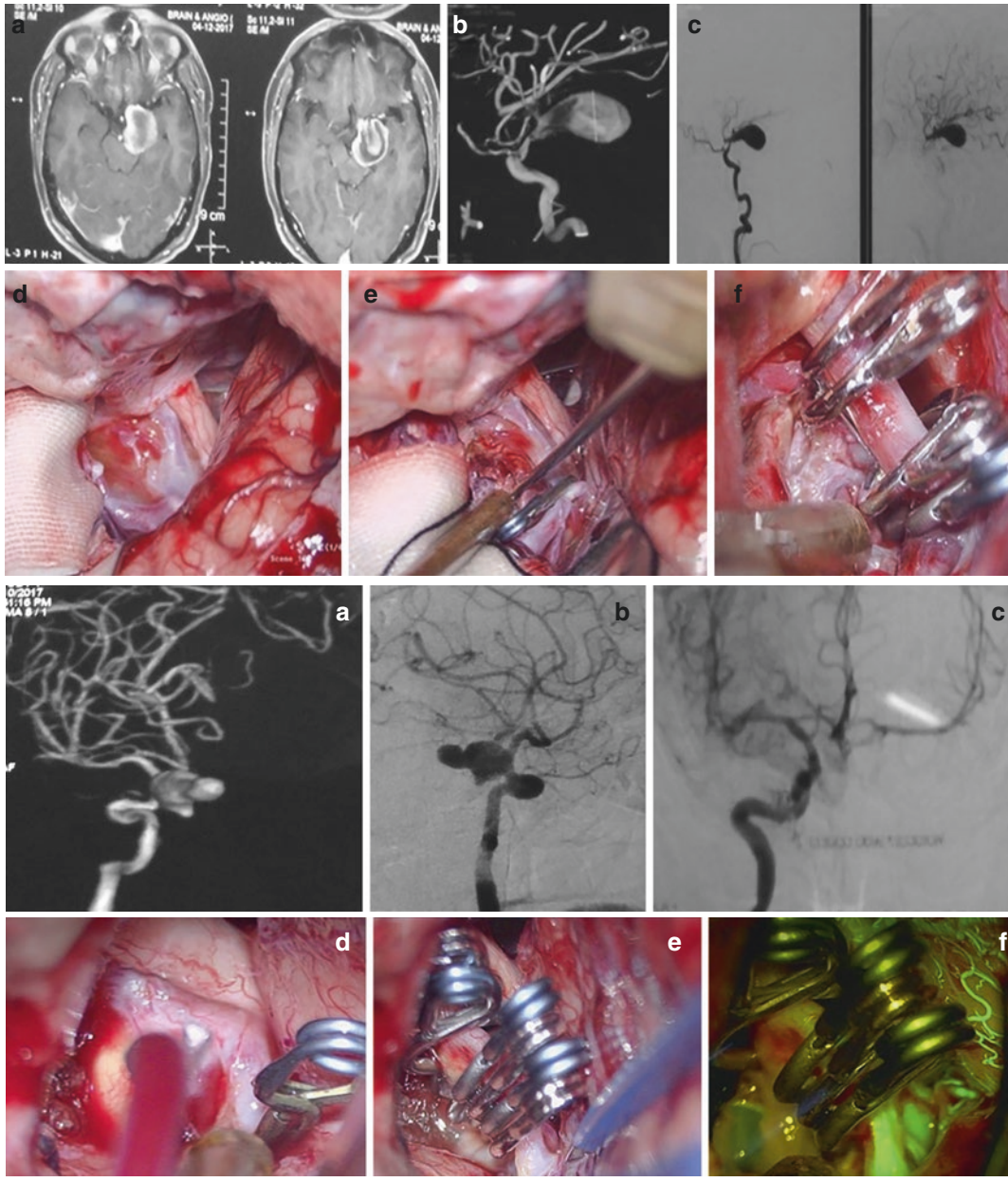


Fig. 16.1 Illustrated Case 1—Giant ICA aneurysm clipping with vessel wall reconstruction. A 48-year-old male presented with left side hemicranial headache and retro-orbital pain without any focal neurological deficit. MRI brain and DSA were suggestive of left supraclinoidal ICA wide neck partially thrombosed giant aneurysm with left side A1 hypoplastic (**a**–**c**). Patient underwent left pterional craniotomy and clipping of aneurysm with multiple clips and vessel wall reconstruction (**d**, **e**). Intra-operative thrombosed aneurysm noted (**f**). ICA flow was confirmed with fluorescence microscope. Patient recovered well. A 41-year-old female presented with sudden headache. CT brain suggestive of subarachnoid haemorrhage. DSA suggested left ICA paraclinoid giant aneurysm. Patient underwent craniotomy and clipping with multiple fenestrated clips. Intra-operative ICA flow was confirmed with fluorescence microscope. Post-operative patient recovered without any neurological deficit

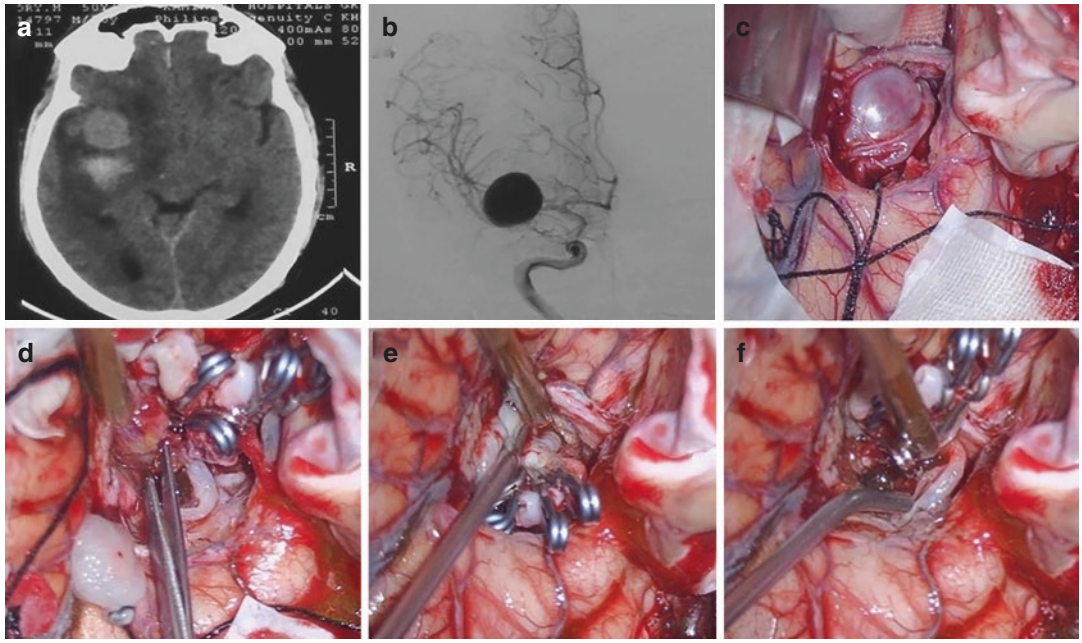


Fig. 16.2 Illustrated Case 2—Giant MCA aneurysm clipping with multiple clips. A 50-year-old male presented with acute headache, vomiting and left side hemiparesis. CT brain showed right Sylvian fissure and temporal acute haemorrhage (**a**). DSA was suggestive of right MCA-M1 Giant partially thrombosed aneurysm (**b**). Patient underwent frontotemporal craniotomy and superior temporal gyrus approach with clipping of aneurysm done with multiple clips. Intra-operative thrombosed aneurysm noted (**c**). Flow in MCA branches was preserved and confirmed with fluorescence microscope and Doppler probe (**d–f**)

16.4.3 Decision Making in Surgical Bypass

1. Cross circulation in DSA: Poor cross circulation needs high flow bypass to obviate need of cerebral perfusion. Ipsilateral A1 hypo plastic can be addressed with low flow STA-MCA bypass with proximal ICA occlusion. Contralateral A1 hypo plastic and ipsilateral dominant circulation needs high flow bypass from ECA to MCA/ICA by saphenous venous graft or radial artery graft.
2. Balloon occlusion test with hypotension challenge: Even with cross circulation in DSA if patient did not tolerate BOT with hypotension challenge, it is preferable to do bypass before ligation of ICA. Some authors prefer to perform a bypass when acute vessel sacrifice is needed because false-negative rates of balloon occlusion tests are significant [19].
3. Tables 16.2 and 16.3 summarize selection criteria for high flow vs low flow bypass. Arterial versus venous graft in bypass surgery is compared in Table 16.4.

