Carotid Artery Disease

Evaluation and Management

Min S. Park
M. Yashar S. Kalani
Adam de Havenon
J. Scott McNally
Editors

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Editors
Min S. Park
Department of Neurosurgery
University of Virginia
Charlottesville, VA
USA

M. Yashar S. Kalani
Department of Neurosurgery
University of Virginia
Charlottesville, VA
USA

Adam de Havenon
Department of Neurology
University of Utah
Salt Lake City, UT
USA

J. Scott McNally
Department of Radiology
University of Utah
Salt Lake City, UT
USA

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This book is dedicated to my wife and children, without whose infinite patience this would not be possible, and to the patients who entrust their care with us every day.

Min S. Park

To my patients, who are a source of inspiration and who have taught me immensely. To Kayhan and Layla for the joy they bring to my life every day.

M. Yashar S. Kalani

This book is dedicated to my wonderful wife, Verena, and son, Lars, who put up with me every day; to my parents, Michael and Georgia, who made it possible for me to pursue my dreams; and to Min and Lorraine, who had tireless devotion herding a bunch of cats masquerading as physicians.

Adam de Havenon

To my family.

J. Scott McNally

Preface

To paraphrase the words of the Australian writer and activist Irina Dunn, the world needs another carotid disease textbook like a fish needs a bicycle. We, along with the publishers, had some trepidation that another textbook discussing disease of the carotid artery would be lost in the dusty bins of libraries or, more likely, remain "unclicked" on a website somewhere. However, this project sprang from a legitimate need to address all facets of the management of carotid artery disease. We have attempted to create a diverse textbook where one can find management recommendations for any process which involves the extracranial carotid artery, be it related to atherosclerotic, traumatic, inflammatory, or even oncologic disease.

This textbook is a somewhat unique offering in the world of medical publishing. It is not often that one can find traditional, and even exclusively, medical conditions within the same binding as surgical or interventional ones. To that purpose, we recruited thought leaders from across medical, surgical, and radiological disciplines to provide expert commentary on the presentation, evaluation, and management of these conditions united by its involvement of one of the most crucial pieces of real estate on the human body. This effort would not be possible without editors from complementary medical disciplines (neurology, neurosurgery, and neuroradiology).

We hope that you find this effort beneficial for your education and clinical practice. The information contained within can serve as an introduction to the disease processes for someone early in their medical training, as well as a refresher course for more seasoned clinicians. It has been an honor and privilege to work with the publisher and colleagues across disciplines on this important endeavor.

Charlottesville, VA, USA — Min S. Park
Oxford, United Kingdom — M. Yashar S. Kalani
Salt Lake City, UT, USA — Adam de Havenon
Salt Lake City, UT, USA — J. Scott McNally

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Contributors

Isaac Josh Abecassis, MD Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Karl R. Abi-Aad, MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Felipe C. Albuquerque, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Matthew Alexander, MD University of Utah, Department of Radiology, Salt Lake City, UT, USA

Rami O. Almefty, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

M. Ali Aziz-Sultan, MD Brigham and Women's Hospital, Harvard Medical School, Department of Neurosurgery, Boston, MA, USA

Bernard R. Bendok, MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Department of Otolaryngology, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Joseph F. Carrera, MD Department of Neurology, University of Virginia, Charlottesville, VA, USA

Leonardo Rangel Castilla, MD Departments of Neurosurgery and Radiology, Mayo Clinic, Rochester, MN, USA

Karen S. Chen, MD Brigham and Women's Hospital, Harvard Medical School, Department of Neurosurgery, Boston, MA, USA

Lynda M. Christel, MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Mayo Clinic, Phoenix, AZ, USA

Dale Ding, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Alexander J. Doud, MD, MS Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

Andrew F. Ducruet, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Nathan Gaines, MD Highland Hospital Division of Neurology, Alameda Health System, Oakland, CA, USA

Bradley A. Gross, MD Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Adam de Havenon, MD Department of Neurology, University of Utah Health System, Salt Lake City, UT, USA

Department of Neurology, University of Utah, Salt Lake City, UT, USA

Benjamin K. Hendricks, MD Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Mariam Ishaque, MD, PhD Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

M. Yashar S. Kalani, MD, PhD, FAANS, FAHA Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

University of Oxford, Oxford, U.K.

Cory M. Kelly, BS Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Chandan Krishna, MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Michael R. Levitt, MD Departments of Neurological Surgery, Radiology, and Mechanical Engineering, University of Washington, Harborview Medical Center, Seattle, WA, USA

David S. Liebeskind, MD, FAAN, FAHA, FANA Neurovascular Imaging Core, UCLA Department of Neurology, Los Angeles, CA, USA

Yince Loh, MD Swedish Neuroscience Institute, Seattle, WA, USA

Jamal McClendon Jr., MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Michael McLaughlin, MD Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA

J. Scott McNally, MD, PhD Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA

Chelsea Meyer, MD Department of Neurology, University of Utah, Salt Lake City, UT, USA

Stephen J. Monteith, MD Swedish Neuroscience Institute, Seattle, WA, USA

Andrew Montoure, MD Medical College of Wisconsin, Department of Neurosurgery, Milwaukee, WI, USA

Peter Nakaji, MD Department of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Pedro Norat, MD Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA

Kamil W. Nowicki, MD, PhD Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Min S. Park, MD Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA

Devi P. Patra, MD MCH Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Lorenzo Rinaldo, MD, PhD Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA

Jerdan Ruff, MD Department of Neurology, University of Utah, Salt Lake City, UT, USA

Paul J. Schmitt, MD Swedish Neuroscience Institute, Seattle, WA, USA

Rajeev D. Sen, MD Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Yilin Shek, MD Cedars-Sinai Medical Center, Department of Neurology, Los Angeles, CA, USA

Cody Smith, MD Department of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Sauson Soldozy, BA Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA

Shlee S. Song, MD Cedars-Sinai Medical Center, Department of Neurology, Los Angeles, CA, USA

Andrew M. Southerland, MD, MSc Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, VA, USA

Ali Sultan-Qurraie, MD University of Washington, Valley Medical Center, Renton, WA, USA

David L. Tirschwell, MD, Msc Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

Ali Turkmani, MD Department of Neurological Surgery, Neurovascular and Skullbase Program, Mayo Clinic, Phoenix, AZ, USA

Juan Vicenty-Padilla, MD Brigham and Women's Hospital, Harvard Medical School, Department of Neurosurgery, Boston, MA, USA

Matthew E. Welz, MS Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA

Robert T. Wicks, MD Department of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Christopher C. Young, MD, PhD Department of Neurological Surgery, University of Washington, Seattle, WA, USA

Osama O. Zaidat, MD Mercy Health System, St. Vincent Medical Center, Toledo, OH, USA

Chapter 1
Introduction to Management of Carotid Disease

Mariam Ishaque, Adam de Havenon, J. Scott McNally, M. Yashar S. Kalani, and Min S. Park

Introduction

Carotid artery disease is a major cause of ischemic stroke and a leading cause of death and disability worldwide. Globally, carotid artery disease is considered to have reached epidemic proportions and its incidence is projected to continue to increase, particularly in younger patients [1]. This results in a significant health and financial burden on patients and the healthcare system, estimated to cost over $30 billion a year in North America alone [2]. Our understanding of the carotid artery in health and in disease has progressively allowed for the development of preventative and therapeutic measures, although much remains to be discerned.

Historical Perspectives

Ancient Greeks recognized the importance of the carotid arteries and their association with neurological dysfunction over 2000 years ago. In fact, some of the current medical terminology used for carotid artery disease stems from ancient Greek medical literature [3]. In the fourth century BC, Hippocrates defined the term *apoplexy*

M. Ishaque · M. Y. S. Kalani · M. S. Park (✉)
Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA
e-mail: MI4FP@hscmail.mcc.virginia.edu; yk6z@hscmail.mcc.virginia.edu; mp2tq@hscmail.mcc.virginia.edu

A. de Havenon
Department of Neurology, University of Utah Health System, Salt Lake City, UT, USA
e-mail: Adam.DeHavenon@hsc.utah.edu

J. S. McNally
Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA
e-mail: scott.mcnally@hsc.utah.edu

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as “to strike down.” He additionally described the signs and symptoms of transient ischemic attacks and strokes accurately, and he recognized that carotid artery lesions could result in contralateral hemiplegia [4, 5]. He proposed that “unaccustomed attacks of numbness and anesthesia” could portend apoplexy [6].

In 100 AD, the Greek physician Rufus of Ephesus is thought to have named the carotid arteries after noting that when mechanically compressed, loss of consciousness or a state of stupor/sleep would occur. The term “carotid” was thus derived from the Greek word *karos* meaning “to stupefy or fall into a deep sleep,’” and the carotids were referred to as the “sleep arteries” or *soporales* [3, 4].

Despite these early descriptions of the carotid arteries and their neurofunctional significance, it would take over 1500 years until their anatomy was depicted. Swiss pathologist Johann Wepfer described the carotid vascular supply to the cerebral hemispheres in his *Treatise de Apoplexiae* in 1658. In this text, he purported the relationship between carotid pathology and symptoms of cerebral artery insufficiency and provided the first known reports of carotid artery thrombosis [3, 4, 6].

Wepfer’s contemporary was the leading neuroanatomist and English physician Thomas Willis. His publication, *Cerebri Anatome*, was one of the most impactful medical texts of this era. Although the vascular anatomy of the *circulus arteriosus cerebri,* known as the Circle of Willis, had been previously described, Willis was the first to propose its physiological importance and the potential consequences of vascular pathology. Through autopsies performed by Willis and later, by Jean-Louis Petit, an eminent French anatomist and surgeon, it was affirmed that unilateral occlusion of the carotid artery could be compatible with life, as asymptomatic and minimally affected patients were found to have near-occlusion of a single carotid on postmortem evaluation [6, 7]. The first hypothesis of a cause for vascular occlusion came from van Swieten in the mid-18th century. He proposed that embolic material arising from the heart and great vessels might flow distally to cause occlusion of the carotid artery [6, 8]. Around the same time in the 19th century, Virchow published *Gesammelte Abhandlungen zur wissenschaftlichen Medicin* (Collected Essays on Scientific Medicine). In this work he described a case of carotid artery thrombosis associated with ipsilateral monocular blindness, and first used the terms thrombosis, ischemia, and embolus. Over the years, both Rokitansky and Virchow detected inflammation within atherosclerosis, though the former thought it was secondary to fibrin deposition whereas the latter postulated a primary role [9]. Additionally, these great pathologists recognized that the atherosclerotic plaque was not randomly distributed throughout the vasculature but occurred specifically at branch points like the carotid bifurcation, and therefore hypothesized a primary role for mechanical or flow related forces in the initiation of plaque. In doing so, they laid the basis for future research into mechanotransduction and inflammatory cascades that continues to this day [9].

In the 19th century, John Abercrombie described other causes of apoplexy, which he referred to as *ramollissement*, or “softening” of the brain, in French. Aside from embolism, he purported that circulatory failure could underlie *ramollissement*, based on observations of his patients with apopletic attacks. He noted in his text in 1828 that in these patients, the internal carotids appeared larger than usual and

"their coats were much thickened" [6]. Robert Carswell, in his 1838 text *Pathological Anatomy: Illustrations of the Elementary Forms of Disease,* made the connection that "if obliteration takes place in the carotid…the greater part or the whole of a hemisphere may be softened…" [10].

This link between extracranial carotid arterial occlusion and cerebral ischemia and infarction continued to develop into the 20th century. Austrian pathologist Hans Chiari first suggested that potential emboli at the carotid bifurcation, specifically plaques or thrombi, place a patient at increased risk for infarction, thus establishing the thromboembolic hypothesis. He proposed post-mortem examination of the carotid arteries in patients with suspected strokes to evaluate them as the potential etiology of apoplexy. In the 1950s, approximately 30 years after the first cerebral arteriogram was performed, Carl Fisher was able to use this technology to demonstrate the association between carotid bifurcation disease and stroke, as Chiari had earlier advocated. Fisher identified grades of carotid stenosis and described their respective cerebral consequences in his seminal manuscripts [6, 11–13]. He even alluded to therapeutic interventions, mentioning the future possibility of bypassing the occluded portion of the vessel to establish distal flow.

Surgical History

The first operations of the carotid artery were largely limited to vessel ligations. The original report of operative ligation of the carotid artery was from Ambroise Pare in 1552. This intervention reportedly prevented the patient, a French soldier, from hemorrhaging, but left him aphasic and hemiplegic [8]. Over the next 200 years, other physicians attempted carotid artery ligations as well, mostly in cases of traumatic carotid injuries. Outcomes in these patients were commonly quite poor and with significant morbidities.

Procedures for carotid aneurysms primarily involved proximal ligations, but there are reports of distal ligations as well. Benjamin Travers was the first to perform carotid ligation for a carotid corpus cavernosum fistula in 1809, and Victor Horsley was the first to successfully ligate the carotid artery for an intracranial aneurysm in England in 1885 [3, 8, 13]. The indications for carotid ligation grew to include tumors, aberrant arteriovenous connections, and other lesions, until the procedure came to be regarded as dangerous in the late 19th and early 20th centuries.

In the 1930s, a new procedure gained ground for treatment of carotid artery occlusion, involving excision of the occluded segment. This was first performed by Chao and colleagues at the Medical College of Peking in 1938, with good neurological outcomes in two patients [3, 14]. In 1948, Sciaroni introduced a procedure wherein an arteriovenous fistula was generated between the common carotid artery and internal jugular vein in hopes of increasing cerebral blood flow. He deemed it "reversal of the circulation of the brain." Sciaroni reportedly had excellent outcomes and the procedure continued to be performed for the next several years [3].

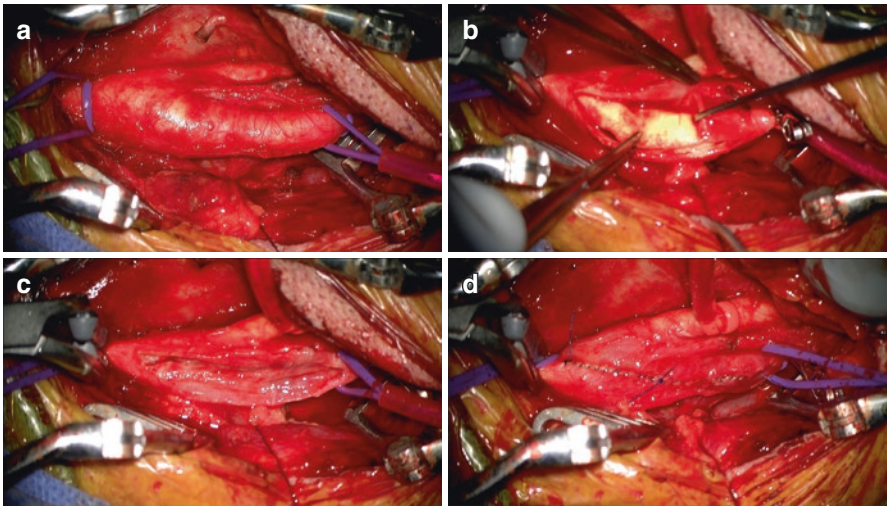

Fig. 1.1 (**a**) Intra-operative photograph of the exposed cervical carotid artery during carotid endarterectomy surgery demonstrating the isolation of the internal carotid artery, external carotid artery, and the common carotid artery (Block). Vessel loops have been applied to the internal and common carotid arteries for possible placement of a shunt. (**b**) A large atheromatous plaque is mobilized following opening of the vessel from the common to the internal carotid artery. A plane of dissection between the plaque and the intima is developed to facilitate removal. (**c**) Intra-operative photograph following removal of the plaque. The intima is carefully inspected prior to vessel closure. (**d**) The artery is repaired with a running suture to ensure a watertight closure. In this instance, given the size of the artery, we elected to repair in a primary fashion without a patch

Surgical procedures aimed at restoring flow in the setting of stenosis and occlusion without ligation or resection of the vessel began in the early 1950s. With the advent of angiography, several methods were developed but ultimately, endarterectomy became the procedure of choice (Fig. 1.1a–d). The first successful carotid endarterectomy (CEA) was performed by Michael DeBakey on August 7, 1953. He removed an atheromatous plaque and a fresh clot from the carotid bifurcation of a 53-year-old male with transient ischemic attacks [3, 6, 15].

DeBakey and colleagues also first described carotid angioplasty in 1967 in the context of fibromuscular dysplasia. This involved serial dilation of the carotid lesions causing stenosis of the vessels, with reportedly excellent outcomes. The dilators initially used for this purpose were biliary dilators borrowed from general surgery colleagues. Denton Cooley recounted the first use of an intravascular shunt during carotid cross-clamping to permit distal blood flow [4]. In 1994, Marks and colleagues at Stanford reported their use of Palmaz stents in the ICA in two patients with carotid stenosis, also with good outcomes [3]. Fine-tuning of techniques and patient selection with angioplasty and stenting continued to demonstrate improvement in outcomes through the 20th century to the present.

Conclusion

Needless to say, the advances in understanding and treatment are predicated on the work of prior generations. Technological improvements and developments have facilitated new diagnostic and therapeutic options to better manage carotid diseases, but there remain many areas warranting further investigation and optimization. The following text will offer a description of the medical and surgical diseases of the cervical carotid artery with a focus on current management and future directions.

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Chapter 2
Anatomy of the Carotid Artery

J. Scott McNally and Michael McLaughlin

Anatomy of the Carotid Artery

The Carotid Space

The left and right carotid spaces are paired tubular spaces contained in a fascial sheath made up of the three deep cervical fascia layers. The carotid space contains the carotid arteries, carotid body, carotid sinus, internal jugular (IJ) veins as well as cranial nerves (CN) IX-XII. The internal jugular nodal chain is associated with the outer sheath, but there are no nodes located within the carotid space itself.

In the suprahyoid neck, the sheath is more incomplete than in the infrahyoid neck. Multiple cranial nerves are present within the suprahyoid carotid sheath including CN IX-XII. Only CN X remains in the infrahyoid neck where the nerve is located in the posterior notch between the ICA and IJ. The sympathetic plexus is found along the posterior aspect of the carotid sheath closely opposed to the prevertebral fascia. The ansa cervicalis is part of the cervical plexus of nerves forming a loop located within the anterior wall of the carotid sheath. The superior root descending over the ICA/CCA is a continuation of CN XII with fibers from the C1 spinal nerve supplying the superior belly of the omohyoid. The inferior root descends around the IJ with C2-C3 spinal nerve fibers and supplies the inferior belly of the omohyoid. The inferior root joins the superior root anteriorly and inferiorly along the CCA to form the ansa cervicalis, which supplies the sternohyoid and sternothyroid muscles.

There are two additional important structures within the carotid sheath, the carotid body and carotid sinus. The carotid body is a chemoreceptor consisting of two types of receptor cells: (1) **Type I cells** (glomus cells) that are derived from the

J. S. McNally (✉) · M. McLaughlin
Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA
e-mail: scott.mcnally@hsc.utah.edu; Michael.McLaughlin@hsc.utah.edu

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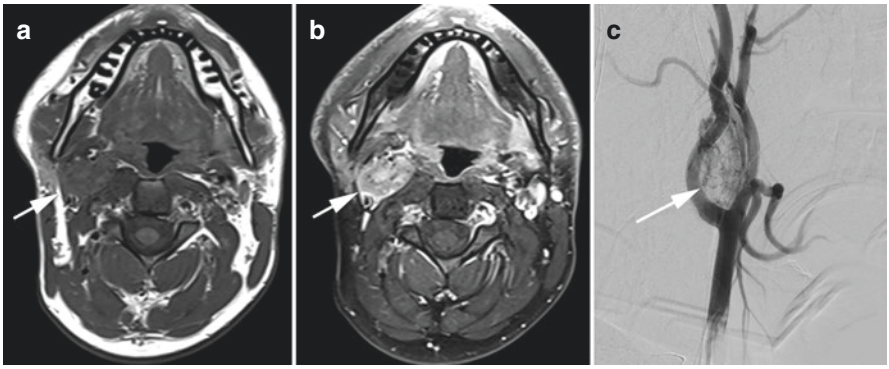

Fig. 2.1 Carotid body paraganglioma. Right carotid body paraganglioma on MRI, with T1 precontrast (**a**), T1 postcontrast (**b**), and pretreatment DSA (**c**) showing an avidly enhancing mass (arrow) splaying the internal and external carotid artery

neural crest and release acetylcholine, ATP, and dopamine when activated, and (2) **Type II cells** (sustentacular cells) which serve as supporting cells. The carotid body monitors blood pH, pCO_2, and pO_2 and senses acidemia, hypercapnia, or hypoxia, respectively. The carotid body can increase sympathetic tone to increase blood pressure, heart rate, and respiratory rate. The carotid body is normally ≤6 mm in size on imaging, but when larger raises the concern for a carotid body paraganglioma (Fig. 2.1) [1]. It is innervated by the carotid sinus nerve, a branch of CN IX that provides sensory innervation. Nerve fibers travel to the nucleus tractus solitarii (NTS) in the medulla oblongata and indirectly modulate sympathetic and parasympathetic tone in the medulla and pons via the hypothalamus. The cell bodies of the afferent neurons reside in the petrosal ganglion and synapse with type I cells. Because this region contains an important baroreceptor and chemoreceptor, avoiding carotid sinus nerve and carotid body during endarterectomy is important to preserve autonomic function [2]. The carotid body is also the target for carotid massage, which can decrease both heart rate and blood pressure. While carotid stimulation can induce bradycardia and even syncope in some individuals, fatal cardiac events following carotid sinus stimulation are rare and often accompanied by the presence of drug abuse and/or cardiac pathology, and may be secondary to underlying predispositions as opposed to the stimulation itself [3].

Carotid Artery Anatomy and Predisposition to Atherosclerosis

Carotid artery anatomy is essential to the understanding of plaque predilection to the carotid bifurcation. Like all arteries, the carotid consists of 3 layers (from inner to outer): tunica intima, media, and adventitia. The intima consists of a single layer of endothelial cells with a collagen matrix underneath. The media consists of a thick layer of vascular smooth muscle cells (VSMC) and matrix. The adventitia is

composed of fibroblasts and adipocytes. Vasa vasorum are found in the carotid artery, primarily located near the bifurcation and bulb, and these course within the adventitia penetrating into the media and nearly reaching the intima [4]. Patients with atherosclerosis have a higher density of vasa vasorum, and the endothelial lining of these small vessels may represent a potential atherosclerosis prevention or treatment target [5].

As a result of their prime location, endothelial cells experience three types of mechanical force: pressure, circumferential stretch, and shear stress or the dragging force created by blood flow. Of these, shear stress may be the most important due to the modulation of genes and controlled release of vasoactive substances [6]. For over a century, pathologists have known atherosclerosis does not occur randomly throughout the vasculature. Instead, plaque occurs at specific anatomic locations such as branch points and non-linear vascular segments. In particular, the outer wall of the carotid artery is highly predisposed to atherosclerotic plaque, and is located 180 degrees opposite the flow divider at the bifurcation and bulb. Blood flow at the carotid bifurcation is non-laminar, in contrast to linear vascular segments.

Linear vessel segments experience laminar flow and are relatively protected from atherosclerosis [7]. Laminar shear stress stimulates endothelial nitric oxide (NO) production, and this accounts for the main atheroprotective effect of aerobic exercise [8]. During exercise, NO causes vasodilation and increased perfusion of downstream tissues. Importantly, NO also counteracts atherogenesis by inhibiting platelet aggregation, VSMC proliferation, leukocyte adhesion, and oxidative damage [9]. Through this mechanism, exercise counteracts the proatherosclerotic conditions of hypertension, diabetes, and hypercholesterolemia which can disrupt endothelial response to laminar shear stress [10, 11].

In contrast, at the carotid bifurcation flow reversal and oscillatory shear stress occur during systole along the outer wall of the carotid bulb. This site is particularly prone to intima-media thickening and atherosclerosis [12, 13]. Studies have shown that early carotid plaque formation is related to an oscillating pure positive and negative shear stress, as opposed to disorganized turbulent flow. In cell culture models, this oscillatory shear stress increases superoxide and oxidase activity [14–16] and correspondingly decreases NO levels [17]. Decreased NO contributes to atherogenesis by increased inflammation, vasoconstriction, VSMC proliferation, leukocyte adhesion, coagulation, and increased oxidative damage. This accounts for the predilection of plaque along the outer wall of the carotid bulb.

Extracranial Arterial Anatomy

Arch Anatomy

There are both left and right common carotid arteries (CCA) with a similar course in the neck, but with different origins. The normal aortic arch configuration of the great vessel origins includes (from right to left) the brachiocephalic, left CCA

and left subclavian arteries. The brachiocephalic artery bifurcates into the right subclavian artery and right CCA. Variations on this anatomy occur, most often related to a common origin of the brachiocephalic and left CCA (often referred to as a“bovine-type” arch, though this bears no resemblance to the bovine arch), direct arch origin of the left vertebral artery, or aberrant right subclavian artery (ARSA) with a retroesophageal course [18]. Congenital aortic arch variants may have important clinical implications as they can be associated with vascular rings, congenital heart disease, and chromosomal abnormalities.

CCA Anatomy

Both CCA's are symmetric in their course and are contained within the carotid sheath. This sheath is in contiguity with the deep cervical fascia and serves as the boundary of the carotid space. In males the average CCA diameter is 6.5 mm and in females is 6.1 mm [19].

Carotid Triangle

The carotid triangle is formed when the sternocleidomastoid is retracted posteriorly. The posterior margin of the triangle is formed by the sternocleidomastoid, the stylohyoid and posterior belly of the digastric muscles the superior margin, and the superior belly of the omohyoid forms the inferior margin. In this triangle, CN XII crosses superficial to the carotid artery (sometimes within the carotid sheath) obliquely from posterosuperiorly to anteroinferiorly.

Carotid Bifurcation and Bulb

The carotid bifurcation occurs at approximately the C4 vertebral body level in most patients, though can be seen as low as T2 or as high as C1-C2. The CCA bifurcates into the internal carotid artery (ICA) and external carotid artery (ECA). In most patients, the ICA originates posterolaterally and the ECA originates anteromedially, though the reverse can be seen about 10% of the time. The bifurcation is mobile and can turn within the sheath during swallowing or vocalization, and the orientation of the ICA-ECA can change between imaging scans (Fig. 2.2). Superior to the bifurcation there is a normal anatomic dilation known as the carotid bulb. Very rarely, there is no bulb and the ECA branches arise directly from the CCA.

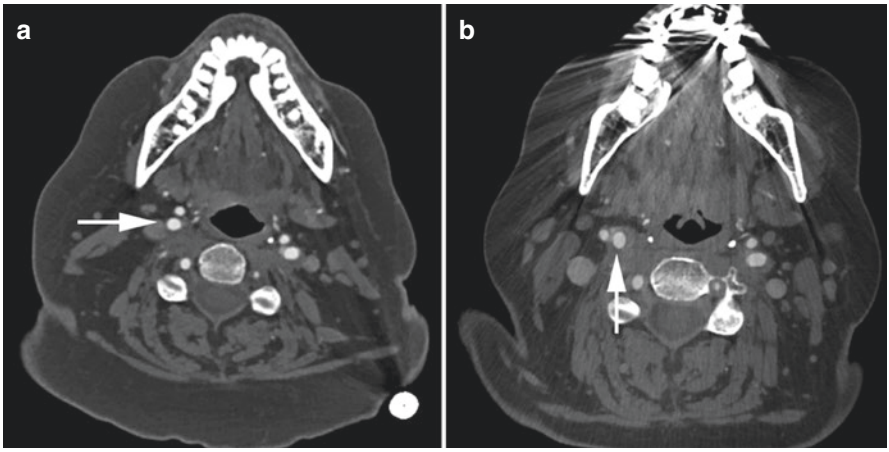

Fig. 2.2 Carotid bifurcation rotation. Two CTA scans 6 months apart showing rotation of the right carotid bifurcation within the carotid sheath. Initially, the right ICA (arrow) was located posterolateral to the ECA (**a**). On the second scan, the right carotid rotated such that the ICA (arrow) was located medial to the ECA (**b**)

External Carotid Artery (ECA)

The ECA is named for external course, and can be distinguished from the ICA by its multiple branches. Potential anastomotic routes can exist between the extracranial and intracranial arteries, so called 'dangerous' anastomoses due to the potential for non-target embolization to the central nervous system during ECA intervention procedures involving the skull base and orbit [20, 21]. The 8 named branches of the ECA are: **superior thyroid, ascending pharyngeal, lingual, facial, occipital, posterior auricular, superficial temporal, and internal maxillary arteries**. These branches supply facial structures and are named according to the structure they supply or their anatomic course:

Superior Thyroid Artery

Usually this is the first ECA branch, though sometimes it arises directly from the CCA below or near the bifurcation. This artery courses inferiorly to supply the superior thyroid gland and larynx, and anastomoses with the inferior thyroid artery arising from the thyrocervical trunk. A rare example of a superior thyroid infarct is shown in Fig. 2.3.

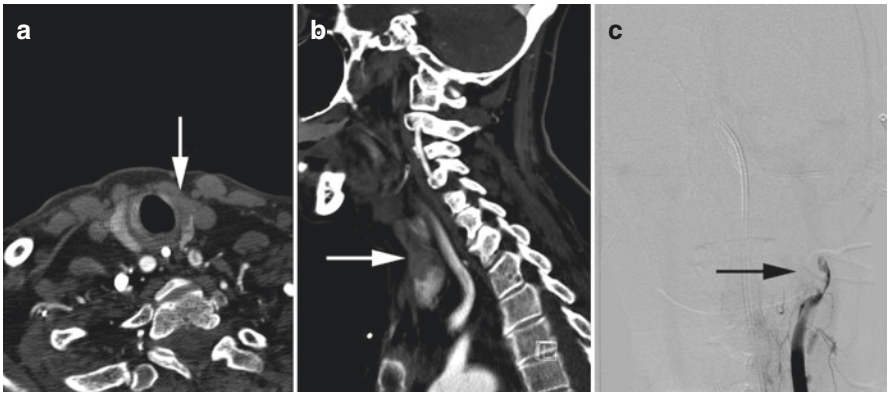

Fig. 2.3 Superior thyroid infarction. Patient with acute left hemispheric infarction related to left carotid occlusion involving both the ECA and ICA. Thrombus extended into the left superior thyroid artery resulting in superior thyroid lobe infarction (white arrows) on axial (**a**) and sagittal CTA (**b**). DSA with delayed imaging confirmed left ICA and ECA occlusion (**c**, black arrow)

Ascending Pharyngeal Artery

This artery is often the second ECA branch though can have a variant origin at the notch of the carotid bifurcation. This vessel courses superiorly between the ICA/ECA and supplies the nasopharynx and oropharynx. Muscular/tympanic branches supply the pharyngotympanic (Eustachian) tube, middle ear and prevertebral musculature. Neuromeningeal branches supply cranial nerves IX-XI and the dura. Potentially dangerous anastomoses are present with the middle/accessory meningeal caroticotympanic and Vidian arteries. An example of an enlarged ascending pharyngeal artery in the setting of an anatomic variant aberrant ICA is shown in Fig. 2.4. In this case, the ascending pharyngeal artery supplies an enlarged inferior tympanic artery, caroticotympanic artery, and then connects with the posterolateral aspect of horizontal petrous ICA.

Lingual Artery

Usually the second ECA branch, the lingual artery courses anteroinferiorly and is the major vascular supply to the tongue, oral cavity and submandibular gland. In some cases the lingual and facial arteries can arise from a common origin.

Facial Artery

The facial artery arises superior to the lingual artery and courses along the cheek to supply the face, lip and cheek as well as the palate. There are potentially dangerous anastomoses along the anterior cheek with the ophthalmic artery branch of the ICA.

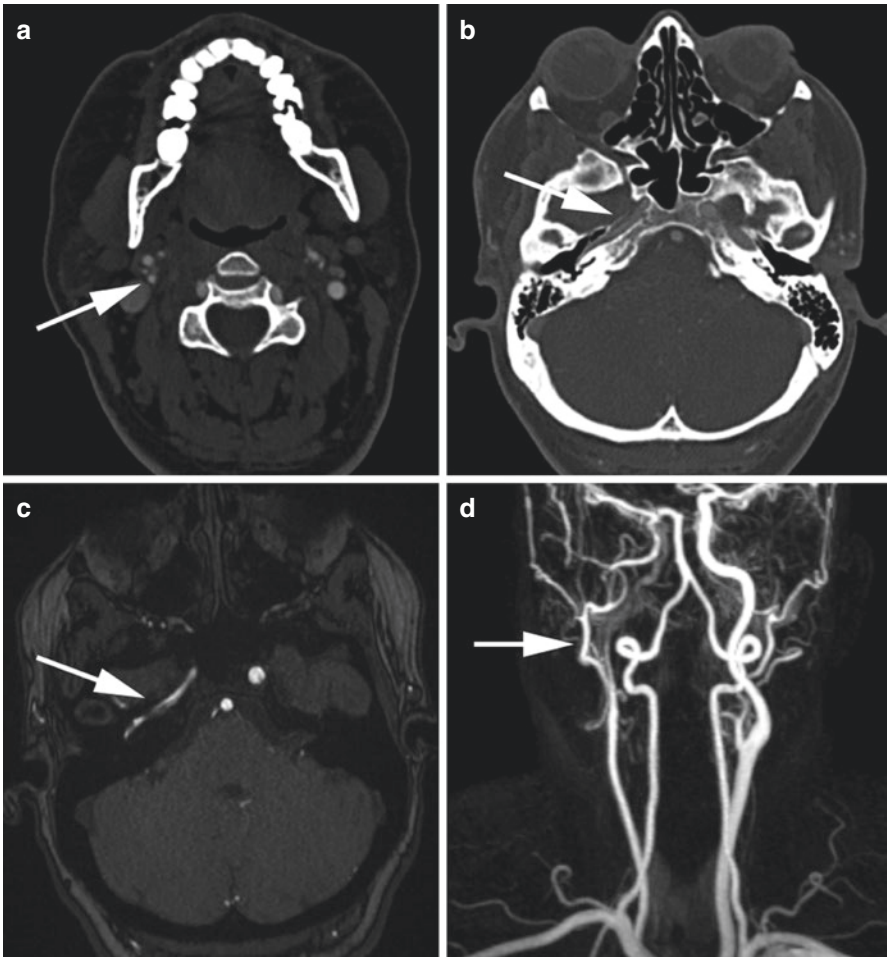

Fig. 2.4 Aberrant internal carotid artery. Patient with an aberrant right ICA. CTA showed an enlarged right-sided ascending pharyngeal artery (**a**, arrow) that coursed along the cochlear promontory with an asymmetrically small carotid canal (**b**, arrow). The ascending pharyngeal artery supplied an enlarged inferior tympanic artery, caroticotympanic artery, and then connected with the posterolateral aspect of horizontal petrous ICA. MRA with TOF (**c**) and contrast maximum intensity projections (**d**) confirmed an aberrant right ICA (arrow)

Occipital Artery

This artery arises from the posterior ECA and courses posteriorly to supply the occipital scalp, upper cervical musculature and dura of the posterior fossa with multiple potential dangerous anastomoses with the vertebral arteries through muscular branches. This artery serves as important embolic access for posterior fossa meningiomas and dural arteriovenous fistulae (dAVF) which commonly occur at the margin of the transverse/sigmoid sinus junction. An example of an

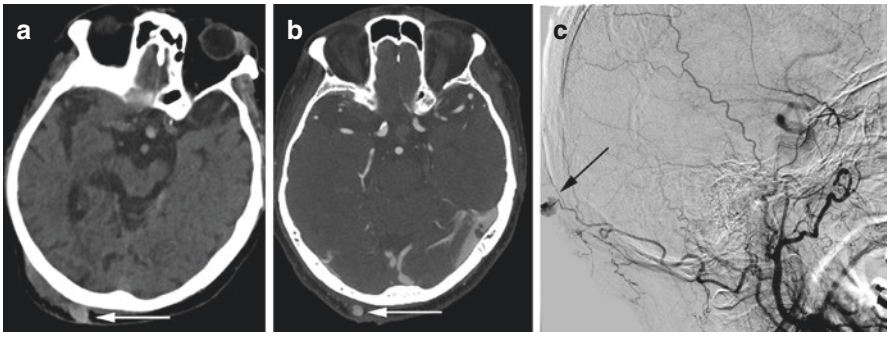

Fig. 2.5 Occipital artery pseudoaneurysm. Patient with a right occipital scalp laceration after ground level fall. Noncontrast CT showed a rounded hematoma along the right occipital scalp (**a**, arrow). The hematoma began to pulsate, and CTA was performed which showed a pseudoaneurysm (**b**, arrow). DSA confirmed the pseudoaneurysm was supplied by the occipital artery (**c**, arrow). This was subsequently embolized

occipital artery pseudoaneurysm related to prior trauma is shown in Fig. 2.5, subsequently treated with embolization.

Posterior Auricular Artery

This branch arises superior to the occipital artery origin and courses posteriorly to supply the pinna of the ear, posterior scalp, external auditory canal and chorda tympani.

Superficial Temporal Artery (STA)

The smaller of the terminal ECA branches is the superficial temporal artery, which courses posteroinferiorly to the mandibular condyle to supply the scalp. This vessel is often biopsied in cases of suspected ECA vasculitis and can present with pseudoaneurysms as shown in Fig. 2.6. An additional case of an STA fistula from stabbing is shown in Fig. 2.7.

(internal) Maxillary Artery (iMAX)

The largest terminal ECA branch is the iMAX, which arises deep to the mandibular condylar neck in the parotid space. The iMAX branches include the middle meningeal artery (MMA) and the sphenopalatine branch. The MMA is an important

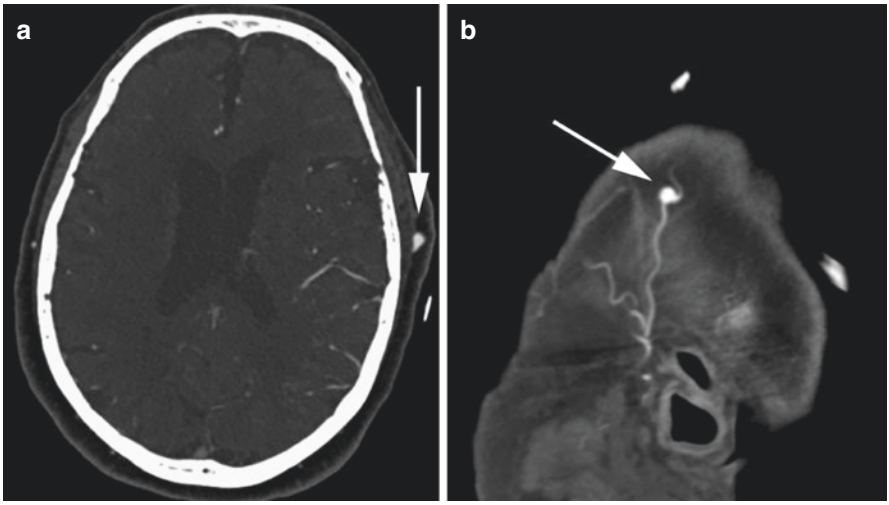

Fig. 2.6 Superficial temporal artery vasculitis and pseudoaneurysm. Patient with headache and vision loss who underwent workup with CTA. Axial (**a**) and sagittal CTA images (**b**) showed a 5 mm left sided superficial temporal artery pseudoaneurysm and the patient subsequently went to biopsy confirming giant cell arteritis

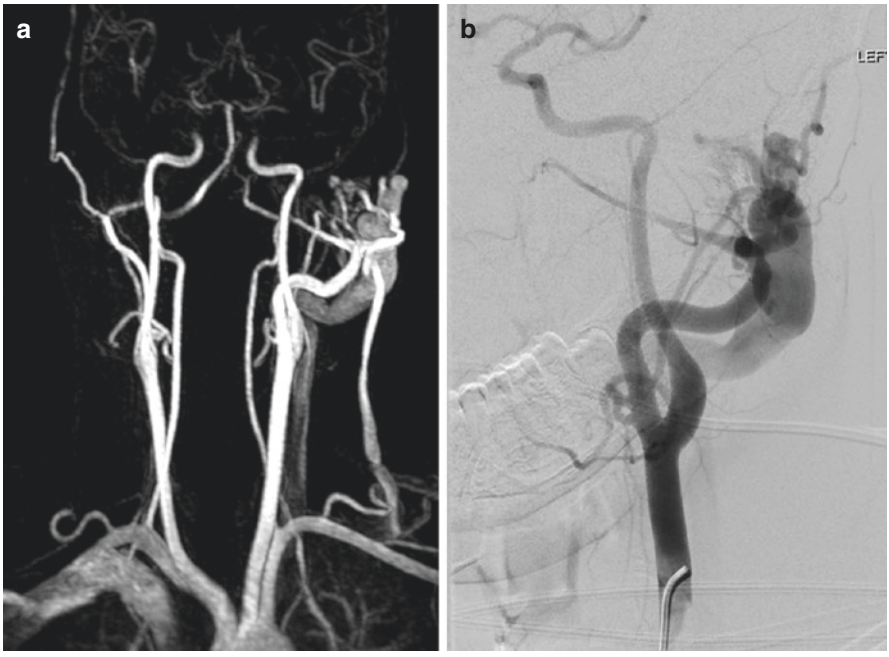

Fig. 2.7 Superficial temporal arteriovenous fistula. Patient with a pulsatile mass at the site of a prior stab wound. MRA (**a**) showed arteriovenous shunting within the left parotid mass, which was found to represent a posttraumatic arteriovenous fistula on DSA (**b**)

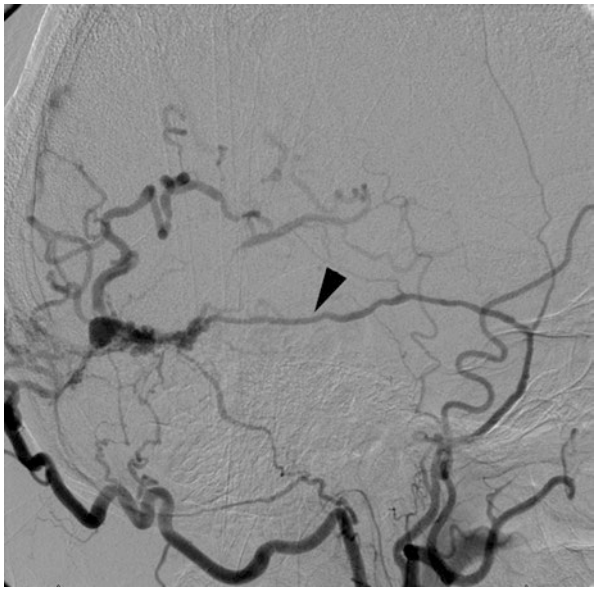

Fig. 2.8 Dural arteriovenous fistula. Patient who presented with worsening left sided headache and vision loss. DSA shows a left sided dural arteriovenous fistula fed by multiple arteries including the middle meningeal artery (arrowhead)

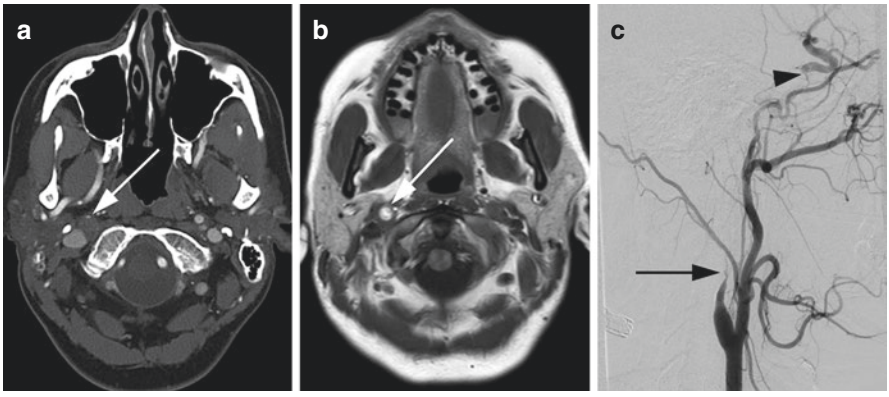

Fig. 2.9 External to internal carotid artery collateral flow. Patient with a right cervical ICA dissection. CTA showed a right ICA dissection with severe lumen narrowing (**a**, arrow). MRI showed a large T1-hyperintense intramural hematoma (**b**, arrow). DSA showed ICA dissection (arrow) along with ECA to intracranial ICA collateral flow (**c**, arrowhead)

access site for embolization of dural tumors (e.g. meningioma) or dAVF as seen in Fig. 2.8. The sphenopalatine branch in the pterygopalatine fossa supplies the deep face and nose, and provides embolization access to tumors in this region (e.g. juvenile angiofibroma) and for nosebleeds. There is also high potential for ECA-ICA collateral flow as shown in Fig. 2.9. Much like the STA, this vessel can be involved with deep face vasculitis (Fig. 2.10).

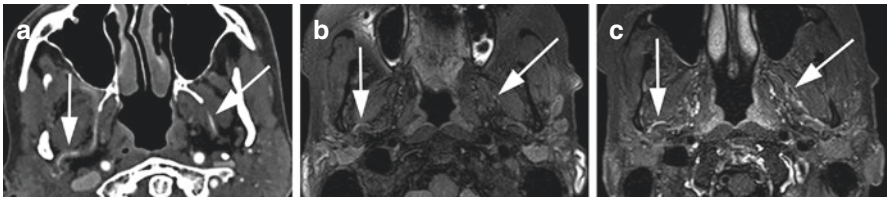

Fig. 2.10 Internal maxillary artery vasculitis. Patient presenting with facial pain and found to have eosinophilic vasculitis on biopsy. CTA showed bilateral internal maxillary artery lumen narrowing and wall thickening (**a**, arrows). MRI also showed wall thickening on T1 precontrast black blood images (**b**, arrows) and enhancement on postcontrast images (**c**, arrows)

Internal Carotid Artery (ICA)

The ICA is named for the more 'internal' path it takes throughout the neck. The first segment of the ICA is the cervical segment and this extends from the bifurcation to the skull base. Within this segment, the carotid bulb is an anatomic dilation measuring approximately 2 cm in length along the outer wall of the proximal ICA. The carotid bulb is particularly predisposed to atherosclerosis as discussed previously. Distal to the bifurcation, the ICA has been studied extensively with classification systems based on anatomy and clinical relevance.

ICA Anatomy

The ICA is divided up into multiple segments with some variation based on classification system. Fischer first devised the ICA segment classification in 1938, but named the segments C1-C5 from superior to inferior to identify skull base lesions based on mass effect on angiography (prior to cross sectional imaging). In 1996, the most widely used 'Modified Fischer Classification' system was devised by Bouthillier with 7 segments (C1-C7) from inferior to superior. This is the primary system used by neurointerventionalists today (Fig. 2.11).

Modified Fischer classification system The following is a description of the modified Fischer classification system used at many institutions. Imaging examples follow each segment description.

Cervical Segment (C1)

The first segment, or 'cervical' segment, extends from the carotid bifurcation to the carotid canal at the skull base. This segment has a rich supply of vasa vasorum centered at the carotid bifurcation and bulb. The cervical ICA is especially prone to

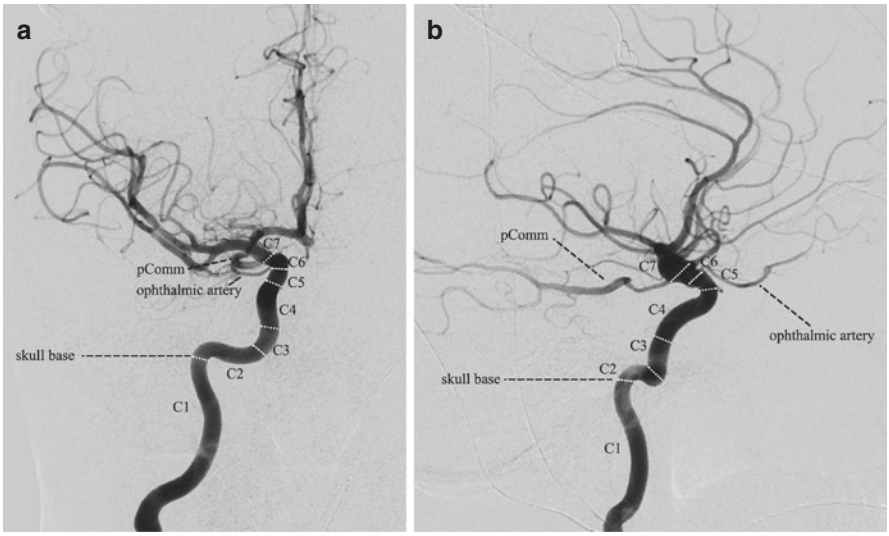

Fig. 2.11 Modified Fischer classification system. The Modified Fischer classification system is shown on frontal (**a**) and lateral (**b**) DSA projections with following segments: C1 – cervical, C2 – petrous, C3 – lacerum, C4 – cavernous, C5 – clinoid, C6 – ophthalmic, C7 – communicating. The skull base, ophthalmic artery and posterior communicating (pComm) arteries are labeled for reference

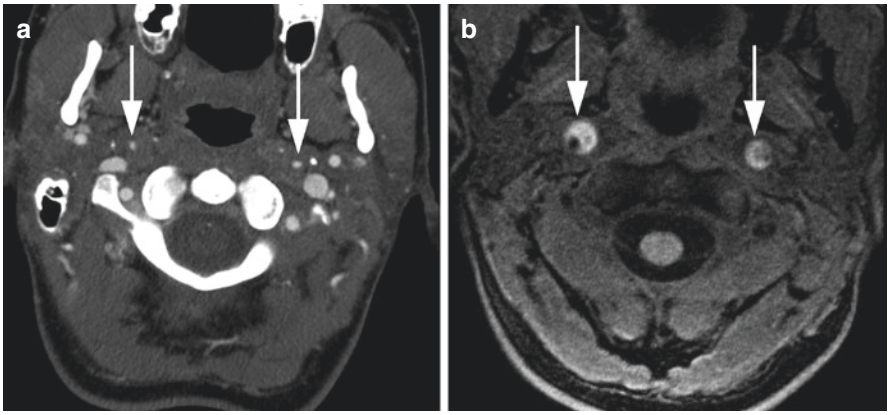

Fig. 2.12 Cervical internal carotid artery dissection. Patient with bilateral cervical ICA dissections. CTA (**a**) showed bilateral severe cervical ICA lumen narrowing (arrows). MRI T1-weighted images (**b**) demonstrated large bilateral T1-hyperintense intramural hematomas (arrows)

dissections, which can occur through direct intimal tear or ruptured vasa vasorum resulting in intramural hematoma. The cervical ICA is also prone to pathology from fibromuscular dysplasia, a form of collagen vascular disease. An example of bilateral cervical ICA dissections is shown in Fig. 2.12.

Petrous Segment (C2)

Once the vessel enters the skull base, it becomes the relatively long 'petrous' segment throughout the carotid canal in the petrous temporal bone. Atherosclerotic plaque, aneurysms, and dissections can occur along the petrous segment. Injury and dissection can occur from high velocity trauma from motor vehicle crashes and resultant skull base fractures. An example of a petrous ICA aneurysm in Fig. 2.13 and petrous ICA dissection in Fig. 2.14.

Lacerum Segment (C3)

After the petrous segment, the ICA extends up to the foramen lacerum where it becomes a short 'lacerum' segment. The petrolingual ligament surrounds a portion of the dorsolateral walls of the lacerum ICA segment, just under the anteroinferior portion of the anteromedial wall of the trigeminal cave [22]. While the lacerum segment is relatively short, the proximity to the foramen lacerum makes this segment especially prone to perivascular spread of disease from head and neck cancer or deep face infection, as shown in Fig. 2.15.

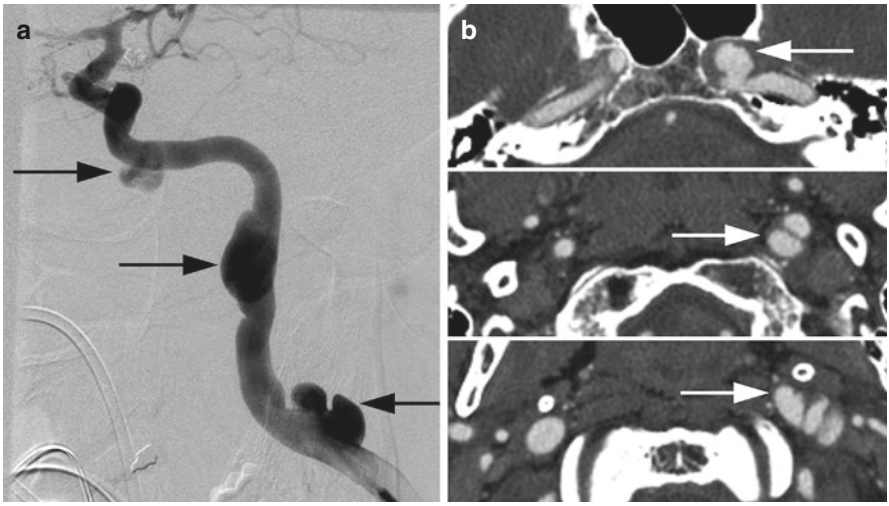

Fig. 2.13 Petrous internal carotid artery pseudoaneurysm. Patient with fibromuscular dysplasia and a petrous ICA pseudoaneurysm. DSA (**a**) and CTA (**b**) demonstrate multifocal cervical ICA lumen corrugation (lower arrow), cervical ICA pseudoaneurysm (middle arrow), and petrous ICA pseudoaneurysm (lower arrow)

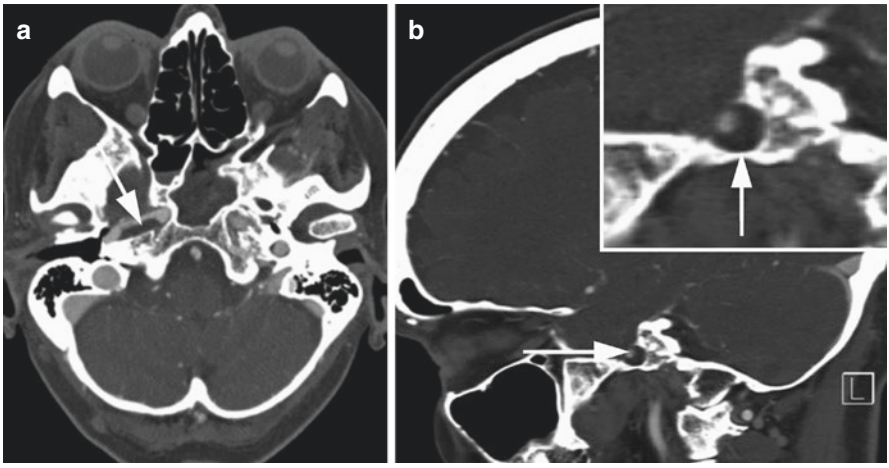

Fig. 2.14 Petrous internal carotid artery dissection. Patient presenting with right hemispheric stroke and right petrous ICA dissection. Axial (**a**) and sagittal (**b**, inset) CTA showed 50% lumen narrowing and intramural hematoma (arrows) indicating dissection of the right petrous ICA

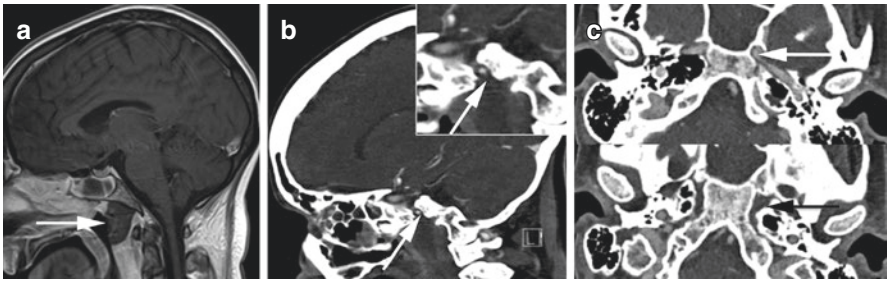

Fig. 2.15 Lacerum internal carotid artery perivascular spread of infection. Patient with intracranial spread of nasopharyngeal mucor infection. Sagittal T1 postcontrast MRI (**a**) shows marked nasopharyngeal mucosal thickening with central nonenhancing tissue extending to the clivus, compatible with vasoinvasive fungal disease (arrow). Sagittal (**b**, inset) CTA shows perivascular spread of infection through the foramen lacerum with narrowing of the ICA lumen (arrow). Axial CTA (**c**) also shows asymmetric narrowing of the ICA (C top, white arrow) and extension through the foramen lacerum (C bottom, black arrow)

Cavernous Segment (C4)

The ICA then passes under the petrolingual ligament, enters the cavernous sinus, and becomes a relatively long 'cavernous' segment from the posterior genu through the anterior genu. The cavernous segment has two important branches, the meningohypophyseal trunk (MHT) and inferolateral trunk (ILT), both of which serve as important access and potential treatment points for dAVF or meningiomas.

One of the most common findings in the cavernous ICA is calcification often identified by CT. Although there is some debate on the causes of these calcifications, significant correlations exist with diabetes, hypercholesterolemia, and hypertension and they are commonly seen alongside microangiopathic disease [23]. Cavernous ICA calcifications are also associated with atherosclerotic risk factors including age, sex, vascular risk factors, serum C-reactive protein, estimated glomerular filtration rate and homocysteine [24]. Still, the cavernous ICA can develop calcification even at teenagers and pathology specimens from children as young as 9 years old show this may relate to internal elastic lamina calcification in young otherwise healthy people [25]. This argues that at least some of the carotid siphon calcification is not related to atherosclerotic change. Furthermore, there are mixed results on the thromboembolic potential of cavernous ICA calcifications, with some studies finding that high-grade calcifications are associated with acute large and small vessel infarcts [26] and other studies showing no correlation between cavernous ICA calcifications and acute infarction [27] or white matter hyperintensities [28]. This segment is also associated with injuries related to high velocity or penetrating trauma, including dissection and AVF, due to its unique anatomy surrounded by cavernous venous sinusoids. An example of a direct CC fistula is shown in Fig. 2.16.

Lastly, the cavernous ICA accounts for 2–9% of intracranial aneurysms with a relatively small risk of subarachnoid hemorrhage (0.2–0.4% per year) given the

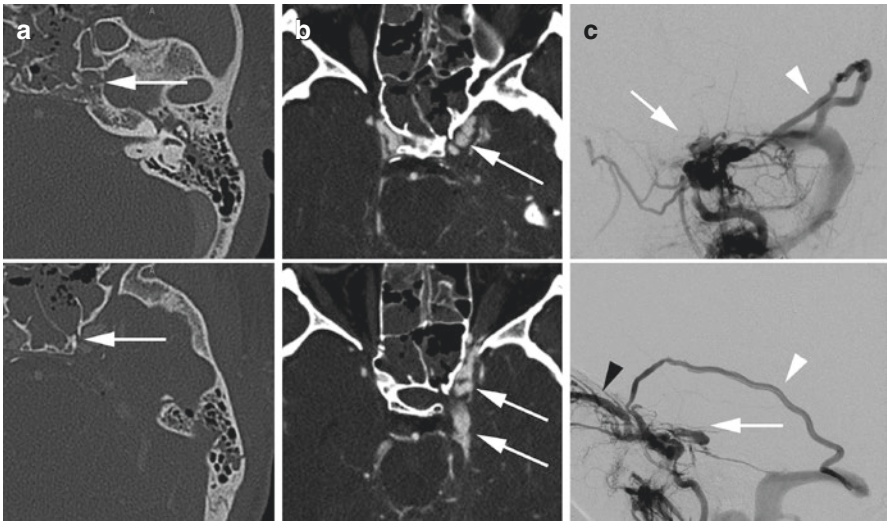

Fig. 2.16 Direct cavernous carotid fistula. Patient following a motor vehicle crash with skull base fractures and left cavernous carotid fistula. CT bone algorithm (**a**, top and bottom) demonstrates extensive skull base fractures through the sphenoid sinus and carotid canal (arrows). CTA (**b**, top and bottom) showed asymmetrically enlarged and irregular left cavernous sinus with arterial phase enhancement (arrows). DSA (**c**, top = frontal projection and bottom = lateral projection) confirmed a posttraumatic direct cavernous carotid fistula (arrow) with cervical ICA injection. Immediate venous contrast enhancement was present in the vein of Labbe (white arrowhead) extending into the sigmoid sinus as well as the superior ophthalmic vein (black arrowhead)

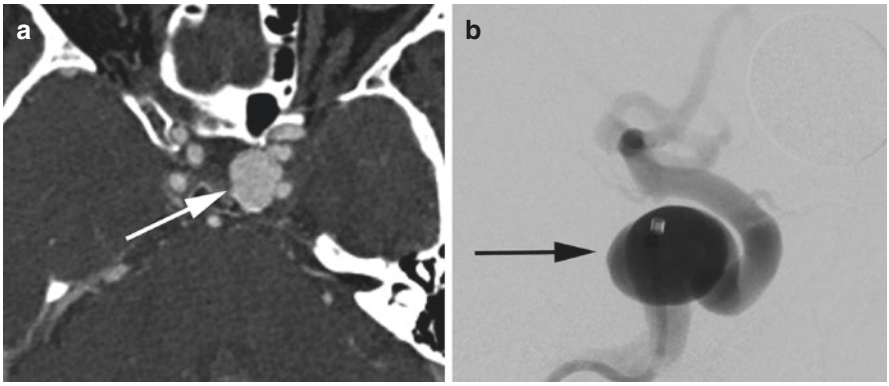

Fig. 2.17 Cavernous internal carotid artery aneurysm. Patient with a large cavernous ICA aneurysm. CTA (**a**) and DSA (**b**) show the large saccular aneurysm involving the cavernous ICA segment (arrows)

location in the cavernous sinus. Still, novel treatments have evolved to cover giant aneurysms in this location which can erode into adjacent structures and cause symptoms from mass effect [29]. An example of a cavernous ICA aneurysm is shown in Fig. 2.17. Further, perivascular spread of sinus disease can occur in this segment, with an example of perivascular spread of sphenoid sinus infection along the cavernous ICA is shown in Fig. 2.18.

Clinoid Segment (C5)

After the anterior genu of the cavernous segment, the ICA passes through the proximal dural ring and becomes a relatively short segment at the level of the clinoid process, the 'clinoid' segment. At this point, the ICA travels through the distal dural ring and becomes subarachnoid. This segment is relatively short, but also an important site of pathology including atherosclerosis, vessel injury and aneurysm, with an example in Fig. 2.19. Special consideration must be given to the 'carotid cave', a subsegment occurring along the medial aspect of the ICA between the clinoid and ophthalmic segments, where a redundant portion of the distal dural ring can project inferiorly into the cavernous sinus. Aneurysms here are *intradural*, but can appear extradural on angiographic imaging Fig. 2.20.

Ophthalmic Segment (C6)

The ophthalmic artery origin occurs just after the distal dural ring, and at this point becomes the 'ophthalmic' segment up to the origin of the posterior communicating artery. This is the site for ophthalmic aneurysms, which occur at the junction of the

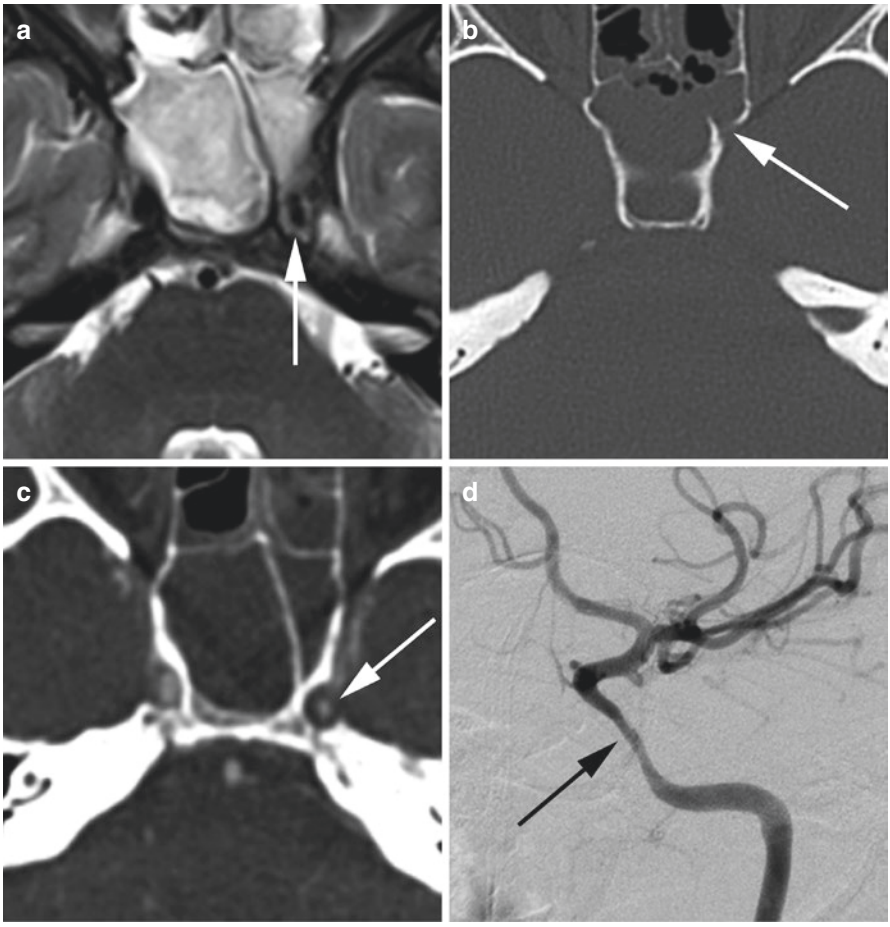

Fig. 2.18 Cavernous internal carotid artery perivascular spread of infection. Patient presenting with headache was evaluated initially with a noncontrast MRI. MRI T2-weighted images (**a**) showed completely opacified sphenoid sinuses and adjacent narrowing of the left cavernous ICA flow void (arrow). CT bone algorithm (**b**) showed dehiscence along the left sphenoid sinus (arrow) with adjacent narrowing of the left cavernous ICA on CTA (**c**, arrow). DSA (**d**) confirmed fusiform narrowing of the left cavernous ICA (arrow). Further testing revealed fusibacterium necrophorum infection of the sphenoid sinuses

ophthalmic artery origin and adjacent ICA (Fig. 2.21). This segment can also be injured along the dorsal ICA, forming the important do-not-miss 'blister' aneurysm or pseudoaneurysm associated with rapid growth rate and high morbidity and mortality (Fig. 2.22).

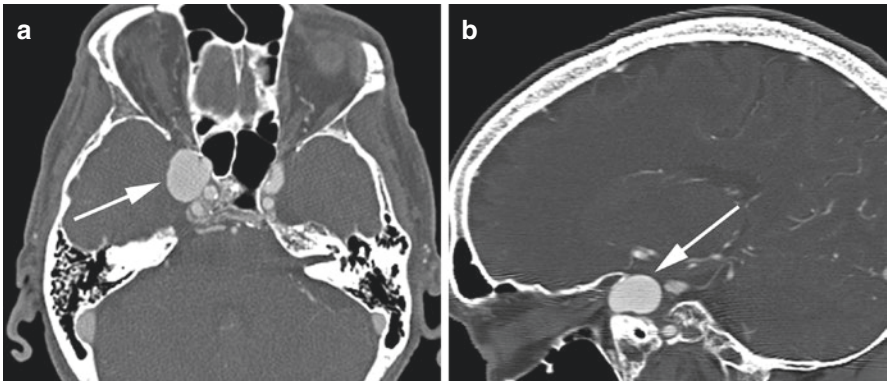

Fig. 2.19 Clinoid internal carotid artery aneurysm. Patient with a clinoid segment ICA aneurysm. Axial (**a**) and sagittal (**b**) CTA demonstrates a large aneurysm involving the clinoid ICA segment (arrows)

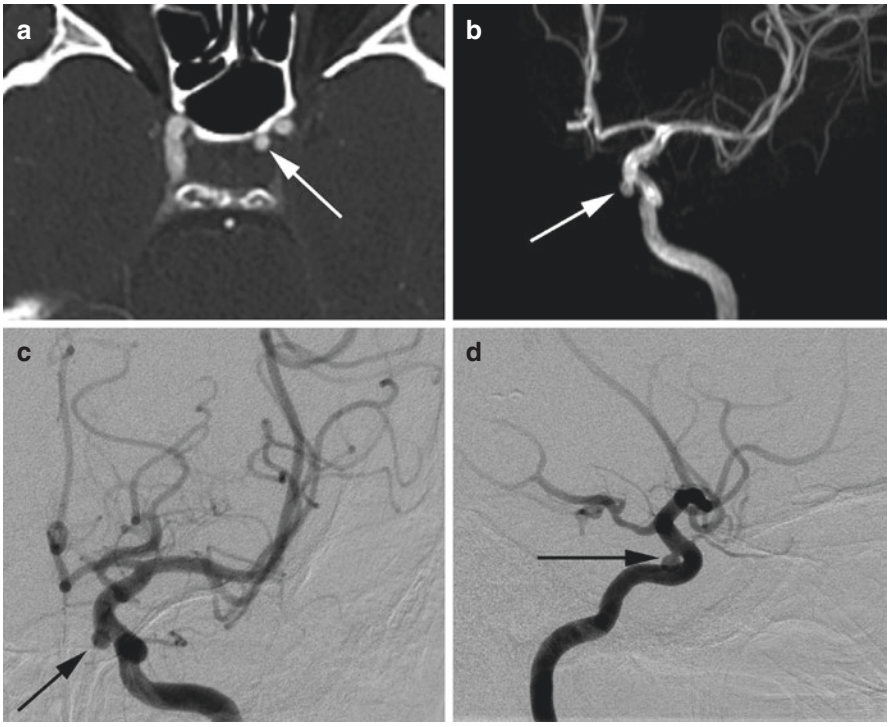

Fig. 2.20 Carotid cave aneurysm. Patient with a left carotid cave aneurysm. CTA (**a**), time-of-flight MRA 3D reformat (**b**), DSA frontal (**c**) and lateral projections (**d**) show a small ICA aneurysm involving the carotid cave (arrow). A carotid cave aneurysm is intradural, but may appear extradural due to inferomedial projection into the cavernous sinus

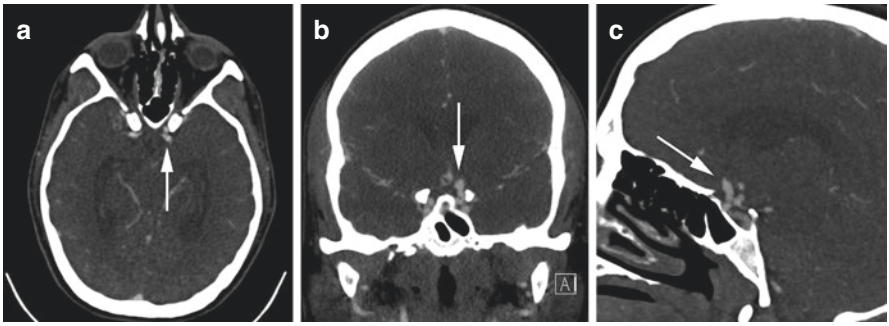

Fig. 2.21 Ophthalmic segment aneurysm. Patient with a left ophthalmic segment aneurysm. Axial (**a**), coronal (**b**) and sagittal (**c**) CTA showing a superiorly projecting left ICA ophthalmic segment aneurysm (arrow)

Communicating Segment (C7)

The terminal ICA segment extends from the posterior communicating artery origin to the ICA terminus and is known as the 'communicating' segment. This segment includes the anterior choroidal artery, which supplies the posterior limb of the internal capsule [30, 31]. Anterior choroidal aneurysms (Fig. 2.23), posterior communicating artery aneurysms (Fig. 2.24) and fusiform aneurysms such as can be seen with HIV vasculopathy (Fig. 2.25) can occur in this segment. At the ICA terminus the vessel divides into the MCA M1 and ACA A1 segments, and from these originate deep brain perforators including both the medial and lateral lenticulostriates supplying the caudate and putamen.

