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Editor

Arterial Revascularization of the Head and Neck

Text Atlas for Prevention and Management of Stroke

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Editor
Horia Muresian
Department of Cardiovascular Surgery
The University Hospital of Bucharest
Bucharest
Romania

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Preface

This volume emerges as the result of the day-to-day practical activity of a team of specialists directly involved in the diagnosis and treatment of cerebrovascular diseases. Practical reasons, informal communication, the need for sharing personal experience, and the desire of solving perplexities or difficult cases have all represented reasons for which the team constituted, first in an "ad hoc" manner, but subsequently becoming a network of specialists with a continuously growing experience and who eventually offered the patients more suited recommendations, more targeted therapeutic indications, and, not least, better results. Perspectives were also open for further research.

The current guidelines are far from being complete or over-encompassing, but these limitations should never diminish the role of the large and randomized studies when compared to individual or center's experience. On the other hand, the clinical practicality that is built on the baseline offered by the guidelines can and should go beyond these, when backed by a thorough motivation. Decisions are sometimes difficult to take, as numerous variables not only enrich but also complicate the clinical picture in the individual patient. Some of the most important factors to be taken into account and, not least, some of the limitations of the current protocols and guidelines are synthetically presented below.

When considering stroke, attention is focused most on the carotid bifurcation, less on the heart (as source of embolism), and least on the vertebrobasilar system. The carotid stenosis cannot be judged in a simple, mechanistic manner: the severity of stenosis and the degree of inflammatory process at the level of the atherosclerotic plaque appear as independent risk factors for stroke.[1] Plaque characteristics (volume, surface, lipid core, hemorrhage, length, and localization) are directly related to subsequent risk of stroke.[2] Lower-degree stenoses do not automatically represent less risk for subsequent stroke as plaque rupture appears to be more probable and more frequent in larger stenoses, where hemodynamic stress over plaque surface is greater.[3] Mechanical and hemodynamic factors and the anatomical variations of the carotid bifurcation have all an important role in the development and the complication of the atherosclerotic plaque.[4] Surgery for mild carotid artery stenosis is currently indicated.[5] A comparison is usually made between the cerebrovascular and the coronary arterial system, although many

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[4]Schulz UG1, Rothwell PM. Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4,627 carotid stenoses. Cerebrovasc Dis. 2003;15(4):244–51.

[5]Kobayashi M, Ogasawara K, Inoue T, Saito H, Suga Y, Ogawa A. Endarterectomy for mild cervical carotid artery stenosis in patients with ischemic stroke events refractory to medical treatment. Neurol Med Chir (Tokyo). 2008;48:211–15.

differences emerge and practical measures appear quite different. The degree of carotid stenosis cannot be considered as an absolute criterion for the therapeutic indication, when considering even the pure, anatomical individual variations of the aortic arch and of the neck vessels.[6] Bilateral carotid stenotic disease is associated with multi-territorial arterial disease and with a higher risk of non-stroke death.[7] A more aggressive medical therapy is warranted and other types of surgery are also indicated, for example, the simultaneous bilateral carotid endarterectomy (SBCE). Many of the lesions in one of the vertebral arteries (VA) are overlooked, as the common opinion is that the opposite VA will compensate for the diseased one. Embolism or extension of thrombosis from the diseased VA represents important causes of stroke in the vertebrobasilar system. The highly stenotic or occluded VA may steal blood from the carotid system (even when the subclavian artery is not occluded). The variations in the intracerebral distribution of the major cerebral trunks and of the arterial circle of Willis and its emerging branches are additional variables in the therapeutic algorithm. Comorbidities and the extant of atherosclerotic disease impose a thorough and a highly individualized strategy and a decision which is not always easy to take.

The authors contributing to this volume have come to constitute a multidisciplinary team, with a rich 10-year experience in the diagnosis and treatment of cerebrovascular diseases, comprising medical therapy (including thrombolysis), endovascular procedures, and surgery. Most of the patients treated were in critical conditions, were admitted as emergency cases, or had a heavy atherosclerotic burden, generally in more vascular territories. The aim of this work is that of sharing from our team's experience and to endow the reader with practical conclusions that ideally should contribute to the choice of the best therapeutic indication in the individual patient.

Department of Cardiovascular Surgery
The University Hospital of Bucharest
Bucharest
Romania

Horia Muresian

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[7]Touze' E, Warlow CP, Rothwell PM. Risk of coronary and other non-stroke vascular death in relation to the presence and extent of atherosclerotic disease at the carotid bifurcation. Stroke. 2006;37:2904–09.

Abbreviations

A1-A3	Segments of the anterior cerebral artery (1 through 3)
ACA	Anterior cerebral artery
ACommA	Anterior communicating artery
ARSA	Aberrant right subclavian artery (retroesophageal subclavian, "arteria lusoria")
ASM	Anterior scalene muscle
BA	Basilar artery
BBB	Blood-brain barrier
BCT	Brachiocephalic trunk ("innominate artery")
C_1-C_7	Cervical vertebrae (1 through 7)
C1-C7	Segments of the internal carotid artery
CAM	Cell adhesion molecules
CAS	Carotid angioplasty and stenting
CCA	Common carotid artery
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CHS	Cerebral hyperperfusion syndrome
CoW	Arterial circle (circle of Willis)
CSF	Cerebrospinal fluid
CT	Computerized tomography
CT-angio	Computerized tomographic angiography
CVD	Cardiovascular disease
DSA	Digital subtraction angiography
EC	Endothelial cells
ECA	External carotid artery
HA	Hypoglossal artery
HDL	High-density lipoprotein
ICA	Internal carotid artery
ICH	Intracerebral (intraparenchymal) hemorrhage
IFN	Interferon(s)
IJV	Internal jugular vein
IL	Interleukins
MCP	Monocyte chemoattractant protein
mLDL	Modified low-density lipoproteins
MMPs	Matrix metalloproteinases
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
OA	Otic artery
P1-P3	Segments of the posterior cerebral artery (1 through 3)
PCA	Posterior cerebral artery
PCommA	Posterior communicating artery
ProA	Proatlantal artery
PTFE	Polytetrafluoroethylene vascular graft

ROS	Reactive oxygen species
SAH	Subarachnoid hemorrhage
SBCE	Simultaneous bilateral carotid endarterectomy
SCA	Subclavian artery
SCM	Sternocleidomastoid muscle
SMC	Smooth muscle cells
TA (persistent)	Trigeminal artery
TNF	Tumor necrosis factor
VA	Vertebral artery
V0-V4	The segments of the vertebral artery (0 through 4)

Contents

The Cerebral Circulation

1

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As in the case of each regional circulation, the cerebral circulation has special characteristics and unparalleled control mechanisms. The brain also holds a particular role, as it lodges the principal centers of the cardiovascular and respiratory control system of the body. The brain and the spinal cord are enclosed in rigid osseous and dural structures. As envisaged centuries earlier by the Monro-Kellie concept, the volume of the intracranial contents cannot change [1], and consequently, a physiologic balance must be maintained between the cerebral parenchyma, cerebrospinal fluid, and blood. The cerebral parenchyma is constituted by nerve cells, nerve fibers, neuroglia, intercellular fluid, and vascular tissue – all enclosed by the meninges. In a simplified scheme, the balance must be maintained between the cerebral parenchyma, cerebrospinal fluid, and the arterial and venous compartments, respectively. Reciprocal volume changes naturally occur, for instance, under normal circumstances, arteriolar dilatation is made possible by a reduction of the venous volume without increasing the resistance to flow. On the other hand, disproportionate vasodilation and subsequent vasogenic edema will increase intracranial pressure generating severe neurologic complications and eventually death.

The brain weighs about 2 % of the body mass but has a high metabolic rate and receives between 15 and 20 % of the total cardiac output and uses 18 % of the oxygen absorbed by the lungs; the resting blood flow and O_2 consumption per unit of mass, of the central nervous system (CNS), are surpassed only by that of the kidneys and myocardium. The cerebral arteriovenous difference is high, being exceeded only by the myocardium and skeletal muscle [2]. A high fraction of the cardiac output and a constant blood flow are essential for the maintenance of the prevalently oxidative metabolism of the brain. The regional distribution of the cardiac output is almost constant in the cerebral circulation either at rest or under light, strenuous or maximal exercise, whereas in the coronary circulation or skeletal muscle, it augments considerably under effort, while it concomitantly diminishes in the splanchnic, renal, or cutaneous territories [3].

Under resting conditions, the cerebrovascular resistance is moderate with the contribution of the large arteries accounting for almost half of the total vascular impedance. However, among the numerous vasomotor stimuli, only a few have constrictor effect; an active contraction of the walls of the vessels of the cerebral circulation is never a strong response, and the tonic sympathetic vasoconstrictor discharge does not characterize the cerebral circulation. The basal state of the cerebral vessels is the result of a combination of factors that produce vasodilatation.

Two major arterial systems contribute to the vascularization of the brain: the carotid and the vertebrobasilar systems. Both belong to the superior aortic system and earn a particular organization and distribution of flow from the very early stages of development with a preferential delivery of oxygenated blood to the brain (the same physiologic adaptation is evident in diving species, including reptiles, chelonians, and crocodilians). Some important features of the arteries vascularizing the brain are as follows. Anastomoses are numerous and multidirectional in the superior aortic system and are constituted between the internal and external carotid, between the carotid and vertebral arteries, between the subclavian and vertebral or external carotid arteries, and between the right and left sides. Venous drainage has similar characteristics, and an important amount of mixing of arterial or venous blood is present under normal conditions or in various disease states. There is an apparent symmetry of the vessels of the brain although unparalleled structures render the right/left division less evident, concomitantly compensating any obstacle or impediment to arterial or venous flow: the basilar trunk, the arterial circle of Willis, the anterior communicating artery, the superior sagittal sinus, the cavernous sinus, and the pterygoid plexus. There is also a wide range of individual variations regarding the ratio between the amount of blood

H. Muresian
Cardiovascular Surgery Department,
The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

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carried by the carotid and the vertebrobasilar system, the individual differences between the right and left vertebral arteries, the difference in the diameter of the internal jugular veins, the inverse relationship between the internal and external jugular veins, and so forth. Numerous anatomical variations in the origin, course, and termination of the cerebral vessels are also encountered including the presence of vestigial vertebro-carotid anastomoses. As a result, the picture of the cerebral vascularization is protean, and the response to the various physiologic or pathologic conditions is varied.

The branches of the cerebral arteries eventually give off pial arteries – vessels on the very surface of the brain lodged within the pia-arachnoid and surrounded by cerebrospinal fluid. These arteries give rise to smaller penetrating arteries, contained within the Virchow-Robin spaces (continuation of the subarachnoid space) and which eventually become parenchymal arterioles once they penetrate the brain tissue; the latter are sheathed by the astrocytic end feet which contribute to the blood-brain barrier. Astrocytes play a major role in capillary function as they regulate the cerebral blood flow, the ion, and water hemostasis. The penetrating and the parenchymal arteries are terminal vessels [4].

The cerebral arteries and arterioles have a well-developed internal elastic membrane but no external elastic membrane; there are also fewer elastic elements in the tunica media. Due to the lack of external elastic membrane, the intracerebral arteries are more prone to rupture. The smooth muscle cells in the tunica media are circularly oriented with a zero-degree obliquity. A similar disposition is present in the larger pial veins. The cerebral veins are devoid of valves. The intracerebral veins are very thin walled.

The density of the intracerebral capillaries is high, as practically every neuron has its own capillary. Various conditions may alter capillary density: chronic hypoxia increases capillary density, while hypertension causes a rarefaction of the vessels. A neurovascular unit (see below) is composed of endothelial cells, vascular mural cells (vascular smooth muscle and pericytes), glial cells (astrocytes and microglia), and neurons. In the intracerebral arteries, vascular smooth muscle cells occupy most of the vascular wall thickness. At the level of brain capillaries, pericytes replace smooth muscle cells and are attached to the vascular basement membrane. Pericytes extend multiple cytoplasmic processes which encircle the endothelial cells; the pericyte/endothelial cell ratio is high in the brain as compared to other organs and tissues [5]. The point of transition from smooth muscle to pericyte remains poorly defined. At each level, mural cells are further surrounded by astrocyte end feet and are in close proximity to neurons and microglia [6].

The veins draining the cerebral hemispheres can be classified in Fig. 1.1. The superficial cortical veins drain the cortex and subcortical white matter. The deep or central veins (the subependymal veins, internal cerebral veins, the basal vein, and the great cerebral vein of Galen) drain the deep white matter and gray matter surrounding the lateral and third ventricles and the basal cistern. The cortical veins empty into the superior sagittal sinus. Both venous systems (superficial and deep) drain blood toward the confluence of sinuses, the sigmoid sinuses, and eventually, the internal jugular veins. The cerebellum is drained by the inferior cerebellar veins and occipital sinuses. The veins draining the brainstem terminate in the inferior and transverse petrosal sinuses.

Collateral circulation in the brain is well developed as anastomoses are present at various levels. The cervical and extracranial anastomoses between the carotid and the vertebral systems were presented before (internal carotid-external carotid, external carotid-vertebral). The major intracranial anastomotic connection is at the level of the arterial circle of Willis (itself depicting however numerous anatomical variations). Distal to this, abundant leptomeningeal anastomoses exist (Heubner's leptomeningeal anastomoses); collateral flow may consequently develop between the distal branches of the anterior, middle, and posterior cerebral arteries. Their functional relevance highly depends on their number and diameter. Venous collaterals exist as well [7]. Different from other organs in the body, the brain has no lymphatic drainage.

The preservation of the particular physiologic milieu of the neural tissue in the brain, spinal cord, and retina is enabled due to the existence of selective "barriers" at the blood-neuronal tissue interface (blood-brain, blood-spinal cord, blood-retina barrier) or blood-cerebrospinal fluid interface. These selective boundaries maintain the neuron water and ion homeostasis and prevent plasma proteins and blood cells from inadvertently passing into the brain parenchyma. The blood-brain barrier (BBB) is a selective barrier between the lumen of cerebral blood vessels and brain parenchyma. The various structures contributing to it are as follows. The endothelial cells connected by tight junctions form the physical barrier of the interendothelial cleft. The endothelial basement membrane envelops the endothelial cells together with the investing pericytes. The astrocyte end feet surround all these structures. This complex is referred to as *the neurovascular unit*. The endothelium of the cerebral vessels that lacks fenestrations has a high number of mitochondria and depicts a low rate of pinocytosis. The BBB is absent from the circumventricular organs (CVO), area postrema, median eminence, pineal gland, neurohypophysis, subfornical organ, and lamina terminalis; circulating substances diffuse into the CVO but not beyond. The release and transport of hormones between the brain and peripheral blood are thus facilitated [8]. The BBB allows the passage of oxygen, carbon dioxide, and small lipophilic substances; it is impermeable to hydrophilic molecules (glucose, amino acids). BBB transporters also

regulate the reuptake and inactivation of neurotransmitters. The main mechanisms involved are specific carrier-mediated transport, receptor-mediated transport, and the active efflux transporter systems together with the transcellular transport. Hydrophilic molecules (including proteins) and univalent cations (Na^+, K^+) do not move freely across the BBB. As a consequence, movement of water into the brain parenchyma as normally driven by hydrostatic pressure is opposed by the osmotic pressure of the retained molecules in the capillary lumen. This protective role of the BBB prevents the development of vasogenic edema [9]. The high resistance of cerebral vascular endothelium to water filtration (in response to hydrostatic pressure) is known as hydraulic conductivity; this parameter encompasses both transcellular and paracellular routes of permeability. The parenchymal arterioles are in intimate contact with astrocytes. Astrocytes can release vasoactive factors and have a role in regulating local blood flow in concert with neuronal demand [10].

The epithelial cells of the choroid plexus form the blood-cerebrospinal fluid (CSF) barrier, while the arachnoid epithelium forms the CSF-blood barrier. At the level of both barriers, the epithelial cells are joined by tight junctions. The CSF has the same electrolyte composition as the interstitial fluid. The capillaries of the choroid plexus are fenestrated. There is a high turnover of the CSF with a rate of production of about 600 ml/day [11]. The CSF, far from being regarded only as a simple filtrate of plasma or possessing merely a mechanical buffering role, stands from the physiologic and biochemical points of view at the crossroads of three vital topics in biology and medicine: active transport, respiration, and neurology [12]. There is a remarkable similarity between the CSF and aqueous humor (and perilymph). Like the aqueous humor, the CSF can be regarded as a two-compartment system: the ventricular space analogous to the posterior chamber and the subarachnoid space analogous to the anterior chamber. The CSF if formed predominantly in the choroid plexuses with an important contribution from extrachoroidal tissue: ependymal cells secrete up to 35 % of the CSF [13]. The half-time for CSF renewal is 270 min. The volume of CSF within the ventricular system of man is about 23 ml, while the quantity in the subarachnoid space of the brain and spinal cord is 117 ml. The CSF pressure is about 150 mm H_2O – almost twice that in the veins. CSF pressure is little influenced by arterial blood pressure but is dependent on venous pressure and the volume of blood in the head.

Pial arteries and arterioles are innervated by "*extrinsic*" nerve fibers originating in the superior cervical (sympathetic), sphenopalatine, otic (parasympathetic), and trigeminal (sensory) ganglia. There is a considerable spatial heterogeneity in what regards the pattern and density of "extrinsic" innervation with substantial innervation in rostral than caudal and carotid more than vertebrobasilar regions. On the other hand, parenchymal arterioles and cortical microvessels receive an "intrinsic" innervation from locus coeruleus, raphe nuclei, basal forebrain, or even from neighboring cortical interneurons. This "intrinsic" innervation appears to target the astrocytes rather than the parenchymal arterioles. The major role of "extrinsic" sympathetic innervation appears to be the elevation of the autoregulation threshold and the consequent protection against increases in venous pressure, disruption of the BBB, and edema formation. Parasympathetic stimulation increases cerebral blood by its vasodilator effects. The trigeminal system is the only sensory (afferent) system in the cerebral circulation, responsible for mediating nociceptive stimuli as, for example, during migraine attacks. Coordinated flow responses occur in the brain due to conducted or flow-mediated vasodilation from distal to proximal arterial segments and to myogenic mechanisms that increase flow in response to decreased perfusion pressure [14].

The maintenance of a fairly constant blood flow despite variations in perfusion pressure is known as the autoregulation of cerebral blood flow. With a perfusion pressure in the range of 60–160 mmHg, the cerebral blood flow is maintained constant, at approximately 50 ml. 100 g brain tissue^{-1}. min^{-1} or: 50 ml / 100 g brain tissue / min (with differences between the white matter and gray matter). Outside these limits the cerebral blood flow varies linearly with the mean arterial pressure. The reduction in cerebral blood flow is compensated for by an increase in oxygen extraction. Signs of ischemia become evident when metabolic needs cannot be compensated anymore by the increased oxygen extraction: dizziness, altered mental status, and eventually cerebral infarction occur. The mechanisms of autoregulation are still not completely understood as, for example, autoregulation is still preserved in sympathetically and parasympathetically denervated animals. The myogenic response seems to play a major role besides other mediators such as neuronal nitric oxide and H^+, K^+, O_2, and adenosine. The loss of myogenic tone (rather than spasm) can produce a three- to fourfold increase in cerebral blood flow – a phenomenon known as autoregulatory breakthrough [15, 16]. The resultant clinical conditions having this common denominator are the hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy syndrome (PRES), reversible posterior cerebral edema syndrome, reversible posterior leukoencephalopathy syndrome (RPLS), hyperperfusion syndrome, brain capillary leak syndrome (however, none of these latter labels appears as satisfactory: the syndrome is not always reversible, and it is not confined to the white matter or to the posterior regions of the brain).

In the context of the particularities of the cerebral circulation presented so far, it appears evident that a strict parallel between the cerebral circulation and other vascular territories is both difficult to draw and of limited benefit. The most used analogy is between the cerebral and the coronary circu-

lations. In both these territories, the most distal arterial branches are terminal vessels, and the occlusion produces ischemic infarction. This may be rapidly followed by hemorrhagic transformation. Adjacent tissues may still be viable but in a dormant, inoperative state. Expedient therapeutic maneuvers (pharmacologic, endovascular, surgical) may limit the damage produced by ischemia, stop the ischemic process, and recuperate adjacent tissues of borderline viability. Yet, the two regional circulations differ substantially. The cerebral and coronary microcirculations differ from each other macroscopically, microscopically, and functionally. A culprit lesion is more readily identifiable in the coronary circulation and more amenable to therapy. On the other hand, cerebral infarctions can be ischemic, ischemic with subsequent hemorrhagic transformation, or hemorrhagic – recognizing different pathophysiologic mechanisms. Moreover, even in the case of cerebral atherosclerosis, definitions based solely on the degree of stenosis may underestimate the extent and the role of intracranial large artery atherosclerosis: advanced atherosclerosis may involve many arterial segments in the absence of severe stenosis [17]. On the other hand, many more mechanisms appear to play a role in the development of stroke as illustrated by the fact that cryptogenic stroke accounts for about 30–40 % of all ischemic strokes [18]. Venous infarctions are also more frequent in the cerebral circulation.

1.1 Clinical and Surgical Anatomy

Different from other parts and regions of the body, the neck depicts many more individual variations and modifications related to body constitution, posture, movement, and physiologic acts such as swallowing, phonation, deep breathing. Particular attitudes can be also produced with disease, pain, pathologic spasms, and vicious contractions. The various disease processes can impinge on the cervical elements, leading on one hand to vascular impediment, edema, or compression of the nervous or visceral structures. On the other hand, normal anatomic elements or morbid formations require adequate positioning of the head and neck for a proper exposure during surgery or for diagnostic interrogation.

The neck depicts a roughly quadrilateral outline on either side between the following landmarks: Anterior: the median line. Posterior: the anterior margin of the trapezius muscle. Inferior: the clavicle. Superior: the base of the mandible continued by the line joining it with the mastoid process. The sternocleidomastoid muscle divides this space in two triangles: anterior and posterior. The muscle itself covers a significant area of the neck, forming a separate region, called the sternocleidomastoid region. Each of the resulting larger triangles is subdivided in the following regions (Fig. 1.2).

1.1.1 Anterior Triangle of the Neck

Digastric triangle, limited by the base of the mandible (superior), the stylohyoid and posterior belly of the digastric (posterior), and the anterior belly of the digastric (anterior). Important structures contained in this area are the branches of the facial and transverse cutaneous cervical nerves, the submandibular gland, the facial vein (superficial to the gland) and the facial artery (coursing deep to the gland), the submental artery, the mylohyoid artery and nerve, the lower part of the parotid gland, and the external carotid artery as it enters the substance of the parotid gland. The internal carotid artery (together with the internal jugular vein and vagus nerve) is separated from the more superficial external carotid, by the styloglossus, stylopharyngeus muscles, and the glossopharyngeal nerve.

Submental triangle, limited by the anterior bellies of the digastric muscles and the hyoid bone. Important structures located in the area of the triangle are the mylohyoid muscles (forming the floor of the buccal cavity) and the origin of the anterior jugular veins.

Carotid triangle is limited by the anterior margin of the sternocleidomastoid (posterior), the posterior belly of the digastric muscle and the stylohyoid muscle (superior), and the superior belly of the omohyoid muscle (anterior). Contents are the distal portion of the common carotid artery, the carotid bifurcation, and the external carotid artery usually placed anterior and medial with respect to the internal carotid artery, although many variations of the bifurcation are frequently encountered regarding both "the height" of the bifurcation and, respectively, the relative position of the external and internal carotid branches to each other. The following branches of the external carotid are encountered in the area of the triangle: superior thyroid, facial, lingual, occipital, and ascending pharyngeal arteries. Their corresponding veins join the internal jugular vein, either separately or with variable degrees of fusion, the most frequent being the so-called thyro-linguo-facial trunk. With the division of these veins, the carotid bifurcation appears evident to the surgeon. The normal height of the carotid bifurcation is usually marked by the origin of the superior thyroid artery. With higher carotid bifurcations, the superior thyroid artery originates separately from the common carotid artery. The internal jugular vein is covered by the sternocleidomastoid muscle, except in the upper part of the triangle. With the head in neutral position, the carotid bifurcation is more readily surgically accessible; apart from that both the vein and the sternocleidomastoid muscle cover the artery, and excessive traction of these structures is required for adequate surgical exposure leading to their potential damage and especially to internal jugular vein thrombosis. The jugular lymph nodes lie in contact with the jugular vein, underneath the sternocleidomastoid muscle. Conspicuous adenopathy

may render difficult the exposure of the carotid bifurcation. The hypoglossal nerve emerges between the internal jugular vein and the internal carotid artery and crosses the internal and external carotid arteries giving off the superior root of the ansa cervicalis; the latter nervous structure runs in the anterior part of the carotid sheath (the posterior root of the ansa lies close to the internal jugular vein). Division of the ansa cervicalis is sometimes necessary for a higher exposure of the more distal internal carotid artery and for a gentle mobilization and protection of the hypoglossal nerve. The superior laryngeal nerve gives off its internal branch below the hyoid bone and more inferiorly its external branch. This latter nervous branch must be protected during dissection of the carotid bifurcation: a damage of the external branch leads to paresis of the cricothyroid muscle and consequent diminished tension of the vocal apparatus and lowered vocal potency. The vagus nerve, the internal jugular vein, and the sympathetic trunk are covered by the sternocleidomastoid muscle.

Muscular triangle is limited by the superior belly of the omohyoid (superior), the anterior margin of the sternocleidomastoid (posterior), and the anterior median line (anterior). Important structures are the thyroid gland (and parathyroid glands), larynx, trachea, pharynx, the infrahyoid muscles, and the recurrent laryngeal nerves.

1.1.2 Posterior Triangle of the Neck

Occipital triangle is limited by the posterior margin of the sternocleidomastoid (anterior), the anterior margin of the trapezius (posterior), and the inferior belly of the omohyoid (inferior). Important structures are: the accessory nerve (entering the sternocleidomastoid muscle at approximately 2–3 cm inferior to the mastoid process, coursing along the levator scapulae muscle, to reach the deep surface of the trapezius; adjacent lymph nodes are also present. The accessory nerve may cross superficial or deep to the internal jugular vein). The superficial branches of the cervical plexus become apparent at the posterior border of the sternocleidomastoid muscle, in its middle portion – and can conveniently be approached for locoregional anesthesia (superficial cervical plexus block).

Supraclavicular triangle is limited by the inferior belly of the omohyoid (superior), the posterior margin of the sternocleidomastoid (anterior), and the clavicle (inferior). Important structures are the supraclavicular nerves, the first rib with the insertion of the anterior scalenus muscle, the phrenic nerve, the third portion of the subclavian artery (emerging between the anterior and middle scalenus muscles), and, in close contact with the artery, the brachial plexus (the upper and middle roots) and the transverse cervical artery. The suprascapular vessels and the subclavian vein usually lie just posterior to the clavicle and actually not in the area of the triangle. The surgical approach to the subclavian artery and origin and first part of the vertebral artery requires a more extensive dissection, beyond the limits of the triangle, by extensively retracting or cutting the clavicular head of the sternocleidomastoid and the inferior belly of the omohyoid muscles.

The sternocleidomastoid region corresponds to the muscle and, due to the mobility of the neck, may cover more or less of the adjacent regions together with the structures contained within these. In any case, the muscle covers most of the internal jugular vein and the adjacent lymph nodes. Between the sternal and the clavicular heads of origin of the muscle, the internal jugular vein depicts a slight dilatation (the inferior bulb of the internal jugular vein) and can be readily accessed (dissected or catheterized) at this level.

All aforementioned spaces and "*triangles*" offer a theoretical and didactic basis for the localization of the main anatomical structures of the neck. However, the soft tissues forming the boundaries of these subdivisions of the neck and the well-known mobility of the cervical segment render somehow artificial a strict delimitation of such regions. From a surgical and practical point of view, it is more important to recall the division of the neck in three anatomical-surgical zones [19, 20].

1.1.2.1 The Three Anatomical-Surgical Zones of the Neck

An alternative classification of the neck in three zones of surgical interest was elaborated in Fig. 1.3.

Zone I extends from the base of the neck to 1–2 cm above the clavicle. This upper limit corresponds to the inferior belly of the omohyoid muscle. *Zone II* is the segment from 1 to 2 cm above the clavicle to the base of the mandible (and the line joining the angle of the mandible with the mastoid process). *Zone III* extends from this latter line to the skull base.

The common carotid artery, the subclavian artery, and the origin of the vertebral artery are all accessible in zone I. However, surgical exposure of the left common carotid artery origin and a lower or aortic origin of the left vertebral artery in zone I may additionally require median sternotomy or the trap-door incision. On the right side, the brachiocephalic trunk can be accessed, dissected, and clamped through an incision in the lower neck. Yet, partial sternotomy is needed in order to gain a safe access on the origin of the trunk.

For a proper exposure of the carotid artery (common carotid, bifurcation, and origin of the internal and external carotid arteries), a single longitudinal, oblique, or transversal cervical incision in zone II is usually sufficient.

Exposure of the internal carotid artery higher in the neck – zone III – may require additional maneuvers, among which are mandibular partial resection, mandibular subluxation,

and pre- or retroauricular extension of the cervical incision (we advocate the latter procedures; see below). A single cervical incision in zone II extended in zone III will allow concomitant access to the carotid bifurcation and the suboccipital (V3) portion of the vertebral artery.

Some further anatomical details of clinical and surgical significance need to be recalled at this very point.

1.1.2.2 The Cervical Fascia and Its Layers

The important vascular, nervous, and visceral structures of the neck are concentrated in the central and anterior part, encircled on the remainder three sides by muscle and bone. A central group of muscles surrounds the cervical spine, being attached to the base of the skull, to the ribs, and to the adjacent vertebrae: the erector spinae (posteriorly), the longus colli and longus capitis (anteriorly), and the levator scapulae and scalene muscles (laterally) [21]. Their investing fascia – the prevertebral fascia – attaches to the base of the skull, to the vertebral bodies and the anterior longitudinal ligament, and to the ligamentum nuchae. The prevertebral fascia covers the origin of the branches of the cervical plexus (comprising the phrenic nerve); inferiorly, the fascia covers the roots of the brachial plexus and the subclavian artery and continues distally with the axillary common neurovascular sheath. This common sheath represents an important and clinically significant structural space facilitating the spreading of morbid pathologic collections or aiding the diffusion of anesthetic agents, as used in the various regional anesthesia techniques. The middle layer of the cervical fascia encloses the visceral component (together with the infrahyoid muscles), being also called for this reason the visceral fascia. Posteriorly, the space occupied by loose areolar tissue interposed between the buccopharyngeal fascia and the prevertebral fascia allows the normal physiologic mobility of the visceral structures (pharynx, larynx, trachea) during swallowing, deep breathing, etc.; on the other hand, it may also offer a route for the spreading of infections, air, or gastrointestinal contents between the neck and the mediastinum, as, for instance, after esophageal injury. The superficial layer of the cervical fascia forms a complete sheath, from the posterior part of the skull base, the zygomatic arch, and the base of the mandible to the sternum, clavicles, acromion, and the spine of the scapula.

1.1.2.3 The Carotid Sheath

The sheath surrounds the carotid artery, the internal jugular vein, and the vagus nerve. It is an aggregation of connective tissue filling the elongated triangular space between the prevertebral muscles, the visceral component of the neck, and the sternocleidomastoid muscles, allowing an easy access to any of the anatomical elements contained. Postoperative or radiation-induced scarring may render more difficult the exposure of the neurovascular elements. Conspicuous cervical adenopathy may also render more laborious the dissection and exposure of the vessels Fig. 1.4.

1.1.2.4 The Carotid Artery

The common carotid artery (CCA) depicts a slightly oblique tract from origin toward its bifurcation (which is usually located at the level of the superior border of the thyroid cartilage, i.e., in correspondence with the C_3–C_4 vertebrae). It can be distinguished from the vertebral artery (VA), the latter showing a somehow opposite disposition, with a slightly more lateral origin and a convergent tract toward the transversal foramen of the sixth cervical vertebra; this disposition is readily apparent on angiogram. The CCA and the internal carotid artery (ICA) usually give off no cervical branch. The origin of the superior thyroid artery can be sometimes located at the level of the distal CCA. It is in fact the superior thyroid artery the element marking the normal level of the carotid bifurcation. In the case of higher bifurcations, the superior thyroid artery still emerges at the normal level, not from the external carotid (ECA) but, instead, from the CCA. A middle thyroid artery may sometimes originate from the CCA, in correspondence with the middle thyroid vein. In rare instances also, the sternocleidomastoid branch of the superior thyroid artery may arise directly from the CCA. At their origins ECA is anteromedial, while the ICA is posterolateral; nonetheless numerous anatomical variations of the bifurcation are encountered, the most frequent being with the two arteries in a sagittal plane (with the ICA posterior), or the bifurcation may appear as "inverted" with the ICA posterior and medial. Such variations may mislead during diagnostic interrogation or surgery (Fig. 1.5). The dilatation at the origin of the ICA – *the carotid sinus/carotid bulb* – is readily apparent in most individuals (in sagittal or inverted carotid bifurcations, the bulb is less apparent). The ECA is easily identifiable, due to its numerous cervical branches. The ICA actually continues the direction of the CCA higher in the neck, and this disposition is evident on angiograms. As a matter of precaution, dissection of the carotid tripod should not proceed deep into the angle between the ICA and ECA, as numerous important structures can be injured: the superior laryngeal nerve, the carotid sinus nerve, the vessels and nerves of the glomus, and the origin of the ascending pharyngeal artery. Hemorrhage from these tiny vessels can be annoying to the surgeon. Dissection of the carotid bifurcation should be performed in the periadventitial layer and just as much as needed: preoperative imaging and intraoperative gentle palpation offer a good account to the surgeon regarding the extent of exposure required during operation. This will lessen the risk of embolization or damage to the neighboring anatomical elements.

The CCA and ICA normally give off no cervical branches. The caliber of the ICA is almost constant up to the cavernous

segment where more conspicuous branches take off. The ICA traverses the osseous carotid canal of the petrous temporal bone. At this level, the encompassing structures confer stiffness to this segment of the ICA annihilating its pulsations and cyclic systolic dilatations. Pressure pulse oscillations change into fluctuations of flow as the tube becomes rigid. More distally, the ICA is contained in the cavernous venous sinus, where numerous fibrous tracts anchor the artery and the venous plexus to the adjacent bony elements and dura. As a result, the vascular lumina are kept open and are not prone to collapse. The ICA becomes "*hyperelastic*" and amenable to dilation on behalf of the adjacent plexus of veins. It is right in this part that the ICA depicts three distinct curves, each oriented in a different plane. Each of the three loops has a small radius which aids to taper off the variations of flow: with higher rates of flow in the ICA, the artery dilates and lengthens at the same time; the three curves consequently become narrower, and the entire intracavernous part of the ICA appears similar to bellows tubing and behaving as a hydraulic variable resistance.

In conclusion, the petrosal part of the ICA dampers the pulsations of the arterial wall, while the intracavernous part controls and levels the distal flow by hampering the excessive current of the blood. The increased resistance to forward flow is transmitted backward, proximally, to the carotid bifurcation, and part of the flow is redirected toward the ECA.

Similar mechanisms can be speculated in the case of the vertebral arteries as the anatomical disposition resembles that in the carotid system and probably serves corresponding roles. The caliber of the VAs in their cervical part appears almost constant in spite of the numerous muscular branches. The VAs traverse the rigid dural-osseous canal at C_2–C_1 level. The superior cervical (C_2–C_1) and atlanto-occipital curves of the VA offer extra length and allow the complex movements of the head and neck (flexion-extension, lateral rotation, lateral flexion, and complex, combined movements). Functionally, these sinuosities may be looked upon as analogous to the intracavernous part of the ICA. The cross-sectional area of the basilar trunk is always less than the sum of the areas of the two VAs. The sum of the areas of the two emerging posterior cerebral arteries is less than the area of the basilar trunk – accordingly, there appears to be a greater resistance to forward flow. However, different from the carotid system, reduced flow in one of the VAs is compensated by the contralateral VA. Furthermore, the loops of the intracavernous ICA are not influenced by movements of the head and neck.

1.1.2.5 The Internal Jugular Vein

The internal jugular vein (IJV) seems to wind around the carotid arterial axis. At the level of the base of the skull, the internal jugular vein is located posterior to the internal carotid artery, between the artery and the styloid process. The facial and the accessory nerves are located posterior to the vein. The glossopharyngeal, vagus, hypoglossal nerves, and the sympathetic chain emerge between the vein and the internal carotid artery (Fig. 1.6). Lower in the neck, the vein lies lateral to the internal and common carotid arteries, while at the root of the neck, the vein is placed, anterior to the common carotid artery. In the carotid triangle, only the posterior root of the cervical ansa (hypoglossal ansa) and the vagus nerve accompany the vein. The vagus nerve lies deep to the vein. Numerous anastomoses between the internal and the external jugular veins are present, the two systems of veins enclosing the sternocleidomastoid muscle between them. In the upper part of the carotid triangle, the retromandibular vein represents an important anastomosis between the external and the internal jugular veins. The anterior jugular veins represent another anastomotic pathway between the two aforementioned systems. There is a physiologic asymmetry of the two internal jugular veins, as the venous drainage through the dural sinuses is also dissimilar. The jugular foramina at the skull base also depict left-right differences, in most individuals (Fig. 1.7). There is also an inverse relationship between the dimensions of the external and the internal jugular veins. Extensive surgical manipulation or prolonged traction of the internal jugular veins can lead to postoperative thrombosis. The facial vein (or the thyro-linguo-facial trunk) represents an important landmark for the underlying carotid bifurcation. Most if not all of the venous tributaries of the internal jugular vein reach its anterior and medial aspects. Extensive dissection and mobilization of the internal jugular vein can be performed more comfortably posterior to the vein, by avoiding all the venous tributaries. Yet, most of the lymphatic vessels and the jugular lymphatic trunk are adjacent to the posterior aspect of the vein. Surgical exclusion of one internal jugular vein (as, e.g., in radical neck dissection for neoplastic disease) might have no particular consequences for the patient; nonetheless, the risk of extensive ante- and retrograde thrombosis and cerebral edema should always be borne in mind and prevented by the use of anticoagulation, heads-up position, and diuretics. Preoperative venogram or Doppler interrogation may offer valuable data on the side of the dominant internal jugular vein and on the status of the external jugular veins – in the given patient.

Variations of the IJV must be kept in mind during surgery: an IJV crossing anterior (superficial) to the carotid bifurcation may render more difficult the approach (Fig. 1.8).

1.1.2.6 The Nerves of the Neck

The spinal nerves contributing to the cervical and the brachial plexuses emerge between the prevertebral muscles. A good reference point is represented by the interscalene space, in the lower and middle part of the neck. Surgical approaches

anterior to the sternocleidomastoid muscle interfere least with the nerves of the superficial cervical plexus. Retrosternocleidomastoid surgical approach has the advantage of not interfering with the tributaries of the internal jugular vein but will interfere with the superficial cervical plexus. The brachial plexus and the phrenic nerve can be damaged with surgical approaches in the lower neck, as, for example, during the exposure of the subclavian and vertebral arteries. A special reference must be made to the long thoracic nerve (C_5–C_7), innervating the serratus anterior muscle: the nerve emerges through the middle scalene muscle, and it can be injured during surgery for thoracic outlet syndrome (winged scapula being the most notable consequence).

The cranial nerves deserve a separate consideration. The surgery for carotid and vertebral extracranial vascular lesions can potentially interfere with the cranial nerves VII (facial), IX (glossopharyngeal), X (vagus), XI (accessory), and XII (hypoglossal) and their branches, especially the superior and recurrent laryngeal branches of the vagus nerve. Injury to any of these structures can have serious consequences to the patient [22].

The facial nerve emerges from the styloid foramen, enters the parotid gland, and branches in the very substance of the gland, the facial plexus lying superficial to the venous and arterial elements being incorporated within the parotid gland. Preauricular incisions allow access to the distal ICA and skull base; in these cases, the facial nerve and its branches must be thoroughly identified and preserved. The marginal mandibular branch of the facial nerve runs close to the mandibular angle in the upper part of the digastric triangle, supplying the risorius and the muscles of the lower lip and chin (mentalis, depressor labii inferioris, and depressor anguli oris). This branch can be damaged in case of extended, higher exposures of the ICA or by extensive retraction. The angle of the mouth will be deviated toward the unaffected side (Fig. 1.9).

The glossopharyngeal nerve emerges at the level of the skull base between the internal jugular vein and the internal carotid artery. It then passes lateral to the internal carotid, in the angle between the ICA and ECA ("*the carotid fork*"), together with the styloglossus and the stylopharyngeus muscles. The nerve spirals toward the anterior surface of the latter muscle and sinks beneath the posterior edge of the hyoglossus muscle. The glossopharyngeal nerve is surgically damaged in rare instances; lesion of its sensory and motor fibers distributed to the tongue and pharynx may lead to aspiration of food and liquids. Deglutition may become difficult [23].

The vagus nerve is located between the ICA and the IJV. At times, it may course on a more anterior plane, being easily confounded with the ansa cervicalis (Fig. 1.10). Although its main trunk is rarely damaged, some of its important branches can be injured either directly or with extensive scarring, on a delayed basis. The external branch of the superior laryngeal nerve innervates the cricothyroid muscle, and although its lesion will not produce vocal cord paralysis, this may induce alterations in the tensioning of the vocal apparatus, with consequent loss of voice intensity – more severe with bilateral lesions. Injury to the recurrent laryngeal nerves is more severe and more disabling, but the nerves are less prone to direct injury; the risk of damage is higher in the mid-neck with extensive surgical manipulation of the main vagal trunk. The left laryngeal recurrent nerve can be directly injured during dissection of the aortic arch and origin of the left subclavian artery. The right laryngeal recurrent nerve is more prone to direct surgical injury with extensive dissection of the brachiocephalic trunk and origin of the right subclavian artery. The existence of a right nonrecurrent inferior laryngeal nerve must be always considered, especially in cases with aberrant right subclavian artery (ARSA) [24–26]. The superior cervical cardiac branches of the vagus nerve travel anterior to the CCA toward the cardiac plexus.

The accessory nerve lies posterior to the IJV, penetrates the sternocleidomastoid muscle, courses along the levator scapulae, and is distributed to the trapezius muscle. This nerve may be injured either at the level of the skull base (exposure of the distal cervical ICA) or during the suboccipital approach to the vertebral artery (V3 segment). At times, the nerve may have a pre-jugular course and the risk of its damage is greater (Fig. 1.11).

The hypoglossal nerve emerges from the level of the hypoglossal canal and lies between the IJV and the ICA, crossing the latter and the ECA at the level of the lingual artery and vein, usually deep to the stylohyoid and digastric muscles before entering deep to the mylohyoid muscle. During the surgical interruption of the lingual vein (for a better exposure of the internal carotid artery), a special attention should be given to the identification of the hypoglossal nerve. Iatrogenic injury to the hypoglossal nerve leads to hemilingual paresis and atrophy; bilateral lesions are grossly disabling to the patient.

The sympathetic trunk is situated on a deeper plane, is attached to the prevertebral fascia, and is separated from the cervical transverse processes by the prevertebral muscles. The trunk adheres to the carotid sheath in the upper neck, where it lies posterior to the ICA and medial to the vagus nerve. Lower in the neck, the sympathetic trunk becomes lateral to the vagus nerve and posterior to the IJV. At the level of the base of the neck and toward the thoracic outlet, the sympathetic trunk separates from the carotid and jugular vessels, coming in closer contact with the neck of the first rib, between the pleural dome, the longus colli muscle, and the anterior scalenus muscle. Important anatomical relationships are established between the sympathetic trunk and ganglia, on one hand, and the origin of the vertebral artery, the inferior thyroid artery, and the proximal part of the CCAs, on the other. An important contribution of the cervical sympathetic

trunk to the autonomic innervation of the head and neck is accomplished through the jugular nerve, the internal carotid nerve, the external carotid nerves, and the laryngopharyngeal branches. The vertebral plexus and nerve have also origin at the level of the sympathetic trunk. The cervical sympathetic trunk also contributes to the autonomic innervation of the superior limb and thoracic viscera, including the heart. Injury to the upper part of the sympathetic trunk or to the cervicothoracic ganglion may produce Horner's syndrome.

Nerve twigs to the carotid body and sinus from the glossopharyngeal, vagus, and superior cervical sympathetic ganglion lie between the external and internal carotid arteries. A great attention has been paid to the carotid sinus nerve (nerve of Herring). Dissection 2 cm or more away from the bifurcation avoids inadvertent lesion of these fine but important structures. Loss of the normal baroreflex adjustment of the blood pressure is known to appear after interruption of the carotid sinus nerve or extensive dissection of the carotid bifurcation. Orthostatic hypotension may occur especially after bilateral carotid endarterectomy.

The visceral component is represented by the larynx, the upper part of the trachea, the pharynx and origin of the esophagus, and the thyroid gland and the parathyroid glands – all enclosed by the middle cervical fascia. Excessive dissection or surgical manipulation of these structures may complicate with neck hematoma, laryngeal edema, dysphonia, and dysphagia – annoying to the patient and not least hazardous, as acute respiratory insufficiency or aspiration may occur anytime during the postoperative period.

The retromandibular space (Fig. 1.12). The narrow space between the mastoid process and the ramus of the mandible, as well as the presence of numerous important nervous structures, limit to a great extent the surgical approach to the distal cervical ICA. This can be however overcome with the application of two surgical principles: expanding the retromandibular space or by approaching the ICA higher up, in the carotid canal or in its intrapetrous portion, by drilling the temporal bone. The newer endovascular procedures have however reduced the need for such extended surgical approaches. A satisfactory access to the retromandibular space can be also achieved from below, after dividing some elements normally crossing the ICA: the lingual and retromandibular veins, the occipital artery, and the posterior belly of the digastric and the stylohyoid. Dissection performed strictly in the periadventitial layer will prevent direct injury to the numerous and important nervous structures contained in this narrow space.

The vertebral artery (Figs. 1.13 and 1.14) originates deep in the neck, from the first portion of the subclavian artery, usually opposite the origin of the internal thoracic artery (and in a much deeper plane that the inferior thyroid artery with which it can be sometimes mistaken). The internal thoracic artery, the thyrocervical trunk, the costocervical trunk, and the vertebral artery originate from the subclavian artery in a radial fashion, with the VA arising superiorly and posteriorly. The VA gives off no cervical branch at this level and can be thus easily distinguished from the remainder arteries branching off from the subclavian artery. The origin of the VA is enclosed in a narrow space bounded by the longus colli muscle (medially) and by the anterior scalene muscle (laterally). The two muscles converge toward the anterior tubercle of the sixth cervical vertebra C_6 (*the carotid tubercle*) but diverge inferiorly toward the thoracic outlet: the longus colli continues over the upper thoracic vertebral bodies, while the anterior scalene inserts laterally on the first rib. The resultant solid angle is occupied inferiorly by the pleural dome over which the subclavian vessels arch. The narrow space between the left and right pleural cavities which is the superior mediastinum communicates freely with the neck spaces. The VA arches over the pleural dome to reach the angle between the longus colli and anterior scalene muscles and reaches the transverse foramen of C_6. This space can however be easily dissected, albeit with caution in order to avoid injury to the numerous adjacent structures. The confluence of the subclavian and internal jugular veins lies on a more anterior plane. The CCA is medially placed. On the left side, the thoracic duct emerges from its deeper situation, between the carotid and subclavian arteries; passes medially, close to the origin of the VA; and ends in the jugular-subclavian venous confluence. The cervical sympathetic trunk and ganglia are located medial to the VA, while the vagus nerve occupies an even more medial position. The vertebral vein is anterior to the artery and confluences with the subclavian vein, close to the termination of the thoracic duct. The vein offers a good landmark for the identification of the artery. The phrenic nerve courses over the anterior scalene muscle from lateral and superior to medial and inferior, lying closer to the VA in the lower neck. Accessory phrenic nerves can be sometimes conspicuous and may limit somehow the dissection at this level. The scalene fat and lymphatic pad fills the anterior and superficial portion of the scaleno-vertebral space, contains the branches of the thyrocervical trunk, and is covered by the middle layer of the cervical fascia and the inferior belly of the omohyoid muscle. Superficial to this, the supraclavicular nerves and the external jugular vein cross the region. A better access to this region is obtained by dividing the clavicular origin of the sternocleidomastoid muscle. Division of the muscle allows a concomitant exposure of the CCA.

The VA usually enters the transversal foramen of the sixth cervical vertebra, although numerous variations are encountered. In the usual manner, the artery courses through all the transversal foramina from C_6 to C_1 and the corresponding intervertebral (intertransversal) spaces, accompanied by one or more venous channels and by the vertebral nerve (sympathetic fibers accompanying the artery and its branches). The cervical spinal nerves exit the vertebral canal posterior to

the artery, partially enclosed in a bony gutter between the anterior and posterior tubercles of each cervical transverse process. Venous tributaries and arterial branches are abounding at the level of the intertransversal spaces; consequently, a better and bloodless approach to the VA is obtained with partial bone excision with a rongeur, in the bony canal rather than between the transverse processes. Extensive exposure of the VA can be necessary in patients with a shorter neck or with stenoses beyond the very origin of the artery. While performing the deep cervical plexus block and in order to avoid the inadvertent puncture of the VA, contact with bone represents a good guiding maneuver.

The transverse foramina of the atlas (C_1) are located more laterally than those of the axis (C_2): at this level, the VA depicts a divergent lateral and posterior course. The artery winds around the lateral masses of the atlas; pierces the posterior atlanto-occipital membrane and, shortly afterward, the dura mater, entering the skull through the occipital foramen; and shifts from a posterior location to an anterior position (Fig. 1.15). At the level of the pons, the two vertebral arteries converge and form the basilar trunk. The tortuosity of the distal cervical (extracranial) VA allows the extensive and complex movements of the neck. This segment of the VA is contained in the triangular space bounded by the suboccipital muscles delimitated by the rectus capitis posterior major (medially), obliquus capitis superior (superiorly and laterally), and obliquus capitis inferior (inferiorly and laterally). The triangle lies deep to the semispinalis capitis and trapezius muscles. A strict posterior approach to this segment of the VA is more demanding for the surgeon being performed only when an associated opening of the posterior cranial fossa is also contemplated.

Not infrequently, the left VA has a separate origin, at the level of the aortic arch, between the origin of the left carotid and the left subclavian arteries. This variation must be sought and identified during angiographic examination. Numerous other variations of the origin, tract, and termination of the VA have been reported [27–33].

The carotid and the vertebral arteries are divided for practical (clinical, diagnostic, and surgical) reasons in various segments. A brief presentation and description of these segments are mandatory, before illustrating the surgical approaches to aforementioned arteries.

1.1.2.7 The Segments of the Carotid Artery

The left CCA has an intrathoracic part as it originates from the aortic arch (normally) or from the brachiocephalic trunk or from a common carotid trunk (the most common variations of origin). The artery is located in the superior mediastinum before reaching the base of the neck. The left phrenic nerve comes into close contact with the left CCA at its aortic origin; the left laryngeal recurrent nerve lies between the left subclavian and the CCA. The trachea and the brachiocephalic trunk are on the right side of the left CCA.

The cervical segments of the right and left CCAs show similar disposition and relationships while depicting an oblique and lateral course in the neck toward their bifurcation.

1.1.2.8 The Segments of the Internal Carotid Artery (Fig. 1.16)

The ICA may be divided for clinical, surgical, and diagnostic purposes in the following segments: cervical, petrous, cavernous, cisternal, and cerebral.

- *The cervical segment* begins at the level of the bifurcation, terminating as the artery enters the carotid canal. The origin and the initial part of the ICA can be easily approached; surgical access to the distal cervical portion of the internal carotid artery (i.e., above the digastric and stylohyoid muscles) requires additional maneuvers (see below).
- *The petrous segment* is contained in the carotid canal of the petrous temporal bone. The internal carotid artery curves anteriorly and medially. After leaving the bony canal, it enters the cranial cavity running upward and medially above the fibrocartilage that fills the foramen lacerum. Finally, it passes between the lingula and the petrosal process of the sphenoid bone. The artery can be approached at this level only by drilling the temporal bone.
- *The cavernous part* is covered by the lining endothelium of the sinus. The artery ascends toward the posterior clinoid process, passes on the side of the body of the sphenoid bone then turns anteriorly and passes lateral to the sella turcica. The artery then bends sharply back on itself under the root of the anterior clinoid process, pointing thus directly posteriorly (the carotid bend).
- *The cisternal segment*: after emerging from the cavernous sinus, the carotid artery penetrates the dura mater medial to the anterior clinoid process and passes under the optic nerve.
- *The cerebral (terminal) part*: the internal carotid artery ascends in the subarachnoid space up to its point of division, participating in the formation of the arterial circle (Willis). Four important arterial branches arise at the level of the terminal part of the internal carotid artery: the anterior communicating artery and the middle cerebral artery, which represent the so-called terminal branches, plus the posterior communicating artery and the anterior choroidal artery.

The ophthalmic artery gives off the central artery of the retina – that can be easily and directly examined through ophthalmoscopy, offering important details on the intracerebral circulation. Branches of the ophthalmic artery anastomose with the angular artery, a branch of the facial artery establishing thus an important communication between the internal and the external carotid arteries. The

direction of blood flow through this anastomosis can be easily demonstrated during the Doppler examination and offers important details on the intracerebral collateral flow between the left and right carotid arteries, also reflecting the degree of severity and hemodynamic significance of ICA stenosis.

Various classifications were elaborated during time, emanating from different premises and aiming distinct scopes. The Fisher classification (in retrograde fashion) addressed the early angiographic imaging requests for localization of regional tumor pathology and its effects on the ICA [34]. The following classifications addressed especially the intracranial aneurysms: Gibo et al. [35], Bouthillier et al. [36], and, later, the interest in microsurgical approaches and techniques focused on the intracranial ICA by Ziyal et al. [37]. Other more refined classifications emphasized the embryologic origins of the various segments of the ICA addressing all manner of cerebrovascular development and variation: Lasjaunias and Santoyo-Vazquez [38]. The classification of Bouthillier et al. which is most widely used nowadays is presented synthetically: C1, cervical; C2, petrous; C3, lacerum; C4, cavernous; C5, clinoid; C6, ophthalmic; and C7, communicating. Fisher's classification was limited by its less accurate anatomical details and not least, because segments were numbered opposite the direction of blood flow. Although widely used, the Bouthillier's classification was challenged by Ziyal et al. who did not recognize a distinct lacerum segment of the ICA. The endovascular (and angiographically based) classification system provided by Shapiro et al. [39] comprises seven segments of the ICA without alphanumeric correspondence: cervical, petrous, cavernous, paraophthalmic, posterior communicating, anterior choroidal, and terminus (and may serve better endovascular purposes). The classifications are not absolute as various diseases (and especially aneurysms) modify the local anatomical relationships. The variation of origination of the meningohypophyseal trunk, of the ophthalmic artery, etc., may render such partitions forced or artificial. Some of the emerging branches of the ICA may not be evident on angiogram (e.g., the caroticotympanic branch) and other landmarks also (the precise location of the petrolingual ligament, the location of the proximal dural ring, and so forth). The classifications contemplating the embryological framework have a limited surgical or endovascular relevance, and there is no single all-encompassing classification serving all purposes.

The segments of the vertebral artery (Fig. 1.17). The widely used and practical classification is reported here [40, 41]:

- *V0 = origin*. The very origin of the vertebral artery is sometimes called the V0 segment. The purpose of assigning a separate name to this portion of the vertebral artery arises from the need for drawing attention toward the adjacent parts of the subclavian artery and of the aortic arch also (in cases with aortic origin of the VA); lesions of these closely related arterial segments may limit, modify, or even contraindicate surgical or endovascular approaches.
- *V1 = pretransversal or extraosseous*. This is the portion of the vertebral artery most accessed in surgery. From its origin the VA ascends in the solid angle between the anterior scalene and longus colli muscles. It is covered by the vertebral vein. With older age or atherosclerotic disease, the V1 portion can show significant kinking. This is the portion of the vertebral artery that can be mobilized most, allowing, for example, its reimplantation in the common carotid artery or in the subclavian artery. This portion of the vertebral artery can be sometimes confused with the inferior thyroid artery. This latter structure lies however on a more superficial plane (anterior to the vertebral artery), crosses almost transversally behind the CCA from lateral to medial, and, characteristically, gives off numerous cervical branches. Another important detail is that the vertebral artery is the first (the most proximal) branch of the subclavian artery.
- *V2 = interosseous*. The VA passes through the transversal foramen of the first six cervical vertebrae. The roots of the cervical spinal nerves and the spinal ganglion are situated posterior to the VA. Surgical access to this part is more striving for the surgeon due to the need for partial bone resection. Exposure between the transverse processes is even more difficult due to the numerous venous tributaries and arterial muscular branches. Lesions of this portion of the VA can be however treated more conveniently and more rapidly, by using endovascular techniques and approaches. The vertebral artery is accompanied by a plexus of veins and by sympathetic nerves derived from the cervical ganglia, the latter forming the vertebral nerve. This segment of the vertebral artery gives off branches to the cervical nerves, vertebrae, intervertebral joints, neck muscles, and spinal branches for the cervical spinal cord. A prominent branch at C5 level anastomoses with the anterior spinal artery. The anastomoses with the deep cervical and with the ascending cervical artery can become conspicuous and offer parallel arterial pathways toward the distal VA (V3 segment). Conversely, such well-developed anastomoses may promote the steal syndrome even in case of occlusion of the vertebral artery at its origin (V0 and V1 segments).
- *V3 = distal extracranial segment or the atlas loop*. The artery runs laterally and then vertically toward the transverse foramen of the atlas (C_1); after passing through the foramen, the artery winds medially along the lateral mass of the atlas, pierces the posterior atlanto-occipital membrane, entering the dura mater and the arachnoid at the level of the foramen magnum. The suboccipital portion of the vertebral artery from the transverse foramen of the axis (C_2) to the posterior atlanto-occipital membrane is a relatively long segment, allowing a proper

surgical exposure for a bypass at this level. Numerous muscular and articular branches must be identified and interrupted, at this level.

- *V4 = intracranial/intradural*. This segment of the vertebral artery lies entirely in the subarachnoid space. Before the confluence of the two VAs, each gives off some important branches in the intracranial portion: the posterior spinal artery, the posterior inferior cerebellar artery (PICA), and the anterior spinal artery. A lower (i.e., more proximal) origin of the PICA may impede surgical maneuvers at the level of the intracranial vertebral artery.

1.1.2.9 The Anatomical Variations of the Vertebral Artery

Variations of the Origin of the VA The most frequently cited variation is the aortic origin of the left VA (this actually represents a variation of the branches of the aortic arch), and the most common site is between the left CCA and the left SCA; rarely the left VA can originate distal to the left SCA. The right VA may originate from the ascending aorta, between the right SCA and CCA (or bicarotid trunk – in the absence of the brachiocephalic trunk), between the left CCA and the left SCA, or even distal to the left SCA. With left-sided origin of the right VA, the artery depicts a retroesophageal course [42]. Rarely, a bilateral origin of the VA is also reported [43, 44]. The VA may originate distal to the thyrocervical trunk, from the thyrocervical trunk, costocervical, or from the inferior thyroid artery. Alternatively, the VA may give off the inferior thyroid artery. These subclavicular variations of origin may mislead the surgeon; more distal exposure of the VA toward the C6 transverse foramen is mandatory for a correct identification of the VA. Rarely, the VA may originate from the CCA, ECA, or ICA.

Variations of the Interosseous/Transversal Segment (V2) The VA may enter any of the transverse foramina from C_7 to C_3; when entering the upper cervical foramina, the VA has a pretransversal course, underneath the longus colli muscle being more exposed to injury during anterior approach to the cervical spine. Rarely, a fibrous band may intermittently compress the VA in extension of the neck. The VA may depict various types of loops, either at the level of the intervertebral disks or bodies, sometimes favored by the growth of osteophytic spurs. Fenestrations of the VA may also occur at this level (Fig. 1.18).

Variations of the Suboccipital Segment (V3) Duplications and fenestrations occur at C_1–C_2 level: one part of the VA follows the usual course, while the second runs intradurally. The condition when only the latter persists is named "*intradural course of the VA*." Calcification of the posterior atlanto-occipital membrane impedes the surgical exposure of the VA.

Variations of the Intradural/Intracranial Segment (V4) Fenestrations of this segment are associated with aneurysms and dissections [45]. The VA may terminate by giving off the PICA, an occipital branch, or a spinal artery – usually unilaterally. Bilateral anomalous termination is extremely rare [46]. An atretic VA does not join the BT, while the hypoplastic VA will join the BT however depicting a reduced caliber (less than 2–3.5 mm) as compared with the major, dominant VA. Usually, the left VA is dominant. It appears nonetheless surprising the fact that with vertebral steal syndrome, the two VAs become of an even caliber, including the V2 segment.

1.2 The Variability of the Territories of the Major Cerebral Arteries (Fig. 1.19)

Contrary to the usually followed schemes depicting the "normal" territories of the major cerebral arteries [47], a considerable interindividual and intraindividual (right-left and anterior-posterior) variation in the diameter and the volume of brain vascularized by each of the major artery was demonstrated [48]. Indeed, the neurodiagnostic of the watershed ischemia based on the location of the infarct appears to be more complex, and the templates of relatively unvarying territories of the major cerebral arteries would be most misleading [49] (Fig. 1.19). In addition, each of the individual territories may change in time as a result of the altering hemodynamic circumstances as well as in stenotic/occlusive arterial disease [50, 51]. A complex interdependence is also demonstrated between the blood flow, the arterial diameter, the resistance of the target tissues, and the volume of distal tissues vascularized. Moreover, there are well-known differences between the vascular resistance and blood flow of the cortical gray matter, white matter, and the gray matter of the basal nuclei. As mentioned before, the cerebral blood flow is maintained constant, at approximately 50 ml per 100 g of brain tissue^{-1}/min^{-1}. The mean flow in the gray matter is 3.9 times as high as the flow in the white matter, and the mean flow in the basal nuclei is only slightly higher than that in the cortex [52, 53]. There is a corresponding higher vascular density in the gray matter. Regarding the intraindividual variations, the most conspicuous asymmetry between the calibers of homonymous arteries was found for the anterior cerebral artery. Consequently, it appears that one of the most relevant elements of the arterial circle of Willis [54] is the anterior communicating artery (ACommA), and this particular may explain the higher prevalence of aneurysm development at this level [55]. Not least, the ACommA has significant branches vascularizing the optic chiasm, lamina terminalis, hypothalamus, diagonal band of Broca, cingulate gyrus, genu of corpus callosum, and pillar of fornix, and injury to these vessels caused either by aneurysmal rupture or surgical manipulation may lead to serious clinical deficits mostly psycho-organic syndromes [56].

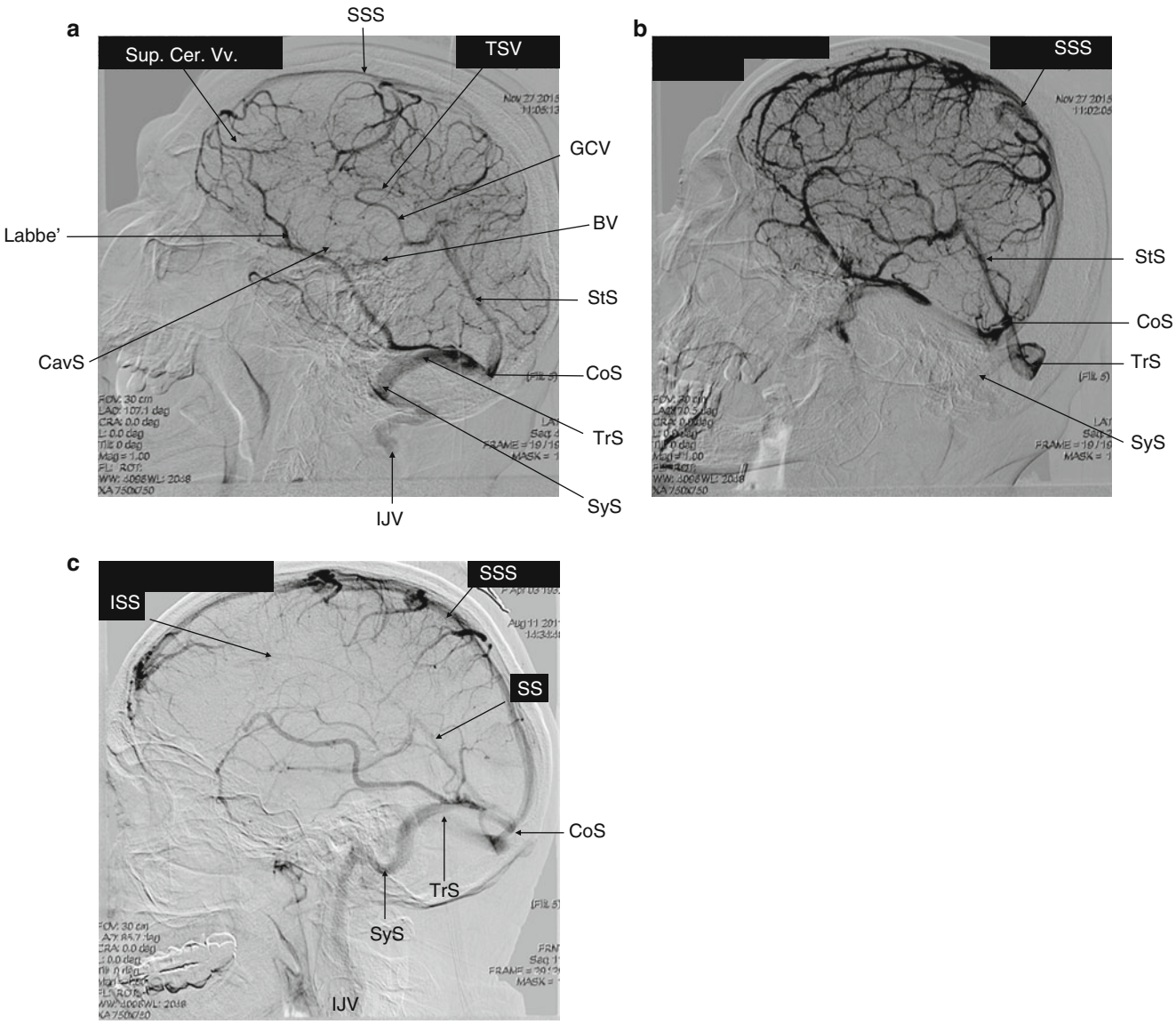
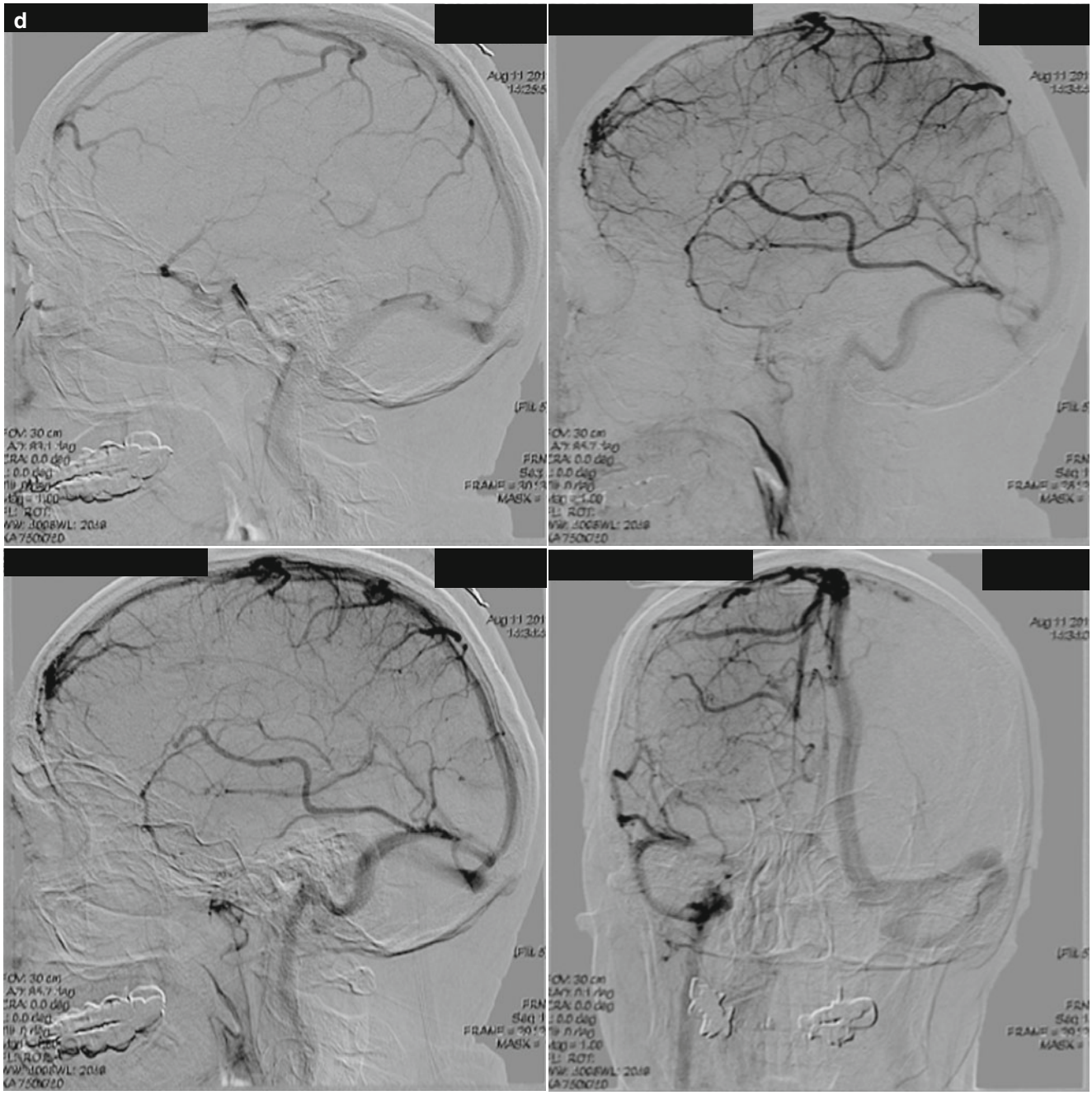


Fig. 1.1 The cerebral veins. Panel (**a**), lateral view of the main cerebral veins. *Sup. Cer. Vv.* superior cerebral veins, joining the superior sagittal sinus (*SSS*). The thalamostriate vein (*TSV*) merges into the great cerebral vein of Galen (*GCV*); after joining the basal vein of Rosenthal (*BV*), they form the straight sinus (*StS*). The StS unites with the transverse sinuses (*TrS*) at the level of the confluence of the sinuses (*CoS*). The TrSs continue with the sigmoid sinuses (*SyS*) eventually becoming the internal jugular veins (*IJV*). A conspicuous anastomosis is represented by the vein of Labbe' (*Labbe'*). The approximate position of the cavernous sinus (*CavS*) is also shown. Panel (**b**), an oblique projection demonstrating better the confluence of the sinuses. Panel (**c**), additional lateral view of the cerebral veins, demonstrating the inferior sagittal sinus (*ISS*), together with the previously mentioned sinuses (see above). Panel (**d**), various phases of venous flow as seen during a routine angiogram. See the legend above for details and abbreviations. Panel (**e**), a sequential demonstration of the cerebellar veins, eventually draining into the IJVs. Lateral view



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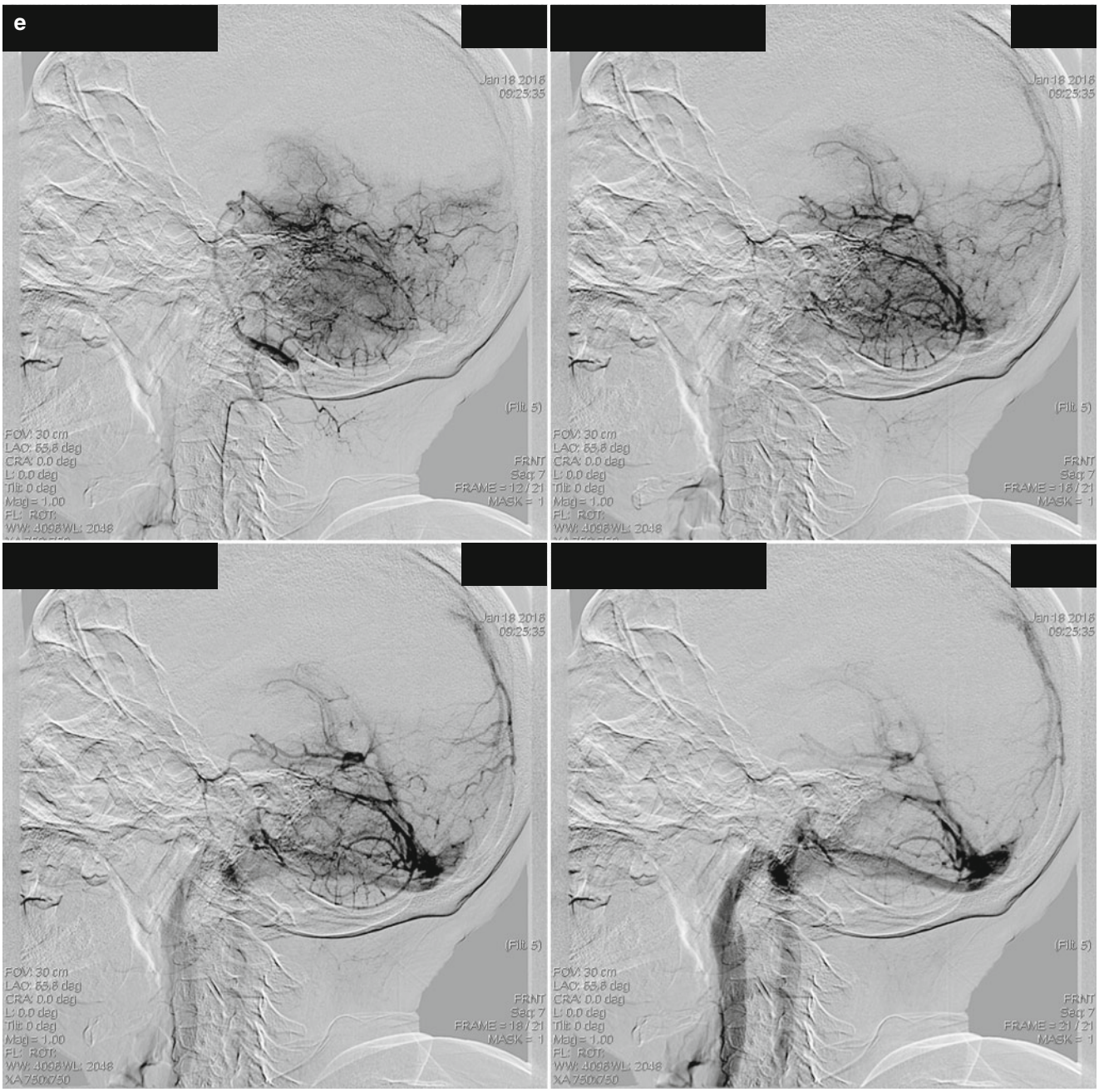

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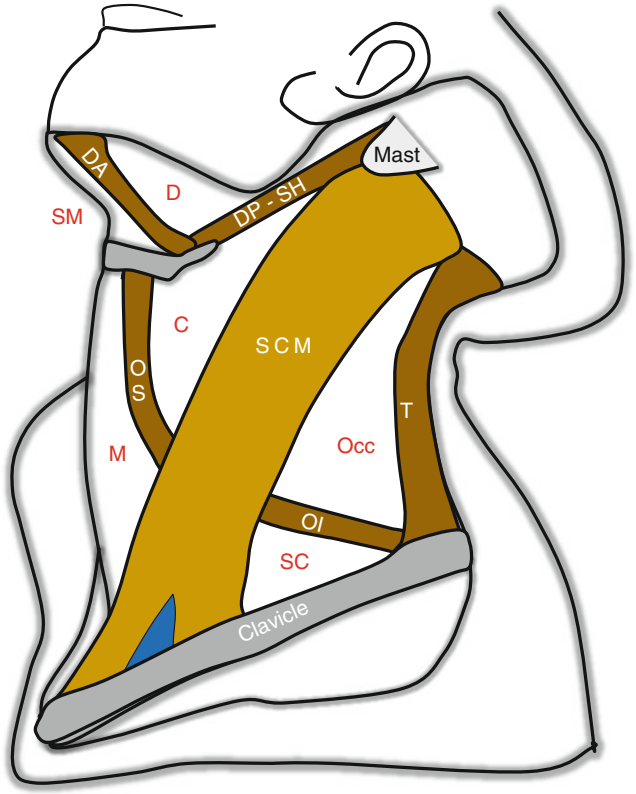


Fig. 1.2 Schematic representation of the neck triangles. Left side of the neck with the head in extension and contralateral rotation. *DA* digastric muscle, anterior belly; *DP-SH* digastric muscle, posterior belly and stylohyoid. *Mast* mastoid process, *OI* omohyoid inferior belly, *OS* omohyoid superior belly, *SCM* sternocleidomastoid muscle (and region). *T* trapezius muscle. The triangles are as follows: *C* carotid, *D* digastric, *M* muscular, *Occ* occipital, *SC* supraclavicular, *SM* submental. The small supraclavicular triangle formed between the clavicular and sternal heads of origin of the SCM is figured in blue; the IJV ("the inferior bulb") lies underneath

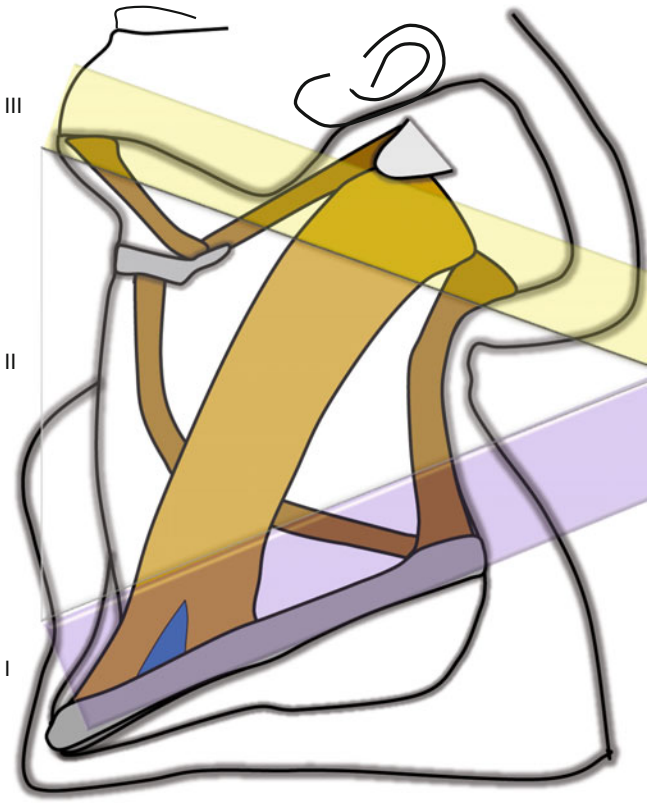


Fig. 1.3 The three surgical zones of the neck. Zone I extending about 1–2 cm superior to the clavicle is represented in violet. It corresponds roughly to the inferior belly of the omohyoid muscle. The small triangle between the two heads of origin of the SCM can be also included in this area. The IJV is readily approachable at this level. Zone II (*light gray*) extends superior to zone I, up to the level of the line continuing the inferior margin of the mandible. Note that with the head in extension, zone II appears more reduced posteriorly. Zone III (*yellow*) corresponds to the cranial base

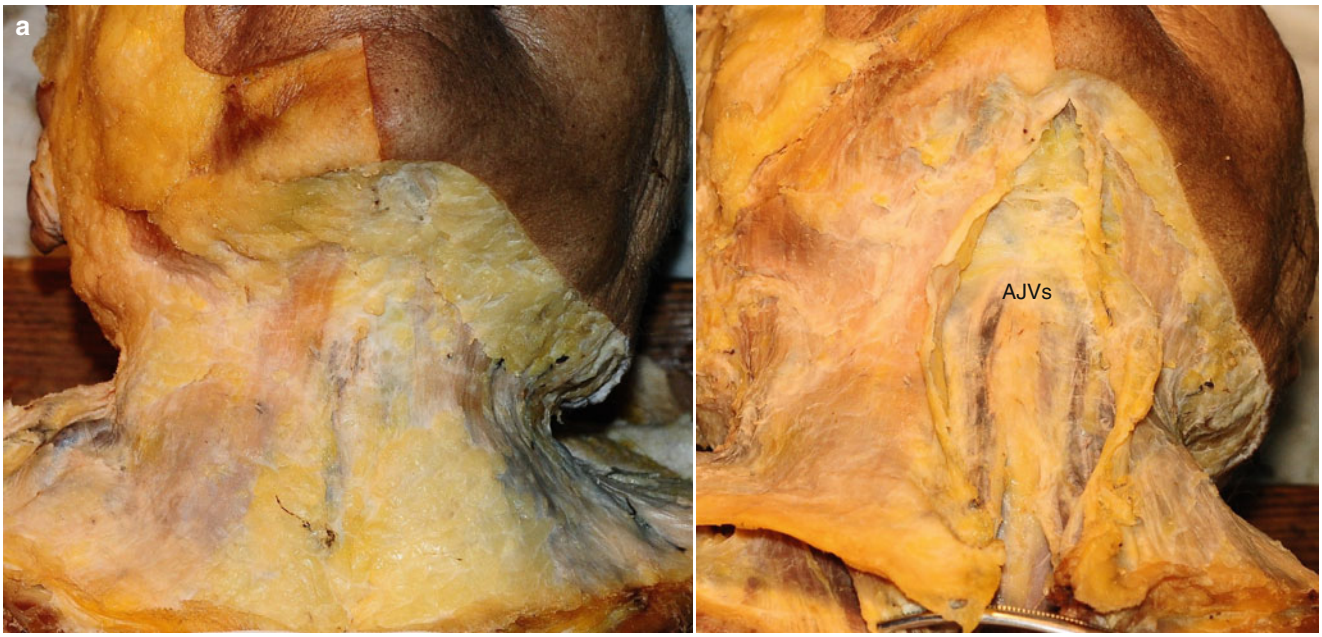
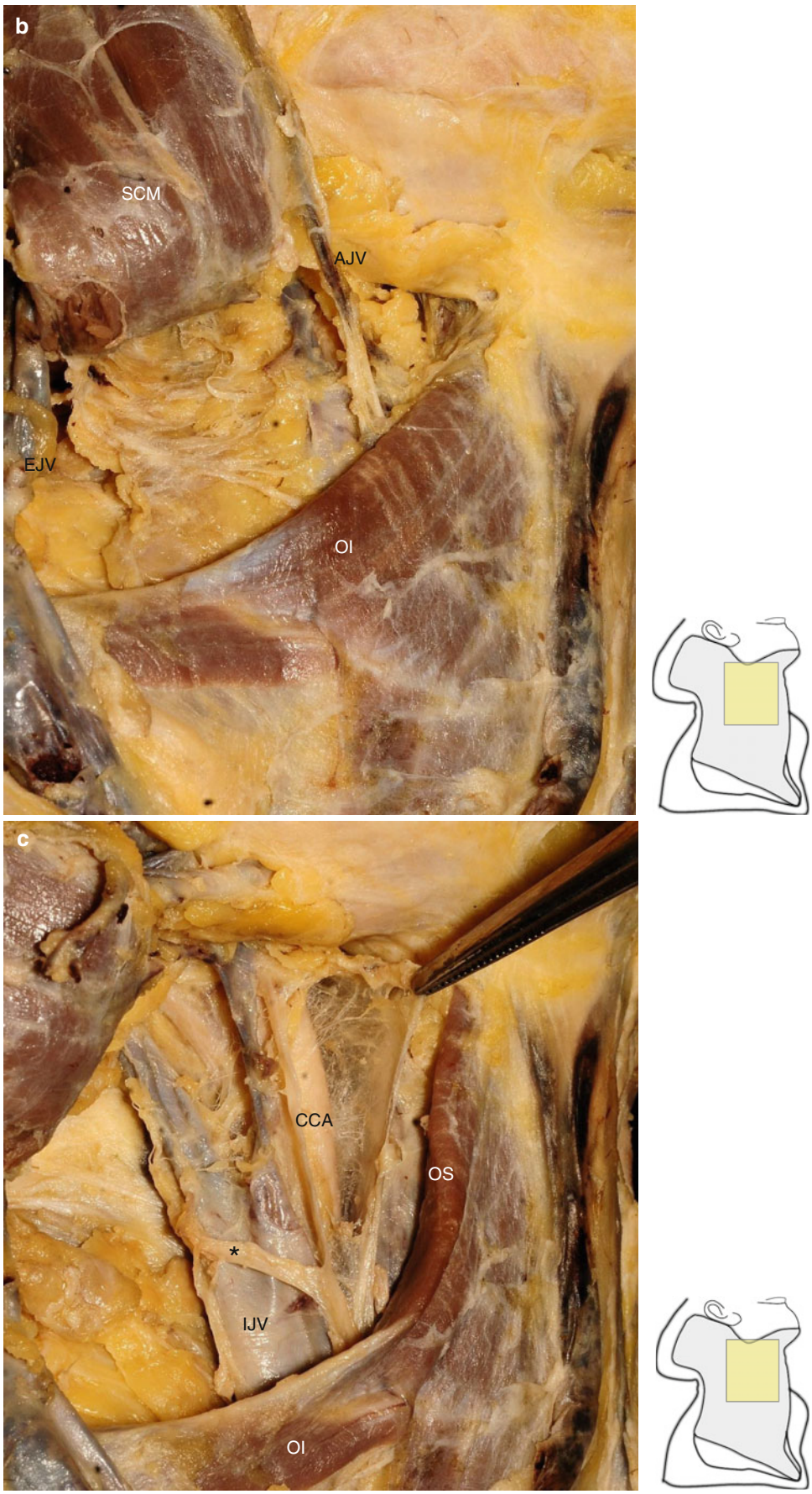


Fig. 1.4 The carotid sheath and the cervical fascia. Panel (**a**), the superficial layer of the cervical fascia and the platysma muscle. The anterior jugular veins (*AJVs*) are also visible. Panel (**b**), part of the carotid triangle appears superior to the omohyoid muscle (*OI* inferior belly). The omohyoid is covered and retained in its position by the middle layer of the cervical fascia (visceral or pretracheal layer). The anterior jugular vein (*AJV*) joins the IJV just underneath the OI. The external jugular vein (*EJV*) is partially visible in the lateral part of the image. *SCM* sternocleidomastoid muscle (cut and retracted). Panel (**c**), the carotid triangle and the carotid sheath. The dissection proceeds deeper, superior to the inferior belly of the omohyoid muscle (*OI*). By opening the sheath, direct access is possible to the common carotid artery and bifurcation (*CCA*), the internal jugular vein (*IJV*), the cervical ansa (hypoglossal ansa*). Note the dense tissue of the carotid sheath (held with pickups). Panel (**d**), further dissection demonstrates the carotid bifurcation, the vagus nerve (*X*), and the sympathetic trunk (*S*); the latter is covered/contained by the prevertebral layer of cervical fascia (the prevertebral fascia was dissected in order to demonstrate the sympathetic trunk). Intraoperative image, at the right for comparison (in the intraoperative image, the sympathetic trunk is not readily visible, being covered by the pretracheal layer of the cervical fascia). Panel (**e**), the pretracheal fascia covers the infrahyoid muscles, the thyroid and parathyroid glands, the trachea, and the larynx. The thyroid gland is visible, together with the superior and inferior thyroid vessels and the recurrent laryngeal nerves (Recc). *CCA* common carotid artery, *ITA* inferior thyroid artery (note its transversal course from lateral to medial), *ITV* right inferior thyroid vein, *X* vagus nerve



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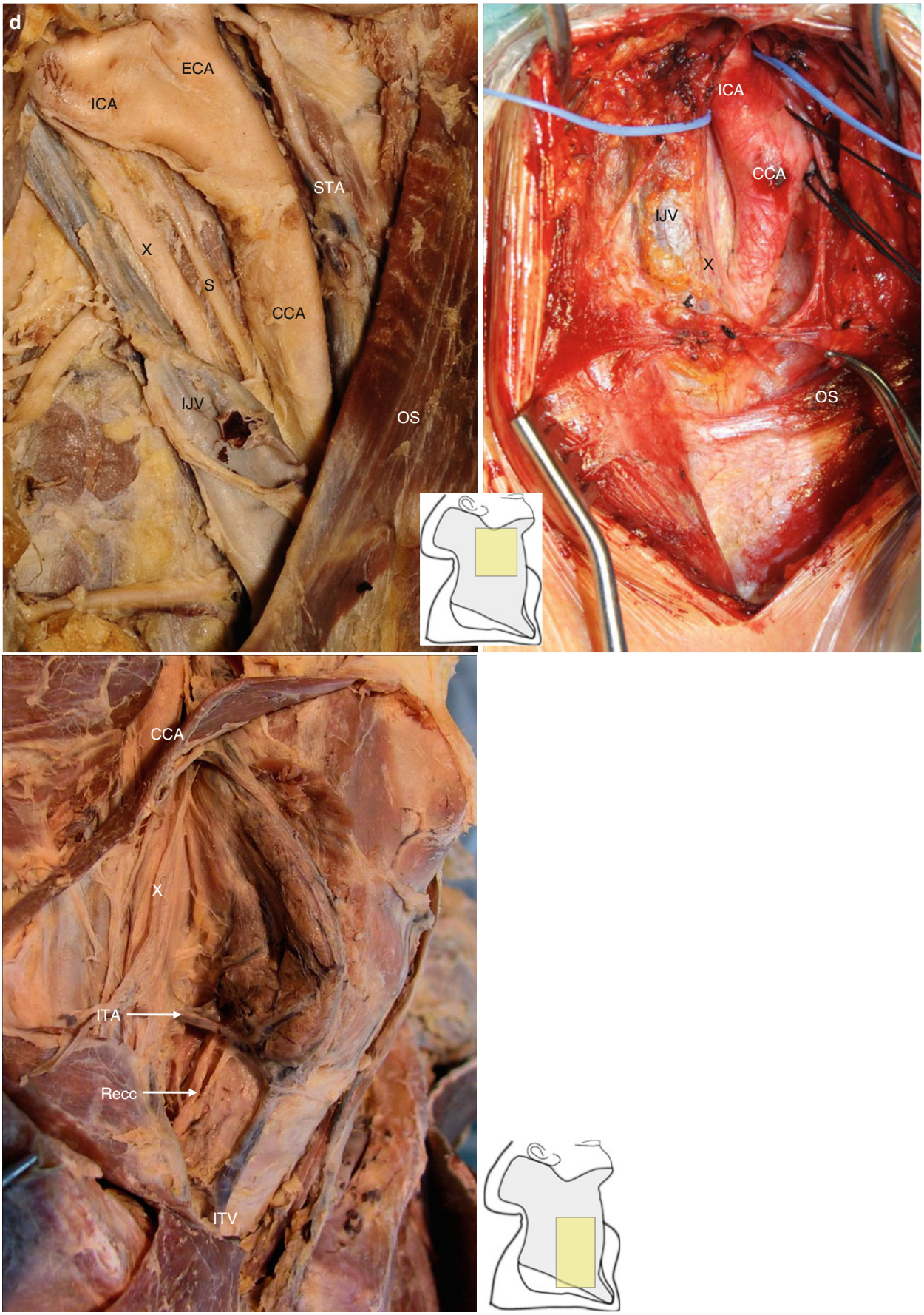

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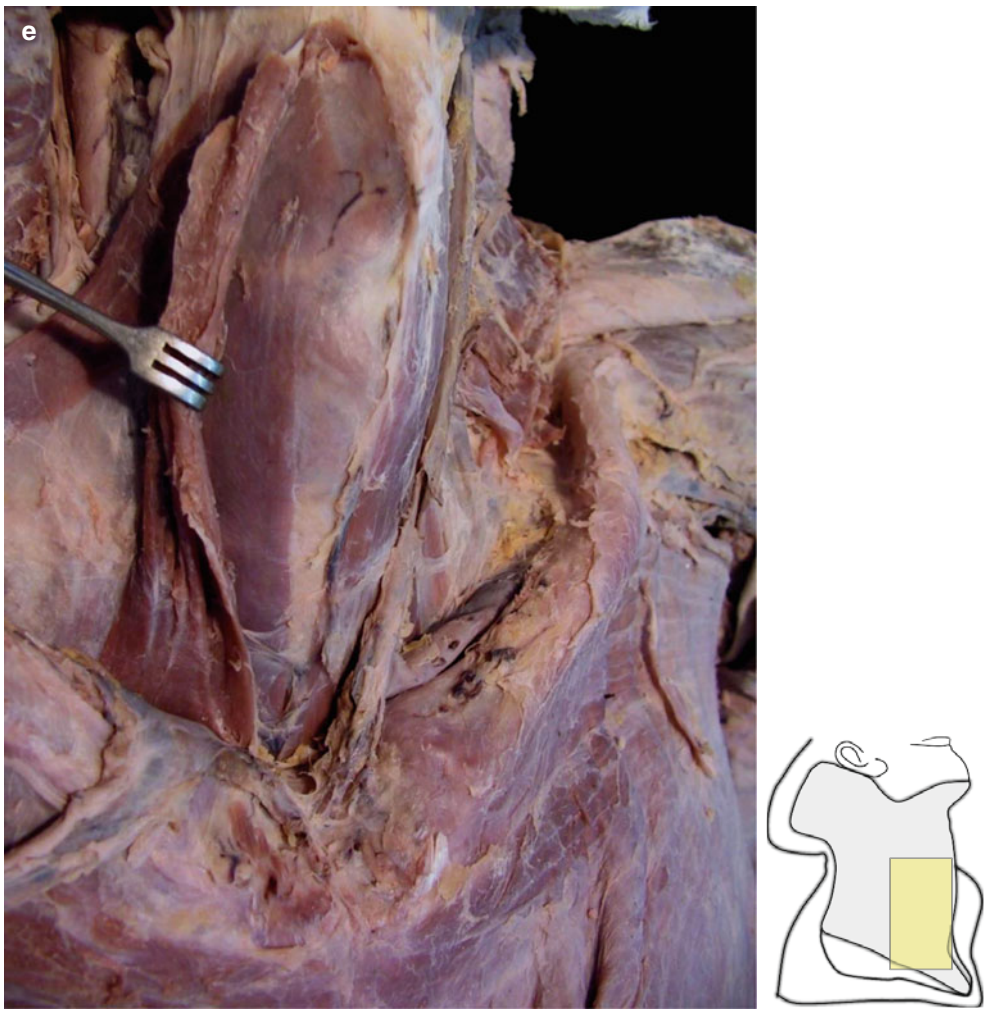

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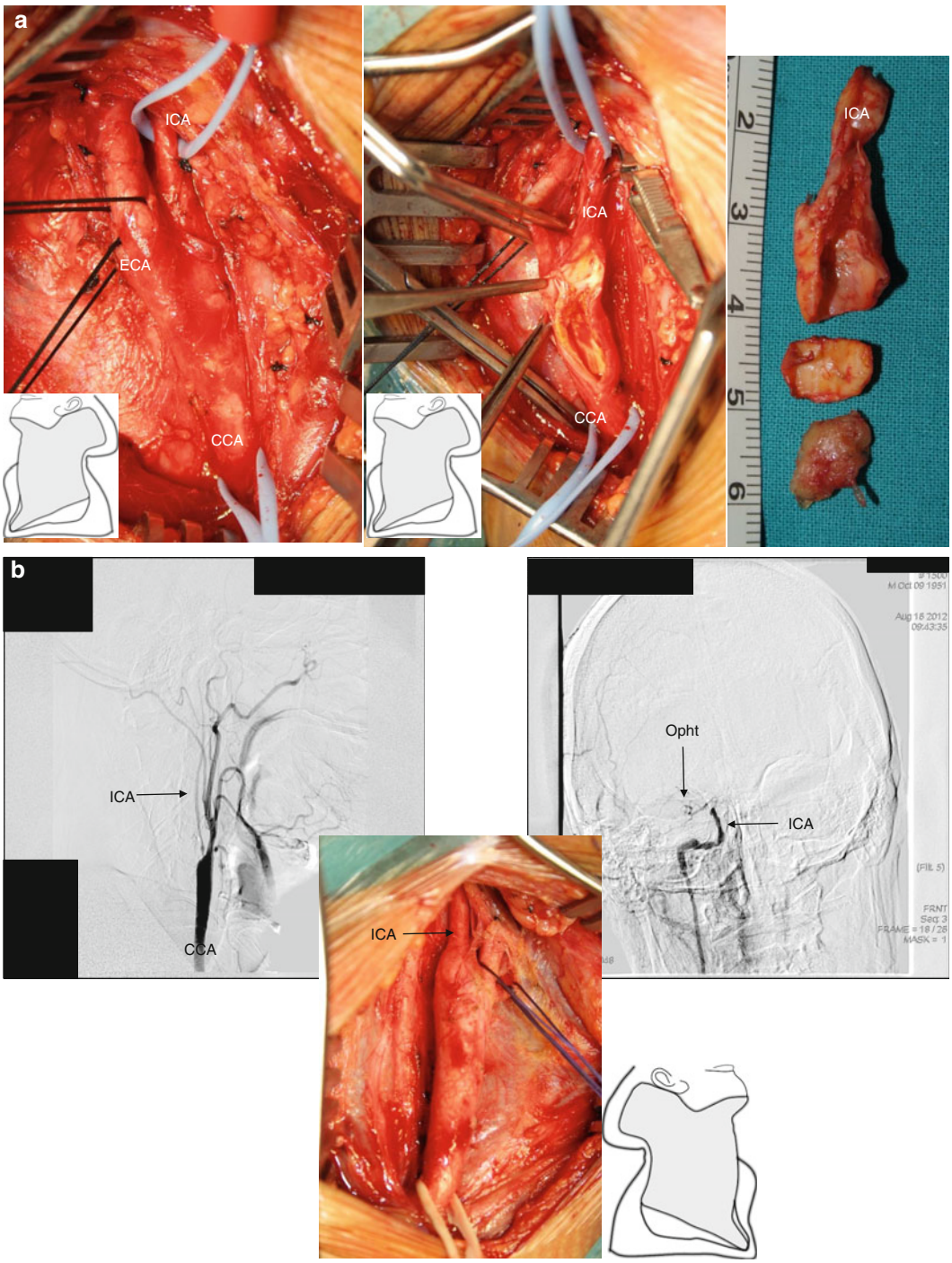
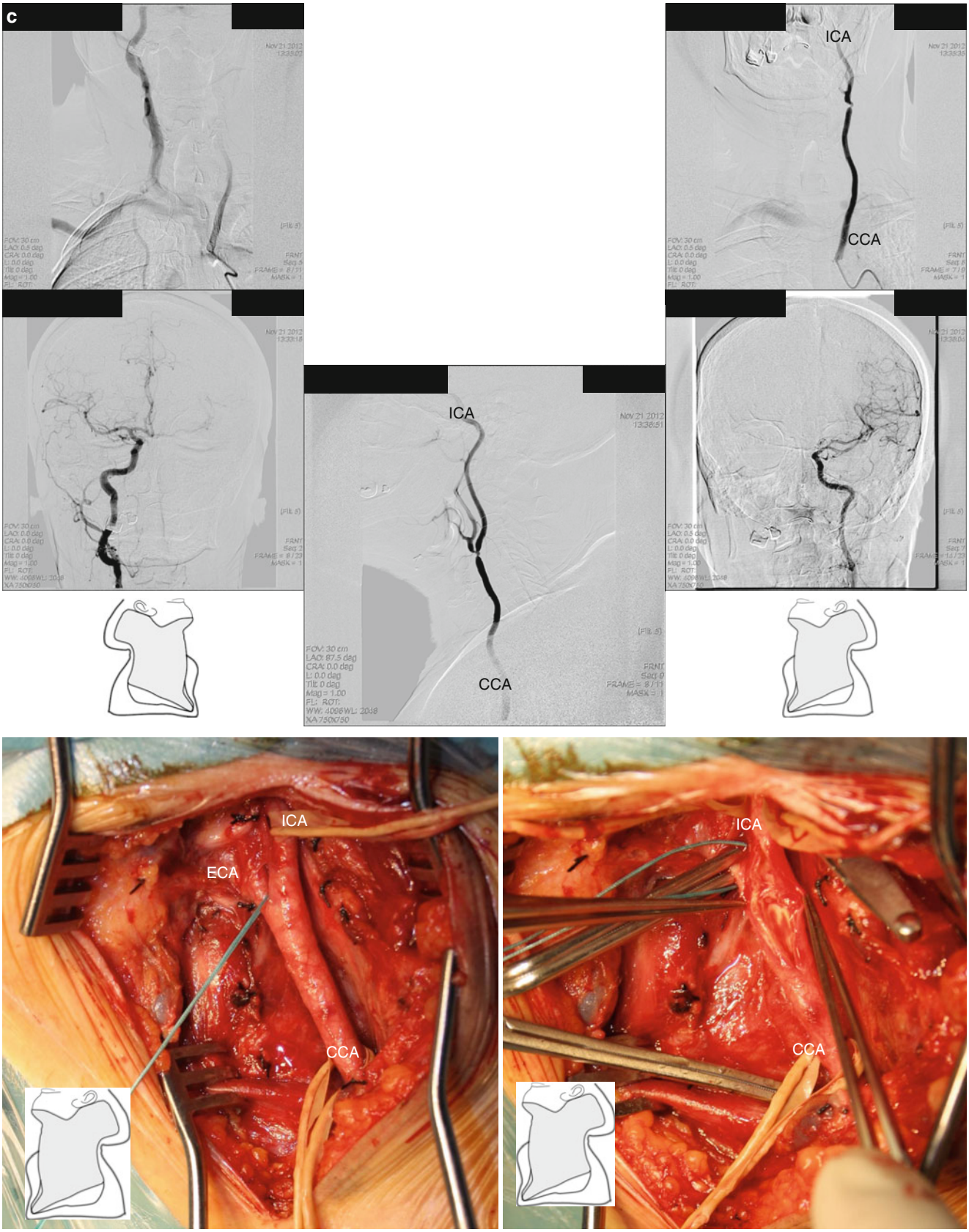


Fig. 1.5 Variations of the carotid bifurcation. Panel (**a**), hypoplastic ICA. The caliber of the ICA is evidently more reduced as compared with the ECA (ICA is about half of the ECA diameter). Note also that the carotid bulb is not apparent. A long atherosclerotic plaque occupies most of the carotid bifurcation and of the proximal segment of the ICA. Intraoperative aspect of left carotid bifurcation and of the excised plaque. Panel (**b**), hypoplastic, slender ICA terminating by giving off the ophthalmic artery (Opht). Panel (**c**), hypoplastic CCA. The CCA has almost the same caliber as the ICA. The right CCA, ICA, is of normal diameter, and there is an important participation of the right carotid system to the vascularization of the brain, with ACA and MCA on the left side fed from the right ICA. Panel (**d**), absence of the carotid bulb. There is no carotid bulb, and the carotid bifurcation appears as a double-barrelled gun with the ICA and ECA of almost even caliber. Panel (**e**), inverted carotid bifurcation. Intraoperative aspect of the right carotid bifurcation. The ECA is anterolateral, while the ICA is posteromedial. Note that in this case also, there is no definite carotid bulb. Panel (**f**), inverted carotid bifurcation: sagittally disposed ICA and ECA. The ECA is superposed over the ICA. *STA* superior thyroid artery. Mobilization of the carotid bifurcation allows a good exposure of the more deeply situated ICA. Panel (**g**), bilaterally inverted carotid bifurcations. On both sides, the ICAs are located posterior and medial. The superior thyroid artery (*STA*) crosses the bifurcation. Panel (**h**), kinking of the CCA and lower bifurcation, approximately at the level of C_4–C_5. Panel (**i**), sagittal bifurcation with ECA anterior and ICA posterior. The superior laryngeal nerve (SLN) passes between the ICA and the ECA



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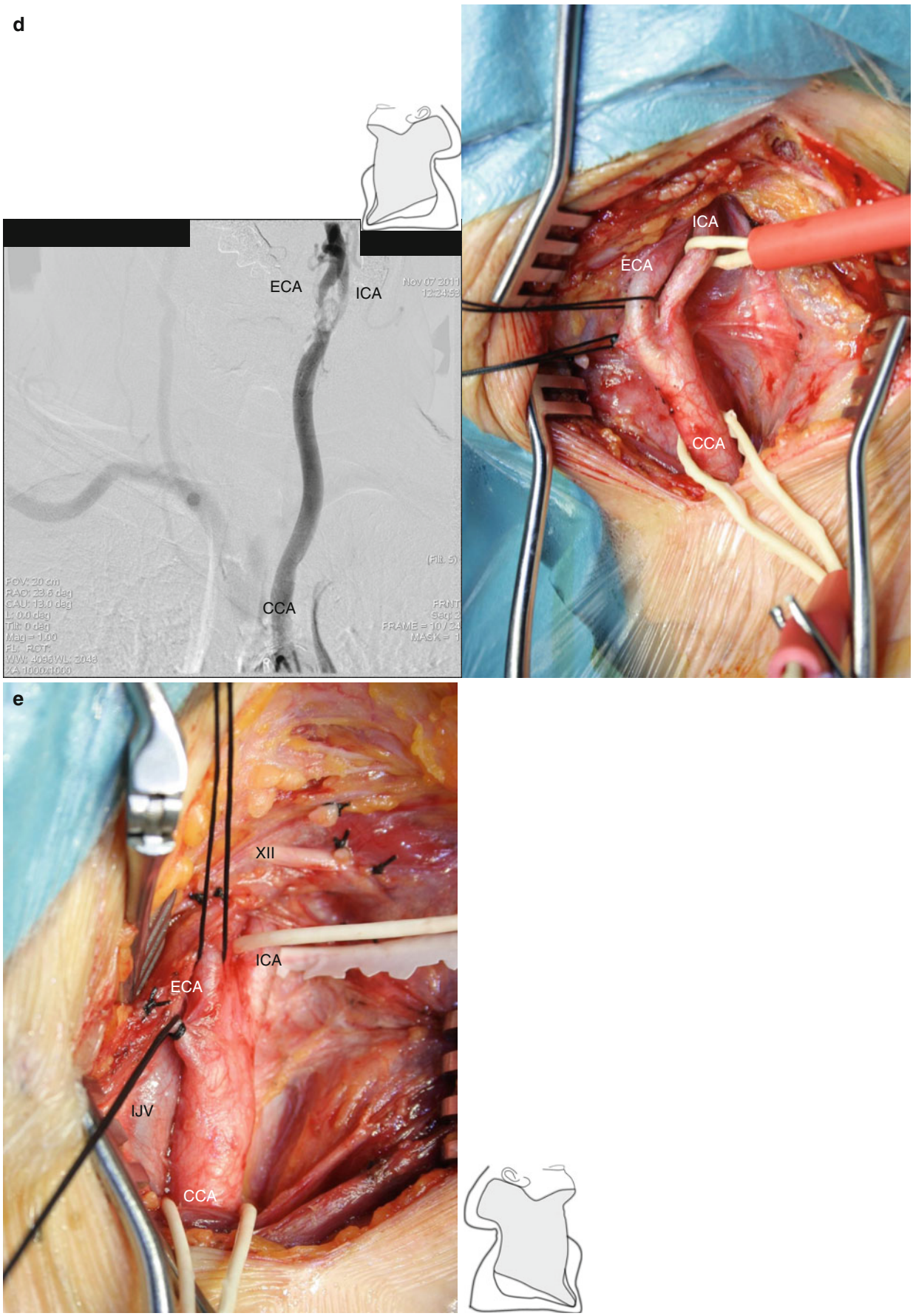

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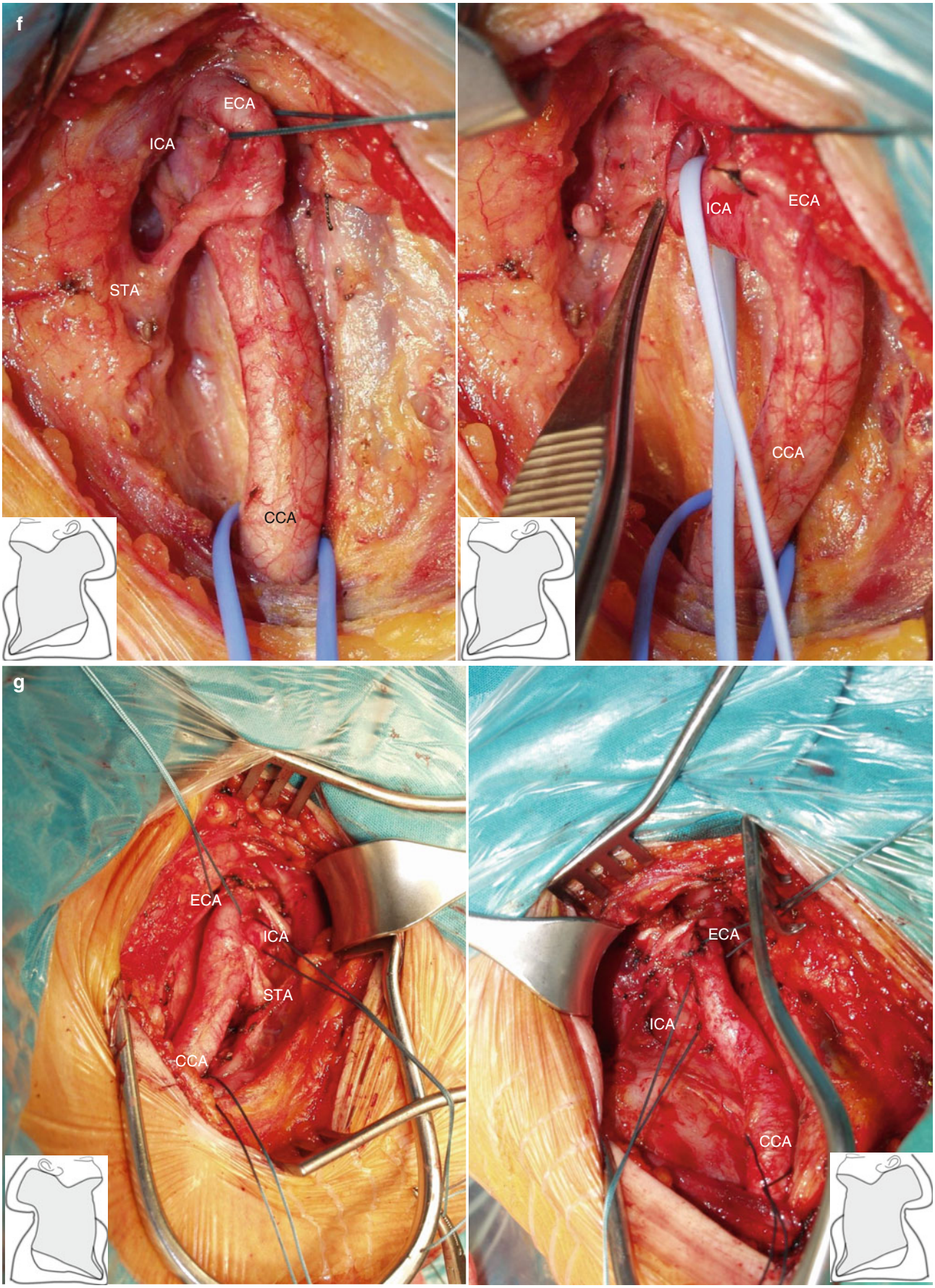

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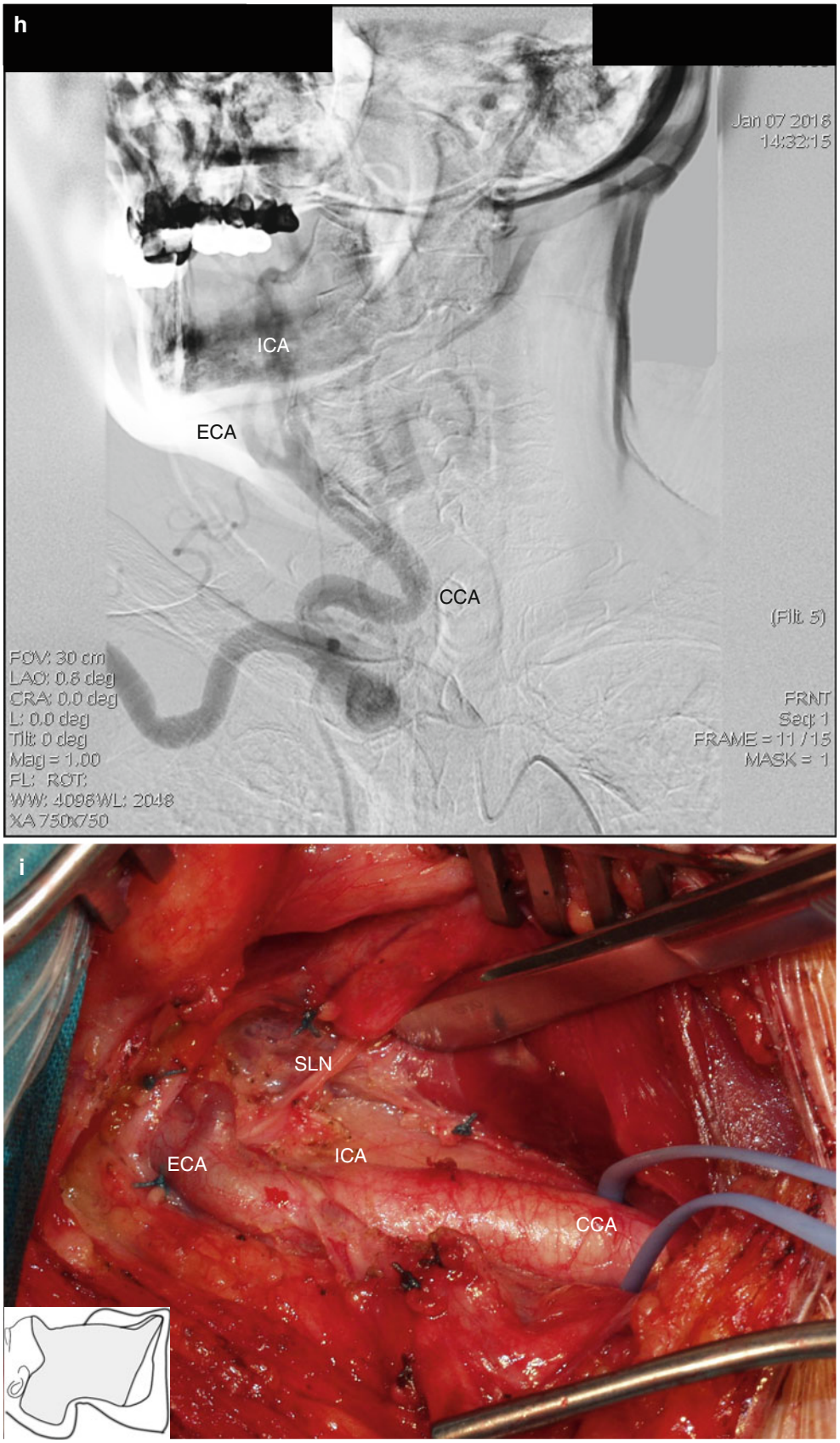

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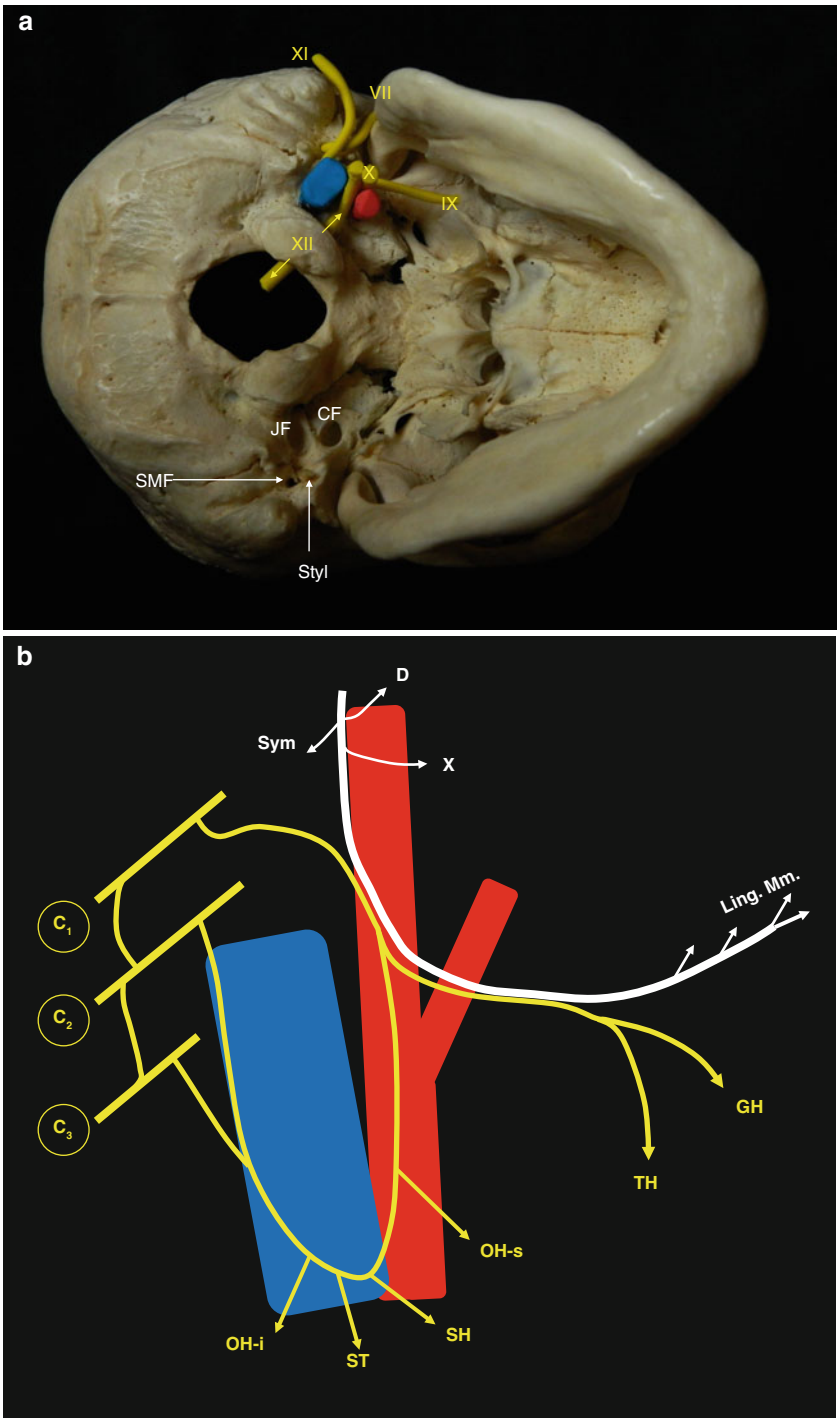


Fig. 1.6 Anatomical relationships at the cranial base. Panel (**a**), a schematic reconstruction and demonstration of the main structures at the cranial base. The ICA is depicted in red, while the IJV in blue. The ICA enters the skull at the level of the carotid foramen (*CF*) accompanied by the sympathetic fibers (not shown). The IJV exits the skull at the level of the jugular foramen (*JF*) sharing the same orifice with the glossopharyngeal (*IX*), vagus (*X*), and the accessory nerve (*XI*). Nerves IX and X are pre-jugular, while XI is retro-jugular in most of the cases. The hypoglossal nerve (*XII*) courses the anterior condylar (hypoglossal) canal and passes posterior to the ICA, IX and X nerves, descending over the ICA down to the level of the bifurcation which it eventually crosses from lateral to medial. The facial nerve (*VII*) exits the stylomastoid foramen (*SMF*) being separated from the ICA by the styloid process (*Styl*) and muscles. Panel (**b**), schematic drawing of the hypoglossal nerve (*XII*) and of the cervical (hypoglossal ansa). The carotid vessels are colored red and the IJV in blue. The hypoglossal nerve is colored in white and the cervical anterior rami in yellow. The branches of the XII nerve are *D* for dura mater, *SYM* communicating with the sympathetic trunk, *X* communicating branch to the superior vagal ganglion. The terminal branches are for the intrinsic lingual muscles (Ling. Mm.). The superior root of the cervical ansa originates in the ventral ramus C1, while the inferior root, from C2 and C2. Branches from the ansa innervate the hyoid muscles: *OHi* omohyoid inferior belly, *OHs* omohyoid superior belly, *ST* sternothyroid, *SH* sternohyoid, *TH* thyrohyoid, and *GH* geniohyoid. The ansa courses over the IJV although numerous variations are encountered

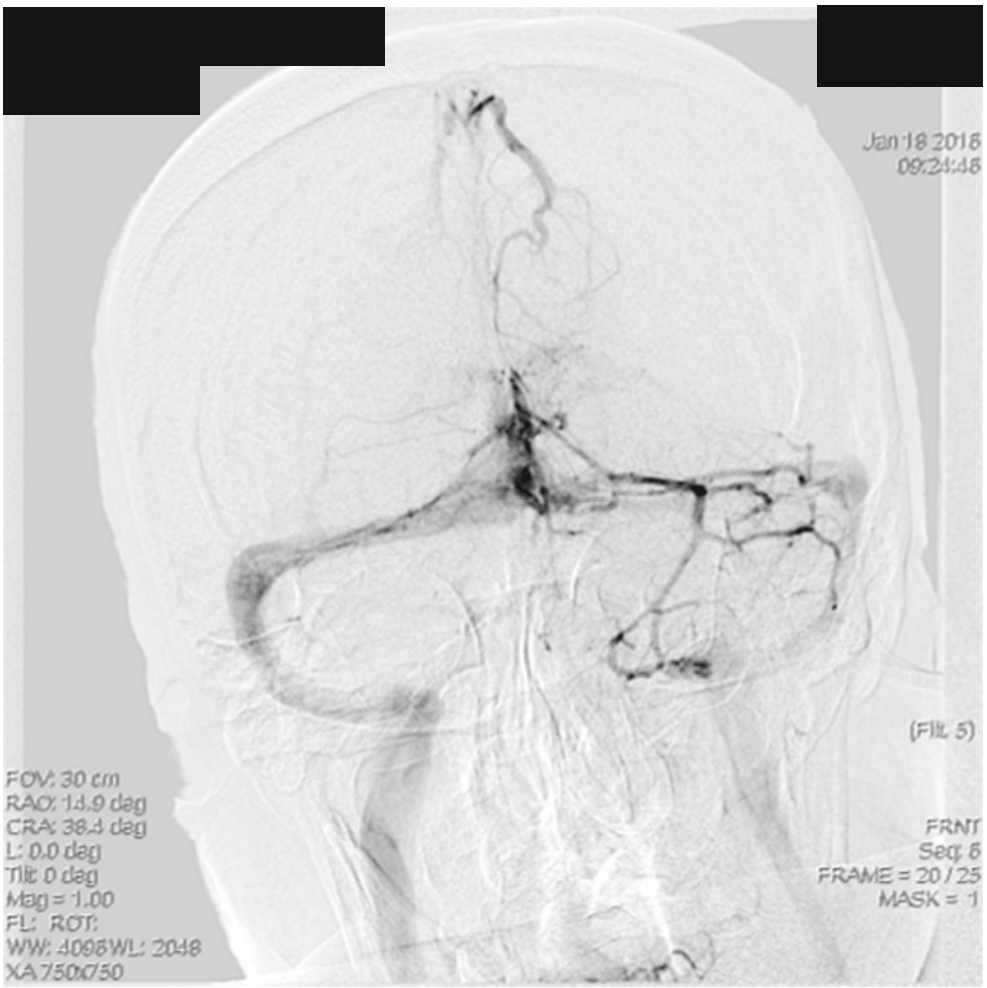


Fig. 1.7 The natural asymmetry of the internal jugular veins. The IJVs are frequently found to be asymmetric, reflecting the differences between the dural transverse and sigmoid sinuses. The jugular foramina (lodging the superior bulb of the IJVs) are also dissimilar. This discrepancy has clinical relevance in case of IJV thrombosis (if the dominant IJV is occluded), central vein catheterization, and, not least, during surgery. At times, the superior IJV can be of small caliber, but after receiving larger tributaries in the upper neck (retromandibular vein, thyro-linguo-facial trunk), it becomes conspicuous. The tract of the IJV can also depict variations of surgical relevance (see Fig. 1.8)

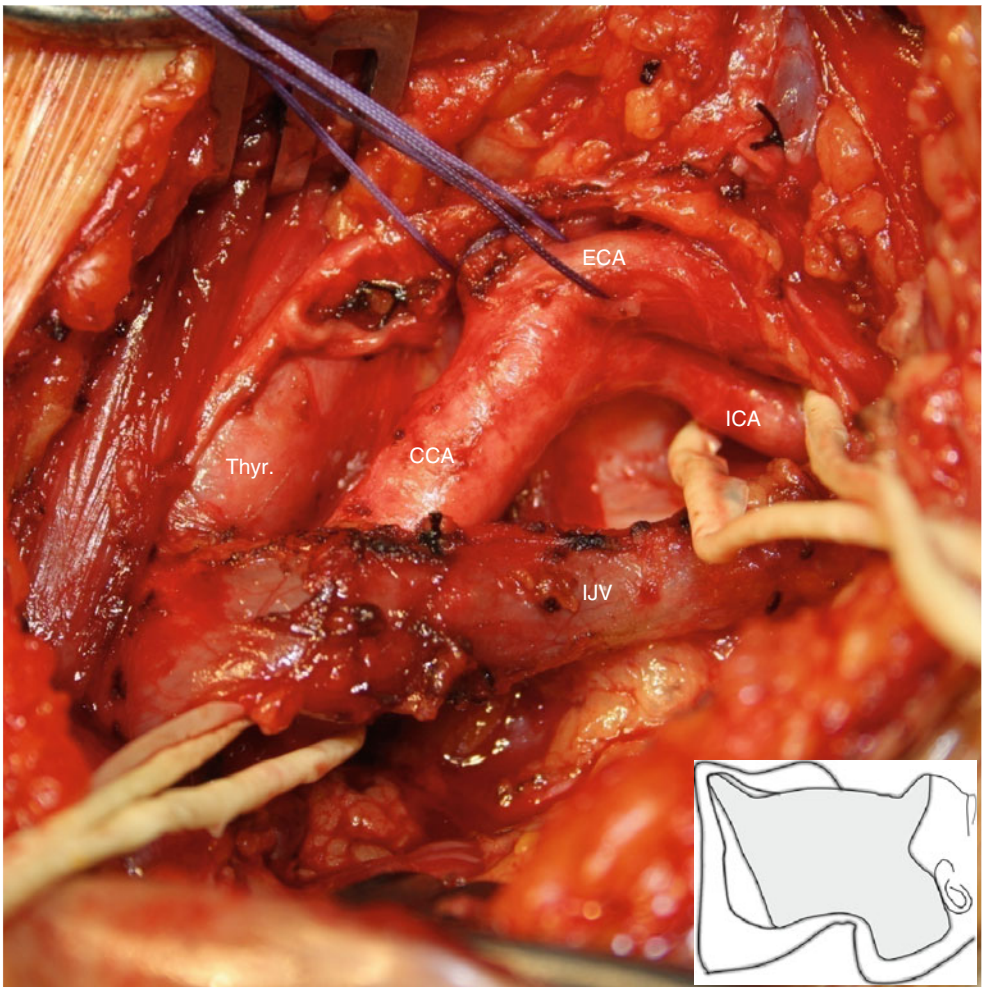


Fig. 1.8 Further anatomical variations of the internal jugular veins. The IJV crosses the carotid bifurcation from lateral to medial. The IJV becomes anterior and medial in position relative to the CCA. This variation has clinical relevance for two reasons: First, the IJV must be protected during surgical exposure of the CCA, as the vein crosses the artery. Additionally, the anteriorly coursing IJV can be mistaken for a collateral branch and inadvertently ligated. Second, there would be a difficult catheterization of the IJV if it lies anterior and medial to the CCA or the CCA can be punctured instead of the vein. For other variations, see Fig. 1.10 b, c