Table 16.3 Selection of bypass—high flow vs low flow bypass [20–22]

	High flow bypass	Low flow bypass
Flow rate	>50 ml/min	<50 ml/min
Indications	Proximal large vessel sacrifice Flow replacement Large area to be revascularized	No vessel sacrifice Flow augmentation Small area to be revascularized Brain cannot handle high flows
Donor vessel	Internal maxillary ECA ICA Free arterial graft(radial ≥2.4 mm) Free venous graft(GSV ≥ 3 mm)	STA (superficial temporal artery) MMA (middle meningeal artery) OA (occipital artery)

16.4.4 Clinical Tips for Successful Surgical Bypass

- Meticulous haemostasis (heparin administration)
- Distension of graft to prevent spasm
- Vein graft should not *reversed*
- Intracranial anastomosis performed first
- Deliver graft without torsion

Table 16.4 Comparison between arterial and venous graft for bypass

Arterial graft	Venous graft
• Better suited to high pressure flow • Short-term patency rates are better (98% at 6 W) • Length is a limitation • No valves • Lumen approximates that of recipient • May not always be available (incomplete palmar arch) • Recipient ≥ 2 mm	• Larger diameter, higher flow rates • Lower short-term patency rates (93% at 6 W) • Length is not a limitation • Almost always available • Valves present • Lumen larger than recipient • Higher procedure related complications • Children < 12 years • Recipient ≥ 2.5 mm

16.4.5 Illustrated Case Examples of Surgical Bypass in GIAs

16.4.5.1 Bypass with Proximal Ligation

As illustrated in Cases 3 and 4, giant proximal and cavernous ICA aneurysm usually treated with proximal ligation of ICA. Need of bypass decided by cross circulation and balloon occlusion test during cerebral angiogram. If poor cross circulation through A1, then bypass is mandatory before proximal ligation of ICA (Figs. 16.3 and 16.4).

16.4.5.2 Trapping of Aneurysm with Bypass

Surgically accessible giant aneurysm, fusiform aneurysm, dissecting aneurysm, cervical ICA

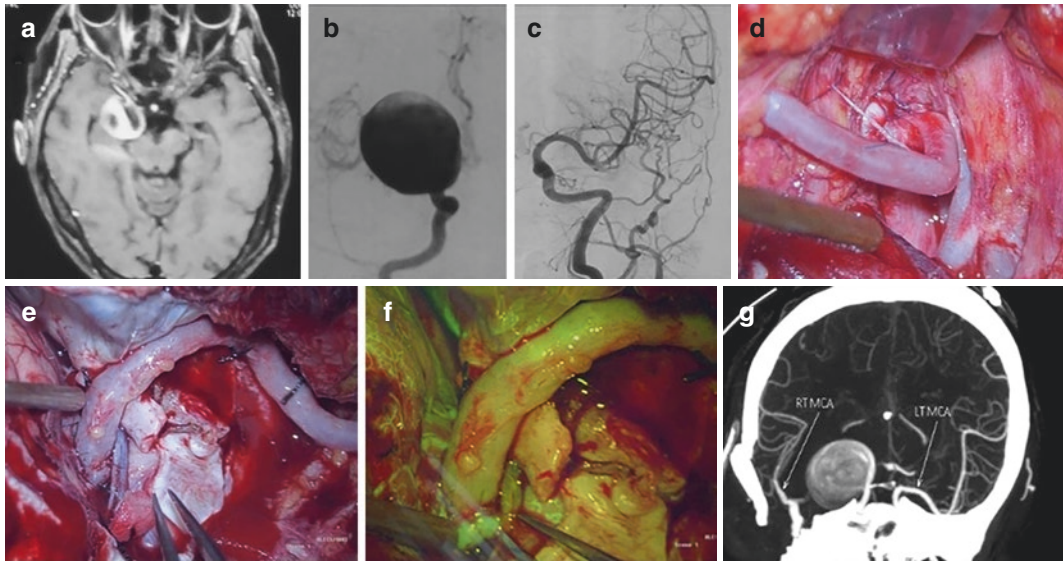


Fig. 16.3 Illustrated Case 3—ICA bifurcation giant aneurysm treated with high flow bypass. A 55-year-old female presented with chronic headache, change in behaviour and acute onset of left upper limb weakness. MRI was suggestive of right ICA bifurcation giant aneurysm (**a**). DSA suggested right ICA bifurcation giant wide-neck aneurysm with felling of both ACA from right ICA (**b**). Left ICA injection suggested hypoplastic left A1 (**c**). Patient underwent right ECA to M1 high flow bypass with saphenous vein graft [ECA-SVG end to side anastomosis (**d**), SVG-M1 end to side anastomosis (**e**, **f**). Patient recovered well. Post-operative CT angiogram shows a patent bypass (**g**). As planned patient underwent second stage procedure stenting of right ICA to right A1 to exclude aneurysm, but this attempt failed and resulted in a fatal rupture of the aneurysm

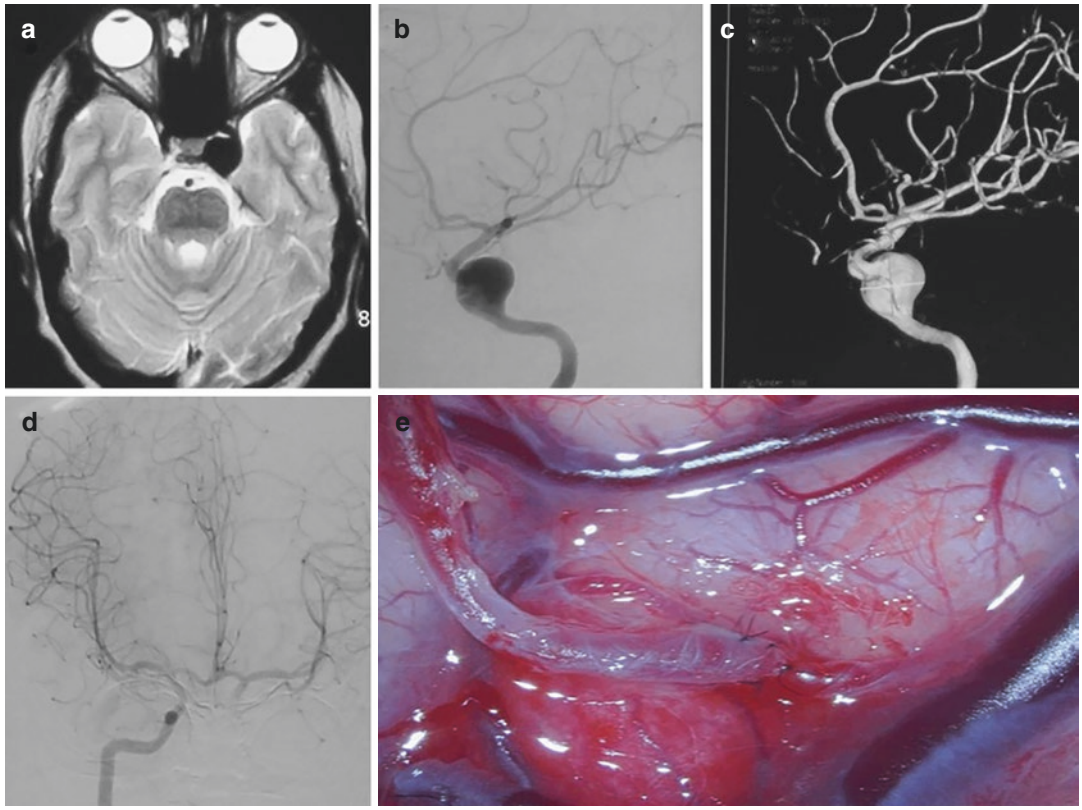


Fig. 16.4 Illustrated Case 4—Low flow bypass with proximal ICA occlusion in Cavernous ICA aneurysm. A 10-year-old girl presented with chronic headache. On evaluation MRI brain revealed left cavernous ICA aneurysm (**a**). DSA was suggestive of left cavernous ICA giant aneurysm feeding from left side (**b**, **c**). There was good cross circulation during right ICA injection (**d**). Patient underwent left STA-MCA low flow bypass (**e**). On third post-operative day, patient underwent left ICA proximal ligation at cervical level. Patient recovered well without any complication

giant aneurysm with poor cross circulation are managed by surgical bypass followed by trapping of aneurysm. During DSA retrograde filling of Cavernous ICA aneurysm indicates trapping of aneurysm, which may later lead to enlargement of aneurysm, illustrated case 5 (Fig. 16.5).

16.5 Endovascular Treatment for GIA

Endovascular flow diversion is a paradigm shift for aneurysm treatment. While coil embolization aims to completely occlude the aneurysm at the time of treatment. Flow diversion is an entirely endoluminal treatment that requires no device to enter the aneurysm itself. Tightly braided flow-diverting stents (FDSs) have low porosity and provide 30%–35% wall coverage, which directs blood flow along the parent artery and away from the aneurysm. Aneurysm occlusion occurs in a delayed fashion, over several weeks or months, as endothelialization occurs, neo-intimal growth proceeds across the aneurysm neck and the parent artery remodels around the FDS [18].