ICA Anatomic Variants

Persistent Carotid-Basilar Anastomoses

There are 4 potential variant anastomoses between the ICA and vertebral artery not including the posterior communicating artery. The most common of these is the persistent trigeminal artery with a lateral or medial course (**Saltzman type I or II**) that occurs in 0.1–0.2% of the population [32]. The second most common is the persistent hypoglossal artery (0.03–0.09%), which arises from the ICA at C1-C2 and passes through the hypoglossal canal to join the basilar artery. The proatlantal intersegmental artery is the third most common variant and arises from the cervical ICA at C2-C3 and joins with a vertebral artery or more rarely ECA to vertebral artery at the craniocervical junction. The fourth variant, the persistent otic artery is extremely rare and connects the petrous ICA to basilar artery through the internal auditory canal.

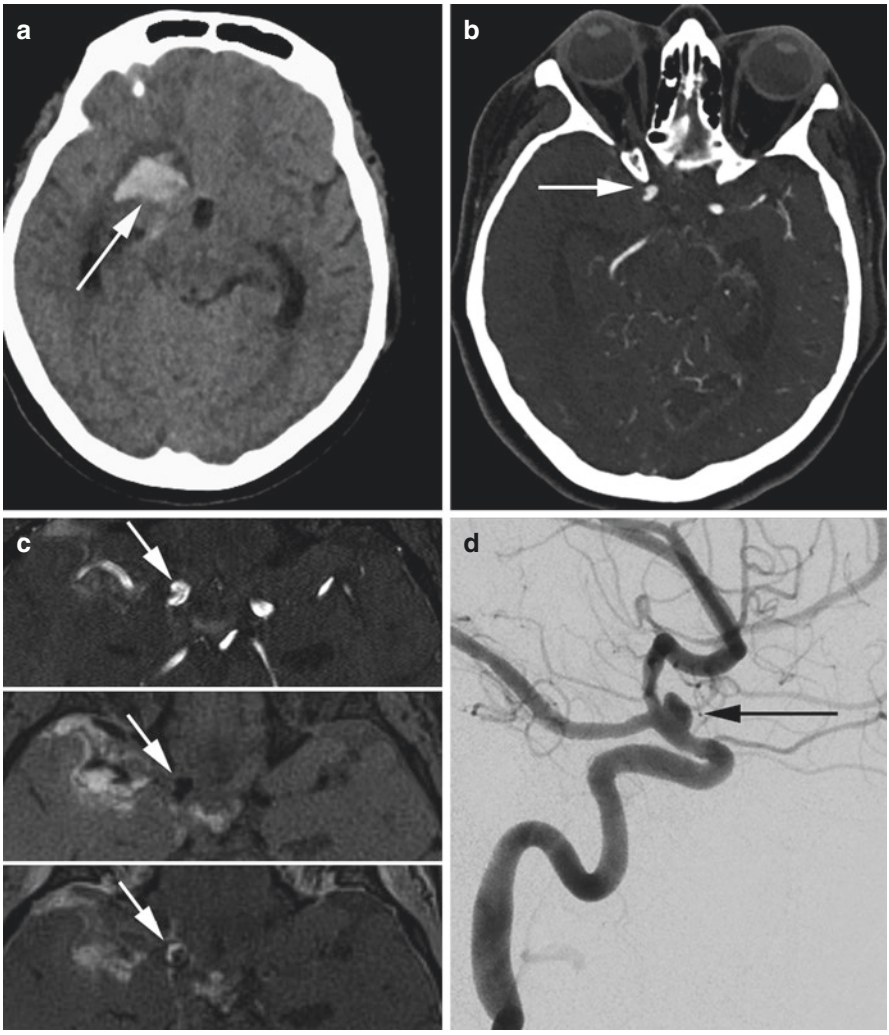

Fig. 2.22 Dorsal variant internal carotid artery pseudoaneurysm. Patient with intraparenchymal and subarachnoid hemorrhage on initial CT scan (**a**). Axial CTA (**b**) shows a right ICA ophthalmic segment blister aneurysm (arrow). Vessel wall imaging was performed with the aneurysm (arrow) on time-of-flight (**c**, top), flow suppressed T1 precontrast (**c**, middle), and with vessel wall enhancement flow suppressed T1 postcontrast (**c**, bottom). DSA (**d**) confirms a dorsal variant ICA pseudoaneurysm (arrow)

Often one clue to the existence of a carotid-basilar anastomosis is a small vertebrobasilar system that abruptly changes to normal caliber, with the anastomosis found on close inspection. One must also search for other variants, since aneurysms are reported in up to 15% of cases as are other anomalies including fenestrations, absent vessels or dAVF. These anomalies are most often asymptomatic and treatment is not required unless there is an associated aneurysm or fistula.

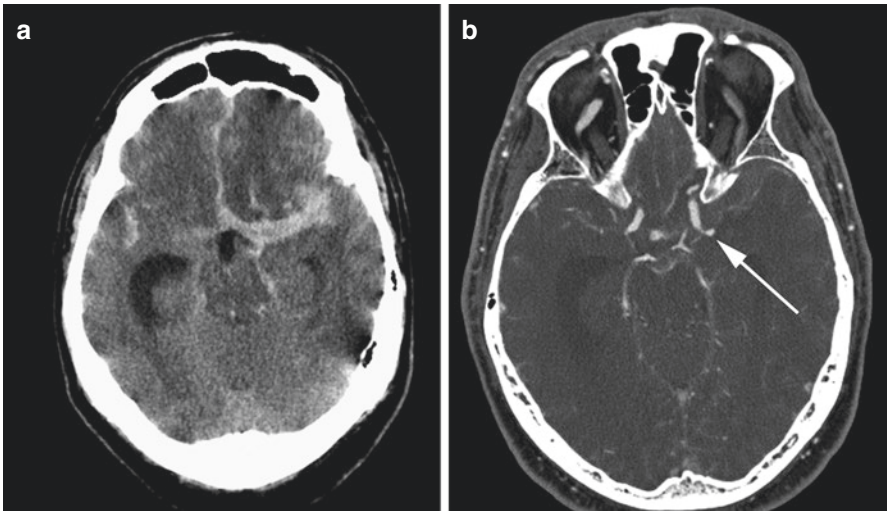

Fig. 2.23 Anterior choroidal aneurysm. Patient presenting with acute subarachnoid hemorrhage asymmetric to the left on noncontrast CT (**a**). CTA (**b**) showed a recently ruptured anterior choroidal artery aneurysm (arrow)

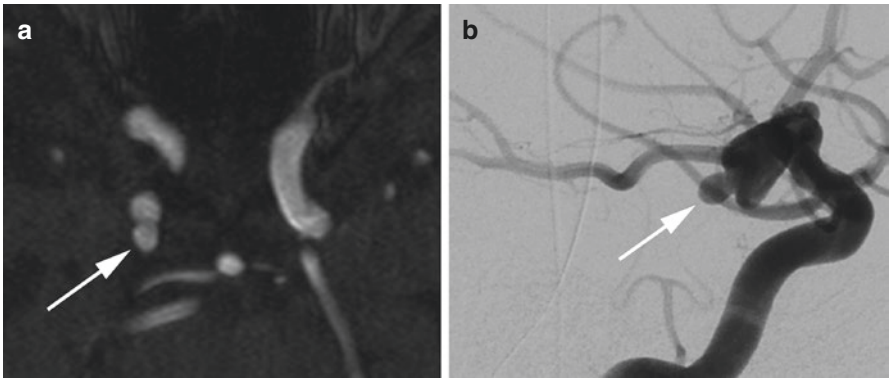

Fig. 2.24 Posterior communicating artery aneurysm. Patient with a right-sided posterior communicating artery aneurysm. Time-of-flight MRA (**a**) and DSA (**b**) demonstrate a wide-necked, irregular 7 × 8 mm posterior communicating artery aneurysm with an associated daughter sac (arrow)

Aberrant ICA

This congenital variant results from failed formation of the extracranial ICA and is actually formed by a collateral pathway from the ascending pharyngeal artery to the inferior tympanic artery then the caroticotympanic artery, finally connecting with the posterolateral petrous ICA. On axial CTA, the aberrant ICA crosses the middle ear from posterior to anterior, with an associated enlarged tympanic canaliculus located anteromedial to the stylomastoid foramen/mastoid segment of the facial

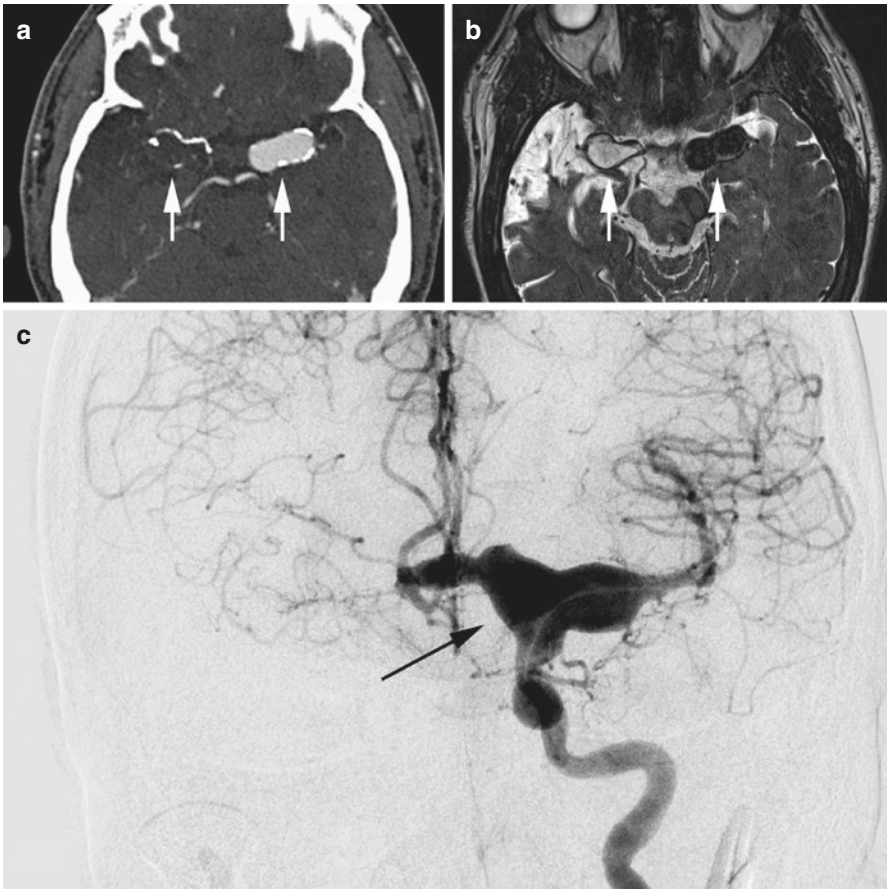

Fig. 2.25 Carotid terminus vasculopathy related to HIV. Patient with longstanding HIV. CTA (**a**) and T2-weighted MRI (**b**) demonstrate fusiform aneurysms involving the bilateral carotid termini (arrows) with occlusion on the right. DSA with left ICA injection (**c**) shows fusiform dilation of the carotid terminus, A1 ACA and M1 MCA segments (arrow)

nerve. 30% have an associated persistent stapedial artery with an absent foramen spinosum and an enlarged anterior tympanic segment of the facial nerve on CT. While often asymptomatic and incidentally found on CTA or otoscopy, these can be associated with pulsatile tinnitus and conductive hearing loss.

Lateral ICA

In this rare variant along the temporal bone, the ICA enters the anterior middle ear cavity more lateral than normal as can be seen in Fig. 2.26. By definition, if the petrous ICA is lateral to the mid cochlea on axial images, the ICA is lateralized.

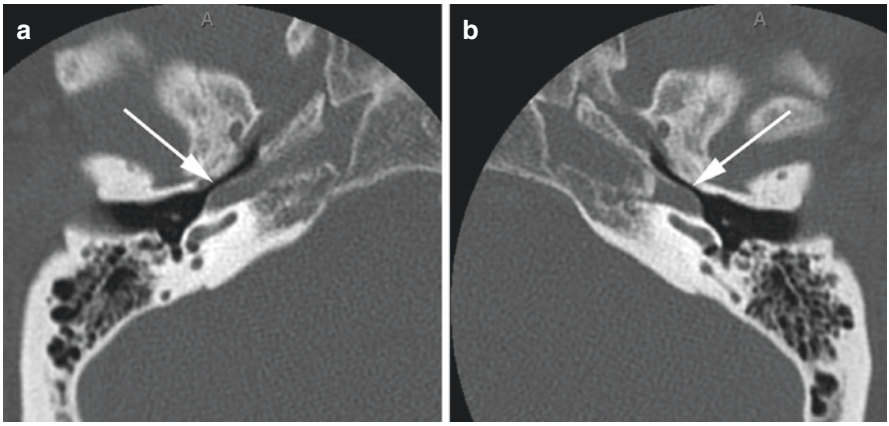

Fig. 2.26 Lateralized internal carotid artery. Patient with asymptomatic bilateral lateralized ICA's. Noncontrast CT of the temporal bones right (**a**) and left (**b**) ICA's coursing along the cochlear promontories (arrows), but without a persistent stapedial artery or enlarged tympanic canaliculus

Often the lateral ICA osseous covering is dehiscent and this can mimic aberrant ICA on MIP images. With a lateral ICA, there is no association with a persistent stapedial artery and the inferior tympanic canaliculus is not enlarged. These are often asymptomatic incidental findings on CTA or otoscopic exam, though some patients can present with pulsatile tinnitus.

Summary

In conclusion, the carotid artery is an important conduit for blood supply to the brain, face and neck. Carotid artery anatomy forms the basis of plaque formation and affects downstream stroke risk. An intricate knowledge is essential for appropriate surgical and endovascular treatment planning.

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Chapter 3
Imaging of the Carotid Artery

Michael McLaughlin and J. Scott McNally

Digital Subtraction Angiography (DSA)

Background

Initially developed in the 1970's, digital subtraction angiography (DSA) allows detailed visualization of the arterial vasculature of the head and neck with high-resolution imaging. High spatial resolution refers to the ability to distinguish between very small structures, usually expressed in line pairs per millimeter. The x-ray technology used in DSA is able to achieve the highest spatial resolution amongst imaging modalities. DSA was previously the primary method of detecting carotid stenosis [1, 2] and is still considered gold-standard for stenosis measurement [3, 4].

DSA requires intra-arterial access, most often through a vascular sheath placed in the femoral artery. A catheter is placed through the sheath and advanced into the arteries of the head and neck for contrast injection. An initial preinjection "mask" image is obtained to subtract background soft tissue, skeletal structures and hardware from subsequent postinjection images. Iodinated contrast is then injected through the catheter while serial fluoroscopic images are obtained. After subtracting the mask image, only high-resolution images of the contrast filled arteries remain. Pixel shifting techniques can be used to account for small amounts of patient motion between pre/post injection as needed.

M. McLaughlin · J. S. McNally (✉)
Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA
e-mail: Michael.McLaughlin@hsc.utah.edu; scott.mcnally@hsc.utah.edu

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Interpretation

Serial fluoroscopic images depict both the arterial and venous phases following contrast injection, and can be examined for pathology affecting either.

The arterial vasculature is examined for stenosis, intraluminal clot or occlusion, luminal irregularity, dissection flap, or aneurysm. Prior to non-invasive cross-sectional imaging, DSA was also used as a primary means to detect mass effect and tumor blush.

Venous phase images are also evaluated to look for venous sinus stenosis or thrombosis.

Images may detect early contrast opacification of a venous structure during the arterial phase, and this arteriovenous shunting can indicate the presence of an arteriovenous fistula or malformation.

Advantages/Disadvantages

In addition to providing the highest resolution vascular imaging, DSA allows real time interventions to be performed during the procedure. This can include vascular stent placement for arterial stenosis; embolization of aneurysms, vascular malformations, or actively bleeding vessels; and clot retrieval or administration of intra-arterial thrombolytics for large vessel occlusions.

DSA was once considered the standard of lumen imaging of the carotid artery due to its high resolution. It does, however, have inherent procedural risks of catheter angiography including vessel injury, bleeding, and stroke. DSA also often has higher radiation doses than other methods of carotid artery imaging [5]. Over time it has been largely replaced with non-invasive methods of imaging the lumen, which include ultrasound, CTA and MRA, though it is still used as a gold standard measurement of stenosis in problematic cases and primarily used for interventional cases.

Ultrasound (US)

Background

Duplex ultrasound (US) of the carotid arteries is named such because of the two methods it uses. One, B-mode US, creates gray scale images that correspond to plaque composition. The second, Doppler US, evaluates blood flow velocity and uses this information to determine percent diameter stenosis based on comparison data between US and DSA.

Interpretation

Doppler US detects flow velocities and detects stenosis indirectly by peak systolic velocity (PSV) and systolic ratio between the ICA and CC (PSV ICA/CC). In addition to PSV, spectral broadening and aliasing are additional criteria supportive of high grade stenosis (Fig. 3.1). The primary criteria used to detect stenosis are SRU criteria as listed in Table 3.1. SRU criteria correspond to NASCET criteria and include the following criteria for 70–99% stenosis: PSV >230 cm/s, Systolic ratio >4 (PSV of the ICA/CCA).

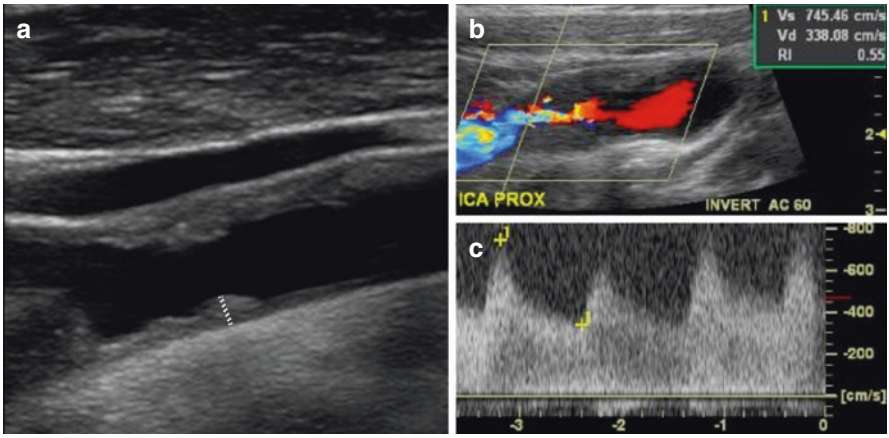

Fig. 3.1 Ultrasound imaging of carotid plaque. Ultrasound in a patient with severe carotid stenosis. B mode (grayscale) ultrasound image (**a**) of the right common carotid artery just proximal to the carotid bifurcation in the longitudinal plane demonstrates mildly echogenic atherosclerotic plaque along the vessel wall with intima to media thickness (IMT) measured by the dotted line. Color Doppler ultrasound at the level of severe stenosis (**b**) shows high systolic velocity of 745.46 cm/s. M-mode ultrasound (**c**) also demonstrates elevated PSV, spectral broadening and aliasing are additional criteria supportive of high grade stenosis

Table 3.1 Society of Radiologists in Ultrasound (SRU) consensus criteria for carotid artery stenosis measurement on ultrasound

	Normal	<50% ICA Stenosis	50–69% ICA Stenosis	≥70% ICA Stenosis	Occlusion
ICA PSV	<125 cm/s	<125 cm/s	125–230 cm/s	>230 cm/s	Undetectable
ICA/CCA PSV Ratio	<2.0	<2.0	2.0–4.0	>4.0	Undetectable
ICA EDV	<40 cm/s	<40 cm/s	40–100 cm/s	>100 cm/s	Undetectable
Plaque or Intimal Thickening	None	Visible	Visible	Visible with Luminal Narrowing	Lumen not Visualized

The interpretation of B-mode US depends on echogenicity of plaque components. In the setting of early disease, B-mode US is also used to measure intima-to-media thickness (IMT) (Fig. 3.1). In later disease, B-mode US can detect calcification, lipid-rich necrotic core (LRNC), and potentially intraplaque hemorrhage (IPH) though the sensitivity and specificity are far lower than MRI compared to pathology. Calcification can be detected by hyperechoic line with posterior acoustic shadowing.

Advantages/Disadvantages

Ultrasound (US) has some particular advantages over other carotid imaging modalities. Because it is cheap, US offers a method to screen for carotid disease without undue burden to the healthcare system. It is also a non-contrast method, eliminating any issues with contrast allergy, renal clearance, or tissue deposition pertaining to contrast. Furthermore, it does not involve a radiation dose. Given its high resolution, US is the method of choice to measure IMT, linked to vascular dysfunction, future cardiovascular disease risk and cognitive deficits. Furthermore, US can measure vessel wall compliance and elasticity using real time measurement of lumen diameter changes during systole and diastole and comparing that to concurrent blood pressure measurement.

There are some disadvantages of both B-mode and doppler US. One major limitation of US compared to DSA, CTA, and MRA is the lack of assessment of the intracranial vasculature for any downstream stenosis or other pathology. Another inherent limitation is related to calcification. When calcification is thick or peripheral in nature, this can limit evaluation of deeper plaque components and velocities due to posterior acoustic shadowing [6]. Another limitation of US is its operator dependence. Sonographers require specific training in order to be accurate in the measurements of velocities that are highly dependent on the angle of insonation. Additionally, Doppler US itself is not as accurate in comparison to CTA and MRA in calculating percent diameter stenosis. A study by Anzidei in 2012 compared MRA, CTA and US to reference standard DSA in 336 carotid arteries [7]. This group found no difference between the accuracy of CTA (97%) or MRA (95%) stenosis measurements compared to DSA, and both out-performed US (76%). Further disadvantages of US include poor delineation of vulnerable plaque components including lipid rich necrotic core and intraplaque hemorrhage relative to gold standard carotid plaque MRI.

Computed Tomography Angiography (CTA)

Background

Computed tomography angiography (CTA) of the carotid arteries involves the acquisition of helical CT images through the neck following the intravenous administration of iodinated contrast. The timing of contrast administration is controlled

using a bolus tracking technique to optimize the opacification of the systemic arterial vasculature. This allows detailed examination of the carotid artery luminal caliber, atherosclerotic plaque calcification, and surrounding structures and landmarks.

The advent of multi-detector CT scanners allowed thin sub-millimeter acquisition, which enables reconstruction of images in all planes (axial, coronal, and sagittal) without visible step-off. Maximum intensity projection (MIP) and 3-D reformatted images may also be generated.

Interpretation

CTA can be used to measure luminal stenosis using NASCET criteria. As with DSA, the diameter of the narrowed segment of the internal carotid artery is measured in cross section (b) and compared to a downstream segment (a) of the internal carotid artery (ICA) without narrowing (Fig. 3.2). Stenosis is then expressed as a

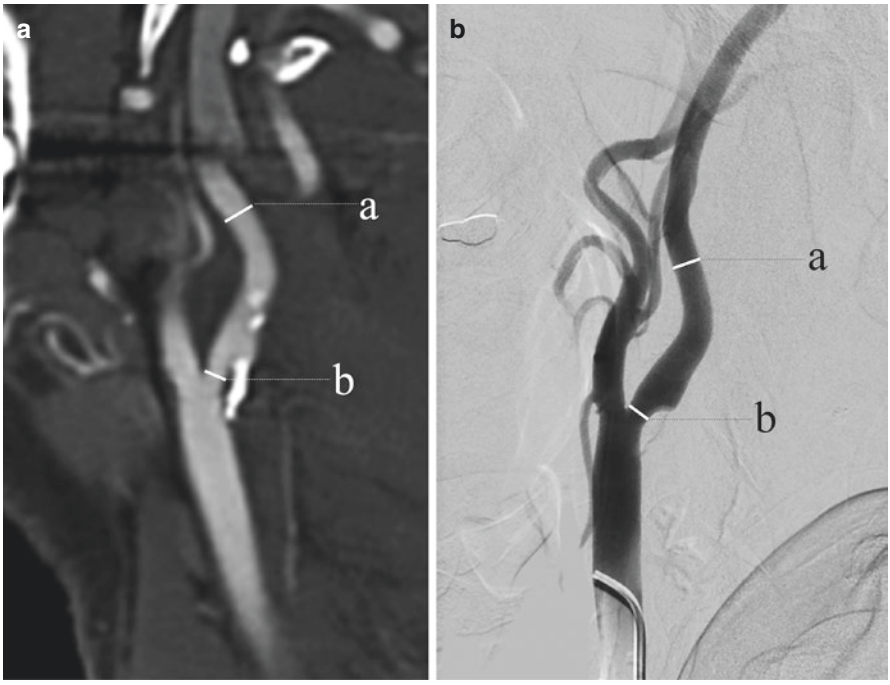

Fig. 3.2 CTA and DSA NASCET criteria for carotid stenosis measurement. Sagittal CTA image through the right carotid bifurcation demonstrates a partially calcified atherosclerotic plaque which results in luminal narrowing of the proximal right internal carotid artery (**a**). Percent diameter stenosis is calculated using NASCET criteria, where the diameter at the stenosis (b) is compared to a downstream segment of the ICA (above the carotid bulb) without narrowing (a). Stenosis is calculated by the equation $100 * (a - b)/a$. DSA in the same patient demonstrates luminal narrowing with NASCET measurements again shown (**b**). Note that DSA in this case provides information about the degree of luminal stenosis only, with no information on plaque composition

percent narrowing of the ICA [100 ∗ (a − b)/a]. Stenosis can also be estimated with a single mm-stenosis measurement on CTA, with thresholds of ≤1.3 mm equivalent to ≥70% stenosis and 1.4–2.2 mm equivalent to 50–70% stenosis by NASCET, as has been shown by Bartlett and Fox in 2006 and 2008 [8, 9].

A special consideration in measuring carotid stenosis is that of a 'near-occlusion'. Near-occlusion was described as part of the NASCET trial by Dr. Fox as meeting these criteria [10]: (1) visible narrowing, (2) downstream ICA caliber of <3 mm, (3) ECA:ICA ratio of <1.25, and (4) if DSA is used, cross filling of contrast is identified from contralateral injection.

CTA also provides information regarding plaque composition [11]. This allows the interpreter to distinguish between heavily calcified plaque and "soft" atheromatous plaque, which may be more vulnerable to plaque rupture [12].

In addition to lumen stenosis, there are many other CTA markers of plaque vulnerability including plaque ulceration, maximum plaque thickness, intraluminal thrombus and patterns of calcification. The 'smoking gun' marker identifying a carotid-source stroke is the intraluminal thrombus which is rare but highly associated with acute ischemic stroke (Fig. 3.3). This is identified by the characteristic 'donut sign' by Menon et al. [13]. Additionally, ulceration has been shown to represent an important marker of carotid plaque vulnerability [14]. On multivariable regression analysis, particular CTA imaging markers identifying intraplaque hemorrhage include the "CTA rim sign", which is defined as a thick soft atheromatous plaque measuring >2 mm surrounded by a thin rim of calcification measuring <2 mm [15] (Fig. 3.4). This is a marker of plaque vulnerability and is highly predictive of intraplaque hemorrhage, indicating a potential carotid source of stroke independent of stenosis.

CTA also allows visualization of the surrounding soft tissues to evaluate for extrinsic compression of the carotid artery or any other incidental pathology in the head or neck, including carotid space masses such as paragangliomas (Fig. 3.5).

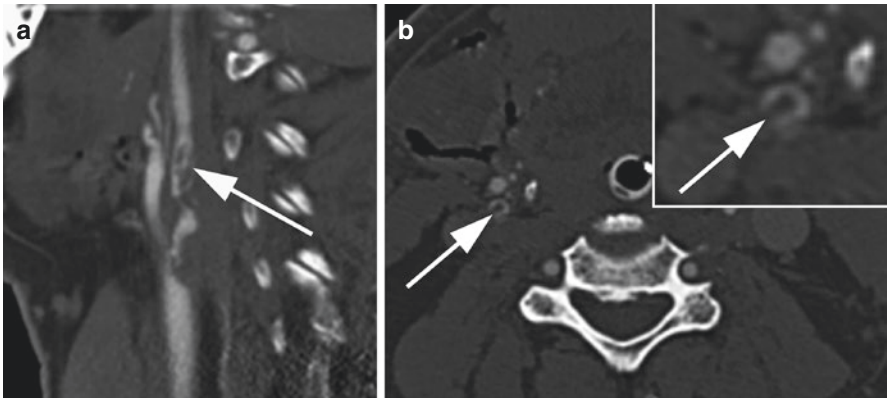

Fig. 3.3 Carotid intraluminal thrombus. Sagittal (**a**) CTA image through the right ICA demonstrates intraluminal thrombus with intraluminal low attenuation clot (arrow). This has the characteristic "donut sign" on axial images (**b**, inset) with central clot (arrow) surrounded by high attenuation contrast

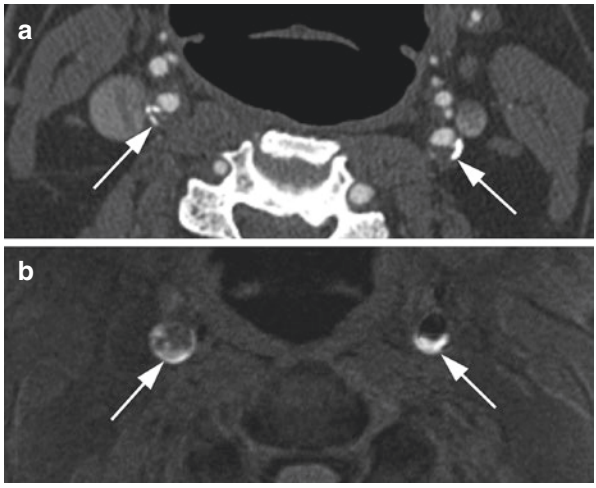

Fig. 3.4 CTA rim-sign indicating carotid intraplaque hemorrhage. This patient presented with bilateral acute infarcts but no cardiac embolic sources after 3 months of monitoring and with <50% carotid stenosis. CTA (**a**), however, demonstrated bilateral 'rim-signs' (arrows) indicating likely carotid IPH. MRI was suggested with MPRAGE (**b**) confirming bilateral carotid IPH (arrows)

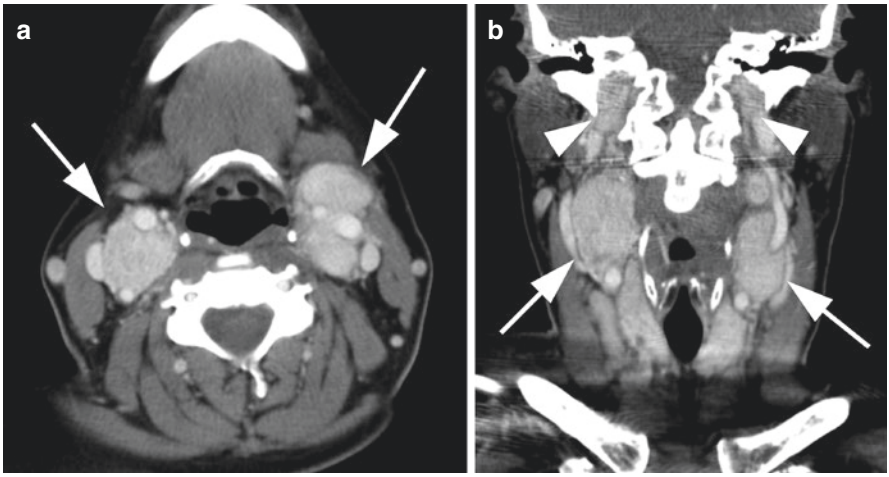

Fig. 3.5 Carotid body paraganglioma. Axial contrast enhanced CTA image through the neck demonstrates bilateral avidly-enhancing masses located within the carotid sheaths (arrows) and splaying the internal and external carotid arteries compatible with carotid body paragangliomas. In addition to the bilateral carotid body tumors, there were bilateral glomus jugulare paragangliomas seen on coronal CTA (**b**, arrowheads) in this patient with succinate dehydrogenase-B (SDH-B) hereditary paraganglioma syndrome

Advantages/Disadvantages

Advantages of CTA include that it can be rapidly acquired and is readily available for stroke workup in every major medical center in the U.S.

CTA allows accurate determination of luminal stenosis in the setting of any calcified atherosclerotic plaque, which often significantly limits carotid ultrasound.

In addition, more proximal and distal stenoses can be accurately identified with CTA compared to US, which is limited in its field of view by the skeleton.

The main disadvantage of CTA is an associated radiation dose, which is often higher than non-contrast CT studies of the head and neck [16]. Medical radiation sources have dramatically increased the average radiation dose per person from an average radiation exposure in the United States of about 3.6 mSv (360 mrem) in the 1980s to 6.2 mSv (620 mrem) in 2006 [16, 17]. Acute stroke workup with CTA and CT perfusion imparts a mean effective dose of 16.4 mSv, approximately 6X the dose of a noncontrast CT head [18]. At these doses, there is a small but significant concern for radiation-induced carcinogenesis. While the individual risk of CT-associated cancer is small, when applied to a large population undergoing CT, this may create a public health issue some years in the future. As reviewed elsewhere, extrapolating data from Hiroshima, Three Mile Island, and Chernobyl radiation workers to current CT use, it has been estimated that about 1.5–2.0% of all cancers in the US may be attributable to the radiation from CT studies [19]. Databases on organ specific doses from CT scans have been developed for future large scale epidemiologic studies which have been proposed to address this important question [20].

In the absence of the rim sign however, CTA is insensitive for the detection of carotid IPH as plaque density on CTA is a very poor detector.

Patients with acutely impaired renal function or a history of contrast allergy may be unable to receive iodinated contrast injection. Patients with contrast allergies can receive premedication prior to CTA to reduce the risk of a reaction, however this can take several hours to accomplish and is often not feasible in the emergent setting. The most effective pretreatment regimen requires 13 h (50 mg prednisone orally 13, 7, and 1 h prior and 50 mg diphenhydramine orally 1 h prior to contrast administration).

MRA

Background

Magnetic resonance angiography (MRA) involves the use of a static magnetic field and multiple radiofrequency pulses to manipulate protons within the body, which then emit a signal dependent on tissue composition. The signal emitted by the tissues is then reconstructed into an image.

MRA may be performed either without or with gadolinium contrast material.

Non-contrast MRA uses the time of flight (TOF) technique in order to image vessels. TOF creates image contrast between flowing blood and the surrounding soft tissues by applying multiple excitation pulses to the same slice or slab. The stationary tissues become saturated by these pulses, while inflowing blood sees fewer exci-

tation pulses and therefore maintains relatively high signal compared to the surrounding tissue [21]. This gives information about the luminal diameter and the direction of flow within that vessel.

Contrast enhanced MRA involves the serial acquisition of MR images following the intravenous administration of gadolinium contrast material, with timing optimized to evaluate the arterial vasculature. This has the advantage of better contrast resolution and decreased imaging artifacts compared to non-contrast TOF. It does not, however, give information regarding flow direction. Many standard clinical protocols incorporate both techniques.

Additional sequences used in the MRA of the carotid arteries include T1 weighted imaging with fat saturation or similar techniques (i.e. magnetization prepared rapid acquisition gradient echo (MPRAGE)), which aid in detecting intramural hematoma in dissection or carotid intraplaque hemorrhage (Fig. 3.6).

Interpretation

As with CTA, the luminal diameter of the internal carotid arteries can be measured and compared to a normalized downstream segment to calculate the percent stenosis according to the NASCET criteria.

The presence of atherosclerotic plaque ulceration and intraluminal thrombus may also be visualized on MRA, similar to CTA.

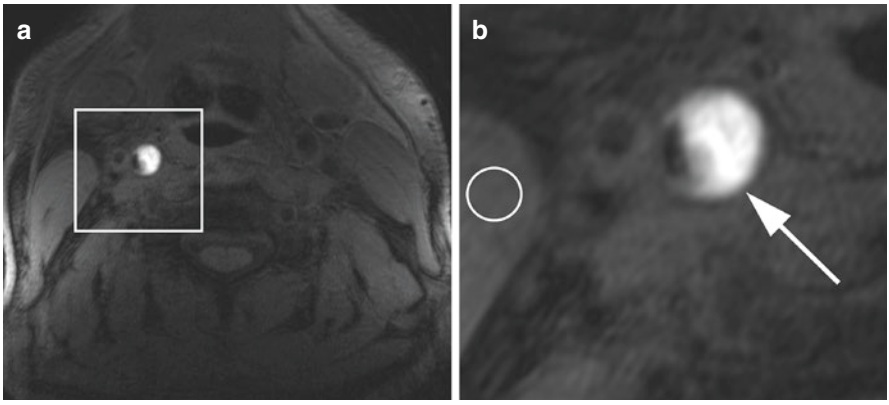

Fig. 3.6 Carotid intraplaque hemorrhage. Axial MPRAGE image through the neck demonstrates high signal in a large right carotid plaque (**a**). Magnified view (**b**) shows greater than 2X the signal in the adjacent sternocleidomastoid muscle (circle) within the large right carotid plaque (arrow) consistent with carotid intraplaque hemorrhage (IPH)

MRA has the added advantage of detecting intramural hematoma or carotid intraplaque hemorrhage on the T1 weighted or MPRAGE sequences, both of which are independently associated with ipsilateral stroke [22, 23].

Advantages/Disadvantages

The major advantage of MRA over CTA is the lack of ionizing radiation associated with the modality.

As previously discussed, MRA is able to detect carotid vessel wall characteristics (e.g. intramural hematoma and intraplaque hemorrhage) that are clinically important but not often visible on CTA.

In patients unable to receive iodinated or gadolinium contrast material due to allergy or acutely impaired renal function, non-contrast MRA techniques may be utilized to visualize areas of severe luminal stenosis and the direction of flow within the carotid and vertebral arteries.

The major disadvantages of MRA include the increased time required to acquire the images and the increased cost of MR imaging compared to CT.

The use of MRI may be limited in patients who have implanted medical devices such as pacemakers, many of which are either MRI conditional or may be incompatible.

Vessel Wall (vw)MRI

Background

Advanced MR techniques have been developed that allow more detailed characterization of carotid atherosclerotic plaque beyond the degree of luminal stenosis and presence of surface irregularity or plaque ulceration.

Additional sequences added to the standard MRA protocols include heavily T1 weighted sequences (i.e. MPRAGE), thin section T2 weighted imaging, and dynamic contrast enhanced T1 weighted imaging.

Interpretation

Intraplaque Hemorrhage (IPH)

The presence of carotid IPH has been shown to be a marker of plaque instability and independent risk factor for ipsilateral ischemic events even in non-stenotic carotid plaques [22]. This is thought to reflect intraplaque rupture related to delamination from tensile and shear forces [24]. It is thought to represent a medically refractory state, and is often present for months to years and stimulates plaque progression [25]. Most importantly, IPH has been shown to be highly associated with future stroke with an annual stroke risk between 15% and 45% and hazard ratios between 4.59 and 12.2 [26–28]. This is despite standard medical therapy including statins, platelet inhibition, treatment of high blood pressure and lifestyle modification.

Carotid IPH can be detected on heavily T1 weighted sequences (Fig. 3.6). It is most easily detected using MPRAGE, and is defined as the presence of increased signal measuring greater than two times that within the adjacent sternocleidomastoid muscle with a sensitivity and specificity for IPH >90% [29]. This sequence compares well with histology, and also discriminates between other plaque components, namely lipid rich necrotic core (LNRC) [30]. Additional sequences have been shown to detect IPH, including Simultaneous Non-contrast Angiography and intra-Plaque hemorrhage (SNAP) [31]. However, other sequences including 3D TOF and conventional T1 fat sat have poor accuracy in diagnosing IPH compared to MPRAGE [32].

Detecting IPH is extremely important. It is one of the optimal carotid imaging factors associated with acute ipsilateral stroke, and acts independently of stenosis [22]. It accounts for many strokes in patients with <50% stenosis, and can identify a potential stroke source in patients that would otherwise have been characterized as cryptogenic [33].

Lipid Rich Necrotic Core (LRNC)

LRNC refers to the fibrofatty elements that compose the majority of the atherosclerotic plaque, often containing macrophages and other inflammatory cells. The presence of a large LRNC has been shown to be a marker of plaque vulnerability and propensity to rupture [34, 35].

LRNC may be identified on T2 weighted MR images as an area of low signal intensity within the atheromatous plaque (Fig. 3.7) [36], but is most easily detected using contrast enhanced T1 weighted MR images as a focal area of non-enhancement within the vessel wall [37, 38].

Like the presence of IPH, the volume of LRNC may be used further to stratify those patients who would benefit from more aggressive lipid lowering therapy.

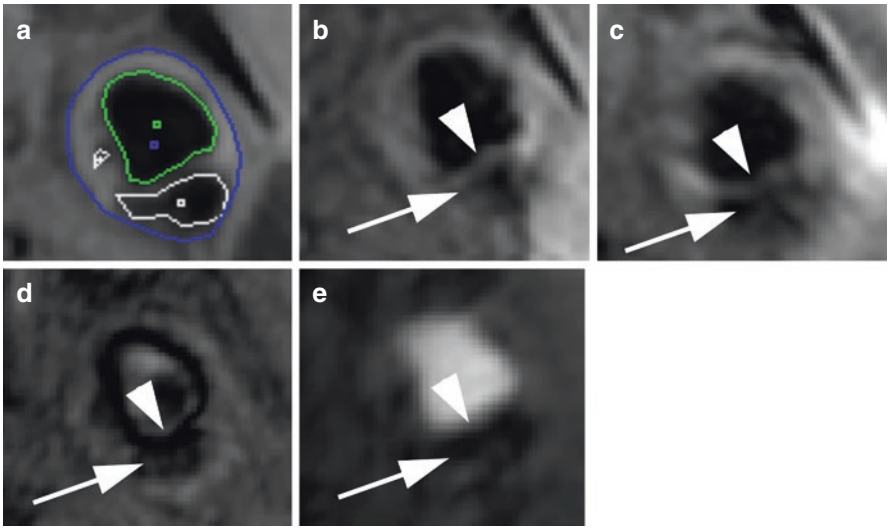

Fig. 3.7 Carotid plaque vessel wall imaging with lipid rich necrotic core and fibrous cap. Segmented left carotid bifurcation plaque on 2D T1-weighted imaging (**a**) with lumen (green tracing), outer wall (blue tracing), and lipid rich necrotic core (LRNC, white tracing). 3D T1-weighted images (**b**) show low signal within the LRNC (arrow) and a thinned fibrous cap (arrowhead). Similarly, 3D T2-weighted images (**b**) show low signal within the LRNC (arrow) and a thinned fibrous cap (arrowhead). 3D MPRAGE (**d**) also shows low signal within the LRNC (arrow) and a difficult to see fibrous cap (arrowhead). On bright blood time-of-flight images (**e**), the LRNC (arrow) and fibrous cap (arrowhead) are not easily seen

Thin Ruptured Fibrous Cap (TRFC)

In addition to IPH and large LRNC, the presence of a thin fibrous cap (Fig. 3.7) overlying the atherosclerotic plaque with areas of fissuring of rupture is an additional marker of plaque vulnerability.

A thick, less vulnerable fibrous cap can be visualized on contrast enhanced T1 weighted images as a high signal intensity band adjacent to the vessel lumen.

If this band of enhancement is not visualized or is interrupted, this indicates the presence of a thin FC. The absence of this band and the presence of a bright gray region adjacent to the lumen indicated fissuring or rupture of the FC [37, 39].

Adventitial Neovascular Dysfunction

Carotid IPH has been linked to adventitial neovascularity with leakage or rupture from neovessels that originate from the adventitia (Fig. 3.8). One method to measure plaque neovessel leakage is carotid plaque dynamic contrast enhanced MRI (DCE-MRI) [40–42]. Contrast leakage can be measured by the DCE-MRI metric K^{trans} (the contrast transfer constant) (Fig. 3.9), and this metric corresponds to both microvessel density and macrophage density as a measure of inflammation.

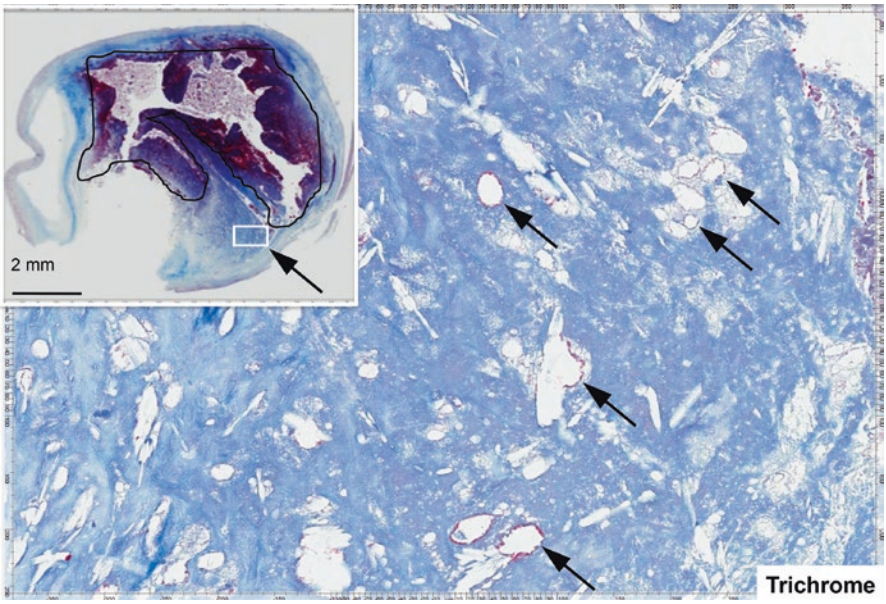

Fig. 3.8 Carotid intraplaque hemorrhage and plaque neovascularity. In this Trichrome stain of a carotid endarterectomy specimen, a large area of IPH (inset, dark purple outlined in black) is present within the LRNC. Adjacent to the large IPH and within the LRNC (rectangle) are multiple plaque neovessels (arrows) representing vasa vasorum, most of which originate from the adventitia

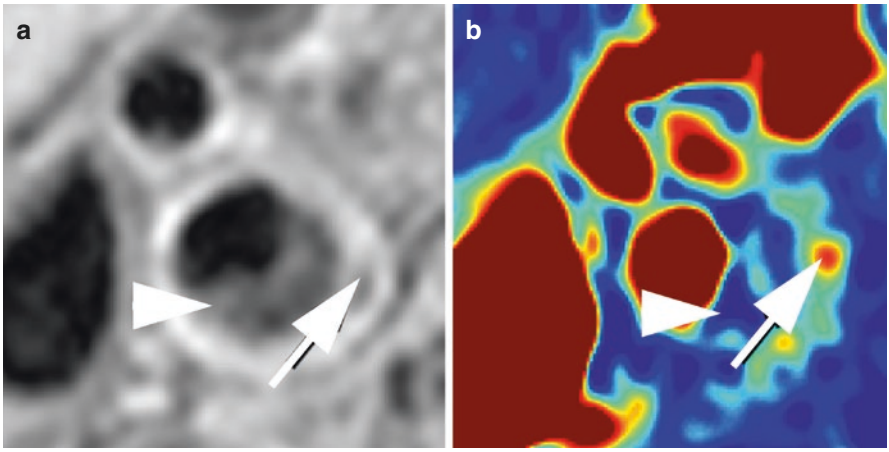

Fig. 3.9 Carotid plaque dynamic contrast enhanced MRI. Carotid plaque dynamic contrast enhanced (DCE)-MRI can allow quantification of plaque neovessel density and permeability. One DCE metric is the contrast transfer constant K^{trans}, which is a measure of tissue blood flow ($F\rho$) and capillary permeability-surface area product ($PS\rho$). In this 3D T1-weighted image (**a**) of a left carotid plaque, there is a large central lipid core (arrowhead) and a rim of higher signal along the adventitia (arrow). Corresponding DCE-MRI K^{trans} map shows elevated K^{trans} along the periphery (arrow), and this correlates with microvessel density, macrophage density and vulnerable plaque features such as IPH

Importantly, K^{trans} correlates with carotid IPH demonstrating a pathophysiological link between adventitial neovascular dysfunction and plaque vulnerability [43]. This method can also be used to monitor treatment response to high intensity lipid lowering therapy [44].

Advantages/Disadvantages

MR sequences optimized for evaluation of the vessel wall and carotid plaque components may be performed on both 1.5 T and 3.0 T MR scanners with or without dedicated carotid coils, and therefore can be implemented in most clinical practices.

The major disadvantages of MR vessel wall imaging include longer imaging acquisition times and the cost associated with MR imaging. In addition, evaluation of LRNC and FC requires the administration of gadolinium based contrast agents which is contraindicated in patients with documented allergies or severe renal failure on dialysis.

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Chapter 4
Introduction to Carotid Atherosclerosis

Chelsea Meyer, Jerdan Ruff, and Adam de Havenon

Historical Perspective

The history of the carotid artery begins in Antiquity. The first known description involving the carotid artery is attributed to Hippocrates (400–200 BC), and his description of the symptoms of apoplexy, meaning "to strike down" [1]. The name carotid is derived from the ancient Greek for sleep/stupor and stems from Rufus of Ephesis's experiments (100 AD), in which external compression of the carotid artery produced sleep in the affected individual [2]. Galen, experimenting in sheep, identified a "rete mirable," a network of blood vessels, which he believed humans also possessed, and mistakenly attributed loss of consciousness to simultaneous ligation of the artery and nerve in the neck. He therefore favored changing the name, but wrote, "The artery has so long retained the name, that I will not deprive it of it, and as at present fixed, so let it remain" [3].

The idea of the rete mirable remained until the Renaissance, when Andreas Vesalius dispelled it in his detailed anatomical description of the brain [4, 5]. The idea of the carotid artery carrying spirits and vapours to and from the brain, however, persisted. In the 1500s, Ambroise Pare described the carotid artery as the "sleepy artery," carrying the Animal spirit, which is created by the arteries and veins of the brain. He noted a humor which blocks the passage of this spirit, results in Apoplexies and Palsies, whereby patients "do languish and seem dead, sometimes destitute of motion, sometimes wanting both sense and motion." The prevailing knowledge of the day was that a blockage of this humor resulted in purulent fluid in

C. Meyer · J. Ruff · A. de Havenon (✉)
Department of Neurology, University of Utah, Salt Lake City, UT, USA
e-mail: Chelsea.meyer@hsc.utah.edu; Jerdan.ruff@hsc.utah.edu; Adam.dehavenon@hsc.utah.edu

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the cerebral ventricle. Pare identified the carotid as a branch off of the great artery "arising forth from the left ventricle of the heart," and traced its course in the neck adjacent to the jugular veins and windpipe. He identified the branches of the internal and external carotid arteries, but wrote that each contributed many branches to the neck, face, and calvarium [6]. Gabriel Fallopio gave the initial description of the circle of Willis, although Thomas Willis was the first to describe its collateral physiology by injecting ink into the vessel and observing its spread [7–10]. Willis actually doubted occlusive vascular disease as the etiology of apoplexy, after dissecting a man "not troubled by astonishing disease" and found both the right vertebral and carotid arteries occluded [8, 9].

It wasn't until 1628 when William Harvey described the circulation of blood, that the idea of the carotid artery being a conduit for the animal spirit was discarded. This description paved the way for the discovery of apoplexy as a cessation of blood flow to the brain, first described by Johann Wepfer [11]. Although more famous for his discovery of intracerebral hemorrhage as a cause of apoplexy, Wepfer theorized that the disease might be caused by occlusion of the carotid artery by small fibrous bodies (preventing sufficient blood from reaching the brain) [12, 13].

One of the first histologic descriptions of atherosclerosis has been attributed to Leonardo Da Vinci who wrote that vessels in the elderly restrict the flow of blood through thickening of the tunics [14] and the first link between atherosclerotic disease of the carotid and apoplexy is attributed to Francois Bayle in 1677 [9, 10, 15]. It wasn't until 1769, when Giambattista Morgagni wrote *De Sedibus et Causis Morborum per Anatomen Indagatis* (The Seats and Causes of Diseases Investigated by Anatomy) that apoplexy was classified as either sanguinous or serous, laying the foundation for the modern classification of stroke as either ischemic or hemorrhagic [9, 16, 17].

Epidemiology

Stroke is the leading cause of long-term disability and the 5th leading cause of death in the United States with 795,000 strokes per year [18]. Of those patients with ischemic stroke, 15–20% are attributed to large artery atherosclerosis [19]. The incidence of carotid artery stenosis in patients with ischemic strokes is ~13 per 100,000 [20]. Large artery atherosclerosis has been separated into intracranial and extracranial atherosclerosis because management strategies differ significantly from primarily medical management to interventional therapies, respectively. The most significant risk factors for atherosclerosis are hyperlipidemia and cigarette smoking, but there are also variations in the prevalence in different populations. For example, intracranial atherosclerosis is more prevalent in Asians and Black populations compared to Caucasians [21].

When evaluating for symptomatic atherosclerosis, the focus has previously been on the amount of stenosis. Large artery atherosclerosis was considered in patients with ≥50% stenosis in the relevant vessel; however, there has been research show-

ing that the plaque characteristics may be more predictive of ischemic stroke [20]. Complex plaques, defined as plaques with neovascularity, ulceration, echolucency or intraplaque hemorrhage, have been shown to have 4 times higher risk of ischemic stroke than standard plaques [22].

Clinical Presentation

Patients with carotid atherosclerosis will have varying clinical presentations and may be asymptomatic. The incidence of carotid atherosclerosis increases with age and is estimated that 7.5% of men and 5.0% of women over the age of 80 years old have ≥50% cervical carotid artery stenosis that are asymptomatic, compared to only 0.7% of men and 0.5% of women less than 60 years old [23]. Carotid atherosclerosis is considered symptomatic when it causes focal neurologic symptoms that are either transient or permanent.

The neurologic symptoms associated with carotid atherosclerosis will vary depending on the degree of ischemic damage. Patients may experience ipsilateral monocular vision loss (amaurosis fugax), contralateral hemisensory loss or contralateral hemiparesis. Patients can also present with contralateral homonymous hemianopia or quandrantanopia if there is damage to the optic radiation. If the ischemia is in their dominant hemisphere, they may have language impairment including expressive and receptive aphasia. If the non-dominant hemisphere is affected, patients are more likely to have contralateral neglect and visuospatial impairment. Syncope is less likely to be caused by carotid atherosclerosis and stenosis unless bilateral carotid arteries are severely stenotic; however, decreased responsiveness can be seen in basilar thrombosis.

On exam, patients may also have a carotid bruit when auscultating the neck on the ipsilateral side of stenosis. A carotid bruit only has a sensitivity of 53% and specificity of 83% for carotid stenosis ≥70% so its predictive value is limited [24]. An ocular bruit can also be auscultating over a patient's closed eye, which can be useful in assessing intracranial arterial stenosis. The ocular bruit can be heard on the ipsilateral side of stenosis or may be more prominent on the contralateral side because of compensatory increased flow, especially with an occluded internal carotid artery [25].

Carotid atherosclerosis can cause stroke by two mechanisms, either thromboembolism or hypoperfusion. Previous studies, like NASCET and ACAS, have been primarily focused on the degree of stenosis of carotid artery atherosclerosis, which correlates to the risk of hypoperfusion associated with that artery [26, 27]. As imaging has advanced, newer studies have focused on the plaque characteristics as markers for instability and thus the risk of thromboembolism.

Patients may present differently depending on whether the underlying etiology is decreased blood flow through a stenotic artery versus an atheroembolic event. If a patient has decreased perfusion through a stenotic vessel the symptoms may be reversible and present as a transient ischemic attack (TIA). These symptoms could

improve once flow was re-established by either an increase in blood pressure or positional changes, like lying flat. Ischemic damage on imaging will first be seen in watershed territories, which are areas between major vascular supplies. For carotid disease this is typically seen between the middle cerebral artery and posterior cerebral artery territories in the posterior parietal and anterior occipital region. When symptoms are secondary to an atheroembolic event, the symptoms are less likely to resolve with an increase in blood pressure or positional changes. Depending on the patient's collateral circulation, they may be able to compensate for the occluded vessel and thus may have some improvement in their symptoms, but that is less common.

Imaging Findings

Clinically, four imaging modalities are commonly used to assist in determining the stability and hemodynamic characteristics of carotid atherosclerotic plaque. These include carotid duplex ultrasound (CUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). While DSA is considered the gold standard diagnostic tool for carotid atherosclerosis, and is a required part of treatment with carotid stenting, it is not commonly done for routine diagnosis and surveillance, as less invasive techniques have become very accurate and confer less risk of complications [28].

Stenosis

DSA allows direct visualization of the degree of carotid stenosis, and allows direct visualization of the flow of contrast across the stenotic region and into the intracranial vessels. CUS allows measurement of the velocity of blood across a stenotic lesion, and the velocity is used to estimate the degree of stenosis in a vessel [28, 29].

Historically, CTA lacked sensitivity and specificity to detect carotid stenosis, but with the advent of dual source CT, increased detector density, and advanced software image processing, the sensitivity and specificity reach 0.93 and 0.94 respectively [28]. Conventional MRA can be performed with contrast (CE-MRA) or without contrast using time of flight (TOF MRA). CE-MRA has been shown to have high sensitivity and specificity for carotid stenosis, however TOF MRA has been shown to overestimate the degree of carotid stenosis at 1.5 T and 3.0 T MRI [30, 31].

Although the degree of carotid stenosis remains the standard indicator of disease severity and is used to make treatments about intervention, there is increasing recognition that factors such as plaque composition and morphology also have an impact on symptomatic carotid atherosclerosis, and can explain the etiology of ischemic stroke in patients with mild or moderate stenosis by standard measurement

criteria [29, 32]. Even the location of the stenosis with regard to the vessel lumen has implications for ischemic stroke risk, as stenotic vessels with an eccentric lumen have been found to confer a greater risk than equal vessels with concentric stenosis [33].

Intraluminal Thrombus

Detection of an intraluminal thrombus in patients who presents with ischemic stroke is a rare but emergent entity. An occlusive thrombus is typically characterized by an abrupt cut-off of the vessel on CTA, MRA, or DSA. A nonocclusive thrombus within the lumen may show a filling defect, and be visualized as a "donut sign," describing the circumferential appearance of blood flow around the thrombus [34]. Small thrombus adherent to the vessel wall is difficult to detect on CT, US, or DSA, and may be interpreted simply as stenosis. However, using advanced MRI techniques, the composition of atherosclerotic plaques is more easily described. Acute thrombus is rich in red blood cells and produces increased T2 signal relative to surrounding muscle [35]. As acute thrombi are rich in methemoglobin, the thrombus produces magnetic susceptibility effect on iron sensitive sequences such as gradient echo (GRE) or susceptibility weighted imaging (SWI). Older, organized thrombi are characterized by decreased T2 signal [35, 36]. Advanced techniques using specialized contrast have been developed for direct thrombus imaging on MRI, but these have mostly been studied in animals, and are not routinely used in clinical practice [35].

Ulceration

Carotid plaque ulceration represents a breakdown of the luminal portion of the plaque, creating an indentation, fissure, or erosion, and exposing the inner necrotic core of the lipid rich plaque directly to the circulating blood. Carotid plaques can be characterized as smooth, irregular, or ulcerated, based on the degree of surface fluctuation. Radiographically, and regardless of imaging modality, it is visualized as a cavity in the region of the atherosclerotic plaque, measuring >1 mm [29, 37, 38].

Lipid-Rich Necrotic Core

As the plaque grows, local hypoxia within the plaque creates intra-plaque necrosis [39]. MRI is the imaging modality of choice for detection of the lipid-rich necrotic core, which appears isointense on T1, hypointense on T2 weighted imaging, and shows less enhancement than fibrous tissues on CE-MRA [36].

Fibrous Cap

The fibrous cap (FC) is a layer of fibrous connective tissue on the luminal side of the atheroma, and plays an important role in the stability of the plaque. Lesions with a thin FC and a large lipid rich cord are thought to be unstable and confer a higher risk of plaque rupture [40, 41]. Thin FC and plaque rupture have both been found to be highly associated with recent stroke or TIA [42, 43]. Detection of FC thickness using US and CT techniques are limited, although on US, a FC can be seen as an echogenic structure, between the hypoechoic core of the atheroma and the anechogenic artery lumen [44]. Using MRI, detection of the FC is accomplished by differences in signal intensity of the lipid-rich core, and its absence limits detection. Thick FC can be seen as a hypointense band between the bright lumen and dark core, and thin FC is characterized by the absence of this band [45]. Detection can be limited by extensively calcified plaque, which can create a hypointense shadow across the FC. CE-MRA can improve detection through better signal differentiation, as the FC appears more hyperintense compared to the atheroma core [46, 47].

Intraplaque Hemorrhage

As the plaque grows, local hypoxia within the plaque promotes neovascularization of the blood vessel wall, which is thought to be due to a VEGF mediated sprouting of the vasa vasorum. These vessels are immature and fragile, with poorly formed basement membrane, and subject to frequent extravasation of blood into the surrounding tissue, similar to neovascularization found in tumors [39]. Intraplaque hemorrhage has been identified as a component of a vulnerable carotid plaque, and its detection has been found to add significant utility in determination of carotid-source stroke [48].

The utility of CT to detect intraplaque hemorrhage is limited due to inadequate soft tissue contrast resolution [49, 50]. Using MRI with a T1-weighted or magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence, intraplaque hemorrhage can be seen as a hyperintensity in the atherosclerotic region of the carotid artery [50–54].

Measurement Criteria – NASCET Versus ACAS

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS) are two prominent studies that evaluated the benefits of carotid endarterectomy for moderate to severe carotid stenosis in symptomatic and asymptomatic patients, respectively, and evaluated the benefits of endarterectomy. For NASCET, the measurement of stenosis was performed on angiograms with the percentage of stenosis calculated

from the narrowest part of stenosis divided by the normal part of the artery just distal to the carotid bulb but proximal to the stenosis [26]. This is limited in patients who have stenosis immediately following the carotid bulb with no normal proximal internal carotid artery preceding the stenosis. It was also using measurements obtained from angiograms, which are more invasive then our current methods of measurement like carotid ultrasounds or CT and MR angiograms.

The ACAS trial used different methods and measurement criteria then NASCET. ACAS also used measurements on angiography if performed within 60 days but if >60 days then they needed to also meet Doppler ultrasound as a means to confirm the stenosis. The ultrasound measurement in ACAS was heterogenous and based on instrument-specific frequency or velocity with a 90% positive predictive value cut-off. On angiography the stenosis is calculated by dividing the diameter of the narrowest part from the diameter at the first point distal to stenosis that has parallel arterial walls [27]. This varies from NASCET because the denominator is the normal artery proximal to the stenosis (but after the carotid bulb) in NASCET, whereas it is normal artery distal to the stenosis in ACAS.

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Chapter 5
Medical Management of Atherosclerotic Carotid Disease

Alexander J. Doud and David L. Tirschwell

Introduction

Medical management of vertebral and carotid atherosclerosis remains a mainstay of therapy for a large population of patients for whom endarterectomy or arterial stenting is not indicated. Here we will review the most recent advancements and clinical guidelines pertaining to the medical management of carotid artery disease. The review will include a discussion of the roles of statin medications, behavioral modifications, antihypertensives and glycemic control as well as the use of antiplatelet and anticoagulant medications as framed in the context of clinical management of extracranial carotid artery atherosclerosis.

Statin Therapy

Statins belong to a class of medications that have been proven to modify the course of atherosclerotic disease through inhibition of the HMG-COA reductase system. They have demonstrated multiple advantageous effects with both lipid modulating and anti-inflammatory benefits shown in multiple randomized controlled trials [1]. Furthermore, use of statins in carotid stenosis may lead to plaque stabilization and regression [2]. The SPARCL trial showed that high-dose atorvastatin (80 mg daily) was associated with a reduction in 5-year risk of ischemic stroke in patients who had suffered a prior stroke or TIA, with the most notable side effect of elevated liver enzymes and mild increase in 5 year relative risk of hemorrhagic stroke [3]. Other

A. J. Doud · D. L. Tirschwell (✉)
Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA
e-mail: jaalex@uw.edu; tirsch@uw.edu

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commonly described adverse patient reactions to statin medications include statin myositis and drug related rash. Simvastatin and pravastatin were found to be most likely to have favorable patient tolerability in a large meta-analysis by Naci [4]. In the same analysis, atorvastatin and rosuvastatin were found to have increased rates of discontinuation, with rates of discontinuation correlated with elevated doses of these medications. A surprising outcome in this analysis was an increased tendency to develop diabetes mellitus associated with statin use. Myopathy was not a demonstrated association, though the studies included in the meta-analysis were not all capable of detecting subclinical muscle toxicity. Given the high degree of tolerability of statins as a class, with overall low incidence of significant side effects, it is reasonable to trial an alternate statin to improve patient tolerance in those patients who have previously discontinued a statin therapy due to myopathy or other adverse side effects.

As of the most recently updated AHA guidelines for secondary prevention of ischemic stroke, there is strong evidence supporting the use of statins in patients with ischemic strokes presumed to arise from vessel-to-vessel atheroembolic origin (Class 1; Level B) [5]. Within the SPARCL cohort, the majority of patients within the high intensity statin group were able to achieve LDL levels of <100 mg/dL, which has subsequently been proposed as a reasonable goal [3]. More aggressive reduction of LDL to a goal of less than 70 has also been proposed for patients with diabetes and was implemented in the CREST 2 trial's maximal medical therapy arm [6, 7].

Quantifying the degree of atherosclerotic disease by the rate at which it progresses affords a useful metric for comparative analysis of therapeutic interventions, such as statins or the newer class of cholesterol lowering monoclonal antibodies called proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Serial assessment by magnetic resonance features of carotid artery plaque has demonstrated plaque stabilization in response to the PCSK9 inhibitor alirocumab in a cohort of three patients with statin-resistant atherosclerotic disease [8]. These agents have been separately shown to reduce risk of stroke and myocardial infarction through the monoclonal antibody binding to PCSK9 and dramatically lowering LDL-C. They are well tolerated, but currently prohibitively expensive without insurance coverage, which has been inconsistent at the time of this article. Nonetheless, the early data demonstrating a favorable effect for PCSK9 inhibition in carotid artery atherosclerotic plaque management warrants further investigation with larger patient populations.

Exercise Therapy/Diet/Lifestyle

The role of lifestyle modifications in the treatment of atherosclerosis may appear intuitive. However, the degree to which diet, exercise and lifestyle modifications influence the natural history of carotid artery disease has undergone recent evaluation in several studies. The AHA 2014 guidelines suggest that weight loss, dietary pref-

erence for fruits, vegetables and low-fat dairy products with occasional fish or poultry are behavioral factors associated with stroke risk reduction. There is level C evidence supporting these behavioral factors [5]. Venojarvi studied the impact of aerobic exercise on a cohort of middle-aged men with impaired glucose regulation and demonstrated improvement on the study's atherogenic index and metabolic syndrome score without substantially influencing measured oxidative stressors [9]. Other researchers have evaluated the role of behavioral modifications in the work environment to promote improved cardiovascular health including fitness wrist trackers, standing desks and periodic motivational interviews [10].

Exercise and lifestyle modifications impact health at multiple stages of life. Basic science investigations in mouse models show atheromatous metalloprotease activity is reduced in mice fed on a western diet participating in an aerobic exercise regimen compared to control mice independent of changes in weight [11]. Metalloprotease activity is related to progression of the atheromatous fibrous cap and produces a variety of cofactors influential in its development. A randomized controlled trial of caloric restriction, endurance exercise therapy, or both produced a reduction in body weight (7% reduction) and greater increase in VO2 in the exercise cohort when compared to caloric restriction, with similar changes demonstrated in systolic and diastolic blood pressure, non-HDL, and triglycerides. No change was identified in HDL cholesterol in this cohort of 52 patients [12].

Carotid intima-media thickness (cIMT) of the arterial wall is a metric of atherosclerotic disease burden that has been proposed as a longitudinal marker to assess the impact of diet, exercise and other behavioral modifications. The rate of change of cIMT has been demonstrated to slow in the setting of lifestyle modifications and aggregate early markers of atherosclerotic risk have been associated with venous O2 during aerobic exercise [13, 14]. Mindfulness-based meditation strategies may impart a chronic reduction in stress with downstream effects on sympathetic nervous system and the hypothalamopituitary axis, although formal scientific studies to assess these effects have not been performed [15]. The American Heart Association updated recommendations for exercise and lifestyle modifications summarized in "Life's Simple 7", an aggregated score ranging from 0 to 14, summarizing a patient's multifactor risk profile (smoking, hypertension, BMI, physical activity, diet, total cholesterol, and glycemic control) with each score allocated as 0 (poor), 1 (intermediate) and 2 (ideal). The inclusion of physical activity and diet in the Simple 7 reflects its importance in stroke prevention, including from carotid atherosclerosis. Additional research is needed to improve patients' ability to meet activity and dietary recommendations.