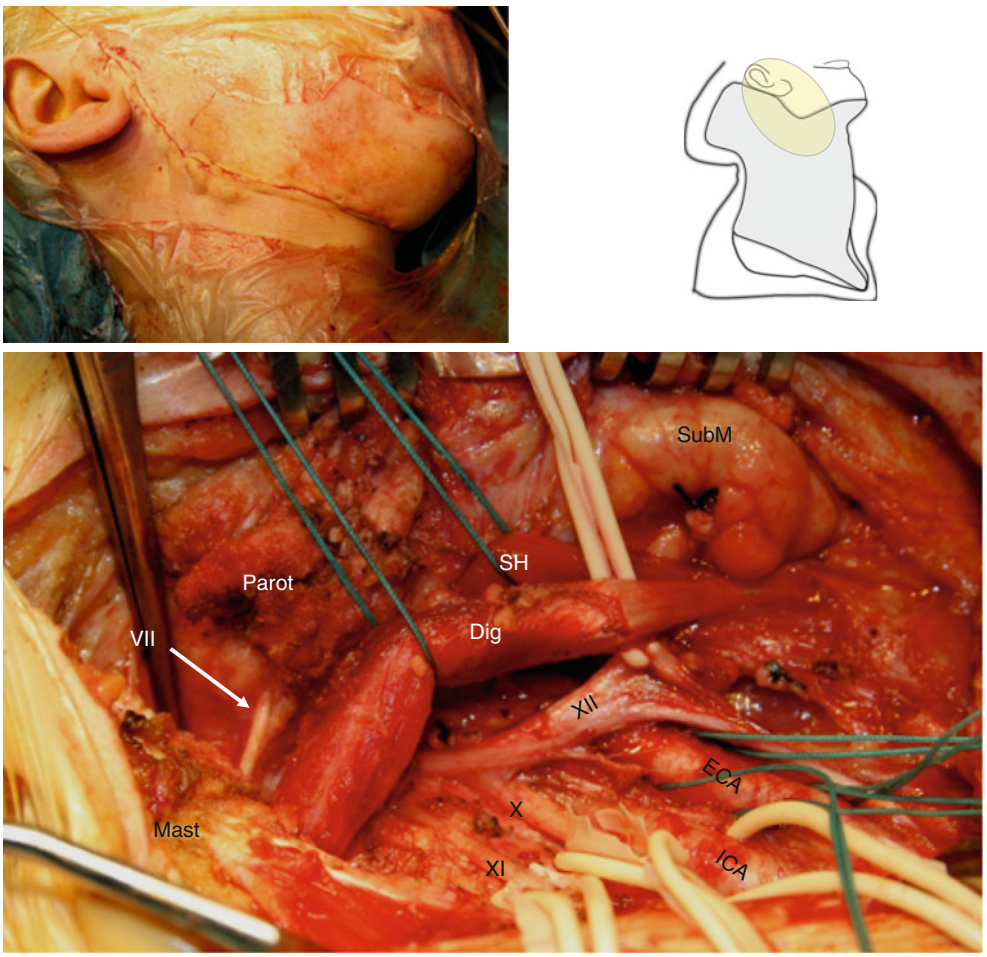


Fig. 1.9 The extracranial portion of the facial nerve and anatomical relationships at cranial base. This aspect is also discussed with the exposure of the ICA high in the neck. Intraoperative aspect. Right side. Preauricular extension of the neck incision. The carotid bifurcation is exposed (*ICA* and *ECA*). The vagus (*X*), accessory (*XI*), and hypoglossal (*XII*) nerves are exposed and circled with elastic tapes. The posterior belly of the digastric muscle (*DIG*) and the stylohyoid muscle (*SH*) are dissected and gently mobilized (in this way, cutting of these two muscles is not necessary). The facial nerve (VII – indicated by arrow) is exposed upon its exit from the stylomastoid foramen, deep to the mastoid process (*Mast*). The facial nerve crosses the retromandibular space to enter the parotid gland (*Parot*). The submandibular salivary gland (*SubM*) is also visible. The main trunk of the facial nerve can be readily identified and protected. It will eventually divide in the very substance of the parotid gland

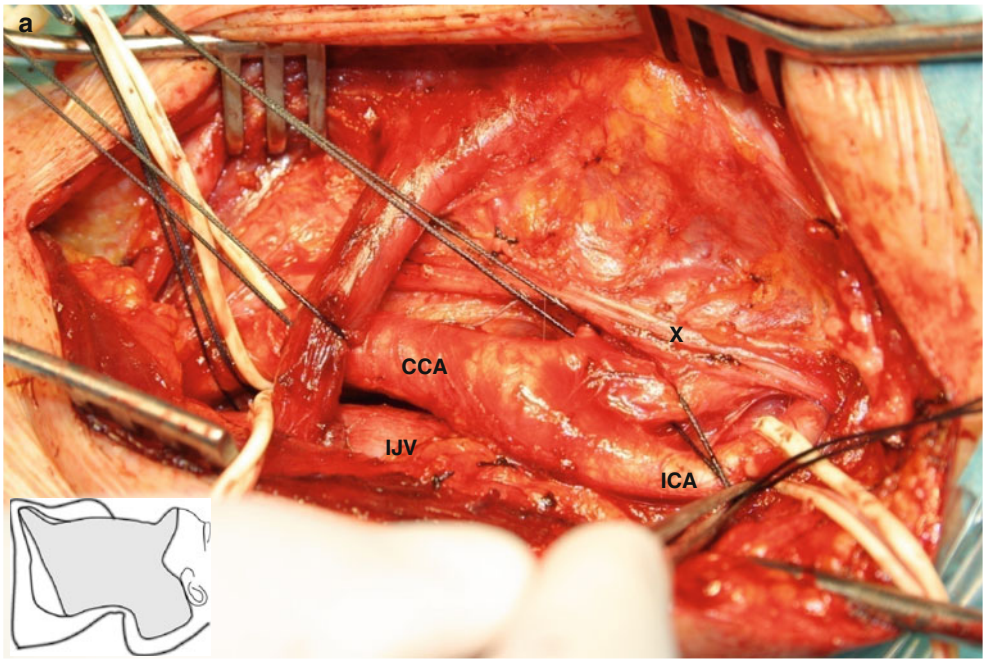
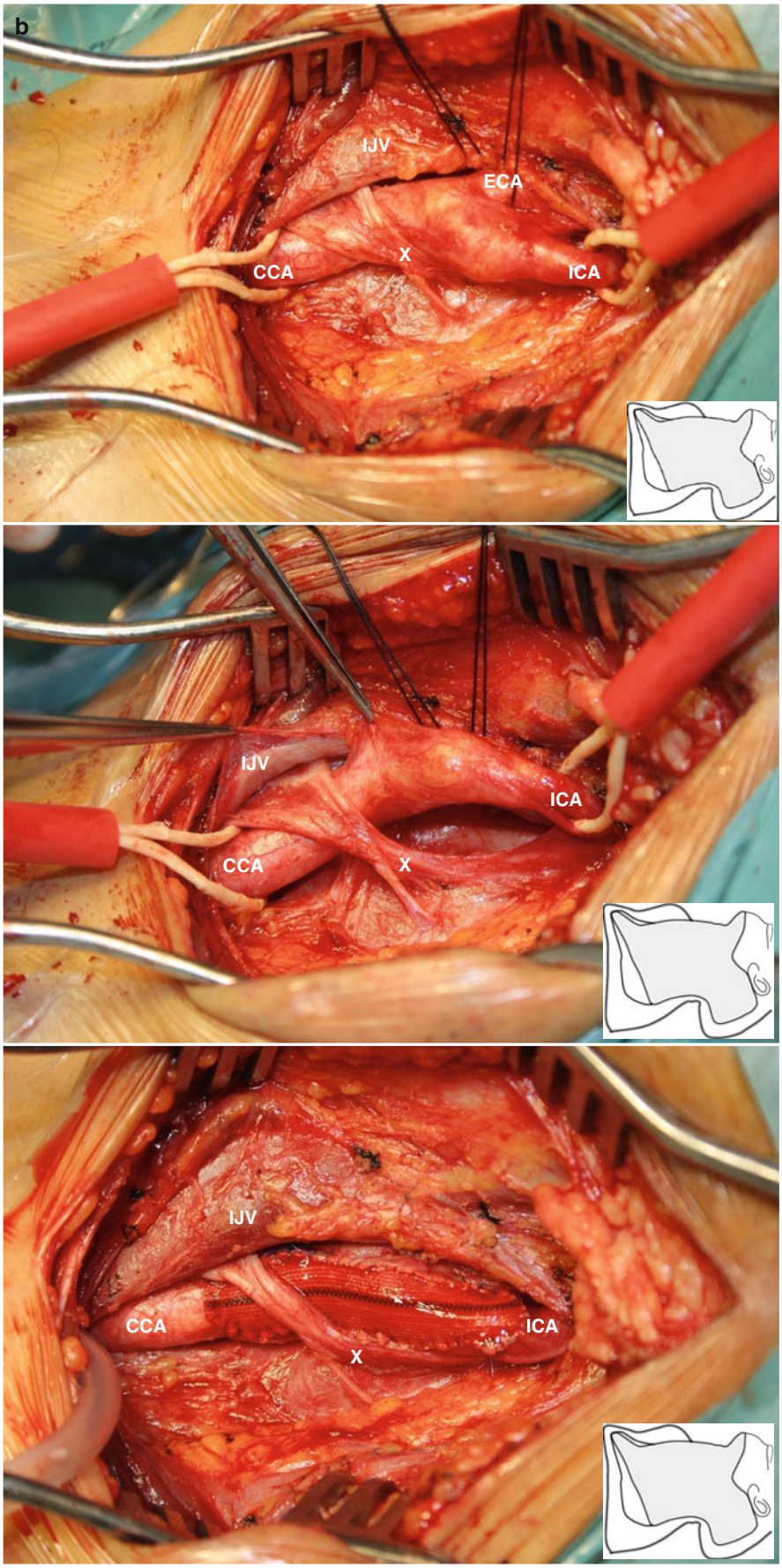
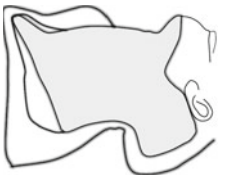


Fig. 1.10 Variations of the vagus nerve in the neck. The normal position of the vagus nerve in the neck is between the ICA (and CCA) and the IJV, on a slightly more posterior plane than the vessels. Sometimes, however, the vagus nerve may depict a different position. Such variations are surgically relevant, and the surgeon must be aware on modified anatomical relationships, in order to avoid any damage of the nerve. During locoregional anesthesia when the anesthesiologist tries to infiltrate the area of the carotid sinus and glomus, inadvertent block of the vagus nerve may ensue. Panel (**a**), vagus nerve in anterior, medial, and superficial position crossing the carotid bifurcation. Panel (**b**), vagus nerve crossing the carotid bifurcation. Note that in this case, the IJV is also in abnormal position, i.e., anterior and medial to the ECA and CCA. Successive images demonstrating the surgical approach, with mobilization of the carotid bifurcation and of the vagus nerve, allowing the endarterectomy and insertion of the synthetic patch

Fig. 1.10 (continued)





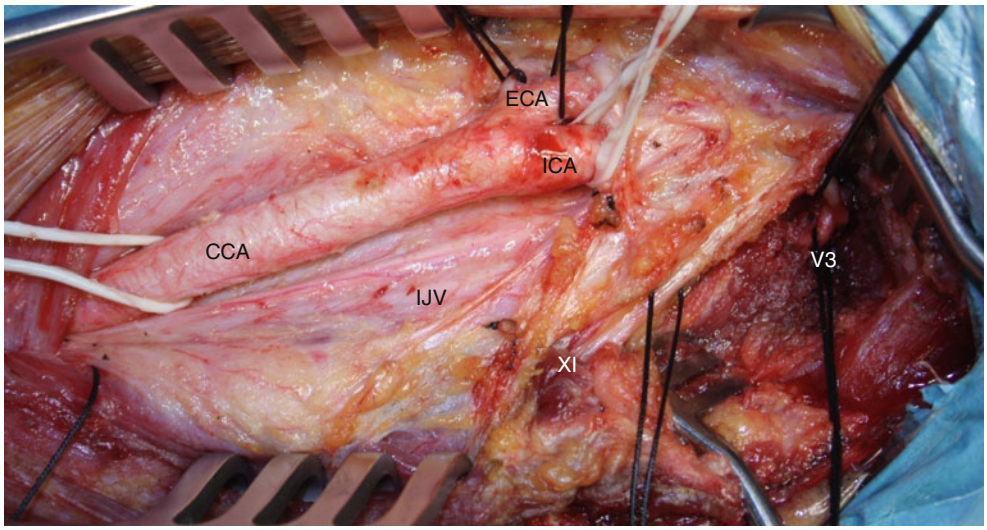


Fig. 1.11 Accessory nerve in pre-jugular position. The accessory nerve (*XI*) may depict a pre-jugular position and may be damaged more easily when exposing the carotid bifurcation during removal of cervical lymph nodes. In the case illustrated, the pre-jugular accessory nerve can be further damaged while approaching the suboccipital vertebral artery (*V3*)

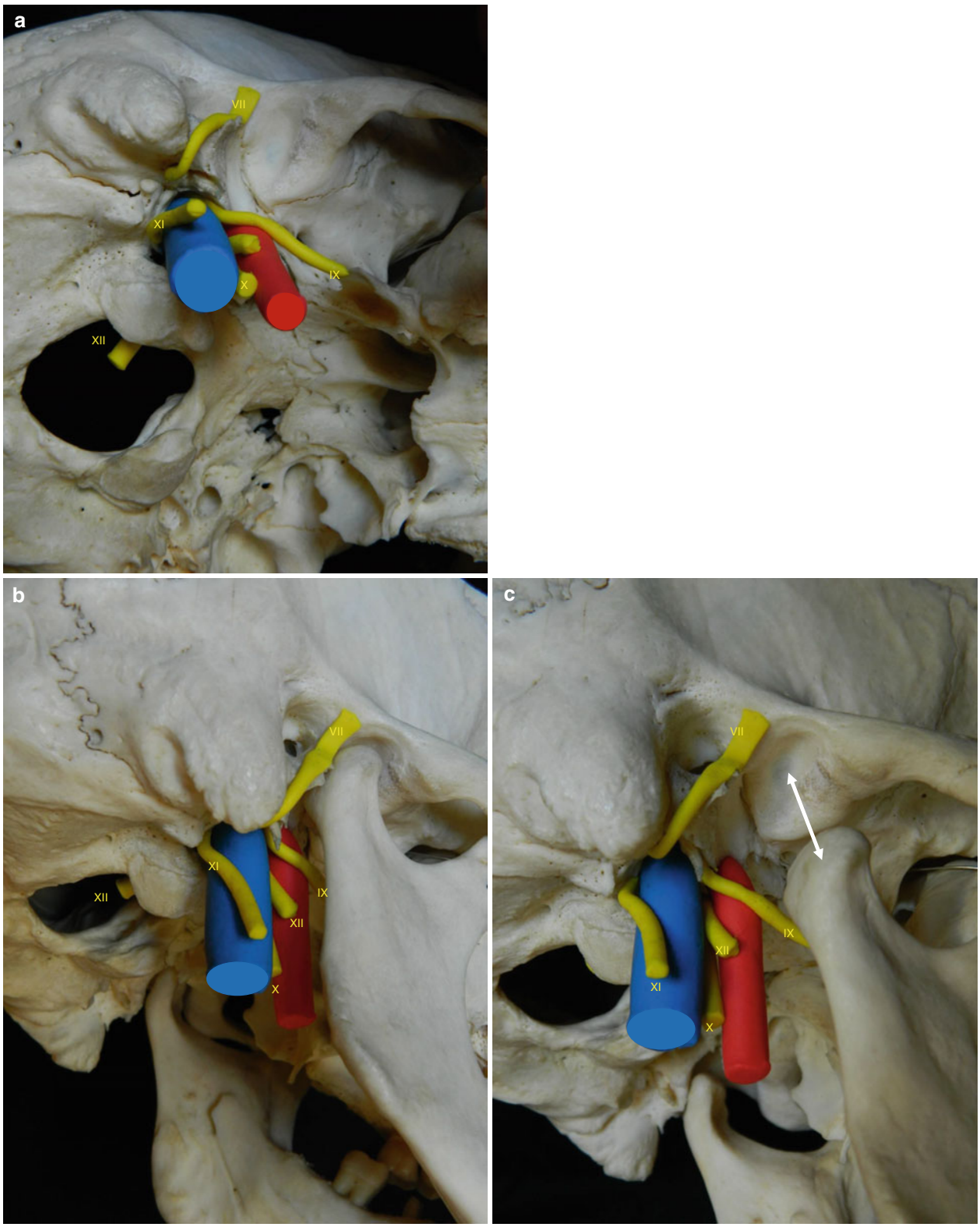


Fig. 1.12 The retromandibular space. Schematic reconstruction as in Fig. 1.6. Panel (***a***), inferior view of the cranial base, with the mandible removed. The IJV (*blue*) and the ICA (*red*) are surrounded by numerous nerves. The vagus (*X*) and glossopharyngeal (*IX*) nerves exit the cranial cavity in a pre-jugular position and the accessory nerve (*X*) retro-jugular. The hypoglossal nerve (*XII*) exits through a separate canal (hypoglossal canal) and passes between the ICA and the IJV. The styloid muscles separate the facial nerve (*VII*) from the remainder. The facial nerve crosses the retromandibular space to reach the parotid gland. Panel (**b**), lateral view with the mandible in place. Note the narrow space between the mastoid process and the mandible and the deeper position of the ICA. Panel (**c**), with mobilization of the mandible (*double-headed arrow*), the retromandibular space can be enlarged, usually no more than 2 cm as the facial nerve can be easily elongated and damaged. Exposure of the distal ICA usually requires division of the styloid muscles

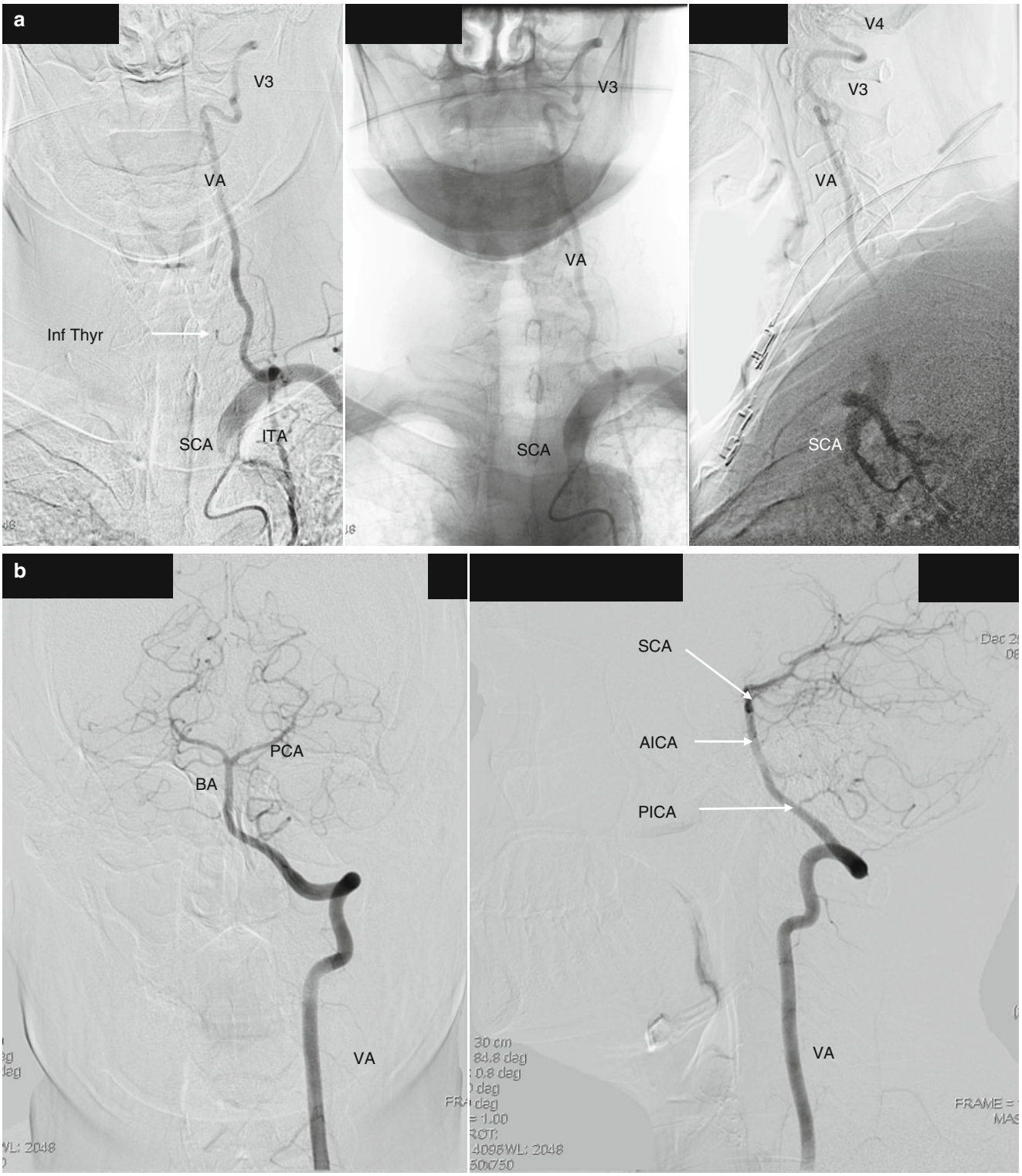


Fig. 1.13 The vertebral artery (1). Angiographic aspect of the vertebral artery (VA). Panel (**a**), the origin is usually in the first portion of the subclavian artery (*SCA*) opposite the internal thoracic (*ITA*). More distal to the VA origin, are the thyrocervical trunk and suprascapular arteries. The first portion (*V1*) is on a deeper plane, between the anterior scalene and longus colli muscle. The artery enters the transverse foramen of the cervical vertebra C_6 (although numerous variations of entrance are described). The C2–C1 and suboccipital curves of the VA are well visible (V3 and V4). *InfThyr* inferior thyroid artery. Panel (**b**), the distal segments of the VA as these appear on angiogram. Anterior and lateral projections. *VA* vertebral artery, *BA* Basilar artery, *PICA* posterior inferior cerebellar artery, *AICA* anterior inferior cerebellar artery, *SCA* superior cerebellar artery, *PCA* posterior cerebral artery

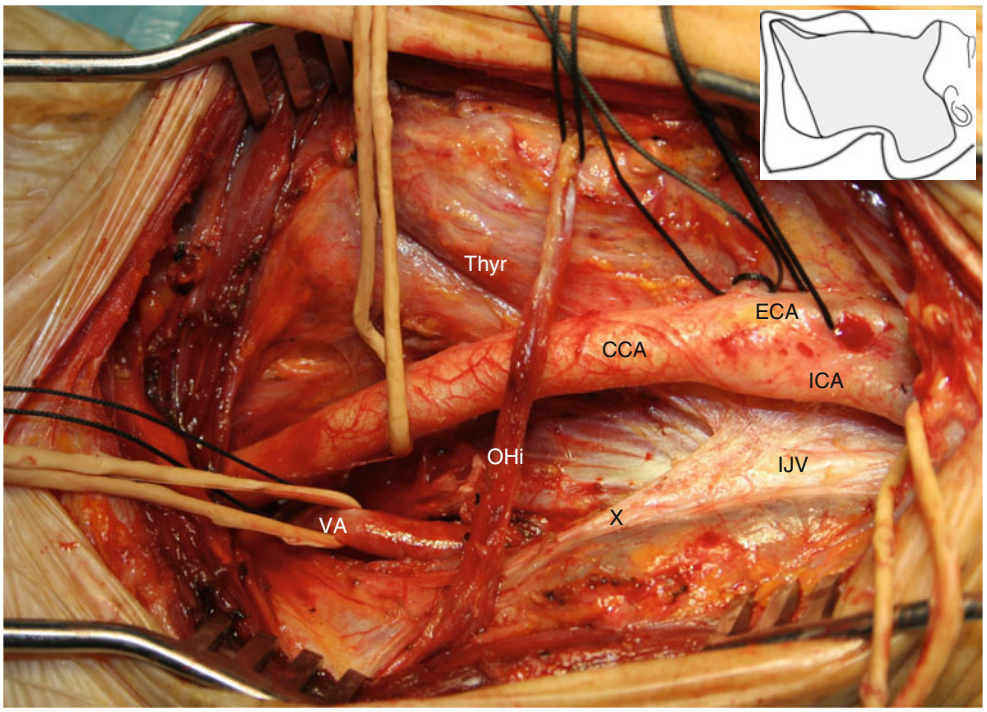


Fig. 1.14 The vertebral artery (2). Intraoperative aspect of the first segment of the VA, from origin in the SCA to the entrance in the transverse osseous canal at the level of C_6. The carotid artery and bifurcation were dissected both inferior and superior to the omohyoid muscle OHi (the pretracheal/visceral layer of the cervical fascia was divided). The VA was approached between the CCA and the IJV (retracted together with the vagus nerve X). The bony canal is covered by the origins of the longus colli (*LC*) and anterior scalene (*AntSc*) muscles. *Thyr* thyroid gland. Note the close relationship between the CCA and the VA, allowing the reimplantation of the VA into the CCA

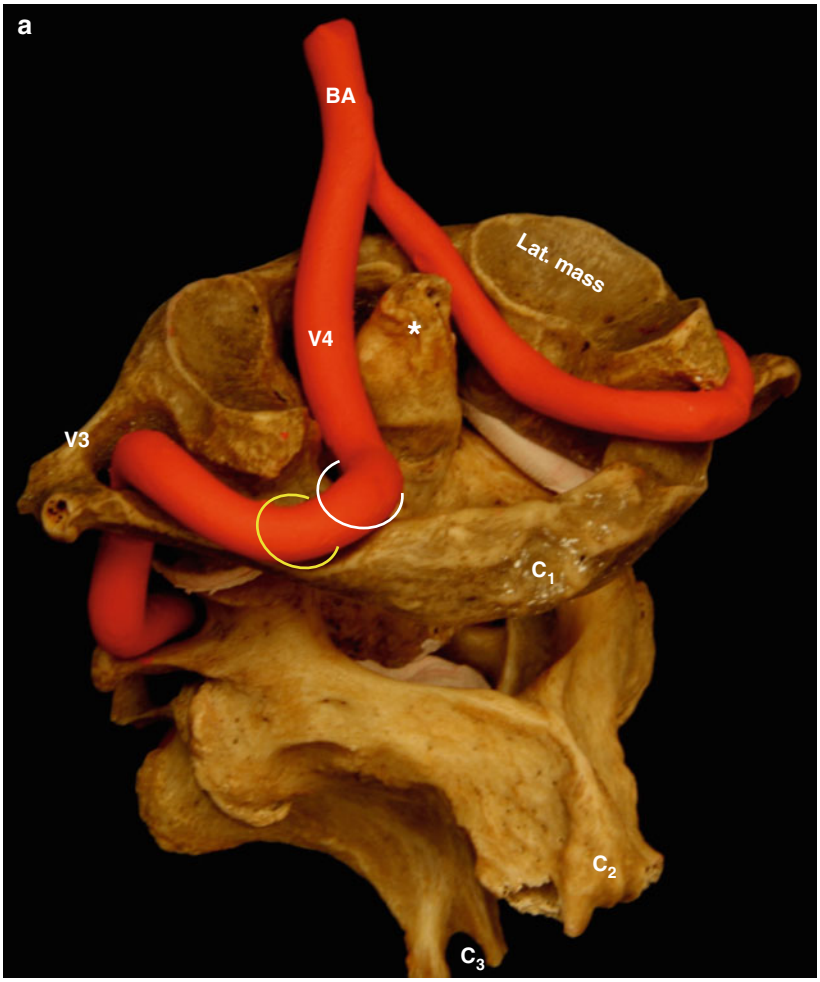
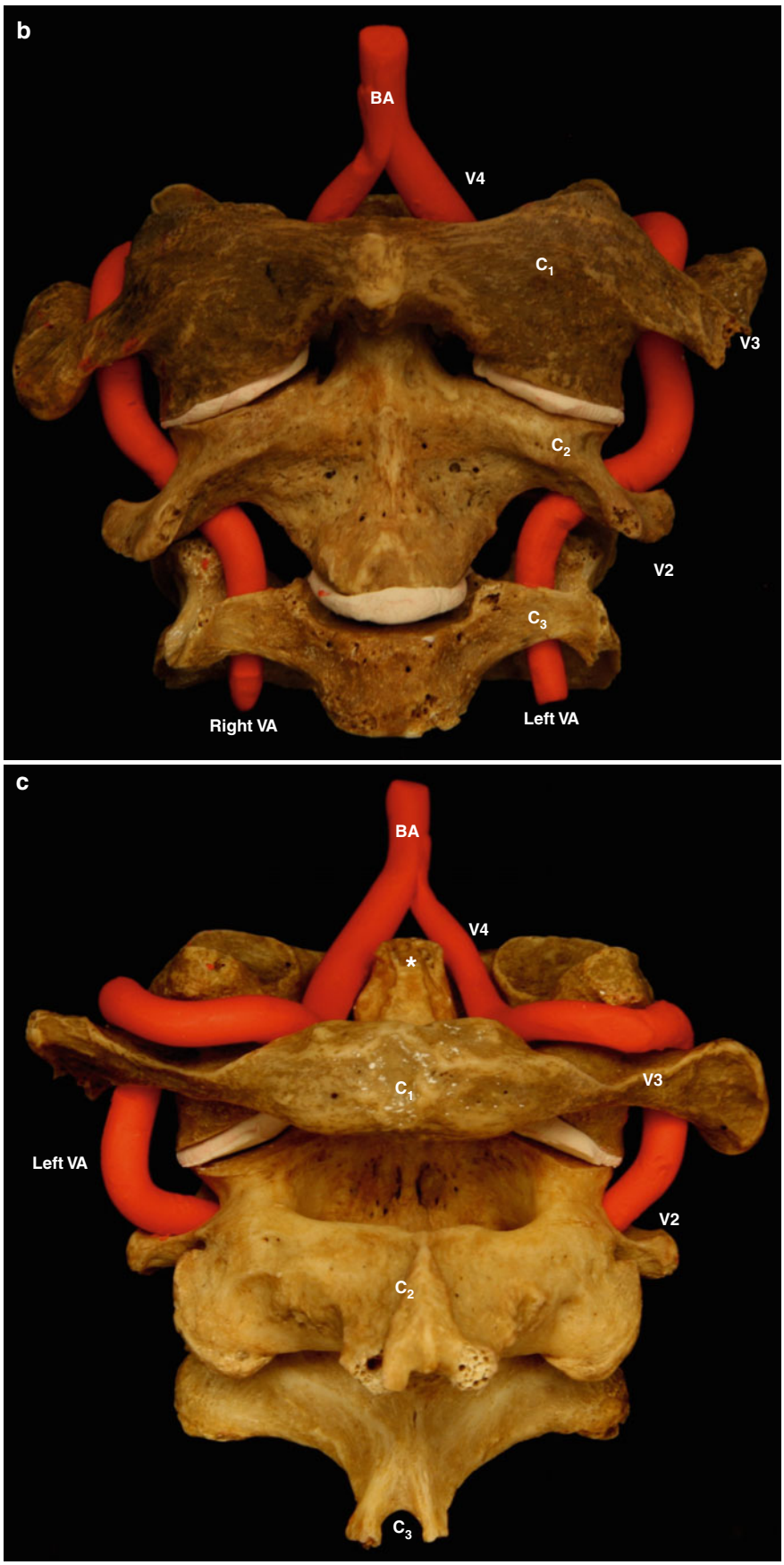


Fig. 1.15 The vertebral artery (3). Panel (**a**), demonstration of the distal ("upper") segments of the VA, as it winds around the lateral masses of the atlas (C_1) and perforates the posterior atlanto-occipital membrane (*yellow ring*) and the dura mater (*white ring*). Note the close proximity with the odontoid process of axis (C_2), the lateral masses of the atlas and the articular surfaces of the latter, with the occipital bone. The spinous process of axis is also the most prominent, allowing for a good radiological identification. Note also that the spinous processes of the cervical vertebrae are bifid. There is also a natural asymmetry of the two VAs. Panel (**b**), anterior view of the same first three cervical vertebrae and the VAs. Note the orientation of the transverse foramina of the axis with the superior part of the orifice oriented laterally. The transverse processes of the atlas are far more lateral than those of the remainder cervical vertebrae, being palpable just underneath the mastoid processes (and offering a good landmark for surgery and for regional anesthesia). Panel (**c**), the same first three cervical vertebrae – posterior aspect. Surgical approach to these segments of the VAs is cumbersome, as the artery is on a deeper plane, covered by the suboccipital muscles. Panel (**d**), anatomical relationships of the VA and cervical nerves. The transverse processes of the cervical vertebrae contain the sulcus of the cervical nerve, immediately posterior to the VA. Inadvertent puncture of the VA may occur with cervical plexus block due to the very narrow space between the two structures. In the same way, the subarachnoid space may also be entered. Panel (**e**), suboccipital segments of the VAs and anatomical relationships. The uppermost portion of the VA is covered by the suboccipital muscles. The VA can be exposed in the "vertebral artery trigone" delimitated by the following muscles: inferior oblique (*ObI*), superior oblique (*ObS*), rectus capitis posterior major (*RCPM*). In the median portion, the rectus capitis posterior minor (*RCPm*) is partially covered by RCPM. In the area of the triangle, the VA is also covered by the posterior atlanto-occipital membrane. The first two cervical nerves are just posterior to the VA (C_1 and C_2). *MAST* mastoid process



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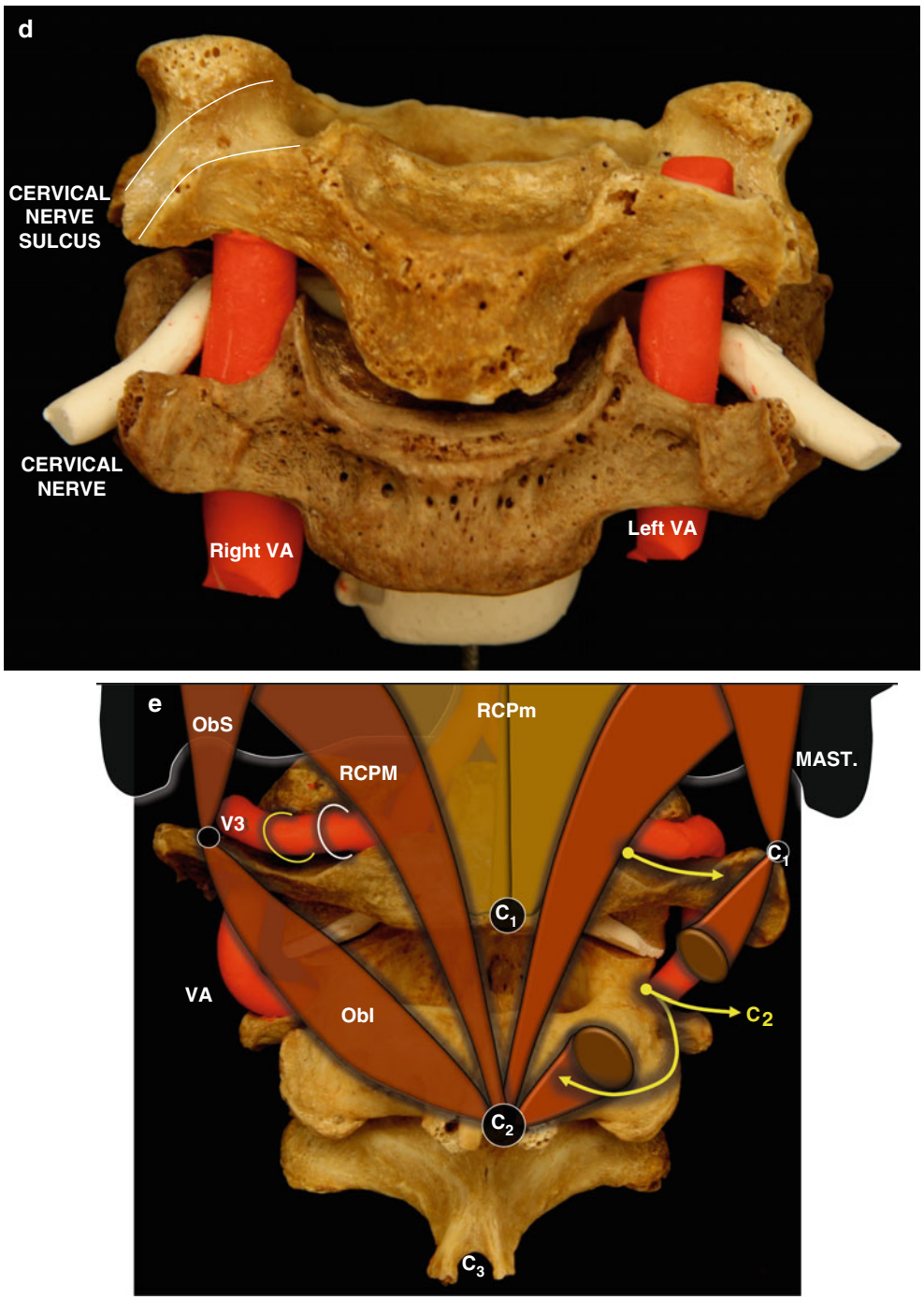

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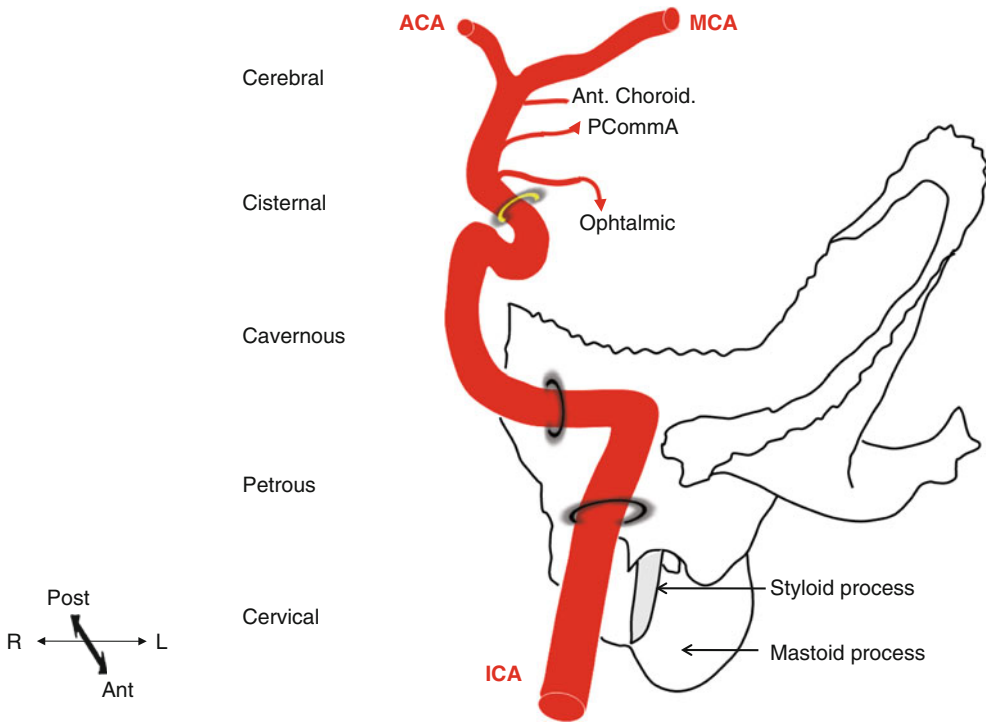

Fig. 1.16 The segments of the internal carotid artery. The drawing illustrates an anterior view of the left ICA and the major curves described by the vessel. Numerous classifications of the ICA segments have been elaborated during time, serving various purposes (see text for details). We present here only the major portions, as the more distal three are frequently subdivided especially for neurosurgical and endovascular purposes. *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *Ant Choroid* anterior choroidal artery, PComm *A* posterior communicating artery

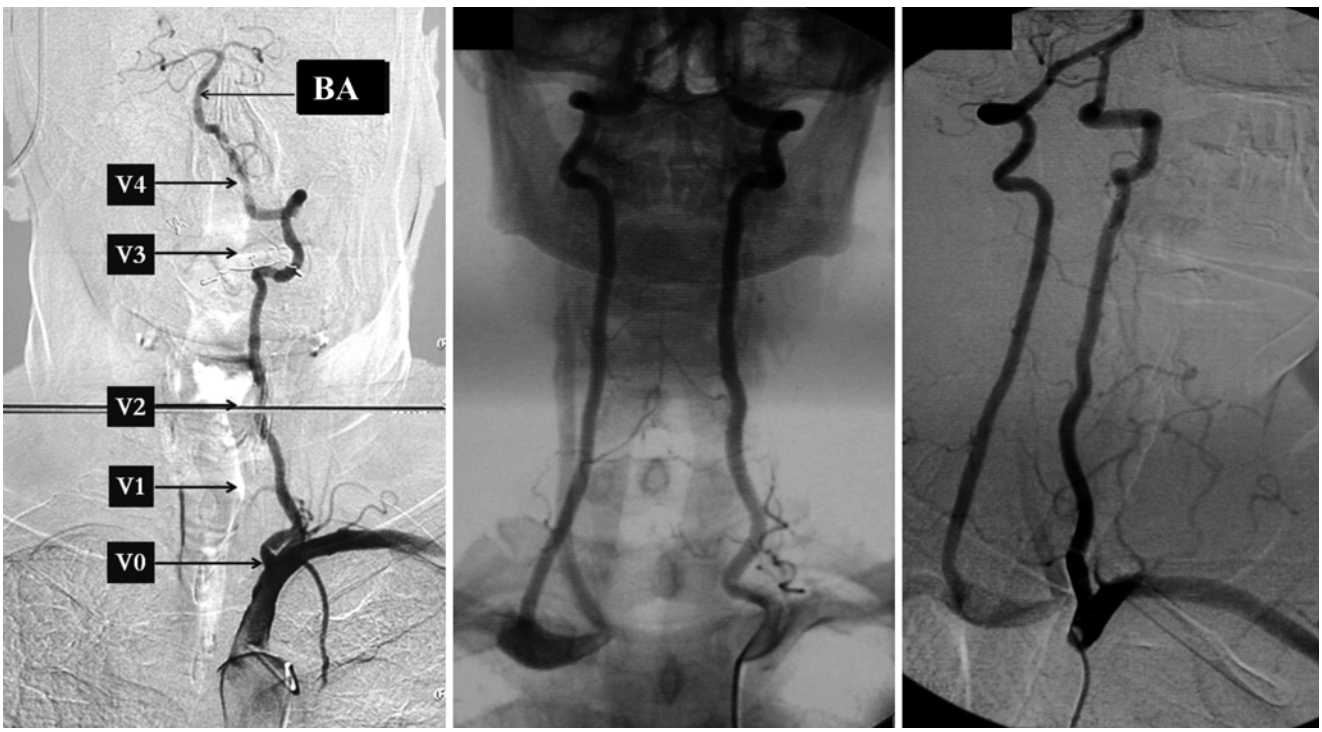

Fig. 1.17 The segments of the vertebral artery. The left panel illustrates the normally appearing angiographic image of the VA and its segments: *V0* the very origin, *V1* the pretransversal (extraosseous) segment, *V2* the intraosseous segment, *V3* the atlanto-occipital loop, and *V4* the suboccipital segment eventually fusing into the basilar artery (*BA*). The remainder two images demonstrate the concomitant visualization of the two VAs in a case with vertebral steal due to occlusion of the brachiocephalic trunk. Note the equal caliber of the two VAs. The case was selected in order to demonstrate the numerous muscular branches of the VA and anastomoses with branches of the SCA and carotid arteries (usually not so well visible)

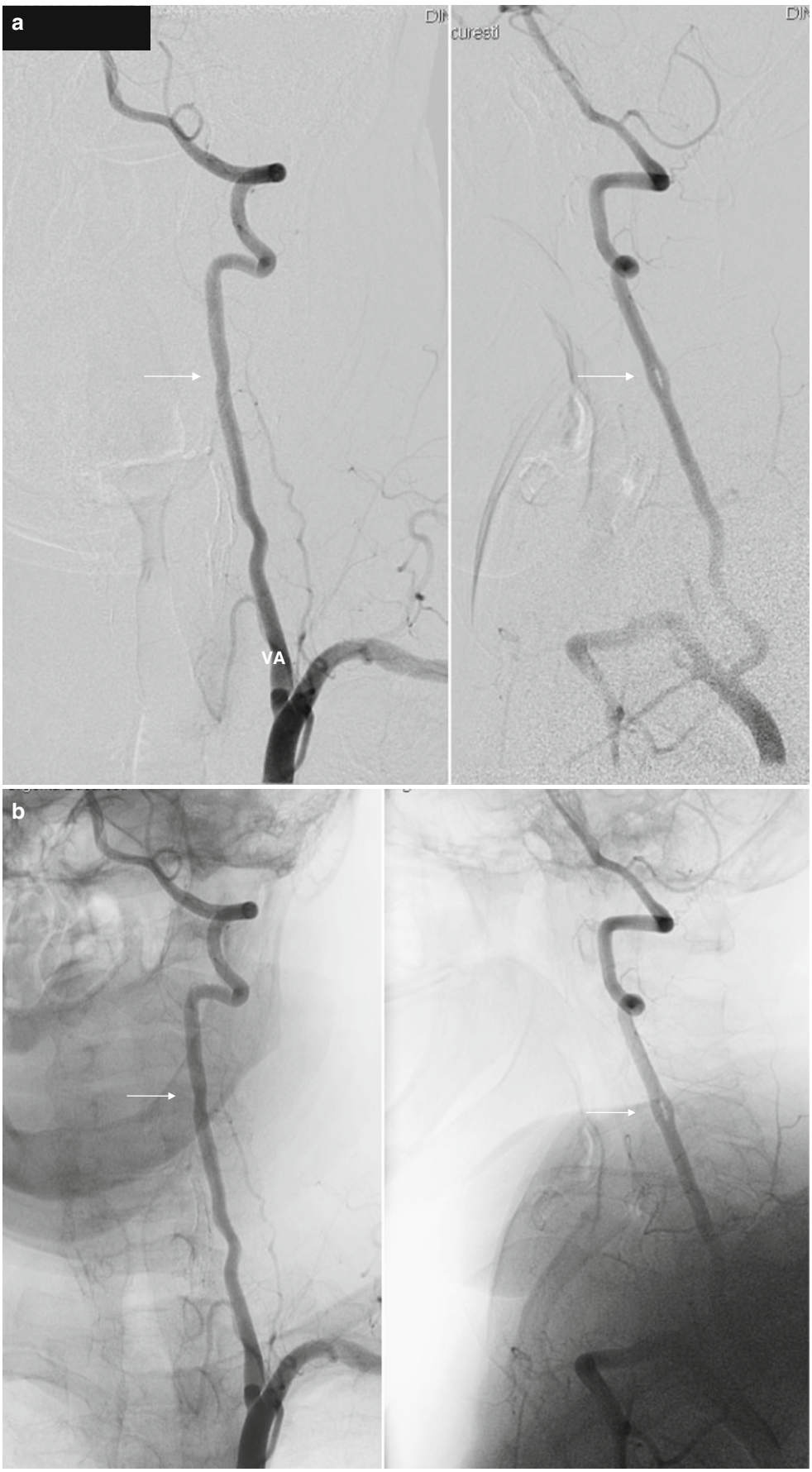

Fig. 1.18 Fenestration of the extracranial vertebral artery. Fenestrations of the intracranial segments of the VA (and of the BA) are more frequent than those involving the extracranial VA. An apparent stenosis (*white arrow*) of the V2 segment is observed on anteroposterior projection. In lateral view, the same area demonstrates a fenestration of the VA. Digital subtraction angiogram in Panel (**a**) and angiogram without subtraction in Panel (**b**)

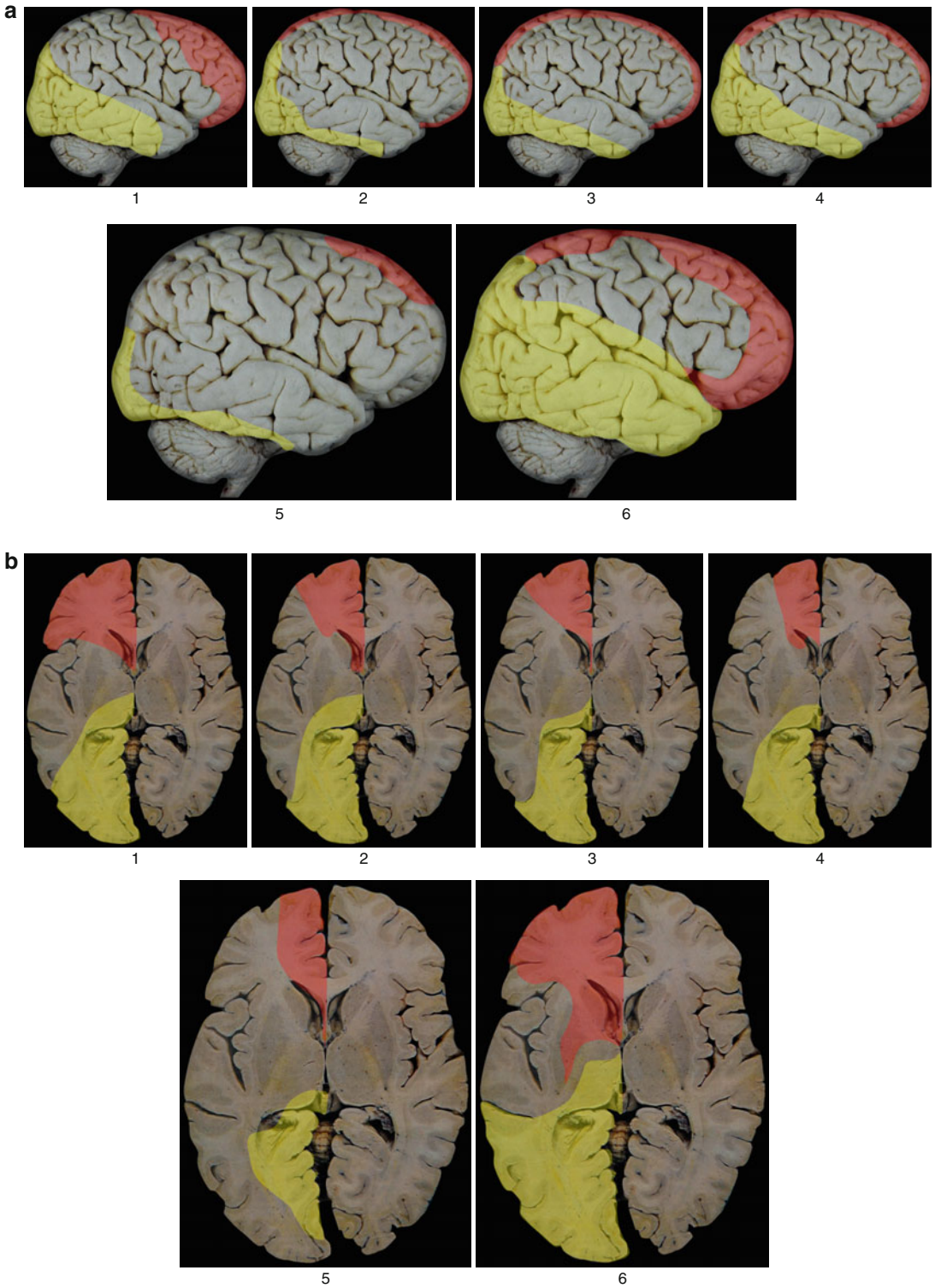

Fig. 1.19 The variability of the territories of the major cerebral arteries. Schematic representations of the territories of the major cerebral arteries: *ACA* red, *PCA* yellow, and *MCA* not colored. In Panel (**a**), the lateral side of the hemisphere is represented, while in Panel (**b**), a horizontal section passing through the middle portion of the cerebral hemispheres is shown, demonstrating the major encephalic structures (thalamic nuclei, basal ganglia, internal capsule, optic radiation, anterior and posterior horns of the lateral ventricles, the third ventricle, insula, and so forth). Numerals 1 to 4 correspond to various studies in which the participation of each of the main cerebral arteries was investigated. Numerals 5 and 6 indicate the maximal (*5*) and minimal (*6*) distribution of the MCA as demonstrated by Beevor CE (cited by van der Zwan and Hillen 1991). Note that there are no fixed landmarks and that besides interindividual variations, there may also be a left-right difference in vascular distribution

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Cerebral Vascular Territories and the Major Neurovascular Syndromes

2

Horia Muresian

The cerebral circulatory system is a component of the superior aortic system, the latter comprising the entire arterial territory originating directly or indirectly from the aortic arch. Different from the arterial system of the superior limbs, of the neck (including the cervical viscera), or of the superior mediastinum, the cerebral territory depicts important particulars (see Chap. 3) which are also reflected in the distinct mechanisms of stroke. Numerous extracerebral as well as intracerebral factors may contribute to the triggering and progression of stroke, and rarely, there is only one component, only a single culprit lesion, or a singular mechanism involved. The multistory arterial anatomical pathway starts at the level of the heart and terminates with the distal, small intracerebral perforating arterioles; morbid changes at any of these levels may cause, adjuvate, or amplify the cerebrovascular accident or ischemia. For example, even well-known mechanisms of ischemic stroke such as artery-to-artery embolism may be accompanied by the extension of atherosclerosis at the site of stenosis into adjacent perforators, thus defining a particular element of cerebral ischemia and suggesting an important determinant of prognosis [1]. Cardioembolism may also manifest with various types of stroke and particular localization of ischemia, due to the size of embolus and to the preferential flow in the branches of the arterial circle of Willis [2].

The major clinical neurological syndromes are defined by and directly related to the pattern of arterial vascularization, to the target tissues vascularized (i.e., the particular cortical areas, centers or tracts), and, not least, to the extant and status of the collateral circulation (and the possible compensatory flow). Interindividual variability addresses all three pivotal elements: arterial distribution, collateral flow, and brain parenchyma; consequently each patient will ask for a thorough, complete, and efficient diagnostic interrogation and ranking of lesions and possible cause(s) of stroke. Therapeutic indication and prognosis are strictly bound to and influenced by this individual diversity, and as a consequence, accurate and all-encompassing comparisons between centers and patient series are still difficult to carry out. In this chapter, all the three elements mentioned above will be considered.

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

2.1 The Arterial Supply of the Brain

The internal carotid artery (ICA) after giving off the ophthalmic artery divides in the following branches (Fig. 2.1): anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior communicating artery (PCommA), and (anterior) choroidal artery. Of all four, the MCA is the largest and appears as the direct continuation of the ICA. The ACA and MCA are collectively labeled as the terminal branches of the ICA. A synthetical description of the ACA, ACommA, and MCA follows. An integrated representation of the major central branches of the ACA, ACommA, and MCA is subsequently given with the detailed description of the arterial circle of Willis.

The anterior cerebral artery (ACA) is divided for surgical and endovascular purposes (Fig. 2.2) in the following segments: A1, from its origin to the offshoot of the anterior communicating artery (ACommA); A2, from the ACommA to the origin of the callosomarginal artery (i.e., at the level of the genu of corpus callosum); and A3, distal to the callosomarginal artery (the ACA accompanies the corpus callosum as the pericallosal artery extending as far as the precuneus and limbic lobe = Brodman areas 7, 31, and 23). As in the case of each cerebral artery, the ACA gives off cortical and central (i.e., deep) branches, respectively. The cortical branches are named according to the territory supplied: orbital branches (frontal lobe, olfactory cortex, gyrus rectus, medial orbital gyrus), frontal branches (corpus callosum, cingulated gyrus, medial frontal gyrus, paracentral lobule), and parietal branches (precuneus). The frontal and parietal

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branches supply also a variable territory of the lateral and superior part of the cortex (corresponding to Brodman areas 9, 8, 6, 4, 3, 1, 2, 5, and 7). Usually, the cortical areas of the ACA supply the cortical motor and somatosensory areas that represent the lower limb. The central branches of the ACA penetrate the anterior perforated substance and are distributed to the corpus callosum (rostrum), septum pellucidum, putamen (anterior part), caudate nucleus (head), and internal capsule (anterior limb). Anteromedial striate arteries originate from A1, A2, or ACommA and are distributed to the anterior part of the head of the caudate nucleus, of the internal capsule and putamen.

The two ACAs are joined by the anterior communicating artery (ACommA). This vessel may depict numerous variations: short, long, absent, or doubled. It should not be looked upon as a mere anastomosis between the two ACAs, as it gives off important branches that supply the optic chiasm, lamina terminalis, hypothalamus, diagonal band of Broca, cingulate gyrus, genu of corpus callosum, and pillar of fornix. Injury to these vessels caused either by aneurysmal rupture or surgical manipulation may lead to serious clinical deficits mostly psycho-organic syndromes [3].

The middle cerebral artery (MCA) follows the direction of the ICA toward the lateral cerebral fissure; from this perspective, the ACA appears to depict a somehow recurrent tract (Fig. 2.3). The MCA travels the lateral fissure and passes over the intervening insula. Hence, the MCA is divided in M1, the sphenoidal segment; M2, the insular segment; M3, the opercular segment, over the insula and superficially emerging between the temporal and frontal lobes; and M4, the terminal or cortical segment. From the M2 segment on, the MCA may bifurcate or trifurcate depicting an upper, a lower, and occasionally a middle trunk. The cortical branches supply the frontal lobe (precentral, middle, and inferior frontal gyri), parietal lobe (postcentral gyrus, superior parietal lobule, inferior parietal lobule), and temporal lobe (lateral surface of temporal cortex). Normally, the MCA supplies the somatosensory cortex (except the area of the lower limb), the auditory area, and the insula. The central branches, the lateral striate/lenticulostriate arteries, supply the internal capsule, the lentiform complex, and the caudate nucleus.

The vertebral arteries (VAs) and their continuation, the basilar artery (BA), exhibit an extensive territory of vascularization (Fig. 2.4a, c) including essential, vital centers: the superior part of the spinal cord, the brainstem, the posterior part of the hemispheres, and the cerebellum. Before converging into the BA, the VAs give off salient branches. The anterior and posterior spinal arteries participate in the formation of the longitudinal arterial system supplying the spinal cord: the unpaired median anterior and the two paired posterior spinal arteries; these longitudinal channels are reinforced by branches from the V2 segment of the VA, ascending cervical, intercostals, and lumbar arteries. The posterior inferior cerebellar artery (PICA) is the largest branch of the VA; sometimes it may be absent. In other circumstances, the VA may terminate giving off the PICA (Fig. 2.4b). Besides the cerebellum, the PICA also vascularizes the medulla oblongata and the choroid plexus of the fourth ventricle. The cerebellar arteries readily anastomose with each other.

The basilar artery (BA) follows the anterior median pontine sulcus up to the superior part of the pons where it divides into the posterior cerebral arteries (PCA). It gives off pontine branches, the labyrinthine artery, the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery (SCerA).

The BA bifurcates in two terminal branches: the posterior cerebellar arteries (PCAs). The segments of the PCA are P1, from origin to the junction with the posterior communicating artery (PCommA); P2, from the junction with the PCommA to the portion in the perimesencephalic cistern; and P3, the calcarine portion (the cortical part, in the calcarine fissure on the medial aspect of the occipital lobe). The cortical branches of the PCA are temporal (for the uncus hippocampi, parahippocampal, medial occipitotemporal, and lateral occipitotemporal gyri), occipital (cuneus, lingual gyrus, posterolateral surface of the occipital lobe), and parieto-occipital (cuneus, precuneus). The PCA supplies the cortical visual area and the other structures in the visual pathway. The central branches supply the thalamus, subthalamus, globus pallidus and lateral wall of the third ventricle, lateral geniculate body, the choroid plexus of the third ventricle, inferior horn of the lateral ventricle, the fornix, colliculi, medial geniculate body, and pineal gland.

The central branches from the arterial circle of Willis are as follows (Fig. 2.5):

The anteromedial (AM) group: origin in ACA, ACommA. Supply the optic chiasma; lamina terminalis; anterior, preoptic, and supraoptic areas of the hypothalamus; septum pellucidum; para-olfactory areas; anterior column of fornix; cingulated gyrus; rostrum of corpus callosum; anterior part of putamen; and the head of the caudate nucleus.

The posteromedial (PM) group: origin in PCommA and PCA (P1). Supply the hypothalamus, pituitary gland, anterior and medial parts of the thalamus, mammillary bodies, subthalamus, lateral wall of the third ventricle, medial thalamus, and globus pallidus.

The anterolateral (AL) group: origin MCA (M1). Striate, lateral striate, or lenticulostriate arteries. Supply the posterior striatum, lateral globus pallidus, anterior limb, and genu and posterior limb of internal capsule.

The medial striate artery: origin from MCA or ACA. Supplies the rostral part of the caudate nucleus and putamen and the anterior limb and genu of internal capsule.

The posterolateral (PL) group: origin from PCA (P2). Supplies the cerebral peduncle, colliculi, pineal gland, the posterior thalamus, and the medial geniculate body.

2.2 The Collateral Circulation

The collateral circulation includes all the arterial and venous channels that stabilize, supplement, or replace the failing main conduits. Residual perfusion in an ischemic zone represents an important determinant of both remnant blood flow and a possible cause of hemorrhagic transformation. Collateral circulation may also facilitate the clearance of fragmented thrombi from more proximal locations [4, 5]. The recruitment of collaterals depends on the diameter and patency of the main trunks and on hemodynamic, metabolic, and neural mechanisms [6]. Hypertension, for example, may impair collateral development (in the setting of carotid occlusion) and, therefore, increase the stroke risk [7]. However, a straight relationship between the status of collaterals, the cerebral blood flow, and clinical symptomatology still remains unclear and under-investigated. The various diagnostic modalities used depict intrinsic limitations in what regard the visualization of some of the collaterals or of the particular patterns of flow; besides, a systematic evaluation of collaterals in all patients with cerebrovascular disease is still not practical. It is also difficult to differentiate between preformed collaterals and collaterals developing after the onset of ischemia. The direction of flow may also change after the infarct through decreased metabolic turnover or flow may exhibit a to-and-fro pattern [8]. Perfusion through collateral circulation plays a critical role in acute cerebral ischemia, but on the other hand, the precise arterial source of sustained perfusion of specific regions in the brain may not appear evident.

The type, size (diameter and length), and location of collateral vessels also appear to have clinical and surgical significance. The collateral arterial channels can be classified in various modes. A first classification regards the location of connections: extracranial or intracranial. From a second point of view, the collaterals are primary, secondary, and, respectively, the rare or inconstant channels (for the latter, see the vestigial anastomoses below).

The extracranial anastomoses are located at cervical or cephalic level. As the common carotid and internal carotid arteries (CCA and ICA, respectively) normally do not give off any cervical branches, the cervical anastomoses are developed between the external carotid artery (ECA), the vertebral artery (VA), the subclavian artery, and their branches. The cervical anastomoses usually do not contribute to the augmentation of intracerebral arterial perfusion, but in some cases, blood can be shunted away from the cerebral circulation through such collaterals: subclavian steal through anastomoses between the VA, the occipital artery, and the deep and ascending cervical arteries (Fig. 2.6). The anastomoses at cephalic level include the extra-to-intracranial arterial communications (and these may be also called peripheral anastomoses) (Fig. 2.7):

- From the facial artery: In the angular artery, the terminal branch of the facial artery (ECA) anastomoses by inosculation with the dorsal nasal branch from the ophthalmic artery (ICA). Hemodynamically important and clinically the most significant, this anastomosis can be readily assessed echographically. In clinical setting (and argot), "the negative ophthalmic artery" (i.e., the reversed blood flow from the ECA toward the ICA) represents a valid sign of ipsilateral ICA significant stenosis or occlusion. On the other hand, severe stenosis or occlusion of the ICA may well be compensated through the circle of Willis, and the ophthalmic artery may still appear as "positive" on ultrasound examination. At orbital level, numerous other anastomoses are encountered between the supraorbital artery (branch of the superficial temporal artery, ECA), the maxillary artery branches (ECA), and the orbital branches of the ophthalmic artery (ICA). None of these latter are by inosculation, as the former anastomosis is. However, the lack of choroidal blush during ICA-selective angiography (and the appearance of a choroidal blush with selective ECA injection of contrast agent) indicates an abnormal supply to the eye from the ECA, a severe stenosis of the ICA, or, rarely, agenesis of the ICA.
- The maxillary artery group (ECA). The sphenopalatine artery (the terminal branch of the maxillary artery) anastomoses with the ethmoidal branches of the ophthalmic artery (ICA). The middle meningeal artery (branch of the maxillary artery) anastomoses with the lacrimal artery, from the ophthalmic artery (ICA). The meningeal branches from the ascending pharyngeal artery anastomose with the meningeal branches from the ICA (see below the meningeal anastomoses) and from the maxillary artery (ECA). The anterior tympanic branch and the stylomastoid artery (from the maxillary artery, ECA) anastomose with the caroticotympanic artery within the tympanic cavity. The recurrent branch of the greater palatine artery (maxillary artery, ECA) anastomoses with the pterygoid artery (vidian artery) from the ICA, within the pterygoid canal.
- The ascending pharyngeal artery (ECA) gives off the posterior meningeal artery which enters the cranial cavity through the jugular foramen or through the condylar canal, anastomosing with dural branches of the posterior fossa (VA).
- The occipital artery (ECA) gives off branches that enter the cranial cavity through the mastoid foramen or parietal foramen anastomosing with meningeal branches from the middle meningeal artery or VA (see the tectal plexus below). The occipital artery via the posterior anastomotic radicular branches of the horizontal segment retains its connections with the vertebrobasilar system [9].

All these collateral channels depict numerous intra- and interindividual variations. Actually, most anastomoses form plexuses, with minute contributing arterial branches: the

orbital plexus, the so-called rete mirabile caroticum (although a genuine rete mirabile – as in other species – has not been observed in man), and the tectal plexus constituted between the supratentorial branches from the PICA and the infratentorial branches of the superior cerebellar artery (both from the vertebrobasilar system). Even the most significant anastomosis between the facial and ophthalmic artery may sometimes be absent, as the facial artery may terminate after giving off the labial branches (consequently, an echographically absent *ophthalmic* artery may appear misleading).

The meninges represent an extensive area where collateral circulation may develop. Some "preformed" communications may account for normally occurring variations: the anastomosis between the middle meningeal artery (ECA) and the recurrent branch of the lacrimal artery (ICA) may be enlarged resulting in the origination of the lacrimal artery from the middle meningeal. On the other hand, recruitment and enlargement of meningeal arteries may ensue not only in ischemic brain disease but also with the development of intracerebral vascular malformations and meningiomas. At the level of the anterior cranial fossa, the dura is supplied by anterior and posterior ethmoidal arteries (from the ophthalmic artery, ICA), branches arising directly from the ICA and branches from the middle meningeal artery (ECA). In the middle fossa, the middle and accessory meningeal branches (from the maxillary artery, ECA), from the ascending pharyngeal artery (ECA), and branches of the ICA and the lacrimal artery (ophthalmic artery, ICA) converge and anastomose. In the posterior fossa, multiple types of anastomoses develop, between the ECA, ICA, and VA: occipital artery, ascending pharyngeal artery (ECA), meningohypophyseal trunk (ICA), and posterior meningeal arteries (VA). Consequently, the bony and dural envelopes of the brain do not represent an absolute and impenetrable barrier to blood vessels. In a similar way, numerous venous emissary veins and collateral venous channels are normally present. Significant bleeding from skull fractures represents a good example of the rich arterial and venous vascularization and of the freely communicating arteries and veins. In a similar way, the spreading of infections from extracranial sources toward the meninges is facilitated by the same anatomical disposition.

The anastomoses presented so far are generally called *secondary anastomoses* in order to be differentiated from the most significant primary or main anastomoses located intracranially, at the base of the brain and forming the arterial circle of Willis (CoW). The CoW appears almost as ring like, although it is essentially a heptagon with the sides formed by the two posterior cerebral arteries (PCA), the two posterior communicating arteries (PCommA), the two anterior cerebral arteries (ACA), and the unpaired anterior communicating artery (ACommA). The CoW represents the most important collateral pathway between the anterior (ICA) and posterior (VA and BA) circulations as well as between the two sides of the brain.

The anterior (internal carotid) cerebral circulatory system is the first to appear during embryologic development and delivers blood to the developing brain. The posterior circulation consists only of a primitive arteriolar mesh fed by penetrating branches of the anterior system and by the carotid-vertebral anastomoses (the trigeminal, otic, hypoglossal, and proatlantal arteries – in rostral-caudal direction). With the development of the hindbrain and occipital lobes, the posterior circulatory system becomes more conspicuous, and the carotid-vertebral communications regress, while the vertebrobasilar system becomes independent and connects to the subclavian artery [10]. The PCommA, originating in the ICA, develops and connects with the distal BA. The proatlantal arteries persist until the VAs are fully developed (a segment of the proatlantal artery becomes incorporated in the definitive V3 segment of the VA and in the distal portion of the occipital artery) [11]. Initially, the contribution to the CoW is as follows: the anterior division of the ICA gives origin to the ACA, MCA, and anterior choroidal artery; the posterior division of the ICA gives origin to the fetal PCA and the posterior choroidal artery. The posterior extensions of the PCommA (with transitory branches from the ICA) will form paired longitudinal neural channels. These latter consolidate and form the BA. The proximal (i.e., caudal) portion of the BA is still connected to the ICA by means of the proatlantal arteries. The VAs form as longitudinal anastomoses between the upper cervical segmental arteries of the dorsal aortae; the VAs eventually connect proximally via the sixth intersegmental artery, to the subclavian system. The formation of the definitive CoW consequently depends on the selection of numerous particular channels and the regression of other, and the many anatomical variations encountered can be thus explained. The arterial circle of Willis depicts a considerable anatomical variability both in left-right and in anterior-posterior coordinates. The identification and classification of the anatomical variations of the CoW must take into account:

- The presence or absence of each of the arterial components normally constituting the CoW
- The size of each component: diameter and length
- Unexpected/atypical features: abnormal tract, fenestrations, peculiar course, or anatomical relationships with adjacent structures, especially with cranial nerves

The *normal* CoW is usually considered when the circle possesses all the contributing arteries although hypoplastic segments (diameter <1 mm) are frequently encountered, especially at the level of the ACommA or PCommA. The diameter of any particular component may also be highly variable

reflecting the individual variations in the development of the CoW while also matching the size of the emerging branches. Not least, the arteries undergo remodeling during lifetime (Fig. 2.8), and whether this compensatory arterial dilatation is beneficial or not remains unknown [12]. The complete absence of an artery is rare and involves the ACommA [13].

The geometry of the constituting arteries of the CoW and of the emerging major branches has a particular significance in the development and progression of atherosclerosis and aneurysm formation. Obtuse bifurcation angles appear to facilitate atherosclerosis [14]. Alteration of parent-to-daughter arterial diameter ratio may lead to increment of turbulence as evidenced by the augmentation of the Reynolds numbers and consequent wall shear stress [15]. Aneurysm formation is facilitated at branch points deviating from the optimal bifurcation geometry where the wall shear stress is augmented [16]. Wall shear stress is also amplified on the side of the branch point where the pressure is lower and the flow is higher, as for example, in arteries feeding arteriovenous malformations at which point aneurysm formation has a higher incidence, and this particular situation was also experimentally reproduced and computed [17].

2.2.1 The Variations of CoW Are Presented in Fig. 2.9

2.2.1.1 Variations of the Feeding or Emerging Arteries from the CoW

- Duplicated MCA. Both MCAs originate independently from the ICA [18].
- Accessory MCA which originates from the ACA [19].
- Azygous ACA (fused A2 segments of the ACA and absent ACommA).
- Bihemispheric ACA: both A2 segments exist, but one is dominant supplying both hemispheres (while the remainder appears hypoplastic or terminates proximally toward the genu of the corpus callosum).
- The third A2 (the small, medial ACA) with origin in the ACommA (normal situation in many vertebrate species) [20].
- The variations of the ACommA are presented with the variations of the CoW.
- BA fenestration/BA duplication, occurring more frequently closer to the confluence of the two VAs.
- The variations of the VAs are presented in Chap. 2.
- Persistence of the fetal origin of the PCA (PCA which originates not from the BA but from the ICA). The variation may also occur in both PCAs.
- Duplicated P1 or P2 segments of the PCA.
- Failure of formation of the P1 segment of the PCA is accompanied by agenesis of PCommA and fetal PCA.

2.2.1.2 Persistence of Vestigial Arteries/ Persistent Carotid-Vertebrobasilar Anastomoses

- Persistent trigeminal artery (TA), the most frequent persistent carotid-vertebrobasilar anastomosis. Various types are reported. Type I: TA joins the BA between the SCA and AICA. Type II: TA joins the BA distal to the origin of the SCA. Type III: TA supplies the SCA and contralateral PCA. TA may also supply directly the SCA, AICA, or PICA, bypassing the BA.
- Hypoglossal artery (HA). The artery connects the cervical ICA with the BA via the hypoglossal canal. VA of PCommA may be absent on one or both sides. Different from the embryonic HA which passes anterior and medial to the rots of the hypoglossal nerve, the adult HA courses posterior and medial to the roots
- Proatlantal artery (ProA). One or both VAs are hypoplastic. Type I ProA originates from the ICA. In Type II, the ProA originates from the ECA. Both types enter the cranial cavity through the foramen magnum and join the V4 segment of the VA (Type I ProA) or the V3 segment of the VA (Type II)
- Otic artery (OA). It connects the petrous part of the ICA with the BA, passing through the internal auditory canal
- Stapedial artery. The persistence of the primitive artery supplying the eye and agenesis of the ICA [21].

The presence, the degree of development, and the functional status of collateral circulation are all highly significant in the clinical setting, as patient outcome may be considerably influenced by the physiological status of the alternative vascular pathways [22]. Current methods of evaluation are evolving. Indeed, anastomoses can be visualized angiographically. The lack of angiographical visualization of a collateral vessel does not actually reflect its absence, as opacification is flow dependent (and flow is also determined by the metabolic status of target brain tissue, which, at its turn, eventually rests on the type of ischemic lesion). Angiographic grading systems for regional collateral flow can predict the location and extent of infarction [23] and may be implemented in larger clinical trials. CT angiography interrogation may reveal the presence of collaterals but with limited benefit regarding the functional status and contribution of anastomoses to the maintenance and/or recovery of the affected brain tissue. Diagnostic imaging addressing the brain parenchyma (CT, MRI) [24] adds important particulars especially regarding the extant and extent of ischemia, the approximate volume of penumbra, the presence of deleterious effects such as edema, or the evaluation of "the misery perfusion" as revealed by the increased oxygen extraction fraction (positron emission tomography). Regional perfusion imaging represents a

noninvasive arterial spin-labeling MR imaging method that can visualize collateral brain tissue perfusion [25, 26]. CT angiography provides a good interobserver reliability [27] while this holds not true for the use of different MR imaging characteristics. Some other techniques are used in the preclinical setting: laser speckle contrast imaging (LSCI), two-photon laser scanning microscopy (TPLSM), and Doppler optical coherence tomography (DOCT) [28].

Various therapies are indicated to improve collateral flow in ischemic stroke: volume expansion and hemodilution, vasodilation, induced hypertension, improvement of collateral flow by growth factors, stimulation of the sphenopalatine ganglion, temporary occlusion of the abdominal aorta, and external counterpulsation. For further reading, see ref. [28] above.

2.3 The Target Tissues Vascularized

As stated before, the major clinical neurological syndromes are defined by and directly related to the pattern of arterial vascularization, to the target tissues vascularized (i.e., the particular cortical areas, centers, or tracts), and, not least, to the extant and status of the collateral circulation (and the possible compensatory flow). Inter- and intraindividual variability is significant and important to consider when interpreting each particular patient. A general view of the major clinical stroke syndromes is offered in Table 2.1. Some of the most frequently encountered syndromes are presented in Tables 2.2, 2.3, 2.4, 2.5, and 2.6.

Table 2.1 Clinical stroke syndromes

Main artery involved	Division/branches	Clinical features
Internal carotid artery (ICA)	Anterior (ACA) and middle cerebral (MCA) arteries, anterior choroid artery, ophthalmic artery	Different degree of severity depending on collateral flow compensation: from asymptomatic occlusion to large devastating stroke in both ACA and MCA regions. In most cases of acute occlusion of ICA, an MCA stroke is the most frequent consequence, but watershed ACA/MCA, MCA/PCA, or deep/superficial MCA strokes are also encountered. Transient monocular visual loss (*Amaurosis fugax*) or anterior ischemic optic neuropathy is also possible in case of severe carotid stenosis or occlusion
Anterior cerebral artery	Cortical branches	Contralateral weakness of leg and shoulder with/without sensory loss
		Left limb dyspraxia, impairment of gait (gait apraxia)
		Contralateral grasp reflex
		Abulia, akinetic mutism, apathy, in rare situation euphoria, disinhibition, mental impairment with perseveration and amnesia
		Urinary (and sometimes fecal) incontinence
		Other specific signs depending on affected side:
		In *left-sided lesions*: initial mutism, then possible evolving toward dysarthria or slight aphasia of transcortical motor type
		In the *right-sided lesions*: could add confusion and agitation, occasionally transient choreoathetosis on opposite limbs
		In *bilateral lesions*: bilateral hemiparesis with pseudoparaplegia, akinetic mutism, severe mood disturbances, stupor, vegetative disturbances, long-lasting incontinence
	Deep, penetrating branches	Lesions in anterior limb of the internal capsule, anterior part of hypothalamus and caudate nucleus
		Transient hemiparesis, dysarthria, abulia or confusional state, or the opposite: agitation and hyperactivity or choreoathetosis in opposite limbs
		Slight aphasia in left-sided lesions or transient left visual neglect in right-sided lesions

(continued)

Table 2.1 (continued)

Main artery involved	Division/branches	Clinical features
Middle cerebral artery	Cortical branches	Paralysis of the contralateral face, arm, and leg (with predominance of arm and face)
	Deep MCA branches	Sensory impairment over the contralateral face, arm, and leg (with disturbance of stereognosis, tactile localization, baragnosis, cutaneographia)
	Total MCA stroke	Paralysis of conjugate gaze to the opposite side
		Homonymous hemianopia (sometimes superior homonymous quadrantanopia)
		Lesions of the dominant cerebral hemisphere: motor speech disorder (Broca variants of aphasia), Wernicke's aphasia, word deafness, anomia, jargon speech, Gerstmann syndrome (agraphia, acalculia, finger agnosia, right-left confusion)
		In nondominant cerebral hemisphere: apractagnosia (amorphosynthesis), anosognosia, hemiasomatognosia
		Unilateral neglect, agnosia for the left half of external space, "dressing apraxia," "constructional apraxia"
		Inaccurate localization in the half visual field, agitated hyperactive state
		Loss or impairment of optokinetic nystagmus
		Basal ganglia and internal capsule infarction with more severe motor deficit of the opposite limbs (frequent hemiplegia with equal distribution on face-arm-leg), dysarthria in right hemisphere or in left hemisphere transient mutism or some features of motor aphasia. Sensory loss is transient and minor
		Severe motor deficit (hemiplegia on opposite side), deviation of gaze toward lesion, hemianopia on opposite side of lesion, mutism, or severe forms of mixed aphasia in left hemisphere lesions (Broca and Wernicke's aphasia); anosognosia, hemiasomatognosia in right hemisphere lesions, Cheyne-Stokes respiration, stupor and coma due to edema and brain herniation, often with a fatal outcome
Anterior choroidal artery		Hemiparesis of face, arm, leg
		Prominent sensory loss, but often temporary
		Homonymous hemianopia
		Absence of other high cortical function deficits
Posterior cerebral artery	Cortical branches	Homonymous hemianopia on opposite side, or quadrant hemianopia
		Unformed visual hallucinations, metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, monocular diplopia
		Impairment of movement perception
		Transient global amnesia or long-term memory problems
		Topographic disorientation
		Left-sided lesion: dysmnesia (for verbal material), pure alexia, optic aphasia (visual anomia), transcortical sensory aphasia
		Hemiachromatopsia, color anomia, visual hemineglect, acute confusional state, acute delirium; dyslexia without agraphia,
		Right-sided lesion: dysmnesia (for nonverbal material), visual hemineglect, palinopsia, impaired mental imagery (Charcot-Wilbrand syndrome)
		Bilateral lesions: cortical blindness with visual deficit agnosia, or tubular vision in partial bilateral lesions with limited peripheral bilateral field and preserved central vision; Balint's syndrome (oculomotor apraxia, optical ataxia, visual simultanagnosia); altitudinal hemianopia; prosopagnosia; visual object agnosia; amnesia
	Deep PCA branches	Thalamic syndrome on the opposite side: sensory loss (all modalities), spontaneous pain and dysesthesias, choreoathetosis, mild intentional tremor, pseudo-athetosis posture of hand, cognitive impairment, confusion, agitation
		Mild hemiparesis produced by subthalamic or midbrain part of pyramidal tract
		Paralysis or paresis of vertical eye movement, skew deviation, possible third nerve palsy with contralateral ataxia or paresis in midbrain lesions

(continued)

Table 2.1 (continued)

Main artery involved	Division/branches	Clinical features
Vertebral arteries		Possible (but rare) cervical spinal cord infarcts
		Lesion of medulla and cerebellum but sometimes associated pontine, midbrain, and PCA artery strokes
		Medullar lesion is frequent in the retro-olivar area producing a *Wallenberg syndrome. On the lesion side* (Horner syndrome, vestibular signs with nystagmus, cerebellar signs, ambiguous nucleus palsy with dysarthria, dysphonia and dysphagia, pain and temperature sensibility trigeminal hypoesthesia) and *on the opposite side* of body (complete loss of pain and temperature sensibility)
		Cerebellar infarcts are frequent in postero-inferior cerebellar artery territory associating vertigo, vomiting, nuchal headache, cerebellar ataxia, falling, and impossibility of gait; possible evolution toward brainstem compression and herniation of the cerebellar tonsils with cardiac and respiratory arrest
Basilar artery	Inferior-middle part of basilar artery	Association of medulla, pons, and cerebellar lesions, frequent on both sides with miosis (pinpoint pupils), various oculomotor palsy (frequent abducens palsy, conjugated ocular gaze deviation toward paralyzed members, skew deviation, one and a half syndrome)
		Ocular bobbing, nystagmus, decreased or abolished corneal reflex, peripheral facial nerve palsy, dysphonia, dysphagia, various combination of motor limb deficits going to tetraplegia, locked-in syndrome, cerebellar ataxia, decerebration, and respiratory disturbances and finally in severe cases coma and death
	Top of basilar	Association of lesion in midbrain, superior cerebellar arteries, and posterior cerebral arteries with bilateral divergent strabismus and mydriasis, multidirectional nystagmus, ocular infraversion, supranuclear vertical gaze palsy, tetraparesis, abolished vesibulo-ocular reflexes, various visual field defects or cortical blindness (detected if patient can cooperate), drowsiness, decerebrate rigidity, respiratory and circulatory abnormalities, coma, and death
Small perforating arteries	Lacunar strokes	Pure motor deficits
		Pure sensitive deficits
		Dysarthria clumsy hand
		Ataxic hemiparesis
		Combined motor and sensitive deficits
		Pseudobulbar palsy in association of many lacunar strokes

Table 2.2 MEDIAL MEDULLARY SINDROME (DEJERINE)

Clinical manifestation/features	Side	Structure injured	Artery obstructed
Hemilingual paresis ± atrophy	I	Hypoglossal nerve fibers (XII)	VA
Hemiparesis or hemiplegia/face spared[a]	C	Corticospinal fibers	Proximal BA
Hemihypoesthesia (or anesthesia) for discriminative touch, proprioception, and vibration[b]/face spared[c]	C	Medial lemniscus	

I ipsilateral, *C* contralateral
[a]Motor nucleus of the trigeminal nerve located in the pons is spared
[b]Pain and temperature sensation preserved: spinothalamic tract not affected
[c]Spinal tract of trigeminal nucleus is located more laterally

Table 2.3 LATERAL MEDULLARY SYNDROME (Wallenberg)

Clinical manifestation/features	Side	Structure injured	Artery obstructed
Loss of pain and temperature sensation from face	I	Trigeminal (V) spinal tract and nucleus	VA
Loss of pain and temperature sensation from limbs and body	C	Lateral spinothalamic tract	PICA
Cerebellar ataxia, dysmetria, dysdiadokokinesia	I	Inferior cerebellar peduncle	Superior, lateral, or inferior medullary arteries
Nausea, vomiting, vertigo, nystagmus, diplopia		Vestibular nuclei	
Palatal myoclonus		Central tegmental tract	
Dysphagia, hoarseness, paresis of soft palate and pharynx, diminished gag reflex	I	Nucleus ambiguus: vagal (X, XI cranial) and glossopharyngeal fibers	
Ageusia	I	Solitary tract nucleus: glossopharyngeal (IX) and vagal (X) special visceral afferent (gustatory) fibers	
Horner syndrome	I	Descending sympathetic fibers	

I ipsilateral, *C* contralateral

Table 2.4 MEDIAL PONTINE SYNDROME [MEDIAN INFERIOR PONTINE SYNDROME (FOVILLE)]

Clinical manifestation/features	Side	Structure injured	Artery obstructed
Spastic hemiparesis	C	Corticospinal tract	Paramedian branches of the BA
Loss of tactile, vibration sensation, and stereognosis	C	Medial lemniscus	
Strabismus/diplopia	I	Lateral rectus muscle paralysis	
Facial nerve palsy	I	Facial (VII) nucleus	

I ipsilateral, *C* contralateral

Table 2.5 LATERAL PONTINE SYNDROME

Clinical manifestation/features	Side	Structure injured	Artery obstructed
Loss of pain and temperature sensation in trunk and limbs	C	Lateral spinothalamic tract	AICA
Loss of pain and temperature sensation from face (facial hemianesthesia)	I	Trigeminal (V) spinal tract and nucleus	
Ataxia (limb ataxia and gait)	I	Inferior and middle cerebral peduncle	
Paralysis of upper and lower face Loss of lacrimation and salivation Loss of taste (anterior 2/3 of tongue) Loss of corneal reflex	I	Facial (VII) nucleus and fibers	
Nystagmus, nausea, vomiting, vertigo	I	Vestibular nuclei and fibers	
Hearing loss/tinnitus	I	Cochlear nuclei and fibers	
Horner syndrome	I	Descending sympathetic fibers	

Table 2.6 SUPERIOR ALTERNATING HEMIPLEGIA (WALLENBERG SYNDROME)

Clinical manifestation/features	Side	Structure injured	Artery obstructed
Parkinsonism	C	Substantia nigra	Paramedian branches of PICA, of BA bifurcation
Hemiparesis	C	Corticospinal fibers before the medullary decussation	
Paresis of lower hemiface and tongue	C	Corticobulbar fibers	
Ophthalmoplegia (paralysis of all extrinsic ocular muscles except inf. Oblique and lateral rectus; of intrinsic muscles = fixed pupil and levator palpebrae superioris = drooping eyelid)	I	Oculomotor (III) nerve fibers	

Image Gallery

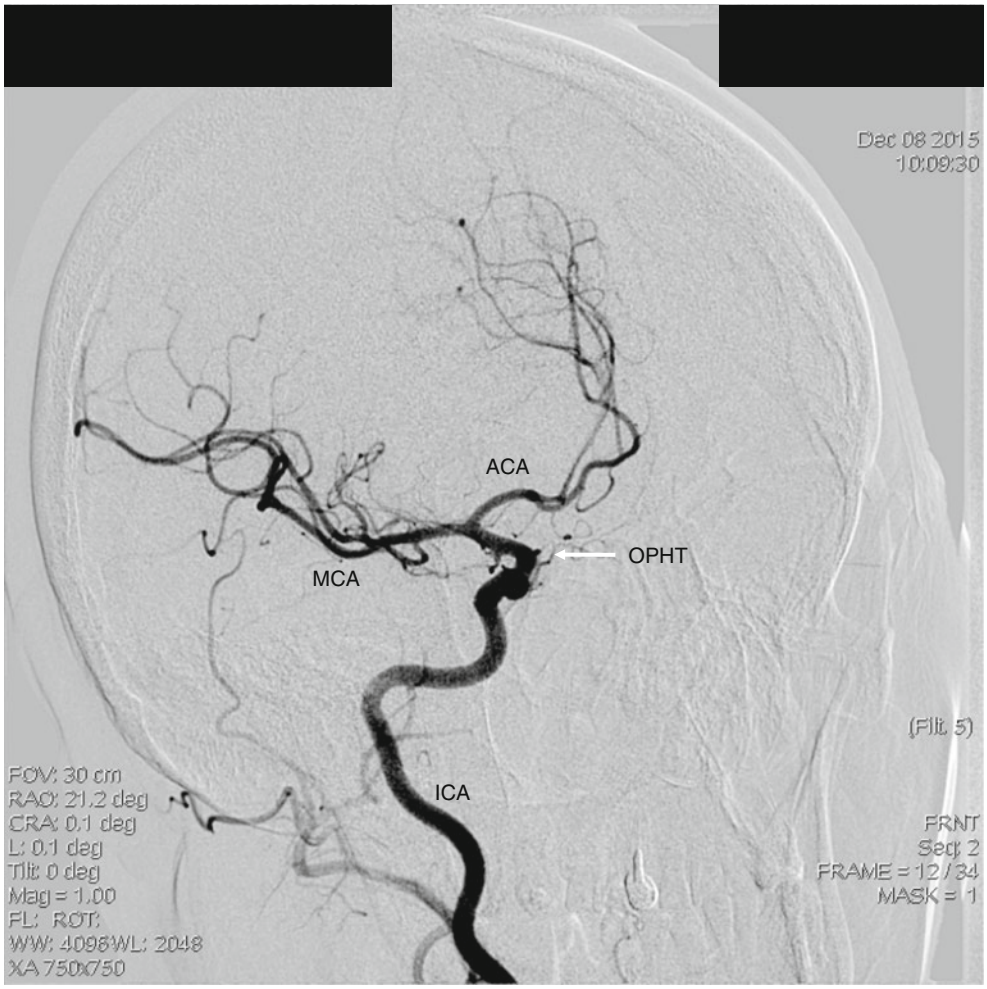


Fig. 2.1 General disposition of the branches of the internal carotid artery. The internal carotid artery (*ICA*) divides into the anterior (*ACA*) and middle (*MCA*) cerebral arteries, after giving off the ophthalmic branch (*OPHT*). Note the curves of the ICA and the diverging ACA and MCA. Frequently, the MCA appears doubled (see also text for details)

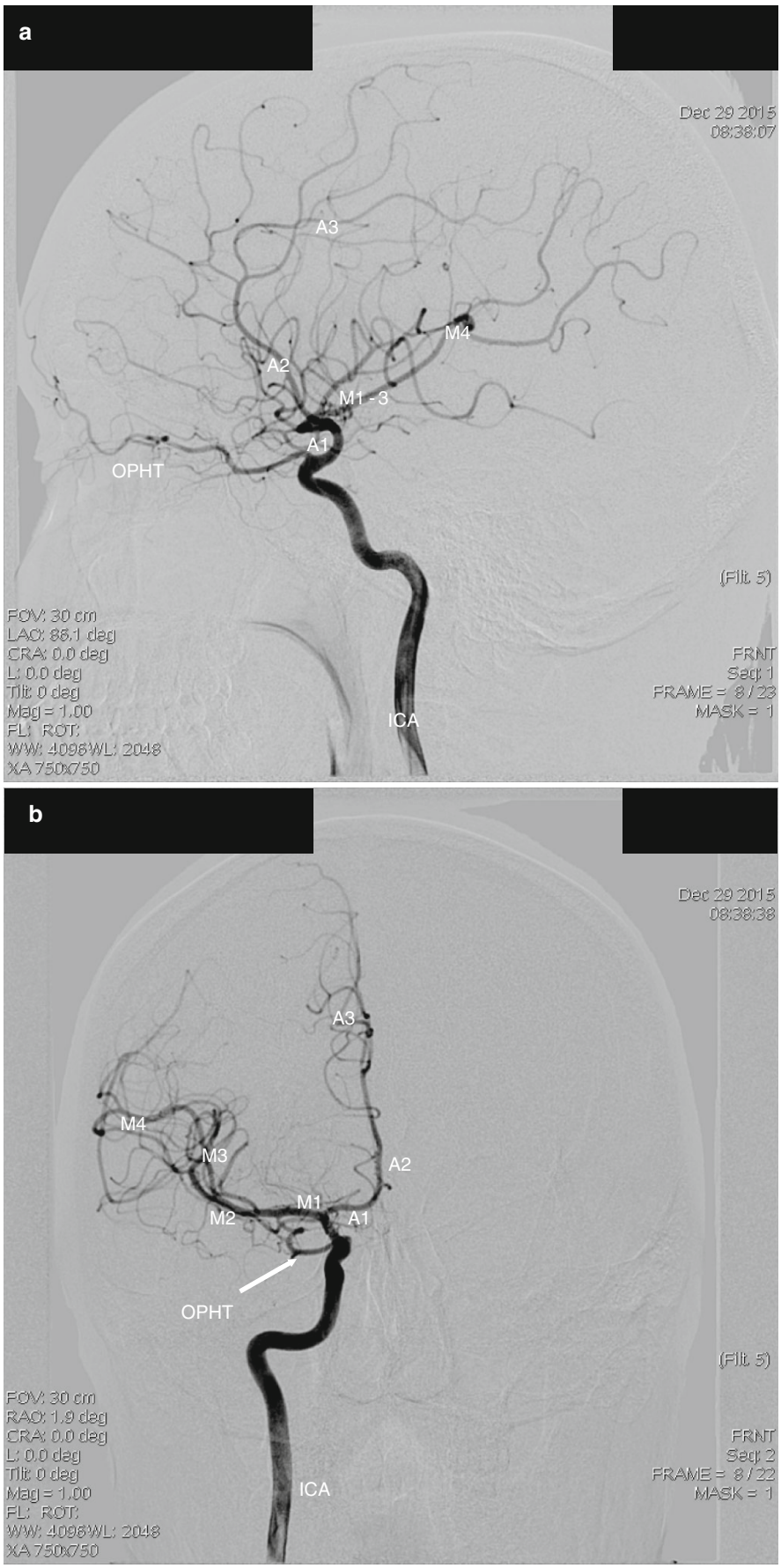


Fig. 2.2 The main branches of the cerebral arteries. Panel (**a**) lateral view. The course of the ACA is better visualized in this projection. A1 extends from origin to the branching of the anterior communicating artery; A2 up to the level of the callosomarginal artery and A3 distal to it. Panel (**b**) anteroposterior view of the main cerebral branches. The segments of the MCA appear clearly: M1 sphenoidal, M2 insular, M3 opercular, and M4 cortical. From M2 onward, the MCA is frequently doubled

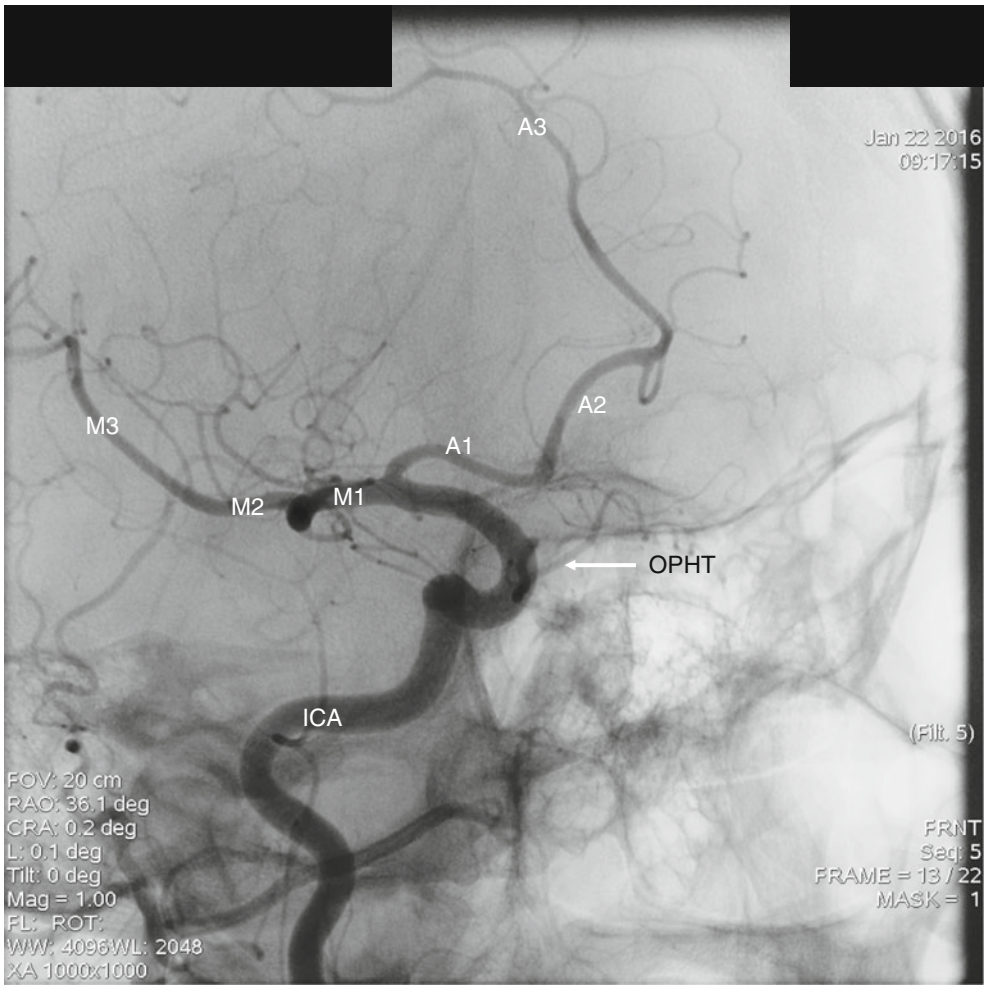


Fig. 2.3 Oblique view of the terminal part of the ICA. Note that the MCA continues the main direction of the ICA and has a more conspicuous caliber as compared with the ACA; this detail explains the more frequent embolization in the territory of the MCA

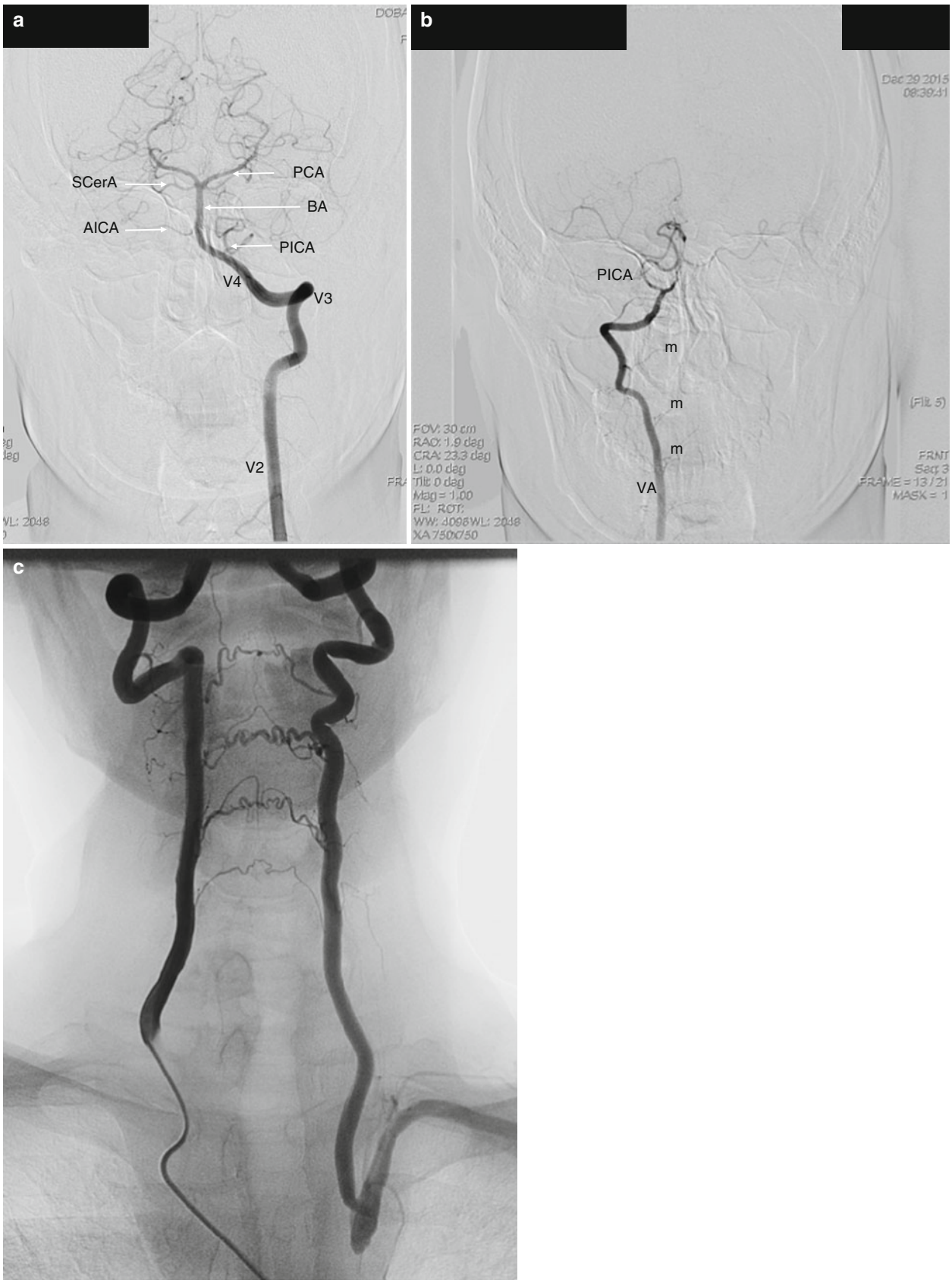


Fig. 2.4 Branches of the vertebral and basilar arteries. Panel (**a**) anterior view of the left vertebral artery (*VA*) continuing with the basilar artery (*BA*). The latter gives off the anterior inferior cerebellar artery (*AICA*) and the superior cerebellar artery (*SCerA*). The VA gives off the posterior inferior cerebellar artery (*PICA*). The BA bifurcates into the two posterior cerebral arteries (*PCA*). The segments of the VA V2 through V4 are also labeled. Panel (**b**) contralateral slender VA terminating with the PICA. Note the small muscular branches (*m*). Panel (**c**) muscular and spinal branches of the VA, appearing more evident in a case with occlusion of the left VA and vertebral steal syndrome

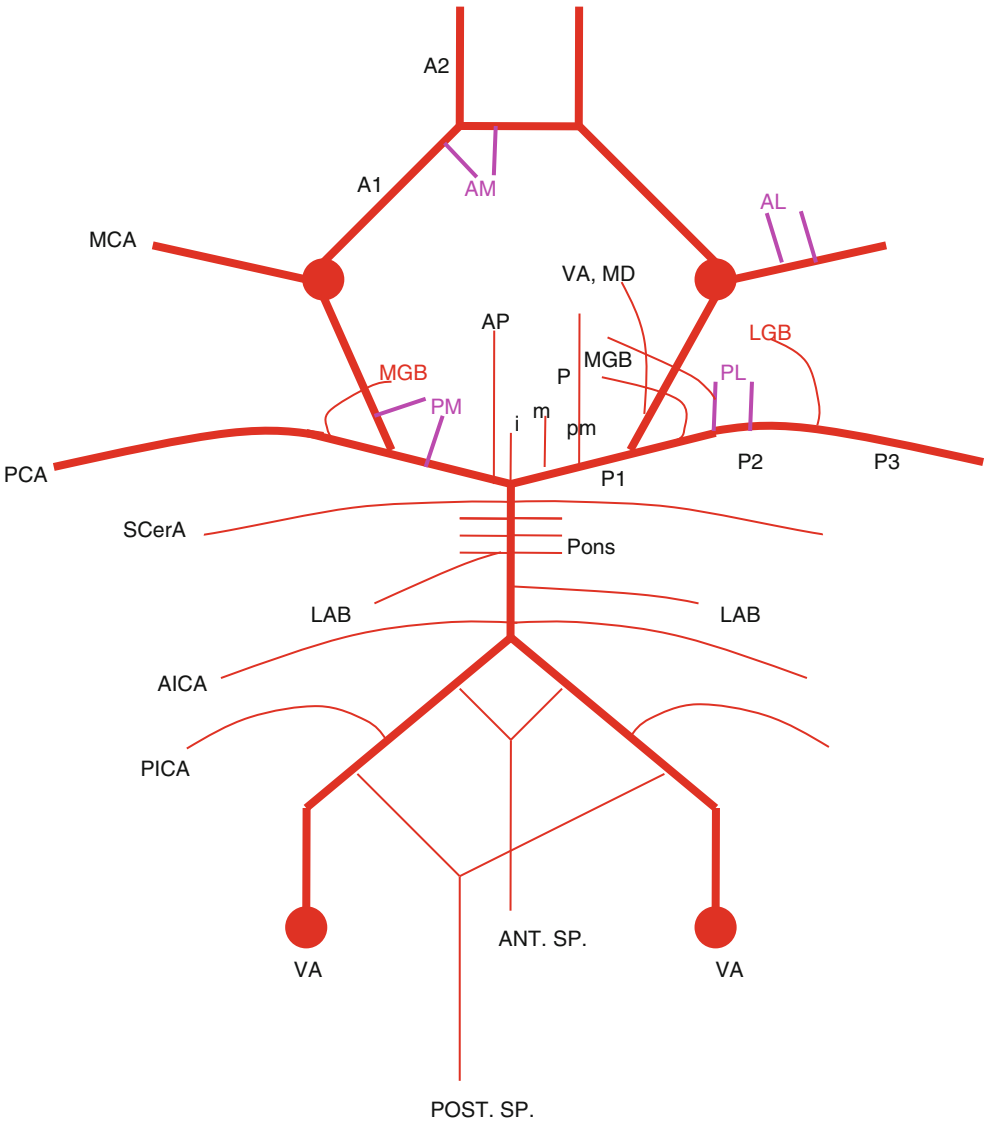


Fig. 2.5 The central branches of the arterial circle of Willis. The VA and the ICA are indicated by red disks. *ACA* and *MCA* anterior and middle cerebral arteries, PCA posterior cerebral arteries, *A1* and *A2* the segments of the ACA, *P1–P3* the segments of the PCA. The VAs give off the anterior and posterior spinal branches (*ANT.SP* and *POST.SP*) and the posterior inferior cerebellar arteries (*PICA*). The basilar artery gives off the anterior inferior cerebellar artery (*AICA*), the superior cerebellar artery (*SCerA*) just immediately upon its bifurcation. The pontine branches (*Pons*) may also give off the labyrinthine artery (*LAB*) when this latter one does not have a separate origin from the BA. The central branches of the CoW are grouped as *AM* anteromedial, AL anterolateral, PM posteromedial, and *PL* posterolateral and are depicted in pink. The main basal nuclei and thalamic and subthalamic nuclei vascularized are indicated (*VA*, *MD*, ventral anterior and median dorsal, P pulvinar, *MGB* and LGB medial and lateral geniculate body). AP artery of Percheron (the *posterior paramedian thalamo-subthalamic artery* which vascularizes the subthalamus, inferior, and anteromedial thalamic areas, *bilaterally*). See text for more details

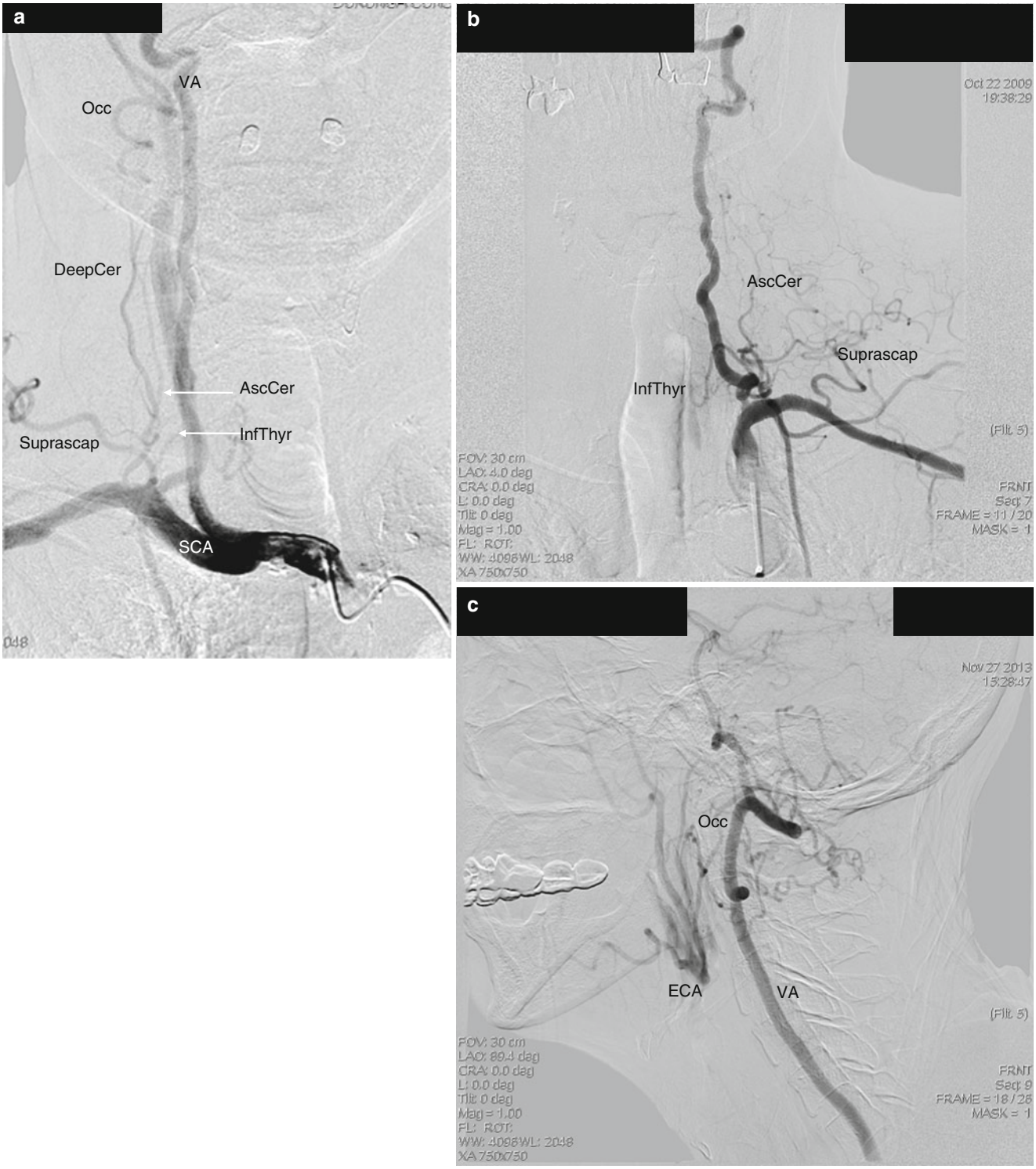


Fig. 2.6 Cervical anastomoses. These anastomoses are established between the VA and the carotid and subclavian arterial systems. The anastomoses become evident and may also facilitate arterial steal, in cases of obstruction or severe stenosis of one of the major arterial trunks (carotid, vertebral, subclavian). The direction of flow is best appreciated during angiogram. Panel (**a**) the anastomotic channel paralleling the VA: the deep cervical (*DeepCer*) and ascending cervical (*AscCer*) branches of the subclavian artery, anastomosing with the occipital artery (*Occ*) from the ECA and the VA. Sometimes, an occluded SCA may be also fed by means of anastomoses with the suprascapular artery (*Suprascap*). Panel (**b**) conspicuous branches at the base of the neck and at the root of the superior limb provide important collateral channels as in this case with stenosis of the SCA and of the VA. The same abbreviations as above. *InfThyr* inferior thyroid artery (from the thyrocervical trunk). Panel (**c**) anastomoses at suboccipital level between the VA and the ECA. This is the case of an occluded origin of the ECA. The ECA and its main branches are filled through collateral circulation from the VA, mainly through the occipital artery

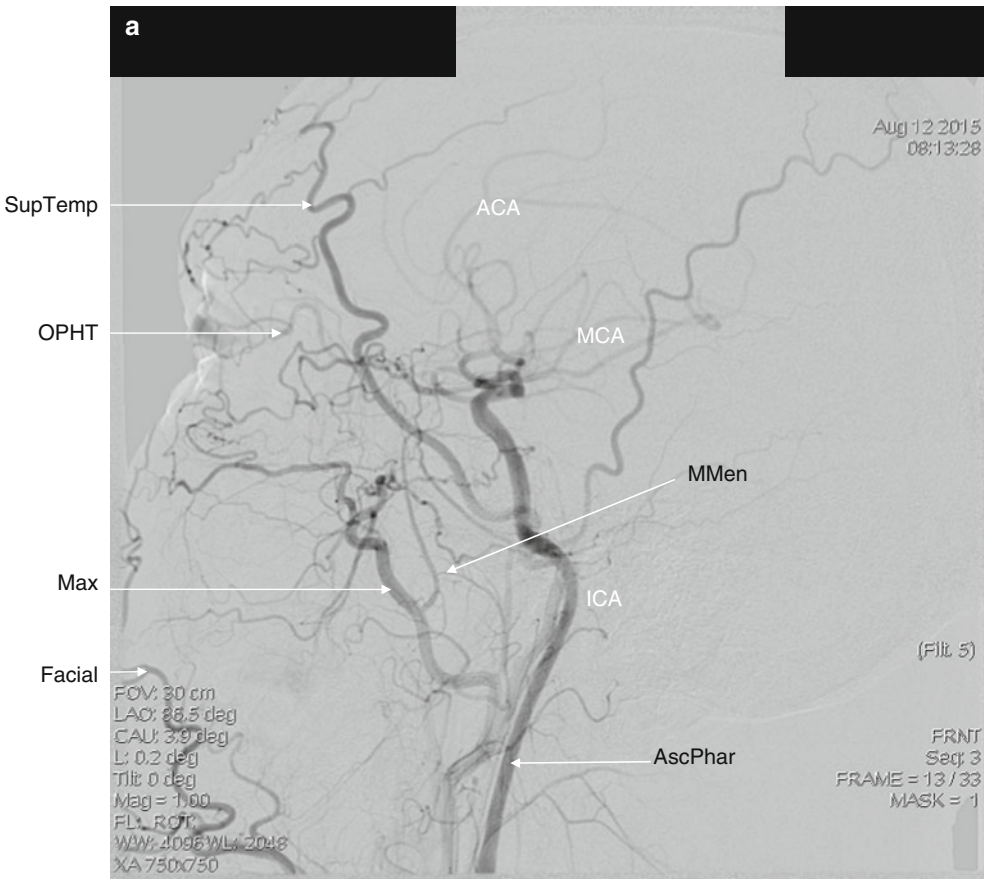
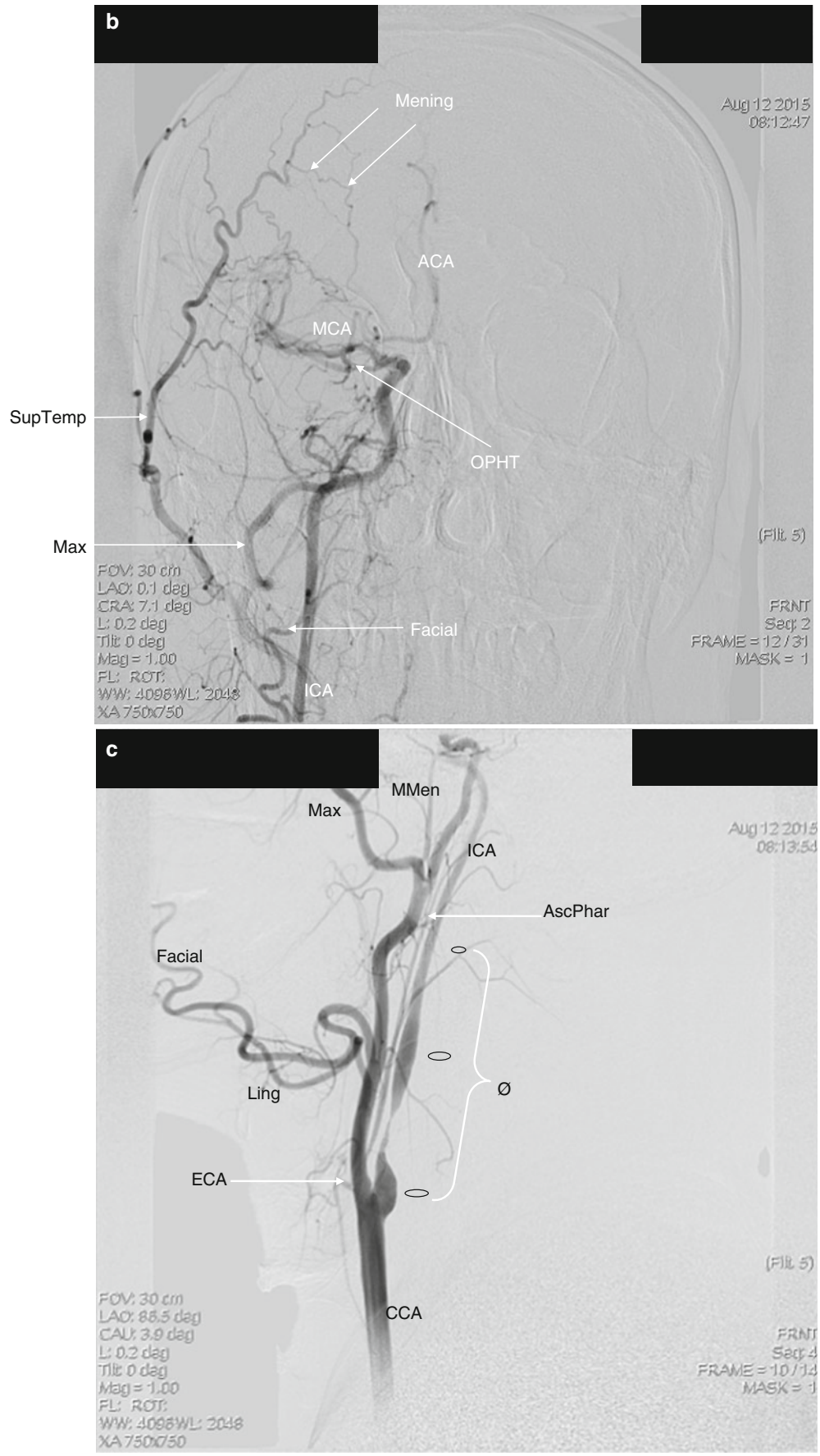


Fig. 2.7 Extra-intracranial collateral circulation. Panel (**a**) lateral view. The ICA and its major divisions (*ACA*, *MCA* and the ophthalmic artery) are feebly filled due to a severe stenosis at the origin of the ICA. The ECA and its branches appear conspicuous. The principal collateral pathways are offered by the facial artery (*Facial*) and its dorsal nasal branch, the maxillary artery (*Max*) with the sphenopalatine artery and the middle meningeal (*MMen*), and the superficial temporal artery (*SupTemp*). Note also the well-visible ascending pharyngeal artery (*AscPhar*), paralleling the ICA and offering an additional collateral pathway. Panel (**b**) anteroposterior view. The same abbreviations as above. Note the anastomoses at meningeal level (*Mening*). Panel (**c**) lateral view of the carotid bifurcation. Note the severe stenosis at the origin of the ICA, sparing the bulb. The ascending pharyngeal artery (*AscPhar*) is well visible. The ECA and superior thyroid artery and the facial, lingual, and superficial temporal branches of the ECA are also well visible. The case is of particular interest, reflecting the caliber of the ascending pharyngeal artery in situations with severe stenosis of the ICA. Note also that the ICA immediately distal to the stenosis appears somehow dilated, while more distally, it becomes narrower. While measuring the degree of a stenosis, it would be difficult to choose which of the ICA diameters represent the best landmark, as the segment after the stenosis appears as a poststenotic dilatation. Panel (**d**) leptomeningeal vessels. A later phase angiogram demonstrates the leptomeningeal arteries. These vessels become conspicuous and easily recognizable in cases with severe stenotic lesions of the ICA. Note the normal filling of the ophthalmic artery and anastomoses with the ECA (direction of flow from the ICA to the ECA branches) in an individual with no stenosis of the ICA (*white arrows*)

Fig. 2.7 (continued)



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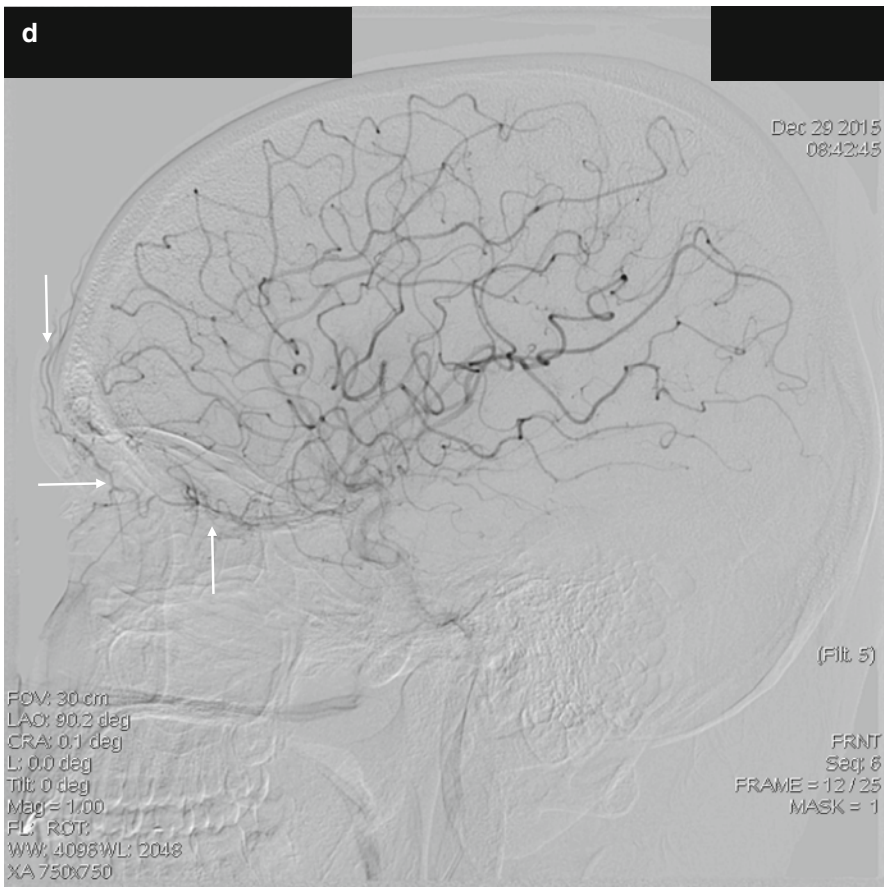

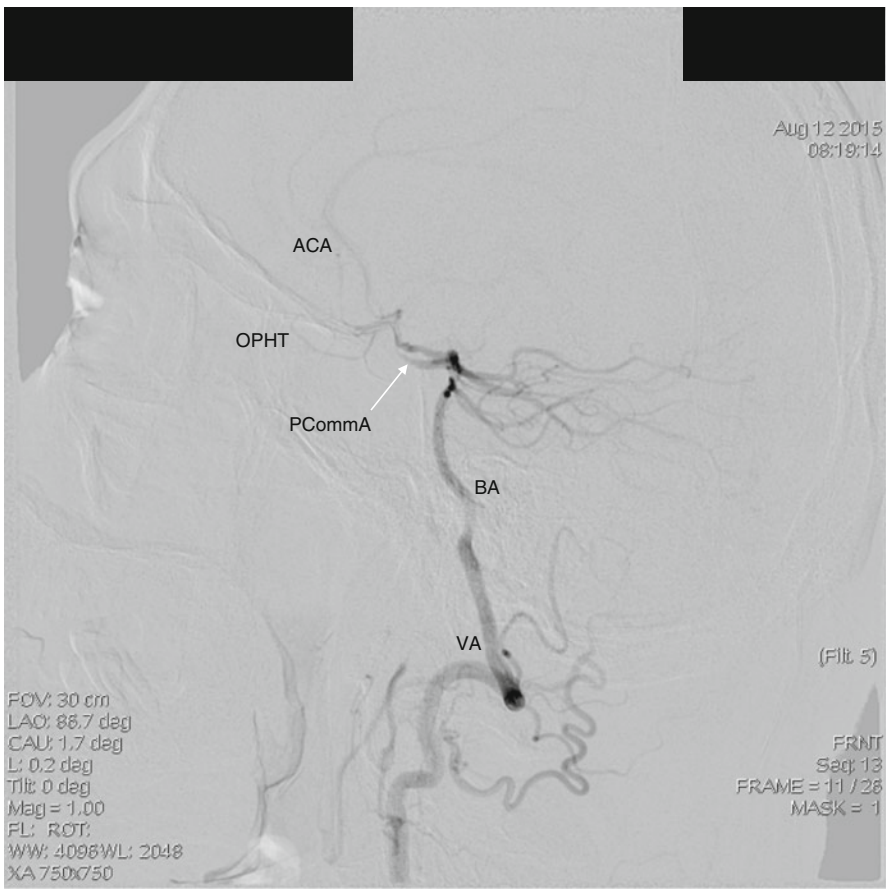

Fig. 2.8 Compensatory dilatation of the posterior communicating arteries. The caliber of the arterial segments constituting the CoW may undergo important changes with age, disease, and shifting hemodynamic conditions. The posterior communicating arteries (*PCommA*) become visible in cases with severe stenosis/occlusion in the carotid or vertebra-basilar system. The case illustrated is of a severe stenosis of the ICA; selective VA angiogram demonstrates filling of the ACA through the PCommA

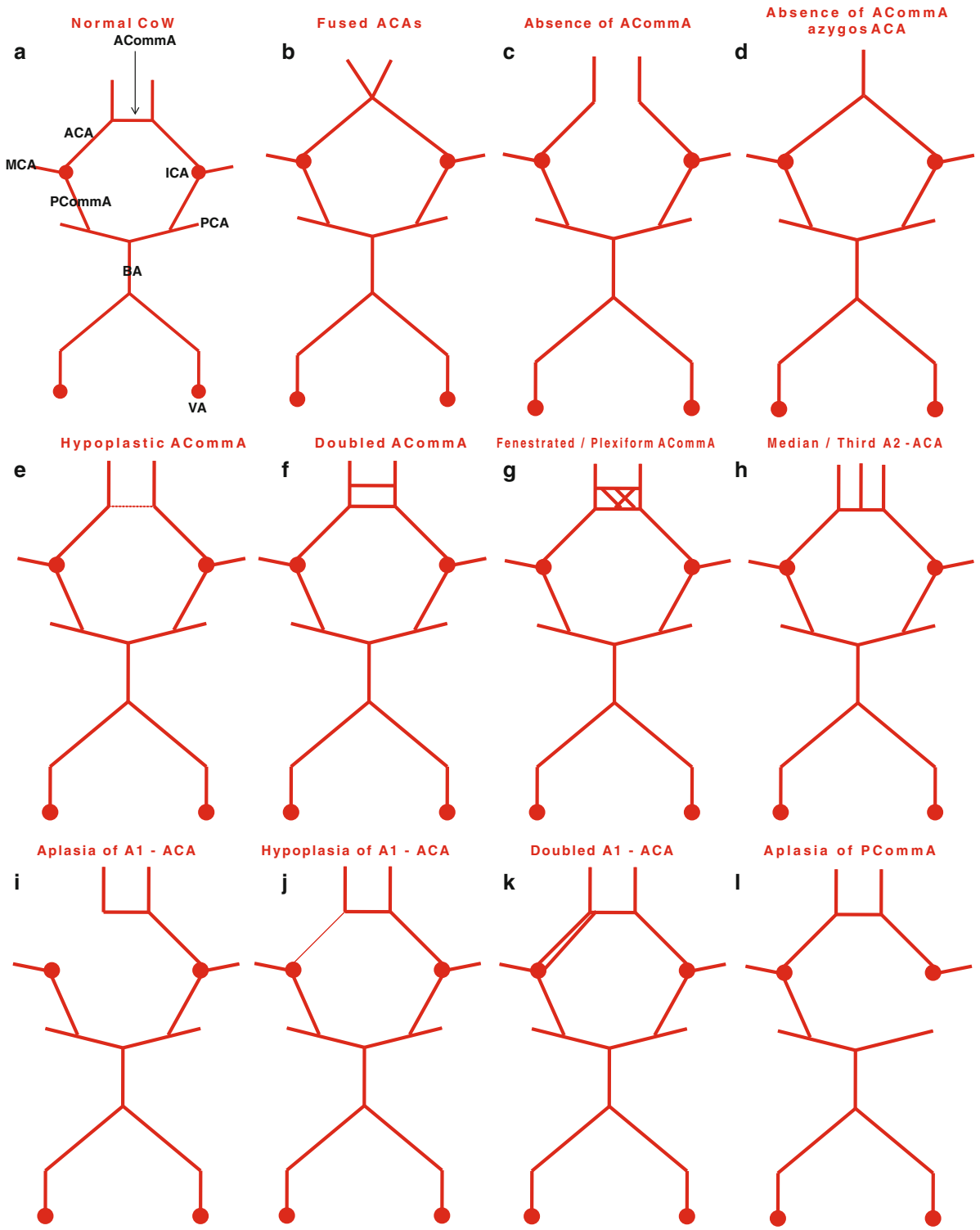

Fig. 2.9 Variations of the arterial circle of Willis. Schematic drawings of the arterial circle of Willis (*CoW*) and its component arterial segments. The feeding arteries are illustrated as red disks: internal carotid artery (*ICA*) and vertebral (*VA*) and basilar (*BA*) arteries. *ACA*, *MCA*, and *PCA* anterior, middle, and posterior cerebral artery, respectively. *ACommA* and *PCommA* anterior and posterior communicating artery, respectively. Panel (**a**) normal CoW. Panels (**b**) through K, variations in the anterior segments of the CoW: *B* fused ACAs. *C* absence of ACommA, *D* absence of ACommA with azygos ACA, *E* hypoplastic ACommA, *F* doubled ACommA, *G* fenestrated or plexiform ACommA, *H* median (*third*) ACA, *I* aplasia of A1 portion of the ACA, *J* hypoplastic A1 portion of the ACA, *K* doubled A1 portion of the ACA, Panels (**l**) through (**v**): variations in the *posterior* segments of the CoW. *L* aplasia of PCommA, *M* hypoplasia of PCommA, *N* fenestration of PCommA, *O* fetal pattern of PCommA, filled from the ICA (*black arrow*). *P* aplasia of P1 portion of the PCA (situation resembling the fetal pattern of PCommA). *Q* hypoplasia of P1 portion of the PCA, *R* duplication of P1, *S* fenestration of P1, *T* common stem of P1 and SCerA (superior cerebellar artery), *U* two separate PCAs, *V* two separate PCAs, in this latter case, one PCA fed from the carotid system, the other from the BA. Note: All these variations must be interpreted not solely from the pure anatomical point of view, as hemodynamic conditions may fluctuate and the direction of flow can also change. There is still probably no perfect diagnostic technique for the quantification of all necessary parameters

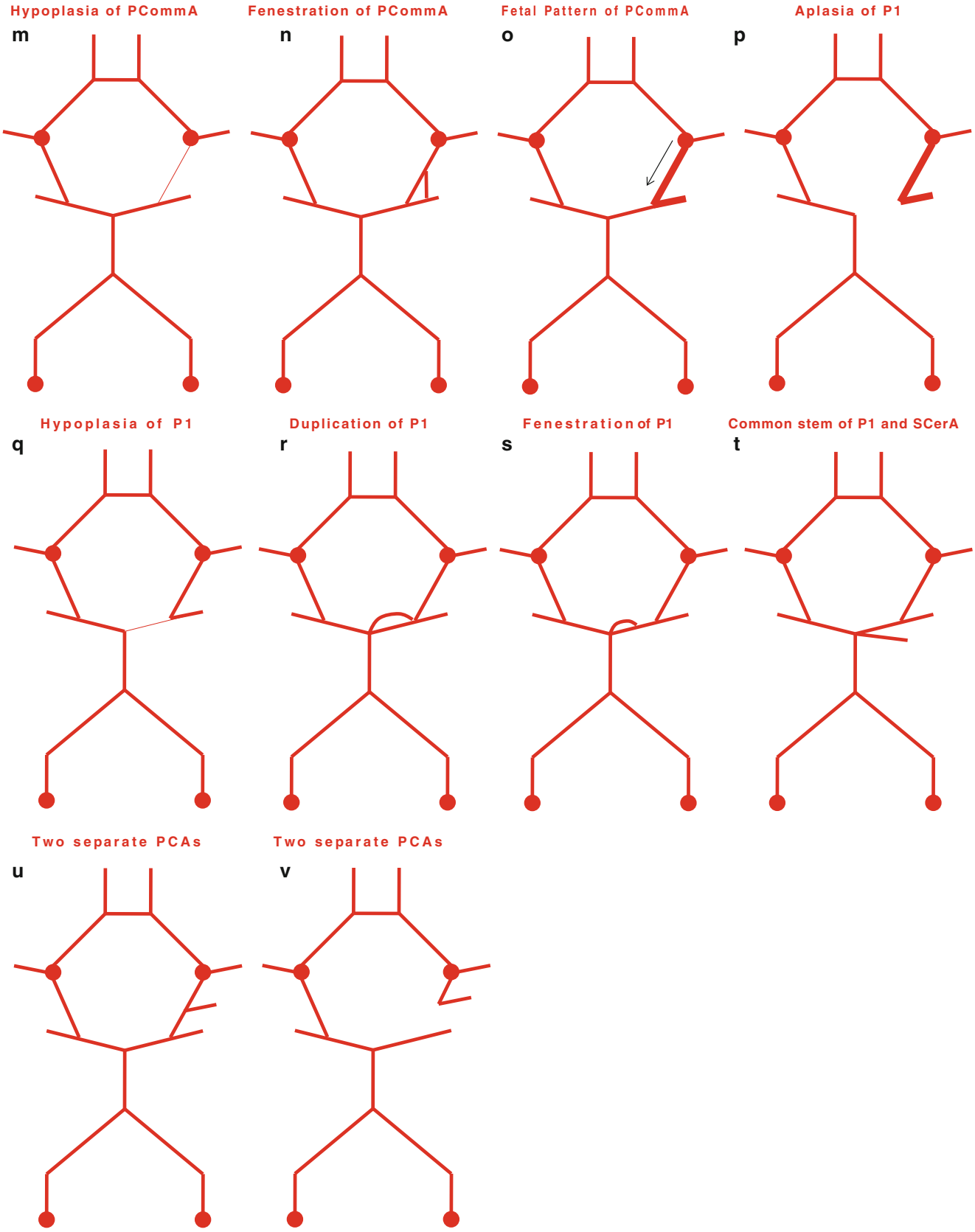

Fig. 2.9 (continued)

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Stroke Subtypes

3

Horia Muresian

3.1 Stroke Subtypes (Tables 3.1, 3.2, and 3.3)

Stroke (*cerebrovascular accident*, *cerebrovascular insult*, or *brain attack*) denotes the clinical pathological condition characterized by cell death induced by altered blood supply to the brain. Stroke is usually caused by a combination of elements and circumstances involving the blood vessels (either large or small or in combination), the clotting system, and hemodynamic factors, consequently appearing as a complex entity. Two main types of stroke are encountered: ischemic and hemorrhagic, and although considered diametrically opposite conditions, there is no absolute separation between them. Ischemic stroke can undergo hemorrhagic transformation; on the other hand, the initial hemorrhagic stroke may induce adjacent cerebral ischemia and vasospasm or may favor venous thrombosis. Additionally, a particular condition is represented by the cerebral venous infarction. Almost three quarters of strokes are of ischemic type (Table 3.1). *Cerebral edema* follows any type of infarct, due to the release of osmotically active substances from the necrotic brain tissue (e.g., arachidonic acid, lactic acid, electrolytes), and the condition is aggravated by further vascular injury and protein leakage into the interstitial space. Severe neurologic complications, coma, and death may ensue as a result of edema and not as much by the loss of brain tissue.