The Pipeline Embolization Device was approved by the FDA in 2011 and by the European Medicines Agency in 2008 for the

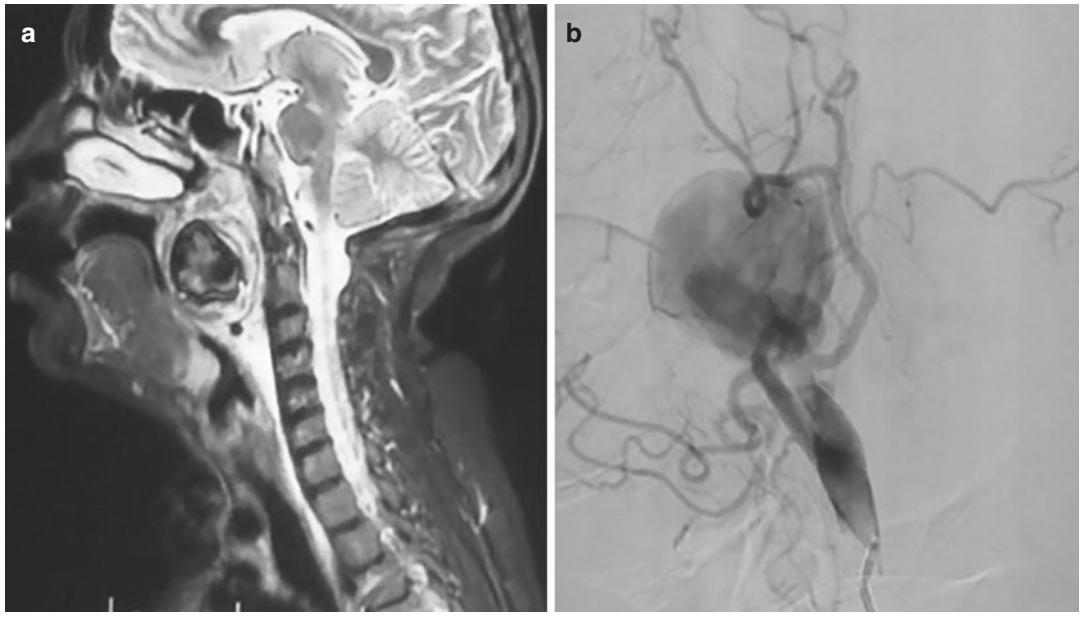


Fig. 16.5 Illustrated Case 5—Trapping of aneurysm and surgical bypass. A 52-year-old female presented with difficulty in swallowing, slurring of speech and cervical bruit. MRI neck and brain revealed cervical ICA giant aneurysm (**a**). DSA was suggestive of right cervical ICA giant aneurysm with no cross circulation (**b**). Patient underwent left side high flow bypass with SVG between CCA to M1 and trapping of cervical ICA aneurysm

treatment of large or giant, wide-neck intracranial aneurysms of the internal carotid artery from the petrous to the superior hypophyseal segments [23]. Flow-diverting stent has not yet been approved for use in the posterior circulation, treatment of aneurysmal subarachnoid haemorrhage or in the anterior circulation beyond the internal carotid artery superior hypophyseal segment.

16.5.1 Complications of Endovascular Management of GIAs

The Flow Diversion in the Treatment of Intracranial Aneurysm Trial (FIAT), conducted in Canada, was stopped prematurely because patients allocated to flow diversion did not reach the primary outcome of angiographic occlusion at 3–12 months and were dead or dependent at 3 months because of procedural complications. These complications included device migration, arterial rupture, delayed aneurysm rupture, distal intraparenchymal haemorrhage and delayed primary vessel occlusions. Although the popularity of flow diversion is increasing, coil embolization remains a suitable treatment for many saccular aneurysms and future trials are needed to compare directly the safety and efficacy of these two modalities [24].

Thromboembolic and Haemorrhagic Risks of Flow Diversion Antiplatelet therapy is required with flow diversion to prevent thromboembolic complications and in-stent stenosis until vessel remodelling occurs and epithelial growth covers the stent lumen. Thromboembolic or haemorrhagic complications occur in 4% of cases of flow diversion [6]. Complications usually include

ischaemic stroke due to device occlusion, thromboemboli, ipsilateral intraparenchymal haemorrhages or aneurysm rupture. Others have noted morbidity and mortality rates between 8% and 10% [25]. Meta-analysis of distal aneurysms has recently suggested reasonably high rates of occlusion (70%) with marked complication rates (20%) [26].

Delayed Aneurysm Occlusion Flow diversion does not result in immediate aneurysm occlusion or complete dome protection. Until aneurysm thrombosis occurs, the aneurysm remains unsecured to an extent, and the risk of rerupture remains real because of the need for antiplatelet treatment, especially in patients at risk of periprocedural bleeding complications.

FDS Migration One of the disadvantages with flow diversion is that it is difficult, if not impossible, to retrieve malpositioned stents after deployment. A failed or malpositioned FDS can obstruct blood flow and be a source of thromboemboli. In some instances, FDS placement may paradoxically induce aneurysm growth and mural destabilization if thrombus formation occurs at a rate faster than it is degraded [27]. In cases of FDS failure, open surgery using bypass with or without parent artery occlusion is a bailout option.

16.5.2 Comparison Between Management Strategies for Complications and Clinical Outcomes

Unruptured Aneurysms A meta-analysis suggested that overall endovascular treatment-related complications reported in various studies were 30% and after reconstructive (coiling/BAC, SAC, flow diversion alone, and flow diversion plus coiling) and deconstructive treatments (parent artery occlusion). Similarly, permanent complications were higher among the reconstructive group (15% versus 8.6%). Most complications were related to ischaemic events (15% and 11% among reconstructive and deconstructive groups, respectively). Worsening of mass effect was comparable between reconstructive and deconstructive treatments (1.7% versus 3.5%). Finally, the rate of haemorrhagic complications was higher after reconstructive techniques (6%) compared with PAO (2%). During follow-up, mass effect symptoms were improved in about 48% of patients after reconstructive treatments and in 77% of patients after PAO [3].

Ruptured Aneurysms The overall rates of complications and permanent complications were slightly higher after PAO (38% and 29%) compared with coiling (34% and 20%). The incidence of ischaemic events was slightly higher after deconstructive compared with reconstructive treatments (33% versus 18.8%), as was worsening of mass effect (14% versus 7%). Haemorrhagic complications were higher after coiling compared with PAO (17% versus 9%). Improvement of compressive symptoms was reported in 24% of reconstructive cases, whereas no data were available among the deconstructive group.

Illustrated cases 6, 7 and 8 depict complications like ICA occlusion post flow diverter, intracranial bleed after coiling and acute infarct post flow diverter, respectively (Figs. 16.6, 16.7 and 16.8).