Antihypertensive Medications

Hypertension has long been identified as an important modifiable risk factor in the management of ischemic stroke and TIA. Recent estimates of prevalence in the United States suggest up to 78 million Americans fit the diagnosis of clinical hypertension,

which is variably defined as systolic blood pressures exceeding 140–160 mmHg systolic. Almost 70% of patients with stroke meet the criteria for hypertension at the time of stroke diagnosis [5].

The recently updated 2014 guidelines from the American Stroke Association recommend initiation of antihypertensive therapy for patients with systolic blood pressure of >140 systolic (or 90 mmHg diastolic) with Class I, level of evidence B. Targeting a lower blood pressure for patients with a systolic <140 prior to initiation of therapy was found to be of Class IIB, level C evidence. However, restarting antihypertensives in patients who previously took the medications is supported with class 1, level A evidence. Restarting these medications in the days following stroke is associated with less stroke recurrence as well as less incidence of other secondary cardiac endpoints [5]. Several days of delay in initiation of blood pressure lowering therapy are likely beneficial to avoid theoretical hypoperfusion of penumbral tissue. The exact timeline and treatment goal to restart antihypertensives is patient specific and likely should take into account the size, severity, laterality and degree of hemorrhagic conversion of a patient's stroke. Typical timelines for reinitiation are within 2 weeks of stroke with adjustment for the above factors.

The association between hypertension management and risk reduction in carotid artery atherosclerosis has not been specifically demonstrated, it is reasonable to expect that similar stroke risk reduction will apply in the setting of carotid artery disease. More objective measurement of IMT in relation to antihypertensive medications demonstrate reduced progression of atherosclerotic vessel wall thickening in association with ACE inhibitors, calcium channel blockers and potentially chlorthalidone [16]. While studies conducted in the early 2000s compared medical management to carotid endarterectomy in patients with carotid stenosis, the medical intervention arms of these studies were often suboptimal when compared to today's standard of antiplatelet, statin or hypertension management. As of yet, there is not a modern study comparing optimal medical management, including aggressive control of hypertension, to surgical intervention in patients with carotid atherosclerosis [16]. The ongoing CREST 2 trial will provide much-needed data on the effects of a modern implementation of optimal medical management protocol, but those results will not be available for several years.

Lowering HgA1c

Patients with TIA or ischemic stroke should underdo screening for diabetes as hyperglycemia is a modifiable risk factor associated with elevated risk of stroke. There is Class IIa, level C evidence supporting screening for diabetes in patients with ischemic stroke or TIA [5]. Significant reduction in cIMT has been shown to correlate with glycemic control in a 11-study meta-analysis by Yokoyama [17]. Biomarkers of carotid plaque risk which have been useful in evaluating the impact of HgA1c reduction include cIMT, percent wall volume (PWV), and presence or absence of a lipid rich necrotic core (LRNC). MRA evaluation of carotid atherosclerosis with attention

to these metrics in a population of patients with ischemic stroke demonstrated an association between vulnerable plaque features and A1c level [18]. Similar multivariate analyses demonstrated that fasting glucose was not useful in making predictions about carotid artery disease, but that A1c levels had a linear relationship with cIMT [19]. A prospective trial demonstrating significant reduction in progression of cIMT in response to A1c lowering would offer more compelling evidence, however the role of glycemic control in luminal remodeling is likely only one of the contributory factors. According to AHA guidelines, for patients with diabetes, glycemic control to A1C <7 is likely beneficial but has not been specifically demonstrated to reduce stroke risk [6].

Antiplatelet Therapy/Antithrombotic Therapy

Asymptomatic Disease

The Asymptomatic Cervical Bruit Study enrolled asymptomatic patients with 50% or more stenosis of at least one carotid artery and randomized them to 325 mg aspirin per day vs. placebo for prevention of vascular events. There were no significant differences found in the outcomes of ischemic vascular events or death [20]. Despite this, the 2014 Guidelines for Primary Prevention of Stroke from the American Stroke Association suggest that patients with asymptomatic carotid artery stenosis be treated with an aspirin for stroke prevention [21]. The level of evidence given is Class 1, Level of Evidence C, which reflects that the recommendation is based on limited data and consensus expert opinion. These 2014 guidelines also recommend that if patients undergo carotid endarterectomy for asymptomatic carotid stenosis, they should be treated with aspirin perioperatively and postoperatively, which is also Class 1, Level of Evidence C.

Recently Symptomatic Carotid Disease

The best antithrombotic medication for recently symptomatic internal carotid artery stenosis, specifically in the period between symptoms and surgical intervention, is not entirely clear. At least one antiplatelet medication should generally be used, and there are no situations with a clear mandate for anticoagulation, despite its use at times. The 2014 AHA Guidelines state "optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke, as outlined elsewhere in this guideline (Class I; Level of Evidence A)" [5]. In 2005, the CARESS randomized trial reported on the effective of dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin vs. aspirin alone in patients with ≥50% carotid stenosis, symptoms in the last 3 months and transcranial doppler ultrasound positive for

microembolic signals (MES). There was a significant decrease in MES positive patients on day 7 in the DAPT group, and though the study was not powered for clinical outcomes, there were less strokes in the DAPT group, suggesting possible greater treatment effectiveness [22]. If a patient does not undergo a surgical carotid procedure after recent symptoms, DAPT may be reasonable as a short-term option but probably should not be continued for long-term secondary prevention. Moreover, antiplatelet medications are clearly preferred over anticoagulation [6].

Perioperative Antithrombotic Use

Guidelines consistently recommend that 81–325 mg/day of aspirin be used before, through and after carotid endarterectomy (CEA) or stenting (CAS) [6]. The ACE randomized trial compared 4 doses of aspirin as perioperative antithrombotic; 81 mg, 325 mg, 650 mg and 1300 mg per day. At 30 days, the composite outcome of stroke, myocardial infarction or death was lower in the low dose groups (81 or 325 mg) compared to the high dose groups (650 or 1300 mg) (5·4% vs 7·0%, $p = 0{\cdot}07$), and at 3 months (6·2% vs 8·4%, $p = 0{\cdot}03$). These results led to the current lower antiplatelet dose recommendation [23]. Despite one small trial that suggested a benefit of DAPT prior to CEA and other supporting observational evidence, this approach is not broadly endorsed [24, 25].

Perioperative management of antithrombotics for patients undergoing CAS consistently includes recommendations for DAPT, given the thrombogenicity of stents. Accordingly, DAPT was used in a number of the large randomized trials including SPACE [26], EVA-3S [27], CREST [28] and ICSS [29]. This is reflected in the 2011 multi-society Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease which states "before and for a minimum of 30 days after CAS, dual-antiplatelet therapy with aspirin (81–325 mg daily) plus clopidogrel (75 mg daily) is recommended" [6]. In current practice, other medications may take the place of clopidogrel, but they are beyond the scope of this discussion.

Special Circumstances

The discovery of dissection of the carotid artery, especially in the setting of recent TIA or stroke mandates treatment with an antithrombotic agent. At the time of publication of the last AHA guidelines in 2011, no randomized trials had been done to inform this question, leading to the recommendation that "antithrombotic treatment with either an anticoagulant (heparin, low-molecular-weight heparin, or warfarin) or a platelet inhibitor (aspirin, clopidogrel, or the combination of extended-release dipyridamole plus aspirin) for at least 3–6 months is reasonable for patients with extracranial carotid or vertebral arterial dissection associated with ischemic stroke or TIA (Level of Evidence: B)." The CADISS (Cervical Artery Dissection in Stroke

Study) trial, published in 2015, randomized patients with extracranial carotid or vertebral dissection with symptoms in the last 7 days to either antiplatelet drugs or anticoagulant drugs for 3 months with the primary outcome of ipsilateral stroke or death. Outcome rates were overall very low, and there was no significant difference found between medication groups [30]. There remains no strong evidence favoring either antiplatelet or anticoagulation for carotid dissection, though many are drawn to the safer profile and ease of use of antiplatelet medications.

Carotid artery webs are a form of focal carotid bulb fibromuscular dysplasia, composed of nonatheromatous intimal fibrous proliferation causing a filling defect on imaging and commonly occur on the posterior lateral wall of the proximal internal carotid artery [31]. These vascular anomalies are increasingly recognized as causing otherwise cryptogenic ischemic strokes, especially in young patients, and in some series are present in up to 30% of such cases. Ischemic stroke related to carotid webs have been reported as having a high rate of recurrence regardless of antithrombotic therapy, and perhaps very low rates of recurrence after open or endovascular surgical intervention [31, 32]. As the pathophysiology is thought to relate to stagnant flow in the shadow of the web, at least one recent review hypothesized that warfarin anticoagulation might be a better antithrombotic than antiplatelet therapy, though more research is needed [32].

Conclusions

Where studies specific to the carotid artery are not available, generalization from research involving other arteries is likely reasonable given a shared underlying pathobiology [6]. Patients should initiate evaluation with minimally invasive diagnostic modalities with escalation to more invasive options only if necessary. AHA guidelines state that symptomatic patients with known carotid stenosis, or stenosis suspected due to detection of a bruit, should initially undergo carotid ultrasound. There may be a role for sonographic carotid screening in patients with multiple stroke risk factors or existing atherosclerosis in other arterial territories, however it is not clear that the addition of ultrasound benefits these patients as indications for initiation of optimal medical management are already present. Once the presence of carotid artery atherosclerotic disease is established, specifics of currently recommended optimal medical management include treatment of blood pressure to a goal of less than 140/90 (Level A evidence) with suggestion that ACE and calcium blocking antihypertensives may lead to most favorable remodeling of the carotid lumen. Dyslipidemia should be corrected with a high-intensity statin agent to an LDL goal of less than 100 (Level B evidence) or LDL less than 70 in patients with diabetes mellitus [6]. A brief summary of an aggressive medical management approach to carotid atherosclerotic disease is provided in Table 5.1 below.

Taken together the optimal medical management of patients with symptomatic and asymptomatic carotid artery disease is best described as a multifaceted approach aimed at reducing modifiable risk factors and providing patients with resources for

Table 5.1 Summary of Recommendations for management of carotid atherosclerotic disease

Statin Therapy	High intensity statin to LDL goal of <100 in general population. Goal LDL <70 in patients with diabetes.
Diet/Exercise Lifestyle	Level B evidence supports smoking cessation in patients with extracranial carotid stenosis. Likely benefit from exercise and dietary counseling.
Antihypertensive Medications	Blood pressure goal <140/90 with recommended agents including ACE inhibitors, calcium channel blockers and thiazide diuretics.
Lowering HgA1c	Likely benefit though no demonstrated reduction in stroke risk associated with A1c <7.0. Regimen including antihyperglycemics and dietary counseling is recommended.
Antiplatelet Therapy (Asymptomatic carotid disease)	Aspirin 81 mg daily. If undergoing carotid endarterectomy recommendations support perioperative aspirin.
Antiplatelet (Recently Symptomatic carotid disease)	Short-term dual antiplatelet therapy if patient unable to undergo a timely vascular intervention. Dual antiplatelet therapy not recommended for long-term management. Antiplatelet monotherapy preferred to anticoagulation.
Perioperative Antithrombotic Therapy	Aspirin 81–325 mg consistently recommended before during and after endarterectomy. Addition of clopidogrel 75 mg if undergoing stenting
Special Circumstances	Consensus support of antiplatelet therapy 81–325 mg for 3–6 months following symptomatic carotid dissection. No evidence demonstrating superiority of anticoagulation vs antiplatelet in this context. Expert support for anticoagulation in setting of carotid web, though limited available research.

their own lifestyle interventions. Furthermore, the comparison of the impact of optimal medical management to modern surgical interventions is an area for further study. However, it is clear that by taking measures aimed at maximal medical management with or without vascular intervention, there is an opportunity for substantial risk reduction as well as the opportunity to positively impact both patient quality of life and to reduce the global health burden attributable to the debilitating deficits of stroke.

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Chapter 6
Carotid Endarterectomy

Pedro Norat, Sauson Soldozy, Min S. Park, and M. Yashar S. Kalani

Indications

Carotid artery disease represents a significant cause of stroke worldwide [1]. Proper patient selection for carotid revascularization depends on carotid stenosis severity and clinical presentation. Patients with carotid stenosis can be classified as either symptomatic or asymptomatic. Carotid stenosis is considered symptomatic in the presence of stroke or transient ischemic attacks (TIAs). Patients are classified as asymptomatic if they have no previous history of either carotid artery or vertebrobasilar-related symptoms, with dizziness or lightheadedness being considered asymptomatic. Consequently, deciding when CEA is indicated has been the topic of much debate, with several randomized controlled trials (RCTs) having been conducted to determine the utility and safety of CEA in both symptomatic and asymptomatic patient populations.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have both established the benefit of CEA over medical management alone in symptomatic patients with severe carotid stenosis, defined as ≥70% stenosis. The NASCET randomized 328 patients to CEA

P. Norat · S. Soldozy · M. S. Park
Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA
e-mail: pn2se@virginia.edu; ss2ah@virginia.edu; Min.park@virginia.edu

M. Y. S. Kalani (✉)
University of Oxford, Oxford, U.K.
e-mail: yashar.kalani@merton.ox.ac.uk

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and 331 patients to medical therapy, but the trial was stopped after 18 months because a significant benefit was found in patients with 70–99% stenosis undergoing CEA. The ipsilateral stroke risk was 9% at 2 years with CEA versus 26% at 2 years with medical therapy alone [2]. In 1998, the NASCET published further results showing less marked benefit of CEA in patients with 50–69% stenosis, with risk of ipsilateral stroke being 15.7% at 5 years with CEA versus 22.2% at 5 years with medical management alone [3]. In patients with <50% stenosis, no benefit of CEA was found. The ECST randomized 2518 patients and reported similar findings, indicating CEA only benefits patients with ≥70% stenosis, with no benefit in patients with 50–69% stenosis [4]. It is currently recommended by the American Stroke Association and the American Heart Association (ASA/AHA) that symptomatic patients at average or low surgical risk undergo CEA within 6 months of symptom onset with ≥70% stenosis on non-invasive imaging (class I; level of evidence: A) or ≥50% stenosis on catheter angiography (class I; level of evidence: B) given the anticipated rate of perioperative stroke or mortality is less than 6%. In older patients, CEA is indicated in the event endovascular intervention is deemed unfavorable (class IIa; level of evidence: B). In patients with TIA or stroke without contraindications to early revascularization, it is better to perform CEA within 2 weeks of symptom onset rather than delaying surgery (class IIa; level of evidence: B). If symptomatic patients are at high risk of complications by CEA because of comorbidities, it is not well established if revascularization provides greater benefit over medical therapy alone (class IIb; level of evidence: B) [5]. Occasionally, a patient may present with bilateral carotid stenosis. While symptoms may be due to occlusion of a single carotid artery, the contralateral carotid artery may also exhibit stenosis. It is recommended that the symptomatic side is operated on first, followed by the other side 1–2 weeks after the first operation. If both sides are symptomatic, the more severe lesion is prioritized. Overall, patients presenting with severe stenosis and symptoms benefit greatly from surgical intervention.

The risk of performing CEA on asymptomatic carotid stenosis patients has also been weighed against the natural history of the disease and undergoing medical therapy. The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) demonstrated the benefit of CEA in asymptomatic patients with greater than 60% stenosis. The ACAS randomized 1662 patients to either medical management with CEA or medical management alone. The trial stopped after 2.7 years due to a net benefit being established in the CEA cohort, with projected 5-year rates of ipsilateral stroke, perioperative stroke, and death being 5.1% for CEA patients and 11% for the medical therapy group [6]. The ACST enrolled 3120 patients with asymptomatic carotid stenosis greater than 60%, reporting 6.4% rate of stroke or death over 5 years in the CEA group versus 11.7% in the medically managed group, providing further evidence that CEA is beneficial in asymptomatic patients with greater than 60% stenosis [7]. When selecting asymptomatic patients for carotid revascularization, individual factors such as comorbid conditions and life expectancy should be considered while discussing the risks and benefits of CEA in addition to understanding patient preferences (class I; level of evidence: C). Given a low risk of perioperative stroke, MI, and death, CEA is indicated in asymptomatic patients with greater than 70% stenosis (class

IIa; level of evidence: A). In asymptomatic patients at high risk of complications for carotid revascularization by CEA due to comorbidities, it is not well established if CEA or medical therapy alone is more effective (class IIb; level of evidence: B). It is important to also note that in the event a patient is found to have complete occlusion of their ICA and are still asymptomatic, then CEA is contraindicated. These patients and should be considered for bypass surgery instead.

Technique

There exist a variety of techniques when performing CEA as reported in literature. The procedure can be performed under three different kinds of anesthesia. The surgeon can choose from either a transverse or longitudinal cervical incision. Choice of monitoring modalities is also up to the discretion of the operating surgeon. Patients may be selectively shunted during the occlusion period of the operation, and the arteriotomy can be closed either primarily or with a patch. Given the different options to choose from when performing CEA, the surgeon should utilize the techniques they are most comfortable with. Regardless of the approach, all patients should be started and maintained on aspirin prior to the surgery. If heparinization was previously initiated, it may be continued throughout the procedure. Blood pressure medications should be continued as well, as the patient should ideally remain normotensive leading up to and throughout the perioperative period.

Positioning and Incision

The patient is positioned supine on the operating table with the arms tucked securely at the side. For obese patients, a small bump of towels should be placed between the shoulder blades to assist with exposure. In all patients the head should be extended slightly towards the floor and turned to the contralateral side to allow for better exposure of the carotid artery. In most patients, the ICA is positioned posterior to the ECA. Rotation of the head to the contralateral side moves the ICA laterally into view, facilitating dissection (Fig. 6.1). The degree of head rotation is determined by preoperative angiography or magnetic resonance angiography (MRA), which displays the anatomical position of the ICA and ECA relative to each other. Minor extension of the patient's neck can increase the operative space (Fig. 6.2), but care must be taken to avoid hyperextension in elderly patients with possible cervical spondylosis.

With the surgical site adequately exposed, the incision site can be identified. In most patients the carotid bifurcation lies two finger breaths below the angle of the jaw but may vary significantly in patients with high or low carotid bifurcations. Upon marking the incision, a surgical skin prep should be performed followed by placement of a drape over the operative site. The surgical incision is then made along the medial border of the sternocleidomastoid muscle, with the midpoint over

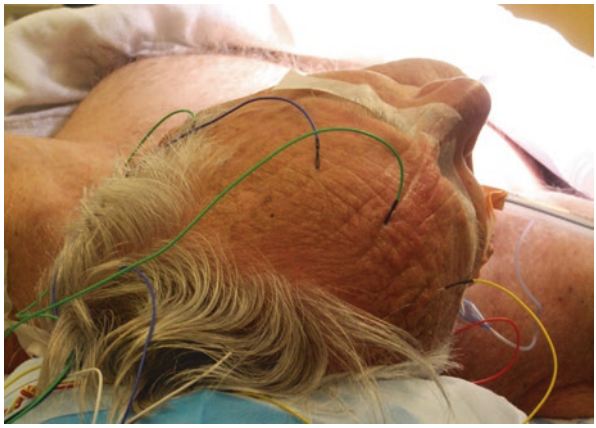

Fig. 6.1 Rotation of the head to the contralateral side in order to move the ICA laterally into view

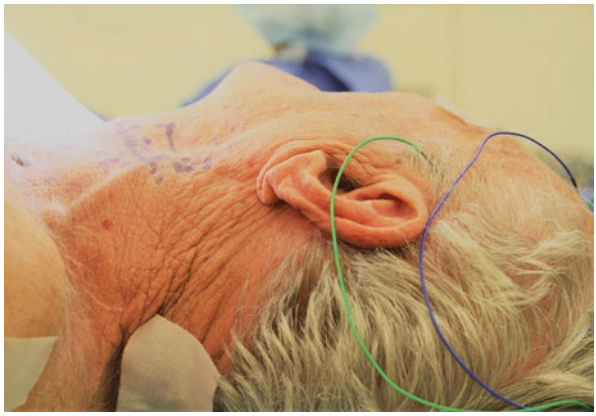

Fig. 6.2 Minor extension of the patient's neck enables a larger operative space

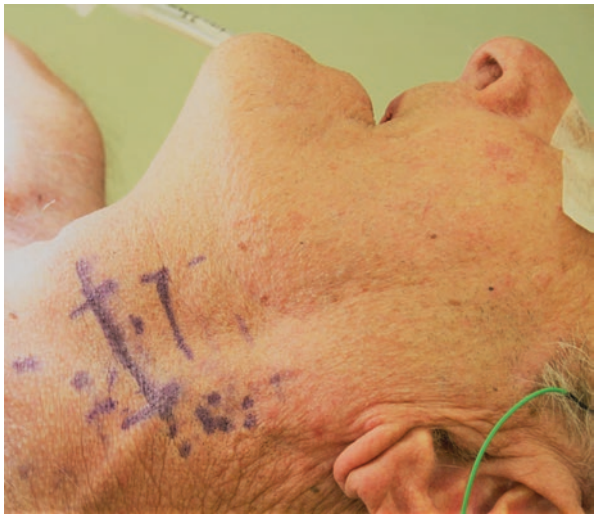

Fig. 6.3 Transverse incision begins 1 cm below the angle of the mandible and ends over the sternocleidomastoid muscle

the carotid bulb. The transverse incision begins about 1 cm below the angle of the mandible and ends over the sternocleidomastoid muscle (Fig. 6.3).

Exposure

After the incision is made, careful anatomic dissection and identification of cervical structures is necessary to prevent bleeding. Bipolar cautery can be utilized to control for superficial bleeding and maintenance of a blood-free field. The platysma muscle is divided with electrocautery. After division of the platysma, fixed metal retractors are placed to maintain field exposure. It is important for the retractors to remain positioned superficially throughout the procedure to prevent injury to the recurrent laryngeal nerve. The transverse cervical sensory nerve may be encountered in the superior portion of the incision and can be sacrificed if necessary.

Below the platysma, the medial border of the sternocleidomastoid muscle must be identified and traced to the internal jugular vein (IJV). When dissecting under the sternomastoid muscle, care should be taken to prevent injury to the spinal accessory nerve. During this portion of the dissection, the common facial vein may be encountered crossing over the carotid bifurcation and can be sacrificed when necessary (Fig. 6.4). The carotid artery lies medially and deep to the vein. The inferior aspect of the dissection is marked by the omohyoid muscle, while the superior aspect is marked by the posterior belly of the digastric muscle. The hypoglossal nerve should be identified and protected during this phase of dissection. It is almost always positioned superficial to the ECA and ICA, directly under the digastric muscle. In rare

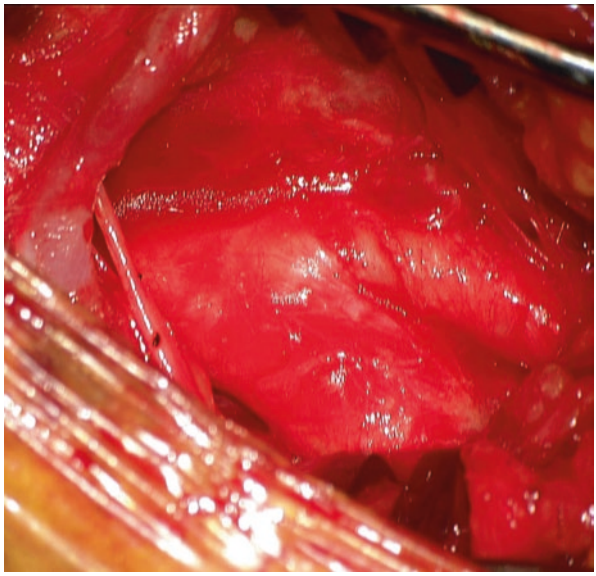

Fig. 6.4 Carotid bifurcation exposure with the facial vein preserved at the bottom part of the field

cases, the descendens hypoglossi may be sacrificed. It is important to remember that atherosclerosis is a systematic disease, often beginning inside the aortic arch, spreading to and covering the walls of the CCA and ICA, and ultimately reaching inside of the skull. For this reason, the authors recommend dissecting as necessary based on the size of the lesion to allow adequate carotid exposure. This enables comfortable application of a Fogarty clamp at the proximal CCA and bulldog clamp at the ICA as well as the ECA beyond the superior thyroid artery (STA) to cover the stenotic area. Elevation of the carotid sheath in the field allows the surgeon to identify the distal extent of the plaque.

Soft vessel loops should be placed around the CCA and ECA. Particularly in symptomatic patients, care should be taken when dissecting the bifurcation and ICA to prevent a thromboembolic event. Distal exposure of the ICA is the most difficult portion of the dissection and is crucial for the success of this procedure. For patients in which either the plaque extends more cephalad than usual or their carotid bifurcation is higher than normal, the surgeon should ensure exposure above the third cervical level. This requires expansion of the incision to the mastoid tip, but care must be taken to not incise the fascia over the parotid gland. Under the temporoparotid fascia, the facial nerve may be located. After exposure of the parotid gland, the surgeon needs to identify and expose the posterior belly of the digastric muscle along with the hypoglossal nerve. The nerve can then be dissected free, isolated with a vessel loop, and gently retracted. Next, the posterior belly of the digastric muscle is incised and retracted to expose the stylohyoid muscle. Dividing this muscle allows for identification and resection of the deeper stylomandibular ligament, resulting in complete exposure of the distal ICA.

The authors recommend the distal extent of the ICA plaque be ascertained before cross-clamping. This can be performed by auscultation of the ICA with a Doppler ultrasound (higher pitch beyond the plaque), visual cues such as arterial wall discoloration (yellow turns pink as the plaque ends), and careful digital (gentle) palpitation of the end of the hard plaque. Vessel loops should be placed around the ICA, ECA and CCA. These loops can assist with mobilization of vessels, and in case the placement of a shunt may be necessary, they can hold the shunt in place.

Endarterectomy

Prior to occluding the carotid branches, heparin is given intravenously at a dose of 5000 IU (or 70 IU/kg). A sterile marking pen is used to draw the arteriotomy line from the CCA, across the bulb, and to the ICA. The surgeon should notify the SSEP and EEG technicians and the anesthesiologist that cross-clamping is imminent. At this moment, the anesthesiologist needs to elevate the systolic blood pressure between 20 and 30 mmHg above the patient's baseline blood pressure and induce burst suppression, often using Propofol. Once EEG monitoring baselines have been verified, the surgeon may begin carotid occlusion.

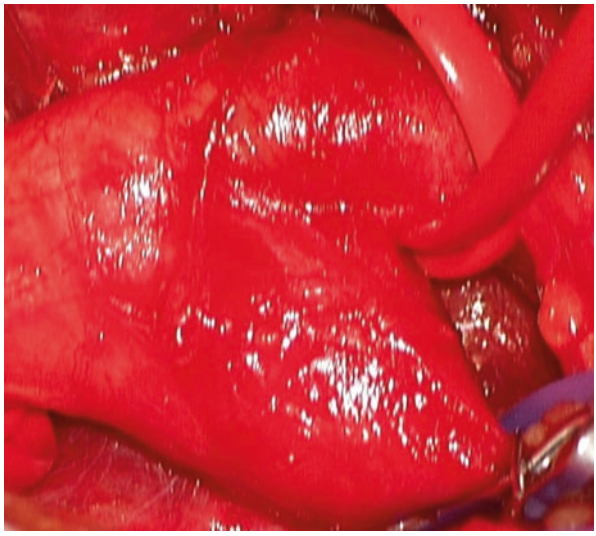

Fig. 6.5 Carotid bifurcation occlusion. First, occlude the ICA with an Aneurysm clip

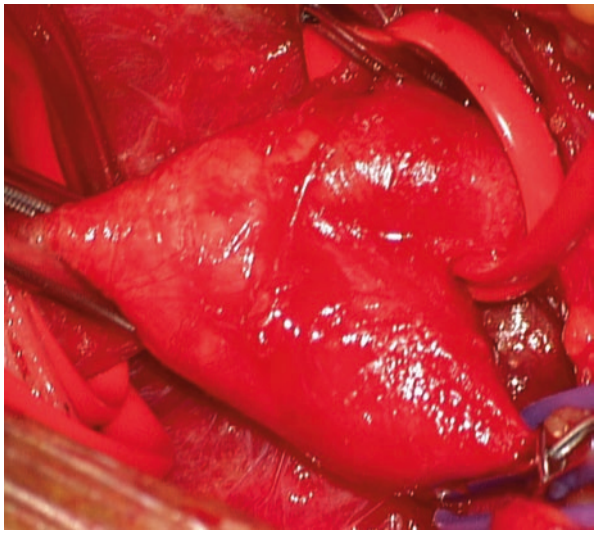

Fig. 6.6 Occlude the CCA with a Fogarty clamp

First, the surgeon occludes the ICA with a small bulldog clamp or an aneurysm clip. The ICA is clamped first to protect the brain from emboli (Fig. 6.5). Second, the CCA is occluded with a Fogarty clamp, taking care not to over close the clamp to avoid injury to the vessel (Fig. 6.6). If the CCA is clamped beyond the STA, the STA must be clipped with an aneurysm clip. Third, the ECA is occluded with a larger bulldog clamp or another aneurysm clip (Fig. 6.7). After ensuring isolation of the stenotic area, the arteriotomy is performed with a 11-knife blade and expanded up and down with Pott's scissors (Fig. 6.8). The arteriotomy should be bigger than

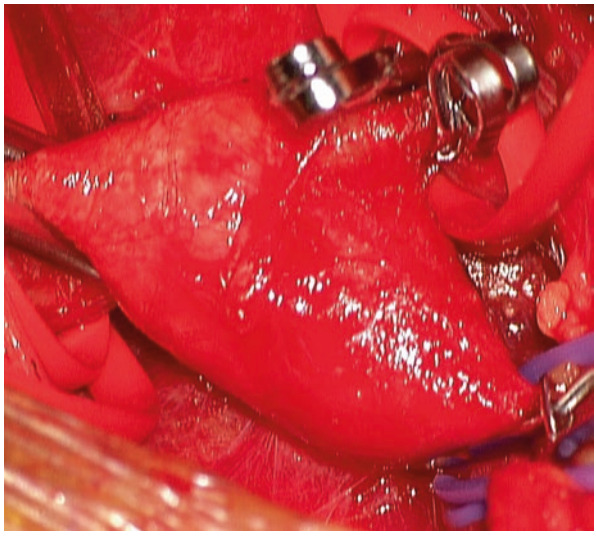

Fig. 6.7 Occlude the ECA with final aneurysm clip

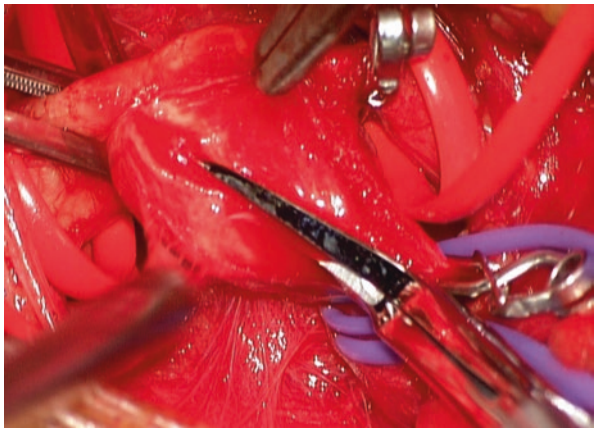

Fig. 6.8 Arteriotomy with 11-knife blade expanded up and down with Pott's scissors

the stenotic area exposing the normal intima distal in the ICA. At this time, the surgeon should check if there is a monitoring change in the EEG ipsilateral to the occluded ICA, and the decision to use a shunt is considered. If a change is noted, a shunt should be placed immediately. Shunt utilization is discussed in more detail later in the chapter.

The endarterectomy begins at the bifurcation, where the lesion is thickest. First, the plaque is separated from the media of the artery with fine vascular forceps and a small spatula, or a 6 Rhoton dissector (Fig. 6.9). Next, plaque removal continues along the lateral wall and toward the back wall of the bifurcation. This process is repeated on the medial side until the plaque has been circumferentially removed. At the proximal CCA, the plaque should be cut away with Metzenbaum scissors

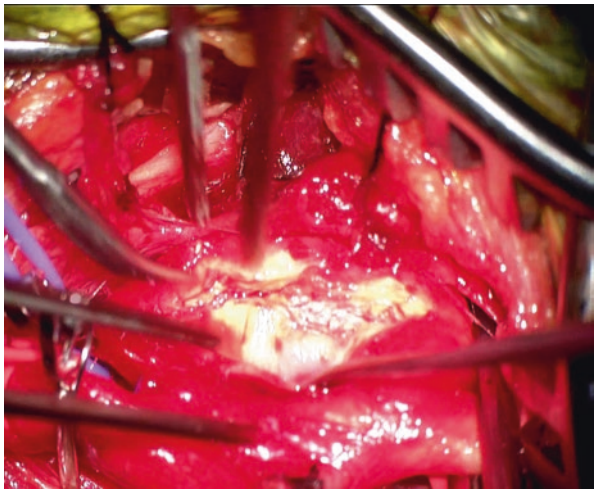

Fig. 6.9 The dissection begins at the bifurcation, with the plaque being separated from the media of the artery with a small spatula

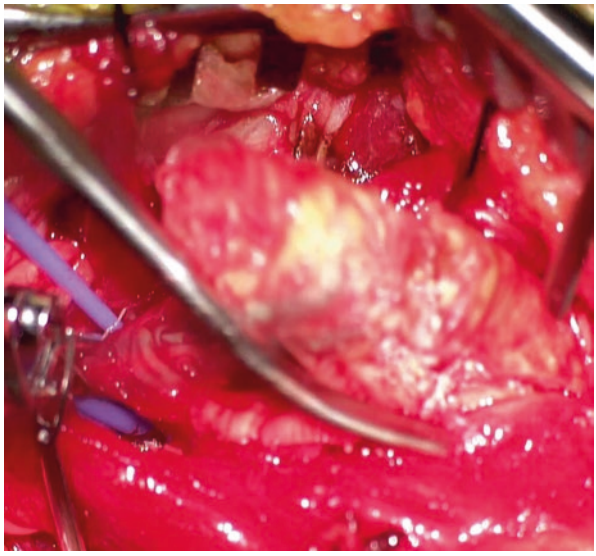

Fig. 6.10 Plaque removal after compete dissection

(Fig. 6.10). To create a uniform transition zone at the ICA, the surgeon needs to use meticulous technique and feather the plaque off the intima, though sharp dissection may be necessary to avoid dissecting the plaque beyond the view of the exposed ICA arteriotomy. The plaque is best removed in a circumferential fashion by peeling. The plaque usually detaches easily from the normal intima and curved microscissors should be used to cut the plaque and create a distal break point. Any loose pieces of plaque that cannot be feathered down at the ICA intima-plaque junction should be tied down using a double armed 6-0 Prolene suture with the knot tied outside the artery wall. The last step of the endarterectomy is dissecting the plaque in the ECA

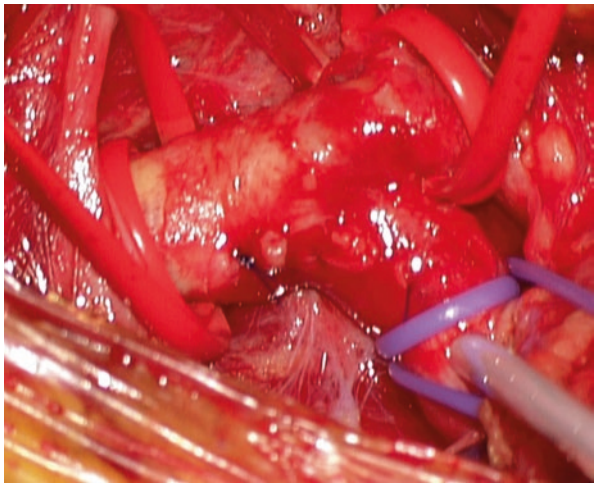

Fig. 6.11 Plaque

orifice with a small mosquito hemostat using the same circumferential technique applied earlier. Rarely, plaque fragments can remain attached within the ECA. If this happens, the surgeon should evert the ECA or extend the arteriotomy into the ECA to allow adequate resection of the plaque. This prevents perioperative thrombus formation and ensures complete plaque removal.

After the plaque is removed (Fig. 6.11), the endarterectomy field needs to be inspected and the artery wall should be peeled with ring-tip forceps. Care should be taken to remove any remaining fragments from the lumen while ensuring a smooth distal plaque transition.

Closure

The authors prefer primary closure and believe that a patch is not necessary for all cases, with use of a patch discussed in more detail below (Fig. 6.12). Before beginning primary closure, the entire field should be washed with heparinized saline and inspected again. Closure is microscope assisted and starts at the distal ICA and proximal CCA with double armed 6-0 Prolene hemo-seal (Ethicon) sutures. First, closure begins at the distal end of the ICA towards the proximal end of the CCA until one fourth of the proximal CCA remains. Then, closure resumes from the proximal end of the CCA toward the distal end of the ICA stopping just before complete closure to allow for sequential bleeding of each carotid branch. After bleeding, a syringe containing 1000 IU of pure heparin is inserted into the artery lumen via the opening and the lumen is filled as the surgeon ties the remaining two loose 6-0 Prolene ends together. Once the final suture is secured, the carotid clamps can be removed. Clamp removal first begins with the

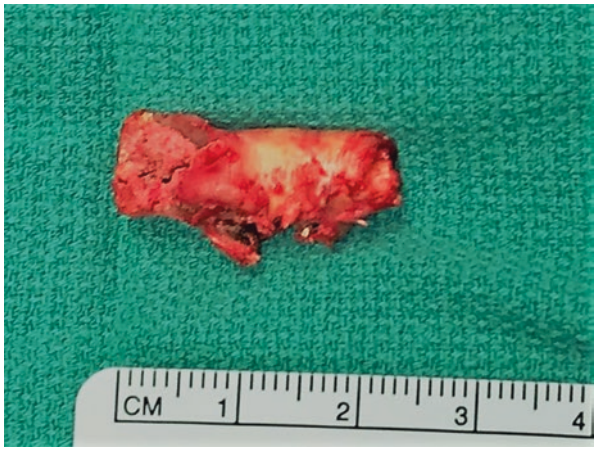

Fig. 6.12 Carotid bifurcation after primary closure. We are checking the blood flow with Doppler over the ICA

ECA, followed by the CCA and then the ICA. This ensures any air or debris travel up the ECA rather than the ICA, thus protecting the brain. At the completion of the procedure the patient's blood pressure should be decreased by 10–20 mmHg below their baseline blood pressure to prevent reperfusion injury and bleeding.

Pre-medication

All patients who are diagnosed with carotid artery stenosis should be started on aspirin, as it reduces the risk of stroke. There is evidence that lower perioperative doses of aspirin (81–325 mg) are more effective than higher doses (650–1300 mg) in reducing risk of postoperative stroke for up to 6 months [8, 9]. It is recommended that aspirin be administered to all patients undergoing CEA, whether they are symptomatic or not.

Patients receiving combined aspirin and clopidogrel have been shown to be at an increased risk for bleeding and reoperation after CEA [10]. Nonetheless we regularly perform CEA with patients on dual anti-platelet medications. Warfarin management is largely individualized during the perioperative period, with patients needing to switch to heparin upon admission. CEA can be safely performed on a heparin drip, with several series having noted only slight increases (0.7%) in postoperative hematomas in patients on heparin drips [11]. The use of statin has been shown to reduce rates of in-hospital mortality and combined ischemic stroke or death in symptomatic patients undergoing CEA; however, asymptomatic patients on statin did exhibit improved outcomes. Blood pressure medications should be controlled in order to keep the patient normotensive during the perioperative period [12, 13].

Awake or Asleep

Patients have the option of remaining awake or asleep during their CEA procedure. The main advantage of an awake CEA is that neurologic function can be directly assessed, especially during the carotid artery cross clamping portion of the procedure. Otherwise, when the patient is asleep, the surgeon must rely on traditional intraoperative monitoring techniques and wait for the patient to wake up to assess their neurologic status. Patients susceptible to anxiety or who are claustrophobic are not recommended to undergo an awake CEA.

Anesthetic Considerations

Several anesthetic options are available to choose from, including general, regional, and local anesthesia. Each carrying their own advantages and disadvantages, the general anesthesia versus local anesthesia for carotid surgery (GALA) trial did not show a clear benefit of one technique over another [14]. Overall, there are no differences in stroke rate, complications, length of stay, or overall outcome among the different anesthetic techniques. If there is an advantage to local or regional anesthesia over general anesthesia, it is that it allows the surgeon to follow the patient's mental status, extremity movements and speech during the procedure.

We recommend general anesthesia for CEA. Typically, the anesthesiologist uses a combination of an inhaled Sevoflurane, intravenous muscles relaxant and opioids. These anesthetic agents significantly reduce the cerebral metabolic rate of oxygen consumption, therefore playing a protective role during carotid occlusion. Another advantage of general anesthesia is that it facilitates a controlled environment that prevents field contamination and patient movement [15].

Utility of Monitoring

Several monitoring tools are available for the surgeon to adequately assess and respond to changes in patient status. In our practice, we use an intraoperative carotid Doppler for vascular monitoring, as well as a standard 16-channel electronencephalogram (EEG) and somatosensory evoked potential (SSEP) monitoring. This allows for observation of cerebral electrical activity in real-time. In addition, changes in EEG are correlated with cerebral blood flow (CBF) [16]. Combining these three modalities, we are better able to identify indicators of reduced CBF and imminent cerebral ischemia. Following arteriotomy closure, an intraoperative Doppler examination is performed on the common carotid artery (CCA), the ICA, and the ECA to ensure patency.

Shunt or No Shunt

If during CEA there are changes in the EEG following carotid occlusion, the surgeon should not hesitate to place a shunt. Several shunt options are available with the Javid (Bard® Carotid Bypass Shunt, Tempe, Arizona) and Loftus (Integra Neurocare, Pleasant Prairie, NJ) shunts being the most commonly used devices. Shunt placement should be performed prior to plaque dissection. The shunt should be flushed with heparinized saline before insertion. Once the shunt is placed in the CCA, a Rummel tourniquet is secured around the shunt to hold it in place. The CCA is then opened temporarily to flush the shunt with blood and to remove any debris or air. After, the ICA clamp is removed and the surgeon gently passes it into the distal ICA. The shunt is then secured above the lesion with a pinch clamp, and the CCA opened to restore flow.

A handheld Doppler over the tubing is used to auscultate shunt flow. If there is low flow or the EEG does not improve after reestablishing flow to the ICA, there is possibility of a distal embolus or occlusion. While exceedingly rare, the shunt should be replaced in this situation. The surgeon must reocclude the arteries, remove the shunt, and assess backflow from the ICA. If there is no flow from the ICA, a Fogarty balloon catheter must be passed into the ICA to remove possible clots.

It should be noted that the use of a shunt makes closure of the arteriotomy more difficult, as more steps are required just before final closure. First, the shunt is clamped with two mosquito hemostats through the final suture line defect and cut into two pieces. Next, the small bulldog clamp is reapplied at the ICA to stop backbleeding, and the Rummel tourniquet is loosened to allow for removal of the first piece of the shunt. The Fogarty clamp is reapplied on at the CCA end and the Rummel tourniquet is loosened to remove the second piece. EEG changes will most likely occur following this procedure, prompting flow restoration as soon as possible.

Patch or No Patch

There are two trials that suggest a lower rate of ipsilateral stroke and a reduction in the frequency of ≥50% restenosis when surgeons utilize patch closure. The authors recommend using a patch when the carotid wall is small and when injury to the wall may occur. The surgeon can choose from several different kinds of patches as described in literature (saphenous vein, jugular vein, bovine pericardium, Darcon, polytetrafluorethylene, etc.) [17, 18]. A systematic review showed no significant differences among different patch materials [19].

When necessary we utilize a Dacron (Hemashield patch) graft. The tips of the patch are trimmed to fit over the arteriotomy defect. The patch is sewn at the distal and proximal ends with double armed 6-0 Prolene sutures. The running stich is first

placed along the medial under microscope magnification. The needle passes through the patch first and then through the artery. Once the running stich reaches the CCA anchoring stitch, it is tied to one of the free ends of that 6-0 Prolene's two arms, and the same can be repeated for the lateral wall. The suture line should be verified to ensure uniform patch closure.

Post-operative Management

Following CEA, the patient should be transferred to the intensive care unit. The neurologic and hemodynamic status of the patient should be monitored closely during the early post-operative period. In addition, routine neck circumference measurements should be performed to monitor for potentially worsening neck hematoma. Heparin reversal with protamine is an option to reduce risk of hemorrhage, although its use is controversial with some studies suggesting it increases stroke risk, with others reporting no association between protamine use and adverse outcomes [20]. Patients are expected to continue taking aspirin indefinitely, and vascular imaging is recommended for all patients in order to determine the patency and new baseline of the carotid artery, although the choice of imaging is at the discretion of the practitioner.

BP Control

Intraoperative alteration of the carotid bulb results in blood pressure fluctuations that can persist post-operatively. This is most likely a result of damage to Hering's nerve, a branch of the glossopharyngeal nerve that innervates the carotid sinus, located within the carotid bulb [21]. Changes in blood pressure that occur early in the post-operative period are often associated with increased risk of myocardial infarction or cerebral vascular accident, making it crucial that extreme hypertension and hypotension are avoided [22]. Ideally, systolic blood pressure should be maintained between 120 and 150 mmHg.

Uncontrolled hypertension can be problematic. Combine this with the fact that many CEA patients are often on antiplatelet therapy, hypertension can contribute to neck hematoma development. In addition, post-operative hypertension can result in cerebral hyperperfusion syndrome (CHS). Often presenting with increasing or severe headache, CHS can result in cerebral edema or intracerebral hemorrhage [23]. Patients with a pre-existing cerebral aneurysm should be especially monitored, since postoperative increased cerebral perfusion can cause rupture, resulting in subarachnoid hemorrhage [24]. Therefore, it is imperative that fast-acting antihypertensive medications be given to post-CEA patients if large increases in blood pressure are observed.

Hypotension should also be managed appropriately to ensure sufficient cerebral blood flow. An electrocardiogram (ECG) may be performed to rule out a cardiac cause. Infusion of intravenous (IV) fluid or colloid solution are usually sufficient in raising blood pressure, with a phenylephrine drip being indicated if hypotension is still not controlled. A central venous catheter (CVC) can also be inserted if the patient fails to respond to initial medical interventions. Occasionally, bradycardia is also observed and can be addressed with atropine administration.

Complications and Management

Myocardial infarction and stroke are two of the most serious postoperative complications of CEA and are often associated with fluctuations in blood pressure, hence the importance of blood pressure monitoring discussed earlier. The presence of a new neurologic deficit suggests that an embolic event has taken place and immediate vascular imaging is warranted, since such deficits are largely reversible if flow is restored quickly. Other complications may arise including neck hematoma, cranial nerve palsy, restenosis and are discussed in more detail below.

Acute Occlusion/Emboli

If the patient presents with a new post-operative neurologic deficit and is hemodynamically stable, a non-contrast CT and CTA of the head and neck should be performed. In the absence of intracerebral hemorrhage, cerebral angiography is indicated to inspect for intracranial emboli and to evaluate collateral circulation. In the event there is evidence of distal emboli and the endarterectomy is patent, heparin anticoagulation should be administered to reduce the risk of further thromboembolic events. Given acute occlusion of the ICA, re-operation is warranted to restore flow, but carries with it its own set of risks discussed below.

Re-exploration

As discussed earlier, progressively worsening neck hematoma is an indication for wound re-exploration. Another major indication for reintervention is when a patient develops a neurologic deficit following CEA in the early perioperative period. Deficits that present during the first 24 hours after CEA are likely due to intraluminal thrombus formation and embolization, and if other etiologies of stroke are ruled out, then immediate re-exploration is necessary [25]. Depending on when re-operation is performed, it can be complicated by scarring and fibrosis of the vessel

wall, making dissection more difficult and thus putting the patient at increased risk of complications, especially cranial nerve palsy. A higher risk of cranial nerve palsy has been reported in patients undergoing second CEA.

Neck Hematoma

Postoperative cervical hematoma is a complication of CEA most often caused by capillary oozing, but in some cases can be due to arterial bleeding. Depending on how neck hematoma is defined, incidence can vary greatly. If it is defined as requiring tracheal reintubation or wound exploration, an incidence of 1–3% is typically reported; in contrast, when defined radiographically as a reduction in airway cross-sectional area or volume, reported incidence is much greater at 26.3%. Sex of the patient is also a factor that impacts incidence, with women having significantly higher risk of developing neck hematomas than men [26]. Some degree of neck hematoma is always present in post-CEA patients, and can even present as a surgical emergency even preceding marked external neck swelling [27]. In the event there is tracheal compression and subsequent airway compromise, reintubation and wound re-exploration is indicated.

Reintubation of the patient becomes complicated by the fact that there is distortion of airway structures, making hematoma evacuation difficult. Fiberoptic tracheal intubation should attempted first, followed by direct laryngoscopy as it has been associated with a high success rate after failed fiberoptic airway management. If both methods fail, successful airway management can be accomplished via tracheostomy [28].

It is not uncommon for patients undergoing CEA to also be on antiplatelet medications. While medically effective, antiplatelet agents, especially combined clopidogrel and aspirin administration, pose a problem for the surgeon, as they are commonly associated with increased bleeding. For this reason, extra care must be taken during carotid closure to reduce the risk of hematoma development and a closed suction drain should be placed. Post-operative bright red blood drainage is indicative of a suture line disruption and warrants re-exploration. Intravenous thrombolytic therapy, though, does not significantly increase the risk of neck hematoma [29, 30].

Cranial Nerve Palsy

Several nerves lie within the vicinity of the carotid artery and its branches, making cranial nerve injury a common neurologic complication of CEA. Dysfunction can vary from mild to severe depending on the mechanism of injury and usually resolves over time, with postoperative incidence generally ranging from 3% to 27%, due in part to variation in study design and measurement error [31]. Despite being tran-

sient in nature and generally well-tolerated, distal cranial nerve palsy is a risk of surgery that patients should be informed about.

Hypoglossal Nerve Typically, the hypoglossal nerve crosses the ICA and ECA 2–4 cm above the carotid bifurcation, but anatomic variations exist where it can cross as low as the carotid bifurcation or adhere to the posterior surface of the anterior facial vein as it crosses. Normally, the hypoglossal nerve is only encountered in patients with a high carotid bifurcation or a particularly caudal plaque. Tongue clumsiness, tongue biting, dysarthria, and difficult mastication and deglutition can also occur due to traction injury in more severe cases. While unilateral hypoglossal nerve injury is typically non-life threatening, bilateral damage can result in upper airway obstruction [32].

Vagus Nerve The vagus nerve exits the skull through the jugular foramen, descending within the carotid sheath posterolateral to the internal carotid and external carotid artery. Occasionally, the vagus nerve can be anteromedial to the carotid artery thereby increasing its risk of injury, especially if the surgeon falsely believes it to be the ansa cervicalis and divides it. Dissection of the carotid artery should be maintained close to the wall of the artery to prevent vagal injury. Additionally, care should be taken when placing vascular clamps on the CCA and ICA to reduce risk of crush injury to the vagus nerve, which typically results in vocal cord paralysis [32, 33].

Recurrent Laryngeal Nerve The recurrent laryngeal is generally not within the operative field during CEA. Despite this, self-retaining retractors that are placed too deep and exert pressure on the trachea and tracheoesophageal groove can cause direct recurrent laryngeal nerve injury. In rare cases, the patient may present with a nonrecurrent laryngeal nerve variant, where the nerve branches off the vagus at the carotid bifurcation and courses medially and posterior to the CCA to enter the larynx directly. For this reason, there is a higher likelihood of injury during dissection of the CCA and carotid bifurcation. Damage to the recurrent laryngeal nerve results in ipsilateral vocal cord paralysis in the median or paramedian position, resulting in mild hoarseness and loss of effective cough mechanism. Patients may present asymptomatically due to contralateral vocal cord compensation [32].

Superior Laryngeal Nerve The superior laryngeal nerve runs behind the ICA and ECA, where it divides into external and internal branches. Due to their close proximity to the proximal superior thyroid artery, care must be taken when dissecting these vessels by staying close to the arterial wall at the carotid-superior thyroid artery junction. Damage to the external branch results in cricothyroid muscle paralysis, causing early fatigability of the voice and inability to produce high-pitched sounds. Internal branch injury results in a reduction of sensation at the laryngeal inlet, causing minor swallowing problems. Unclamping and reclamping of the vessels during backbleeding can also damage both branches [32, 34].

Marginal Mandibular Branch of Facial Nerve Emerging from the parotid gland, the marginal mandibular branch of the facial nerve runs across the masseter muscle just deep to the platysma. Several factors are at play that put this nerve at risk of harm. In positioning the patient, when the neck is hyperextended and rotated to the opposite side, the nerve becomes pulled down closer to the operative field. Transverse and longitudinal skin incisions the reach the mastoid tip also place the nerve at risk, but this can be avoided by posterior displacement of longitudinal incision toward the mastoid process as one approaches the angle of the mandible. Drooping of the corner of the mouth and, in severe circumstances, difficulty holding fluids in the mouth, can occur if this nerve is injured [32, 33].

Glossopharyngeal Nerve Due to the position of the glossopharyngeal nerve, it is rare that injury to this nerve will occur during CEA. Only when dissection of the ICA must go above the level of the hypoglossal nerve and division of the posterior belly of the digastric muscle is necessitated will there be possible injury. Symptoms of glossopharyngeal nerve damage can be mild dysphagia or loss of gag reflex. Severe symptoms include chronic aspiration and malnutrition due to disrupted deglutition, necessitating a tracheostomy and feeding jejunostomy [32].

Follow-Up

Follow-up routines vary, with Doppler ultrasound being recommend 3–4 weeks postoperatively, followed by repeat ultrasound at 6 months and then annually. Some practitioners follow patients with CTA.

Incidence and Management of Re-stenosis

Recurrent stenosis, defined as stenosis >50%, is a complication of CEA that has been reported to occur in 1–37% of patients, with 0–8% of those patients being symptomatic. Among patients with recurrent stenosis, there is a 5.5% chance of ipsilateral stroke occurring [35]. Carotid re-stenosis is categorized as being “early” (≤2 years after the initial procedure) or “late” (>2 years after primary CEA). The time of presentation is indicative of the pathogenesis of the lesion.

Early restenotic plaques have been shown to be rich in fibroblasts and smooth muscle cells due to an inflammatory reaction known as myointimal hyperplasia. This proliferative response can be triggered due to damage of the intima by vascular clamps or by surgical technique, as wounding of endothelial cell monolayers by scratching results in increased replication and migration [36]. Late re-stenosis is usually related to recurrent or progressive atherosclerosis [37].

Prior studies suggest that smoking history, being under the age of 65, women, and metabolic syndrome are all significant risk factors of restenosis [38–41]. Despite this, there exist conflicting information with a more recent study reporting age,

hyperlipidemia, smoking, and sex to not be significant predictors of restenosis. Instead, they noted that only family history of stroke was found to be a significant factor that influenced re-stenosis [42]. In reducing risk, lipid lowering drugs have been found to serve a protective role against restenosis. While hyperlipidemia may or may not be a risk factor of re-stenosis, lipid lowering drugs have been found to serve a protective role against restenosis [43].

If a patient presents with re-stenosis, reintervention is often not necessary; despite this, if a patient presents with either asymptomatic re-stenosis >80% or symptomatic re-stenosis >60%, then therapeutic intervention is required [44]. A repeat CEA is one option, but is made difficult by periarterial scarring and thickened fibrosis of the arterial wall. For this reason, carotid artery stenting (CAS) has been supported specifically for recurrent stenosis after CEA, due to the relative ease of stenting. Despite this, literature does not favor CAS over CEA in cases of re-stenosis, with combined death and stroke rates being 3.7% and 3.1% after CEA and CAS, respectively. The only clear benefit of CAS over CEA is the avoidance of cranial nerve palsy [35]. Conflicting reports exist, with one group stating that an endovascular approach utilizing percutaneous angioplasty and stenting (PTAS) in their patient cohort and others resulted in lower complication rates than those reported after secondary CEA [45].

EC-IC Bypass

The efficacy of EC-IC arterial bypass surgery in the treatment of patients with symptomatic carotid artery occlusion (CAO) has been assessed in several studies. One notable trial was the International Cooperative Study of Extracranial/Intracranial Arterial Anastomosis (EC/IC Bypass Study), which in 1985 concluded anastomosis of the superficial temporal to the middle cerebral artery (STA-MCA) failed to prevent stroke in patients with symptomatic CAO [46]. One major criticism of the EC/IC Bypass Study was that it failed to distinguish patients with thromboembolic stroke from hemodynamic stroke [47]. With subsequent advances in positron emission tomography (PET) in the following decade, it became possible to identify patients suffering from stroke related to hemodynamic failure. Since then, evidence began to emerge that cerebral hemodynamic failure is an independent risk factor for subsequent stroke in medically treated patients [48]. Combine this with the fact that EC-IC arterial bypass improves hemodynamics distal to the occluded artery, it substantiated the need for a new prospective randomized trial to assess EC-IC bypass and its role in reducing subsequent stroke in this subgroup of patients, thus forming the basis for the Carotid Occlusion Surgery Study (COSS) discussed below [49].

Carotid Occlusion Surgery Study

The COSS was a prospective, parallel group, 1:1 randomized, open-label, blinded-adjudication treatment trial designed to test the hypothesis that STA-MCA anastomosis, when combined with best medical therapy, would reduce the 2-year risk of subsequent ipsilateral ischemic stroke at 2 years in patients by 40% when compared to best medical therapy alone [50]. Between June 2002 and June 2010, patients were screened to determine if they had complete symptomatic atherosclerotic occlusion of an internal carotid artery. If these patients presented with transient ischemic attack (TIA) or ischemic stroke in the ipsilateral hemisphere within 120 days of screening, they underwent PET imaging to assess for hemodynamic failure. Ipsilateral-to-contralateral ratios of mean regional carotid territory oxygen extraction fraction (OEF) were calculated, with a ratio greater than 1.130 being required for inclusion. Out of 4958 patients assessed, 195 were eligible and 98 were randomized to receive no surgery and 97 to receive surgery.

The surgery group underwent end-to-side anastomosis of a STA branch, most often the parietal or frontal branch, to a cortical branch of the MCA. In the event the STA was unsuitable for use (diameter <1 mm), the occipital artery (OA) was used instead. After surgery, patients remained on 81 mg or 325 mg aspirin for a perioperative period of at least 30 days, with patients returning to the preferred antithrombotic therapy as determined by their physicians. Participants in the surgical group underwent a repeat PET scan 30–60 days postoperatively, with follow-up visits every 3-months afterward until 24 months was reached. Graft patency was determined via doppler ultrasound examination during follow-ups. The primary end-point for the surgery group was the combination of all stroke and death from surgery through 30 days after surgery, while the primary end points for the nonsurgical group was all stroke and death from randomization to randomization plus 30 days and ipsilateral stroke within 2 years of randomization.

The study was terminated early given that the nonsurgical group resulted in an unexpectedly low rate of primary endpoints such that a clinically meaningful difference in favor of surgery would require an unattainable increase in sample size. The 2-year rates for ipsilateral stroke were 21% for the surgical group and 22.7% for the nonsurgical group ($p = 0.78$, z-test). Perioperative stroke rates of ipsilateral ischemic stroke were 14.3% in the surgical group and 2.0% in the nonsurgical group. This is in spite of the excellent graft patency and improved cerebral hemodynamics achieved in the surgical group.

Conclusion

Carotid endarterectomy continues to be the preferred treatment modality for carotid artery disease. The procedure is well-tolerated by patients, and effectively reduces the risk of stroke. While clinical indications are clearly established for symptomatic patients with severe stenosis, there continues to be debate on the best treatment

approach in patients with varying amounts of stenosis and asymptomatic presentation. As medical therapy and endovascular techniques improve, clinical decision making will continue to evolve as we work to identify the best and safest treatment modalities available to patients.

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Chapter 7
Carotid Artery Stenting

Lorenzo Rinaldo and Leonardo Rangel Castilla

Indications

Despite an extraordinary amount of research dedicated to the study of this procedure, the indications for carotid artery stenting (CAS) in the treatment of carotid stenosis have yet to be clearly defined. This ambiguity stems primarily from persistent uncertainty as to whether CAS is equivalent to carotid endarterectomy (CEA) as a primary treatment option. Recent large, randomized clinical trials did not demonstrate a difference in outcomes between CEA and CAS in non-selected patient populations [1–3], though a concurrent randomized trial suggested a greater risk of peri-procedural adverse events in patients treated with CAS [4]. Accounting for some of these discrepancies, results of meta-analyses studies comparing the efficacy and safety of CEA and CAS appear to indicate greater risk associated with CAS in certain patient populations [5, 6], highlighting the importance of patient selection to the optimal utilization of CAS. In this section we will briefly summarize indications for CAS in the setting of both symptomatic and asymptomatic carotid stenosis according to the most recent American College of Cardiology/American Heart Association guidelines [7, 8], with a focus on demographic and anatomic characteristics that may favor CAS, as well as those that may warrant preference for CEA.

L. Rinaldo
Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA

L. R. Castilla (✉)
Departments of Neurosurgery and Radiology, Mayo Clinic, Rochester, MN, USA
e-mail: RangelCastilla.Leonardo@mayo.edu

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General Indications

Symptomatic Carotid Artery Stenosis

In general, invasive treatment of symptomatic carotid stenosis is indicated when the degree of stenosis surpasses 50% according to established criteria, and strongly indicated when stenosis exceeds 70% [9–11]. According to recent guidelines, CAS can be considered as an alternative to CEA for treatment of symptomatic stenosis if these conditions are met and the estimated peri-procedural risk of stroke or death is less than 6% (Level of evidence: Class IIb) [7, 8]. The value of 6% represents the perioperative risk of stroke or death after CEA noted in large observational studies [12], thereby serving as the minimum standard of operator safety necessary to justify selection of CAS.

The timing of carotid intervention relative to the symptomatic event also appears to be relevant to treatment choice. Historically, patients included in randomized trials were classified as having symptomatic stenosis if they experienced an ipsilateral ischemic or embolic event within 120 days of revascularization [9–11], however patients are often considered for treatment during or shortly after hospitalization for initial stroke work-up and management. Indeed, the benefits to revascularization appear most pronounced if surgery is performed within 2 weeks of the symptomatic event [13]. In pooled subgroup analyses from large randomized studies, the risk of peri-operative stroke when intervention is performed within 7–14 days after symptom onset appears to be significantly higher in patients treated with CAS relative to CEA [14, 15]. These findings should be considered when determining treatment in recently symptomatic patients, and may warrant the favoring of CEA in this setting unless other contraindications are present (See below).

Asymptomatic Carotid Artery Stenosis

Indications for CAS in the setting of asymptomatic carotid artery stenosis are perhaps even less clear than those for symptomatic stenosis, stemming from uncertainty on the indications for the invasive treatment of asymptomatic stenosis in general. Landmark randomized trials observed benefit to CEA in terms of subsequent stroke risk reduction for patients with at least 60% asymptomatic stenosis [16, 17], thus establishing a threshold for intervention that would be employed for the subsequent two decades. Patients in the control arm of these trials were treated with best medical therapy, which at the time often consisted solely of daily baby-dose aspirin. Moreover, modifiable risk factors for cerebrovascular disease, for example hypertension and hyperlipidemia, were not uniformly or aggressively treated [7]. Significant advances in the sophistication of medical management since the enrollment period of these initial trials has brought with it an unsurprising decline in the stroke risk for patients with asymptomatic stenosis treated medically [18], and thus previously established indications for surgical treatment of asymptomatic stenosis are now outdated [19]. In this setting, recent guidelines do not provide clear indications

for treatment of asymptomatic stenosis, and instead recommend decision-making regarding intervention and treatment selection should be performed on a case-by-case basis and should hinge on perceived risk of intervention and life expectancy [7, 8]. The second iteration of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST-2), enrollment for which is ongoing, will compare outcomes of both CEA and CAS to that of best medical therapy in separate study arms [20]. The results of this trial will hopefully clarify the indications for treatment of asymptomatic stenosis and more clearly define the role of CAS in this clinical setting.

Risk Modifiers Relevant to Treatment Selection

Age

A finding that has been consistently observed in contemporary randomized trials and associated meta-analyses is a greater risk of peri-operative stroke and mortality in elderly patients treated with CAS when compared to similarly aged patients treated with CEA, an effect that appears to manifest when patients reach 70 years of age [4–6, 21]. The mechanism underlying this effect is not well understood, as in an analysis of patient characteristics from enrollees in the initial CREST study, only carotid plaque length was found to both increase with age and be associated with increased likelihood of peri-procedural adverse events [22]. Importantly, plaque length accounted for only a fraction of the increased risk of CAS in this patient population, suggesting the presence of other unidentified age-related factors [22]. Regardless, the preponderance of evidence suggesting a detrimental effect of elderly age on outcomes after CAS prompted recent guidelines to recommend CEA be considered as the primary option to treat patients older than 70 in the absence of other contraindications [7, 8]. Interestingly, since publication of the CREST results, utilization of CAS in septuagenarians and above has actually increased relative to utilization prior to CREST [23], highlighting the importance of familiarity with current guidelines.

Patient Comorbidities

A perceived advantage of CAS over CEA is the less invasive nature of the procedure, thus making it an attractive treatment option for patients at greater risk of cardiopulmonary events during and immediately after open surgery. The use of CAS in this setting was validated in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, in which outcomes after CAS and CEA in patients deemed to be at high risk for complications after surgery were found to be comparable [24, 25]. A number of studies have identified specific risk factors that may increase the risk associated with CEA, and these unsurprisingly include traditional cardiovascular risk factors such as diabetes,

hyperlipidemia, hypertension, prior stroke, renal disease, and smoking history [26–29]. Importantly, the risk of adverse events may increase proportionally as the number of patient comorbidities increases [26, 29]. According to recent guidelines, CAS is thus considered a reasonable alternative to CEA for patients with a significant comorbidity burden including these conditions (Class IIA, Level of Evidence: B) [7, 8]. It should be noted, however, that while CEA may be associated with greater risk of perioperative cardiac events [1], patient quality of life appears to be impacted more significantly by even a minor stroke when compared to the effect of myocardial infarction [30]. As such, the risk of specific complications and how these are affected by a patient's unique comorbidity profile should be considered when selecting treatment.

Anatomic Risk Modifiers

Current guidelines describe several circumstances related to patient anatomy and prior surgical or treatment history in which CAS may be considered a safer treatment option than CEA. Traditionally, low- or high-riding plaques located at the level of the clavicle or the second cervical vertebra, respectively, are relatively surgically inaccessible and CAS is considered a reasonable alternative in these situations [31]. Carotid artery occlusion contralateral to the target stenosis may also be a relative contraindication to CEA. Analysis of patient outcomes from the North American Symptomatic Carotid Endarterectomy Trial revealed a significantly increased risk of perioperative stroke in the presence of contralateral carotid occlusion [32], however more recent data suggests the risk in this setting may not be prohibitive [33]. Similarly, the risk of stroke associated with repeat CEA has been noted to be significantly higher than that after initial CEA [34], though, again, more modern series have found the risks in experienced operators to be acceptable [35]. Finally, CAS is often selected in patients with a history of neck radiation [36], a circumstance which will be discussed in a subsequent chapter. Inevitably, operator experience with both CEA and CAS in anatomically complex patients is a critical component to the treatment-selection process.

Technique

CAS is performed in an angiography suite with biplane fluoroscopy. The procedure can be performed with or without general anesthesia, though it is our preference to proceed under monitored anesthesia care. The patient is positioned supine on the operating table and, under conscious sedation, the groin is infiltrated with local anesthetic. Arterial access is obtained via a micropuncture kit, after which a 6–8 French (F) sheath is inserted into the common femoral artery using standard Seldinger technique. The common carotid artery is accessed using a 0.035″ glidewire and a 6F guide catheter. Anteroposterior and lateral images of the stenosis are

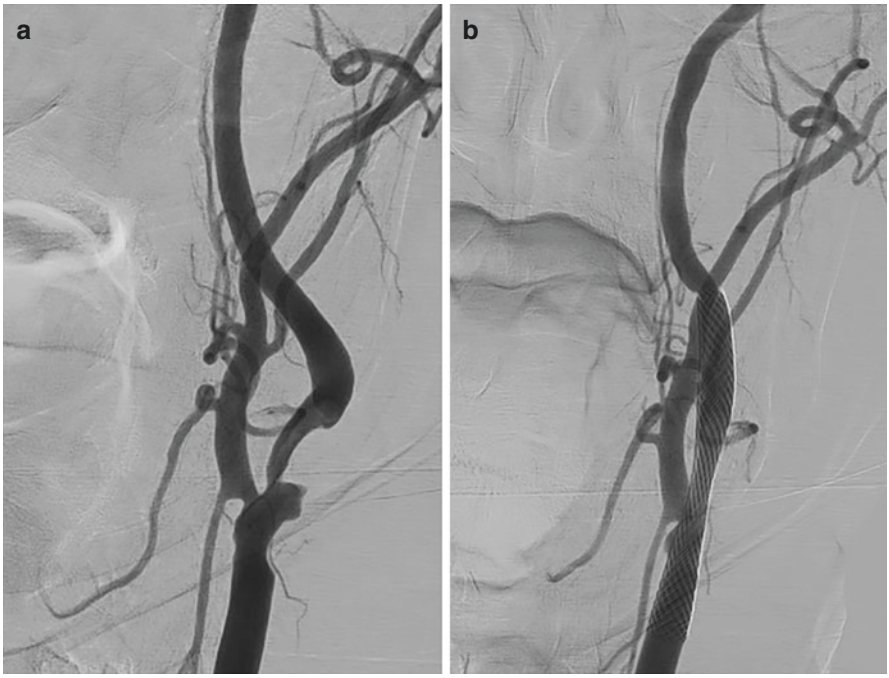

Fig. 7.1 Left carotid stenting. The patient was a 46 year-old male presenting with symptomatic left carotid stenosis in the setting of right carotid occlusion. (**a**) Anteroposterior angiogram demonstrating moderate to severe left internal carotid stenosis. (**b**) Anteroposterior angiogram after stent deployment

subsequently obtained, and the length of the stenotic segment and width of the internal carotid artery are measured to determine stent sizing and maximize wall apposition. Prior to stent deployment, heparin is administered with a goal activated clotting time of at least 250 seconds. Under roadmap guidance, a distal embolic protection device is deployed at about the C1 level. The stent is then navigated to the stenotic lesion and deployed. An example of CAS in a patient with symptomatic left carotid severe stenosis in the setting of right carotid occlusion is shown in Fig. 7.1.