Stroke affects all tissue elements in the brain: neurons, glia, and vessels. Neurons do not regenerate, while the other elements undergo various changes eventually resulting in the formation of the glial scar. The major effects of stroke include alteration and deep dysfunction of the cerebral activity, matching the infarcted areas. Besides the sheer nervous deficit, deleterious effects may alter the overall brain metabolism and the turnover of the cerebrospinal fluid or may induce neuroendocrine dysfunction. The alteration in nervous function is protean and includes various degrees of somatic and vegetative dysfunction as well as psychic disturbances. This is well reflected by the numerous scales and tests used for the grading of stroke and addressing both the stroke types and consequences (National Institutes of Health Stroke Scale, Pediatric National Institutes of Health Stroke Scale, European Stroke Scale, Canadian Neurologic Scale, the specific neurologic impairment scales testing motor impairments, balance, arm/hand function, mobility, aphasia, cognition, the degree of depression, the quality of life – and so forth). The equilibrium between ischemia and hemorrhage is very delicate, and hemorrhagic transformation is very likely to occur both spontaneously, as during the development and evolution of stroke (e.g., more frequently in embolism), after endovascular or surgical revascularization or favored by thrombolytic or antiplatelet therapy (see also Chap. 8).

The *ischemic penumbra* is defined as the zone surrounding the area of total and irreversible ischemia and necrosis. Tissue elements in the penumbra appear metabolically dysfunctional but not yet structurally damaged and can be salvaged by means of thrombolytic medication and endovascular or surgical revascularization – however if applied during a short interval of time after the debut of infarction (usually 3–4 h).

A particular category of patients will depict fluctuating neurologic dysfunction after stroke, requiring prompt distinction between the extension of infarcted area with alteration of penumbra and augmentation of edema or metabolic alterations, respectively. In the first case, expeditious revascularization is essential.

Lacunar infarcts are characteristically smaller infarct areas with deeper localization (brain stem, white matter, hippocampal regions, basal ganglia, and thalamus) which are produced by occlusion of the deep penetrating branches of the main arterial trunks and typically are not accompanied by cerebral edema. The neurologic deficit can be however substantial if important neuronal routes are interrupted as in the case of lacunar infarcts involving the internal capsule or the brain stem. Lacunar infarcts are characteristic of arterial hypertension, diabetes, and old age (lipohyalinosis, hyaline

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

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Table 3.1 Stroke types and etiology

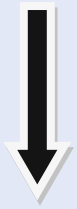
Intrinsic vascular lesions	Atherosclerosis	*Ischemic* 
	Lipohyalinosis	
	Hyaline arteriolosclerosis	
	Dissection	
	Aneurysm	
	Inflammation	
	Amyloid	
	Arteriovenous malformations	
Embolizing lesions/diseases	Cardiac source	
	Aorta (ascending, arch, thoracic)	
Hemorheologic factors	Vascular collapse	
	Hyperviscosity	
	Polycythemia	
Vessel rupture/leakage	Subarachnoid hemorrhage	*Hemorrhagic*
	Intraparenchymal/intracerebral hemorrhage	
Disruption of the blood–brain barrier	Lacunar syndrome	
Cerebral venous thrombosis		

Table 3.2 Characteristics of stroke subtypes

	Hemorrhagic		Ischemic		
Parameter	ICH	SAH	Thrombosis	Embolism	Hypoperfusion
Dynamics of symptoms	Do not begin abruptly Not maximal at onset	Abrupt Maximal at onset	Fluctuate Remit or progress	Abrupt. Maximal at onset Multiple vascular territories/ multiple sites	Diffuse Non-focal
Focal neurologic signs	Gradual Progressive (minutes to hours)	None or not relevant	Fluctuating (stuttering progression). Lacunes develop in hours to days	Maximal deficit at onset May improve quickly	Characteristic: bilateral
Headache		Maximal at onset (onset headache) Severe Widespread			
Age	Adolescents and young adults		Age over 40 years. Under 40, in patients with severe risk factors or family history		Usually in older age
TIAs	Not a feature of brain hemorrhage		Same vascular territory	More vascular territories (cardiac and aortic source of emboli)	Not characteristic

Table 3.3 Symptoms indicating particular types of stroke

Symptom	Type of stroke
Headache at onset	SAH
Headache: progressive and neurologic signs	ICH
Nausea, vomiting	SAH/ICH Large vertebrobasilar ischemic stroke
Seizures	SAH/ICH Embolism
Reduced alertness/coma	SAH/ICH Large ischemic strokes/pontine strokes
Fever	Embolism/endocarditis
Infection	Thrombosis

arteriolosclerosis). Ischemia determines the loss of axons and myelin (leukoaraiosis and leukoencephalopathy) eventually leading to vascular dementia. The loss of elasticity from destruction of smooth muscle cells in the arteriolar wall favors the development of aneurysms with consequent microbleeds or larger severe intracerebral hemorrhage (complicating minor, trivial head trauma).

Hemorrhagic stroke ensues as blood leaks from necrotic capillaries or from collateral vessels (as when the occluding thrombus or embolus breaks up and the infarcted area is reperfused). Macroscopically, the area appears stippled with petechiae or may depict larger, confluent hemorrhagic zones (especially in necrotic gray matter). Hemorrhagic transformation is a possible complication with thrombolytic therapy or anticoagulation or after endovascular or surgical revascularization. Two subtypes of hemorrhagic stroke are described: intracerebral (intraparenchymal) hemorrhage (ICH) and subarachnoid hemorrhage (SAH). *ICH* denotes direct bleeding into the cerebral tissue from small arteries and arterioles. The blood accumulates in minutes to hours, and consequently, the neurologic symptoms and signs do not begin abruptly, are not maximal at onset, and develop progressively. *SAH* represents a direct consequence of intracerebral aneurysmal rupture; flooding of the subarachnoid space and the brisk raise of the intracranial pressure rapidly complicate with coma and death. Onset headache, instantly severe and widespread, is a characteristic of SAH while significant neurologic signs are not. In *meningocerebral hemorrhage*, bleeding occurs in the brain and subarachnoid space concomitantly, combining the signs and symptoms of ICH and SAH. Transient ischemic attacks are not a feature of brain hemorrhage.

Ischemic stroke may develop abruptly (as with embolism) or during a matter of hours (atherothrombosis). The latter condition may be preceded or not by transient ischemic attack(s). The ischemic area appears as poorly demarcated and softened, during the first 24–48 h circa. Microscopical examination reveals axonal swelling and myelin breakdown and deterioration and vacuolization of the white matter. Early in ischemic stroke, CT imaging is generally negative (especially with brain stem infarcts); during this period, MRI appears more sensitive, the infarct appearing hypodense and bright on T2 MRI.

Subsequently, the infarcted tissue appears better demarcated; after about 2 weeks the infarcted area disintegrates progressively leaving behind a cavity. As the core of the infarcted area disintegrates, endothelial cells proliferate from the peripheral areas and neo-capillaries fill the necrotic area. The process of neovascularization, which peaks at about 2 weeks, accounts for contrast enhancement observed with imaging techniques. Monocyte–macrophage reaction activates from the early stages and peaks at 3–4 weeks; the products of degradation of neurons and myelin are absorbed and dispatched and the phagocytic cells appear as lipid-laden macrophages. The final glial scar is completed at about 2 months, with astrocyte proliferation from surrounding areas.

Thrombotic strokes follow the obstruction of large or small cerebral arteries; atherosclerosis represents the main cause of larger artery occlusion. The neurologic symptoms fluctuate, partially remit, or progress while generally matching a particular cerebral vascular territory.

Embolic strokes develop abruptly with neurologic symptoms maximal at onset and covering an arterial wider range or over multiple sites, revealing the heart or the aorta as the probable source of embolic material. A rapid recovery also favors embolism.

Silent brain infarcts are diagnosed by neuroimaging as the patients do not reveal or relate any evident clinical history or previous TIAs. However, the presence of cognitive deficits indicates that this particular category of infarcts is not totally asymptomatic and the denomination of *covert brain infarcts* appears more appropriate (most patients demonstrated a significant decline in the Modified Mini-Mental State Examination and the Digit Symbol Substitution tests) [1]. Covert brain infarcts are more frequent than symptomatic strokes [2, 3]. Patients with severe atherosclerotic disease may have silent brain infarcts at a younger age. As revealed by the Cardiovascular Health Study [*ref above*], most of the silent brain infarcts detected were single, small, subcortical, and without acute symptoms recognized as TIA or stroke but with subtle cognitive changes. Patients with silent brain infarcts, with more than one infarct, and with more lesions of the white matter were at higher risk for subsequent stroke [4] and at risk for dementia [5]. A particular issue indubitably follows: should patients with asymptomatic carotid stenosis and silent brain infarcts be considered as symptomatic? This will be taken again in discussion later.

The *transient ischemic attack* (TIA) denotes a focal and reputed reversible neurological deficit typically lasting less than 24 h. The mechanism of TIAs is uncertain. Most ischemic strokes are preceded by TIAs, sometimes in a *crescendo* fashion. TIAs in the carotid system depict more typical signs as compared with TIAs in the vertebrobasilar system (Table 3.4). Neuronal dysfunction may persist however beyond the symptomatic period of the TIA, and neurologic deficits can be medically reactivated (e.g., with midazolam) [6]. The diagnosis of TIA is not always straightforward, as numerous conditions may mimic TIAs: metabolic conditions (hypoglycemia, acute intermittent porphyria), electrolyte disturbances (hypo- and hypercalcemia, hyperkalemia), infectious diseases (toxoplasmosis, cryptococcal meningoencephalitis, Lyme disease, tuberculous granuloma of the central nervous system), neurologic and psychiatric diseases (Meniere disease, multiple sclerosis, epilepsy, hyperventilation, carotid sinus hypersensitivity, anxiety, hysteria), and miscellaneous (cervical spondylosis, dural sarcoidosis, subdural hematoma, hypovolemia, adverse drug reactions) [7].

Amaurosis fugax or *transient visual loss* can be correlated and equated with TIA. The preferred term is however

Table 3.4 Clinical features of TIAs in the vertebrobasilar system versus carotid system

Vertebrobasilar	Carotid
Vertigo, dizziness, unstable gait	Contralateral hemiparesis (at times, predominantly brachial)
Ipsilateral facial paresthesia	Transient monocular visual loss (*amaurosis*)
Contralateral limb paresthesia Impaired vision: diplopia	Slurred/difficult speech
Hoarseness	Conscious state not altered
Dysphagia	
Rarely: hemiparesis	
Polymorphous and less characteristic symptomatology	*Clinical signs are more characteristic*

transient monocular visual loss (TMVL) and *transient binocular visual loss* (TBVL). The diagnosis of the episode is made in retrospection, as generally the patient presents after the event has already resolved. However, some symptoms and clinical signs help in distinguishing the cause and mechanism of transient visual loss. Ischemia caused by carotid artery lesions frequently manifests as TMVL, with a rapid onset, descending over the visual field like a curtain and lasting typically less than 10 min. Headache accompanying the former symptoms usually characterizes giant cell arteritis. Retinal vasospasm and retinal migraine may also represent a cause of TMVL in young individuals. On the other hand, TBVL occurs with vertebrobasilar ischemia. If only one hemisphere is ischemic, the patient will experience homonymous visual field loss contralateral to the lesion; signs of brain stem ischemia (dysarthria, dysphagia, vertigo, diplopia) or of cerebral ischemia (hemiparesis, hemisensory loss, aphasia) may accompany the TBVL. Diagnostic workup must be thoroughly performed in order to differentiate and exclude other possible conditions for transient visual loss, among which ocular disease (e.g., glaucoma, spontaneous hyphema, vitreous floaters, congenital optic disc anomalies, compressive optic neuropathy, optic neuropathy, retinal vasospasm and retinal migraine, retinal vein occlusion), giant cell arteritis, migraine, and seizures. Ophthalmologic and neurologic clearance is mandatory even in the presence of a known carotid stenosis.

The phenomenon of *delayed stroke* (stroke occurring many months after total carotid occlusion) may be due to distal propagation of thrombus or embolism from the more distant portion of the clot [8]. Impaired vasoreactivity is associated with an increased risk of ipsilateral ischemic stroke in individuals with high-grade carotid stenosis or occlusion.

Although comparisons have continuously been made between the pathogenesis of plaques in the carotid and in the coronary circulations, the conditions in the former case are less well understood. Rupture of the carotid plaque appears as a consequence of various factors, among which the most relevant and most studied are morphologic (plaque geometry, thickness of the fibrous cap, intraplaque hemorrhage, endothelial erosion), hemodynamic (wall shear stress and local pressure, both involving the more proximal portion of the plaque), and oxidative stress and inflammation (the possible clinical use of FDG-PET to target high-risk plaques, still remains to be determined). [*A detailed account of the inflammation and oxidative stress is given in* Chap. 18]. *Intraplaque hemorrhage* represents an important marker of risk, and diagnostic workup should ideally aim in defining the presence and characteristics of the vulnerable plaque [9, 10]. Increased number of emboli (as detected by ultrasound, in the carotid and intracranial circulations) in patients with more than 50 % asymptomatic carotid stenosis places these individuals at higher risk for further symptoms [11]. Ulcerated plaques are highly associated with symptoms and thrombus formation [12].

Clinical signs and symptoms are important in the planning of the diagnostic interrogation. However, the carotid bruit, ocular bruits, and facial pulse asymmetry are all poor predictors of future stroke in asymptomatic patients, as all these signs cannot be accurately correlated with the degree of stenosis and with plaque morphology. Classically, a high-pitched or a long-duration bruit will suggest a tight carotid stenosis (over 75 % or with a residual lumen of less than 1.5 mm). These details should not limit the thorough and extensive clinical evaluation of the patient, including the palpation of pulses and auscultation of the main arteries (carotid, subclavian, femoral, abdominal aorta, and iliacs). Important data pertaining not only to the cerebral circulation but also to the remainder arterial system can be revealed during physical examination orienting the clinician toward the best and most suited diagnostic exploration in the given patient.

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Surgical Approaches for Cerebrovascular Revascularization

4

Horia Muresian

In this chapter, the surgical exposure of the carotid, subclavian, and vertebral arteries is considered. The approach to carotid and vertebral arteries includes exposure from origin to the cranial base, combining the anatomical, clinical, and surgical particulars. The gross anatomy and relevant relationships of the aforementioned arteries were previously presented in Chap. 2 "Cerebral Vascular Territories and the Major Neurovascular Syndromes."

This presentation can be perceived and understood in two ways: on the one hand, the classical description of the exposure of the carotid and vertebral arteries from origin, up to the base of the skull. On the other hand, the approach guided by practical reasons, comprising:

1. The principal target artery or the most frequent site of exposure, i.e., the carotid bifurcation, the V0 and V1 segments of the vertebral artery, and the subclavian artery
2. Additional arterial segments: common carotid arteries, origin of the right common carotid artery, bifurcation of the brachiocephalic trunk, the distal internal carotid artery, and the distal and suboccipital (V3–V4) segments of the vertebral artery
3. More distant donor arterial segments: ascending aorta, brachiocephalic trunk, aortic arch, and origin and intrathoracic segment of the left subclavian artery and left common carotid artery
4. Additional approaches for concomitant or more extensive exposure: more than one arterial segment of the same artery or more arteries
5. Particular exposure for selected pathologies: aneurysms and tumors
6. Approaches for the harvesting of venous grafts

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

4.1 Surgical Approach to the Principal Target Arteries

4.1.1 Exposure of the Carotid Bifurcation

The "normal" level of the carotid bifurcation is located at the level of the superior border of the thyroid cartilage and is contained in the carotid triangle. Numerous variations regarding the height of the bifurcation are however encountered. With higher bifurcations, surgical approach may become difficult or impossible. Lower bifurcations may be associated with particular relationships with nerves (vagus, superior laryngeal) and veins and may be confusing for the surgeon, as a clear distinction should be made with other arterial variations (e.g., proatlantal artery, conspicuous thyrocervical trunk, separate origin of the ECA from the aortic arch, extra-transversal course of the vertebral artery). Preoperative imaging (ultrasound, CT-angio, MRI, or angio) must offer clear details to the surgeon regarding not only the level of the carotid bifurcation but also some other variables, for example, unusual location of the ECA with respect to the ICA (sagittal bifurcation, "inverted" bifurcation), marked hypoplasia of the ICA, extreme kinking, and so forth. The superior thyroid artery offers a sound landmark for the normal level of the carotid bifurcation: with higher bifurcations, the superior thyroid artery originates from the CCA. Conversely, with lower bifurcations, the ECA depicts a longer trunk until giving off its main branches.

The type of incision is chosen after taking into account the planned surgery to be performed and the possible additional exposures. With lesions limited at the level of the bifurcation, a smaller longitudinal, oblique or transversal cervical incision anterior to the sternocleidomastoid muscle (SCM) will suffice (Fig. 4.1). Otherwise, the longer longitudinal incision is recommended (Fig. 4.2). The entire neck is prepared, including the supraclavicular regions (in case with highly diseased CCA, the SCA may offer a good donor vessel). We do advocate only a slight extension and minimal contralateral rotation of the head with minimal tension on the

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tissues and in order to avoid the superposition of the SCM and of the IJV over the carotid vessels that occurs with extensive rotation. The patient is in head-up position, with the operating table flexed almost as a recliner chair. This allows maximal comfort for the patient under locoregional anesthesia, facilitates ventilation, and diminishes venous pressure. Both arms are adducted. The oblique or transversal incision is performed at 3–4 cm under the mandible from the upper level of the thyroid cartilage to the anterior border of the SCM. These incisions will probably interrupt less superficial cervical nervous branches, although no study has revealed any particular advantage, except cosmetic, with less retractile or keloid scars (Fig. 4.3). If the head is not extensively rotated, the dissection and retraction of the SCM are minimal. We do not routinely dissect the IJV and prefer having it retracted together with the SCM with minimal interference with the venous flow. Some of the main tributaries of the IJV must be selectively ligated (superior and middle thyroid veins, lingual, facial vein, or variant common trunks) together with the sternocleidomastoid branch of the superior thyroid artery (this artery may be more conspicuous or even the superior thyroid artery may cross the bifurcation in cases with "inverted" carotid bifurcation when the ECA is lateral to the ICA; see Chap. 1 for details). The hypoglossal ansa has very different lengths and relationships. Its identification is important not for its preservation (as it may be cut without major consequences) but for correctly identifying the hypoglossal nerve and variations of the superior laryngeal nerve or of the vagus nerve (see Chap. 1 for details). The vagus nerve may depict a more anterior disposition, sometimes adherent to the carotid bulb and must be well identified and preserved. Bradycardia may follow manipulation of the vagus nerve and of the carotid sinus area; spraying or infiltration of the area with local anesthetic and/or atropine i.v. will usually reverse the dysrhythmia. The accessory nerve can be injured at the upper pole of the incision and especially if it has a pre- or trans-jugular tract. Inflamed or enlarged lymph nodes may impede a direct access to the carotid bifurcation and require selective excision. Ectopic thyroid tissue must be identified. We routinely perform histologic examination of any tissue excised during operation even if performed solely for tactical reasons. The distal CCA, ICA, and ECA are subsequently dissected (Fig. 4.4). We perform minimal manipulation of the vessels, at least until clamping. The atheromatous plaque is usually well visible through the wall of the ICA, allowing the necessary exposure of the ICA, ideally circa 5 mm distal to it (a segment of ICA of good quality is necessary for safe clamping and shunt insertion if needed). The solid angle between the ICA and ECA is not routinely dissected, in order to preserve the nerves of the sinus and glomus. The hypoglossal nerve crosses the ICA and ECA and is accompanied by the occipital artery. The ICA must be sometimes exposed superior to the hypoglossal nerve; division of the ansa facilitates mobilization of the nerve and its gentle retraction. The superior laryngeal nerve crosses deep to the bifurcation, but it may sometimes pass between the ICA and ECA or, rarely, anterior to both. A nonrecurrent inferior laryngeal nerve may be present on the right side either associated with an aberrant right subclavian artery (ARSA) or as a singular variant. Its identification is mandatory especially with more extensive exposure of the CCA and branches. An extensive and circumferential dissection of the bifurcation is seldom necessary, mostly when the version technique or resection and bypass are contemplated. There is no clear consensus regarding the proper handling of the nerves of the sinus: to denervate or to preserve, in order to avoid postoperative hypertension; this particular is even more important in cases with bilateral carotid endarterectomy (either staged or simultaneous). The ascending pharyngeal artery (Fig. 4.5) originates in the solid angle of the carotid bifurcation, either from the ECA or rarely from the very origin of the ICA (an ascending pharyngeal artery originating from the ICA may contribute to the maintenance of the patency of the ICA in cases with proximal near-occlusive or occlusive lesions). If larger than usual, the artery must be selectively isolated and clamped in order to avoid back bleeding when opening the carotid bifurcation. The mandibular branch of the facial nerve can be injured [1] with higher incisions or after extensive retraction at the upper pole of the wound, leading to asymmetry of the mouth (the buccinator muscle is spared).

4.1.2 Exposure of the Vertebral Artery: The Segments V0 and V1

The VA from its origin up to the transverse foramen of the sixth cervical vertebra (V0 and V1 segments) can be approached either through a horizontal transverse supraclavicular incision or by a longitudinal, anterior cervical incision (Fig. 4.6). The position of the patient is the same as above. In our experience, extension of the head appears of more help than contralateral rotation.

Supraclavicular Approach to the VA (Fig. 4.7) This incision allows a good and concomitant exposure of the VA, SCA, and CCA. The skin incision is performed at about 1–2 cm superior to the clavicle from just lateral to the sternoclavicular joint and is extended laterally to the level of the external jugular vein (which usually can be preserved); the external jugular vein indicates approximately the middle of the clavicle. The platysma muscle is divided, along with small branches of the supraclavicular nerves (with longer incisions, the resultant paresthesia in the infraclavicular and pectoral regions can be disturbing to the patient). For a good exposure, we divide the clavicular head of origin of the SCM. The SCM is retracted medially. The IJV is identified

and partially dissected after cutting the middle layer of the cervical fascia. The inferior belly of the omohyoid muscle can be retracted superiorly and laterally, without having it divided. The pre-scalene fat pad and lymph nodes are either partially dissected and retracted or excised. Numerous lymph nodes can be identified at the lateral and posterior border of the IJV, and some need to be excised for a good exposure of the IJV and of the underlying CCA and vagus nerve. The suprascapular artery crosses the field from medial to lateral and usually needs to be ligated. If the CCA is needed for VA reimplantation, the CCA is dissected over a distance of about 4 cm and mobilized, *posterior* to the IJV and vagus nerve. The thoracic duct and any larger cervical and supraclavicular lymphatic ducts are identified and ligated. For a better exposure of the VA or for exposure of the SCA, the anterior scalene muscle is divided, after identifying the phrenic nerve (the nerve courses on the anterior surface of the anterior scalene muscle, from superior and lateral to inferior and medial). The position of the VA is indicated by the solid angle between the anterior scalene and longus colli muscles; the artery appears as the deepest anatomical element, hidden by the inferior thyroid artery, the sympathetic fibers, middle sympathetic cervical ganglion, and the vertebral vein. The C_6 transverse process can be easily palpated and offers a good guide for the VA. Just inferior to C_6, the inferior thyroid artery crosses from lateral to medial; if larger than usual, it can be easily mistaken for a VA. The vertebral vein is interrupted allowing the direct approach to the VA. (The vertebral vein represents also a good landmark for the thoracic duct: the vein joins the subclavian vein close to the jugular-subclavian venous confluence. The thoracic duct approaches the venous confluence and passes just anterior to the vertebral vein.) Alternatively, dissection may follow the SCA from lateral to medial and identifying its main branches up to the VA. A particular care must be given to the preservation of the sympathetic and parasympathetic nerve fibers (cervical ansa, cardiac branches, middle cervical and stellate ganglia, etc.). Extensive dissection and interruption of sympathetic nerves can lead to Horner's syndrome. Before proceeding with the planned surgical procedure, we recommend a thorough examination of the VA (palpation and a precise measurement of the obtained length and, not least, the distance from the VA to the SCA or CCA) as sometimes the quality of the wall of the VA or its length is not sufficient. Consequently, exposure of the VA in the transverse canal of C_6 must be performed by opening the bone with a rongeur. The C_6 nerve trunk may limit the superior extension of the VA exposure.

Anterior Cervical Approach to the VA (Fig. 4.8) This incision allows also a good and concomitant exposure of the VA, SCA, CCA, and, if extended superiorly, the carotid bifurcation. The full incision follows the anterior border of the SCM and higher in the neck is slightly curved underneath the mandibular angle. If the carotid bifurcation need not to be exposed, the skin incision will end superiorly at the level of the thyroid cartilage. The platysma and the cervical fascia are divided; the SCM is retracted laterally. Again, the superior belly of the omohyoid muscle can be retracted without division. The carotid sheath is dissected, and the CCA, IJV, and vagus nerve are identified. Subsequently, the elements of the supraclavicular fossa are dissected. Even with this incision, we divide the anterior scalene muscle after identification of the phrenic nerve. The remainder of the approach proceeds as above. If the carotid bifurcation needs to be exposed for concomitant lesions at this level, we recommend two approaches: either the full length anterior cervical incision or two horizontal and parallel incisions, one supraclavicular (for the CCA, SCA, and VA), and one submandibular (for the carotid bifurcation). The choice depends on the conformation of the neck and of the extension of the lesion on the ICA, distally. With the anterior cervical approach, less supraclavicular nerve fibers are interrupted, but the skin incision appears less esthetical and more prone to retractile scar.

The pleural dome is usually not at risk when approaching the VA or the CCA. The more extensive dissection of the SCA may bring additional risk for opening the pleura. It is however more important to recognize the lesion than the lesion itself.

Exposure of the VA in the interosseous segment (V2) may be necessary in trauma when acute control of hemorrhage is needed. The anterior cervical approach is favored, and exposure of the V2 in the bony canal is facilitated by contralateral (medial) retraction of the cervical viscera, carotid vessels and IJV, and adjacent sympathetic fibers. Identification of the bony landmarks and nerve trunks is mandatory. Opening of the bony canal will lead to additional hemorrhage from the branches of the VA and venous tributaries, and a good vision is impeded both by the numerous bleeding branches and by the already formed cervical hematoma. Endovascular procedures have reduced or eliminated the need of such a surgical approach for which we have no personal experience.

4.1.3 Exposure of the Subclavian Artery

This paragraph does not deal with the approach to the origin of the left SCA, a topic that will be discussed later in this chapter.

The entire cervical portion of the SCA can be approached through a cervical incision, either horizontal supraclavicular (Fig. 4.9) or anterior longitudinal (Fig. 4.10) (see above the exposure of the VA). The same steps as above are usually taken, and both incisions allow a good exposure of the SCA, of its main branches, and of the CCA. If reimplantation of the SCA into the CCA or CCA-to-SCA bypass is contemplated, the same retro-jugular exposure of the CCA is

advocated. The SCA is best exposed after dividing the anterior scalene muscle and gentle manipulation of the phrenic nerve. The more distal SCA is in intimate relationship with the brachial plexus and difficult to approach. Alternatively, the axillary artery can be dissected immediately infraclavicular just below the subclavius muscle and after cutting the clavipectoral fascia, through the same supraclavicular skin incision (or rarely, requiring an additional infraclavicular incision). Consequently, should the third (extrascalenic or postscalenic) segment of the SCA not be suited for a recipient artery, the axillary artery may offer a sound alternative (Fig. 4.11). In trauma patients, the approach of the SCA above the clavicle and of the axillary artery inferior to the clavicle precludes the sectioning of the bone (Fig. 4.12). The supraclavicular approach to the SCA allows also the exposure of the first rib and its resection for the treatment of the thoracic outlet syndrome (Fig. 4.13).

4.2 Surgical Approach to Additional Arterial Segments

4.2.1 Exposure of the Common Carotid Arteries and Origin of the Right Common Carotid Artery

The entire right CCA and cervical portion of the left CCA are approached in the lower neck (see Chap. 1: the three anatomical-surgical zones of the neck, Zone I) either by a supraclavicular or by an anterior longitudinal incision. The type of incision and its length depend on the particular disease and surgical procedure planned, as during surgery the CCA is approached together with other arterial segments: carotid bifurcation and SCA. The same steps followed are as above. Particular attention must be given to the thoracic duct on the left side and to the autonomic nerve fibers on both sides. A strict periadventitial dissection will facilitate the preservation of most if not all nervous elements. It is important to note the different relative position of the CCA and SCA on the right and left sides. On the left, the SCA is posterior to the CCA, while on the right, as the brachiocephalic trunk does not bifurcate in a sagittal plane, the SCA appears more lateral to the CCA. It is also on the right side that the vagus nerve lies in closer contact with the CCA; the right recurrent laryngeal nerve winds around the right SCA just at the level of the bifurcation of the brachiocephalic trunk and comes in contact with the very origin of the right CCA. The presence of a right inferior nonrecurrent laryngeal nerve must be also borne in mind when approaching the origin of the right CCA. The CCA is covered in the lower neck by two layers of fascia: the superficial and the middle, the latter "packing" the infrahyoid muscles and hiding the CCA. An enlarged thyroid gland may also partially cover the CCA. It is also important to underline the relative position of the CCA and IJV: the latter is posterior to the carotid vessels at the level of the cranial base, becoming lateral, and then anterior to the CCA in the lower part of the neck. As a consequence, the CCA is in a deeper position in Zone I.

The CCAs usually do not give off cervical branches except a middle thyroid artery (rarely). In cases with a high carotid bifurcation, the superior thyroid artery appears as a branch of the CCA, quite distinct from the ECA. Consequently, the caliber of the CCA is constant. It is important to examine thoroughly the quality of the CCA, as lesions can extend into the CCA; the presence of ulcerated plaques and multiple atheromatous lesions may modify the surgical technique.

4.2.2 Exposure of the Brachiocephalic Trunk and Its Bifurcation

The approach to this arterial segment is sometimes needed especially with lesions limited at this very level or when the brachiocephalic trunk (BCT) is needed as a donor vessel for more distal bypasses. The origin of the BCT cannot be safely approached only through a cervical incision requiring at least partial upper sternotomy (Fig. 4.14). The BCT is generally approached through a right supraclavicular incision, an anterior longitudinal cervical incision (Fig. 4.15), or a combination of both (an inverted L-incision with a lateral "hinge"). The IJV needs to be dissected and mobilized; the sympathetic fibers and the vagus, recurrent, and phrenic nerves must be identified and preserved. The left brachiocephalic vein needs also particular care as it crosses anterior over the BCT. The cervical approach allows an adequate exposure of the BCT but not of its origin. The surgeon must explore by palpation the origin of the BCT and adjacent portion of the aortic arch just before clamping of the BCT in order to not overlook lesions at these levels. A gentle traction of the BCT can be applied with a vessel loop or after clamping. In case of bleeding or rupture of the BCT, the surgical team must be prepared for an emergency sternotomy; hence, the patient must have the chest prepped.

The BCT and the cervical segments of the CCAs are also approached for extra-anatomical bypasses in de-branching procedures, in the context of hybrid treatment of thoracic aorta aneurysms (arch and proximal descending).

4.2.3 Exposure of the Distal Cervical Internal Carotid Artery

The distal cervical ICA is approached in the upper neck, defined as Zone III (see Chap. 2), an area extending superior to the level of the mandibular base. Higher atheromatous lesions, aneurysms, traumatic lesions, and para-vascular

tumors may require this particular exposure of the ICA. The approach is limited in two ways: on the one hand, the confined retromandibular space which needs to be either extended or "emptied" of its contents. On the other hand, by the fact that the ICA enters the skull and distal clamping and vascular procedures require at least 4–5 mm of a good-quality artery. In our experience, the major impediment is not due to the narrow retromandibular space but to the reduced length of the ICA just before entering the carotid foramen. Consequently, we do not advocate mandibular (partial) resection, mastoid osteotomy, or mandibular subluxation: our standard approach comprises the preauricular extension of the cervical incision and isolation of the facial nerve (see below) [2, 3].

The carotid bifurcation is approached in the usual manner through an anterior longitudinal incision; the skin incision is extended superiorly just posterior to the mandibular angle and ends at the level of the zygomatic arch and tragus (Fig. 4.16). The carotid bifurcation and the adjacent cranial nerves (X, XI, and XII) are dissected first and circled with vessel loops for subsequent mobilization. The posterior belly of the digastric muscle is also dissected, mobilized, and cut if necessary (we did not find this maneuver obligatory). The occipital artery and vein are divided. The parotid gland is isolated starting with its inferior portion and proceeding posteriorly. The styloid process is identified by palpation. Next, the facial nerve is identified, isolated, and gently mobilized. Generally, the trunk of the facial nerve can be isolated for a length of about 1–1.5 cm. The stylohyoid muscle is cut first in order to identify the glossopharyngeal nerve. Subsequently, the remainder styloid muscles and stylohyoid ligament are divided close to the styloid process (the process can be also excised with a rongeur). It is important to note the fact that the ICA cannot be mobilized by pulling on it toward inferior and, hence, no additional length can be obtained. Clamping may be difficult and, sometimes, endovascular clamping with a Fogarty catheter may help. However, as stated before, the dissection of the distal segment of the ICA must allow gaining at least 4–5 mm of arterial wall. Division of the styloid muscles and of course lesion of the glossopharyngeal nerve will cause major difficulties in deglutition [9].

4.2.4 Exposure of the Distal Cervical Vertebral Artery (V3)

This distal segment of the VA is generally approached for VA revascularization [4]. The V3 segment usually remains patent due to the numerous anastomoses with the carotid system and especially with the occipital artery and with the deep cervical artery (from the SCA). Surgical approach is also facilitated by the wider space between the C_1 and C_2 vertebrae, by the more lateral winding of the VA, and, not least, by the adequate landmark offered by the anterior ramus of the C_2 nerve. The V3 segment is also somehow more superficial than the V4 segment of the VA (between C_1 and occipital bone).

The patient is supine with the neck extended and with the head rotated to the contralateral side. The head must be rotated more than with carotid exposure while the extension must be moderate. It is also important to lower the shoulder, as much as possible. If a saphenous vein graft is needed, the leg must be prepped.

The skin incision starts with an anterior longitudinal incision from the level of the thyroid cartilage reclining posterior just under the angle of the mandible and extending 1 cm underneath the mastoid process (Fig. 4.17a). With the head rotated, the transverse process of C_1 (atlas) is located anterior to the transverse processes of the remainder cervical vertebrae. It is important to localize the transverse process of C_1 as it may be easily confused with the mastoid process (this is why we advocate incisions below the mastoid process). The SCM is identified. The carotid bifurcation is dissected, as generally revascularization of the V3 is performed either from the bifurcation or from branches of the ECA. The cranial nerves X, XI, and XII are identified and isolated. The particular position of the accessory nerve (XI) is important because it must be mobilized more extensively anteriorly and because the SCM must be divided (at least partially, the anterior half). The accessory nerve may also depict a prejugular tract in rare instances. It usually perforates the SCM at about 2 cm under the mastoid process. The prevertebral muscles covering the transverse processes of C_1 and C_2 are divided. The anterior ramus of the C_2 nerve is identified and followed making a good guide to the VA. The nerve can be isolated with a vessel loop and gently mobilized. A segment of about 2 cm of the VA can be readily exposed between C_1 and C_2 vertebrae (Fig. 4.17b). The dissected segment usually allows space for a proper clamping and anastomosis. Sometimes, smaller muscular branches may bleed rendering dissection cumbersome. The distal end of the (venous) graft is anastomosed first (Fig. 4.17c).

Exposure of the VA in the suboccipital (V4) segment (between C_1 and the occipital bone) is indicated for the treatment of more distal lesions [5]. The surgical approach is rendered more difficult due to the deeper position of the VA requiring division of conspicuous muscular masses. One advantage of this approach is the concomitant exposure of the distal ICA. We have not performed this surgical approach so far.

4.3 Surgical Approach to More Distant Donor Arteries

Numerous arteries outside the neck area may be approached surgically, mostly serving as donor vessels especially when extra-anatomical bypasses (e.g., carotid-to-subclavian,

carotid-to-carotid, subclavian-to-subclavian, etc.) are not contemplated, not indicated, or impossible to perform (e.g., aortic arch syndrome). Under these circumstances, other more distant arteries are available for surgical reconstruction: the ascending aorta and aortic arch, the brachiocephalic trunk, and the origin and intrathoracic segments of the left CCA or SCA. These arteries are approached intrathoracically either through sternotomy, thoracotomy, or combined incisions such as the trap door thoracotomy.

The ascending aorta represents an adequate and advantageous donor vessel due to the high flow, relative sparing from the atherosclerotic process, and easy access. Grafts from the ascending aorta can be easily tunneled up to the cervical area to reach the SCA, CCA, or carotid bifurcation. With lateral clamping and thoroughly monitoring of hemodynamic parameters, the anastomosis on the ascending aorta can be easily performed, on beating heart and without cardiopulmonary bypass. The surgical approach for the ascending aorta will generally require complete median sternotomy. The BCT may represent an alternative donor vessel. Moreover, lesions of the BCT need complete exposure of the BCT and adjacent aorta. The BCT can be approached through a limited upper sternotomy. The left SCA and left CCA are approached in the thorax through a left anterolateral thoracotomy or the trap door incision. As most of these approaches represent classical surgical procedures [6], we will stress only some important particulars of clinical relevance.

The skin incision for *median sternotomy* (Fig. 4.18) is performed from about 2 cm under the jugular notch to the lower part of the sternal body, and the sternum is divided from superior to inferior (in this way, the xiphoid process need not be dissected down to the linea alba). In cases when concomitant cervical approach is required, we advocate to carry out a separate incisions in the neck (and not continuous sterno-cervical incisions). For a better identification of the arch branches, we isolate and mobilize the left brachiocephalic vein. More extensive dissection of this vein allows a better retraction of the two sternal halves as required, for example, for the exposure of the left CCA or left SCA and distal arch. The BCT can be accessed extrapericardially, but we advocate full pericardiotomy for approaching the ascending aorta. The caliber of the ascending aorta must be evaluated preoperatively by ultrasound or CT before choosing the surgical tactic. We prefer circling the ascending aorta with tape; this facilitates the lateral clamping of the ascending aorta. Direct visualization of the heart is also important during the lateral clamping of the aorta as dilation of the heart or reduced contractions are easily and readily observable before hemodynamic compromise. Temporary pacemaker wires are also inserted. After completion of the bypass from the ascending aorta, the pericardium is left open, and only the thymic remnants are approximated, between the graft and the sternum.

The limited upper sternotomy (see above Fig. 4.14) is performed from the jugular notch to just below the sternal angle (third intercostal space). The midline sternal incision is extended on both sides at the level of the third intercostal space without interfering with the internal thoracic vessels. For a safer and better exposure of the BCT, right CCA, and SCA, the incision is continued with a right cervical incision (supraclavicular or anterior longitudinal). The vagus nerve, sympathetic trunk, and their branches must be protected as mentioned above. The tributaries of the left brachiocephalic vein (especially the inferior thyroid veins and the thymic veins) must be identified and safely divided. The vein itself needs to be dissected and isolated. If necessary, the origins of the sternothyroid and sternohyoid muscles can be divided (for a bloodless field, we usually do not divide these muscles). Excessive retraction of the two sternal blades is also avoided. The thymus and its adipose remnants are sometimes well developed and require careful dissection and division (the thymus has numerous vascular pedicles, lacking a main portal). We recommend closing the upper sternotomy with two steel wires in the form of "X."

The left anterolateral thoracotomy (see also below: the trap door incision) offers access to the origins of the left SCA and left CCA. The patient is supine, with both arms adducted (alongside the thorax). We do not advocate the abduction of the left arm, for two reasons: first, the thorax must be slightly rotated to the right and the left arm may be inadvertently hyperabducted. Second, the position with the abducted arm limits access to the supraclavicular area. Consequently, we place the patient supine, with a rolled pat underneath the left shoulder and spine while the left arm lies at the level of the operating table. The left side of the thorax is exposed enough in order to permit a full size anterolateral thoracotomy with no impediment to access the neck. The incision is curvilinear from the left sternal border to the anterior axillary line, under the lower contour of the greater pectoral muscle and below the breast in female patients. The fourth intercostal space is entered. Selective lung intubation may assist the proper dissection and access to the left CCA and left SCA, although we deflate the left lung only in selected cases. In most instances, we do not divide the internal thoracic vessels. The distal aortic arch and the origins of the left CCA and left SCA are visible under the mediastinal pleura. The pleura is incised distal (i.e., posterior) to the vagus nerve and its recurrent branch. The thoracic duct is not visible but usually courses posterior to the left SCA. With dissection close to the left SCA, the thoracic duct is theoretically protected from injury. Drainage and closure of the thorax are performed in the usual manner.

The trap door incision is a combination of the supraclavicular cervicotomy, limited upper sternotomy, and anterolateral thoracotomy (Fig. 4.19). It is mostly indicated in emergency cases with major bleeding from an injured left SCA or adjacent arch and for obtaining the direct access to

treat aneurysms of the origin of the left SCA, Kommerell diverticulum, and so forth. It is more time-consuming and with more blood loss than any of the other thoracic incisions. The internal thoracic vessels on the left side are also interrupted. The two horizontal incisions are performed first: the anterolateral thoracotomy (for an initial, rapid examination of the distal arch and left SCA and left CCA at their origin) and the supraclavicular incision (for access to the CCA and SCA in the neck). These are followed by the upper partial sternotomy, from the jugular notch to (generally) the fourth intercostal space. In order to allow a complete retraction, the SCM and omohyoid muscles are divided. In spite of being more cumbersome and bleeding, this incision allows probably the best vision and access to the distal arch and origin (and proximal segments) of the left CCA and left SCA (and adjacent structures). Another advantage is represented by the fact that the patient is supine, allowing access to the head, neck, thorax, abdomen, and limbs – this particularly being very important to take into account in unstable patients (e.g., trauma and polytrauma). Postoperative pain and limited capacity of ventilation may pose important problems in many patients; whenever possible, a thoracic epidural catheter is inserted preoperatively.

4.4 Concomitant or More Extensive Arterial Exposure

With wider and more severe stenotic and occlusive disease in the superior aortic system, the need of a complete repair becomes evident. In our experience, we encounter numerous patients with occlusion of one or more of the neck vessels, and these patients can be grossly divided in two groups: First are patients with advanced atherosclerotic lesions, neurologically unstable, with many associated diseases, and having an important anesthetic and operative risk. These patients will mainly require an improvement of the neurologic status and prevention of recurrent strokes. Second are younger patients, with advanced and severe atherosclerotic lesions in the superior aortic system requiring a complete and long-term arterial repair, the major goal being the social and familial reintegration.

In the case of the first category of patients, most of the planned procedures are basically more limited, less aggressive, and, whenever possible, to be performed under locoregional anesthesia and in many more steps. Combined procedures (endovascular and surgical) are also highly indicated. It is sometimes sufficient having or obtaining a single arterial trunk in the neck that will eventually offer a fair inflow to the remainder arteries, after performing extra-anatomical bypasses. The second category of patients will require complete and extensive revascularization, with extensive surgical approaches and needing a thorough preoperative evaluation, preparation, and perioperative monitoring.

For extra-anatomical arterial reconstruction in the neck, one or two concomitant incisions are generally sufficient. The SCA, VA, CCA, carotid bifurcation, ICA, and ECA can be easily approached by means of a single more extensive cervical incision or by two incisions, as presented before. If the donor artery is located on one side and the recipient artery (arteries) is located on the other side of the neck, two limited incisions are generally indicated. As with any bilateral concomitant procedure, a great attention must be paid for the protection of the cranial nerves [7] and to avoid devascularization of some viscera, e.g., bilateral ligature of the ECA or of the lingual artery (see simultaneous bilateral carotid endarterectomy in Chap. 13: "Extensive Cerebrovascular Arterial Revascularization"). Depending on the shape of the neck, a single horizontal cervical incision may allow access to arteries on both sides. Closely placed and parallel incisions must be also avoided. The extra-anatomical bypasses have the theoretical advantage of being easy to explore both clinical and by ultrasound, in the postoperative period.

For a complete arterial revascularization, the donor and the recipient sites must be thoroughly assessed in the preoperative clinical and imagistic evaluation. The natural history of the stenotic-occlusive disease must also be taken into account: most of the patients will require vascular reconstructions in the future, including renal arteries, abdominal aorta, and inferior limbs. Not least, most of these patients will be expected to undergo coronary revascularization. Teamwork is essential in these cases, as staged and combined procedures are highly indicated. The cardiologist, neurologist, interventional radiologist, and cardiovascular surgeon must establish a pertinent and continuous dialogue for the proper planning of the therapeutic procedures and, not least, for a most efficient follow-up.

In younger patients, we recommend a complete arterial revascularization, the ascending aorta representing the first choice as donor artery (Fig. 4.20). This will not preclude the surgical coronary revascularization in the future, if necessary. In patients with concomitant severe arterial lesions in the inferior aortic system, a concomitant ascending aorta-to-femoral bypass can be easily performed (Fig. 4.21). If the BCT is of good quality, this artery can be used as the main inflow and accessed through a limited upper sternotomy.

4.5 Particular Exposures for Selected Pathologies: Aneurysms, Tumors

Tumors and aneurysms located in the neck will ask for more extensive approaches that permit access to the vessels and adjacent nervous structures. Most of the patients will have a long cervical incision through which the proximal and distal ends of the diseased artery are efficiently controlled and the accompanying cranial and cervical nerves and sympathetic

trunk are identified and preserved (Fig. 4.22). For tumors, the IJV and lymphatic structures will need complete exposure. Whenever the case, a single, unique cervical incision or two separate incisions will satisfy the requests of a good exposure. The choice of the graft is also important. Potentially septic aneurysms or tumors will contraindicate the use of prosthetic material, favoring the use of autologous vein or homograft. In selected patients, combined tumor and carotid surgery (comprising simultaneous bilateral carotid endarterectomy) is indicated [8].

4.6 Approaches for Harvesting of Venous Grafts

Venous grafts are not routinely used for cerebrovascular reconstruction nowadays, as numerous types of artificial conduits and synthetic patches are available. Two particular cases are still important: the presence of infection and bypass on the distal VA or distal cervical ICA. The use of autologous vein in infected sites is well known. On the other hand, if a bypass on the distal VA or ICA is contemplated, the best graft is the autologous vein. The generally recommended graft is the saphenous vein, while the superficial cervical veins remain as a second alternative. The saphenous vein depicts numerous qualities and represents the type of graft mostly studied in various situations and for different types of revascularization (inferior limbs, coronary bypass, carotid surgery). The site for harvesting of the saphenous vein (upper or lower leg) depends on the caliber of the vein and on that of the target vessel. With a supraclavicular incision, the external jugular vein can be also harvested. The vein is however more prone to dilatation and the obtained length is usually not above 4 cm. Its caliber and tract are sometimes highly variable. As in the case of other venous bypasses, the orientation of the venous valves must be clearly kept in mind. If only a limited length of vein graft is needed, alternative grafts must be also considered, for example, the lesser saphenous vein (leaving the greater saphenous vein available for other types of bypasses, in the future). Clinical and ultrasound preoperative venous mapping is essential.

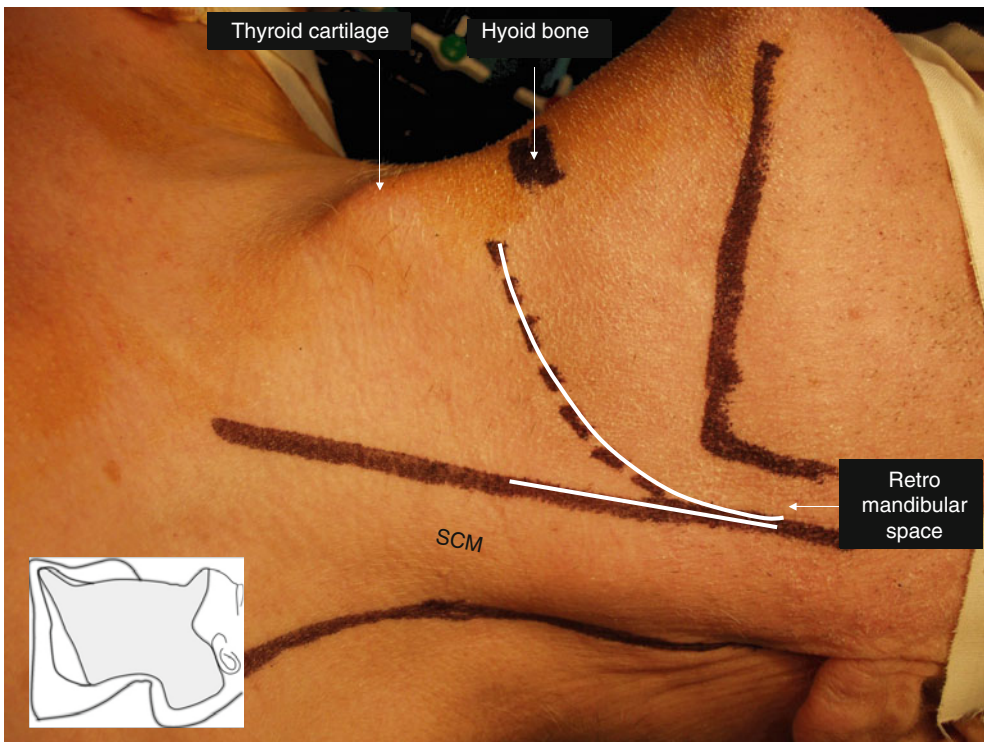


Fig. 4.1 Surgical approaches to the carotid artery and bifurcation. In cases when only the carotid bifurcation must be approached, a more limited incision is recommended, either longitudinal or oblique (less, transversal). Usually, the inferior part of the skin incision will not go beyond the thyroid cartilage (inferior) and the mandibular angle (superior)

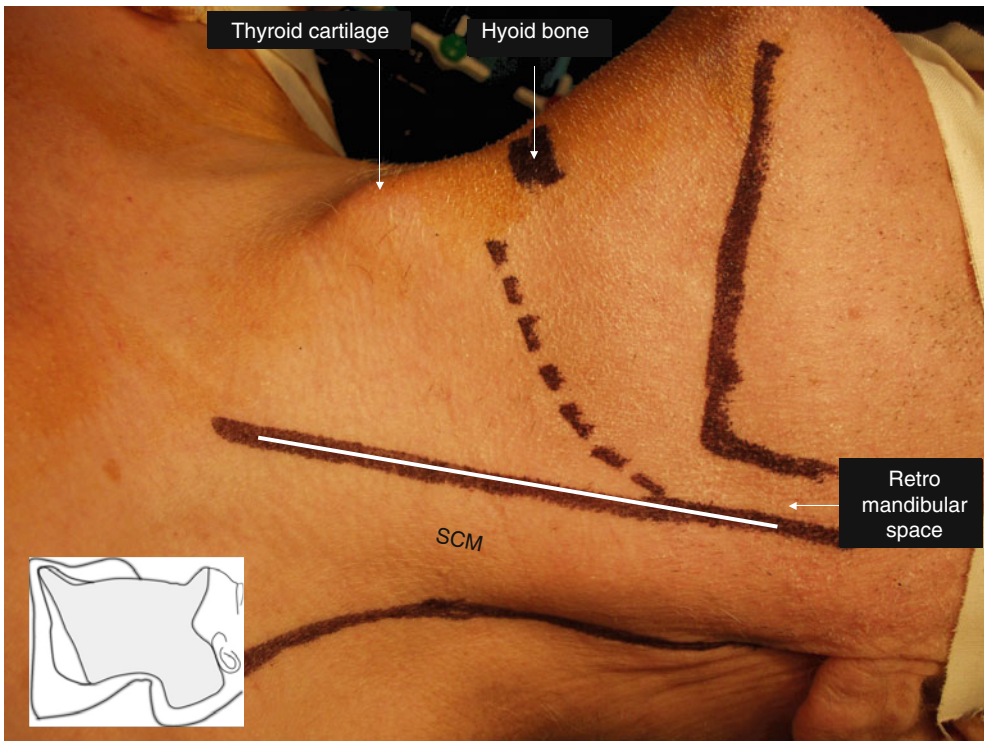


Fig. 4.2 Surgical approach to the entire cervical carotid artery. With a longitudinal incision anterior to the SCM, the entire cervical portion of the carotid artery can be approached, both inferior and superior to the omohyoid muscle. This longer incision allows concomitant exposure of the SCA, VA, IJV, and adjacent nerves

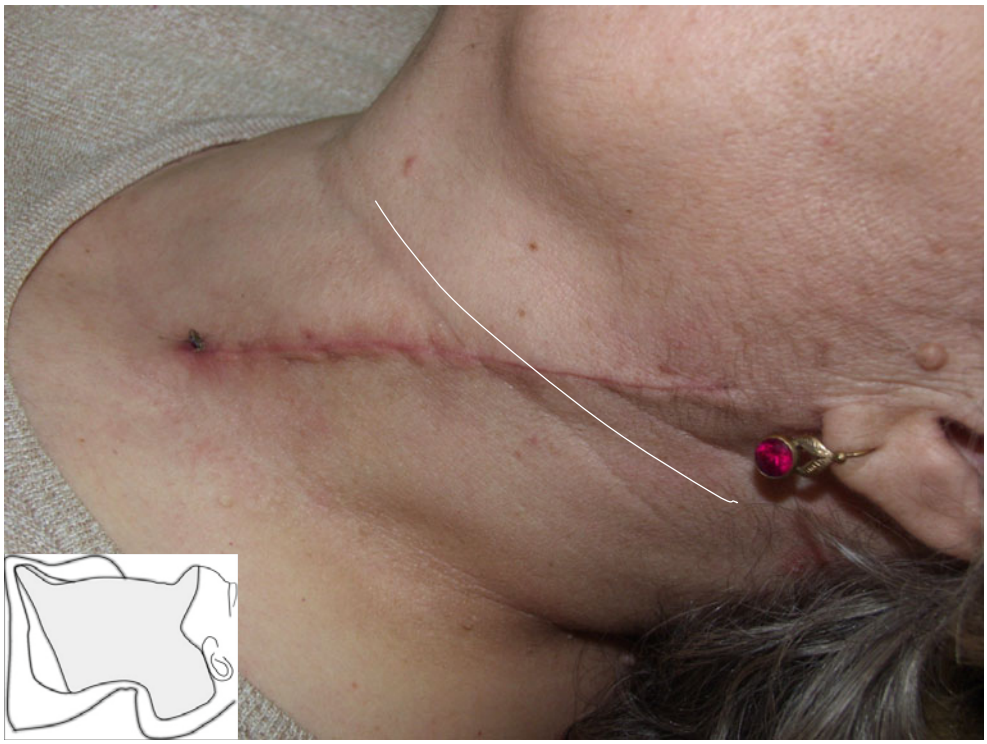


Fig. 4.3 Advantages of the oblique incision. The best cosmetic results are obtained with the oblique incision, matching and following the natural skin creases and folds; retractile and keloid scars are less probable. Not least, the oblique incision may interrupt less superficial nerve fibers with less paresthesias

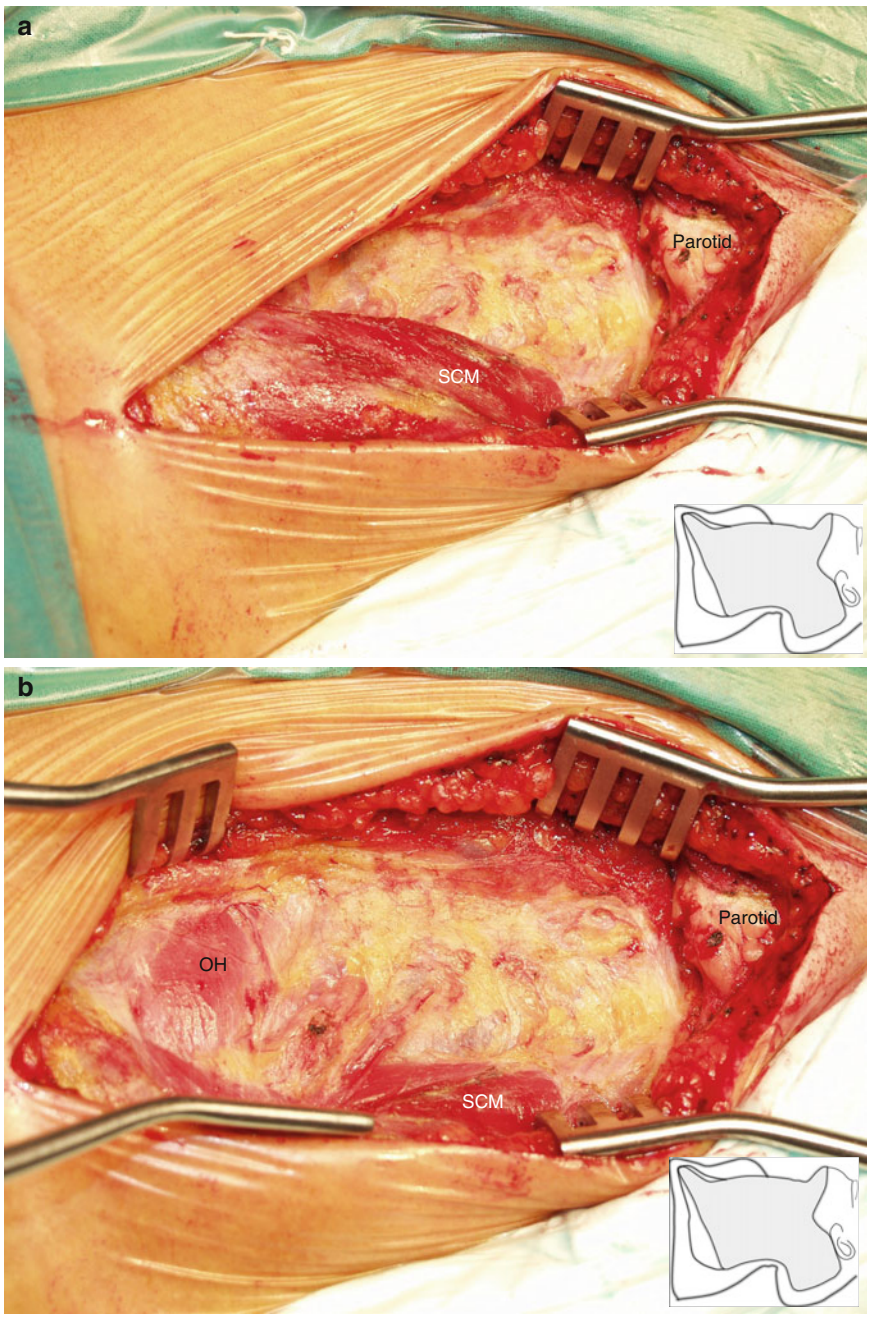
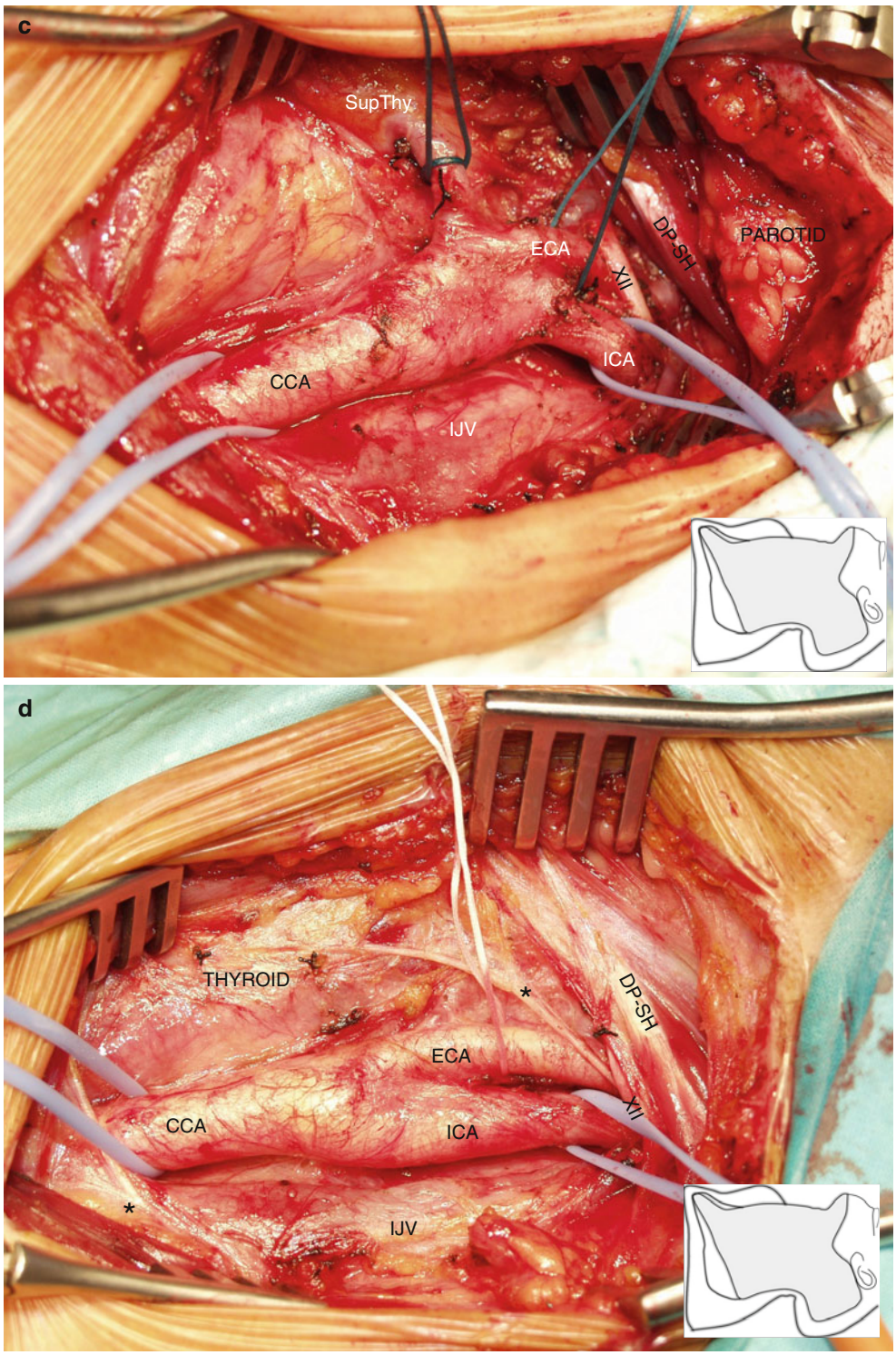


Fig. 4.4 The main steps in surgical exposure and endarterectomy. Panel (**a**): the longitudinal skin incision is deepened into the superficial layer of the cervical fascia, anterior to the SCM. If not particularly requested, the area inferior to the omohyoid muscle is not approached. In order to be properly retracted, the SCM must be freed from its fascial covering. Panel (**b**): the deep fascia and the carotid sheath are approached. The parotid gland must be protected, especially in individuals with a larger gland. Panel (**c**): exposure of the carotid bifurcation (CCA, ECA, and ICA), the internal jugular vein (IJV), and the hypoglossal nerve (XII), under the digastrics posterior belly and stylohyoid (DP-SH). The superior thyroid artery (SupThy) is usually isolated with a separate loop for a better control of back bleeding. Panel (**d**): another carotid bifurcation exposed for endarterectomy. Note the two roots of the cervical (hypoglossal) ansa (marked with *). Panel (**e**), F and G: the sequence of endarterectomy, with plaque isolation and excision, in a patient with temporary CCA-to-ICA shunt. Vessel exposure must take into account the necessity of extra length, e.g., for shunt insertion, and this may be cumbersome in patients with higher bifurcation or with longer carotid plaques. Panel (**h**): insertion of a synthetic patch, starting from the distal end of the arteriotomy, after the distal end artery was secured with separate stitches. Panel (**i**): a view of the almost entirely sutured patch and the shunt still in place, just before the removal of the latter. Panel (**j**): intraoperative aspect of a carotid bifurcation after endarterectomy and direct suture. Panel (**k**): exposure of the carotid bulb and the line of incision for arteriotomy. The arteriotomy must avoid the sinus and glomus nerves. Panel (**l**): demonstration of the excision of the plaque after creating a cleavage plane in the very substance of the carotid wall. The remaining portion of the arterial wall must not be too thin, as this condition will predispose to late dilatation of the carotid bifurcation or dehiscence of the suture. Panel (**m**): intraoperative aspect of the carotid bifurcation after endarterectomy. Note that the distal end artery on the ICA appears thicker than the endarterectomized zone, almost in step-like fashion. We routinely tackle the end artery with 2–4 separate stitches, in order to prevent formation of intimal flaps. The lateral and the anterior parts of the ICA end artery will be sutured to the patch. Panel (**n**): the final result, with the patch inserted. Note that in numerous cases, the patch may be longer, if the plaque extends farther on the ICA, CCA, or both. The width of the patch, although not well standardized, must allow the restoration of the initial dimension of the carotid bulb and origin of the ICA and must be large enough not to angulate or constrict the entrance into the ICA and fitted in such a way of not creating a discrepancy between a larger-than-normal carotid bulb and a too narrow ICA

Fig. 4.4 (continued)



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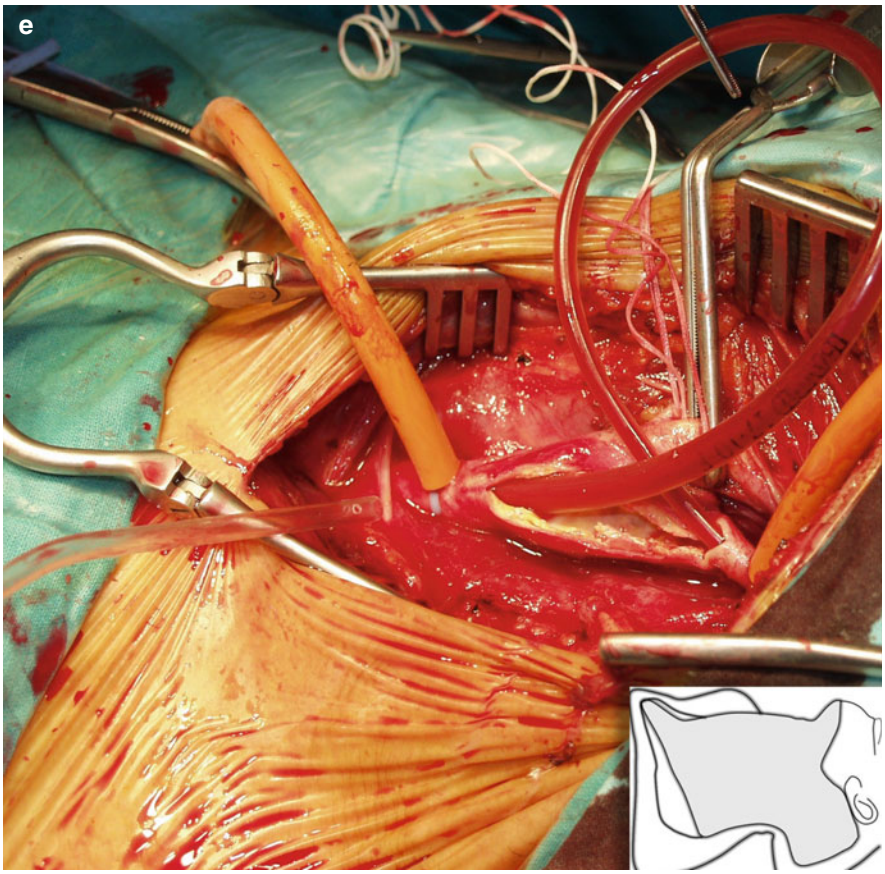

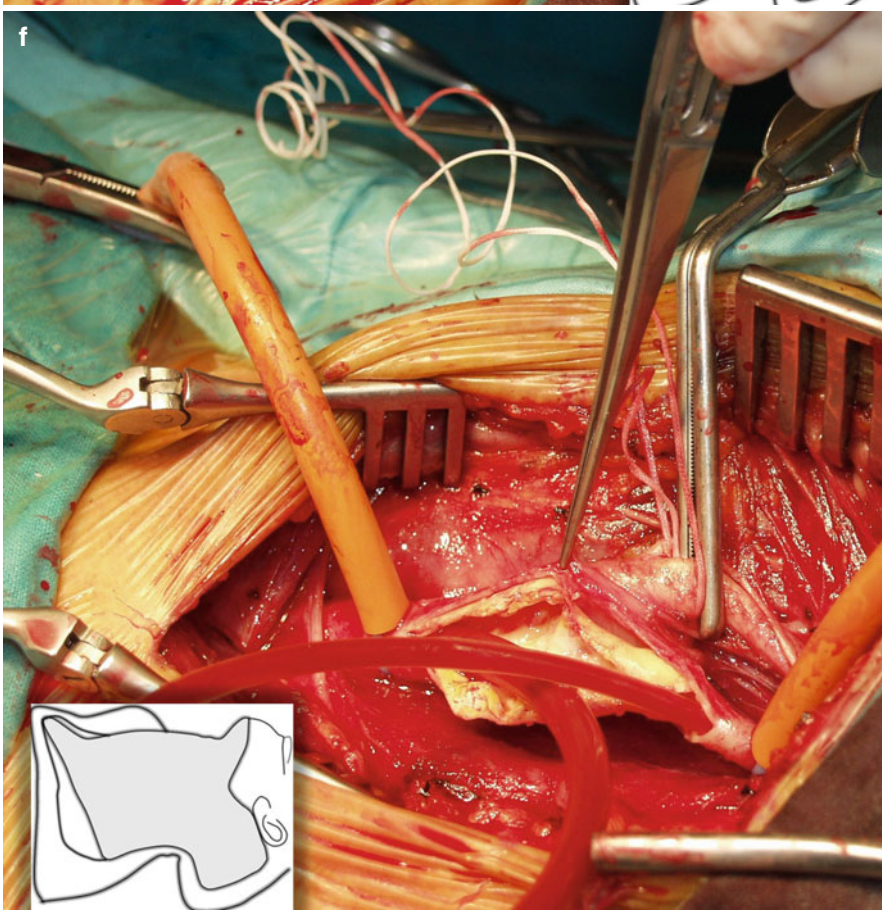

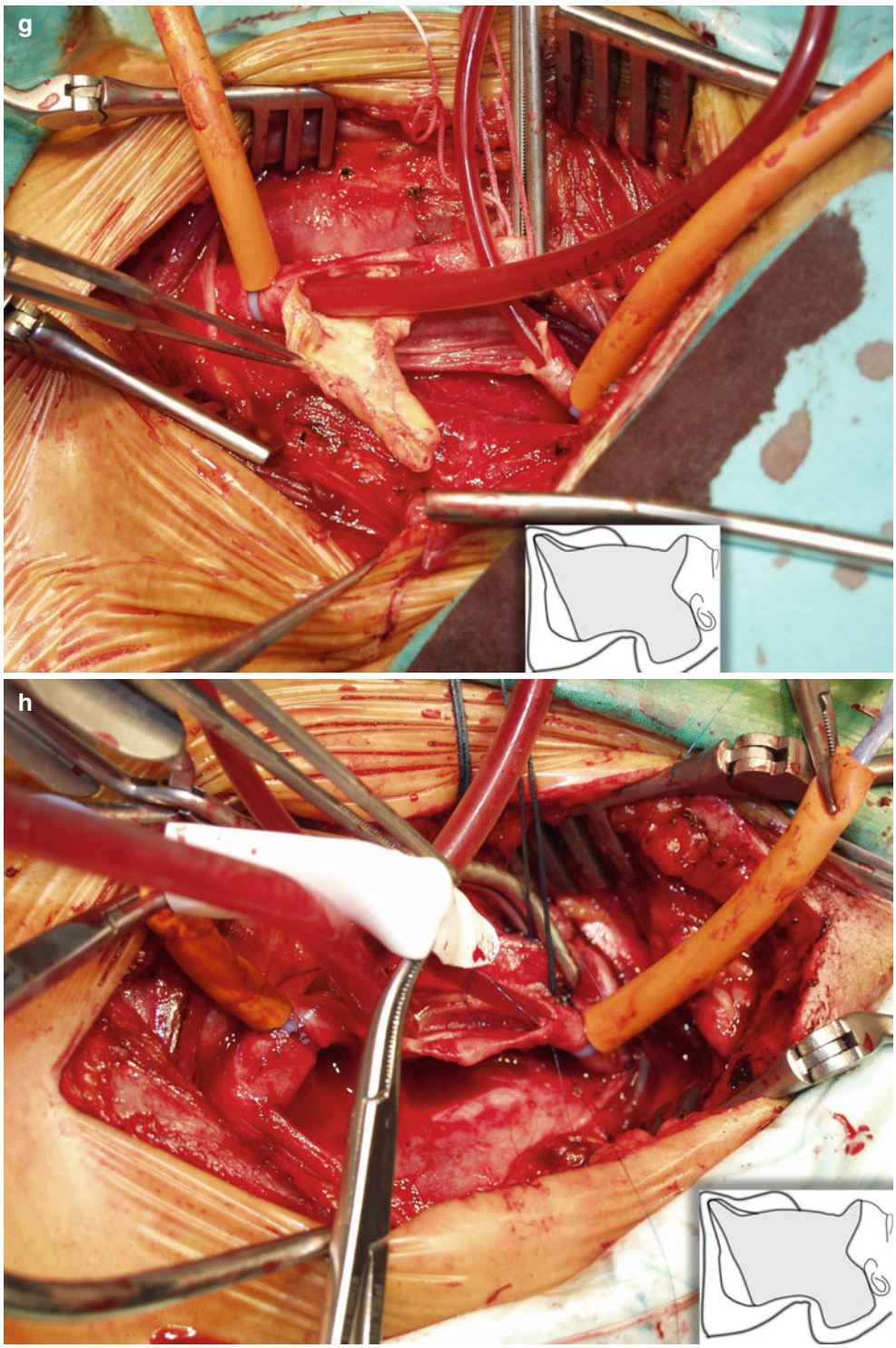

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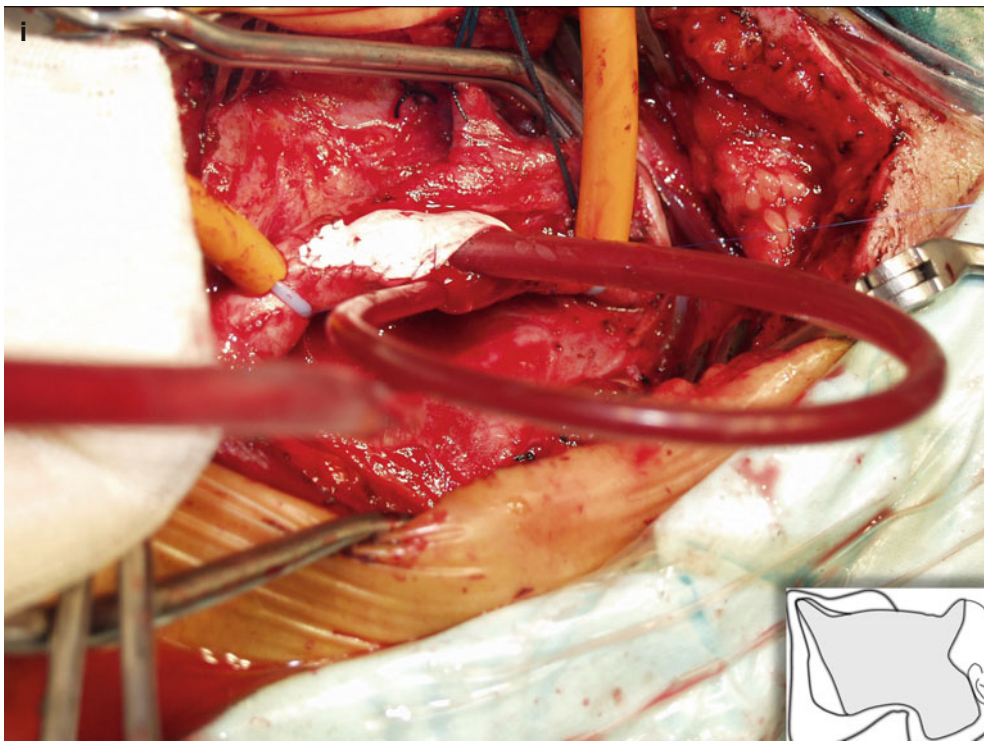

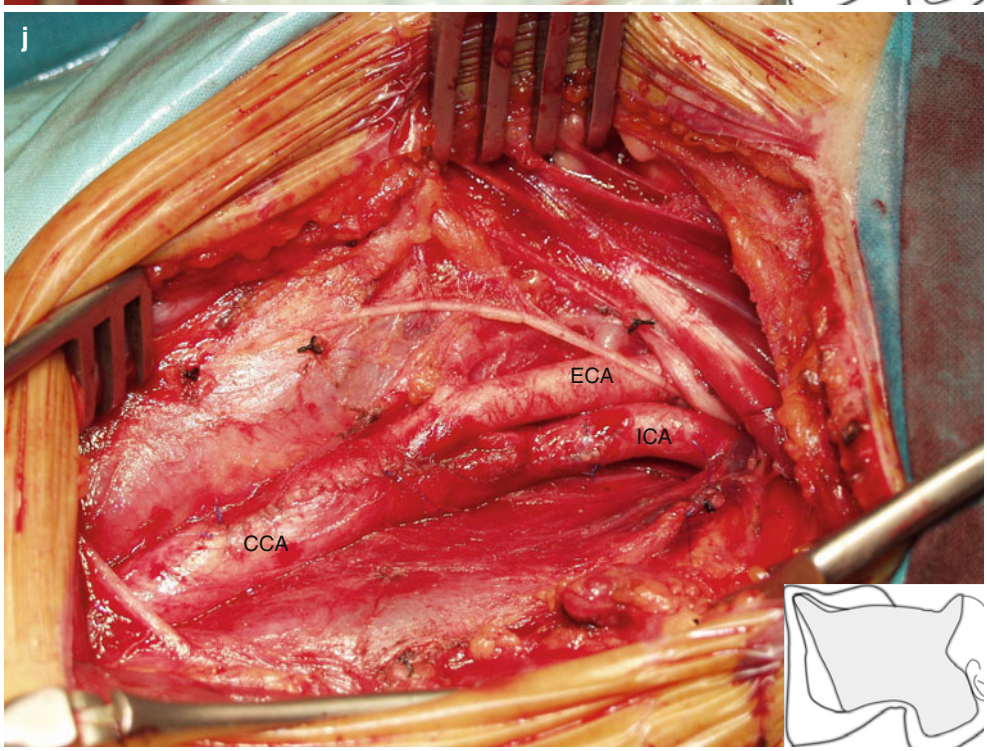

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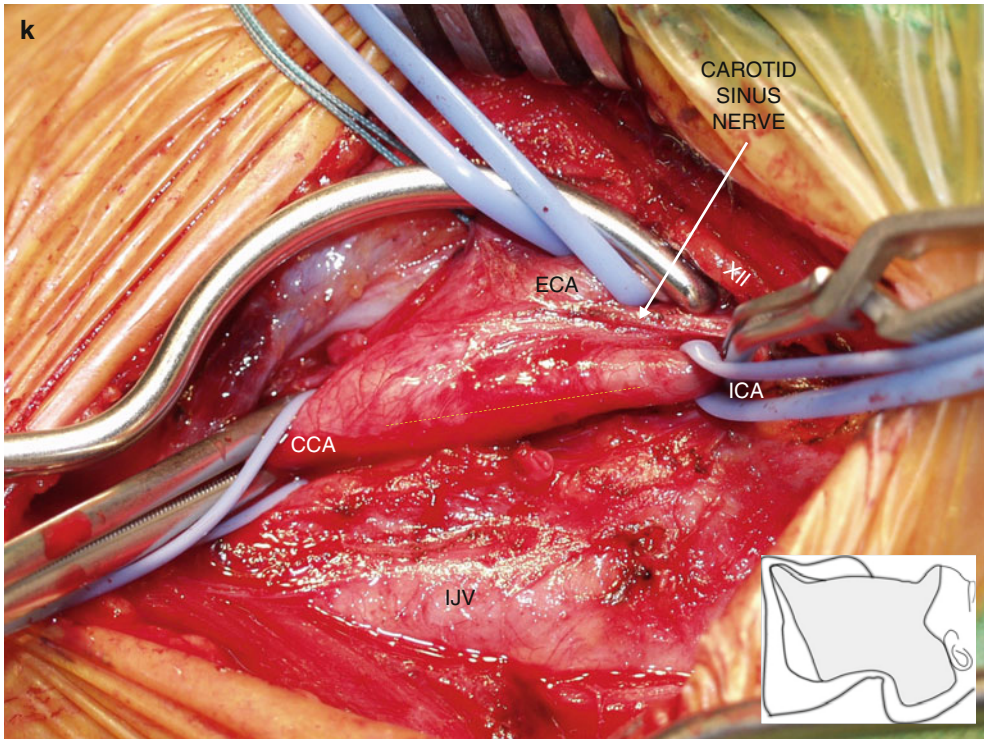

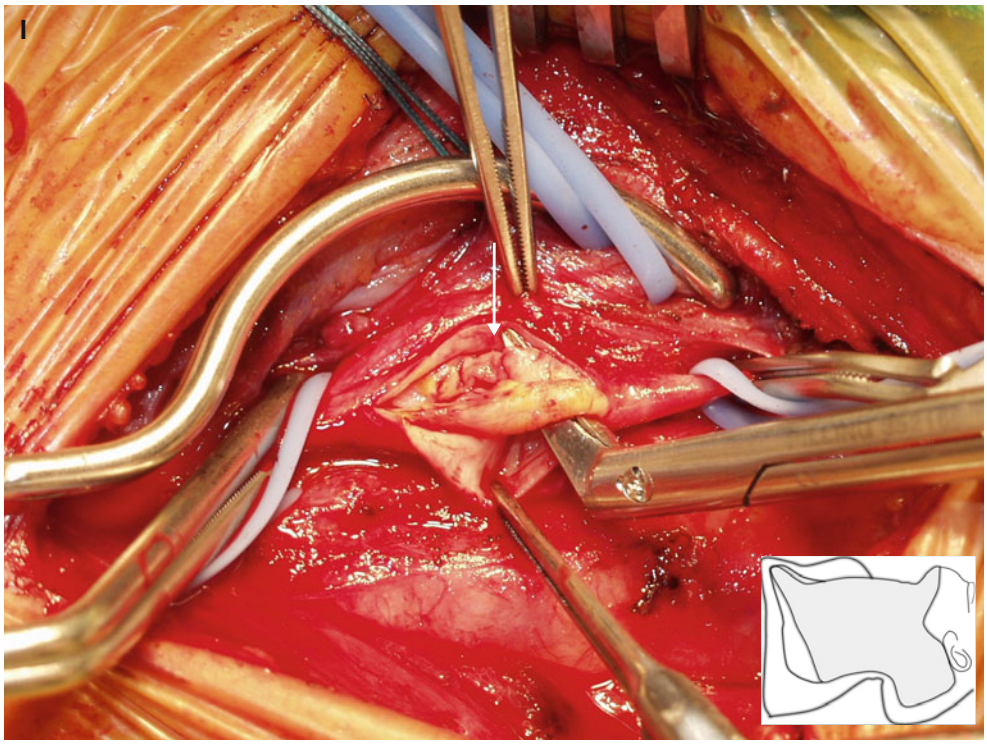

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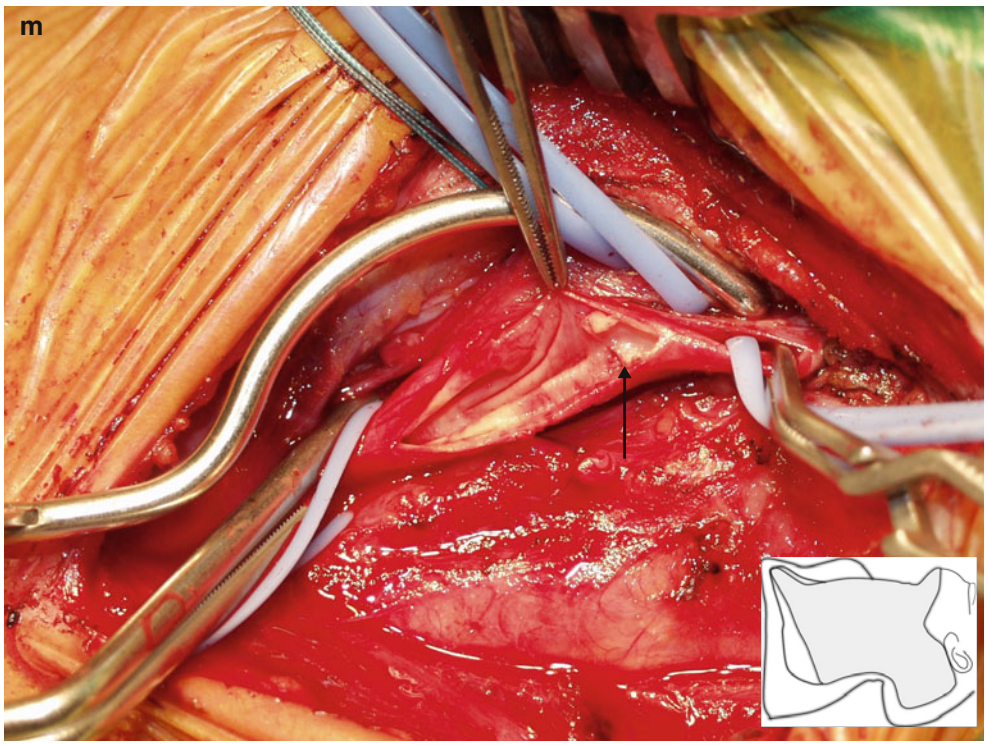
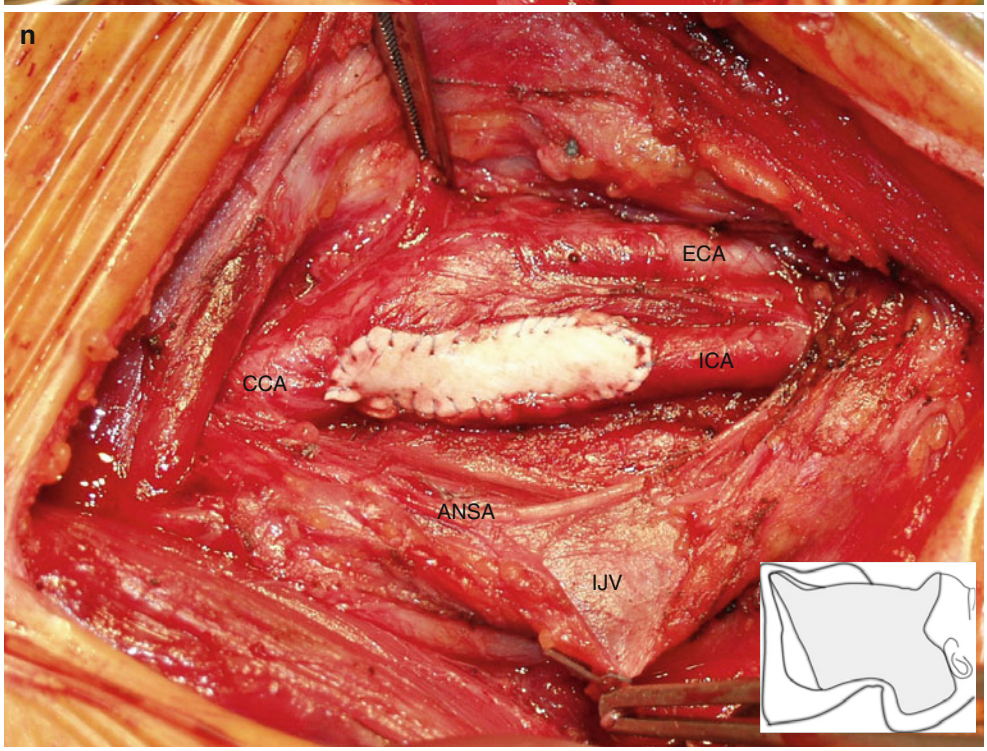




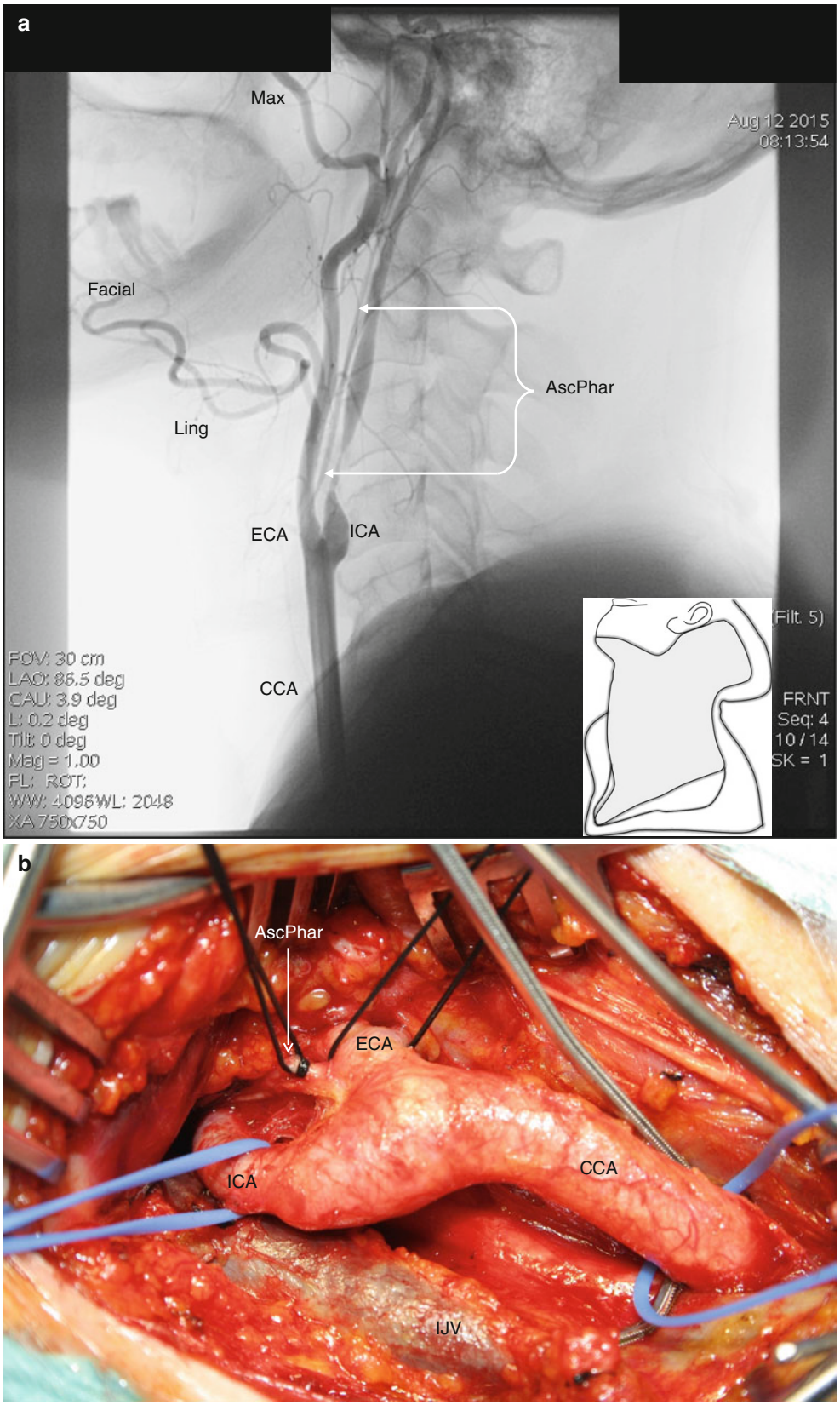


Fig. 4.5 The ascending pharyngeal artery. Panel (**a**): angiographic demonstration of a well-developed ascending pharyngeal (AscPhar) artery, paralleling the ICA. The AscPhar offers anastomoses with the intracranial ICA in cases with severe stenosis of the latter. If the AscPhar originates in the very proximal segment of the ICA (at the bulb), it may maintain the patency of the ICA even in cases with highest degree stenoses. During surgery, a larger AscPhar must be isolated and temporarily clamped to avoid troublesome back bleeding. Panel (**b**): intraoperative aspect of the right carotid bifurcation and a larger AscPhar artery

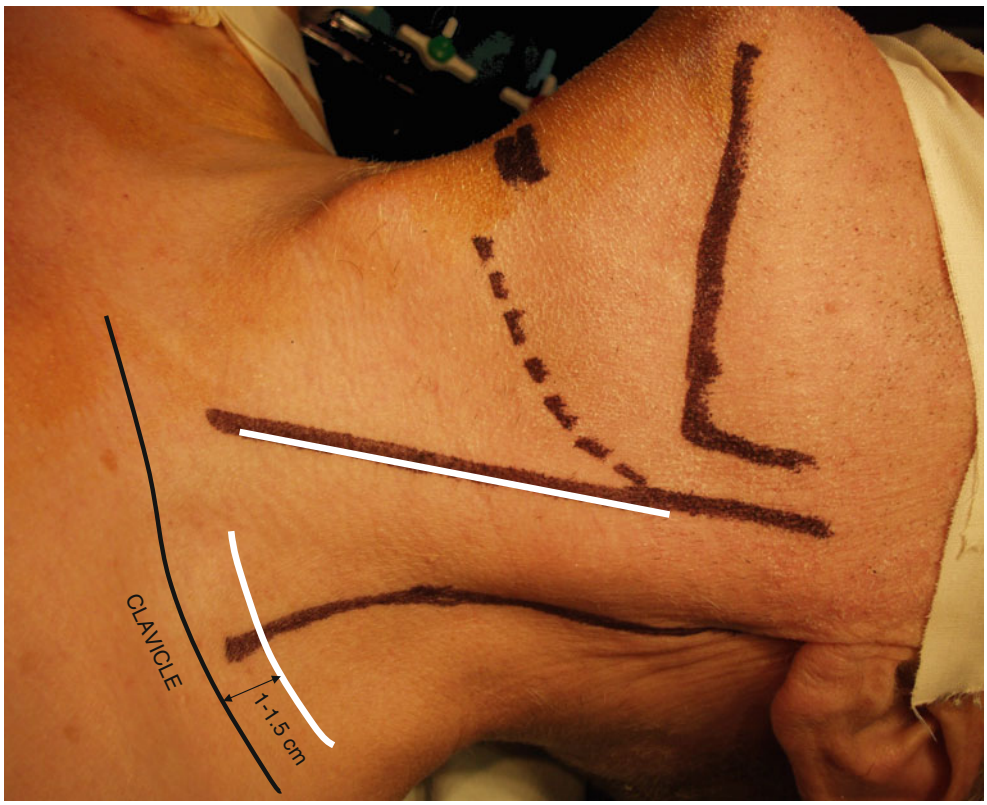


Fig. 4.6 Surgical exposure of the vertebral artery. The V0 and V1 segments of the VA can be approached either by a supraclavicular horizontal incision or by a longitudinal incision, anterior to the SCM and starting at the level of the sternoclavicular joint. In both situations, the concomitant exposure of the CCA is possible. With the supraclavicular approach, the SCA can be also accessed. Access to the V2 segment of the VA is possible through the longitudinal incision (see also text for further details)

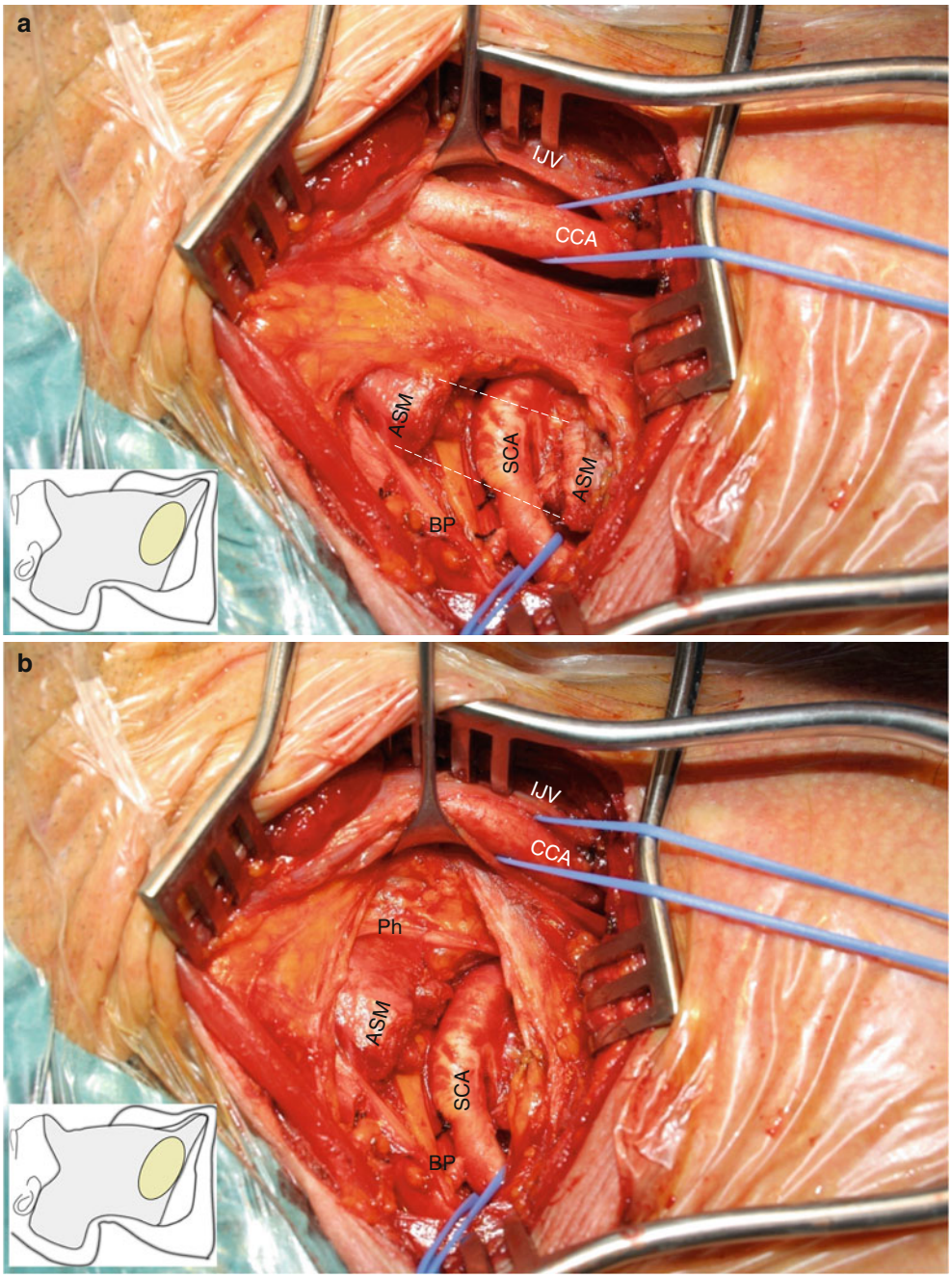


Fig. 4.7 Supraclavicular approach. Intraoperative view. Panel (**a**): the clavicular head of the SCM is cut, allowing the exposure of the CCA and IJV. The latter is retracted toward anterior and medial; thus, bypasses or reimplantations into the CCA will be in a retro-jugular position. The vagus nerve must also be identified and preserved. The SCA is best exposed after cutting the anterior scalene muscle (ASM) this maneuver facilitating the approach. Laterally, the brachial plexus (BP) limits the exposure of the SCA. Dissection may proceed inferiorly over both the CCA and SCA, to the level of the bifurcation of the brachiocephalic trunk (only on the right side). Panel (**b**): with more extensive retraction, the phrenic nerve is identified and protected (Ph). All the branches of the SCA can be identified

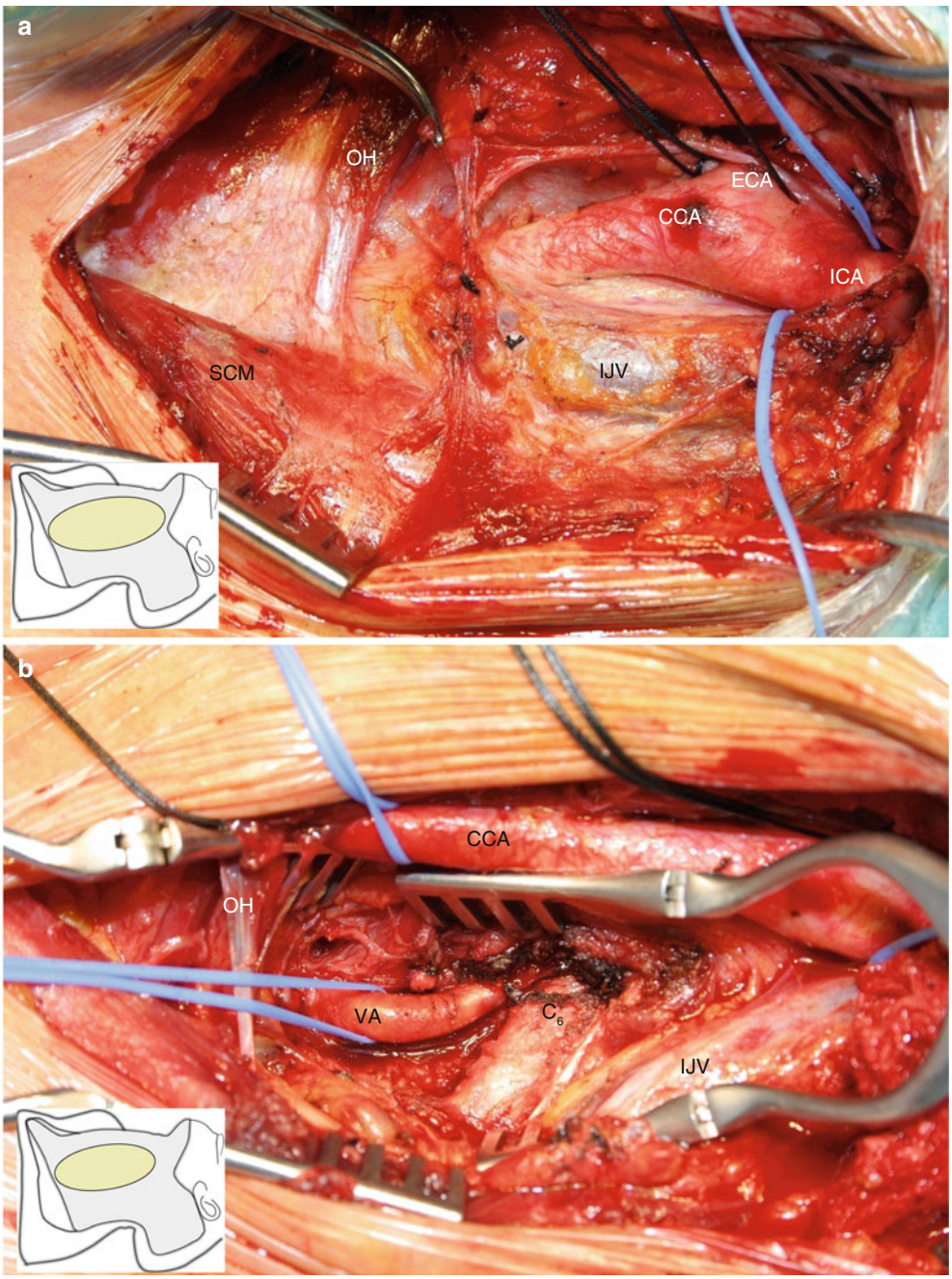


Fig. 4.8 Anterior cervical approach to the VA. Concomitant exposure of the SCA, CCA, and bifurcation can be obtained through this incision. Panel (**a**): dissection starts as with a regular approach to the carotid bifurcation and more proximal CCA. Note the omohyoid muscle (OH) still contained in the pretracheal (visceral) layer of the cervical fascia. Panel (**b**): the OH was retracted inferiorly and dissection proceeded between the CCA and IJV. The vagus nerve is retracted together with the IJV laterally. The VA is identified in the solid angle between the anterior scalene and the longus colli muscles (the two converging at the level of the anterior tubercle of C_6). The VA is usually covered by the vertebral vein. On an intermediate plane, the inferior thyroid artery crosses the VA anteriorly and the CCA posteriorly, from lateral to medial. The inferior thyroid artery may be divided for surgical access, if necessary. Numerous sympathetic fibers encompass this portion of the VA and these must be preserved as much as possible. Dissection proceeds toward the origin of the VA from the SCA. If necessary, the transverse vertebral canal can be opened with a rongeur

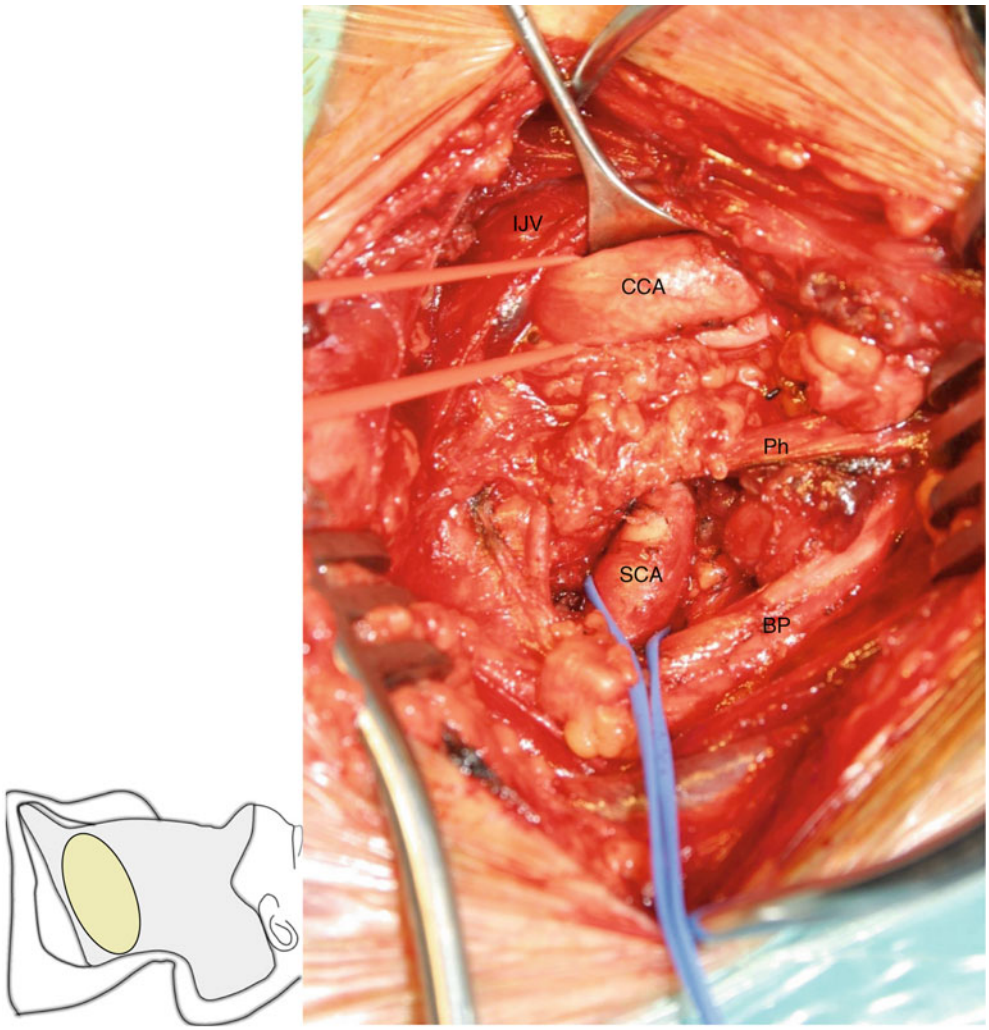


Fig. 4.9 Exposure of the cervical SCA through supraclavicular incision. The incision starts at the level of the sternoclavicular joint and proceeds laterally to the clavicular midpoint (division of the external jugular vein is not necessary). The pretracheal (visceral) layer of the cervical fascia is cut, the OH muscle is retracted toward superior, and the scalene fat pad is excised partially or retracted (caution to ligate the suprascapular vessels and lymph channels). The anterior scalene muscle is identified, together with the phrenic nerve (the latter courses over the anterior surface of the muscle from lateral and superior to medial and inferior – although variations may be encountered). When needed, the scalene muscle is divided (we do this maneuver routinely). Staying close to the SCA will prevent inadvertent entry into the pleura. Through the same incision, access to the CCA and VA is also possible

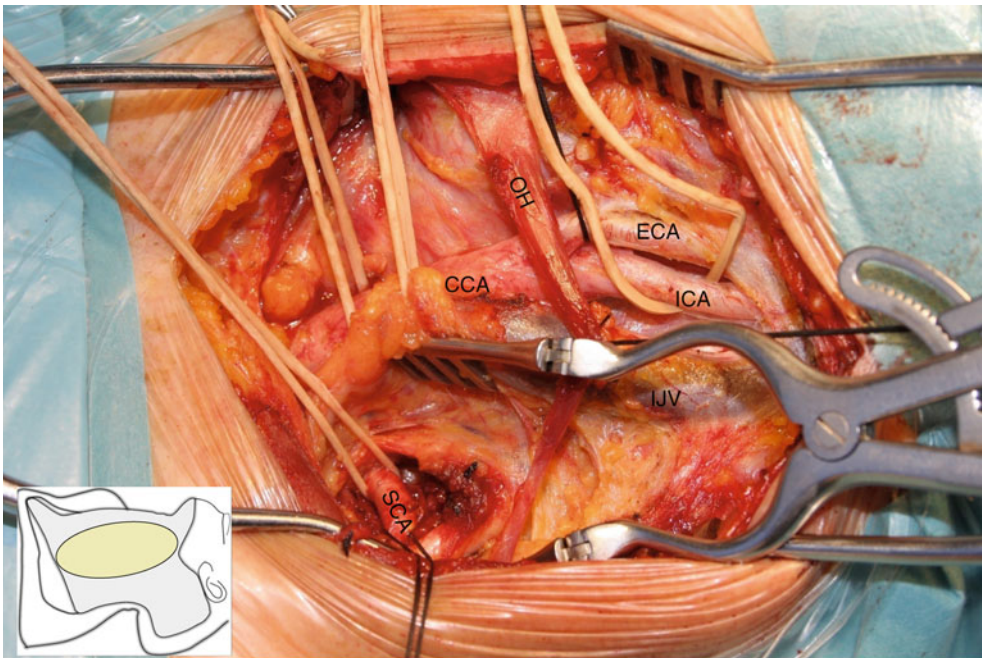


Fig. 4.10 Exposure of the cervical SCA through longitudinal incision. This incision allows a comfortable and concomitant exposure of the VA, CCA, carotid bifurcation, and SCA. In the image presented, the anterior scalene muscle was divided

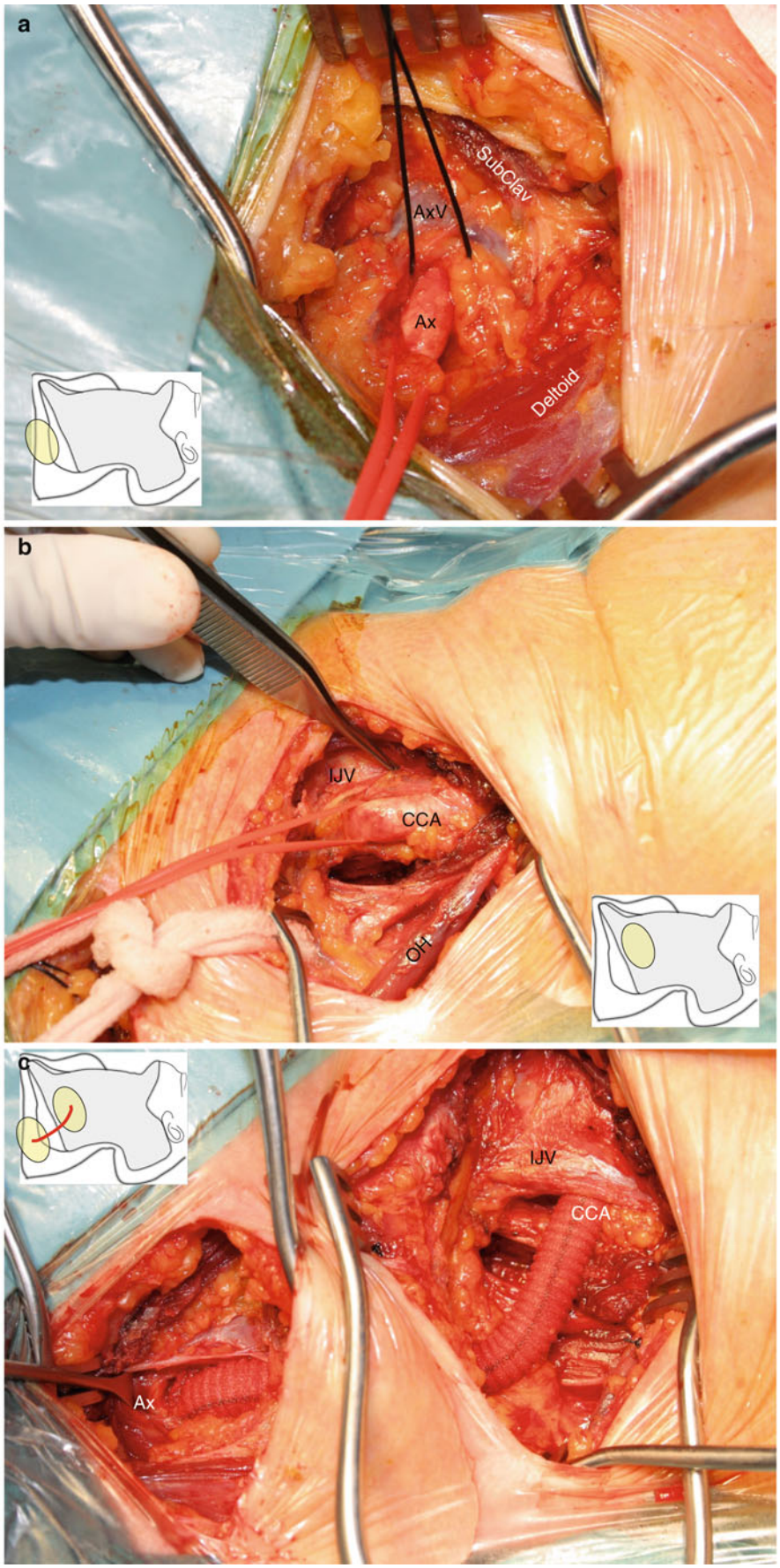


Fig. 4.11 Exposure of the axillary artery. When the distal SCA cannot be approached or when of scarce quality, the axillary artery (Ax) offers a sound alternative. Figure 4.11 offers an example of a CCA-to-Ax artery bypass. Panel (**a**): the Ax is approached by a subclavicular incision and prepared. Tex Ax is lateral to the axillary vein AxV. The fascicles of the brachial plexus encompass the artery except its anterior aspect. Usually, the Ax is prepared at the level of origin of the thoracoacromial artery (crossed by the pectoral ansa). Panel (**b**): the CCA is approached by a supraclavicular incision (again, posterior to the IJV). Panel (**c**): the CCA-to-Ax bypass. The vascular graft in tunneled under the clavicle

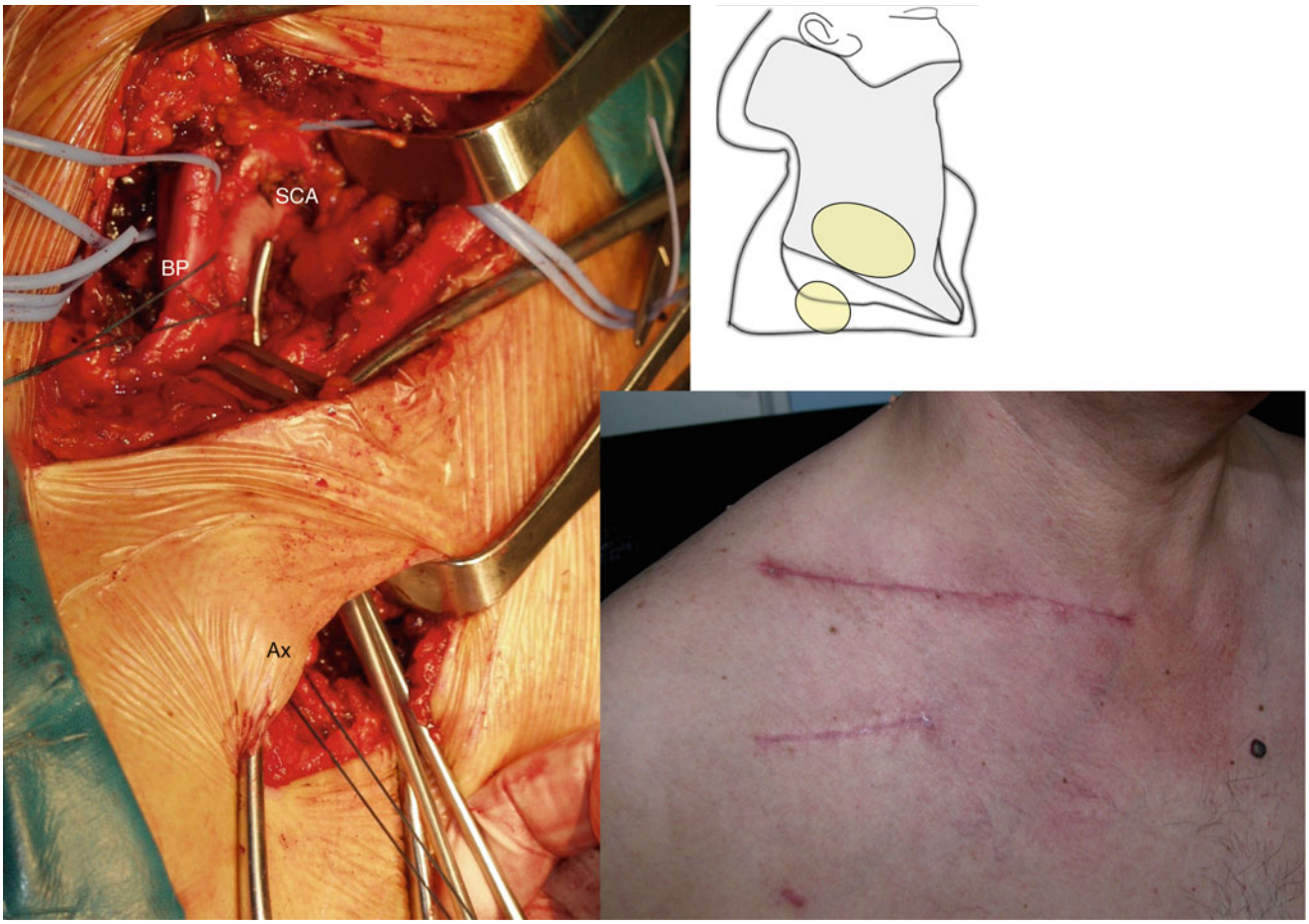


Fig. 4.12 Simultaneous supra- and infraclavicular approach. Even in emergency cases (e.g., trauma), there is no need for dividing the clavicle, as a good approach is offered by the two incisions. Any tunnel under the clavicle must be performed over the artery or just lateral to it, in order to protect the subclavian vein

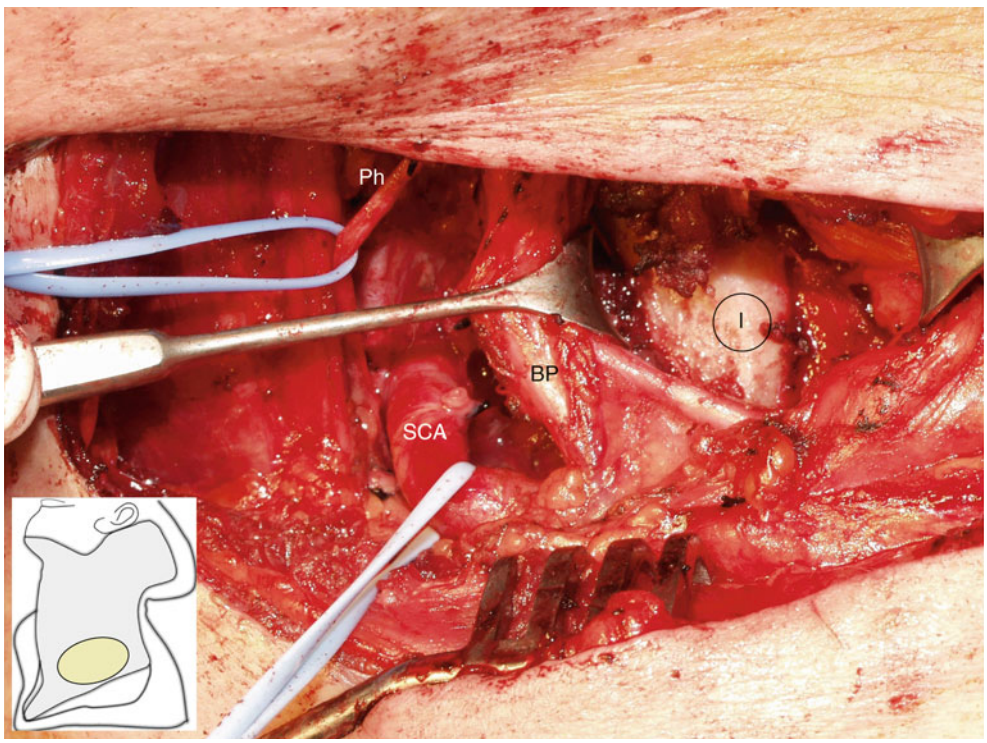


Fig. 4.13 Exposure of the first rib. In cases with thoracic outlet syndrome, excision of the first rib (or additional cervical rib) can be performed through a supraclavicular incision. The SCA and BP are dissected and protected. The anterior scalene muscle can be safely divided. The middle scalene muscle can be also divided with caution to the long thoracic nerve (C_5–C_7) as it perforates the latter muscle

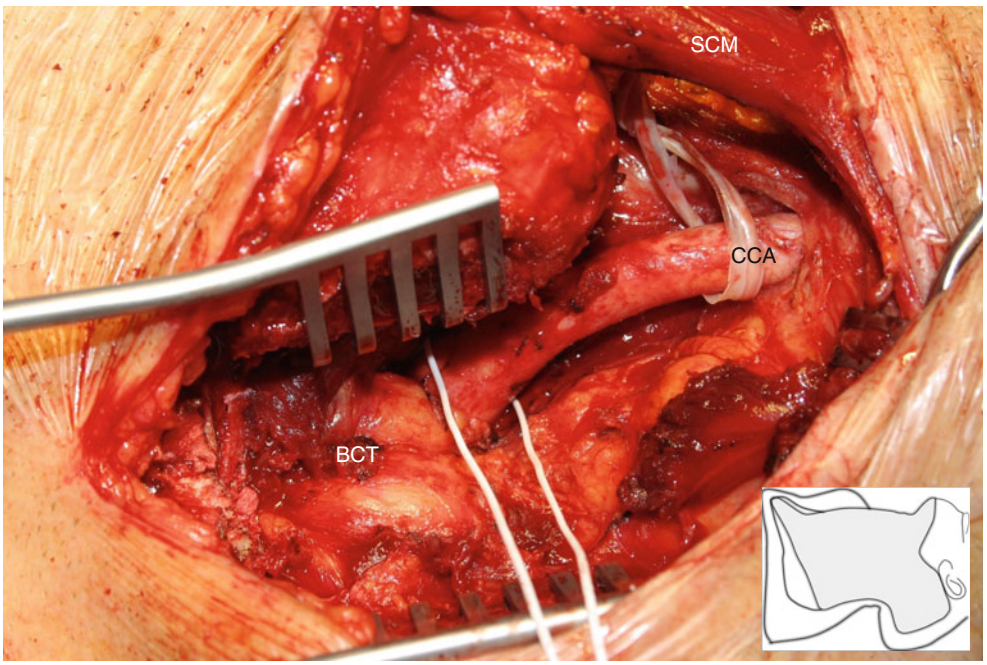


Fig. 4.14 Exposure of the brachiocephalic trunk. Upper sternotomy. The BCT cannot be safely isolated only through a cervical incision, and partial upper sternotomy is required, especially if clamping of its origin (or adjacent aorta) is needed. The sternal incision can be united with the right supraclavicular incision or not. The sternum is cut to the level of the manubrium and partially retracted. The right laryngeal recurrent, the vagus, the sympathetic ansa, and the phrenic nerve must all be protected. A graft anastomosed on the BCT can be easily tunnelzed to cervical level