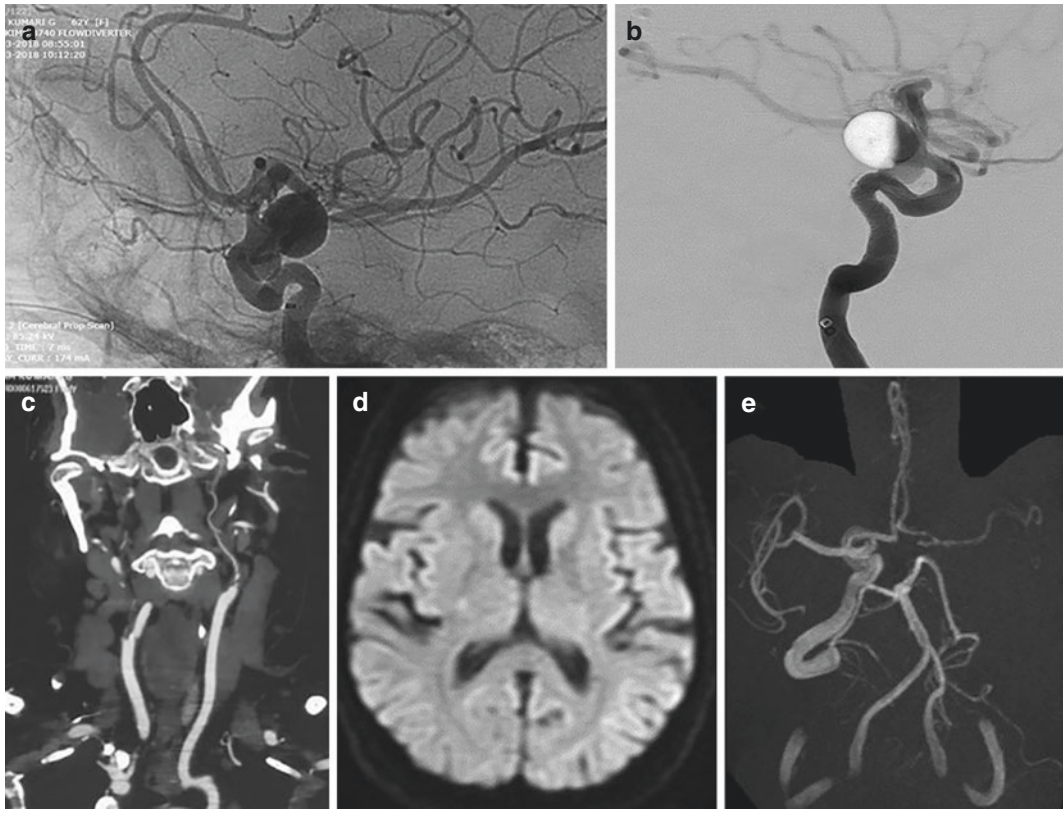


Fig. 16.6 Illustrated Case 6—Post flow diverter ICA occlusion. 65 years female presented with chronic headache and retro-orbital pain. DSA was suggestive of left supraclinoid GIA (**a**). Patient underwent flow diverter placement (**b**). Subsequently, patient presented with symptoms of TIA and a CT angiogram confirmed complete occlusion of left ICA (**c**). MRI DWI did not reveal infarct perhaps due to good cross circulation (**d**, **e**)

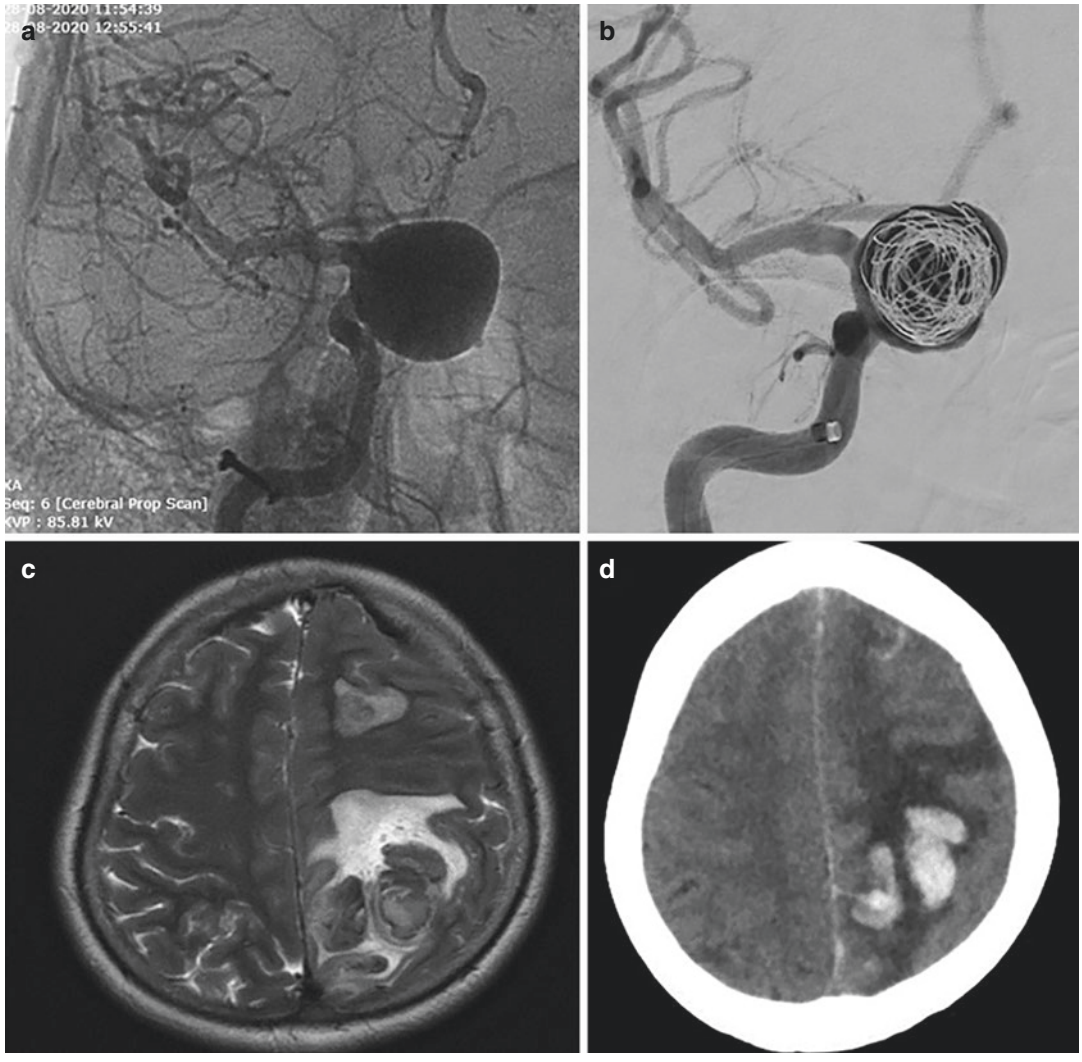


Fig. 16.7 Illustrated Case 7—Post coiling intracranial bleed. 49 years female with left cavernous ICA unruptured giant aneurysm underwent coiling (**a**, **b**). On the second post-operative day, patient complained of drowsiness and headache with right-sided weakness. MRI brain suggested left frontal parietal IC bleed (**c**). The patient was managed medically and a follow-up serial CT brain-post flow diverter day 5 (**d**). Patient partially recovered from right side weakness

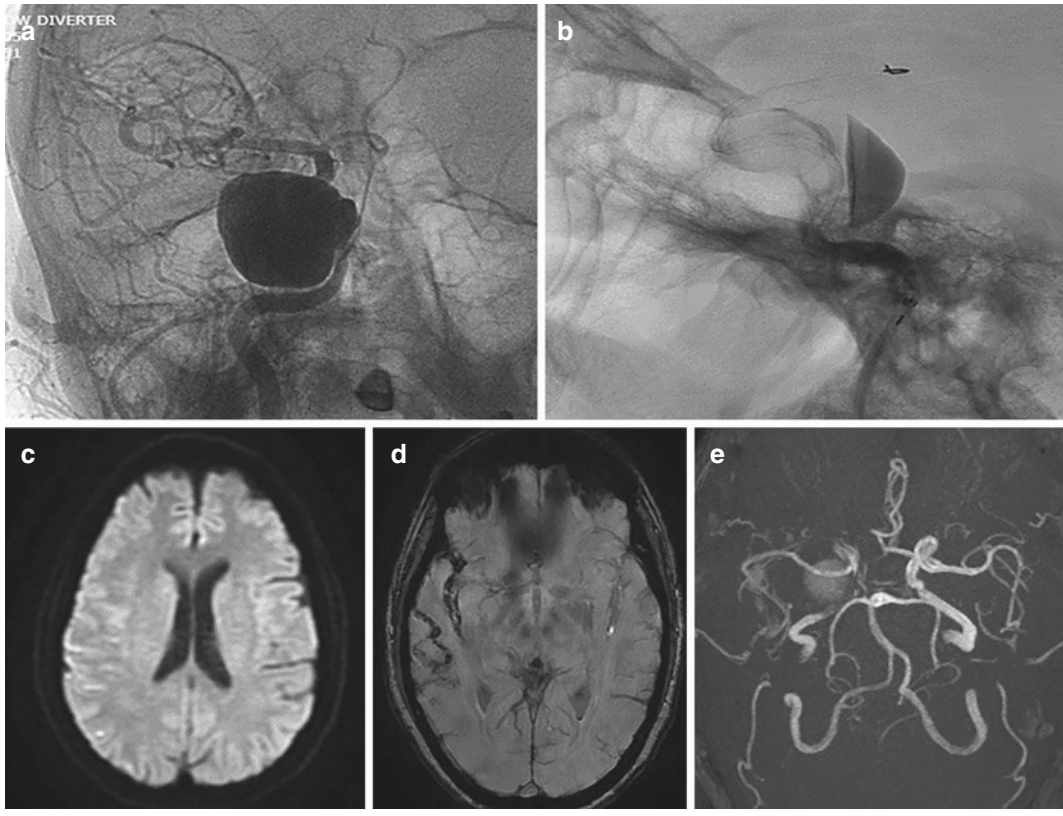


Fig. 16.8 Illustrated Case 8—Post flow diverter bleed and acute infarct. 59 years female with right cavernous giant ICA unruptured aneurysm underwent flow diverter placement (**a**, **b**). On post-operative day 4, patient developed acute headache and left-sided weakness. MRI brain was suggestive of mild SAH and infarct in MCA distribution (**c**–**e**).