Pre-medication

Patients typically receive dual antiplatelet therapy prior to stent placement. Patients who require urgent stent placement can alternatively be loaded with Aspirin 650 mg and Clopidogrel 600 mg, or an alternative $P2Y_{12}$ receptor antagonist, on the day prior to the procedure. Additional information on pre- and postoperative antiplatelet therapy is detailed below.

Anesthetic Considerations

General anesthesia is typically unnecessary during routine CAS placement, and can be eschewed in favor of mild sedation and local anesthetic, even for transcervical access to the carotid [37]. There is some evidence to suggest that hemodynamic instability, specifically bradycardia and hypotension in response to baroreceptor stimulation in the carotid sinus during balloon angioplasty and stent deployment [38], may be less frequent with use of general anesthesia [39]. Given the benign nature of most instances of such hemodynamic instability [40], however, it is unlikely that this potential benefit justifies the routine use of general anesthetic.

Access

The carotid artery can be accessed via transfemoral and transradial approaches, as well as directly through percutaneous carotid injection. We will briefly review advantages and disadvantages of each approach and discuss available data investigating the relative incidence of associated complications.

Femoral Access

The femoral artery is the most common site of access for carotid stenting and endovascular procedures in general, and is generally well tolerated with a low rate of complications [41]. The most common complication associated with the transfemoral approach is an access site hematoma, with less common but more serious complications including retroperitoneal hemorrhage, femoral artery branch perforation, femoral artery dissection or occlusion, and formation of pseudoaneurysms or arteriovenous fistulae, the incidence of which vary considerably in available literature [42]. Access site hematomas are associated with increased hospital length of stay and need for transfusion [43], and thus there has been considerable interest in lowering their incidence.

Radial or Brachial Access

Radial or brachial access is the most commonly employed alternative to the transfemoral approach, most frequently in patients with complex aortic arch anatomy complicating access to the common carotid artery. Whether or not the routine use of transradial access is justifiable is unclear. A recent randomized clinical trial comparing the incidence of complications after CAS performed via a transradial versus

transfemoral approach did not demonstrate differences in the incidence of major access site complications or cardiac or cerebral events. The transradial approach was associated with a greater frequency of crossover to alternative approaches, as well as with higher cumulative radiation dose [44]. Nevertheless, transradial access is a safe and occasionally necessary in the performance of CAS.

Direct Carotid Access

CAS can also be performed through direct carotid access. The utilization of transcarotid access is less frequent compared to that of transfemoral and transradial approaches, at least in part due to lack of operator familiarity, review of outcomes of this approach demonstrate safety and comparable efficacy in experienced hands when compared to traditional approaches [45, 46].

Distal Protection Device

Distal embolic protection devices (DEPD) are filters placed distal to the target stenosis and serve to protect against embolic events during CAS. An example of a DEPD utilized during CAS can be seen in Fig. 7.2. Analyses of outcomes from randomized trials in which the utilization of EPDs was non-uniform suggested a protective effect against stroke and/or death when an EPD was deployed [47], garnering support for the routine usage of these devices. On the other hand, placement of DEPDs has been associated with an increased number of microembolic events detected by transcranial Doppler [48], mostly during passage of the DEPD across the stenotic lesion, and has not been shown to reduce the frequency of ischemic lesions visualized on post-procedural MRI [49]. A randomized trial comparing radiographic outcomes after CAS with and without use of an EPD also did not show a benefit to use of DEPDs, though this study was limited by small sample size [50]. Nevertheless, a number of studies have reported a benefit with regard to reduced incidence of ischemic events with DEPDs [51], and in trained operators can be performed with acceptable rate of complications or adverse events [52]. Larger randomized studies may be needed to further validate their use.

Balloon Guide Catheter (Proximal Protection)

An alternative method of embolic protection during CAS involves the use of a balloon guide catheter. In contrast to the distal protection afforded by EPDs, balloon guide catheters provide cerebral protection by temporarily occluding the external

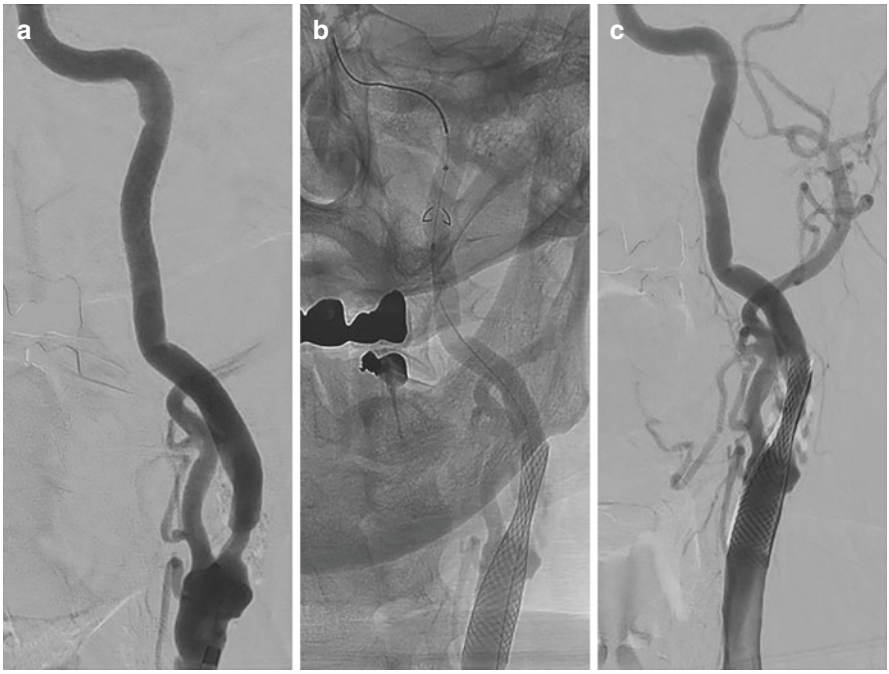

Fig. 7.2 Distal protection device. (**a**) Angiography demonstrating left carotid stenosis. (**b**) Distal protection device in place with stent deployed. (**c**) Final angiographic run after removal of distal protection device

and common carotid arteries, thereby allowing deployment of the stent under conditions of flow reversal. This method obviates the need for the protection device to cross the stenosis, which has been associated with microembolic events during use of DEPDs [48]. The use of proximal protection during CAS has been associated with a low rate of peri-procedural ischemic events [53, 54]. For example, in the Proximal Protection with the Mo.Ma device during Carotid stenting (ARMOUR) trial, investigators reported a 98% and 93% device and procedural success rate, respectively, with a 30-day major stroke rate of 0.9% [55]. Moreover, there is evidence to suggest that proximal protection catheters may confer a safer risk profile for octogenarians [56], a traditionally high risk population for CAS [21]. However, a comparison of outcomes of CAS with use of distal versus proximal embolic protection using data contained within a large multi-center registry did not demonstrate significant differences in the rate of adverse events within 30 days of the procedure [57]. Though there is no randomized data suggesting equivalency between distal and proximal protection, both methodologies appear to have acceptable safety profiles in experienced operators.

Bare Metal Versus Drug Eluting Stents

The first generation of carotid stents were bare metal stents, with initial iterations composed of stainless steel. Newer models are now typically composed of nitinol [58], an alloy of nickel and titanium with the properties of supraelasticity and shape-memory, allowing stent shape to conform to the arterial wall, maximizing wall apposition, and resist deformation over time [59]. Despite significant technologic advances in stent design, however, in-stent restenosis remains a significant issue, with an incidence of greater than 10% in long-term follow-up of patients enrolled in recent large clinical trials [2, 60]. To combat the problem of restenosis, there has been significant interest in the utilization of drug-eluting stents (DES) for CAS. DESs are typically coated with immunosuppressive agents that inhibit cell proliferation, thereby preventing neointimal formation and associated stent restenosis [58]. Drugs typically used include Sirolimus, an inhibitor of Mammalian Target of Rapamycin, and Paclitaxel, a microtubule assembly antagonist, both of which have shown efficacy in preventing restenosis in animal models [61, 62]. Data on outcomes of DES placement for carotid stenosis in humans is limited, though preliminary studies have shown technical feasibility and promising results with regard to incidence of restenosis [63, 64]. Additional, larger studies with long-term follow-up will be needed to validate the use of DES.

Postoperative Management and Duration of Anti-Platelets

Prior to proceeding with CAS, patients should receive dual anti-platelet therapy (DAT) with Aspirin 325 mg and clopidogrel 75 mg; patients with intolerance to clopidogrel can be treated with a substitute $P2Y_{12}$ receptor antagonist such as Prasurgel or Ticagrelor [7, 8]. If pre-operative DAT is not possible, patients can alternatively be loaded with Aspirin 650 mg and Clopidogrel 600 mg on the day prior to the procedure. Post-operatively, the patient's hemodynamic and neurologic status should be closely monitored in a general or intensive care setting, the former of which may be associated with lower costs without an increased risk of adverse events [65]. Patients should remain on DAT in the immediate postoperative period, though the adequate duration of postoperative DAT is less well-defined. In the CREST trial, DAT was continued for at least 4 weeks post-operatively, followed by lifelong aspirin monotherapy [1]. Current guidelines support this practice [7, 8], and surveys of contemporary practice patterns reveal a consensus on the necessity of temporary DAT in the postoperative period, though the duration is somewhat variable, followed by indefinite antiplatelet monotherapy [66]. Regarding the utility of prolonged DAT after CAS, there is limited evidence to suggest this is beneficial [67], and certain studies suggest an association with increased all-cause mortality [68].

Patient's individual response to specific antiplatelet agents may also influence postoperative anti-platelet regimens. $P2Y_{12}$ receptor antagonists such as Clopidogrel irreversibly antagonize the $P2Y_{12}$ receptor, which triggers platelet aggregation after binding of adenosine diphosphate. Clopidogrel is a prodrug that is metabolized to its active form by the hepatic cytochrome P450 system. Polymorphisms in the P450 system, particularly in the CYP2C19 enzyme, have been shown to result in clinically significant differences in platelet reactivity after exposure to Clopidogrel [69]. According to their catabolic genotype, patients can be classified as ultrarapid, extensive, intermediate, or poor metabolizers, the latter two of which may result in insufficient levels of the active metabolite and consequent increased levels of platelet reactivity and aggregation if treated with Clopidogrel [70]. Platelet function assays assessing aggregation after $P2Y_{12}$ receptor activation are available in point-of-care form [71, 72], and though there is no randomized evidence to support the routine use of these assays as part of the preoperative evaluation, studies have correlated high platelet reactivity with increased incidence of ischemic events after CAS [73, 74]. Strategies to mitigate poor $P2Y_{12}$ receptor antagonist metabolism include increasing Clopidogrel dosage from 75 to 150 mg daily, though the utility of this approach has not been validated in prospective studies [75, 76]. Alternative strategies include substitution of Clopidogrel with other $P2Y_{12}$ receptor antagonists such as Prasurgel or Ticagrelor [70], or the phosphodiesterase inhibitor Cilostazol [77]. The role of platelet reactivity testing in the pre-operative evaluation for CAS is likely to be further refined with future studies.

Complications and Management

CAS is generally well tolerated, though a number of complications can occur. The rate of perioperative ischemic events causing significant disability was 4.8% in data pooled from recent large clinical trials, while the perioperative mortality rate was 1.9% [1]. Among non-neurologic complications, bradycardia and subsequent hypotension in response to baroreceptor stimulation in the carotid sinus during balloon angioplasty and stent deployment is a common occurrence [38], though the majority of these events are transient and do not appear to be associated with periprocedural ischemic complications [78]. Myocardial infarction can also occur, though is less common than after CEA [6]. Arterial dissection and vessel perforation are other potential complications, though are fortunately uncommon [79].

Acute Occlusion

Acute stent occlusion is a rare complication with potentially devastating consequences if not corrected rapidly. The incidence of acute occlusion after CAS is not well-defined, but is estimated to be less than 1% [80]. Risk factors for acute occlusion

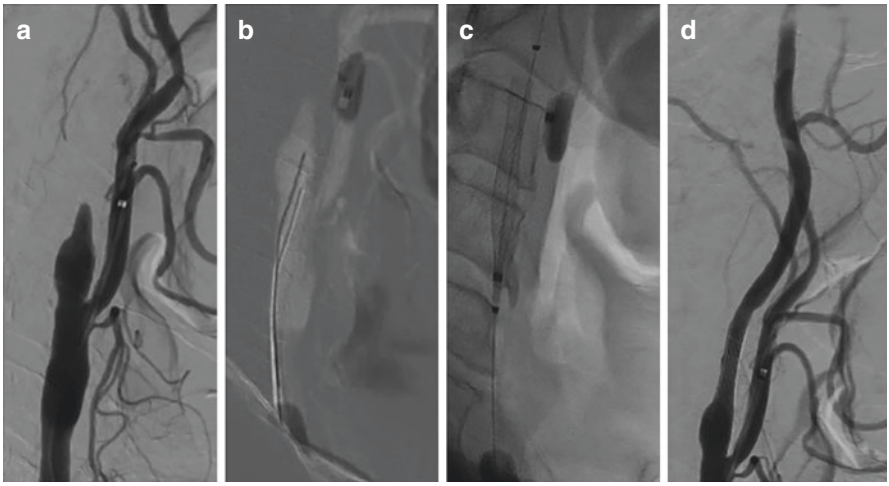

Fig. 7.3 Proximal protection with the Mo.Ma device. (**a**) Angiography demonstrating right carotid occlusion. (**b**) Immediately prior to crossing stenosis with microwire with Mo.MA catheter positioned within the external and common carotid arteries. (**c**) Stent deployment. (**d**) Successful carotid revascularization

include inadequate antiplatelet therapy or resistance to preoperatively administered antiplatelets and inherited thrombotic disorders [80]. Procedural events inciting acute occlusion include arterial dissection and prolapse of the atheromatous plaque through the stent wall [80]. Occlusion of a DEPD can also lead to acute occlusion and cessation of flow through the internal carotid. Flow can typically be restored by withdrawing the DEPD, though embolic events can occur during this process [81]. Acute intraprocedural occlusion necessitates prompt restoration of flow, acceptable strategies for which include thrombolytic therapy, aspiration of thrombus with or without thrombolytics, mechanical thrombectomy, repeat angioplasty, or surgical evacuation [80]. Figure 7.3 demonstrates a case in which the patient experienced neurologic symptoms attributable to an intraluminal thrombus manifesting 2 weeks after initial stent placement (Fig. 7.3c, d). Asymptomatic patients can be managed with anticoagulation with acceptable results [82].

Follow-Up

In addition to routine clinical follow-up, patients should undergo radiographic follow-up to evaluate for stent patency and occurrence of restenosis. Non-invasive imaging, most commonly in the form of duplex ultrasonography, is an adequate monitoring modality, and is typically performed at predetermined intervals after CAS according to the operator's practice [7]. In patients for whom quality ultrasonography is technically difficult, computed tomographic or magnetic resonance

angiography are reasonable alternatives. In the absence of new neurologic symptoms, after 1 year the interval between imaging studies can be extended, and studies should be obtained for as long as the patient is a candidate for procedural intervention [7].

Incidence and Management of Re-stenosis

While long-term follow-up data on patients undergoing CAS is limited, available evidence suggests that the rate of moderate (≥50%) and severe (≥70%) restenosis in patients with 5- to 10-year follow-up may be greater than 40% and 10%, respectively [2, 60]. Risk factors for restenosis after CAS may include female sex, diabetes, hyperlipidemia, and smoking [83]. The clinical significance of restenosis after CAS is uncertain. In an analysis of long-term outcomes of patients enrolled in the International Carotid Stenting Study (ICSS), ≥50% restenosis was more common among patients treated with CAS relative to those treated with CEA, and was associated with increased risk of ipsilateral stroke when compared to that of the general population [84]. Whether this increased risk justifies re-intervention, however, is unclear, particularly if restenosis is detected on routine follow-up and the patient is asymptomatic. The natural history of asymptomatic carotid restenosis after CAS is not well understood, and thus the risks of re-operation versus those of continuation or intensification of medical therapy should be carefully considered [85]. On the other hand, the rate of peri-procedural events after CAS for recurrent stenosis has been observed to be relatively low [86], and thus repeat CAS after restenosis appears to be a reasonable treatment option, especially in patients who are symptomatic.

Percutaneous transluminal angioplasty is the most commonly employed technique to treat recurrent stenosis, though may be associated with recurrent stenosis, necessitating multiple subsequent treatments [87, 88]. An emerging treatment option for refractory recurrent stenosis is angioplasty with a drug-eluting balloon. Preliminary evidence suggests the use of drug-eluting balloons may limit the need for additional angioplasty [89], though this treatment requires further validation. Repeat CAS has been shown to be safe and effective for restenosis after CEA [90, 91], though data on repeat stenting after CAS is limited. Figure 7.4 depicts a case of a patient with in-stent stenosis after initial CAS. The patient was successfully treated with repeat CAS, with the second stent overlapping the proximal end of the first. The patient experienced in-stent luminal thrombosis 2 weeks after initial stent placement requiring mechanical thrombectomy. Finally, CEA with stent removal has also been shown to be feasible in experienced operators, though again, evidence is limited to small case series [92].

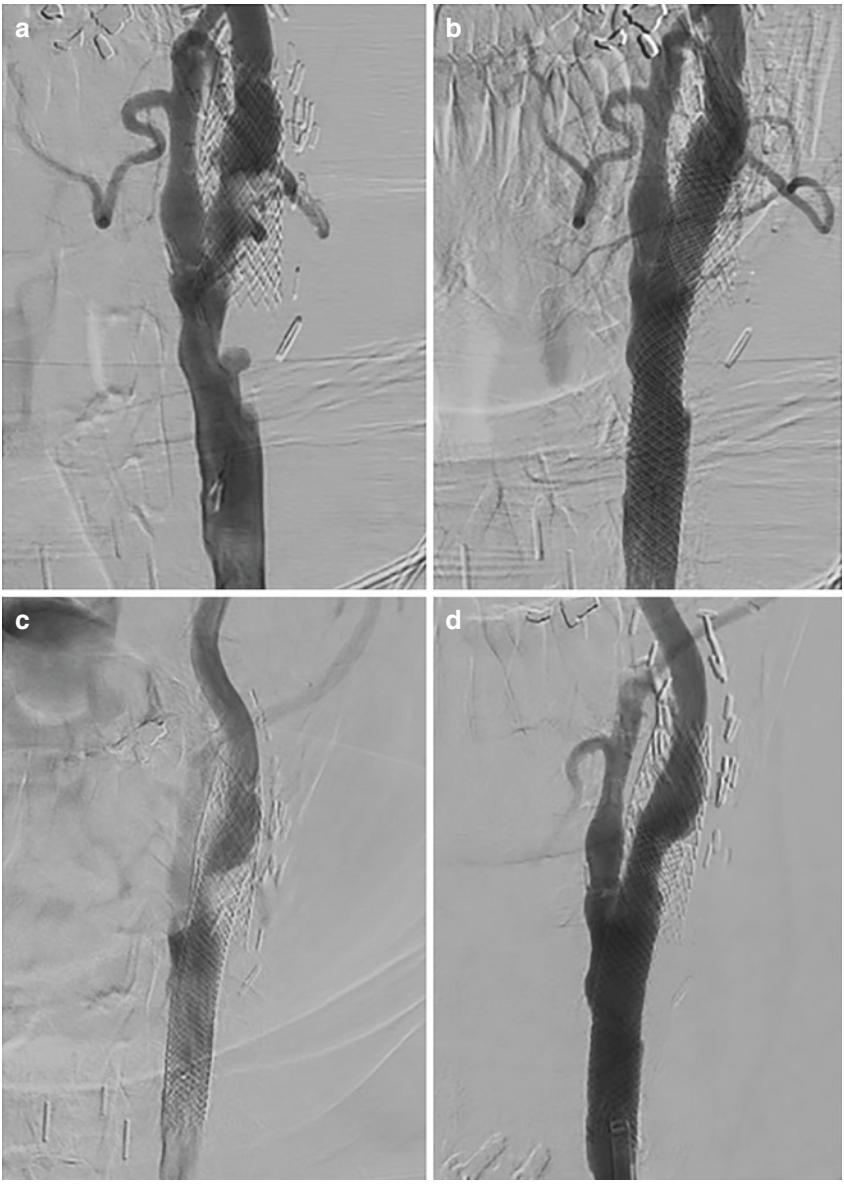

Fig. 7.4 Left carotid restenosis treated with repeat stenting, complicated by intraluminal thrombus. The patient was a 56 year-old female with a history of left CEA complicated by restenosis, managed with CAS. She presented with acute-onset right sided hemiparesis and was found to have significant left-sided carotid restenosis. (**a**) Anteroposterior view demonstrated significant restenosis. (**b**) Anteroposterior view after placement of an overlapping stent. (**c**) The patient subsequently presented 2 weeks after stent placement and was found to have significant restenosis, likely due to intraluminal thrombus. (**d**) The patient was treated with mechanical thrombectomy, with restoration of flow seen on final anteroposterior angiographic runs. Abbreviations: CAS Carotid artery stenting, CEA Carotid endarterectomy

Conclusions

Carotid artery stenting is an important tool in the armamentarium of neurointerventional practitioners. While the indications for treatment of carotid artery disease have been established from multiple, multi-center, randomized, controlled trials, modern medical practices may have improved the risks of ischemic events with medical therapy. Thus, the decision to proceed with CAS requires a careful review of the patient, the carotid pathology and anatomy, and indications and contraindications of use. Fortunately, CAS is a relatively straightforward and safe procedure when performed by experienced operators in the appropriate patient.

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Chapter 8
Radiation-Induced Stenosis

Isaac Josh Abecassis, Christopher C. Young, Rajeev D. Sen, Cory M. Kelly, and Michael R. Levitt

Introduction

Concurrent to the development of modern oncologic treatment regimens that include radiation therapy, there has been an increased presence of radiation-induced side effects, particularly after cranial and neck neoplasm-related treatments. These include vasculopathy [1] with [2] or without necrosis, cerebral aneurysms and pseudoaneurysms [3], cavernous malformations [4], and capillary telangiectasias [5]. With longer survival periods, the prevalence of these complications, including both intra- and extracranial arterial stenoses, has gradually increased.

Radiation-induced intracranial stenosis is thought to occur more rapidly than extracranial disease (average of 5.1 vs 13.4 years after radiation, respectively) [6], though it is less commonly symptomatic than atherosclerotic intracranial stenosis. Regardless of the vessel site, endothelium dysfunction, injury to the vasa vasorum, and accelerated atherosclerosis all set the stage for recurrent transient ischemic attacks (TIAs) or permanent stroke [7], necessitating prompt diagnosis and treatment. Treatment options include carotid endarterectomy (CEA), surgical bypass, and endovascular stenting and/or angioplasty. The common carotid artery (CCA) and internal carotid artery (ICA) are most susceptible to radiation induced stenosis compared to similar control groups of patients untreated with radiation (78% versus 22%), but the disease also affects the external carotid artery (ECA) (45% versus 2%) and vertebral artery (VA) (7% versus 0%), the latter comparison not achieving statistical significance [8].

I. J. Abecassis · C. C. Young · R. D. Sen · C. M. Kelly
Department of Neurological Surgery, University of Washington, Seattle, WA, USA
e-mail: abecassi@uw.edu; cyoungmd@uw.edu; rdsen@uw.edu; kellycm@uw.edu

M. R. Levitt (✉)
Departments of Neurological Surgery, Radiology, and Mechanical Engineering, University of Washington, Harborview Medical Center, Seattle, WA, USA
e-mail: publications@neurosurgery.washington.edu

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Here we will provide an overview of radiation induced stenosis (RIS). We will summarize the literature regarding treatment options, though there is a paucity of prospective, randomized trials guiding medical decision making (level 1 evidence). Currently there is only one level 2 study, which was comparing endovascular stenting in RIS to the same treatment for atherosclerotic disease [9]; the remaining literature is of evidence level 3 or higher.

Presentation and Incidence

There are several studies that have evaluated the incidence of RIS of head and neck arteries. Initially considered to be a rare phenomenon, RIS has become more clinically relevant due to highly sensitive imaging and more effective oncologic treatments leading to increased life expectancies.

Lam and colleagues conducted a cross-sectional study of the extracranial carotid arteries of 71 patients who underwent radiation therapy (RT) for nasopharyngeal carcinoma using Doppler ultrasound and compared their results to those of 51 radiation-naïve controls with newly diagnosed nasopharyngeal carcinoma. They found a significantly higher rate of carotid artery stenosis in the radiation group (78% vs. 22%) and, of those with post-radiation stenosis, 36/51 had more than 50% reduction in luminal diameter [10].

In an attempt to determine the true prevalence of RIS, Cheng and colleagues conducted a prospective cross-sectional study by screening patients who underwent RT for nasopharyngeal carcinoma and healthy controls using color flow duplex ultrasonography. This study had a mean post-RT interval of 80 months and found that 28% of post-RT patients had internal carotid artery stenosis of more than 30%, and 13% of patients had stenosis of greater than 70%. In contrast, only 8% of patients in the healthy control group had stenosis between 30 and 70%. No healthy patients had severe stenosis greater than 70% [11].

At a structural level, Huang and colleagues found that the intima-media thickness of the common carotid artery was significantly increased in post-RT nasopharyngeal carcinoma patients as compared to the control group. Furthermore, linear regression analysis revealed that duration of RT was an independent predictor of intima-media thickness along with age, HbA1c and gender [12].

While these studies confirm that irradiation increases the rate of carotid artery stenosis, there is a high degree of variation among cited rates. This is likely due to the heterogeneity between studies with regards to patient population, follow up time, amount of radiation and other factors.

Clinical presentation of RIS is associated with luminal narrowing and subsequent cerebral hypoperfusion, which can often be subtle and may go undetected [13]. Common manifestations include paresis, aphasia and amaurosis fugax. Less common are dizziness, diplopia, amnesia, and headache [14]. If the stenosis is severe enough, a carotid bruit can be appreciated on physical exam. The interval between irradiation and stroke can range between months to decades [15].

In a large, retrospective study, Smith and colleagues evaluated 6862 patients who underwent either RT alone, surgery plus RT, or surgery alone for head and neck malignancies. They found that the 10-year incidence of cerebrovascular events was 34% in the RT only group compared to 26% in the surgery only group ($p < .01$) [16]. A recent review identified 17 epidemiological studies, both retro- and prospective, and concluded that the relative risk of TIA or ischemic stroke is at least doubled by head and neck radiation therapy [17].

Management

Medical Management

For intracranial stenosis, the first step in management is dual anti-platelet therapy, as well as attention to modifiable risk factors such as cholesterol, diabetes and hypertension. Radiographic and/or clinical progression may require endovascular or surgical treatment. In general, similar efficacy and safety has been demonstrated between CEA (the main surgical treatment choice) and carotid artery stenting (CAS, the main endovascular treatment choice) in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) in both short and long term follow up periods [18]. However, the CREST trial studied primarily atherosclerotic carotid artery stenosis, and patients with prior radiation treatment to the neck were excluded, so results of this trial should be generalized to the RIS population with caution. Very rarely, cerebral bypass for reperfusion can be considered.

Endovascular Management

Although the gold-standard treatment for symptomatic carotid stenosis is CEA, the American Stroke Association guidelines recommend consideration of CAS in "high risk" patients, including those with radiation-induced carotid stenosis due to diminished healing capacity, scar tissue from prior neck dissection surgery or radiation therapy [19], and more proximal stenosis in the common carotid artery compared to atherosclerotic disease [20, 21]. While the safety and efficacy of CAS was first demonstrated for atherosclerotic disease in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) in 2004 [22], similar positive results have been observed in smaller cohorts for radiation induced stenosis. Dorrestejeijn et al. prospectively followed 24 patients with symptomatic carotid stenosis from radiation therapy treated with CAS for 3.3 years and reported no deaths or disabling periprocedural strokes, only an 8% rate of peri-procedural TIA and 4% rate of non-disabling strokes. During the follow-up period, there was 1 ipsilateral TIA (4%), but 1 (4%) contralateral TIA, and 2 (8%) contralateral disabling strokes. Restenosis (>50%) rates were significant, with 33% at 12 months and 42%

at 24 months, though all were asymptomatic. These low rates of peri-procedural events but high rates of asymptomatic restenosis echo the results of 2 other observational studies in the literature with 16 [23] and 23 patients [24], the latter of which demonstrating that radiation induced carotid stenosis patients fared clinically similar to the atherosclerotic cohort (127 patients), but with higher rates of late, asymptomatic restenosis.

One of the major risks with CAS is a dissection due to difficulty in catheterizing the true lumen of the vessel. Some authors advocate utilizing an ultrasound to follow the microcatheter as it traverses the stenosis to ensure intraluminal location [25, 26]. Thromboembolic complications can occur at any time during the procedure as well, but the risk can be reduced using proximal balloon inflation for flow-reversal with aspiration [27], distal protection, and consideration of a long dilatation balloon [26].

Endovascular Case Example (Reproduced from From Nico et al., Endovascular recanalization of the common carotid artery in a patient with radio induced chronic occlusion. *J Neurointerv Surg*. 2017;9(6):e23. With permission from BMJ Publishing Group Ltd.)

A 41-year old male presented with acute onset of postural symptoms and right hemiparesis. Medical history was significant for oropharyngeal undifferentiated carcinoma 23 years prior to presentation that was successfully treated with neck radiation therapy.

MR brain was significant for diffusion restriction in the bilateral watershed areas between anterior cerebral artery (ACA) and middle cerebral artery (MCA) territories. Further diagnostic studies including digital subtraction angiogram (DSA) and two-dimensional perfusion imaging [28] revealed evidence of bilateral watershed arterial insufficiency between the ACA and MCA territories, as evidenced by prolonged mean transit time. Single photon emission CT (SPECT) also demonstrated decreased global uptake of 99mTc-ethyl cysteinate dimer.

Computed tomography angiography (CTA) demonstrated occlusion of bilateral common carotid arteries and the right vertebral artery, as well as 70% stenosis at the origin of the left vertebral artery.

DSA confirmed the above CTA findings and that brain perfusion relied on quite limited flow from the right ICA, with collateral supply from the right ECA, deep cervical artery, and additional contribution from a stenotic left VA (via a patent posterior communicating artery). The left ICA filled retrograde via posterior communicating arteries with no inflow from the anterior circulation.

Given the clinical and radiographic evidence of cerebral arterial insufficiency, the patient was offered endovascular revascularization with balloon angioplasty of the right CCA followed by deployment of a right CCA stent. The patient was premedicated for 3 days with aspirin and clopidogrel, and heparinized for the case. Coaxial catheter systems were introduced via the common femoral artery and brought to the residual limb of the right CCA. With the assistance of angiographic roadmapping, the microwire was carefully advanced through the occlusive lesion. In order to prevent intimal injury and arterial dissection, microwire advancement was carefully monitored using duplex doppler to ensure its luminal location.

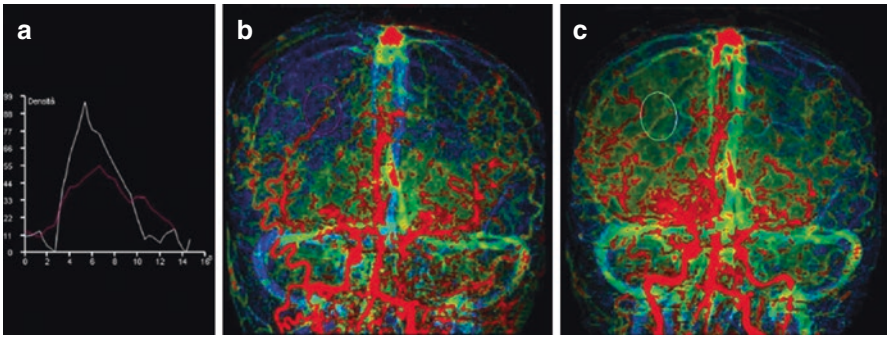

Fig. 8.1 DSA two-dimensional perfusion images preformed with pigtail injection before (**b**) and after (**c**) treatment, providing time-density information (**a**), confirms the improvement (white slope) of hemispheric parenchyma perfusion with reduction in mean transit time from 4.0 to 2.7 s. (Reproduced from From Nico et al. [26]. With permission from BMJ Publishing Group Ltd.)

After the microwire was successfully navigated into the ICA, a 3 × 150 mm balloon (Savvy Long; Cordis, CA, USA) was inflated to perform the angioplasty which resulted in satisfactory dilation of the CCA lumen. This was followed by sequential deployment of two 5 × 30 mm and 7 × 40 mm conjoined self-expandable stents (Precise Pro Rx; Cordis) across the entire CCA. Post-dilation with a peripheral long balloon (5 × 220 mm; Savvy Long; Cordis) was performed. Distal thromboembolism was minimized using the proximal stop flow technique with the inflation of a proximal occlusive balloon.

Excellent angiographic result was achieved with significant immediate and delayed improvement of cerebral perfusion. At 1 year follow up, the patient had not experienced further TIA or ischemic episodes. (Figs. 8.1, 8.2, 8.3, 8.4, and 8.5).

Surgical Options

Radiation therapy in the neck is well known to be associated with both arteritis and accelerated atherosclerosis and vessel stenosis. Despite valid concerns regarding CEA in the context of prior radiation, as well as association of possible prior surgical intervention in the neck, CEA is well tolerated for simple carotid stenosis following radiation [29]. Interestingly, despite higher rates of cranial neuropathies after CEA post-radiation, CEA was associated with a lower rate of restenosis and lower incidence of delayed cerebrovascular events compared to CAS [30].

Combined Open and Endovascular Case Example [31]

The complex nature of radiation associated intracranial and extracranial carotid stenosis occasionally warrants a combined open and endovascular treatment strategy.

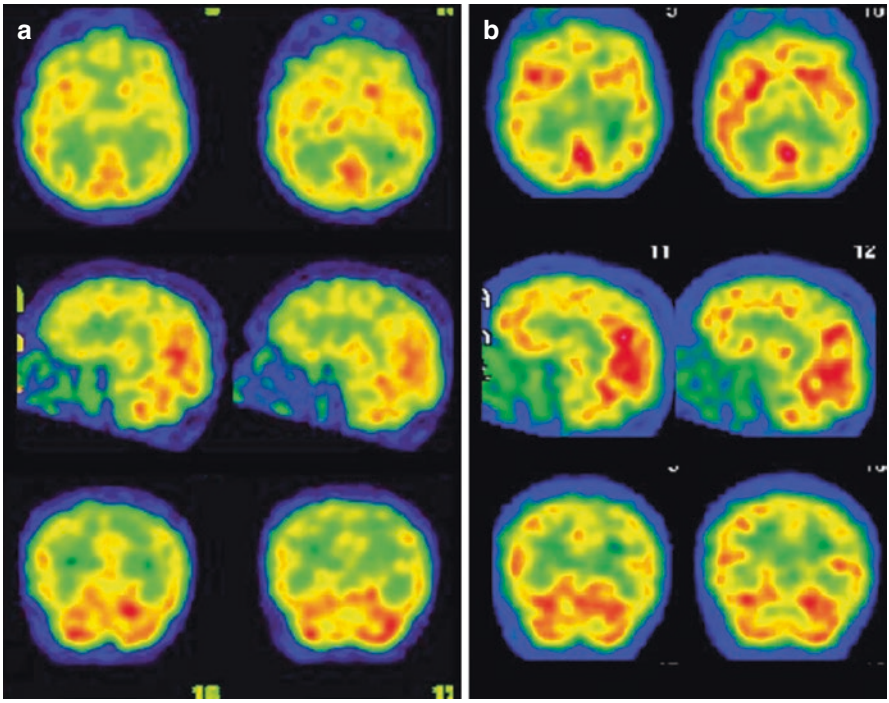

Fig. 8.2 Axial, sagittal, and coronal single photon emission CT images. (**a**) Preoperative images revealed decreased uptake. (**b**) Six months after treatment, the images confirmed global improvement in cerebral parenchyma perfusion. (Reproduced from From Nico et al. [26]. With permission from BMJ Publishing Group Ltd.)

A 63-year-old male presented with subacute progressive right hemiparesis over a 10 day period. Medical history was significant for previous pharyngeal carcinoma treated with radical left neck dissection followed by 60 Gy of radiation therapy 10 years before presentation. MRI brain revealed bilateral (left greater than right) scattered areas of diffusion restriction. MRA demonstrated bilateral ICA occlusion, with the left ECA vessels also filling poorly, suggestive of possible left CCA occlusion.

DSA showed complete occlusion of bilateral ICAs with retrograde filling from bilateral posterior communicating arteries. There was also high grade stenosis of the proximal left ECA with attenuated filing of the left superficial temporal artery. SPECT studies demonstrated reduced cerebral blood flow to the left MCA and bilateral ACA territories with decreased cerebral vascular reserve following acetazolamide challenge.

The patient's bilateral strokes were deemed likely secondary to left ICA insufficiency, exacerbated by an underlying dominant left A1 segment. The treatment strategy was to augment left ICA perfusion by (1) restoring left ECA supply via CAS, followed by (2) open STA-MCA bypass.

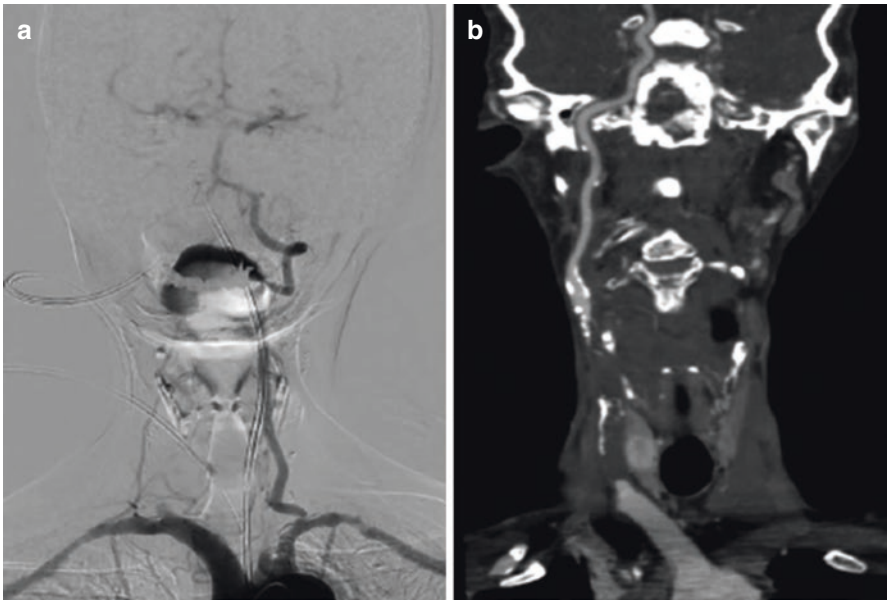

Fig. 8.3 Preoperative DSA (**a**) and CT angiography (**b**) demonstrates three vessel chronic occlusion with residual supply by the left vertebral artery. (Reproduced from From Nico et al. [26]. With permission from BMJ Publishing Group Ltd.)

Firstly, a left CAS was performed by deploying a 9 × 40 mm stent (Precise Pro Rx; Cordis) on aspirin and cilostazol. This restored ECA perfusion significantly. Subsequent restenosis after 2 weeks was treated with the deployment of a second stent (10 × 24 mm; Carotid WALLSTENT; Boston Scientific, MA, USA) and balloon angioplasty respectively. Once stability of the left ECA was achieved, a left STA-MCA bypass was performed with excellent clinical and radiographic outcome. DSA of the left CCA showed successful re-perfusion of the left ICA territory via the bypass graft, with SPECT studies showing improved perfusion and physiological reserve to acetazolamide challenge. At 2 years follow-up, the patient had not experience any further ischemic episodes.

Incidence of Restenosis

Despite continually improving endovascular techniques and technologies, restenosis after treatment remains a significant challenge when treating RIS. In a prospective study comparing outcomes of angioplasty and stenting in radiation induced stenosis to atherosclerotic stenosis, restenosis at 2 years was significantly higher in the radiation-induced group (25.7% versus 4.2%) and symptomatic restenosis at 2 years was also more common (6.8% versus 0.8%) [9].

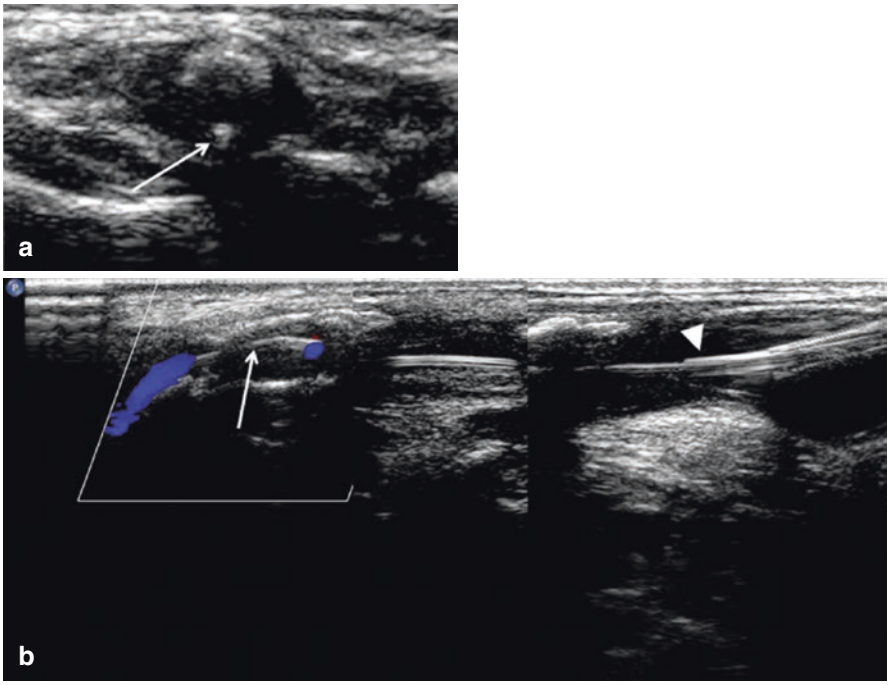

Fig. 8.4 Ultrasound check of the catheter (white arrowhead) and the microwire tip (white arrow) in axial (**a**) and longitudinal (**b**) images. (Reproduced from From Nico et al. [26]. With permission from BMJ Publishing Group Ltd.)

Moon and colleagues found a restenosis rate of 26.3% in patients with a hostile neck (defined as those that had been irradiated or had undergone previous carotid endarterectomy). In comparison, atherosclerotic controls had a rate of restenosis of 10.5%. Of the four instances of symptomatic restenosis, 3 were from the hostile neck group [32]. Tallarita and colleagues compared treatment modalities for radiation induced stenosis. The incidence of restenosis at 7 years was large for both the surgical and endovascular groups with no significant difference (80% versus 72%) [33]. Although Eskandari and colleagues found no difference in restenosis rates between the hostile neck group and de novo lesions (4.5% vs. 2.0%), this is likely due to the short follow up time of 30 days [34].

Overall, these studies demonstrate the significantly higher rate of restenosis of irradiated arteries after treatment. While the mechanism of this phenomenon is unclear, it is likely related to the original pathophysiology of RIS involving acceleration of inflammatory, fibrotic and atherosclerotic processes that are not reversed by interventions such as stenting or angioplasty.

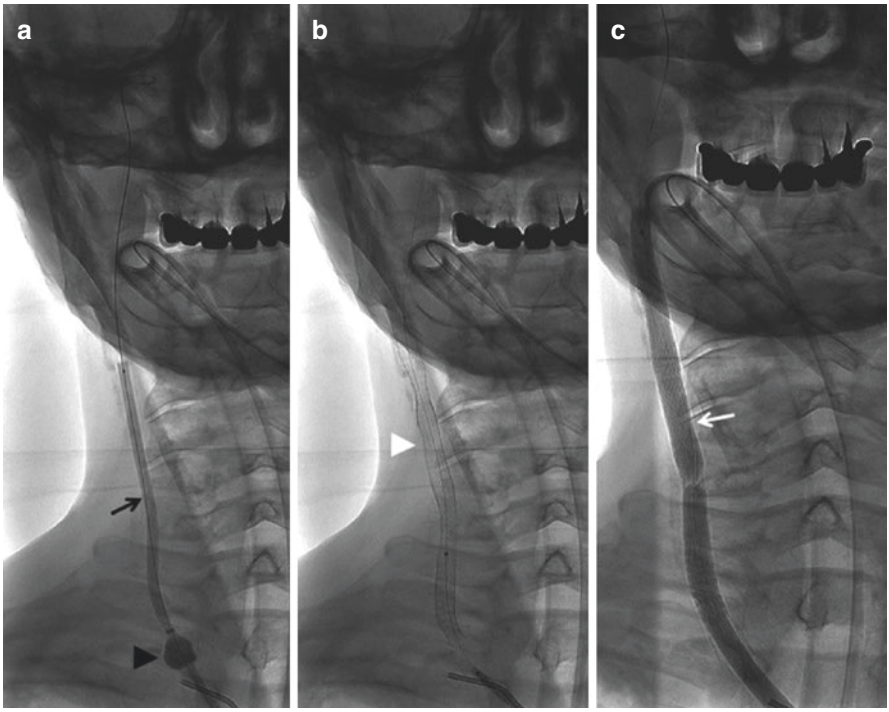

Fig. 8.5 Endovascular procedure. Pre-dilation (black arrow) using a 3 × 150mm balloon during the balloon stop flow (black arrowhead) technique (**a**), the conjoined self-expandable stent (white arrowhead) technique (**b**), and post-dilation with the peripheral 5 × 220 mm balloon (white arrow) (**c**). (Reproduced from From Nico et al. [26]. With permission from BMJ Publishing Group Ltd.)

Conclusions

RIS represents a significant potential complication for patients undergoing radiation therapy for primary oncologic disease. Interventions such as CAS, CEA, or bypass can be utilized on a case-by-case basis for treating patients refractory to medical management, or progressive symptoms. Careful follow-up must be maintained in order to detect restenosis.

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Chapter 9
Acute Carotid Occlusion

Paul J. Schmitt, Yince Loh, and Stephen J. Monteith

Background

Presentation

The carotid arteries are the major conduits of the anterior intracranial circulation. Disruption of one or both of these conduits can lead to decreased cerebral perfusion and acute ischemic stroke. In the United States, stroke is the leading cause of long-term and preventable disability and the fifth leading cause of death. Each year, approximately 800,000 people in the United States experience a new or recurrent stroke. It is estimated that 75% of these are new strokes and the remainder are recurrent.

Ischemic strokes account for 87% of all strokes and the remainder are due to intracranial hemorrhage. Risk factors for stroke include advanced age, male gender, hypertension, a history of stroke or transient ischemic attack (TIA), atrial fibrillation, valvular heart disease, diabetes mellitus, carotid artery stenosis, hypercoagulable diseases, and smoking. Of these risk factors, hypertension is the single most important risk for ischemic and hemorrhagic strokes.

For purposes of this chapter, acute carotid occlusions will be discussed as the acute progression to the final occlusive state of an underlying carotid artery stenosis, which typically occurs secondary to atherosclerotic plaque formation in the common carotid artery (CCA) or internal carotid artery (ICA). Stenosis or occlusion can also be the result of dissection, either spontaneous or traumatic, or congenital conditions such as fibromuscular dysplasia.

P. J. Schmitt · Y. Loh · S. J. Monteith (✉)
Swedish Neuroscience Institute, Seattle, WA, USA
e-mail: Paul.Schmitt@Swedish.org; Yince.Loh@Swedish.org; Stephen.Monteith@swedish.org

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Acute carotid occlusion can present with transient or minimal symptoms, or even be completely asymptomatic. In such cases, the decision to revascularize the carotid itself can be difficult. Techniques are described later in this chapter. Alternatively, patients with acute occlusions can present in extremis and with high scores on the National Institutes of Health Stroke Scale (NIHSS).

Mechanisms

One of the main stroke mechanisms resulting from acute carotid artery occlusion is a hypoperfusion state. Patients can present with high NIHSS scores, but typically present with fluctuating dysfunction, often parietal and sensory, as the "watershed zones" are the most vulnerable to the low-flow state. These zones can be deep in the posterior periventricular, subcortical white matter, as well as superficially, in the shared border zones of the anterior cerebral artery (ACA) and middle cerebral artery (MCA), MCA and posterior cerebral artery (PCA), and ACA, MCA, and PCA. As mentioned above, the natural history of patients with acute carotid occlusion and a low NIHSS that present with fluctuating or progressive symptoms or a perfusion abnormality is not known; however, it may be reasonable to recanalize in such a setting [1].

Another common mechanism by which carotid artery occlusions can lead to acute stroke is from artery-to-artery embolization, where formation of thrombus on an atherosclerotic plaque or rupture of the plaque leads to local thrombus formation. This process culminates in dislodgment and embolization into the intracranial circulation, with or without complete occlusion in the cervical segment. Patients with such tandem occlusions most often present with clinical syndromes consistent with the intracranial large vessel occlusion (LVO). Tandem occlusions can also occur following cervical carotid arterial dissections, where the dissection can lead to local thrombus formation with eventual dislodgement into the intracranial circulation, or complete cervical occlusion with intracranial thrombus migration. As we will explain, recanalizing in the setting of a tandem occlusion is less ambiguous, as the treatment effect of the intracranial LVO is much larger and better established.

A less common cause of acute carotid artery occlusion is thrombus in the vessel itself. This can arise from cardioembolism or migration of thrombus from the more proximal great vessels including the aorta.

Recent History

In 1991 it was first identified that proximal M1 and ICA occlusions resulted in large hemispheric strokes and worse outcomes [2]. The TOAST trial identified significant morbidity and mortality rates of 40% and 20% respectively in the 10% of patients that were found to have acute carotid occlusion [3]. Intravenous tissue plasminogen activator (tPA) is less effective at improving patients outcomes when those patients

are suffering from an acute ICA occlusion when compared to patients with an MCA occlusion [2, 4].

Since the introduction of stent-retrievers (nondetachable, microcatheter based, stent-like devices) and second-generation aspiration catheters, there has been a significant increase in the number of endovascular therapies (EVT) performed for acute stroke [5–7]. The frequency of EVT saw another surge after the publication of the results of several randomized controlled trials that compared outcomes in patients receiving medical management with those undergoing EVT [8–12].

Although these studies did not set out to study acute cervical carotid occlusions, several did not exclude them if there was a tandem intracranial LVO. Thus, much of the current endovascular practice in the management of acute carotid occlusive disease is based on a foundation that was laid by the expansion and advancement of endovascular techniques aimed at intracranial therapies.

Imaging

The primary imaging modality used in the work up of an acute carotid occlusion vary by institution, but the most common modalities include CT angiography (CTA), MR angiography (MRA), doppler ultrasound (DUS), and digital subtraction angiography (DSA) (Fig. 9.1). In addition to its invasive nature, DSA cannot demonstrate the three dimensional morphology of the carotid plaque [13].

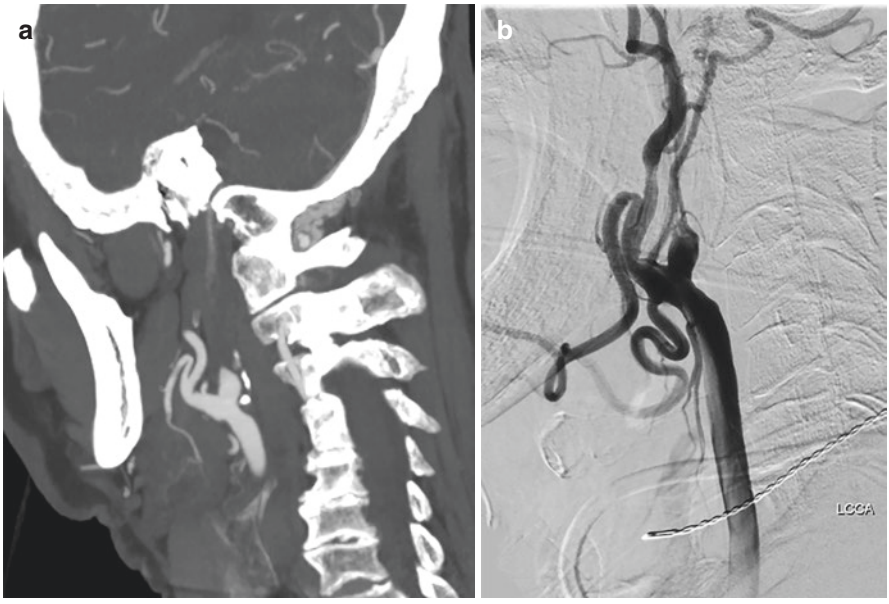

Fig. 9.1 CTA (panel **a**) and DSA (panel **b**) images demonstrating an acute carotid occlusion. Note the tapered stump in both images, indicative of an acute occlusion

The exact location of the occlusion can be elusive with every imaging modality. As an example, pseudo-occlusion occurs when the plane of CT image acquisition overtakes slow-flowing contrast in an artery with a downstream occlusion. On CTA or MRA of the neck, this may appear identical to a cervical ICA occlusion, in which the more distal segments of the ICA may be collapsed or contain a stagnant, unopacified column of blood. Only subtle aspects of each imaging modality can help suggest the exact location of the occlusion.

DUS is often used in the work up of carotid stenosis, but there is some debate surrounding its utility as a stand-alone test in the diagnosis of acute occlusion. The Society of Radiologist in Ultrasound recommends that all DUS examinations be performed using color doppler, grayscale, and spectral DUS [14]. They further recommend stratification of stenosis into the following categories: normal (no stenosis), less than 50% stenosis, 50–69% stenosis, greater than or equal to 70% stenosis to near occlusion, near occlusion, and total occlusion [14].

Peak systolic velocity (PSV) and the presence of plaque are used to stratify patients (Table 9.1). A normal carotid ultrasound PSV is defined as a PSV less than 125 cm/sec with no plaque or intimal thickening, Less than 50% stenosis has a PSV <125 cm/sec with visible plaque or intimal thickening, 50–69% stenosis is when the PSV is 125 to 230 cm/second and plaque is visible, > or = 70% to near occlusion is when the PSV is more than 230 cm/second and visible plaque and lumen narrowing are seen, near occlusion occurs when there is a markedly narrowed lumen on color Doppler US, and total occlusion occurs when there is no detectable patent lumen on grayscale US and no flow on spectral, power, and color Doppler US [14]. Depending on the institution, DUS may not be readily obtainable in an emergency, whereas other modalities may be more routinely staffed.

With respect to an acute ICA occlusion, DUS may be helpful in diagnosing downstream occlusion, as the stagnant column of blood in the carotid bulb should be mobile and the bulb may still be compressible. Conversely, a segment of solid, echogenic material representing the underlying atherosclerotic (and now occlusive)

Table 9.1 Society of radiologists in ultrasound consensus regarding Doppler US for assistance in the diagnosis of carotid artery stenosis [14]

Category	PSV	Plaque or intimal thickening
Normal	<125 cm/sec	Absent
<50 Stenosis	<125 cm/sec	Present
50–69% Stenosis	125–230 cm/sec	Present
≥70% Stenosis to near occlusion	>230 cm/sec	Present
Near occlusion	Markedly narrowed lumen on color Doppler US	
Total occlusion	No detectable patent lumen on grayscale US; and no flow on spectral, power, or color DUS	

PSV peak systolic velocity, *DUS* Doppler Ultrasound

plaque suggests that the source of the occlusion is at the ICA origin. In such situations, however, acuity of the occlusion may still be difficult to decipher.

MRA is a noninvasive modality that can be performed with or without gadolinium (Gd) contrast. In the absence of Gd, MRA is acquired using a time of flight (TOF) sequence. Although Gd is not required, it can often improve the quality of the images. Since the MRA utilizes flow to enhance its images, an acute ICA occlusion will appear similar whether the occlusive lesion is at the bulb or in the intracranial circulation.

CTA, which utilizes intravenous iodinated contrast, is widely available and requires a short acquisition time. It is the most frequently used study in the evaluation of acute carotid occlusion, particularly in the emergent setting. Shortcomings of CTA include potential contrast reaction, radiocontrast-mediated nephropathy, and radiation exposure. Additionally, CTA can overestimate the frequency of suspected occlusion. In a post hoc analysis of the ESCAPE trial, [15] investigators found that approximately 25% of patients with suspected ICA occlusion had pseudo-occlusions with a normal carotid bifurcation on a formal catheter angiogram.

Perfusion imaging with MR and CT is useful to assess cerebral blood flow, blood volume, and transit time. CT Perfusion (CTP) has emerged as a valuable tool for evaluating which patients will respond to thrombectomy, especially in cases where the window between a patient's last known normal (last known time with a normal neurological exam) and presentation is extended. Perfusion imaging is a method of selecting patients with a mismatch between the severity of neurological deficit and volume of infarcted tissue. The DAWN [16] and DEFUSE-3 [17] trials have helped delineate CTP parameters that can be used to define the core and penumbra, as well as patient specific parameters that can help in selecting patients for revascularization procedures. Volumes of the infarct core and ischemic penumbra are calculated with commercially available software (RAPID, iSchemaView).

At many institutions, patients who are considered for any EVT undergo perfusion imaging. As part of the perfusion protocol, multiphase CTA can be collected. The ASPECTS score on the unenhanced CT, [18] infarct volume, ischemic penumbral volume, penumbra-to-core ratio, core size, and collateral supply are all considered. While most decisions are primarily based on infarct core volume and penumbra-to-core ratio, the information provided by a collateral score can help in situations where there is uncertainty [19–23].

Despite its shortcoming as an invasive diagnostic tool, DSA is dynamic and has a relatively customizable temporal resolution. DSA provides a means of visualizing delayed contrast flow and evaluating the collateral circulation, including the leptomeningeal collaterals (the cortical arteriolar-arteriolar network of connections), the communicating arteries, and the collateral supply between the internal and external carotid arteries. Regardless of its diagnostic utility, DSA is most often utilized in the acute setting because it is a necessary means to obtain endovascular access to an intracranial LVO or when the decision has been made to revascularize the acute cervical carotid occlusion.

Treatment

Indications

In general, indications for recanalization of an acute carotid occlusion follow the same principles as those for recanalization of an intracranial LVO. When there is a significant portion of the hemisphere at risk for infarct in the absence of a large infarct core, an intervention should be attempted (Fig. 9.2). In the case of an isolated ICA occlusion it is especially important to assess the intracranial circulation. If there is no ischemia, an occluded ICA is not a stand-alone indication for revascularization [24]. If there is a concomitant intracranial occlusion, the proximal ICA may need addressing only as a means to allow access to an intracranial LVO. The following sections describe different techniques in the setting of acute symptomatic ICA occlusion in which revascularization is deemed a necessary, life or function-preserving intervention.

Carotid Angioplasty and Stenting for Acute ICA Occlusion

General Procedure

When considering carotid angioplasty and stenting (CAS) in the setting of acute carotid occlusion, there are several important preoperative considerations. A CTA of the head and neck can be helpful in evaluating the aortic arch, anomalous or variant vessel origins, the degree of vessel tortuosity, the length of the stenotic segment to be treated, the presence of suspected tandem lesions, and the relationship of the stenosis to the normal vessel segments. A comprehensive knowledge of all available imaging is necessary in order to develop an appropriate strategy for catheter and implant selection.

A long 80 or 90 cm 6F or armored 8F × 25 cm sheath provides distal stability, especially in the context of tortuous aorta and/or iliofemoral vessels, respectively. If an armored 8F groin sheath is used, an 80 or 90 cm 6F sheath can still be advanced through the groin sheath over a 5 or 6 French Bernstein, vertebral, or other multipurpose curve (MPC) diagnostic catheter to access the carotid artery. Alternatively, an 8F delivery or balloon guiding catheter (BGC) can also be used. A 125 cm Vitek may be required to maneuver a long sheath across a Type 3 arch. An 0.035 or 0.038 inch wire is used to access the distal CCA, taking care to remain proximal to the diseased segment. The wire can be navigated into the ECA for additional support if proximal vessel tortuosity is limiting selection or advancement of the sheath into the CCA. The diagnostic catheter is then brought up into the distal CCA, followed by the BGC and/or long sheath. Ideally, the BGC or long sheath terminate in the distal CCA, just proximal to the carotid bifurcation and the diseased segment. Once the sheath or BGC are properly situated, baseline cervical and cranial angiograms can be completed.

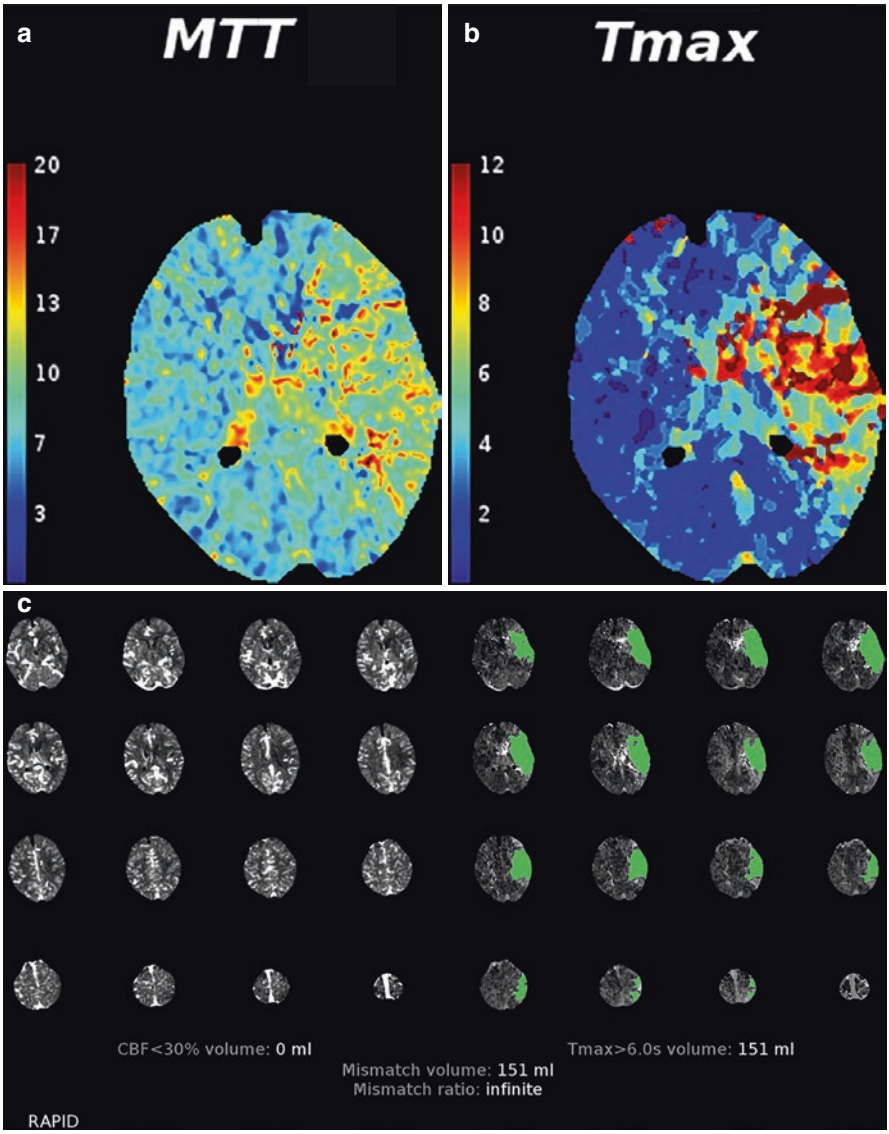

Fig. 9.2 Post-processed images produced by the RAPID software demonstrates markedly elevated mean transit time (panel **a**) and maximum transit time (panel **b**). Using standard thresholds, there is no infarct core in this case, but the ischemic penumbra indicates that a large portion of the left hemisphere is at risk (panel **c**)

Cervical ICA opacification will not occur in acute ICA occlusions. If it does, it typically occurs through retrograde filling of higher ICA segments via external-internal carotid collateral flow (Fig. 9.3). Another means where opacification of the cervical ICA can rarely occur is through a tiny channel across the

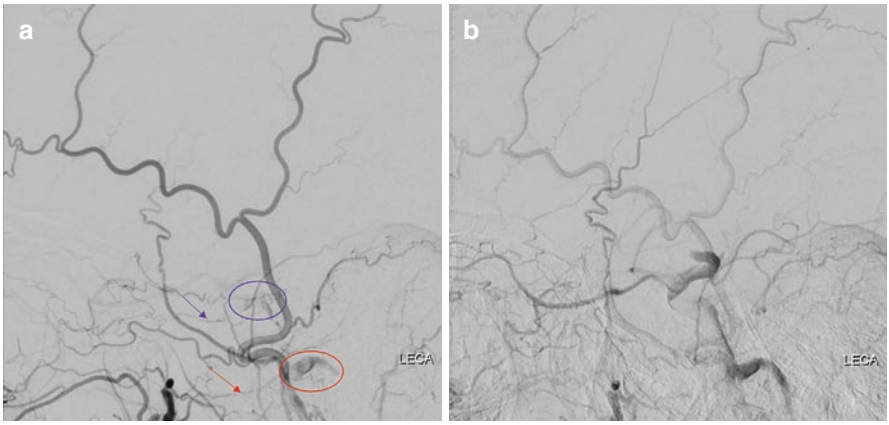

Fig. 9.3 A lateral view of the cranial vasculature during a common carotid artery injection demonstrates filling of the ICA distal to the occlusion through external carotid artery collaterals, indicating that the vessel is not chronically occluded. Panel **a**: Note the filling of the petrous segment of the ICA (red ellipse) via the vidian artery (red arrow), and filling of the cavernous segment (purple ellipse) via the artery of the foramen rotundum (purple arrow). Panel **b**: Later during the injection, there is slow, antegrade filling of the ophthalmic artery, and the intracranial segments of the ICA are more visible

occlusion, such as a "string sign." Thus, it is often impossible to calculate the length and diameter of the distal protection device, balloons, and stents that will be used during the procedure.

Crossing the Lesion

In the case of an occlusion, the operator must decide whether the lesion is due to a dissection or atherosclerotic disease. The distinction is important, as dissections are not likely to require pre-stent angioplasty. Depending on the location of the dissection, it may need to be treated with a stent prior to performing the distal thrombectomy. Current generation aspiration catheters are narrow enough to navigate the true lumen of most cervical carotid dissections. Dissections nearer to the skull base may require treatment in order to allow access to the intracranial ICA segments.

If the lesion is atherosclerotic and cannot be traversed, a standalone angioplasty is preferred as a temporizing treatment. The stent can be deployed at a later date once the stroke burden is known. Delayed stenting avoids having to traverse the stent with a microsystem when performing the intracranial thrombectomy. When performing a balloon angioplasty in the setting of a tandem lesion, the utility of distal embolic protection is unclear.

Crossing the ICA occlusion blindly can be troublesome. The takeoff of the ICA stem often dictates the technique. In acute ICA occlusions in which the ICA stem originates in a fairly cephalad direction from the bifurcation, it is possible to cross the lesion with a microsystem such as a 0.014 wire and 0.0165 inner diameter (ID) microcatheter. There are very low-profile microcatheters that allow for 0.014

microwires yet are only 1.3F (Headway Duo, Microvention, Tustin, CA). Particularly useful in these situations are dedicated 1.5F low-profile crossing catheters which can fit in a 0.035 diagnostic catheter and are stiffer at the tip (Trailblazer (Medtronic, Dublin, Ireland); Quick-Cross (Spectranetics, Colorado Springs, CO)). Once across, gentle contrast injection into higher cervical ICA segment via the microcatheter can determine the thrombus burden and its extent.

In the occluded ICA stem that courses posteriorly, support for crossing is very tenuous, as the tip of the sheath or BGC is oriented at a right angle to the angle of approach. In such cases, the microsystem technique described above should still be the first attempt. Should the angle of attack be too great, a 45 degree or even 90 degree angled diagnostic catheter can be used, with an exchange-length 0.014 microwire. If needed, up to a 0.018 microwire may allow for more maneuverability through the occlusion. The tip of the angled diagnostic catheter is positioned to allow for the wire to have optimal support during crossing. When using this technique, an exchange-length version of the microwire is necessary, as the diagnostic catheter will not be able to cross the lesion over the wire. Once the tip of the microwire is well into the high cervical or petrous ICA segments, the diagnostic catheter is exchanged for a low profile microcatheter as described above.

In either ICA takeoff angle, the underlying atherosclerosis may be difficult to cross with a microwire due to the softness of its tip. At this point, the operator should reassess the intent of the procedure. Is there a tandem distal occlusion that is causing the symptoms? Or is the patient dependent on the carotid flow due to an isolated hemisphere? Presumably restoring ICA flow is critical and the indication for performing the procedure. At this point, crossing the occlusion with a stiffer wire, such as a 0.018 or even 0.035 wire may be necessary. The aforementioned low-profile crossing catheters are also particularly useful to exchange between 0.035 or 0.018 wires and 0.014 systems. The operator has to accept that in such situations, there is a chance that he or she is in the false lumen and needs to verify where the tip is positioned with gentle contrast injection. Even if the tip is in the true lumen distally, this technique may have resulted in the catheter entering a false lumen across the lesion then crossing back into the true lumen distally. In such a situation, the true crossing site may not be known until formal carotid angioplasty and stenting is performed at a later time.