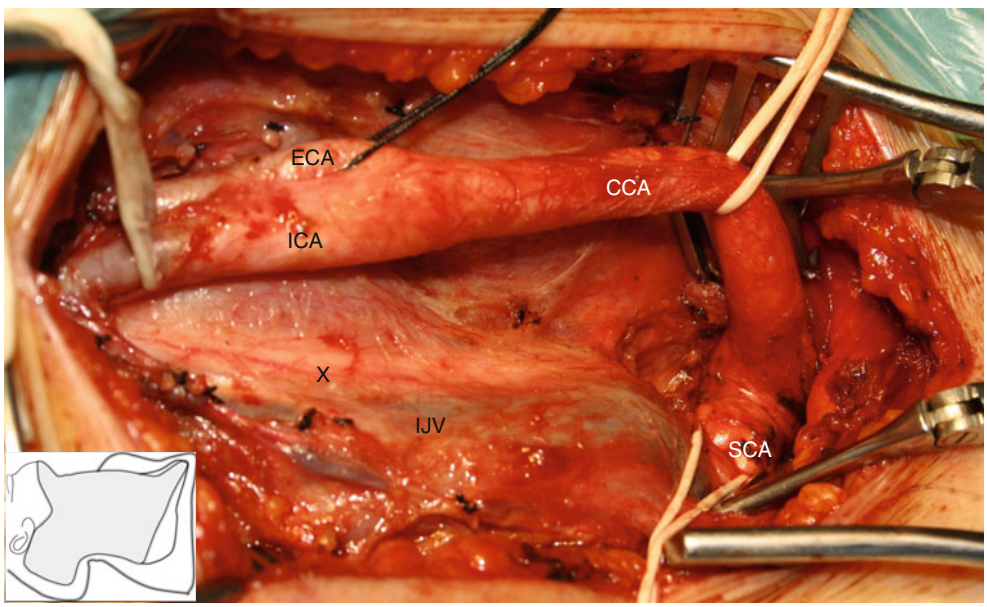


Fig. 4.15 Exposure of the brachiocephalic trunk. Cervical approach. A supraclavicular transverse or anterior longitudinal cervical incision will allow access to the BCT and its bifurcation (less to its origin from the aorta). The nerves mentioned above must be thoroughly protected. The CCA, VA, and SCA are approached comfortably. Should the more distal SCA be exposed, this will require medial traction of the IJV

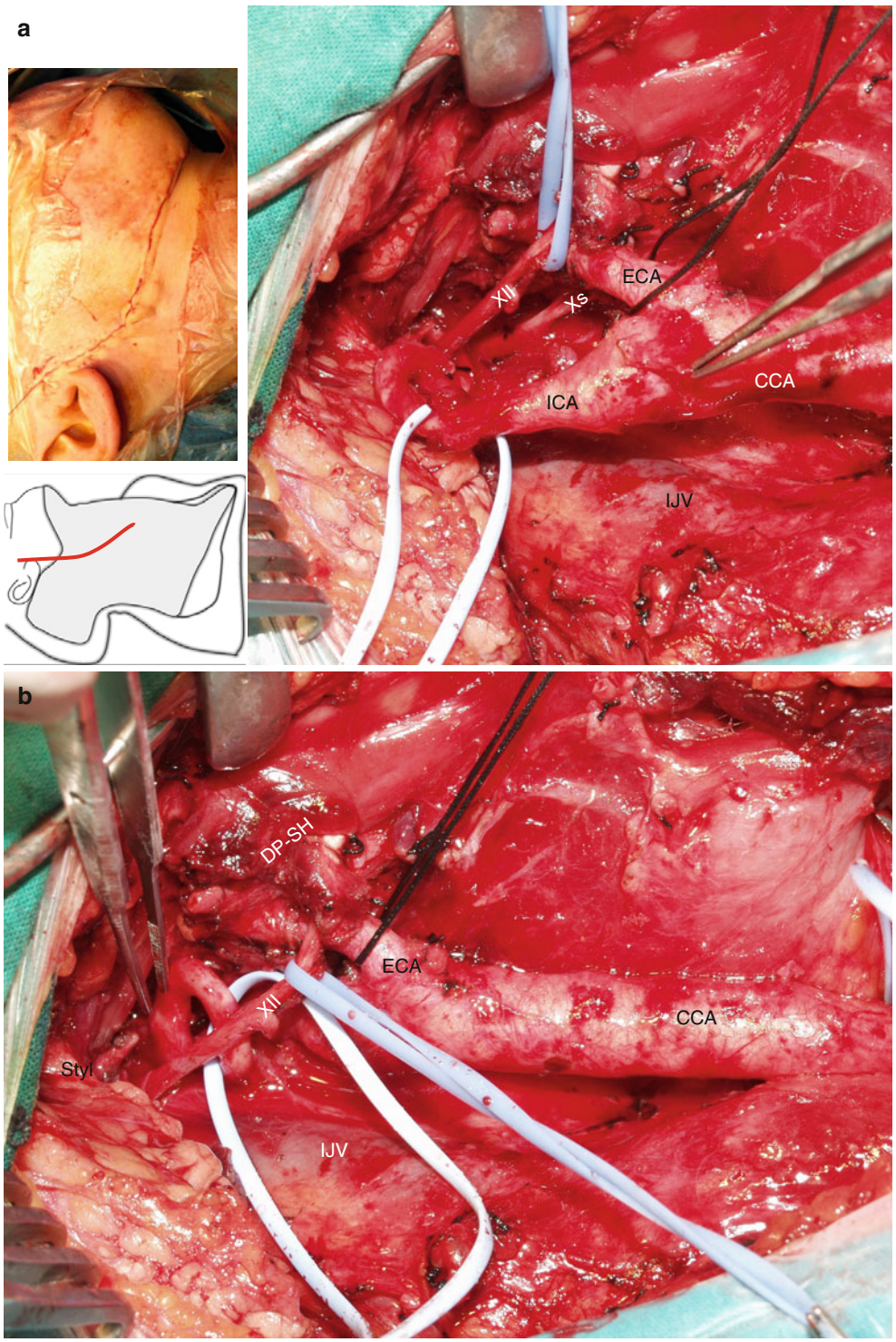


Fig. 4.16 Exposure of the distal internal carotid artery. Panel (**a**): preauricular extension of the cervical incision (the latter may be either submandibular or longitudinal). Isolation of the carotid bifurcation and adjacent cranial nerves. The posterior belly of the digastric muscle and stylohyoid are either divided or retracted (in the case presented, the muscles are divided). By entering the retromandibular space, the distal ICA is exposed. Note the kinking of the ICA. Hypoglossal nerve = XII. Superior laryngeal nerve = Xs. Panel (**b**): further dissection of the distal ICA up to the level of the carotid foramen. The styloid process (Styl) was isolated after dividing the origin of the styloid muscles. If necessary, the styloid process can be excised. The petrous temporal bone can be easily palpated and the ICA is exposed up to the carotid foramen

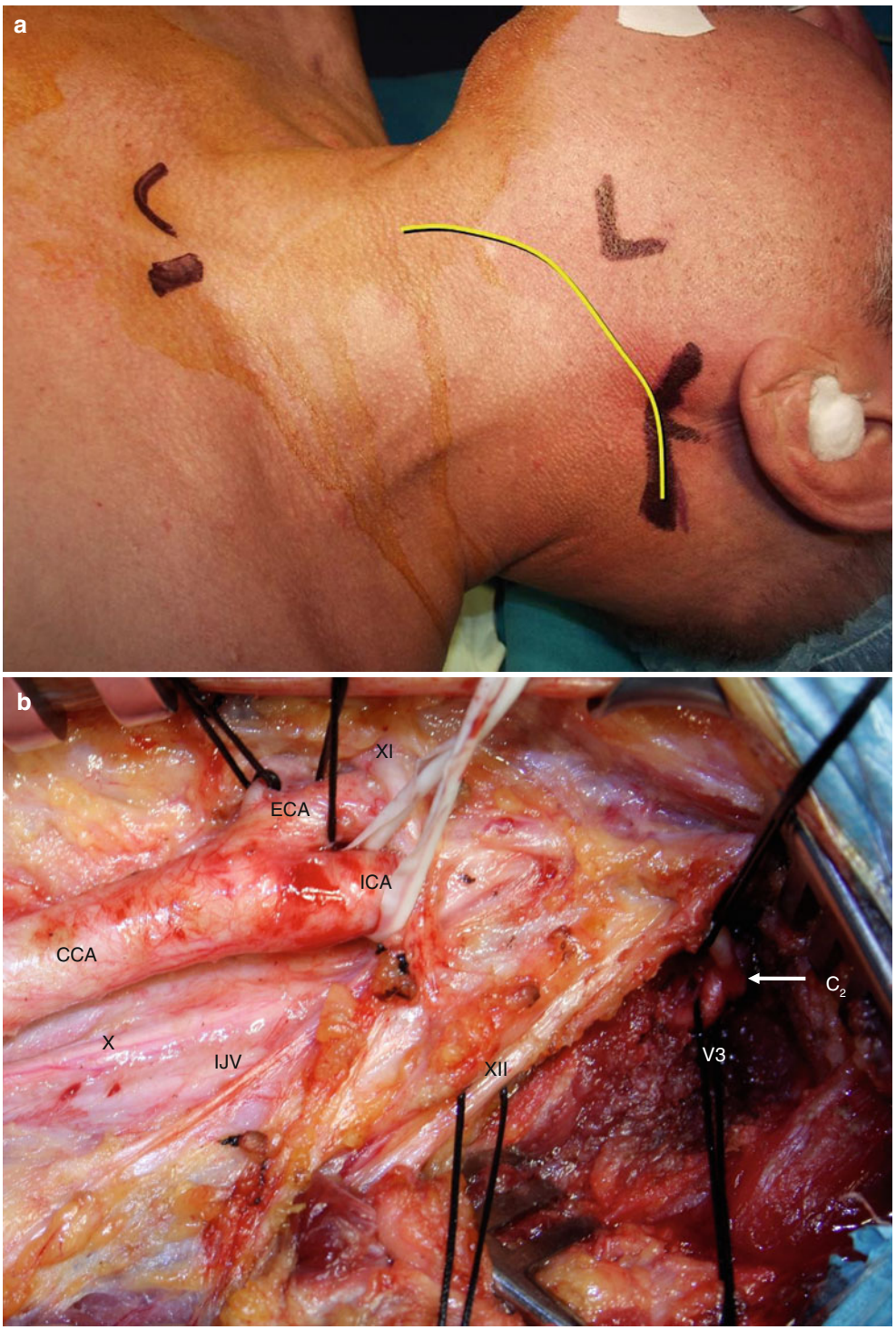
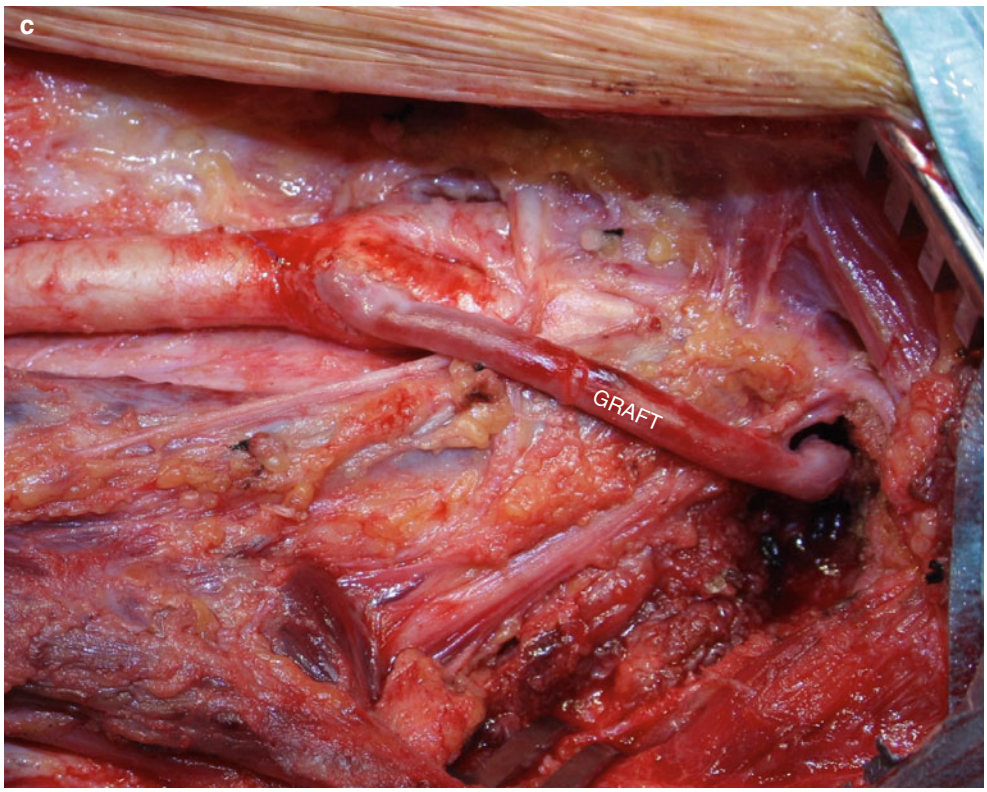


Fig. 4.17 Exposure of the distal vertebral artery V3. Panel (**a**): the incision for the V3 segment of the VA will pass just under the tip of the mastoid process, surpassing the process by approximately 2 cm. The anterior part of the incision is reclined toward the thyroid cartilage; this allows the concomitant exposure of the carotid bifurcation. Panel (**b**): the incision is deepened after dividing (partially or totally) the origin of the SCM and after identifying the accessory nerve (XI). Note that, in the case illustrated, the XI nerve is in pre-jugular position. Dividing the prevertebral muscles, the anterior ramus of the cervical nerve C_2 is visible, marking the loop of the VA between the C_2 and C_1 vertebrae. Usually, approximately 1.5 cm of the VA can be thus exposed. Bleeding from adjacent plexiform venous channels can be sometimes troublesome. Panel (**c**): bypass completed. A saphenous graft was inserted from the carotid bifurcation to the V3. Alternatively, branches of the ECA can be directly anastomosed to the V3 segment of the VA



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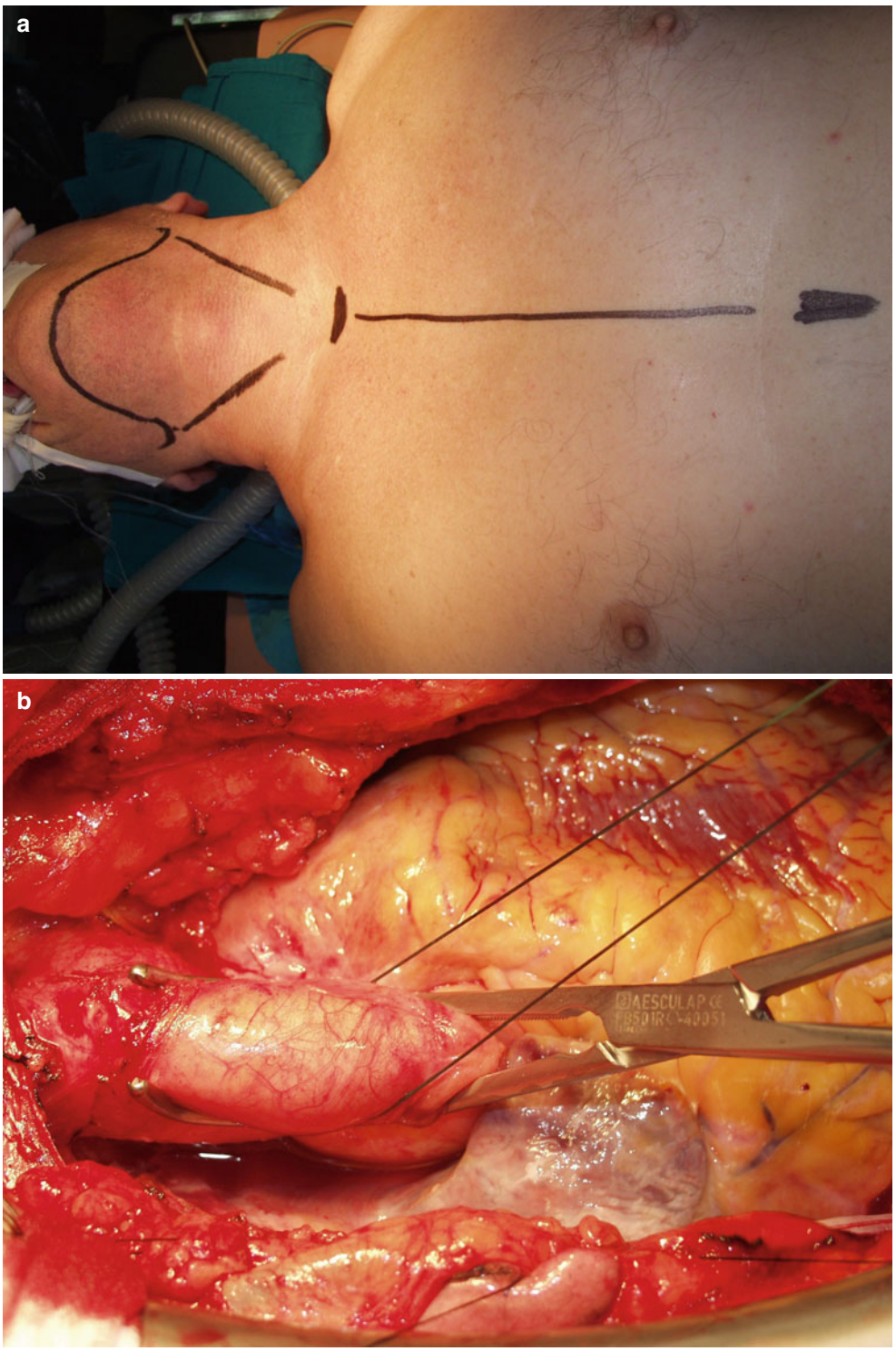
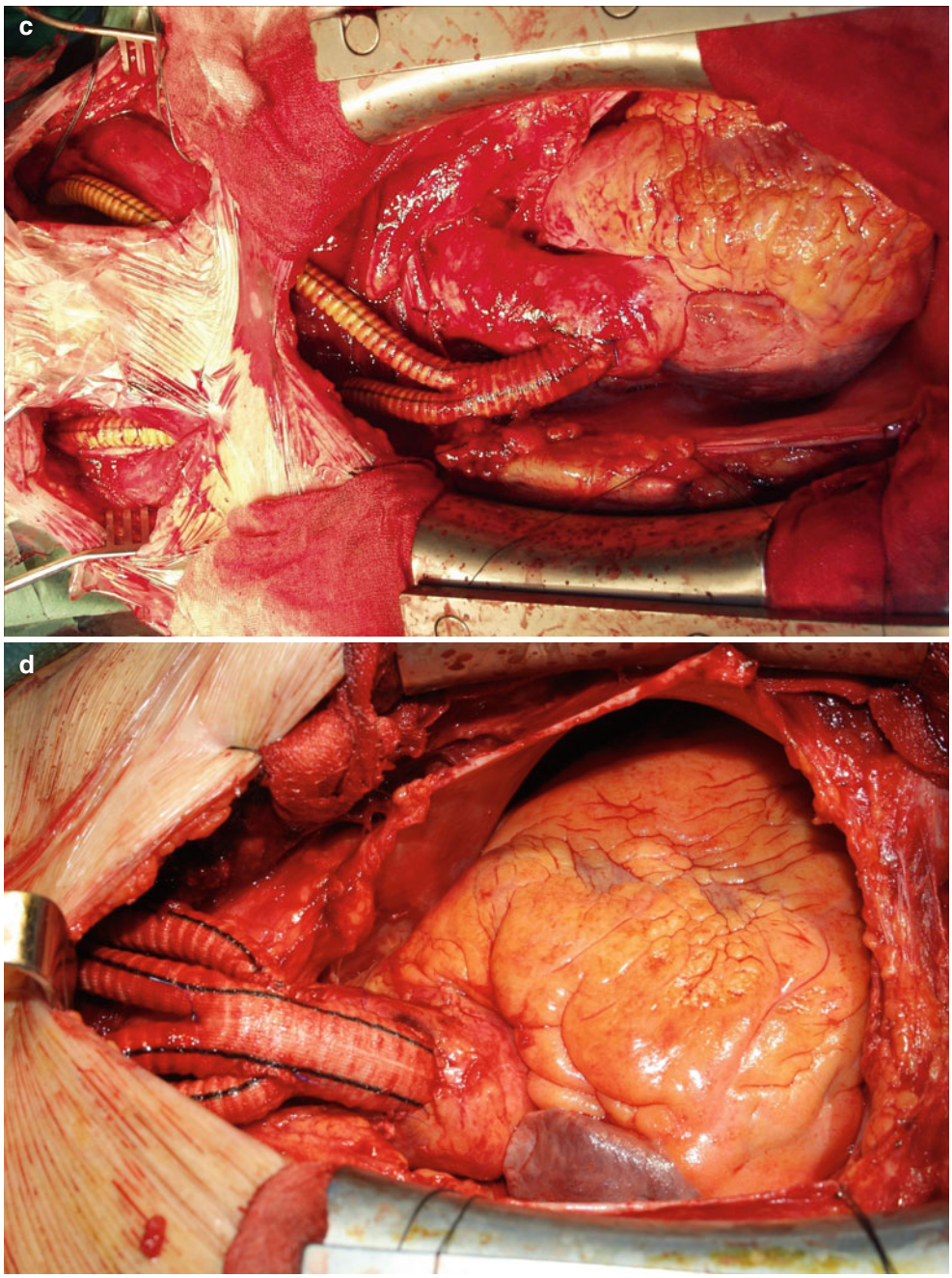


Fig. 4.18 Approach to ascending aorta through median sternotomy. Panel (**a**): patient prepared for median sternotomy (and additional cervical incisions for exposure of the carotid and subclavian arteries). Panel (**b**): the ascending aorta can be also isolated without opening the pericardium; however, a safer approach and control are offered by opening the pericardial cavity. The aorta is explored and palpated before clamping. A lateral clamp can be applied after the anesthesia team controls blood pressure and rhythm. Panel (**c**): a bifurcated prosthesis is anastomosed on the ascending aorta. In this particular case, the patient underwent an ascending aorta-to-bicarotid bypass. Note the lateral position of the graft, not immediately underneath the sternum. Panel (**d**): another patient in whom the ascending aorta is the donor vessel. In this case, a quadrifurcated graft (with two additional branches inserted "ad hoc") was anastomosed on the aorta: the patient underwent an ascending aorta-to-bilateral carotid and bilateral subclavian artery bypass



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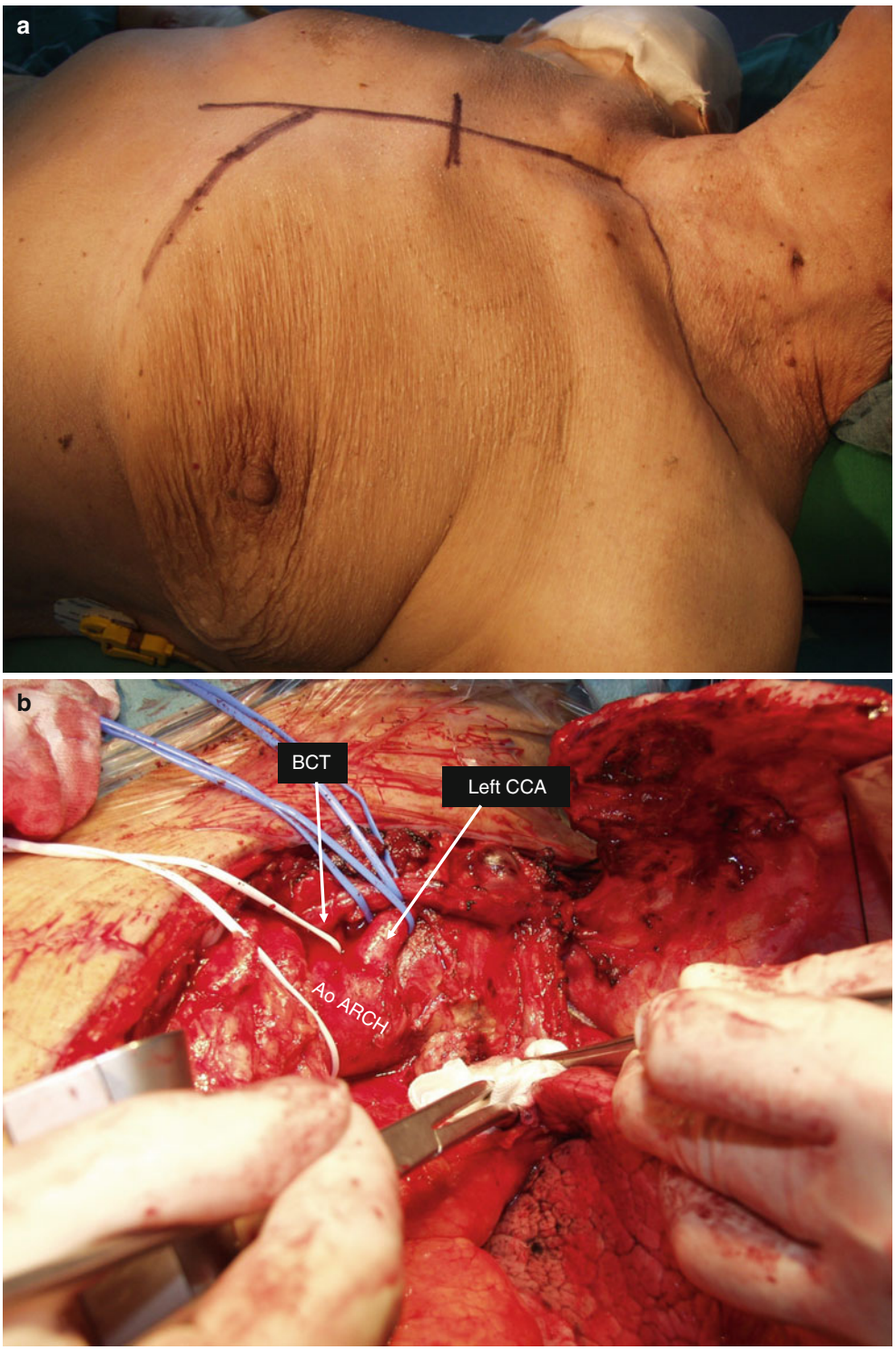
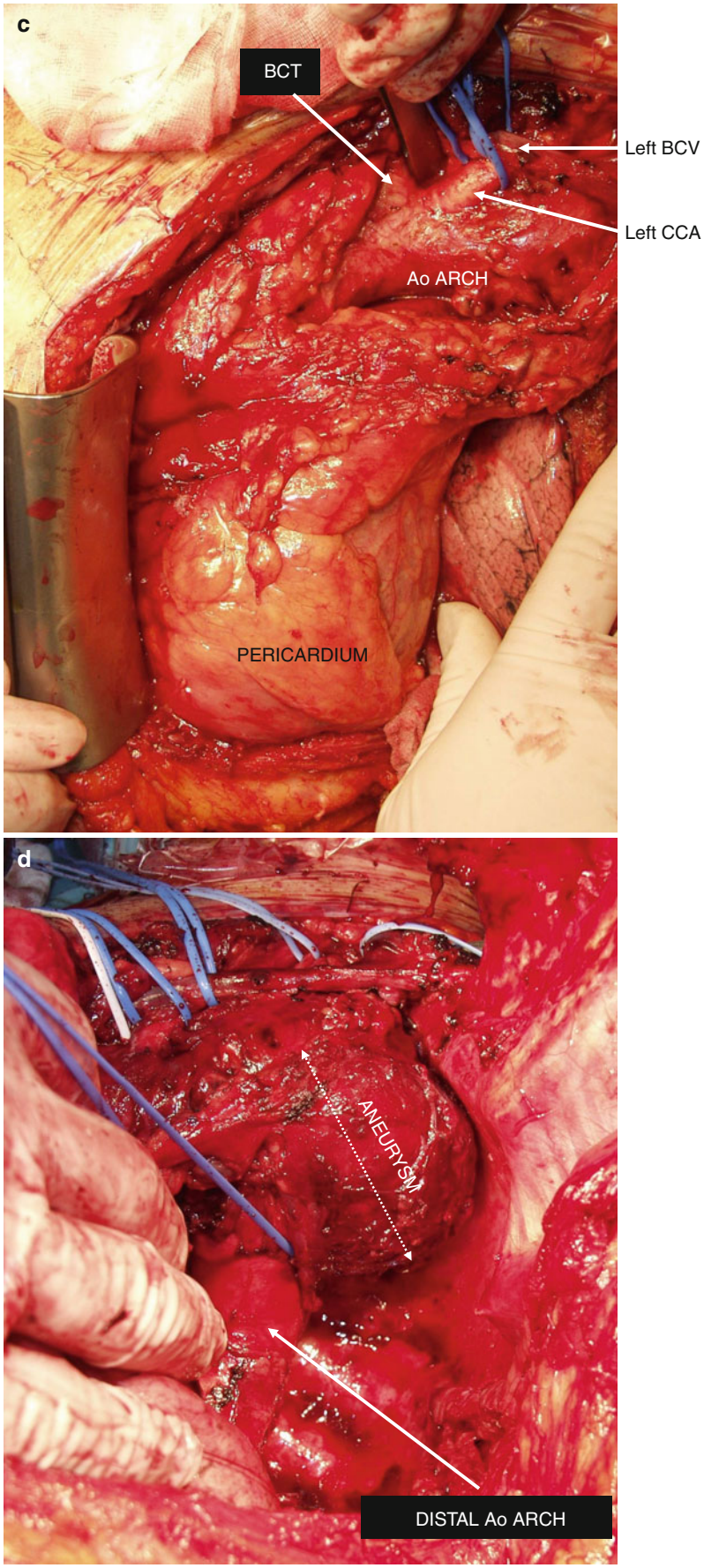


Fig. 4.19 The trap door incision. Panel (**a**): the trap door incision combines an anterolateral left thoracotomy and supraclavicular cervicotomy with median sternotomy. Panel (**b**): a good vision is offered to the aortic arch, to the origin of the arch vessels, and to the proximal descending thoracic aorta. In the present case, the patient had an aneurysm of the origin of the left subclavian artery. Panel (**c**): selective intubation and deflation of the left lung will bring additional advantages to this approach. Panel (**d**): note the voluminous aneurysm at the origin of the left subclavian artery and the possibility of controlling the distal arch and proximal descending thoracic aorta, through the trap door incision. Panel (**e**): if necessary, the pericardium can also be opened gaining access to the ascending aorta. In this case, a purse string suture is made on the ascending aorta, for the insertion of a temporary bypass between the aorta and a femoral artery

Fig. 4.19 (continued)



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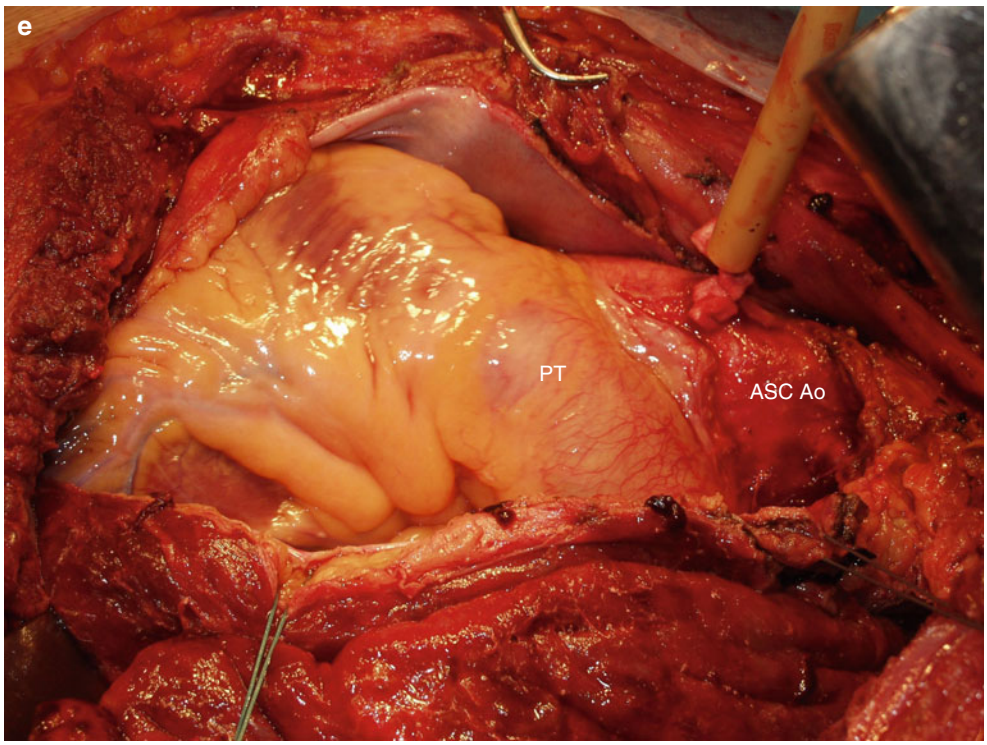

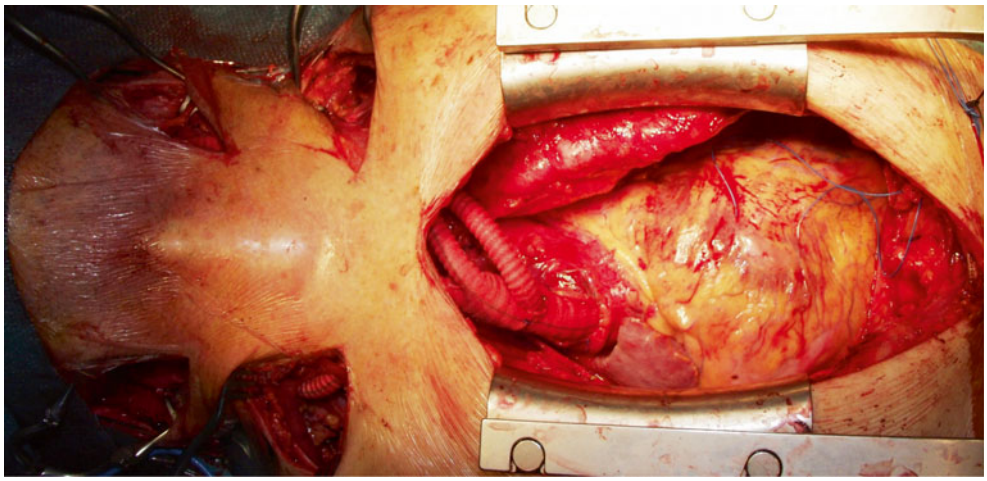

Fig. 4.20 Extensive arterial exposure. Intraoperative aspect of a patient who underwent ascending aorta-to-bilateral carotid and bilateral subclavian artery bypass, through median sternotomy and bilateral cervical incisions. We prefer limited and parallel cervical incisions instead of a single longitudinal cervical incision when the SCA and carotid bifurcations must be approached

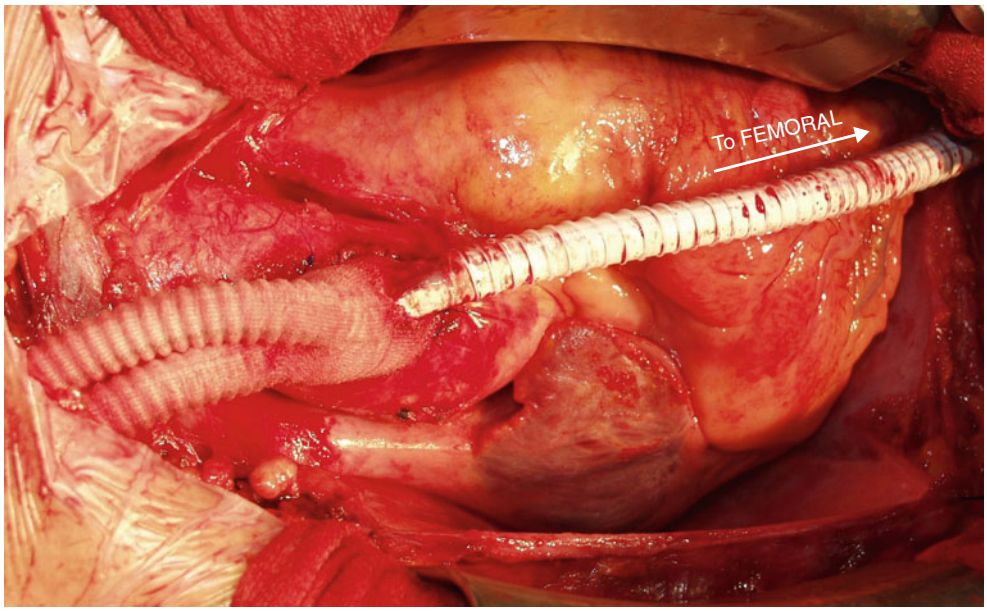

Fig. 4.21 Concomitant arterial disease in the lower extremities. In selected cases, a concomitant revascularization of the inferior aortic system is required. A side branch of the graft can be tunneled (extraperitoneally but not subcutaneously) to one of the femoral arteries. The remainder two branches are directed to the right SCA and right CCA

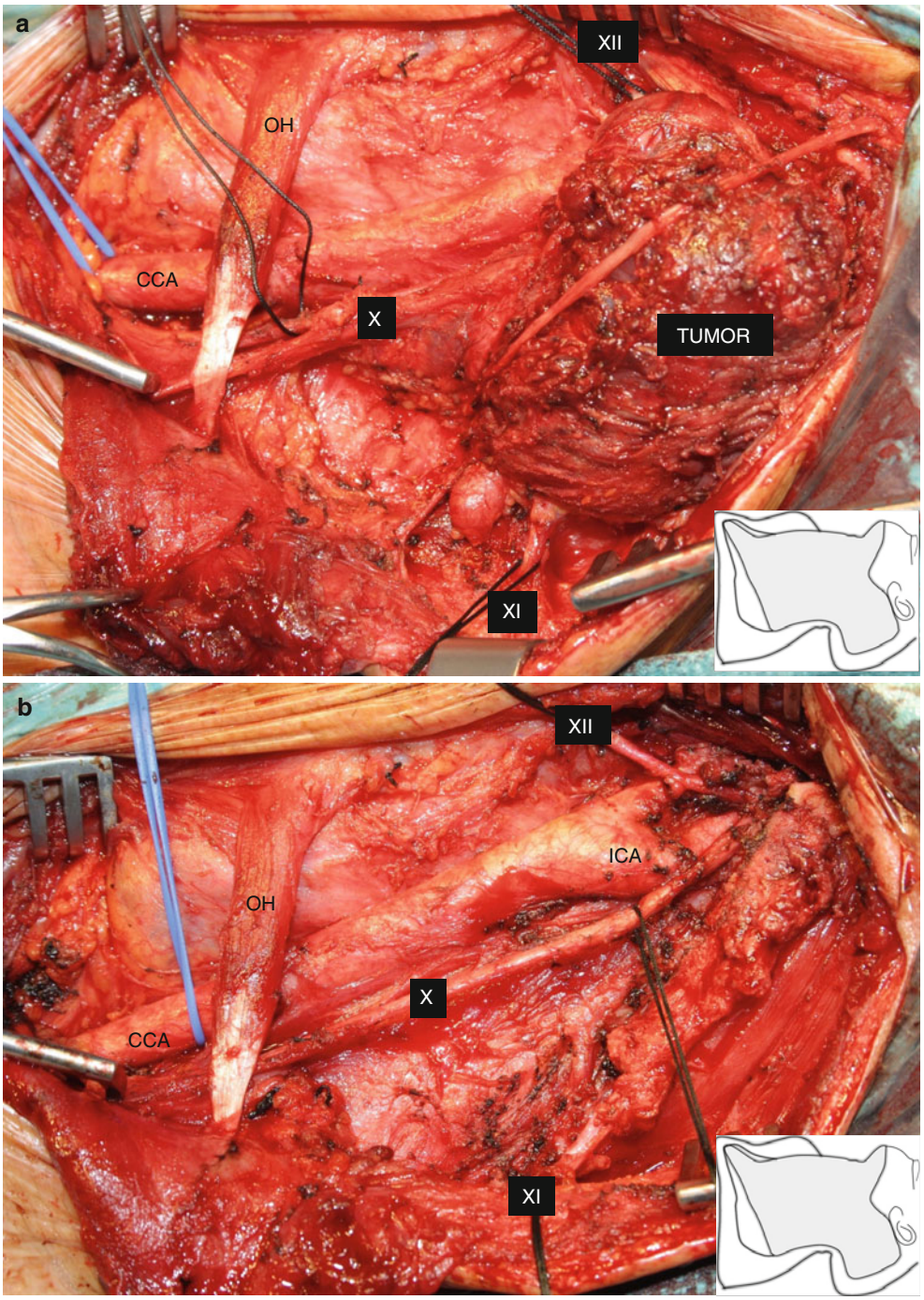

Fig. 4.22 Particular exposures for tumors and aneurysms. Cervical tumors and aneurysms of the carotid artery require more extensive cervical approaches for the proper removal of the aneurysm or tumor and for a safe control of the vessels. Cranial nerves and the sympathetic trunk must also be preserved. Panel (**a**): tumor developed over the carotid bifurcation. Note the position of the carotid artery and of the cranial nerves X, XI, and XII. Panel (**b**): intraoperative aspect after removal of the tumor. The cranial nerves were preserved. The carotid vessels were exposed high in the neck. Part of the SCM was excised, as this was infiltrated by the tumor

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Diagnostic Approach to Cerebrovascular Disease: Ultrasound

5

Andrei Nistorescu and Horia Muresian

In an era of a more complex and sophisticated medicine, the ultrasound exploration of the extra- and intracerebral vessels can become, as well as other complementary techniques, either the best or the worst of examinations. Undoubtedly, it will be the worst if trivialized, if practiced at every street corner and out of the clinical context, thus bringing about either a false sense of security or that of unmotivated fear.
Marie-Germaine Bousser

The substantial advantages of this method [i.e., ultrasound] are counterbalanced by the subjectiveness in gaining and portraying the graphic or acoustic input signals. Data obtained from our patients should be interpreted in the general clinical context; as in other fields of biology, treatment options do not emanate solely from an EEG trace or from a blood test. The practice of treating an echographic image or a Doppler wave must certainly vanish from ultrasonographical practice.
Pierre-Jean Touboul

The echographic evaluation of the cerebral circulation must be considered and included into the more general context of the superior aortic system, i.e., the efferent arteries of the aortic arch. The limits between the upper thorax, the mediastinum, the superior limbs, the neck, and the head are not sharply demarcated either from the normal anatomical, clinical, or pathological points of view, and this is implicitly reflected in the diagnostic approach to the supraaortic arterial trunks.

The ultrasound interrogation of the superior aortic system includes the approach to diverse arterial segments pertaining both to the extracranial and to the intracranial segments of the circulation. The so-called carotid Doppler examination actually comprises more imaging techniques and modalities addressing the various arterial segments. From the first point of view, the well-established modalities include carotid duplex ultrasound (CDUS), transcranial Doppler (TCD), contrast-enhanced ultrasound, 3D ultrasound, and compound ultrasound. From the second point of view, the carotid system and the vertebrobasilar system are approachable either directly or indirectly (TCD). Additionally, the subclavian and axillary arteries are also imaged.

The main *advantages* of these approaches and techniques reside in the following: they are safe, noninvasive, and less expensive (as compared to angiography, CT-angio, or MRA), there is no risk for anaphylactic shock or allergic reactions, and the examination can be repeatedly carried out with no additional risks for the patient. Not least, the routine use of the intraoperative ultrasound devices in the future will allow a more precise checkup at the end of the surgical procedure and eliminate the technique-related complications. The imaging of the arterial wall represents a major advantage of ultrasound over angiography.

Another advantage resides in the possibility of a rapid and efficient communication of the results, with static and dynamic images recorded both on virtual media (electronic support) and on prints. This allows a quick evaluation and comparison of serial examinations in the same patients, performed over longer periods of time. Prints can be simply stored by the patients also similar to an ECG trace.

Numerous anatomical particulars can be precisely identified during ultrasound interrogation; among these, the most salient are the *height* of the carotid bifurcation, the orientation of the carotid bifurcation (normal, transposed, sagittal), the kinking of the ICA or CCA, the measurement of intima-media thickness (IMT: a valid parameter in the follow-up of patients), and the relative caliber of the neck arteries. The carotid arteries generally appear of even caliber, while the VAs are usually asymmetric (velocities in the VAs may be different not solely because of the differential caliber but also due to the distinct origin of the right and

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A. Nistorescu
National Institute of Neurology and Neurovascular Diseases Bucharest, Bucharest, Romania
e-mail: nandrei50@yahoo.com

H. Muresian (✉)
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

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left VA, including the angle of origination and distance from the aortic arch).

Another advantage is that the patient can be easily examined under natural circumstances and hemodynamic conditions or in various positions (supine, seated, with the table tilted up or down, etc.) as chosen by the examiner (if relevant and whenever necessary). Compression of the carotid artery will elicit higher flows in the VA and will allow a clinically valid proof of patency of the CoW (obligatory, carotid compression is performed *after* imaging the carotid). Also, if necessary, the patient can be examined after administering various types of drugs, as, for example, vasodilators, antihypertensive, vasopressors, and so forth. In this respect, the ultrasound examination is more clinically related as important and significant details can be obtained by using relatively simple maneuvers.

The presence of adenopathy, cervical tumors, and thyroid disease can be also quickly evaluated during the ultrasound examination. The IJVs can be assessed, and this is relevant as numerous variations of the IJV are encountered: asymmetry, fenestrations of the IJV, anomalous course, asymptomatic thrombosis (pre- or postoperatively), and spontaneous contrast in the IJV.

Not least, the echographist can easily and promptly check the general vascular condition of the patient: the femoral and renal arteries and the presence of abdominal aneurysm. Such particulars may either complete or change the principal indication for carotid revascularization (either by CEA or CAS) and assist in a better risk stratification.

The *disadvantages* and the *limits* of these methods can be seen as residing in the technique proper, the patient's body habitus and disease characteristics on the one hand, and in the expertise of the ultrasonographer, on the other hand.

Limits of the Technique The aortic arch and the intrathoracic origin of the brachiocephalic trunk (BCT), of the left common carotid artery (CCA), and of the left subclavian artery (SCA) cannot be directly assessed; flow velocity, turbulences, and resistance will all raise suspicion of lower, intrathoracic arterial lesions (some of these can be evaluated by transthoracic echocardiography (TTE) by using the suprasternal window or by transesophageal echocardiography (TEE)). CDUS is less accurate in estimating stenoses <50% (and probably also stenoses <70%). As a consequence, performing CEA based on CDUS solely appears to result in a significant number of unnecessary surgeries [1]. Some authors also stress the fact that CDUS tends to overestimate the degree of ICA stenosis [2, 3].

CDUS images only the extracranial segment of the ICA (TCD examines the major intracerebral arteries through the various *windows*: orbital and cranial base [temporal, occipital] contributing to the quantification of the severity of ICA stenosis and offering details on the compensatory capacity of the CoW). Numerous types of lesions and diseases are not directly identifiable by CDUS, e.g., intracranial aneurysm (although vasospasm in ruptured aneurysms can be diagnosed and monitored by TCD), vascular malformations, tumors, and the presence of vestigial anastomoses (and, additionally, in the neck: bicarotid trunk, ARSA, proatlantal artery, the atypical forms of subclavian steal in cases with occlusion of the V1 segment of the VA). The shorter tract of the facial artery, lacking the anastomosis with the ophthalmic artery (a normal anatomical variation), may mislead the examiner when looking for a *positive* or a *negative* ophthalmic artery.

Regarding plaque morphology, the CDUS cannot distinguish between intraplaque hemorrhage and a conspicuous lipid core, although the mere identification of an echolucent, unstable, or ulcerated plaque already offers important particulars to the examination and for the surgical indication.

Severe stenosis (with hairline residual lumen) can be missed on CDUS [4], while a patent ascending pharyngeal artery can be wrongly interpreted as a pre-occluded ICA or as a rechanneled ICA thrombosis.

Contrast-enhanced ultrasound may help to distinguish complete ICA occlusion from near occlusion and to evaluate the neovascularization in the plaque – a possible marker for plaque instability [5, 6]. A better and quantitative evaluation of plaque volume and morphology is offered by 3D ultrasound; however, this technique is not routinely used. Visualization of plaque texture and surface is also obtained with compound ultrasound – a technique, again, not routinely used. Hence, it appears evident that CDUS should ideally be coupled and completed with a second imaging modality in high-risk patients and in individuals referred for CEA or CAS.

Patient Body Habitus and Disease Characteristics Obese patients with short necks, accentuated kyphosis of the cervical spine (e.g., rheumatoid arthritis), torticollis, previous radiotherapy, and enlarged submandibular and parotid glands – all these may limit the accuracy of the CDUS. Severely kinked CCA and ICA and heavily calcified arterial wall may render the ultrasound imaging difficult, insufficient, or incomplete.

The expertise of the examiner represents one of the major points and reasons influencing the efficacy of the test. We would like to underline the twofold importance of the ultrasonographer's skills and experience. Well-trained and certified specialists (ideally neurologists or cardiologists) are the best choice, but the second additional factor is represented by the possibility of confronting the results with other diagnostic imaging techniques and with surgery. Not all examiners have the chance of a feedback with angiography, CT-angio, or MRA, and even fewer can establish a direct relationship with the surgeon. The comparison with all the particulars offered by the macroscopic examination of the lesion (the actual degree of stenosis as found intraopera-

tively, the aspect and composition of the plaque) is essential for the continuous upgrade of the ultrasonographer. In the current practice of our team, the confrontation between CDUS, angiography (or, alternatively, CT-angio), and the intraoperative aspect does exist. The continuous feedback with anatomy is also essential for a good echographist.

Furthermore, the examiner must know well the clinical data of the patient (the major neurological signs, the general vascular status) and must be aware of comorbidities such as diabetes, heart disease, and so forth; the examination should proceed with calm and patience and proceed beyond the first diagnostic impression.

How Should the Ultrasound Examination Proceed? Figs. 5.1, 5.2, 5.3, and 5.4 Extracranial Doppler (ECD) examination and echotomography offer valid hemodynamic and morphologic data. ECD brings unparalleled data regarding the type and dynamics of flow; an experienced ultrasonographer will readily distinguish between the acoustic signal of the normal flow and that of the stenotic flow (and may also gauge the severity of stenosis) and also recognize the patterns encountered with arterial hypoplasia or arterial dissection. The velocity curve is best obtained with ECD, and the technique allows the diagnosis of vertebral steal also. The origin of the VA and the ophthalmic artery is also best examined with ECD. TCD will follow in selected circumstances and with special indications as it is more time-consuming and requires more skilled operators. The windows for TCD (Figs. 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, and 5.14) are transorbital (targeting the ophthalmic artery, the carotid siphon, and the opposite ACA), transtemporal (targeting the ACA, MCA, and PCA), and occipital (targeting the VA, BA, PICA, and PCA). In order to correctly identify the intracranial artery visualized, it is necessary to consider three parameters: the depth of the vessel examined, the direction of flow, and the modifications after compression of the contralateral carotid artery.

The ultrasound examination should be as comprehensive as possible, offering useful details not solely for risk stratification and the general indication for therapy (CEA or CAS) but to point out in the mean time all the necessary elements for CAS or surgery. These include the evaluation of stenoses (number, localization, shape, severity, tandem lesions, plaque characteristics – including heavily calcified artery) and the impact on flow (pressure, velocity, resistance, arterial distensibility, steal syndrome), the height of the carotid bifurcation, the presence of hypoplastic segments (e.g., a hypoplastic ICA distal to a stenosis, may contraindicate surgery), the transposition of the carotid bifurcation (and other various reciprocal positions of the ICA and ECA that may render more difficult the endovascular or surgical approach), the extreme kinking of the CCA and ICA, the associated lesions such as aneurysms of the ICA, the measurement of IMT, and the general quality of the arterial wall (including very thin-walled carotid arteries or diffusely thickened artery, as in inflammatory states, vasculitides, or after radiotherapy). Even in the case of significant stenosis at the level of one carotid bifurcation, a thorough evaluation must be performed as atherosclerotic lesions develop bilaterally (in spite of the clinical manifestations which may appear predominantly/initially unilaterally) and comprise both the extra- and intracranial segments.

The indication for CEA or CAS goes well beyond the severity of stenosis [7]; complicated plaques or plaques submitted to higher hemodynamic stresses are more likely to become symptomatic, and treatment of mild carotid stenosis in these cases is indicated [8]. Plaque morphology was variously characterized, initially as type A = mild ulceration, type B = extended ulcerations over the plaque, and type C = deep and irregular ulcerations with multiple cavities. Subsequent criteria [9] were added: echogenicity (from echolucent to intense echogenic), texture (homogenous, heterogeneous), and plaque surface (regular, irregular, ulcerated). A more detailed classification was obtained, by combining the various elements [10]: type I = uniformly hypoechogenic plaque with hyperechogenic cap; type II = predominantly hypoechogenic plaque with few scattered hyperechogenic areas, <25 %; type III = predominantly hyperechogenic plaque with few hypoechogenic areas, <25 %; and type IV = uniformly hyperechogenic plaque. The thinness of the fibrous cap represents an important element; it appears to be directly proportional to a larger necrotic core [11] and to the risk of rupture.

Various elements are linked to plaque rupture: the plaque volume and composition, the thinness of the fibrous cap, and the presence of inflammatory process. The rupture of the vulnerable plaque is also determined by hemodynamic and biochemical factors: hemodynamic stress appears to be greater with mild carotid stenoses; reduced elasticity as with age increases the stress over the arterial wall and plaque. Not least, anatomical variations of the carotid bifurcation may also play a role [12].

The NASCET [13] and ECST [14] studies have evaluated only the severity of stenosis, characteristic to the advanced stages of cerebrovascular atherosclerosis while overlooking some important details, among which are the presence and severity of atherosclerotic disease in the opposite carotid artery or in the vertebrobasilar system, the morphology of the plaque, and the concomitant presence of intracerebral arterial disease. Carotid artery stenosis has a progressive natural history spanning from low-degree narrowing of the lumen to near occlusion and occlusion and from asymptomatic to severely symptomatic. As a consequence, it is difficult to draw a clear demarcation line between symptomatic patients with >70 % carotid stenosis – the genuine candidates

for CAS or CEA – and patients in any other state. Integration of clinical and imagistic data in the individual patient and a multidisciplinary team approach undoubtedly represents the best management beyond the current guidelines.

Practical Guidelines An apparent discrepancy between the Doppler and the tomographic ultrasound data may show up; again, plaque morphology and the presence of symptoms may indicate surgery or CAS. Bruits in the neck may not always reflect carotid stenosis: higher velocities can be elicited from the superior thyroid artery (Fig. 5.3) especially in cases with polynodular thyroid or goiter and sometimes when the carotid bifurcation is *inverted*, i.e., the ECA originates lateral and the ICA medial (with the superior thyroid artery crossing the carotid bifurcation). The superior thyroid artery usually marks the level of the carotid bifurcation and represents a good guide for the echographist. However, with higher bifurcations the superior thyroid artery has a separate origin from the CCA.

The VA can be targeted from its origin from the SCA (V0 and V1) up to the V3 segment (the V4 and the BA are approached TCD through the occipital window). The diameter of the VA represents an important element to be quantified, as VAs of small caliber are more difficult to reimplant (or reimplantation will no more be indicated). Severe kinking of the V1 segment may sometimes mislead the echographist, as the signal may appear both positive and negative, depending on the portion of the VA loop that is examined (in a way, similar to V3 segment where the signal has positive and negative components – see below). The level of entry of the VA into the intraosseous portion can be readily assessed, and if different from C_6, this will be signaled to the surgeon. Extrinsic compressions over the V2 segment of the VA appear also evident. Patients with severe arthritic lesions of the cervical spine may depict important extrinsic stenoses of the V2 segment of the VA; some sites of stenosis may appear more evident with extreme rotation of the head (such maneuvers are more difficult to elicit during angiography).

The V3 segment of the VA can be recognized after compression of the ipsilateral carotid artery. The distinction between the V3 and the occipital artery (branch of the ECA) must also be accomplished, as the occipital artery may depict a similar velocity signal as the VA. The velocity amplitude in V3 is directly proportional with the patency of the PCommA. The arterial loop of the VA at C_2-C_1 level depicts both a positive and a negative signal.

TCD is not routinely applied unless ECD raises the supposition of intracranial arterial disease. The approach through the various ultrasound windows and the particulars routinely obtained are presented in Figs. 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, and 5.14. Valid data are also obtained on the CoW. Patients with bilateral occlusion of the ICA and angioplasty of the ECA (either endovascular or surgical) are periodically evaluated by TCD (see Chaps. 6 and 13 for angioplasty of the ECA).

Carotid artery stenosis (Figs. 5.15, 5.16, and 5.17) can be readily and precisely assessed by ultrasound especially with segmental, circumscribed stenoses. The deceleration of flow at the level of the CCA is directly related to the severity of the more distal stenosis. The modifications of the acoustics and the spectral analysis of the Doppler signal allow a stratification of ICA stenosis corresponding to the classification of Touboul (grades I through V). The characteristics of poststenotic flow are demonstrated at the level of the more distal ICA, ACA, and MCA. The OA varies from *positive* to *negative*. All these parameters become normalized after CAS or CEA. The morphology of the plaque must be also examined: volume, length, thickness, echolucent core (reflecting lipid core or hemorrhage), calcifications, and ulcerations. The classification of the plaque characteristics was presented before. An indirect sign of ulceration is the turbulence over the surface of the plaque.

Carotid artery dissection represents a distinct condition (see for details Chaps. 7 and 15) eventually leading, as the atherosclerotic plaque, to carotid thrombosis. However, the sequence of events is usually speedier, requiring a prompt diagnosis and treatment. The dissected segment of the artery may be limited, or the dissection can progress distally to the intracranial portion of the ICA. ECD depicts the characteristic stump flow; the thrombus in the false lumen appears as a hypoechogenic mass. A thorough and complete examination of the cerebral arteries must be performed, as dissection may involve both carotid arteries and, not infrequently, the VA, in the same patient (Figs. 5.18 and 5.19).

Transposition of the carotid bifurcation represents a generic denomination for the most frequently encountered anatomical variations of this particular arterial segment (see also Chap. 1 for anatomical variations of the carotid bifurcation). Transposition actually refers to the reciprocal shift in position of the ECA (originating lateral) and the ICA (originating medial), i.e., vice versa than the normal anatomical disposition (Fig. 5.20). Other situations include the sagittally disposed ECA (anterior) and ICA (posterior) or the absence of the carotid bulb. These particulars may mislead the echographist in identifying correctly the ECA and the ICA. For the surgeon it is important to learn about such variations that might render the exposure of the vessels more difficult. An inverted carotid bifurcation with the ICA in the position usually occupied by the ECA and with no apparent bulb at origin may cheat the echographist (and not least, the surgeon), taking the ECA as an ICA, especially with lower carotid bifurcations – a condition in which the branches of the ECA are not apparent in the proximity of the bifurcation.

The two subclavian arteries have different origins. The right SCA is readily approachable at cervical level, while the origin of the left is not. Indirect signs of SCA stenosis are available: post-stenotic flow evidenced on the distal SCA and axillary or better on the brachial artery. A different blood pressure in the two arms raises the suspicion of SCA stenosis or aortic dissection, and sometimes, it is difficult to tell the difference between the two conditions without performing the CT or TEE. Stenosis of the origin of the left SCA can be also accompanied by similar lesions at the origin of the BCT and of the aortic arch, even if the origin of the right SCA and of the right CCA is not (severely) diseased. Patterns of flow more difficult to interpret may appear with an atherosclerotic ARSA and Kommerell diverticulum.

Stenosis of the SCA proximal to the origin of the VA may be accompanied by *the subclavian steal syndrome*. This syndrome does not appear in all cases, as its presence depends on the caliber and length of the VA of the same side: the syndrome will not develop in case of hypoplastic VA or in case with a left VA with aortic origin. Moreover, not all patients with steal syndrome are symptomatic (and asymptomatic cases should not be operated). In other circumstances, the proximal segments of the VA are also occluded (V0 and V1 and sometimes even the V2), while the subclavian steal is apparent, through highly developed collaterals between the V3, ECA, and SCA on the same side (see Chap. 7 for details). Consequently, the ultrasound diagnosis of SCA stenosis and the presence of steal syndrome is not always at hand and not always achievable in its totality. The steal syndrome may fluctuate with the cardiac cycle (positive systolic complexes alternating with negative diastolic complexes, in the SCA) and may diminish while performing the cuff test (the cuff of the sphygmomanometer is inflated above the systolic blood pressure). Retrograde flows in the VA are characteristic and may be elicited over the V2 segment of the VA and more difficult at the level of the V3. With TCD the V4 segment and the BA may be approached, certifying the steal syndrome (basilar steal syndrome). In experienced hands even a laminar flow in the BA can be elicited with different directions of flow in the right and left sides of the BA. At TCD, the cerebellar arteries originating on the side with subclavian steal depict a post-stenotic pattern of flow.

The postoperative/post-endovascular treatment is routinely assessed by ultrasound. Ultrasound in the follow-up of patients represents a valuable tool (Figs. 5.21, 5.22, 5.23, 5.24, 5.25, 5.26, and 5.27). We usually recommend the first control at approximately 1 month after patient's discharge and afterward, on a biannual basis. The numerous types of arterial reconstruction can be readily checked and measured, including the CAS. Complications, technical failures, accelerated atherosclerotic process, and the development of plaques in untreated arterial segments are all readily diagnosed by ultrasound. Another important parameter in the evaluation of the results of the therapy is represented by the measurement of the IMT. We recommend guiding statin therapy by taking into account not solely the lipid profile but also considering the IMT.

The spontaneous contrast in the IJV (see Fig. 5.28 for details) may appear as an accidental finding or during the postoperative checkup. It is still difficult to assign a precise cause to the phenomenon or to indicate a particular treatment. Patients must be evaluated for a possible hypercoagulable state. The spontaneous IJV contrast may also appear in cases with a notable asymmetry of the two IJV.

Conclusive Remarks In contemporary medicine, it is highly advisable that clinicians train in and perform one imaging technique. Ultrasound appears more at hand as compared with angiography or CT (and does not require a radiological competence, including a longer training); ultrasound appears even more clinically related as compared with the alternative diagnostic modalities. Ultrasound can be performed on ambulatory basis too. However, as stated before, the clinician should ideally be a neurologist or cardiologist well trained and a *connoisseur* of the anatomy and clinical manifestations of the cerebrovascular diseases. Conversely, specialists dedicated to diagnostic imaging must be endowed with all the particulars regarding the clinical status of the patient; otherwise, the final image will be a standard one with least practical significance. As a consequence, a pertinent and continuous dialogue must be established between all the specialists who diagnose and treat cerebrovascular diseases.

In spite of the advantages offered by the versatility of the technique, the lower costs, the reduced space for lodging the ultrasound equipment and for patient examination, the echographical approach, and the final diagnosis are dependent, in a very high degree, on the operator. Not least, the operator should be looked upon as the member of a complex team of specialists approaching the patient with cerebrovascular diseases from different angles but focusing on a common target which is the best therapy with the best outcome.

Image Gallery

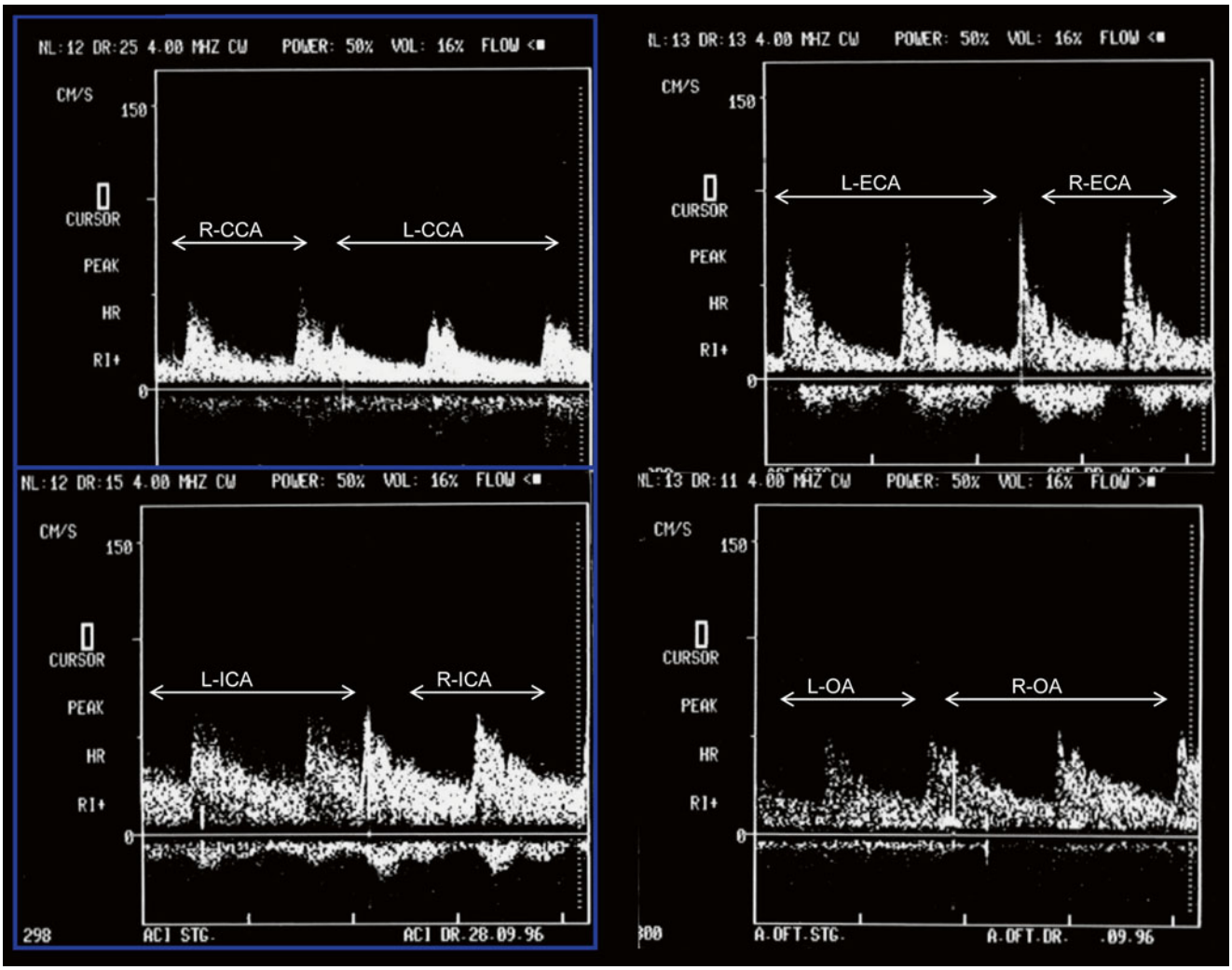

Fig. 5.1 Normal flow pattern – carotid artery. Laminar flow at the level of the carotid and ophthalmic arterial axis. Note the "ultrasonic window" at the level of the ICA (base of the spectral frequencies), reflecting a normal flow pattern. *CCA* common carotid artery, *ICA* internal carotid artery, *ECA* external carotid artery, *OA* ophthalmic artery, *L* left, *R* right

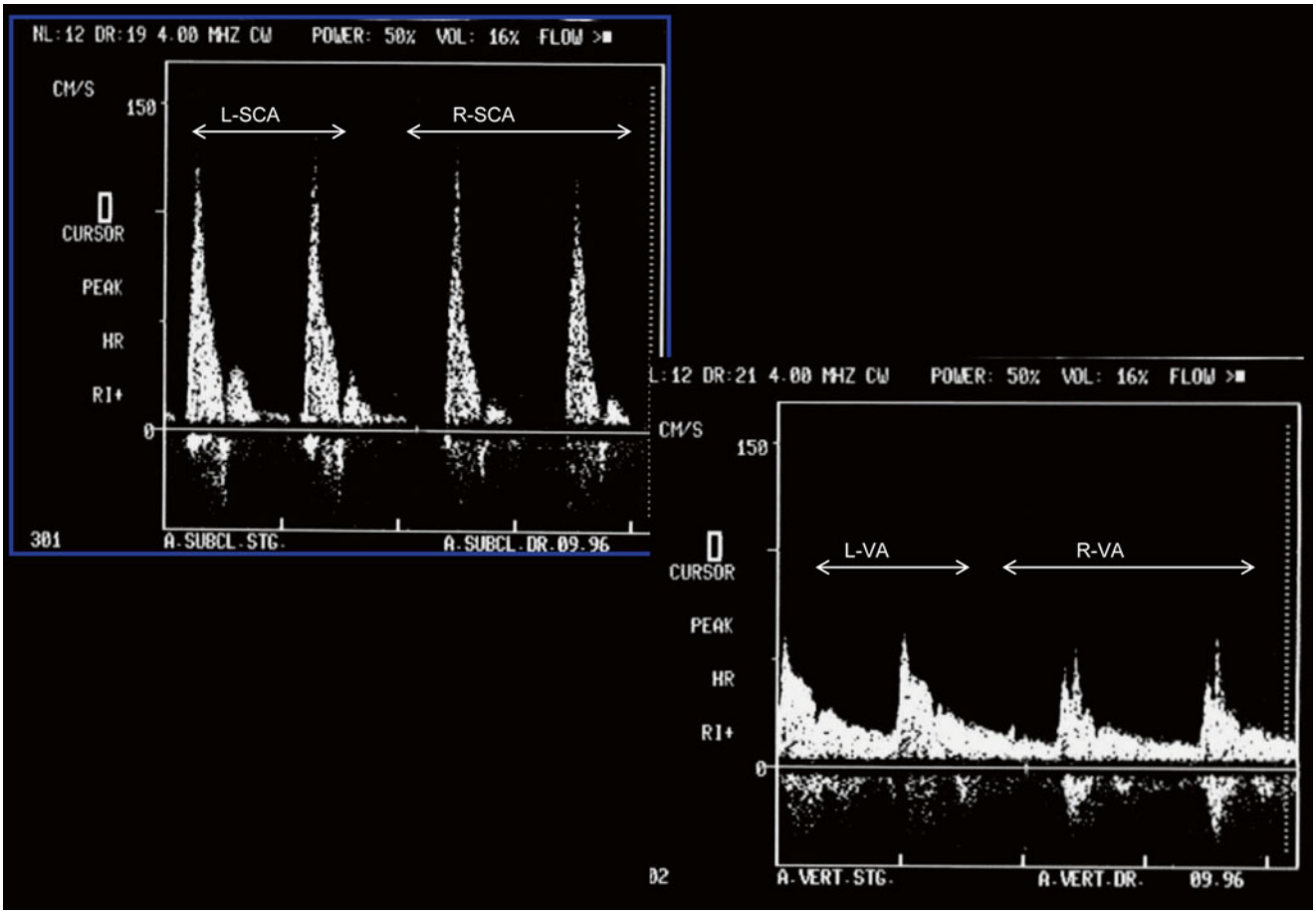

Fig. 5.2 Normal flow pattern – subclavian and vertebral arteries. The normal flow pattern in the subclavian artery (*SCA*) and vertebral artery (*VA*)

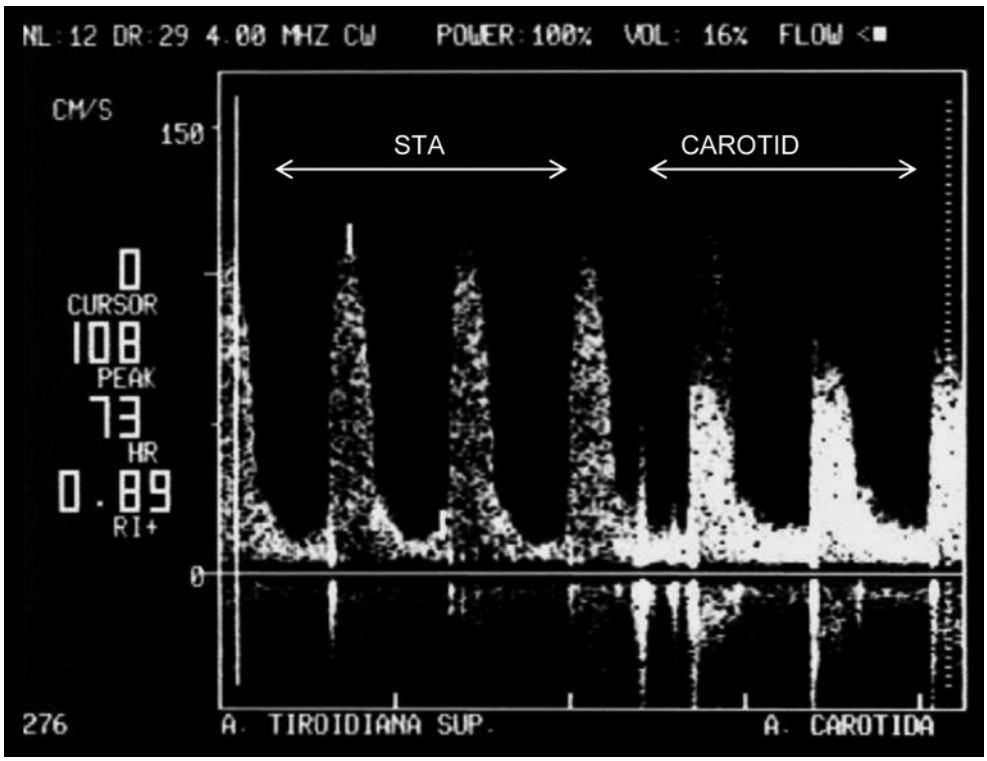

Fig. 5.3 Superior thyroid artery. Passage of the ultrasonic wave from the superior thyroid artery (STA) to the carotid. In many patients the laterocervical bruit originates in the STA. The STA serves as a good marker for the carotid bifurcation

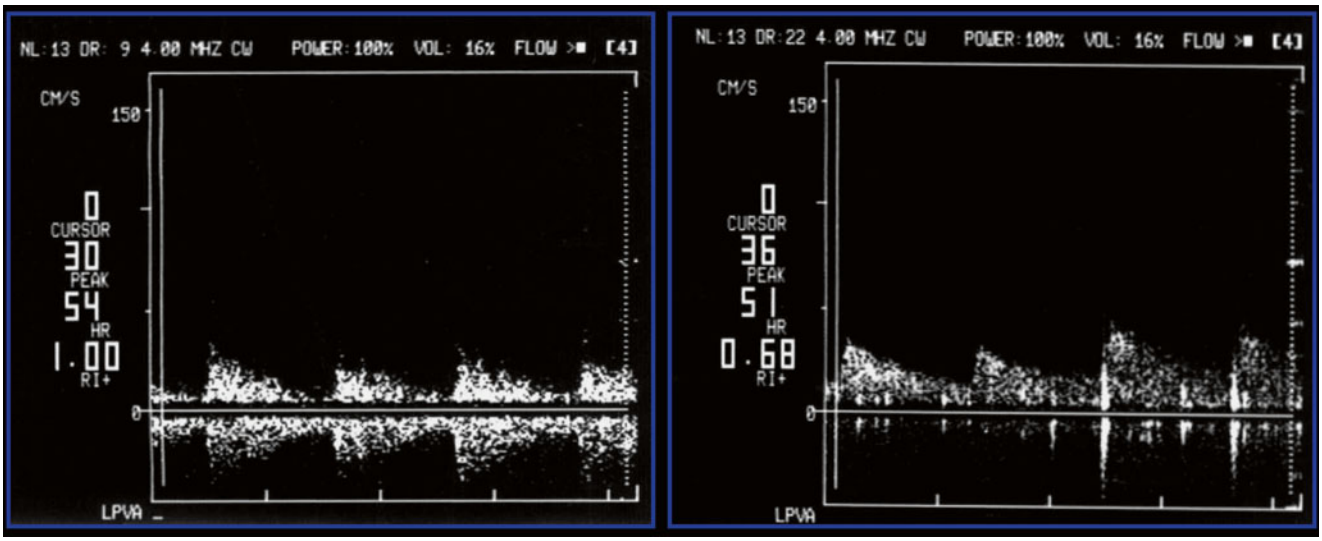

Fig. 5.4 V3 segment of the VA. The atlas loop appears with both a positive and negative signal pattern

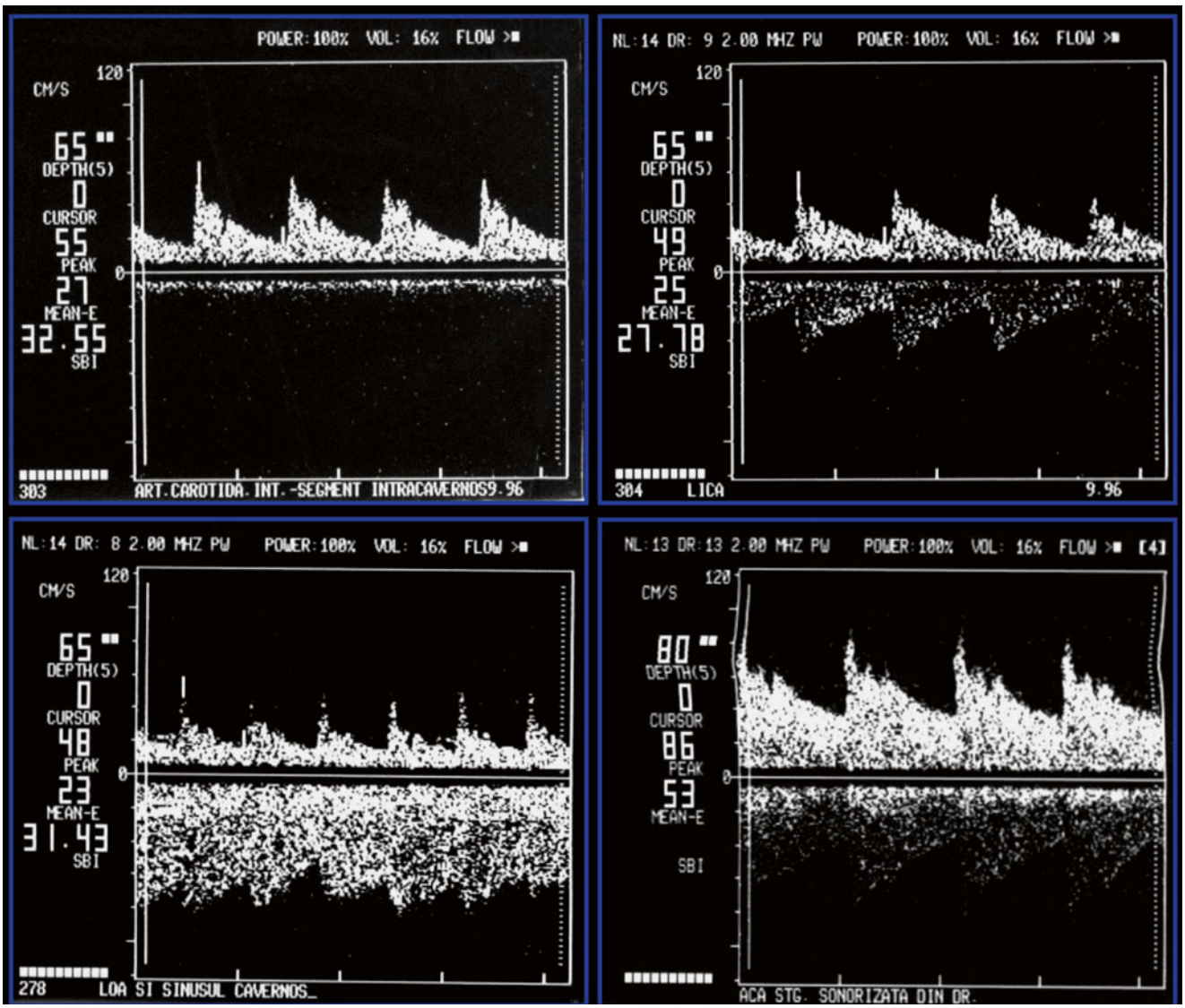

Fig. 5.5 TCD – ophthalmic window. Imaging of the intracerebral segments of the ICA. The intracavernous segment (depth 65 mm) appears positive while the supraclinoid segment, negative. The positive OA and the venous flow in the cavernous sinus are discernable at the same depth

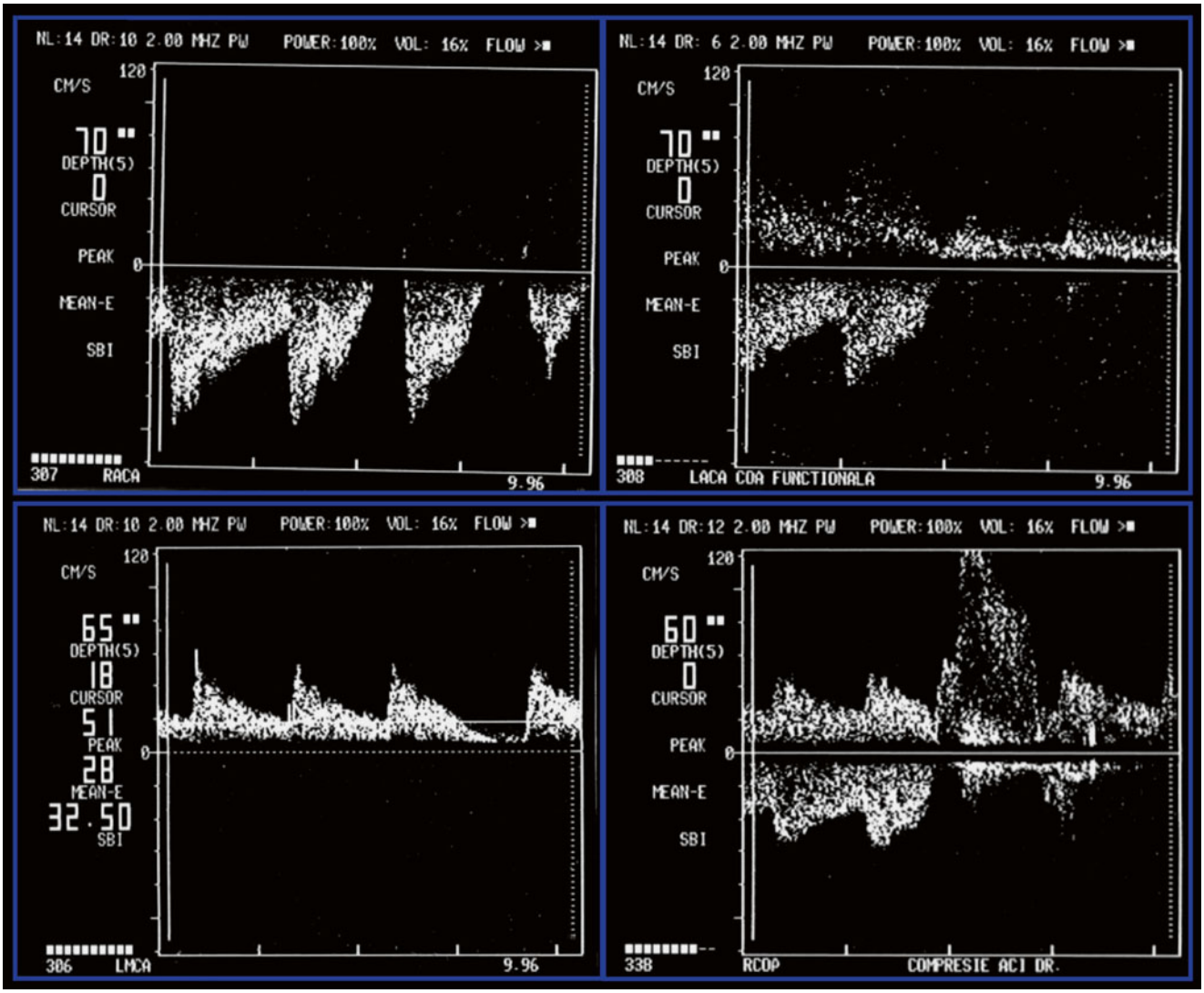

Fig. 5.6 TCD – temporal window. The A1 segment of the ACA appears at a depth of 70 mm (*upper left panel*) with a negative signal. Compression of the ipsilateral carotid (*upper right panel*) is followed by the disappearance of signal, reflecting a nonfunctional PCommA. The signal over the M1 segment of the left MCA (*lower left panel*) disappears with ipsilateral carotid compression, while the signal over the P1 segment of the PCA increases in amplitude, reflecting a patent and efficient PCommA on the same side (*lower right panel*)

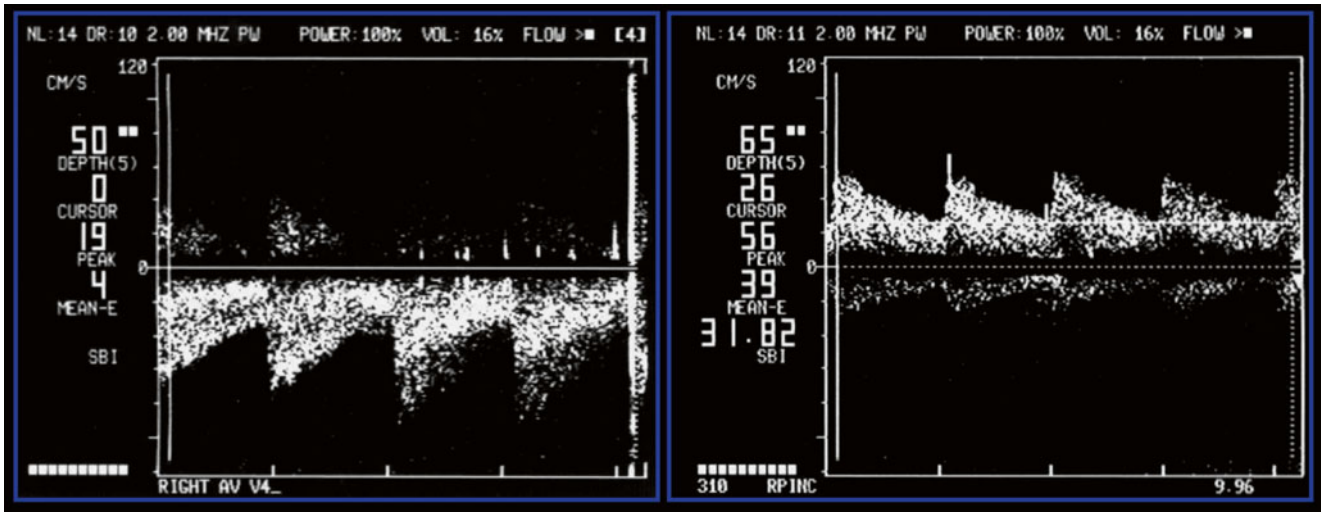

Fig. 5.7 TCD – occipital window. The V4 segment of the V4 can be imaged through the foramen magnum at a depth of 50–65 mm (negative signal, *left panel*). Increases in velocity in V4 after ipsilateral carotid compression reflect a patent and functional PCommA. The PICA can be individualized after orienting the probe slightly lateral, at a depth of 65 mm

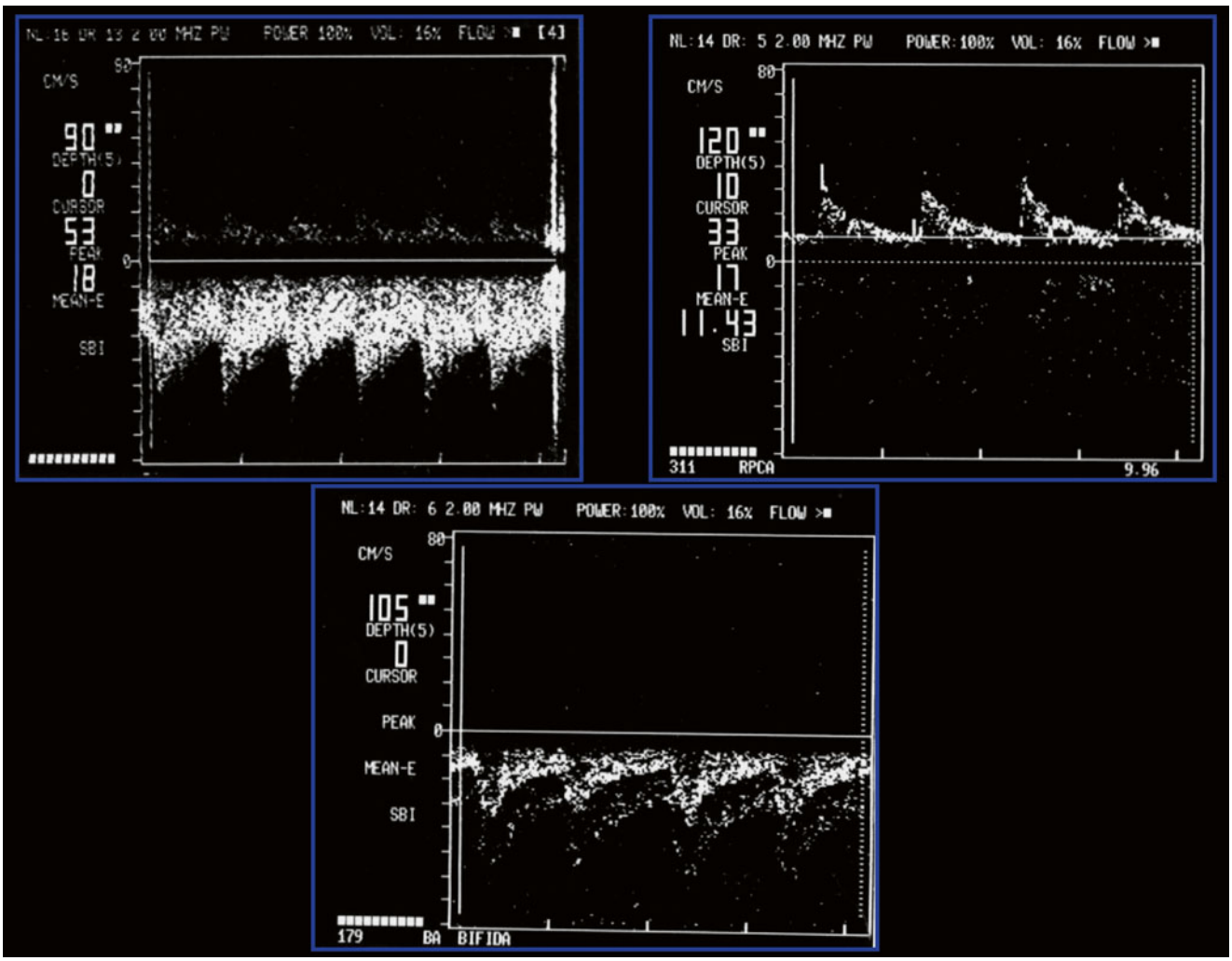

Fig. 5.8 TCD – the basilar artery. The BA appears with a negative signal at a depth of 75–120 mm (*upper left panel*). The positive signal is from one of the superior cerebellar arteries (*upper right panel*). The PCommA appears with a positive signal at a depth of 100–120 mm. The bifid BA represents a normal variation of this artery (*lower panel*)

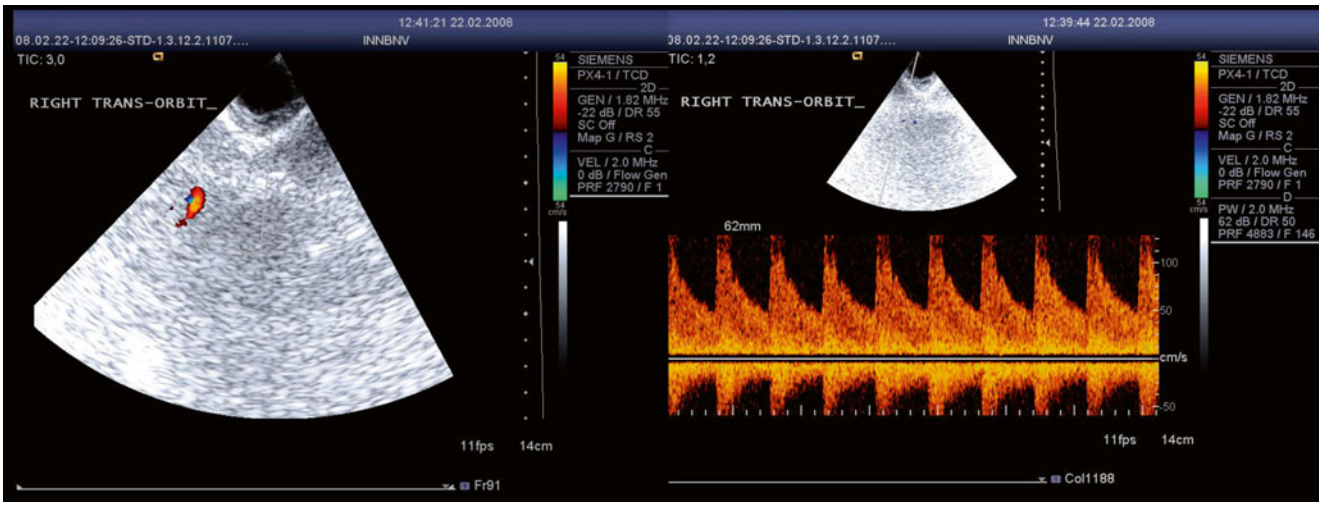

Fig. 5.9 Transcranial color-coded sonography (TCCS) – orbital window. The OA (*left panel*) can be imaged with a transocular approach (orbital window). Using the same approach, the carotid siphon is identified (*right panel*), with a positive signal (the intracavernous segment of the ICA) and with a negative one (the supraclinoid segment)

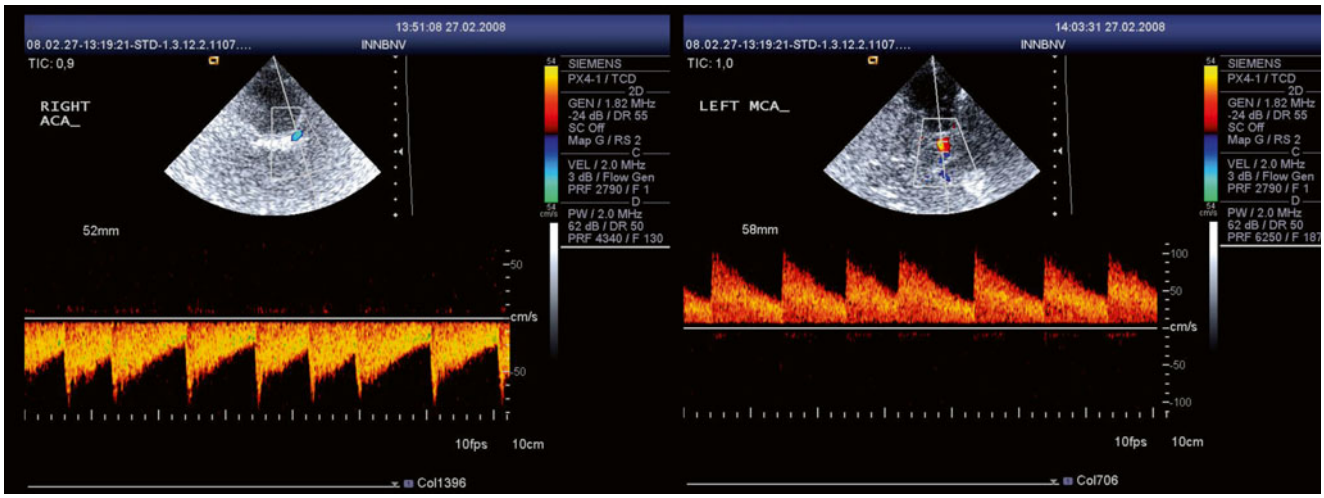

Fig. 5.10 TCCS – temporal window (1). The ACA appears in blue color and depicts a negative velocity signal (*left panel*), while the MCA appears in red color and with a positive signal (*right panel*)

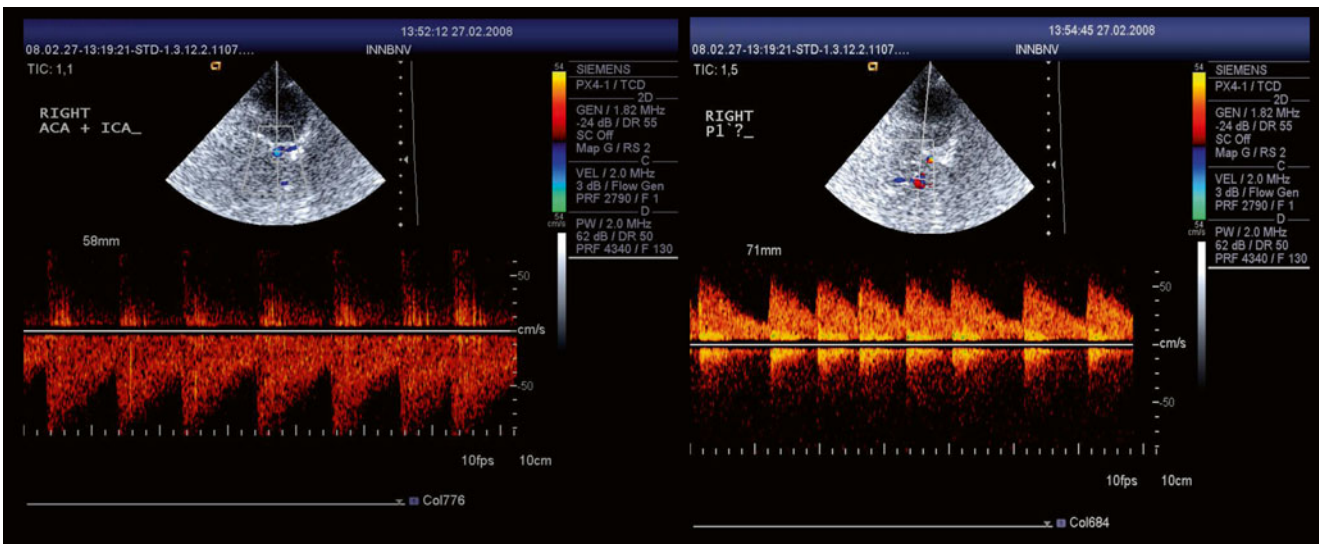

Fig. 5.11 TCCS – temporal window (2). The terminal part of the ICA appears with positive signal (*left panel*) and ACA at its origin (with a negative signal). Through the same window, the P1 segment of the PCA appears with a positive signal (*right*)

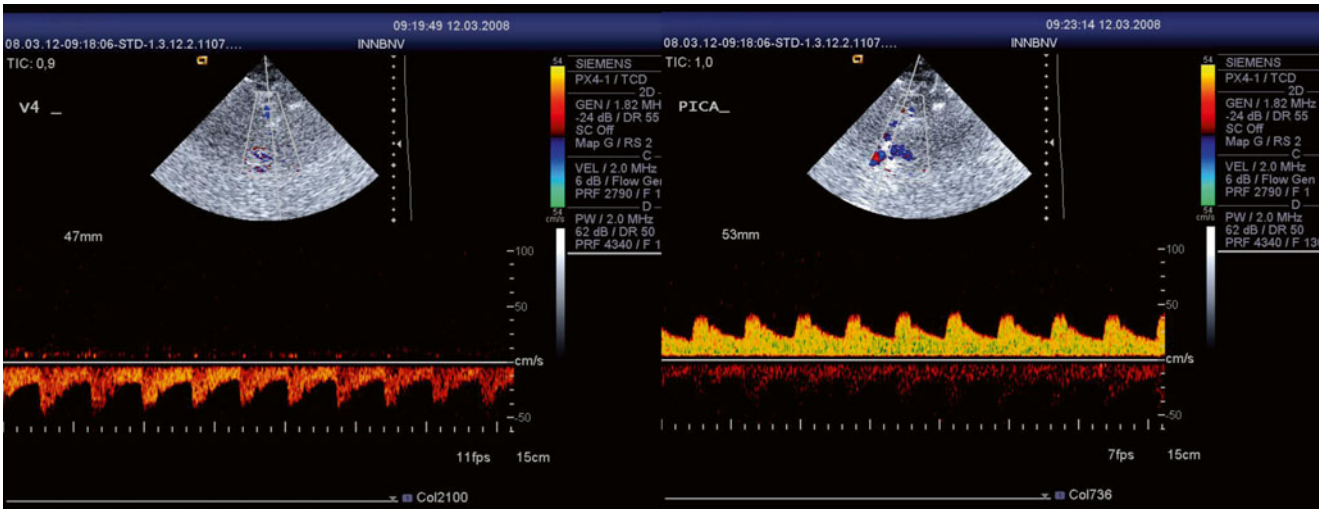

Fig. 5.12 TCCS – occipital window (1). The VA appears in blue color and negative signal (*left panel*); deeper, the PICA appears with a positive signal (*right*)

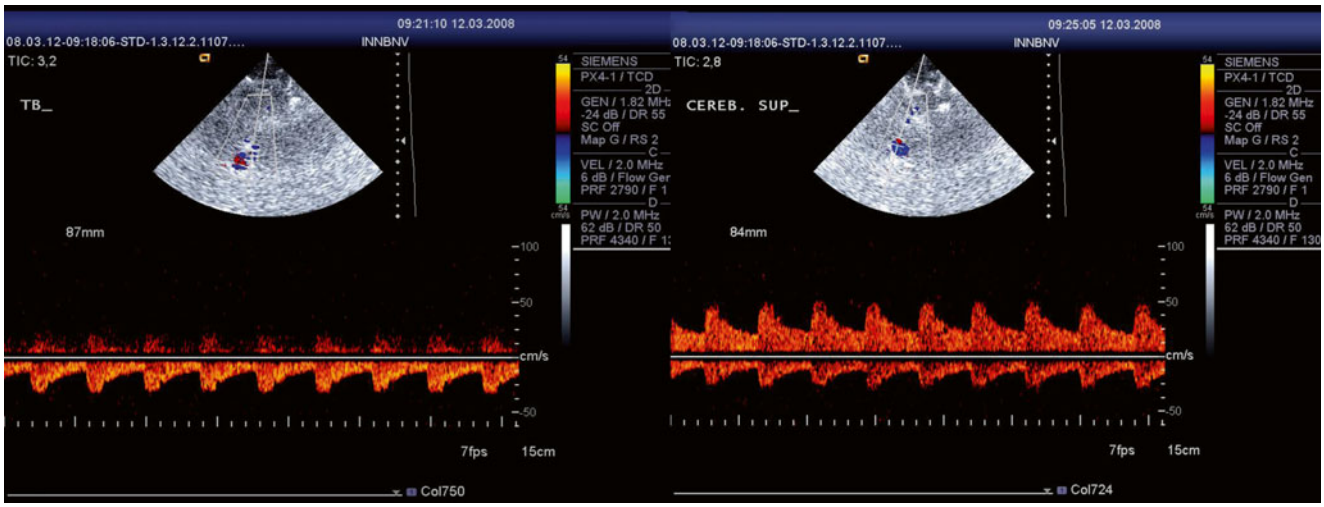

Fig. 5.13 TCCS – occipital window (2). The BA is visible at depths between 75 and 120 mm (*negative and blue color*). The SCA is visible at depths between 80 and 100 mm (*positive – right panel*)

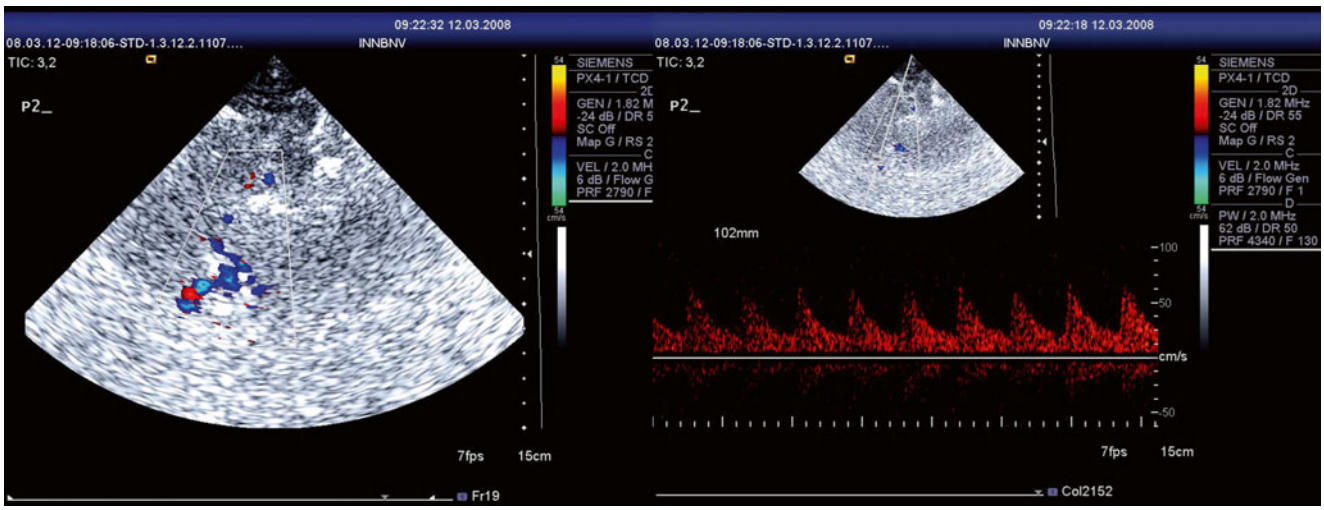

Fig. 5.14 TCCS – occipital window (3). The P2 segment of the PCA is visible at depths between 100 and 120 mm (*red color and positive*)

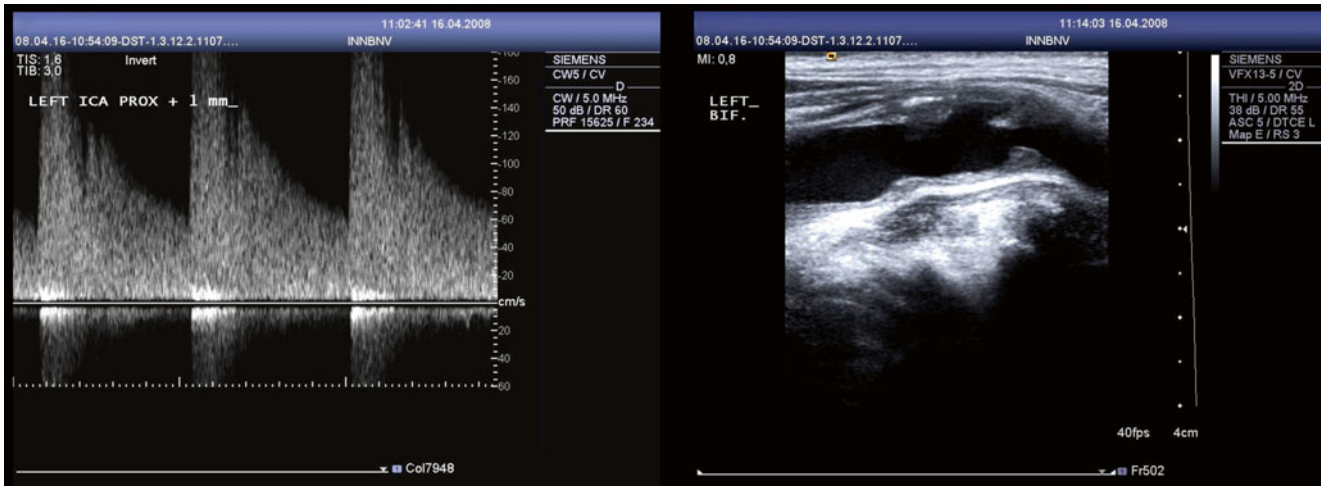

Fig. 5.15 Stenosis of the carotid artery (1). ECD with spectral analysis: high-grade stenosis (75–90 %) of the ICA at origin (*left panel*) and imaging of the stenotic area (*right panel*)

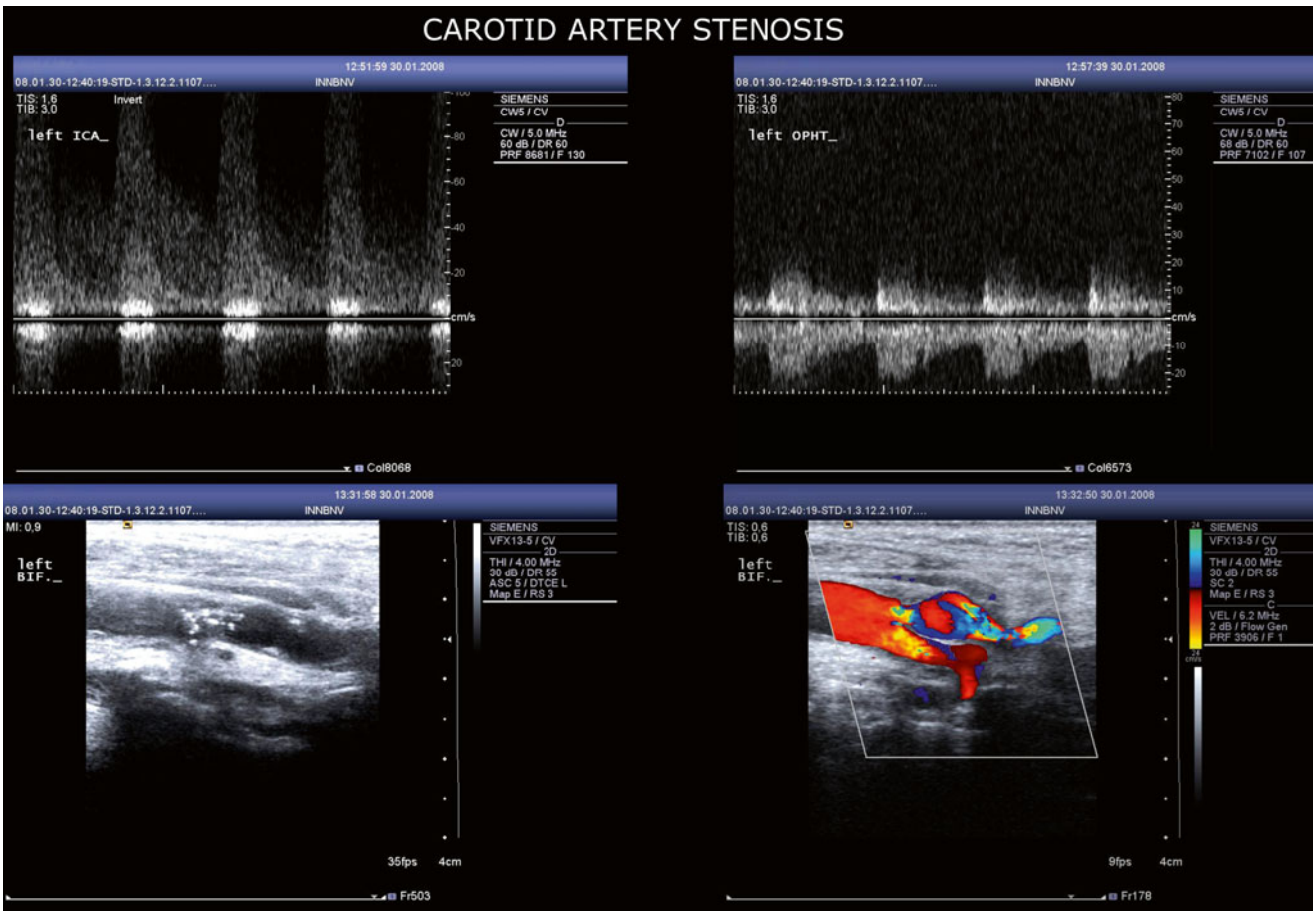

Fig. 5.16 Stenosis of the carotid artery (2). Higher-grade carotid stenosis (>90 %) with flow inversion in the OA (*upper panels*). Aspect of the plaque and flow, in the same patient (*lower panels*)

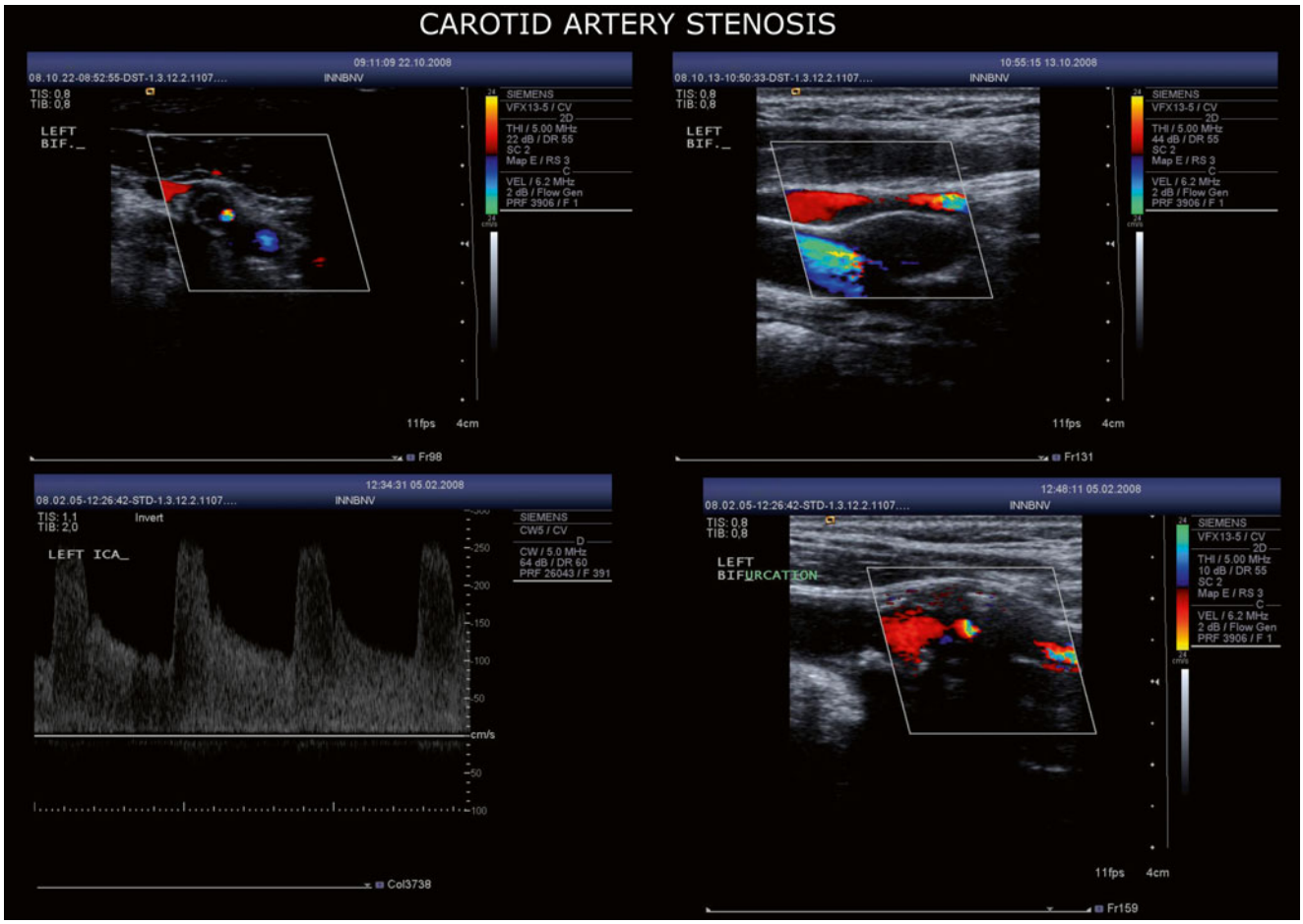

Fig. 5.17 Stenosis of the carotid artery (3). Color-coded image of the ICA at origin, transversal section (*upper left panel*). The narrow residual lumen appears (at 3 o'clock) in red-blue color (reflecting a highly turbulent flow). A high-degree stenosis produced by a homogenous, hypoechogenic, and voluminous plaque (*right upper panel*). Milder stenosis (grades III–IV) produced by an irregular, nonhomogenous, and predominantly hypoechogenic plaque (turbulences at the surface of the plaque; *lower panels*)

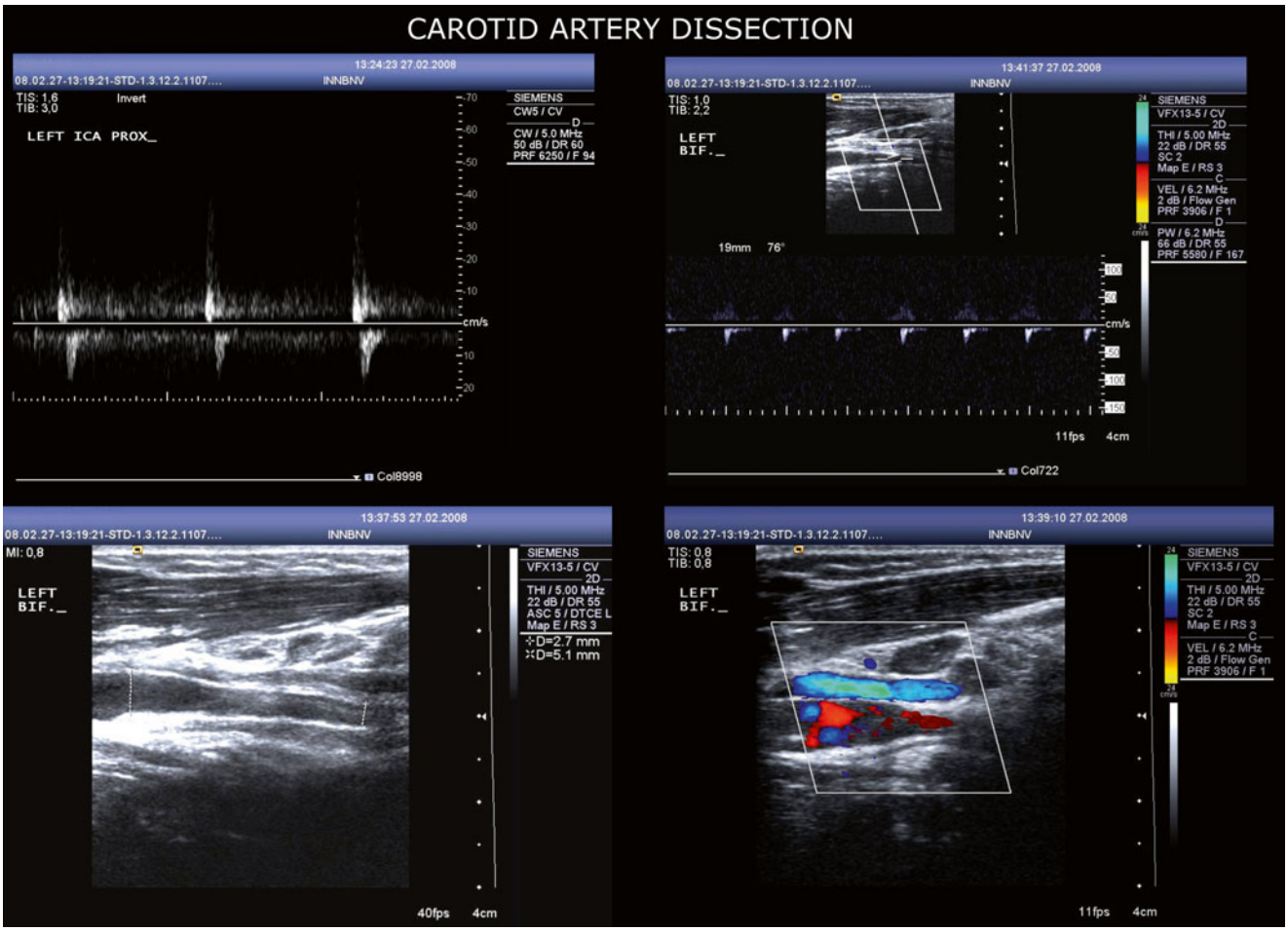

Fig. 5.18 Carotid dissection (A) and Carotid dissection (B). ECD with spectral analysis and Duplex demonstrate stump flow at the level of the carotid bulb (*upper panels*). Echography (*black and white*) demonstrates the hypoechogenic thrombus in the ICA (*lower left panel*) and with color-coded echo, the disappearance of flow distal to the bulb (*lower right panel*)

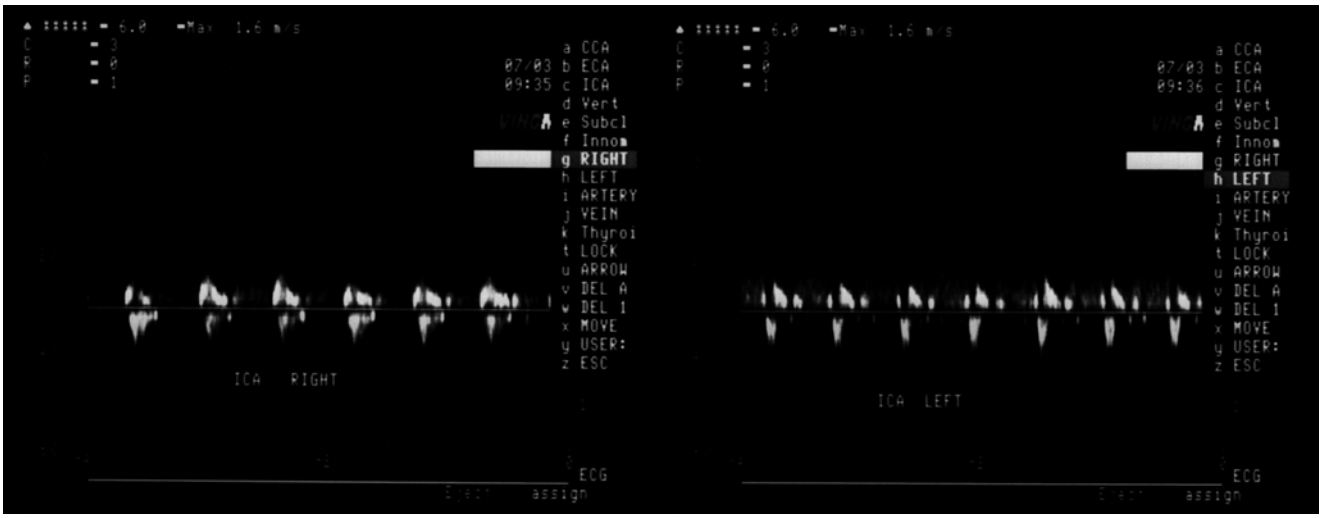

Fig. 5.19 Carotid artery dissection (2). Spontaneous bilateral dissection of the ICA: ECD examination demonstrating stump flow

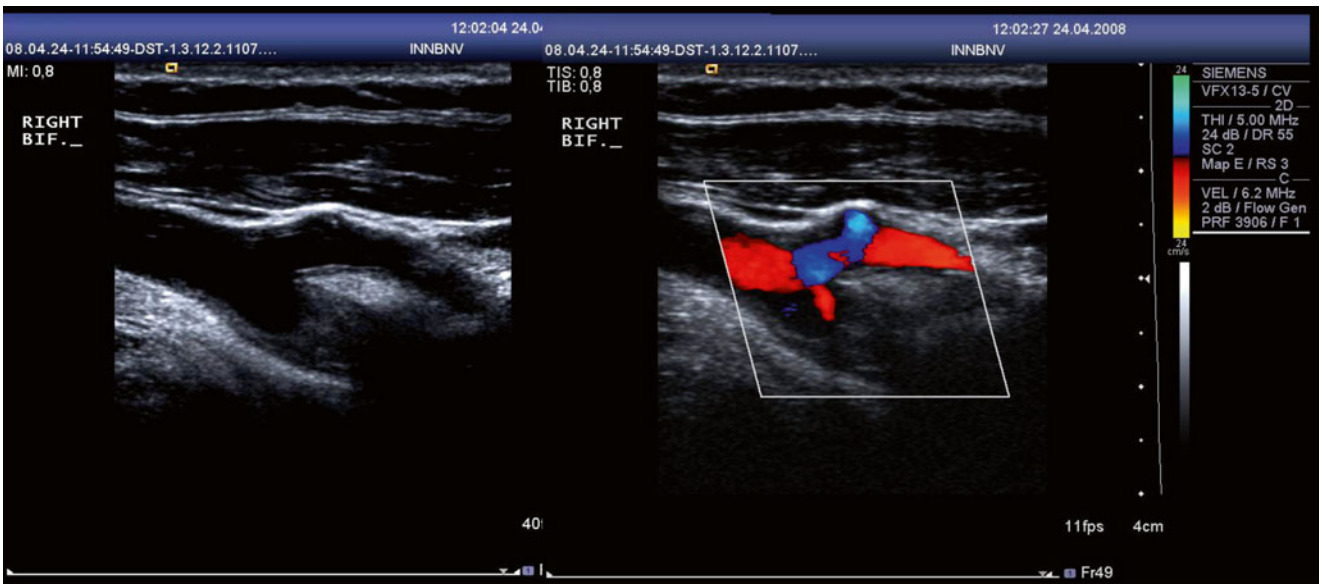

Fig. 5.20 Transposition (inversion) of the carotid bifurcation. This variation can be readily demonstrated with ICA placed medially and the ECA laterally. Note that in this patient, the ICA is thrombosed (absent flow – *right panel*)

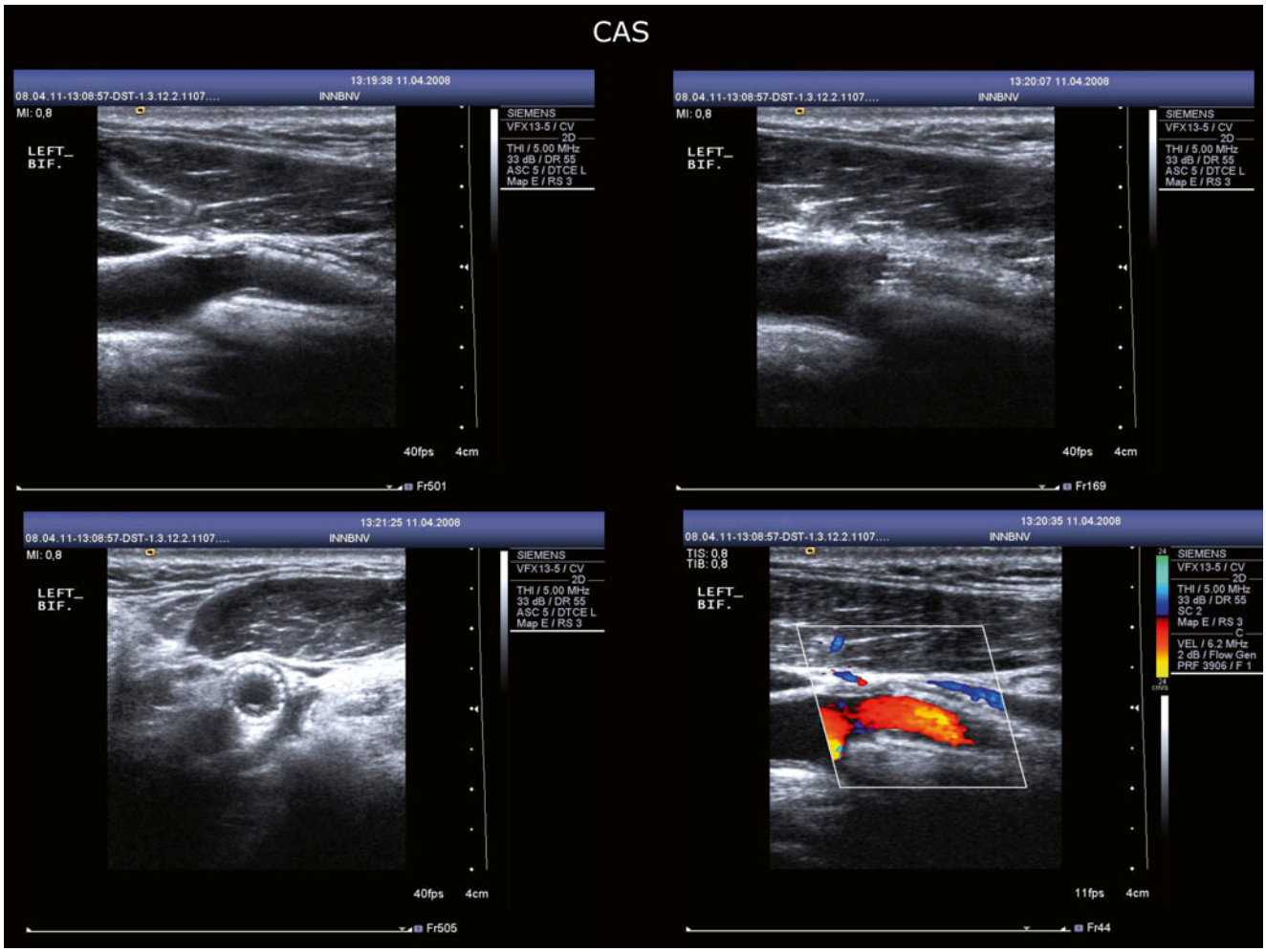

Fig. 5.21 CAS. Echotomographic aspect of the stented ICA and of the carotid bifurcation, seen longitudinally (*upper panels*) and transversally (*left lower panel*). The flow in the ICA appears normalized (*right lower panel*)