16.6 Conclusion

Anatomical factors like wide neck distort the anatomy of parent and branch arteries at the base of GIAs making it dangerous to coil and difficult to obliterate completely, leading to the advent of endovascular treatment including flow diverter. Flow diversion may yet offer some meaningful treatment options, particularly with basilar trunk and some basilar apex aneurysms where surgical morbidity rates are particularly high. However, level 4 evidence for both flow diversion and bypass techniques suggests that neither is superior, laying emphasis for further studies. Therefore, microsurgical aneurysm occlusion still appeals to many patients who prefer a single, definitive and durable therapy.

References

1. Walcott BP, Stapleton CJ, Choudhri O, Patel AB. Flow diversion for the treatment of intracranial aneurysms. JAMA Neurol. 2016 Aug 1;73(8):1002–8. https://doi.org/10.1001/jamaneurol.2016.0609.
2. Pandey AS, Gemmete JJ, Wilson TJ, et al. High subarachnoid hemorrhage patient volume associated with lower mortality and better outcomes. Neurosurgery. 2015;77:462–70.
3. Cagnazzo F, Mantilla D, Rouchaud A, Brinjikji W, Lefevre P-H, Dargazanli C, Gascou G, Riquelme C, Perrini P, di Carlo D, Bonafe A, Costala V. Endovascular treatment of very large and giant intracranial aneurysms: comparison between reconstructive and deconstructive techniques—a meta-analysis. AJNR Am J Neuroradiol. 2018;39:852–8.
4. Lawton MT. Basilar apex aneurysms: surgical results and perspectives from an initial experience. Neurosurgery. 2002;50:1–8.
5. Jafar JJ, Russell SM, Woo HH. Treatment of giant intracranial aneurysms with saphenous vein extracranial-to-intracranial bypass grafting: indications, operative technique, and results in 29 patients. Neurosurgery. 2002;51:138–44.
6. Sharma BS, Gupta A, Ahmad FU, Suri A, Mehta VS. Surgical management of giant intracranial aneurysms. Clin Neurol Neurosurg. 2008;110(7):674–81.
7. Sughrue ME, Saloner D, Rayz VL, Lawton MT. Giant intracranial aneurysms: evolution of management in a contemporary surgical series. Neurosurgery. 2011;69:1261–70.
8. Chalouhi N, Tjoumakaris S, Gonzalez LF, et al. Coiling of large and giant aneurysms: complications and long-term results of 334 cases. AJNR Am J Neuroradiol. 2014;35:546–52.
9. Jahromi BS, Mocco J, Bang JA, et al. Clinical and angiographic outcome after endovascular management of giant intracranial aneurysms. Neurosurgery. 2008 Oct;63(4):662–74.
10. Lopes DK, Jang DK, Cekirge S, et al. Morbidity and mortality in patients with posterior circulation aneurysms treated with the pipeline embolization device: a subgroup analysis of the international retrospective study of the pipeline embolization device. Neurosurgery. 2018;83:488–500.
11. Wang CB, Shi WW, Zhang GX, et al. Flow diverter treatment of posterior circulation aneurysms: a meta-analysis. Neuroradiology. 2016;58:391–400.
12. Chalouhi N, Tjoumakaris S, Dumont AS, et al. Treatment of posterior circulation aneurysms with the pipeline embolization device. Neurosurgery. 2013;72:883–9.
13. Gaberel T, Borha A, di Palma C, et al. Clipping versus coiling in the management of posterior communicating artery aneurysms with third nerve palsy: a systematic review and meta-analysis. World Neurosurg. 2016;87:498–506.
14. Sughrue ME, Saloner D, Rayz VL, Lawton MT. Giant intracranial aneurysms. Neurosurgery. 2011;69:1261–71.
15. Al-Mufti F, Amuluru K, Gandhi CD, et al. Flow diversion for intracranial aneurysm management: a new standard of care. Neurotherapeutics. 2016;13:582–9.
16. Hoh BL, Putman CM, Budzik RF, Carter BS, Ogilvy CS. Combined surgical and endovascular techniques of flow alteration to treat fusiform and complex wide-necked intracranial aneurysms that are unsuitable for clipping or coil embolization. J Neurosurg. 2001;95:24–35.
17. Isla A, Alvarez F, Roda JM, Muñoz J, Morales C, Garcia Blazquez M. Serpentine aneurysm: regrowth after a superficial temporal artery-middle cerebral artery bypass and internal carotid artery ligation: case report. Neurosurgery. 1994;34:1072–4.
18. Mazur MD, Taussky P, Park MS, et al. Contemporary endovascular and open aneurysm treatment in the era of flow diversion. J Neurol Neurosurg Psychiatry. 2018;89:277–86. https://doi.org/10.1136/jnnp-2016-314477.
19. Linskey ME, Jungreis CA, Yonas H, et al. Stroke risk after abrupt internal carotid artery sacrifice: accuracy of preoperative assessment with balloon test occlusion and stable xenon-enhanced CT. AJNR Am J Neuroradiol. 1994;15:829–43.
20. Sanai N, Zador Z, Lawton MT. Bypass surgery for complex brain aneurysms: an assessment of intracranial-intracranial bypass. Neurosurgery. 2009;65:670–83.
21. Sekhar LN, Kalavakonda C. Cerebral revascularization for aneurysms and tumors. Neurosurgery. 2002;50:321–31.

22. Kalani MY, Rangel-Castilla L, Ramey W, et al. Indications and results of direct cerebral revascularization in the modern era. World Neurosurg. 2015;83:345–50.
23. Walcott BP, Stapleton CJ, Choudhri O, et al. Flow diversion for the treatment of intracranial aneurysms. JAMA Neurol. 2016;73:1002–8.
24. Turk AS, Martin RH, Fiorella D, et al. Flow diversion versus traditional endovascular coiling therapy: design of the prospective LARGE aneurysm randomized trial. AJNR Am J Neuroradiol. 2014;35:1341–5.
25. Raphaeli G, Collignon L, De Witte O, et al. Endovascular treatment of posterior circulation fusiform aneurysms: single-center experience in 31 patients. Neurosurgery. 2011;69:274–83.
26. Yan Y, Zhu D, Tang H, et al. Safety and efficacy of flow diverter treatment for aneurysm in small cerebral vessels: a systematic review and meta-analysis. World Neurosurg. 2018;115:54–64.
27. Bowers CA, Taussky P, Park MS, et al. Rescue microsurgery with bypass and stent removal following pipeline treatment of a giant internal carotid artery terminus aneurysm. Acta Neurochir. 2015;157:2071–5.

Training Protocols for Neuroendovascular Surgery

17

Vikram Karmarkar, Rakesh Singh, Krishna Shroff, and C. Deopujari

Abstract

There is an increasing adoption of neuroendovascular surgery in clinical practice worldwide, which represents an important paradigm shift in the management of patients with diseases of the vasculature of the central nervous system. As newer generations of neuroendovascular "specialists" are trained, they must practice their specialty at a certain basic standard that ensures competent care and the ability to prevent and also deal with complications as and when they may arise. Therefore, there is an increasing need for the adoption of standardized training protocols in the field. Training for neuroendovascular procedures is necessary for the safe conduct of procedures and to advance the field. In this chapter, we shall discuss the current needs and protocols, taking certain prototypical training guidelines into account.

Keywords

Neuroendovascular · Surgery · Training Neurointervention · Interventional neuroradiology

V. Karmarkar (✉) · K. Shroff · C. Deopujari
Department of Neurosurgery, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

R. Singh
Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

17.1 Introduction

Neuroendovascular surgery (or NES) (also called interventional neuroradiology/endovascular neurointervention/neurovascular intervention) is the medical subspecialty that uses minimally invasive catheter-based technology and radiological imaging combined with clinical and technical expertise to diagnose and treat diseases of the vasculature of the central nervous system, including the head, neck, and spine. In specific clinical scenarios, endovascular procedures have augmented the efficacy of, and also replaced, open surgical operations. There is increasing adoption of neuroendovascular surgery in clinical practice worldwide, which represents an important paradigm shift in the management of patients with diseases of the vasculature of the central nervous system. As newer generations of neuroendovascular "specialists" are trained, they must practice their specialty at a certain basic standard that ensures competent care and the ability to prevent and also deal with complications as and when they may arise. Therefore, there is an increasing need for the adoption of standardized training protocols in the field.

Vascular pathology and its repercussions on the central nervous system may frequently be devastating. Hence the physician involved in treating these problems needs to focus on prevention, salvage, and augmentation of nervous

X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_17

system function. Training for any skills based specialty consists of many interlapping processes.