Thrombectomy

Once access across the occlusion is achieved, the next steps are dictated by whether or not there is thrombus in the ICA or whether it is collapsed. If it is the latter, the microcatheter can be exchanged for a distal embolic protection device (EPD), and the otherwise routine procedure of carotid angioplasty and stenting can commence (see below). This can be done with proximal protection as well, if a BGC is utilized. It is important to keep in mind that the smallest EPD delivery systems are still 3.2F. Thus, if the crossing profile of the EPD delivery system is too large, a low-profile balloon such as a 2.5F Gateway balloon (Stryker Neurovascular, Kalamazoo,

MI) may be necessary for pre-procedural balloon dilatation in order to position an EPD into the distal vasculature. If a BGC is not used, this maneuver is completely unprotected.

If there is thrombus in the ICA, the technique becomes more complex and entirely depends on blind proximal dilatation in order to deliver distal thrombectomy devices. The microcatheter is first exchanged for a low-profile balloon such as an Aviator (Cordis, Milpitas, CA) or Gateway. A BGC provides an advantage in this scenario, as it provides proximal embolic protection in the absence of any distal protection. Since an exchange-length wire is in position, either a monorail/rapid exchange or an over-the-wire system can be used. Following this pre-CAS angioplasty, care must be taken not to inject vigorously during post-dilatation control angiography so as to avoid dislodging free-floating thrombus. Once sufficient luminal diameter is achieved following balloon dilatation, either an aspiration or intermediate catheter should be advanced across the lesion. This allows for either direct aspiration or deployment of a stent-retriever, while preserving access across the lesion. If direct aspiration is used, one should consider doing so over an exchange-length 0.014″ wire so as to maintain access across the lesion.

Several other techniques have been described when performing CAS across an occluded ICA stem when there is concern for thrombus lying within the occlusion or within the distal collapsed carotid. These can utilize BGCs and balloon microcatheters, but will not be described in detail in this chapter [25].

Tandem lesions will be described later in this chapter; however, it is useful to discuss this scenario with respect to how the carotid lesion is addressed. If the underlying ICA lesion cannot be crossed with anything other than a microwire or microcatheter, the operator is forced to decide whether to definitively treat the ICA first or to wait to do so after the intracranial LVO is removed, or even in a delayed fashion. No guideline exists as to which occlusion should be treated first, nor is there agreement whether acute or delayed stenting is superior [15, 26–29]. It is also useful to note, that the standard Committee on Medicare and Medicaid Services (CMS) guidelines for carotid artery stenting (Table 9.2) are not necessarily applicable here.

Traditional Carotid Angioplasty and Stenting

Once access across the occlusion is obtained and any thrombus in the distal vasculature removed, traditional techniques for CAS can be utilized. In isolated acute ICA occlusions, this is likely as the decision to intervene was made solely on the need to revacularize the ICA, taking into account any existing stroke burden and risk of reperfusion injury. In the setting of tandem lesions, it is reasonable to forego CAS completion to assess the infarct burden and the clinical status of the patient.

After its deployment, the distal EPD's rail serves as the rapid exchange system for the remainder of the case. Once the EPD is in place, the pre-stent dilatation can proceed. We recommend using a rapid exchange system, again choosing a balloon system based on a low crossing profile.

Table 9.2 Current CMS criteria for carotid artery stenting

1.	Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis ≥70%
2.	Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with category B IDE clinical trials regulation
3.	Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥80% in accordance with the category B IDE clinical trials regulation
High risk surgical criteria	
	Age ≥80;
	Recent (<30 days) MI;
	LVEF <30%;
	Contralateral carotid occlusion;
	New York Heart Association Class III or IV congestive heart failure;
	Unstable angina: Canadian Cardiovascular Society Class III/IV;
	Renal failure: end-stage renal disease on dialysis;
	Common Carotid Artery lesion(s) below clavicle;
	Severe chronic lung disease;
	Previous neck radiation;
	High cervical (ICA) lesion(s);
	Restenosis of prior CEA;
	Tracheostomy;
	Contralateral laryngeal nerve palsy
	Other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stunting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II

It is reasonable to place cardiac pacer leads prior to beginning the procedure, as manipulation of the carotid bulb can result in cardiac arrhythmia. Furthermore, the anesthesia team should have atropine and/or glycopyrrolate readily available. It is imperative to avoid over-inflating the balloon. After the initial angioplasty, another angiogram is performed to evaluate the success of the dilatation and to assess for embolic complications.

Stent Considerations

Stent placement follows the angioplasty. The angiograms are used to measure the vessels, select an appropriate size stent, and determine the optimal origin and termination zones for the stent. The vertebral bodies are used as backup landmarks for the "safe zone" for stent deployment, in anticipation of patient movement rendering roadmap images inaccurate. Self-expanding, open cell stents are the convention in CAS. Tapered stents are particularly useful when the suspected underlying pathology of the occlusion is atherosclerotic, and, more specifically, at the stem of the ICA. In such cases, optimal positioning of the proximal aspect of non-tapered stents (or the "landing zone") can be difficult, and require landing in the CCA. In this

scenario, the distal aspect of a non-tapered stent should be oversized to the ICA, so as to minimize undersizing of the proximal aspect relative to the CCA. Longer tapered stents are advantageous, as the proximal aspect is typically 2 mm larger than the distal aspect to provide better wall apposition in the larger proximal common carotid artery.

Once the stent reaches the diseased segment, it is crucial to refrain from forcing it across the stenosis. If the stent will not advance, it is withdrawn and an additional dilatation is performed with a 4–5 mm balloon. Alternatively, a short balloon-expandable stent can be deployed first, followed by the definitive self-expanding stent. Consider oversizing the self-expanding stent: using 8 mm or 10 mm stents when the proximal end is deployed in the CCA and 7 mm or 8 mm stents when they are deployed entirely in the ICA. The stent is deployed from within the healthy segment of the ICA across the diseased segment. It is less important that the proximal end of any tapered stent is located in the CCA.

Care must also be taken in properly sizing the stent relative to the curvature of the carotid. When there is much redundancy and thus ectasia of the carotid, placing a long stent may inadvertently kink the carotid at its edges, since stents are somewhat rigid and will straighten the stented segment. Kinks have the potential of being flow-limiting in and of themselves. In extremely tortuous vessels, advancing the stent may also be difficult. These should be considerations when deciding between stenting and endarterectomy. After stent deployment, another angiogram is performed to confirm adequate positioning and assess for thromboembolic complications. If the results are not satisfactory, a post-stent angioplasty can be performed with a larger balloon.

In most cases, the stent will cover the origin of the ECA. Rarely, the ECA may become stenosed or occluded after post-dilatation. Once angioplasty and stenting have successfully been performed, final cervical and cranial angiograms are performed to make sure all branches and vessels are patent without evidence of thromboembolic complications. The distal EPD is carefully removed using the retrieval catheter. If a BGC was used, it is deflated. Femoral or radial artery closure proceeds per surgeon preference.

Carotid Endarterectomy for Acute Carotid Occlusion

The details of this procedure are described elsewhere, so we will focus more specifically on the decisions made in the setting of carotid occlusion. Treatment of an acutely occluded carotid artery has traditionally been limited to medical management [30]. Even with early studies indicating that there were subsets of patients who were at risk for serious neurological sequelae, results of clinical trials favored medical management over surgery [31–35]. With the advent and dispersion of perfusion imaging, carotid revascularization in selected patients in the acute and subacute setting has come back into favor. When patients present with an acute or subacute carotid occlusion, limited or no stroke burden, evidence of hypoperfusion, and no

contraindications to surgery (Table 9.2), they should be considered for revascularization via endarterectomy (CEA).

Immediate preoperative, intraoperative, and immediate postoperative transcranial doppler (TCD) with emboli monitoring may be useful. TCD provides information regarding the direction of flow at baseline, during cross-clamping, and after the endarterectomy. Emboli monitoring is also helpful in making decisions regarding adjuvant therapies to avoid postoperative complications, such as dextran infusions and additional or alternative antiplatelet agents. Intraoperative neuromonitoring, consisting of EEG and SSEP recordings, is also a useful adjunct, if available.

The decision to use a shunt during cross-clamping is mostly guided by TCD findings and augmented by intraoperative monitoring signals. If there are no changes within the first 2 minutes, one can proceed without a shunt. A 30% reduction in flow velocity is concerning, but if the operator is confident that the endarterectomy can be completed quickly, it is reasonable to proceed. A 50% reduction in velocity necessitates a shunt. Likewise, a loss of SSEP signals despite adequate blood pressure augmentation is an indication to shunt. The placement of Rommel tourniquets prior to cross-clamping allows for rapid shunting should the need arise.

If there is limited back-bleeding after the thromboendarterectomy is complete, there may be additional thrombus distal to the arteriotomy. In this situation, a Fogarty balloon can be used to perform a blind thrombectomy [36]. The deflated balloon catheter is passed into the distal cervical ICA. The balloon is gently inflated until back-bleeding subsides. The inflated balloon catheter is then slowly pulled back through the arteriotomy. This technique can be repeated until satisfactory back-bleeding is observed.

There have been multiple technical notes published regarding the use of a hybrid technique for carotid recanalization [37, 38]. A hybrid technique employs some combination of a standard thromboendarterectomy and a mechanical thrombectomy. The thrombectomy component may be performed while the carotid bifurcation is exposed, or immediately after closure. In both settings, a hybrid room is necessary for expeditious management.

Tandem Lesions

As discussed previously, a tandem lesion refers to an acute M1 or carotid terminus occlusion in the setting of an occlusion or stenosis of the cervical carotid artery. Following the publication of multiple randomized controlled trials, (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, and SWIFT PRIME) intracranial large vessel occlusion is now a disease necessitating urgent treatment [9–12, 39]. It is widely accepted that tPA is not as effective in the case of tandem occlusions and we have already discussed its relative ineffectiveness in acute ICA occlusions [40]. The management strategy for these lesions is controversial and thus heavily operator dependent. Multiple studies have demonstrated improved clinical outcomes after successful revascularization of tandem occlusions [15, 37–39]. As mentioned earlier, no guideline

exists as to which occlusion should be treated first, or whether acute or delayed stenting is superior [15, 26–29].

When deciding the order of intervention, the operator should consider the global perfusion of the patient. In most cases, the perfusion of the intracranial circulation is tenuous, and the distal lesion should be treated first [27, 41]. Newer generation aspiration catheters have made proximal-to-distal treatment possible, as they are easily navigable into the intracranial circulation. However, they require a minimal luminal size through which to pass in order to reach the intracranial circulation.

The BGC or long sheath is positioned near the origin of the ICA. The previously described techniques are applied in order to cross the lesion and remove any ICA thrombus. Assuming this is all successful, a diameter has been nominally achieved that allows passage of an intermediate catheter or even an aspiration catheter. If the lumen is still too small to accommodate an intermediate or aspiration catheter, the operator may be forced to stent the carotid prior to clearing any thrombus from within the ICA. Use of a BGC is an advantage in this scenario as it allows for proximal flow arrest. If the operator is forced to stent the carotid first, care should be taken in subsequently advancing any aspiration or intermediate catheter. In fact, if a stent-retriever is favored for the intracranial LVO or to address any ICA thrombus, an intermediate or aspiration catheter must be used so that the stent-retriever is not pulled across a freshly placed cervical carotid stent during each retrieval attempt.

In the case of an isolated hemisphere, the proximal lesion may first need treatment to prevent hypoperfusion of territories that are not affected by the distal occlusion. The anterior and posterior communicating arteries can allow the operator to perform the distal thrombectomy and then determine whether or not the proximal lesion remains flow-limiting once distal flow has been restored. Often, the act of passing a microcatheter, followed by an intermediate or aspiration catheter, will open the proximal lesion, much like the Dotter angioplasty technique (Fig. 9.4). Any residual stenosis can be addressed at the conclusion of the procedure, or in a delayed fashion after assessing the final stroke burden. Stenting the cervical carotid prior to performing the intracranial thrombectomy poses a theoretical risk of causing fragmentation of the intracranial thrombus, and thus downstream embolization into branches that may be less accessible for thrombectomy.

Summary

Acute and subacute carotid occlusion represents a challenging clinical scenario. Treatment paradigms are shifting towards being more aggressive with revascularization. In patients with a symptomatic occlusion and a favorable infarct burden, revascularization should be considered. Multiple imaging modalities, including DUS, CTA, MRI, perfusion imaging, and traditional catheter angiography should be used to draw a comprehensive picture of the patient's intracranial perfusion and

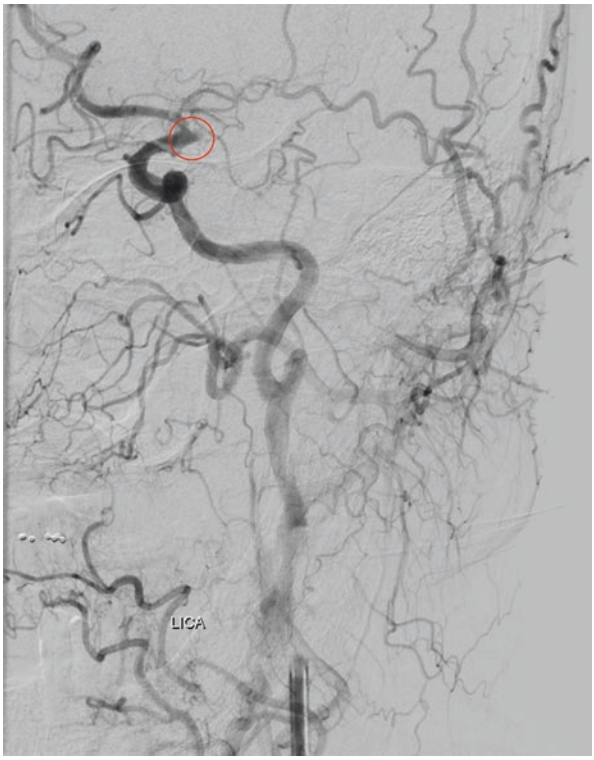

Fig. 9.4 After passing the occlusion in the proximal ICA, it is evident that the majority of the vessel remains open. Furthermore, the tandem occlusion in the M1 segment is appreciated (red ellipse)

reserve at the time of presentation. Questions regarding the superiority of open versus endovascular treatment, angioplasty and stenting versus angioplasty alone, and proximal-to-distal versus distal-to-proximal treatment order have yet to be answered.

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Chapter 10
Chronic Carotid Occlusion

Ali Sultan-Qurraie, Andrew Montoure, Matthew Alexander, and Osama O. Zaidat

Introduction

The definition of chronic carotid artery occlusion (CAO) is variable, with some authors applying the prefix *chronic* after 4 weeks of complete occlusion [1]. As the timing of occlusion is often unknown, the diagnosis is presumed based on patient presentation and angiographic features. Complicating its definition is the accurate diagnosis of occlusion, with "near-occlusion without ICA collapse" or high-grade internal carotid artery (ICA) stenosis instead being frequently misdiagnosed.

The annual incidence of symptomatic CAO is considered to be at least 6/100,000 [2]. Conservative management is generally accepted for asymptomatic CAO, because presently published rates of procedural risk appear to exceed the risk of natural history. Management of symptomatic CAO is more controversial—while bypass or recanalization is an ostensibly reasonable option, no randomized study to-date has demonstrated the benefit of these approaches. Endovascular trials are underway to evaluate the feasibility and benefit of symptomatic CAO revascularization.

A. Sultan-Qurraie (✉)
University of Washington, Valley Medical Center, Renton, WA, USA
e-mail: ali_sultan@valleymed.org

A. Montoure
Medical College of Wisconsin, Department of Neurosurgery, Milwaukee, WI, USA
e-mail: amontoure@mcw.edu

M. Alexander
University of Utah, Department of Radiology, Salt Lake City, UT, USA
e-mail: matthew.alexander@hsc.utah.edu

O. O. Zaidat
Mercy Health System, St. Vincent Medical Center, Toledo, OH, USA
e-mail: oozaidat@mercy.com

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Definitions

Part of the complexity of CAO is due to its multiple etiologies. Proximal, distal, and tandem lesions can cause CAO either by direct obstruction of antegrade flow or, secondarily, by an inability of antegrade flow to overcome a pressure gradient. Variability in etiology of occlusion has led to variability in the definition of carotid occlusion, which includes both the common carotid artery (CCA) and ICA. In this article, we define two conceptual categories of carotid occlusion, "true total occlusion" and "near-occlusion *with* ICA collapse."

True Total Carotid Occlusion

Carotid occlusion may occur secondary to the same etiologies that cause stenosis—in younger patients, arterial dissection is a common cause; in older patients, progressive atherosclerosis is more likely. Radiotherapy, thromboembolism, granulomatous disease, and moyamoya disease are other possible causes of CAO. CAO of the ICA often tapers to a "stump," allowing the angiographer to perform to a "stumpo-gram" to distinguish true occlusion from a high-grade stenosis or "string-sign" (Figs. 10.1 and 10.2).

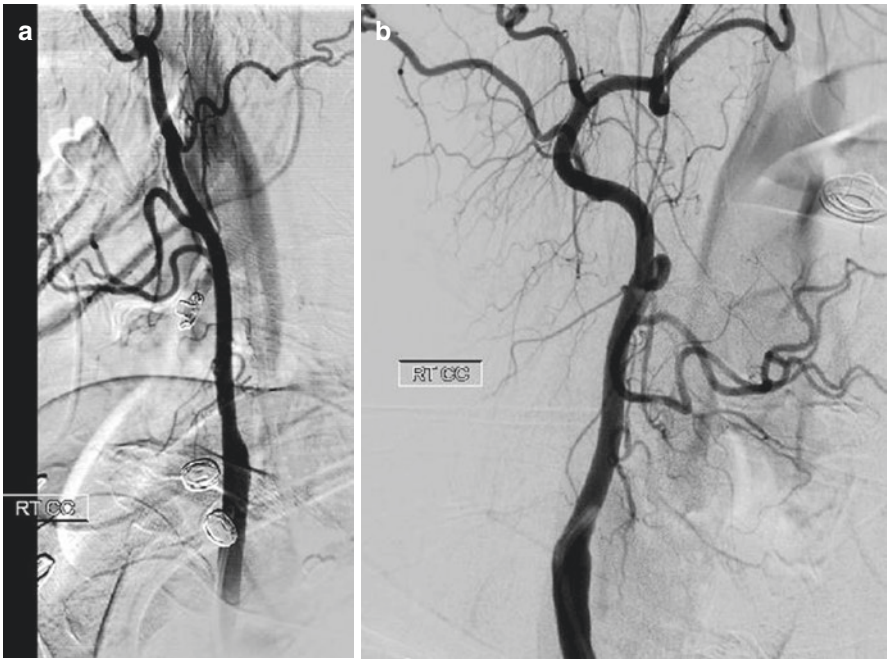

Fig. 10.1 Right CCA angiogram, demonstrating right external carotid artery (ECA) opacification; the ICA is occluded at its origin and not seen in its usual posterior-lateral position

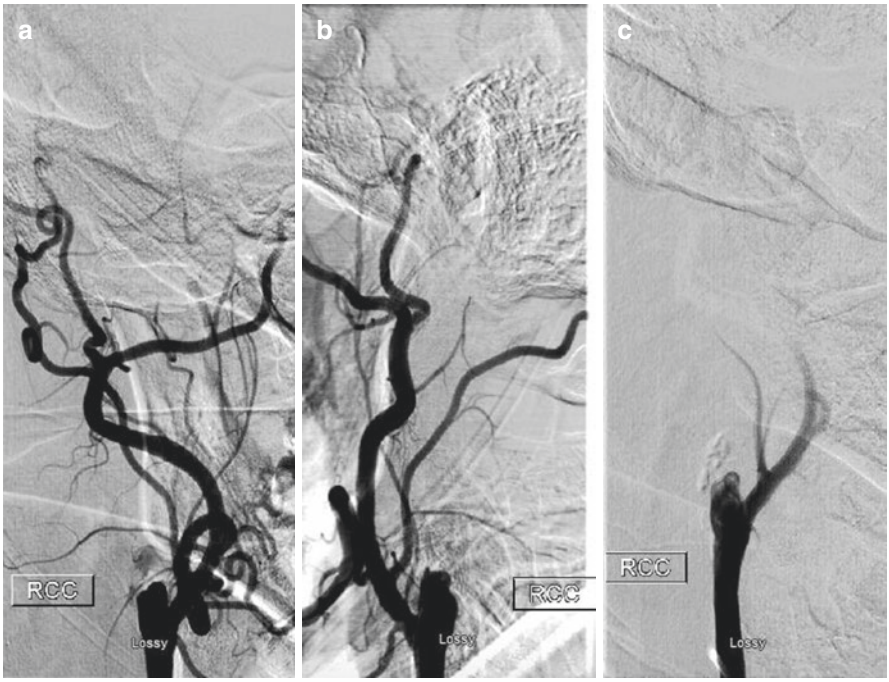

Fig. 10.2 Oblique (**a**) and lateral (**b**) views of a "stumpogram." Angiography is performed with the diagnostic catheter in the 'stump' of the proximal ICA, which is occluded presumably secondary to advanced atherosclerosis with evidence of heavily calcified plaque seen on DSA (**c**)

Near-Occlusion with ICA Collapse

Near occlusion with ICA collapse is defined by the angiographic appearance of a collapsed ICA distal to a high-grade stenosis, accompanied by faster filling in the external carotid artery (ECA), and preferential filling of the intracranial circulation from collateral vessels (Fig. 10.3). In this scenario, there is a hemodynamic basis to occlusion, with antegrade flow pressure in the ICA being unable to overcome intracranial pressure. In the extreme sense, the same concept occurs even in the absence of carotid stenosis in brain death and elevated ICP (Fig. 10.4) [3, 4].

Terms such as "string-sign," "pseudo-occlusion," "slim sign," or "post-stenotic narrowing" appear in the literature and are often meant to be synonymous with near-occlusion. These terms may be confusing as there is no agreement in their definitions. For example, while "string-sign" was first described by Ojemann and intended to denote distal ICA collapse in the setting of ICA dissection, the term has been used by subsequent authors in relation to other causes, both with and without ICA collapse. Johansson and Fox nicely delineate the various terms historically used to describe near-occlusion [5]. Regardless of the term, the result of near-occlusion is a reduced diameter of the ICA distal to the high-grade stenosis with ICA collapse even more distally. When collapse does not occur, the reduction in ICA diameter distal to the stenosis is considered to be "virtual" by Fox et al. and in subgroup analyses of the NASCET and ECST studies the

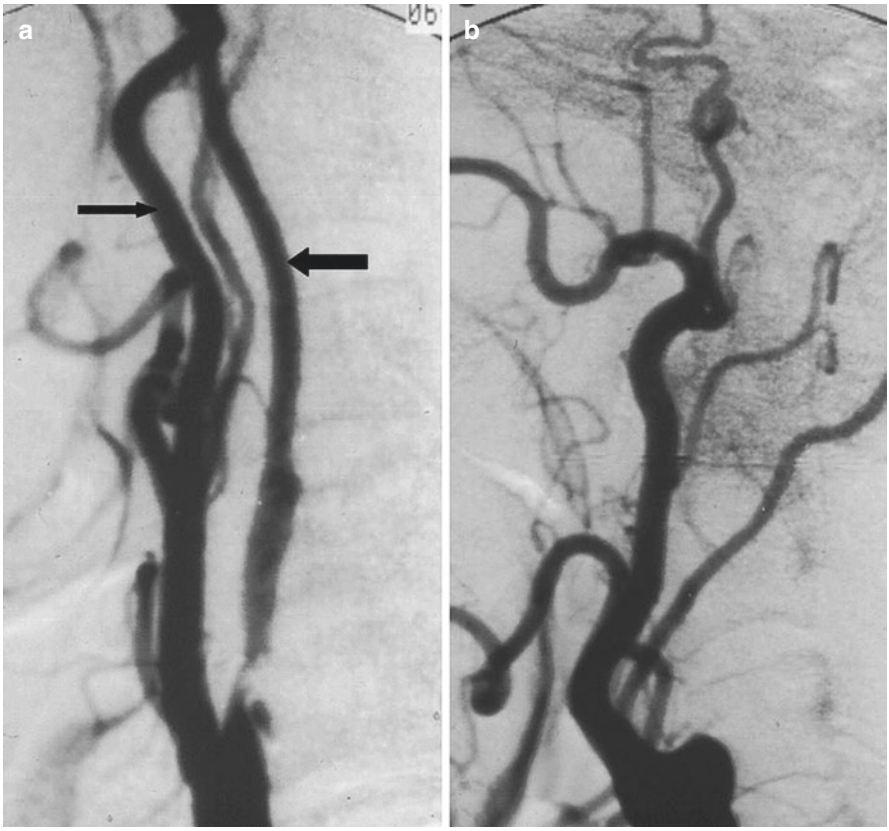

Fig. 10.3 Progression of near occlusion to occlusion. (**a**) Lateral carotid angiogram shows ulcerated stenosis causing near occlusion with ICA diameter beyond the stenosis (*larger arrow*), reduced in diameter to be smaller than the distal ECA diameter (*smaller arrow*). It should be about twice that diameter. (**b**) Lateral carotid angiogram of the same carotid as *A* about 8 months later shows that the near occlusion has progressed to occlusion [49]. (Republished with permission of the American Society of Neuroradiology, from Fox et al. [49]; permission conveyed through Copyright Clearance Center, Inc.)

benefit of carotid recanalization in these patients was found to be "muted." The explanation for this is presumably due to healthy collaterals via the ECA and other territories. Recent research, however, contradicts the subgroup analyses of NASCET and ECST and suggests that "best medical therapy" is not superior to endarterectomy or stenting in improving 1 month or 1 year stroke/death risk in these patients [6].

Natural History and Clinical Manifestations

Patients with chronic carotid occlusion can present with ipsilateral TIA or stroke. However, the magnitude of stroke risk is variable. Cote et al. prospectively followed 47 patients and, in a 34.4 month period, 23.5% (11 patients) suffered ipsilateral stroke.

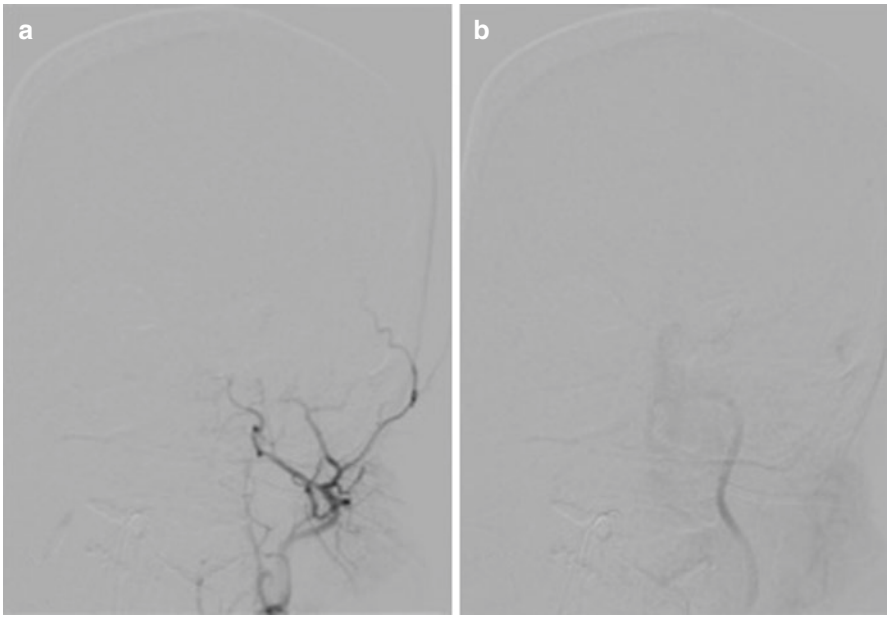

Fig. 10.4 Early anterior-posterior (A) and late AP (B) projections of a left CCA injection demonstrate the concept of ICA "collapse" in brain death. The ICA does not fill distal to the cavernous segment. In this scenario, Intracranial Pressure exceeds extracranial ICA pressure

den Hartog et al. cite a 17% 5 year and 20.8% 10 year risk of stroke for patients with CAO [7]. Flaherty et al. extrapolate the annual incidence of symptomatic CAO to be 6 in 100,000, 15–20 thousand incident cases in the US annually, although the true incidence is assumed to be greater. In their study, they identify a temporal risk of ipsilateral stroke with stroke being more likely earlier after occlusion. Risk of cerebral infarction during follow-up was 8% at 30 days, 10% at 1 year, and 14% at 5 years. Five of 11 cerebral infarctions occurred within the first week after diagnosis of occlusion. Likewise, risk of myocardial infarction increased with time. Risk of death was 7%, 13%, and 29%, respectively, in these time epochs. Furlan et al. retrospectively studied 138 patients with CAO who were either not symptomatic or had "minimal" deficits, finding a 2% annual risk of ipsilateral stroke for the first 4 years after occlusion. Hankey et al., on the other hand, in a review of 12 prospective studies (1261 patients with angiographically documented CAO followed for a mean 45.5 months), reported the average risk of death was 9.5% per year (95% confidence interval (CI): 8.4–10.7%), the risk of stroke was at least 7.0% per year (95% CI: 6.2–7.7%) and the risk of stroke ipsilateral to the carotid occlusion was 5.9% per year (95% CI: 4.3–7.5%) [8]. Therefore, it is apparent that there is a wide variability of reported stroke risk following CAO, with higher risk likely being associated with initially symptomatic occlusions with reduction of yearly risk over time. Nonetheless, as Hankey states, "it is clear that carotid occlusion is not a stable condition, and patients should benefit from measures aimed at the prevention of subsequent major cardiovascular as well as cerebrovascular events."

Is there a difference between stroke rates in true total carotid occlusion versus near-occlusion with collapse? To our knowledge, no study has looked at stroke risk based on occlusion type. Stroke risk in symptomatic near-occlusion with ICA collapse may be high, but the existing data is not robust. A number of small studies suggest a high risk of stroke recurrence in cases of symptomatic near-occlusion with ICA collapse. Ringelstein et al. suggested "mandatory" surgical recanalization in these patients [9–11]. NASCET and ECST included only a small subset of near-occlusion patients with collapse (n = 16) and pooled these patients with near-occlusion without collapse. Therefore, robust prospective data is lacking, but the few small existing studies suggest that symptomatic near-occlusion with ICA collapse, similar to symptomatic true total occlusion, has a high risk for stroke recurrence.

In patients with hemodynamically significant occlusion, the stroke risk may be as high as 28.2% [12]. "Stump" emboli, emboli from the ECA, transhemispheric emboli, and hypoperfusion have been postulated mechanisms of stroke [13]. The consideration of hemodynamic insufficiency as a cause of stroke in these patients led to EC-IC bypass studies, described below. Limb shaking, in the absence of epileptiform activity on EEG monitoring, and retinal artery occlusion with bright light stimulus are considered clinical manifestations of hypoperfusion in the setting of CAO [14–16].

Headaches, or facial pulses, as described by Fisher can occur as a result of "dilatation of the vessels that carry anastomotic flow from the branches of the ECA into the distal internal carotid artery." [17] Chronic ocular ischemia is prevalent but is generally not clinically manifested [18]. Syncope has also been associated with CAO, both with and without contralateral ICA stenosis [19].

Compared to carotid stenosis, fewer studies have assessed the impact of CAO on cognitive function. Postulated mechanisms of cognitive impairment in this setting include progression of white matter lesions, ischemic strokes, and cerebral hypoperfusion. Oudeman et al. published a systematic review of 4034 articles (ultimately including 8 articles that met their study criteria), reporting that cognitive impairment is present in "about half to two-thirds of patients" with CAO. The cognitive impairment was not found to be restricted to specific cognitive domains. They could not, however, find an association between systemic hemodynamic impairment and cognitive functioning [20].

Stroke risk with asymptomatic CAO appears significantly lower. Powers et al. report ischemic stroke occurring in 1 of 30 of "never-symptomatic" patients (3.3%) and 15 of 81 of symptomatic patients (18.5%; $p = 0.03$) within an average 32-month follow-up period. Similarly, Yang et al. found that the rate of stroke in asymptomatic CAO is low, <1% [21]. In their cohort of 316 patients with asymptomatic CAO (free of ipsilateral stroke for the past 18 months), only 0.9% (3 patients) had ipsilateral stroke in follow-up (mean duration of follow up was 2.56 years). As a result of the relatively low risk of asymptomatic CAO, endovascular or surgical intervention of an asymptomatic carotid artery has not been justified within the existing body of medical literature [22].

Several studies have reported the spontaneous recanalization of chronic CAO. Delgado et al. reported that 7 (5%) of 136 patients with "symptomatic athero-

matous ICA occlusion" demonstrated spontaneous recanalization on follow up imaging >3 months after initial occlusion. Morris-Stiff reported that 8 (10.3%) out of 77 patients with follow-up imaging demonstrated recanalization at a median follow up of 53 months. Of 153 patients with CAO, 38 (25%) had ipsilateral stroke [23]. Camporese et al. reported a recanalization in 16 of 696 patients (2.3%; 95% confidence interval, 1.3–3.7%) with ICA occlusion after a mean interval of 38 months from the diagnosis of occlusion [24].

Diagnosis

Some authors deem carotid occlusion greater than 4 weeks to constitute a 'chronic' designation; others prefer >3 months as a cut-off [25]. In practical terms, when patients present with symptomatic CAO, the time of initial occlusion may be assumed but not definitively known. Various techniques have been used to diagnose CAO and are used to distinguish acute from chronic occlusion.

Michel et al. used CT angiogram to report that a "carotid ring" sign—defined as hypodensity in the carotid artery signifying thrombus and/or contrast within the carotid wall (vaso vasorum)—had high sensitivity (88.9%) in diagnosing acute occlusion (imaging being obtained <1 week from presumed occlusion) [26].

Time is one variable by which carotid occlusion is defined; hemodynamics and ICA location of occlusion is another. Grossberg et al. suggest that routine CTA is unable to discern an intracranial occlusion from an extracranial occlusion, because both result in the appearance of cervical ICA occlusion and in 33% of patients the appearance of intracranial occlusion mimicked a carotid dissection on CTA [27]. Therefore, these and other authors advocate for super selective angiographic microcatheter exploration for accurate diagnosis. In cases of intracranial ICA occlusion, microcatheter angiography performed in the distal ICA will result in 'backfilling' of contrast and demonstration of proximal ICA patency.

Management

Medical Management

There is no clear consensus on the "best medical treatment" of chronic CAO, but "intensive medical therapy," which is advocated for asymptomatic carotid stenosis, seems reasonable [28]. "Intensive medical therapy," according to Spence et al., should constitute "healthy lifestyle choices (not smoking, moderate alcohol intake, a body mass index <25, 30 min of daily exercise and a healthy diet score in the top 40%), a Mediterranean diet, effective blood pressure control, antiplatelet therapy, intensive lipid-lowering therapy, and treatment with B vitamins (with methylco-

balamin instead of cyanocobalamin).” However, even in patients treated with anticoagulant or antiplatelet therapy, the overall risk of subsequent stroke is 5–7% per year, and the risk of stroke ipsilateral to the occluded carotid artery is 2–6% per year [29].

Surgical Management

Surgical indications for treating chronic CAO are limited and are not widely accepted in today’s practice. DeBakey reports performing direct carotid revascularization for carotid occlusion in 1953 [30]. Subsequent studies of carotid endarterectomy in the chronic setting were met with high failure rate and complication risk, assumed in part due to intracranial extension of thrombus [31]. These early failures led to indirect revascularization techniques, as with ECA-ICA (EC-IC) bypass—the most common of which is arterial bypass via the superficial temporal artery (STA), or occipital artery to the middle cerebral artery (MCA). Nevertheless, there have been no randomized control studies to support surgical treatment to date. Two major landmark studies which have explored this topic and shown no benefit for surgical intervention include the International Extracranial-Intracranial Bypass Study (EC-IC Bypass Study) [32] and the Carotid Occlusion Surgery Study (COSS) [33].

The EC-IC Bypass Study was a multi-center randomized control study originally published in 1985. It compared best medical therapy (Aspirin and medical optimization of other co-morbidities) to EC-IC bypass in addition to best medical therapy. Overall, 714 patients were randomized to the best medical care arm and 663 were randomized into the surgical group. The primary outcome event was post randomization fatal or non-fatal strokes. The rate of major perioperative stokes in the surgical group was 4.5%, compared to the medical group rate of 1.3% [33]. This study failed to show a benefit or reduction in the rate of subsequent stokes within the surgical arm and actually demonstrated a higher frequency and earlier stroke occurrence compared to medical therapy alone [33]. The authors concluded that EC-IC bypass surgery was not effective in decreasing the rate of stroke and stroke-related deaths in patients with symptomatic disease [34].

Due to the results of the EC-IC Bypass Study, surgical intervention for this patient population have been discarded. However, one of the major critiques for the study was an inability to separate patients who were at high risk for subsequent strokes due to hemodynamic factors versus embolic factors [35–37]. With imaging advancements, positron emission tomography could show the oxygen extraction fraction (OEF) and hemodynamic compromise. The risk of stroke in patients with impaired hemodynamics (increased OEF) is greater than those with a normal OEF [2]. Finally, in patients with stage 2 hemodynamic failure a STA-MCA bypass has demonstrated return of the OEF to normal values post operatively [34, 38–40]. This was the basis for the COSS trial.

The COSS trial was a prospective, randomized trial. Participants in the trial had symptomatic CAO with a stroke or TIA within 120 days and hemodynamic ischemia with an increased OEF as demonstrated by PET scan. Ninety-seven were in the surgical arm and 98 were randomized into the medical arm [41]. The surgical patients underwent an STA-MCA cortical branch anastomosis. The primary outcome measure was the occurrence of ipsilateral ischemic stroke within 2 years of randomization; results demonstrated a primary endpoint of 21% for the surgical group and 22.7% in the medically treated group [42]. There was also a high rate of ipsilateral stroke within the 30-day postoperative period (15%) [42]. The authors concluded that despite graft patency of 96% and decreasing the OEF, STA-MCA bypass did not provide a benefit or reduce the risk of ipsilateral strokes compared to medical treatment alone [42]. Given the results of these studies, there remains no universally accepted indication for the surgical management of CAO.

Endovascular Studies

Terada appears to be the first to report endovascular revascularization of a chronic CAO [42]. Chen et al. attempted endovascular recanalization in 138 patients with chronic CAO [43]. They reported successful recanalization in 61.6% of cases. Several factors were associated with *lower* chance of recanalization including absence of prior neurological events, a non-tapered stump, distal ICA reconstitution via contralateral injection, and distal ICA reconstitution at the communicating or ophthalmic segments. In their retrospective study, six patients (4.3%) suffered serious events such as major stroke and intracerebral hemorrhage, and two patients died. Lin et al. attempted recanalization in 54 patients and reported technical success in 65% of patients [44]. Thomas et al. reported two successful cases of endovascular revascularization by angioplasty and stenting of two total CAO [45]. Contrary to the report by Chen et al., Thomas et al. suggest that retrograde filling of the distal ICA is a predictor of increased success of recanalization. Lee et al., in a study of 19 patients with occlusion proximal to the clinoid ICA segment, reported 89% technical success, 0% complication, and 0% re-occlusion; while 23 patients with occlusion at or distal to the clinoid segment reportedly had 52%, 22%, and 91% technical success, procedural complication, and re-occlusion.

Even if carotid revascularization is feasible, future studies are needed to determine which patients would benefit from such procedures. Emboli monitoring or assessment of cerebrovascular reserve have been shown to identify patients at highest risk for stroke in patients with carotid stenosis [11]. These and other tools may also have a role in selecting the optimal patient with CAO. Liberman et al. found a high rate of microemboli on TCD monitoring in patients with recently symptomatic carotid occlusion [46]. Prospective studies evaluating endovascular revascularization and EC-IC bypass (in a subgroup of patients refractory to medical management) are currently being conducted [47, 48].

Conclusion

There is a dearth of data relating to chronic carotid occlusion. It is a challenging entity both because of pitfalls in its diagnosis and because of its heterogenous etiologies. In this chapter we have defined true total CAO and near-occlusion with ICA collapse; each of which may portend different symptom risk and be prone to different feasibility of treatment. Reports regarding incidence of stroke, cognitive impairment, and other symptoms are variable. Inefficacy of surgical bypass compared to medical management was demonstrated by randomized trials. While retrospective endovascular studies have suggested feasibility and benefit to CAO revascularization, validation in prospective studies is ongoing and required.

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Chapter 11
Carotid Artery Dissection

Benjamin K. Hendricks, Dale Ding, Rami O. Almefty, Felipe C. Albuquerque, and Andrew F. Ducruet

Abbreviations

2D TOF	2-dimensional time of flight
CAD	Carotid artery dissection
CADISS	Cervical Artery Dissection in Stroke Study
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
ICA	Internal carotid artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging

Introduction

Arterial dissections are defined as the presence of intramural hematomas within the smooth muscle of the arterial wall. They can vary in anatomical location, etiology, and clinical implication. Carotid artery dissection (CAD) is a relatively infrequent type of dissection within the vascular system, with an annual incidence of 1.7–3 per 100,000 [1, 2], which is approximately three times more frequent than vertebral artery dissection [2]. Epidemiologically, CADs account for only 1–2% of all ischemic strokes, but they comprise approximately 10–25% of all strokes in patients younger than 50 years of age [3–7]. This incidence implicates CAD as a major contributor of morbidity in this younger population.

B. K. Hendricks · D. Ding · R. O. Almefty · F. C. Albuquerque · A. F. Ducruet (✉)
Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA
e-mail: Neuropub@barrowneuro.org

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CADs can be either extracranial or intracranial, with extracranial dissections occurring more commonly [7]. These injuries are further categorized as "traumatic" or "spontaneous" based on their etiology, although the literature suggests that spontaneous dissections likely occur in patients with predisposing conditions who sustain an unrecognized mild trauma [8, 9]. Most of the recent CAD literature covers spontaneous extracranial CAD after minor trauma, with extracranial dissections in patients with major trauma and intracranial dissection locations being discussed less frequently [8, 10, 11]. The pathogenesis underlying the vascular injury is thought to result from abnormal acute force generated within the tunica media, resulting in an intramural hematoma [6, 7, 12]. The hemorrhagic source is variable, originating either from the vascular lumen after a tunica intimal tear or from the traversing vasa vasorum [13]. The false lumen propagates longitudinally and, in doing so, results in partial or complete occlusion of the true lumen [14]. This occlusion imparts an ischemic risk to all tissues with distal perfusion; combined with the prothrombotic state resulting from exposure of luminal blood to the subluminal contents, an additional risk of thromboembolic stroke is incurred in these patients [1, 15].

Historical reports suggest that patients with untreated traumatic CADs have high rates of morbidity (40–80%) and mortality (20–40%) [16–18]. The highest risk after dissection is believed to occur shortly after the onset of symptoms, with a risk of secondary stroke after presentation ranging from 15% to 20% [3, 10, 19, 20]. Given the high associated morbidity of stroke, urgent treatment is warranted. Management options include medical therapy, endovascular intervention, or open surgical treatment.

The discussion of CAD in this chapter begins with a historical perspective on this topic, followed by a discussion regarding traumatic versus spontaneous etiologies of CAD. Clinical presentation and risk factors are discussed in detail, followed by the management of patients with CAD, stratified into medical and interventional strategies. We conclude with a discussion of the recurrence of CAD and preventative strategies.

Historical Perspective

CAD is rarely reported in the historical literature, with the earliest case reported in 1959 [21] and only 30 cases reported by 1980 [16]. The original diagnosis of CAD was noted by the presence of a "string sign" on digital subtraction angiography (DSA) along the extracranial internal carotid artery (ICA) [22]. Screening for traumatic CAD after significant trauma began in 1999 when a report in the *Journal of Trauma* demonstrated the efficacy of computed tomography angiography (CTA) for this purpose [23]. Further study in trauma patients demonstrated the importance of follow-up arteriography within 7–10 days after diagnosis of a CAD because of the risk of injury progression [24]. As the diagnosis and classification

of CAD progressed, management of these lesions also evolved. In 1999, the Biffl scale (also referred to as the Denver grading scale) for blunt cerebrovascular injuries was proposed to characterize the radiographic severity of injury in adult patients [25]. These advances in classification were augmented by the increased use of screening tools to identify these injuries before patients were impacted neurologically.

The early management for CAD was surgical, involving proximal and distal trapping with excision of the diseased segment, endarterectomy, and interposition graft placement [22, 26–28]. Outcomes after these interventions were poor, with many patients developing persistent neurological deficits postoperatively [22, 26, 27]. For those lesions at or above the skull base, nonoperative management was considered the standard of care because of the inaccessibility of the lesion for open surgical repair [25].

The use of antithrombotic agents for patients with CAD was proposed in the late 1970s, based on the suspected pathogenesis of CAD-associated stroke [29]. However, randomized clinical evidence to validate this treatment strategy was lacking [30]. Anticoagulation was introduced in 1980 as a potential treatment for CAD after a case report described how the use of medical therapy (3 weeks of heparin) provided a favorable neurological outcome, as well as complete recanalization of the ICA [31]. The use of an implantable infusion device for continuous intravenous heparinization for 5 months was proposed in 1981 [32]. In 1994 a large multicenter study of systemic heparinization with 49 patients demonstrated improved neurological outcomes in CAD patients who were heparinized compared to those who did not receive anticoagulation [33]. In 1996 a large, single-institution series utilizing systemic heparinization for traumatic CAD in 47 patients demonstrated similar results [34], suggesting that heparinization was the treatment of choice for surgically inaccessible lesions [25]. Nevertheless, clinicians recognized that the use of systemic heparinization was not always possible, particularly in patients affected by trauma.

Procedural intervention became the second-line therapy for patients with CAD, and it was generally reserved for patients who suffered persistent cerebral ischemia despite adequate anticoagulation or antiplatelet therapy [35]. Prior methods of surgical intervention [22, 26–28] were abandoned after multiple reports of success with extracranial-to-intracranial bypass procedures in the 1990s [36–38]. Endovascular intervention was a late arrival in the management scheme for CAD, given the concern in the late 1980s about possible cerebral infarction after an initial endovascular approach, such as selective arterial embolization or balloon occlusion of the ICA [39]. Advances in endovascular technique led to the use of stents as a potential treatment for CAD in 1997, with promising results [40, 41].

The evolution of treatment recommendations for CAD demonstrates a trend toward initial medical management. It is followed by procedural intervention for persistent cerebral ischemia that is dependent on the individual patient's clinical scenario and extent of injury.

Spontaneous Versus Traumatic Carotid Artery Dissection

Traumatic CADs are observed after either blunt or penetrating trauma to the cervical ICA, although CADs occur more frequently in patients with blunt injury. Overall, traumatic CAD is a rare entity, with previous reports suggesting that CADs only occur in approximately 1–2% of adult patients with severe, nonpenetrating neck injuries [42, 43] and in 0.03–0.9% of pediatric patients with traumatic brain injuries [44–46]. Blunt trauma produces multiple potential mechanisms of injury, including acute hyperextension of the neck, related to compression of the ICA between the mandible and cervical vertebra, and a stretch injury occurring across the cervical lateral mass [13, 47, 48]. Penetrating injury, a less frequent etiology, is generally observed after a stabbing, a gunshot wound, or an iatrogenic injury sustained during cervical spine interventions [13]. Traumatic CADs are often misdiagnosed or undetected initially because of multiple coexisting factors that can mask the clinical presentation.

Spontaneous CAD is a rare entity, with an annual incidence ranging from 1.7 to 3 per 100,000 [2, 12, 49, 50]. Most of these incidence calculations are based on observational registries in the United States and Europe, thereby potentially biasing the estimated incidence of CAD in other countries. Traditionally, to be classified as a spontaneous dissection, a history of preceding trauma must be absent [13]. Some authors believe that spontaneous CADs are actually a result of minor trauma in a patient with predisposing anatomical or genetic factors that precipitate the dissection in the absence of a recognized major trauma [9, 35, 51]. Since most of the recent CAD literature has focused on lesions of the extracranial ICA, that is the focus of the remainder of this chapter.

Diagnostic Imaging

DSA has historically been the preferred diagnostic modality, with the carotid string sign being the most common radiographic finding [22, 52]. This sign is observed with the remnant anterograde filling of the true lumen on angiography, surrounded by the irregular long-segment narrowing from the dissection [22, 52]. The more pathognomonic sign for CAD is a double lumen or the isolation of the intimal flap observed on imaging, although this finding is observed in less than 10% of patients with CAD [35, 52, 53]. DSA is a highly accurate diagnostic modality, but it harbors a 2–3% risk of complications, including a risk of stroke with permanent disability of 0.1–0.2% [12, 54, 55]. As a result, noninvasive imaging, including CTA, magnetic resonance angiography (MRA), and carotid ultrasound, have become the standard for screening patients with a suspected carotid artery injury [35, 52]. The integration of noninvasive imaging into the diagnostic protocol for CAD has greatly increased the frequency of its diagnosis.

CTA provides high-resolution vascular imaging from the aortic arch to the circle of Willis. The common findings in patients with a CAD are the irregular long-segment narrowing of the extracranial ICA, crescent-shaped mural thickening, annular enhancement, and the identification of an intimal flap [56, 57]. MRA or magnetic resonance imaging (MRI) is a non-ionizing modality for the diagnosis of CAD. Imaging features for CAD on MRA or MRI include an intramural hematoma, which changes in appearance depending on the age of the blood. Within the first 48 hours, the hematoma appears hypointense on T1-weighted and T2-weighted sequences, and then at 48 hours to 8 weeks, it becomes hyperintense on T1-weighted sequences, resembling a crescent shape with adjacent aberrant flow within the ICA on MRA. Thereafter, the hematoma becomes isointense with the adjacent anatomy [35, 52]. A more reliable early diagnostic feature of CAD on MRA is a relatively enlarged external arterial diameter compared to the narrowed intraluminal diameter for anterograde flow on MRA. The pathognomonic sign of an intimal flap is often difficult to visualize on a contrast-enhanced MRA because of the signal intensity of adjacent blood flow, which lends an advantage to the use of cross-sectional MRI in visualizing this feature [58]. MRA evaluation can be augmented by the acquisition of 2-dimensional time-of-flight (2D TOF) MRA, and this modality has been reported to permit excellent visualization of subacute intramural hematoma [52]. Contrast-enhanced MRA, an alternative imaging sequence to 2D TOF, provides a comparable field of view to CTA and has faster acquisition with fewer artifacts than 2D TOF [52]. The diagnostic capability of cross-sectional MRI combined with a contrast-enhanced MRA sequence is reported to have a sensitivity of 95% and specificity of 99% for CAD [59].

A comparison of the sensitivity, specificity, positive predictive value, and negative predictive value of CTA versus MRA for CAD has been performed. This comparison showed no statistically significant difference in capability between the two modalities [58]. A comparison of MRI to MRA also did not demonstrate a statistically significant difference in diagnostic capabilities [59]. The efficiency of CTA is advantageous in evaluating patients after a major trauma, and this modality is therefore generally favored in such patients.

The alternative noninvasive modality for the diagnosis of CAD is carotid ultrasonography. Several sequences within the ultrasound evaluation can be used, including gray-scale ultrasonic evaluation, color Doppler, and spectral analysis of Doppler flow velocity signals [54]. The ultrasonic evaluation is focused on identifying the intimal flap or the presence of a double lumen during direct ultrasonic visualization [54]. A visualized intramural hematoma also indicates the presence of a dissection [54]. The diagnostic feature of a CAD seen during Doppler analysis is the presence of a high-resistance flow pattern imparted by the dissection [35]; this feature has been demonstrated in up to 68% of all CADs [60]. Those CADs with increasing severity of luminal compromise are most accurately detected by ultrasonic evaluation, whereas those with minimal stenosis of the true lumen are less accurately identified [61].

Table 11.1 Denver grading scale for blunt carotid injury (also referred to as the Biffl scale)

Injury grade	Description
I	Luminal irregularity <25% stenosis
II	Dissection or intramural hematoma with ≥25% luminal stenosis
III	Pseudoaneurysm presence
IV	Carotid occlusion
V	Carotid transection

Data from Biffl et al. [25]

After the identification of a CAD on imaging, the Denver grading scale (also referred to as the Biffl scale, see Table 11.1) can be used to evaluate the angiographic severity of the CAD [25]. This scale was designed for use in patients with blunt carotid artery injury, and it ranges from grade I to grade V, with both prognostic and therapeutic implications [25]. Grade I injuries are defined as an irregularity of the carotid artery with less than 25% luminal stenosis. The level of stenosis is calculated based on a comparison of the diseased segment to the diameter of the normal vessel proximal to the dissection. Grade II injuries are those in which the intramural hematoma contributes more than 25% luminal stenosis or when an intraluminal thrombus or intimal flap is visualized. Grade III injuries are defined by the presence of a pseudoaneurysm. Grade IV injuries are defined by vessel occlusion. Grade V injuries are defined by vessel transection with active contrast extravasation [25].

Radiographic risk factors for CAD after blunt cerebrovascular injury have been analyzed in both the adult and the pediatric populations, resulting in the Memphis criteria and the Utah score, respectively, which can indicate the need for further screening of these patients. The Memphis criteria, which were designed to stratify patients as being at higher risk for blunt cerebrovascular injury on the basis of their radiographic and clinical findings, include the following [62]:

- Basilar skull fracture with involvement of the carotid canal
- Cervical spinal fracture
- Cerebral imaging that does not explain neurological findings
- Horner syndrome
- LeFort II or III fracture patterns
- Neck soft tissue injury (e.g., hanging, seatbelt sign, or hematoma)

The presence of any of these high-risk features on radiographic evaluation should prompt noninvasive angiographic evaluation for possible dissection. The Memphis criteria were further modified to improve the sensitivity of diagnosis by including basilar skull fracture with involvement of the petrous bone [63]. These criteria provide stratification for the recommendation for screening angiography to evaluate the presence of carotid or vertebral artery injury.

Blunt carotid artery injury with dissection was analyzed in the pediatric population to devise the Utah score (ranging from 0 to 11, see Table 11.2), which is a

Table 11.2 Utah score for stratification of a pediatric patient's risk for blunt cerebrovascular injury

Utah Score Variable	Score
GCS score ≤8	1
Focal neurological deficit	2
Fracture through the carotid canal	2
Fracture of the petrous temporal bone	3
Cerebral infarction diagnosed on CT	3

CT computed tomogram, *GCS* Glasgow Coma Scale
Data from Ravindra et al. [64]

stratification score to guide the need for screening imaging evaluation in pediatric patients [64]. Risk factors that were identified included a Glasgow Coma Scale score ≤8 (1 point), a focal neurological deficit (2 points), fracture through the carotid canal (2 points), a petrous temporal bone fracture (3 points), and cerebral infarct on computed tomography (3 points) [64]. These independent risk factors were determined by multivariate regression analysis and externally validated, with a score ≥3 (categorized as high risk) associated with an 18.1% probability of having a blunt cerebrovascular injury [64, 65]. Conversely, patients with a score ≤2 (categorized as low risk) had a 2.7% probability of blunt cerebrovascular injury. This scoring system misclassified 16.6% of the patients in the external validation study [65]. The Utah score provides a meaningful method to stratify a pediatric patient's blunt cerebrovascular injury risk based on imaging findings and basic clinical evaluation.

Clinical Presentation

The clinical presentation of patients with CAD classically consists of the triad of unilateral pain (head, face, or neck), partial Horner syndrome, and neurological deficits related to cerebral or retinal ischemia [12]. In clinical practice, less than one-third of CAD patients present with all of these findings [6, 12, 66], more than 50% have a clinical presentation not suggestive of the diagnosis [67], and up to 5% are asymptomatic [54].

Pain is the most common feature of CAD and the first presenting feature of affected patients, with headache being present in 44–69% and neck pain in 25–49% [8, 35]. Pain is the isolated clinical feature in less than 10% of patients with CAD [68]. Headache is generally characterized as non-throbbing and gradual in onset, although a sudden, "thunderclap" onset or throbbing quality has also been reported [7, 35, 69, 70]. Neck pain is commonly ipsilateral along the upper anterolateral cervical region [35, 71].

Neurological deficits secondary to cerebral or retinal ischemia are observed in 50–95% of patients with CAD, and these deficits are related either to vascular insufficiency from flow-limiting ICA stenosis or to thromboembolic stroke [6, 8, 12, 35]. Thromboembolism has been reported to be the underlying cause of stroke in most

cases [72], with hypoperfusion accounting for only about 5% of ischemic strokes in these patients [69, 72]. Overall, 71–84% of CAD patients present with a cerebral infarction, 13–20% present with symptoms consistent with those of a transient ischemic attack, 3% with amaurosis fugax, and 1% with retinal infarction [8, 12, 35, 38, 70]. The impact of thromboembolism is supported by transcranial Doppler ultrasonography studies demonstrating the presence of cerebral microemboli and an embolic pattern of infarction on neuroimaging [10, 15, 73, 74].

A partial Horner syndrome, observed in up to 50% of CAD patients and comprising ptosis, miosis, and lack of anhidrosis, relates to local mass effect from the mural hematoma on the sympathetic nerve fibers ascending along the arterial wall. Anhidrosis is a component of complete Horner syndrome. The lack of anhidrosis in CAD patients is explained by the fact that the sympathetic fibers responsible for hidrosis of the face travel along the external carotid artery, and are therefore generally not affected by a dissection of the ICA. Thus, the presentation of a patient with spontaneous unilateral partial Horner syndrome warrants investigation for the presence of CAD [6, 12, 35].

Risk Factors

Risk factors for CAD include hypertension, diabetes mellitus, hyperlipidemia, smoking, exogenous estrogen supplementation through oral contraceptives, and connective tissue disorders (e.g., fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome type IV, autosomal dominant polycystic kidney disease, and osteogenesis imperfecta type I) [6, 12, 13, 38, 69]. Several other conditions have also been associated with CAD, including predisposing genetic conditions, migraine headache, pregnancy, infection, connective tissue disease, hypertension, remote minor cervical trauma, and a history of strangulation [6, 8, 9, 66, 75–79]. Spontaneous CAD related to a connective tissue disease is typically associated with fibromuscular dysplasia (15%) and less frequently occurs with other connective tissue diseases (<5%) [12, 13, 20, 38, 80].

Traumatic injuries can be categorized into major versus minor events. Major prior cervical trauma underlies the traditionally labeled traumatic CADs. The minor prior cervical traumas are events that, alone, would be unlikely to generate a CAD, but in patients with any of the aforementioned risk factors would promote the development of a spontaneous CAD. Correlative major traumatic injuries include traumatic brain injury, spinal cord injury, major thoracic trauma, and fractures of facial bones, the skull base, or the cervical spine [81]. These injuries denote high-intensity trauma, which is most likely necessary to initiate the pathological process underlying CAD. Correlative minor prior cervical traumas include cervical manipulation therapy [82–84], heavy lifting [47, 48], extreme head movements [47, 48], and recreational activities [85]. These minor correlative factors, which are often normal components of daily life, suggest an insufficient contribution for minor cervical traumas in the pathogenesis of CAD. Engelter et al. [9] evaluated the role of prior

cervical traumas in CAD (966 patients with CAD, 651with ischemic stroke not related to CAD, and 280 healthy subjects) and concluded that prior cervical trauma was not an independent predictor of CAD. Instead, the trauma should be more appropriately termed a "mechanical trigger event," given that it is most likely a contributor to a multifactorial milieu precipitating the dissection. In summary, the diverse presenting features and risk factors for CAD make accurate diagnosis and estimation of its true incidence challenging.

Management

Medical management stands as the first-line treatment for prevention of primary and recurrent stroke. Interventional therapy should be considered for CAD patients who experience persistent ischemia or infarction despite medical therapy.

Medical Therapy

The goal of treatment after a diagnosis of CAD is preservation of the at-risk penumbra and minimization of further cerebral ischemia. Prevention of adverse neurological outcomes generally leads to favorable clinical results, given that the dissection itself usually heals spontaneously [8]. Historically, the treatment protocol for CAD included either anticoagulation (initial administration of intravenous heparin followed by maintenance therapy with warfarin) or antiplatelet therapy with aspirin [12]. The typical duration of medical therapy is 3–6 months, because previous reports indicate that recurrent stroke often occurs within that interval [12, 35, 72]. Until 2015, no randomized controlled trials had compared the efficacy of anticoagulant therapy and antiplatelet therapy for CAD [7, 10, 68].

The comparative efficacy of a particular agent for prevention of recurrent stroke after CAD was examined in the Cervical Artery Dissection in Stroke Study (CADISS) [10]. In this randomized trial, patients had either extracranial carotid or vertebral artery dissections with an onset of symptoms within 7 days of presentation. A total of 250 patients (118 with CADs, 132 with vertebral artery dissections) were enrolled, and the primary endpoint was ipsilateral stroke or death. The results showed no statistically significant difference in the primary outcome between the anticoagulant and antiplatelet cohorts, with an overall rate of 2% (ipsilateral stroke in 4 patients, including 3 in the antiplatelet cohort and 1 in the anticoagulant cohort). There were no deaths during the study. The secondary endpoints were also noted to be similar between the two groups [10]. CADISS provides the highest level of currently available evidence that no difference exists in the efficacy of anticoagulant versus antiplatelet therapy for extracranial carotid or vertebral artery dissection, which supports similar data from prior nonrandomized studies [1, 6, 30, 86]. Therefore, medical treatment with either agent is acceptable for patients with CAD.

Thrombolytic therapy has not been thoroughly evaluated for the treatment of CAD patients who have signs and symptoms of a severe stroke. The use of a thrombolytic agent in patients with an intramural hematoma has the potential to expand the hematoma, promote subarachnoid hemorrhage, and dislocate a mural thrombus, causing thromboembolism [87]. Despite this risk, a retrospective analysis found that intravenous thrombolysis in patients with acute CAD and moderate-to-severe neurological deficits (median National Institutes of Health Stroke Scale of 16) did not result in worse outcomes compared to matched controls [88].

Intervention

The medical literature regarding outcomes after interventional therapy for CAD is relatively sparse [89]. Current recommendations for endovascular or surgical management of CAD are based on retrospective, nonrandomized studies [8, 35, 90]. For CAD patients requiring intervention because of neurological deterioration due either to flow-limiting stenosis or to recurrent thromboembolism, endovascular treatment is the preferred first-line therapy. The general indications for endovascular intervention include recurrent ischemia despite adherence to medical therapy, contraindications to antithrombotic therapy, or insufficient cerebral blood flow [6, 89, 91–93]. The American Heart Association/American Stroke Association guidelines support the use of endovascular intervention for CAD. Notably, the guidelines do not clearly describe a time point past which medical therapy is considered a failure and intervention should be undertaken. The preferred endovascular treatment of CAD is carotid stenting because it preserves the parent vessel [93–97].

Patients who are unable to undergo stenting because of anatomical or lesional factors may be considered for endovascular ICA occlusion, although a balloon test occlusion is necessary prior to sacrifice of a parent artery. Unlike patients with carotid stenosis caused by extracranial atherosclerotic disease, most CAD patients may not require angioplasty before stenting if the luminal diameter of the stenotic segment is sufficient (approximately 2 mm) to allow the stent to be advanced primarily. Whereas atherosclerotic lesions of the extracranial ICA tend to be localized to the proximal ICA at the carotid bulb immediately distal to the common carotid artery bifurcation, CADs are more likely to be localized to the distal cervical ICA, where the vessel transitions from a mobile (cervical) to a fixed (petrous) segment. A case example of carotid artery stenting for CAD is demonstrated in Fig. 11.1.

Clinical outcomes after surgical intervention for CAD are not as well defined as those for endovascular treatment [89] but carry a similar recommendation from the American Heart Association/American Stroke Association. Specifically, surgical intervention should be pursued for medically resistant CAD patients, but it is not recommended for patients with vertebral artery dissection. Current indications for the surgical treatment of CAD include severe persistent symptomatic stenosis, formation of an arteriovenous fistula, presence of subarachnoid hemorrhage, or major contraindications to the antiplatelet therapy that is necessary after carotid stenting [6, 35, 89, 91, 93].

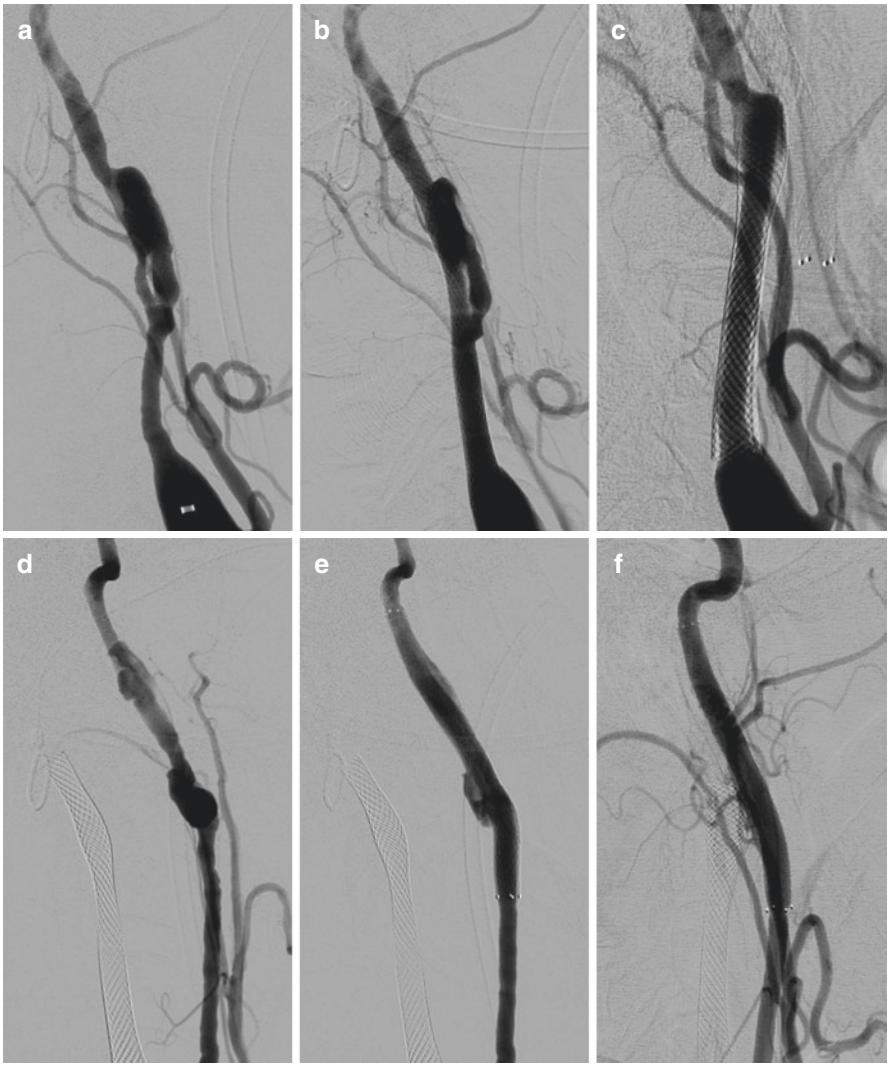

Fig. 11.1 A 71-year-old man presented to the emergency department with multisystem trauma after being hit by a car while riding his bicycle. (**a**–**f**) The patient was found to have bilateral cervical internal carotid artery (ICA) dissections, for which he was treated with stenting. (**a**, **d**) Lateral angiograms demonstrating Biffl grade III right and left ICA dissections, respectively. (**b**, **e**) Lateral angiograms demonstrating bilateral carotid stenting of the high-grade, flow-limiting, right and left luminal stenosis, respectively. The patient demonstrated immediate improvement in luminal diameter and a decrease in the size of the pseudoaneurysms on interval angiograms obtained at 6 months, 9 months, 12 months (**c**, **f**, lateral angiograms for right and left ICAs, respectively), 3 years, and 6 years. The patient did not experience any procedural complications, thromboembolic events, or ischemic sequela related to the intervention. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona)

The currently available surgical strategies for CAD include carotid artery occlusion, thromboendarterectomy with patch angioplasty, and extracranial-to-intracranial bypass [7, 35, 98, 99]. Prognostic data from surgical interventions are sparse and heterogeneous, and a larger-scale evaluation would be necessary to effectively compare outcomes for endovascular management and medical management [36, 37, 39]. This lack of data is compounded by the fact that CAD is a clinically diverse condition with multiple clinical and radiographic variables, making the assessment of therapeutic efficacy challenging.

Outcomes

The rate of recurrent stroke or transient ischemic attack within the first 3–6 months after a CAD are reported to range from 1.4% to 16.7% [3, 51, 86, 100], with the CADISS randomized trial reporting a 2% incidence in a population adherent to medical therapy [11]. Recurrence of CAD has been reported in up to 25% of patients [101]. Recurrent dissection is most commonly observed in the first several months after the initial dissection [95, 102, 103]. Factors that predispose a patient to recurrent CAD are a family history of CAD, Ehlers-Danlos syndrome type IV, fibromuscular dysplasia, and younger age at onset [6].

Multiple series have reported encouraging patient outcomes after endovascular intervention for CAD [97, 104, 105]. Asif et al. [97] analyzed 22 patients with 27 CADs treated with carotid stent placement and identified only one (4.5%) recurrent transient ischemic attack after a median follow-up of 14 months. Ohta et al. [105] analyzed a series of 43 patients with 44 CADs, in which stent placement was successful in 43 cases (97.7%) and recanalization was achieved in 42 cases (95.5%), with no recurrent strokes during a mean follow-up of 19.2 months. At discharge, a modified Rankin Scale score of 0–2 was observed in 36 patients (83.7%) [105]. Moon et al. [104] published a large series that included 93 patients with CAD treated with carotid stenting. All 93 patients underwent successful stent placement, 3 demonstrated clinically significant restenosis (3.2%), 1 required retreatment (1.1%), and 14 patients (15.1%) with a modified Rankin Scale score ≥3 at discharge demonstrated improvement to scores of 0–2 within a mean follow-up of 47.5 months [104].