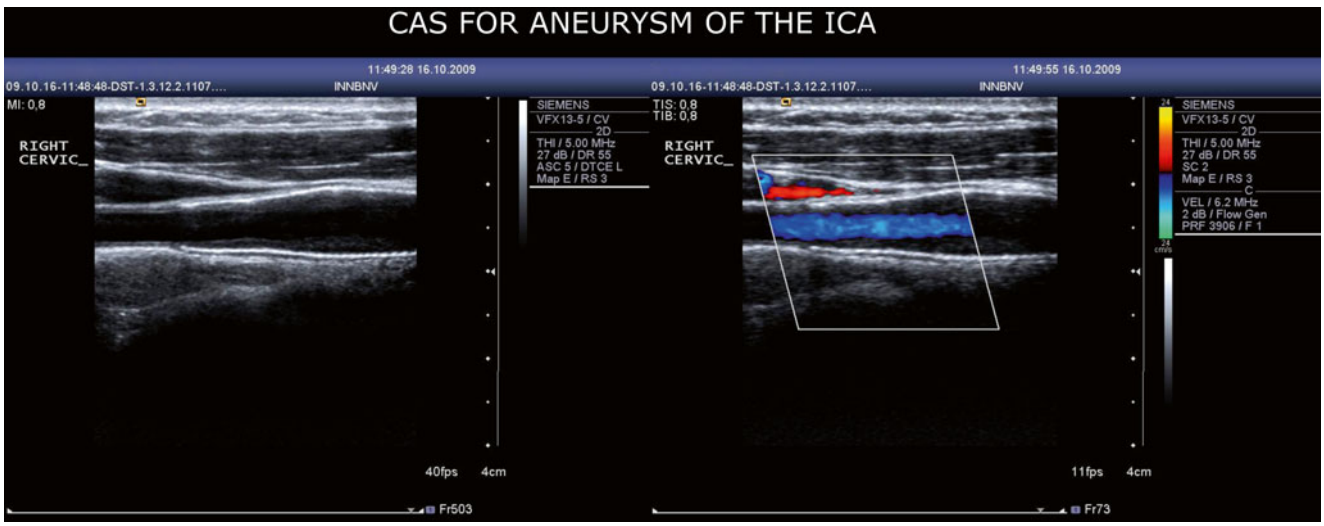

Fig. 5.22 Aneurysm of the ICA – endovascular repair (1). A black and white (*left panel*) and color (*right panel*) imaging of an internal carotid artery stenting (after ICA traumatic dissection). Normal flow pattern

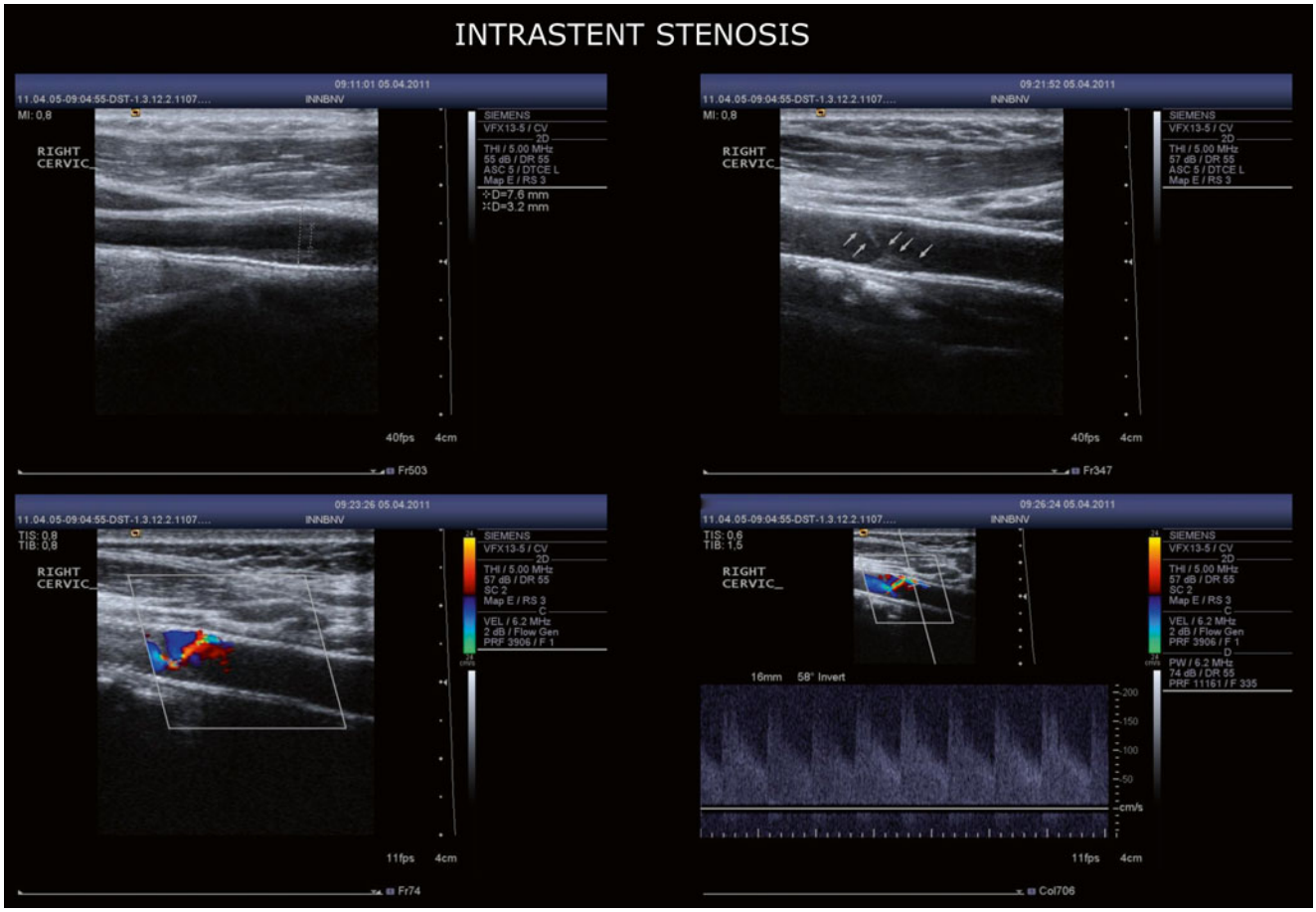

Fig. 5.23 Intrastent stenosis. The same patient as in Fig. 5.22 at 1-year checkup. There is an intrastent stenosis; the hypoechogenic thrombus is well visible (*upper panels*). Restriction of flow and stenosis measurement (*lower panels*): the degree of stenosis amounting at approximately 50–60 %

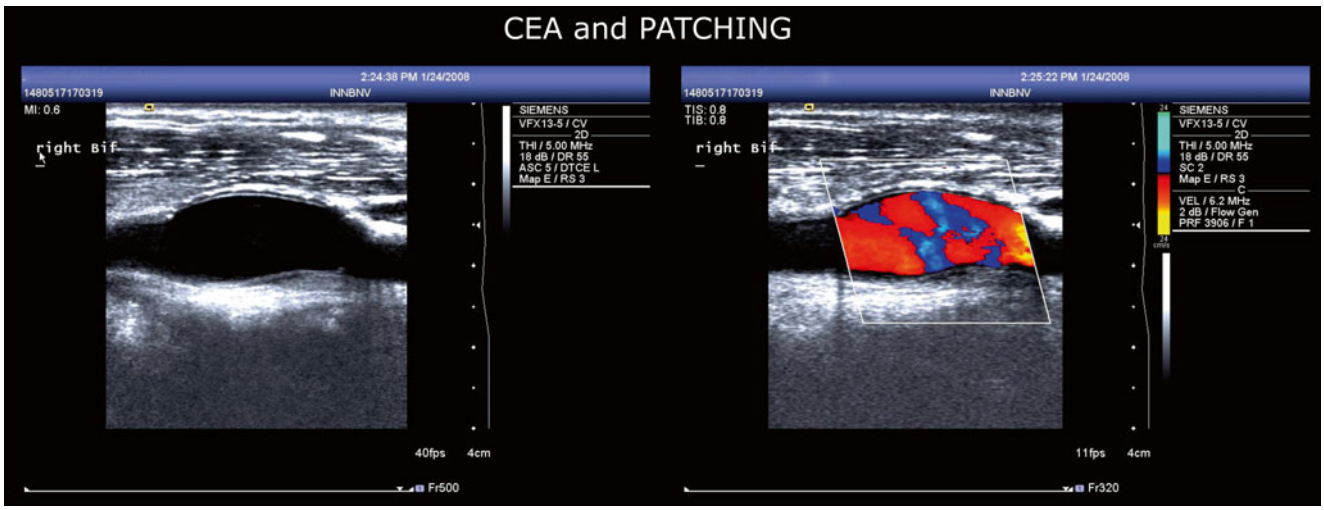

Fig. 5.24 CEA and patching. The aspect of the carotid bifurcation after CEA and insertion of a synthetic patch

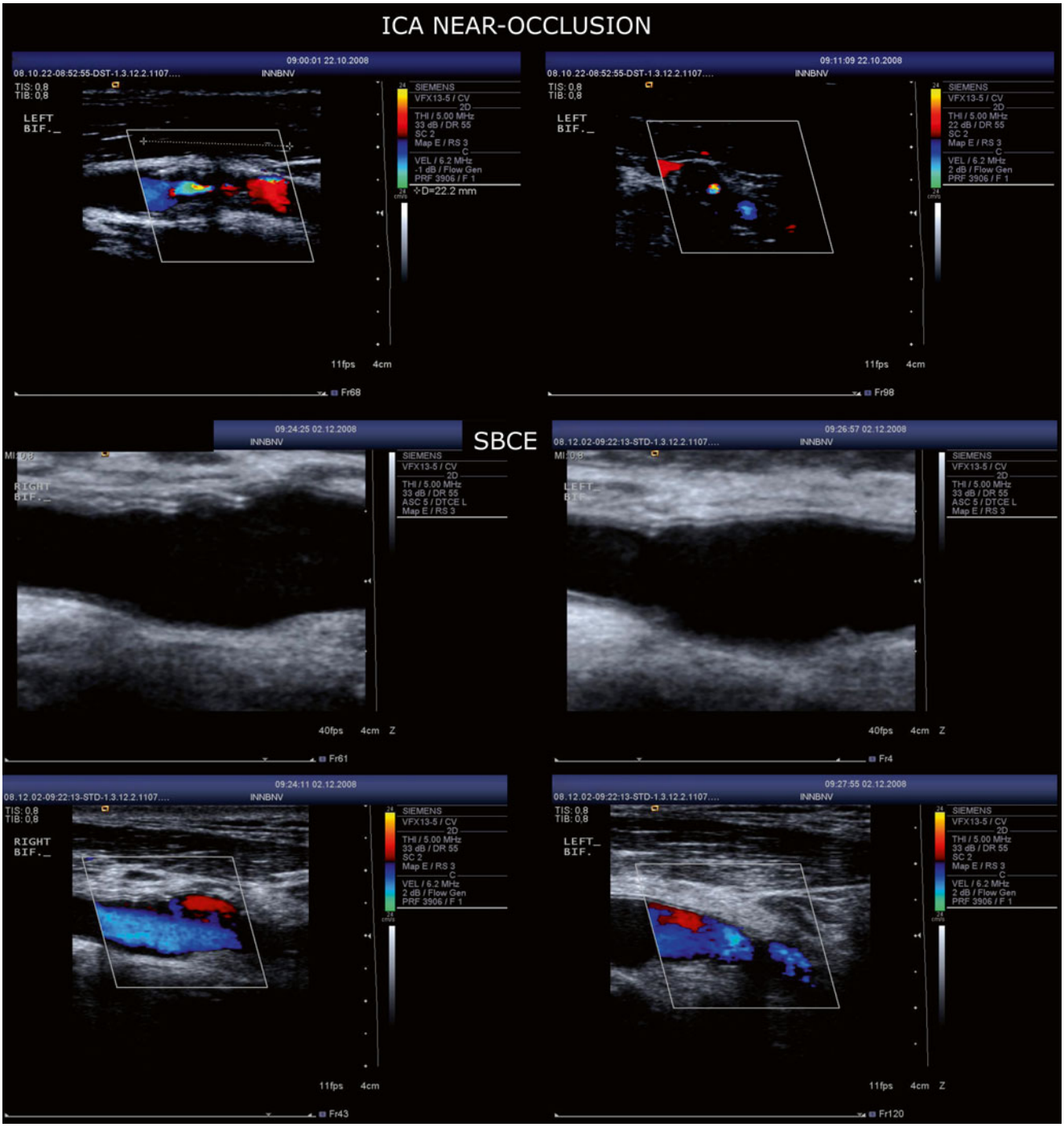

Fig. 5.25 SBCE. Panel (**a**): echographic aspect of a severely stenosed carotid bifurcation in a patient demonstrating the same type of lesion on the opposite side also. The patient underwent SBCE. Panel (**b**): the result of SBCE. Both carotid bifurcations are enlarged with synthetic patches. Flow is normalized. Note the slight folding of the patch (*upper left panel*) but with no consequences on flow

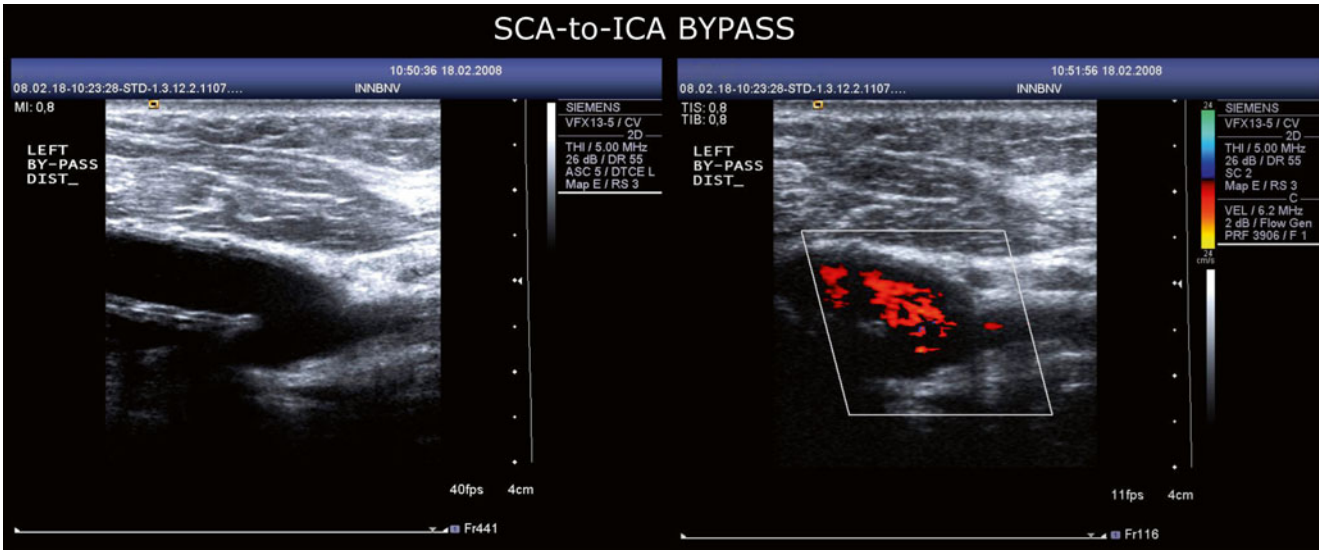

Fig. 5.26 Control of bypasses in the superior aortic system (1). SCA-to-ICA bypass by using a PTFE graft. This patient had occlusion of the CCA on the left side. The carotid bifurcation and the ICA were patent (patency was maintained through retrograde flow in the ECA from the numerous collaterals in the neck). The graft was inserted between the SCA and the carotid bifurcation (it is still patent after 7 years) and is tunneled under the SCM

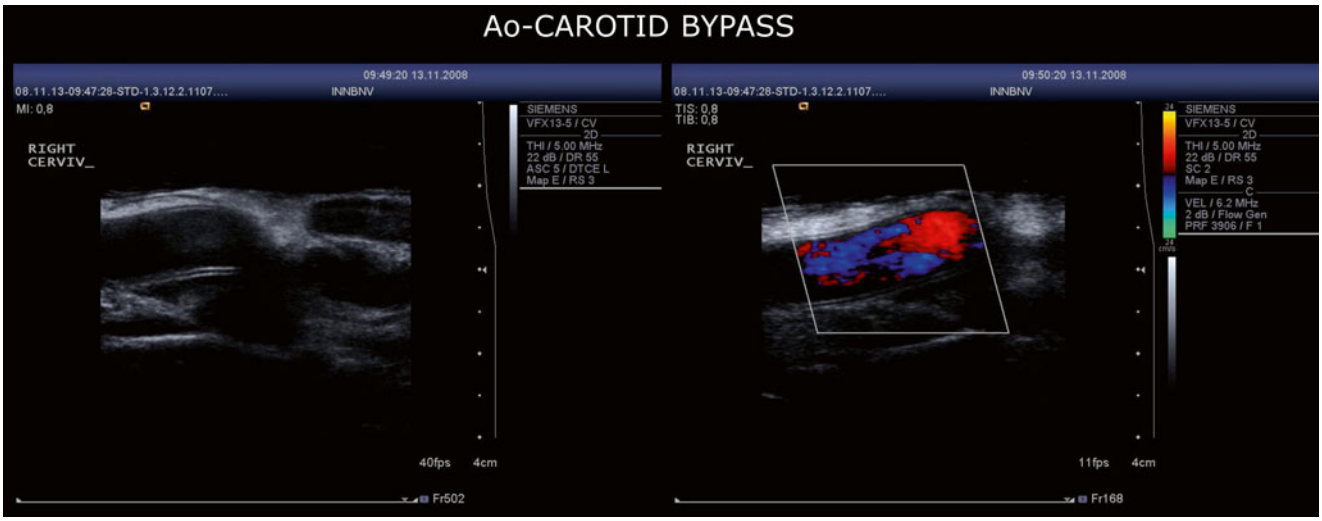

Fig. 5.27 Control of bypasses in the superior aortic system (2). The superior limb of an ascending aorta-to-right carotid artery bypass (as performed for aortic arch syndrome). In this case, the right CCA was occluded. The bypass comprised a common trunk of the graft and two or more branches, reaching the supraaortic trunks. In case of concomitant lesions at the level of the carotid bifurcation, CEA is concomitantly performed (see Chap. 14)

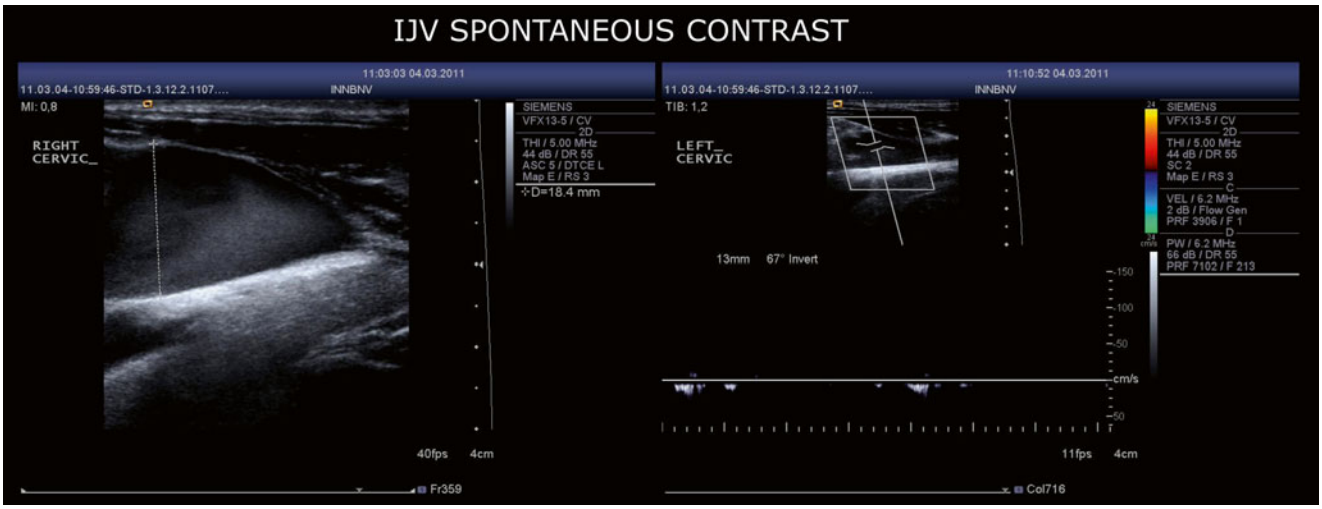

Fig. 5.28 Spontaneous contrast in the IJV. Faint hypodensities resembling a moving cloud are sometimes noticed in the lumen of the IJV. On transversal sections these appear as concentric waves with a center-to-periphery development. At times, these hypodense shapes depict a flow in opposite direction toward the head. The spontaneous contrast is encountered postoperatively (possible after excessive traction of the IJV), after placement of a central venous catheter and in hypercoagulable states. The phenomenon may also appear in patients with TIAs or minor ischemic events. The low flow in the IJV was confirmed at MRA. No obstructive venous lesions are encountered in these cases, and this may reflect a predisposition for a hypercoagulable state (although this was not certified by coagulation tests). Should these patients be put on oral anticoagulant medication still remains an open question. In some cases, the same spontaneous contrast was noticed at the level of CCAs with a heavier atherosclerotic load, after CEA of the bifurcation. This raises again the question of performing or not more extended endarterectomies over the CCA also (even in cases with CCAs that show only diffuse atherosclerotic lesions with no critical stenosis)

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Endovascular Approach: From Diagnosis to Therapy

6

Horia Muresian and Bodgan Dorobat

In cardiovascular medicine, angiography, while included among the diagnostic procedures, is continuously reappraised and compared with other techniques and, not least, criticized for its invasive potential regarding the need for direct arterial access, administration of contrast agent, and the radiation dose applied to the patient. Although initially considered as "the golden standard" for imaging carotid and vertebral artery lesions, a more recent inconsideration of the method developed when compared to complementary techniques allegedly more innocuous or less invasive and which may offer comparable diagnostic data.

From the pure diagnostic point of view, angiography however has particular advantages and conveys unparalleled information. Furthermore, the therapeutic potential is mostly overlooked. It is worthwhile underscoring the fact that angiography is generally performed in larger centers where the possibility of applying endovascular procedures and the surgical backup does normally exist. Trained interventionalists and surgical teams usually complete the background of the angiography laboratory. This holds true especially in cardiovascular medicine and particularly for cerebrovascular disease, where the both endovascular and surgical treatments should be readily available and, most often, complete each other. As a consequence, this chapter will display and endorse the particular role and advantage of *a technique that should be perceived in its entirety*.

Angiography consents the evaluation of the entire cerebral arterial system: carotid and vertebral extra- and intracranial circulation and of the remainder superior aortic system. Particulars on the direction of flow, velocity of flow, collateral circulation, and parenchymal distribution complete the pure arterial mapping. Venous circulation can be also optimally visualized. Complex atherosclerotic lesions and characteristics of the plaque are adequately imaged particularly tandem stenoses, ulcerated plaques, and thrombus formation on plaque. An accurate evaluation of the intracerebral arterial disease is of utmost importance as this will select a category of patients who will benefit from CEA: patients with moderate carotid stenosis and intracranial arterial disease [1]. Eccentric plaques may not be precisely and rigorously evaluated especially if only standard projections are employed. Plaque morphology evaluation does not represent a main characteristic of angiography with the exception of ulcerated and calcified plaques. Whenever required, an angiographic imaging of the coronary circulation, renal arteries, and inferior aortic system can be also performed. Generally speaking, a patient undergoing angiographic interrogation has a complete and precise vascular assessment in a relative short period of time and in a single session. Digital subtraction angiography (DSA) has enabled reduction of the dosage of contrast agent along with the use of smaller-caliber catheters and has shortened the duration of the examination.

The main limits of angiographic diagnosis include its invasive nature (arterial puncture, contrast agent, radiation), costs, and periprocedural morbidity and mortality (hematoma at puncture site, arterial dissection, distal embolism in the cerebral circulation, and stroke; death). The risk is proportional with age and comorbidities: diabetes, arterial hypertension, renal failure, cerebrovascular disease, and peripheral artery disease. Patients under dual antiplatelet therapy or triple antithrombotic therapy are at particular risk for the development of rapidly extensive hematoma from the puncture site. Subclinical or silent cerebral embolism after angiography may occur with a higher frequency than expected [2] most probably from the manipulation of diseased arteries or from inadvertently passed air, in spite of rigorous preventive measures. The best imaging is obtained by selective catheterization of each main vessel; in patients with more severe and extensive lesions of the supra-aortic

H. Muresian (✉)
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

B. Dorobat
Interventional Radiology Laboratory, The University Hospital of Bucharest, Bucharest, Romania
e-mail: bdorobat@gmail.com

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arteries, the hazard of cerebral embolism is consequently far greater. Not least, the selective catheterization of the neck vessels is best achieved from the femoral route; in patients with aorto-iliac disease, the angiographic imaging resulting from accessing the brachial route may result unsatisfactory.

In the context of no-nil risk, angiography will remain a second-choice diagnostic tool in asymptomatic patients and in patients in whom no surgical or endovascular therapy is contemplated. In these patients, ultrasound examination is followed by either angio-CT or MRA if there is suspected disease at more proximal level (origin of CCA, aortic arch). Even in severe multivessel disease (carotid and vertebral artery disease, subclavian arteries, vertebral steal syndrome, etc.), valid information can be obtained by using noninvasive methods (a detailed diagnostic workup also appears questionable in asymptomatic patients, and some authors prefer performing only a periodic follow-up by ultrasound). Angiography remains to be indicated in symptomatic patients and in patients who will theoretically undergo endovascular or surgical repair or when non-atherosclerotic disease is suspected (vasculitis, dissection). CT and MRI also have the additional advantage of imaging the cerebral parenchyma and are more indicated in patients with recent stroke. Detection of silent or multiple small brain infarcts may change the therapeutical strategy, and CT and MRI have particular advantages over angiography in these cases.

Angiography appears to be superior to other diagnostic tests in detecting near occlusion of the ICA – an important detail for further therapeutic planning, as total occlusion of the ICA contraindicates any revascularization maneuver. On the other hand, the accuracy of noninvasive methods appears to be reduced in diagnosing carotid stenoses between 50 and 69 % (as compared with stenoses of higher degree); in this respect, angiography may select a particular category of patients in whom a complete mapping of the cerebral circulation may be beneficial for stroke prevention (patients with concomitant intracranial stenotic lesions). Angiography allows the clear distinction between near occlusion of the ICA and occlusion of the same but with a patent ascending pharyngeal artery simulating on ultrasound interrogation a near-occluded ICA (the ascending pharyngeal artery having a deep cervical course similar to that of the ICA toward the cranial base). Longstanding stenoses of the ICA at origin may complicate with hypoplasia of the distal (intracranial) ICA and with the development of collateral circulation from the contralateral carotid and/or from the vertebrobasilar system. In these cases, revascularization has little (if any) effect and the therapeutic indication can be adjudicated with angiography.

Angiography is not routinely used as a screening test or as initial diagnostic tool. Patients are generally selected following the clinical examination and the ultrasound interrogation. Bypassing angiography before surgery requires that noninvasive tests be highly specific as well as sensitive [3]. Combining ultrasound and MRA may obviate the need for angiography but only when the two diagnostic methods do agree [4, 5]. (The particular indications of each of the remainder diagnostic methods are presented in Chaps. 5 and 7).

As mentioned before, the evaluation of flow represents an important feature of angiographic evaluation. The direction of flow (e.g., the presence of inverted flow in one of the VAs), the velocity, and, not least, the direction of flow in collateral vessels are all details easily and quickly obtainable with angiography (as compared with other diagnostic techniques). The significance of a carotid stenosis can be readily appreciated when the ACA and MCA are filling from the opposite ICA. The same applies when arteries pertaining to the anterior circulation are filled from the posterior circulation through the PCommA.

Angiography allows a speedier evaluation of technical failures after CAS or CEA and the prompt treatment of these. Distal stenosis, spasm of the ICA, distal embolization, thrombus developing at the origin of the ICA, distortion of the carotid bifurcation after CAS of CEA, intimal flaps (plus/minus more distal dissection), and so forth are all amendable by the endovascular route after completion angiogram.

Longer, tandem, serial, or atypical arterial stenoses (e.g., spur-like; stenosis and adjacent ulceration) are difficult to appreciate by echo, CT-angio, or MRA and especially regarding the hemodynamic impact of the lesions, considered both singularly and in conjunction. An important question arises however at this point: "what is the real hemodynamic impact of serial carotid stenoses or do these become critical under certain conditions?" Two comparisons are offered by the coronary circulation and by the arterial circulation in the lower legs: with augmented demand (as under stress or effort), sequential stenoses may have similar hemodynamic impact as a singular high-degree lesion leading to angina or claudication. Should this apply in the cerebral circulation, it will select a category of patients who could benefit from CEA.

Lesions at the level of the CCA may build up additional hemodynamic burden over those at the origin of the ICA, but some other aspects merit a more detailed discussion. The CCA may appear more diffusely diseased in some instances with plaques that do not appear as "hemodynamically significant" but which will limit clamping either due to calcifications or due to their unstable nature. Not least, the evolving potential of such lesions is difficult to envisage. Occlusion of the CCA may occur postoperatively at some time, leading either to total occlusion of the CCA and ICA or only to a limited occlusion of the CCA up to the level of the bifurcation (the ICA remaining still patent while fed through the ECA). Angiographic evaluation can assist in determining which patients could benefit from a more extensive surgery. In our experience, we carefully examine the CCAs both angiographically and intraoperatively; a safe clamping is obtained by a more extensive exposure of the CCA and by

choosing a disease-free segment of the CCA. If multiple and especially "unstable, vulnerable, soft, or ulcerated" plaques are encountered, the CCA is treated also either by performing an enlarged CEA and patching or by segmental excision of the CCA and replacement with a vascular graft (Fig. 6.1). Alternatively, the carotid bifurcation is treated surgically and the lesion(s) on the CCA is stented (Fig. 6.2).

Another advantage of angiography resides in *the evaluation of the disease in the ECA* (Fig. 6.3). Carotid plaques frequently extend into the ECA for variable distances. The atheroma in the ECA is generally pulled out during CEA. More severe or more extended lesions in the ECA cannot however be removed safely in this manner, and occlusion of the ECA may supervene after CEA; thrombosis may either propagate or embolize into the ICA. Advanced disease involving the ECA can be identified during the routine preoperative angiographic evaluation and, thereupon, efficiently treated by endarterectomy extended into the ECA, double patching, etc.

Angiographic interrogation may also select patients with occluded ICAs who will benefit from either *CAS or CEA of the ECA*. The assessment of the origin, divisions, and anastomoses of the ECA branches with the intracranial ICA will best predict in which patients the mentioned procedure is profitable. So far, no other diagnostic technique appears superior to angiography in this respect. Computational fluid dynamics will undoubtedly deliver important and clinically useful data in the future [6–8].

Particular lesions are also best evaluated and quantified with the aid of angiography: *coexistence of aneurysm and stenosis* of the cervical ICA ± kinking. The 3-D reconstruction of the complex lesion brings unparalleled details of surgical relevance (Fig. 6.4).

Angiography allows also the best appraisal of flow in the revascularized vertebral artery (VA reimplantation into the CCA), including the intracerebral distribution and direction of flow (Fig. 6.5).

Completion angiogram remains a rapid and most valuable method of detecting and treating suspected problems and complications presenting after the operation. The results of the technique applied can be readily verified and quantified with the aid of intraoperative ultrasound Doppler probes: flow measurements, presence of inadvertent turbulences, intimal flaps, residual or recently formed thrombi, and such protocols should ideally follow any carotid operation. When Doppler examination is either not available or in cases with suspected failures or imperfection of the surgical construction and/or distal embolization into the cerebral circulation, the urgent angiographic examination is mandatory. Selective catheterization of the carotid artery and multiple projections are deployed. Extra- and intracranial circulations are visualized. Whenever the case, patients are selected for redo surgery or CAS. Cerebral vasodilators (e.g., nimodipine) are administered if cerebral vasospasm is evidenced or in cases with multiple distal embolisms (Fig. 6.6).

Angiography probably diagnoses best and speediest, certain *anatomical variations of the arch vessels*. In our surgical experience, we operated on three patients with ARSA (aberrant right subclavian artery, with retroesophageal course), to correct the anomaly associated with aneurysmatic dilatation, voluminous Kommerell diverticulum, or esophageal compression (Fig. 6.7). The aortic origin of the left VA (the most common variation of origin of the VA) must be accurately diagnosed, differentiating this condition from the occlusion of the VA. Atypical clinical symptoms may also appear in relation with anatomical variations of the supra-aortic arteries and are best revealed through angiography [9].

Various patterns of *vertebral steal syndrome* are best evidenced with the aid of angiography including the atypical situations with occluded V0 and V1 (and even V2) segments of the VA but with important steal through collateral circulation (Fig. 6.8).

Some particular situations will be presented, in order to underscore the significant role of endovascular diagnosis and therapy.

Mega-dolicho internal carotid artery (Fig. 6.9). The first case illustrated is that of a 22-year-old male patient with aneurysma-like dilatations of the ICA with intervening arterial segments of almost normal caliber. It is interesting to note the fact that the disease was unilateral and with normal vertebrobasilar system also. The ICA distal to the lesions was successfully obliterated. The second case (Fig. 6.10) comprised kinking, stenoses, and dilatations of the cervical segment of the ICA, and the entire diseased portion was stented (with three stents).

Thrombosis of the ICA origin developing on otherwise normally appearing arterial wall and no history of trauma, either unilateral or involving both ICA origins. No particular risk factors were present, except smoking and hypercholesterolemia. The two cases serve as sound paradigms also, as one patient was treated by endovascular thromboaspiration (Fig. 6.11), while the other was referred to surgery (Fig. 6.12) – see figure legend for details. The recanalization can be obtained by either balloon angioplasty, mechanical clot disruption and thrombolysis, endovascular microsnare device, the whirling roto-rooter clot maceration (X-ciser), EPAR (endovascular photoacoustic recanalization) laser device, or self-expanding Nitinol capture baskets.

Excessive kinking of the CCA or ICA is not an absolute contraindication for performing the CAS. Angio-CT and MRA cannot offer the dynamic image of the carotid bifurcation and even less details about the feasibility of passing the sheath beyond the loops of the CCA (Fig. 6.13).

Late *restenosis after CEA* is generally diagnosed by ultrasound, subsequently confirmed, and treated by angiography and CAS. However, early suspicion of restenosis or technical

failure of CEA (or whatever surgical technique used) is best evaluated by angiography and expeditiously treated (Fig. 6.14).

Aneurysm of the cervical ICA can be conveniently treated by endograft insertion and exclusion of the aneurysm. This represents a good alternative to conventional surgery (Fig. 6.15).

Concomitant ICA stenosis (extra- and intracranial) plus intracranial aneurysm can be treated in a single procedure: CAS and aneurysm embolization (Fig. 6.16).

One of the major advantages of angiographic examination is *diagnosing near occlusion of the ICA* and differentiating it from total occlusion, with eventual recuperation of the carotid system. In the example shown in Fig. 6.16, the general aspect was that of ICA occlusion. The patient had a symptomatic aneurysm of the MCA and angiography revealed an almost occluded ICA on the same side.

Revascularization of the ECA in patients with bilateral occlusion of the ICA (Fig. 6.17). This procedure can be performed either by endovascular route or surgically (the surgical approach is presented in Chap. 13). These patients are symptomatic (dizziness, unstable gait, pre-syncope and syncope, and so forth), either with previous strokes or not. Angiography probably offers the best details regarding the total occlusion of the ICA, the status of the VAs (and possible lesions in the vertebrobasilar system), the intracerebral hemodynamics, and, not least, the status of collateral circulation between the extra- and intracranial vessels. Such data are best correlated with transcranial Doppler examination (as this later technique is used for patient follow-up also). The side with less collateral flow is selected first.

Speediest and precise diagnosis of critical clinical conditions represents another major, unparalleled attribute of angiography. We are illustrating here the case of a 28-year-old female patient with SAH, in whom 4-vessel angiogram (arterial, parenchymal, and venous phases) was negative: no intracerebral aneurysm or any other type of vascular malformation was found (Fig. 6.18). A quick angiographic evaluation of the *spinal* vascularization revealed the presence of vascular malformation as the cause of SAH.

Image Gallery

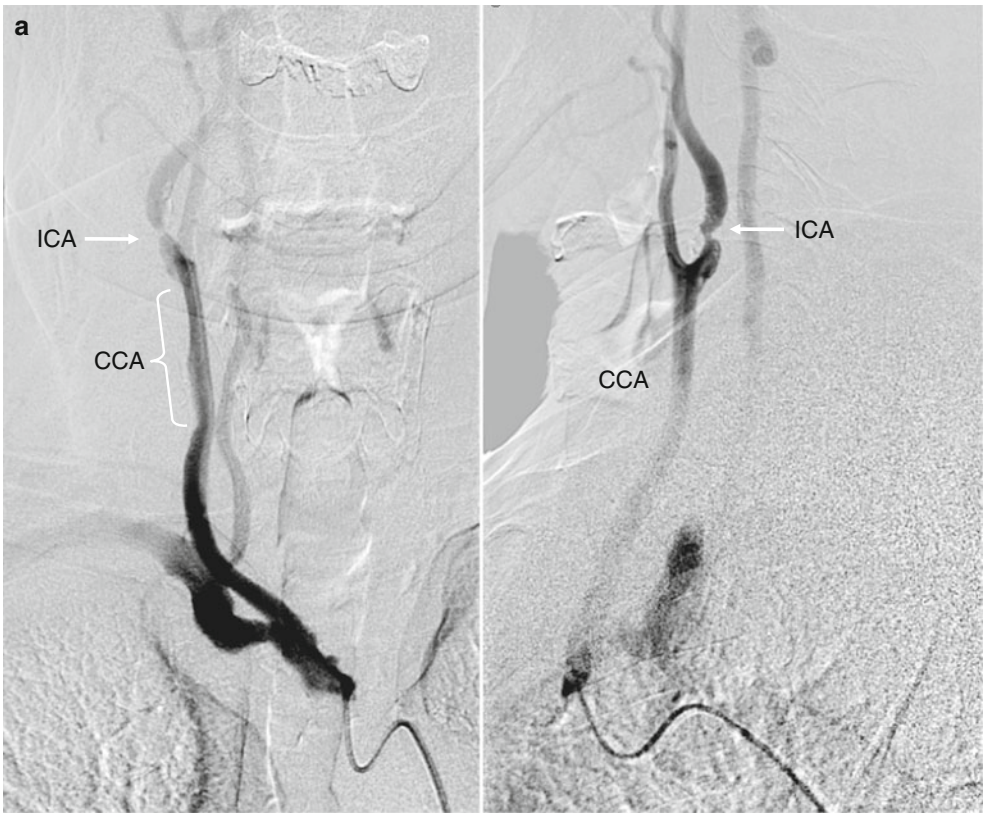


Fig. 6.1 Treatment of lesions at the level of the CCA – surgery. Atherosclerotic lesion of the CCA can present and become significant, in various modes. On the one hand, stenosis can appear significant or serial stenoses can add their hemodynamic impact; on the other hand, plaques on the CCA can be ulcerated or with a conspicuous lipid core. Not infrequently, both conditions may associate. Panel (**a**): angiographic aspect of stenosis of the ICA and of the CCA. Note the tight, severe lesion on the ICA and the lengthier stenosis of the CCA. Panel (**b**): an intraoperative demonstration of the significance of such lesions of the CCA. In this particular case, a wider exposure of the CCA, ICA, and ECA was performed. Panel (**c**): because of the extensive and severe lesions of the almost entire right CCA, a resection of the vessel was performed, followed by graft (G) interposition. Panel (**d**): macroscopic aspect of the excised arterial segments. From the ICA, the plaque was excised by using the eversion technique. The ICA plaque and the segment of the CCA excised were both sliced, to demonstrate the extension and the severity of the lesions

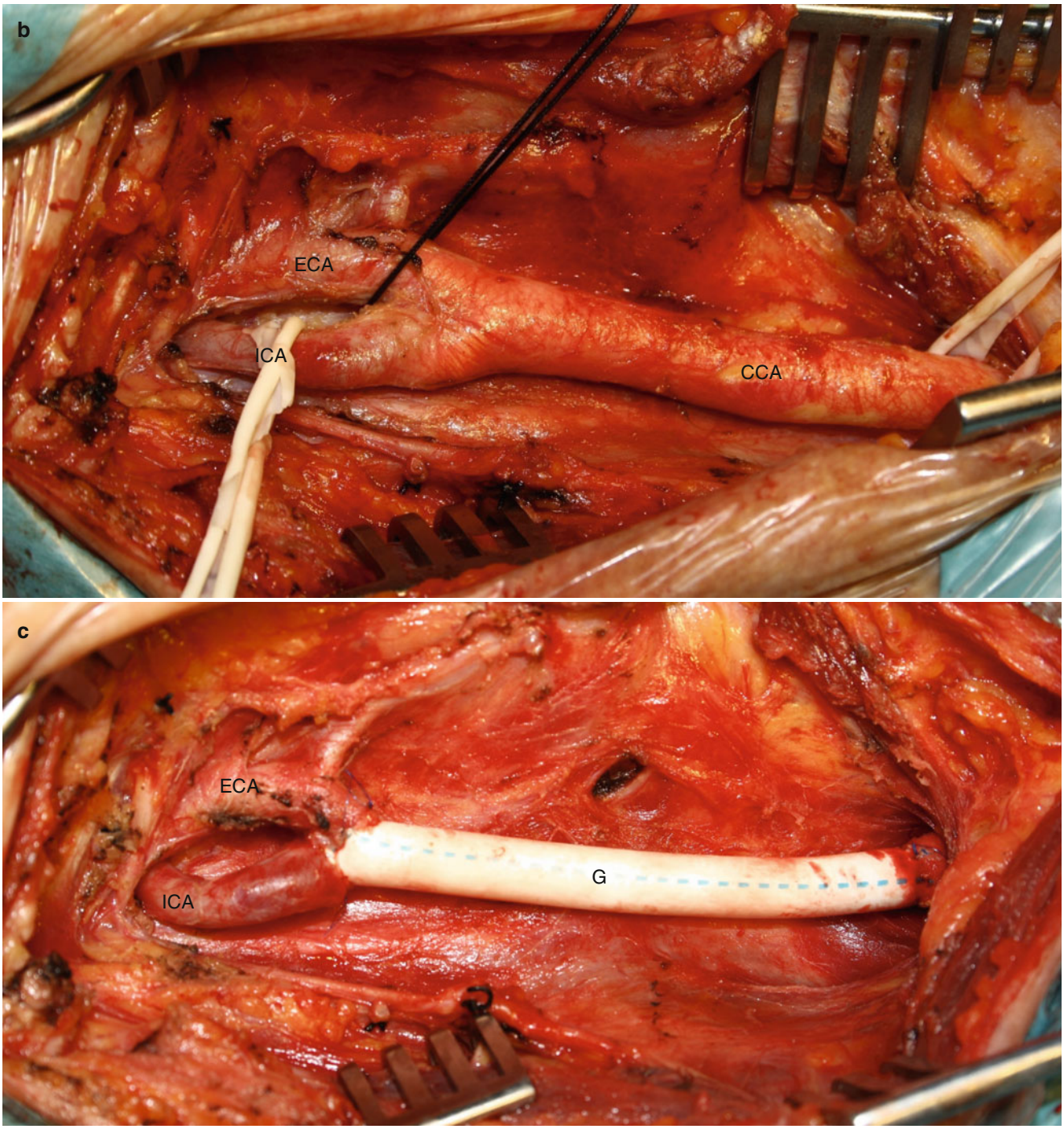
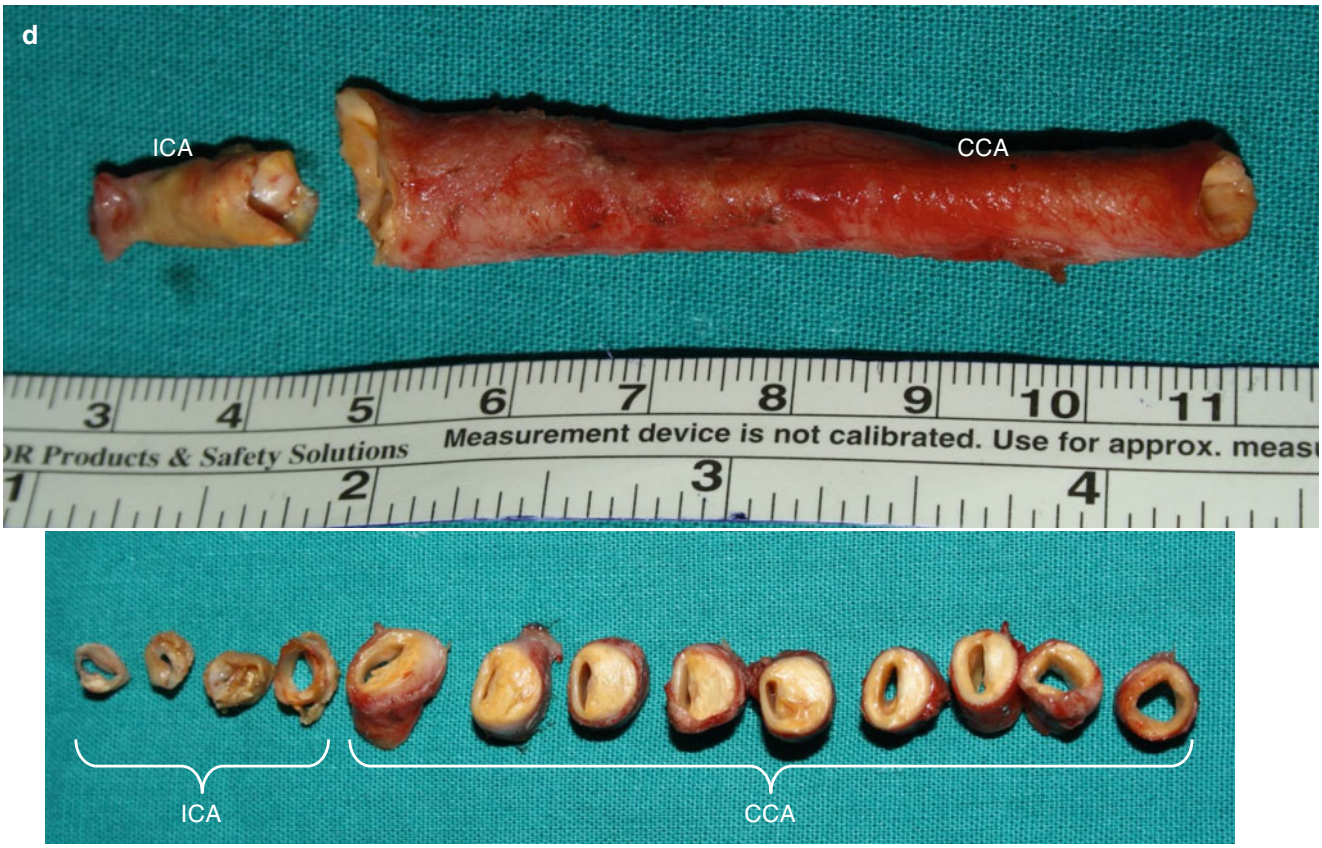


Fig. 6.1 (continued)



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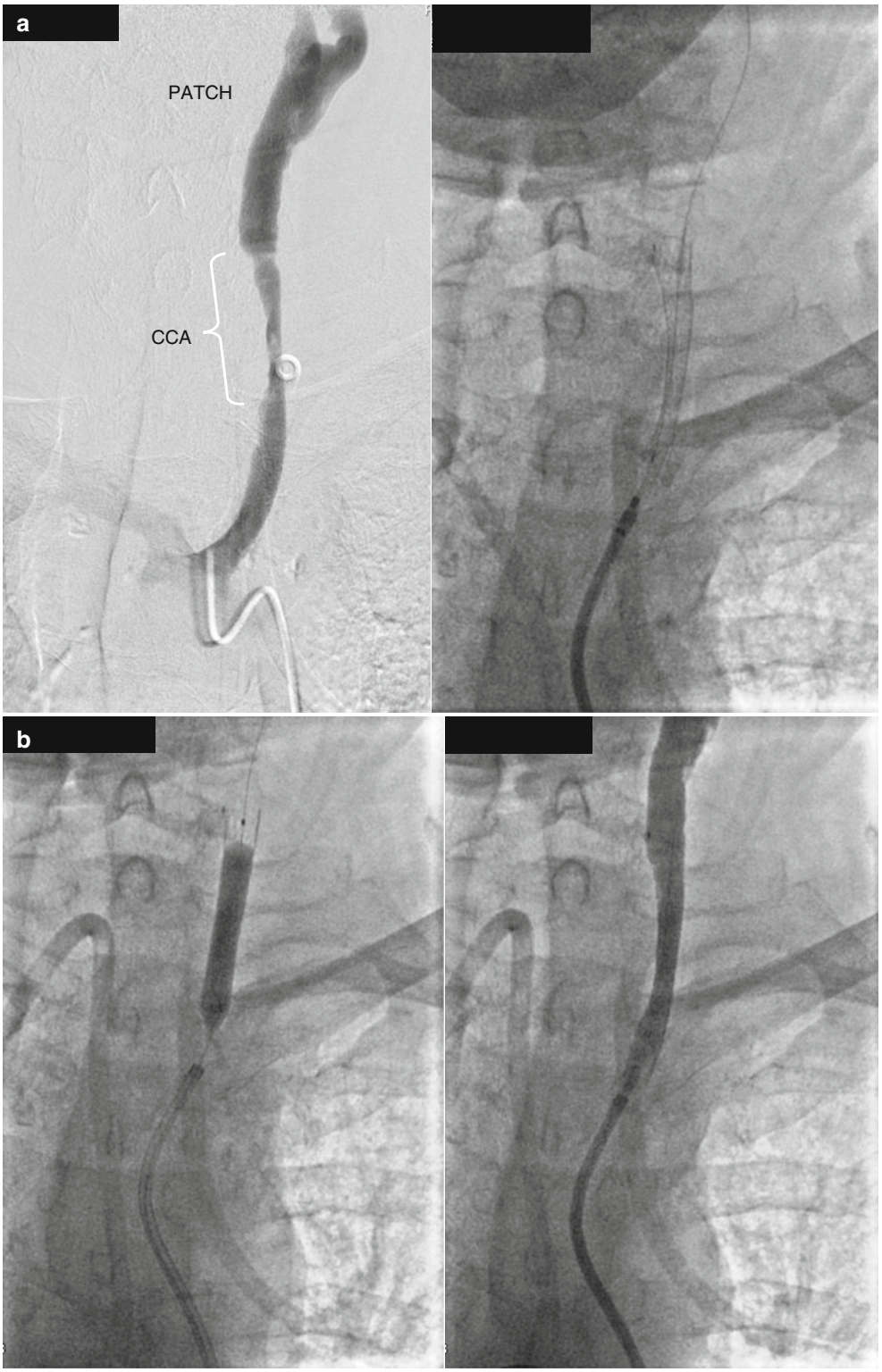


Fig. 6.2 Treatment of the lesions at the level of the CCA – combined. Panel (**a**): angiographic aspect of the left carotid bifurcation in a patient who underwent CEA and patching of the bifurcation. Note the long and tight stenosis of the CCA. A stent was placed into the CCA from the femoral route. Panel (**b**): the severe stenosis required post-dilatation. On the right side, note the final result

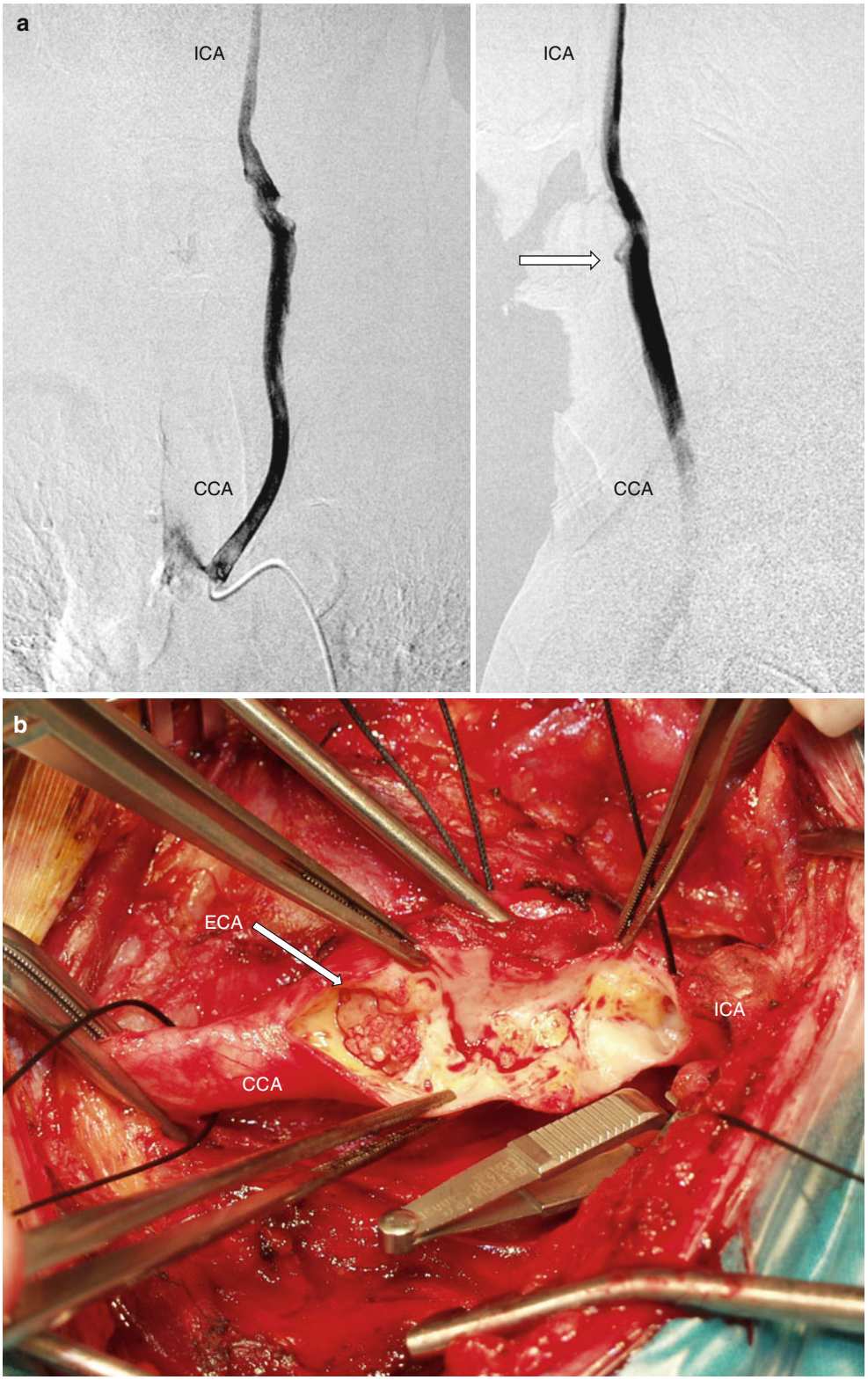
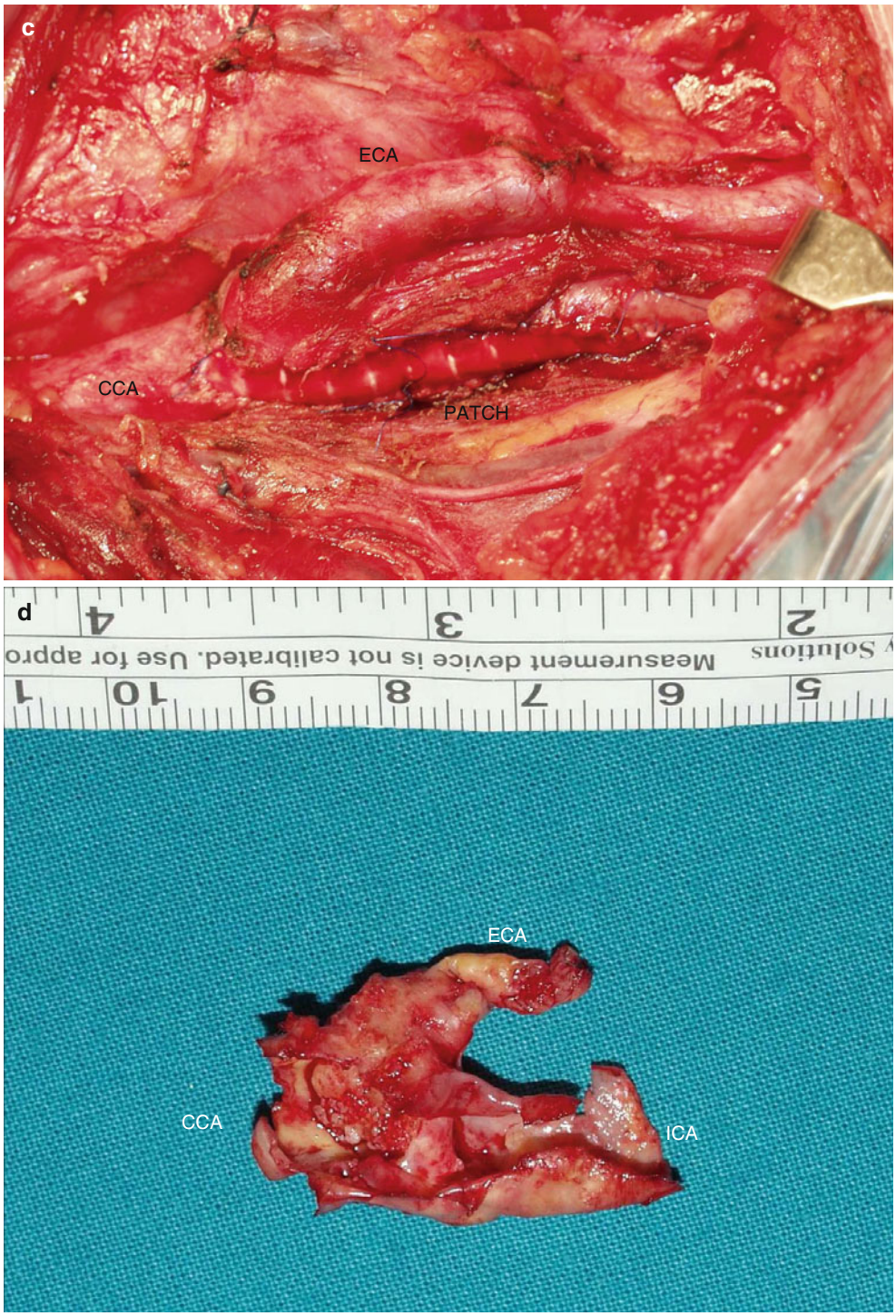


Fig. 6.3 Angiographic evaluation of the diseased ECA. Panel (**a**): angiographic aspect of the left carotid. The origin of the ECA is not visible. Only the superior thyroid artery origin is visible (*white arrow*). Panel (**b**): intraoperative aspect of the opened carotid bifurcation. The origin of the ECA is occluded (*white arrow*). Note also the highly irregular and ulcerated plaques at the level of the bifurcation. Panel (**c**): following the data offered by angiography, and the intraoperative aspect, endarterectomy of the origin of the ECA was complementary performed. The origin of the ICA was enlarged with a PTFE patch (the patch is partially visible). Note the enlarged caliber of the ECA. Panel (**d**): the excised plaque at the origin of the ICA and ECA. Note the extension of the plaque into the ECA (scale in cm and inch, above)

Fig. 6.3 (continued)



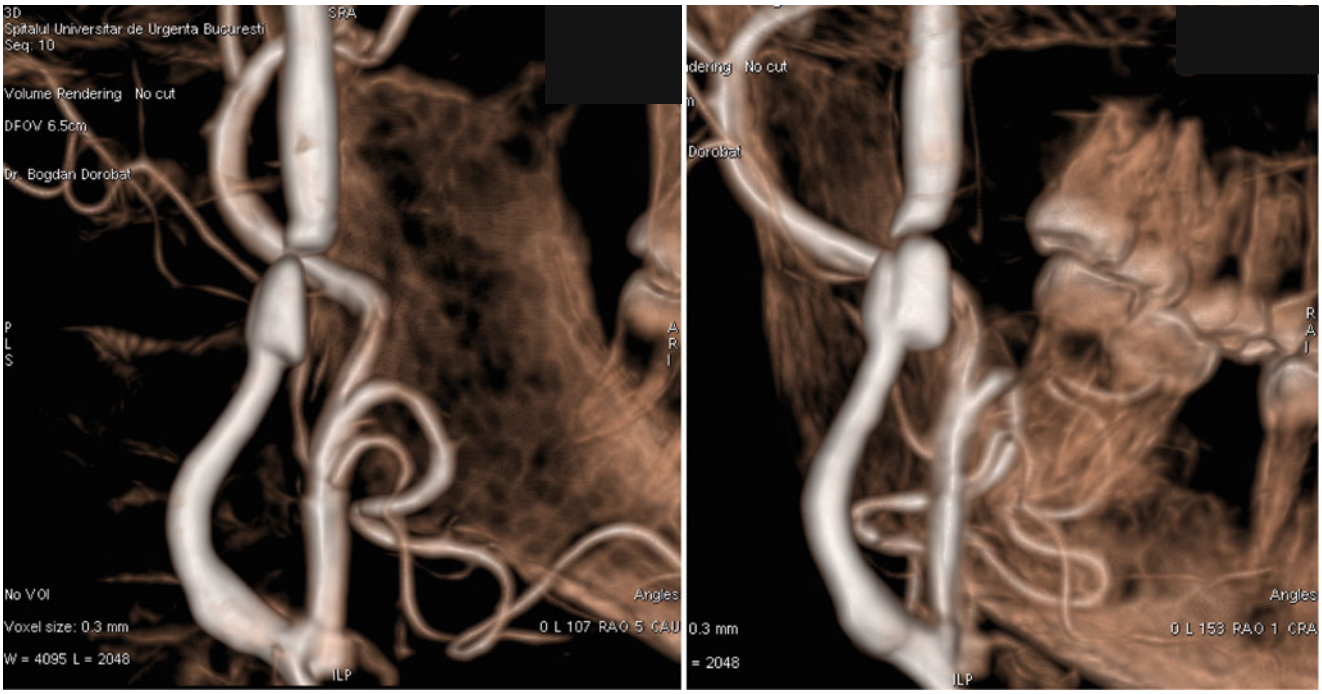


Fig. 6.4 Angiographic evaluation of particular lesions (stenosis + aneurysm). Angiography offers valid data on particular conditions such as coexistence of stenosis and aneurysm. The height of the lesion can be best assessed, while osseous artifacts will not distort the final image (as, e.g., during CT-angio). 3-D reconstruction offers particulars comparable with CT-angio

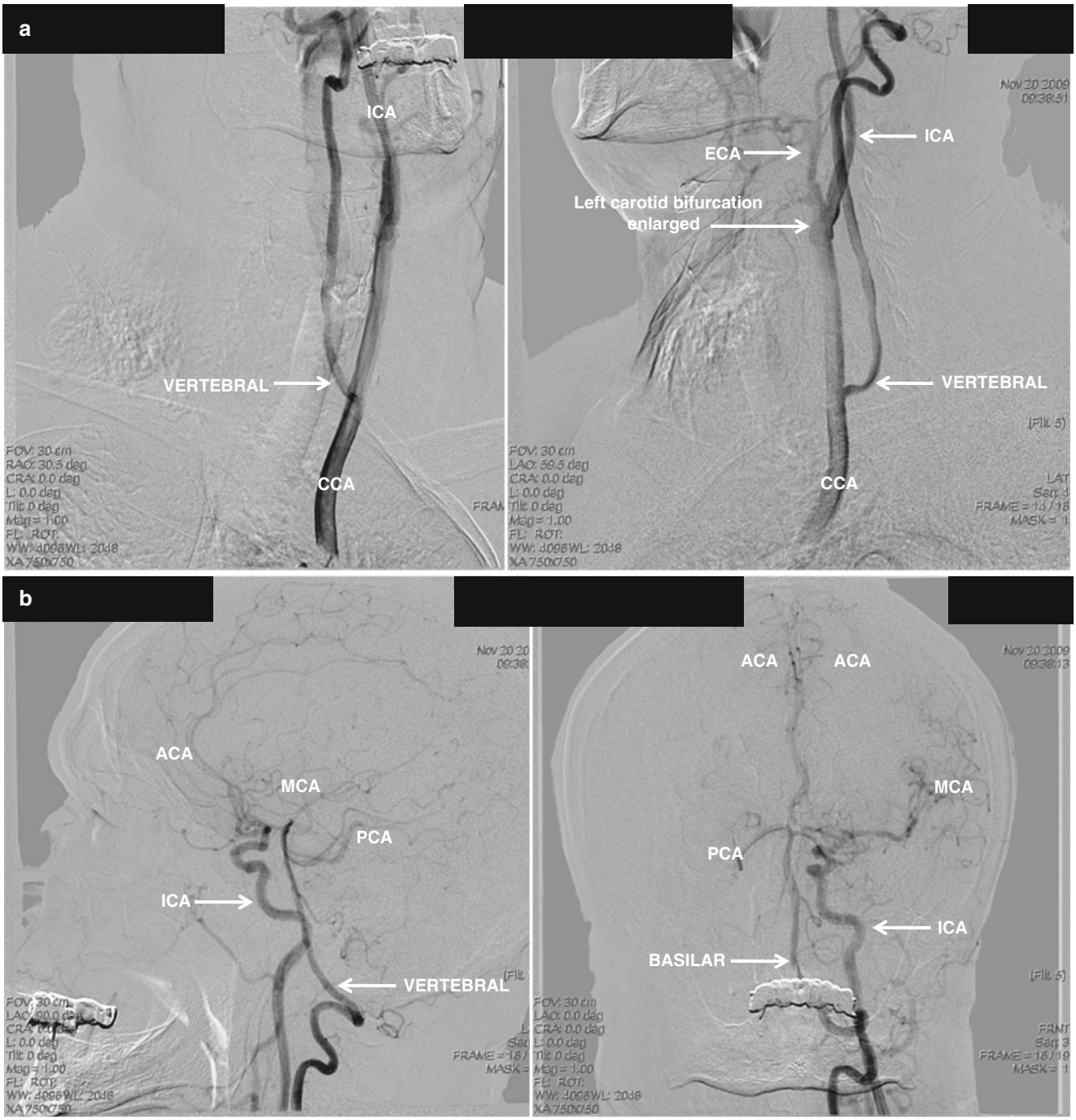


Fig. 6.5 Evaluation of arterial reconstructions. Panel (**a**): angiographic demonstration of the result of arterial reconstruction consisting of CEA and patching of the carotid bifurcation + VA reimplantation into the CCA. Besides the anatomical data, angiography offers important details on the direction of flow, flow velocity, and intracranial distribution, including the hemodynamics of the CoW (Panel (**b**))

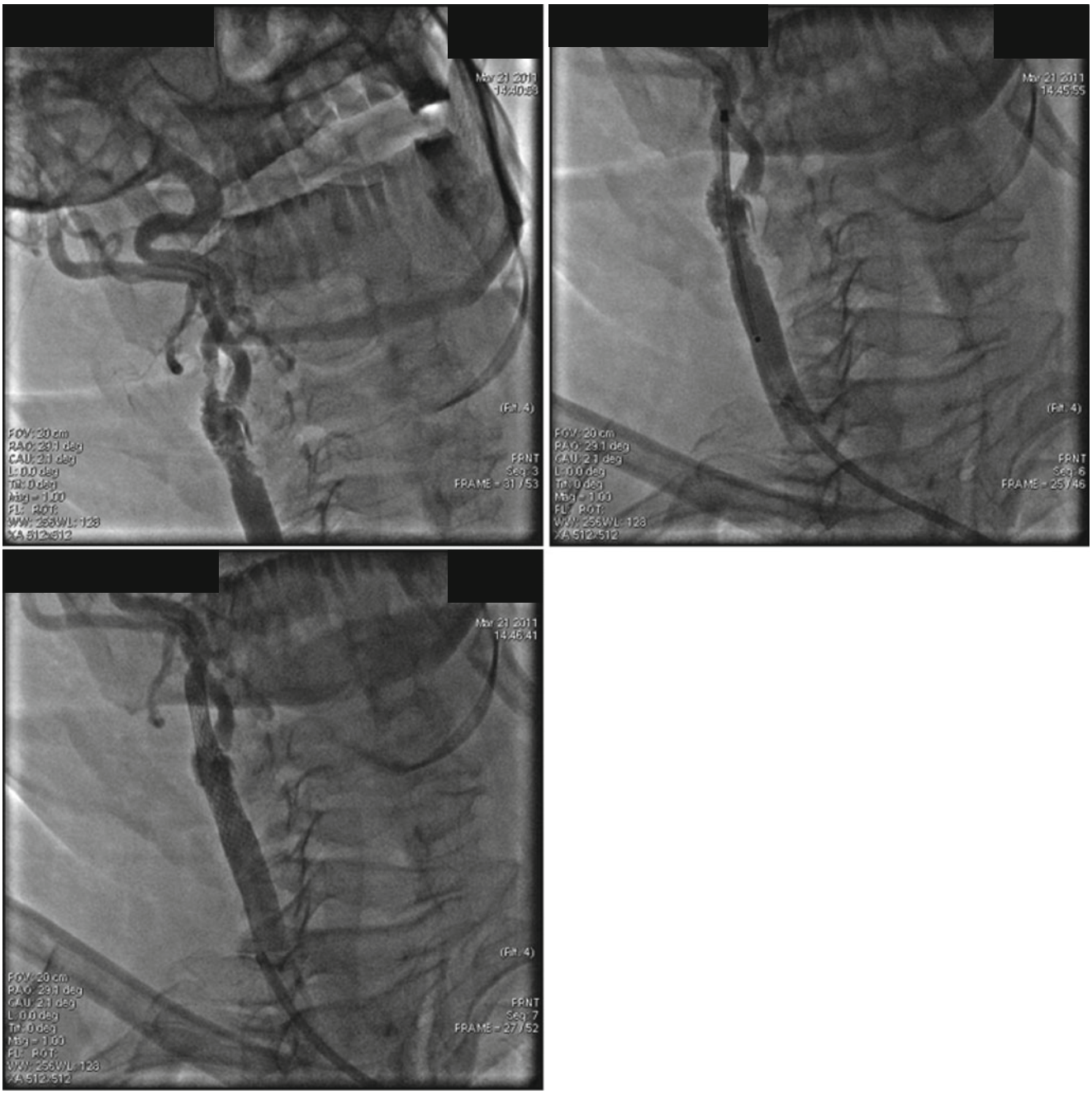


Fig. 6.6 Completion angiogram. The paradigm is offered by a patient operated and who developed cerebral ischemia. Angiography performed as emergency procedure reveals thrombosis of the operated zone; the diseased zone was stented with reversal of clinical signs and complete recovery of the patient

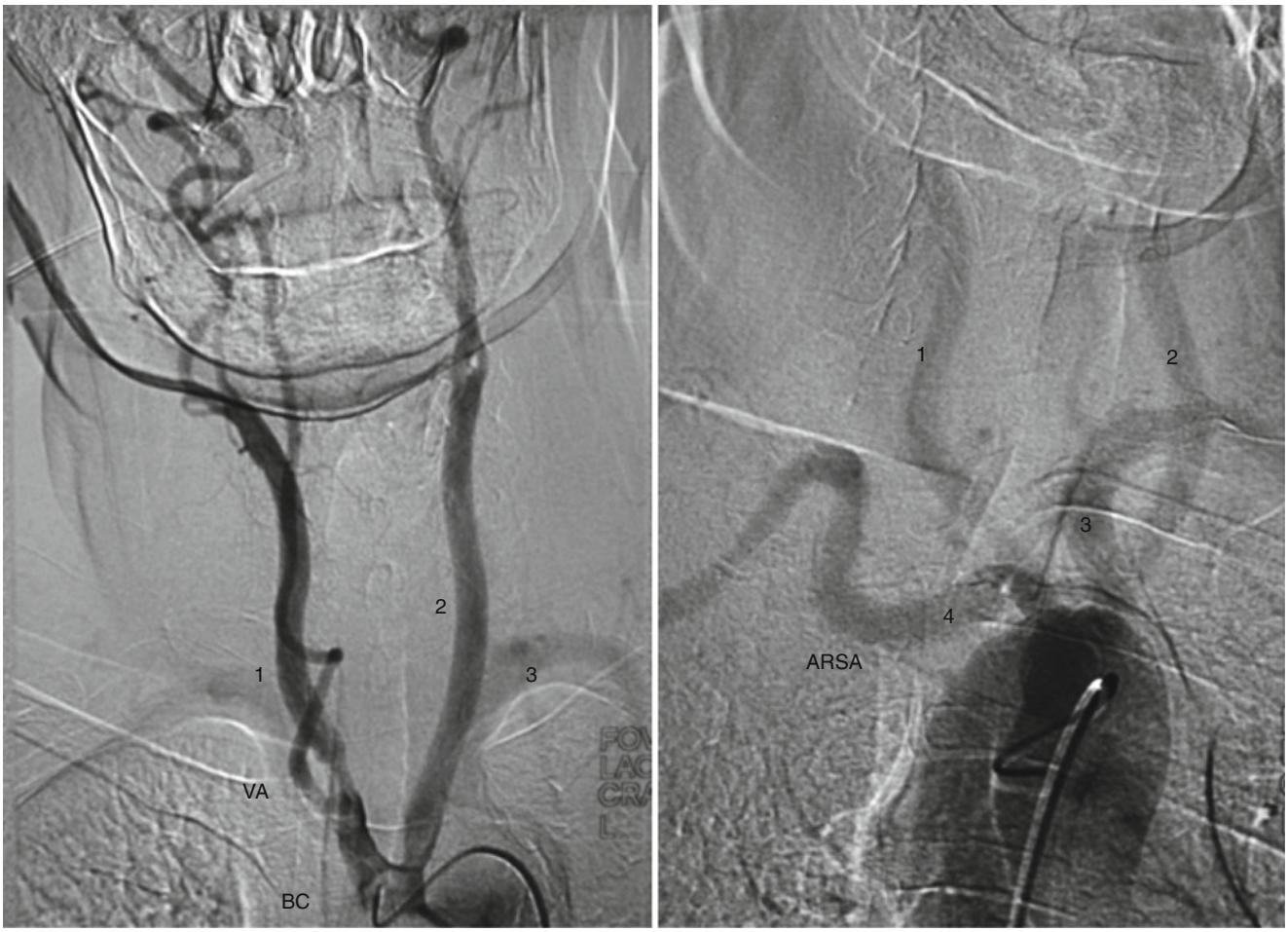


Fig. 6.7 Anatomical variations of the arch vessels. An example is offered by the aberrant right subclavian artery (ARSA): this is probably the most frequent anomaly of the arch vessels as its incidental finding surpasses 5%. Angiographic examination offers best and rapid data on the anatomical variation and hemodynamics. In this particular case, the right VA originated from the right CCA. Both carotid arteries originated from a common trunk (*BC* bicarotid trunk). The order of emergence from the aortic arch is as follows: *1*=right CCA; *2*=left CCA (in this case, actually 1 and 2 have a common aortic origin); *3*=left SCA; *4*=right SCA actually ARSA

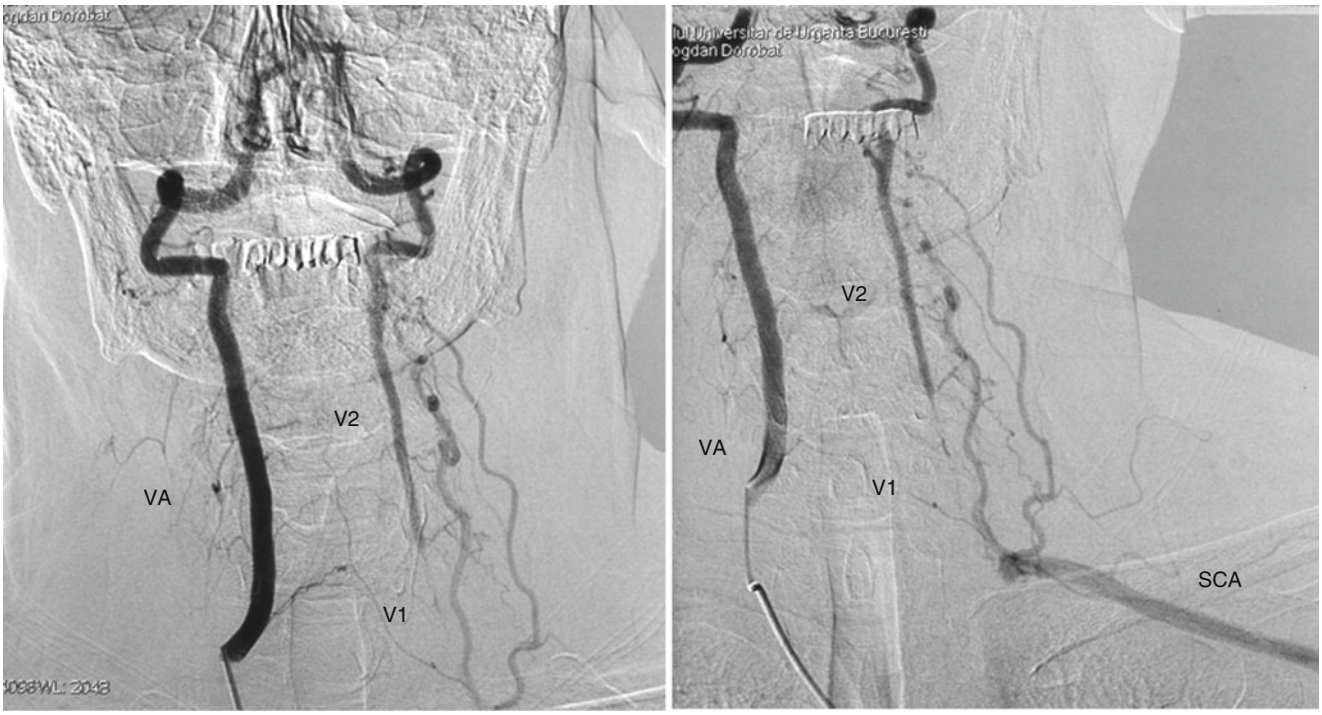


Fig. 6.8 Vertebral steal syndrome. Besides the "classical" vertebral steal syndrome, there are also some "atypical" forms. The Doppler examination in this particular patient revealed an occluded origin of the left VA, while the flow in the V2 segment of the left VA was difficult to ascertain. The patient experienced vertigo. Angiography shows an atypical type of vertebral steal: in spite of the occluded V0 and V1, blood is stolen from the VA through anastomoses with the SCA (deep cervical and ascending cervical arteries). Note the good opacification of the left SCA, not directly through the VA but through collateral circulation. This patient had palpable distal pulse in the left hand

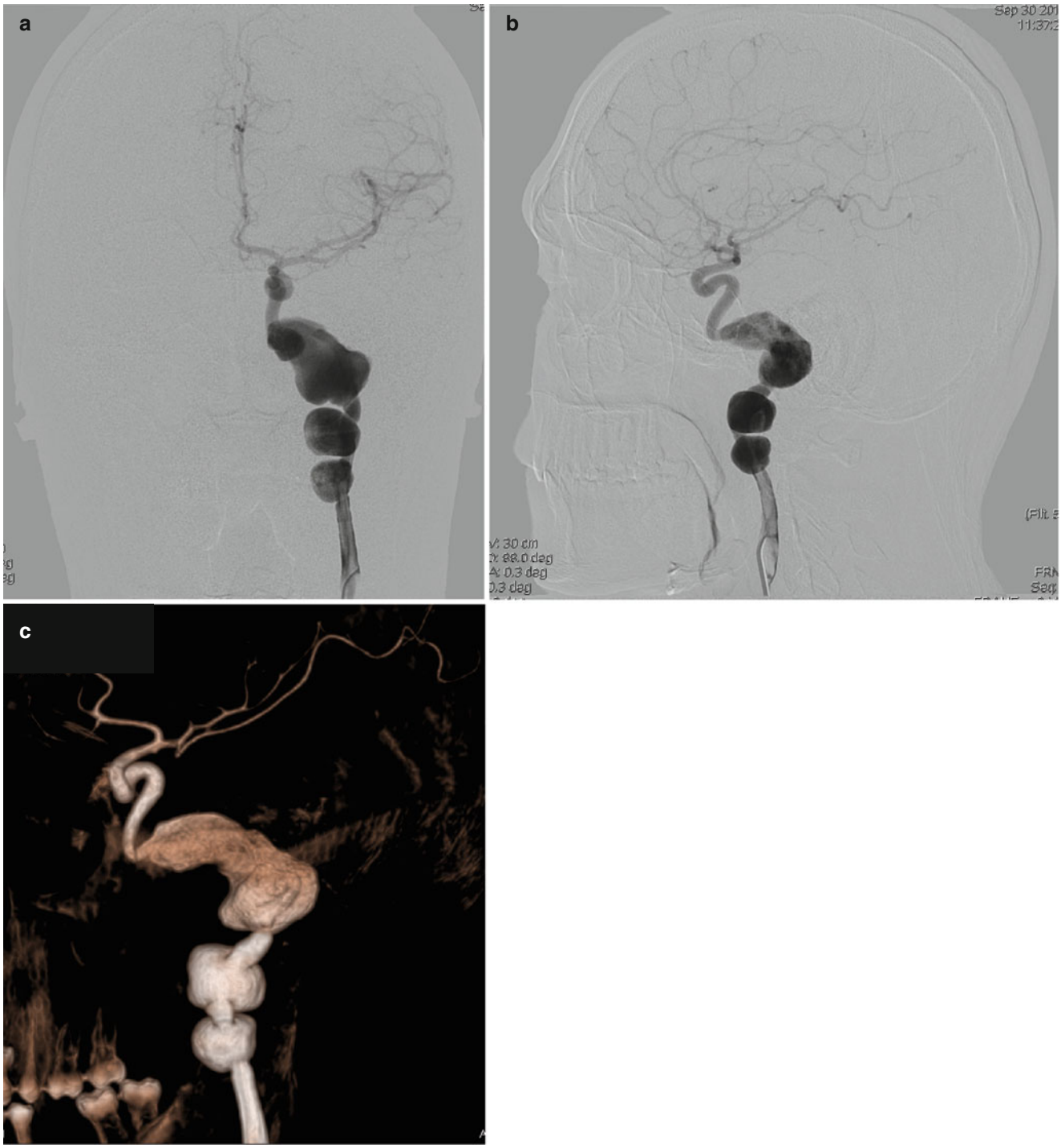


Fig. 6.9 Mega-dolicho ICA (1). Enormous dilatations of the ICA in a younger patient, in whom the remainder cerebral arteries were normal. A good collateral circulation developed, both from the opposite ICA and from the vertebrobasilar system, allowing the exclusion of the diseased left ICA from the circulation. Panel (**a**): anteroposterior view. Panel (**b**): lateral view of the lesions. Panel (**c**) offers a 3-D reconstruction of the same. Panel (**d**): obliteration of the aneurysmatical segments with distal coils and proximal balloon

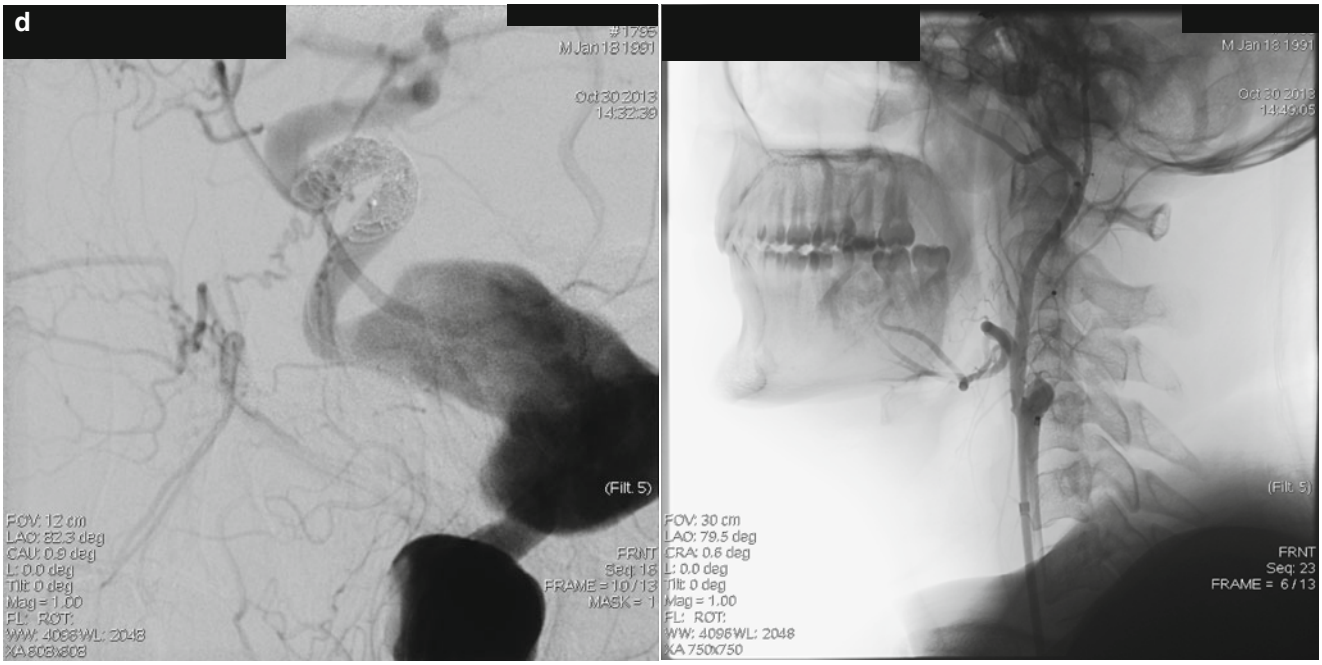


Fig. 6.9 (continued)

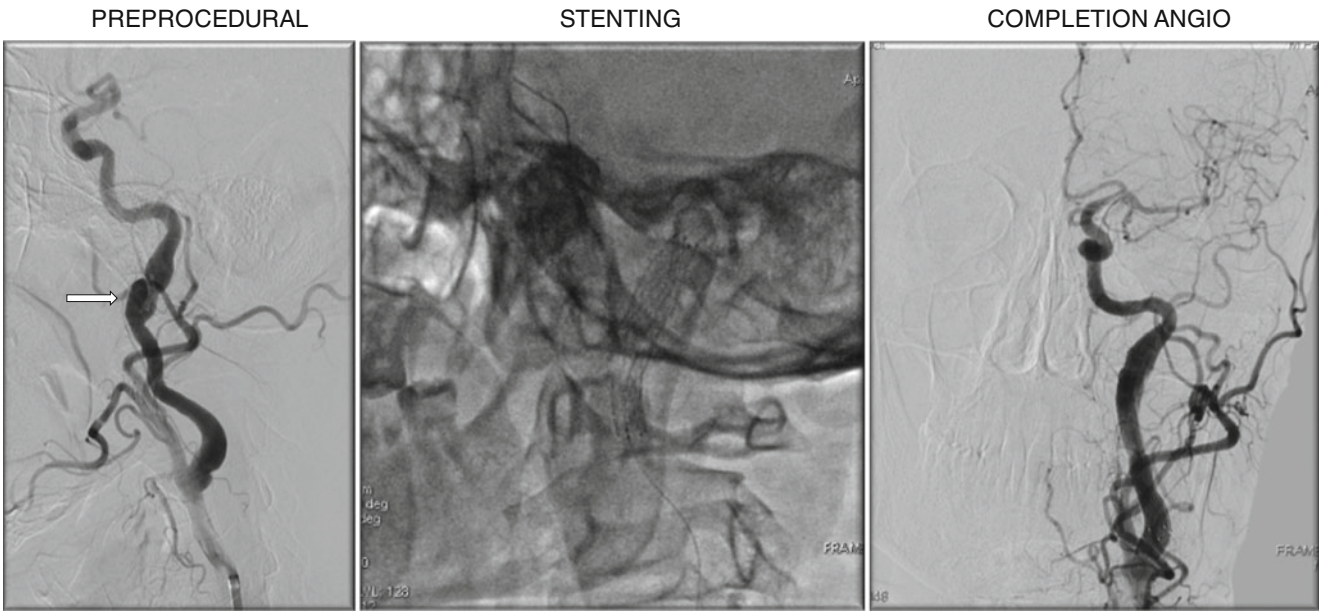
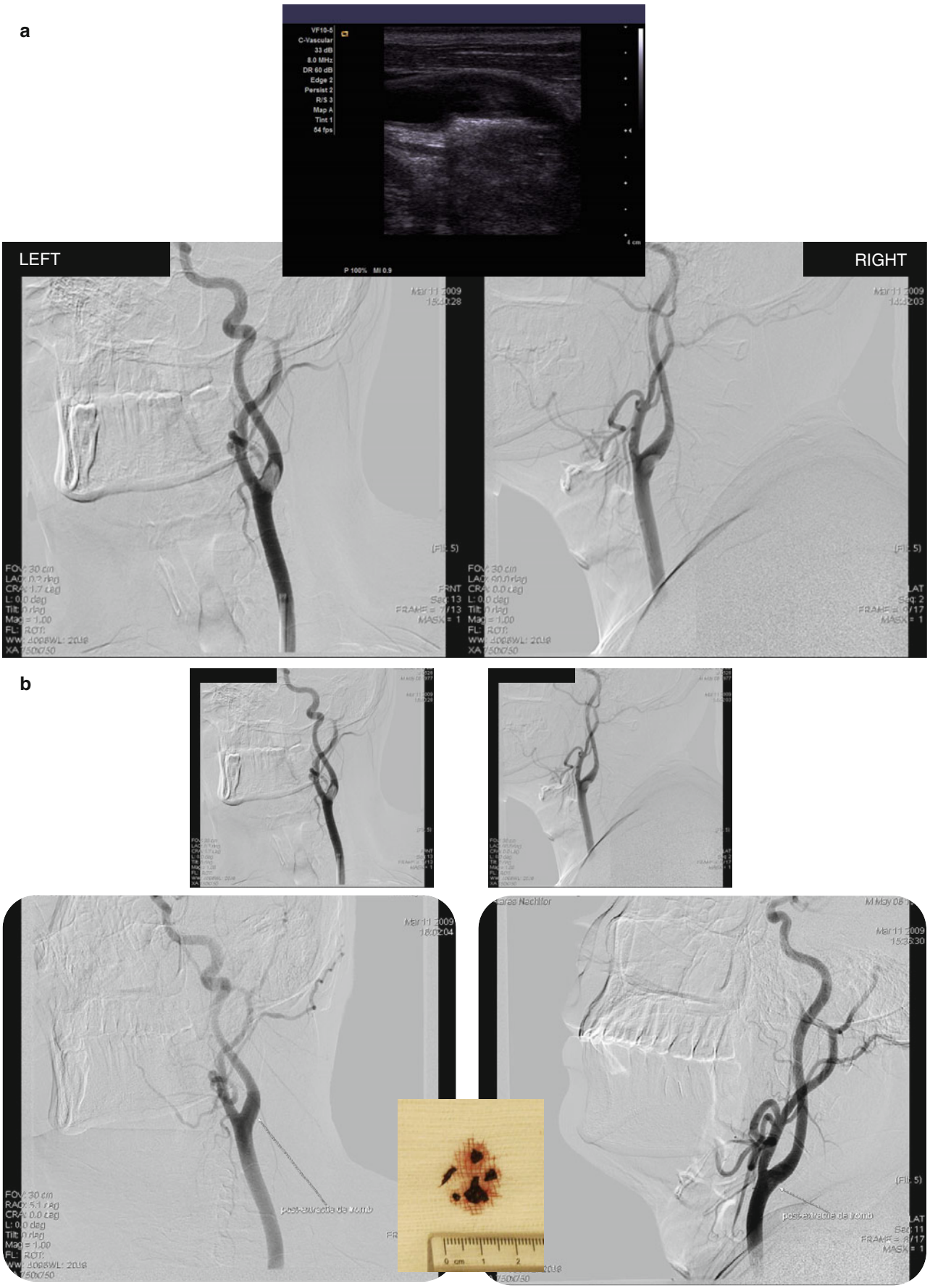


Fig. 6.10 Mega-dolicho ICA (2). Kinking of the cervical ICA appears very frequently associated to the stenotic lesions of the carotid bifurcation. In some patients, the excessive length is accompanied by aneurysm-like dilatations. Many patients are symptomatic (TIAs sometimes related to particular positions of the head). These lesions may extend high in the neck making surgery cumbersome or impossible. The example in the figure demonstrates both the length of the lesion and the result after stenting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b

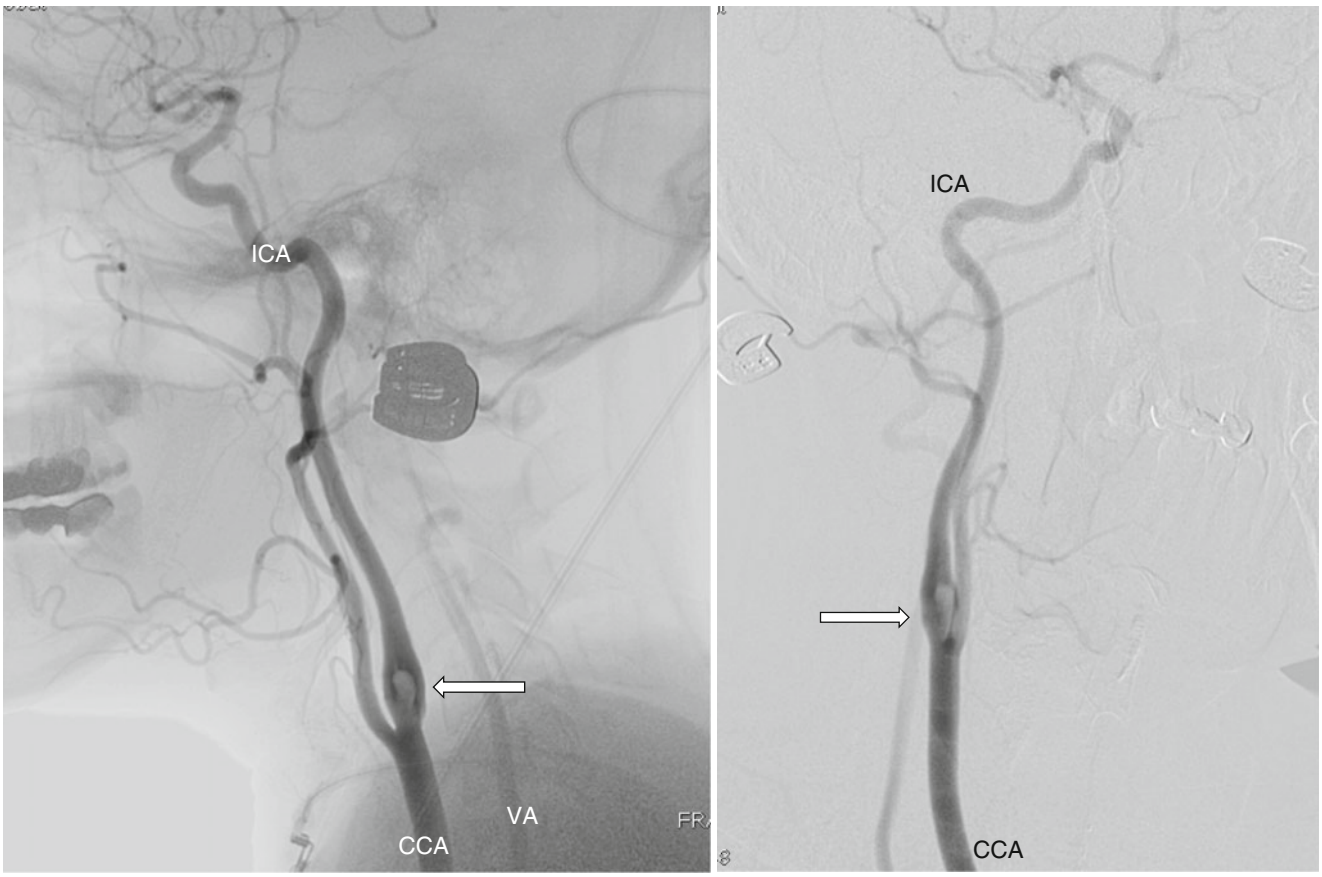


Fig. 6.12 Thrombosis at the origin of the ICA (2). Similar angiographic aspect in an older patient with thrombosis of the right ICA at origin (*white arrow*). Note again the absence of any particular lesion of the carotid and vertebral arterial axis. This patient was referred for surgery while taking into account the longer time interval of symptomatology, suggesting a longer evolution and the higher risks for an incomplete thromboaspiration

Fig. 6.11 Thrombosis at the origin of the ICA (1). A spontaneous thrombus formation at the level of the carotid bulb was encountered in two patients. The patients had ischemic strokes of different ages, by embolization. It is interesting to note that none of these two patients had particular risk factors, no coagulation dysfunction, and no previous trauma (and so forth). The carotid bifurcations appeared normal both on eco and angio (Panel (**a**)). Panel (**a**): younger patient with bilateral ICA thrombosis, symptomatic on the left side. Panel (**b**): angiographic control after bilateral endovascular thrombectomy. Insert: thrombotic material (scale in cm)

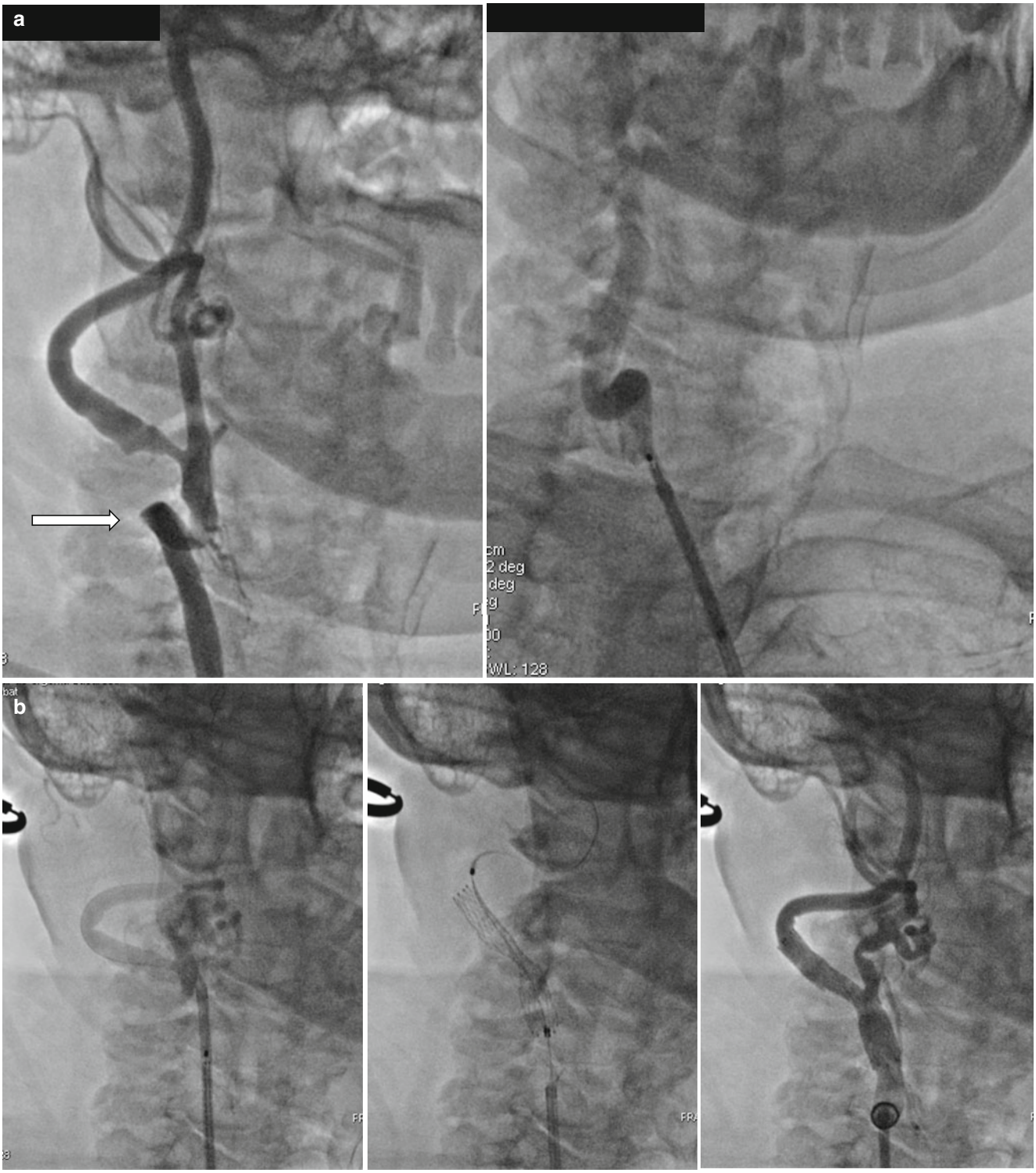


Fig. 6.13 Excessive kinking (*white arrow*) of the CCA and ICA – and CAS. Angiography offers a dynamic picture of the carotid bifurcation (over the CT-angio or MRA) and of the possibility of performing the CAS or not in selected patients. Panel (**a**): excessive kinking of the CCA that theoretically (and especially after CT-angio or MRA) would contraindicate the CAS. Panel (**b**): progression with the sheath will straighten the CCA but will transfer the excessive curve to the ICA. However, in spite of these limitations, a good result was eventually obtained. Not least, note that the distal portion of the stent does not angulate the ICA

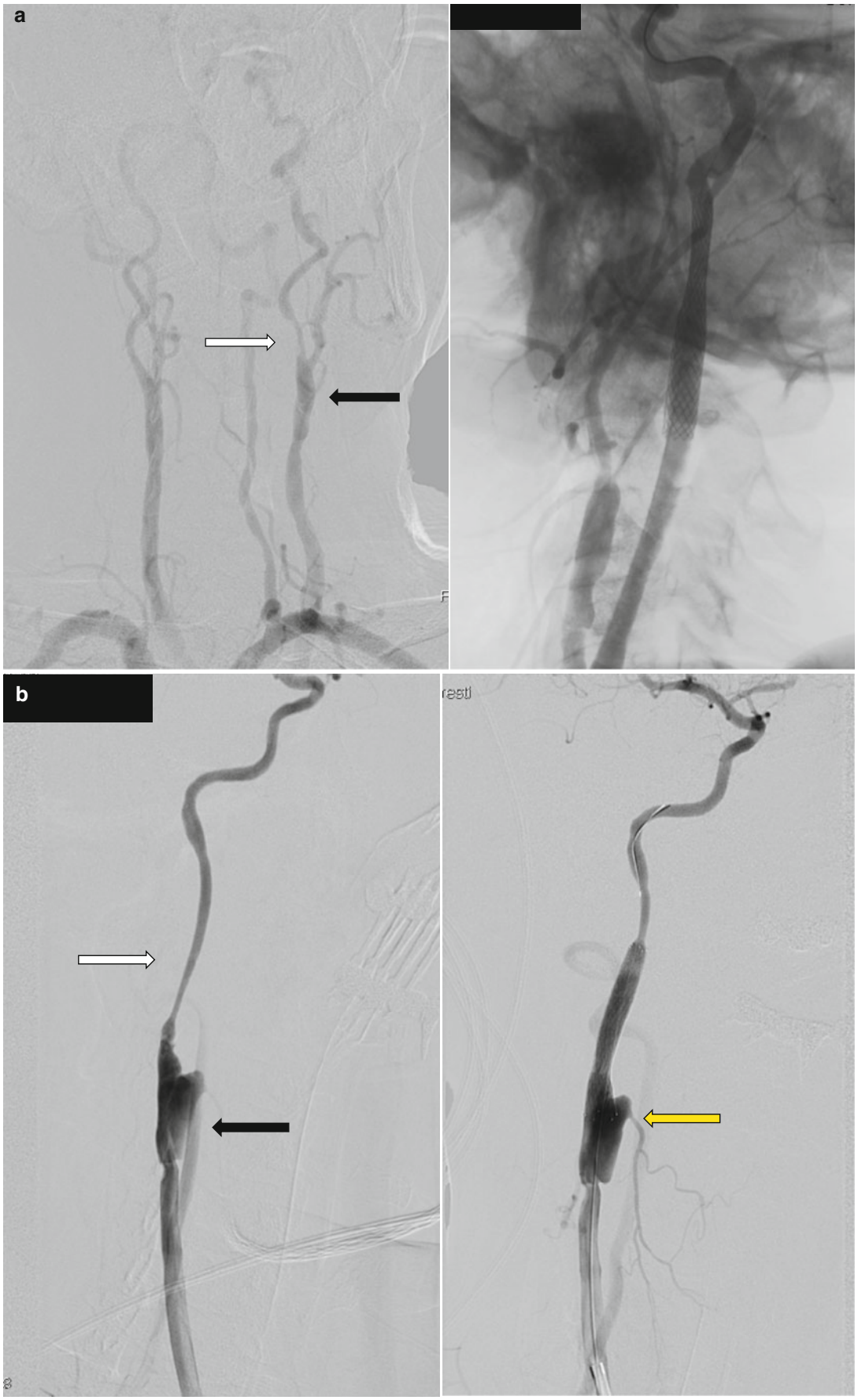


Fig. 6.14 Endovascular treatment of later restenosis after CEA. Panel (**a**): stenosis of the ICA (*white arrow*) distal to the patch (*black arrow*). On the right side, the final result after stenting. Panel (**b**): stenosis of the ICA distal to the patch (*black arrow*) and associated arterial spasm (*white arrow*). Note that the ECA is occluded after surgery. On the right, angiographic aspect after stenting; from the ECA only the superior thyroid artery patent (*yellow arrow*)

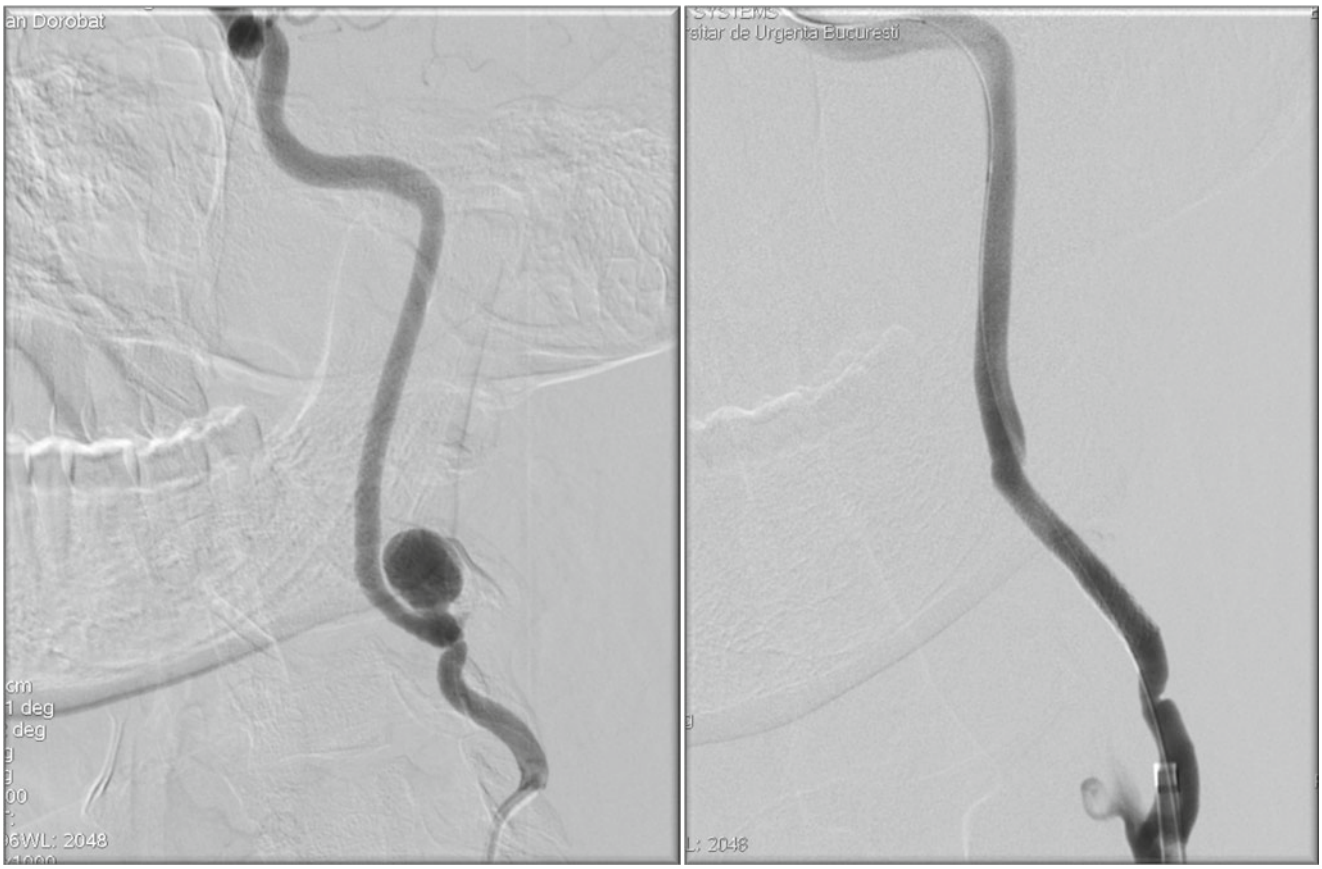


Fig. 6.15 Endoprosthesis for exclusion of ICA aneurysm. Aneurysms of the ICA can be elegantly treated without surgery, either by stenting or by inserting and endoprosthesis (as in the case illustrated here). As in the case of surgical treatment, the choice of the type of procedure is dictated by numerous factors, among which are condition of the patient, type and localization of the aneurysm, dimensions, presence of associated symptoms produced by compression, presence of infection, etc.

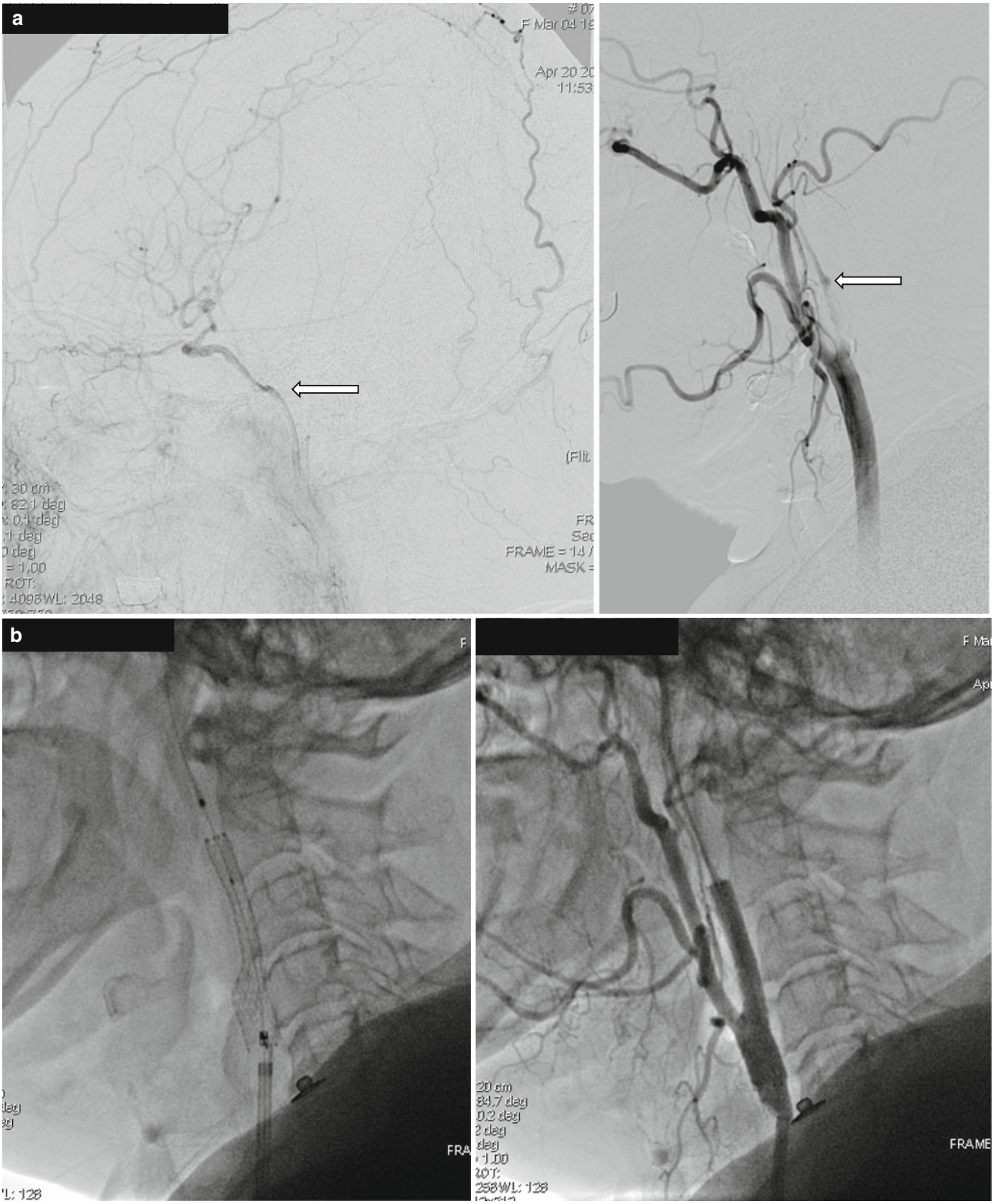


Fig.6.16 Intracerebral aneurysm + stenosis of the ICA (*white arrow*). The case presented is of a patient with bleeding from an intracerebral aneurysm (of the MCA). Access appears difficult if not impossible due to an almost occluded ICA. The case is particularly interesting and clinically significant because the ICA appeared in some angiographic images as occluded, with a rich collateral circulation that eventually filled the distal ICA (Panel (**a**)). The ICA appears thin, from its origin up to its termination. Panel (**b**): the bifurcation and origin of the ICA were stented. Panel (**c**): access to the distal ICA and the aneurysm was obtained. Note that even after CAS, the ICA appears diffusely diseased. The aneurysm was coil embolized (*white arrow*)

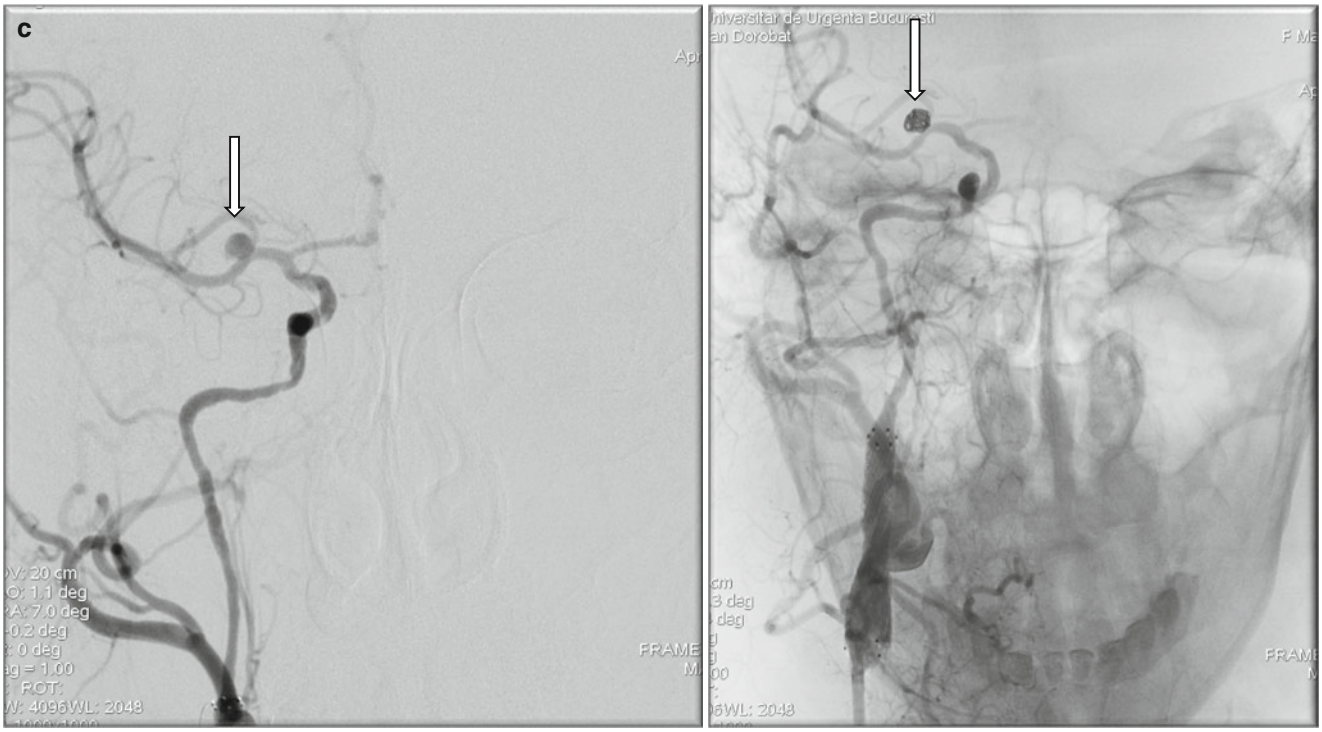
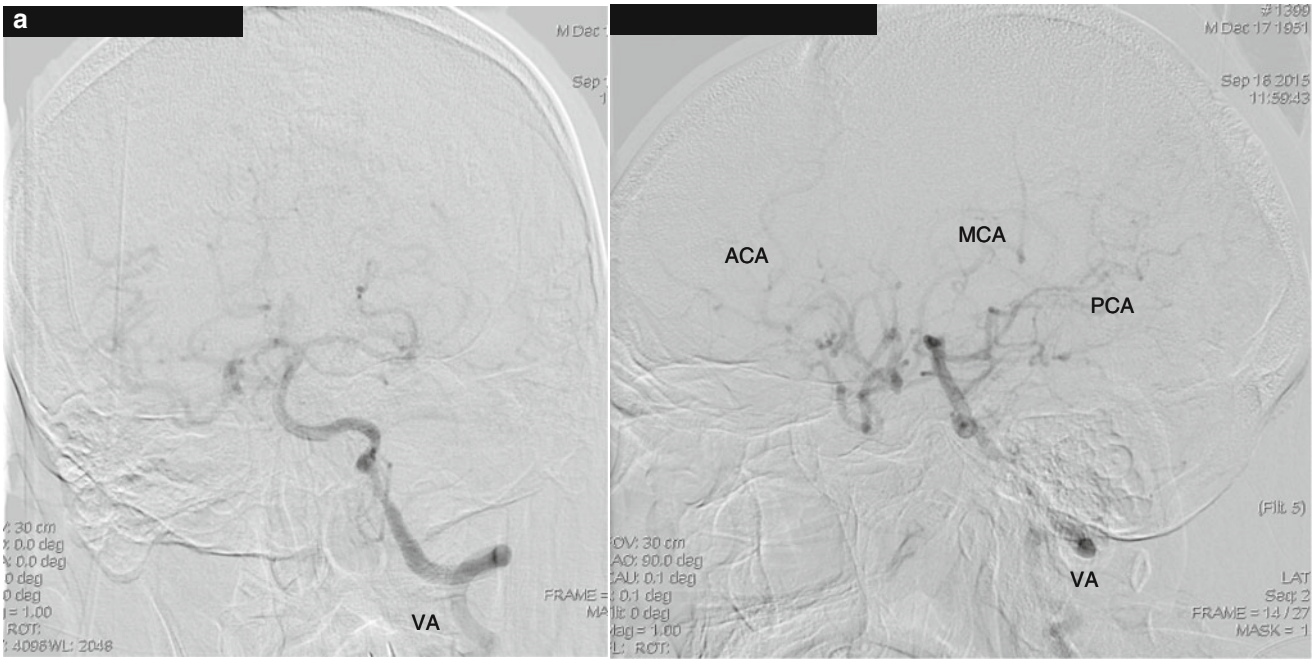


Fig. 6.16 (continued)

Fig. 6.17 CAS of the ECA. Bilateral occlusion of the ICA limits the surgical and endovascular procedures of direct revascularization (extra-to-intracranial bypass except). Indirect revascularization can be obtained by enlarging the origin of the ECA and by allowing higher flow through collaterals. Panel (**a**): left VA angiogram, revealing the patent PCommA and filling of the anterior system from the VA. Panel (**b**): severe, pre-occlusive stenosis at the origin of the left ECA. ICA is occluded. Panel (**c**): stenting of the ECA. Panel (**d**): completion angiogram illustrating the filling of the distal ICA through collaterals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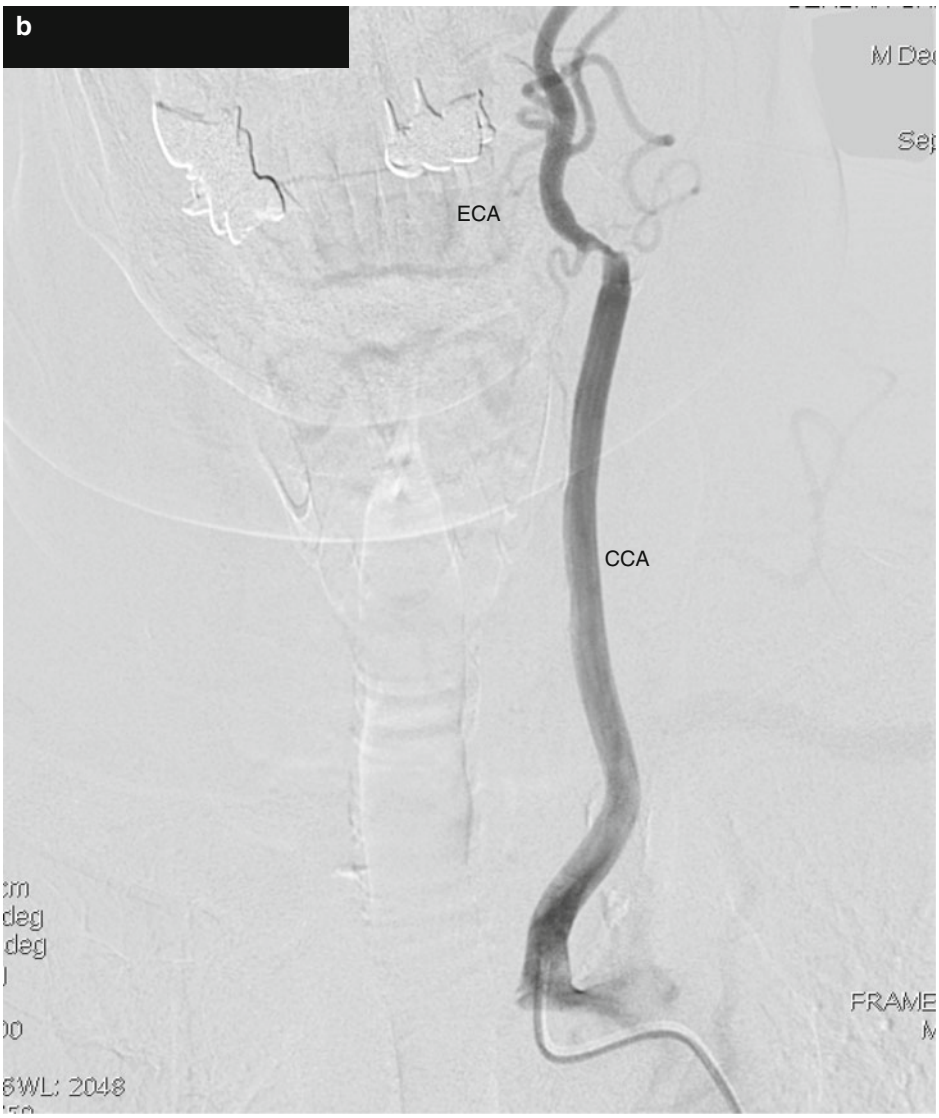
VA
ACA
MCA
PCA
VA


b
ECA
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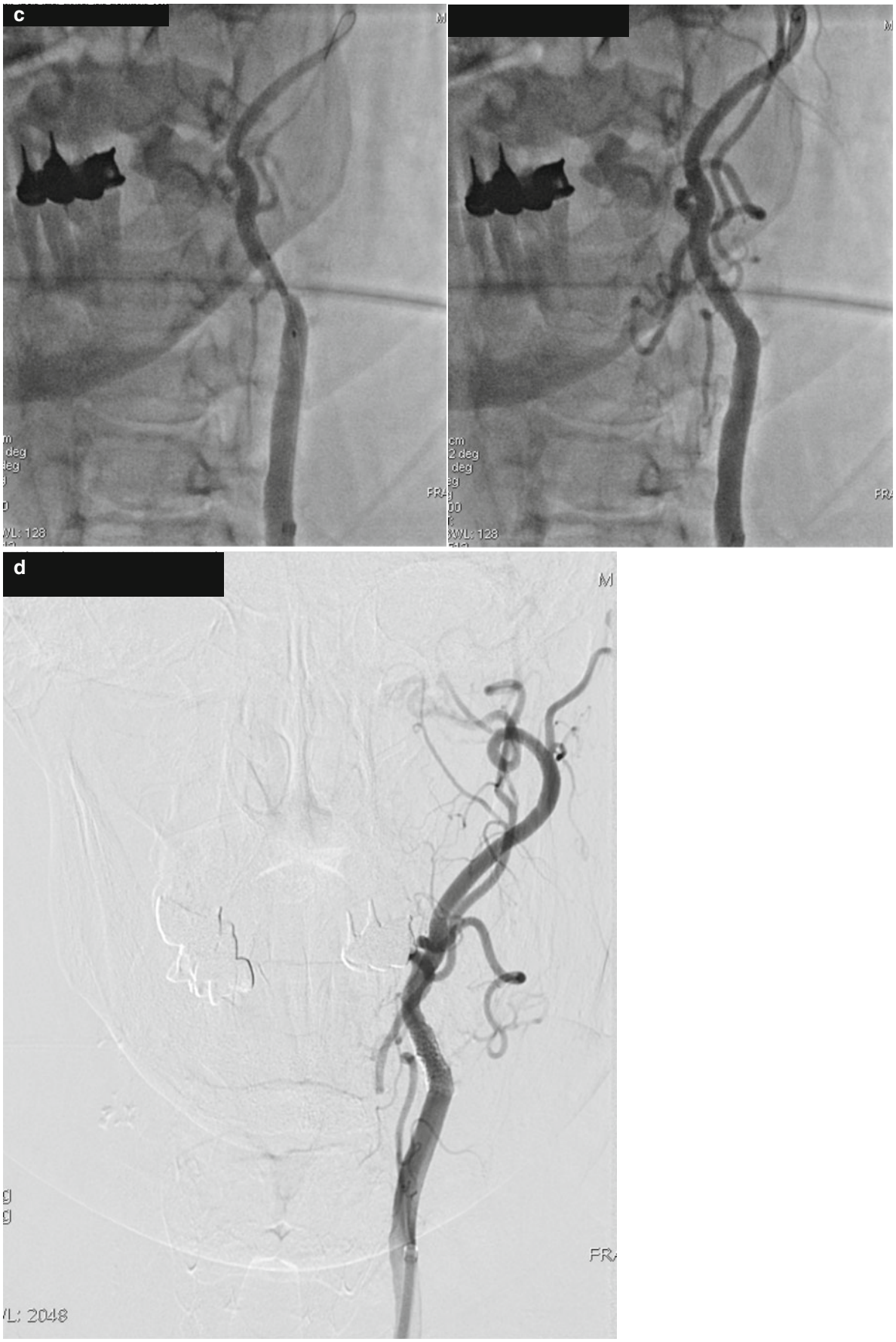

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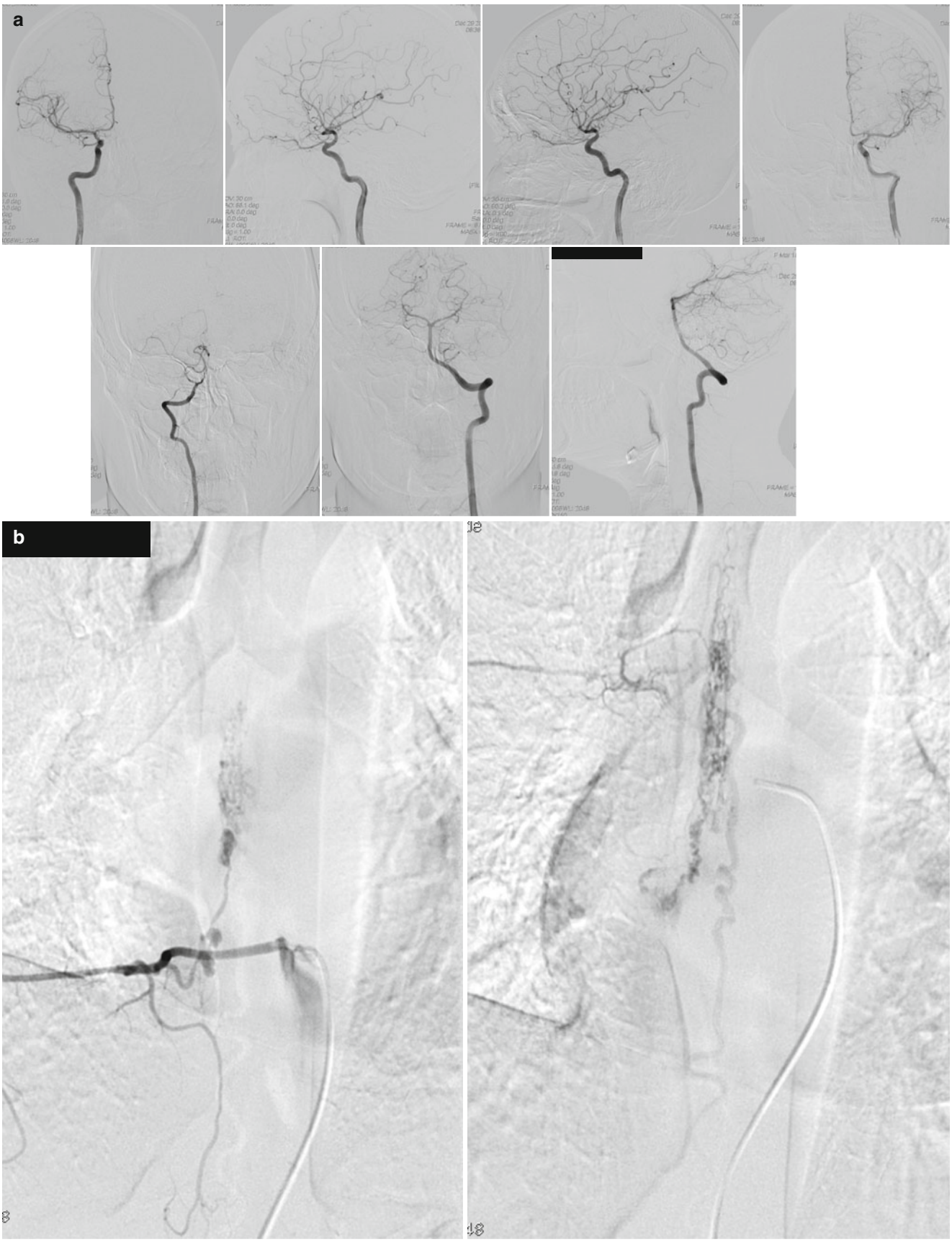

Fig. 6.18 SAH in patient with spinal vascular malformation. Panel (**a**): 4-vessel angiogram reveals normal aspect (in this figure, only the arterial phase is illustrated). Note that the right VA terminates by giving off the PICA (normal anatomical variation). Panel (**b**): selective angiography of intercostal branches reveals spinal vascular malformation fed from multiple arterial sources, especially from the right-sided arteries; the malformation extends into the capillary and venous segments also

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Diagnostic Approach to Cerebrovascular Disease: CT and MRI

7

Alina Ioana Nicula

7.1 Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide, hence becoming a serious public health problem. About 88 % of strokes are ischemic, the rest being hemorrhagic [1]. The degree of stenosis alone is a relatively poor prediction of neurological events [1–6], but patients with substantial carotid narrowing are at increased risk for major stroke. Identifying and investigating plaque morphology and instability (specific plaque characteristics being associated with ischemic brain injury) consume a great deal of efforts in research. However, a reliable in vivo imaging method which can monitor both plaque progression and components is needed in order to understand the mechanisms behind the vulnerable plaque [1, 2].