The most basic requirements are cognitive skills. In the beginning, the trainee must be familiar and conversant with the unique anatomy, physiology, and pathological aspects. In this specialty, this would entail knowledge of the nervous system, its function, its vascular connections and the pathologies associated with the vasculature which affect the nervous system. An important point, in our opinion, is to focus on the neurological outcome for prevention, mitigation, salvage, or augmentation of function and not just successful radiological outcomes.

Physicians coming to train in this specialty typically come from either radiology or a neurosurgical and, more recently, from a neurology background. In different parts of the world, the proportions vary. Hence training must factor for this diversity. A trained neuroendovascular specialist has to be able to work in a team with the related specialties of traditional neurosurgery, neurology, and neurocritical care specialists.

The basic technical skills needed are similar to endovascular techniques used in other systems in the body. Neuroendovascular skills may differ because of the differences and unique characteristics in the vasculature of the central nervous system. Familiarity with and ease of use of various devices, catheters, and embolics, need to be introduced and mastered. In this chapter, we shall discuss the current needs and protocols, taking certain prototypical training guidelines into account. Many nations have their guidelines, which has overlap. Some systems are discussed below.

17.2 Training Protocols

17.2.1 Europe

The European guidelines for training in the field of neuroendovascular surgery (interventional neuroradiology) have been have been developed by a working group of the European Society of Neuroradiology (ESNR) and the European Society of Minimally Invasive Neurological Therapy (ESMINT) on the initiative and under the umbrella of the Division of Neuroradiology/Section of Radiology of the European Union of Medical Specialists (UEMS) [1].

17.2.1.1 The Program

The primary goal of the training program, as laid down in the guidelines, is to provide the trainee with a broad knowledge base, the procedural skills and experience, professional judgment, and self-criticism required to practice interventional neuroradiology safely [1].

National professional licensing bodies, or in their absence, a European association/society/organization (UEMS or European subspecialty societies—for example, ESNR, ESMINT or boards cooperating with UEMS) provide a general program for accrediting teaching institutions. This is a voluntary procedure aimed at securing high quality and good standards of practice in the teaching program [1].

The teaching program must be within a clinical neuroscience institution, or a network of such institutions, with all the appropriate related specialties represented. The patient population at the institution must have a diversity of illnesses (brain, head and neck, spine) from which broad experience in interventional neuroradiology can be obtained by the trainees [1].

Training could be limited to a specific area of interventional neuroradiology—for example, spinal interventions or endovascular treatment of ischemic stroke, including the management of complications, provided that the minimum annual activity for the specific area (as outlined in the section on requirements/criteria for institutions), is fulfilled and site conditions and operational guidelines are guaranteed by the training institution, according to the ESNR/ESMINT/UEMS guidelines for standards of practice in interventional neuroradiology [1].

For training that is limited to specific areas of interventional neuroradiology, such as endovascular treatment of ischemic stroke, the requirements of existing multi-society global recommendations should be applied [1]. Recommendations include “Training guidelines

for endovascular ischemic stroke intervention: an international multi-society consensus document [2] and the Standards of practice in acute ischemic stroke intervention: international recommendations [3]."

17.2.1.2 Requirements/Criteria for Trainees

Trainees must have a valid license to practice medicine within their respective countries, which must be recognized at the country/countries where training in interventional neuroradiology is to take place [1].

Before entering interventional neuroradiology training, trainees are required to be qualified physicians in a training program of a medical specialty or have accomplished training in a recognized medical specialty [1].

The education and training needed to become a specialist physician with a particular qualification in INR consists of [1]

- 12 Months *mandatory* dedicated training in diagnostic neuroradiology.
- 24 Months *mandatory* dedicated training in interventional neuroradiology
- 12 Months *recommended* clinical training in neuroscience.

Depending on previous training, these durations may be reduced as credit is given for previous training and clinical skills. Assessment of previous training and clinical skills, and evaluation of the remaining training time has been laid out to be the responsibility of the director and each of the co-directors of the program after thorough and careful assessment of previous training and experience [1].

Trainees should keep a trainee portfolio containing details of previous training posts, examinations passed, lists of publications and presentations at meetings, courses attended, cumulative procedural totals, and copies of assessment forms from the different training periods [1].

Trainees are to familiarize themselves with knowledge pertaining to neuroanatomy (with focus on vascular anatomy) and neuroembryology (with focus on vascular embryology), spine biomechanics, neurobiology including molecular genetics, neurophysiology, and biology of pain, pathology with a focus on vascular diseases, including inflammatory and autoimmune diseases and the natural history of neurovascular diseases [1].

Trainees are to be capable of taking a clinical history and performing a neurological examination and to communicate with patients and relatives, fellow residents, other clinicians and hospital staff and administration [1].

Trainees must be competent in the selection of various treatment options (indications/contraindications) based on knowledge and communication in a multidisciplinary environment and must be capable of carrying out appropriate pre-procedural and peri-procedural management such as patient preparation before the procedure, intraprocedural maintenance of homeostasis and organization of follow-up procedures. They must also possess adequate knowledge of the relevant clinical pharmacology, including drug–drug interactions, pre- and post-procedural drug management, and also neurointensive care [1].

Trainees must also possess adequate knowledge of radiation physics, radiation biology, and radiation protection [1].

Trainees must possess adequate knowledge of the technical aspects, the proper selection, and the interpretation of various neuroradiological studies, including digital subtraction angiography, CT, MRI, and ultrasound, including the management aspects of various contrast materials such as their interactions and complications [1].

Trainees are expected to know about appropriate pre- and post-procedural patient management, relevant clinical neuropharmacology, as also with the technical aspects of the procedure (such as percutaneous access to the vascular system, the head and neck compartments, and the spine, the use of delivery systems like needles, catheters, wires, and rinsing systems, skillful management of radiological equipment, post-procedural management of the puncture site, procedure risks and limitations and complication management) [1].

Technical interventional neuroradiology expertise to be attained [1].

Percutaneous Treatments

Each trainee should perform *50 spine procedures as the first operator*, including a case mix of disk treatments, epidural spine treatments, nerve blocks, facet joint treatments, and vertebral bone augmentation treatments.

Neuroendovascular Procedures

- Each trainee should perform *100 digital subtraction angiography scans as the first operator before starting interventional endovascular* procedures.
- Each trainee should participate in *a minimum of 150 interventional endovascular procedures, of which in at least in half of the procedures, the trainee is the principal operator*. The *diversity* of these procedures should include endovascular treatment of aneurysms, acute ischemic stroke, extracranial, and intracranial angioplasty/stenting, embolization of brain arteriovenous malformation and dural arteriovenous fistula, and external carotid embolization.
- Each trainee should participate in a *minimum of 50 cases of revascularization and 50 cases of embolization* (*in either group in at least half of the procedures as the principal operator*).
- If the trainee does not complete the required number of procedures during the training period, the training should be prolonged accordingly.

The guidelines also state that trainees should have a firm knowledge of experimental design, performance and interpretation of results and basic knowledge of medical statistics. They are advised to participate in research projects conducted by the faculty or other trainees or to undertake projects as principal investigators and are encouraged to submit their work for presentation at national and international meetings. They should also understand the ethical aspects of research and what constitutes a conflict of interest [1].

Trainees are to keep a personal logbook for documentation of their skills and experience acquired during training. The logbook should be based on the picture archiving and communication (PACS) system and the radiology information system (RIS) of the clinic [1] and should state whether the trainee acted under supervision or was self-responsible. Trainees will have to demonstrate that they have participated in a wide spectrum of procedures which should include a balance of supervisor-assisted procedures and procedures performed personally under supervision. The logbook is to be produced by them at their examinations [1].

Trainees are to undergo evaluation of their progress (which includes assessment of the trainee's knowledge, technical skills, attitudes, and interpersonal relationships, decision-making skills and clinical management skills) at least twice a year during their program. This is to be conducted by the program director in consultation with the co-directors and the faculty [4].

17.2.1.3 Requirements/Criteria for Institutions

The optimal training program in interventional neuroradiology must take place and be organized in a single institution or in a network of institutions/departments in which the interventional neuroradiology unit is the core and is surrounded by clinical and diagnostic neuroscience units, and operating in accordance with the "Standards of practice in interventional neuroradiology: Consensus document from the ESNR/ESMINT/UEMS."

To qualify as a training program, the following conditions must be fulfilled [1]:

- The director and co-directors must have senior appointments in a recognized training institution that may be affiliated with academic institutions. Commercial interests cannot be involved in the organization and scientific content of the training.
- Ideally, the network should be involved in active interventional neuroradiology research.
- There should be ready access to general medical/neuro interventional texts and scientific

journals. Computerized literature search facilities should be available.