Conclusions

The diagnosis and management of CAD has evolved along with the growing body of literature evaluating this diverse clinical entity. Early diagnosis and initiation of medical therapy are critical for the successful management of these patients. Patients with progressive neurological deterioration or recurrent thromboembolic events caused by flow-limited stenosis of the ICA or unstable intramural or intraluminal

thrombus should be referred for endovascular or surgical intervention. Endovascular therapy is the preferred treatment for most CAD patients, although surgical options can be considered when endovascular treatment is not possible. Overall, most patients with CAD who are appropriately managed have excellent long-term clinical outcomes. Additional investigation of the efficacy and timing of intervention for CAD is warranted.

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Chapter 12
Extracranial Carotid Artery Aneurysms

Devi P. Patra, Matthew E. Welz, Chandan Krishna, Karl R. Abi-Aad, Jamal McClendon Jr, Ali Turkmani, Lynda M. Christel, and Bernard R. Bendok

Introduction

Aneurysms in the extracranial carotid artery are rare and account for less than 1% of all arterial aneurysms [1–4]. Large case series describing more than 50 patients are limited to 5–6 reports in the medical literature. In an angiographic study of 5000 patients, House and Baker et al., found extracranial ICA aneurysms only in 8 (0.16%) patients [5]. Given the rarity of such lesions, limited knowledge is available about their true incidence and natural history. Despite this, the lesion is considered to be of significant clinical importance, mostly for its potential for giving rise to embolic and occlusive strokes, which may occur in as high as 50% of cases [6].

Various etiologies have been described for the occurrences of these rare aneurysms including atherosclerosis, trauma, connective tissue disorders, etc. In most instances, the presenting symptoms are either due to stroke or local compression. Recently, a significant number of asymptomatic patients are being diagnosed incidentally. Although all segments of the extracranial carotid artery (ECCA) can be

D. P. Patra · M. E. Welz · C. Krishna · K. R. Abi-Aad · J. McClendon Jr
Department of Neurological Surgery, Neurovascular and Skullbase Program, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA
e-mail: Patra.Devi@mayo.edu; welz.matt@mayo.edu; Krishna.Chandan@mayo.edu; Abiaad.Karl@mayo.edu; McClendon.Jamal@mayo.edu

A. Turkmani · L. M. Christel
Department of Neurological Surgery, Neurovascular and Skullbase Program, Mayo Clinic, Phoenix, AZ, USA
e-mail: Turkmani.Ali@mayo.edu; Christel.Lynda@mayo.edu

B. R. Bendok (✉)
Department of Neurological Surgery, Neurovascular and Skullbase Program, Department of Otolaryngology, Precision Neuro-therapeutics Innovation Lab, Neurosurgery Simulation and Innovation Lab, Mayo Clinic, Phoenix, AZ, USA
e-mail: Bendok.Bernard@mayo.edu

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affected, the internal carotid artery is the most common location with the external carotid artery as the rarest. Treatment depends on the symptoms and etiology, along with the location. While small and/or asymptomatic lesions are likely best managed conservatively, symptomatic and/or enlarging asymptomatic aneurysms may require intervention to reduce the risk of stroke and rupture. Depending on anatomic and physiological issues related to collateral circulation, both reconstructive and deconstructive techniques with or without bypass may be needed. The treatment plan should consider all open microsurgical and endovascular techniques and tools.

Classification

ECCA aneurysms can be classified as true or false (pseudo) aneurysms based on their etiology and pathological characteristics. True aneurysms are surrounded by all three vessel wall layers (intima, media, and tunica) but, have a dilation of at least 50% when compared to the normal diameter [7]. Pseudoaneurysms are caused by the disruption of the arterial wall and may contain a hematoma in the arterial lumen. Common causes of pseudoaneurysms are trauma, dissection, or local infection. Literature showing the relative prevalence of extracranial true vs pseudo carotid artery aneurysms varies between studies. In a study, describing 42 cases, the incidence of pseudo vs true aneurysms were nearly equal [8]. However, in another larger study published by the Mayo Clinic describing 141 patients, 82% were pseudoaneurysms as compared to 18% of true aneurysm [9]. A classification scale based on anatomical segment has been established which has importance in treatment planning (Fig. 12.1 and Table 12.1).

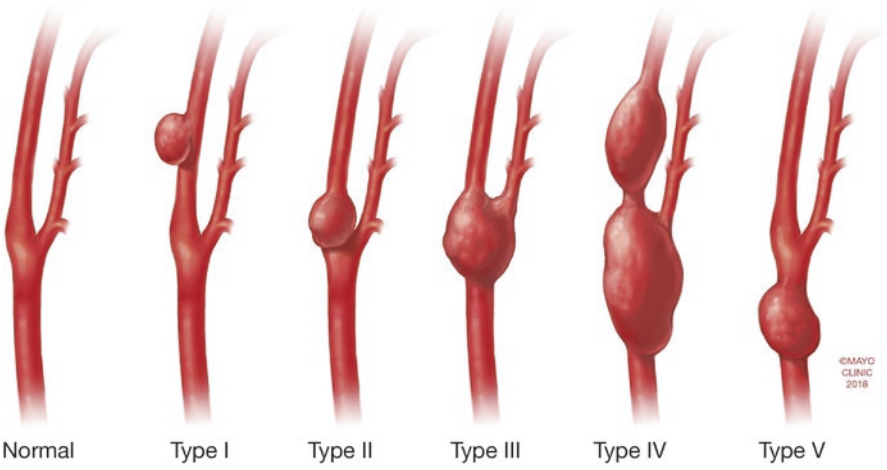

Fig. 12.1 Classification of external carotid artery aneurysms. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Table 12.1 Classification of external carotid artery aneurysms

Normal	Type 1	Type 2	Type 3	Type 4	Type 5
Natural looking artery	Isolated Aneurysm of internal carotid	Aneurysms of the internal carotid artery with involvement of the bifurcation	Aneurysms of the carotid bifurcation	Combined aneurysms of the internal and common carotid artery	Aneurysm of the common carotid artery

Although any segment of the extracranial carotid artery can give rise to aneurysms, the segment around the carotid bifurcation has a higher tendency for aneurysm formation, because of the higher burden of atherosclerotic disease. This segment is also most exposed to external trauma and surgery (carotid endarterectomy, neck dissection for tumors) which increases its vulnerability to pseudoaneurysm formation. Although, the carotid bifurcation is not commonly involved per se, the diseased artery at the bifurcation can lead to increased flow velocity and stress in the internal carotid artery just distal to the bifurcation and may pose risk for aneurysm formation. In the Mayo Clinic series, 81% of the aneurysms were located in the internal carotid, 8% in the common carotid, 10% at the bifurcation, and 1% in the external carotid [9]. In a literature review of 1332 ECCA aneurysms, Welleweerd et al. found that the ICA was the most common location comprising 46% of cases followed by the bifurcation which accounted for 20% of cases [10].

Etiology and Risk Factors

The etiology of aneurysm formation in the extracranial carotid arteries is multifactorial and is broadly due to hemodynamic changes from atherosclerotic changes or from weakness of the arterial wall due to direct or indirect injury. Atherosclerosis is the most likely cause for formation of true aneurysms in elderly individuals. In the review by Welleweerd et al., atherosclerosis accounted for up to 38% of the aneurysms [10]. Although arterial wall degeneration has been shown as the most common mechanism, another study from these same authors analyzing the histological characteristics of these aneurysm identified arterial dissection as another important etiology [11]. No patients presented with a prior history of arterial dissection, but the histological findings of arterial dissection suggests that some degree of dissection, even in asymptomatic patients, may lead to the future development of aneurysms. A more frequent association is also seen with coronary artery disease and chronic obstructive pulmonary disease [12]. Other etiologies for formation of true aneurysms especially in younger patients include fibromuscular dysplasia, connective tissue disorders, inflammatory diseases, Marfan syndrome, Ehler-Danlos Syndrome, tuberous sclerosis, and cystic medial necrosis [9, 13].

Pseudoaneurysms are normally caused by prior intervention or infections. Both true and false aneurysms can be caused by blunt or penetrating trauma depending on the severity of the arterial wall injury [12]. Primary and secondary infection of the

neck can also lead to ECCA aneurysms. Primary infections are rare with only 100 cases reported in the literature [14]. Carotid endarterectomy has been historically shown to cause less than 1% of pseudoaneurysms of all procedures performed [15]. However, in the Mayo Clinic series, prior endarterectomy was implicated in the formation of 24% of the psuedoaneurysms [9]. Blunt injury and penetrating cerebrovascular injury can also lead to pseudoaneurysms. Additionally, the timing of delayed aneurysm formation can be as long as 20 years [9]. Spontaneous carotid dissections can also give rise to aneurysm formation [16]. Nearly 30% of patients with spontaneous dissections ultimately developed aneurysms [17]. Radiation, another risk factor for formation of ECCA aneurysms, may result in radiation-induced changes of the arterial wall with subsequent degeneration and weakening [18]. In one study, 70% of the patients who received a second course of radiotherapy developed a pseudoaneurysm [19]. Whether this justifies surveillance with MRA or another modality merits study.

Presentation

ECCA aneurysms are rare, but can present in patients of any age. Rupture and thrombotic events are similarly rare. Due to an increase in neurovascular imaging and improvements in imaging techniques, a greater number of ECCA aneurysms are being reported. In one study, half of the ECCA aneurysms were asymptomatic and discovered incidentally [9]. The common modes of presentation are outlined below.

Stroke

ECCA aneurysms can present as a transient ischemic attack (TIA) or strokes which can occur in almost half of patients. An asymptomatic, pulsatile mass is the second most common form of presentation found in nearly one third of patients [10].

Compression

Another important mode of symptomatic presentation is compressive symptoms due to pressure on surrounding structures. Local compression can cause pain in the neck and retro-orbital areas along with headaches [12]. It is rare to have a ruptured aneurysm compress the pharyngeal muscles resulting in dysphagia [9]. Compression of the glossopharyngeal nerve can cause angular pain dysphagia and pharyngeal dysfunction. If compression involves the sympathetic chain, a Horner's Syndrome can result. Vagal compressions can result in hoarseness and hypoglossal compression can cause tongue deviation and decrease in function [6].

Rupture

However rare rupture of ECCA aneurysms are, one cannot minimize its risks, as fatal airway compressions may occur. Infected aneurysms are more likely to rupture, compared to non-infected aneurysms [13]. Pseudoaneurysms following radiation treatment are also known to rupture and must be kept under surveillance [19].

Inflammation

ECCA aneurysms that are infected can present as an expanding, pulsating cervical mass associated with local pain, tenderness fever, dysphonia and dysphagia [14].

Diagnosis and Imaging

A pulsatile mass in the neck is found in nearly 90% of the patients [20, 21]. Ultrasound is the initial imaging modality for evaluation of neck masses. But further imaging with computer tomographic angiography (CTA) or magnetic resonance angiography (MRA) is usually required to help define the aneurysm. CT or MR angiograms give a better view of the aneurysm and its location, diameter, and/or the presence of a thrombus. It can also provide information about both intracranial and collateral circulation. Catheter arteriography is highly sensitive and can play a role in both diagnosis and collateral assessment. Imaging of other areas is recommended to document associated aneurysms, especially in patients with connective tissue disorders and in patients with a strong family history of aneurysms. In a 48-patient study, 24% of patients with true aneurysms had an associated aneurysm. The most common place was the abdominal aorta [22].

Treatment

Given the rarity of ECCA aneurysms, the optimal management protocol for these lesions is less clearly defined. But broadly, the management options include observation, open surgical repair, and endovascular treatment. The primary goal of treatment is to prevent thromboembolic complications and alleviate local compression. The current evidence on management of ECCA aneurysms is based primarily on observational studies. A randomized control trial is largely impractical because of low prevalence rates of the disease. Therefore, most of the cases are usually managed at the discretion of the physician based on individual patient factors. Conservative management for large and symptomatic lesions may not be advisable. Older literature suggested a high incidence of mortality from observed symptomatic

lesions (as high as 71% described in older literature [23]) in untreated patients. This has not be substantiated in more modern series which include a much higher number of more benign incidentally discovered lesions. An expansion of treatment options including endovascular management has lowered the threshold for treatment in select cases. A summary of treatment options is outlined in Table 12.2. A general guideline has been developed from the current evidences and is depicted in Fig. 12.2.

Conservative Treatment

Conservative treatment is usually advocated in asymptomatic and incidentally detected aneurysms. Medical management focuses on prevention of progression of atherosclerosis using statins and prevention of thromboembolic episodes using antiplatelets (aspirin with or without clopidogrel) or anticoagulation (warfarin or apixaban). Anticoagulation may be preferred if an acute dissection is suspected, particularly if a thrombus is present. In select low risk patients, observation and follow up with serial imaging can be judiciously used.

Open Surgical Management

Open surgical management for extracranial carotid artery aneurysms dates back to 1805 when Sir Astley Cooper performed ligation of the common carotid artery to treat an aneurysm [24]. Unfortunately the patient died 48 hours later. However, this opened the door to technical advances and subsequent reports of successful ligation were reported. Till the mid twentieth century, carotid ligation was the preferred method of treatment of such aneurysms, although with a risk of perioperative stroke of 30% [25]. Surgical treatment options can include resection of the aneurysm and end to end anastomosis, resection followed by dacron or saphenous graft anastomosis, and/or aneurysmorrhaphy.

The type of surgical intervention depends upon the size and location of the aneurysm, the etiology, and patient factors like age, associated comorbidity, and/or type of presentation. In the series by Radak et al., most of the Type 1 aneurysms were managed with resection and end-to-end anastomosis, Type 2 aneurysms by resection, shortening, and ICA re-implantation, and Type 3 and 4 aneurysms by resection with tubular graft insertion [26]. Although atherosclerotic aneurysms are relatively easier to repair, pseudoaneurysms especially from a previously operated artery, prior infection, or radiation are challenging. Meticulous dissection, removal of the diseased segment including the suture line, and/or use of an appropriately sized graft are basic nuances for successful repair. The most described complication after surgical repair are thromboembolic complications and postoperative cranial nerve dysfunction. Proper use of carotid clamping tech-

Table 12.2 Summary of management options for extracranial carotid artery aneurysms

Treatment Option	Treatment modality	Indications	Advantages	Disadvantages/complications
Observation		Asymptomatic, incidentally detected aneurysms Medical comorbidities precluding surgery	No risk of intervention	Risk of stroke Risk of progression with compressive symptoms Requires frequent follow ups
Surgery	Carotid ligation	Evidence of good cross circulation	Simple approach	Risk of stroke
	Resection and reconstruction (End to end anastomosis; graft interposition; aneurysmorrhaphy)	True aneurysms Short segment aneurysms Low lying aneurysms	Surgical excision/elimination of the aneurysms Relieves compression symptoms	Cranial nerve damage Anastomotic leak/dehiscence Pseudoaneurysm formation at anastomosis site Graft failure Graft stenosis
	Bypass procedure	High riding aneurysms Complex aneurysms Extensive scarring or adhesion of the neck	Allows carotid ligation and exclusion of the aneurysms with a very distal extension	Major surgery Risk of graft failure Risk of graft stenosis Risk of stroke due to graft insufficiency
Endovascular treatment	Covered stents	Pseudoaneurysms with relatively straight arterial segment	High rate of aneurysm obliteration Low risk of endoleak	Stiff constructs which are difficult to navigate in tortuous vessels Vessel perforation Thromboembolism Requires perioperative anticoagulation

(continued)

Table 12.2 (continued)

Treatment Option	Treatment modality	Indications	Advantages	Disadvantages/complications
	Bare metal stents	Aneurysms with tortuous vessels	Flexible constructs which are easily navigated in tortuous vessels	High rate of endoleak Risk of aneurysm regrowth due to persistent flow Requires perioperative anticoagulation
	Flow diversion	Aneurysms with tortuous vessels	Flexible constructs and can be navigated in tortuous vessels High metal coverage with low flow into the aneurysm High obliteration rate	Risk of stent migration Risk of thrombo-embolic complications Requires perioperative anticoagulation

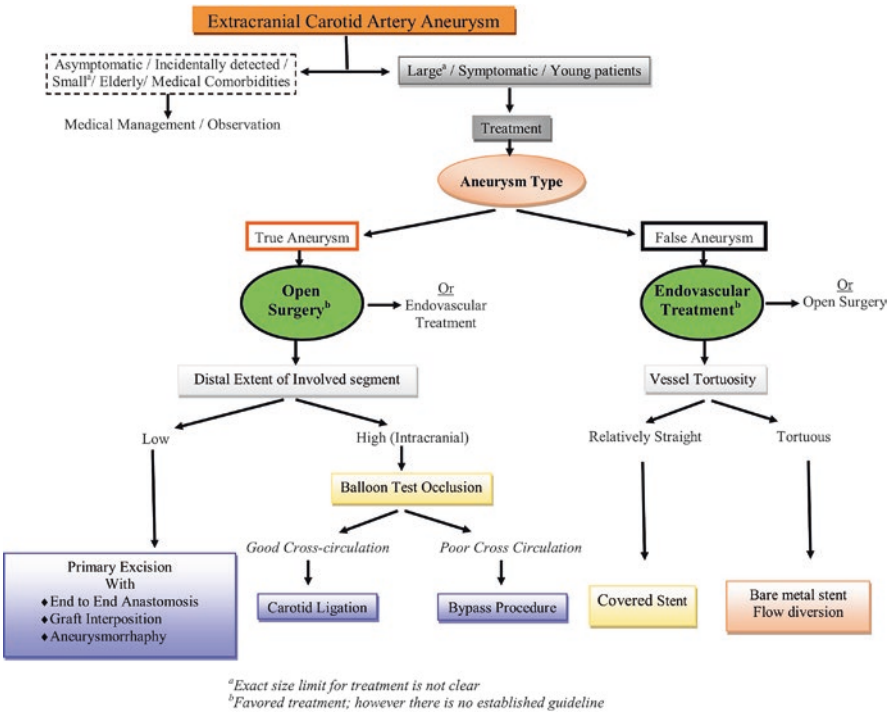

Fig. 12.2 A general guideline for treatment options, developed from the current evidence

niques and intraoperative anticoagulation are important to prevent potential clot migration. Similarly, careful dissection during manipulation of the posterior wall is essential to prevent postoperative cranial nerve dysfunction. The rates of postoperative stroke in the literature range from 11% to 22% with a permanent deficit of 3% to 13% [21, 27–31]. Some of the common surgical procedures are discussed below.

Carotid Ligation

Carotid ligation is a simple and relatively straightforward procedure. In an early series of 22 patients reported by Schievink et al. in 1994, five patients underwent carotid ligation without any ischemic or other neurological complications with a long term follow up of 8.8 years [32]. The most obvious requirement to determine candidacy for ligation is documentation of adequate collateral flow by a preoperative balloon occlusion test with possible inclusion of a perfusion study such as xenon-133 cerebral blood flow monitoring or single photon emission computed tomography (SPECT) [33–36]. Despite good cross circulation during testing, there is still a risk of ischemia in the ipsilateral circulation. The newer trend of surgical

management is towards anatomic reconstruction of the affected segment rather than ligation. In the review by Welleweerd et al., carotid ligation consisted of only 5% of all open procedures in 1102 surgically treated aneurysms [10].

Resection of the Aneurysm and Reconstruction

Resection of the aneurysm is now the most commonly performed open surgical procedure. Options for restoration of flow after resection include direct anastomosis, interposition graft, partial resection followed by patch graft, and aneurysmorrhaphy. Aneurysms above the carotid bulb with short segment involvement of the ICA can be resected with primary end-to end anastomosis. However, carotid bulb involvement or long segment disease usually requires the use of an interposition graft. Other important considerations in this regard include the health of the vessel wall, tension on the ends, and the history of radiation or infection of the surrounding tissues. Fusiform dilation of the carotid bulb or the carotid bifurcation can be suitably managed with partial resection of the aneurysm wall followed by reconstruction with primary closure. Extensive circumferential involvement by false aneurysms may need a venous patch graft or an artificial dacron patch graft for reconstruction of the lumen.

An important concern regarding aneurysm resection is the exposure of distal involved segments of the ICA. Different approaches for high cervical exposures have been described in the literature. In most cases, this can be achieved by mobilization of the parotid gland with elevation of the facial nerve. The occipital artery may need division along its course. A higher exposure can be obtained with fracture and removal of the styloid process, along with division of the posterior belly of the diagastric muscle along its origin. The most distal segment of the extracranial ICA is accessed by drilling of the mastoid tip with exposure of the stylomastoid foramen. A more extreme form of the skull base approach has been described by Fisch et al., which can expose the proximal portion of the petrous segment [37]. This surgery involves mobilization of the facial nerve proximal to the geniculate ganglion by drilling its canal in the mastoid bone and middle ear with anterior transposition of the nerve. This safely exposes the bony canal of the proximal petrous carotid segment. Drilling of the thin bone of the petrous bone in the tympanic and mastoid portion, along with division of the fibrous ring around the ICA at its entrance into the canal, enables mobilization of the artery. This procedure requires extensive middle ear manipulation with the sacrifice of the ossicles and necessarily comes with the cost of hearing loss.

The most common complication associated with cervical carotid exposure and manipulation is cranial nerve damage. The most common nerve involved in the exposure is the vagus nerve and its branches including the pharyngeal and superior laryngeal nerves. This usually leads to dysphagia and dysphonia in the immediate post-operative period. Damage to the spinal accessory nerve is also possible during mobilization of the sternocleidomastoid muscle. The facial nerve is the other cranial nerve which can be damaged, especially with high cervical exposures which is at

risk during parotid manipulation or manipulation around the stylomastoid foramen. Other complications related to anastomosis or reconstruction include anastomotic leak or dehiscence leading to a neck hematoma, thromboembolism, or complete graft thrombosis. Chronic complications include graft stenosis at the anastomosis site and/or formation of pseudoaneurysms.

Extracranial (Cervical) to Intracranial Bypass

An extracranial to intracranial bypass procedure may be needed when the proximal extent of the aneurysm is too high for a safe resection, with complex aneurysms, or with a history of prior infection or radiation with extensive scarring of the neck. An important consideration during the decision making process for a bypass procedure is the type of bypass needed. A balloon test occlusion (BTO) provides objective evidence to determine the degree of tolerance to vessel occlusion and the adequacy of cross flow from the contralateral and posterior circulations. This test can help in determining the type of bypass, high flow or low flow, needed to sustain the circulation. The BTO usually consists of four components which are performed during the temporary occlusion of the ipsilateral vessel [36]. It includes clinical assessment in which the patient's neurological status is assessed while awake; hemodynamic assessment in which an angiogram may be performed from the contralateral vessel; neurophysiological assessment in which the EEG waveforms may be monitored; and finally a provocative assessment in which the mean arterial pressure is decreased using pharmacologic agents and clinical and neurophysiological tests are repeated.

Surdell et al. have described three broad groups based on the BTO findings [35]. The patients who pass all four modalities have adequate cross circulation and, therefore, should tolerate a permanent vessel occlusion alone. Patients who only pass in their clinical assessment have moderate cross circulation and may need at least a low flow bypass (typically superficial temporal artery to middle cerebral artery bypass) in addition to vessel occlusion. Patients who fail the clinical assessment have poor cross circulation and may require a high flow bypass to sustain the circulation. Pedicled arterial grafts including the superficial temporal artery (STA) or occipital artery (OA) are used for a low flow bypass. The free arterial (radial artery) or venous grafts (saphenous vein) are used for high flow grafts. High flow bypasses are technically more challenging, but are associated with high patency rates if successful. The saphenous vein graft proximal connection can be to an external carotid artery branch, including the superficial temporal artery proximal to its bifurcation. The size of the parent arteries and the location of the aneurysm help define the best anatomic solution. Distal anastomosis can be to the supraclinoid carotid artery or to a large branch of the middle cerebral artery after its first bifurcation. In any of the bypass procedures, the major risk is failure of the anastomosis with subsequent ischemic stroke. Vasospasm can affect outcomes with radial artery bypass. This can be mitigated with postoperative infusion of a vasodilator and by keeping the graft integrated with its venous circulation [38].

Endovascular Management

With increasing technical advancements, endovascular management has grown in feasibility and efficacy. Challenging Type 1 and low Type 4 lesions, aneurysms associated with scarring, and aneurysms with other unfavorable local conditions may be better treated with endovascular reconstruction with stents. Endovascular treatment may have a more effective long-term outcome in pseudoaneurysms as compared to true aneurysms, possibly due to the self-limiting nature of pseudoaneurysm etiology and the lower incidence of intraluminal thrombus in pseudoaneurysms [9]. The rationale of using endovascular stenting as a treatment in presence of compressive symptoms by the aneurysm is controversial. Theoretically, compression symptoms should preclude endovascular procedures, as it does not decompress or remove the aneurysm. However, proponents of endovascular treatment argue that the thrombosis of the aneurysm with subsequent remodeling reverses the compression of the surrounding structures. In the series by Leng Ni et al., two patients presented with compressive symptoms who underwent endovascular stenting [39]. One patient who had swallowing difficulty improved. However, the other patient had persistent hoarseness after stenting.

Currently, the options for endovascular treatment include either covered or bare metal stents, stent placement with coil embolization, or vessel occlusion. Covered stents may be more effective as they exclude the aneurysm from the circulation and also prevent endoleak and recanalization [18]. Li et al. in their systematic review on endovascular procedures demonstrated a significantly lower incidence of endoleak, re-intervention, and late complications with covered stents [40]. However, the major disadvantage of covered stents, as compared to bare metal stents, is their stiff construct which precludes their use in tortuous anatomy. Another important limitation of covered stents is the discrepancy in parent artery diameter when aneurysms involve the ICA bifurcation. This scenario is associated with in increased risk of endoleak when covered stents are used. Nonetheless, a number of authors have reported promising results in carefully selected patients. Leng Ni et al. in their series, successfully used PTFE covered stents, such as Viabahn endoprosthesis, which has significant flexibility and conformability to the vessel configuration and neck movement [39]. Welleweerd in their series of 7 patients described successful use of bare metal stents [41]. Although, the metal coverage of the stents used were less than 10%, an 86% exclusion rate in their series was demonstrated.

With the advent of flow diverting stents, there is a paradigm change in the treatment of extracranial aneurysms, especially pseudoaneurysms. Flow diverting stents (which have been designed and approved for select intracranial aneurysms) provide a more flexible construct that can easily be navigated through tortuous segments. Initially, the major concern was stent migration due to the increased caliber of the cervical ICA, increased mobility of the artery, and tendency of the cervical vessel to change with neck movements [42]. In the early description by Rahal et al., a second, non-flow diverting stent was used as an anchoring support to mitigate the potential

for foreshortening and migration of the flow diverting stent [43]. Chen et al., in 2016, described their successful use of multilayer stents by covering multiple bare stents. They achieved a 100% occlusion rate in their 8 patients [44]. Subsequently, there have been several published reports describing successful use of flow diverting stents in cervical pseudoaneurysms [45–47]. The continued evolution of stent configurations may make endovascular treatment a more feasible and safer option for these ECCA aneurysms.

The common complications described after endovascular treatment include post procedure strokes, stent restenosis, and occlusion. Adequate anti-thrombosis in the perioperative and post-operative period is essential. In their review, Li et al. demonstrated a 92.8% procedure success rate and 93.2% stent patency rate with a very low complication rate. Another review specifically addressing carotid artery dissection associated pseudoaneurysms demonstrated a 98.3% occlusion rate with use of an endovascular stent with or without coiling [48]. The restenosis rate after stenting is reportedly around 6%, which usually occurs adjacent to a bent or kinked carotid artery [39].

Conclusion

ECCA aneurysms are rare lesions with limited validated recommendations for their management. Although a significant number of patients are asymptomatic, these lesions can still give rise to thromboembolic complications. Given the rarity of ECCA aneurysms, a definite recommendation regarding their management is still not available. Several factors play a role in determining the optimal treatment modality, including aneurysm type, location, and cause. Similarly, other important factors include a prior history of radiation or neck surgery, associated comorbidities, age, and functional status. Open surgery with resection of the aneurysm and primary anastomosis or graft reconstruction is favored for true aneurysms and large aneurysms with compressive symptoms. Endovascular treatment with covered or bare metal stents is another emerging treatment with comparable results. Pseudoaneurysms, especially with prior infection or radiation may be better treated by endovascular means. Balloon test occlusions can help define extracranial to intracranial bypass options or support parent artery occlusion as a treatment option. Observation and follow up is an option, especially for smaller asymptomatic aneurysms or in patients who are otherwise not candidates for intervention.

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Chapter 13
Carotid Blowout Syndrome

Kamil W. Nowicki and Bradley A. Gross

Historical Perspective

Carotid Blowout Syndrome (CBS) is a rare, and catastrophic event resulting in rupture of the carotid artery, or one its branches, and resulting hemorrhage. CBS is an emergency with historical mortality rates as high as 50–100% before the advent of endovascular therapy [1]. Patient populations at risk for CBS include those in which the structural integrity of surrounding supporting adventitia has been compromised such as in local spread of malignancy, post-radiation changes, and wound dehiscence or infections.

Hemorrhage is a common complication in the oncologic population with rates as high as 10% and 30% in the general and hematologic malignancy patients, respectively [2]. CBS represents perhaps one of the most serious hemorrhagic complications in oncology patients. The risk for CBS in the surgical population with head and neck malignancies can be as high as 4.5% [1]. In multiple studies, re-irradiation has been reported to pose a separate and significant risk for CBS in head and neck cancer patient population. In fact, repeat radiation therapy results in nearly eight-fold increased risk for carotid artery rupture [3]. Moreover, those with cumulative radiation dose of more than 70 Gy had a 14-fold increased risk for CBS. Conversely, the rate of CBS falls to almost half when patients who have not undergone radiotherapy are analyzed as a separate subgroup. Pre-operative irradiation raises the risk of CBS up to 3% [4].

More than two-thirds of CBS patients present with acute hemorrhage [5]. Consequently, the risk of CBS has been classified as threatened, sentinel, or active, depending on the exposure of the vessel to the environment or oral cavity, bleeds controlled by conservative management, or ongoing hemorrhage, respectively [6]. Timely intervention is directly associated with patient survival [7]. In the past, open

K. W. Nowicki · B. A. Gross (✉)
Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
e-mail: Nowickik@upmc.edu; grossb2@upmc.edu

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vascular repair or vessel ligation in the operating room was the only available treatment [8]. Recurrent CBS most often occurs due to disease progression rather than treatment failure [9]. Although historically muscle flaps were not reported to decrease risk of CBS in patients undergoing surgery, [10] more recent prospective study by Cordova et al. suggests that chimera anterolateral/vastus lateralis flaps reduce future complications by almost half [11]. Rapid ligation and sacrifice of the common carotid artery (CCA) or internal carotid artery (ICA) without balloon test occlusion has been reported to result in higher rates of cerebrovascular accidents (CVA) [7]. Mortality in open vascular cases of CBS have been reported to be as high as 100% [7]. Historically, on average 54% of patients died of acute hemorrhage or neurological sequalae before leaving the hospital [12]. More severe hypotension on admission was noted to be an ominous sign and a predictor of neurological deficit. Furthermore, a review of five decades of CBS studies showed that between 10% and 20% of patients were reported to have permanent neurological deficits [1]. Recently, the reliance on open vascular approaches as the first treatment of choice has decreased to as low as 7% with endovascular approaches taking the lead as the prime therapeutic and diagnostic option in the armamentarium of CBS management [5].

The goal of endovascular approaches in CBS is to provide both diagnostic and therapeutic intervention. Digital subtraction angiography (DSA) is the gold standard in evaluation of head and neck vasculature. In hemodynamically stable patients, balloon test occlusion (BTO) can be performed at the time of the DSA to evaluate the risk of ischemia if there is a need to sacrifice the carotid artery [8, 13]. However, in hemodynamically unstable patients with active profuse hemorrhage, the BTO may not be able to be performed. In such scenarios, the interventionist has to rely on his evaluation of the angiogram of the contralateral vasculature and its ability to support perfusion of the ipsilateral side.

Depending on the results of the BTO or urgency of treatment, either endovascular embolization or repair with covered stents can be attempted [13]. Agents typically used for embolization including coils and vascular plugs [14]. Onyx embolic agent is a fairly new option in endovascular treatment that was first approved for intracranial aneurysms in 2007 [15]. Gandhi et al. published their experience with onyx in emergency treatment of traumatic carotid artery injury in 2011 [16]. Amplatzer vascular plugs are specialized detachable devices that were first described in treatment of extracranial carotid aneurysms in 2008, [17] and CBS in 2011 [18].

Mortality rates for patients undergoing endovascular embolization management have been reported to be about 8% compared to 10% in covered stenting in a study of 1218 patients [19].

Pathophysiology

Anatomy of the carotid artery, especially the common carotid and cervical internal carotid arteries, is unique due to the high hemodynamic requirements. In fact, rupture of the carotid artery rather than one its tributaries, is an independent predictor

of poor patient outcome [7]. Due to the size of the carotid artery, especially the thickness of the media, the vasa vasorum contained in the adventitia provide most of the nutritional and oxygen needs to the deeper layers. The mean flow rate across each common carotid artery has been reported to be around 395 mL/min, which corresponds to about 8% of total blood volume [20]. Burst pressure of the carotid adventitia is in excess of 250 kPa, while the media can support much lower pressure of 60 kPa [21]. Interestingly, a small cadaveric study demonstrated that atherosclerotic carotid adventitia provides significantly more ultimate mean strength in both axial (1996 ± 867 kPa) and circumferential directions (1802 ± 703 kPa) than the media (519 ± 270 kPa and 1230 ± 533 kPa, respectively) [22]. For comparison, a typical car tire is usually pressurized to about 200–300 kPa.

During surgical exploration, extensive neck dissection not only removes the structural component of the adventitia, but also may abolish the critical blood supply. Radical neck dissection with exploration of the carotid sheath removes the adventitia which provides the blood and nutritional supply via the vasa vasorum. Because the common carotid artery (CCA) depends on the vasa vasorum more heavily than its external or internal branches, it's not surprising that most of the ruptures occur prior to the carotid bifurcation [8]. Interestingly, pseudoaneurysm formation after surgery or radiation has been reported to occur in patients as far as 20 years out from the original procedure [23].

In CBS patients who recently received repeat radiation therapy, rupture of the carotid artery had mortality rates as high as 76% [24]. The adventitia provides more than 3/4ths of the blood and nutrition supply to the wall of the carotid artery. Radiation therapy induces thrombosis of vasa vasorum, fibrosis of the adventitia, and results in structural weakening of the vessel wall. The average time from repeat radiation to CBS was reported to be 7.5 months [24]. In one case, CBS occurred acutely during repeat radiation therapy. Hyperfractionation of doses spread over longer periods of time decreases the risk of CBS [24]. Concurrent chemotherapy does not appear to significantly increase the risk of CBS [24].

Similarly, surgical site infections can lead to CBS by inducing inflammation and thrombosis of the vasa vasorum in the adventitia, tissue breakdown or formation of fistulas [1]. Almost four out of ten patients with CBS present with bacterial infections [25]. Out of those patients, between 40% and 63% had a pharyngocutaneous fistula [25, 26]. More than half of the patients also display necrosis of the soft tissue flap overlaying the surgical site [25, 26].

Presentation

A 67 year old male patient with laryngeal squamous cell carcinoma (SCC) secondary to external beam radiation therapy and laryngectomy 7 years prior, first presented to our facility with dehiscence of soft tissues around the left common carotid artery (CCA) and a previously placed covered-stent for CBS at an outside facility (Fig. 13.1). Given the concern for infection of vascular structures with retained

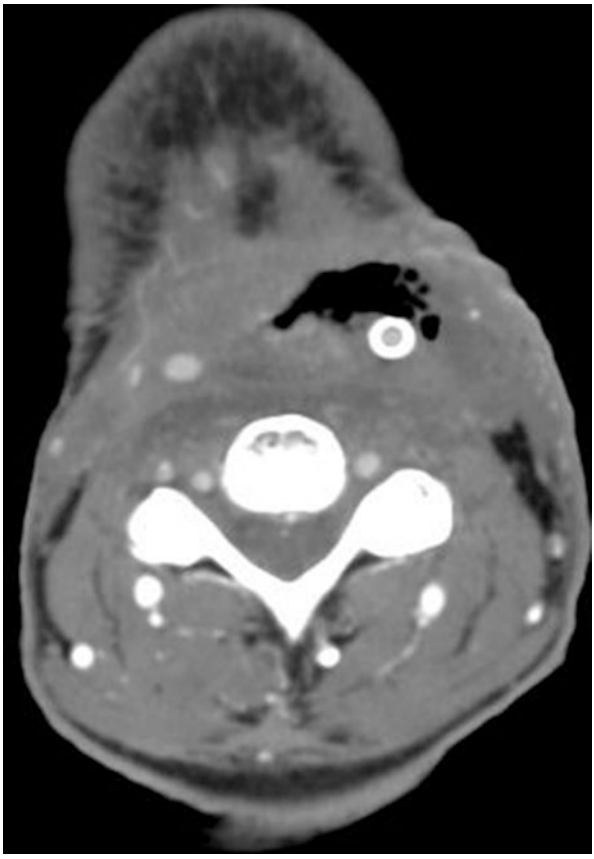

Fig. 13.1 CT neck angiogram showing deep soft tissue emphysema with concern for dehiscence of the soft tissue anterior to the previously stented left common carotid artery

hardware, the decision was made to take him to the operating room for left CCA ligation, resection, removal of hardware and wound debridement. A BTO was performed in the angiography suite prior to his carotid artery ligation.

The same patient then re-presented at 77 years of age with oropharyngeal dysphagia. He was admitted to the trauma intensive care unit and on hospital day three, he developed acute worsening of oropharyngeal bleeding with CTA imaging concerning for right carotid blowout. The hematoma compressed his oropharyngeal structures and the patient entered hemorrhagic shock (Fig. 13.2). Bilateral CBS is very uncommon and has been reported in only 2% of all CBS patients [25]. The patient underwent resuscitation with a total of seven units of packed red blood cells, two units of fresh frozen plasma, and two units of platelets. He had a six Shiley cuffed tracheostomy placed in the laryngectomy stoma and was given propofol once hemodynamically stable. His throat was packed with kerlex dressing and he was immediately referred for angiography and moved to the interventional radiology suite.

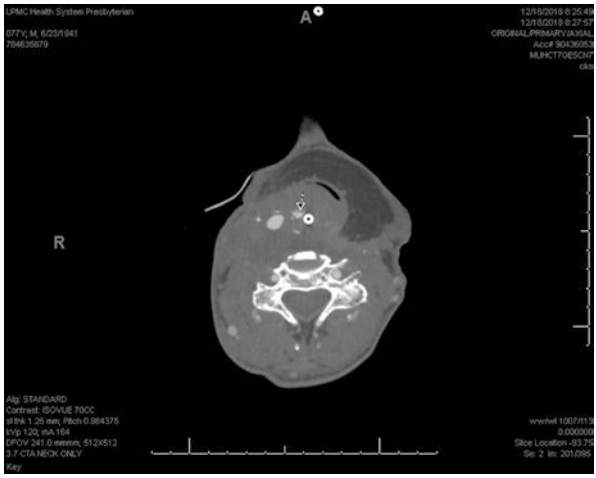

Fig. 13.2 CT neck angiogram showing active right common carotid artery contrast extravasation

Imaging

As discussed above, the patient initially underwent a CTA head and neck, which showed active extravasation of the right common carotid artery at the C4–5 level (Fig. 13.2). He was then taken for a DSA. Imaging showed a known proximal left common carotid signal cut off corresponding to the area of ligation and resection, with supply to the left ECA via the left vertebral artery. Antegrade flow in the left posterior communicating artery supplied the left ICA and MCA candelabra. Supply to the left hemisphere was via the right ICA (AComm) and vertebral artery (PComm) (Fig. 13.3). Upon visualization of a mid-distal cervical CCA pseudoaneurysm, an 8 French shuttle sheath was advanced over the Simmons into the distal CCA. A Viabahn 7 mm × 39 mm stent was advanced to the tip of the shuttle, the shuttle withdrawn, and the stent deployed by inflating the balloon to nominal pressure (12 atm) (Fig. 13.4a–c).

Treatment

Modern management of carotid artery blowout is centered around vessel reconstruction with endovascular therapy being the preferred first approach. However, during emergencies, the clinician may not have the luxury of time to proceed with vessel sparing techniques.

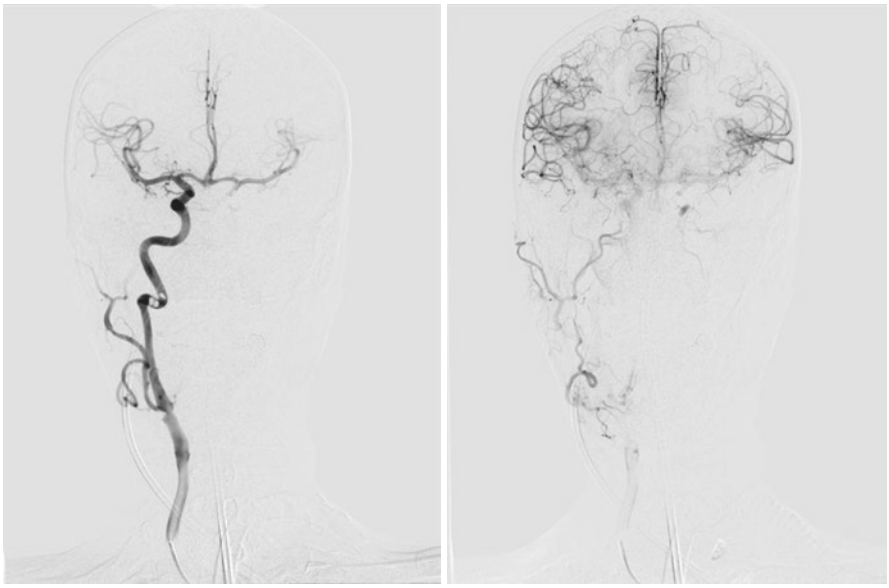

Fig. 13.3 Selective angiography of right internal carotid artery. DSA of right ICA showing supply to the left hemisphere via the right ICA and AComm

Surgical

Given the patient's prior history of left CCA resection, a vessel-preserving approach was necessary for his right carotid system. The patient was taken for immediate head and neck angiography to be evaluated for covered-stent revascularization. However, it is still illustrative to discuss the patient's prior open surgical management. As discussed above, the patient presented with threatened blowout due to soft tissue dehiscence and exposed left CCA with retained hardware. He was taken to the operating room with a joint team composed of a plastics and reconstructive team, head and neck surgeon, and a vascular surgeon. He was placed under general anesthesia and initial exposure and neck dissection was performed. Once the carotid system was visualized, the external carotid artery was ligated with double-stranded 0 silk ties. The proximal common carotid artery was also transected and oversewn with 5-0 Prolene suture in a Blalock's fashion. Distally, a clamp was applied in the distal segment and the internal carotid artery was transected about 2 cm proximal to it. The Viabahn graft was still noted to be in the internal carotid artery. The Viabahn

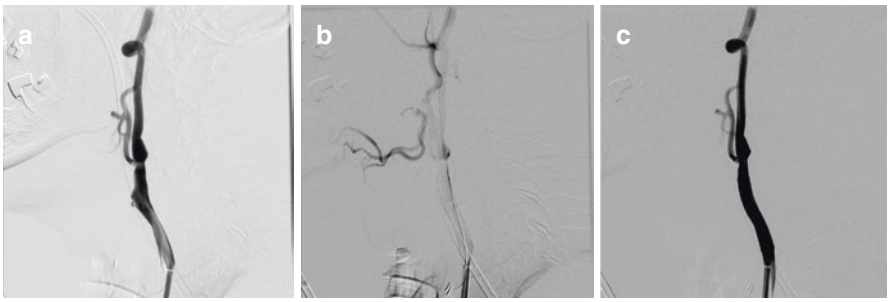

Fig. 13.4 Selective angiography of the right common carotid artery pre- and post-stent. (**a**) DSA of the right CCA showing mid-distal pseudoaneurysm, with (**b**) Viabahn stent deployed, and (**c**) final result post-reconstruction

graft was then separated out from the intima and was gently pulled while the clamp was released. The remainder of the Viabahn graft was then easily removed. The distal internal carotid artery was ligated and oversewn in Blalock's fashion with a 5-0 running Prolene suture. Both internal and common carotid artery stumps were occluded. The entire carotid artery was then resected en bloc. The patient was then brought out from anesthesia and woke up without any significant neurological deficit.

Endovascular

Modern endovascular therapy presents a perfect avenue for treatment of carotid blowouts. In this case, during the second presentation, vessel sparing approach was required given the prior left CCA ligation and resection. Vascular access was obtained via right common femoral artery using a micropuncture set and an 8 French 90 cm Cook Shuttle sheath via Seldinger technique. Through the sheath, a 5 French Simmons II catheter was advanced coaxially over an 0.038 glidewire into the aortic arch. Upon visualization of a mid-distal cervical CCA pseudoaneurysm and blowout, the shuttle was advanced over the Simmons into the distal CCA. The patient received 4000 units of heparin and 10 mg of IV integrillin. The distal right CCA pseudoaneurysmal blowout was then treated via deployment of a Viabahn 7 mm × 39 mm stent without residual angiographic opacification of the lesion post-stent (Fig. 13.4a). Hemostasis was then achieved using an endovascular closure device (Angioseal). The patient was transferred to the intensive care unit in stable condition.

Post-operative Course

The patient was recovered in the ICU post-procedure. Three days later he underwent esophagoscopy demonstrating an ulcerative and exophytic mass along posterior right nasopharynx. Biopsy results confirmed an invasive squamous cell carcinoma (keratinizing) of the right pharynx. Six days post endovascular therapy, a G-tube was placed given persistence of severe oropharyngeal dysphagia and odynophagia. On hospital day nine, he was discharged to home with home health care nursing and palliative services.

Disclosures

Bradley A. Gross is a consultant for microvention and medtronic.

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Chapter 14
Carotid Artery Fibromuscular Dysplasia

Joseph F. Carrera and Andrew M. Southerland

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-inflammatory, non-atherosclerotic vascular disease characteristically affecting small or medium sized arteries [1–3]. FMD most commonly affects the renal and cervico-cephalic (carotid and vertebral) arteries, but multi-vessel involvement is common, and coronary, visceral, upper extremity, and lower extremity arteries can also be involved [1]. For the purposes of this chapter, we will focus predominantly on carotid artery FMD and its manifestations.

Historical Perspective

Leadbetter and Burkland are credited with the first description of FMD in 1938. They presented a case of a 5½-year-old boy with marked hypertension and an intra-arterial mass of smooth muscle in his renal artery, whose hypertension was cured following unilateral nephrectomy. [4] In 1958, McCormack et al. first introduced the term "fibromuscular hyperplasia" in a description of three patients with hypertension and renal artery stenosis [5]. McCormack went on to publish a detailed pathological-arteriographic correlation of types of FMD, as well as a pathologic classification system, breaking down FMD into three subtypes based on the most pathologic arterial layer (medial, intimal, adventitial) [6, 7]. This histologic

J. F. Carrera
Department of Neurology, University of Michigan, Ann Arbor, MI, USA
e-mail: josephfc@med.umich.edu

A. M. Southerland (✉)
Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, VA, USA
e-mail: as5ef@virginia.edu

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classification system was a mainstay until more recent consensus statements have favored use of angiographic appearance for classification [1, 2].

Cerebrovascular FMD was first identified and described as a non-atherosclerotic cause of internal carotid artery (ICA) stenosis by Palubinskas and Ripley in 1964 [8]. Shortly thereafter, Connett and Lansche published the first histologically proven case of FMD in the internal carotid arteries of a 34-year-old woman who experienced sudden onset of right-sided hemiparesis and aphasia found secondary to an occluded left ICA [9]. In 1971, Houser et al. described a series of 52 patients with "cephalic arterial" FMD with involvement of the internal carotid arteries and/or vertebral arteries [10]. Stanley et al. published a series in 1974 of 15 female patients with FMD, and described a co-prevalance of renal artery involvement as well as intracranial aneurysms. In that landmark publication, the authors also suggested hormonal influences and traction to the vascular wall as contributors to the development of FMD [11]. In 1982, Mettinger published a review of nearly 1100 patients with FMD, including 300 with aorto-cranial involvement, also confirming the strong female predominance and co-prevalence of intracranial aneurysms [12]. More recently in 2014, consensus statements published by multi-specialty groups in the United States and Europe proposed a revised classification system for FMD [1, 2].

Classification of FMD

The original classification scheme focused on the segment of maximal arterial wall involvement (intimal, medial, and adventitial subtypes) [6, 7]. Under this system, the vast majority of cases fell into the medial subtype, followed by intimal and adventitial subtypes (Table 14.1) [7, 13, 14]. As arterial tissue specimens are rarely obtained in modern clinical care, more recent classification systems have focused on the radiographic appearance of FMD. Both the European consensus statement and American Heart Association (AHA) scientific statement advocate use of a classification system dividing patients into multifocal or focal FMD [1, 2]. The term unifocal and focal are used interchangeably, though for purposes of standardization, we will use focal FMD.

Multifocal FMD is the most common subtype and generally manifests with alternating areas of stenosis and dilatation, resulting in the so-called "string of beads" radiographic appearance (Fig. 14.1). Multifocal FMD requires two or more

Table 14.1 Histiological fibromuscular dysplasia classification system

Histiological fibromuscular dysplasia classification system [7]	
Medial	Medial fibroplasia (60–70%) Perimedial fibroplasia (15–25%) Medial hyperplasia (5%–15%)
Intimal	Intimal fibroplasia (1%–2%)
Adventitial	Adventitial fibroplasia (<1%)

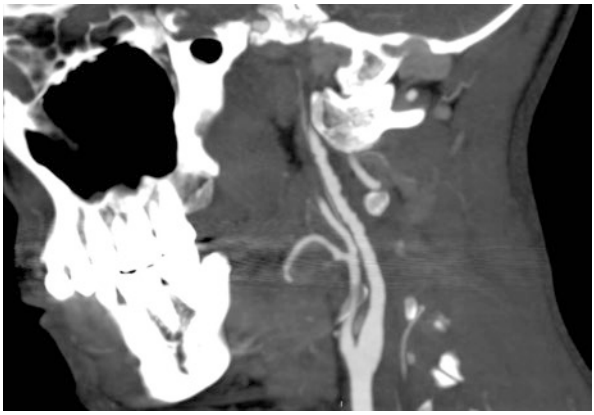

Fig. 14.1 String of Beads. An example of multifocal internal carotid artery fibromuscular dysplasia on computed tomography angiography resulting in the so-called "string of beads". Notice the involvement of the mid- and distal portions of the internal carotid artery

Table 14.2 Pathologic-angiographic correlation of classifications schemes

	Multifocal	Focal
Angiographic appearance	Alternating stenoses and dilatation resulting in "string of beads" Occurs in the mid and/or distal portions of the internal carotid artery	Focal concentric (<1 cm) or tubular (>1 cm) stenosis
Histologic subtype	Medial fibroplasia (most common) Perimedial fibroplasia (rare)	Intimal fibroplasia (most common) Adventitial fibroplasia (rare) Medial hyperplasia (rare)

stenoses in a given vessel segment, which typically involves the mid- to distal portions of the artery [15]. It is thought to be associated with medial fibroplasia given findings in pathological-angiographic correlation studies (Table 14.2) [6, 16]. Focal FMD is defined by the presence of unifocal concentric (<1 cm in length) or tubular (≥1 cm in length) narrowing, and is more associated with intimal or adventitial histologic subtypes [1]. Relative to focal FMD, patients with multifocal FMD are typically diagnosed at older ages, more likely to be female, and less likely to be current smokers [15].

Epidemiology

The prevalence of carotid artery FMD in the general population is unknown because, in many cases FMD is clinically silent or discovered incidentally. Published cohorts of FMD are largely of European ancestry with a paucity of published epidemiological data about FMD in other race/ethnic groups. Renal FMD has been estimated to be as high as in 4% of the general population [17, 18]. One source of prevalence data for renal FMD has been from potential living kidney transplant donors. In a retrospective review of 716 potential kidney donors, in whom 80% had angiogram data, a 6.6% prevalence was reported [19].

Prevalence of carotid artery FMD is thought to be potentially smaller, with studies describing a range from 0.3% to 3.2% prevalence as identified by routine catheter angiography [20]. More contemporary reports describe similar prevalence of carotid artery and renal artery involvement [13, 21–23].

Amongst patients with FMD, involvement of multiple vascular beds is relatively common. In the US FMD Registry, renal artery involvement was reported in nearly 65% of patients with cervical artery FMD. Similarly, 65% of patients with renal FMD in that registry also have cervical artery FMD [21]. In the French ARCADIA Registry, in patients with cervical artery FMD, prevalence of renal FMD was substantially higher in patients with a history of comorbid hypertension (66.3% vs 41.4%) [22].

FMD primarily affects young to middle-aged women. In the US Registry (n = 447), 91% of patients were women, and the median age of diagnosis was 51.9 years [21]. Nearly all other published series mirror this predilection for women. For instance, the ratio of women to men was 3:1 in the large Cardiovascular Outcomes in Renal Atherosclerotic Lesions database [24]. Not surprisingly, given the demographic breakdown, hormonal factors have been implicated in the disease process, but little evidence exists to support a hormonal role except the sex and age distribution of FMD patients.

Genetic Risk

FMD likely has a complex genetic basis, and genetic and genomic studies hold promise in advancing our understanding of the disease. Unfortunately, there are a number of factors which have hampered development of heritability estimates of FMD. These include the relative rarity of the diagnosis, frequency of asymptomatic phenotypes, influence of environmental modifiers, and inaccurate characterization of family histories. In modern registries, patients rarely identify an affected family member with FMD (1.9–7.3%) [21, 22]. In a subset of patients, an autosomal dominant inheritance has been suggested [25, 26]. A more recent study requiring imaging confirmation in family members with FMD suggested that 11% of FMD was classified as familial [27]. Although FMD shares similar phenotypic features with a number of monogenic connective tissue diseases (e.g. Ehlers-Danlos, Marfan's, and Loeys-Dietz syndromes), systematic screening of these known genetic mutations have failed to demonstrate a consistent association with FMD [28, 29]. In a genome-wide association study, an intronic variant (rs9349379-A) in the *PHACTR1* gene (6p24) conferred an association with FMD (odds ratio 1.39) [30]. Notably, the *PHACTR1* rs9349379-A single nucleotide polymorphism risk-allele is associated with a number of FMD-associated conditions such as hypertension, migraines, and cervical artery dissection, and in an inverse association with atherosclerotic coronary artery disease [31–35]. Using CRISPR-edited stem cell-derived endothelial cells, Gupta et al. have demonstrated that this PHACTR1 variant regulates the downstream expression of endothelin1 (EDN1), further supporting a shared common pathophysiology between FMD and these related phenotypes [36].

Environmental Factors

In addition to the aforementioned genetic risk allele, a number of environmental factors have been implicated with an associated risk of FMD. Current smoking (OR 2.5–4.1) and ever smoking (OR 1.8–4.1) have both been associated with renal FMD [37, 38]. Further, Sang et al. reported a case-control study suggesting a dose-dependent relationship between cigarette smoking and risk of FMD in 94 patients [39]. This finding has not been replicated in more recent studies [20, 22]. A significantly higher rate of aneurysms was reported in FMD patients with a history of smoking as opposed to those who had never smoked, and current smokers experienced an earlier age of diagnosis of both FMD and hypertension than non-smokers [38, 40]. Despite these associations, only 37% of FMD patients in the US Registry reported a history of ever smoking, which is comparable to the general population [21].

Given the strong female predominance in FMD, exposure to endogenous or exogenous estrogen has also been associated with FMD, although the nature of this association remains murky. FMD was not associated with oral contraceptives, hormone replacement therapy, or number of pregnancies [39]. Interestingly, an abnormal ratio of estrogen and progesterone receptors was found in renal artery samples of patients undergoing surgery for renal FMD in a recent case-control histology study. This study found marked progesterone receptor expression within the nuclei of smooth muscle cells in the renal arteries of patients with FMD relative to controls [41].

Few studies have evaluated molecular targets and FMD, but Sang et al. reported an association with human lymphocytic antigen (HLA) type DRw6 and FMD when compared to matched renal donor control subjects or matched health ambulatory controls. More recent studies were unable to replicate these findings [39, 42].

Presentation

Carotid artery FMD presentations may be quite variable and non-specific, which presents a diagnostic challenge. Further, carotid artery FMD is often asymptomatic and incidentally discovered on imaging obtained for other indications. Common signs and symptoms associated with carotid artery FMD include headaches, dizziness, pulsatile tinnitus, and auditory bruits. Less common but more dreaded cerebrovascular complications include cervical artery dissection, intracranial aneurysms, and ischemic or hemorrhagic stroke. These associations are outlined in further detail.

Headache

Headaches are the most common presenting symptom associated with FMD, reported in up to 70% of cases, and approximately half are migraines [1, 3, 22]. In the US Registry, over 30% of patients reported current headache at the time of their

presentation, with an additional ~40% reporting a history of headaches [3]. Mettinger and Ericson reported recurrent headache in nearly 80% of patients with carotid artery FMD, with most patients reporting symptom onset <10 years before diagnosis [26]. As such, later age at headache onset may be a clinical clue for FMD. Despite a high co-prevalence of headache in patients with FMD, the pathophysiology behind this association is unclear and likely multifactorial. Posited mechanisms include heightened dural pain sensitivity, uncontrolled hypertension, turbulence of flow within the cerebrovasculature, and structural injury (e.g. dissection or microtrauma) [43].

Pulsatile Tinnitus

Pulsatile tinnitus, often described by patients as an auditory "swishing" or "whooshing" sound was the presenting symptom for over a quarter of patients in the US Registry [21]. This often corresponds to a carotid bruit, the result of turbulent flow in the FMD segment. Isolated cervical bruit may be the only sign of carotid artery FMD, estimated to be the presenting sign in approximately 20% of patients [1]. Neck pain, non-pulsatile tinnitus, and dizziness are other reported symptoms in 20–26% of patients [20, 21, 26]. The dizziness described is typically lightheadedness, as opposed to true vertigo [1]. Other less common presentations reported in the US Registry include jaw claudication (5.2%) and oculosympathetic defect or Horner's syndrome (4.7%) [21]. Notably, even in a registry database subject to presentation bias, 5.6% of patients exhibited no symptoms or signs of their FMD [21].

Cervical Artery Dissection

The association between cervical artery dissection and FMD has been well described as far back as the 1970s [44–48]. Severe headache and neck pain are common presenting symptoms of carotid artery dissection. Cranial nerve deficits may also occur, particularly of the lower cranial nerves. This results from interruption of the vascular supply to these nerves fed by the internal carotid artery. A partial Horner's syndrome can also result in patients with carotid dissection, which occurs secondary to interruption of the sympathetic nerve fibers which ascend along the carotid artery wall. Generally, these patients do not experience anhidrosis, as the sudomotor fibers supplying the sweat glands travel along the external carotid, and hence ICA dissection typically presents with an incomplete Horner's syndrome manifesting as tarsal lid ptosis and miosis.

Dissection is the most common cause of ischemic stroke or TIA in patients with carotid artery FMD, due to carotid occlusion or thromboembolism. As many as 15–20% of individuals who experience cervical artery dissection have FMD, and

this figure may be even higher in individuals presenting with multiple cervical dissections [49–51]. Concomitantly, carotid and vertebral artery dissections were reported by 16% and 5% of patients, respectively, in the US FMD Registry. Among the FMD patient population who do experience dissections, the most likely artery involved is the carotid artery (64%), followed by multiple arterial dissections (37%), and finally isolated vertebral artery dissection (21%) [21].

Typically, cervical dissection in patients with FMD occurs in the mid- to distal segments of the extracranial ICA. This location is where the carotid is under greatest traction and is further strained by extension and lateral rotation of the head and neck [52]. Following cervical artery dissection, there is a higher risk of short term recurrence while the rate of long term recurrence is low (<2%/yr.), with greater risk in those with multiple artery dissections. Whether there is a greater risk of recurrence in patients with FMD remains unclear [53].

Additionally, patients with FMD are also at higher risk for spontaneous coronary artery dissection, which should be considered in patients with carotid FMD presenting with acute cardiac symptoms [54].

Intracranial Aneurysm

Similar to the association between FMD and arterial dissection, the association between FMD and cerebral aneurysms has been well described. Initial case series had widely variable rates of intracranial aneurysms in FMD patients, with rates as high as 50% reported [12, 20]. A meta-analysis of more than 500 patients with cervico-cephalic FMD reported a prevalence of unruptured intracranial aneurysm of 7%, higher than the estimated 5% in the general population [55]. There does not appear to be a difference in the prevalence of intracranial aneurysm between patients with renal FMD or cervico-cephalic FMD. [56] The US Registry reported a 12.9% rate of intracranial aneurysm in women with FMD, and 4% of these patients had more than one intracranial aneurysm. Notably, these aneurysms did tend to be larger than those in the general population, with nearly 30% of their aneurysms being at least 5 mm in diameter [21]. Although their larger size may portend a higher risk of aneurysmal rupture, it remains unclear if aneurysmal rupture rates are higher in FMD patients than in the general population.

Transient Ischemic Attack or Ischemic Stroke

At time of enrollment in the US Registry, 13.4% of patients had experienced a TIA, and 9.8% had suffered a stroke. Further, an additional 5.2% had experienced amaurosis fugax [21]. It is important to keep in mind that these are likely overestimates of the natural history of FMD given the reporting and selection bias associated with registry data. The etiology of ischemic events in carotid FMD could

be secondary to a number of potential mechanisms, including dissection, artery-to-artery thromboembolism, or hypoperfusion across a severe stenosis. Patients with carotid FMD and migraine may also experience frequent episodes with neurological aura that can mimic TIA, further challenging the diagnosis of associated ischemic events.

Subarachnoid Hemorrhage

As aforementioned, patients with carotid FMD have higher prevalence and larger size of intracranial aneurysms than the general population, which can put them at risk for subarachnoid hemorrhage. Another source of subarachnoid hemorrhage in patients with FMD may be dissection of the distal vertebral artery into the intracranial segment. According to the ARCADIA FMD Registry, prevalence of subarachnoid hemorrhage in patients with FMD was approximately 3%, but notably 20% of patients with cerebrovascular presentations were for subarachnoid hemorrhage [22].

Pediatric FMD

Although not the primary focus of this chapter, it is important to review the common presentations of FMD in the pediatric population. A case series described by Kirton and colleagues of pediatric patients (birth to 18 years) with FMD highlights the differences from the adult FMD population with regard to epidemiology, histology and common clinical presentations [57]. In the pediatric population, both genders are affected equally. Average age at diagnosis is 7-years-old, however nearly a third of patients are diagnosed in their first year of life. Histologically, cases of pediatric FMD tend to be focal, and characterized by intimal fibroplasia, whereas the more predominant multifocal FMD with medial fibroplasia seen in the adult population is very rare. Unfortunately, ischemic stroke is the most common presentation (63% of cases), which is thought to be predominantly the result of intracranial stenoses [57]. Moyamoya syndrome is another common presentation in patients with pediatric FMD [58–61]. Prognosis for these patients is poor, with a high rate of recurrent stroke or death estimated at 36% and 44% respectively, with a mean follow-up of 43 months [57]. Stenotic aortic lesions have also been described in association with pediatric FMD, often presenting as atypical aortic coarctation or middle aortic syndrome. This is another point of differentiation with FMD in the adult population, where stenotic aortic lesions have not been well described [62, 63]. Given the numerous distinguishing features of pediatric FMD, it is thought that this may be a separate clinical entity altogether [1].

Differential Diagnosis

Imaging and clinical findings in carotid artery FMD can be subtle, and understanding the unique clinical and imaging findings for these patients is critical for distinguishing it from other pathologic entities of the cerebrovasculature.

Given the increasing burden of vascular risk factors and atherosclerosis in younger adults, the ability to differentiate FMD from more common atherosclerosis can be challenging. Carotid artery FMD and cervical artery atherosclerosis can be comorbid, and are best differentiated based upon the location of the imaging abnormalities [1, 21]. Atherosclerosis occurs most frequently at arterial branch points, or in the proximal segments of an artery, as opposed to FMD, which is more likely to affect the mid- to distal portions of vessels.

As opposed to FMD, which is a non-inflammatory process, vasculitis is characterized by inflammation of the arteries. Although arterial stenoses can be present in some large-vessel vasculitic conditions, such as giant-cell arteritis and Takayasu arteritis, the presence of raised inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) can help distinguish them from FMD, in which these are typically normal [1, 64].

Segmental Arterial Mediolysis (SAM) is also a non-inflammtory arterial disease characterized by spontaneous dissection, aneurysms, and occlusive stenoses [65, 66]. SAM typically presents with abdominal symptoms due to involvement of the visceral vessels, but has been described to involve intracranial arteries as well [67]. On imaging alone, SAM can be indistinguishable from FMD, and the two conditions are better differentiated based upon distinct histological features and clinical course [68, 69].

There are also a number of monogenic connective tissue disorders which can result in a higher predilection for aneurysm and dissection and thus mimic or overlap with FMD. Examples include vascular Ehlers-Danlos Syndrome, Loeyz-Dietz syndrome, and Neurofibromatosis type 1. [49, 70, 71]

Radiographically, standing waves are another entity commonly mistaken for changes related to carotid artery FMD. Standing waves are regular undulations in an arterial wall thought to be related to spasm induced either by a catheterization or contrast material. The regular nature of these undulations helps differentiate from FMD, which tends to be more irregular. Another differentiating point is that standing waves will reverse with infusion of a vasodilator, in contrast to FMD [72, 73].

Reversible cerebral vasoconstriction syndrome (RCVS) can also be confused with FMD, but tends to be intracranial as opposed to FMD which is often exclusively extracranial. Stenoses in RCVS are classically smooth and tapered, differentiating them from the more beaded stenoses in FMD. Another distinguishing feature of RCVS from FMD is that RCVS typically responds to administration of vasodilatory substances such as calcium channel blockers.

Imaging

Although conventional angiography remains the gold standard imaging modality for the diagnosis of FMD, non-invasive imaging studies such as duplex ultrasonography, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) have become the preferred initial imaging modalities at most centers. While there is inadequate data to recommend one non-invasive study over another for the diagnosis of carotid artery FMD, there are several anatomical associations that are universal regardless of modality. As previously mentioned, segmental beading vasculopathy in the mid- and distal segments of the ICA is almost pathognomonic for carotid FMD. Hypertortuosity in the form of an "S curve" or tonsillar loop in the mid to distal portion of the internal carotid artery is also commonly seen in patients with carotid FMD. Sethi et al. described an S curve in 34% of patients with FMD compared to 2.7% of age- and sex-matched controls without FMD under the age of 70 [74]. Carotid elongation and redundancies are non-specific and can more commonly result from chronic hypertension, although more often in older ages compared to those presenting with FMD.

Duplex Ultrasonography

Duplex ultrasonography has the benefit of being a non-invasive and widely available modality. In addition to the structural analysis of the gray-scale imaging, with addition of Doppler, ultrasonography has the capability to assess flow velocities and turbulence. Although there are no validated diagnostic criteria for FMD on ultrasound imaging and no published studies comparing ultrasound to other modalities, a number of ultrasound characteristics can be highly suggestive of FMD. Turbulence, elevated velocities, and tortuosity of the mid and distal portions of the carotid is suggestive of FMD, as this is an area much less likely to be affected by atherosclerosis [1, 2]. In contrast, atherosclerotic related changes in velocity and turbulence typically are visualized at or just distal to the carotid bifurcation [1]. Beading of the vessel can also be visualized on Doppler imaging in patients with FMD (Fig. 14.2), however this is more difficult to appreciate with ultrasound than in other modalities.

Given that characteristic FMD findings on ultrasonography are most commonly visualized in the mid and distal segments of the ICA, it is crucial that any study in a potential FMD patient interrogate the entire cervical segment of the artery as opposed to a more routine study, which may focus predominantly at the carotid bulb and bifurcation.

Although carotid duplex imaging has a number of attractive features, there are a number of limitations in its utility as well. First, ultrasound is very limited in its ability to visualize the intracranial circulation and thus has a limited role in evaluating for intracerebral aneurysms or intracranial involvement of the FMD. Transcranial ultrasound is able to evaluate intracranial flow velocities, but lacks specificity in diagnosing the etiology of increased velocities.

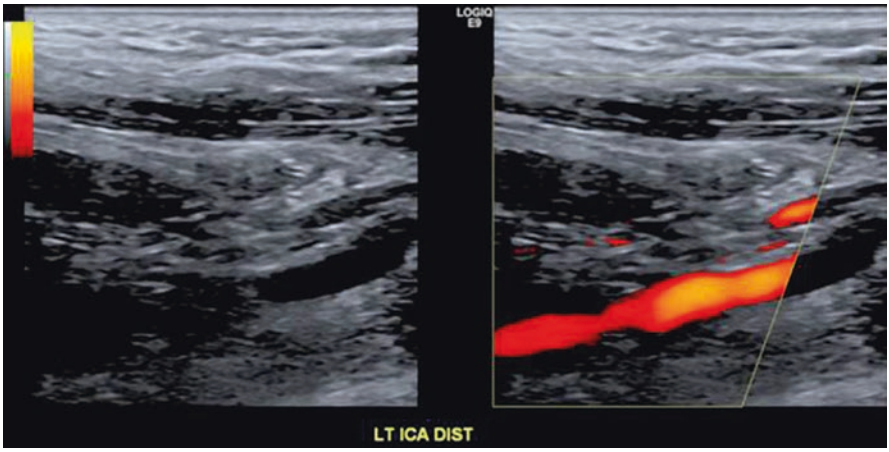

Fig. 14.2 Fibromuscular dysplasia on ultrasound of a left internal carotid artery. Although more difficult to appreciate on carotid artery ultrasound, beading of the vessel can be identified on duplex ultrasound. Other common sonographic findings of fibromuscular dysplasia include turbulent flow and elevated velocities in the mid- and distal portions of the artery

In addition to initial assessments, carotid duplex ultrasound is thought to be a useful modality for interval follow-up and surveillance of carotid FMD given the low-cost, portability, and ease of access. The 2011 multi-societal extracranial carotid and vertebral artery disease guidelines suggested annual imaging of carotid FMD with carotid duplex ultrasound as a *Class IIa* recommendation [75].