Accurate measurements of the degree of stenosis have become extremely important. Initially, based on the results of the North American Symptomatic Endarterectomy Trial (NASCET), only a discrimination made between 50–69 % and 70–99 % stenosis was considered to be important. However, subsequent studies have made use of more and different cutoff values for patient selection, using stenosis degree of 50, 60, 70, and 80 %, depending on the presence of symptoms as well as comorbidity [7–10].

Initially, stenosis grading was based on intra-arterial digital subtraction angiography (DSA); in time, less invasive techniques such as duplex ultrasound, magnetic resonance angiography (MRA), and computer tomography angiography (CTA) have gradually replaced this technique [11].

Little appreciation is being given, in the medical literature, to the role of observer variability in reporting, having the purpose of explaining the disagreement between methods, which is most often attributed entirely to test characteristics. When one method is compared with another and disagreements emerge, it is not readily apparent how much of the disagreement is caused by the process of measurement, unless observer variability data are also presented, and how much by the method used [12].

7.2 Carotid Atherosclerotic Vascular Disease (CAVD): Diagnostic Imaging

1. *Definitions*: CAVD is a disease impacting large- and medium-sized arteries, characterized by atheromatous plaques in the intima of large- and medium-sized arteries, being a degenerative process resulting from progressive intimal accumulation of lipid, protein, and cholesterol esters in arterial walls [13, 14].
2. *Location* (Fig. 7.1):
   - Cervical arteries, most commonly involving the proximal internal carotid artery (*ICA*) at the level of the carotid bulb [15]
   - May involve also any of the extracranial cerebral arteries while other typical locations of involvement include the large vessel origins from the aortic arch
3. *Imaging*: Major trials published in the 1990s such as NASCET, ECST, and ACAS were based on conventional angiography, thus making it to be considered the standard method for evaluating carotid stenosis. Lately however, the introduction and development of ultrasound Doppler, CT angiography (CTA), and MR angiography (MRA) have been replacing angiography for diagnostic purposes, essentially reserving it for endovascular treatment.

CTA offers both high spatial and contrast resolution, and it is probably the best noninvasive imaging modality with current multi-detector capabilities, since high-quality multiplanar reformats can be routinely obtained. CTA is a fast process, with images of the head and neck acquired over a time interval of around 15 s during contrast injection. It provides an

A.I. Nicula
Department of Radiology, The University Hospital of Bucharest, Bucharest, Romania
e-mail: alinapavel74@yahoo.com

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anatomic study of arteries (enabling the possibility to evaluate extracranial arteries simultaneously with delineation of soft tissues [16]), allowing for direct evaluation of carotid stenosis; it also has the ability to visualize the vasculature in relation to the surrounding structures (difficult to obtain via other types of explorations), a fact which can be desirable in patients with anatomical variations [17, 18]. Another advantage of CTA is that it provides information about surrounding anatomy, such as osseous structures, that is useful in surgical planning [19]. The anatomic orientation of carotid arteries running perpendicular to the imaging plane is favorable for CTA [20].

Multiplanar reconstructed CTA may be obtained from thin, contiguous axial images acquired after intravenous administration of radiographic contrast material. Rapid image acquisition and processing, continuous image acquisition ("spiral CT"), and multiple detector systems have made high-resolution CTA clinically practical [21–27]. CTA provides anatomic imaging from the aortic arch through the circle of Willis, while multiplanar reconstruction and analysis allow even the evaluation of very tortuous vessels. Unlike ultrasonography or MRA, CTA provides direct imaging of the arterial lumen suitable for evaluation of stenosis, but in severe stenosis, volume averaging impacts the accuracy of measurement as the diameter of the residual vessel lumen approaches the resolution limit of the CT system.

It is possible to narrow the nominal section thickness in order to obtain a submillimeter dataset for evaluation of carotid arteries and the cerebral vasculature, and this ability, combined with 3D image rendering, provides an "unprecedented volumetric spatial resolution for any imaging technique" [18]. In order to assess the relative benefits of CTA in reference to safety, time, and related lower cost than DSA, we suggest that it is compelling to use CTA when the indication for angiography is not to make an interventional procedure, but to accurately characterize the degree of stenosis.

Improvements are expected when using 16, 64, or even more channels, especially when needed to minimize venous filling, although this is not an artifact for neck carotid imaging, because arteries are easily recognized as distinct from veins. Other techniques are commonly used in clinical practice, such as duplex ultrasonography and the ubiquitous MRA, though both are more dependent upon flow and are thus indirect tools for evaluating anatomic carotid stenosis [28–31].

It is important to recognize that both CT and MR modalities continue to show important advances along the time, thus making such relative comparisons changing with further advancements. With CTA, images can be acquired in a few seconds starting from the aortic arch to the vertex, with a narrow axial field of view, thus resulting in high resolution, while CE-MRA for neck and head is acquired in a coronal direction with a wide field of view, yielding a lower resolution [32]. Despite these advantages, MRI is unique in its ability to demonstrate methemoglobin within wall plaque [33].

With CTA, DSA, and CE-MRA, the vessel lumen is evaluated via a contrast-filled luminogram. CTA allows for direct and accurate submillimeter measurements of the vessels, which are not possible with DSA, while additional advantages of CTA include its 3D abilities, which provides an advantage over conventional DSA [34, 35].

A recent meta-analysis of the diagnostic accuracy of CTA for the assessment of carotid stenosis reviewed 28 studies which compared CTA with DSA.CTA was found to be highly accurate for diagnosing the degree of carotid occlusion, with an overall sensitivity of 97 % and specificity of 99 %. For severe stenosis (70–99 % range), CTA was found to be reliable, with sensitivity of 85 % and specificity of 93 %. Measurement of residual lumen diameter by CTA compares favorably to DSA, MRA, and ultrasonography [36–40].

When compared with MRA, CTA is less susceptible to artifacts because – like DSA – it is a digital subtraction technique that relies on intraluminal contrast rather than signal changes attributable to alterations in blood flow. Also, because it is a much faster process, artifacts introduced by patient motion are less common [32].

CTA has become an integral part of hyperacute stroke evaluation. In this regard, an initial NECT scan, usually performed to rule out hemorrhage, is followed by a CTA +/− CT perfusion study. The entire evaluation can be completed in less than 30 min, including time to peak, cerebral blood flow, and cerebral perfusion calculations done using commercially available software [17].

3.1. *CT*: The CT technique allows either high resolution, smaller volume, imaging with isotropic voxel size, or imaging of a larger coverage of anatomic areas, that is, the whole cerebrovascular circulation from the aortic arch to intracranial arteries [41]. CTA facilitates good quality 3D reconstructions or 2D reformats and accurate measurements [20]. Carotid artery CTA has a sensitivity of 65–100 % and a specificity of 88–100 % for atherosclerotic stenosis [36, 42–45]. The percentage ranges represent differences in the degree of stenosis, level of lesions, and post-processing techniques used for image reconstruction.

- *NECT*:
  - Calcified CAVD plaque at CCA bifurcation +/− ICA (compared with other imaging studies, more calcifications in the carotid arteries can be detected with CT angiography) (Fig. 7.2).
  - May show thromboembolic or hemodynamic cerebral infarction.
- *CECT*: decreases the ability to visualize calcified plaque (Fig. 7.3).
- *CTA*: CTA is a safe, noninvasive technique that performs accurate measurements of carotid artery area reduction

and provides a clear anatomic depiction of the carotid bifurcation, which could be helpful in preoperative evaluation. With this technique, the current standards for carotid artery imaging may need to be reevaluated and the precise role for helical CTA more clearly defined [46]. The interpretation of the complex vascular system necessitates the visualization of several contiguous sections or views, and usually the interpretation of CT angiograms is performed interactively on a workstation [47]. Three-dimensional reconstructions such as volume rendering (VR) or shaded surface display (SSD) are able to display complex arterial anatomy and the findings in a single view. The powerful computers of the workstation today allow easy generation of the 3D views; thus, for example, VR views are quickly available for the overview of the vascular anatomy and for demonstration of findings to the referring physician [48].

- The CTA also depicts a variety of additional abnormalities, including loops, aneurysms, and ulcers, while the sensitivity of CT angiography seems to be excellent for the detection of distal lesions in the ICA [37] (Fig. 7.4).
  - *CTA technique*: A full diagnostic imaging resulted from a single session (starting from the heart and going all the way to intracranial vessels) in a neurological patient for search of, e.g., source of embolism, is facilitated by improved temporal and spatial resolution of CT. Also, cerebral CT can be combined with CT perfusion study for the brain, providing additional information about cerebral blood flow and helping determining the hemodynamic significance of stenotic lesions in the extracranial and intracranial arteries that supply the brain. In the same way, in the same session, CT angiography for supra-aortic arteries can be performed as a valuable evaluation set for stroke patients [20].
  - Most of the CTA values presented below were taken from investigations made on a Philips CT machine with 32 detectors:
    - Locator: under the tracheal bifurcation
    - Tracker: positioning of the tracker inside the pulmonary trunk.
    - CTA acquisition is cranio-caudal (reduces venous artifacts at the circle of Willis level)
    - Thickness: 1 mm (or less)
    - Increment: –0.5 mm
    - kV: 120, mAs/slice: 180
    - Threshold: 120
    - Post threshold delay: 3.7 s
    - Contrast material: 50–60 ml
    - Flow rate: 4 ml/s
  - Can *characterize plaque composition*:
    - Slow hemorrhage, ulceration, fibrous cap; patchy/homogeneous low density in wall may be seen with large necrotic/lipid plaque.
- Plaque morphologic features and composition have been suggested as a complement to luminal narrowing measurements for assessing carotid atherosclerotic disease, giving rise to the concept of "vulnerable plaque" [49–53].
  - Several carotid morphologic features have been reported as being associated with an increased risk for stroke, the most studied descriptor being the common carotid artery (CCA) intima-media thickness (maximal carotid wall thickness ≥4 mm is predictive of future carotid ischemic stroke) [54–59] (Fig. 7.5).
  - Carotid plaques with a thin fibrous cap and a large lipid core are also considered to increase the risk for stroke [60, 61], as are ulcerated plaques [62] (MIP and MPR reconstructions: detection of ulceration – up to 94 % sensitivity, 99 % specificity) (Figs. 7.6 and 7.7).
  - Neovascularization and inflammatory changes in the plaque are thought to accompany the processes which lead to plaque rupture and – for a given degree of stenosis – may serve to further stratify acute stroke risk [63, 64]. A recent study based on this reasoning has shown that enhancement of the vasa vasorum adjacent to severe carotid plaque during arterial phase CTA suggests a higher likelihood of symptomatic disease (TIA or stroke) [32, 65] (Fig. 7.8).
- In contrast, plaques with high calcium content, especially when located superficially (Fig.7.9), are thought to be associated with a lower risk of stroke [66, 67].
- Some authors observed in their study that CTA is the best modality for analyzing plaque irregularities because it allows visualization of the atheromatous plaque [59].
  - Visualizes the *degree of stenosis vs. occlusion*:
- CTA is the most appropriate noninvasive method, short of DSA, for differentiating pseudo-occlusion from true complete occlusion (Fig. 7.10) because:
  - CT is unaffected by slow flow and has high spatial resolution; when we have a very slow flow in the presence of a critical focal proximal ICA stenosis, a delayed CTA scan immediately following the arterial phase bolus administration is often helpful for the detection of hairline lumen (pseudo-occlusion) and for the presence of collateral vessels [32, 68].
  - May evaluate the modifications of distal ICA caliber reduction in comparison to its expected size, the contralateral ICA, and the ipsilateral ECA.
- CTA is a highly accurate and precise technique for determining the percentage of stenosis [59].

Precision is reported [46] to depend more on the measurement technique than on the acquisition parameters. The accuracy of stenosis measurement depends on the scanning plane, which ideally should be perpendicular to the carotid artery, used to obtain magnified transverse oblique images [69].

- Axial sections provide the most reliable measurements for stenosis when comparing CTA with DSA and are the most reliable carotid stenosis measurement for different reasons [13, 24, 36, 43, 70–72]:
  - Axial images allow good visualization of the patent lumen apart from vessel wall plaque, even with calcium on the sides (Fig. 7.11).
  - When the residual lumen is elongated in the axial plane, the stenosis at its narrowest point can be measured with much more accuracy than on angiograms (Fig. 7.12).
  - Direct measurement of the ICA, from inner wall to inner wall including any plaque, requires the interpreter to identify the actual ICA wall, not just the contrast-filled lumen; therefore, CTA is the only current angiographic method that allows such high-resolution images of contrast-filled vessels, plaque, and surrounding soft tissues [72, 73] (Fig. 7.13).
  - Axial sections provide stenosis without requiring subsequent post-processing such as calcification subtraction; therefore, calcifications are not a limiting factor; despite difficulty with quantification in such cases, CTA still has an advantage over other imaging techniques by defining the morphology of the calcification, which may have implications regarding the treatment strategy [73].
  - In the case of very coarse wall calcifications, properly wide window level settings can reduce beam-hardening artifacts so that the residual contrast-filled lumen, plaque, and the noncalcified vessel wall can be confidently evaluated [73] (Fig. 7.14).The radiologist interpreting CT angiography studies must therefore have a good clinical experience.
  - The scan plane, which has to be perpendicular to the carotid artery, influences the accuracy of stenosis measurement on axial images (this limitation suggests that axial sections must not be used as the sole means of measuring lesions).
  - Axial sections are obtained by using a post-processing reconstruction technique, such as MIP and/or SSD reconstruction (MIP is more reliable than SSD) (Fig. 7.15); these techniques require lengthy post-processing time and are less efficient in cases with circumferential arterial wall calcification.
  - In very severe stenosis, the decrease in distal ICA diameter precludes an accurate measurement of the degree of stenosis by the NASCET method and usually leads to a classification of cases with ICA diameter lower than that of the external carotid artery as near occlusion (confusion between ICAs and external carotid arteries may be a theoretical limiting factor, particularly in cases with near occlusion) [28, 70] (Fig. 7.16).
- *MIP* and *MPR* reconstructions:
  - MPR: This type of reconstruction offers informative images, better interobserver agreement, and fast and efficient method to analyze both the vascular lumen and the arterial wall.
  - MPR identifies the carotid orientation in order to ensure true cross-sectional measurements, and the analysis of carotid stenosis is performed at the narrowest portion of the carotid bulb on the axial data. Internal carotid arteries (ICAs), identified as passing oblique to the axial plane, are measured perpendicular to their own oblique carotid axis, these measurements being verified with measures from reformats, in order to ensure accuracy in obtaining the narrowest diameter in a true cross-sectional plane [74].
  - The interactive interpretation of CT angiography includes scrolling of axial source images together with two MPR views in orthogonal directions (sagittal and coronal), and if necessary, additional MPR-angled views can be taken; in cases of very short stenosis, the assessment of the stenosis on axial images can become difficult, in which cases MIP reconstructions can help [74] (Fig. 7.17).
  - This technique can lead to an overestimation of stenosis severity and, in cases of tortuous vessels, make interpretation of images difficult (Fig. 7.18). Moreover, this method necessitates a proficient and trained operator [19, 75]. Finally, calcifications can be removed from axial sections by using manual segmentation [19, 76] or sophisticated software [69], but this procedure is time-consuming and can result in an overestimation of stenosis severity with the removal of neighboring pixels [77].
  - MIP provided angiogram-like images and correctly classified most stenosis in different studies.
  - MIP images are used to identify the point of maximal stenosis and to visualize overall vascular anatomy. Mural calcifications constitute a drawback for MIP reconstructions, but the combination of axial and MIP imaging enables an accurate estimation of the degree of stenosis severity in most cases [77].

- Calcifications are easily detected on MIP and can artificially shrink the diameter of the artery, but this might theoretically be avoided with multiple view angles (differentiating between vascular wall calcification and contrast material) [78] (Fig. 7.19).
- In MIP images, the readers attempt to select a windowing producing the best available edge detection for each vessel, in these cases the concentration of contrast medium in the arteries as well as the patient anatomy having an effect on the selection of the best windowing [79] (Fig. 7.20).

– *SSD*:
- The advantage of SSD resides in the possibility of moving, rotating, and adjusting for tilt (Fig. 7.21), therefore providing a better view of the vascular loops, providing more accurate images than conventional angiograms in some cases [70].
- However, even in the absence of calcification, SSD frequently underestimated the degree of stenosis, probably due to the arbitrary selection of the lower threshold (Fig. 7.22), and did not provide a reliable assessment of carotid stenosis [80]. When atherosclerotic plaques are not calcified, MIP reconstructions provide a more reliable measurement of the vascular lumen than SSD [70].
- The 3D display methods offer an additional tool for visualizing the artery anatomy, being used by the physician for the search of possible sites of pathology, useful for demonstration of the diagnosis [20].
  – Some authors [69, 75] consider that accuracy is reduced if extensive calcification is present, but this limitation (even when circumferential calcified plaques are present) can be avoided when MPR and MIP reconstructions are used (Fig. 7.23). With this technique, the whole bifurcation including calcifications at this level can be visualized.
  – Even if the stenosis is located near intramural calcification, decreasing the volume of reconstruction can be used to better visualize the residual lumen. In the case when volume reconstruction is not available, transverse oblique reconstruction can help. So, calcifications should not, therefore, be considered limitations of CTA [59].
    - When using an automated 3D CTA analysis program, several misregistrations of the enhanced carotid artery lumen were noticed (but are quite easy to recognize and correct – Fig. 7.24) [20]:
      – Intramural calcifications (leading to the misregistration of the borders of contrast-enhanced lumen in the carotid bifurcations) [81]
      – Adjacent bypassing vessels
      – Partial volume effects from short segment stenosis
      – Intraluminal low contrast media density
      – Bifurcating vessels [80]
      – Inability of the radiologist to perform accurate placements of the digital calipers in a stenosed artery which has a very small diameter
- *Other limitations and pitfalls*
  – The major disadvantage of the technique is represented by the need to post-process data to remove calcifications, veins, and bone structures from the images (Fig. 7.25).
  – Technical solutions for the reduction of the radiation dose should be aggressively used as the radiation dose of CTA studies is significant.
  – It is not allowed to administer intravenous iodinated contrast substances to patients with renal disease (these patients are indicated to perform US and MRA).
  – In CTA, iodinated contrast agents must be injected at a relatively high flow rate.
  – Metallic implants, stents in the carotid artery (Fig. 7.26), or clips in the neck may cause severe streak artifacts [82]. Pacemakers and defibrillators implanted in the chest are not impediments to CTA of the cervical arteries.
  – Very obese patients are suboptimally imaged (Fig. 7.27).
  – Uncooperative (moving) patients are difficult to scan (accurately motion artifacts appearing in the reconstruction – Fig. 7.28).
  – Dental amalgam may impact the result visualization (dental amalgam artifact – Fig. 7.29).
  – In case of total carotid occlusions, the ascending pharyngeal branch of the external carotid artery can be mistakenly interpreted as a hairline open ICA. This pitfall can be avoided by following the proximal internal carotid artery into the petrous canal at the skull base [79] (Fig. 7.30).

3.2. *MRI*. The unique feature of MRI, in vascular imaging, is represented by its ability to provide excellent contrast between the vessel wall (by offering tissue information) and the adjacent lumen, by using flow-sensitive pulse sequences (flowing blood). This feature, as a noninvasive characterization of plaque morphology, can be used to help prospectively identify the unstable lesion and in assessing the progression or regression of the disease [83].

MRA can be performed without contrast and has no risks related to ionizing radiation [82]; but its utilization as a screening method is limited by the elevated costs and by frequent artifacts.

MRA does not exclude extracranial disease, when it identifies a normal flow in the intracranial vessels [82]. When a hemodynamically significant stenosis is suggested on MRA, a secondary imaging modality needs to be performed [82], because an overestimation of low-flow states on MRA leads to diagnostic uncertainty (sometimes apparent MRA occlusion are in fact proven to be patent vessels, via ultrasound, CTA, or DSA).

Contrast-enhanced MRA (*CE-MRA*) has added further value to MRA. Remonda et al. [97] studied time-resolved CE-MRA in comparison to DSA in a large study population, showing that CE-MRA could become an alternative to DSA in the evaluation of patients with carotid disease. The introduction of contrast material-enhanced carotid MR angiography (MRA) has increased the confidence in MRA imaging because of better depiction of arterial detail [85, 86]. The contrast-enhanced three-dimensional (3D) MRA technique is a rapid acquisition that eliminates many of the TOF-MRA artifacts [87].

- *MR technique:*
  - A surface coil, ideally bilateral, is placed immediately under the mandibular angle, compared to the carotid bifurcation. It is important to ask the patient not to swallow during data acquisition.
  - A standard examination comprises several series of contiguous sections perpendicular to the axis of the explored vessel and covering the whole of the plate, with T1 weighting, proton density (PD), and time of flight (TOF). For the T1 weighting, PD, and TOF, a sequence of type 2D turbo spin echo with fat saturation, ECG synchronization, and black-blood module (double or even quadruple inversion recovery) is used. Note that, for the T1 weighted, it is possible not to use cardiac synchronization to shorten the TR of the sequence but at the cost of increased artifacts related to the movement of the wall.
- *MR findings*: MRI of carotid atherosclerosis provides a unique method to characterize plaque morphology and tissue composition (it can examine the fibrous cap status in vivo, thus making it a powerful tool to identify high-risk plaques and is also well suited for studying atherosclerosis progression and regression) and to a certain extent, plaque inflammation [2]. The multi-weighting analysis of the plaque makes it possible to identify the components based on the signal of the adjacent muscle and on the main morphological characteristics of plaque instability (rupture of the fibrous cap, the presence of a lipid core, ulceration, intraplaque hemorrhage, loose matrix, and calcification). We can identify:
  - *Calcifications* which, in the absence of protons, appear as a signal on all weights.
    - The role of calcification as a criterion of instability or stability of the plaque is subject to controversy [88].
  - *The lipid core* (Fig. 7.31) which is formed mainly of cholesterol monohydrate in crystalline phase and cholesterol esterified by fatty acids in semiliquid phase having a low mobility and non-fluid physical state – all these give a complex signal, variable, different from the usual signal of the fat (e.g., subcutaneous). It appears as low-intensity TOF, variable signal in T1 and DP, and more often as intermediate signal in T2 [88].
    - The presence of a lipid core is considered a risk factor of thromboembolism due to the ability of this material to embolize the downstream bed in case of rupture of the fibrous cap.
  - *The fibrous cap* that oversees the plaque appears as a band adjacent to the light on the isointense signal or even as slightly hyperintense signal relative to muscle in T1, T2, and PD and as a signal in TOF. Intraplate fibrosis has an identical signal [88].
    - Several studies showed an increase of the relative risk of ipsilateral stroke of about 20 in cases of ruptured fibrous cap on the reference MRI. Intravenous injection of contrast media based on gadolinium seems useful to highlight the neovascularization indicator of inflammation within the plaque but also to better delineate the lipid core (because this core does not enhance after injection, unlike the surrounding fibrous tissue) as well as the fibrous cap.
    - The ulceration is the combination of the rupture of the fibrous cap and the more or less complete cleansing of the heart of the plaque. It is responsible for the jagged, craggy aspect of the plaque. It may be associated with the presence of intraluminal contact thrombus.
  - *The loose matrix* is much hydrated and thus appears as low intensity on T1 and as hyperintensity signal on T2 and DP.
    - The amount of loose matrix would be greater in the plaques which have undergone proliferation/repair mechanism than in intact plaques, since this matrix corresponds to a sparse proliferation of smooth muscle cells in response to plaque rupture. However this loose matrix is often difficult to individualize from the rest of the plate and seems to be a secondary end point of instability [88].
  - The presence of a possible *intraplaque hemorrhage* appears as hyperintense signal in TOF and T1 and, depending on the age of hemorrhage, as low-intensity signal on DP and T2 (recent hemorrhage) or as hypersignal on DP and T2 (less recent hemorrhage).
    - The intraplaque hemorrhage is described as an instability of the plate/plaque histology factor. Takaya et al. [108] reported a relative increased risk of stroke by 5 in the case of intraplaque hemorrhage. In addition, for the same team, an increased risk is related to the size of the bleeding.
  - The presence of a *possible intraluminal juxta-plaque thrombus*, shown more as hyper-signal in TOF and in T1 as it is more recent.
  - Magnetic resonance angiography can be combined with multicontrast, *high-resolution black-blood spin-echo MRI sequences* [90].

    - MRA provides information on the severity of stenotic lesions and their spatial distribution.
    - The high-resolution black-blood sequences allow the characterization of plaque composition.

    This strategy may potentially allow patient risk stratification and selection of the adequate treatment modality [91].
  - Intravenous injection based on the gadolinium contrast agent seems useful to highlight the neovascularization indicating the inflammation within the plaque but also to better delineate the lipid heart as well as the fibrous cap.
  - The contrast enhancement of the plate after intravenous injection of gadolinium corresponds to two passive phenomena:
    - Increasing the permeability of the wall
    - Neovascularization
  - It is thus possible to show a contrast enhancement greater in the symptomatic plaques than in stable plaques and a different kinetics of the contrast enhancement as a function of the intensity of neovascularization.
  - In addition, the contrast enhancement appears clearly more important in fibrosis (especially strong neovascularization area) than the lipid heart (because it does not enhance after injection, unlike the surrounding fibrous tissue). The maximum contrast difference between the two structures is reached 10 min after injection and lasts for the next 20 min [88].
- *MRA*: The techniques commonly used for carotid MRA are time-of-flight imaging (*TOF-MRA*), which can be done either with *2D* or *3D* acquisition, and gadolinium contrast-enhanced angiography (*CE-MRA*).
  - *TOF-MRA* is susceptible to degradation by phenomena such as turbulence and slow flow (which disrupt smooth linear flow of blood through the vessel lumen), because the technique relies on the movement of magnetized blood through the volume being imaged. 3D TOF provides better spatial resolution than 2D TOF, but takes longer, with greater likelihood of patient movement during the exam.
    - TOF-MRA closely approximates catheter-based stenosis measurements [92–94] and has the added advantage of not requiring contrast agent administration.
    - TOF-MRA is usually acquired through the carotid bifurcation only and with a higher spatial resolution (providing an elevated ability to detect small ulcers), while CE-MRA is typically optimized for coverage from the aortic arch to the skull base.
    - This technique has a lower sensitivity to vascular calcification and is very useful in excluding a hemodynamically significant vascular stenosis.
    - TOF-MRA is often inadequate for detecting tandem lesions [95] because it leads to signal loss within a severely compromised lumen [96, 97].
    - There will be a tendency to classify normal arteries as mildly stenosed, if a combination of reversed flow and non-laminar flow occurs in the normal carotid bulb giving rise to apparent flattening of the bulb on MRA, more pronounced with the 2D technique.
    - Recirculating blood proton saturation could also affect the signal within an ulcer crater [98].
    - Apparent signal gaps can occur with the 2D magnetic resonance angiogram techniques utilizing a traveling saturation slice [99]. This most commonly occurs when there is a loop in the artery and creates a peculiar discontinuity in the apparent course of the vessel (in these cases, a 3D technique can be useful to clearly view the loop).
    - Distal to severe stenoses, flow is often turbulent rather than laminar, resulting in signal loss due to intravoxel dephasing, as well as the admixture of magnetized and demagnetized blood in a single voxel. This phenomenon is called "signal dropout." TOF-MRA is inadequate to distinguish between true complete occlusion and cases with slow flow distal to a severe stenosis ("hairline lumen"), because signal dropouts appear in both cases [32].
    - Apparent discontinuities can also occur if the patient moves appreciably during the acquisition of the 2D MRA. This is easy to identify, and unless the slice being imaged at the time of motion is in a critical position, such as at the stenosis, it is not usually a serious problem [99].
    - Two approaches are suggested to overcome poor visualization of the arch origins as well as motion and "venetian blind" artifacts [82]:
      1. Review source images for artifacts.
      2. Add a contrast-enhanced neck MRA as a "belt and suspenders" technique in case the 2D TOF fails.
    - A recently formed thrombus can generate quite high signals to the extent that it may show on the processed MRA. This could theoretically be mistaken for blood flow, although the signal from thrombus has a different quality, which can be recognized with experience.
    - *3D TOF-MRA* with various "angiographic-like" reconstructions (Fig. 7.32) is able to accurately demonstrate hemodynamically significant stenosis of carotid arteries [19, 42, 100–102]. Besides these reconstructions, the reviewing of axial source images is of value for the definition of the degree of stenosis [13, 103–105].

- Recent studies proved 3D TOF-MRA to be moderately accurate for evaluation of minor atherosclerotic changes in carotid arteries [106].
- The post-processing technique of MIP used to convert the original axial sections into a projection angiogram can lead to apparent reduction in vessel diameter, overestimation of blood turbulence or stenosis, and poor visualization of small vessels or vessels with slow flow, because the technique results in some loss of the lower intensity features of vessels [107].

– *CE-MRA* is superior to TOF sequences and provides better visualization of the arterial lumen [32] (Fig. 7.33):
- CE-MRA is significantly less sensitive than TOF-MRA to flow artifacts, though intravoxel dephasing can still reduce accuracy. This is because CE-MRA is physiologically more analogous to conventional angiography, relying primarily on the presence of endovascular contrast rather than on blood flow for luminal measurement. This lumen-filling characteristic allows depiction of slow or stagnant flow, including that in ulcers [87].
- Another advantage of the contrast-enhanced technique is the ability to image from the aortic arch through the intracranial circulation.
- In their study, M. Etesami et al. indicate that CE-MRA detects more carotid plaque ulcers than TOF-MRA and these misses are influenced by hemodynamic patterns of blood flow that depend on ulcer orientation (proximally pointing), position relative to narrowing, and geometry (low neck-to-depth ratio) [67].
- With gadolinium-enhanced MRA, overestimation of the degree of stenosis tends to occur, as shown by many studies [94, 101]. These artifacts can be due to excessive section thickness, causing a partial volume effect [11, 109]. Concerning stenosis degrees greater than 70 %, the residual lumen is smaller than pixel size. Despite a short echo time, intravoxel dephasing can occur. The presence of hemodynamic modifications can also explain the signal loss; overestimation of stenosis with gadolinium-enhanced MRA can occur because the stenosis causes a decreased flow that leads to a reduced concentration of contrast agent in the distal arterial lumen [110]; this phenomenon appears especially in cases of evaluating the degree of stenosis in small vessel lumens [59].
- Due to its lack of spatial resolution, CE-MRA is not sufficiently sensitive for the detection of plaque irregularities [59].
- Image quality in CE-MRA is highly dependent on correct contrast bolus timing and imaging parameters [111].
- Venous contamination may occur with the contrast-enhanced neck MRA; however, reconstructing the source images into the axial plane can resolve questions due to overlap of venous and arterial structures on the coronal and sagittal MIP reconstructions [82].
- CE-MRA may also be inaccurate in the presence of metallic surgical clips which introduce susceptibility artifacts [112], although this occurs with TOF imaging as well.

- *Brain T2WI*, *FLAIR*, and *DWI* – look for secondary signs of extracranial ASVD in the brain.
- *Other limitations and pitfalls*
  – Pitfalls in MRA evaluation of CAVD include overestimation of stenosis (more frequently in non-contrast examinations) when compared with DSA. However the rate of misclassifications appears to be low enough to outweigh the risks of DSA (up to 1 % risk of stroke at some centers and in some trials) [44, 113]. In part responsible for the discrepancy between MRA and DSA is the fact that DSA, compared with rotational angiography, may underestimate the degree of carotid stenosis. Hence it can be concluded that underestimation by DSA, rather than overestimation by MRA, is in part responsible for the discrepancy [32, 114]. In this line of thought, it is also important to note the MRI inability to discriminate between subtotal and complete arterial occlusion.
  – Evaluation of the post-stented carotid can also be limited by a signal dropout from metallic susceptibility or incompatible implanted devices (such as pacemakers, defibrillators, cerebral aneurysm clips or in those who have undergone certain other medical procedures). Also problematic is the inability to examine the substantial fraction of patients who have claustrophobia, extreme obesity, etc.
  – The relative insensitivity to arterial calcification of the MRA represents one of its notable strengths relative to carotid ultrasound and CTA. MRI may be used, in the same way as sonography, to assess atheromatous plaque morphology [115, 116], but further validation is required in order to assess the utility of this application in clinical practice.
  – The lack of generally accepted protocols with standardized sequences for multicontrast imaging leads to methodological limitations which in turn limit its application to hospital with MRI physicists able to modify these imaging parameters. In addition, a validated automated operator-independent software for quantitative assessment of plaque dimension and composition does not seem to have been developed [90].
  – Finally, the high costs associated with this technique will limit the use of MRI for screening purposes [90].

7.3 Conclusions and Future

In general practice, duplex sonography is performed as a screening examination. Cervical and intracranial CTA are most commonly performed as part of an acute stroke evaluation. Cervical CTA is most commonly performed for patients in whom the detail of the carotid stenosis is needed prior to surgery and for the ones who have contraindications for MRI (e.g., pacemaker, aneurysm clip). Cervical MRA using a TOF technique now represents the most commonly performed follow-up examination for asymptomatic patients with significantly abnormal carotid duplex ultrasound results as well as for symptomatic patients. Those patients in which the TOF study is not adequate require a CE-MRA of the cervical circulation to be performed [17].

Current imaging research does not try to simply measure a vascular caliber change, but instead is focused on modalities that improve the identification of potentially vulnerable atherosclerotic plaque. Currently, standard NASCET criteria miss the detection of ulcerative or irregular plaques having unstable characteristics that are at high risk of embolization. MRI-based techniques such as high-resolution vessel wall imaging, black-blood, and conventional gadolinium-based enhanced vessel wall imaging are all very useful in plaque characterization [82]. In that respect, we can conclude that MRI might permit a noninvasive means of determining the response to medical management or even the potential for targeted therapy.

Among the advantages of CE-MRA, we can mention reliable venous suppression and high spatial resolution, despite imaging times approaching 1 min. The use of contrast material provides an examination physiologically analogous to conventional angiography and allows depiction of subtle vascular irregularities and ulceration. The performance and accuracy of CE-MRA appears to be adequate to replace conventional angiography in the preoperative evaluation of patients prior to carotid endarterectomy [87]. However, MRI methods capable of imaging other important aspects of atherosclerotic disease in vivo, such as inflammation, neovascularization, and mechanical forces, have surged and may aid in advancing the understanding of the atherothrombotic disease [57, 90, 117].

MRI can also be combined with other imaging modalities such as ultrasound and nuclear medicine to create a comprehensive evaluation of carotid atherosclerosis starting from tissue compliance, composition, all the way to inflammation [2].

Like MRA, CTA is undergoing rapid technological evolution. Faster, higher-resolution imaging and larger fields of view are all facilitated by the increase in the number of detector rows, and 16-, 32-, 64-, 256, and 320-row detector and dual-source systems are already in clinical use [118, 119]. This type of scanners, with increased number of detector rows, offers faster acquisition times during the arterial phase. They also reduce motion and respiratory artifacts and lessen the volume of contrast required. Equipment, imaging protocols, and interpreter experience factor heavily into the accuracy of CTA [120–123], but in contemporary studies, CTA was compared favorably with catheter angiography for evaluation of patients with CAVD, with 100 % sensitivity and 63 % specificity (95 % CI 25–88 %); the negative predictive value of CTA demonstrating <70 % carotid artery stenosis was 100 % [38]. However, according to a study that compared sonography, CTA, and MRA performed with and without administration of intravenous contrast material, the accuracy of noninvasive imaging for evaluation of cervical carotid artery stenosis seems to be generally overestimated in the literature [124].

As is the case with carotid duplex sonography, transcranial Doppler sonography, MRI, and radionuclide imaging to assess cerebral perfusion, there is no convincing evidence that available imaging methods reliably predict the risk of subsequent stroke, and there is no adequate foundation on which to recommend the broad application of these techniques for evaluation of patients with cervical arterial disease [17].

Image Gallery

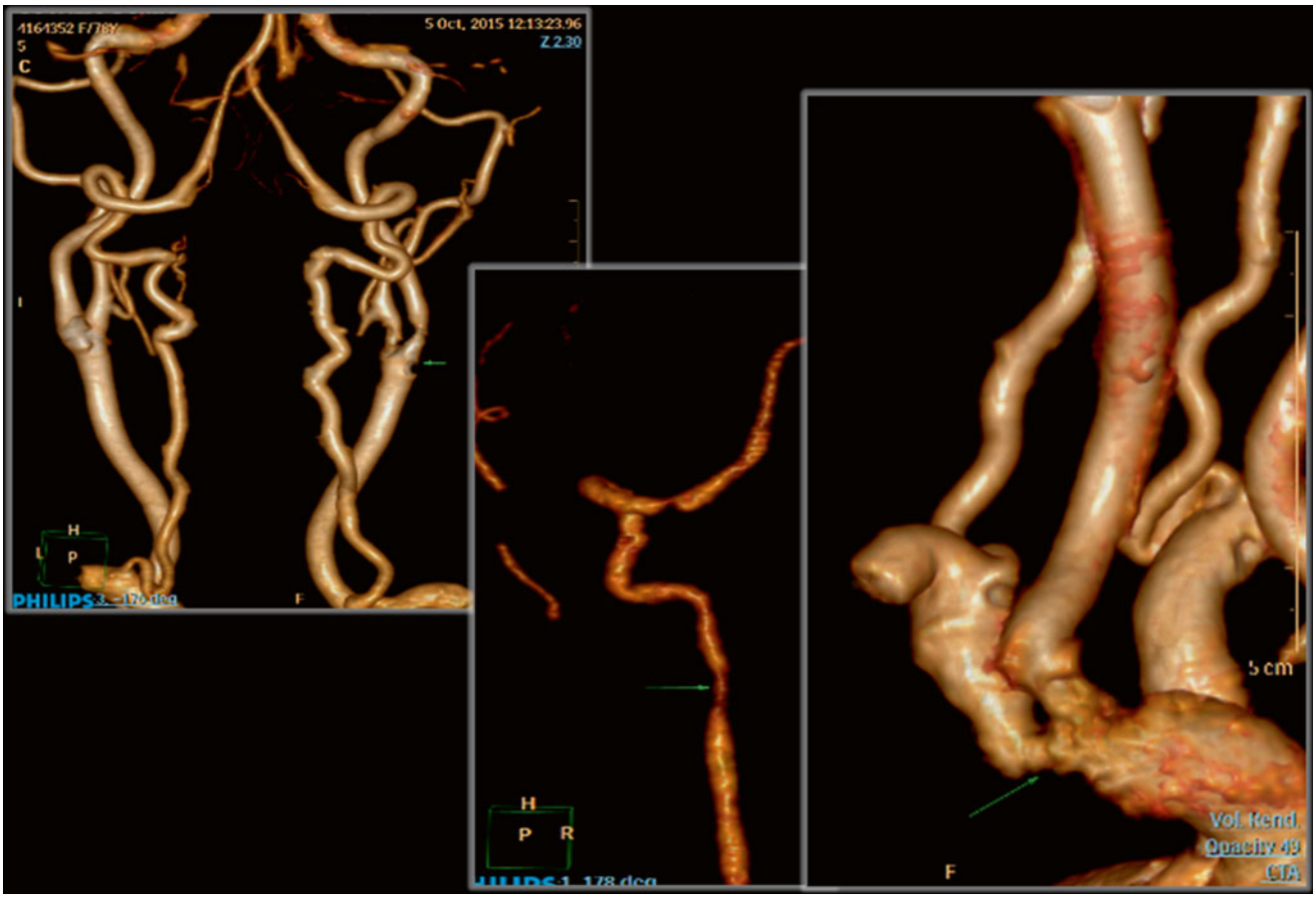

Fig. 7.1 CAVD most commonly involving the carotid bulb, but may involve also any of the extracranial cerebral arteries and the large vessel origins from the aortic arch

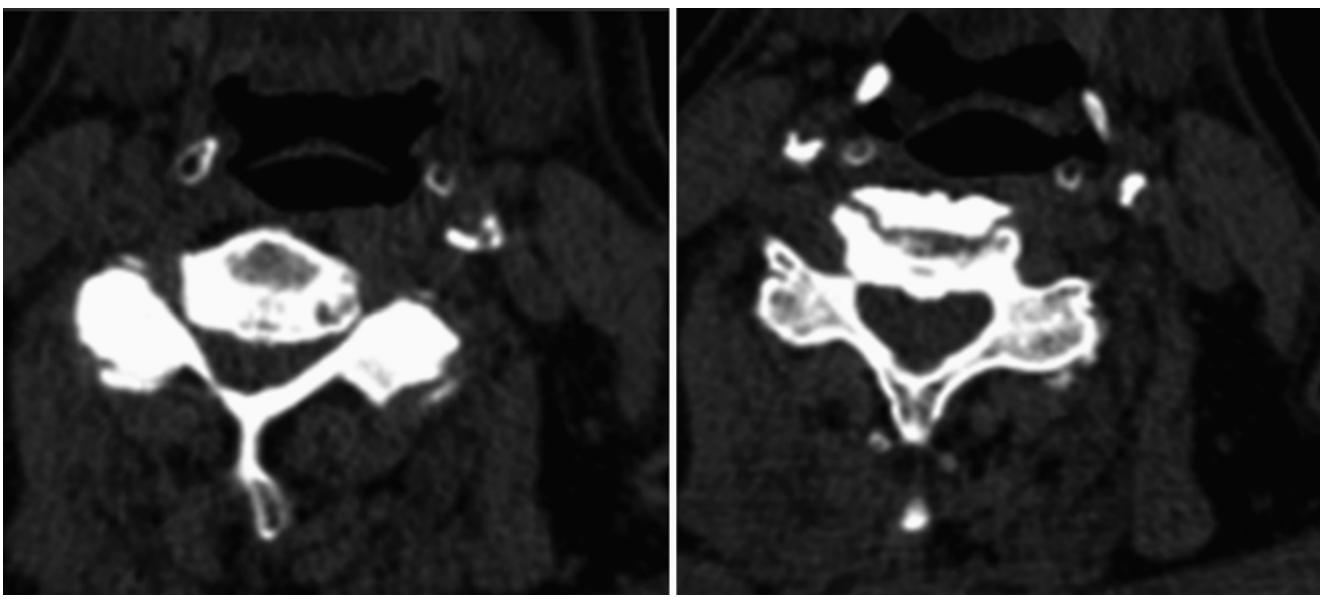

Fig. 7.2 Calcified CAVD plaque at CCA bifurcation

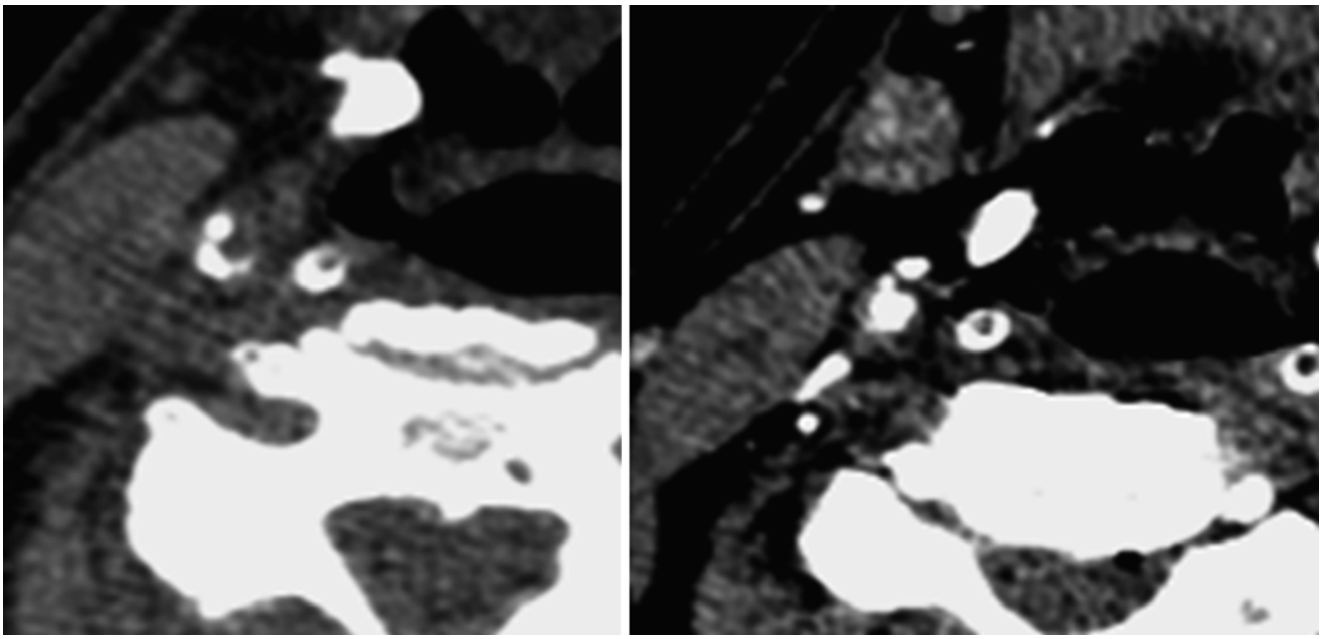

Fig. 7.3 CECT decreases the ability to visualize calcified plaque

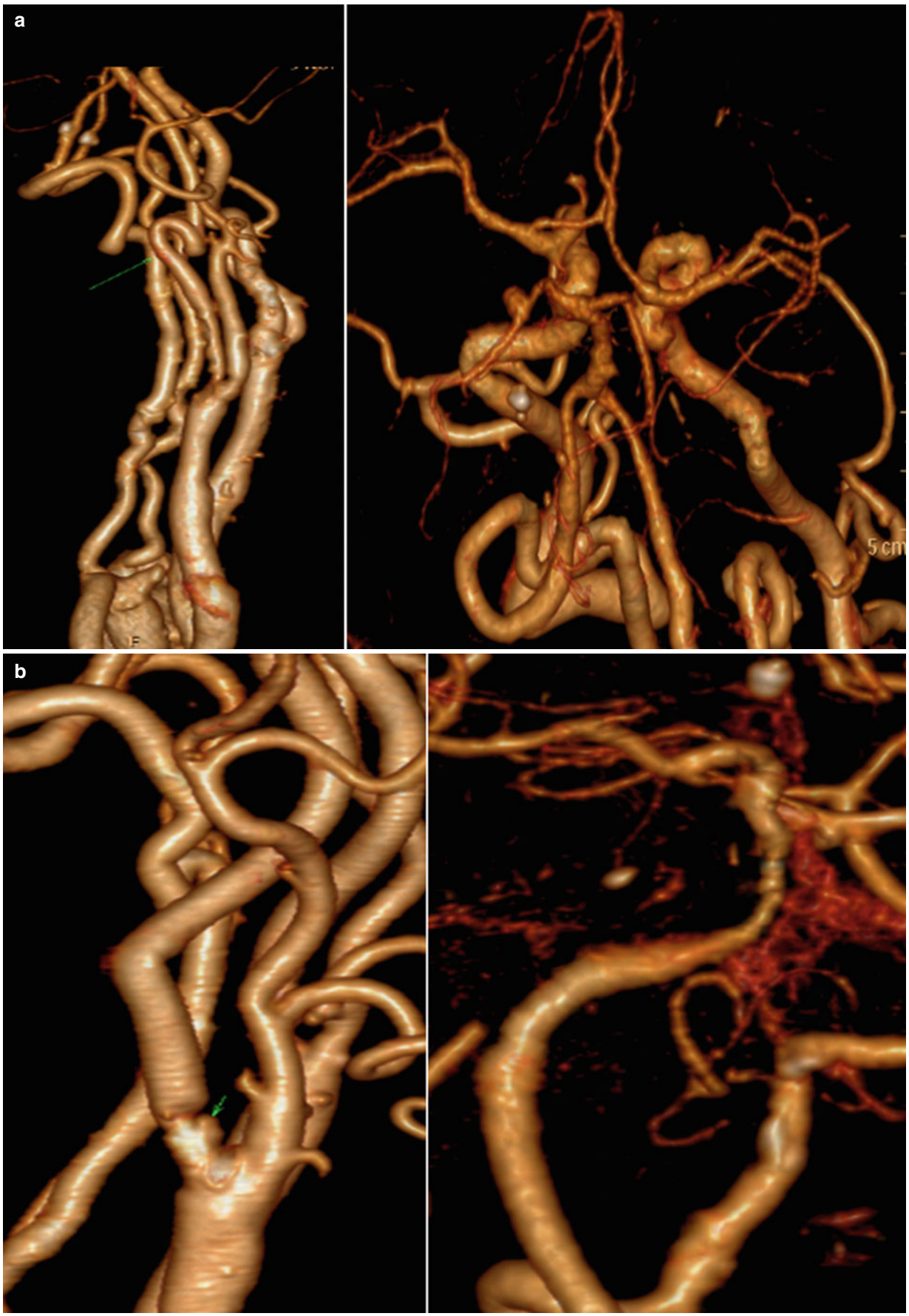

Fig. 7.4 The CTA depicts a variety of additional abnormalities: loops, aneurysms, ulcers, and distal lesions in the ICA

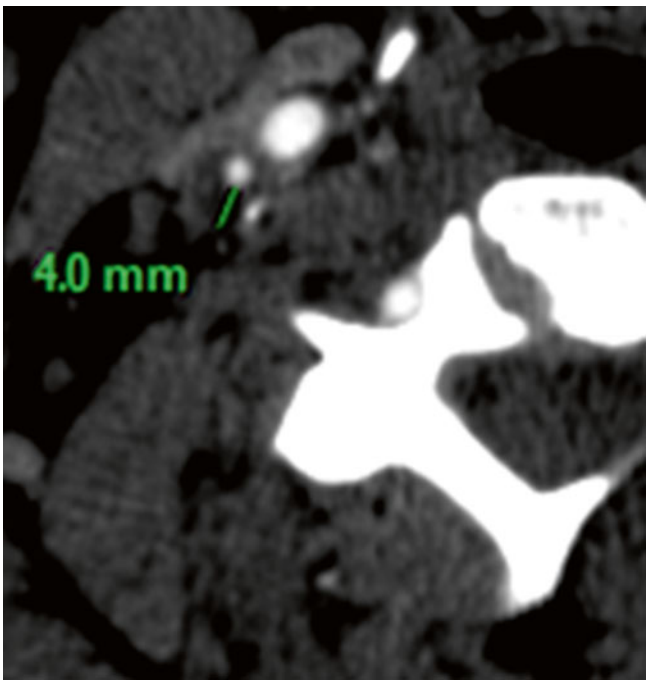

Fig. 7.5 Maximal carotid wall thickness ≥4 mm is predictive of future carotid ischemic stroke

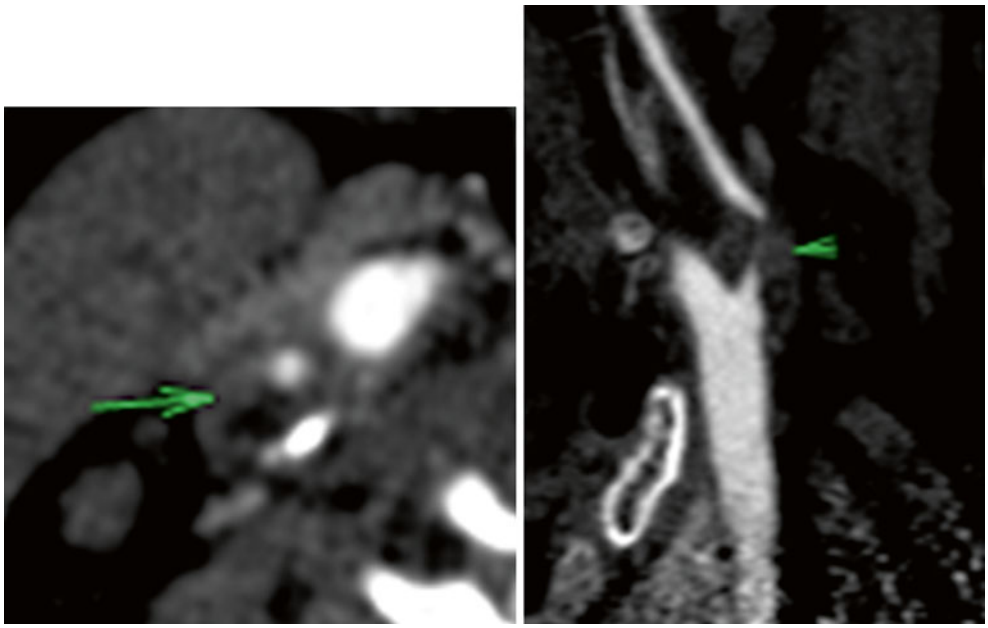

Fig. 7.6 Carotid plaques with a thin fibrous cap and a large lipid core (indicated by arrow in image) are considered to increase the risk for stroke

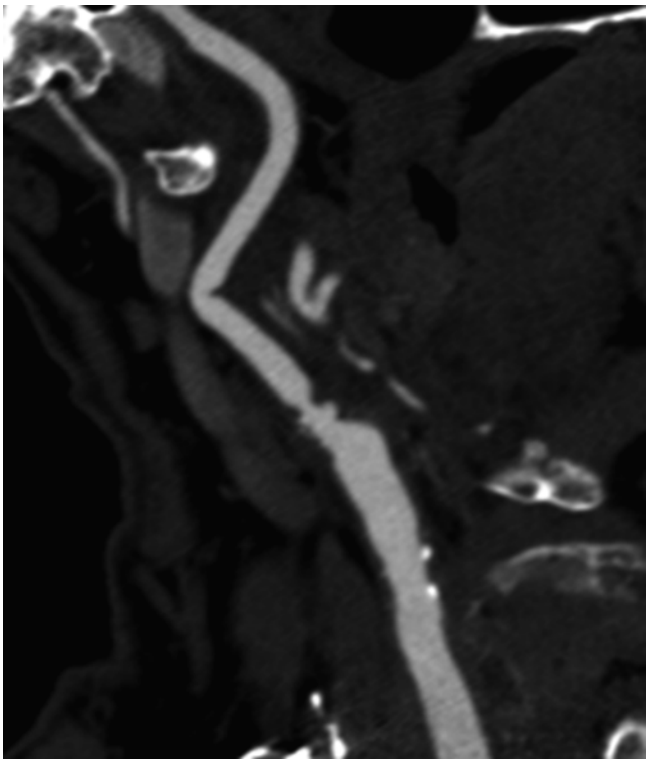

Fig. 7.7 Ulcerated plaques (MIP reconstruction)

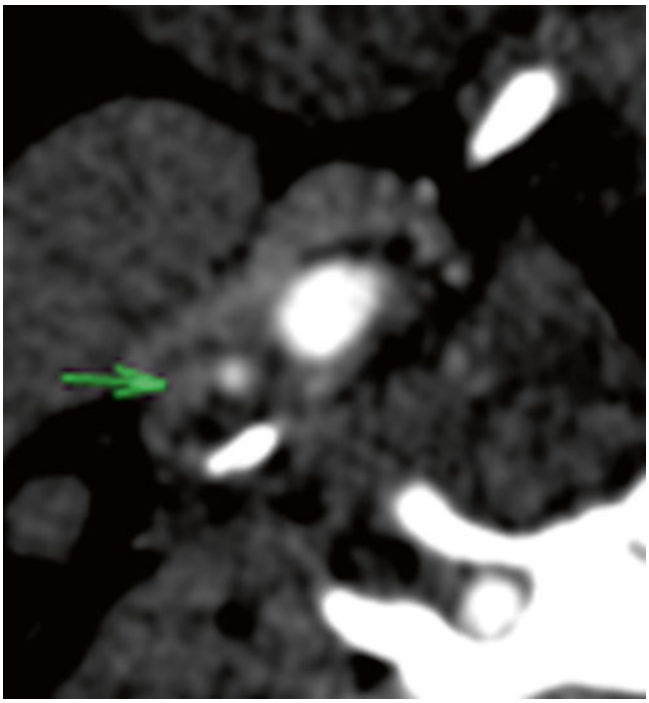

Fig. 7.8 That enhancement of the vasa vasorum (indicated by arrow in image) adjacent to severe carotid plaque during arterial phase CTA

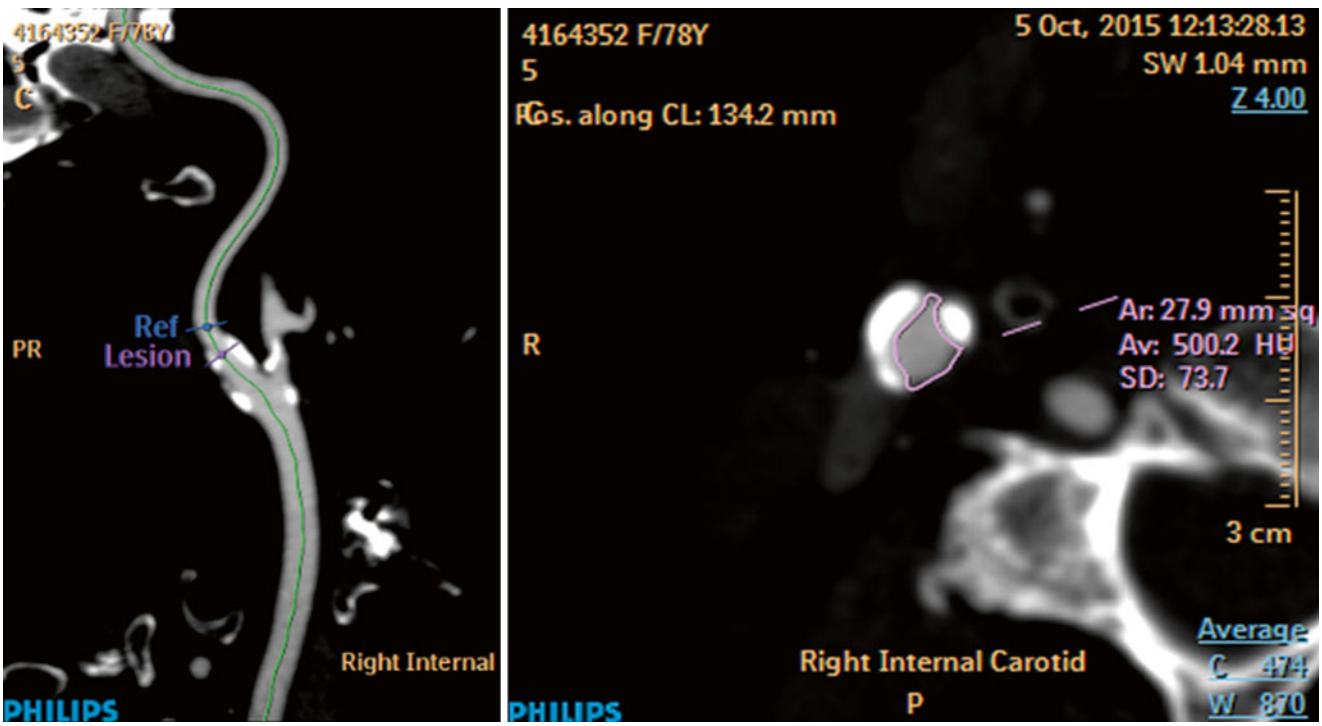

Fig. 7.9 Plaques with high calcium content

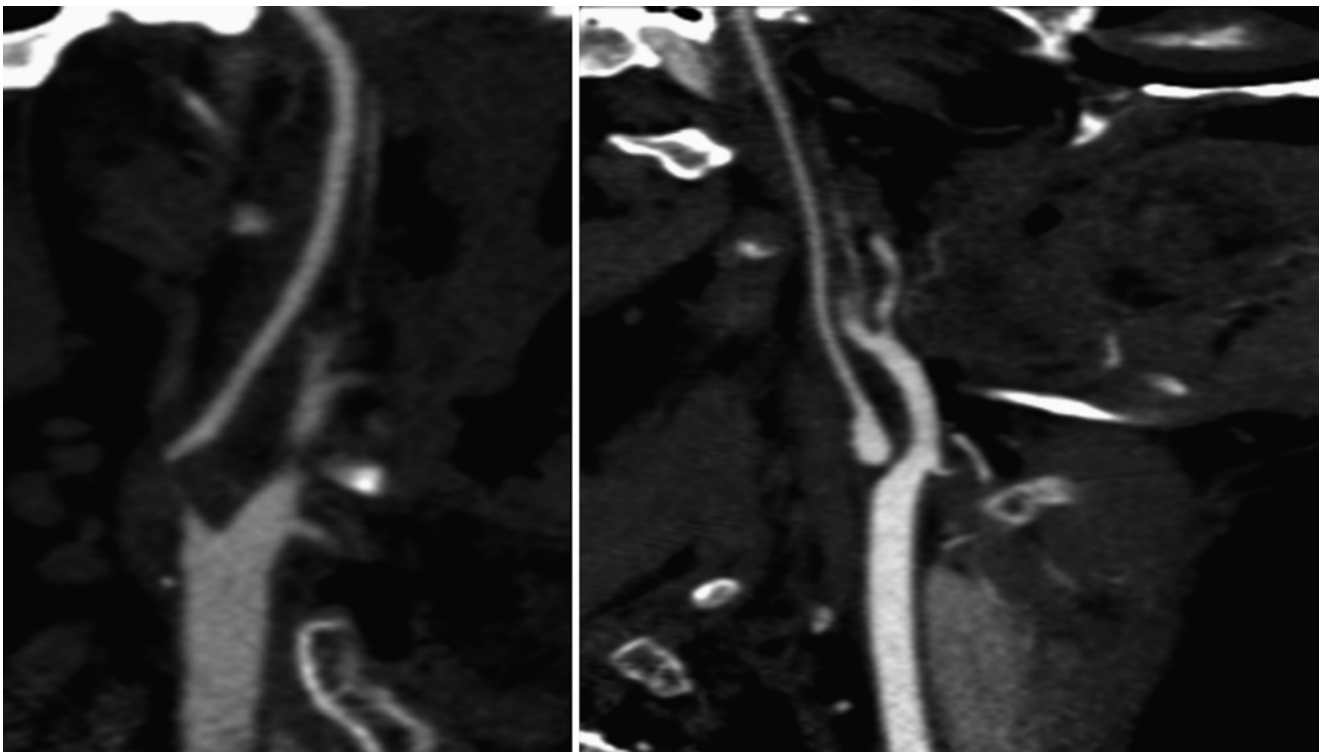

Fig. 7.10 CTA is the most appropriate noninvasive method, short of DSA, for differentiating pseudo-occlusion from true complete occlusion

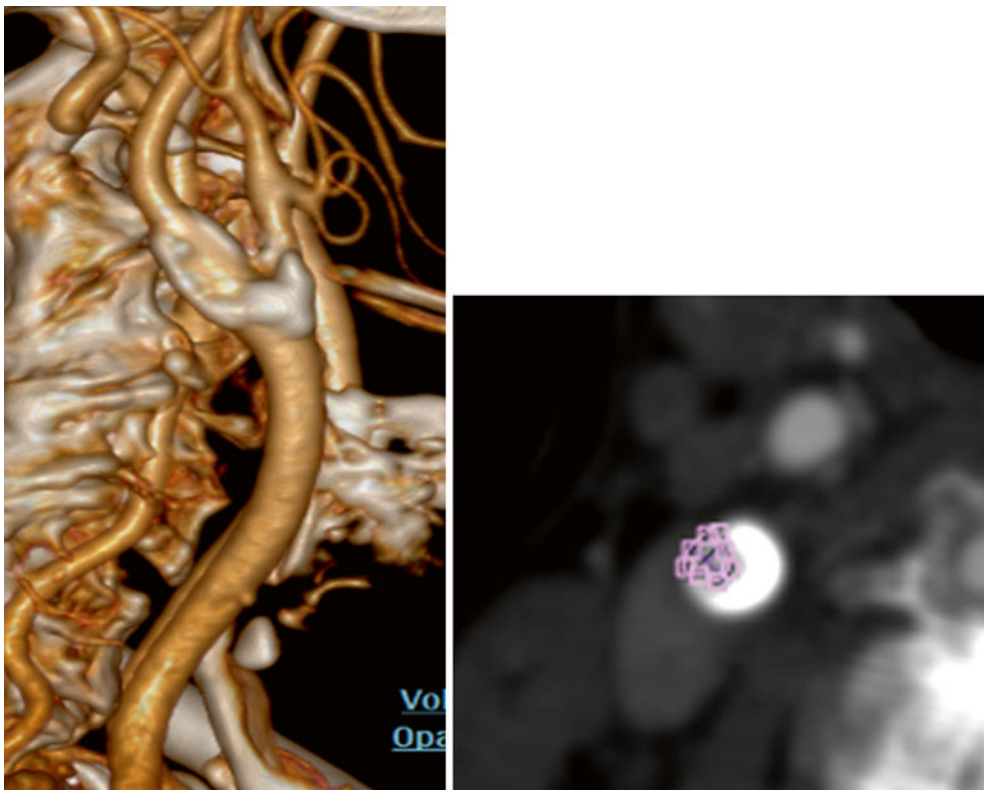

Fig. 7.11 SSD and axial image: Axial images allow good visualization of the patent lumen apart from vessel wall plaque, even with calcium on the sides

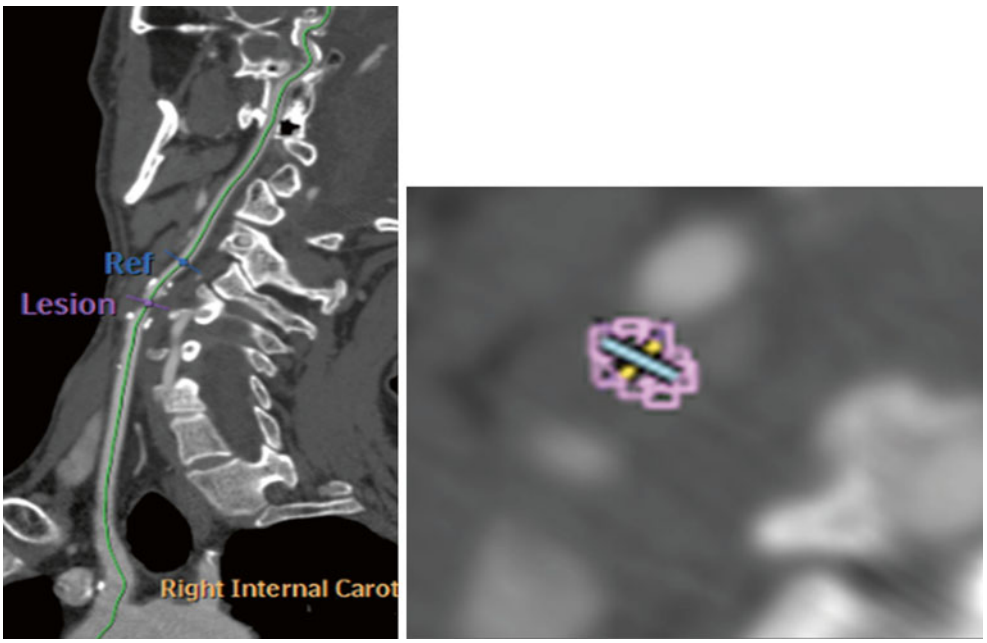

Fig. 7.12 When the residual lumen is elongated in the axial plane, the stenosis at its narrowest point can be measured with much more accuracy than on angiograms

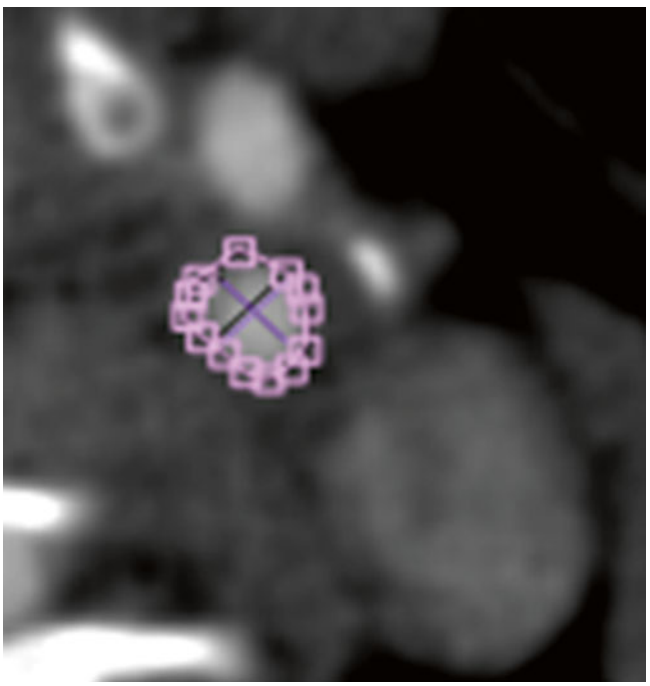

Fig. 7.13 CTA is the only current angiographic method that allows such high-resolution images of contrast-filled vessels, plaque, and surrounding soft tissues

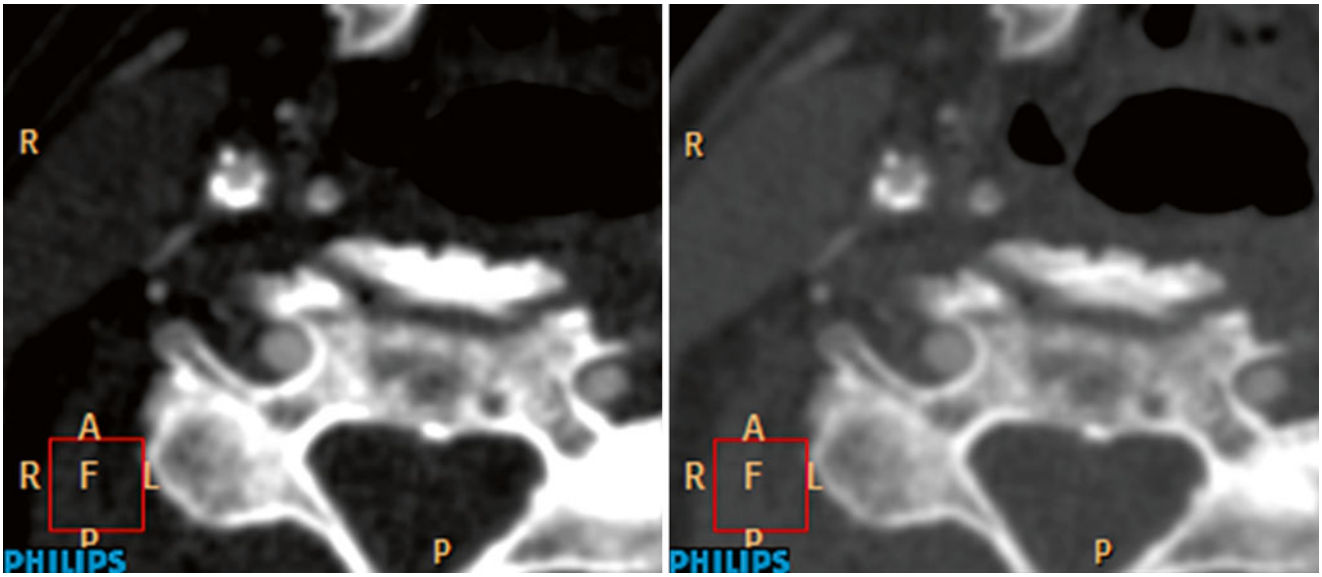

Fig. 7.14 In the case of very coarse wall calcifications, properly wide window level settings can reduce beam-hardening artifacts

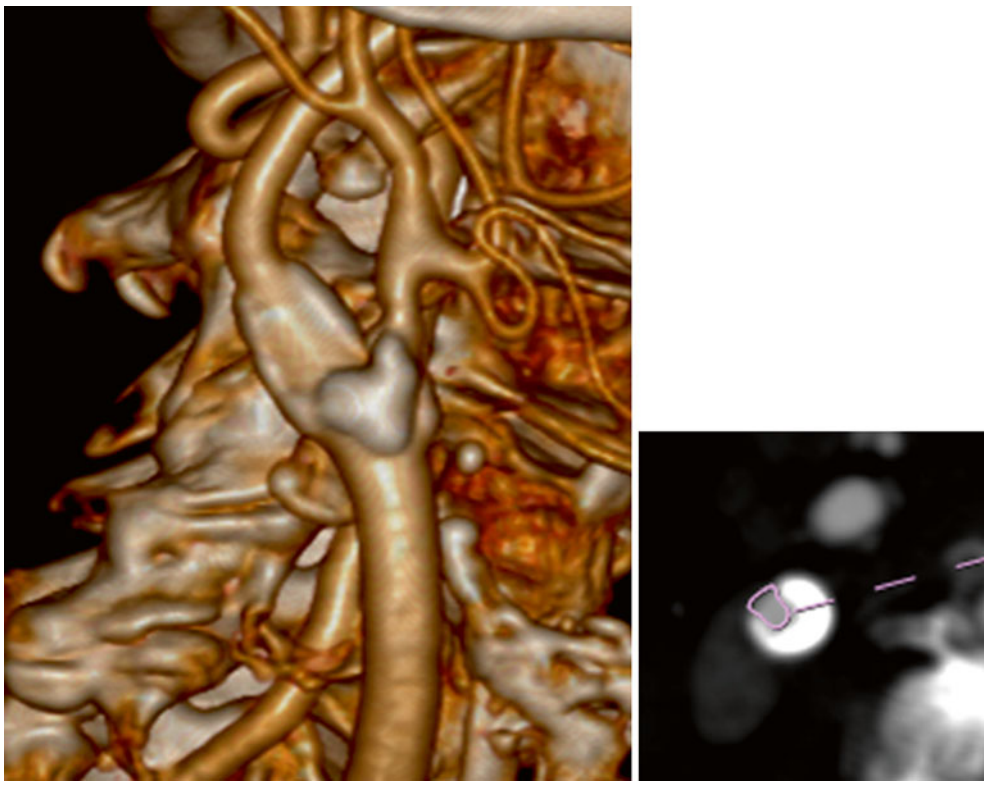

Fig. 7.15 Axial sections are obtained by using a post-processing reconstruction technique, such as MIP and/or SSD reconstruction (MIP is more reliable than SSD)

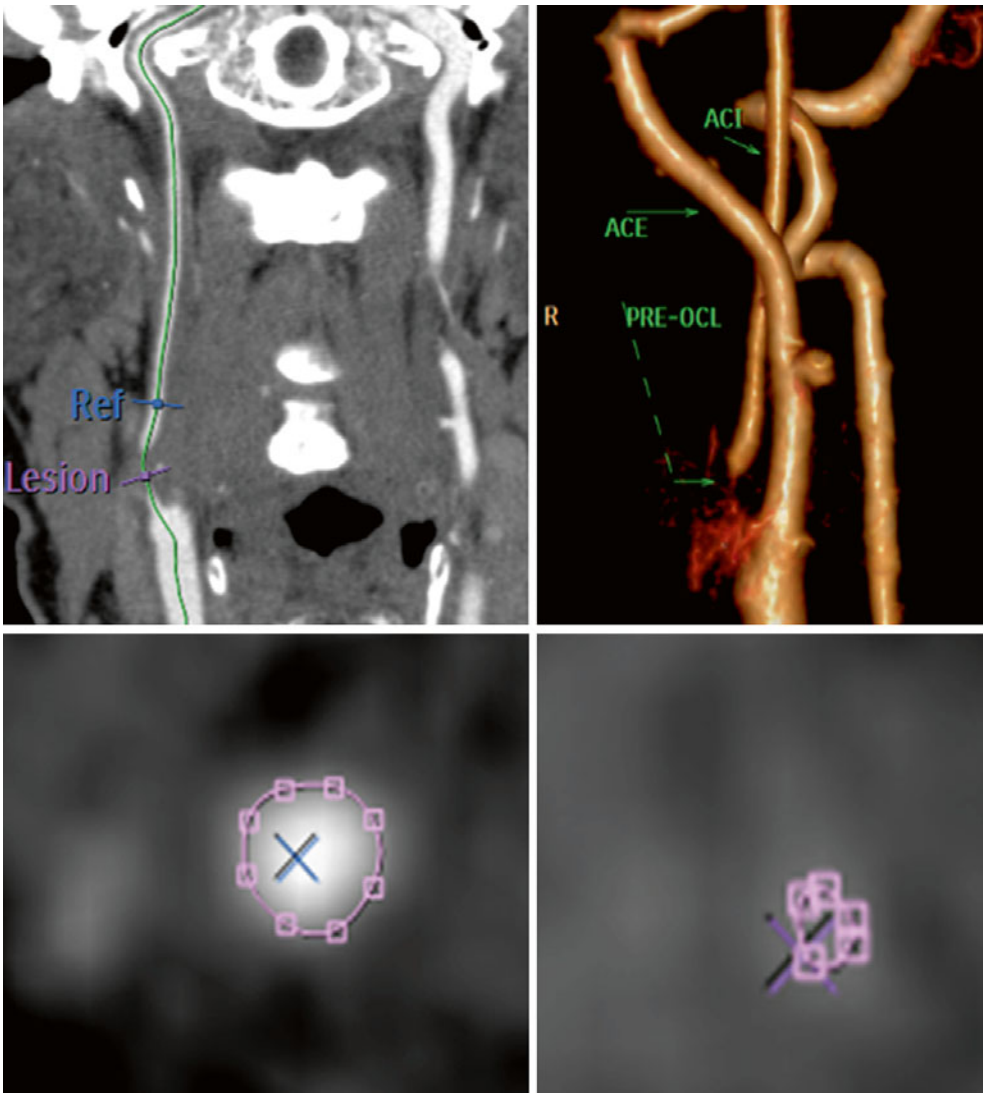

Fig. 7.16 In very severe stenosis, the decrease in distal ICA diameter precludes an accurate measurement of the degree of stenosis by the NASCET method and usually leads to a classification of cases with ICA diameter lower than that of the external carotid artery as near occlusion (in image ACI, ACE - Internal and External Carotid Arteries, PRE-OCL - Preocclusion)

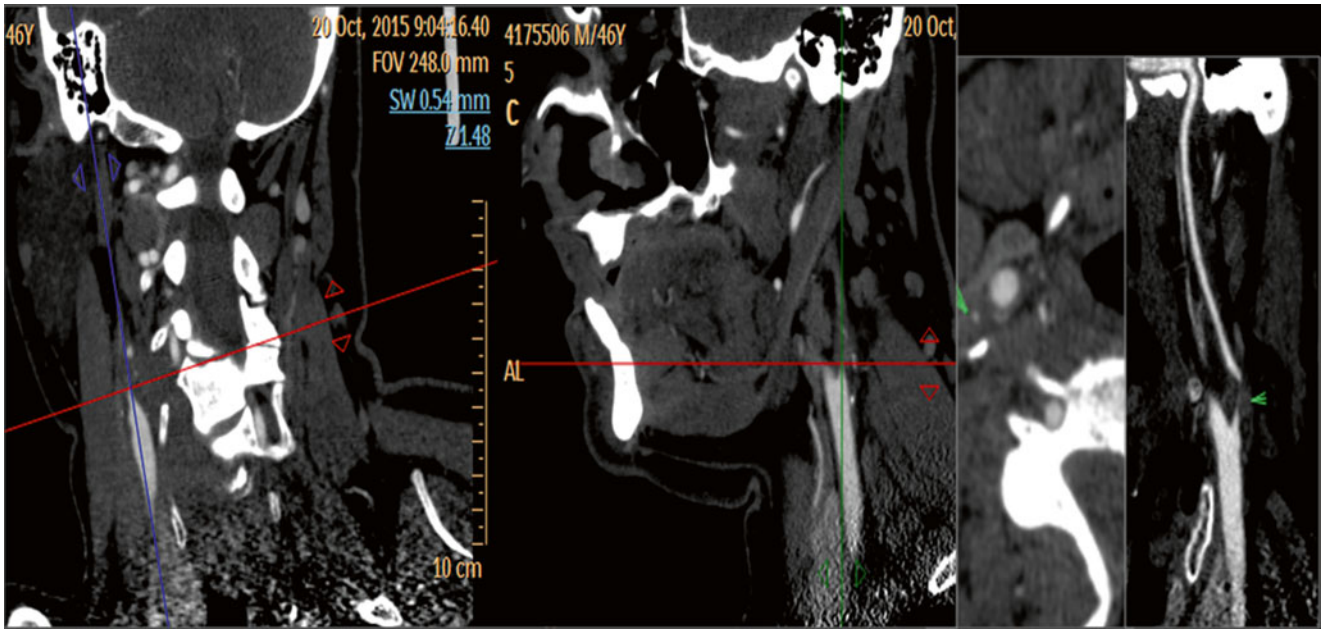

Fig. 7.17 MPR: in cases of very short stenosis, the assessment of the stenosis on axial images can become difficult, in which cases MIP reconstructions can help

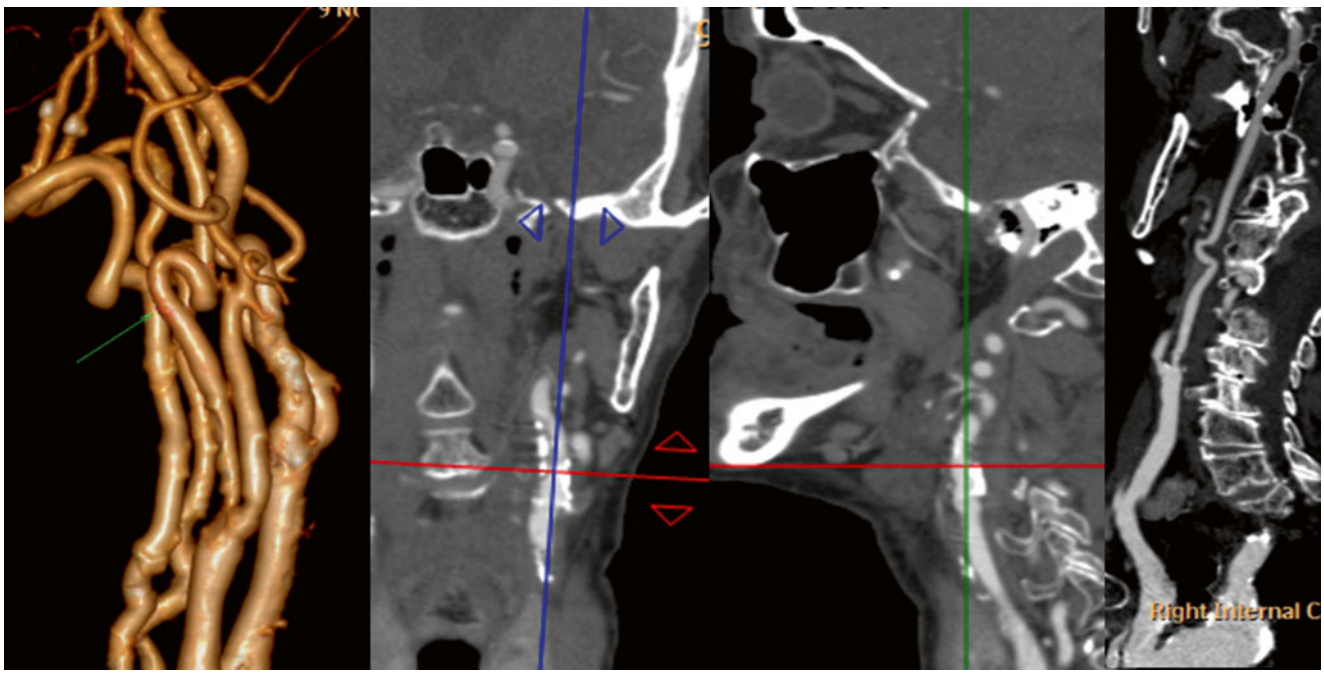

Fig. 7.18 In cases of tortuous vessels, make interpretation of images difficult; MIP reconstructions can help

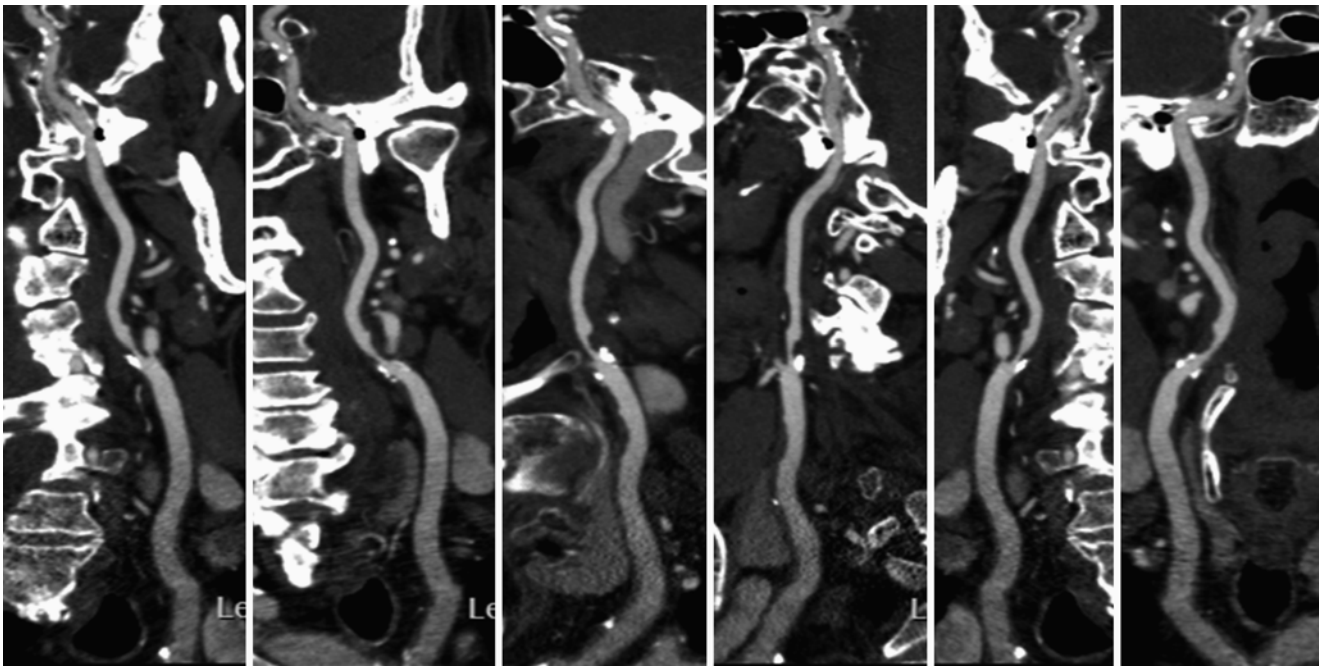

Fig. 7.19 MIP: calcifications are easily detected on MIP and can artificially shrink the diameter of the artery, but this might theoretically be avoided with multiple view angles

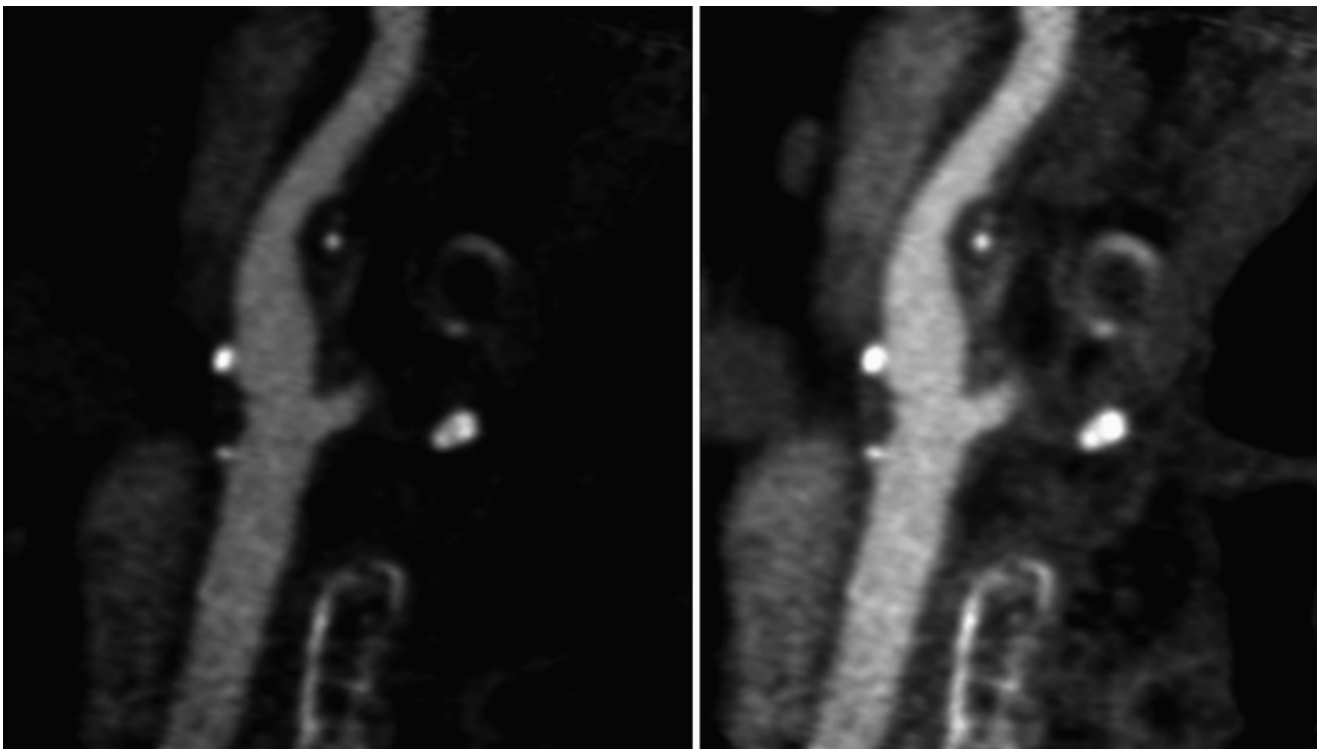

Fig. 7.20 MIP: the readers attempts to select a windowing producing the best available edge detection for each vessel

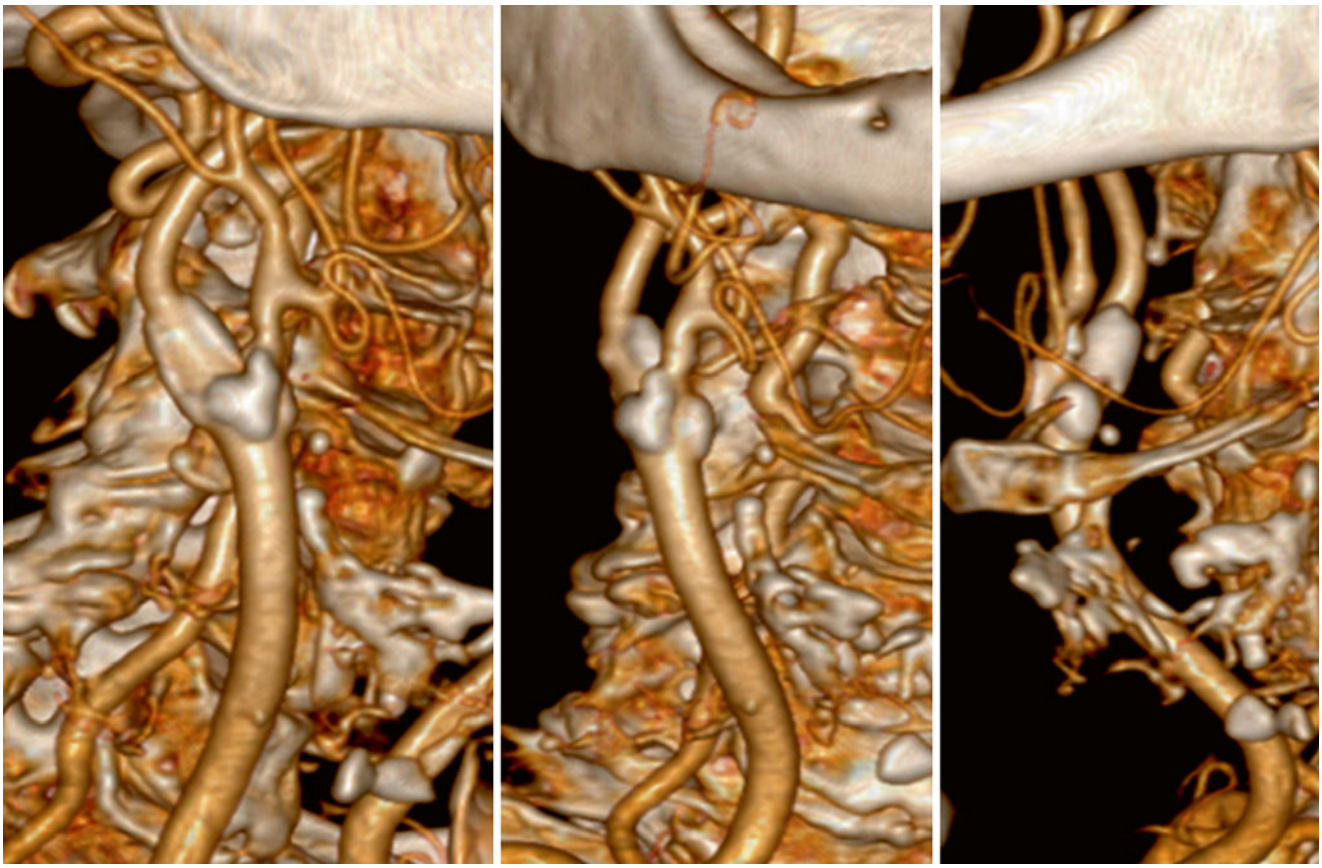

Fig. 7.21 The advantage of SSD resides in the possibility of moving, rotating, and adjusting for tilt

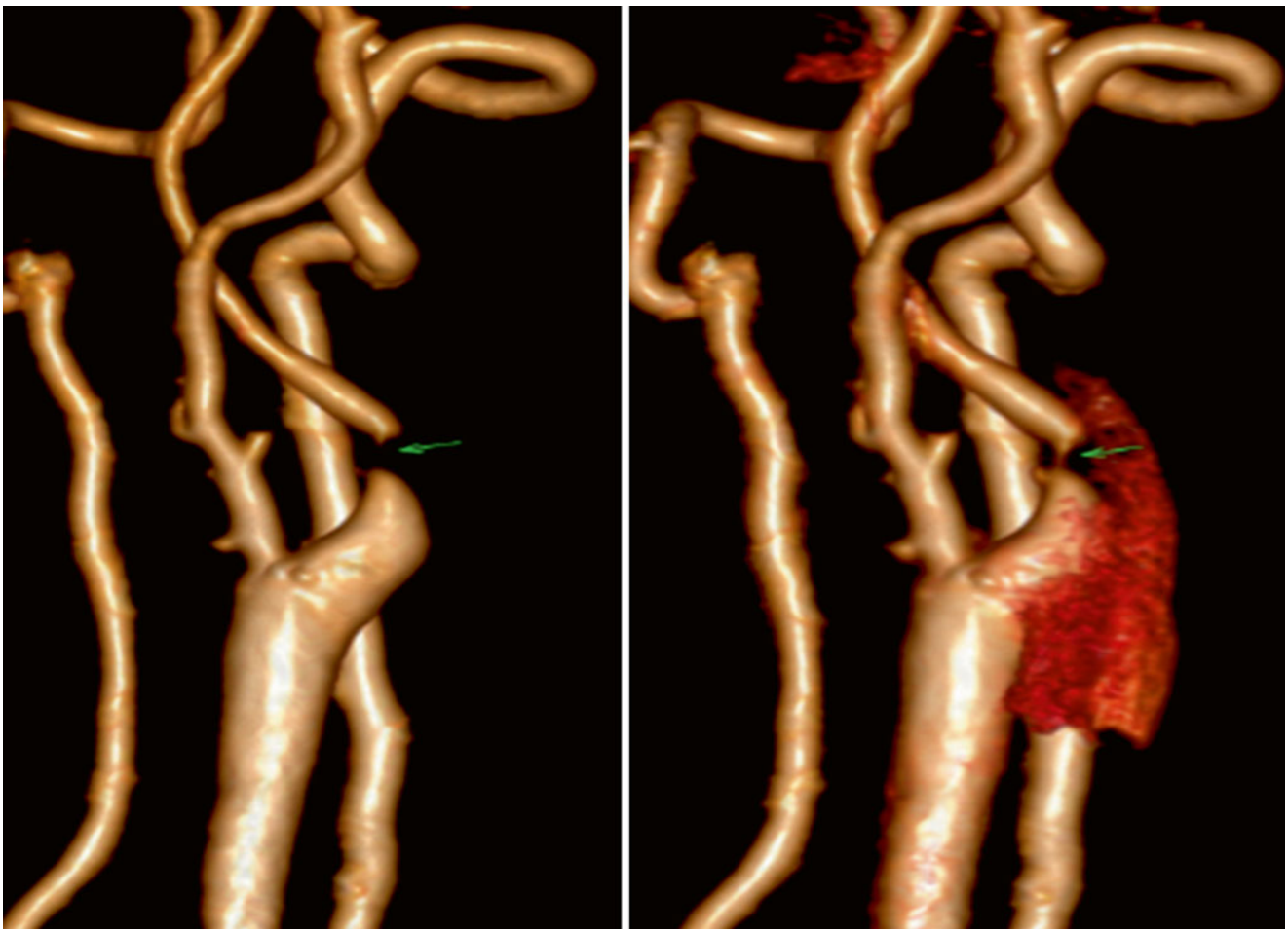

Fig. 7.22 Even in the absence of calcification, SSD frequently underestimated the degree of stenosis (indicated by arrow in image), probably due to the arbitrary selection of the lower threshold

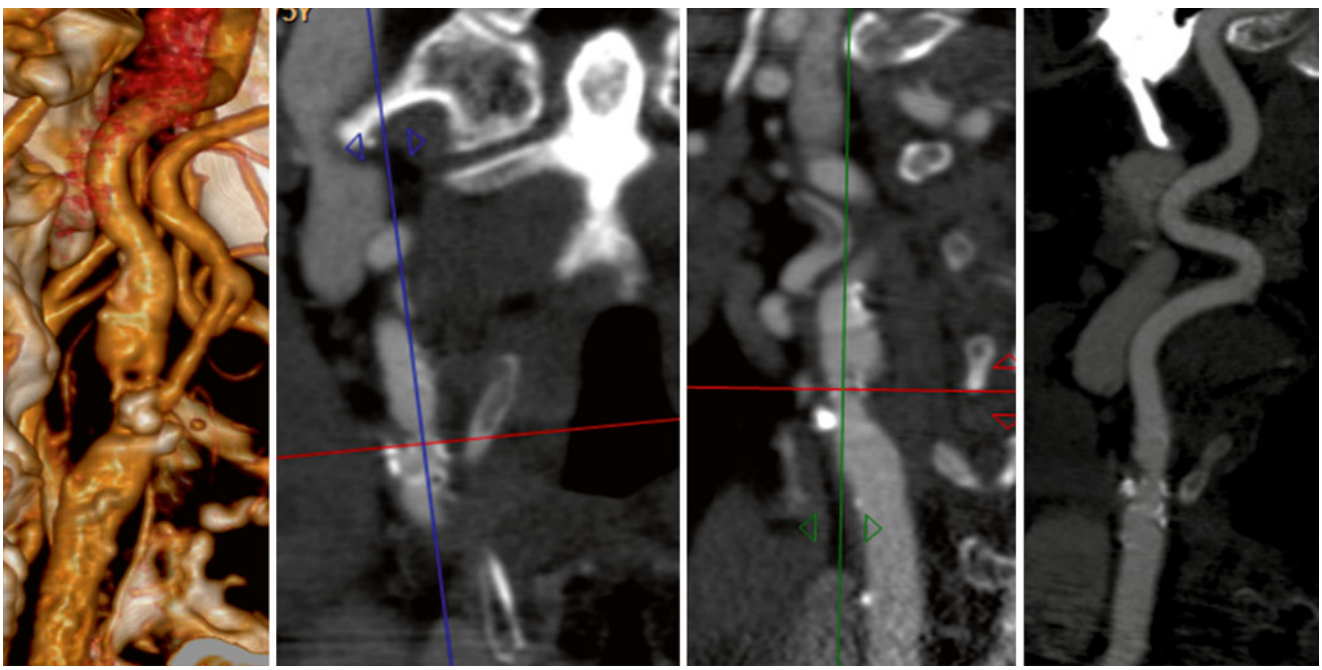

Fig. 7.23 SSD, MPR, and MIP reconstructions: accuracy is reduced on SSD reconstruction if extensive calcification is present, but this limitation can be avoided when MPR and MIP reconstructions are used

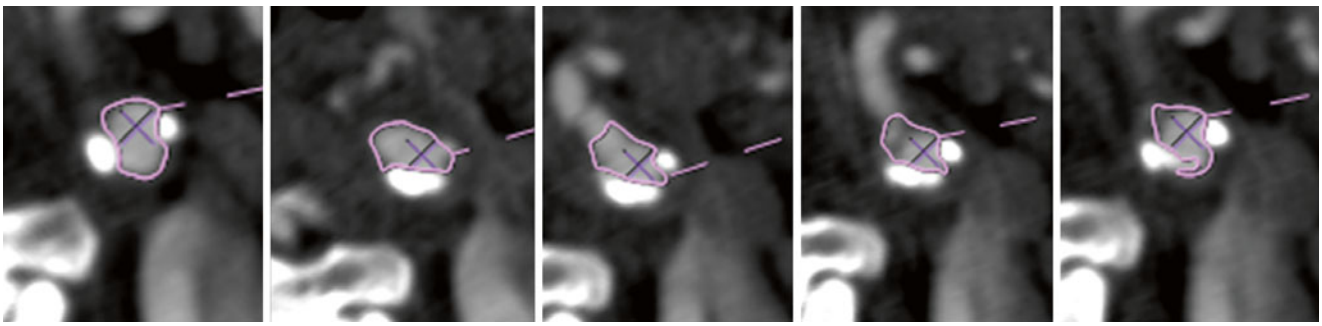

Fig. 7.24 When using an automated 3D CTA analysis program, several misregistrations of the enhanced carotid artery lumen were noticed

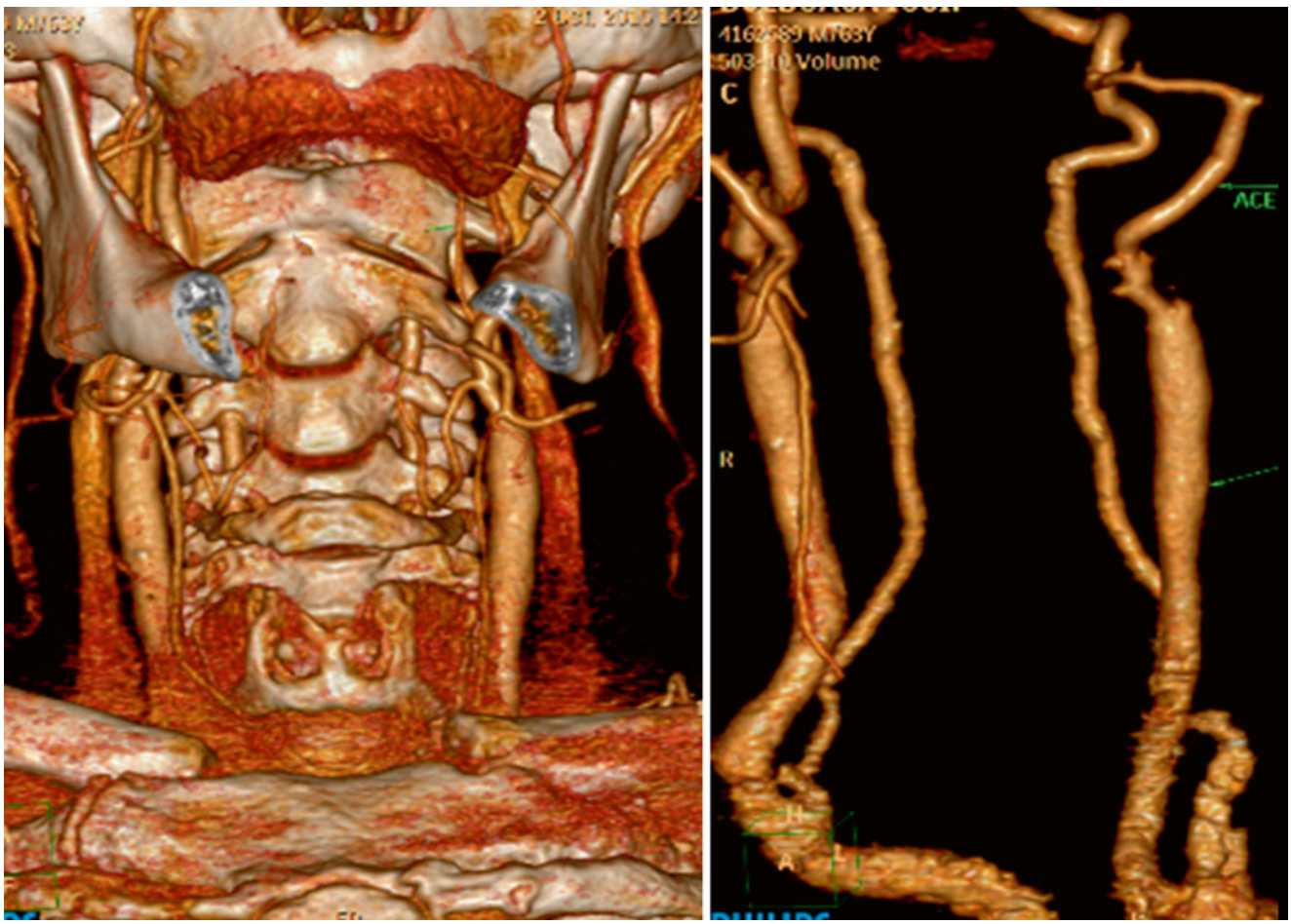

Fig. 7.25 The major disadvantage of the technique is represented by the need to post-process data to remove calcifications, veins, and bone structures from the images

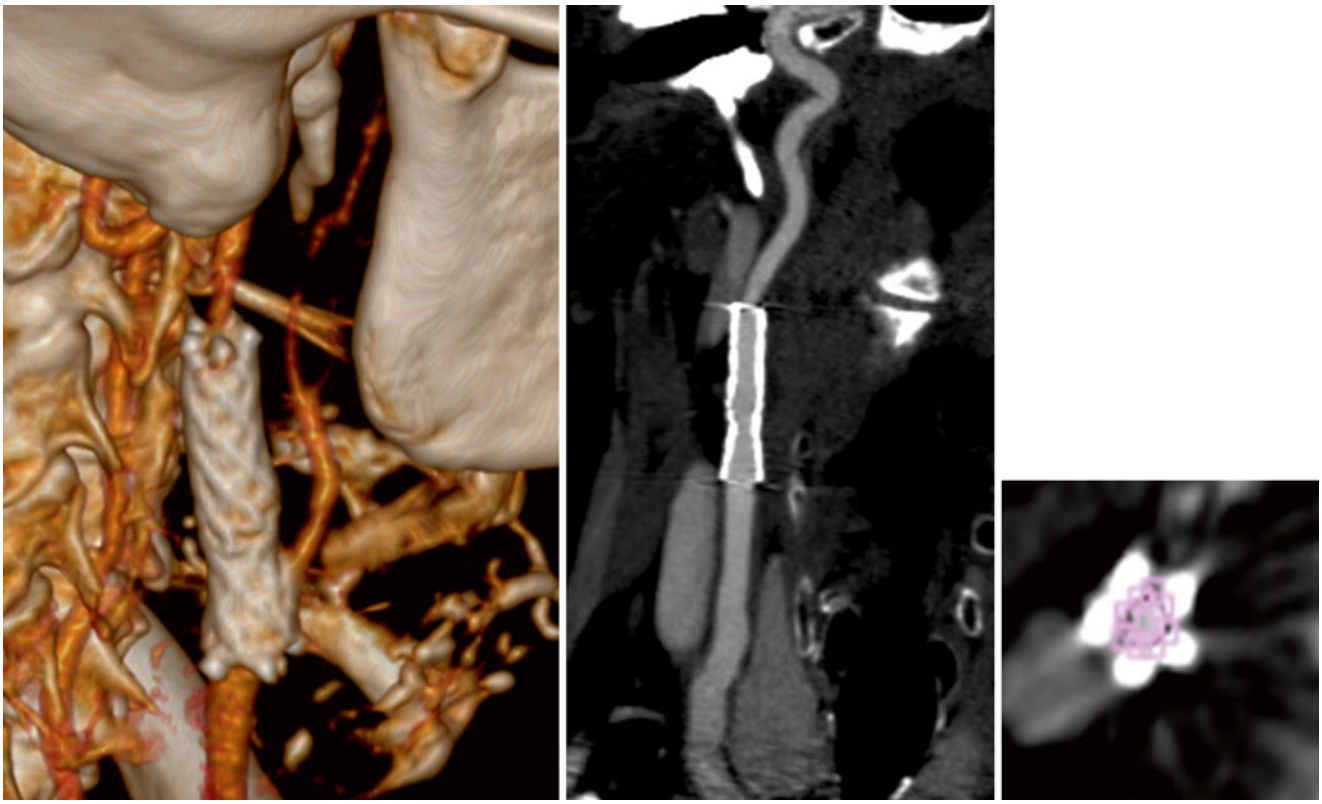

Fig. 7.26 Stents in the carotid artery may cause severe streak artifacts

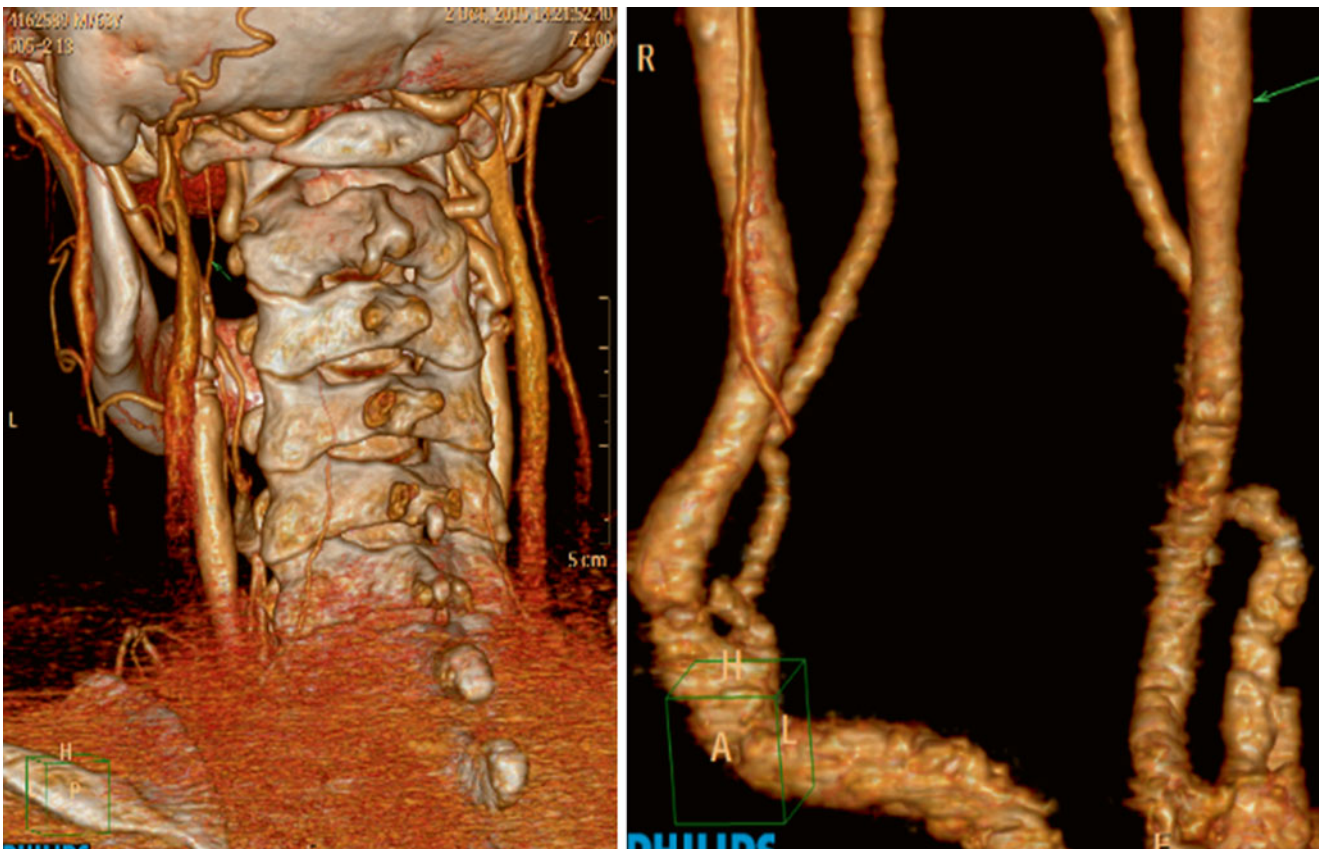

Fig. 7.27 Obese patients are suboptimally imaged

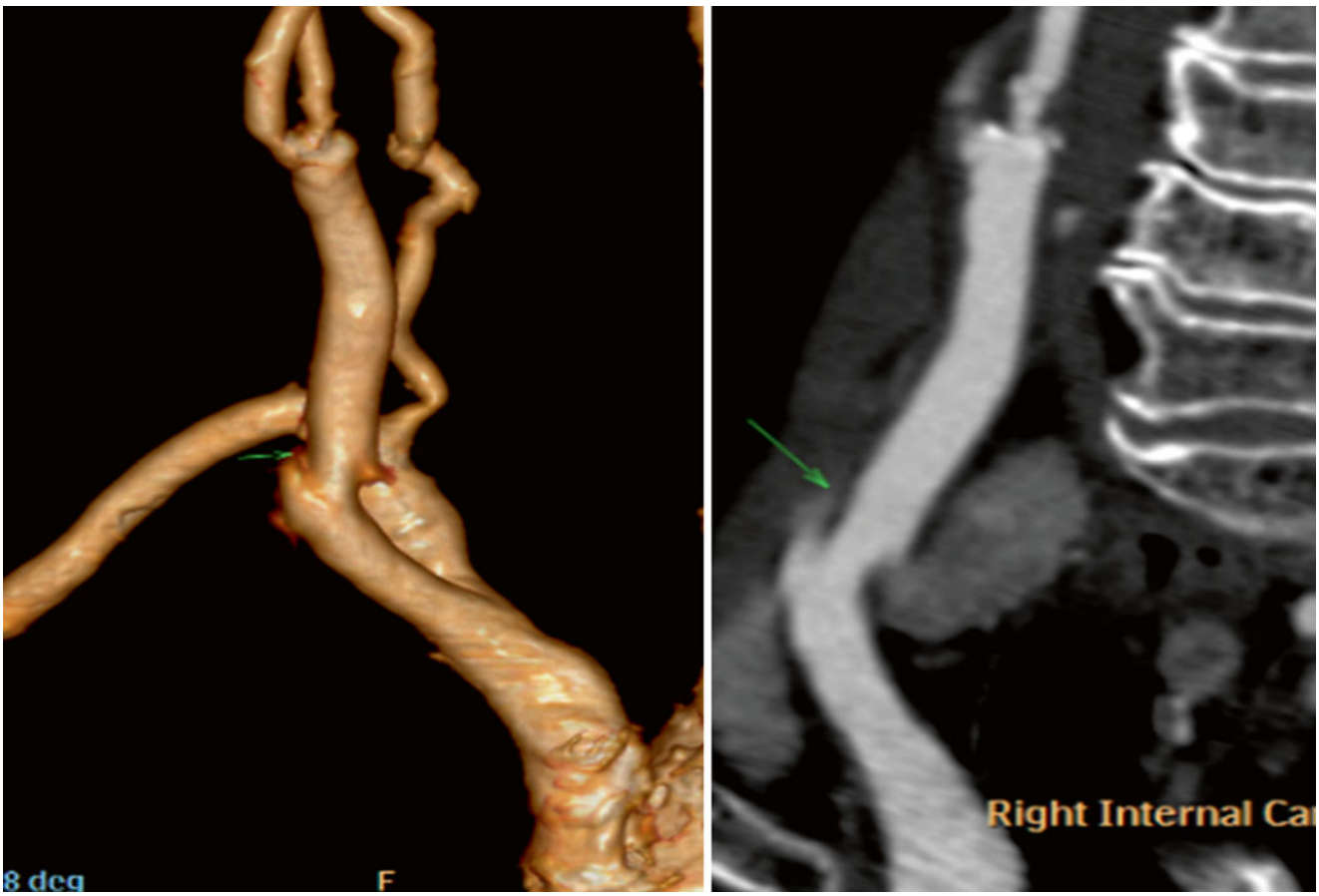

Fig. 7.28 Motion artifacts (as shown by arrow in image)

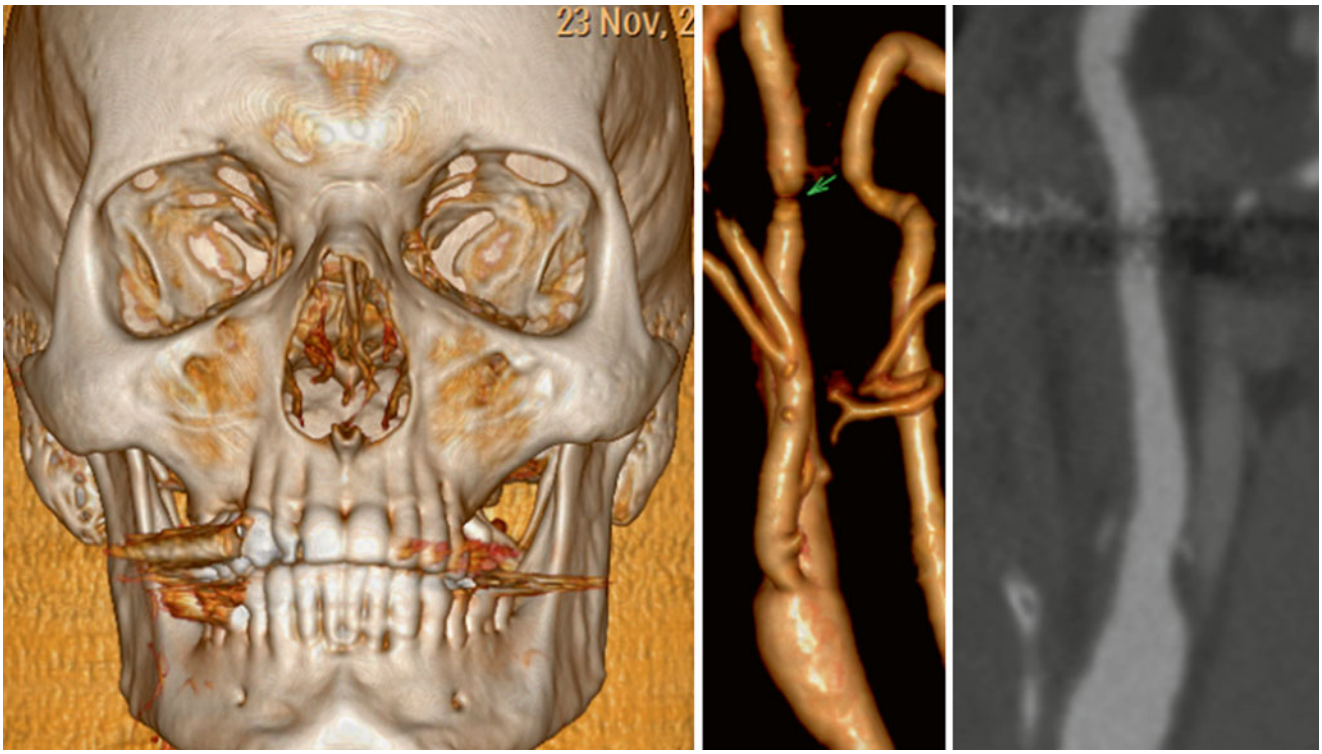

Fig. 7.29 Dental amalgam artifact (as shown by arrow in image)

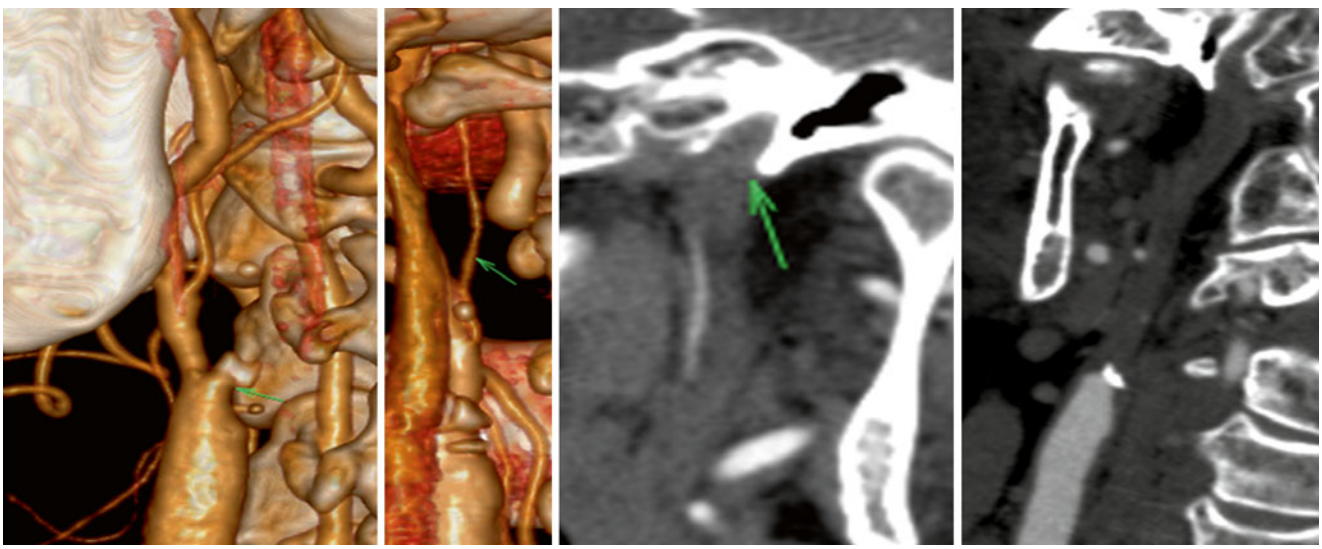

Fig. 7.30 Total carotid occlusions: the ascending pharyngeal branch of the external carotid artery can be mistakenly interpreted as a hairline open ICA

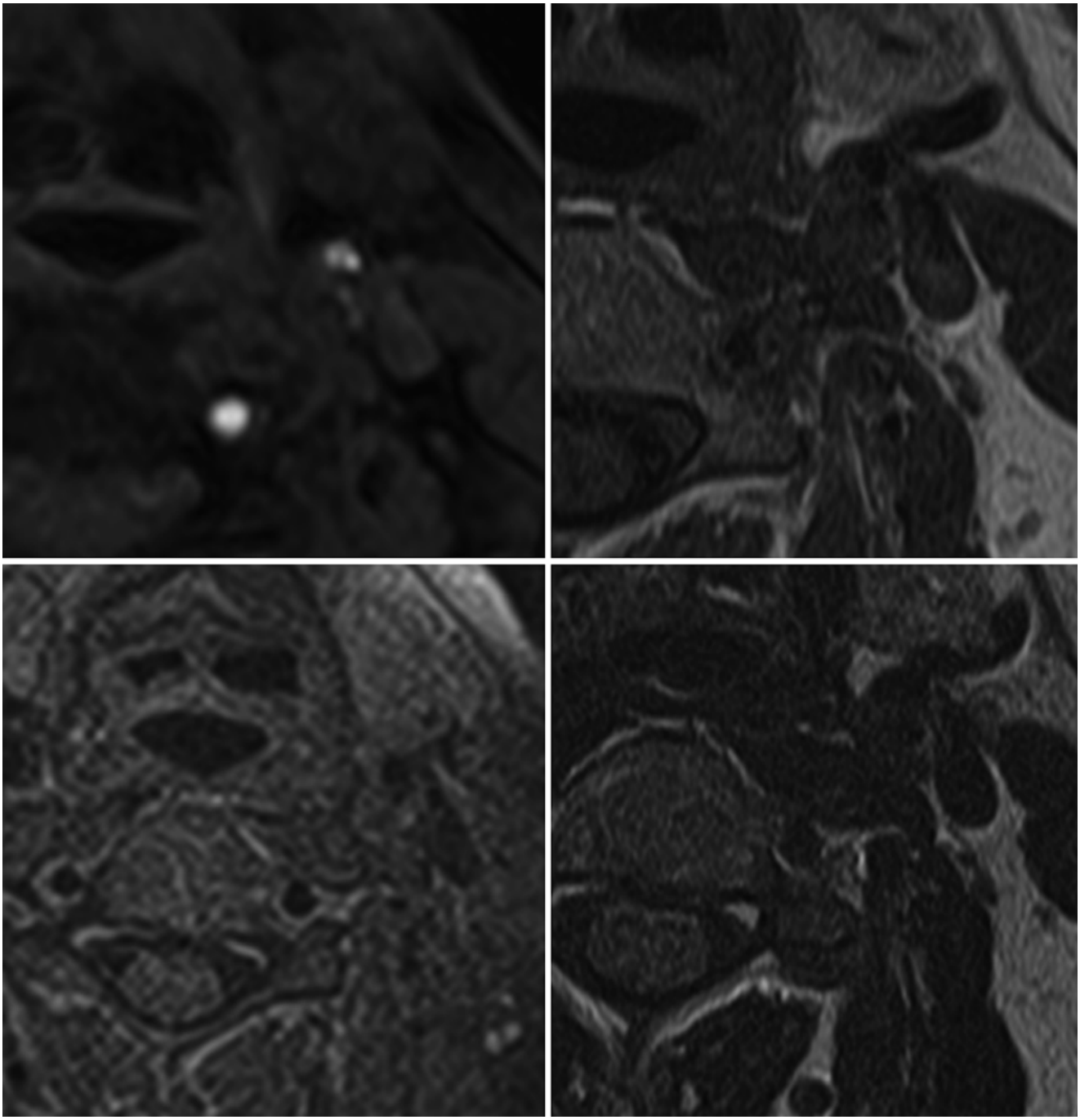

Fig. 7.31 The lipid core appears as low-intensity TOF, variable signal in T1 and DP, and more often as intermediate signal in T2

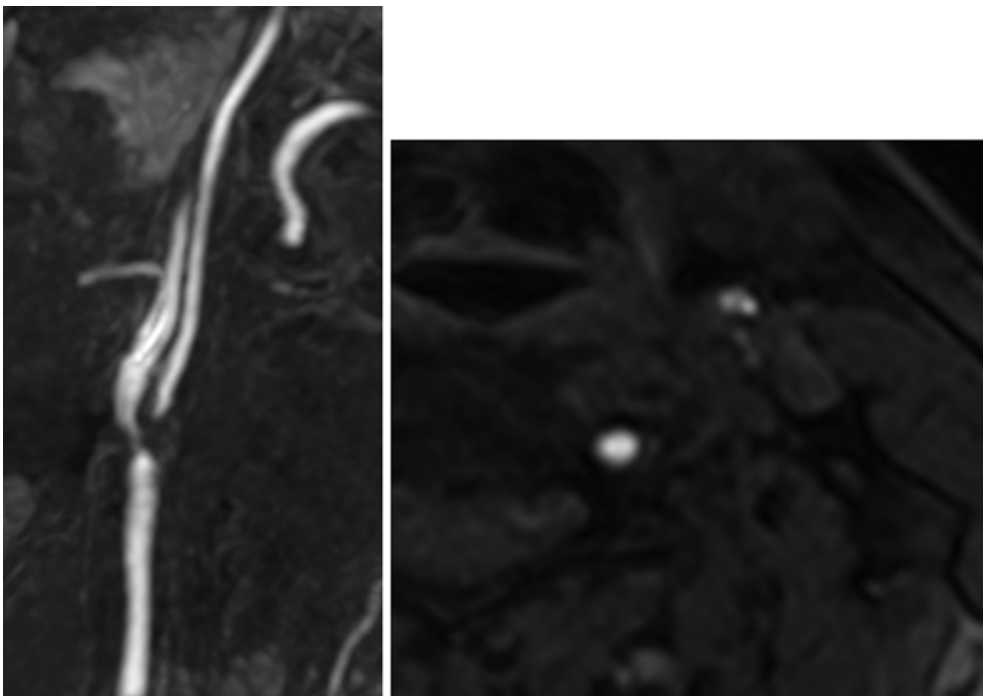

Fig. 7.32 3D TOF-MRA with "angiographic-like" reconstructions and axial source image

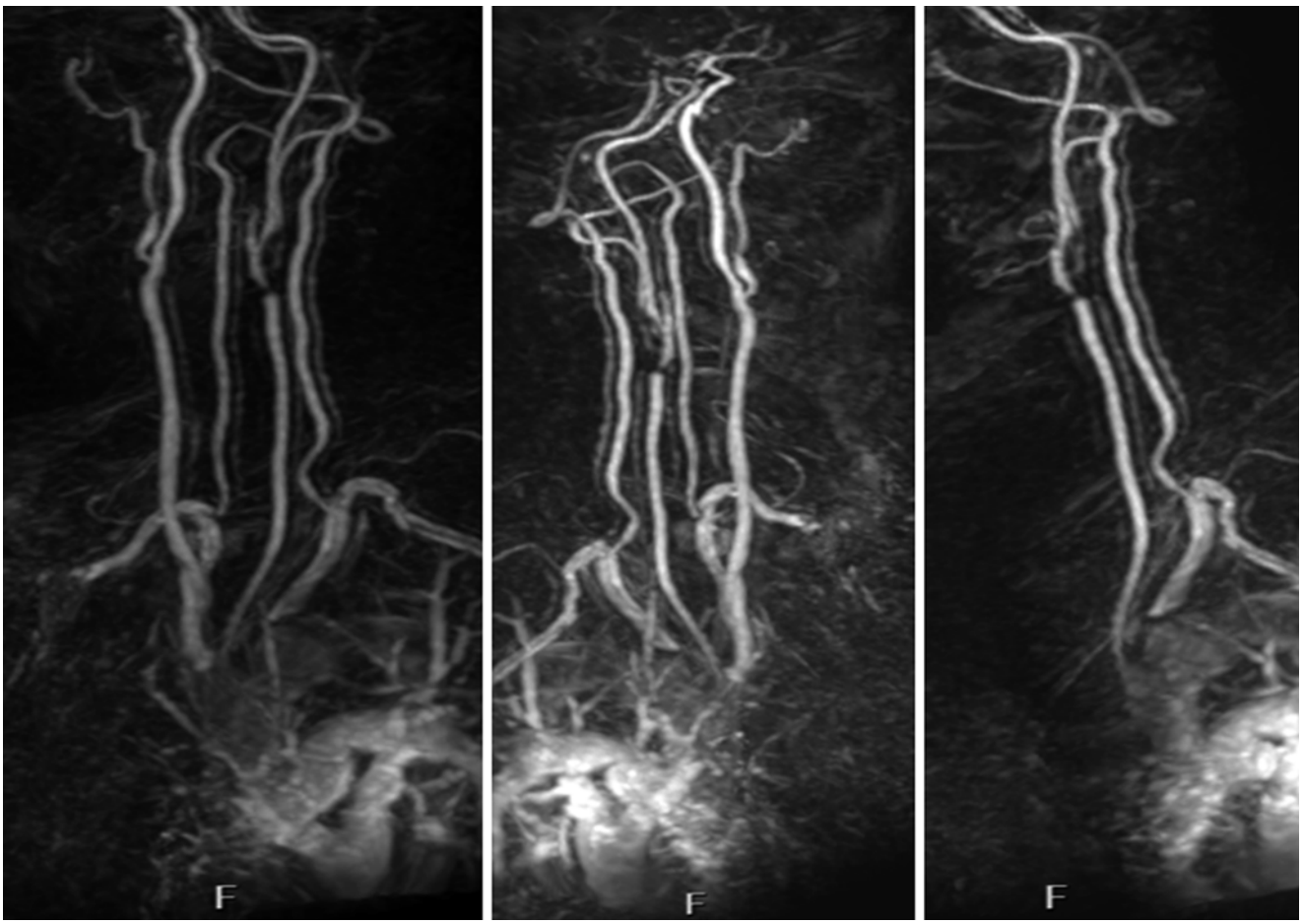

Fig. 7.33 CE-MRA

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Pharmacological Measures for the Treatment and Prevention of Stroke: The Choice of Initial Therapy

8

Sorin Tuta

In spite of progress in reducing the disease burden (especially in developed countries in the last decades), stroke still represents the second leading cause of death and third leading contributor to disability-adjusted life-years all over the world. Due to the aging of population and inherent limits of therapies, even in developed industrialized countries, stroke incidence had reached a plateau level. Correct and prompt treatment in the acute stroke phase, as early as possible, and adequate measures for secondary prevention together with measures of population health strategies and specific primary prevention are the cornerstones for limiting fatalities and disability related to this disease.