- The Interventional neuroradiology core must fulfill the following conditions
  - Interventional neuroradiology *caseload of a minimum of 100 cases/year of endovascular interventions and 50 cases/year of percutaneous spinal interventions*. INR case mix should include a *diversity* of vascular diseases, such as acute ischemic stroke, aneurysms, arteriovenous malformations, dural arteriovenous fistula, and spinal vascular malformations, in the respective percentages according to their prevalence. If accreditation is limited to percutaneous spinal interventions, the minimum caseload is 50 cases/year. If accreditation is limited to endovascular treatment of ischemic stroke, the minimum caseload is 50 cases/year.
  - The faculty of the training program must include *at least two members* practicing interventional neuroradiology.
  - The proportion of INR trainers to trainees must not exceed a *1:1* ratio.

17.2.1.4 Requirements/Criteria for Faculty and the Director of the Program

As laid down in the guidelines, the director of the training program must be an active interventional neuroradiologist certified according to the national regulations or in their absence by the UEMS cooperating European board.

The program director may have a senior academic appointment or a senior leading position as an interventional neuroradiologist in a nonprofit training institution.

The program director coordinates the network that constitutes the training program.

A network co-director should be well experienced and well respected as an interventional neuroradiologist or as a medical specialist in another appropriate specialty such as radiology, neuroradiology, neurosurgery, or neurology.

A director or co-director should participate in appropriate continuing medical education/continuing professional development activities according to the national regulations.

It is the responsibility of the program director and co-directors for enforcing the training charter and for selecting and supervising the trainee and faculty members.

The program director is expected to ensure that the program meets the required academic standard.

The program director should seek or need (if available) the national accreditation of the program by a national authority or the respective national neuroradiological professional.

17.2.2 USA

The guidelines for training in neuroendovascular surgery in the USA have been laid down by the Joint Section of Cerebrovascular Surgery for the American Association of Neurological Surgeons and Congress of Neurological Surgeons (JSCVS), the Society of NeuroInterventional Surgery (SNIS), and the Society of Vascular and Interventional Neurology (SVIN), jointly; to standardize and optimize the training program accreditation and individual certification processes for neuroendovascular surgery under the aegis of the CAST (Committee for Advanced Subspecialty Training) program of the Society of Neurological Surgeons (SNS) [5].

17.2.2.1 The Program

Participating societies connected to neuroendovascular surgery, including neurosurgery, neuroradiology, and neurology, have also agreed within an Accreditation Council for Graduate Medical Education (ACGME)–sponsored training curriculum and summary document [6]. Before starting a neuroendovascular surgery fellowship, this document requires that a trainee must complete an ACGME-accredited residency in neurosurgery, neurology, or radiology. The document also clarifies the need for preliminary training in stroke, critical care, and neuroradiology required for neurologists and radiologists [5].

The neuroendovascular surgery (NES) training program must foster a rich educational environment that includes frequent interactions between open vascular neurosurgery, critical

care, stroke neurology, neuroradiology, and state-of-the-art neuroimaging. Trainees must have the opportunity to participate in research and other scholarly activities. Each program must ensure that the learning objectives of the program are not compromised by excessive reliance on trainees to fulfill service obligations [5].

The Neuroendovascular Surgery Advisory Committee (NESAC) will operate through the CAST infrastructure to advise and assist CAST in the development and implementation of guidelines for accreditation of training programs and certification of individuals. NESAC comprises three persons from each of the neuroscience specialties of neurosurgery, neurology, and neuroradiology, working in concert with the CAST Chairman and Secretary.

17.2.2.2 Requirements/Criteria for Trainees

As per the guidelines, neuroendovascular training shall consist of three different phases [5].

1. *Preliminary Specialty Training*
   Each trainee should first fulfill requirements for their respective specialties.

   For neurosurgeons, they must first satisfactorily complete an ACGME-approved residency in neurological surgery and must be eligible for certification by the American Board of Neurological Surgery (ABNS) and must be in good standing in the ABNS.

   For neurologists, they must first satisfactorily complete an ACGME-approved residency in neurology and must be eligible for certification by the American Board of Psychiatry and Neurology and must be in good standing in the American Board of Psychiatry and Neurology. They must also complete an ACGME-accredited Vascular/Stroke Neurology Fellowship including, or in addition to, at least 3 months in the neurointensive care unit, or completion of and certification by a United Council for Neurological Specialties or CAST-approved.

   Neurocritical Care Fellowship.

   For radiologists, they must first satisfactorily complete an ACGME-approved residency in diagnostic or interventional radiology and must be eligible for certification by the American Board of Radiology and must be in good standing in the American Board of Radiology. They must also satisfactorily complete an ACGME-accredited neuroradiology fellowship including, or in addition to, at least 6 months of clinical service in neurological surgery, vascular neurology, or neurocritical care program before entering the advanced year of neuroendovascular surgery fellowship.

   As a result of the foregoing training, the fellowship candidate should have the expected level of competence required to enter neuroendovascular surgery. The candidate should be knowledgeable about the pathophysiology of cerebrovascular disease and skilled in the interpretation of neuroradiological studies. They are also to be well versed in the essentials of the intensive care unit management of neuroendovascular surgery patients, the complexities of anticoagulation and its reversal algorithms, and the manipulations of central and cerebral hemodynamics in patients with cerebral ischemia. They are also to be well versed with the specific management issues in neuroendovascular surgery patients requiring mechanical ventilation, with elevated intracranial pressure requiring clinical or invasive monitoring and with other conditions routinely encountered in an intensive care unit [5].
2. *Pre-Requisite Training*
   Candidates pursuing neuroendovascular surgery training must be technically competent in catheter access and manipulations within the vasculature supplying the brain and spinal cord. They are also expected to have a working knowledge of radiation biology in order to ensure patient and operator safety.

   The specific details of pre-requisite training include

- Performance of *at least 200 catheter-based diagnostic and interventional cerebral angiographic* procedures as a primary operator.
- Demonstrated competency in catheter techniques as validated by the NES Fellowship Program Director.
- ABNS Milestones one to four for cerebrovascular diseases and NES, completed and signed off by both the residency and NES fellowship program directors.

All candidates must demonstrate competency in catheter techniques and must perform *200 catheter-based diagnostic and interventional cerebral angiographic procedures as a primary operator before starting their focused NES training year*, regardless of their primary specialty. In a multi-year neuroendovascular surgery fellowship program, this pre-requisite may be obtained during the first year for any of the specialties [5].

3. *Advanced Neuroendovascular Surgery Training*

The specific details for all primary specialties (neurology, neurosurgery, and neuroradiology) include

- *Twelve continuous months* of a dedicated neuroendovascular surgery fellowship experience, during which the fellow performs a broad spectrum of endovascular procedures as defined by the core-competency requirements, to be performed after completion of their preliminary specialty and subspecialty requirements. For neurosurgeons, the 12-month neuroendovascular surgery fellowship may occur during residency but not before Post Graduate Year 6.
- *A minimum of 250 interventional treatment procedures should be performed as primary operators* to ensure that the trainee is exposed to *diverse* cerebrovascular diseases and the endovascular procedures used in their treatment. As a general guideline, those performed should have a core experience consisting of:
  - Forty aneurysm treatments, including ten presenting with rupture
  - Twenty intracranial embolizations (arteriovenous malformation, arteriovenous fistula, tumor)
  - Twenty-five intracranial or extracranial stent placements (at least five in each category and may include stents or flow diverters for aneurysms)
  - Thirty acute ischemic stroke treatments
  - Ten intracranial infusions (e.g., vasospasm, chemotherapy, and stroke)
  - Ten extracranial embolizations
  - Five spinal angiograms and embolizations

The guidelines state that those candidates who are unable to complete the required interventions during the 12 months should extend their training or seek training at other institutions. The continuity of care must be of sufficient duration, so the trainee is familiar with the natural history of each disease and the outcome of these treatment procedures [5].

17.2.2.3 Requirements/Criteria for Institutions

The institution where the training program is based should have an emergency room, a dedicated neurointensive care unit, ACGME-accredited residency programs in neurology and radiology, and ACGME, United Council for Neurological Specialties, and CAST-accredited fellowship programs in stroke and vascular neurology, neurocritical care, and neuroradiology.

There should also be a robust open surgical neurovascular program, meeting ACGME accreditation requirements at the same institution, a designated Comprehensive Stroke Center, and access to both adult and pediatric patients.

The imaging equipment and procedure rooms must be appropriately equipped and available for all neuroendovascular procedures. Imaging equipment should include biplanar fluoroscopy with digital subtraction and roadmap capability and rotational 3D imaging. The training program

must be hospital based to provide adequate inpatient, outpatient, emergency, and dedicated neurointensive care. Ancillary up-to-date imaging, such as MRI and CT with perfusion analysis, and ultrasound, are also necessary.