Computed Tomography Angiography (CTA)

CTA is an imaging modality that allows for more detailed anatomic imaging and visualization of the cervical and intracranial vasculature via one bolus of intravenous contrast administration. CTA has excellent spatial resolution (0.5 mm), and is able to be reconstructed into 3-D multiplanar and volume-rendered images. CTA also has a relatively short acquisition time and is less susceptible to motion artifact when compared to MRA imaging. Common FMD related abnormalities on CTA include the "string of beads" appearance for patients with multifocal FMD or a tubular stenosis for patients with focal FMD. Unlike duplex ultrasonography, CTA is a very reasonable, if not preferred, imaging modality to evaluate for cerebral aneurysms. Relative to conventional angiography, CTA has a high sensitivity and specificity in detecting cerebral aneurysms, particularly those that are at least 3 mm in diameter [76, 77]. Although there are no published studies rigorously comparing CTA to conventional angiography for the diagnosis of carotid FMD, CTA is highly accurate (97%) in measurement of atherosclerotic carotid stenosis [78].

Despite many advantageous aspects of CTA for non-invasive imaging of patients with FMD, there are a number of limitations in its application. CTA imaging requires administration of iodinated contrast material for opacification of the cerebrovasculature, which may be nephrotoxic. Given the high prevalence of renal artery stenosis and secondary hypertension in patients with FMD, CTA should be used with caution if there is any concern for concomitant kidney disease. In patients with a glomerular filtration rate of <30 mL/min/1.73m^2, CTA should be avoided unless emergently indicated or the patient is on dialysis. Aside from concerns related to contrast administration, CTA of the head and neck does submit the patient to a non-inconsequential radiation exposure [79]. Particularly given that most FMD patients are young to middle-aged women, discretion is advised before utilizing CTA as a means of surveillance in this population.

Magnetic Resonance Angiography (MRA)

Contrast-enhanced MRA is a reasonable option for imaging of changes related to FMD, particularly in patients with an allergy to iodinated contrast material. As with CTA, there are no studies published validating use of MRA compared to conventional angiography for the purposes of evaluating for carotid artery FMD. Benefits of MRA over CTA include the lack of iodinated contrast, and lack of radiation exposure, the latter of which is particularly appealing in imaging younger patients [80, 81]. In evaluating patients with concern for cervical arterial dissection, use of T1 fat-saturation images may enhance detection, as MRA is generally preferred over CTA for this indication [80]. Similar to CTA however, contrast-enhanced imaging is limited in patients with a glomerular filtration rate of <30 mL/min/1.73m^2, given concerns of precipitating nephrogenic systemic fibrosis with use of gadolinium-based contrast agents. Limitations of MRA include poorer spatial resolution (1–2 mm) as well as an increased likelihood of motion artifact due to much slower imaging acquisition (Fig. 14.3).

Conventional Angiography

Conventional, catheter-based angiography remains the gold standard imaging modality for visualization of changes related to carotid artery FMD (Fig. 14.4). This is in large part a result of its superior spatial resolution (<0.1 mm). Conventional angiography provides optimal visualization of the cerebrovasculature, has unsurpassed ability to detect intracerebral aneurysms, as well as dynamic flow-related information not obtainable via CTA or MRA. Despite this, conventional angiography is not frequently performed for diagnostic purposes in patients with suspected FMD due to logistical challenges, invasiveness, and a theoretical higher risk for iatrogenic dissections in this population [82]. Conventional angiography is thus usually reserved for carotid FMD cases with diagnostic uncertainty, need for intervention, or to identify small cerebral aneurysms.

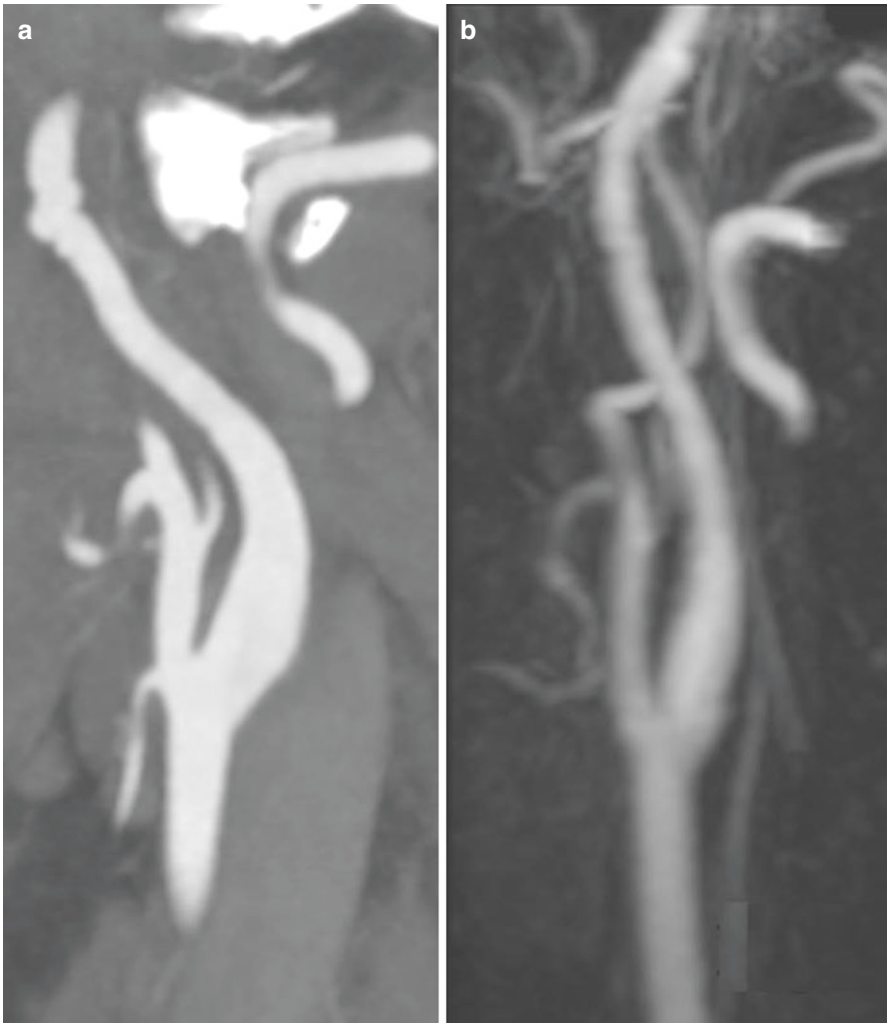

Fig. 14.3 Right internal carotid fibromuscular dysplasia. Alternating dilitation and stenoses in a right internal carotid artery with multifocal fibromuscular dysplasia as identified on computed tomography angiography (**a**) and magnetic resonance angiography (**b**). Note the improved spatial resolution on the CTA relative to the MRA

Management

Migraine and Pulsatile Tinnitus

As discussed earlier in the chapter, headache and pulsatile tinnitus are two of the most common and disabling symptoms of carotid artery FMD, and therapy can be targeted to address these conditions. It is important to consider that although

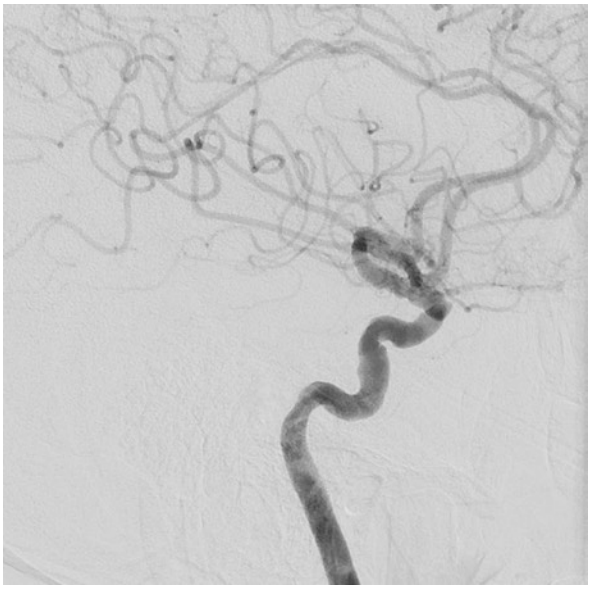

Fig. 14.4 Conventional angiography. Subtle "string of beads" as identified by conventional angiography with selected injection of contrast into the distal left internal carotid artery. Note the unsurpassed spatial resolution and the ability to visualize the intracranial circulation concurrently

migraine is the most common type of headache in patients with carotid artery FMD (including 38% of patients of the US Registry, and 28% in the ARCADIA study), headaches can also result from uncontrolled hypertension or cervical arterial dissection [21, 22]. No studies have been performed prospectively assessing medical interventions for migraine specifically in FMD patients. It is unclear at this time if migraineurs with FMD exhibit differential responses to typical migraine therapy, or if any classes of pharmacotherapy may have any specific effects in FMD-related migraine headaches. Thus, similar medical management as in the general migraine population is advised, with the exception of use of caution with abortive triptan or other sympathomimetic agents, which have the potential of causing symptomatic vasoconstriction or exacerbating hypertension. In carotid artery FMD patients with a history of cervical or coronary artery dissection, triptans, ergots, and other vasoconstrictive agents may be contraindicated [43]. As for pulsatile tinnitus, patients may respond to reassurance and education. Those with more severe symptoms may warrant a trial of sound or cognitive behavioral therapy, although this has not been studied specifically in the carotid artery FMD population [83–85]. Audiology and/or otolaryngology consultation may be helpful to rule out other potential etiologies of tinnitus aside from carotid artery FMD.

Hypertension

In the absence of any studies evaluating a specific blood pressure target in patients with carotid FMD, it is reasonable to treat patients with carotid artery FMD according to general recommendations such as the 2017 American College of

Cardiology/American Heart Association Multisocietal Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [86]. Patients with comorbid migraine headaches may obtain dual benefit from certain classes of antihypertensive medications (e.g. beta blockers, calcium channel blockers). Adequate control of hypertension is of particular import in carotid artery FMD patients with intracranial aneurysms. Aside from medical management, in patients with concurrent renal FMD, particularly in those with resistant hypertension (i.e. failure to achieve adequate blood pressure control despite an appropriate 3-drug regimen including a diuretic), revascularization of the renal artery becomes a consideration [1].

Carotid Artery FMD Without Cerebrovascular Complications

Given the high prevalence of FMD in other vascular beds in those found to have carotid artery FMD, a multidisciplinary approach to these patients is recommended [2]. In patients with carotid artery FMD who have not experienced any cerebrovascular complications, use of a low-dose (75 to 100 mg/day) daily aspirin is thought to be a reasonable option for prevention of stroke or TIA, acknowledging that there is an absence of rigorous prospective data to support the use of antiplatelet agents for the indication of primary stroke prevention [1, 3, 20]. This is supported by a *Class IIa* recommendation from a 2011 multisocietal guideline statement [75]. Treatment of co-morbid hypertension is indicated, as above. Surgical or endovascular intervention upon asymptomatic carotid FMD, including asymptomatic arterial dissection, is not recommended regardless of the severity of the stenosis [75].

Carotid Artery FMD with Cerebrovascular Complications

In patients experiencing acute ischemic stroke or TIA secondary to carotid artery FMD, recommended management is similar to those without carotid artery FMD [48]. Treatment of acute ischemic stroke with intravenous thrombolysis and/or endovascular thrombectomy are thought to be safe [87, 88]. As with stroke or TIA in the general population, secondary stroke prevention regimens should be tailored to the underlying stroke mechanism and their vascular risk factors.

Similar to TIA and stroke, management of intracerebral hemorrhage or aneurysmal subarachnoid hemorrhage in patients with carotid artery FMD should be unchanged from that in the general population [89, 90].

In the case of cervical artery dissection, endovascular therapy is typically reserved only for patients with ongoing cerebral ischemia despite optimal medical therapy [88, 91, 92]. During endovascular intervention in patients with carotid FMD, operators should use caution to avoid potential iatrogenic vascular injury given theoretical vulnerability due to dysplasia of the arterial wall.

As the pathophysiology is drastically different in carotid artery FMD and typical atherosclerosis of the cerebrovasculature, the role for statin therapy is unclear. A retrospective study failed to demonstrate any impact of statin therapy on rate of restenosis in renal FMD patients [93]. Given the lack of association between dyslipidemia and carotid FMD, statins should only be recommended when indicated for comorbid atherosclerotic disease.

Lifestyle Modification and Other Considerations

A major modifiable risk factor for patients with carotid artery FMD is smoking cessation. Impact of smoking cessation has not been studied rigorously with regard to rate of progression of FMD related changes, but Savard and colleagues have suggested that FMD patients that are current smokers may have a more aggressive course than non-smokers with FMD [38]. Given the association of smoking with cerebrovascular events, smoking cessation should be strongly recommended to any patients with carotid artery FMD [1, 94, 95].

As discussed above, no data exist linking exposure to oral contraceptives or hormone replacement therapy with development or progression of FMD, but there is a possible concern for interaction with intracranial aneurysm growth and rupture or thromboembolism. Thus, it is generally recommended that any hormonal therapy be administered at the lowest effective dose, and for the shortest duration necessary in women with a history of intracranial aneurysm or stroke, particularly if they are current smokers.

Screening for FMD in Other Vascular Beds

As discussed previously, the majority of patients found to have carotid artery FMD have involvement of other arterial beds. As such, a one-time screening of the renal arteries with either ultrasound or CTA is recommend in patients with carotid FMD. If not already performed at the time of diagnosis of carotid artery FMD, imaging of the intracranial arterial vasculature with either CTA or MRA is also recommended to rule out intracranial involvement and the presence of cerebral aneurysms.

Conclusion

Carotid FMD is an idiopathic, non-inflammatory, non-atherosclerotic arteriopathy characteristically seen in the mid or distal segments of the ICA and often easily diagnosed with non-invasive vascular imaging. Although the etiological risk factors

associated with carotid FMD remain largely unclear, recent genomics studies confirm shared associations with cervical artery dissection, migraine, and an inverse association with atherosclerotic disease. Despite a higher risk for carotid artery dissection and intracranial aneurysms, the overall natural history of carotid FMD is generally favorable and supports reassurance for patients in which it is discovered incidentally. Management of migraine and pulsatile tinnitus can improve quality of life for symptomatic patients. Ongoing collaborative research and involvement in patient registries is needed to better understand the pathophysiology and optimal prevention and management of its cerebrovascular manifestations.

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Chapter 15
Giant Cell Arteritis

Nathan Gaines and David S. Liebeskind

Introduction

Giant Cell Arteritis (GCA) is the most common systemic vasculitis [1]. It targets large and medium caliber vessels and its classic symptoms result from a predilection for the cranial branches of the carotid arteries. It is a disorder of middle to older age and rarely affects individuals younger than 50. Diagnostic dilemmas frequently result from clinical presentations that can be highly variable and diagnostic tests that are often nonspecific or unreliable. The consequences of missing the diagnosis are high, with permanent vision loss occurring in 15 to 20% of patients [2]. However, because it is a disease of older patients, often with medical comorbidities, standard treatment with systemic corticosteroids is far from benign in many cases. Accurate diagnosis and effective treatment require a high index of suspicion in nonspecific presentations, careful examination and diagnostic workup, and at times, tolerance for uncertainty in choosing the best clinical approach for each patient in which GCA is suspected.

Historical Perspective

An excellent review of the early history of GCA is provided by Gene Hunder in the Mayo Clinic Proceedings [3]. Early descriptions by Hutchinson in the 1890s included a case report of a man in his late 70s with bilateral tender, red streaks on his scalp that Hutchinson attributed to swollen superficial temporal arteries [4].

N. Gaines (✉)
Highland Hospital Division of Neurology, Alameda Health System, Oakland, CA, USA

D. S. Liebeskind
Neurovascular Imaging Core, UCLA Department of Neurology, Los Angeles, CA, USA

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Pulsations in the arteries weakened with time and as the visible inflammation resolved, firm thrombosed vessels were all that remained. Little more was published on the subject until the 1930s when Horton and colleges reported two cases of patients with several weeks of constitutional symptoms, headache, jaw claudication, and tender areas of the scalp along the course of the temporal arteries. Biopsy specimen of these cases showed identical chronic arteritis. Over that same decade additional cases were reported with similar clinical findings in patients aged from their mid-50s to 70s. [5–7]

After excluding common infections as the underlying etiology, Horton explored the possibility of an autoimmune condition by injecting ground temporal artery specimen into the scalp of 5 healthy volunteers in their 70s and into the forearm of one woman in her 60s who carried the diagnosis of GCA [8]. His suspicion of an autoimmune condition was supported when the healthy volunteers showed no reaction but the woman with GCA developed fever, anemia, and elevated erythrocyte sedimentation rate (ESR).

In the 1930s and 40s reports of visual manifestations began to surface. In the 1950s Wagener and Hollenhorst reviewed the ocular findings of 122 patients with GCA seen at the Mayo clinic, of which 44% had experienced loss of vision, with ischemic optic neuropathy being the predominant fundoscopic finding [9]. Horton and Magath presented on GCA in a meeting of the American Medical Association in the 1950s but it would still be decades before physicians were widely aware of the disease. There are no reliable sources for estimating the prevalence of GCA prior to the twentieth century and while increased recognition is undoubtedly a factor in its apparent increase, aging of the population likely also plays a significant role since it almost exclusively affects individuals over the age of 50.

Over the years GCA has had many names. Hutchinson initially labeled his patients as having thrombotic arteritis of the aged, while Horton used the term temporal arteritis. Horton's disease, cranial arteritis, granulomatous arteritis, senile arteritis, and polymyalgia arteritica also appear in the earlier literature [3]. The two most persistent labels have been giant cell arteritis and temporal arteritis. The terms are interchangeable but, for consistency, this chapter will use GCA except when alternate names were used by references.

Clinical Presentation

Epidemiology

GCA is the most common systemic vasculitis in the United States with the biggest risk factors being non-modifiable: age, gender, and ethnicity. It almost exclusively affects individual over age 50 with the majority of cases occurring in one's 70s [10]. Incidence is highest among individuals of Scandinavian descent (about 17 per 100,000 persons over age 50), intermediate among Southern European and Middle Eastern populations (about 10 per 100,000 persons over age 50), and thought to be

rare among African American, Latino, Asian, and Arabic populations, though data in these groups are limited and inconsistent [11]. True incidence may be higher due to undiagnosed cases: one Swedish study looking at postmortem analysis of temporal arteries reported evidence of GCA pathology in 1.6% [12]. Females are more commonly affected with a ratio of about 3:1 compared to males [1].

Common Symptoms

The most common symptoms of GCA at presentation are headache, constitutional symptoms, muscle and joint pain due to polymyalgia rheumatica (PMR), jaw claudication, and visual complaints [13]. While most practitioners would correctly diagnose this constellation of symptoms, many patients with GCA present with normal physical exams and only a few, often non-specific symptoms. Common chief complaints such as headache, fatigue, and muscle aches are highly prevalent in the general population and more specific complaints such as jaw claudication are less common and often not volunteered by patients unless specifically asked about by the practitioner. A high index of suspicion and careful, detailed questioning is often required. Depending on the order of symptom onset, or which symptoms are most troubling, patients can present to a variety of clinical settings including primary care clinics, urgent care or emergency departments, optometry or ophthalmology clinics, headache specialists, general neurology clinics, stroke clinics, etc. For this reason it is important that all physicians are familiar with variability of clinical presentations since delays in diagnosis in any of these settings could result in irreversible blindness that might have been avoided.

As with most secondary headaches, the subjective quality of headache in GCA can present in almost any fashion in a diffuse or focal location. Patients typically describe a throbbing pain but the full range of pain descriptors will be encountered in clinical practice. Bitemporal headache occurs in about half of cases and may be associated with scalp tenderness, a finding that could help differentiate GCA from the much more common bitemporal tension headache. The key feature that should raise concern for GCA and other secondary headaches is new onset headache in patients over age 50 (or change in headache type in the case of chronic headache patients) [14].

Jaw claudication is one of the few symptoms with high specificity for GCA but must be distinguished from the many other, more common causes of jaw pain [10]. Jaw pain from the temporomandibular joint (TMJ) occurs at the onset of chewing as a direct result of stress on the joint. In contrast, jaw claudication from GCA occurs due to reduced blood flow to the muscles of mastication with delayed onset after chewing starts and subsequent improvement with jaw rest. In some cases, jaw fatigue, rather than frank pain, might be reported.

Visual complaints vary as well. Sudden, monocular vision loss is more common but any type of ischemic visual disturbance is possible including stuttering visual loss, transient monocular vision loss (amaurosis fugax), bilateral vision loss,

hemianopia, and even diplopia from ischemia to cranial nerves 3, 4, or 6, or direct ischemia to the extraocular muscles. Diplopia occurs in only about 5% of patients but has been found to be one of the few symptoms with relatively high specificity when GCA is suspected [13]. Visual release hallucinations (Charles-Bonnet Syndrome) can occur with just about any cause of ocular or neurologic visual loss and have been reported in GCA. Persistent visual deficits or dysfunction can often be correctly classified by careful neuroophthalmological exam but identifying the exact nature of transient visual symptoms is limited by the quality of the history. Differentiating transient monocular vision loss from hemianopsia after the fact is often unreliable unless the patient had the presence of mind to cover each eye one at a time or they are able to describe hallmark features of ocular ischemia such as a "curtain coming down" appearance that reflects the distal to proximal loss of blood flow in an ischemic retinal artery. About 80% of cases of vision loss are due to arteritic ischemic optic neuropathy (AION), followed by central retinal artery occlusion (CRAO) causing about 10%, and branch retinal artery occlusion (BRAO) being uncommon at less than 5%. Vision loss due to ischemia is not reversible with corticosteroid therapy [10]. This topic will be discussed further below.

Joint and muscle aches are common at presentation due to polymyalgia rheumatica (PMR), which commonly co-occurs with GCA. PMR occurs in about 40–50% of patients with GCA while GCA develops in about 15% of patients with PMR [15]. Despite its name, the condition is not a myopathy but rather an inflammatory polyarthritis with tendon or bursa involvement. Patients typically describe pain and stiffness in the neck, shoulders, and hips with referred myalgias to the shoulders and hips that is worse in the morning [16].

Constitutional symptoms such as fever, anorexia, weight loss, and fatigue are common but again, non-specific. Neoplasm or infection, especially in this older age group should always be a concern. Fever and weight loss are typically mild or low grade but can be more severe. Constitutional symptoms appear to correlate to some extent with the markers of systemic inflammation, which will be discussed further on. About 15% of fever of unknown origin cases in the elderly are due to GCA [17].

Physical Exam and Laboratory Findings

While physical exam findings can be dramatic in some cases, most patients have unremarkable physical exams at presentation. Presence of fever and unintentional weight loss are non-specific but important findings regardless of their etiology. Palpation of the temporal arteries starting just anterior and superior to the tragus of the ear and tracing upward may demonstrate tenderness, decreased pulsation, redness and swelling, or firmness. Visibly necrotic skin of the scalp or tongue can occur. Fundoscopic exam may show signs of ischemic optic neuropathy (pale and swollen disk) or, less commonly retinal artery occlusion (pale retina with cherry red spot due to spared blood flow through collaterals to the macula).

ESR is typically highly elevated in GCA, up to 100 mm/hr [18], as is c-reactive protein (CRP). Modestly elevated or normal ESR or CRP does not, however, exclude the disease and does not appear to indicate a more benign disease course. A minority of patient, around 10% or less in several studies, had ESR values below 50 and in less than 5% of cases the ESR was normal [19–21]. However ESR and CRP are non-specific markers of inflammation; elevated levels carry a very broad differential diagnosis. IL-6 may offer a better marker of disease activity in GCA but is not widely available and typically not necessary [22].

Other common laboratory abnormalities include normocytic anemia, reactive thrombocytosis, modestly decreased serum albumin, and modestly increased hepatic enzymes, all of which typically improve or resolved after starting glucocorticoids. White blood cell counts are typically normal at the time of presentation even in the presence of systemic inflammatory symptoms.

Diagnostic Value of Symptoms, Exam and Laboratory Findings

One common challenge when approaching the patient who presents with only a few signs or symptoms suggestive of GCA is how much diagnostic value to place on different findings. Smetana and Schmerling provide an excellent investigation of the comparative value of diagnostic findings in GCA in their article "Does this Patient Have Temporal Arteritis" [13]. In their study the only findings that increased the likelihood of a positive temporal artery biopsy were jaw claudication, diplopia, and temporal artery abnormalities while normal ESR significantly decreased the likelihood of a positive biopsy. Unfortunately these findings offer poor sensitivity for diagnosing GCA; as do nearly all of the common GCA symptoms. Clinicians are left with the difficult task of evaluating the clinical picture in its entirety and often proceeding with diagnostic uncertainty.

Patterns of Disease and Histopathology

The prototypical vasculitis of GCA causes inflammation of medium and large vessels at all vessel layers with granuloma formation in the media, destruction of the elastic lamina, and rapid, concentric intimal hyperplasia. Intimal thickening is a non-specific response to vascular injury found in various inflammatory and non-inflammatory vasculopathies. Luminal narrowing, and not thrombus formation, is the major mechanism of ischemia in GCA. Necrosis is not a feature of GCA pathology and apart from fragmentation of the elastic lamina the other components of the arterial wall are typically not fully destroyed [23].

However, GCA is a heterogenous syndrome and clinical presentation appears to be affected by the differences in immune response and pathologic patterns. PMR likely represents one end of the clinical spectrum with a robust systemic syndrome

very similar to GCA occurring in the absence of any detectable vasculitis. Interleukin-1 (IL-1) and interleukin-6 (IL-6) are secreted but destructive interferon---producing T cells are not recruited [18]. IL-6 is a key inducer of the systemic inflammatory response but inversely correlates with vascular ischemic injury. One possible explanation is that IL-6 has potent angiogenic properties and may induce collateral flow pathways around ischemic lesions [19]. Another explanation could be that those patients with strong inflammatory responses and readily apparent systemic symptoms are identified and treated more rapidly than those for which ischemic injury is the sentinel event. GCA with prominent ischemic symptoms but no systemic symptoms has been referred to as an "occult" variant, while prominent systemic symptoms without ischemic complications has been labeled the "silent" variant.

Adding to the variability, vasculitis in GCA has stenotic and non-stenotic patterns, likely due to different T-cell responses. In patients with ischemic disease, luminal stenosis from intimal hyperplasia results from growth factors and angiogenic factors that are attempting to repair the affected vessels. Other patients have vascular inflammation and injury but lack the reactive intimal hyperplasia that underlies the ischemic sequelae [18]. There is also histopathological variation depending on the stage of disease with giant cells possibly absent at both early and late stages, perhaps contributing to their absence in about 60–70% of biopsy samples [24].

GCA's affinity for the elastic lamina correlates with its predilection for the aorta and its proximal branches with typical sparing of the intracranial arteries, which have little or no elastic fibers. Intracranial arteries also lack vasa vasorum that may allow for infiltration of inflammatory cells in GCA. For the extracranial cervical arteries, the vertebral arteries are more commonly involved than the carotid arteries. Involvement of intracranial arteries has been reported but appears to represent a rare subset of GCA with a fulminant course and resistance to corticosteroid therapy [25].

While extracranial vasculitis in the head and neck are the hallmark features of GCA, large vessels outside this area are also frequently involved. Signs and symptoms of aortic and upper or lower extremity vasculitis (e.g. claudication, cold extremities, weak pulsation and asymmetric blood pressures) are the presenting features in 20–80% of GCA patients and may precede the diagnosis. Many of these patients will not have the classic cranial manifestations such as headaches, abnormalities of the temporal arteries, or ophthalmologic complications, but do manifest the systemic inflammatory symptoms characteristic of GCA including PMR. Aortitis secondary to GCA is typically clinically silent but the aorta is uniquely prone to dilation and aneurysms, which do not typically occur in other arteries due to GCA, and may present as back pain, abdominal pain, dyspnea, or be asymptomatic. Aortic rupture has been reported [19].

Vision Loss, Stroke, and Other Neurologic Complications

Vision loss from GCA occurs in about 20% of patients before they have been started on glucocorticoid therapy; reports of GCA prior to the glucocorticoid era estimate a higher rate of vision loss, around 35–60%. Since the most common causes of vision

loss are AION (80%) and CRAO (5–15%), the pattern of vision loss is typically painless, sudden onset, and monocular. Binocular vision loss also occurs either through a subsequent ischemic event in the contralateral eye or, in rare cases, both eyes simultaneously. Transient monocular vision loss is estimated to occur in 10–15% of patients and may herald impending permanent ocular ischemia much in the same way crescendo TIAs might warn of progressive carotid artery disease and impending large vessel stroke. Vision loss from GCA is irreversible and unfortunately occurs as the presenting symptom for many patient with the occlusive, vasculitic variety of the disease [26].

Diplopia, as mentioned above, is one of the few highly specific symptoms for GCA but occurs in fewer than 10% of patients. It typically results from ischemia to cranial nerves or extraocular muscles, resulting in disconjugate gaze [27].

Approximately 1.5–7% of GCA patients suffer from stroke or transient ischemic attach (TIA), more commonly in the posterior circulation from involvement of the extradural vertebral arteries followed by the extradural carotid arteries [21]. Along with ocular causes of vision loss, stroke represents a major cause of morbidity in GCA; since mortality does not appear to be increased in GCA, patients often deal with the GCA related disabilities for many years. Special attention should be given to symptoms of posterior circulation strokes (brainstem, cerebellum, occipital lobe, thalami) and vertebrobasilar insufficiency (e.g. vertigo on rising especially if accompanied by focal neurologic deficits). Devastating bilateral vertebral artery occlusions have been reported [28].

Strokes typically occur during the clinically active phase of the disease – most often from symptom onset to about 1 month after corticosteroids are started – and are not commonly a late complication of GCA. The vascular mechanism appears to be ischemia more than thrombosis. Major risk factors for stroke in GCA appear to include traditional cardiovascular risk factors of hypertension, smoking, and male gender as well as prior ischemic events. As previously discussed, a strong systemic inflammatory response appears to decrease the risk of stroke, likely due to angiogenic properties of IL-6 that may increase collateral blood supply, earlier identification and treatment of patients [29], and because it may represent a different pattern of disease with a natural history that includes fewer vasculitic complications.

Imaging

Imaging of patients with suspected GCA should be tailored to the clinical presentation as well as the capabilities at specific institutions. Color doppler ultrasound of the temporal arteries can be very helpful in the diagnostic workup and will be discussed in the next section.

For patients with focal symptoms attributable to large arteries, MR and CT angiography (MRA, CTA) are the modalities of choice to look for underlying abnormalities such as stenosis or dilation but they are not reliable for imaging medium and small vessels. Both CTA and MRA are excellent for showing segmental luminal stenosis or dilation. Contrast enhanced MRI may show vessel wall enhancement of

the temporal or occipital arteries with small studies reporting sensitivity of 68–89% and specificity of 73–97% [30]. Carotid ultrasound might also be useful to screen for carotid stenosis but CTA or MRA would offer much greater diagnostic value in differentiating the cause of stenosis, especially since patients with GCA are older and thus more prone to atherosclerotic carotid stenosis independent of GCA.

Fluorodeoxyglucose positron emission tomography (FDG-PET) may be helpful to demonstrate vasculitis in cases where symptoms are non-localizing, such as fever of unknown origin or other constitutional symptoms. Sensitivity and specificity are around 77% and 66% respectively and uptake can persist for at least 6 months even after initiating glucocorticoid treatment [30]. In each of these modalities differentiating atherosclerosis from vasculitis is not always possible, including FDG-PET in which active atherosclerotic lesions can also take up tracer.

Work Up and Management

Diagnostic Workup

Definitively diagnosing GCA is challenging. The threat of vision loss in possible cases has resulted in a practice of treating as soon as the diagnosis is strongly suspected but the risk of adverse effects of long-term glucococorticoid therapy in older patients who may have diabetes mellitus or other conditions that complicate steroid treatment leads to a desire to prove the diagnosis. The major diagnostic tool remains tissue examination via a temporal artery biopsy. While the procedure is typically outpatient and generally safe, the high risk of false-negative outcomes does little to alleviate diagnostic uncertainty; biopsies return positive in only about 25–30% of cases [31].

While biopsy may not exclude GCA, it remains the definitive diagnostic proof. Yield is thought to improve with sections at least 5 mm long and, ideally, frozen section of the first biopsy can be done so that, if negative, a sample can be taken from the contralateral side. Inflammation is discontinuous along the course of a vessel with so-called “skip lesions”, likely accounting for some of the variability, although many false negatives may reflect early or late disease stages lacking the hallmark pathologic findings, or reflect a variant pattern of GCA with more prominent systemic inflammation and/or large artery vasculitis rather than involvement of the cranial arteries (as described above). Biopsy sensitivity ranges from about 70–90%; specificity is not quite 100%. Fortunately, biopsy yield does not appear to decline much until 1 or 2 weeks after initiating steroid therapy, allowing for prompt treatment without losing the opportunity to make an accurate diagnosis [24].

The major alternative to biopsy is color-duplex ultrasonography of the temporal arteries but its utility is limited to centers with the necessary technical expertise. Positive studies identify a “halo sign” consisting of a hypoechoic ring around the arterial wall due to vessel wall edema. Sensitivities and specificities vary between studies, ranging from 55–100% and 78–100% respectively, likely due in part to

technologist experience. The halo sign disappears as soon as 2–3 weeks after starting steroids but may persist for a few months [30]. As described above, MRI, CTA, and FDG-PET may also help make the diagnosis, especially when the pattern of disease varies from the prototypical cranial artery vasculitis picture.

Differentiating GCA from related inflammatory disorders can typically be done clinically. Takayasu arteritis, the other major large vessel vasculitis, can present similar to the large artery variety of GCA (e.g. with subclavian involvement) but does so in much younger patients and rarely manifests with vision loss. Some small and medium vessel vasculitides such as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and polyarteritis nodosa (PAN) can affect the temporal arteries, mimicking GCA but they typically affect distinctively different vascular territories.

Ultimately, GCA is often a clinical diagnosis. History, exam, labs, imaging, and biopsy need to be taken as a whole and some degree of diagnostic uncertainty is common.

Management

Glucocorticoids are the primary treatment of GCA and should be started as soon as there is strong suspicion of the diagnosis to hopefully avoid ischemic complications like vision loss. Dosing practices vary but typically start with a prednisone equivalent dose of 40–60 mg for 2–4 weeks followed by a taper of about 10 mg equivalent dose every 2 weeks with close monitoring for relapse [30]. Once doses of 20 mg daily are reached, tapering should be slowed, typically by 2.5 mg every 2 weeks until 10 mg daily dose then very slowly by 1 mg every 2–4 weeks. Relapses are more likely to occur below 20 mg daily. When relapses occur, dose increases should be proportional to the clinical event, i.e. vision loss or other ischemic complications would justify restarting at induction doses while milder constitutional symptoms may only require more modest increases to the pre-relapse dose. If patients present with ischemic complications or they occur during tapering, high-dose intravenous methylprednisolone (500–1000 mg daily for 3 to 5 days) followed by high dose prednisone can be considered though there is insufficient evidence of superiority over oral steroids alone to recommend this routinely. ESR and CRP are imperfect biomarkers of disease activity and cannot be solely relied upon to monitor for relapse.

Adjunctive therapies with methotrexate or tocilizumab are also options, especially for patients with contraindications to steroid therapy. Tocilizumab is an IL-6 receptor antagonist that has been shown to improve remission rates when compared to glucocorticoids alone and reduce the cumulative glucocorticoid dose burden [32]. One consequence of tocilizumab use is a rapid normalization of ESR and CRP as a direct effect so that relapse monitoring needs to be done clinically. As a new medication its optimal role in GCA management is yet to be determined, including whether it addresses underlying vasculitis or has a more supportive role by reducing the systemic

inflammatory response. Methotrexate appears to be of modest benefit in GCA but may also help reduce cumulative glucocorticoid dose burden [30], which is very important for the many patients who are poorly tolerant of steroids.

Improvement in constitutional symptoms and pain, including headache, can occur within days of starting steroids as does a decrease in blood levels of systemic inflammatory markers. Steroids may prevent vision loss but do not reverse it once it has occurred and progression of vision loss over several days may even occur despite starting treatment [33].

Conclusions

GCA is a heterogenous, diagnostically challenging condition without high value biomarkers, clear and valid diagnostic criteria, or a highly sensitive gold standard diagnostic test. In spite of those challenges and, in fact, because of them, it is important for all physicians to be aware of this complex disease since patients may present to a variety of clinical settings and a missed diagnosis may result in prolonged illness as well as avoidable, permanent vision loss and other ischemic complications.

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Chapter 16
Takayasu's Arteritis

Yilin Shek and Shlee S. Song

Historical Perspective

Takayasu's arteritis is a chronic nonspecific arteritis affecting mainly the aorta and its large branches, such as the carotid, subclavian, brachiocephalic, vertebral, renal arteries, and as well as the pulmonary and coronary arteries. It is rare, but most commonly seen in young Asian adults, usually presenting in the second and third decades of life [1]. Cases have been reported globally in the United States, Europe, and South America. The first published description of this arteritis was given by Japanese physician, Rokushu Yamamoto, in 1830 [2]. Yamamoto described the case of a 45-year-old man suffering from persistent fever associated with weight loss and dyspnea, who became pulseless in the radial artery and carotid arteries. At the 1908 Annual Meeting of Japanese Ophthalmology Society, Dr. Mikito Takayasu, professor of ophthalmology at Kanazawa University Japan, presented a case of a 22-year-old woman with blurry vision and characteristic fundal arteriovenous anastomosis [3]. In the same year, Ohnishi described a similar case of a 22- year-old presenting with absent radial pulses [4]. The first post-mortem case of Takayasu's arteritis was published in 1920 which revealed large vessel arteritis. This provided support for fundal findings most likely caused by retinal ischemia [2]. Arterial inflammation is the hallmark of the disease associated with variable degrees of a systemic acute-phase response. The pathogenesis of Takayasu's arteritis remains poorly understood, but immune-mediated injury to the arteries appears to play a major role [5]. Microscopically, the arteritis consists of an acute, florid, inflammatory phase and a chronic fibrotic phase. In the acute phase, the lymphohistiocytic inflammatory infiltrates are seen in the media, along with occasional multinucleated giant cells. There are findings that include vasa

Y. Shek · S. S. Song (✉)
Cedars-Sinai Medical Center, Department of Neurology, Los Angeles, CA, USA
e-mail: shlee.song@cshs.org

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vasoritis in the adventitia and intimal hyperplasia. In the chronic phase, fibrosis and scarring with destruction of elastic tissue are more prominent. Macroscopically, the inflammatory lesions result in arterial wall thickening and arterial remodeling, followed by myofibroblast proliferation. This leads to subsequent arterial stenosis formation of aneurysms and thrombosis [6, 7].

Presentation

Takayasu's arteritis commonly presents in patients under 40 years of age with nonspecific constitutional symptoms such as low-grade fever, malaise, anorexia, arthralgia, myalgia, and weight loss. Nonspecific symptoms often lead to a delay in diagnosis and treatment. As the arterial inflammation progresses and steno-occlusive lesions of the carotid, subclavian, brachiocephalic, vertebral, and other arteries develop, the symptoms of vascular disease become clinically apparent. Among the aortic branches, the most commonly involved arteries are the subclavian and common carotid arteries. In most studies, steno-occlusive lesions are reported in 90% of patients, whereas aneurysmal diseases are found in up to 25% [1]. Clinical presentations range from asymptomatic disease found as a result of impalpable pulses to catastrophic disease with neurological impairment [2, 8]. In 30–50% of patients, the constitutional symptoms can be absent at presentation [1]. The following characteristic features can be seen:

Absent or diminished peripheral pulses: Takayasu's arteritis is also known as pulseless disease, since 84–96% of patients have diminished pulses or absent pulses in the arms [9]. Most patients have blood pressure discrepancies between the arms (>10 mm Hg) due to subclavian stenosis. Arterial bruits are often audible over the carotids, subclavian, and abdominal vessels [10]. Coolness of the hands, claudication of extremities, with arterial pain and tenderness caused by reduced blood flow, may be observed.

Hypertension develops in 33–83% of patients, which most often reflects renal artery stenosis or narrowing and reduced elasticity of the aorta and its branches [10, 11].

Carotidynia, a special type of cervicofacial pain that could be induced by pressure on the common carotid arteries, is observed in 10–30% of patients at presentation, which provides an important clue to the diagnosis [1, 12].

Up to 37% of patients develop Takayasu retinopathy [13, 14]. Pulmonary arteries are affected in up to 50% of patients, which may lead to pulmonary hypertension [15, 16]. Cardiac complications are common, including aortic insufficiency resulting from dilatation of the ascending aorta. Myocardial ischemia related to coronary arteritis may occur or coronary artery ostial narrowing from aortitis. There also may be congestive cardiac failure associated with hypertension, aortic insufficiency, and dilated cardiomyopathy [9, 11]. Other manifestations include abdominal pain, and gastrointestinal bleed resulting from mesenteric artery ischemia, and erythema nodosum over the legs [11].

Involvement of extracranial cerebral arteries causes cerebral hypoperfusion and ischemia. This is manifested clinically as postural dizziness, syncope, headaches, amaurosis, transient ischemic attacks, and strokes. A recent meta-analysis from Duarte et al. found a pooled stroke-TIA prevalence of 15.8% among patients with Takayasu's arteritis [17]. Stroke may be the initial presentation without other systemic symptoms. Bond et al. found in their study of 79 patients that 11.4% patients presented with acute ischemic stroke, 6.3% with TIA, and 1.3% with symptomatic intracranial hemorrhage [18]. In a more recent French study, the authors demonstrated that stroke has a significant impact on prognosis in Takayasu's arteritis patients since 59% of patients sustain neurological impairment, 35% had a recurrent stroke, and 24% suffered from epilepsy [19]. Several underlying mechanisms of ischemic stroke in Takayasu's arteritis are proposed, including arterial occlusion secondary to vasculitis and arterial thrombosis, proximal embolism (artery-to-artery embolism or embolism from cardiac disease), cerebral hypoperfusion due to hemodynamically significant stenosis or vascular steal, or rarely, carotid artery dissection, and moyamoya disease [18–24].

In the natural course of Takayasu's arteritis, a triphasic process has been suggested with initial systemic inflammation and pre-stenotic disease, progressing to stenotic or aneurysmal vascular injury, followed by a final stage of burnt out fibrotic disease [10, 14]. The duration and course of each of these disease phases varies between patients. The disease presentation appears to vary between different populations as well. Moriwaki et al. demonstrated in their study of a Japanese cohort, that female patients predominately present with pulselessness and dizziness. More of these patients also suffer from aortic regurgitation and prolonged severe inflammatory activity. On the other hand, Indian patients, of whom 37% were male, tend to present with headache and hypertension [25]. Kerr et al. demonstrated in the study of 60 patients, that 20% of patients had monophasic self-limiting disease, whereas 80% had a protracted course requiring medical therapy. Furthermore, about 50% of patients who achieved remission later relapsed of whom 88% demonstrated disease progression [11]. Ishikawa et al. reported the 15-year survival rates have improved from 79.9% (1957–1975) to 96.5% (1976–1990) in their study of a Japanese cohort [26]. Death resulted mostly from cerebrovascular disease and cardiac failure [13]. In the recent French nationwide study of 318 patients, Comarmond et al. found that 42.7% of patients with Takayasu's arteritis relapsed and 38.4% had vascular complications with mortality of 5% after a median follow up period of 6.1 years [27].

Imaging

Takayasu's arteritis is an idiopathic systemic inflammatory vasculopathy that typically progresses to result in end-organ ischemia. The heterogeneous nature of its clinical presentation, as outlined above, frequently leads to delayed diagnosis. Even once the diagnosis is established, it is not easy to accurately monitor disease activity,

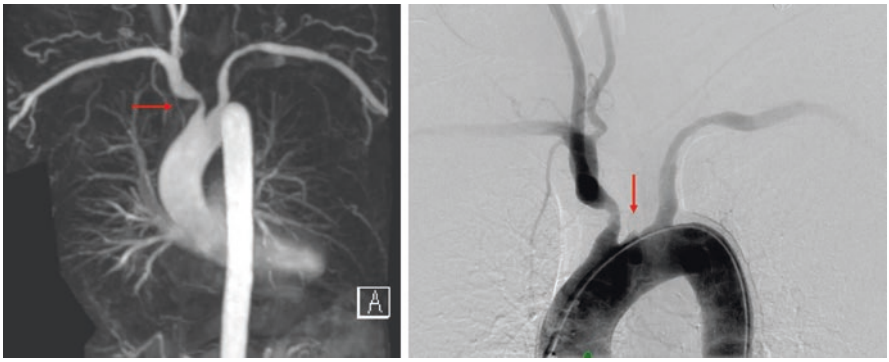

Fig. 16.1 Aortic arch in a patient with Takayasu's Disease. MRA on the left shows moderate-to-severe narrowing involving the proximal innominate artery (arrow). The left common carotid artery is occluded near the origin. There is luminal irregularity within the proximal left subclavian artery. Figure on the right shows angiographic view of the arch confirming MRA findings. There is only a proximal stump seen for the left common carotid artery (arrow)

progression, and response to therapy. In addition to a comprehensive clinical assessment, vascular imaging techniques play an important role in this setting. Imaging studies may be utilized to detect inflammation within the affected arterial wall and the presence or absence of clinically relevant vascular damage, such as steno-occlusive lesions, dilatation, aneurysm formation, or thrombosis (Fig. 16.1), and can aid in diagnosis and treatment decisions. The demonstration of arterial wall inflammation and detection of multiple large vessel lesions with luminal abnormalities in the correct clinical setting are clues to the diagnosis of Takayasu's arteritis. Moreover, the demonstration of arterial wall inflammation may provide a useful tool to assess disease activity and monitor response to therapy during the progression of Takayasu's arteritis. Different imaging modalities which allow for analyzing arterial morphology and/or functional characteristics of the vessel wall include ultrasonography, echocardiography, MRI, MRA, CTA, PET, and intra-arterial angiography [28–32].

High-resolution color doppler ultrasound can be used to assess the common carotid and proximal subclavian arteries, which can aid the diagnosis of Takayasu's arteritis. Vascular ultrasound may demonstrate the characteristic macaroni sign in Takayasu's arteritis, namely a circumferential midechoic thickening of the arterial wall of the affected arteries, indicating underlying vessel wall edema [33, 34]. Furthermore, duplex ultrasound provides information about blood flow and estimates blood flow velocities, allowing functional evaluation of stenotic segments, which makes ultrasound a valuable tool for monitoring disease progression and to guide management [35]. Abdominal ultrasound may be used for screening abdominal aortic aneurysmal dilation. More recently, microbubble contrast-enhanced ultrasound (CEUS) was shown to be able to improve the depiction of the blood vessel wall, enhancing the arterial lumen, and allowing detection of adventitial neovascularization, which may represent the main portal of entry for inflammatory cells into the arterial wall [36, 37]. Recent evidence by Giordana et al., suggests that carotid CEUS may be used to diagnose and monitor treatment response in Takayasu's arteritis [38, 39]. They reported that on carotid CEUS, the pretreatment scan demonstrated a

marked arterial wall thickening with multiple vasa vasorum in a patient with Takayasu's arteritis. These ultrasound imaging abnormalities changed progressively under steroid treatment with markedly reduced arterial wall and vasa vasorum enhancement, which correlated with a dramatic improvement of patient's symptoms. The advantages of ultrasound imaging include noninvasiveness, widespread availability, non-expansiveness, and lack of ionizing radiation. The main limitations are its inability to insonate through bone and operator-dependence.

Conventional intra-arterial angiography is an important imaging modality for diagnosis and accurate visualization of the aorta and its branches. It also facilitates preoperative assessment and surgical planning. Its drawbacks include invasiveness and the inability to delineate the arterial wall and periarterial structures. Therefore, it may fail to detect the early pre-stenotic disease process in which arterial wall inflammation is present with preserved lumen diameter [40].

In contrast, iodine or gadolinium contrast-enhanced CTA or MRA can analyze both arterial luminal morphology and detect vessel wall inflammation. In early vasculitis, CT angiography typically shows concentric mural thickening of the affected arteries [41, 42]. On pre-contrast imaging, the inflamed arterial wall can be differentiated from normal vascular lumen by higher attenuation. However, in healthy controls, the aortic wall could not be identified on pre-contrast images and transverse arterial-phase CTA revealed an aortic wall of less than 1 mm thickness [43, 44]. On post-contrast images, a double ring enhancement pattern due to poorly enhanced swollen intima and a more obviously enhanced outer ring of inflamed media and adventitia is typical of early-phase Takayasu's arteritis [44, 45]. In advanced disease, CTA is useful in identifying complications such as aneurysms, steno-occlusive lesions, and thrombosis [42]. Compared with conventional angiography, the sensitivity and specificity of CTA in the diagnosis of Takayasu arteritis involving the thoracic aorta and its major branches was 95% and 100%, respectively [46]. Furthermore, coronary CTA can help identify coronary artery involvement in Takayasu's arteritis [47, 48]. Kang el al. demonstrated in their cohort of 111 patients with Takayasu's arteritis that 53% of patients had coronary artery lesions (mainly coronary ostial stenosis, non-ostial coronary arterial stenosis, and coronary aneurysm) on coronary CTA [47]. CTA benefits from its widespread availability and short scan time, however the drawbacks are exposure to ionizing radiation and risks associated with the use of iodinated contrast material. In contrast, MRI is attractive for diagnosing Takayasu's arteritis, monitoring disease progression, and identifying relapse, particularly in the characteristically young affected population, due to high-resolution depiction of both arterial wall and lumen and the advantage of avoiding radiation. Time of flight (TOF) MRA is the most frequently used non-contrast enhanced MRA technique, which can be useful in patients with contraindications to contrast. Contrast-enhanced MRA can provide assessment of vessel lumen with improved spatial resolution [49]. Another added benefit of MRI in assessment of Takayasu's arteritis is the possibility to perform cardiovascular MRI (CMR) to allow the evaluation of cardiac complications by assessing myocardial function and aortic regurgitation in addition to imaging the aorta and its branches [50, 51]. Limitations of MRA include overestimation of the degree of vessel stenosis, longer scan times, artifacts and safety concerns related to implanted devices.

[18F]-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is increasingly used in the evaluation of patients with Takayasu's arteritis. [18F]-FDG is a radiolabeled glucose analog and [18F]-FDG-PET imaging utilizes the metabolic accumulation of deoxyglucose in activated inflammatory cells in the affected vessel wall [52]. Generally, more intense uptake than that of the liver is considered specific for vasculitis [53, 54]. The accumulation of radiolabeled deoxyglucose is useful in diagnosing Takayasu's arteritis in the early pre-stenotic stage and it reveals the extent of the disease by delineating the arterial wall inflammation [37, 55, 56]. The reported ranges of sensitivity for FDG-PET are 65%- 100% in the diagnosis of Takayasu's arteritis [56, 57]. Although PET has a relatively poor spatial resolution, the combination of PET images with CTA or MRA has been shown to improve the diagnostic accuracy with better visualization of the arterial wall abnormalities and more precise anatomical localization of functional data [58–61]. Furthermore, data from a recent prospective study to assess the use of PET-CT in patients with Takayasu's arteritis and giant cell arteritis versus those with diseases mimicking large vessel vasculitis or healthy controls, demonstrated that FDG-PET scan activity during clinical remission may predict future clinical relapse [62]. Thus, PET scans provide a valuable tool not only for early diagnosis of Takayasu's arteritis, but also for disease monitoring. A limitation of [18F]-FDG-PET imaging is the lack of specificity for inflammatory cells, since FDG is taken up by any metabolically active tissue. More recently, a novel PET ligand [11C]-PK11195, specifically binding to the translocator protein (TSPO), which is highly expressed in monocytes and neutrophils, has been investigated in diagnosing Takayasu's arteritis [63, 64]. Pugliese et al. reports that [11C]-PK11195 PET-CTA imaging demonstrated markedly increased arterial wall uptake in all 6 symptomatic patients with Takayasu's arteritis or giant cell arteritis, but in none of the asymptomatic controls [65]. Second-generation radiolabeled ligands with longer physical half-life are being tested for wider clinical applications [66].

In addition to the above-mentioned imaging modalities, transthoracic (TTE) and transesophageal (TEE) echocardiography is used to evaluate cardiovascular complications in the course of Takayasu's arteritis, including aortic valve insufficiency, aortic root dilatation, and myocardial disease. TTE is generally the first test used to assess the ascending aorta and aortic valve and provides valuable information about anatomical and functional characterization of the aortic root and aortic valve. Compared with TTE, TEE is more invasive, but provides superior high-resolution images and is useful in identifying aortitis complications such as aortic dissection and intramural hematoma [29].

Work Up and Management

Work Up

Takayasu's arteritis is a rare large vessel vasculitis affecting predominantly young adults, associated with substantial morbidity and mortality. It is essential to make the diagnosis early, ideally in the pre-stenotic phase, so that aggressive treatment

can be initiated to prevent vital organ damage. Clinicians should have a high level of suspicion to include the disease as part of the differential diagnosis in patients with suggestive clinical findings. Comprehensive clinical assessment includes detailed history-taking, careful physical examination, measurement of systemic inflammation using analysis of acute phase reactants as well as utilizing appropriate imaging modalities. The 1990 American College of Rheumatology (ACR) selected six criteria for the traditional classification of Takayasu's arteritis [67]: (1) onset at age less than or equal to 40 years, (2) claudication of an extremity, (3) decreased brachial artery pulse, (4) greater than 10 mm Hg difference in systolic blood pressure between arms, (5) bruit over the subclavian arteries or the aorta, and (6) arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The diagnostic sensitivity and specificity were 73.6% and 98.3% respectively and there is recognized need for updated classification and diagnostic criteria for large vessel vasculitis [68]. For example, Yoshida et al. has demonstrated that age is not an absolute diagnostic criterion, with 15–20% of patients with Takayasu's arteritis having a disease onset after 40 years of age [69]. Furthermore, noninvasive imaging techniques, which have improved diagnostic sensitivity, should be included in the updated ACR criteria.

In young patients presenting with the above mentioned signs and symptoms, or with an unexplained acute phase response or hypertension, further investigation is warranted. There are no specific diagnostic laboratory tests such as specific autoantibodies or other serologic abnormalities for Takayasu's arteritis [70]. The measurement of acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), certainly provide a useful tool to support the presence of a systemic inflammatory process. However, they do not reliably identify vascular inflammation and disease progression [11, 13, 14, 71]. Moreover, active disease can be present in the setting of normal ESR and CRP levels [11, 71].

Vascular imaging techniques provide a valuable tool for the diagnosis of Takayasu's arteritis, localizing its disease activity, and establishing the extent of vascular involvement at baseline, routine follow up, and evaluation of treatment response. Multiple modalities provide distinct and often complimentary imaging findings, guiding clinical management. Noninvasive methods are obviously more desirable and appropriate. Doppler ultrasound is easily applied to the extracranial vessels and can measure the arterial wall thickening and luminal narrowing of the most commonly affected carotid and proximal subclavian arteries. In addition, it may provide complimentary information to MRA or CTA hemodynamics [29]. For the diagnosis of those suspected to have early pre-stenotic disease, [18F]-FDG-PET-CT is a well suited diagnostic imaging modality by detecting arterial wall inflammation [1]. A thorough assessment of the arterial tree of the chest, head and neck, abdomen or other areas by MRA or CTA to determine the luminal configuration and vessel wall thickness is recommended upon diagnosis [72]. MRA is the favorable choice for long-term follow up to monitor disease progress due to lack of radiation exposure.

The diagnosis of Takayasu's arteritis is seldom made by histopathological findings due to the lack of easy access to biopsy material. Histological examination is limited to those cases undergoing revascularization procedures or aneurysm repair.

The histopathological findings can be helpful in establishing diagnosis and determining the state of the disease (e.g. active inflammation versus inactive fibrosis), which may lead to changes in disease management.

Management

Management of patients with Takayasu's arteritis is challenging, mostly due to uncertainty of the disease course, difficulties in assessing actual disease activity, and response to treatment. The combination of clinical data consisting of assessment of patient symptoms, measurement of acute-phase reactants and the findings of imaging studies should be utilized to search for active disease, monitor disease progression, and to help guide management. In addition, it is important to recognize prognostic predictors of Takayasu's arteritis, which may help identify a subset of patients who require more aggressive therapy and close follow-up. Ishikawa et al. found that the presence of either a major complication (Takayasu retinopathy, secondary hypertension, aortic regurgitation, or aneurysm) or a progressive course were predictors of poor outcome. The presence of both a major complication and progressive course was the worst prognostic indicator with a survival rate of 43% at 15 years. No patient died in the uncomplicated disease group [26]. More recently, Comarmond et al. identified male gender, elevated CRP level, and carotidynia as risk factors associated with relapse of Takayasu's arteritis. Furthermore, they reported that a progressive disease course and retinopathy were associated with an increased risk of vascular complications by 2 and 3.4-fold, respectively [27].

The rationale of medical treatment is to suppress both vascular and systemic inflammation with appropriate immunosuppression. The major therapeutic goal is to prevent arterial disease progression, such as stenosis or aneurysm formation. Corticosteroids form the mainstay of therapy for Takayasu's arteritis. Evidence suggests that corticosteroid therapy alone can achieve clinical remission, or at least once, in up to 60% of patients [11, 73]. Hall et al. showed in their study that eight of 16 steroid treated patients had a return of absent arterial pulsation after a delay of a few months [14]. However, in up to one-half of all patients with Takayasu's arteritis, corticosteroid therapy alone does not provide sustained remission and relapses are frequently observed when corticosteroids are tapered [74]. In this setting, treatment with conventional immunosuppressive agents such as methotrexate, azathioprine, and cyclophosphamide are required [73, 75, 76]. The additional benefit of conventional immunosuppressive agents is to minimize potential adverse effects of corticosteroids. A small open-labeled study of methotrexate in 16 steroid unresponsive patients demonstrated disease remission in 81% of patients. However, 44% of patients relapsed when the steroids were weaned off [74]. In cases of refractory disease, biological-targeted therapy with TNF-alpha and anti-IL-6 antagonists such as etanercept, infliximab, and tocilizumab may be tried with reported control of disease activity in 60–70% of patients [77, 78]. In a randomized, placebo-controlled trial of tocilizumab in 36 patients with refractory

Takayasu's arteritis, tocilizumab had favorable outcomes over placebo in regard to time to relapse [79]. Overall, despite the above outlined medical therapy, disease relapse is not uncommon during the course of Takayasu's arteritis, particularly if treatment is tapered. Thus, detailed follow up with vessel imaging studies is essential, initially every 6 months, to monitor response to therapy and disease progression [80, 81].

In cases of symptomatic steno-occlusive lesions or aneurysmal dilatation, endovascular interventions and surgical procedures may be indicated [82–84]. Indications for vascular intervention include stenotic-occlusive lesions leading to cerebral or cardiac ischemia, uncontrolled hypertension secondary to critical renal artery stenosis, aneurysmal enlargement with risk of rupture, and severe aortic regurgitation. In general, surgery should be performed during inactive disease periods to avoid complications such as re-stenosis, formation of anastomotic aneurysms, and thrombosis [85, 86].

Finally, the other important aspect of treatment in Takayasu's arteritis is management of associated cardiovascular risk factors and complications, which includes hypertension, accelerated atherosclerosis due to inflammation, pulmonary hypertension, cardiac failure, and stroke. This emphasizes the need to take a multidisciplinary approach when managing patients with Takayasu's arteritis.

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Chapter 17
Carotid Body Tumors: Pre-operative Management and a Review of the Literature

Karen S. Chen, Juan Vicenty-Padilla, and M. Ali Aziz-Sultan

Introduction: Pathology and Clinical Presentation

Carotid body tumors (aka Carotid paragangliomas or Glomus caroticum) are tumors that originate from the carotid body. This diminutive yet important structure belongs to a system grouped as the autonomic paraganglia. These small organs are mainly composed of glomus cells, a non-neuronal, neural crest derived tissue that has a close association to the autonomic system. Normally, these reside along nerves and vessels to detect physiological alterations and, through the secretion of neurotransmitters, have an important role in regulating homeostasis through autonomic responses. The carotid body's normal function as a chemoreceptor is to detect changes in blood oxygen and carbon dioxide levels and signal responses in respiration and vasomotor activity via the glossorpharyngeal nerve (Hering's nerve) and sympathetic nervous system [1, 2].

Glomus tumors or paragangliomas are neoplasms of the autonomic paraganglia and consequently come in two flavors: parasympathetic and sympathetic. The glomus cells receive input from the sympathetic nervous system and secrete catecholamines that bring them to clinical attention from paroxysmal hypertension associated with headache, palpitations, and sweating [3]. Sympathetic paragangliomas can exist anywhere in the body along the parasympathetic chain of the thorax, abdomen, and pelvis. They tend to favor (75% of the time) the abdomen in the organ of Zuckerkandl flanking the aorta just proximal to the iliac bifurcation or the sympathetic plexus of the urinary bladder or kidneys [4]. When located in the adrenal gland, sympathetic paragangliomas are called pheochromocytomas. This distinction is important because of its clinical implications for multifocality, risk of malignancy, and genetic testing [5].

K. S. Chen (✉) · J. Vicenty-Padilla · M. A. Aziz-Sultan
Brigham and Women's Hospital, Harvard Medical School, Department of Neurosurgery, Boston, MA, USA
e-mail: kchen21@bwh.harvard.edu; jvincenty-padilla@bwh.harvard.edu; asultan@bwh.harvard.edu

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Parasympathetic paragangliomas receive input from the parasympathetic nervous system but are generally thought of as nonfunctional [4] and are oftentimes discovered due to cosmesis or a palpable neck mass [6]. Otherwise, they present with extrinsic compression, arising in four distinct locations: along the Jacobson's nerve of CN IX at the cochlear prominence in the middle ear (tympanicum), along Arnold's nerve of CN X in the jugular foramen (jugulare), the vagus nerve within the carotid sheath of the cervical ICA (vagale), or at the carotid body nestled within the carotid bifurcation (caroticum). Because of these locations, patients can present with hoarseness, dysphagia, Horner's syndrome, facial palsy, or tinnitus. Paragangliomas of the head and neck are associated with known mutations in approximately 18% [7] of nonfunctional tumors, but 49% [8] of secreting tumors. Hereditary syndromes associated with paraganglioma and pheochromocytoma include multiple endocrine neoplasia types 2A and 2B, neurofibromatosis type 1, von Hippel Lindau, and Carney-Stratakis syndrome with mutations in VHL, RET, NF1, and SDH (SDHD, SDHB, SDHC) [3, 7, 8].

Although less than 5% of paragangliomas are functional [9], biochemical screening is necessary to avert potentially life threatening cardiovascular complications due to neurosecretory imbalances. Sensitive urinary or plasma assays for catecholamines such as epinephrine, norepinephrine, and dopamine or its metabolites (metanephrine and normetanephrine) should be evaluated preoperatively, keeping in mind that secretion may be sporadic [10].

The most common paraganglioma of the head and neck region is glomus caroticum, [9] (Fig. 17.1) while the glomus vagale (Fig. 17.2) is much more rare. In fact, some studies report that carotid body tumors account for 60% of the cases of head

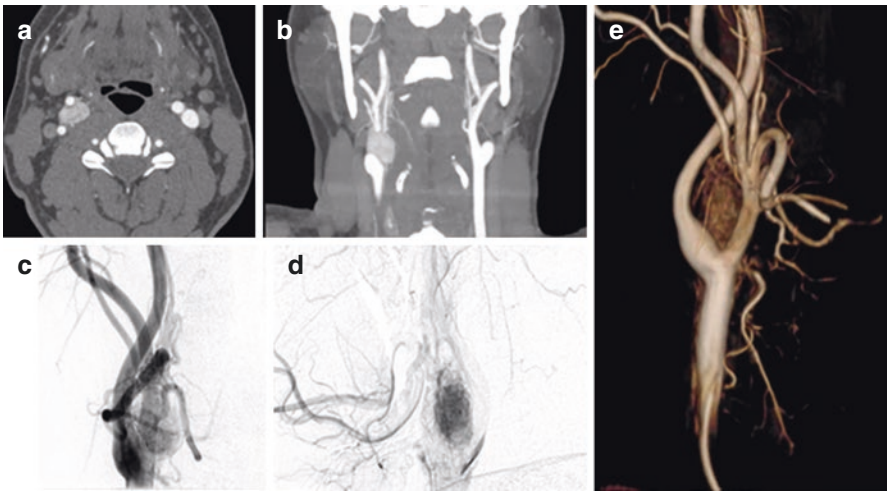


Fig. 17.1 Axial (**a**) and coronal (**b**) MIP CT images demonstrating an avidly enhancing mass splaying the right internal and external carotid artery origins. The mass is centered within the carotid bifurcation. AP (**c**) and lateral (**d**) digital subtraction angiograms demonstrate late arterial (AP) and capillary phase (lateral) images of the tumor with dense contrast staining. 3D shaded surface display (**e**) image demonstrating carotid body tumor

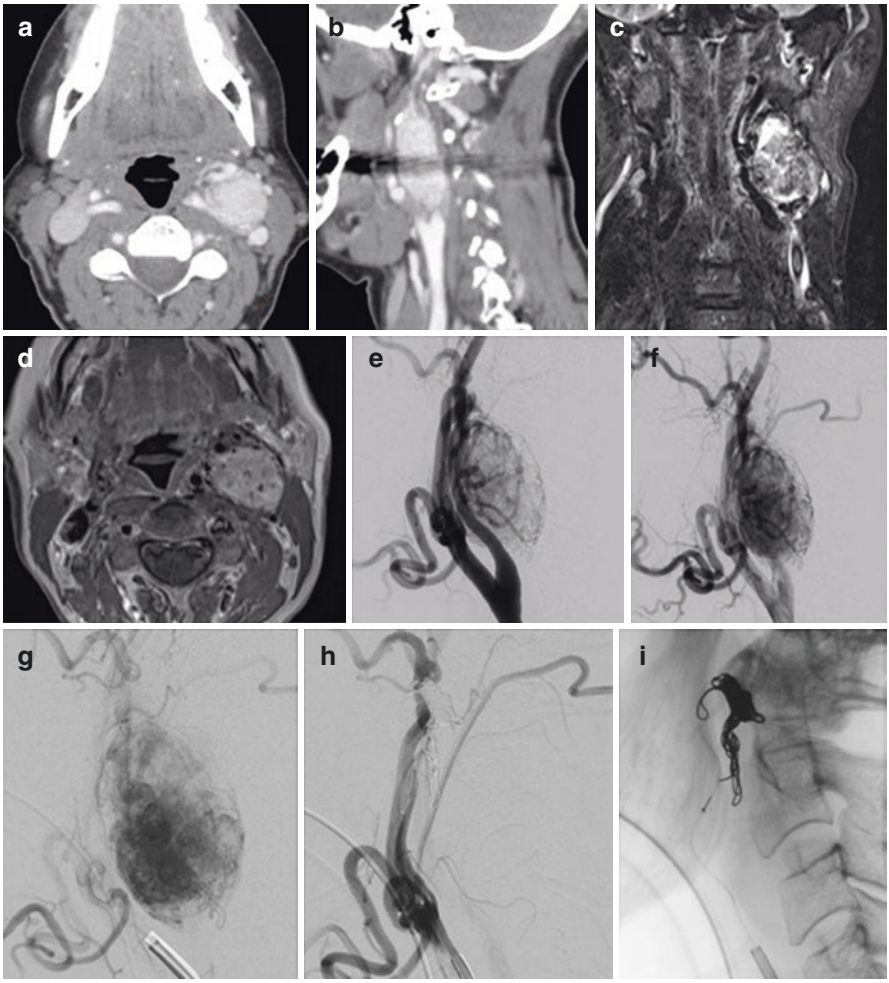


Fig. 17.2 Glomus vagale tumor is a less common type of glomus tumor, but is often confused for a glomus caroticum. Contrast enhanced axial (**a**) and sagittal (**b**) CT views demonstrate an avidly enhancing tumor within the carotid sheath, slightly above the bifurcation. Internal carotid and external carotid arteries are not splayed but displaced anteriomedially. Coronal STIR (**c**) and axial post contrast T1 weighted (**d**) images demonstrate a T2 hyperintense enhancing (isointense on pre contrast T1 sequences) mass of the carotid sheath. Dark flow voids against the background of a T1 hyperintense tumor demonstrate the classic "salt and pepper" appearance of a glomus tumor. Left common carotid digital subtraction angiography demonstrates an avidly enhancing mass in the early arterial (**e**), late arterial (**f**), and capillary (**g**) phase *above* the carotid bifurcation. Subtracted (**h**) and unsubtracted (**i**) post 100–300 micrometers embospheres and coil embolization of the ascending pharyngeal artery angiography demonstrates complete devascularization of the tumor. Estimated operative blood loss was 50 cc

and neck paragangliomas [11]. As mentioned, a clear majority of these tumors are found as painless, slow growing masses of the anterior cervical triangle with or without associated compression neuropathy of the vagus or hypoglossal nerve. Occasionally, some carotid paragangliomas may extend cephalad and invade the skull base and cause lower cranial nerve palsies. The natural history is unclear and has subsequently led to multiple debates in the literature regarding its management.

Cervical Anatomy

To better understand these entities a thorough knowledge of the regional anatomy is of the utmost importance. A precise understanding of the parapharyngeal and carotid space and their neurovascular interactions is mandatory.