Compared with myocardial infarction, stroke has a more complex and heterogeneous pathology; the two major categories of stroke, hemorrhagic and ischemic, are opposite conditions regarding to treatment at least, but on the other hand they could be connected through common lesions like small vessel disease (cause of ischemic and hemorrhagic stroke), common risk factors like arterial hypertension, or treatment (cerebral hemorrhages induced by antithrombotic treatments of ischemic stroke). Although much rare, subarachnoid hemorrhage and cerebral venous and sinus thrombosis are another two separate categories of stroke.

Pharmacological treatment of cerebral hemorrhage is unfortunately limited compared to ischemic stroke, since trials like FAST [1] (with recombinant activated factor VII) and other hemostatic therapy failed to prove significant benefit, so the mainstream treatment is based on prompt decrease of high blood pressure values (under 160 mmHg systolic values and if possible and tolerated to 140 mmHg for systolic values in the first 24 h from onset [2]) and general supportive therapy and prevention of complications. Except the much more rare situations of medical, non-aneurysmal cases of subarachnoid hemorrhage, treatment of aneurysmal or malformative hemorrhages is surgical or endovascular (interventional). The opposite situation of a more complex pharmacological treatment (and recently interventional, endovascular) is currently available for ischemic stroke and cerebral venous and sinus thrombosis, where the antithrombotic treatment is usually the first-line therapy.

8.1 Acute Ischemic Stroke

The reduction of cerebral blood flow (CBF) under 10–12 ml/100 g cerebral tissue per minute produces irreversible necrosis in a few minutes in the core region of ischemia (the region with the minimum flow within the hypoperfused area), while in the surrounding penumbral area where CBF is around 12–22 ml/100 g/min, the neuronal survival is variable, depending on metabolic factors and collateral flow, but in majority of cases being up to 3–6 h from onset. The complete restoration of flow in this period of time could reverse the neuronal and glial ischemic changes in the penumbral area, with salvage of brain tissue at risk and improving or reversing the neurologic deficit quantified by clinical scores like NIHSS and modified Rankin score.

From this point of view, the main priority of treatment of the ischemic stroke is the rapid restoration of flow in the obstructed artery followed by reperfusion of the ischemic cerebral tissue.

After the successful 1995 NINDS trial [3], the recombinant tissue plasminogen activator alteplase was approved for intravenous (i.v.) therapy of acute ischemic stroke.

The analysis of the results [4] showed no significant difference compared to placebo in the first 24 h after administration, but at 3-month evaluation, the chances for favorable results with active therapy were 1.7 times greater, and the number needed to treat for a favorable outcome (defined by a modified Rankin scale of 0–1) was 11 (or

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S. Tuta
Head of Stroke Unit, National Institute of Neurology and Neurovascular Diseases, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
e-mail: sorin.tuta@gmail.com

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only 3 if we consider 1 point decrease for any step in Rankin score), with no differences in mortality, and a number needed to harm of 30.

The symptomatic intracerebral hemorrhage within 36 h after the onset of stroke occurred in 6.4 % of patients given t-PA, but the definition of the symptomatic hemorrhage in this trial was very permissive – any new cerebral bleeding with any increase of the neurologic deficit scores and included cases where a small hemorrhage was not the cause of decline of neurological status score like NIHSS. The positive results were obtained in all subtypes of ischemic stroke: large vessel diseases, cardioembolism, or small vessel disease.

Since NINDS trial the dosage of alteplase is 0.9 mg/kg, 10 % being administered as i.v. bolus and the rest in continuous i.v. infusion during 1 h. The initiation of therapy should have been done in the first 3 h from onset [3].

The successful NINDS trial for i.v. alteplase used for ischemic stroke in the first 3 h from onset was doubled by the ECASS III trial, which further prolonged the time window for i.v. alteplase to 4.5 h from stroke onset. In this trial the chance for good outcome was increased by 34 % (independency defined by an mRankin score 0–2), without additional increasing of death rate [5].

Other trials tried to explore longer time windows for thrombolysis in acute ischemic stroke patients: IST3 up to 6 h [6] did not find significant differences for the group of patients alive and independent at 6 months, and DIAS 3 using desmoteplase [7] and patients selected between 3 and 9 h from onset using the penumbra concept (with MRI or CT scan proved mismatch) also failed to reveal improvement in functional outcome compared to placebo.

The cerebral hemorrhage rate was higher than placebo, like in the other trials with i.v. alteplase (2.4 % symptomatic intracerebral hemorrhage (SICH), with 4 points increase in NIHSS score), but was lower than before (7.9 % in NINDS trial, 7 % in IST3 trial, 5.3 % in ECASS II). In-hospital mortality is significantly higher in patients with symptomatic cerebral hemorrhage after alteplase than in those without (75.0 % vs 16.9 %) and represents one of the major predictive factors for death [8]. Unfortunately treatment for correction of coagulation in cerebral hemorrhages after i.v. alteplase did not change the outcome.

Several prognostic scores have been developed to predict the risk of symptomatic intracranial hemorrhage after ischemic stroke thrombolysis (the safe implementation of treatments in stroke (SITS)-SICH score, the SEDAN score (the acronim SEDAN coming from main items used for the score: **S**ugar -glucose level, **E**arly infarct signs, (hyper) **D**ense cerebral artery sign on admission computed tomography scan, **A**ge and **N**IH Stroke Scale on admission), the hemorrhage after thrombolysis (HAT) score, and the Multicentre Stroke Survey score, but neither proved to be very reliable, ranging in moderate level of predictive performance [9].

The SEDAN score performed a little better, its total sum components ranging between 0 and 6 points. The component parameters of the score are mentioned in Table 8.1, as well as the corresponding absolute risk of cerebral hemorrhage at any score points [10].

Other scores (SITS-SICH score) took into account (beside the mentioned parameters of SEDAN score) other factors associated with an increased risk of cerebral hemorrhage like the antiplatelet treatment before thrombolysis therapy, high systolic blood pressure values, history of hypertension, a longer than 180 min time from onset to treatment, and a weight more than 95 kg [11]. A meta-analysis [12] of the main randomized trials with alteplase for acute ischemic stroke evaluated the results from 6756 patients included in nine clinical trials. The i.v. thrombolytic treatment increased the chances for a favorable outcome with functional independence (modified Rankin score 0 and 1) especially for those treated in the first three hours (32.9 % of active-treated patients compared with 23.1 % with placebo). In the 3–4.5 h interval from stroke onset, the results were also positive, but the magnitude of effect was lower (35.3 % vs 30.1 %), and a nonsignificant therapeutic effect was noticed after 4.5 h from onset. The benefit was independent of age or lesion severity (up to National Institutes of Health Stroke Scale (NIHSS) score of 25, less than one-third of MCA territory, or CT Alberta Stroke Program Early CT score (ASPECTS) above 6). As expected, the risk of symptomatic cerebral hemorrhage (at least 4 points increase of the NIHSS score due to the hemorrhage) increased from 1.3 to 6.8 %, but in spite of more death due to cerebral hemorrhage in the first week, at 90 days from treatment, the death rate did not differ significantly (17.5 % vs 16.5 %) because of delayed increase of death rate in non-thrombolyzed large ischemic stroke. The cerebral hemorrhage rate was independent of time from onset, or the lesion extension within one-third MCA rule, for the first 3 h, but with an increasing rate after 3 h or large cerebral lesions (more than one-third of MCA territory).

A Cochrane meta-analysis from 2014 included 27 trials, and 10187 participants also demonstrated that the i.v. thrombolysis in the first 3 h from onset of ischemic stroke was more efficient than standard treatment in reducing the combined risk of death and dependence [13].

Because as time passes the central core of necrosis expands in ischemic brain in the penumbral area, the effect of recanalization of occluded artery will be better when time from onset to treatment and reperfusion is shorter. The benefit of treatment is visible decreasing with time; intravenous alteplase initiated within 1.5 h of symptom onset was associated with an odd ratio of almost three times higher rates for favorable outcome at 3 months compared with placebo, while within 1.5–3 h was about 1.5 times higher compared with 1.4 times within 3–4.5 h and not significant effect anymore after 4.5 h [14]. The short therapeutic window of

Table 8.1 SEDAN score for predicting post i.v. thrombolysis cerebral symptomatic hemorrhage [10]

Parameter	Allocated points for parameter	Total obtained points	Absolute risks ICH (%)
Blood glucose 145–216 mg/dl	1 point	0	1
Blood glucose >216 mg/dl	2 points	1	3.5
Early infarct signs on baseline CT	1 point	2	5.1
Hyperdense cerebral artery sign	1 point	3	9.2
Age >75 years	1 point	4	16.9
Baseline NIHSS score ≥10	1 point	5	27.8

Table 8.2 Indication and exclusion criteria for i.v thrombolysis of acute ischemic stroke

Indication criteria	Exclusion criteria
Diagnosis of ischemic stroke causing a measurable neurological deficit	Significant head trauma or prior stroke in previous 3 months
	Symptoms suggest subarachnoid hemorrhage
Onset of symptoms <3–4.5 h before beginning treatment	Arterial puncture at noncompressible site in previous 7 days
	History of previous intracranial hemorrhage
Aged ≥18 years	Intracranial neoplasm, arteriovenous malformation, or aneurysm
	Recent intracranial or intraspinal surgery
	Elevated blood pressure (systolic >185 mmHg or diastolic >110 mmHg)
	Active internal bleeding
	Acute bleeding diathesis, including but not limited to:
	Platelet count <100,000/mm^3
	Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal
	Current use of anticoagulant with INR >1.7 or PT >15 s
	Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT or appropriate factor Xa activity assays)
	Blood glucose concentration <50 mg/dl (2.7 mmol/L)
	CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
	Relative exclusion criteria
	Only minor or rapidly improving stroke symptoms (clearing spontaneously)
	Pregnancy
	Seizure at onset with postictal residual neurological impairments
	Major surgery or serious trauma within previous 14 days
	Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
	Recent acute myocardial infarction (within previous 3 months)

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3–4.5 h from onset is one of the main limiting factors for the proportion of patients possible to be treated; except of late arrivers, another significant part (15–25 % of patients) has an unknown time from onset or a wake-up stroke. Imaging strategies like the MRI DWI–FLAIR time mismatch are studied in ongoing trials to confirm the usefulness and safety of this approach for time estimation of onset and to apply a thrombolytic treatment for these patients [15].

Other trials with extended time window up to 6 h like IST3 - which included more than 3000 patients - did not find significant benefit after 4.5 h, but due to a large number of older than 80-year-old patients included it confirmed that these patients did not benefit less than the younger ones, although the benefit is especially achived if they were treated in the first 3 h from onset [6]. Other trials like DIAS 3 using desmoteplase [7] in a 3–9-h time window and multimodal imaging (diffusion–perfusion MRI) for target mismatch selection of patients having enough viable cerebral tissue and a small necrotic core failed to prove a significant benefit in this extended time window.

To date, the accepted time window for intravenous thrombolysis with alteplase is up to 4.5 h from the onset for 18–80-year-old patients and 3 h for those after 80 years old; the most frequently used inclusion and exclusion criteria for treatment are listed in Table 8.2.

There are many predictive factors related to the possible recanalization and reperfusion rate and also the chance for functional independence rate at 3 months (defined by a modified Rankin score between 0 and 2). Reperfusion in the first 6 h was consistently superior to recanalization in predicting tissue and clinical outcome. Reperfusion without recanalization was frequent and probably related to retrograde

reperfusion through leptomeningeal collaterals [17]. From this point of view, higher chances of reperfusion of the ischemic cerebral area are associated with a lower NIHSS score (marginally) and two to four times higher rate if there is a smaller infarct core size, smaller total ischemic area, lower clot burden, distal thrombus location, and good collateral score [18]. Therapeutic benefit of i.v. thrombolysis was independent of neurological NIHSS deficit score in the 3–4.5 h time frame, and up to 6 h in the IST 3 trial, but the proportion of patients with very good outcome (mRankin 0 and 1) decreased with higher NIHSS score: 79.1 % for NIHSS under 8, 60.8 % for a NIHSS between 9 and 15,, and only 26.2 % in case of a severe stroke with NIHSS above16, all these results being independent of time from onset [19]. The explanation comes from the fact that the NIHSS score correlates well with the location of arterial obstruction: a NIHSS score above 9 in the first 3 h from the onset of stroke is predictive (in more than 85 % of patients) of a large artery occlusion (internal carotid artery or the M1 or M2 segments of the middle cerebral artery (MCA)), but the correlation does not apply for vertebral and basilar artery strokes [20].

As was mentioned, the faster reperfusion of the ischemic brain tissue, the greater are the chances for recovery with minimal or without any neurological impairment. Anyway, there is a direct relationship between the dimension of thrombus, the caliber of occluded artery, and the chances of recanalization and reperfusion rate. In middle cerebral artery stroke, intravenous thrombolysis has nearly no potential for recanalization of occluded vessels if thrombus length exceeds 8 mm [21], while for basilar artery in spite of linear inverse relationship between length of thrombus and recanalization rate, for a maximal length of basilar artery thrombi over 30 mm, there is still a recanalization rate of 20–30 % [22]. A favorable outcome with complete functional independence was obtained in only one-quarter of strokes due to large vessel occlusion compared with 70 % in the rest of cases, the corresponding mortality being almost four times higher in the first group (42.1 % versus 11.7 %) [23]. There are significant differences between i.v. alteplase recanalization rates depending on occluded artery: 44 % for distal ACM M1, 30 % for proximal M1 ACM, 27 % for a tandem internal carotid artery and MCA, 30 % for basilar artery, and only 6 % for the terminal intracranial internal carotid artery (the ICA T segment) occlusion [24].

Finally in the latest (2014) meta-analysis [12], the i.v. thrombolysis for acute ischemic stroke is associated with an absolute increase of chances for a very good functional outcome (mRankin 0–1) with 9.8 % for treatment in the first 3 h from onset (number needed to treat (NNT) = 10 for one totally independent patient) and 5.2 % for the 3–4.5 h interval (NNT = 19) but with an increased risk of symptomatic cerebral hemorrhage (absolute increase risk 5.5 % with a number needed to harm (NNH) of 18) and a borderline (but statistically not significant) increase of mortality 1.4 % (NNH = 71). This emphasized the need for administration of treatment as soon as possible (preferable in the first three hours) and to individually analyze the potential benefit and risk in the 3–4.5 h after onset, especially in the older patients (over 80 years) or where the estimation for the risk of cerebral hemorrhage is considered to be high.

The low rate of successful recanalization and reperfusion and the lack of improvement in a significant proportion of patients with large vessel occlusion gave rise in the last decade to development of techniques for endovascular treatment with local intra-arterial fibrinolytic drugs (like urokinase in PROACT II trial), but especially mechanical thrombectomy.

Three major randomized controlled trials (RCTs) of endovascular mechanical thrombectomy in acute ischemic stroke – IMS III, MR RESCUE, and SYNTHESIS – could not demonstrate the superiority to i.v. thrombolysis alone. However, these studies had several limitations: the use of first-generation thrombectomy devices and intra-arterial thrombolytic agents to achieve recanalization, suboptimal patient selection due to the lack of vascular imaging techniques employed, and lengthy delays to initiation of treatment (mean time to groin puncture 208 min in IMS III and 381 min in MR RESCUE) [25, 26].

The recent series of successful endovascular mechanical thrombectomy recanalization randomized studies using stent retrievers such as Solitaire, Trevo, and Revive have demonstrated markedly improved recanalization rates compared to earlier generation like MERCI devices. The incorporation of these devices, improving imaging-based patient selection and more expedient treatment times, has resulted in positive findings from seven trials: MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, THRACE, and THERAPY, supporting the superiority of the intra-arterial approach associated with previous i.v. alteplase (bridging therapy) in large artery occlusion over i.v. alteplase alone [27].

Endovascular mechanical thrombectomy with stent retrievers within 6 h from stroke onset is actually indicated in patients over 18 years treated with i.v. thrombolysis within the first 4.5 h from onset, with prestroke mRankin score of 0 and 1, and proved occlusion of internal carotid artery or proximal MCA (M1), with an NIHSS and ASPECTS score of more than 5. Although the benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries [28].

The proportion of patients to benefit thrombolytic therapy or endovascular mechanical thrombectomy is still low, and a large proportion of ischemic stroke patients need other kinds of antithrombotic treatments in the acute phase.

Unfractionated heparin was frequently used in the past with the hope of reducing the early recurrence of embolism (especially cardiac embolism) and the progression of arterial thrombus with total occlusion or extension of thrombus with blocking of some collateral arteries and extension of ischemic area. Progressing stroke and cardioembolic stroke were considered the elective indication for heparin treatment. In the last two decades, some series of clinical studies proved that progressive stroke is due especially to reduction of penumbra tissue in favor of necrosis, edema development, and some other factors implicated in worsening of clinical status of patients like fever, hypo- or hyperglycemia and infection, and low blood pressure, all of these being not responsive to heparin treatment.

In the last edition of Cochrane review [29] of heparin treatment in acute ischemic stroke (2015), the anticoagulants tested were standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. Over 90 % of the evidence relates to the effects of anticoagulant therapy initiated within the first 48 h of onset. Based on 11 trials (22,776 participants), there was no evidence that anticoagulant therapy started within the first 14 days of stroke onset reduced the odds of death from all causes. The slight reduction of early ischemic recurrence of embolism and deep venous thrombosis with pulmonary embolism was offset by an increase (two to three times higher rates) in cerebral and systemic symptomatic bleeding with no reduction in death rate or dependency at the end of follow-up. The data do not support the routine use of any of the currently available anticoagulants in acute ischemic stroke. Anyway, fractioned heparin in doses to prevent deep venous thrombosis is mandatory in all bedridden stroke patients.

Although the evidence-based proof of efficacy of antithrombotic treatment is weak in *cerebral veins and sinus thrombosis* (only two small randomized trials with a total of less than 100 patients and more case series of patients), the heparin (unfractionated heparin and low-molecular-weight heparin) treatment in cerebral venous and sinus thrombosis with or without cerebral ischemic lesions (or even cerebral hemorrhage due to venous thrombosis) is a widely accepted and recommended therapy [30]. The purpose of this treatment is to help the recanalization of occluded vein and to limit thrombus extension and secondary to prevent deep venous thrombosis with pulmonary embolism and to prevent new venous thrombosis in case of thrombophilia or other coagulation disorders. Guidelines on the treatment of cerebral and sinus venous thrombosis [31] without contraindications for anticoagulation indicate that these patients should be treated either with adjusted doses of i.v. heparin or body-weight-adjusted low-molecular-weight heparin. A case control study and a randomized clinical trial support the preference for low-molecular-weight heparin.

Today the standard antithrombotic treatment for acute phase of ischemic stroke is still aspirin with a loading dose of 300 mg in the first day, followed by 75–100 mg daily in the next period until starting of oral anticoagulants for cardioembolic strokes, or continuation with antiplatelet for most atherothrombotic strokes. In a meta-analysis [32] of antiplatelet therapy for acute ischemic stroke, eight trials involving 41,483 participants confirmed there was a significant decrease in death or dependency at the end of follow-up. For every 1000 people treated with aspirin, 13 people would avoid death or dependency (number needed to treat 79). Antiplatelet therapy was associated with a small but definite excess of symptomatic intracranial hemorrhages, but this small hazard was significantly outnumbered by the benefit – the reduction in recurrent ischemic stroke and pulmonary embolism.

Other antiplatelet drugs like intravenous GPIIb-IIIa inhibitor abciximab or tirofiban did not significantly reduce long-term death or dependency and had no effect on deaths from all causes, but were associated with a significant increase in symptomatic intracranial hemorrhage [33].

There are some hopes for dual antiplatelet (clopidogrel and aspirin) in the acute phase of ischemic stroke; the results from the CHANCE trial [34] and some pooled analysis of antiplatelet treatment in subgroups of patients included in early phases of stroke [35] (in post-acute stroke trials) showed some supplementary benefit of dual antiplatelet compared with aspirin in patients with TIA or minor stroke who can be treated within 24 h after the onset of symptoms, reducing the risk of stroke in the first 90 days without an increased risk of hemorrhage.

Two ongoing major trials analyzing combination of antiplatelet therapy for acute stroke (POINT and TARDIS) [36, 37] will add some more solid data regarding the benefit and risks of these combinations compared to standard treatment (aspirin).

8.2 Secondary Prevention After Transient Ischemic Attack (TIA) and Ischemic Stroke

TIA defined as a transient episode of neurological dysfunction caused by a focal brain, spinal cord, or retinal ischemia, without acute tissue infarction, shares the same mechanisms and risk factors with ischemic stroke, between the two being rather a continuum depending on time and severity of ischemic exposure of the brain. Early MRI with diffusion-weighted sequences (DWI) can show modification up to 50 % of cases of clinical defined TIA, proving the existence of tissue lesions similar to stroke, although of a smaller size and reversible, but the sensitivity for detecting these changes vary with duration of TIA (the longer the greater the chances) and also the time since onset to examination.

The most important fact related to TIA is the increased risk of stroke after such an event, with stroke rates as high as 35 % in some subgroups in the first 7 days [38], but the risk of a stroke is starting very early after TIA (about 1 % at 6 h, 2 % at 12 h, 3 % at 2 days, 5 % at 7 days) [39].

Clinical prediction scores have been developed to improve early stroke risk stratification after TIA and to help physicians in their daily clinical routine because patients with TIA are a heterogeneous group in terms of prognosis. One of the most used prediction scores is the ABCD2 score [40] (age ≥60 years [1 point]; blood pressure ≥140/90 mmHg [1 point]; clinical features of weakness [2 points] or speech impairment [1 point]; duration of symptoms ≥60 min [2 points] or 10–59 min [1 point]; diabetes mellitus [1 point]). Further analysis of performance of this score in different cohorts of patients and real-life situation proved that the ABCD2 score does not reliably discriminate all patients at low and high risk of early recurrent stroke or identify patients with carotid stenosis or atrial fibrillation needing urgent intervention, so further improvement of predictive power of the score was proposed by adding some new parameters like MRI DWI cerebral signals and carotid and cerebral artery evaluation, adding items like previous TIA [41–43], or generating new score variant like ABCD3I [44]. Finally these "ultimate" scores reproduce in fact the day by day attitude to be followed with every TIA-suspected patient who should be admitted for complete medical work-up assessment (neurologic and general examination, vascular imaging, ECG, echocardiography, cerebral imaging, and so on) for correct patient management. As was demonstrated in SOS TIA and EXPRESS studies [45, 46], early initiation of existing treatments after TIA or minor stroke was associated with an 80 % reduction in the risk of early recurrent stroke but that suppose a rapid evaluation of the mechanisms of TIA for a correct treatment. Following the results of the complete workout, the etiology of TIA or stroke should be classified into TOAST (Trial of Org 10172 in Acute Stroke Treatment), within the subtypes of large vessel disease, small vessel disease, cardioembolic stroke, other identifiable cause, and undetermined cause, the therapeutic measures for secondary prevention depending on these specific TOAST subgroups.

8.2.1 TIA and Stroke Due to Cardiac Sources of Emboli

Cardioembolic TIA (frequent cardiac sources of emboli are dominated by atrial fibrillation, followed by other possible causes like rheumatic heart disease, prosthetic valves, acute myocardial infarction and ventricular thrombus, persistent foramen ovale associated with septal aneurysm, infective endocarditis, and atrial myxomas) is a much rare encountered event compared with cardioembolic stroke, due to the large size of cardiac emboli and consequently large artery occlusion with little chance for spontaneous lysis and transient clinical manifestation. After a first TIA the following event in our experience is more frequently a stroke than a second TIA, so urgent measures are needed to prevent further developing and embolization of left atrial thrombi.

After a stroke or TIA the sequential cardiac monitoring of different levels of complexity discovered atrial fibrillation up to 23.7 % of all patients [47].Since the risk for recurrence of cardioembolism in the first 30 days after a first episode is between 3 and 6 % half of this could happen in the first week [48] and up to 13 % in the first year [49], urgent anticoagulation after a cardioembolic TIA (and also following an acute stroke after a delay depending on the size of lesion, as presented later in this chapter) is recommended, unless a firm contraindication exists. An exception is bacterial endocarditis where anticoagulation is delayed and rapid institution of effective antibiotic therapy represents the emergent treatment to reduce the mortality and morbidity from embolic complications and heart failure. In this case an extensive evaluation of embolic risk with echocardiographic assessment of the degree of valve vegetation and a comparison with the risk of cerebral hemorrhage (large size of cerebral lesion, the presence of cerebral microbleeds detected with T2* or SWI MRI sequences) could give a better time window for introduction of anticoagulant therapy [50]. The traditional approach was the administration of oral antivitamin K (AVK) anticoagulants with a target international normalized ratio (INR) between 2 and 3, overlapped for the first days with heparin, usually unfractionated, because of delayed anticoagulant effect of AVK and of a transient hypercoagulable state at the start of VKA therapy (higher risk of embolic events during the first 30 days of warfarin but particularly during the first week of therapy with a hazard ratio of 1.71, in a large meta-analysis [51]).

Aspirin is not an alternative to oral anticoagulants, the modest reduction of embolism being statistically nonsignificant [52], and the net clinical benefit (the difference between prevented ischemic events and induced hemorrhages) is negative [53].

The association of aspirin and clopidogrel, although superior to aspirin in reducing the embolic risk of atrial fibrillation in ACTIVE A study [54], have had an increased risk of hemorrhages, almost equal to AVK (in the ACTIVE W [55]), so dual antiplatelet is not an option, except in extreme cases when any of existing oral anticoagulant medication is not possible to be used. On the other hand when compared to aspirin in AVERROES study [56], apixaban significantly and with a large margin (55 % relative risk reduction compared to aspirin) reduced the risk of embolism, while the hemorrhage rate did not differ significantly, so overall we can say that antiplatelet therapy should not be used in prevention of

cardiac embolism (and especially in secondary prevention after a previous TIA or stroke of cardiac origin).

Overall the AVK therapy reduced the risk of embolism with almost two-thirds (64 % relative risk reduction) [49] compared to control patients with atrial fibrillation but also is associated with increased risk of hemorrhages, including cerebral hemorrhage. Ninety percent of fatalities under treatment with oral AVK anticoagulants are due to cerebral or intracranial hemorrhages, and survivors of these hemorrhages have severe disabilities [57]. The INR over 3 increased by 2.6 times the risk of death due to cerebral hemorrhage [58], and the death rate is almost two-thirds higher in an AVK-induced cerebral hemorrhage compared to a hypertensive hemorrhage of the same volume [59, 60].

The maximum hemorrhage risk especially in the first months after initiation of AVK is 1–3 %/month in the first three, subsequently decreasing to 0.8 %/month up to 1 year, and remaining thereafter about 0.2–0.6 %/year [61]. Not only the hemorrhage risk but also the embolic risk is higher in the first 30 days after the initiation of therapy with an AVK oral anticoagulant [62]; both facts could be an argument for the new non-antivitamin K anticoagulants which do not share these limits.

Initiation of oral anticoagulant therapy in patients with atrial fibrillation is based on estimation of net clinical benefit assessed by comparison of the risk of cerebral and systemic embolism and that of significant hemorrhages. Although these events are unpredictable in a specific patient, an estimation of risks is possible through some risk scores well validated in large cohorts. The most used today are the CHA_2DS_2-VASc stroke risk assessment score [63] for the embolic risk and the HAS-BLED score for the risk of hemorrhage [63] (Tables 8.3 and 8.4).

A CHA_2DS_2-VASc score above 1 is a clear indication for anticoagulant therapy, while the score of 1 is a possible (and generally recommended) option for anticoagulant therapy. The HAS-BLED score above 2 is associated with an increased risk of hemorrhages and recommends caution in selecting the dosage for some anticoagulants and indication to correction of some factors if present (arterial hypertension, antiplatelet without indication, alcohol abuse), but it is not by itself an absolute contraindication for oral anticoagulants.

In spite of significant reduction in stroke risk (64 % relative risk reduction), warfarin is not used in 30–60 % of eligible patients with known atrial fibrillation; poor anticoagulant control is common and associated with an increased risk of stroke, major bleeding, hospitalization, and death. AVK have many pharmacological limitations including a slow onset and offset of action, a narrow therapeutic index requiring frequent coagulation monitoring, frequently very limited in disabled post-stroke patients who are between those with very high risk of new embolism, an unpredictable anticoagulant effect related to genetic factors, and numerous interactions with foods and medications [64].

Table 8.3 CHA2DS2-VASc stroke risk assessment

Congestive heart failure/left ventricular dysfunction	**1**
Hypertension	**1**
Age ≥75 years	**2**
Diabetes mellitus	**1**
Stroke/transient ischemic attack/systemic embolism	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	**1**
Age 65–74 years	**1**
Sex **c**ategory (i.e., female gender)	**1**

Table 8.4 HAS-BLED bleeding risk score

Hypertension	**1**
Abnormal renal or liver function (1 point each)	**1 or 2**
Stroke	**1**
Bleeding diathesis	**1**
Labile INR	**1**
Elderly (age >65 years)	**1**
Drugs or alcohol (1 point each)	**1 or 2**

Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× upper limit of normal, in association with AST/ALT/ALP >3× upper limit normal, etc.). Bleeding refers to previous bleeding history and/or predisposition to bleeding (e.g., bleeding diathesis, anemia, etc.). Labile INRs refer to unstable/high INRs or poor time in therapeutic range (<60 %). Drugs/alcohol use also refers to concomitant use of drugs, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, etc.

In the last years a new generation of oral anticoagulants were tested in large phase III trials and compared with warfarin. These new non-antivitamin K oral anticoagulants (NOAC) are the direct factor IIa (thrombin) inhibitor dabigatran etexilate and the oral direct inhibitors of factor Xa, rivaroxaban and apixaban, with another one – edoxaban – being in the process of approval. The NOAC have several advantages over warfarin, including a more rapid onset of action (time to peak about 2–4 h), a more predictable anticoagulant effect enabling them to be given in fixed doses without routine coagulation monitoring, and a lower risk of food and drug interactions [64].

There are some differences between the three available NOAC (dabigatran, apixaban, and rivaroxaban), regarding pharmacokinetics and dosage [64–67]. The usual dosage for dabigatran is 150 mg twice daily (b.i.d.), but because 80 % of this drug is eliminated through renal pathway, the dose is reduced to 110 mg b.i.d. when creatinine clearance is between 30 and 50 ml/min, especially in patients considered as having a high risk for bleeding, and is not used any more if creatinine clearance drops under 30 ml/min. The same dosage of 110 mg b.i.d. is used for patients over 80 years or in association with verapamil. In the United States the 110 mg was not approved; instead for patients with creatinine clearance between 15–30 ml/min, a dosage of 75 mg b.i.d. is used. Apixaban and rivaroxaban are less excreted through the kidneys (about 25 % and 35 %, respectively), and the usual dosage is 5 mg b.i.d. for apixaban and 20 mg daily (q.d.) for rivaroxaban. These doses are reduced to 15 mg q.d. for rivaroxaban if the creatinine clearance is between 15–49 ml/min and to 2.5 mg b.i.d. for apixaban only if two of the three following criteria are met: age over 80 years, weight under 60 kg, creatininemia more than 1.5 mg/dl. The inferior limit of creatinine clearance that allows the use of apixaban is also 15 ml/min, although the European Society of Cardiology Guidelines recommends a 30 ml inferior limit for all three NOAC (dabigatran, apixaban, rivaroxaban); under this limit only the oral AVK anticoagulants could be used.

In terms of efficiency and safety (compared to warfarin) in the phase III trials [65–67] of the NOAC, there were some slight differences between them: dabigatran 150 mg b.i.d. and apixaban 5 mg b.i.d. were superior to warfarin in reducing the composite index of stroke (ischemic and hemorrhagic stroke) and systemic embolism, while rivaroxaban 20 mg b.i.d. and dabigatran 110 mg b.i.d. were non-inferior. For ischemic stroke only dabigatran 150 mg b.i.d. was superior to warfarin in reducing the event rate, while apixaban 5 mg b.i.d., dabigatran 110 mg b.i.d., and rivaroxaban 20 mg q.d. were non-inferior. All three drugs (dabigatran, apixaban, rivaroxaban) reduced significantly (around 55 % relative risk reduction) the intracranial hemorrhage (including cerebral hemorrhage) rate, while dabigatran (at statistic limit) and apixaban reduced mortality. Major hemorrhages were reduced with apixaban and the 110 mg dosage of dabigatran. The gastrointestinal bleedings are increased by the 150 mg dosage of dabigatran and rivaroxaban. The influence on myocardial infarction was minimal, with only an insignificant trend toward reduction with apixaban and rivaroxaban and insignificant increase with dabigatran. All these major endpoints of the NOAC (including the edoxaban results) are presented in Table 8.5.

All the data in post-marketing surveillance of the NOAC confirm the profile obtained in the phase III trials, so the clinician could have some arguments in decision of selection of one NOAC or another or warfarin. In favor of NOACS are the possibility of administration without frequent check of INR levels (but the values of creatinine should be checked, although at larger intervals than INR), a fact that is useful in older or post-stroke patients with restricted mobility or living in remote areas; a reduced time to peak blood values (2–4 h) allowing avoidance of heparin bridge at initiation of AVK anticoagulation and reduced hospital length of stay; lower rate of intracranial and cerebral hemorrhages (the main cause of death due to any hemorrhages with anticoagulant therapy); and shorter offset time (useful when temporary interruption is needed). The recent approval of an antidote

Table 8.5 Major endpoints of efficiency and safety of non-AVK anticoagulants compared with warfarin [65–67]

	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke and systemic embolism	Superior	Non-inferior	Non-inferior	Superior	Non-inferior	Non-inferior
Ischemic stroke	Superior	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Hemorrhagic stroke	Superior	Superior	Superior	Superior	Superior	Superior
Major bleeding	Non-inferior	Superior	Non-inferior	Superior	Superior	Superior
GI bleeding	Inferior	Non-inferior	Inferior	Non-inferior	Inferior	Superior
All-cause death	Superior[a]	Non-inferior	Non-inferior	Superior	Non-inferior	Superior

GI gastrointestinal
[a]Borderline ($p = 0.051$)

for dabigatran (idarucizumab) [68, 69] and in the next future for the anti-Xa class of oral anticoagulants (andexanet alfa [69, 70] and others like aripazine [69]) will further increase the safety and easier management of hemorrhages or urgent major surgical interventions in patients treated with NOAC.

The oral AVK anticoagulants still remain the major option for patients with a significant heart valve disease associated with atrial fibrillation (medium and severe mitral stenosis, prosthetic heart valves) and patients with severe renal function impairment (creatinine clearance below 15–30 ml/min) or patients for a long time on AVK treatment with an excellent TTR (time in therapeutic range above 70 %) and depending on frequent meeting and support from doctors for a good compliance.

Selection of a specific non-AVK anticoagulant (NOAC) could be a difficult task, since direct comparison trials between them were not done and probably will be not (more than 50,000 patients are required for non-inferiority only). However, some published adjusted network meta-analyses have indirectly compared dabigatran, rivaroxaban, and apixaban vs. warfarin as the common basis of comparison. The results showed the following [64]: (1) dabigatran 150 mg and apixaban are significantly superior to dabigatran 110 mg and rivaroxaban but not significantly different from each other regarding the primary efficacy endpoint, which was any stroke or systemic thromboembolism; (2) apixaban and dabigatran 110 mg are superior to rivaroxaban and dabigatran 150 mg but are not significantly different from each other regarding the primary safety endpoint, which was major bleeding for all trials except the ROCKET AF, as assessed by the International Society on Thrombosis and Haemostasis criteria; and (3) myocardial infarction occurs less frequently on either rivaroxaban or apixaban (not different from each other) compared to both doses of dabigatran. Based on all information it looks that dabigatran 150 mg is the drug with the best profile in patients with very high risk of embolism when the bleeding risk is not high, or in recurrent embolism under any of the other drugs, followed by apixaban, especially when the risk of bleeding is higher. For those with previous gastrointestinal bleeding or peptic ulcer, apixaban and warfarin are better suited and apixaban or dabigatran 110 mg for those with high general bleeding risk. For myocardial infarction or unstable angina, the factor Xa inhibitors look better placed than dabigatran, although this is not an absolute choice, since some large post-marketing registry data did not confirm increased risk of myocardial infarction with dabigatran [71].

In case of recurrent cardioembolic stroke under correct treatment with AVK or NOAC, it looks that dabigatran 150 mg b.i.d. is the possible replacement if it is not used or if there are not contraindications for this dose, since this is the only drug with significant superior result in reducing ischemic stroke over warfarin. A recent meta-analysis [72] of six trials showed that the risk of recurrent stroke under warfarin is higher in patients of older age, female sex, previous stroke/transient ischemic attack, vitamin K antagonist naive status, renal impairment, previous aspirin use, and higher CHADS2 score.

Other than this we should be assured that there is not another more probable cause of recurrent ischemic stroke than atrial fibrillation like a tight carotid stenosis (or other cervical–cerebral artery stenosis). In almost one-fourth of patients with atrial fibrillation and TIA (or stroke), a significant atherosclerotic lesion (more than 50 % stenosis) is detected on the arterial axis responsible for the TIA or stroke [73, 74]. It is often difficult in such cases to precisely establish the cause of stroke as being cardioembolic or due to arterial stenosis. Some stereotype TIA preceding the stroke or a progressive stroke with watershed distribution of cerebral lesions suggesting a hemodynamic mechanism of stroke could help in some instances and point to the carotid stenosis as the culprit. Anyway in most cases a stenosis of more than 70 % NASCET could be a trigger for a decision for revascularization procedures; in this situation (associated with atrial fibrillation and oral anticoagulants) carotid endarterectomy is a better option than stenting, whenever possible, allowing for avoidance of supplementary hemorrhage risk associated with triple therapy (oral anticoagulant and dual antiplatelet therapy – clopidogrel and aspirin). If the local anatomy imposes carotid stenting, bare metal stents allow a shorter period of time for triple and dual antithrombotic therapy (anticoagulant and antiplatelet). If only a large stenosis (50–69 % NASCET) or not stenotic plaques are discovered, association of statins (high doses at the beginning until stabilization of plaque) is a useful option (and mandatory in atherosclerotic disease with tight carotid stenosis also, in spite of surgical or endovascular treatment, or associated significant coronary or peripheral artery disease). Although the antiplatelet is the classic option for atherothrombotic stroke, we should remember that in the ESPRIT [75] and WARSS [76] studies, warfarin was at least equally effective as aspirin in preventing ischemic stroke in carotid disease, but the safety profile of warfarin-treated patients was worse (and was the reason for preference of antiplatelets), so if patients with atrial fibrillation are already taking warfarin, that should cover also the risk of carotid atherosclerosis thromboembolism. If we can extrapolate this to NOAC is still unproven in any trial, but on the other hand, the same rate of prevention with NOAC as with warfarin of myocardial infarction (more

than 90 % related to atherosclerosis) proved in the phase III trials of NOAC can give confidence about the efficiency of this class in treating carotid atherosclerosis in these situations, so we should maintain this therapy and not switch to AVK if the patient is already treated with NOAC.

The addition of aspirin to dabigatran or apixaban in the post hoc analysis of RE-LY [77] or ARISTOTLE [78] trials did not prove any supplementary benefit in reducing ischemic events, but increased the hemorrhagic events. However, some experts agree that if in spite of correct anticoagulation and statin treatment stereotype, TIAs reoccur in a territory of a large stenosis (without indication for revascularization procedures), a short period (1–2 months) of aspirin added to the anticoagulant drugs could be done.

The moment of introduction of oral anticoagulants after the onset of an acute ischemic stroke is not precisely defined, but depends of the dimensions of lesion. Based on small case series and group of patients with early acute phase of stroke included in the past trials of warfarin for secondary prevention, some experts recommend immediate treatment for TIA and minor stroke, a delay up to 3–5 days for less than lobar strokes, 1 week for medium size lesions (lobar), and up to 2 weeks for large strokes (multilobar) [79].

Much difficult is the decision to reintroduce oral anticoagulants after an intracerebral hemorrhage (ICH); this depends on the location of ICH (lobar vs. nonlobar), presence of reversible causes of ICH (e.g., severe hypertension, incidental elevated INR), probability of amyloid angiopathy, level of neurologic deficit and dimensions of hemorrhage (influencing the speed of resorption), and the competing risk of arterial thromboembolism. If the hemorrhage is lobar, large, and with MRI indicating frequent associated lobar cerebral microbleeds suggestive of amyloid angiopathy, the benefit of restarting anticoagulation is low compared with higher risks. If the arguments are in favor of resumption of anticoagulants, the minimum period from the onset of hemorrhage is not clearly defined; the AHA/ASA guidelines [2] recommend at least 4 weeks, but this period is much shorter (depending of the type and position of valve) when patient has prosthetic cardiac valves and when i.v. heparin in dosage to cover at least the lower level of efficiency is probable a safer option until resumption of oral anticoagulants.

8.2.2 TIA and Ischemic Stroke Due to Large Artery Disease

TIA and ischemic stroke due to large artery disease are most frequently associated with atherosclerosis, from aortic arch and large cervical arteries to intracranial large arteries. Large vessel inflammatory diseases and dissection are much rare but should be taken into account in specific situation.

Aortic atherosclerosis is unfortunately the gray zone between the heart and cervical–cerebral arteries often missed as the cause of arterial embolism and stroke. Large atheroma (more than 4 mm thick) or mobile thrombus, ulcerated aortic plaques, and stenosis at the origin from the aorta of large cervical arteries are associated with increased risk of ischemic stroke [80–82].

Even the descending thoracic aorta could be a neglected source of cerebral emboli and stroke through retrograde flow [83] and emboli from complex plaques, so a transesophageal echocardiography (TEE) (as gold standard) and high-definition four-dimensional flow-sensitive MRI (if available) are useful tools to complete the work-up in both determined and especially apparent cryptogenic stroke and could explain embolism to multiple brain territories. Sometimes the clinical features of stroke through embolism from aortic atheroma could be quite unusual; the diffuse spreading of small emboli in different cortical areas presenting as transient confusion with bizarre behavior is easily misinterpreted if a MRI DWI examination is not done (Fig. 8.1).

It is still an unsolved dilemma about the best antithrombotic treatment to prevent further embolization from aortic arch atheroma. First opinions were based on retrospective case series and divided between antiplatelet (aspirin) and warfarin use. Later randomized trials (PICSS [82]) showed that large aortic plaques remain associated with an increased risk of recurrent stroke and death at 2 years despite treatment with warfarin or aspirin, and complex plaque morphology increases the risk. The event rates were similar in the warfarin and aspirin groups (16.4 % versus 15.8 %), so a conclusion between the best choice – antiplatelet or warfarin – was not drawn.

The possible association of clopidogrel to aspirin further raised the bar in favor of the antiplatelet therapy compared to warfarin, so the ARCH trial [84] was designed to compare this treatment possibilities but unfortunately was finally stopped after 8 years from initiation due to lack of inclusion of the planned number of patients. This proved how difficult it is in real life to provide transesophageal echocardiography to all patients supposed to benefit for detection of such lesion and why aortic arch atheroma embolism is still underdiagnosed. Although underpowered because of smaller number of included patients, the trial did not find an advantage of warfarin over dual antiplatelet (clopidogrel and aspirin) in terms of strokes and major hemorrhages including intracranial hemorrhages, but vascular death was in favor of antiplatelet therapy. Finally based on this data, it looks that in most cases dual antiplatelet therapy (clopidogrel and aspirin) is a reasonable option and only in case of association of aortic atheroma with atrial fibrillation or other sources of cardiac embolism, or in case of failure of antiplatelet therapy-warfarin (or other AVK anticoagulants) could be used instead. Adding a statin

treatment in this situation is highly recommended like in all cases of significant large artery atherosclerosis.

8.2.2.1 Cervical (Carotid and Vertebral) Atherosclerosis

Acceptance of cervical artery (carotid and vertebral) atherosclerosis as a cause of ischemic stroke varies from 30 to 60 % with any degree of stenosis documented by noninvasive imaging or angiography, and the attributed proportion of stroke due to extracranial or intracranial atherosclerosis is around 20–25 % [85], but there is a frequent overlapping with other causes of ischemic stroke like cardiac embolism and small vessel disease. Atherosclerosis of large arteries was associated with first ischemic stroke between 46 % in the 2002–2005 period evaluation and decreased to 25 % a decade after, a fact probably explained by better treatment of arterial hypertension and use of statins, and also significant changes in lifestyle (smoking cessation, healthy diet, and so on). There was an opposite trend for increasing prevalence of cardiac embolism (probably proportional with increasing life span of population). The rate of recurrence is higher for large artery disease stroke compared to other causes: 19.2 % of patients with index stroke caused by large artery disease, 4.9 % with small vessel disease, 8.2 % with cardioembolic cause, 5.6 % with cryptogenic cause, and 12.8 % with other and undetermined cause combined [86, 87].

The main mechanism for ischemic stroke produced by atherosclerosis of cervical or cerebral arteries is related to unstable atheroma and local thrombosis and occlusion, associated or not with distal arterial embolism, or hypoperfusion through hemodynamic mechanism leading to watershed-type infarcts.

Primary and secondary prevention in atherosclerosis of large cervical and cerebral arteries should be applied in all patients, but there are differences between indication for medical therapy or interventional procedures (endarterectomy or stenting) in patients with asymptomatic stenosis or atherosclerotic plaques, where medical treatment only is frequently enough and those who have had a TIA or ischemic stroke.

Antithrombotic Treatment

Antiplatelet therapy is an establish treatment for secondary prevention after a TIA or stroke related to atherosclerotic large artery disease starting with trials like Dutch TIA [88], UK-TIA, [89], and ESPS2 [90] in the early 1990s, with a proven reduction stroke risk and death with small doses of aspirin (under 325 mg/day, usually 75–100 mg/day). Since then this treatment became a standard and also recommended in asymptomatic carotid stenosis (more than 50 % degree of stenosis) but not in isolated, asymptomatic, non-stenotic plaques where the risk-benefit ratio was less favorable and where treatment of risk factors (arterial hypertension, hypercholesterolemia with statins, cessation of smoking, diabetes treatment) is a better approach.

Since the ESPRIT [75] and WARSS [76] trials did not prove a superior effect of warfarin over aspirin (only similar results) in reducing the risk of stroke associated with cervical artery atheroma, and overall warfarin induced more frequent hemorrhagic events, oral anticoagulants (antivitamin K) are not an option for prevention of ischemic stroke in patients with cervical artery atherosclerosis.

In ESPS2 [90] aspirin and dipyridamole were more efficient than placebo, and their combination was more efficient than aspirin alone in reducing the risk of fatal and nonfatal stroke.

Clopidogrel 75 mg/day in the CAPRIE [91] phase III trial, compared with aspirin, reduced supplementary with about 8 % (but without reaching a statistical significance) the recurrence of an ischemic cerebral event, but had a significant reduction of the overall index of vascular deaths and vascular events in cerebral, coronary, and peripheral arterial beds. This study and further positive studies with combination of clopidogrel and aspirin in coronary heart diseases imposed clopidogrel as the drug of choice when ischemic large artery cerebral disease is combined with coronary or peripheral ischemia or when a patient has an "aspirin failure " or intolerance.

The addition of aspirin 75 mg/day in patients already treated with clopidogrel 75 mg/day was compared with clopidogrel 75 mg/day alone in MATCH study [92], without supplementary reduction in ischemic cerebral event, but an increase in the hemorrhages rate, with an overall negative benefit. The same negative result was obtained for dual antiplatelet (clopidogrel and aspirin) versus aspirin in the CHARISMA trial [93] (including asymptomatic and symptomatic patients with atherosclerotic lesions of cerebral, coronary, and peripheral arteries) as overall result of the trial and also for patients with asymptomatic carotid atherosclerosis (part of the whole study). The result of these two studies emphasized that the association of clopidogrel and aspirin has an overall negative net benefit in the balance of prevented ischemic and induced hemorrhagic events and mortality, so it is not recommended in usual situation of asymptomatic atherosclerotic lesions of large artery or after a TIA or stroke.

A particular situation is the existence of a recent stent (carotid or coronary) or a recent (first year) myocardial infarction, situations where there is a clear indication for dual antiplatelet therapy (aspirin and clopidogrel if a previous stroke exists) with a duration depending on the stent type (bare metal stent or drug-eluting stent) and the associated risks of hemorrhage but generally extended to no more than 1 year after stent implantation.

In PRoFESS trial [94] clopidogrel 75 mg/day was compared with the combination of 25 mg of aspirin plus 200 mg

of extended-release dipyridamole twice daily for secondary prevention of stroke as primary outcome. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. The trial did not meet the predefined criteria for non-inferiority of the combination therapy but showed similar rates of recurrent stroke with combination of aspirin and dipyridamole as clopidogrel. There was no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.

These results recommend clopidogrel 75 mg/day or combination of low-dose aspirin (25 mg) associated with controlled-released dipyridamole (200 mg) over aspirin (75–150 mg/day) alone after ischemic stroke caused by large cervical artery atherosclerosis, especially in the first 6–12 months after the event, when recurrence rate is higher, in patients with recurrent event while on aspirin (although the results of this attitude is not supported by trials) or for the patients considered as having a high risk, or in patients that have (in case of clopidogrel) associated coronary or peripheral artery lesions.

For rapid onset of action like in recent TIA, aspirin needs a first loading dose of 300 mg, the same being true for clopidogrel.

In case of frequent recurrent TIA in spite of loading dose of antiplatelet monotherapy (usually aspirin 300 mg), the so-called resistant TIAs, an active statin in high dosage (like 80 mg atorvastatin or 40 mg rosuvastatin) for anti-inflammatory and plaque "stabilization" through pleiotropic effects, could be useful. Rapid evaluation of arteries could discover frequently a not stenotic ulcerated plaque, and if the symptoms of TIA reoccur, another possible option is to add (with a loading dose of 300 mg) clopidogrel to aspirin for a limited period of time (1–2 months) to avoid the increased bleeding risk associated with long-term dual antiplatelet therapy. This approach could be justified by the results of CARESS trial [95] where compared with aspirin monotherapy, the dual clopidogrel and aspirin treatment reduced asymptomatic embolization (the microembolic signals detected by transcranial Doppler) and also new TIA and stroke in patients with recent symptomatic carotid stenosis over 50 %.

Anyway, in case of severe cervical carotid stenosis, especially associated with frequent TIAs, carotid endarterectomy (CEA) (or stenting) should be the priority treatment as soon as possible, and this should not be delayed by the introduction of clopidogrel therapy (which is interrupted usually 5 days before CEA, but not before stenting [96]).

Instead, aspirin is initiated before, maintained during, and continued after CEA. Anyway in this situation the 30-day rate of death or stroke after carotid endarterectomy in this situation with crescendo TIA/stroke in evolution is much higher: 13.3 % compared with 2.71 % among asymptomatic patients with no history of stroke/transient ischemic attack, 4.06 % among asymptomatic ones with a distant history of stroke/TIA, 5.62 % among those operated for carotid TIA, and 7.89 % of those with minor stroke [97].

In case of hemodynamic TIA in critical carotid stenosis, reducing blood pressure under the limit of tolerance should be avoided (sometimes the limit could be 160–170 mmHg systolic values), the patient is asked to maintain a decline position, and isotonic saline or plasma expander solutions are administered through intravenous infusion. Repeated TIA after completing all these measures could be associated with another overlooked stenosis of intracranial arteries or at the origin of cervical arteries from the aortic arch, so if it was not already done before, the vascular imaging of the whole arterial axis from the aortic arch up to the cerebral arteries should be done. Other alternative diagnosis than TIA should also be borne in mind in case of normal findings in all work-up for "resistant TIAs."

In case of cervical artery dissections, both antiplatelet (usually aspirin) and heparin are used, the criteria for selection of one or another being empirical and depending on personal experience and preferences of the treating physician. Most often dissection associated with large cerebral or cerebellar strokes, intracranial propagated dissection, and occlusions of the dissected artery are reasons for antiplatelet therapy, while recurrent stroke or TIA under antiplatelet therapy, large intraluminal thrombus, cervical large aneurysm with thrombus formation is in favor of anticoagulant therapy. The randomized trial CADISS [98] did not find any difference in efficacy of antiplatelet and anticoagulant drugs for preventing stroke and death in patients with symptomatic carotid and vertebral artery dissection, and stroke was much rare in both groups than reported in some previous observational studies. In case of hemodynamic deterioration or recurrent stroke under best medical treatment, there are reported series of cases with successful endovascular recanalization. Thrombolysis in the first 3–4.5 h from stroke onset is allowed if there is not an associated subarachnoid hemorrhage or immediate risk for this. The antiplatelet therapy is maintained lifelong if local occlusion, stenosis, or vessel wall irregularity are present, but in the rest of the cases 6 months to 1 year after event could be enough, if a structural defect of the arteries or other systemic arterial diseases (with risk of recurrence) was not found.

Antihypertensive Treatment

Meta-analyses of randomized controlled trials (RCTs) performed primarily among stroke-free individuals have shown that blood pressure lowering is associated with a 30–40 % stroke risk reduction. Risk reduction is greater with larger reductions in blood pressure. Treatment of arterial hypertension should start after the first days of ischemic stroke onset depending on clinical situation (but not

earlier than the first 24 h) in patients known as hypertensive or in those with persistent blood pressure value above 140/90 mmHg [99].

The target value for the upper levels of blood pressure in primary prevention of vascular events was a continuous debate in the latest published guides (JNC 8 [100], 2013 ESH/ESC Guidelines [101], ASH-ISH 2014 Guidelines [102]), and the conclusion is that it should be under 140/90 mmHg in the vast majority of patients and between 140–150 mmHg for some of the older people, especially after 80 years, but these values should be adapted to individual tolerance.

Blood pressure values under 140 mmHg for those over 60 years or even 80 years old were considered as possible to be obtained for further reduction of risk and were a matter of contradictory opinions in some specialist groups [103]. As prevention of stroke is the most consistent benefit of antihypertensive therapy and has been observed in almost all large randomized trials using different drug regimens, all antihypertensive class medications are acceptable for stroke prevention provided that blood pressure is effectively reduced. The European Cardiology Society specifies that calcium channel antagonists may have a slightly greater effectiveness on stroke prevention, but a diuretic in combination with an angiotensin-converting enzyme (ACE) inhibitors has also a proven efficacy in other trials, while the ASH-ISH considers an ACE inhibitor or angiotensin receptor blockers (ARB) to be the first option for patients with previous TIA or stroke, and after that if necessary thiazide diuretic or calcium channel blockers could be added. Greater cerebrovascular protective effects have also been reported for ARBs associated with some protective effects in cognitive decline [104, 105].

An old concern of neurologists was related to the potential harmful effect of significant decreasing of blood pressure values in patients with carotid stenosis, which facilitates a decrease of cerebral perfusion under the limit of tolerance and autoregulation, precipitating an acute stroke or a slow impairment of neurocognitive function. In a retrospective population analysis [106], the risk of stroke was increased with higher values of blood pressure in unilateral carotid stenosis and bilateral large stenosis (but less than 70 % degree of stenosis); however, for bilateral carotid stenosis of more than 70 %, systolic blood pressure values between 140 and 160 mmHg were associated with a minimal rate of events.

The different outcome in acute ischemic stroke patients with the same age and location of arterial occlusion is vastly dependent on the vasomotor reactivity status and collateral circulation, so different levels of blood pressure tolerance could be found and need an individual exploration.

This assumption could be true in some studies [107] with patients having symptomatic carotid stenosis and quantitatively evaluated baseline hemodynamic status using positron emission tomography (PET) and ^{15}O-gas. Overall, a higher total stroke risk was observed for systolic blood pressure lower than 160–170 mmHg in patients with impaired perfusion and at lower systolic blood pressure (less than 140 mmHg) in patients without. Overall, the relationship between SBP and total stroke recurrence was J-shaped, so based on blood pressure values, the therapeutic strategies to prevent recurrent strokes should differ between patients with and without hemodynamic compromise.

After carotid endarterectomy or stenting, prompt treatment of arterial hypertension with systolic blood pressure reduction to 120–130 mmHg should be done to avoid the cerebral hyperperfusion syndrome [108], especially when transcranial Doppler shows a 150–300 % increase in the ipsilateral middle cerebral artery flow velocity. The normalization of hyperperfusion through blood pressure reduction corresponds with clinical improvement and avoids manifestation such as seizures or devastating cerebral hemorrhage. Labetalol and clonidine are the drugs of choice for management of hyperperfusion syndrome, because the rest of antihypertensive drugs could have a vasodilatation effect. Mannitol for cerebral edema treatment and antiepileptic drugs in case of seizures are also recommended.

Statin treatment for atherothrombotic stroke is now well established although in the past some conflicting evidences emerged. Compared to myocardial infarction, stroke is a very heterogeneous disease as etiology, where cardioembolic and small vessel disease and other vasculitis or dissection have little causative connection with hypercholesterolemia. A meta-analysis [109] of trials including over 165,000 patients concluded that reduction of LDL cholesterol with 38 mg/dl reduced the relative risk of stroke with 21.1 %, and after a first stroke, an intensive reduction of LDL (although only four study subgroups from SPARCL, LIPID, CARE, and HPS were included) further reduced with 12 % the relative risk of fatal and nonfatal stroke.

The SPARCL trial [110] is the only one where patients with previous stroke without evidence of coronary heart disease were included, with a starting LDL between 100–190 mg/dl, and the effect of 80 mg/day atorvastatin was compared with placebo. The active-treated patients had a 16 % lower relative risk of stroke, and 43 % less fatal strokes, but the same overall mortality. In the subgroup of patients with carotid stenosis, the risk of stroke was one-third less than the placebo subgroup. Patients who succeeded to reach the recommended target LDL level (less than 50 % of initial level) had a lower rate of stroke and major coronary events (33 % and 37 % less, respectively) without any increase in any hemorrhage. For a level of LDL cholesterol under

70 mg/dl compared with those under 100 mg/dl, a post hoc analysis proved a supplementary 28 % reduction of stroke rate [111].

Although lowering the LDL levels represents the main mechanism of action connected to the clinical benefit of statins, there are also some pleiotropic effects [112] like improvement of endothelial dysfunction, stimulation of nitric oxide synthase, anti-inflammatory effect on the atheroma core, and reducing the volume of lipid core of plaques and reduction of the risk of plaque rupture or thrombosis. The decrease in the rate of progressing of atheroma was proven through serial ultrasound measurement of carotid intima media thickness in different studies [113]. These pleiotropic effects (especially the anti-inflammatory and plaque stabilizing) need higher doses and are earlier than that of decreasing LDL cholesterol, a fact that could explain the positive results in treatment of recurrent TIA associated with an unstable atheroma or stenosis or in the acute phase of ischemic stroke.

8.2.3 Intracranial Large Artery Stenosis

Intracranial large artery stenosis causes about 5–10 % of strokes in white people, 15–29 % of transient ischemic attacks or strokes in black people, and up to 30–50 % of strokes in Asian people [114, 115].

It shares the same major risk factors with cervical atherosclerotic stenosis: hypertension, smoking, diabetes mellitus, and hyperlipidemia. The majority of recurrent strokes occur in the initial symptomatic intracranial artery stenosis territory, and nearly half of these strokes are disabling [116].

To establish more efficacious secondary prevention strategies, it is essential to clarify the predictors of recurrent ischemic stroke.

Patients with cortical and subcortical or multiple lesions on initial MRI DWI images were more likely to have severe stenosis, whereas those with subcortical lesions only were more likely to have milder stenosis, both situations being associated with an increased risk of recurrent stroke, although higher in the first situation [117].

In the WASID trial, patients with at least 70 % stenosis of a major intracranial artery had an increased risk of recurrent stroke in the territory of the stenosis compared with patients with 50–69 % stenosis [118]. However, the presence of robust collaterals in patients with greater than or equal to 70 % stenosis mitigated the risk of recurrent stroke [119].

In the past these patients were frequently treated with anticoagulants, but after the 2005 result of WASID trial [120], these changed in favor of antiplatelet therapy. The only surprising thing was the dose of aspirin used in WASID trial – 1300 mg/day, a dose that at the time of the study, and even more now, is considered higher than the upper standard limit (less than 325 mg, usually 75–100 mg/day). The ischemic stroke rate was the same for every of the two drugs, but the rate of hemorrhages, myocardial infarction, and any deaths were significantly lower with aspirin.

Since in many cases in spite of antiplatelet and statin therapy, the risk of recurrent severe stroke was high when a severe intracranial stenosis was the cause, and having in horizon the successful coronary and cervical carotid stenting, progressive attempts for stenting the symptomatic cerebral arteries were done, and the positive results from some registries gave some hopes.

Unfortunately two randomized trials – SAMMPRIS [121] and VISIT [122] – came to the same conclusions: that in patients with intracranial arterial stenosis, aggressive medical management was superior to angioplasty and stenting with the use of the Wingspan or Vitesse intracranial stent system, both because the risk of early and delayed stroke after stenting was high and because the risk of stroke with aggressive medical therapy alone was lower than expected. Treatment recommended in the medical arm consisted in dual antiplatelet therapy – clopidogrel 75 mg/day and aspirin 75 mg/day in the first 3 months, followed by a single antiplatelet drug, associated with 20 mg rosuvastatin or 80 mg atorvastatin to maintain LDL cholesterol under 70–100 mg/dl, and adequate treatment of arterial hypertension with systolic blood pressure values maintained under 140 mmHg. The reduction of blood pressure is also indicated in intracranial stenosis over 70 %, since higher values than 160/80 mmHg were associated with an increased risk of stroke, and the same is true for values above 120/80 mmHg for stenosis under 70 % [123].

8.2.4 Cerebral Small Vessel Disease

Cerebral small vessel disease is responsible for about 25 % of strokes but is frequently asymptomatic or manifested through progressive cognitive impairment and underdiagnosed if MRI examination of the brain (the method of choice for diagnosis) is not done. The anatomical basis of cerebral hemorrhage is also related to small vessel disease in a vast proportion of patients.

Etiology of this entity is very heterogeneous, most frequent being associated and caused by arterial hypertension and diabetes with lipohyalinosis and also small artery atherosclerosis. Inflammatory diseases of small arteries are another group, due to infections, autoimmune diseases, and other types (not septic or autoimmune) of inflammation

(like in Cogan or Behçet syndrome). There are many genetically determined cerebral small vessel diseases of the central nervous system, the best known being CADASIL, but others are also recently described or supposed to have a genetic background. Because of these heterogeneous causes of small vessel diseases, the treatment of lacunar strokes or small vessel-related TIA depends on identification of specific causes, and if possible, a specific treatment is recommended when it exists (like corticosteroid treatment or pulse cyclophosphamide, rituximab in autoimmune vasculitis, and so on).

The mechanisms of cerebral ischemia in lacunar stroke are also heterogeneous and sometimes unclear – some are caused by proximal perforating small artery atheroma; in this case a larger lacunar infarct in the proximal basal ganglia associated with progressing symptoms is more frequent. Lacunar stroke caused by lipohyalinosis or arteriolosclerosis is thought to be more likely when additional features of small vessel disease (e.g., white matter hyper intensities, widespread small lacunes) are evident. In a large number of cases, there are not classical risk factors, and atherosclerosis of parental vessel was not identified – so in this case it was supposed that a diffuse process that started in the endothelium and consisted of failure of the cerebral arteriolar and capillary endothelium with thickening of the vessel wall and luminal distortion would eventually lead to secondary perforating arteriolar thrombosis, luminal occlusion, and infarction [124, 125].

In case of hypertensive and/or diabetes-associated cerebral small vessel disease, or atherosclerosis of the small penetrating arteries of the brain, correct treatment of arterial hypertension (with target values below 140/90 or 130/80 mmHg if cerebral hemorrhage was associated) and proper treatment of diabetes are the first steps.

Antiplatelets are the antithrombotic treatment of choice for small vessel disease, but the effect is not very well evaluated due to previous mentioned heterogeneity of the causative factors. Aspirin is most frequently used in standard 75–100 mg/day. SPS3 was a double-blind, multicenter trial [126] involving patients with recent symptomatic lacunar infarcts identified by magnetic resonance imaging. Patients were randomly assigned to receive 75 mg of clopidogrel or placebo daily; patients in both groups received 325 mg of aspirin daily. The primary outcome was any recurrent stroke, including ischemic stroke and intracranial hemorrhage. The study was stopped earlier than planned because dual antiplatelet therapy did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death, so single drug therapy with aspirin in standard small doses (75–325 mg/day) remains the main antithrombotic therapy in this case. The same study added in post hoc analysis some important findings – first, the fact that patients with recurrent stroke under aspirin do not benefit from adding clopidogrel, the stroke rate remains the same, and the risk of hemorrhage was significantly increased [127]. Second, in this patient group with recent lacunar stroke and aggressive blood pressure management, prior symptomatic lacunar ischemia, diabetes, black race, and male sex independently predicted ischemic stroke recurrence [128].

Aggressive management of hypertension with a target systolic value under 130 mmHg did not significantly reduce new lacunar strokes but decreased the rate of cerebral hemorrhages, and because of that it is the target value recommended in lacunar strokes. No subgroup of patients had a significant reduction in recurrent stroke rate by either randomized intervention (aspirin or dual antiplatelet therapy).

Some questions are related to the value of statin therapy in pure lacunar stroke. Some studies demonstrated the positive effects of improving vasomotor reactivity as marker of endothelial dysfunction in small vessel disease [129, 130], and in part of these cases, there is an associated large vessel atherosclerotic disease, explaining the fact that in SPARCL trial the treatment with 80 mg atorvastatin was associated with reduction in stroke recurrence in those (more than 50% of all patients) with lacunar stroke at inclusion [131], so overall, treatment with statins in lacunar strokes seems justified.

A particular situation is that of repeated lacunar pure motor TIA, apparently resistant in many cases to any therapy – antiplatelet (single or dual), heparin, or even thrombolysis – leading to lacunar stroke, often severe, with lesion located in internal capsule or paramedian pontine regions, the so-called capsular or pontine "warning syndrome" [132–134]. Escalating the available antithrombotic treatment mentioned above and avoidance of lowering the blood pressure during the period of attacks could be the measures to be applied, with variable results. The exact mechanisms of this kind of resistant attacks are not quite clear, being a matter of debate.

Image Gallery

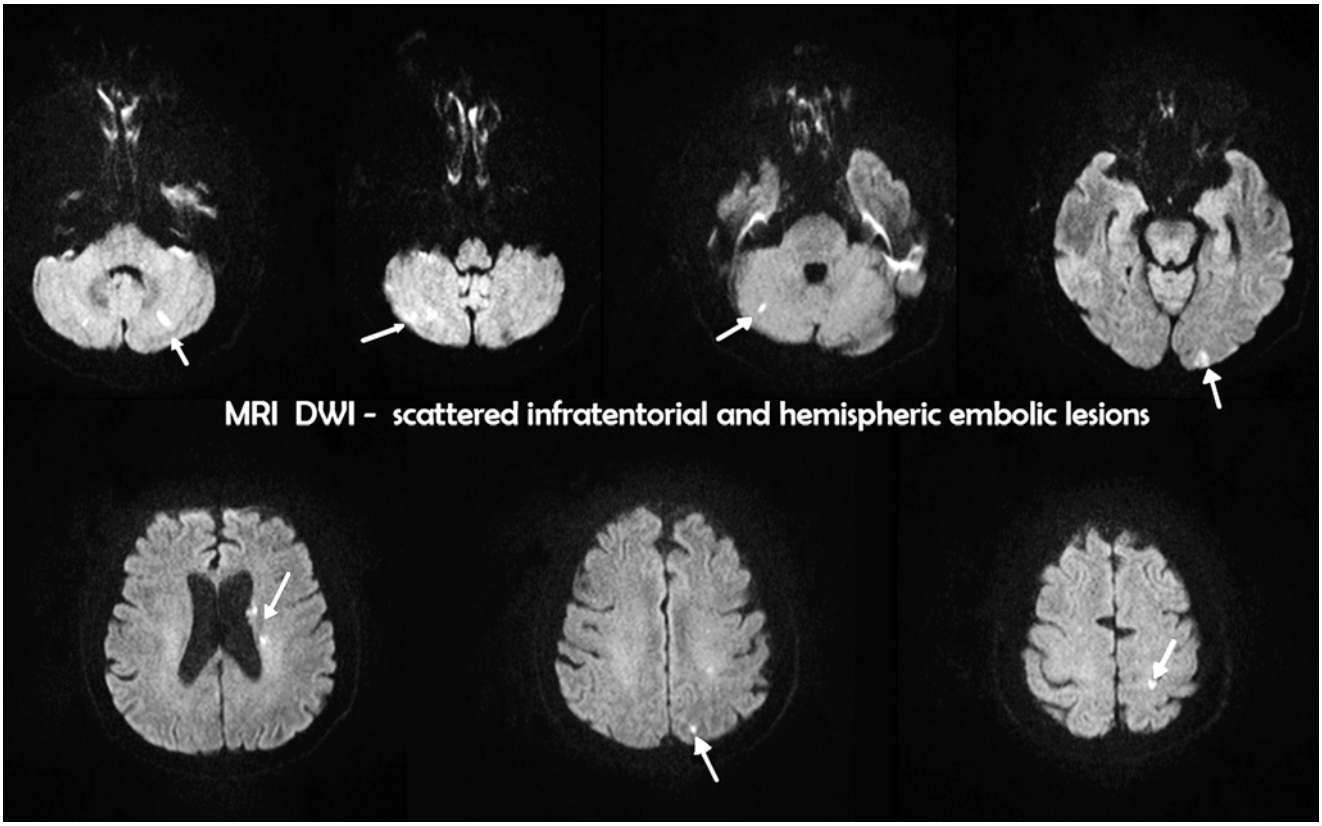

Fig. 8.1 MRI DWI – scattered infratentorial and hemispheric embolic lesions

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Anesthesia for Carotid Surgery and Stenting: Neuromonitoring and Perioperative Care

9

Cristina Tudor and Ramona Jemna

9.1 General Preoperative Evaluation for Carotid Endarterectomy

A comprehensive evaluation of comorbidities and medical condition must be considered for a patient candidate for carotid endarterectomy. Physical examination and medical history are included to identify cardiac and noncardiac problems as well as for stratification of surgery risk.

History
1. Cardiac history
2. COPD (smoking, bronchospasm)
3. Alcohol (cirrhosis)
4. Diabetes (wound infections, risk of protamine reaction)
5. Neurologic symptoms (transient ischemic attacks, remote stroke, previous carotid endarterectomy, neurologic deficit)
6. Urologic symptoms (antibiotics, catheter placement problems)
7. Ulcer disease/GI bleeding (stress prophylaxis)
8. Active infections (urinary tract)
9. Current medications – antiangina, diuretics, antiplatelet or anticoagulant drugs, bleeding history
10. Drug allergies
11. Previous surgery
Physical examination
1. Skin infections/rash
2. Differential arm blood pressures – differential pressures may identify possible subclavian artery stenosis
3. Heart/lungs
4. Neurologic examination (deficits)
Laboratory data
1. Hematology: CBC, PT, PTT, platelet count
2. Chemistry: electrolytes, BUN, creatinine, blood glucose, liver function tests (baseline for use of statins)
3. Arterial blood gases if room air O_2 saturation is <90 %
4. Hemoglobin A1c level (assessment of diabetic control)
5. Urinalysis
6. Chest x-ray PA and lateral
7. Electrocardiogram
8. Pulmonary function testing – not reliable because of poor compliance of neurological patients

C. Tudor (✉) • R. Jemna
Cardiovascular Anesthesia and Intensive Care Clinic,
The University Hospital of Bucharest, Bucharest, Romania
e-mail: georgescucristina@yahoo.com; monicaraiciulescu@gmail.com

Symptomatic classification of patient's *cardiac symptoms* should be performed; the preanesthetic evaluation must detect and optimize cardiac conditions. Cardiac evaluation should be considered since this kind of patients has cardiovascular comorbidities, and myocardial infarction is the main complication of carotid endarterectomy.

Current and prior patient medications are important. Particular attention should be given to anti-ischemic, antiplachetar/anticoagulant, and anticonvulsant medication:

1. All *antianginal* medication *should not be discontinued* in the morning of surgery to prevent the cardiac event.
2. *Diuretics*, *b-blockers*, or *calcium channel blockers* used for hypertension can be given preoperatively to prevent rebound hypertension. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be withdrawn due to the risk of hypotension.
3. *Anticoagulation/antiplatelet therapy*
   (a) *Aspirin* is beneficial for the primary and secondary prevention of cardiovascular disease and is given routinely to patients inhibiting platelet aggregation for 7–10 days. Most studies [1] have shown that preoperative use of aspirin increases perioperative blood loss, but studies also recommend to continue administering aspirin 81 mg daily, bearing in mind the high risk of myocardial infarction associated with carotid endarterectomy.
   (b) *Clopidogrel* is a thienopyridine that should be discontinued 5–7 days preoperatively for patients undergoing elective surgery. Most of the patients that receive clopidogrel also receive aspirin, producing dual antiplatelet activity. Studies [1] have shown that clopidogrel taken within 5 days of surgery is associated with an increased risk of bleeding and increased rates of transfusion and re-exploration for bleeding. However, in case of urgent surgeries, the surgery should not be delayed, but the surgeon should be aware of the potential risk of bleeding and the need for platelet transfusion (usually 2–4 units). The platelet

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transfusion would be less efficient if given in the first 4–6 h after the administration of the maintenance dose of clopidogrel because of the endogenous metabolites.

(c) *Prasugrel* is a third generation of thienopyridine, ten times more potent than clopidogrel with the same limitation for surgery. Prasugrel is associated with a higher risk for bleeding than clopidogrel and should be discontinued 7 days before surgery.

(d) *Ticagrelor* is a reversible inhibitor of the P2Y12 receptor that has a more rapid onset of action and more pronounced inhibition of platelet function than clopidogrel. It has a reversible effect on platelet function with a half-life of 7–8 h, which is translated into a lower risk of operative bleeding. It must be stopped 1–2 days before surgery.

(e) *Warfarin/acenocoumarol* should be stopped 3–5 days before surgery until the normalization of INR; in the meantime, a LMWH or heparin should be given for antithrombotic prophylaxis.

(f) *New oral anticoagulant drugs* (*NOADs*) are an alternative for vitamin K antagonists; these anticoagulants do not require routine INR monitoring and possess favorable pharmacological properties. Dabigatran is a highly specific and competitive direct thrombin inhibitor, which is orally administered as an inactive drug and, after complete esterase-mediated conversion to its active form, reaches peak plasma levels within 2–3 h. It has a rapid onset of action (1–2 h), has a short half-life (12–17 h), and has an 80 % renal excretion. It must be stopped 3 days before surgery (skip four doses) for carotid endarterectomy. Rivaroxaban is a competitive and dose-dependent direct inhibitor of factor Xa. It has a half-life of 9–13 h with 35 % renal clearance. It also must be stopped 3 days before surgery (skip two doses). Apixaban is a direct, reversible, competitive, and selective inhibitor of factor Xa and it must be stopped 3 days before surgery (skip four doses) [2].

(g) *Unfractionated heparin* (*UFH*) requires monitoring by a partial thromboplastin time (PTT) to ensure a therapeutic range of approximately 50–60 s. In patients being bridged, heparin is usually stopped about 4 h before surgery with a PTT under 40 s.

(h) *Low-molecular-weight heparin* (*LMWH*) is simple to use, with no requirement for blood monitoring. It needs to be stopped 18–24 h preoperatively to minimize perioperative bleeding.

4. *Statins* should not be discontinued perioperatively; the use of statins in symptomatic patients undergoing CEA may be associated with improved outcome.
5. *Sedative-analgesic medications* and *anticonvulsants* should be continued because of rebound risk, but we need to take into account that they should be administered only after the patient's neurologic examination has been documented.
6. *Prophylactic antibiotics* – Administration of antibiotics prior to carotid endarterectomy is recommended in order to control surgical site infection due to the frequent use of prosthetic material. Second-generation antithrombotic must be given 2 h before surgery.

Chronic obstructive pulmonary disease (COPD) is a term often applied to patients with a significant smoking history independent of the degree of respiratory impairment. However, the degree of COPD is best defined by pulmonary function testing (PFTs).Although this is not essential in patients without functional limitations, failure to perform spirometry testing may lead to underreporting of COPD and thus to an underestimation of the risk of adverse outcomes. Pulmonary function tests might identify patients at high pulmonary risk (generally an FEV1 <0.6). At this type of patients, with preexistent severe pulmonary disease, the locoregional anesthesia is indicated.

Diabetes mellitus is a condition associated with more extensive and diffuse atherosclerotic disease. It may range in severity from mild hyperglycemia controlled with diet or oral medications to patients requiring insulin. Oral hypoglycemics and insulin are held in the morning of surgery. Monitoring of intraoperative glucose levels and aggressive treatment to maintain blood glucose <180 mg/dL is essential to reduce neurologic morbidity and the risk of infection. Management of postoperative hyperglycemia with a defined protocol is needed.

Ulcer disease/GI bleeding in patient history may indicate the need of evaluation by endoscopy, bearing in mind that the patient will require postoperative anticoagulation/antiplatelet treatment.

Neurologic symptoms should be evaluated before surgery because of the possible postoperative neurologic deficit and for early detection of stroke.

Any past medical history and medication, previous surgical interventions, or psychiatric history should be detailed in the medical record. A review of medical history is needed to identify other comorbid conditions likely to affect the outcome of surgery.

9.2 Choice of Anesthesia

The type of anesthesia used in carotid revascularization is generally decided by surgeon's preference and patient characteristics, choices for this kind of intervention being to administer general anesthesia or locoregional anesthesia [3].

The most important anesthetic goals for carotid revascularization – regardless of anesthetic technique – are to avoid the variation of blood pressure and heart rate, to maintain cerebral perfusion, and to ensure early neurological evaluation for stroke detection at the end of surgery.

Studies have shown that the anesthetic technique used does not impact the long-term prognosis, but changes in perioperative blood pressure or hypotension caused by general anesthesia can have impact on cerebral blood flow. Locoregional anesthesia was associated with fewer patients' hemodynamic status changes. Meta-analysis showed that there was no significant difference in the rate of stroke at 30 days between patients who received general anesthesia and those who received locoregional anesthesia, though locoregional anesthesia is associated with a trend of decreasing mortality, but with no differences in rates of postoperative bleeding, myocardial infarction, pulmonary complications, and length of hospital stay. The same study showed that for locoregional anesthesia, the time of surgical intervention is shorter and anesthesia is less expensive.

9.2.1 General Anesthesia

General anesthesia for carotid endarterectomy is sometimes preferred because it is much more comfortable for the patient and is recommended for uncooperative patients, with neurological dysfunctions or anxiety syndromes [4]. General anesthesia does not prevent hemodynamic response of manipulation of the carotid sinus (severe vagal response) and can cause significant changes in blood pressure and/or pulse rate, especially upon intubation and emergence. Due to comorbidities of the patients (i.e., CAD, MI) and of the nature of surgery, it's important to avoid this hemodynamic modification. Also we need to ensure a quick emergence, a very important fact for quickly assessing the neurological function. General anesthesia for carotid endarterectomy (surgery is typically lasting less than 2 h) is obtained with short-acting drugs to ensure a quick anesthetic emergence.

Induction of anesthesia is generally obtained with etomidate (0.2–0.3 mg/kg) or propofol (2 mg/kg), slowly injected and titrated to maintain hemodynamic stability. The addition of a low dose of opioid (fentanyl 1–2 mcg/kg or remifentanil 1 mcg/kg) and/or lidocaine (1 mg/kg) helps (to) prevent hemodynamic response during endotracheal intubation.

Anesthetic *maintenance* can be achieved using either a volatile or intravenous anesthetic technique.

1. *Volatile anesthetic agents* – Desflurane and sevoflurane are preferred for carotid endarterectomy because they have a low solubility and facilitate a more rapid emergency from anesthesia. Nitrous oxide is not preferred as adjuvant for volatile anesthetic gas because it can increase risk of postoperative nausea and vomiting which can raise incidence of neck hematoma. Also nitrous oxide showed in some studies cardiac toxicity and exacerbation of ischemic cerebral injury.
2. *Intravenous anesthetic agents* – Propofol and remifentanil in combination can maintain the general anesthesia for carotid endarterectomy. The combination of an opioid and a hypnotic is decided by anesthesiologist.

Clinical studies failed to demonstrate that inhaled anesthesia is superior to intravenous anesthesia regarding postoperative pain relief or hemodynamic response. There are also controversies about the use of endotracheal intubation or laryngeal mask. The laryngeal mask has the advantage of less hemodynamic response during anesthetic induction and emergence, but because of the limited access to the head of the patients, it's safe to use the endotracheal intubation. Regardless of the anesthetic method we used, we should consider maintaining normocapnia during the surgery. Permissive hypercapnia may increase cerebral blood flow and by that mechanism decrease the carotid cross-clamping ischemia, but there are adverse reactions like intravascular "steal" because of the increase blood flow in the normally perfused brain tissue. Also, cerebral vasodilatation can increase risk of cerebral embolization. Hypocapnia is decreasing cerebral blood flow by vasoconstriction mechanism causing cerebral ischemia.

The best method for cerebral monitoring during general anesthesia is not yet established, particularly in patients with preexisting neurologic deficit [5–7]. We should not forget that on one side general anesthesia decreases the brain metabolism rate and reduces the effect of cerebral ischemia, but on the other side under general anesthesia may occur ischemic phenomena that were initially undetectable.

9.2.2 Locoregional Anesthesia

9.2.2.1 Cervical Plexus Block

Locoregional anesthesia offers a greater hemodynamic stability than general anesthesia and provides a better evaluation of intraoperative neurological function. It is usually supplemented with intravenous sedation to maintain patient comfort during the procedure, but the sedation is minimized in order to allow neurologic exams to be performed at frequent intervals during the procedure.

The patients receiving locoregional anesthesia can be *followed* during the procedure by monitoring clinical mental status, speech, and function of the extremities. Continuous neurological evaluation during the carotid endarterectomy is a simple, qualitative, continuous, and sensitive method for predicting the cerebral perfusion.

The disadvantage of this technique is the low patient's comfort during surgery *and sometimes that can be converted to general anesthesia*.

The most commonly used nerve block techniques for carotid endarterectomy are superficial and/or deep cervical plexus block. The superficial and deep cervical plexus block are often performed together to provide adequate cutaneous anesthesia.

1. *Pharmacologic choice*

Carotid endarterectomy does not demand significant muscle relaxation; thus, lower concentrations of anesthetics are appropriate with this technique. Example: 1 % lidocaine or 0.25 % bupivacaine or 0.5 % ropivacaine. The studies have shown that the combination with corticoid (dexamethasone 10 mg) and opioid (fentanyl 50 mcg) increases the duration of peripheral nerve block analgesia. More data for dexamethasone are needed prior to its widespread use, especially related to potential dose-response-related neurotoxicity when combined with local anesthetics. It is also reported that a single administration of an opioid may also induce a long-lasting increase of threshold pain sensitivity, leading to delayed hyperalgesia.

2. *Techniques*

The patient is placed in the supine position with the head and the neck turned opposite the site to be blocked.

(a) *Deep cervical plexus block* (Fig. 9.1)
- Palpate the mastoid process behind the ear.
- Draw a line at the posterior border of the sternocleidomastoid muscle connecting the tip of the mastoid process and the Chassaignac tubercle (i.e., transverse process of C6).
- 3 separate injections: at 2 cm below the mastoid process where there is the transverse process of C2, at 2 cm below C2 where there is the transverse process of C3, and another 2 cm below C3 where there is the transverse process of C4.
- 22 G needle is advanced perpendicular to the skin and slightly caudal until contacting the transverse process (depth about 1.5–3 cm).
- Aspiration to detect artery puncture or intrathecal puncture.
- Inject 3–4 ml of anesthetic solution.

(b) *Superficial cervical plexus block* (Fig. 9.2)
- Anesthetize C2–C4 branches (Fig. 9.3).
- Midpoint of the posterior border of the sternocleidomastoid muscle at the intersection with the internal jugular vein.
- 5 ml local anesthetic injected subcutaneously posterior and immediately deep to SCM.
- Redirect needle up than down along the border of the SCM and inject 5 ml at each site.
- Aspirate frequently and with each redirection to detect intravascular injection.

3. *Complications of cervical plexus block*
- Intravascular injection (vertebral artery, carotid artery, internal jugular, external jugular)
- Intrathecal injection (epidural/subarachnoid anesthetic)
- Paralysis of the ipsilateral diaphragm (partial phrenic nerve block)
- Laryngeal block causing hoarseness, coughing, and dysphagia
- Seizures caused by intravascular injection of local anesthetic or of large amounts anesthetic

9.2.2.2 Cervical Epidural Anesthesia

Cervical epidural anesthesia is a technique with high rate of complications (dural puncture, venous puncture, respiratory muscle paralysis) and because of that, it is not preferred for carotid endarterectomy. Also, it can affect the cervical plexus making early neurological assessment difficult.

9.2.3 Conversion from Local/Regional to General Anesthesia

The locoregional anesthesia needs to be sometimes converted to general anesthesia. The most often causes are inadequate analgesia, severe agitation or uncooperative patient, hypoxemia, seizure, or severe neurological deficit.

Sometimes it can be difficult to approach the airways because of the open incision for carotid endarterectomy, and a rapid intravenous induction is needed to allow the anesthesiologist to promptly secure the airway. The intubation can be facilitated by allowing the head to return a neutral position.

9.3 Neurologic Monitoring

Cerebral ischemia is one of the main complications that may occur during carotid endarterectomy, with perioperative incidence of 1.1–7.5 % [7]. It is caused by embolic events, carotid artery cross-clamping, position of carotid artery shunt, and cerebral edema after revascularization.

Cerebral perfusion is interrupted during carotid revascularization to remove the atheromatous plaque, cross-clamping the common carotid artery, external carotid artery, and internal carotid artery. During carotid endarterectomy, the

ischemic risk is correlated with the dependency between the cerebral circulation, the ipsilateral internal carotid artery, the cerebrovascular reserve of the contralateral cerebral hemisphere, and the presence and functioning of circle of Willis.

Neurologic monitoring is important to estimate the decreased of cerebral blood flow and to determine/predict the need for carotid shunt to improve cerebral oxygen delivery [7].The method of intraoperative neurological monitoring during carotid endarterectomy must have relevant results in order to control neurological comorbidities associated with this surgery, to enable to detect the reduction of cerebral blood flow during carotid cross-clamping, and to indicate the action required (setting up carotid artery shunt or increase mean arterial pressure).

The studies showed that 80–85 % [7, 8] of patients tolerate well cross-clamping of carotid artery, without requiring carotid shunt. But cross-clamping of the carotid arteries and performing the surgical intervention without temporal carotid shunt may cause a decrease of cerebral blood flow that cannot be compensated by contralateral hemisphere. On the other side, the carotid artery shunt can cause perioperative cerebral ischemia by embolic events (potential displacement of atheromatous debris, introduction of air embolism, or thrombosis of shunt), carotid artery dissection or increasing local complications (nerve injury, hematoma, occurrence of restenosis), and increase surgical time and makes surgical field less than optimal. Also, during the setting up of the carotid artery shunt, there are still two moments of low cerebral blood flow: placement and removal of the carotid shunt [9]. We should not forget that there are some patients to which shunt insertion is not always technically possible.

There is no agreement on the best neurological monitoring technique, the choice depending on the type of the anesthesia, the surgical technique, and the shunting criteria. Given the fact that no type of monitoring does not accurately detect the occurrence of ischemic phenomena, in patients under general anesthesia, it is preferable to use two types of monitoring [8, 10]. Awake patient with locoregional anesthesia is the best method for neurological evaluation of the patient.

There are several ways to monitor cerebral perfusion, each of which has its limitations:

Cerebral monitoring
1. Awake locoregional anesthesia
2. Electroencephalography
3. Processed electroencephalography (bispectral index)
4. Somatosensory evoked potentials
5. Transcranial Doppler ultrasound
6. Carotid stump pressure
7. Jugular oxygen saturation
8. Conjunctival oxygen tension (pcj O_2)
9. Cerebral blood flow measurement with ^{133}Xe
10. Near-infrared spectroscopy – cerebral oximetry

1. *Awake Locoregional Anesthesia*

Technique Neurological assessment is carried out throughout the ongoing surgical intervention, especially during carotid artery cross-clamping. Grip strength of the contralateral hand and responsiveness to verbal commands are evaluated.

Indicators of cerebral ischemia
- Agitation, confusion
- Drowsiness
- Seizures
- Muscle weakness in the extremities

Advantage
- Gold standard for cerebral monitoring of carotid endarterectomy [11].
- Makes possible early detection of cerebral ischemia events.
- Clinical evaluation of the awake patient with locoregional anesthesia is associated with the lowest rate of intraoperative placement of the carotid artery shunt (studies show <5 % of patients).

Limitation
- Low degree of patient comfort during surgery.
- Sometimes locoregional anesthesia needs to be converted to general anesthesia.

2. *Electroencephalography* (*EEG*)

Technique Multiple EEG channels are monitored simultaneously to enhance the chance of detecting ischemia and to allow comparison with the contralateral hemisphere. Cerebral ischemia causes well-defined EEG changes that can be classified into mild, moderate, and severe. Moderate ischemia causes loss of high-frequency activity. More pronounced ischemia causes large amplitude and low-frequency activity, and severe ischemia completely obliterates EEG activity [12, 13].

Indicators of cerebral ischemia
- Greater than 50 % decrease in waveform amplitude in a generalized or lateralized distribution, delta waves, or disorganized rhythm.
- Laman et al. (2005) [22] clarified which EEG parameters are able to indicate the need for installing shunt.
  - For anesthesia with isoflurane, SEF 90 % is the best single parameter in order establish whether shunt is necessary or not, and the four best derivations are F3-Cz, P4-Cz, C4-Cz, and F7-Cz.
  - For sedation with propofol, the best single parameter is the relative delta power, and its four best derivations are F8–Cz, T4–Cz, C4–Cz, and F4–Cz.

Advantage

- Gives ability to assess both focal and global changes

Limitation

- Indirect method for determining the cerebral blood flow.
- Limited sensitivity and specificity (69 % and 89 %, respectively, in the study by Evans and 73 % and 92 %, respectively, in the study by Stoughton) [14, 15].
- EEG needs to be interpreted by neurologists and can have delays up to 3 min before detecting ischemic phenomena.
- EEG is influenced by hypothermia, general anesthesia agents, hypo-/hypercapnia, hypotension, and previous ischemic phenomena.
- Reflects ischemic impairments in the most superficial layer of cerebral cortex, but does not provide information about subcortical structures.

3. *Processed Electroencephalography* (*Bispectral Index*/*Cerebral Entropy*)

Technique Cerebral entropy and bispectral index (BIS) are electroencephalographic (EEG)-derived multivariate scale that measure the depth of anesthesia. Changes in EEG patterns that correlate with changes in cerebral blood flow can also correlate with cerebral entropy and BIS values. Studies [13, 14] have shown that sudden decrease in cerebral perfusion was associated with lower BIS value.

Indicators of cerebral ischemia Under general anesthesia, a sudden modification of BIS/cerebral entropy after carotid artery clamping may be suggestive of cerebral ischemia.

Limitation

- Decreased BIS has been reported in awake patients requiring a shunt, although the BIS did not fall in a patient who developed a pure motor deficit with no change in level of consciousness.
- Monitors only frontal lobes, supplied by anterior communicating artery, and cannot estimate the blood flow in the middle cerebral artery.
- Is not a specific or sensitive method for detecting cerebral ischemia, especially in patients with locoregional anesthesia.
- Unable to differentiate global versus focal changes.

4. *Somatosensory Evoked Potentials*

Technique Evoked potentials are the electrical signals generated by the nervous system in response to sensory stimuli. Somatosensory evoked potentials (SSEPs) are produced by electrically stimulating a peripheral sensory nerve and recording over the appropriate region of the sensory cortex [16]. For monitoring during CEA, median nerve SSEPs are used because they are reliable and relatively easy to obtain, and the relevant sensory cortex is within the MCA vascular territory.

Indicators of cerebral ischemia

- A common criterion for diagnosing ischemia is a ≥50 % reduction in SSEP amplitude.
- The parameter suggested by Haupt et al. and subscribed by Rowed which best relates with the neurological outcome after CEA is a reduction of 50 % of P25 width.

Advantage

- SSEPs can detect subcortical ischemia.

Limitation

- Explore subcortical part of the brain, but a more limited cortical territory than EEG.
- Intraoperative strokes which occur outside the middle cerebral artery are sometimes cannot be detected by SSEP.
- Less reliable on patients with previous neurological deficit.
- SSEPs values are impaired by inhalational anesthetics.

5. *Transcranial Doppler Ultrasound* (*TCD*)

Technique TCD noninvasive monitoring of the velocity of blood flow in the middle cerebral artery via the temporal window (area above the zygomatic arch in front of the ear). Middle cerebral artery signals are identified at a depth of around 45–55 mm from the skin [8, 9]. TCD measures the ipsilateral mean middle cerebral artery velocity (VMCAi) during carotid endarterectomy; changes in velocity are proportional to cerebral blood flow changes based on the assumption that the vessel diameter (middle cerebral artery) and blood viscosity remain constant [13, 17].

At the moment of carotid clamping an initial decrease of the VMCAi is followed by partial recovery in the next 15 s, recovery that occurs due to the cerebrovascular reserve of the contralateral cerebral hemisphere.

Indicators of cerebral ischemia

- A greater than 40 % reduction of VMCAi determines the need for shunt placement [17].

Advantage

- Allows the detection of embolic phenomena – solid emboli (detected during dissection or during wound closure are predictive of postoperative stroke) and gaseous emboli (after release of the carotid artery clamp)
- Allows the detection of hypo- or hyperperfusion of cerebral tissue
- Identify the occurrence of the postoperative hyperperfusion syndrome

Limitation
- Doppler signal is difficult to maintain during surgery.
- At 10 % of patients, skull conformation prevents transmission of ultrasound.

6. *Carotid Stump Pressure*

Technique Measurement of pressure in the internal carotid artery above the cross-clamping can provide an estimate of the blood flow in the middle cerebral artery. Because the arterial pressure depends on the flow and on the vascular resistances, carotid stump pressure can have values between 25 and 75 mmHg [10].

Indicators of cerebral ischemia Carotid stump pressure tries to predict [10, 13, 14] the need for temporary shunt placement. >50 mmHg indicates adequate collateral circulation, and <40 mmHg indicates the need for temporary shunt placement.

Limitation
- Hypo-/hypercapnia, body temperature, and anesthetic agents can influence vascular resistances.
- It measures pressure only at the beginning of the procedure without subsequent monitoring.
- Method used with caution in patients with preexisting ipsilateral stroke where there is a poor correlation between adequate perfusion pressure and cerebral ischemia.
- There is no threshold of carotid stump pressure which defines a safe lower limit in all patients; multiple studies have found stump pressure to be very poorly predictive of cerebral ischemia with high rates of false-positive or false-negative results.

7. *Jugular Oxygen Saturation*

Technique Measurement of oxygen saturation at the level of ipsilateral jugular bulb

Limitation It has a very low sensitivity and specificity because venous blood may originate from different brain regions.

8. *Conjunctival Oxygen Tension (pcj O_2)*

Technique Some studies showed a correlation between conjunctival oxygen tension (pcj O_2) and cortical oxygen tension. It is not a specific or sensitive method for detecting cerebral ischemia, used only for experimental studies.

9. *Cerebral Blood Flow Measurement with ^{133}Xe*

Technique This technique has two main limitations: cannot be applied routinely in the operating room and is a discontinuous method. Also, this technique identifies only perfused brain areas and not areas with reduced or absent blood flow.

10. *Transcranial Cerebral Oximetry: Near-Infrared Spectroscopy*

Technique Transcranial cerebral oximetry uses near-infrared technique spectrophotometry (NIRS) to noninvasive measurement of cerebral oxygenation [3, 4, 18]. The principle of measuring cerebral oxygen saturation is the difference of absorption in the infrared spectrum of oxyhemoglobin and deoxyhemoglobin. Cerebral saturation display (rSO_2) is largely venous oxygen saturation, given the fact that cerebral blood flow is composed of 75 % of venous blood and 25 % of arterial blood. Two sensors are placed bilaterally on the forehead (Fig. 9.3b) to differentiate changes of non-ischemic source of cerebral saturation (low blood pressure that causes global hypoperfusion) from ischemic changes during carotid clamping. Light penetrates the scalp and the skull to reach the gray matter in the brain. Each sensor has two detectors: closer detector collects reflected light from extracerebral tissue only, and further detector collects reflected light from entire path. Patented algorithm solves the hemoglobin concentration while minimizing influence from extracerebral tissue.

Indicators of cerebral ischemia Normal values of rSO_2 may vary even in healthy adults, so we take into account as a sign of decreased cerebral blood flow a rSO_2 decrease by >20 % from baseline value and not the decrease of rSO_2 from a set value (e.g., rSO_2 <60).

Being a continuous monitoring of cerebral perfusion, rSO^2 can be used to evaluate the placement and functionality of carotid shunt. It is useful also in postoperative monitoring because a decrease of rSO_2 postoperatively after carotid endarterectomy can demonstrate early carotid artery occlusion.

Limitation The sensitivity and specificity using NIRS cerebral oximetry to detect ischemia depend on establishing limit rSO_2. It depends too much on arterial pressure variation, so blood pressure must be the same at the moment of baseline value and at the moment of cross-clamping for the measurement to be relevant.

9.4 Management of Intraoperative Cerebral Ischemia

The main complications during carotid endarterectomy are neurologic events and are causes by embolization from carotid or by insufficient collateral blood flow during carotid cross-clamping. The recognition of cerebral ischemia depends on type of anesthesia used and on neurological monitoring.

The most common ischemic event is cerebral hypoperfusion given by hypotension. This can be treated with fluid resuscitation and vasopressors. The intraoperative mean arterial pressure needs to be maintained at a level up to 20 % from the preoperative values to ensure adequate blood flow from the collateral arteries [2, 19].

If cerebral hypoperfusion is not determined by hypotension, the insufficient cerebral blood flow needs immediate correction by carotid shunt insertion. The use of shunt, however, does not always guarantee sufficient blood flow to the ischemic zones.

Also to ensure the best cerebral perfusion, we should maintain normocarbia throughout the intervention, knowing that hypo- or hypercapnia can change cerebral vascular tonus.

The embolic phenomenon can occur during surgical dissection and insertion of carotid shunt and after carotid closure. Intravenous 30 ml bolus of dextran 40 followed by 50 ml/h for 12 h postoperative can show some benefit [2, 19].

Dissection and thrombosis of carotid artery during surgical intervention are rare complications that can lead to significant diminution of blood flow or to complete occlusion. The main intervention is by surgical intervention or by angiography.

The role of postoperative anticoagulation in case of ischemia is controversial because of the risk of hemorrhagic transformation of ischemic area, but antiplatelet therapy is commonly used (aspirin alone or in combination with clopidogrel/prasugrel). Also glycoprotein IIb–IIIa receptor blockers, such as intravenous abciximab or tirofiban, can have a potential role in the management of early cerebral ischemia after carotid revascularization.

9.5 Cardiovascular Monitor and Management

The choice of anesthesia for carotid endarterectomy does affect the intra- and postoperative hemodynamic profile. Patients with regional anesthesia tend toward hypertension during the period of carotid cross-clamping and hypotension after restoration of cerebral blood flow and into the postoperative period. In contrast, the usual pattern under GA is relative intraoperative hypotension and postoperative hypertension. It is beneficial to avoid intraoperative hypotension, particularly during the period of carotid cross-clamping, whereas after restoration of flow, it is necessary to avoid hypertension.

Electrocardiography (ECG) Continuous ECG monitoring is necessary to detect arrhythmias and/or myocardial ischemia. ST-segment changes should indicate for improvement of myocardial oxygen supply and for reducing myocardial oxygen demand. The presence of intraoperative and postoperative ST-segment changes is associated with cardiac morbidity and mortality in patients at high risk for myocardial ischemia during noncardiac surgery.

Invasive arterial blood pressure monitoring is mandatory to detect and correct rapid arterial pressure variation and for the management of vasoactive drugs. Patients with carotid disease usually have systemic atherosclerotic disease, which can result in blood pressure differences between the arms. Also, it must be considered that in the patients with subclavian artery surgery, blood pressure should be measured at the contralateral side.

Central venous catheter is rarely indicated during endarterectomy, mainly due to the intervention area. Two large venous peripheral lines are used.

Hemodynamic management The continuous arterial pressure monitoring intra- and postoperatively is recommended. During intervention, and especially during cross-clamping, the arterial pressure should be maintained up to 20 % above the patient's baseline blood pressure, in order to optimize collateral cerebral perfusion. This is necessary, even if a shunt is used.

Vasoactive drugs are necessary throughout the perioperative period to maintain cardiovascular stability and treat rhythm disturbance (tachy- or bradyarrhythmias) or arterial pressure modification (hypertension or hypotension). In order to obtain that, we can use atropine (0.2–0.4 mg boluses), phenylephrine (100–200 mcg boluses), ephedrine (5–20 mg boluses), vasopressin (1 unit boluses), nicardipine (100–500 mcg boluses), labetalol (e.g., 5–10 mg/mL injected as 5–20 mg boluses), esmolol (10 mg/mL injected as 10–50 mg boluses), urapidil (25 mg bolus and than 2 mg/min), and nitroglycerin (10–400 mcg/min; 0.1–4 mcg/kg/min).

Fluids Large amount of fluids are rarely required considering that carotid endarterectomy is not associated with excessive blood loss. The administration of fluid must be done to maintain normovolemia.

9.6 Perioperative Complication

Perioperative mortality after carotid endarterectomy ranges from <0.5 to 3 % [20–22]. The two major complications of this intervention are myocardial infarction and stroke.

Cardiac complication (myocardial infarction) is the main issue after carotid endarterectomy having in mind cardiovascular comorbidities of these patients [20, 21].

Stroke [21] is the second most common cause of mortality. Etiopathogenetic mechanisms for perioperative stroke are embolic, ischemic, and hyperemic. There are multiple

causes: intraoperative clamping ischemia, thromboembolic event at manipulation of the carotid, perioperative hypotension, and postoperative hyperperfusion syndrome.

Hyperperfusion syndrome is a rare and serious complication that arises after carotid revascularization. Hyperperfusion is defined as the increase in cerebral blood flow compared to preoperative or baseline values, expressing a hemodynamic parameter of cerebral circulation. The cerebral hyperperfusion syndrome is most common in patients with cerebral blood flow increases of more than 100 % compared with baseline values after carotid revascularization and is rare in patients with increases in perfusion less than 100 % compared with baseline values [23].The main mechanism implicated in the pathogenesis is impaired autoregulation as a result of endothelial dysfunction mediated by generation of free oxygen radicals. The increase of cerebral blood flow, which cannot be controlled by autoregulatory mechanisms, leads to transudation of fluid into the interstitium with subsequent cerebral edema. The most important risk factors in CHS are diminished cerebrovascular reserve, postoperative hypertension, and hyperperfusion lasting more than several hours after carotid endarterectomy. Other risk factors are diabetes mellitus, contralateral carotid occlusion, incomplete circle of Willis, and intraoperative ischemia. Clinical presentation is characterized by ipsilateral headache, hypertension, seizures, and focal neurological deficits. Having in mind that the main complications of cerebral hyperperfusion syndrome are severe brain edema, intracerebral or subarachnoid hemorrhage, and death, treatment strategies are directed toward regulation of blood pressure and limitation of rises in cerebral perfusion. The endpoints of treatment are permissive hypotension, antiseizure prophylaxis, and close neurologic monitoring for the need of neurosurgical intervention.

Other complications after carotid endarterectomy are:

- Nerve injury – vagus nerve, recurrent laryngeal nerve, facial nerve, hypoglossal nerve, and glossopharyngeal nerve
- Bleeding resulting in neck hematoma
- Airway swelling and edema
- Infection

Image Gallery

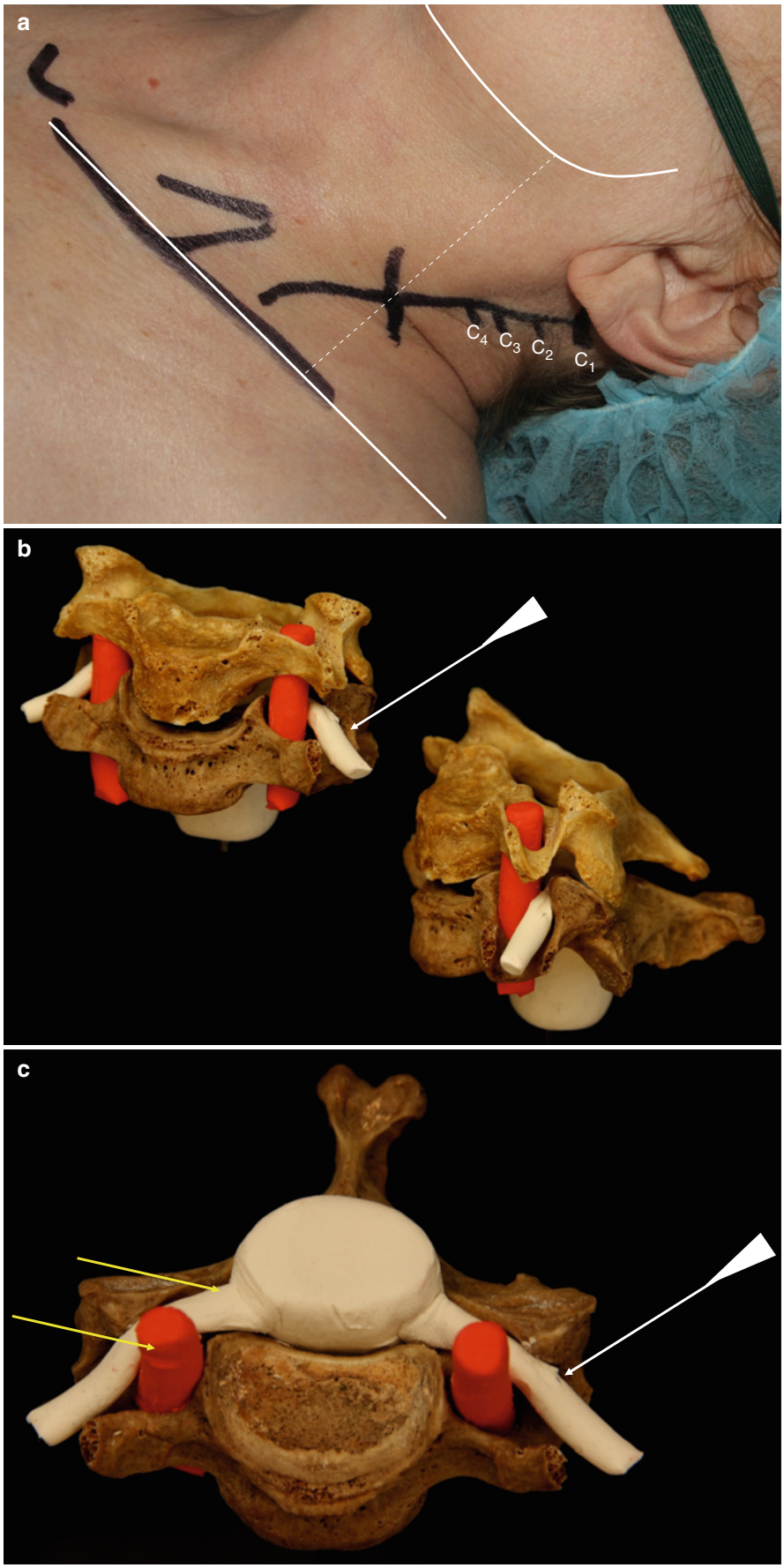


Fig. 9.1 Deep cervical plexus block. Panel (**a**) Anatomical surface landmarks for performing the cervical plexus block. The mandible and the clavicle are marked with white lines. The approximate course of the external jugular vein is from the mandibular angle to the midclavicle. The vein can be easily identified as the patient performs a Valsalva maneuver (or in Trendelenburg position). The posterior border of the SCM is also easily identified. The tip of the mastoid process is palpated and marked. The tip of the transverse processes C1 through C4 is marked. The relative height of the nervous point (where branches of the superficial part of the cervical plexus become subcutaneous in position) is also marked. Panel (**b**) Schematic representation of the reciprocal anatomical relationship between the cervical nerves, the vertebral artery, and the osseous landmarks. Note the cervical nerve sulcus, the posterior position of the latter, and the direction of the injecting needle. Panel (**c**) Possible incidents that may occur during regional anesthesia – inadvertent puncture of the VA and entrance to the subarachnoid space/ intrathecal injection (*yellow arrows*). Compare with the normal position, on the right (*white arrow*). Panel (**d**) Demonstration of injection technique, to block the cervical nerves C2 through C4

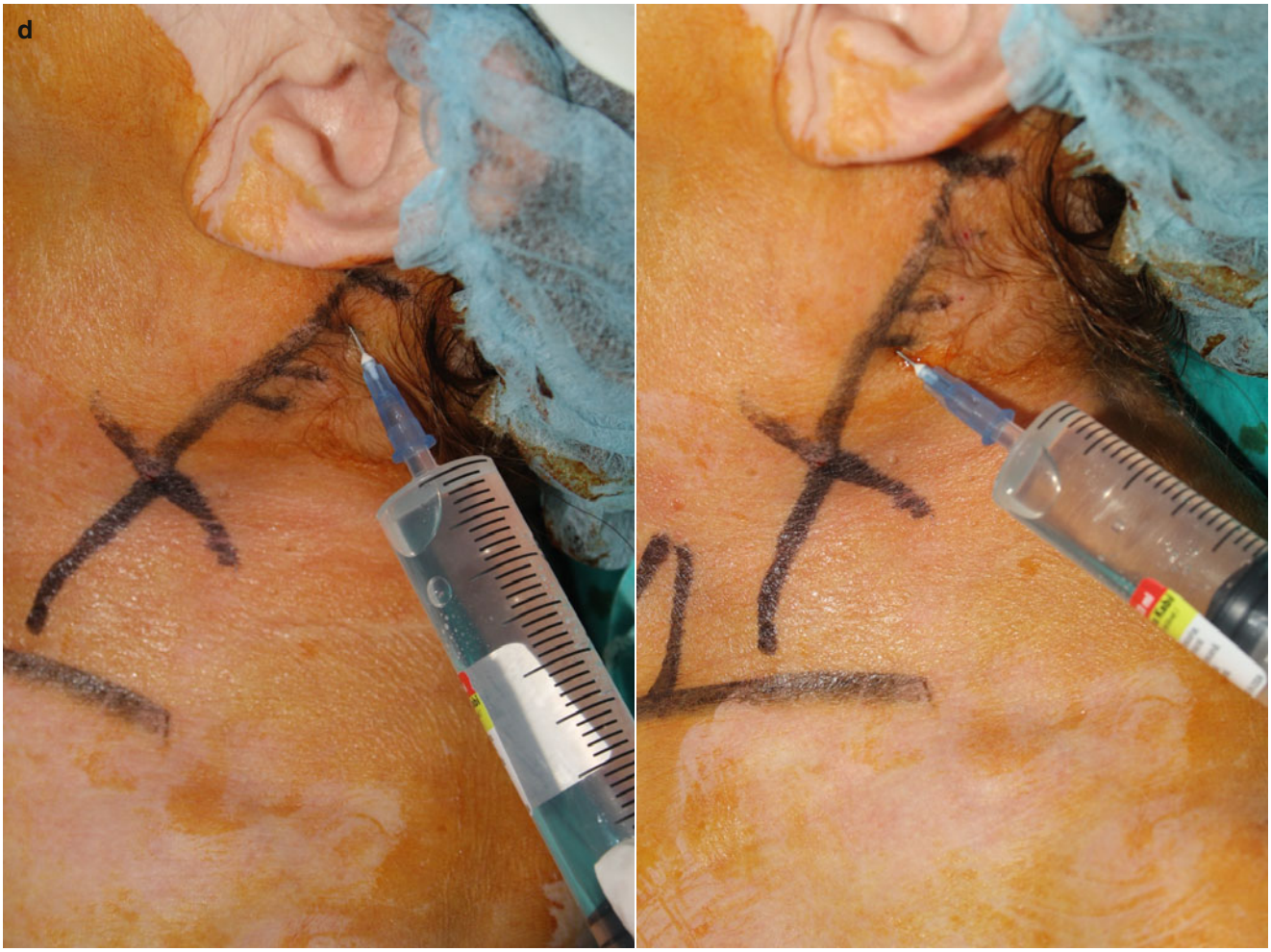
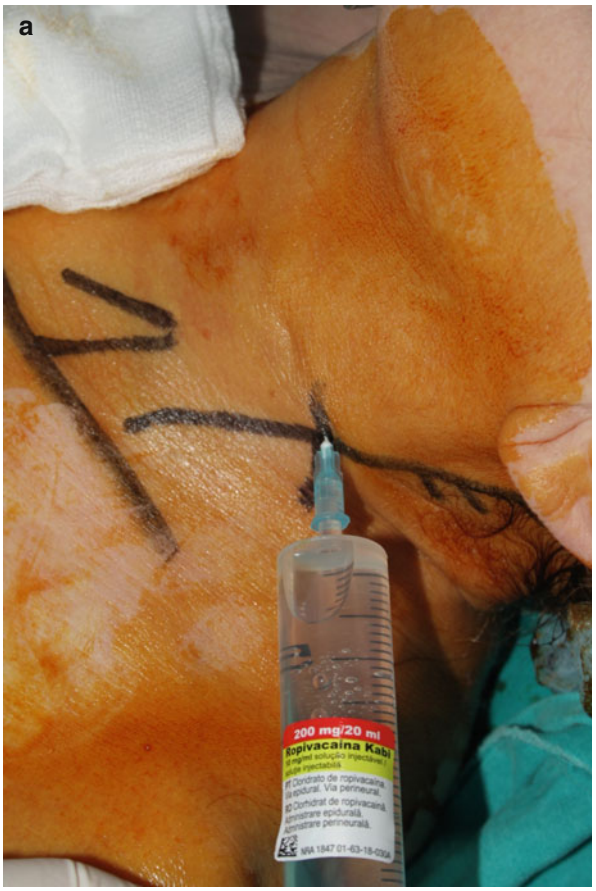


Fig. 9.1 (continued)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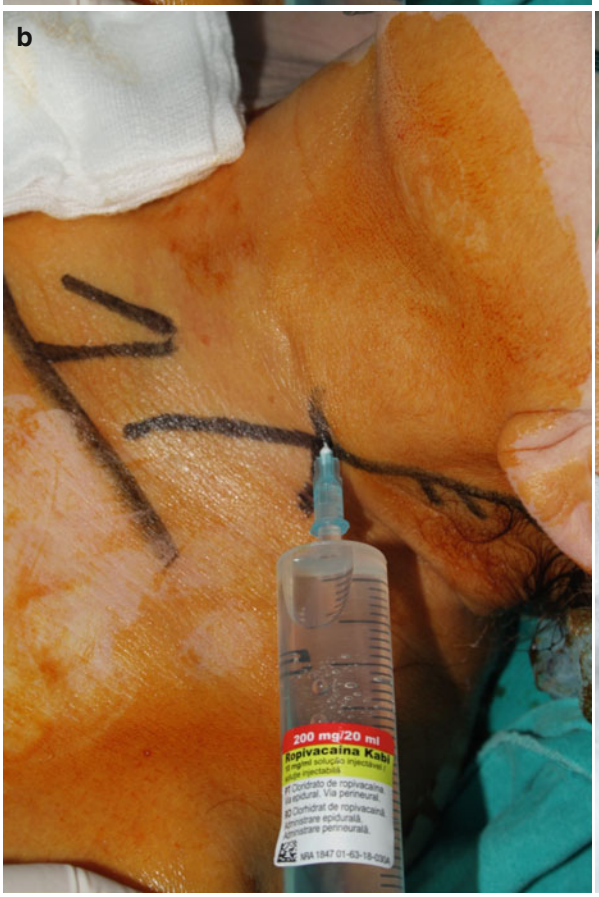
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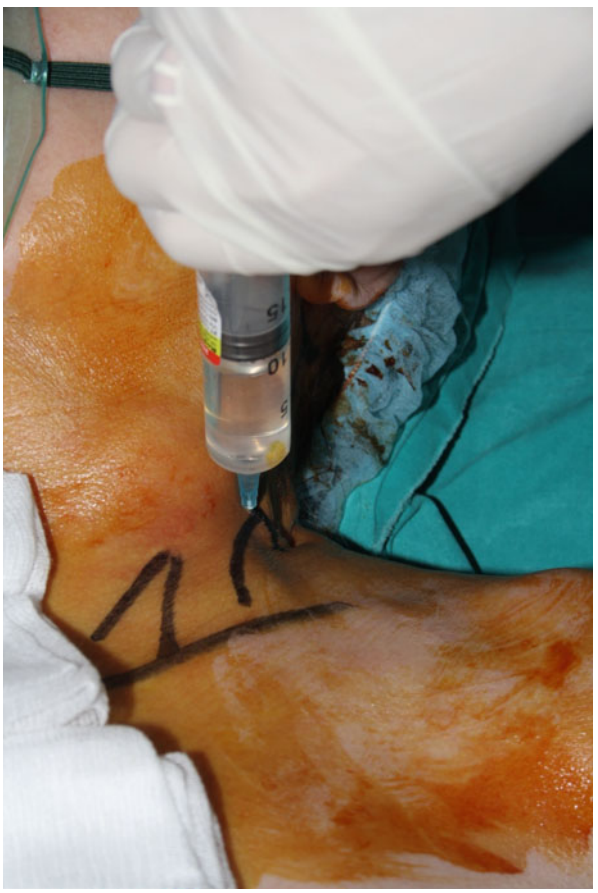

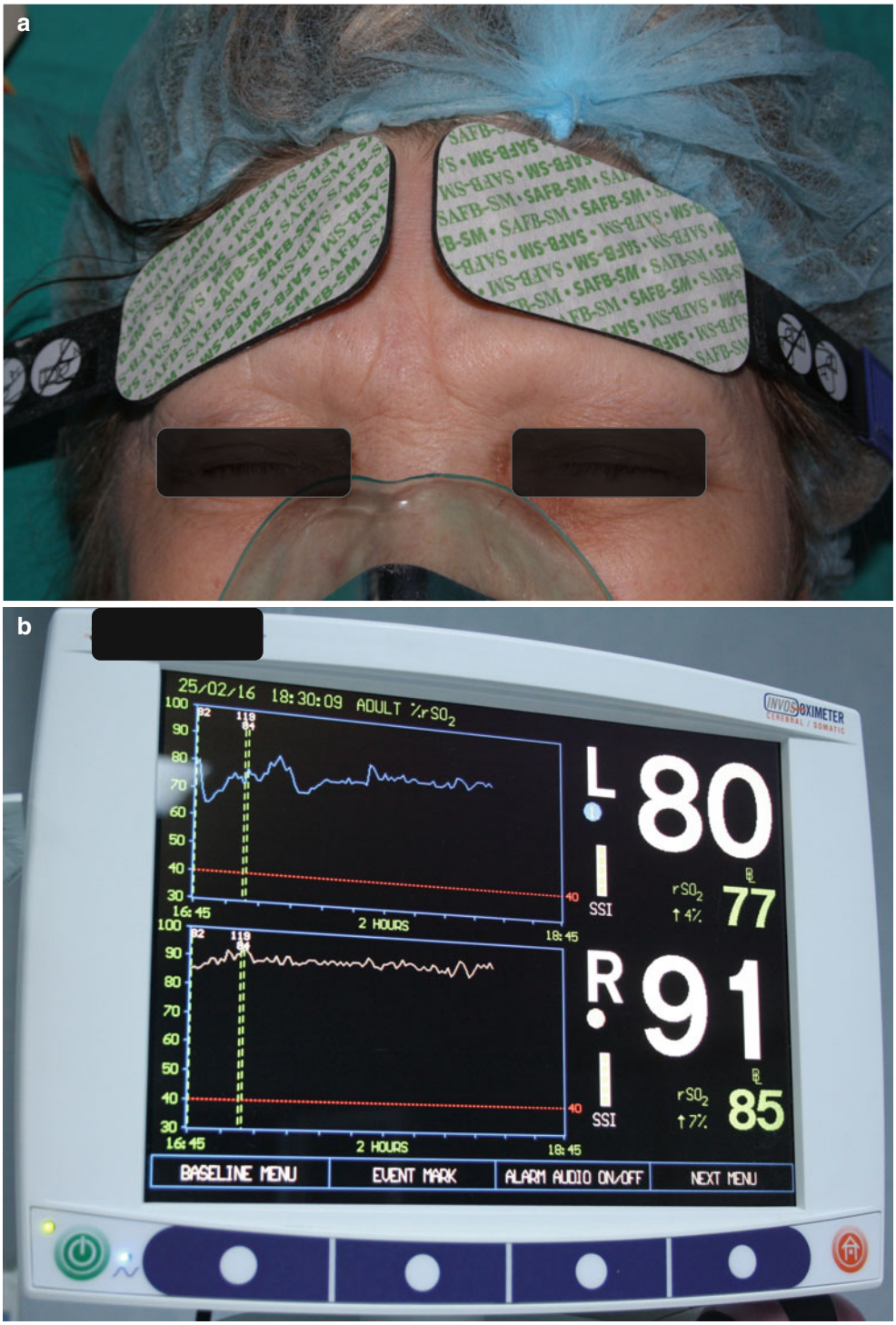

Fig. 9.3 Near-infrared spectroscopy – cerebral oximetry. Panel (**a**) Placement of the electrodes/sensors. Panel (**b**) Illustration of the monitoring system

Fig. 9.2 Superficial cervical plexus block. Panel (**a**) All superficial branches of the cervical plexus can be blocked by injecting at the level of the midposterior border of the SCM. Needle oriented toward the anterior. Panel (**b**) Superficial plexus block is completed by injecting in posterior and inferior direction (especially for the supraclavicular nerves). The supraclavicular part of the brachial plexus can be also additionally anesthetized, when access to the SCA or VA is concomitantly required

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Carotid Angioplasty and Stenting

10

Florina Antochi, Cristina Laza, and Bogdan Dorobat

10.1 Introduction

Stroke is a worldwide burden – every year 15 million people suffer a new or recurrent stroke [1]. In Europe, as in the rest of the world, the impact of stroke varies considerably among countries, being noticeably higher in low-income countries compared to high-income ones [2]; the incidence alone varies greatly among European states, with 101–239 new strokes per 100,000 in men and 63–159 new strokes per 100,000 in women [3]. Even though stroke incidence dropped by more than 40 % in developed countries during the last half of century (as a consequence of implementing public health prevention policies), in low- and middle-income states, the same parameter has more than doubled in the same time frame [4]. This burst in stroke incidence is partly due to the increase in life expectancy – age being one of the unchangeable vascular risk factors. Thus, aging of the world's population produces an increase in the number of people at risk for a stroke [5]. This is why the World Health Organization (WHO) predicts that the yearly number of stroke events will rise in Europe, only on the grounds of demographic aging, from 1.1 million in 2000 to 1.5 million in 2025 [6].

In the United States of America, stroke prevalence amounts to roughly 3 % of the country's entire population, being responsible for 1 in 18 deaths [7]. Worldwide, stroke accounts for 10 % of all deaths, being the third most common cause of death in developed countries, surpassed only by neoplasia and ischemic heart disease [1]. One third of the persons suffering a stroke die within the following 12 months and another one third are permanently incapacitated [1]. Mortality rates increase with time: more than half (52 % of men and 56 % of women) of stroke patients aged 45 or more die during 5 years following the first acute cerebrovascular event [7].

Given these numbers, it is no surprise that stroke is a very expensive affliction. During 2010 alone, the cost of stroke in Europe was about € 64 billion [8] and in the United States over € 65 billion ($ 74 billion) [9].