The environment at the institution should be education friendly and include frequent interactions between open vascular neurosurgery, critical care, stroke neurology, neuroradiology, and state-of-the-art neuroimaging. Trainees should be given the opportunity to participate in research and other scholarly activities. Each program must ensure that the learning objectives of the program are not compromised by excessive reliance on trainees to fulfill service obligations. Didactic and clinical education must have priority in the allotment of fellows' time and energy [5].

17.2.2.4 Requirements/Criteria for Faculty and the Director of the Program

A neuroendovascular surgery fellowship must have a fellowship *program director or co-director* who:

- Is certified by CAST and the American Board of Neurological Surgery (ABNS), American Board of Radiology, or the American Board of Psychiatry and Neurology.
- Has fulfilled all other respective specialty and subspecialty requirements, including Maintenance of Certification (MOC).
- Has special expertise in neuroendovascular surgery, with his/her practice concentrated in this field.
- Is appointed or co-appointed by and responsive to the Chair of the sponsoring ACGME-accredited program in neurological surgery, in consensus with the chairs of the ACGME programs in neurology and radiology if these specialties are represented as faculty in the CAST neuroendovascular surgery fellowship program. [5]

Trainee and faculty evaluations must be performed regularly and reviewed by the sponsoring CAST fellowship program director and any other appropriate institutional review committee to ensure the educational efficacy of the neuroendovascular surgery program.

The program must include *at least two faculty members* with special expertise in neuroendovascular surgery who are board-certified or tracking for certification by the ABNS or certified by the American Board of Radiology or American Board of Psychiatry and Neurology and possess all other additional required educational qualifications as determined by CAST and its NESAC. To ensure adequate teaching, supervision, trainee evaluation, and their academic progress, the trainee-to-faculty ratio must be *at least two* full-time neuroendovascular surgery faculty for the first graduating trainee completing the training program each year. More faculty members will need to be recruited to gain additional numbers of CAST-approved fellowship spots.

17.2.3 India

In India, the standards of training in neuroendovascular surgery have only recently (2019) been set by the National Board of Examinations, New Delhi, as a two-year post-doctoral fellowship program in Neurovascular intervention.

17.2.3.1 The Program

The objectives of the training program for the candidates are that they should [7]

- Understand symptomatology and signs of diseases that are amenable to neurovascular intervention.
- Perform basic neurological examination to evaluate patients with these disorders.
- Understand the pathophysiology and natural history of these disorders

- Understand the basics of imaging modalities, radiation physics and radiation biology and integrate information available from imaging studies and apply it to their practice.
- Communicate effectively with their patients and their relatives, and other doctors and colleagues.
- Know the indications and contraindications of the procedures in neuro intervention.
- Be well versed with the clinical and technical aspects of the procedures.
- Accurately report diagnostic and follow-up Cerebra Digital Subtraction Angiograms as well as Neuro Interventional procedures.
- Discuss medical and surgical alternatives to the neuro intervention procedures.
- Be competent in the pre- and peri-procedural management of patients undergoing neurointerventional procedures.
- Know how to prevent, recognize, and manage complications associated with these Neuro Interventional procedures.
- Handle neurointensive care management in consultation with Neuro-intensivists.

The program is a post-doctoral fellowship program (FNB) of 2 years duration.

17.2.3.2 Requirements/Criteria for Trainees

Candidates eligible to enter into the training program in the country are neurologists, neurosurgeons, and neuroradiologists. Accordingly, they must be in possession of recognized DM/DNB Neurology, MCh/DNB Neurosurgery and DM Neuroradiology qualifications, respectively. They must appear for an entrance examination and must qualify as per the rules and norms of the National Board of Examinations (NBE), New Delhi.

Candidates are put through the following rotations during their 2-year training period (depending upon their primary specialty).

Area of posting	Background qualification of trainee		
	Neuroradiology	Neurosurgery	Neurology
Neuro imaging	NA	1 month	2 weeks
Neurosurgery OT	2 weeks	NA	2 weeks
Neurology	2 weeks	2 weeks	NA
Neuro ICU	2 weeks	NA	NA
Other recognized Center for training in neurovascular intervention	1 month	1 month	1 month

At the end of their training period, candidates must appear for and pass the exit examination to be awarded the FNB Neurovascular intervention [7].

17.2.3.3 Requirements/Criteria for Institutions

The institution where training in neuro intervention is to be provided should have total beds in conformity with existing NBE norms [7].

The institute should have an in-house Neurology, Neurosurgery, and Neuroradiology set up. The requirement of minimum beds in parent super-specialty departments (Neurology/Neurosurgery) should be fulfilled [7].

The department should attend the minimum required patient load for the program as under [7]:

- *At least 100 Diagnostic Cerebral and Spinal Angiograms per annum.*
- *At least 50 Therapeutic Neurovascular Interventions per annum,* including the following:
  - Cerebral Thrombolysis—Arterial and Venous
  - Internal Carotid & External Carotid Angioplasty and Stenting

- Endovascular treatment of brain and spine Aneurysm
- Endovascular treatment of AVM, Dural fistulas and other malformations of brain and spine. Balloon test occlusion
- Pre-Op embolization
- Inferior Petrous sinus sampling
- Percutaneous embolization

17.2.3.4 Requirements/Criteria for the Program Personnel

The department should have *at least two full-time consultants*. One of them should be a Senior Consultant whereas the other consultant may be a Junior Consultant, meeting the criteria as outlined below:

Senior Consultant: Should have a *minimum of 5 years of exclusive experience* in neurovascular intervention *after having qualified* MCh/DNB/DM or equivalent post-doctoral qualification in either *Neurosurgery or Neurology or Neuroradiology*; alternatively, a *minimum of 10 years of exclusive experience* in neurovascular intervention *after having qualified* MD/DNB or equivalent in the specialty of *Radiodiagnosis*. The consultant should have supportive documentary evidence for his/her exclusive experience in the field of neurovascular intervention.

Junior Consultant: Should have a *minimum of 2 years of exclusive experience* in neurovascular intervention *after having qualified* MCh/DNB/DM or equivalent post-doctoral qualification in either *Neurosurgery or Neurology or Neuroradiology*; alternatively, a *minimum of 5 years of exclusive experience* in neurovascular intervention *after having qualified* MD/DNB or equivalent in the specialty of *Radiodiagnosis.* The consultant should have supportive documentary evidence for his/her exclusive experience in the field of neurovascular intervention.

Senior Residents: Two senior residents are *desirable* in the department. They must be in possession of a recognized degree qualification in the specialty of General Medicine or General Surgery or Radiology. The degree should not have been awarded more than 60 months earlier than the date of filing the application. Those in possession of an MCh/DNB/DM degree in Neurosurgery or Neurology or Neuroradiology shall be considered as senior residents in the department till they become eligible to qualify as Junior Consultants, i.e., upto 2 years post-MCh/DNB/DM [7].

The Indian system differs in that there is currently no central body to oversee the processes. This is bound to change in the near future as the training programs become more streamlined.

17.3 Conclusions

Training for neuroendovascular procedures is necessary for the safe conduct of procedures and to advance the field.

References

1. Sasiadek M, Kocer N, Szikora I, et al. Standards for European training requirements in interventional neuroradiology guidelines by the Division of Neuroradiology/Section of Radiology European Union of Medical Specialists (UEMS), in cooperation with the Division of Interventional Radiology/UEMS. J Neurointerv Surg. 2020;12:326–31.
2. Lavine SD, Cockroft K, Hoh B, Bambakidis N, Khalessi AA, Woo H, Riina H, et al. Training guidelines for endovascular ischemic stroke intervention: an international multi-society consensus document. Am J Neuroradiol. 2016;37:E31–4.
3. Pierot L, Jayaraman MV, Szikora I, et al. Standards of practice in acute ischemic stroke intervention: international recommendations. Am J Neuroradiol. 2018;39:E112–7.
4. UEMS. Standards of practice in interventional neuroradiology. Consensus document from the ESNR/ESMINT/UEMS, 2019.
5. Day AL, Siddiqui AH, Meyers PM, et al. Training standards in neuroendovascular surgery: program accreditation and practitioner certification. Stroke. 2017;48:2318–25.
6. Accreditation Council for Graduate Medical Education. ACGME program requirements for graduate medical education in endovascular surgical neuroradiology, 2020; p. 1–54.
7. Delhi N. National Board of Examinations Introduction of FNB NEUROVASCULAR INTERVENTION Programme Attention: All Hospitals/Institutes/Medical Colleges desirous of seeking accreditation, 2019.