- **Carotid Space:** The carotid sheath serves as the boundary for this region and can be divided in two vertical segments with the hyoid bone as its dividing mark. The superior space or suprahyoid compartment extends to the skull base and contains the internal jugular vein, internal carotid artery, cranial nerve 9–12 and sympathetic plexus. The infrahyoid space drops to the thoracic outlet and contains the bifurcation, common carotid artery and internal jugular vein [12].
- **Parapharyngeal space:** This space is intrinsically associated to the superior carotid space. It is commonly described as an inverted pyramid. The roof limit is the temporal bone and its inferiorly pointing tip is the hyoid bone. Its medial limit is the buccopharyngeal fascia while its lateral limit is defined as the pterygoid muscle's fascia. Important neurovascular structures reside in the interior of this fat-filled potential space. Some of these structures are cranial nerves IX-XII, as well as the internal carotid artery and the internal jugular vein [13].
- **Vascular relationships:** CBTs arise within the adventitia of the posteromedial carotid bifurcation in a small cluster of cells known as the carotid body. The carotid bifurcation itself, although classically defined as located at the C3–4 vertebral region, is highly variable in its vertical position. This ultimately may compromise surgery of pathologies at this location, and in extreme instances, may require additional surgical maneuvers such as styloidectomy, mandibulotomy or mandibular subluxation [14]. Most CBTs will be supplied by branches of the external carotid artery, specifically the ascending pharyngeal artery as well as the vasa vasorum of the carotid. Typically the ascending pharyngeal will be observed as abnormally enlarged [15]. Besides the aforementioned arterial relationships, either due to direct tumor adherence or surgical manipulation, special care must be taken with the internal jugular system since many series have described direct injury or need for sacrifice [16].
- **Neural relationships:** The anatomy related to CBTs is simplified by using the vertical divisions of the carotid space, Some series have described the vagus nerve as the most common transitory or permanent nerve injury, followed by the hypoglossal neve; although injury to the glossopharyngeal, spinal accessory, and

Table 17.1 Common neurological complications of CBT surgery

Operative management of CBT: neurological complications	
Stroke	Sympathetic fiber injury
Hypoglossal nerve injury	Spinal accessory injury
Glossopharyngeal nerve injury	Marginal mandibular branch injury
Superior laryngeal nerve injury	Vagal nerve injury

superior laryngeal nerves can be encountered [17]. The longitudinal course of the vagus nerve through the carotid sheath makes it particularly vulnerable to both tumor involvement and manipulation. The vagus nerve also sends important laryngeal branches via the superior laryngeal nerve on the posteromedial aspect of the bifurcation or internal carotid artery. On the other hand, the hypoglossal nerve, although variable in its location, has a close association (antero-lateral) to the carotid bifurcation. Cranial nerve IX can be affected by vertical tumor extension to the infratemporal fossa, as well as through its natural innervation of the carotid body through Hering's nerve. Sympathetic injury to the postganglionic fiber can occur as internal carotid dissection takes place. Some of the most common neurologic complications are best summarized for the reader in Table 17.1.

Preoperative Assessment

The management of carotid body tumors (CBT) has been extensively discussed in the literature. It has been widely accepted that excision through surgery remains the gold-standard for a definitive cure [18]. Surgical resection is a challenge not only due to its inherent association to the carotid bifurcation and both external and internal carotid arteries; but also, due to its size, cranial extension, and degree of vessel infiltration or encasement [18]. The anatomic relationship of nervous and venous structures contributes considerably to the task of resection as well [19]. A comprehensive perioperative plan will aid in reducing the cost of morbidity and mortality of this complex pathology [2, 20–24]. That is why in 1971, Shamblin et al., proposed a combined anatomical and radiological classification as an aid to the surgical plan [2] (Table 17.2). This important classification emphasized the need of a stepwise approach to these entities to avoid major surgical complications [21]. However, although still widely used, the original Shamblin classification does not specifically address tumor size and does not predict the likelihood of vessel infiltration [22]. Also, some authors have stressed the fact that the original classification does not anticipate the risk of postoperative complications [23]. Nevertheless, Shamblin's classification was a milestone in carotid body tumor surgery and has led the way towards other more comprehensive classifications that take into account other elements. Two of these proposed classifications are by Luna-Ortiz et-al [25] and Prasad et al. [24]. The first one specifically addressed tumor size and degree of vessel infiltration. As mentioned before, tumor size does not necessarily entail vascular infiltra-

Table 17.2 Shamblin classification of carotid body tumors [2]

Type I	Small Localized tumor. Dissected in peri-adventitial plane
Type II	Large and adherent tumor. Subtotal vessel encasing.
Type III	Large tumor with total vessel encasement.

Table 17.3 Luna-Ortiz et al. modified Shamblin classification of carotid body tumors [22]

	Size	Vessel encasement or infiltration	Excision
Type I	<4 cm	None	No difficulty
Type II	>4 cm	Partial	Difficult
Type IIIa (original III)	>4 cm	Intimate	Difficult, may need vascular sacrifice or vessel replacement
Type IIIb (original I, II or III)	Any size	Intimate	

tion (Table 17.3). This classification also anticipates the risk for intraoperative vascular sacrifice and risk of neurologic injury. In a separate publication, Prasad et al. described how the association of the CBTs to the concept of circumferential involvement of the internal carotid artery [26] and its vertical extension to the parapharyngeal space and infratemporal fossa may require preoperative stenting, as well as possible intraoperative sacrifice of nerves [24] (Table 17.4).

Some have suggested that these modified classification systems more accurately reflect neurovascular morbidity [22], which ranges from 0% to 38% [6, 17, 25, 27–30] in the perioperative period and is invariably related to carotid vessel damage. In-hospital mortality has been reported at 5% [31], while cranial nerve specific morbidity is reported to range from 7% to 40% [6, 31–34]. A 2015 review reported an overall rate of 4%; there were 23 permanent cranial nerve injuries in 526 carotid body tumors removed from 465 patients [34].

Other factors must be taken into account when planning carotid body tumor intervention. Although a majority of these tumors are metabolically silent, some may possess epinephrine-related granules. That is why screening with urine or serum metanephrines is sometimes undertaken in the perioperative period. Also, due to the possibility of laryngeal nerve damage by these tumors, a preoperative vocal cord assessment is sometimes warranted. The anesthesiologist should also assess the probability of a difficult airway and hemoglobin status due to high volume blood loss.

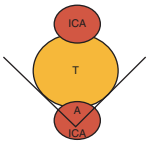
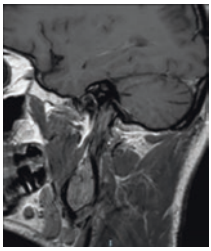
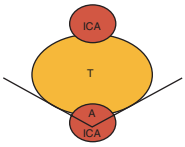
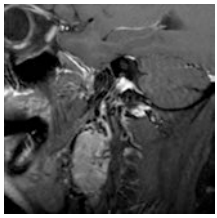
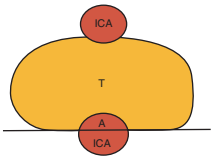
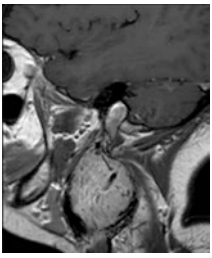
Preoperative Angiography

Preoperative angiography is used to delineate tumor blood supply, confirm diagnosis, and evaluate for multifocal/contralateral disease (Figs. 17.1 and 17.2). Supply typically originates from small branches of the ascending pharyngeal artery, occipital artery, thyrocervical trunk, and even penetrating arteries of the adventitia when

the tumor becomes intimately associated with the carotid artery wall [35]. Preoperative angiography also affords the opportunity to perform balloon test occlusions and preoperative embolization.

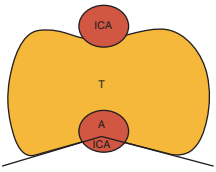
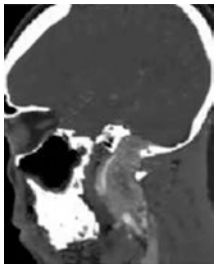
Balloon occlusion of the ICA ipsilateral to the tumor tests whether the patient would tolerate vessel sacrifice during surgery. A contrast filled balloon is navigated to the internal carotid artery, just beyond the carotid bulb along a straight segment of the cervical ICA. The balloon is inflated and gentle test injections of contrast

Table 17.4 Prasad et al. classification on carotid body tumors [24]

Tumor type	Description	Extent	Intn-arterial stenting	Approach
Class I	Tumor is limited to the carotid bifurcation (lower compartment of the porapharyngeal space) Tumors with an angle of contact of <90 degrees with the wall of the internal, external or the common carotid 		Not indicated	Transcervical approach
Class II	Tumor is limited to the middle compartment of the parapharyngeal space Tumors with an angle of contact of >90 degrees but <180 degrees with the wall of the internal, external or the common carotid 		Not Indicated	Transcervical (±transparotid) approach
Class III	Tumors extending into the upper compartment of the parapharyngeal space +/- infratemporal fossa Tumors with an angle of contact of 180 degrees with the wall of the internal, external or the common carotid 		Indicated	Transcervical-transmastoid approach

(continued)

Table 17.4 (continued)

Tumor type	Description	Extent	Intn-arterial stenting	Approach
Class IV	Tumors extending into the upper compartment of the parapharyngeal space and infratemporal fossa and involving the jugular bulb Tumors with an angle of contact of >90 degrees with the wall of the internal, external or the common carotid 		Indicated	Infratemporal Fossa Approach type A

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proximal to the balloon confirm complete occlusion. Then the patient is tested for symptoms of stroke including speech, strength, sensation, attention, and visual fields. Compensatory circulation is further stressed by driving the patient's blood pressure 20 mmHg below baseline with repeat neurologic testing. Alternatively, a second catheter can be used to perform cerebral angiography of the contralateral ICA to assess hemispheric capillary and venous phases while the balloon is inflated. A >2 second delay in visualization of the venous phase ipsilateral to the occluded ICA would constitute a failed test suggesting intolerance of carotid sacrifice. A third variation for balloon test occlusion utilizes the first pass effects of technetium labeled HMPAO, which is administered intravenously. The agent reaches the brain via the contralateral ICA and passively diffuses across the lipophilic membrane at a relatively high first past rate, mimicking compensatory perfusion if the ipsilateral ICA were no longer patent. Despite the multiplicity of tests, post ligation mortality and morbidity in patients demonstrating adequate flow on BTO ranges from 22% to 44% [36–38] in small case series reports.

Preoperative Transarterial Embolization

Reports of preoperative embolization up to the year 2000 heavily utilized embolic particles, measuring 150–500 microns, and gelfoam (Table 17.5). Later studies reveal an increased use of liquid embolic agents and coils, corresponding to the uptick in coil suppliers and the introduction of Onyx into the market in 2005 [39].

To date, there are no randomized controlled studies examining the effect or incremental morbidity associated with preoperative embolization. There have been

Table 17.5 Single arm studies for transarterial embolization

Study ID	Year	No pts./tumors/ glomus/surgery/ TA					Agent	Operative time (min)	Blood loss (ml)
Schick	1980	1	1	1	0	1	Ivalon sponge emboli	NR	4000
Kumar	1982	6	6	3	0	3	Microfibrillar collagen	NR	NR
Hennessy	1984	1	1	1	0	1	Gelfoam	NR	NR
DuBois	1987	1	2	2	0	2	PVA 250–500 microns	NR	NR
Iafrati	1999	1	1	1	0	1	Not reported	NR	NR
Kafie	2001	2	2	2	0	2	Onyx, embolyx	NR	200
Horowitz	2002	1	1	1	0	1	100 alcohol	NR	NR
Persky	2002	47	53	53	0	53	Multiple agents, not listed	NR	CBT: 517, VP 450, JP 494
Yilmaz	2003	5	5	5	0	5	PVA 100–500 microns	NR	100–250
Puggioni	2005	1	1	1	0	1	PVA	NR	NR
Pecorari	2008	1	1	1	0	1	PVA 150 microns	NR	450
Siedek	2009	6	6	6	0	6	Coils, cyanoacrylate	NR	NR
Hall	2010	1	1	1	0	1	Not reported	NR	NR
Gemmete	2011	1	1	1	0	1	Coils and embospheres	NR	NR
Shah	2011	7	7	7	0	7	Onyx	NR	55 (embo only)
Yang	2011	2	2	2	0	2	1:3 nBCA	NR	<100
Alaraj	2012	1	1	1	0	1	Onyx and covered stent in ICA	NR	500
San Noberto	2012	1	1	1	0	1	Poloxamer 407	78	115
Cvjetko	2013	1	1	1	0	1	Coils	NR	230
Kalani	2013	11	13	13	0	12	Onyx (9), onyx and coils (1), nBCA (2)	NR	192
Griauze	2013	27	27	27	0	17	PVA 100–500	276	475

NR not reported, *CBT* carotid body tumor, *VP* vagal paraganglioma, *JP* jugulotympanic paraganglioma, *PVA* polyvinyl alcohol embolic particles, *TA* transarterial embolization

numerous reviews compiling a large number of case reports and small volume case series which have reported conflicting results [34]. Many single arm studies have reported outcomes such as intraoperative blood loss, operative time, and complication rates (Table 17.5) for those undergoing transarterial embolization with or without adjunct maneuvers including covered stent placement [40, 41], temporary balloon inflation in the ICA or ECA [29, 42–49], or direct puncture embolization (Table 17.6). Mean operative blood loss ranges from 50–4000 cc for those who go on to surgical resection [50, 51]. There have been reports of TIA [27, 29, 52–55], strokes [17, 27, 53, 56–60], death [30, 61], and vessel sacrifice from nontarget embolization [41]. Many small case series do not support the use of preoperative embolization with regard to intraoperative blood loss [23, 53, 56, 62–65], operative time [23, 52, 53, 56, 60, 65], hospital stay [32, 53, 56, 58, 66], or perioperative morbidity [56]. Other studies comparing the two techniques found that preoperative

Table 17.6 Small case series reporting use of adjunctive devices in transarterial embolization

Study ID	Year	No. pts	No. tumors	No. glomus tumors	Excision only	TA only	Agent	Adjunct treatment
Hennessy	1984	1	1	1	0	1	Gelfoam	Balloon inflated in ECA
Horowitz	2002	1	1	1	0	1	100 alcohol	Balloon occlusion ICA and distal ECA
Yilmaz	2003	5	5	5	0	5	PVA 100–500 microns	Balloon in ICA for 2 pts
Abud	2004	9	9	9	0	9	Glubran	Balloon occlusion of VA feeder in one jugulare tumor with TA: PVA
Krishnamoorthy	2007	1	1	1	0	1	nBCA	Balloon occlusion of the ICA
Wanke	2009	4	6	6	0	6	Onyx	Balloon occlusion proximal ICA
Li	2010	62	66	66	30	36	PVA 300–500 microns	ICA balloon inflated for 3 TA cases.
Avgerinos	2011	27	29	29	20	4	PVA	ECA covered stent in one pt. with TA and 4 ECA covered stents
Alaraj	2012	1	1	1	0	1	Onyx	Covered stent in ICA
Weigand	2010	1	1	1	0	1	Onyx	Balloon in ICA
Yang	2011	2	2	2	0	2	1:3 nBCA	Balloon occlusion ICA

TA transarterial embolization, *ECA* external carotid artery, *ICA* internal carotid artery, *VA* vertebral artery

embolization was associated with statistically significant decreased operative complexity, less ICA clamping, and less blood loss [60]. In fact, larger more recent studies have demonstrated the benefit of preoperative embolization for blood loss [29, 30, 40, 52, 60, 67–73], operative time [29, 30, 52, 56, 60, 67–70], and hospital stay [29, 67]. However there was no statistically significant impact on complications such as temporary or permanent cranial nerve injury, death, or stroke. This may be more a reflection of the diverse ways complications are reported in the literature and lack of statistical power to demonstrate much effect of any one type of complication. For example, some papers report total complication rates, inclusive of cranial nerve injury, vessel ligation or reconstruction, and stroke. Others report in

painstaking detail which patients present with existing cranial nerve deficits, cases where surgical resection of the nerve is performed, and individual permanent or temporary postoperative cranial nerve deficits. Because of the wide variation in reporting, these statistics should be interpreted with caution, particularly in subgroup analysis of relatively small cohorts. A comprehensive list of comparative studies with transarterial embolization is listed in Table 17.7.

Few studies have the sample sizes to control for known predictors of mortality and morbidity such as the Shamblin classification [30, 74]. Other studies should be interpreted with caution because many preoperative embolization cases are undertaken in larger more complex Shamblin type III tumors. Given that tumor size is a predictor of blood loss [52, 75], a non-statistically significant finding could reflect that embolization does not afford any operative benefit or it may indicate how embolization simplifies complex surgical cases [72].

The most compelling evidence for the efficacy of preoperative embolization comes from meta-analyses published in 2015 and 2019, which reported a statistically significant benefit of preoperative embolization in operative blood loss and operative time. There was no significant difference in tumor size between the two treatment cohorts [76]. The 2019 meta-analysis compiled results from 25 studies comprising 1326 patients and demonstrated statistically significant differences of operative blood loss (weighted mean difference − 135.32 [CI −224.58, −46.06], p = 0.000) and operative time (weighted mean difference − 38.61 [CI −65.61, −11.62], p = 0.000) [75]. In subgroup analysis, length of stay was shorter in the preoperative embolization group for those receiving embolization 24–48 hours prior to surgery. Cranial nerve palsy, stroke, or TIA were not statistically significantly different between the two groups in all three meta-analyses. A study using National Inpatient Sample data also found no mortality or stroke benefit, but could not comment on cranial nerve deficits, which were not recorded in this dataset [58]. An earlier meta-analysis of 12 studies comprising 295 tumors reported similar benefits of preoperative embolization on blood loss (OR -0.52 [CI −.77, −.28], p < .0001) [76]. For operative times, the meta-analysis found 6 reports comprising 174 tumors with adequate data also showing shorter operations for those undergoing preoperative embolization (−0.46, [CI −.77, −.14], p = 0.004). There was no significant difference in complication rates using limited dataset as many studies report complications for the entire cohort rather than by embolization status.

It is likely that these large studies are still insufficiently powered to perform meaningful risk assessment. This is highlighted by another meta-analysis which was published at the same time but included fewer studies for each outcome of interest [77]. Despite a large overlap in the reported studies included in this meta-analysis, 6 studies comprising 176 tumors were used to evaluate the effect of preoperative embolization on blood loss. While the point estimates were statistically significant in favor of embolization in the fixed effects model, the authors gave greater interpretive weight to the random effect model. Although the point estimate was even more in favor of the benefit of embolization, the confidence interval was wider rendering it non-significant. For operative time, the authors examined 3 studies comprising 105 tumors with similar findings to the prior meta-analysis, but

Table 17.7 Comparative studies comparing outcomes of glomus tumor resection with and without preoperative embolization

Study ID	Year	No of pts	Glomus tumors	Excision/ embolization		Agent	Operative time: NE vs TA (min)	Blood loss: NE vs TA (cc)
Ward*	1988	16	6	10	6	PVA 100–250 microns	280 vs 105	1375 vs 397
Robison	1989	6	7	2	5	Not reported	NR	332 (combined)
LaMuraglia	1992	17	19	8	11	PVA 150–300 microns, gelfoam	270 vs 246	609 vs 373
Fruhwirth	1996	16	18	15	3	Gelfoam and coils	NR	NR
Litle*	1996	21	22	11	11	PVA 200–500 micron	234 vs 306	764 vs 1123
Muhm	1997	24	28	14	8	PVA 250 microns	NR	NR
Tikkakowski*	1997	19	27	15	12	PVA 150–250 microns	288 vs 204	1374 vs 588
Westerband	1998	31	32	26	6	PVA	NR	NR
Ramos	1998	23	23	12	11	Not reported	No difference	No difference
Liapis	2000	18	18	13	3	PVA 150–300 microns, gelfoam	NR	700 vs 400
Wang	2000	29	36	18	17	Not reported	NR	625 vs 855
Dardik	2002	25	27	5	22	Not reported	NR	307 vs 395
Tasar	2004	17	18	3	18	Coils, coils, PVA 300–1000 microns	NR	NR
Antonitsis	2006	13	14	2	11	Microcoils	NR	NR
Kollert	2006	22	34	7	20	Not reported	NR	NR
Liu	2006	25	25	15	8	PVA 250–350 and gelfoam	NR	600 vs 238
Kasper	2007	20	25	12	13	PVA 100–750	NR	360 vs 365
Karatas	2008	1	3	1	2	PVA 355–500 microns	NR	NR

(continued)

Table 17.7 (continued)

Study ID	Year	No of pts	Glomus tumors	Excision/ embolization		Agent	Operative time: NE vs TA (min)	Blood loss: NE vs TA (cc)
Ozay	2008	14	14	9	5	Not reported	NR	411 vs 372
Karaman	2009	26	27	3	22	Microcoils	NR	NR
Martinelli	2009	12	15	8	7	Not reported	NR	NR
Vogel	2009	2117	NR	1686	129	Not reported	NR	NR
Zeitler	2010	25	25	15	10	PVA	NR	266 vs 305
Li*	2010	62	66	30	36	PVA 300–500 microns	225 vs 170	656 vs 355
Lim*	2010	13	15	7	6	PVA	360 vs 360	400 vs 550
Avgerinos	2011	27	29	20	4	PVA	NR	747 vs 301–415
Fennessy	2011	1	3	1	2	PVA	NR	NR
Gwon	2011	16	17	3	14	PVA and gelfoam	NR	NR
Nazari	2012	45	50	47	3	Not reported	NR	NR
Power*	2012	131	98	71	33	PVA 150–1000 microns	265 vs 250	599 vs 263
Zhang*	2012	32	32	11	21	PVA 150–500 microns, coils	220 vs 180	450 vs 280
Fruhmann	2013	50	63	55	8	Not reported	NR	NR
Sen	2013	32	34	19	15	Gelfoam, PVA	NR	NR
Bercin*	2015	13	13	6	7	PVA	160 vs 172	375 vs 283
Law*	2017	20	21	12	9	Not reported	269 vs 264	667 vs 530
Liu*	2018	58	58	27	31	Not reported	188 vs 111	140 vs 396
Basel	2018	104	114	100	14	Coils	NR	NR
Ikeda*	2018	150	94	18	76	Not reported	Shamblin class: 229, 262, 461	Shamblin class: 78, 229, 404
Zhang*	2018	29	29	18	11	PVA, coils, onyx, or combo	160 vs 120	200 vs 80
Arnold*	2009	15	15	5	4	PVA 300–450, gelfoam	180 vs 127	700 vs 150

PVA polyvinyl alcohol embolic particles, *NR* not reported, *NE* not embolized, *TA* transarterial embolization. Bold text highlights studies where operative time and blood loss were quantified allowing for comparison between embolized and non-embolized cases. Asterisk denotes studies reporting both parameters for meta-analysis [75]

again statistically non-significant in the random effects models. Ultimately, it is the authors' opinion that statistical power was insufficient in the latter study in light of the findings from the most recent meta-analysis where the random effects model was used along with a larger number of studies demonstrating a statistically significant benefit of preoperative embolization for intraoperative blood loss and operative times [75]. In all meta-analyses, there was no statistically significant effect on any complication including cranial nerve injury, stroke, TIA, or death.

Intratumoral Percutaneous Embolization

Direct puncture (Fig. 17.3) for preoperative embolization was developed for tumors whose feeding pedicles are too small to catheterize in 1992 in Paris [78]. Since then, there have been scattered reports of direct puncture alone with glue [43, 46, 47, 79–81] or onyx [48, 50, 81–83]; in combination with transarterial particle or liquid embolic agents [81] and with balloon assistance [43, 47]. There was one report of delayed migration of the glue cast with resulting hemiparesis and stroke [47]. In the remaining cohort, one case of transient hypoglossal nerve palsy [57] and another of transient mandibular [43] nerve palsy were reported, but without permanent neurologic deficits.

Complete devascularization was achieved in 19 of 61 cases (43%), although this is likely an underestimate since not all studies reported whether complete devascularization was achieved for each patient. One group reported their findings in two different papers with probable overlap, as evidenced by the re-use of illustrative case images in their studies (Fig. 17.1b [83], d [83] and Fig. 17.1c [84], f [84]). The earlier of which was not included in the above estimate. Table 17.8 lists studies reporting the use of direct puncture either for preoperative embolization or definitive therapy.

Further adjunctive techniques used to complement percutaneous embolization include covered stent placement [41, 85], temporary balloon occlusion [43, 44, 47], and concomitant endarterectomy [31, 58]. There are also reports of temporary intraoperative embolization of the ECA with a novel thermosensitive nonthrombogenic polymer [86]. Once the Shamblin type II tumor was excised, the polymer was dissolved with cold saline, restoring flow in the right ECA. Surgical management with case illustrations will be discussed in the following chapter.

Radiosurgery

The earliest reports of radiotherapy for glomus tumors appeared in the literature in the mid 80s [87, 88]. These cohorts were generally among those for whom surgery was not an option due to location and resulting surgical morbidity [88, 89]. Small case series with long term follow up have demonstrated stable disease or tumor

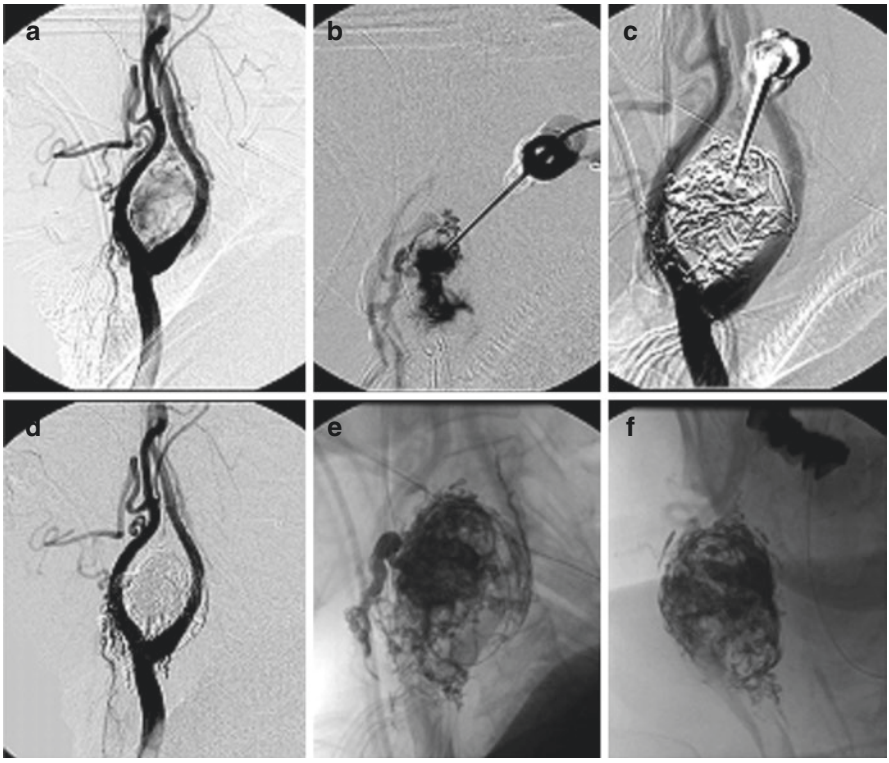

Fig. 17.3 Direct puncture for onyx embolization of a carotid body tumor. Arterial phase digital subtraction angiography (**a**) demonstrates an enhancing mass splaying the carotid bifurcation. Under blank roadmap (**b**), the tumor is infiltrated with onyx via a needle placed percutaneously. Post embolization DSA (**c**, **d**) demonstrated complete devascularization of the tumor and no evidence of non-target embolization. Unsubtracted angiographic views (**e**, **f**) show the onyx cast within the tumor

regression with radiotherapy alone [87, 90]. Tumor recurrence is more common with glomus tympanicums [90]. Starting in the late 1990s, stereotactic radiosurgery was used for adjuvant therapy in treating residual or recurrent disease [91]. Multiple case series have shown high rates of tumor control with long term follow up, as well as symptomatic relief of tinnitus, dysphagia, and tongue weakness [92]. In a review comparing surgery and radiation for glomus jugulare tumors, lower recurrence rates were seen with radiotherapy despite the presence of residual tumor in 100% of patients. Average follow up was 49 months in the surgery group and 39 months in the radiosurgery group. The authors concluded in the short term, at least, radiosurgery was safe and efficacious [93]. A subsequent metanalysis demonstrated adjuvant radiosurgery resulted in lower tumor control rates comparing subtotal resection, gross total resection with and without radiosurgery, and stereotactic radiosurgery alone [94]. Of the four treatment strategies, stereotactic radiosurgery alone yielded the highest tumor control with a mean follow up rate of 5 months. These patients

Table 17.8 Case series using direct puncture for intratumoral embolization

Study ID	Year	No. of tumors	Glomus tumors	Agent	Complete devascularization	Adjunct treatment (microns)
Chaloupka	1999	34	8	Histoacryl	3	5 with TA: Pva, coils
Casasco	1999	65	22	1:1 histoacryl and lipiodol	NR	Balloon in ECA
Abud	2004	9	9	Glubran	5	Balloon occlusion of VA feeder in jugulare tumor with TA pva
Harman	2004	1	1	nBCA	1	
Krishnamoorthy	2007	1	1	nBCA	1	
Elhammady	2009	1	1	Onyx	1	
Wanke	2009	6	6	Onyx	6	Balloon in ICA
Gemmete	2010	15	9	Onyx 18 or 34	8	Coils, PVA 150–300 or 300–500
Ozyer	2010	10	10	1:2 to 1:4 histoacryl	2	6 with TA: PVA 355–500 or 500–710
Weigand	2010	1	1	Onyx	1	Balloon in ICA
Sahin	2011	12	12	1:3 glubran and lipiodol	NR	3 with TA: PVA
Yang	2011	2	2	1:3 nBCA	1	Balloon high in ICA
Elhammady	2012	18	12	Onyx 18, 34, or both	NR	None
Shah	2012	7	7	Onyx 34	7	None
Abdel-Aziz	2013	5	5	Onyx	4	Balloon in ICA
Griauzde	2013	17	10	Onyx	NR	None

PVA polyvinyl alcohol embolic particles, *VA* vertebral artery, *ECA* external carotid artery, *ICA* internal carotid artery, *NR* not reported, *TA* transarterial embolization

also had lower rates of post treatment cranial nerve deficits compared to the gross total resection group.

Most of these studies however are predominately comprised of glomus jugulare tumors. As surgical resection is the primary mode of treatment, mentions of radiosurgery for glomus caroticum or vagale are usually reserved for those who either refuse surgery [95], have large tumors undergoing preoperative radiotherapy to shrink the tumor [27], recurrent tumor, or a malignant tumor with possible local metastases [30]. Given the original impetus to turn to radiosurgery was to avoid surgical morbidity, the lower cranial nerve surgical morbidity with glomus caroticum than glomus jugulare may explain why surgeons have been slower to adopt alternative treatments.

Nonetheless, a recent review of 67 articles comprising 2175 surgical patients and 17 articles comprising 127 radiosurgery patients demonstrated similar tumor resection rates of 93.8% and 94.5%, respectively, over a mean follow up period of 81 months [96]. New cranial nerve injuries were much more prevalent with open surgery (22% versus none, $p < 0.004$) compared to radiosurgery. With advancing technology, treatment strategies for carotid body tumors are improving on all fronts, providing an optimistic outlook for patients with this challenging disease.

Conclusion

Carotid body tumors are peculiar entities encountered by the neurovascular specialist that benefit from a multidisciplinary approach to avoid the associated high risk of morbidity and mortality. A thorough perioperative assessment and surgical strategy are paramount when addressing these tumors. Concise understanding and knowledge of the regional anatomy and imaging are a principal factor when designing a treatment plan. Endovascular techniques have proven to be of singular importance to complement a possible cure via surgical resection. Tailoring these procedures to specific patient needs will result in the best outcomes.

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Chapter 18
Surgical Management of Carotid Body Tumor with Case Illustrations

Robert T. Wicks, Cody Smith, and Peter Nakaji

Introduction

Carotid body tumors (CBTs) are lesions of the chemoreceptors surrounding the dorsal aspect of the carotid bifurcation [1, 2]. While they are the most common neuroectodermal tumors of the head and neck, their overall incidence is estimated to be approximately 1 in 1,000,000 in the Caucasian population, based upon the Dutch National Cancer Registry [3]. Additional population studies are limited, although a similar incidence was estimated based upon the United States National Inpatient Sample database [1]. The actual incidence, however, may be as high as 1 in 30,000 as not all tumors require immediate surgical resection [4]. The majority of presentations are benign. Approximately 5% are malignant, and only discovered due to the detection of distant metastases [5, 6]. The mean age of onset is approximately 50 years, but presentations can be much younger in familial forms [7]. Most series show a slight predilection for women in the sporadic form [8, 9]. In 10% of cases, CBTs can be bilateral and 30% of patients with bilateral tumors have a hereditary form.

CBTs are often categorized as sporadic, hereditary, or hyperplastic [6]. The most common form is the sporadic form, which accounts for between 70% and 85% of cases [10]. Hereditary forms occur in younger patients and are more likely to be malignant. The hyperplastic form is far more common in patients exposed to chronic hypoxia. Risk factors include living at high altitude (>5000 feet above sea level), chronic obstructive pulmonary disease (COPD), or cyanotic heart disease.

Jansen et al. retrospectively reviewed 26 patients with 48 paragangliomas of the head and neck that underwent no interventions with serial imaging [11]. A volume

R. T. Wicks · C. Smith · P. Nakaji (✉)
Department of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA
e-mail: Neuropub@barrowneuro.org; Neuropub@barrowneuro.org; Neuropub@barrowneuro.org

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increase of greater than 20% was seen in 60% of the paragangliomas, whereas the remaining 40% revealed minimal growth with a mean follow-up time of 4.2 years. The median growth rate was 1.0 mm/year and the mean tumor doubling time was 4.2 years. Due to this slow growth rate, CBTs can be asymptomatic for years. It is not uncommon for the period of time between the first symptoms and diagnosis to be between 4 and 7 years.

The most common clinical presentation is an asymptomatic palpable neck mass immediately lateral to the hyoid or sometimes projecting in the lateral oropharynx [9]. They can often be pulsatile due to their adherence to the carotid vasculature and intrinsic vascularity. As the tumor further enlarges, symptoms secondary to cranial nerve or sympathetic chain compression can occur – including Horner's syndrome, hoarseness, dysphagia, and shoulder drop due to spinal accessory nerve compression [12].

Treatment Options Operative Versus Non-operative

While growth can be slow, CBTs have a natural history of continued size increase with eventual encasement of adjacent neurovascular structures. Early treatment is, therefore, recommended in most cases [13]. The primary treatment options for CBT are surgery for resection or radiotherapy (RT). Given the anatomical location, surgical treatment of CBTs can be associated with significant morbidities. These include the risks of cranial nerve injuries (IX, X, XI, XII), the need for carotid bypass or vein grafts, stroke, and death [10]. Postoperative mortality is between 1% and 3% for CBTs greater than 5 cm in size [6].

Despite these risks, surgical intervention is recommended except in presentations in the elderly and in those patients with significant medical contraindications. Series now show rates of cerebrovascular complications to be 5% or less with permanent cranial nerve deficits as a result of surgery occurring in 20% or less of cases [8]. The complication rates depend heavily on the size and location of the CBT. Asymptomatic patients who are elderly with limited life expectancy or who have multiple other medical comorbidities may be considered for observation only [14].

Surgical Anatomy of the Carotid Body

The carotid body is a light-brown structure within the adventitial layer on the dorsal aspect of the common carotid artery bifurcation. The carotid body is an important paraganglionic organ that functions to regulate the body's response to hypoxia by stimulating the medulla to regulate heart rate and blood pressure through alterations to the vasculature and to increase the rate and depth of respirations through stimula-

tion of the external intercostal muscles and diaphragm [10]. The primary nervous innervation is from the carotid sensory branch of the glossopharyngeal nerve known as the nerve of Hering, named for the Austrian physiologist [15]. The carotid body is composed of three cell types (Fig. 18.1a–c): type I – chief cells produce catecholamines and are arranged in cluster formation called zellballen; type II cells, known as sustentacular cells, surround the type I cells to provide support, similar to Schwann cells; type III cells are sensory nerve endings that function as the afferent limb for the chemoreceptor reflexes.

The tumors that develop in this location tend to be extremely vascular with predominant ascending pharyngeal artery vascular supply. Shamblin et al. reported a surgical classification scheme that can assist in predicting difficulty in tumor resection [16]. Type I surgical tumors are restricted to the space between the ICA and ECA and generally dissect easily from surrounding structures. Type II tumors will partially encompass the vasculature and involve greater adherence to the adventitia. Type III tumors encase the ICA and invade the adventitia into the muscularis, to the point that it is often not possible to dissect the tumor from the vessel without entering the vessel lumen. The superior laryngeal and hypoglossal nerves may also traverse the tumor.

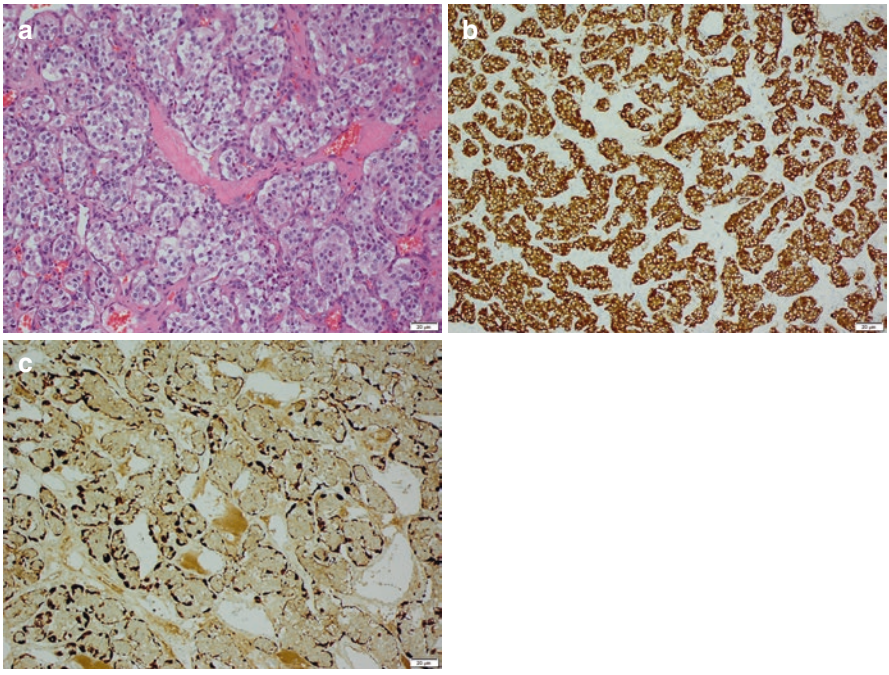

Fig. 18.1 Representative pathologic images of the carotid body paraganglioma described in case example 1. (**a**) Hematoxylin and eosin (H&E) stain under high power revealing the zellballen growth pattern; (**b**) Synaptophysin immunohistochemistry highlights the Type 1 – chief cells; (**c**) S100 immunohistochemistry highlights the Type 2 – sustentacular cells

A similar tumor sometimes included in discussions of carotid body region tumors are the glomus vagale tumors, which often originate between the carotid bifurcation and the jugular foramen. These tumors can have similar clinical effects of carotid artery invasion, destruction of the skull base, and cranial neuropathies [17]. Browne et al. proposed a system of classification including type 1 tumors that lie entirely within the parapharyngeal space without invasion of the jugular foramen; type 2 tumors that invade the jugular foramen, but are not associated with bone destruction; and type 3 tumors that deeply invade the jugular foramen and middle ear with bone destruction and possible involvement of the carotid canal.

Preoperative Management

When surgical intervention is anticipated, perioperative morbidity and mortality can be significantly reduced through appropriate pre-operative planning. Initial endocrine evaluation should be considered in any patients in which a surgical intervention is considered, especially in patients who have noted symptoms of elevated blood pressure or tachycardia [18]. There is a potential for the presence of comorbid pheochromocytomas and some carotid body tumors are also known to secrete catecholamines [19]. Preoperative urine metanephrine studies should be performed. In the case where there is a background of catecholamine hypersecretion, beta blockade as a sole initial intervention can produce fatal complications of cardiovascular collapse. Alpha adrendergic blockade should be induced approximately 2 weeks prior to surgery. Once alpha blockade is induced, beta blockade can be established, and the perioperative surgical risks can then be mitigated.

Preoperative tumor embolization has become an important consideration in the multidisciplinary approach to paragangliomas of the head and neck [20]. Goals include decreased intraoperative blood loss and early tumor necrosis allowing for a more controlled resection resulting in decreased injury to cranial nerves. Some groups perform embolization within 6 days, but in our experience the greatest benefit is seen when performed within 48 h of surgical resection [21]. Liu et al. reported a series of 58 patients with Shamblin Type II and III tumors [22]. 31 patients underwent preoperative embolization of feeding arteries within 48 h of surgical resection of the tumor. In the remaining 27 patients, no preoperative embolization was performed. In those patients who underwent pre-operative embolization, they noted a decrease in mean operative time of 77 min, decrease in mean blood loss of approximately 250 mL, and statistically significant decrease in total complications from 33.3% to 9.7%.

The practice remains controversial, however. A recent paper by Cobb et al. analyzing all CBT resections in 5 states over the period 2006–2013 using the Healthcare Cost and Utilization Project State Inpatient Database (total of 547 patients) found no significant difference in mortality, cranial nerve deficit, or intraoperative blood loss when pre-operative embolization was performed vs. not performed [23]. In our opinion, the benefit is likely limited to those large tumors meeting the Shamblin Type II and III criteria or when complex intraoperative dissection is anticipated for

other anatomical reasons. It should be noted that the ascending pharyngeal artery usually lies on the deep side of the tumor and enters it at its apex superiorly. For those tumors in which the top of the tumor is very high, endovascular devascularization of this portion may facilitate surgical resection of this less accessible area.

In large tumors, especially Shamblin Type III, endovascular balloon test occlusion (BTO) should also be considered in the event prolonged carotid occlusion is required during surgery, an anterior wall patch graft reconstruction is required, or if carotid sacrifice is anticipated [24]. BTO will also help with prediction of whether intraoperative shunting would be required. In those Shamblin Type III tumors in which patients fail a BTO, potential carotid stenting may be considered with preoperative embolization. The carotid stent can improve the structural integrity of the carotid wall, potentially facilitating establishment of a surgical dissection plane [25].

Surgical Approach

Smaller Shamblin Type I tumors can typically be addressed through a small horizontal, transverse incision through a skin crease (Fig. 18.2). Larger tumors will require a longer incision in line with the anterior border of the sternocleidomastoid muscle (SCM) in order to allow for more distant proximal and distal control of the

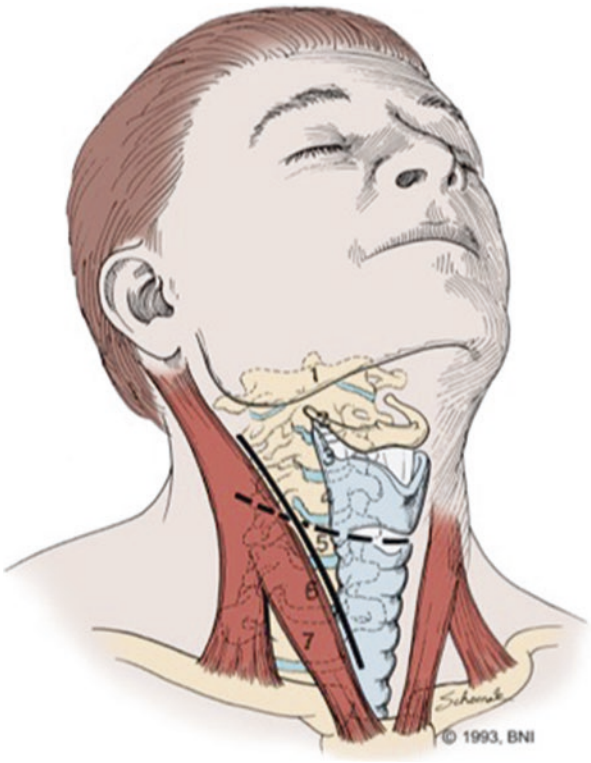

Fig. 18.2 Representative illustration of the incision options for carotid body tumors. Smaller Shamblin Type I tumors can often be approached through a horizontal incision located within a prominent skin crease (denoted by the dashed line) with the lateral edge of the incision approximating the medial border of the sternocleidomastoid muscle. Shamblin Type II and III tumors often require a longer incision along the medial border of the sternocleidomastoid muscle in order to gain adequate proximal and distal control of the carotid vasculature (denoted by the solid line). *(Used with permission from Barrow Neurological Institute, Phoenix, AZ)*

carotid artery. After division of the platysma muscle in line with the skin incision, dissection is carried along the medial border of the SCM until the common facial vein is identified. The common facial vein is then divided. The internal jugular vein can then be retracted laterally along with the SCM to expose the medial contents of the carotid sheath. Once the carotid sheath is opened widely, the proximal and distal carotid artery must be identified and secured with vessel loops above and below the mass. CN 10 and CN 12 are identified if they are not involved with the tumor. CN 12 is typically displaced superiorly and posteriorly. Tumor involvement of the carotid artery is seen in Shamblin Type III tumors; therefore, slow, tedious dissection is required. The tumor is then mobilized from the internal and external carotid arteries using bipolar electrocautery and Metzenbaum scissors. Once fully devascularized, the tumor can be amputated from its pedicles and removed.

Radiation Therapy

Radiotherapy (RT) for CBT is not without risk and has been heavily debated within the literature. In general, patients in good medical condition with limited tumors that are predicted to be resectable with minimal anticipated morbidity should be considered for surgical resection. In those patients with multiple medical comorbidities or advanced tumors that would require extensive sacrifice of neurovascular structures, RT may be considered [26].

For patients appropriately selected to undergo RT, the goal of treatment is to diminish or halt the growth of the tumor. Although an asymptomatic residual mass may still remain following treatment, this is still considered to be an effective therapy so long as the tumor is no longer progressing [27]. The optimal fractionated dose for a benign paraganglioma is believed to be 45 Gy in 25 fractions [14, 26]. Malignant tumors, as defined by those presenting with metastatic adenopathy or distant metastases, would require a higher dose. Stereotactic radiosurgery may be considered in those cases in which a small, less than 3 cm, paraganglioma is identified.

Mendenhall et al. recently reported their retrospective, single institution series of 149 patients with benign head and neck paragangliomas treated with RT, 44 patients of which had carotid body tumors [14]. Median follow-up was 10 years. The local control rate was noted to be 99%, 96%, and 95% at 5-year, 10-year, and 15-year follow-up. Cause specific survival was 98%, 98%, and 98%, respectively. No patients were noted to have malignant transformation of a benign paraganglioma. Subtotal tumor resection had been performed in 19 paragangliomas and was not felt to improve the likelihood of local control and increased the overall morbidity of treatment. Subtotal surgical resection followed by radiation treatment, therefore, is not recommended if gross total resection is not felt to be achievable at the time of surgery. Krych et al. reported on their retrospective, single institution series of 33 patients with paragangliomas of the head and neck region that were treated with RT over the period from 1967 to 1994. The series included 4 patients with carotid body

tumors. Median follow-up was 13 years. The 10-year tumor control rate was 92% and no patients were noted to have a radiation-induced malignancy at last known follow-up.

Other smaller case series specifically investigating CBT treated with RT report similar results. For example, Guedea et al. reported six cases of either CBTs ($n = 5$) or glomus vagale ($n = 1$) treated with RT. [28] Of the six patients, one experienced complete regression, two noted partial regression, and two remained stable (without progression). One patient died of locally recurrent disease 5 years after re-irradiation, after having received extensive treatment at another institution. Evenson et al. published the results of 15 patients with 23 paragangliomas of either the carotid body or glomus vagale [29]. The 10-year local control rate was 100% for the subset of 22 lesions without prior RT. [18]

With the use of intensity modulated radiation therapy (IMRT) and stereotactic radiosurgery, where possible, the acute toxicity of RT is low. The risk of severe late complications such as radiation-induced malignancy appears to be very low. In addition, the risk of delayed radiation complications must be weighed against the slow growth of benign paragangliomas and the immediate potentially permanent risk of cranial nerve deficits from surgical resection.

Case Examples

Case 1 – Left Carotid Body Tumor

A 71 year-old lady was discovered to have a left carotid body tumor on work-up of symptoms of left arm numbness, left facial droop, and aphasia. Her transient ischemic attack (TIA)-like symptoms resolved over the course of 30 min and she was treated for hypertensive crisis. CT angiogram performed revealed a 1.8 cm × 1.6 cm enhancing mass located at the carotid bifurcation and projecting superiorly, splaying the left internal carotid artery and external carotid artery (Fig. 18.3a). Endocrinology work-up was negative. She was determined to be otherwise healthy and was offered the options of observation vs. surgical resection. She wished to proceed with resection.

Given that the tumor was located entirely between the ICA and ECA without encompassing the vasculature, it was graded as a Shamblin Type I. We determined, therefore, that the benefits of preoperative tumor embolization in this situation were limited. A horizontal skin incision was selected within a prominent skin crease and based lateral at the medial border of the SCM. Intraoperative SSEP neuromonitoring was performed throughout the case, in addition to EMG monitoring of cranial nerves 9 and 10 via the endotracheal tube. The platysma muscle was incised in line with the incision and subplatysmal dissection was performed. The common facial vein was suture ligated and divided, exposing the carotid sheath. The carotid sheath was then opened exposing the carotid bifurcation and the tumor (Fig. 18.3b). The common carotid artery was loosely secured with a vessel loop. Circumferential

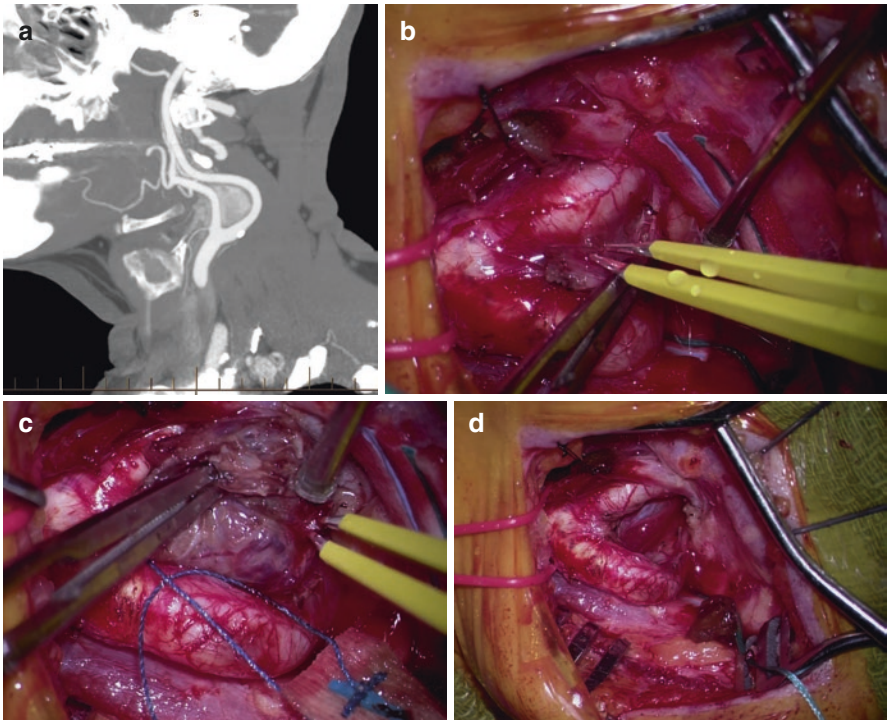

Fig. 18.3 (**a**) Oblique reconstruction of the CT angiogram revealing the location of the left carotid body tumor in case example 1. (**b**) Intraoperative photography of the carotid bifurcation and carotid body tumor after opening the carotid sheath. The vessel loop loosely secures the common carotid artery. (**c**) Circumferential dissection around the carotid body tumor is performed. (**d**) Photograph of the carotid bifurcation after gross total resection of the carotid body tumor. The horizontal skin incision located within a skin crease approximately 2 fingerbreadths below the mandible is also displayed

dissection of the tumor was then performed without noted invasion of the vascular adventitia of either the external or internal carotid arteries (Fig. 18.3c). An en bloc gross total resection of the tumor was performed (Fig. 18.3d). Hemostasis was achieved, and the incision was closed in a layered fashion. The patient recovered well without post-operative neurologic deficit.

Case 2 – Left Glomus Vagale Tumor

A 57 year-old lady with prior history of ovarian cancer presented to the emergency room with acute onset transient dizziness, blurry vision, and word finding difficulty. The symptoms resolved after 3 h. CT angiogram was performed due to concern for TIA. This revealed a large 2 cm × 2 cm mass between the left cervical ICA and IJ at the levels of C1-C3 without carotid occlusion or stenosis (Fig. 18.4a and b). The

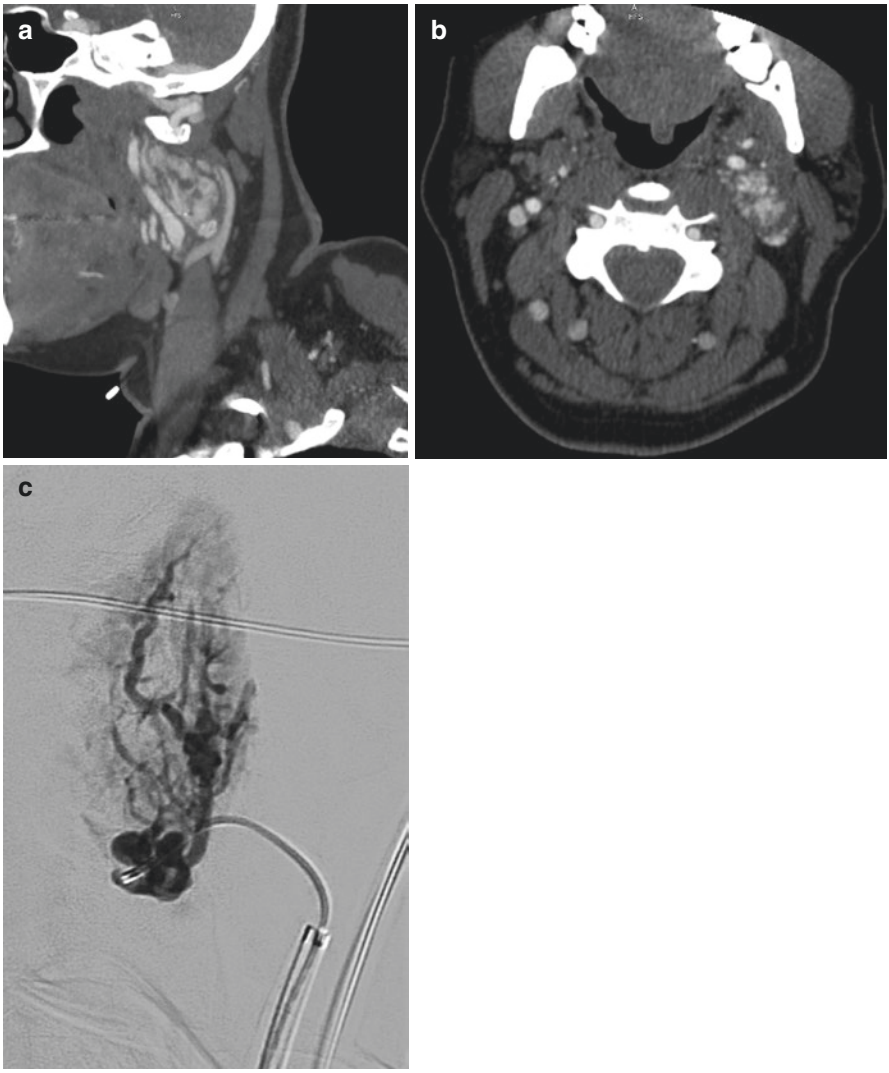

Fig. 18.4 (**a**) Oblique reconstruction of the CT angiogram revealing the dimensions of the left glomus vagale tumor described in case example 2. (**b**) CT angiogram axial slice revealing the glomus vagale tumor on the left approximating the internal carotid artery with no evidence of vessel narrowing. (**c**) Digital subtraction angiography lateral view with selective injection of the tumor prior to selective embolization

mass was noted to be posterior and superior to the carotid bifurcation. Her ovarian cancer had reportedly been in remission for 15 years after receiving chemotherapy and radiation therapy.

Preparations for potential surgical resection were made including laboratory evaluation for urine and serum metanephrines. She was started on phenoxybenzamine for prophylactic alpha blockade until the above lab results were found to be

negative. Given the tumor size and location, the decision was made for evaluation by the endovascular surgery team of potential preoperative embolization, which was performed approximately 48 h prior to surgery (Fig. 18.4c).

At the time of surgery, she was placed under general anesthesia and positioned supine with her head turned to the right. A prominent skin crease was selected approximately 1 fingerbreadth below the mandible. The skin was incised through the platysma. The common facial vein was ligated and divided. The carotid sheath was opened once fully exposed and a vessel loop was placed around the common carotid artery. The tumor was noted to be more consistent with a glomus vagale type variety as there was no splaying of the carotid bifurcation. It arose mostly posterior and superior to the bifurcation and displaced the internal jugular vein laterally. Given the preoperative embolization, the tumor was largely devascularized which allowed for circumferential dissection and removal of the mass. Cranial nerves 10 and 12 were stimulated with a handheld stimulator and revealed normal responses. Irrigation was performed and hemostasis was achieved. No post-operative complications were noted.

Case 3 – Bilateral Carotid Body Tumors

A 58 year-old gentleman presents with a 6-month history of a palpable right neck mass. He had imaging performed that revealed bilateral carotid body region tumors. He otherwise denied any difficulty with swallowing, discomfort, or pain. He also denied any symptoms of flushing, anxiety, or prior history of hypertension. A CT angiogram was performed that revealed bilateral carotid body region tumors. The right mass measured 2 cm × 3 cm and the left mass measured 1 cm × 1.6 cm (Fig. 18.5a–c).

The decision was made to first pursue surgical resection of the smaller left sided tumor in order to minimize the risk of cranial nerve injury. If his vocal cord and swallowing function showed no deficit, then embolization and surgical resection of the right carotid body tumor would follow. His head was turned to the right and the neck was placed in slight extension. An incision was based along the medial border of the SCM. The dissection was continued along the sternocleidomastoid muscle until the carotid sheath was identified. The carotid sheath was opened and the tumor could be visualized within the carotid bifurcation. The tumor was dissected free from the walls of the carotid bifurcation and vasculature. Cranial nerves 10 and 12 were visualized and protected during dissection in addition to cranial nerve 11 in the region of the posterior belly of the digastric. He tolerated the procedure well with no difficulty in swallowing or speaking. Final pathology revealed paraganglioma.

He then underwent resection of the right carotid body tumor approximately 1 month later. Preoperative embolization was performed 24 h prior to surgical resection (Fig. 18.5d, e). The patient was positioned supine with the head turned to the left and the neck placed in slight extension. An incision was made along the medial border of the sternocleidomastoid. Once the carotid bifurcation was identified, a

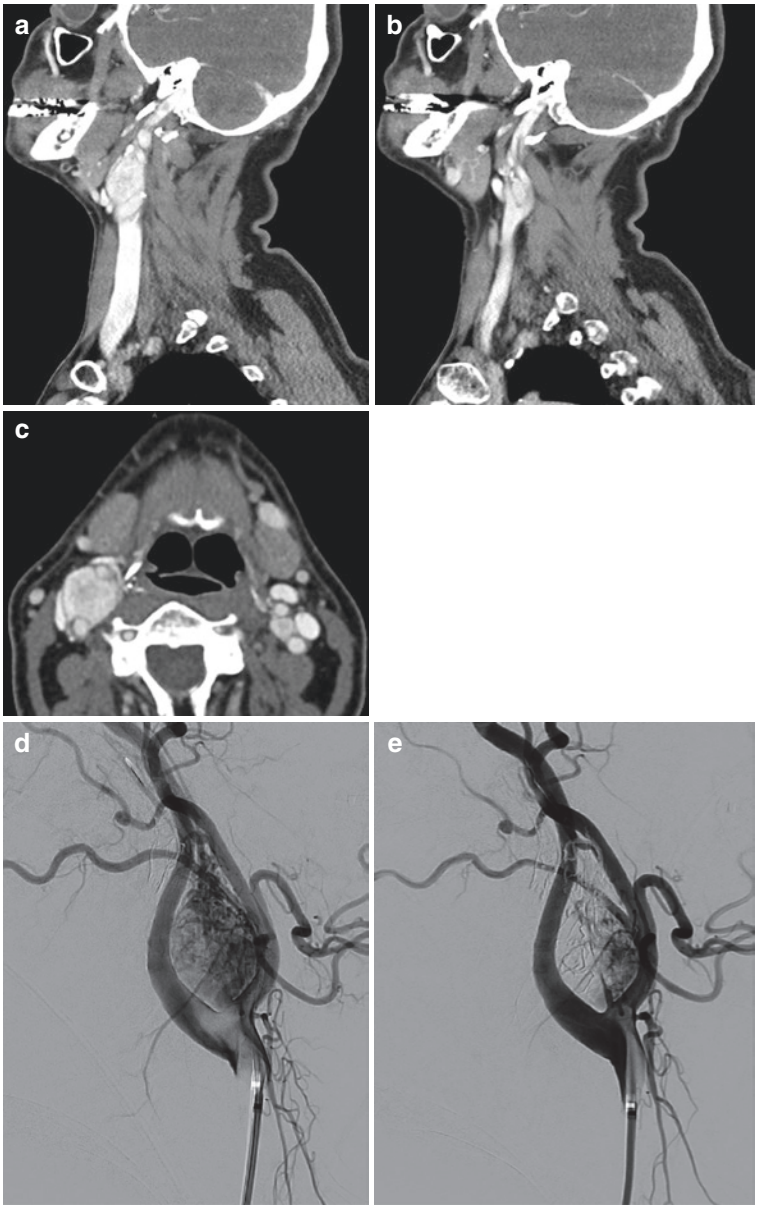

Fig. 18.5 Representative images of the bilateral carotid body tumors noted in case example 3. (**a**) CT angiogram oblique reconstruction of the left carotid bifurcation revealing the left carotid body tumor. (**b**) CT angiogram oblique reconstruction of the right carotid bifurcation revealing the smaller, right carotid body tumor. (**c**) CT angiogram axial image of the bilateral carotid body tumors displaying both internal and external carotid arteries. (**d**) Digital subtraction angiography anterior posterior projection of the left carotid bifurcation during selective embolization of the left carotid body tumor. (**e**) Digital subtraction angiography anterior posterior projection of the left carotid bifurcation after completion of selective embolization of the left carotid body tumor

vessel loop was placed around the common carotid artery. The internal and external carotid arteries distal to the mass were identified. A plane was identified between the tumor and the bifurcation. We were then able to work circumferentially around the tumor. Cranial nerve 12 was noted to be overlying the tumor and was preserved. Any feeding vasculature were coagulated and divided. Cranial nerves 10 and 11 were also preserved. The tumor was removed en bloc. He tolerated the surgical procedure well. Of note, he experienced hoarseness following the preoperative embolization procedure that had improved but not resolved at 6-week post-operative follow-up. He also experienced a few episodes of syncope and near syncope after surgical resection of the second tumor, which had resolved by his 6-week follow-up.

Conclusions

CBTs can present a formidable management and surgical challenge to the surgeon. Because of their frequent slow growth rate, no intervention with monitoring through serial imaging can be considered for asymptomatic CBTs in the elderly or those patients with multiple medical comorbidities that present unnecessary risks to intervention. Surgical intervention should otherwise be a consideration in most patients. In those patients meeting the Shamblin Type II or III classification, preoperative embolization should be a consideration. Careful evaluation with potential BTO should be considered in those patients meeting the Shamblin III classification. Although limited evidence exists directly regarding the treatment of carotid body tumors with RT, it appears to be a viable option for a select group of patients who are otherwise at high risk for surgical resection.

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Chapter 19
Carotidynia

Michael McLaughlin and J. Scott McNally

Definition/History

Carotidynia is defined by pain and tenderness along the carotid artery centered at the bifurcation. The condition was first described in 1927 by Fay et al. [1]. Importantly, pain from other causes, such as vessel dissection, thyroiditis, vasculitis, infection, mass, or osseous pathology (fracture or cervical spondylosis), must be excluded. The syndrome has had a controversial history throughout the twentieth century. In the first International Classification of Headache Disorders in 1988 it was classified as an idiopathic neck pain syndrome [2]. After describing the controversial aspects, in 1994, Biosse and Bousser declared carotidynia a myth [3]. In 2004, it was removed as a distinct entity given that the two defined clinical signs were not always present [4].

In a landmark multicenter series of 47 patients in 2017, Lecler et al. described patients with acute carotidynia and vascular/perivascular imaging findings centered around the carotid artery bifurcation in less than 5% of patients presenting with acute neck pain [5]. They proposed that these patients be classified under a new clinico-radiologic entity: Transient Perivascular Inflammation of the Carotid Artery (TIPIC) syndrome.

Demographics/Imaging

In the early 2000's with advances in imaging techniques, multiple case reports described the entity on US [6, 7], CTA, MRI [8], and even PET-CT [9, 10] and other imaging [11]. These imaging techniques revealed thickening of the vessel wall near the carotid bifurcation as well as perivascular inflammatory changes.

M. McLaughlin · J. S. McNally (✉)
Department of Radiology, University of Utah Health System, Salt Lake City, UT, USA
e-mail: Michael.McLaughlin@hsc.utah.edu; scott.mcnally@hsc.utah.edu

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Most patients presented in the fifth decade with unilateral cervical pain (4% bilateral) with a minority (17%) having associated neurologic symptoms, such as transient dizziness, diplopia, contralateral dysethesia, contralateral motor deficit, or ipsilateral facial nerve palsy [5].

Laboratory evaluation in patients with TIPIC syndrome was non-specific, with a minority of patients demonstrating elevated erythrocyte sedimentation rates (ESR), elevated levels of C-reactive protein (CRP), and elevated serum immunoglobulin-M antibodies. The majority of patients did not show elevation of systemic inflammatory markers.

Risk factors associated with the development of TIPIC syndrome included the presence of vascular risk factors (i.e. hypertension, dyslipidemia, diabetes mellitus, and smoking) and a history of autoimmune disease (i.e. ankylosing spondylitis, autoimmune thyroid disease, Sjogren's disease, systemic lupus erythematosus, and rheumatoid arthritis).

Imaging characteristics that suggested the presence of TIPIC syndrome included:

Perivascular inflammation, defined as soft amorphous tissue replacing the fat adjacent to the carotid artery with stranding or haziness of the fat [5]. The majority of patients demonstrate perivascular inflammation on imaging, most often in a posterolateral location. This also reportedly corresponds to increased radiotracer uptake within the carotid sheath on 18-FDG PET/CT imaging [12].

Fewer than half of patients showed a soft intimal plaque at the carotid bifurcation with mild narrowing of the vessel lumen on imaging. In several cases, there was resolution of the soft plaque on follow up imaging. None of the patients showed ipsilateral ischemic stroke on brain MRI, therefore the connection between the carotid symptoms and imaging findings and the presence of neurological symptoms attributable to an ipsilateral cerebral vascular territory remains unclear.

Additional findings reported include the presence of ipsilateral lymph node enlargement and contiguous inflammation of the pharynx or larynx.

Case reports have demonstrated additional imaging findings that may be associated with carotidynia, including the presence of carotid intraplaque hemorrhage [13] (Fig. 19.1).

Imaging abnormalities may persist after clinical resolution, possibly due to development of fibrosis with low-grade chronic active inflammation [14].

Treatment/Prognosis

All patients presenting with clinical and imaging findings of TIPIC syndrome had a full clinical recovery, with the median time to resolution of approximately 2 weeks.

The majority of patients were treated with anti-inflammatory medications (NSAIDS or high doses of ASA), with a minority receiving steroids, clopidogrel [9], or no treatment at all [8].

Approximately 20% of patients demonstrated a clinical relapse within 6 months of their initial presentation, returning with the same symptoms and imaging findings as they did previously. The most common risk factor for clinical relapse was

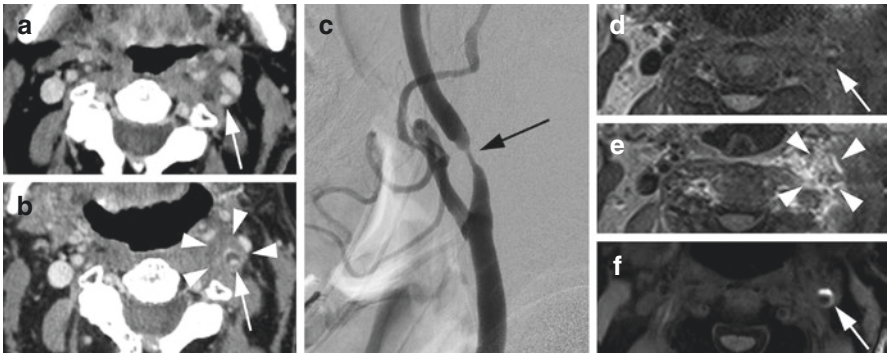

Fig. 19.1 85-year-old male with prior radiation therapy for squamous cell carcinoma with CTA scan 1 year prior (**a**) and on presentation with acute left neck pain localizing to the left carotid artery (**b**). ICA stenosis progressed between the two scans (arrows), and there was active inflammation on CT with perivascular stranding and indistinct fat planes (arrowheads). DSA was performed (**c**) confirming severe left proximal ICA stenosis (arrow). Vessel wall MRI pre (**d**) and post (**e**) contrast T1-weighted flow-suppressed images demonstrated indistinct fat planes around the left ICA (**d**, arrow) and avid periadventitial enhancement (**e**, arrowheads) with contrast leakage into the surrounding soft tissues. MPRAGE (**f**) also revealed T1-hyperintense intraplaque hemorrhage (arrow)

the presence of autoimmune disease, with most of these patients also presenting with an acute exacerbation of their autoimmune symptoms in addition to carotidynia.

Diagnostic Criteria of TIPIC

There are 4 major criteria proposed for the diagnosis of TIPIC syndrome [5]:

- The presence of acute pain overlying the carotid artery, which may or may not radiate to the head.
- Eccentric perivascular inflammation seen on imaging (US, CT, or MRI).
- Exclusion of another vascular or nonvascular cause with imaging.
- Improvement within 2 weeks either spontaneously or with anti-inflammatory treatment.

An additional minor criterion, a self-limited soft intimal plaque, has also been proposed.

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