But more important than being a social and economic burden, stroke is most of all a personal tragedy for the individuals that suffer from it. Ischemic stroke accounts for about 80 % of strokes, and large artery disease is one of the major three subtypes of ischemic stroke according to the TOAST and CCS classification systems [10]. A patient suffering from an ischemic stroke loses 1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers *every minute*; for every hour such a patient is left untreated, their brain ages the equivalent of 3.6 years [11]. Things become even more dramatic when we consider that the recurrence rate of ipsilateral stroke in patients with a 50–99 % carotid artery stenosis at 3 months after the first minor neurovascular event (amaurosis fugax, retinal artery occlusion, transient ischemic attack, or minor stroke) is almost 20 % [12] and that mortality rates are almost double in patients with recurring strokes than in patients with a first-ever stroke [13].

All these being said, it is only natural that prevention plays a major part in the care a stroke patient receives. As neurologists, we rarely get to treat the patient before the first neurovascular event, so we mainly focus on secondary prevention, which, in the cases of stroke caused by large artery disease, consists of best medical treatment, carotid endarterectomy (CEA), and/or percutaneous transluminal angioplasty and stenting (PTAS).

10.2 Method

PTAS is a less invasive method than CEA for treating carotid stenosis. Over the past 10 years, 616 such interventions were performed in our department. The procedure is most frequently performed under local anesthesia for the femoral artery puncture, with continuous ECG and BP monitoring of

F. Antochi (✉) • C. Laza
Department of Neurology, University Hospital Bucharest, Bucharest, Romania
e-mail: flrant@yahoo.com

B. Dorobat
Department of Interventional Radiology, University Hospital Bucharest, Bucharest, Romania
e-mail: bdorobat@gmail.com

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the patient. A catheter is placed into the aortic arch, and an arch aortogram and carotid and cerebral angiograms are obtained to confirm the degree of stenosis and to exclude other pathologies. A guiding catheter is placed into the common carotid artery (CCA), and a microwire is advanced through the stenotic lesion of the internal carotid artery (ICA). Using this microwire, an embolic protection device (EPD) is placed distal of the lesion; even if EPDs are a standard in today's practice, in many of the first studies comparing carotid artery stenting (CAS) with CEA, their use was optional at best (Fig. 10.1).

After placing the EPD, the stenotic lesion may be predilated using an angioplasty balloon passed over the microwire; the balloon is replaced by the stent delivery device used to deploy the stent. When needed, balloon angioplasty after stent deployment might also be performed. Finally, new carotid and cerebral angiograms are obtained in order to check the results of the intervention.

There are several types of embolic protection devices:

- Distal filtration device which stops debris might miss small particles but doesn't block the blood flow through the ICA, so angiogram can be performed during protection – this type is used in the interventions performed in our department.
- Distal protection balloon which stops the debris but also blocks the blood flow through the ICA and doesn't allow angiogram during protection.
- Continuous particle evacuation device consists of proximal protection balloons placed in the CCA and external carotid artery (ECA), leading to reversed flow through the ICA which allows for continuous evacuation of embolic material.
- Stents can also be categorized based on deployment method:
  - Balloon-expandable stents – rarely used today
- Self-expandable stents – used in our department, which can be further divided into:
  - Open-cell stents.
  - Closed-cell stents.
  - Hybrid stents; the decision of using this type of stent over the other is based on vessel anatomy, plaque anatomy, and the risk of embolism.

10.3 History, Studies, Current Recommendations

Although the first transluminal carotid angioplasty was performed in 1979 and the first carotid stent was deployed a decade later, the first randomized studies of CAS versus CEA started in the middle of the 1990s and had conflicting and disappointing results for CAS supporters.

The *Ca*rotid and *V*ertebral *A*rtery *T*ransluminal *A*ngioplasty *S*tudy (*CAVATAS*) enrolled patients with symptomatic and asymptomatic ICA stenosis suitable for surgery (degree not specified) from 1992 to 1997. 504 patients were randomized: 251 were treated by PTA with or without stenting and 253 by CEA. The major outcome at 30 days after the procedure did not show significant statistical differences between treatments: the rate of major stroke or death in the PTA group was 6.4 % versus 5.9 % in the CEA group, and the rate of any stroke lasting more than 7 days or death was 10 % for PTA versus 9.9 % for CEA. However, the rate of severe (70–99 %) ipsilateral carotid stenosis was 14 % for the PTA group compared to 4 % in the CEA group just 1 year after the procedure.

At 3 years, there was no significant difference in the rate of ipsilateral stroke between the two groups [14]. Follow-up studies showed that the 5-year risk of restenosis was three times greater after PTA than after CEA and that it was associated with ipsilateral neurovascular symptoms [15], but that the 8-year incidence of ipsilateral non-perioperative stroke was low in both groups and none of the differences in the stroke outcome measures was significant [16]. Even though these results might seem disappointing, we have to bear in mind the times and conditions under which the study was performed. Some of the most frequent criticism against CAVATAS consists of the following [17]:

- No high-risk patients were included.
- The threshold of carotid stenosis degree is not specified.
- Both symptomatic and asymptomatic patients were included.
- Patients treated by PTA before 1994 did not benefit from stenting, and even after 1994, stent deployment was not mandatory in the angioplasty group, resulting in just 26 % of the patients in the PTA group being stented and the rest 74 % being treated by balloon angioplasty.
- No EPDs were used.
- Double antiplatelet therapy was not enforced either before the procedure or afterward.

After CAVATAS the studies began to systematically use EPDs and stenting and the following three major trials enrolled only symptomatic patients.

The *E*ndarterectomy *v*ersus *A*ngioplasty in Patients with *S*ymptomatic *S*evere Carotid *S*tenosis (*EVA-3S*) trial randomized 527 patients with symptomatic carotid artery stenosis of at least 60 % according to the NASCET criteria (Fig. 10.2), with the primary end point being the incidence of stroke or death at 30 days after treatment. The trial was stopped early on safety and futility concerns: the incidence of the primary end point was significantly higher after CAS (9.6 %) than after CEA (3.9 %) [18]. The shortcomings of this study consist of:

- No high-risk patients were included.
- Limited operator's experience for CAS.

- Great heterogeneity with type of stent and EPD used.
- ~8 % of CAS procedures did not use EPDs.
- Dual antiplatelet therapy was recommended but not mandatory, resulting in monotherapy with aspirin for 17 % of CAS patients before the procedure and 15 % afterward.

A 4-year follow-up study of the EVA-3S trial showed that stenting was as effective as endarterectomy for middle-term prevention of ipsilateral stroke [19].

The *S*tent-Supported *P*ercutaneous *A*ngioplasty of the *C*arotid Artery versus *E*ndarterectomy (*SPACE*) trial randomized 1200 patients with symptomatic severe (>70 %) carotid artery stenosis, with the primary end point of ipsilateral stroke or death occurring between randomization and 30 days after treatment. Even though the incidence of the primary end point was similar for the two treatment groups, 6.84 % for CAS versus 6.34 % for CEA, the study failed to prove noninferiority of stenting compared to endarterectomy [20].

The 2-year follow-up analysis revealed similar rates of recurrent ipsilateral stroke for CAS and CEA patients, but a significantly higher incidence of recurrent carotid stenosis after CAS versus CEA [21].

Some of the flaws held against the SPACE trial design are:

- Not including high-risk patients.
- Heterogeneity of stent used.
- EPDs were used in only 27 % of patients undergoing CAS.

The latest trial in this category is the *I*nternational *C*arotid *S*tenting *S*tudy (*ICSS*). More than 1700 patients with at least 50 % symptomatic carotid artery stenosis were enrolled. The primary end point – disabling stroke or death occurring in the first 120 days after the procedure – was recorded in 4 % of the CAS group and 3.2 % in the CEA group; the incidence of stroke, death, or procedural myocardial infarction was 8.5 % in the stenting group versus 5.2 % in the endarterectomy group; the risk of any stroke and all-cause death was also higher for CAS patients [22].

The shortcomings were similar to those of EVA-3S and SPACE trials:

- Limited experience of CAS operators – a physician, surgeon, or interventionalist was deemed experienced with having performed at least ten stenting procedures of the carotid artery.
- Despite the fact that EPDs were recommended, in 20 % of CAS procedure, no EPD was used.
- Enrolling patients with 50–70 % carotid artery stenosis.

What the ICSS trial brought as a novelty was an MRI substudy which demonstrated that new ischemic lesions on DWI (diffusion weighted-imaging) posttreatment sequences were three times more frequent in the stenting group than in the endarterectomy group and that EPDs did not seem to be effective in preventing cerebral ischemia. However, only 17 % of DWI lesions in the stenting group and 53 % in the endarterectomy group were associated with signal changes on FLAIR imaging 1 month later [23].

A major turning point for the place of angioplasty and stenting in medical practice came after the *S*tenting and *A*ngioplasty with *P*rotection in *P*atients at *Hi*gh *R*isk for *E*ndarterectomy (*SAPPHIRE*) trial. The study randomized 334 patients with more than 50 % symptomatic carotid artery stenosis or more than 80 % asymptomatic carotid artery stenosis, patients that were considered at high risk of complications after endarterectomy. The trial's primary end point was the cumulative incidence of a major cardiovascular event during the first year after treatment: a composite of death, stroke, or myocardial infarction within 30 days after the intervention or death or ipsilateral stroke between 31 days and 1 year. The analysis of the primary end point showed that carotid artery stenting was not inferior to endarterectomy, and the secondary analysis of the cumulative incidence of the primary end point at one year showed a nearly significant difference between CAS and CEA. The trial demonstrated that CAS with the use of EPD is not inferior to carotid endarterectomy in the prevention of stroke, death, or myocardial infarction among patients for whom surgery poses an increased risk [24]. In the long-term (3-year) follow-up study, no significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli protection device and those who underwent endarterectomy [25].

The improvement in study design in the SAPPHIRE trial consisted of systematic use of embolic protection devices and a rigorous double antiplatelet treatment starting 24 h before stenting and lasting 2–4 weeks afterward. However, SAPPHIRE was far from perfect and its major flaw was that approximately 70 % of randomized patients were asymptomatic [24].

Still, the results were compelling enough so that the AHA/ASA Stroke Prevention Guidelines were updated in 2006 to state that:

- Among patients with symptomatic severe stenosis (>70 %) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA; CAS is not inferior to endarterectomy and may be considered (Class IIb, Level of Evidence B).
- CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4–6 %, similar to that observed in trials of CEA and CAS (Class IIa, Level of Evidence B) [26].

The most recent study results published come from the *C*arotid *R*evascularization *E*ndarterectomy versus *S*tenting *T*rial (*CREST*), perhaps the largest study to date; it

randomized over 2500 patients, with both symptomatic carotid artery stenosis of over 50 % and asymptomatic carotid artery stenosis of more than 60 %. The novelty in study design comes from the standardized type of stents and EPDs used, the mandatory (when not contraindicated) double antiplatelet treatment starting 48 h before stenting and continuing at least 30 days after treatment, and last but not least, the rigorous credentialing of interventionalists performing CAS [27, 28].

It is important to mention that 47 % of the randomized patients were asymptomatic, only 13 % of the total cohort presented with carotid artery stenosis of less than 70 %, and in 96 % of the cases that were treated by stenting, an emboli protection device was used [29].

The incidence of the primary composite end point: stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after treatment did not differ significantly between the CAS and CEA groups. There were, however, differences in periprocedural myocardial infarction incidence, which was lower for CAS (1.1 %) than CEA (2.3 %), and periprocedural stroke incidence, which was higher for CAS (4.1 %) than CEA (2.3 %). After the first 30 days, the incidences of ipsilateral stroke were comparably low for both groups [29]. Also, no significant difference in treatment effect was reported by symptomatic status or sex, but age was shown to modify results: the outcomes were better after stenting for patients younger than 70 years and after endarterectomy for subjects aged over 70 [30].

The publication of the CREST results was followed by another AHA/ASA Guideline change in 2011:

- CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70 % by noninvasive imaging or >50 % by catheter angiography (Class I; Level of Evidence B).
- Among patients with symptomatic severe stenosis (>70 %) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered (Class IIb; Level of Evidence B).
- CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4–6 %, similar to those observed in trials of CEA and CAS (Class IIa; Level of Evidence B) [31].

These consequences might seem impressive but the CREST received its share of criticism, mainly regarding the following:

- Inclusion of asymptomatic patients that decreased the power and significance of results.
- Equal consideration of minor myocardial infarction and stroke and death for the short-term end point but not for the long-term one.
- Probably most importantly the fact that even though there was no initial report of the outcomes being influenced by symptomatic status or sex, subsequent analysis showed that CAS was associated with higher rates of stroke or death in symptomatic patients and women [32].

Not long after the AHA/ASA Guidelines had been revised that the Cochrane Stroke Group updated a systematic review of the results obtained from randomized trials comparing carotid artery stenting and carotid endarterectomy. Sixteen trials comprising over 7500 patients with symptomatic or asymptomatic carotid artery stenosis were included in the review that concluded that endovascular treatment presented a higher risk of periprocedural stroke or death when compared with surgery [33]. This was followed by the latest version of the North American Guidelines that recommends:

- CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70 % by noninvasive imaging or >50 % by catheter-based imaging or noninvasive imaging with corroboration, and the anticipated rate of periprocedural stroke or death is <6 % (Class IIa; Level of Evidence B) (revised recommendation).
- It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (i.e., older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (i.e., stroke, MI, or death) and long-term risk for ipsilateral stroke (Class IIa; Level of Evidence B) (new recommendation).
- Among patients with symptomatic severe stenosis (>70 %) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable (Class IIa; Level of Evidence B) (revised recommendation).
- CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6 % for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies (Class I; Level of Evidence B) (revised recommendation) [34].

Nobody knows what future recommendations will look like, but the only thing we feel confident will happen is that the guidelines will continue to change as technology and technique evolve and as trials become more focused on patient subgroups and update their methodology to provide more personalized insight.

10.4 Our Personal Experience

10.4.1 Inclusion and Exclusion Criteria

616 stenting procedures have been carried out in our department during the past ten years. Patients benefiting from angioplasty and stenting in our service had 70–99 % internal carotid artery stenosis according to the NASCET criteria, had been symptomatic, and were not suitable candidates for endarterectomy or would not consent to surgery. In Fig. 10.3, you can see the images from a percutaneous angioplasty and stenting performed in a patient with restenosis after carotid endarterectomy.

Angioplasty and stenting were not performed for carotid artery occlusion (Fig. 10.4) or carotid artery intraluminal thrombosis (Fig. 10.5).

Other exclusion criteria were:

- Severe peripheral arteriopathy with iliac artery occlusion which prevented the femoral endovascular approach
- Severe kidney, liver, or hematologic dysfunction that would prevent double antiplatelet and high-dose statin treatment
- Life expectancy of under a year

10.4.2 Medical Treatment and Ultrasound Follow-Up

Every patient had to receive double antiplatelet therapy with low-dose aspirin and clopidogrel bisulfate at least 24 h before angioplasty as well as statin treatment. On the first day of dual antiplatelet treatment, the dose of clopidogrel bisulfate was of 300 mg and the maintenance dose was of 75 mg/day. The aspirin plus clopidogrel regimen was continued for at least one month after angioplasty followed by single antiplatelet long-term treatment, usually with clopidogrel bisulfate 75 mg/day, if not otherwise indicated.

The first ultrasound evaluation of the stent was usually performed a week after angioplasty if no incidents occurred; the patient was required to return for periodic ultrasonic evaluation of the vascular prosthesis at 1, 3, 6, and 12 months and yearly afterward. See Fig. 10.6 for ultrasonic imaging of the carotidian stent.

10.4.3 Early Complications

The most frequent but also the most manageable complication we encountered was *hemodynamic instability*. As many as 20 % of patients suffered from bradycardia and/or a drop in systolic blood pressure of 30 mmHg or more, during or immediately after carotid angioplasty and stenting, despite adequate fluid balance. Our analysis showed that a stenosis of 90 % or more, the length of stenosed segment of over 6 mm, and the use of beta-blockers were independent factors associated with the appearance of hemodynamic instability after CAS [35].

Microemboli signals (MES) detection is another rather frequent finding in our patients (see Fig. 10.7). Though still a limited number of patients have been monitored for MES, more than 80 % of them had at least three times more MES detected on the stented side during the first week after CAS, and over 65 % maintain a high number of MES detected in the territory of the stented carotid artery one year after the intervention. MES presence at one year after CAS might be predictive of cognitive decline in patients undergoing carotid angioplasty and stenting [36].

The more severe complications we encountered were five ischemic strokes (<1 %), two of which occurred through an embolic mechanism, despite the use of embolic protection devices, and the other three had hemodynamic etiology, following carotid artery spasm. We were also confronted with a single case of acute intrastent thrombosis (Fig. 10.8).

We also experienced one case of severe reperfusion syndrome in an elderly woman patient with severe stenosis of her left internal carotid artery; she presented with markedly elevated blood pressure in the first 15 min after CAS, focal neurologic deficit, seizures, altered mental status, and eventually, despite all our efforts, fatal intracranial hemorrhage (Fig. 10.9). The explanation we found for this outcome was that the patient had a long-standing (at least 2 years) severe stenosis which resulted in chronic hypoperfusion and subsequently in the impairment of the autoregulation capacity of the cerebral microcirculation.

Other severe periprocedural complications of CAS cited in the literature are arterial dissection and, extremely rare, arterial wall perforation and contrast agent encephalopathy – which, fortunately, we did not encounter.

10.4.4 Late Complications

The most feared late complication of carotid stenting is restenosis caused by endothelial proliferation. This occurred in 15 of our 616 patients (~2.4 %) and was resolved by balloon angioplasty (Fig. 10.10). Aside from restenosis, the only late local complication of stenting we encountered was a case of late stent occlusion that occurred in a posterior circulation stent (Fig. 10.11).

10.4.5 Other Uses of Angioplasty and Stenting in the Carotid Territory

In the years of experience with carotid artery angioplasty and stenting, we noticed a subpopulation of patients – patients with symptomatic internal carotid artery occlusion *and* homolateral external carotid artery stenosis. In these patients, the ECA plays a decisive role in the intracranial loading of the anterior circulation through anastomoses with the distal portion of the ICA. We have nine such patients so far, four of which have bilateral ICA occlusion, patients for whom we decided to perform *angioplasty and stenting of the ECA* (Fig. 10.12).

Even though *intracranial endovascular treatment* is not commonly performed, we found that in particularly highly selected cases, it can be extremely useful. In the past 6 years, we have had eight patients with hemodynamically significant intracranial stenosis of the distal ICA or M1 segment of the middle cerebral artery (MCA), patients that were symptomatic in spite of maximal medical treatment; for these patients, we decided to try endovascular treatment.

There were two patients with distal ICA stenosis that were treated by angioplasty and stenting with a balloon-expandable stent (Fig. 10.13) and six patients with stenosis of the M1 segment of the MCA that were treated by low-pressure balloon angioplasty (Fig. 10.14). The results were excellent, without major complications; all patients continued to receive maximal medical treatment indefinitely.

Endovascular treatment has been one of the major improvements in vascular medicine in the past two decades, and carotid angioplasty and stenting are just one small part of this ever-growing field. The hope is that, given the time, the technology, materials, and techniques will become so safe, widespread, and routinely used, as to provide a valid alternative to more invasive procedures.

Image Gallery

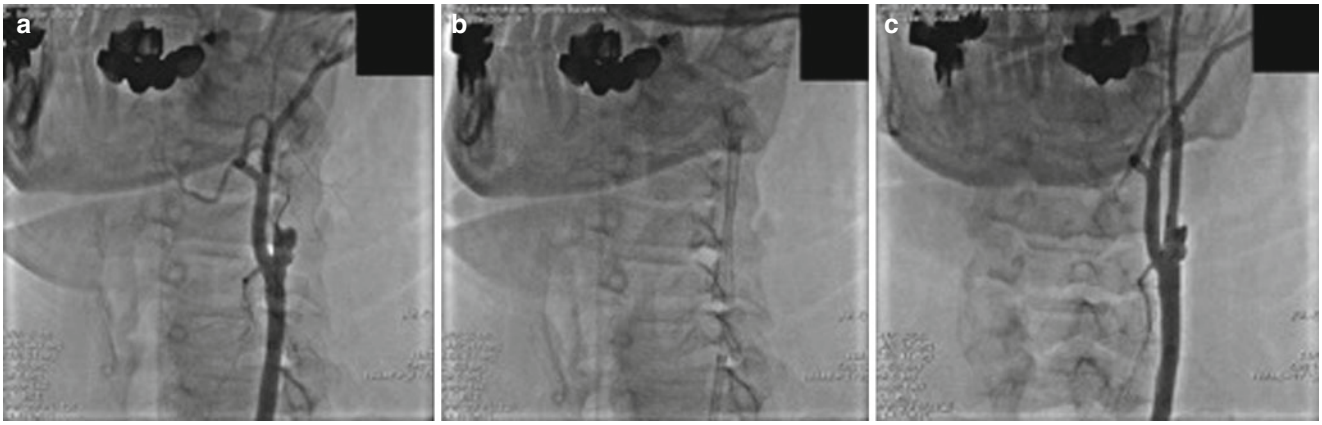

Fig. 10.1 Stenting of the left ICA: panel (**a**) initial carotidogram; panel (**b**) after stent deployment; panel (**c**) final result

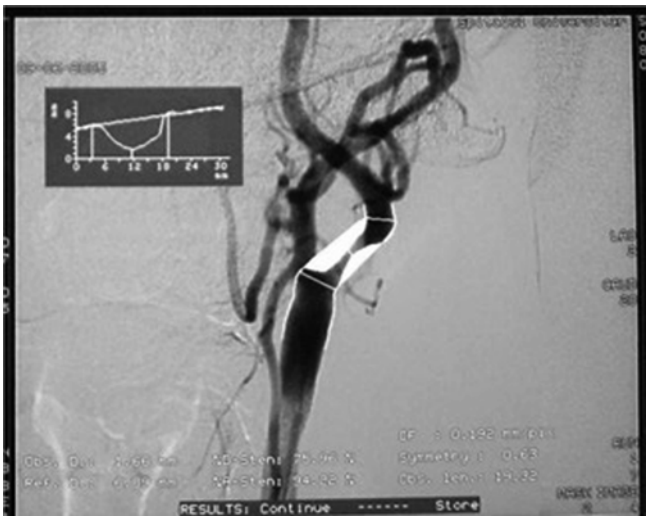

Fig. 10.2 Degree of stenosis measured according to NASCET criteria

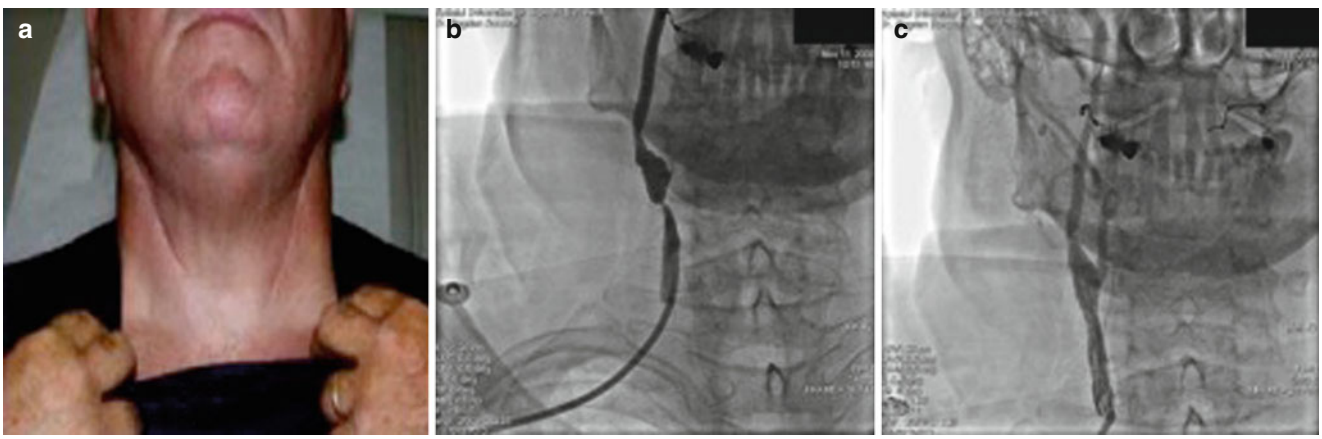

Fig. 10.3 Angioplasty and stenting of the right ICA for restenosis after CEA: panel (**a**) external appearance of patient's cervical region; panel (**b**) initial carotidogram; panel (**c**) end result

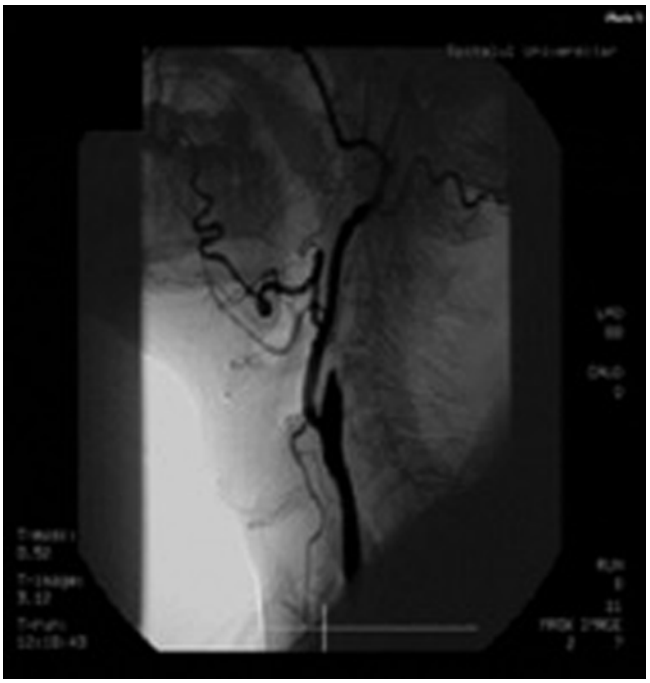

Fig. 10.4 Occlusion of the ICA is not suitable for endovascular revascularization

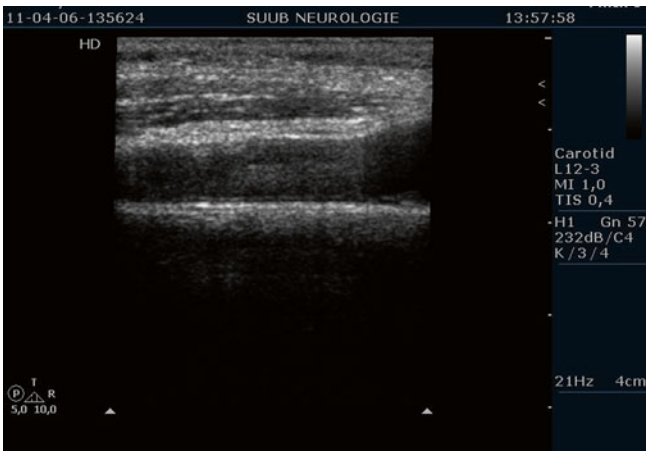

Fig. 10.5 Echographic imaging of intraluminal thrombosis excludes revascularization by CAS

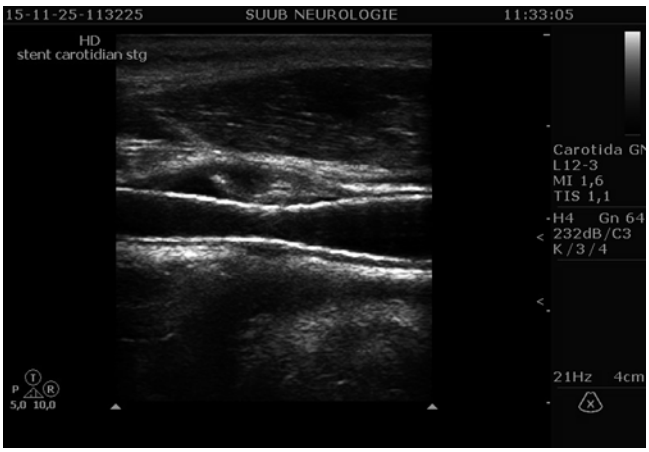

Fig. 10.6 Ultrasonic imaging of a carotid stent

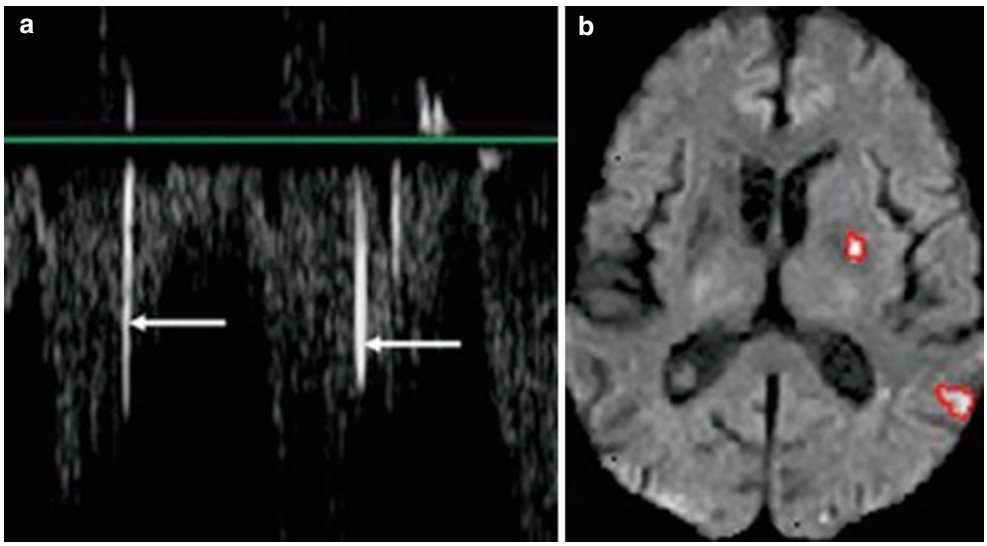

Fig. 10.7 Microemboli: panel (**a**) identified on Duplex velocimetric complexes (*white arrows*); panel (**b**) microinfarcts seen on diffusion-weighted magnetic resonance imaging

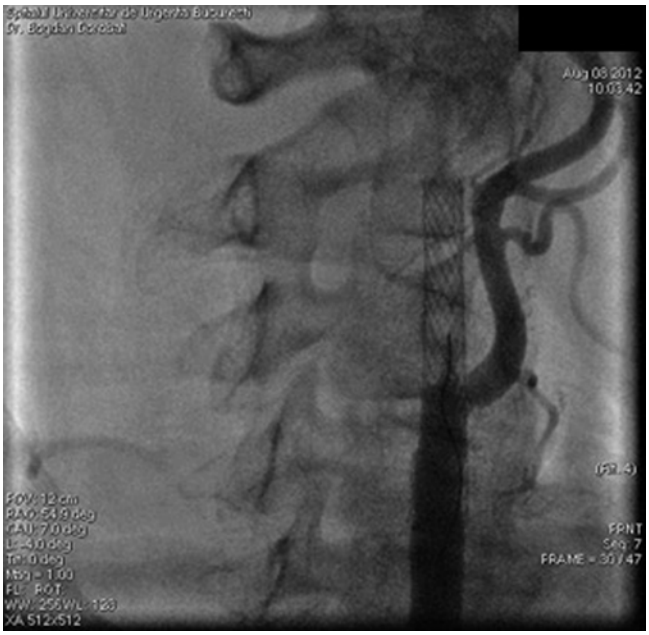

Fig. 10.8 Acute intrastent thrombosis

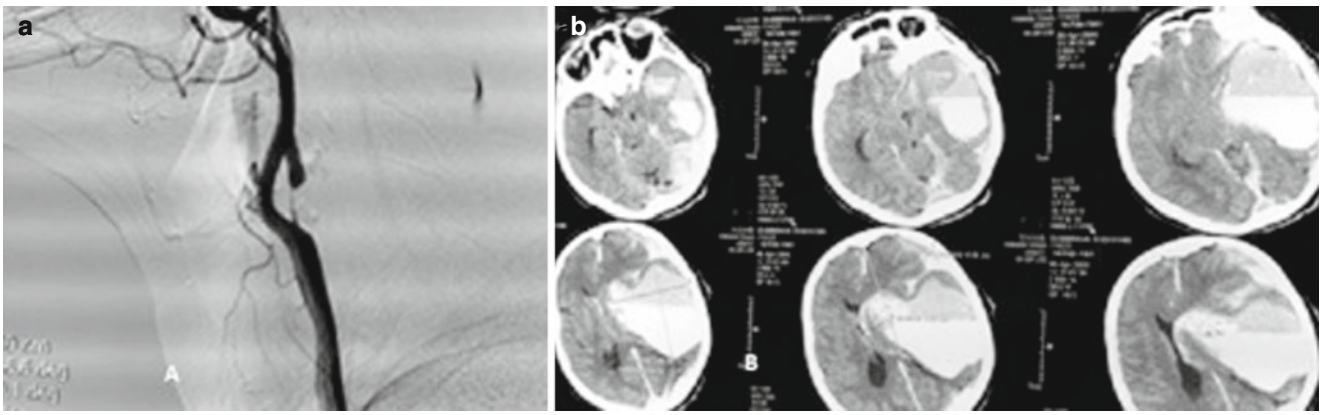

Fig. 10.9 Severe reperfusion syndrome: panel (**a**) initial carotidogram showing severe left ICA stenosis; panel (**b**) CT scan obtained 30 min after successful CAS

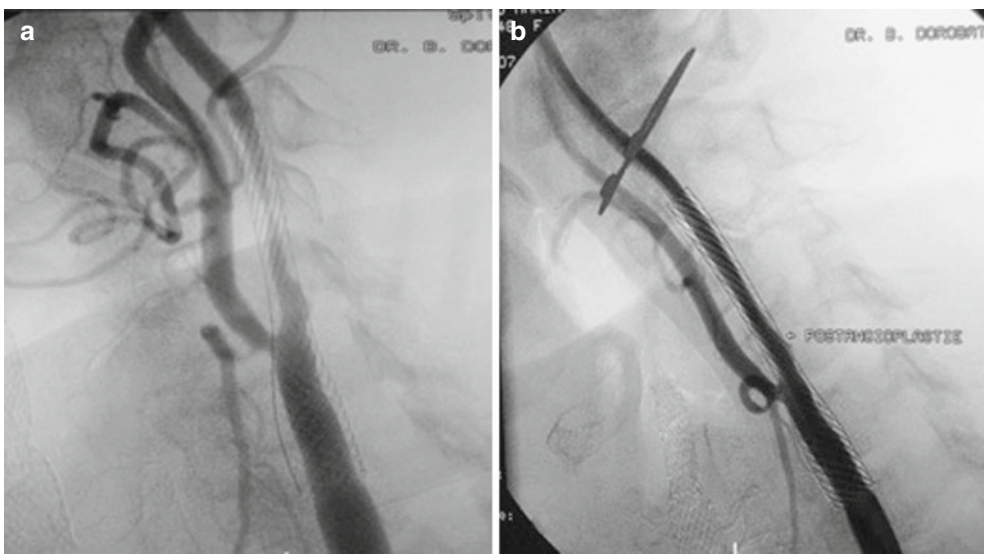

Fig. 10.10 Endothelial proliferation and restenosis after CAS: panel (**a**) initial carotidogram; panel (**b**) carotidogram after balloon angioplasty

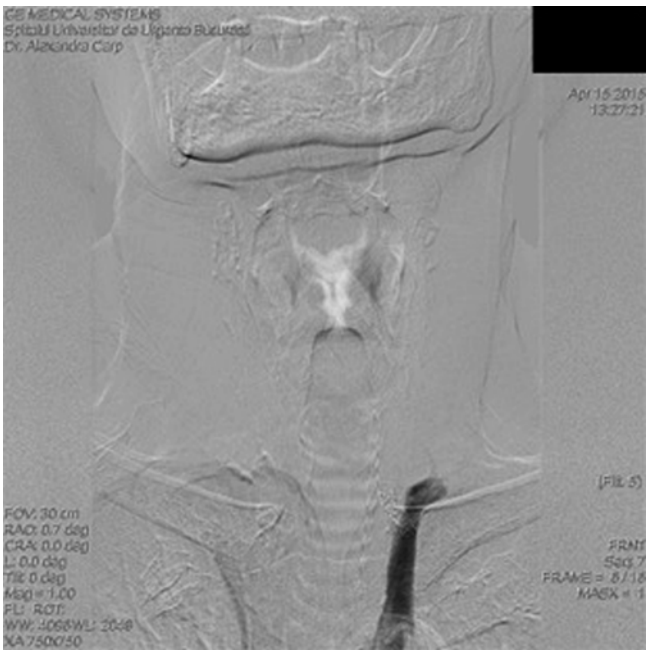

Fig. 10.11 Late stent occlusion in the posterior circulation, clinically asymptomatic

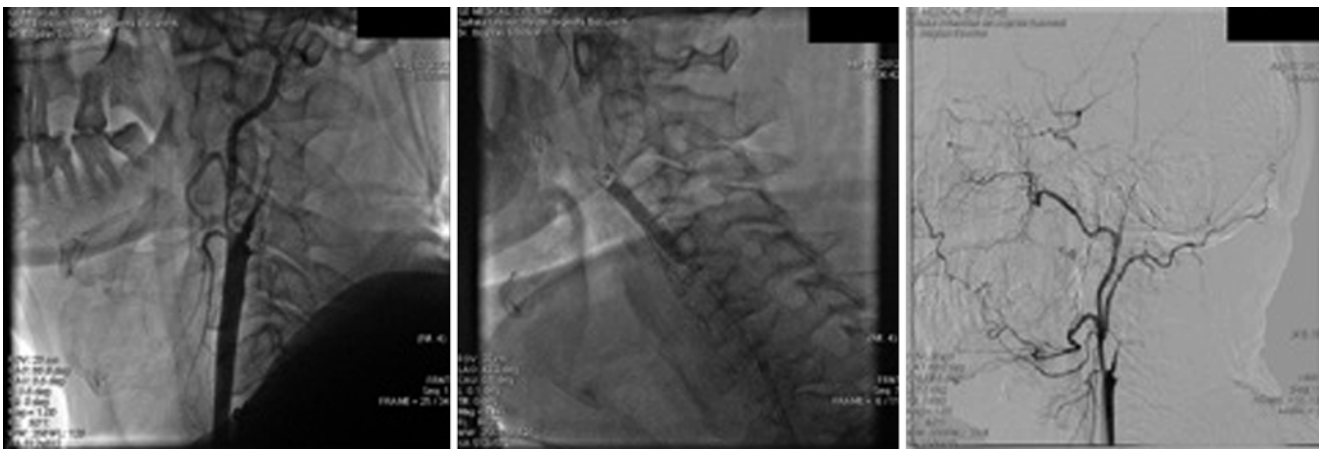

Fig. 10.12 Angioplasty and stenting of the ECA: initial carotidogram, balloon-expandable stent deployment; end result

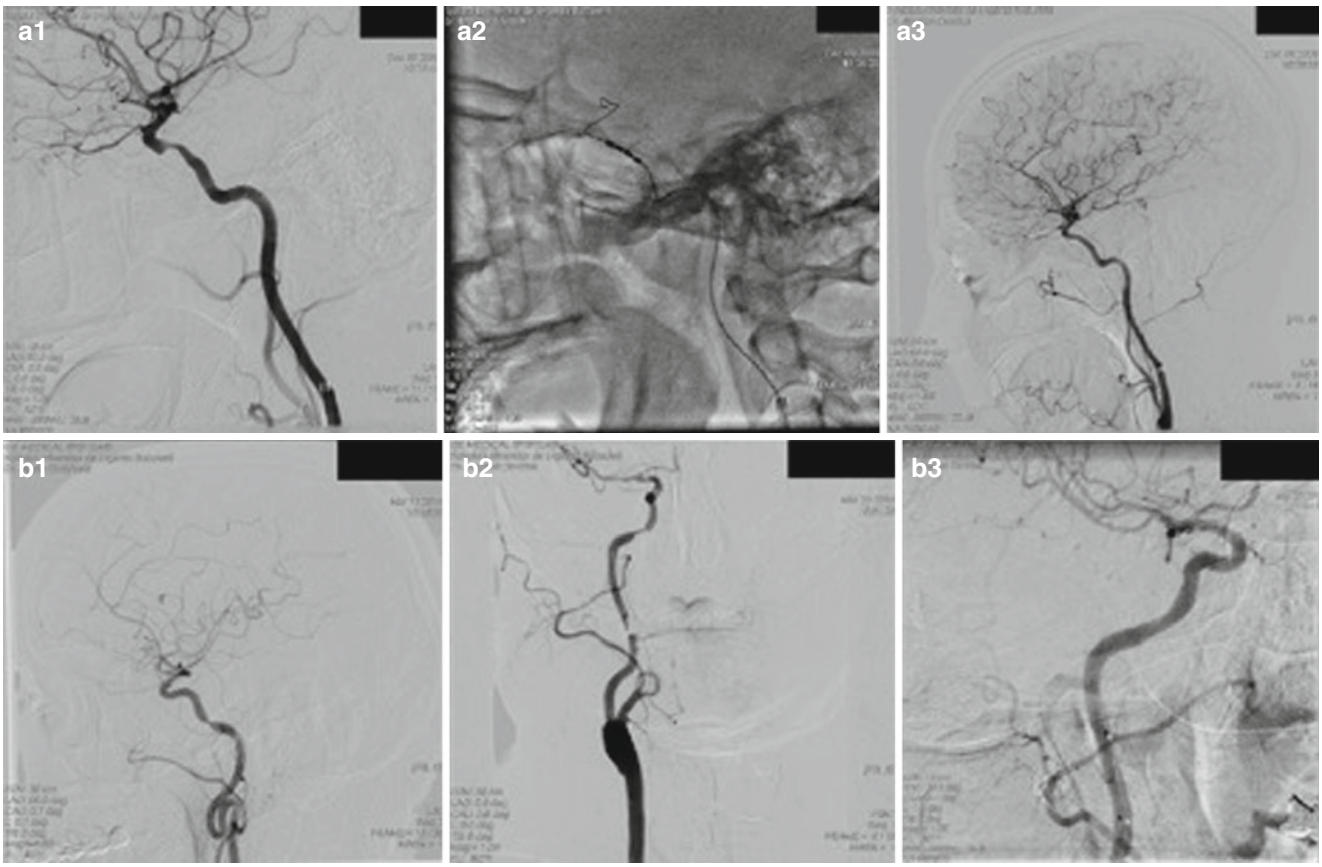

Fig. 10.13 Angioplasty and stenting for symptomatic intracranial stenosis of the distal ICA: patient. (**a**) (Panels A1–A3) – initial carotidogram, balloon-expandable stent deployment, final result; patient. (**b**) (Panels B1–B3) – diagnostic angiography, repeated carotidogram, final result

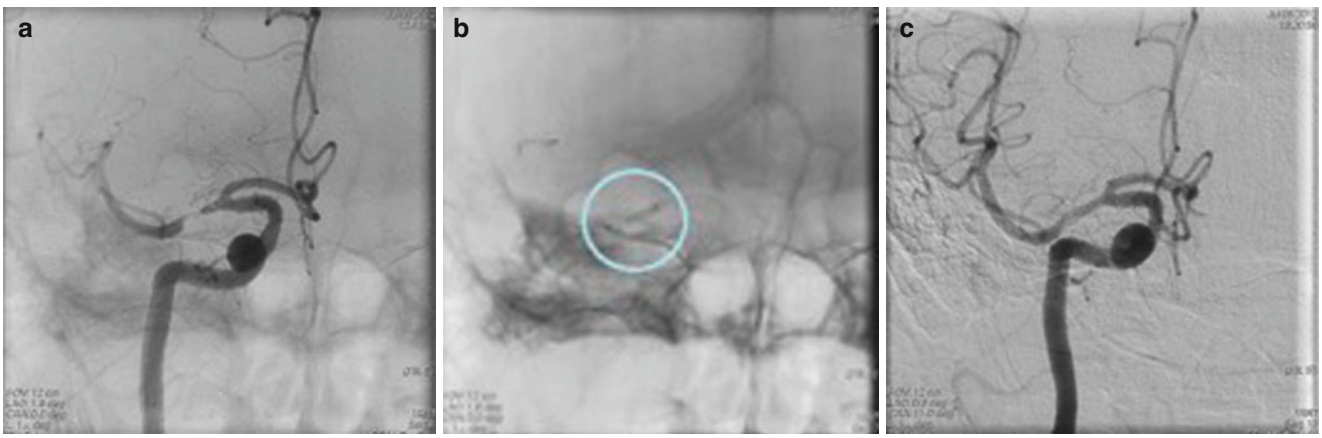

Fig. 10.14 Balloon angioplasty for symptomatic stenosis of the M1 segment of the right MCA: panel (**a**) initial appearance; panel (**b**) balloon inflation; panel (**c**) final result

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Carotid Endarterectomy

11

Horia Muresian

Particular attention has been focused on lesions at the level of the carotid artery bifurcation as most lesions (considered as the culprit lesions) develop preferentially at this site. Randomized trials have underscored the beneficial effects of treating the stenotic lesions of the carotid bifurcation, either by endovascular procedures or surgery. However, one should also consider associated facts when discussing the indications and the results of carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS): First, many of the studies were performed before the implementation of statin therapy and antiplatelet therapy and before the era of modern medical control of hypertensive disease and diabetes and the reduction of smoking. Second, diagnostic imaging offers a better mapping of the entire superior aortic system (including the intracerebral circulation) and plaque morphology, allowing for a better stratification of risk in the given patient and for a more precise and efficient therapy. Third, again diagnostic imaging allows the identification of silent brain ischemia in asymptomatic patients or in patients with uncharacteristic clinical signs and symptoms. This represents a particular category of patients who will benefit from CAS or CEA. Fourth, staged and/or combined (*hybrid*) procedures may be more advantageous and beneficial to selected patients, thus leaving less room for a direct comparison between the various types of therapeutic measures. Fifth, surgery and endovascular procedures represent heterogeneous procedures (i.e., various techniques and devices are used either indicated by patient's disease or by center's preference), and numerous aspects are overlooked when merely comparing CEA to CAS. Sixth, diagnostic and therapeutic efficiency and results are operator dependent and directly related to the personal experience and that of the center. Seventh, carotid stenotic-occlusive disease develops bilaterally; hence, the significance of a carotid stenosis must be evaluated and interpreted in the context of bilateral disease and taking into account the status and potential of compensatory collateral circulation. The natural history of carotid stenosis and eventual occlusion appears protean. Bilateral carotid occlusive disease increases the risk for complications during and after unilateral CEA [1]. Eighth, a particular category of patients have bilateral carotid stenoses and are symptomatic on the site with the lower-degree stenosis. This raises an important question: which side should be treated first – the symptomatic or the highest-degree stenosis? Or should a bilateral CEA be performed? This also depends on the status of the dominant hemisphere: is it on the symptomatic side or on the higher stenosis side? Ninth, the method of stenosis measurement (Fig. 11.1) is also different in the various studies performed: NASCET [2], ECST [3], and common carotid method [4, 5]. Further particulars and special situations regarding stenosis measurement, difficulties, and pitfalls are presented in Fig. 11.2.

Consequently, the guidelines must be interpreted and used as baseline indications (Table 11.1) [6], while the definite emerging strategy must follow a thorough clinical and diagnostic workup, ideally, as a result of teamwork (neurologist, cardiologist, interventionalist, surgeon). Clinical experience and technology will undoubtedly develop. The discussion that follows must be looked upon in this general context.

The main points to be considered for carotid revascularization are the benefit for the patient (prevention of future strokes, improvement of neurologic status, increased life expectancy, lower risks for other surgeries), the periprocedural morbidity and mortality, the risk of restenosis, and, not the least, the costs and efforts for the health system. Addressability of the patient is quite different in the various health systems, and there is no ideal screening for the prevention of stroke and for the early diagnosis of individuals who must be referred for CAS or CEA. On the other hand, efficiency and lowest risks characterize larger centers and well-trained professionals.

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

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Table 11.1 Major recommendations for carotid revascularization

Clinical status % stenosis	Main indication	Notes
TIA, ischemic stroke (6 months), 70–99 % stenosis	CEA	If perioperative morbidity and mortality <6 % No contraindication to early revascularization (2 weeks)
TIA, ischemic stroke, 50–69 % stenosis	CEA	Depending on patient-specific factors (age, sex, comorbidities[a]) and if perioperative morbidity and mortality <6 %
<50 % stenosis	No CAS or CEA indicated	Important to follow plaque morphology and symptoms
Older patients	CEA favored over CAS	
Symptomatic patients with >70 % stenosis by ultrasound or >50 % stenosis by angio	CAS	
Occluded ICA and severe disability	No indication for revascularization	The only absolute contraindication for CEA
Recurrent carotid stenosis	Repeat CAS or CEA	
Unfavorable neck anatomy	CAS	High bifurcation, high and longer stenosis, previous radiotherapy, tracheostomy, contralateral vocal cord paralysis (see text for further details and discussion)

CAS carotid angioplasty and stenting, *CEA* carotid endarterectomy, *ICA* internal carotid artery, *TIA* transient ischemic attack
[a]Comorbidities increasing the risk of revascularization (both CAS and CEA): heart failure NYHA class III–IV, left ventricular ejection fraction <30 %, class III–IV angina, left main or multivessel coronary disease, need for cardiac surgery within 30 days, myocardial infarction within 4 weeks, severe chronic lung disease

Selection of the patients for CEA includes the following situations:

High-grade carotid stenosis in symptomatic patients
Asymptomatic patients with "silent" brain infarcts
Asymptomatic patients with high-degree stenosis scheduled for major surgeries including coronary revascularization and resection of abdominal aortic aneurysm (the so-called prophylactic CEA)
Patients with neck tumors and moderate carotid stenosis but who will undergo radiation therapy after tumor excision
Patients with extreme carotid kinking who need intracranial stenting or intracranial aneurysm embolization
Aortic arch syndrome (with stenotic-occlusive lesions at the origin of the aortic arch and branches and with only moderate lesions at carotid bifurcations and who will undergo ascending aorta-to-cervical artery bypass)
Revascularization of the distal cervical VA from a moderately diseased carotid bifurcation
Subclavian-to-carotid artery bypass for occluded or highly stenosed CCA and with only moderate stenosis of the carotid bifurcation
One can easily see that the guidelines cover only partially the various situations mentioned above. In this chapter, we will focus on some of the particular situations beyond the already known guidelines.

Bilateral carotid stenosis represents a challenging topic both for the neurologist and surgeon. From a diagnostic point of view, a clear stratification of symptoms and signs and relation of these with the carotid lesions must be performed. It is also difficult to appreciate the patient evolution and the future risk of stroke after treating only one of the two carotid stenoses. These latter aspects obviously depend most on the evolution of stenosis on the nonoperated side, plaque morphology, collateral circulation, compliance to treatment, and efficiency of therapy regarding the control of comorbidities and elimination of risk factors. We advocate a personalized approach, therapy, and follow-up, preferring to treat however both lesions. In cases with severe bilateral carotid lesions, we also indicate bilateral CEA in most of the cases in a single operation (*see details on simultaneous bilateral carotid endarterectomy in* Chap. 13).

The case of *the prophylactic carotid endarterectomy* is also open to debate. The risk of the CEA as compared with the risk of perioperative stroke and mortality in surgeries such as coronary revascularization, resection of aortic aneurysms, and major abdominal surgery must be weighed against each other, as no randomized trials have been performed so far. Patients in this category are either symptomatic or asymptomatic, and the carotid lesions are either unilateral or bilateral. With the advent of CAS and CEA under locoregional anesthesia, treatment options appear more tempting, and indications will undoubtedly broaden. Whenever possible, we advocate performing the CEA under locoregional anesthesia in patients who will undergo major surgeries, treating one or both sides. This is possible even during the same hospital stay. In case of emergent operations, we try to avoid hypotension, hypovolemia, hypocapnia, etc. In situations requiring full-dose heparin (e.g., cardiac operations), there is also the risk of favoring intraplaque hemorrhage. Another theoretical valid alterna-

tive is performing off-pump coronary revascularization although blood pressure fluctuations can sometimes be more significant as compared with a well-conducted cardiopulmonary bypass.

Some patients depict stenotic lesions both at the carotid bifurcation and in the *intracranial* segments. Should the intracranial segment stenosis be severe, we recommend treating both types of lesions (CEA plus intracranial angioplasty or CAS plus intracranial angioplasty)

Intracranial aneurysms and stenosis at carotid bifurcation raise the question regarding the future risk of aneurysm rupture. On the other hand, one should take into account the fact that systemic hypertension appears also as a rebound mechanism in severe carotid stenosis/stenoses. Most of the patients require less antihypertensive medication after treating the carotid lesion. The intracranial aneurysm is usually fed from multiple sources (this is reflected in the fact that ligature of the ICA or VA has only a temporary effect on the development of the aneurysm), and the continuous presence of hypertension will favor aneurysm development and rupture. In the few patients, we treated with both types of lesions, the arterial hypertension was controlled well after CEA, and intracranial aneurysms remained stabled and asymptomatic. Moreover, after performing CEA, the aneurysm can be more safely treated, without the risk of embolization from a diseased carotid bifurcation.

Another category of patients will present with *intracranial aneurysms and extreme kinking* of the cervical ICA and mild or moderate stenotic lesions of the carotid bifurcation. Kinking makes impossible access to the intracranial ICA, and these patients are first treated by CEA (the eversion technique). The same applies to patients with concomitant *severe, pre-occlusive intracranial stenosis of the ICA and extreme kinking* (± stenosis) (Fig. 11.3).

Neck tumors pose particular problems. Postsurgical and/or post radiation cervical scarring will limit or even contraindicate CEA (one should also bear in mind the fact that even the results of CAS are limited in time in such cases). The diameter of the CCA and ICA can be altered while the arterial wall may be of a defective quality; the risk of infection and wound nonunion is also higher in these patients. Patients with laryngectomy have also permanent tracheostomy. In our experience, this represents only a relative contraindication, as we performed CEA in such patients both under general and locoregional anesthesia, both unilateral and simultaneous bilateral (Fig. 11.4). Some authors also perform simultaneous bilateral carotid endarterectomy plus laryngectomy in selected groups of patients. On the other hand, should radiotherapy be indicated after carotid revascularization, we recommend performing CEA instead of CAS.

Aortic arch syndrome is associated with moderate lesions at the level of carotid bifurcations. These patients require revascularization of the neck vessels with bypass from the ascending aorta. Should the distal end of the prosthesis be inserted only at the level of the CCA leaving the bifurcations(s) untreated, or should the CEA be concomitantly performed (or should the bypass be inserted at the level of the carotid bifurcation after endarterectomy)? We recommend simultaneous CEA and distal anastomosis of the prosthesis on the endarterectomized carotid bifurcation(s). The same recommendation applies for VA revascularization from a moderately diseased carotid bifurcation: the CEA is performed first and the saphenous vein graft serves as a patch for enlargement of the carotid bifurcation, which is identical for subclavian-to-carotid bypass in cases with occluded CCA.

The diagnostic workup in patients selected for CEA includes cardiological and neurological clearance, spirometry, and evaluation and control of renal failure and diabetes. ENT examination is also used in selected patients to rule out cranial nerve deficits of possible difficulties to intubate the patient. Baseline cardiological examination comprises ECG and cardiac ultrasound; in patients with advanced and multi-territory atherosclerotic lesions, coronary angiogram is also indicated. The aim of the neurological examination is establishing the neurological status or deficits and is followed by duplex ultrasound (ideally performed by the same neurologist). Severe heart disease and severe pulmonary dysfunction, older age, renal failure, uncontrolled diabetes, and presence of stroke as the indication for CEA all are associated with poor outcome. It is also important in stressing the fact that patient population shows a tendency toward combination of more than one major risk factor. Anesthetic and perioperative risk stratification is usually performed by the anesthesiology team.

The principal *imaging techniques* generally accepted and deployed in most centers are duplex ultrasound, angiography, CT and CT-angio, and MRI and MRA. The choice of the diagnostic imaging procedure depends on the preference of the center and of availability. However, most of patients will have at least a baseline ultrasound examination. Even in these cases, a thorough ultrasound reevaluation is mandatory as not all examinations are performed by well-trained specialists or neurologist before the hospital admission of the patient. In our daily practice, we rely on ultrasound examination performed by a trained neurologist (including the transcranial modality). It is only the neurologist who can better appreciate the ultrasound data and particulars in the clinical context. In our experience, we base our therapeutical indication on *two complementary imaging tests*, usually ultrasound and angiography or ultrasound and CT-angio (for the sensibility, specificity, and particular details and indications of each technique, see the dedicated chapters). The two tests are complementary and together offer a reliable anatomical and functional picture. We

would like to underscore the importance of examining the entire superior aortic system and not merely the cervical portions of the carotid and vertebral arteries. A thorough visualization of the vertebrobasilar system is also obligatory. CT and MRI are used mostly for evaluation of brain parenchyma (and in order to exclude other pathologies such as tumors, hematomas). Generally, these are completed by CT-angio and MRA if performed in specialized centers where CAS or CEA is contemplated.

Preparation of the patients for CEA includes administration of aspirin (75–100 mg daily), statins, and prophylactic antibiotics and an efficient control of arterial hypertension, dysrhythmias, and diabetes. Aspirin is not discontinued. On the other hand, we advocate discontinuing clopidogrel (ideally 7 days before CEA). Patients previously on oral anticoagulant therapy are converted on LMWH for the perioperative period.

The type of *anesthesia* chosen, drugs, intra- and postoperative monitoring, and strategy are described in detail in Chap. 9.

11.1 Surgical Technique

Under the name "carotid endarterectomy," various techniques are contemplated. This renders even more difficult the comparison between different centers, as some procedures are preferred over others. In selected instances, it is the type of lesion and the patients' characteristics which dictate the use of a particular surgical technique (see below). The main steps in treating by surgery the carotid lesions include: (1) The adequate exposure of the carotid bifurcation allowing sufficient length of arterial segments for a proper, efficient, and atraumatic clamping of the vessels. (2) The possibility of broadening the operative field and to access alternative donor arteries whenever necessary. (3) The least interference with adjacent structures (cranial nerves, nerves for the carotid sinus and glomus, etc.). (4) Complete excision of the atherosclerotic lesion. (5) Securing the distal intima/end artery of the ICA in order to avoid intimal flaps (leading to early thrombosis or dissection). (6) Closure of the arteriotomy in such a way to prevent restenosis and to avoid angulations and kinking. The techniques we use and recommend are:

1. *CEA and direct closure of the arteriotomy* (Fig. 11.5). A longitudinal arteriotomy is performed at the level of the distal CCA extended over the ICA ideally on the posterolateral aspect of the vessels (to interfere less with the sinus nerves). The arteriotomy must go beyond the carotid lesion (both proximal and distal). A cleavage plane is developed within the arterial wall, usually at the level of the media. The plaque is subsequently removed together with a portion of the media. However, some plaques are more extensive, and the remaining portion of the arterial wall is sometimes too thin after endarterectomy, requiring alternative procedures such as resection and bypass. The distal intima at the origin of the ICA must be secured with separate stitches, in order to avoid the formation of intimal flaps. The arteriotomy is closed with a continuous suture (*surjet*) and flow is reestablished after careful de-airing. The technique has some theoretical advantages: the endarterectomy is performed under direct vision; no synthetic material is necessary; and clamping time of the carotid artery is reduced. On the other hand, some limitations of this technique must be reminded: the technique is not indicated in cases with narrower arteries; the distal portion of the suture constricts the entrance into the ICA. The CEA and direct closure are consequently used only in few, selected cases.
2. *CEA and patch closure* (Fig. 11.6). This technique is widely used. The first steps are similar to the abovementioned one, including the tacking of the intima of the ICA. Closure of the arteriotomy is achieved by inserting a patch (either synthetic or autologous vein). The patch is usually inserted starting from the distal part (i.e., toward the ICA). The main advantages of patch closure are: A better matching between the caliber of the CCA and ICA. There is least risk of restenosis. The patch helps in tacking the lateral aspects of the distal intima of the ICA. The patch allows the enlargement of the entrance into the ICA. The patch can be also tailored in such a way to enlarge the entrance into the ECA too. In cases in which a thinner wall results after endarterectomy, the patch will reinforce the carotid bifurcation, allowing also deeper bites to be taken. The synthetic patch will not predispose to aneurysmal dilatation of the bifurcation. There are some limitations and precautions of this technique. It is more time consuming. The patch must be adequately tailored in order to avoid major discrepancies between the CCA and ICA (e.g., a too much enlarged bifurcation and a slender distal ICA, favoring jet lesions and intimal hyperplasia). The patch can favor angulation at the origin of the ICA if not properly inserted (the long axis of the patch and of the ICA must coincide.
3. *The eversion technique* (Fig. 11.7). The ICA is disconnected and the outer media and adventitia are peeled off of the plaque. The plaque is extracted and the ICA is reanastomosed. This technique is indicated in patients having limited lesions at the level of the proximal ICA (in cases with more extensive lesions, the ECA can be also disconnected and the eversion can be performed over the ECA and CCA too). Kinking of the ICA represents a major indication for eversion, as the ICA can be tailored, shortened, and adapted to the proper length. The technique is less time consuming and uses no synthetic

material. There are however numerous limitations. Disconnecting the ICA will interfere with the innervation of the sinus. The extraction of the plaque is mostly a blind maneuver and intimal flaps may develop. The reanastomosis of the ICA can create a visible threshold at the very origin of the ICA (predisposing to hyperplasia). It is more difficult to treat the more proximal lesion on the CCA. A few modifications of this technique lead to important improvements: in case of excess ICA (kinking of the ICA), a longitudinal arteriotomy can be performed on the ICA up to the distal end of the plaque, and the extraction of the plaque will be no more a blind maneuver. The excess tissue on the ICA can serve as a patch when reanastomosing the ICA to the CCA. Additionally, the CCA can be incised longitudinally, in order to allow a complete removal of the inferior portion of the plaque. More oblique (almost vertical) arteriotomy for disconnecting the ICA will allow a complete removal of the plaque and facilitate reanastomosis.

4. *Resection and bypass* (Fig. 11.8). This is indicated in the case of very diseased bifurcations or with the presence of carotid plaques ulcerated toward the outside or when the resultant arterial wall becomes extremely thin after endarterectomy. The bifurcation is replaced by vascular graft or autologous vein. The ECA may be ligated or reimplanted in the previously CCA-to-ICA bypass (this will depend on the caliber of the ECA and, not the least, on the quality of the contralateral carotid bifurcation). A reimplanted ECA also assists in a better de-airing before declamping. The distal anastomosis on the ICA is performed first. The graft can be tailored in such a way to allow the concomitant anastomosis of the ICA and ECA. In some instances, the wall of the CCA appears very diseased, with ulcerated plaques; in these cases, the CCA is also removed (almost entirely), together with the bifurcation.
5. *Combined technique: eversion plus patch*. This is used in case of ICA kinking but with an ICA of reduced caliber. The ICA is disconnected, the plaque is removed as in the eversion technique, and ICA is reattached to the CCA except the anterior portion, where the anastomosis is completed by inserting a patch. This permits both the elimination of kinking and enlargement of the bifurcation and origin of the ICA.
6. *Combined technique: patch plus bypass* (Fig. 11.9). If the ICA has a smaller caliber and/or the wall of the ICA is thin and fragile, we do not routinely anastomose directly the graft to the ICA, but start patching the ICA from distal to more proximal. The graft is subsequently anastomosed to the ICA which is enlarged by the patch.
7. *Endarterectomy and "ascent" of the carotid bifurcation* (Fig. 11.10). The longitudinal incision over the ICA is paralleled by another one performed on the ECA, and the ECA serves to enlarge the origin of the ICA. Alternatively, a patch can be inserted between the anterior portions of the ICA and ECA.

Shunting for CEA This additional procedure has the theoretical advantage of minimal interruption of cerebral blood flow and eliminating the stress on the surgical team regarding the clamping time. There are however limitations and precautions regarding the use of shunt: First, vessel exposure must be broadened in order to allow a safe and rapid insertion and removal of the shunt. There might be a problem especially with higher bifurcations and longer plaques where less ICA is available for clamping. Second, insertion of the shunt is not an innocuous maneuver: flaps and dissection may supervene as well as dislodgements of plaques. Third, insertion of the shunt requires increased doses of heparin. Additionally during longer procedures, clots may develop between the shunt and the arterial wall. Fourth, the position of the shunt especially in the distal ICA is difficult to appreciate, and the shunt may be partially obstructed if the artery is angulated or if the shunt is against the carotid wall. The patient needs a good intraoperative monitoring for a constant evaluation of the functional status of the shunt. Fifth, there is risk of air embolism at insertion and removal. Sixth, there is reduced field for the surgeon and greater difficulty in removing the plaque and inserting the patch.

We routinely do not use shunting (except in selected cases). Intraoperative monitoring and especially the routine use of locoregional anesthesia have dramatically reduced the need for shunting (see Chap. 10). We also administer low doses of heparin (2500 UI before clamping) with no need of reversing the heparin. Unfractionated heparin is started postoperatively at about 3 h after the intraoperative bolus (UFH is usually kept for about 24 h and subsequently replaced by LMWH). The opened carotid is intermittently rinsed with heparinized saline during CEA. Upon completion of the suture (patch, reanastomosis, or direct suture), the ICA is declamped first, and then it is reclamped; the suture is completed and the ECA and CCA are declamped. Blood flow is directed into the ECA for about 1 min and afterward the ICA is declamped. The site is checked for bleeding; the pulsations of the arteries are checked as well as the presence of any thrills. Intraoperative ultrasound evaluation of the technical results should become a routine. Neuromonitoring assists in evaluating the effects of the operation. The wound is closed in the usual manner after insertion of an aspiration drainage (generally kept for 48 h). We recommend separate stitches in order to avoid the development of neck hematoma. Patients are mobilized the very next morning. Until that moment, the patients are kept in the ICU and under monitorization. Fluid intake is allowed a few hours after the admittance in the ICU and regular meals, on the next day.

11.2 Conclusive Remarks

It is evident that there are numerous techniques and modifications of the classical techniques, collectively termed "CEA." *First*, observation is that there is no singular infallible surgical technique and that the surgeon has to master more types of procedures; versatility in choosing the type of operation represents a "sine qua non" in carotid surgery. *Second*, statistics of various centers are still difficult to compare, due to the procedures performed. For the same type of carotid lesion, therapeutic methods may vary between centers and surgeons (and interventionalists). As a consequence, some would prefer extensive surgery, while others will adopt combined (hybrid procedures). In our opinion, randomized studies will be very difficult to conceive for this reason. *Third*, patient's preference may count: some would opt for a "definitive type of surgery," while others will prefer endovascular or combined procedures. The surgeons and experience and rate of complications (as well as those of the center) will count very much in patient's choice. *Fourth*, most if not all the operations limited to the cervical area can be safely performed under regional anesthesia (cervical ± brachial plexus block), even when performed bilaterally and simultaneous. This will select an important category of patients who would be at higher risk if operated under general anesthesia and who will benefit of the surgical treatment: improvement of quality of life and more efficient prevention of stroke).

Communication between the various categories of specialists and centers is favored. The multidisciplinary teamwork will undoubtedly lower or even eliminate biases in choosing the best therapeutic strategy.

Image Gallery

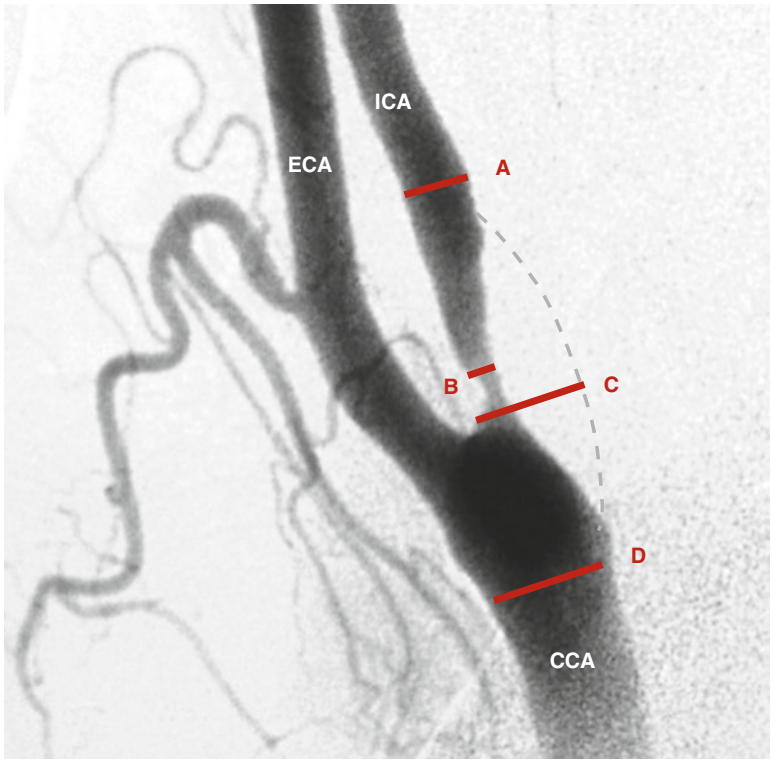
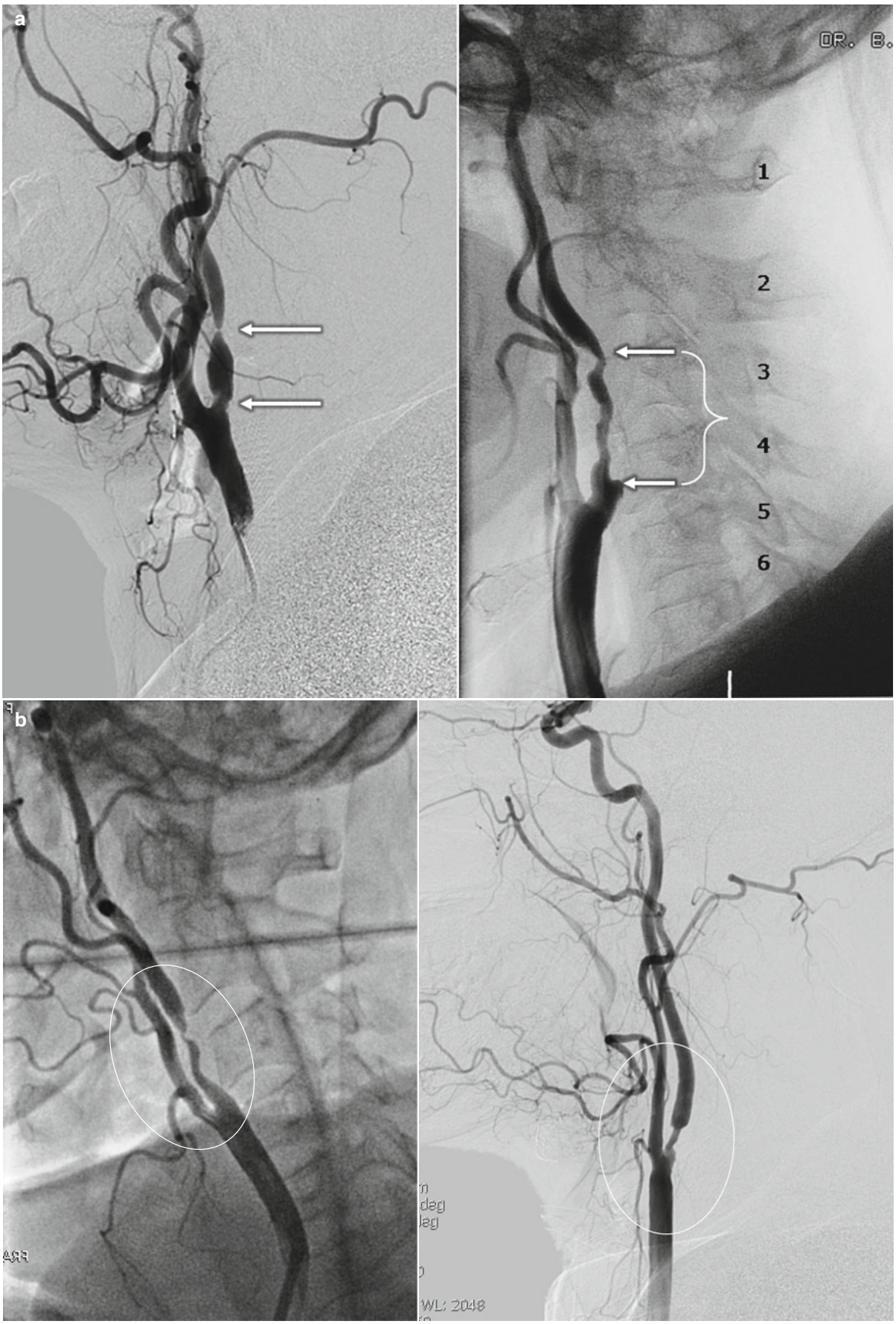


Fig. 11.1 Comparison between the various methods of stenosis measurement. The zone of stenosis (the tightest area) is measured against the common carotid, the internal carotid (distal to the stenotic lesion), or the estimated width at the level of the carotid bulb. The ECST measurement underestimates the degree of stenosis. For further limits and critics of these methods, see Fig. 11.2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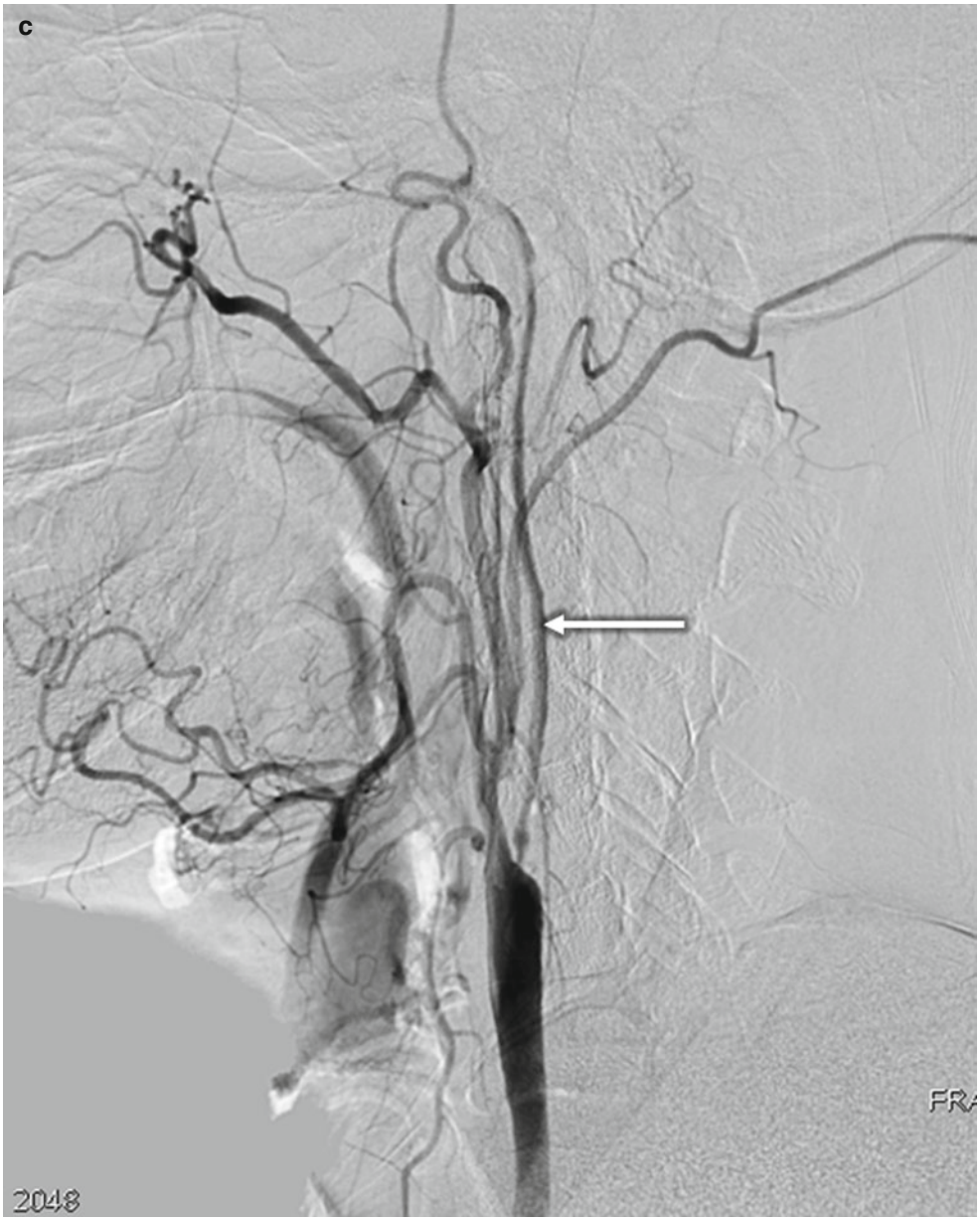
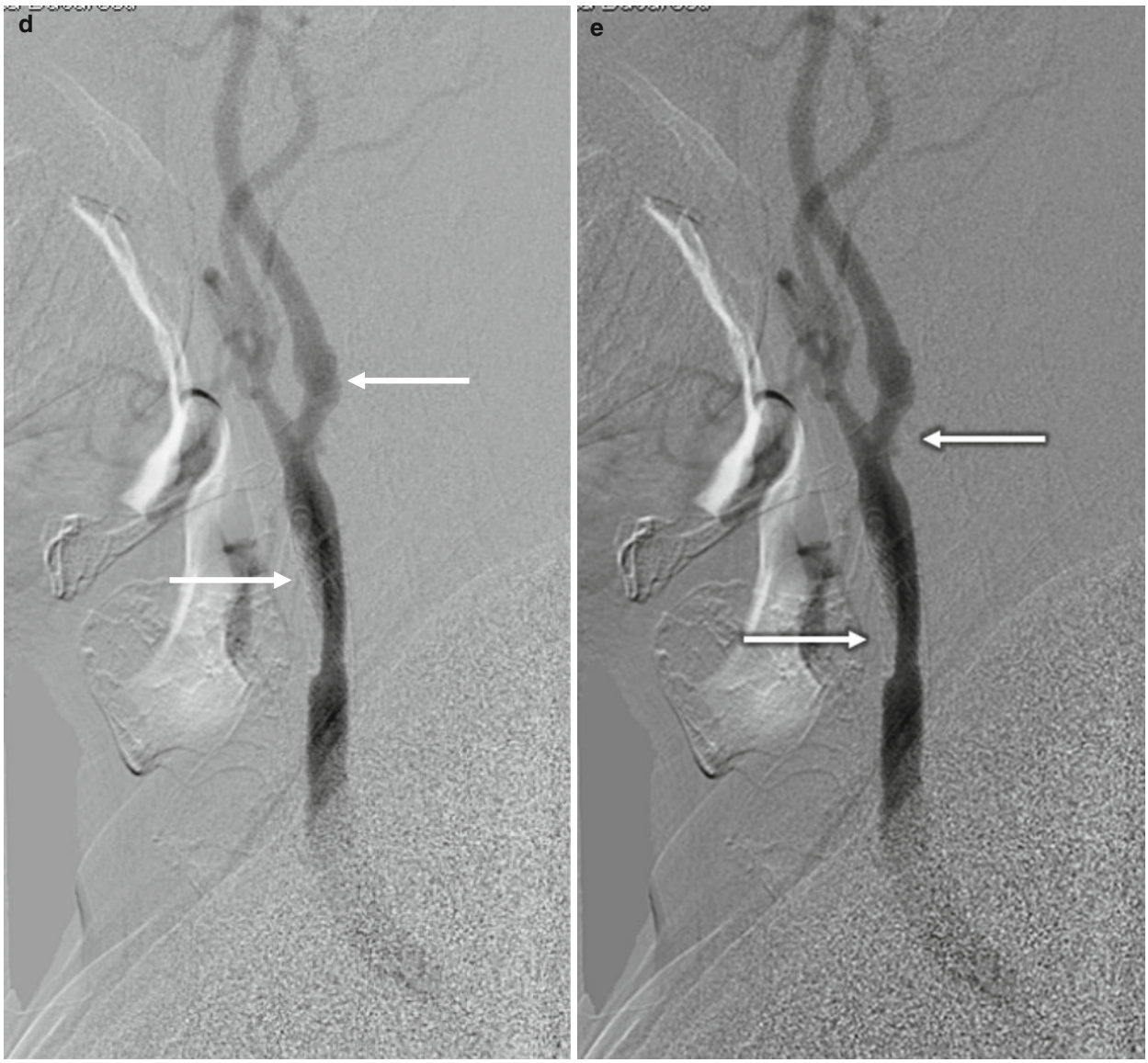


Fig. 11.2 (continued)

Fig. 11.2 Limits and precautions for stenosis evaluation. Panel (**a**): two types of stenoses are presented. Two stenoses with almost normal arterial caliber in between (*left panel, white arrows*) and long, almost tubular-like stenosis (*right panel, white arrows*). From the pure morphologic point of view, it is difficult to estimate the severity and the clinical significance of the lesion. Ultrasound may miss the impact on flow of the more distal stenoses. 1–6 = spinous processes of the cervical vertebrae one through six. Panel (**b**): difference in the shape of stenosis. A fusiform stenosis is presented in the left image, while on the right, a tubular, stepped stenosis is shown. Although the degree of stenosis might be similar, the visual perception may be different. Panel (**c**): stenosis over a hypoplastic ICA (*white arrow*) which makes difficult the correct appreciation of the hemodynamic impact and the surgical indication. Panel (**d**): stenosis of the ICA + stenosis of the more proximal CCA (*white arrows*). The stenosis on the CCA appears frequently as long, eccentric, and apparently not severe. However, the plaque may depict characteristics of severity (ulceration, rough surface, and increased volume). Endarterectomy performed only at the level of the origin of the ICA may compromise in time due to the progressive stenosis of the CCA. A more extended endarterectomy and longer patch are recommended or stenting of both lesions. Panel (**e**): stenosis at the origin of the ICA with hypoplastic CCA (*white arrows*). The hemodynamic impact of the ICA stenosis may be difficult to appreciate. In cases with an ICA of normal caliber and clinically symptomatic patient, CEA of the bifurcation and graft replacement of the hypoplastic CCA might represent a valid solution



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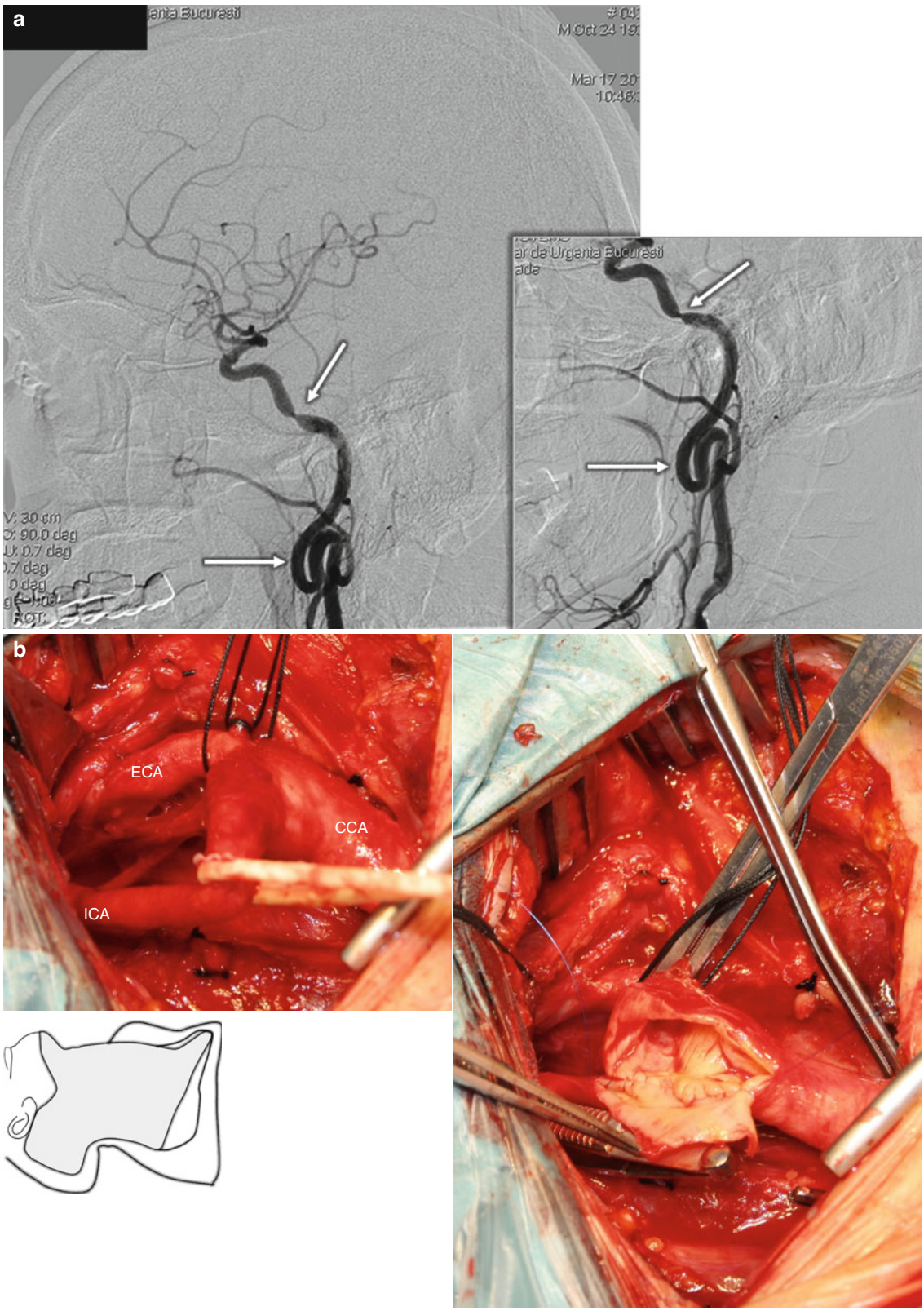


Fig. 11.3 Intracranial stenosis of the ICA and kinking of the cervical ICA (*white arrows*), precluding the endovascular access. Panel (**a**): angiographic appearance of the stenosis of the intracranial segment of the ICA (symptomatic patient) and the extreme kinking of the cervical portion of the ICA. Panel (**b**): intraoperative aspect, demonstrating the excess of length of the cervical ICA. The ICA was partially resected (as with the eversion technique) and reanastomosed to the CCA. Panel (**c**): completion angiogram, after surgery. The carotid bifurcation appears enlarged, the kinking was eliminated, and the distal ICA can be easily accessed (*white arrows*). Panel (**d**): angioplasty and stenting of the intracranial stenosis of the ICA (*white arrows*)

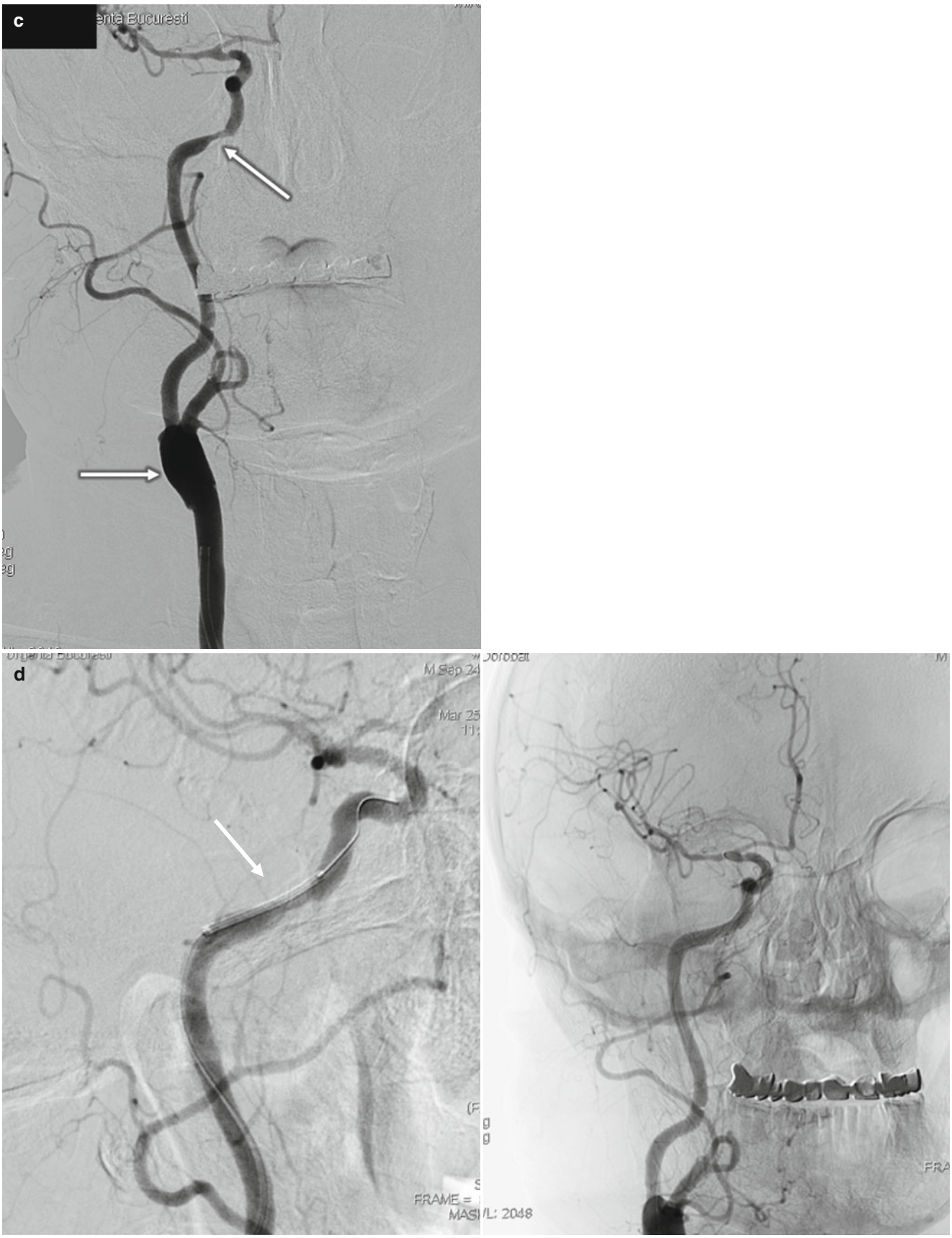


Fig. 11.3 (continued)

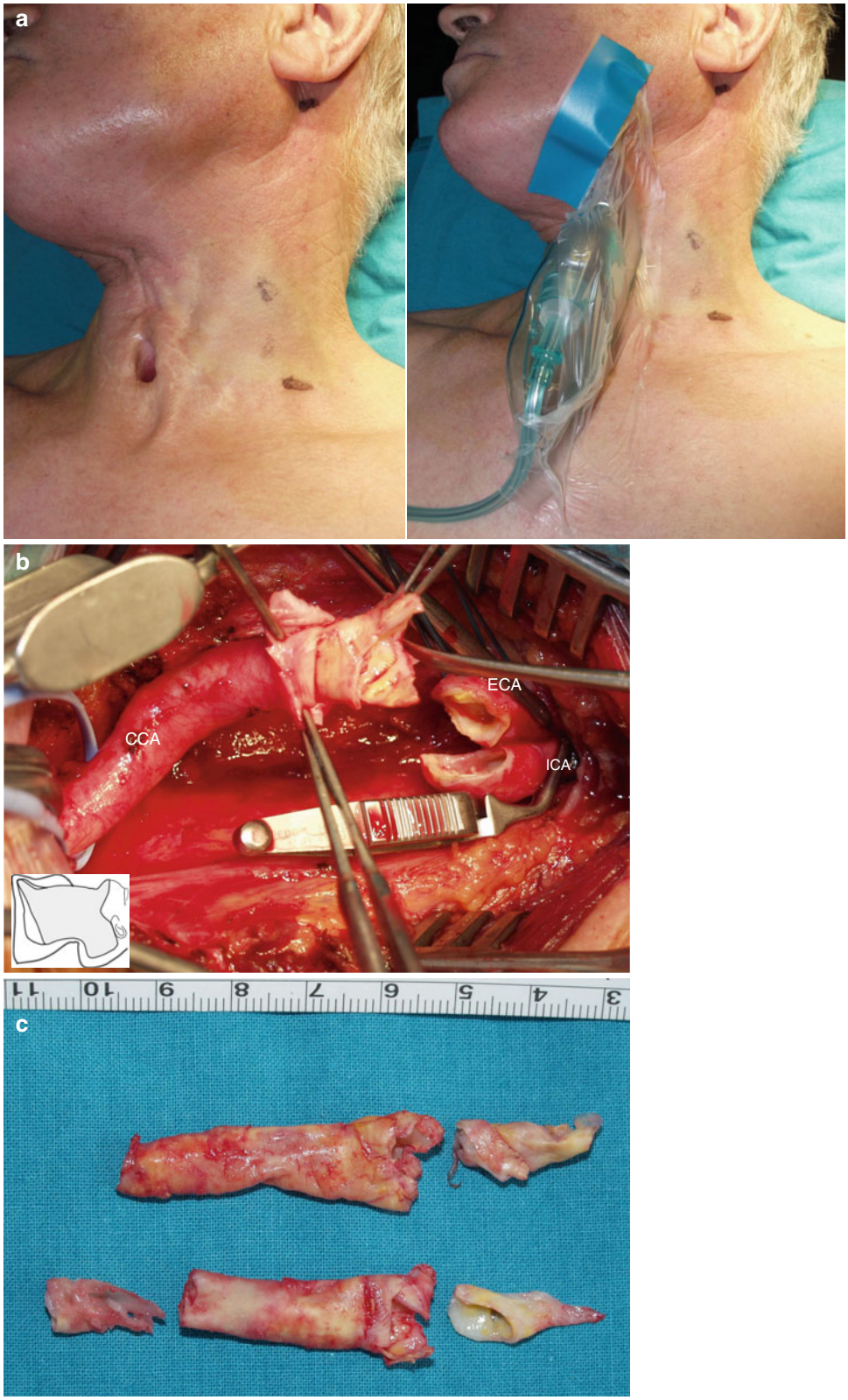


Fig. 11.4 Simultaneous bilateral carotid endarterectomy in patient with permanent tracheostomy after laryngectomy for laryngeal cancer – under bilateral cervical block (awake patient). Panel (**a**): preparation of the patient. Aspect of the tracheostomy. Application of a face mask for oxygen delivery during the operation. Bilateral cervical plexus block was applied in this patient. Panel (**b**): intraoperative aspect of the left carotid bifurcation, prepared for eversion. The ECA and ICA are disconnected from the CCA. In spite of previous bilateral neck irradiation, the arterial and periarterial tissues are not difficult to dissect. The IJV and vagus nerve are also easily isolated. Previous irradiation represents only a relative contraindication for surgery. Panel (**c**): aspect of the excised plaques from both carotid arteries, including longer plaques from the CCAs (see also the eversion technique)

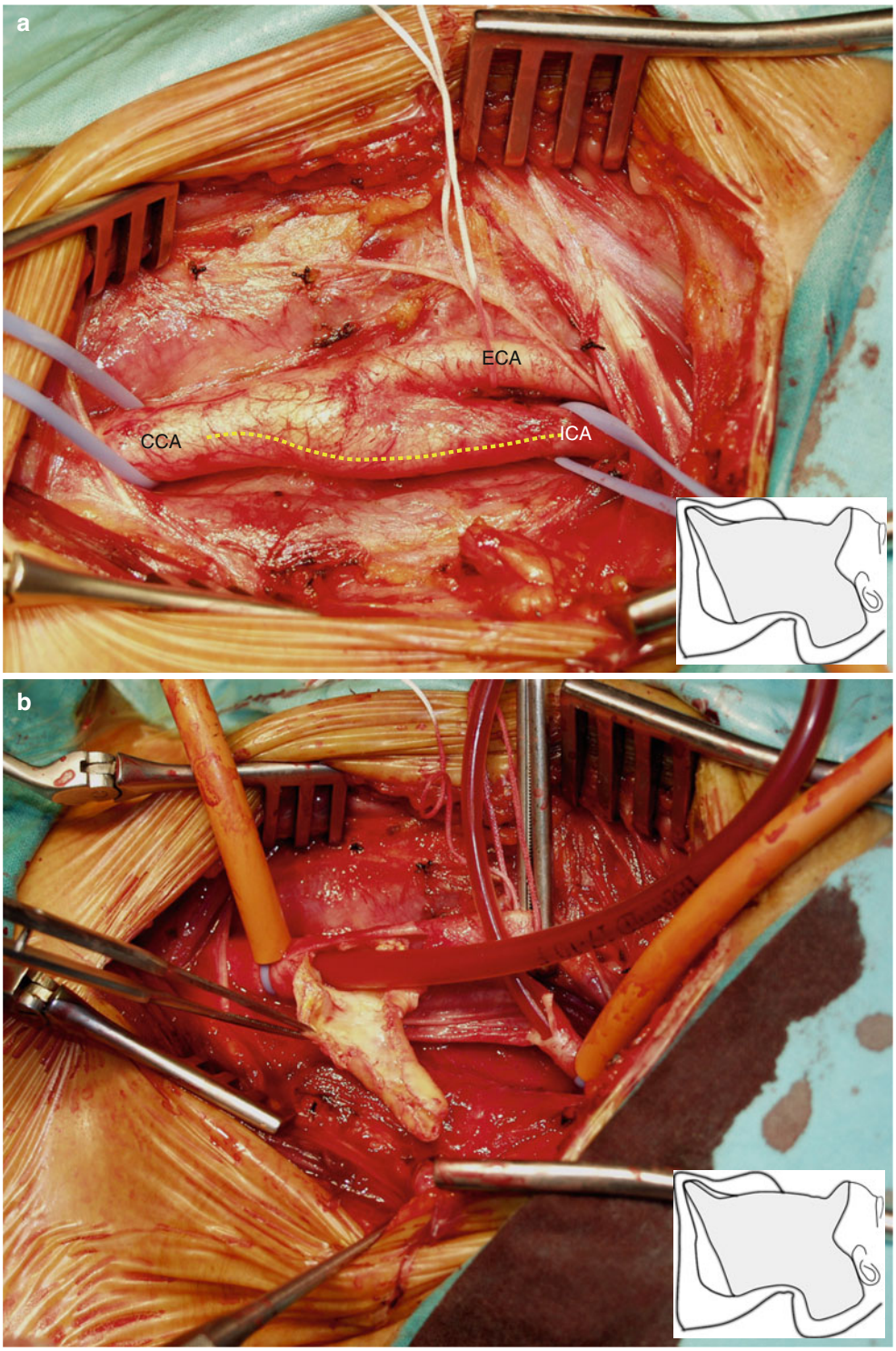


Fig. 11.5 CEA and direct closure of the arteriotomy. Panel (**a**): preparation of the carotid bifurcation. Note the placement of the arteriotomy, at the level of the posterior and lateral portion of the CCA and ICA, avoiding the nerves of the carotid sinus and glomus. Panel (**b**): excision of the carotid plaque, in a patient in whom shunting was deployed. Note the volume of the plaque and the aspect of the remaining carotid wall. Panel (**c**): operation completed. The image on the left demonstrates a carotid bifurcation after direct closure of the arteriotomy. Compare with the shape of the *neo-bifurcation* obtained with patching (*on the right side*)

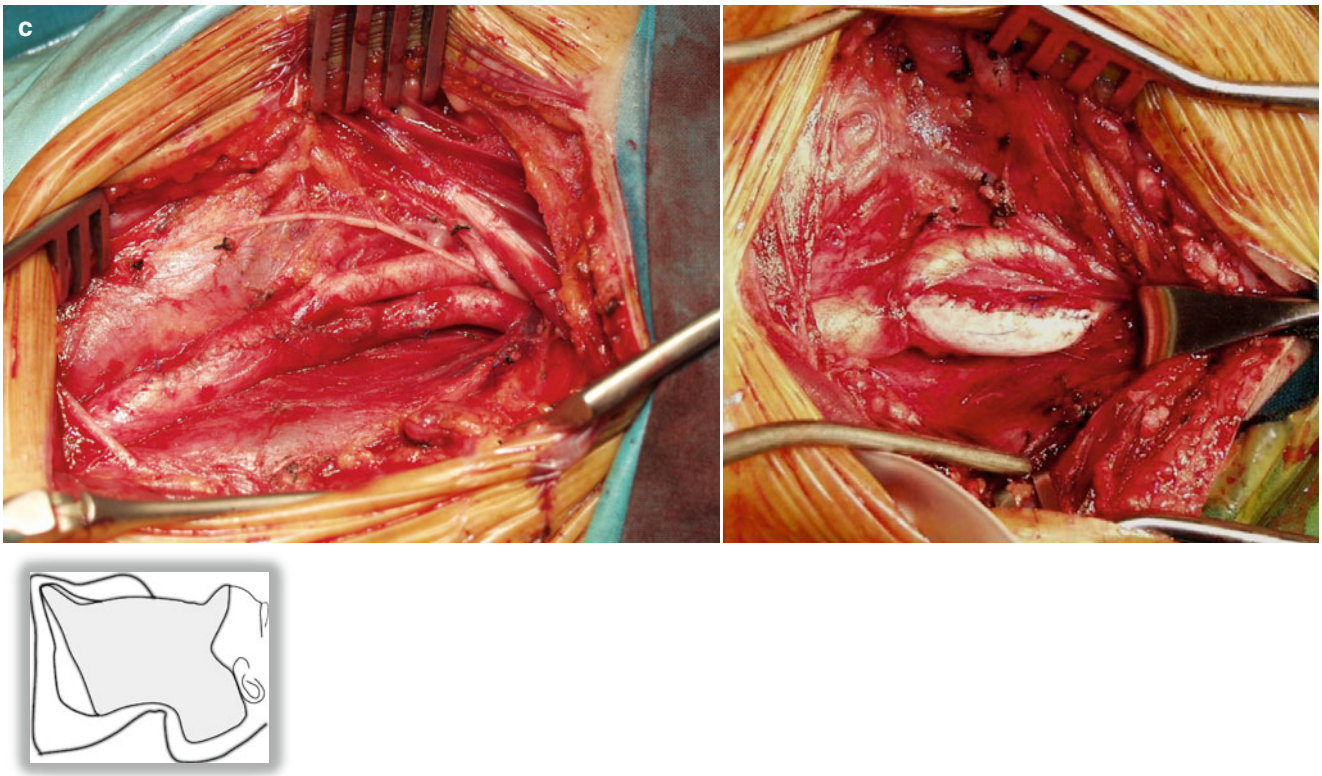


Fig. 11.5 (continued)

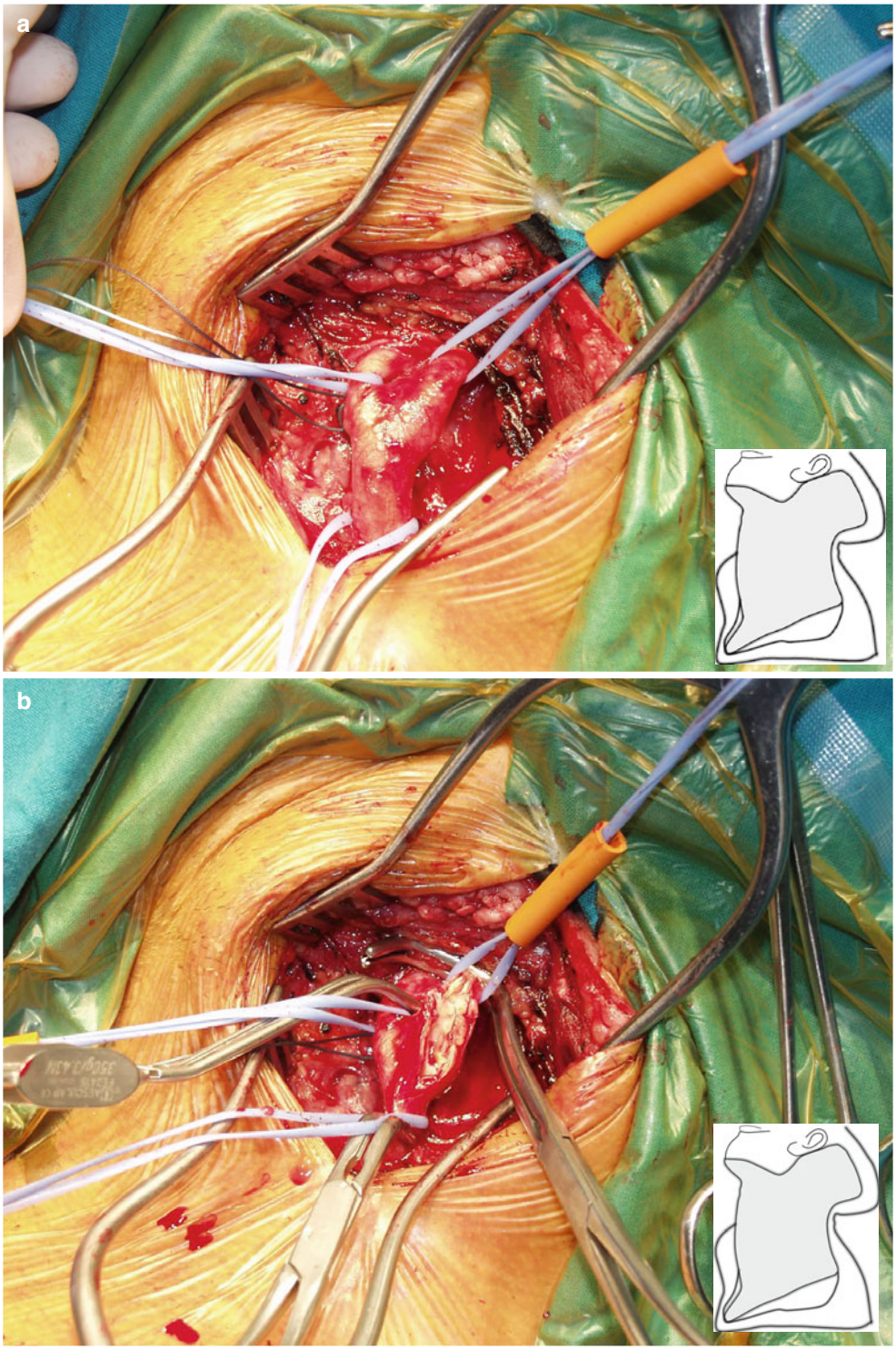
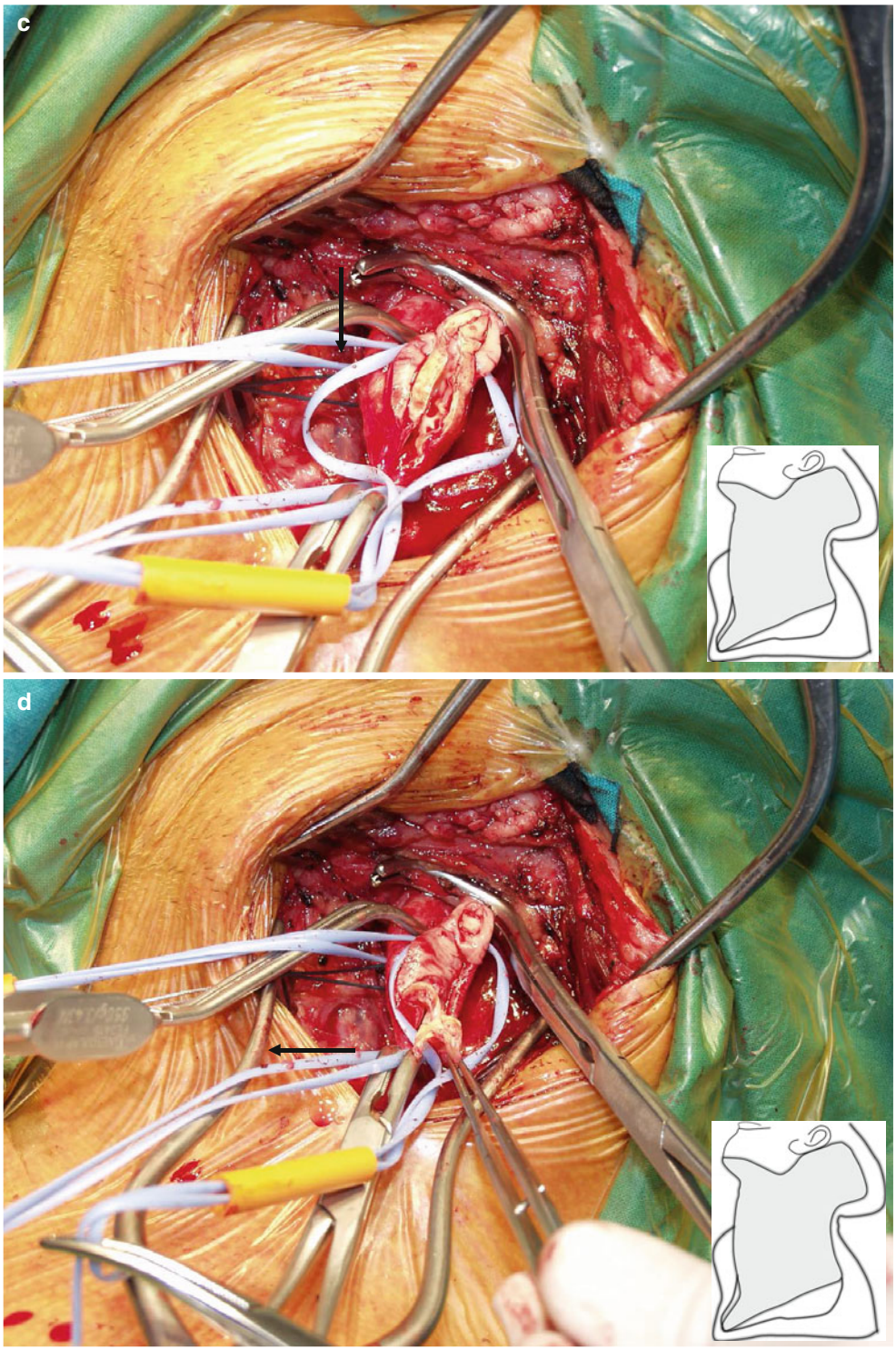


Fig. 11.6 Carotid CEA and patch closure. The main steps of the operation are presented. Panel (**a**): preparation of the carotid bifurcation. Panel (**b**): arteriotomy and identification of the plaque and of the cleavage plane between the plaque and the remaining arterial wall. Panel (**c**): removal of the plaque. Panel (**d**): after plaque removal, note that the remaining arterial interior surface might not result smooth all around, especially when there is no definite cleavage plane around the plaque. Note also that in the distal portion, the end artery over the ICA appears thicker than the rest. We secure the ICA end artery with separate stitches, in order to avoid intimal flaps. Panel (**e**): insertion of the patch, starting from the distal portion. In this way, the most important segment of patch closure will be inspected and any remaining or possible flaps are resecured. The entrance into the ICA can be also well calibrated. In cases with a slender ICA, a curved patch might be more indicated. This can be obtained from a vascular graft, properly tailored. Panel (**f**): operation completed. Note the more natural shape of the carotid bifurcation after patching, as compared with direct closure. Panel (**g**): alternatively, CEA of the origin of the ECA can be additionally performed and a bifurcated patch can be inserted



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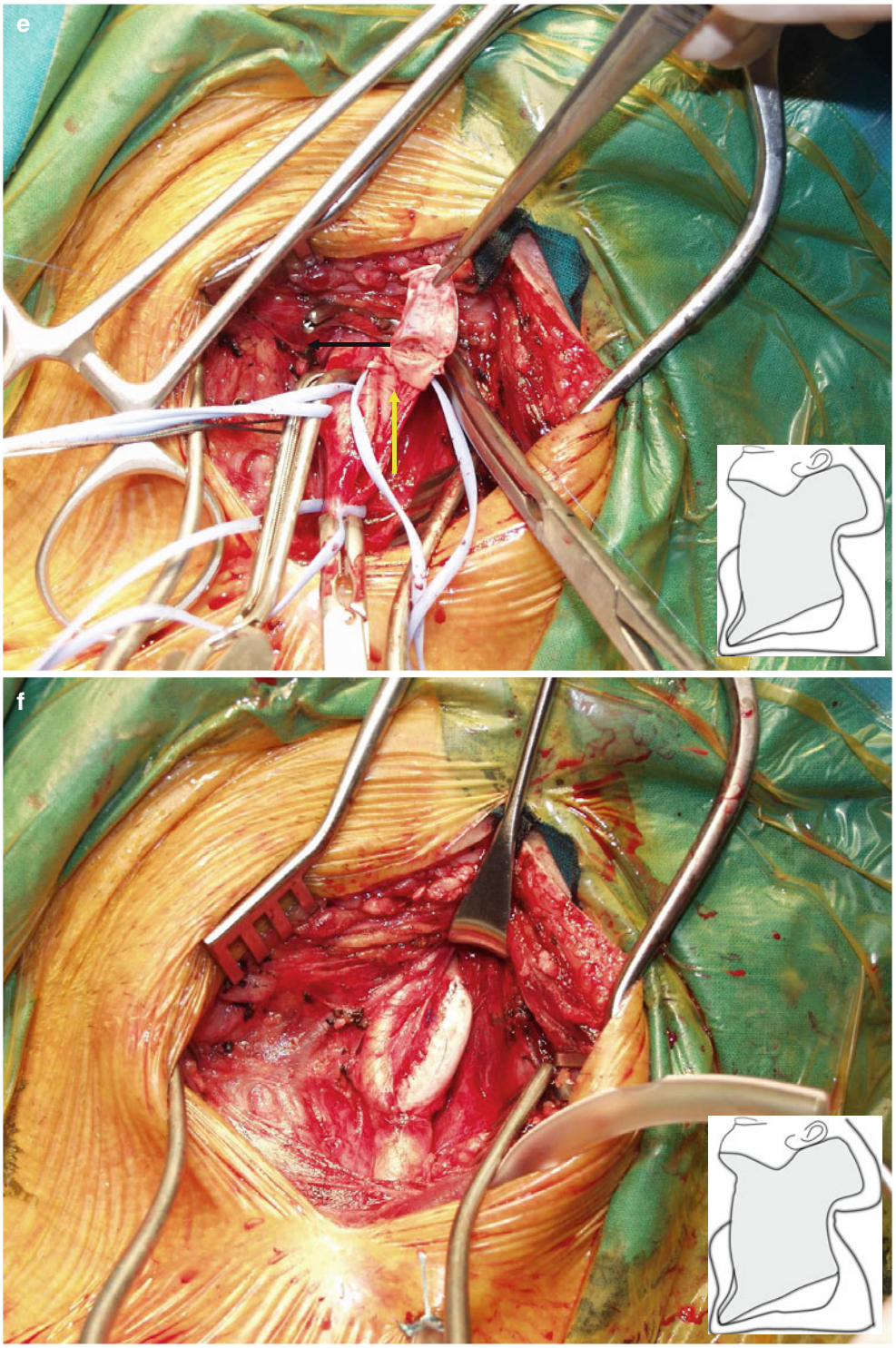

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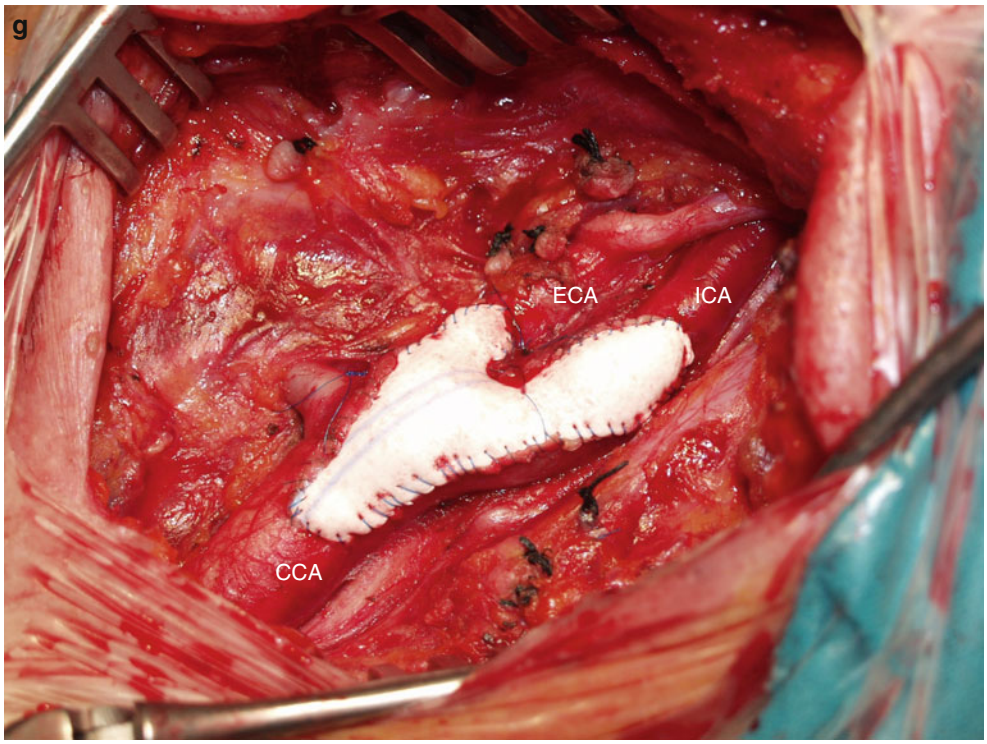


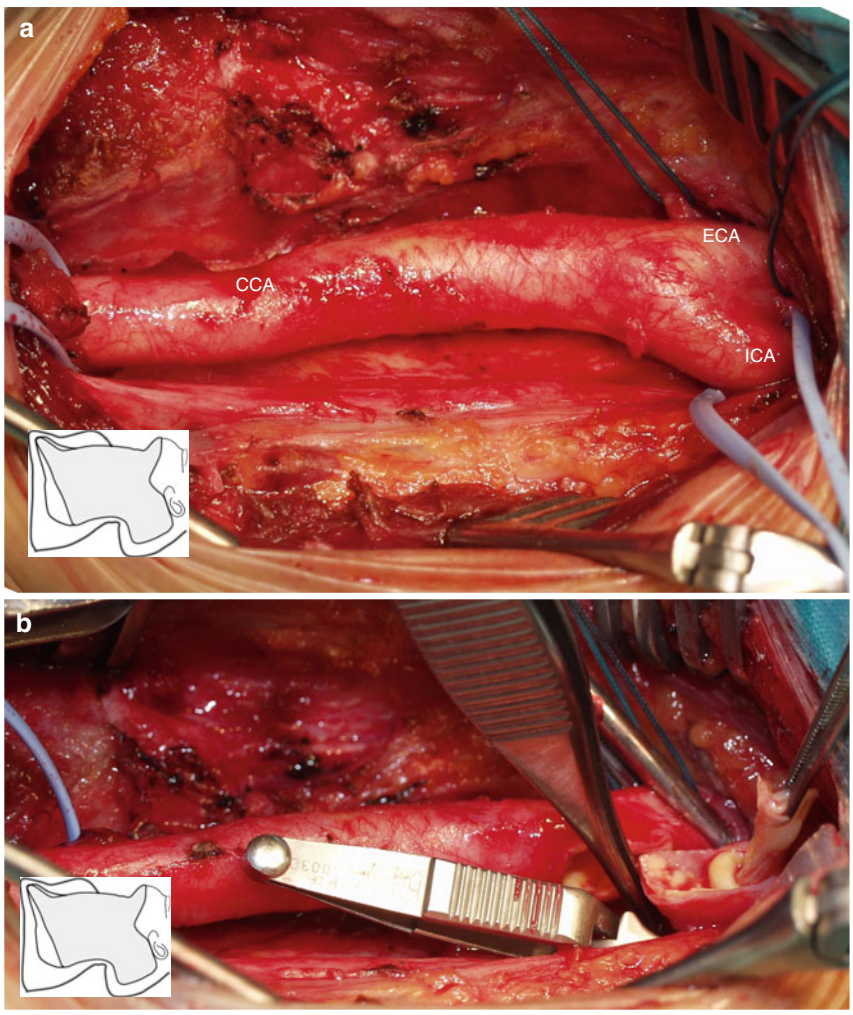
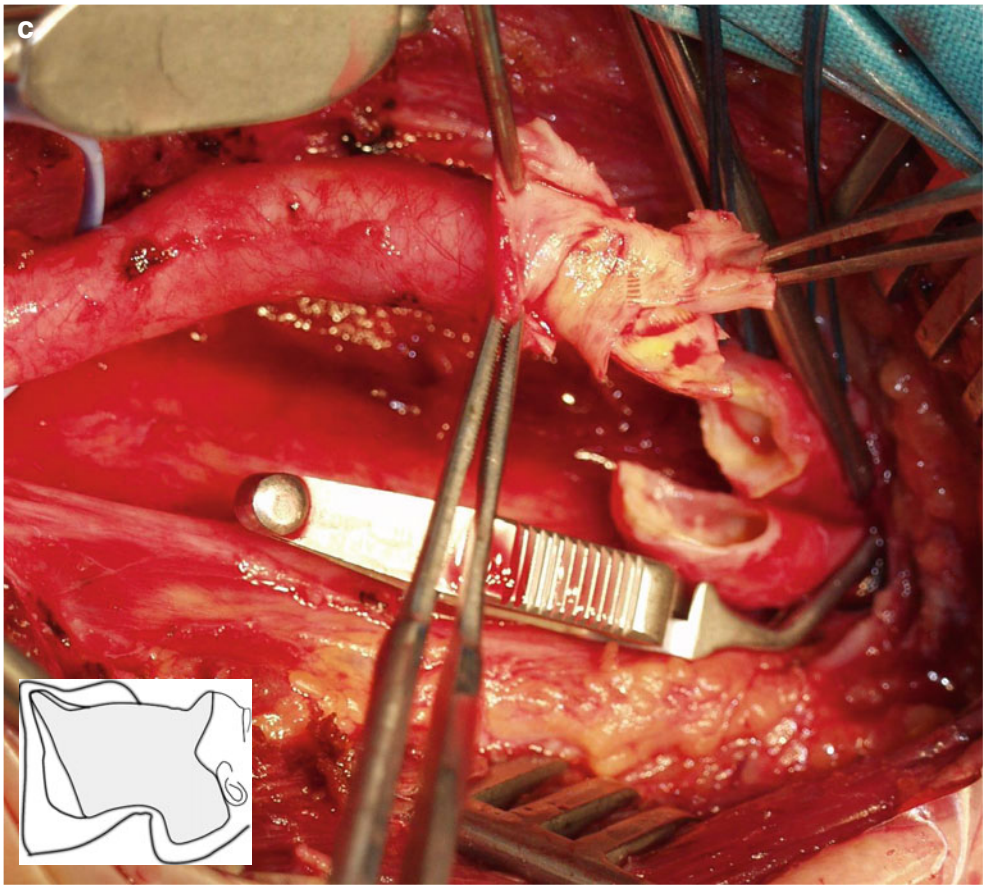
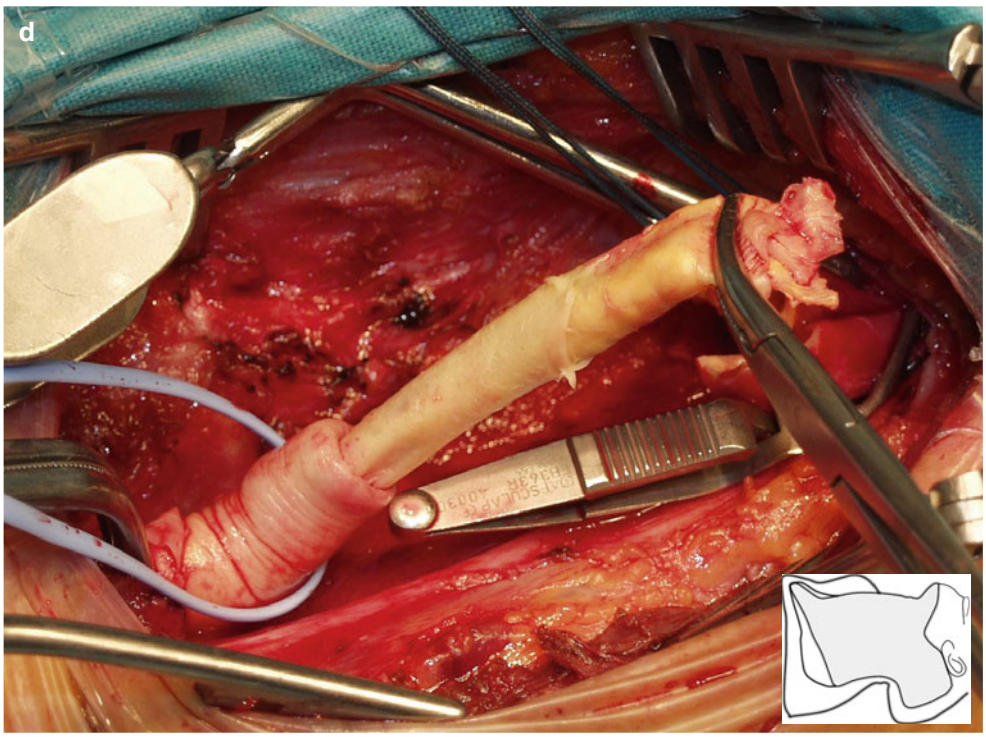


Fig. 11.7 Eversion technique. Panel (**a**): the carotid bifurcation (and a longer segment of the CCA in this particular case) is prepared. Panel (**b**): the ICA and ECA are disconnected from the CCA. The plaque on the ICA is identified and pulled out, while the remaining arterial wall is being everted. Panel (**c**): the same is applied in this case, to the plaque occupying most of the cervical portion of the CCA. Panel (**d**): a longer plaque from the CCA is pulled out, while the CCA is everted. Panel (**e**): the ICA and the ECA are reanastomosed to the CCA. In cases in which the reanastomosis might appear stenotic or when a larger portion of the anterior wall appears deficient, a patch can be also inserted. Panel (**f**): reanastomosis completed

Fig. 11.7 (continued)





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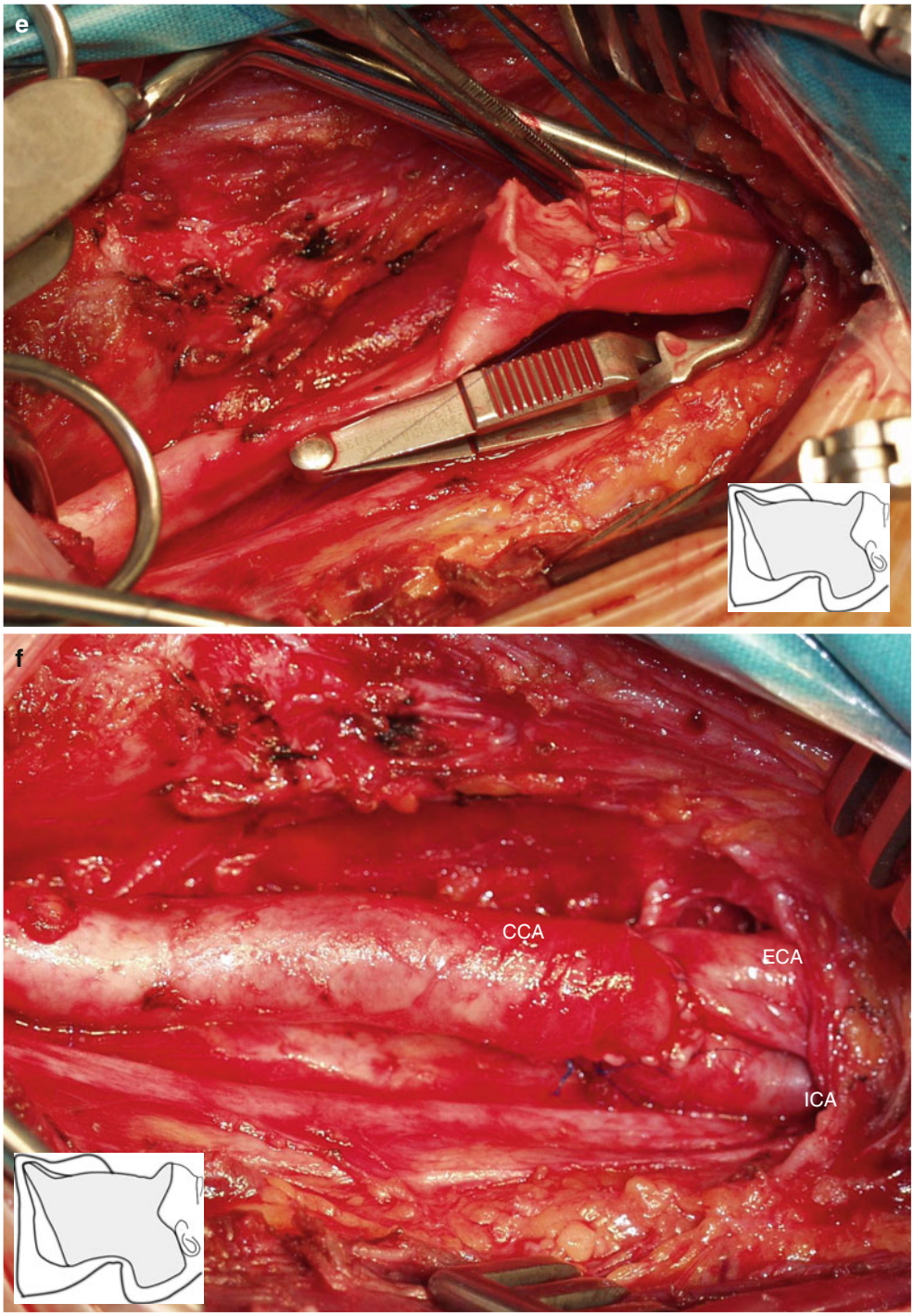

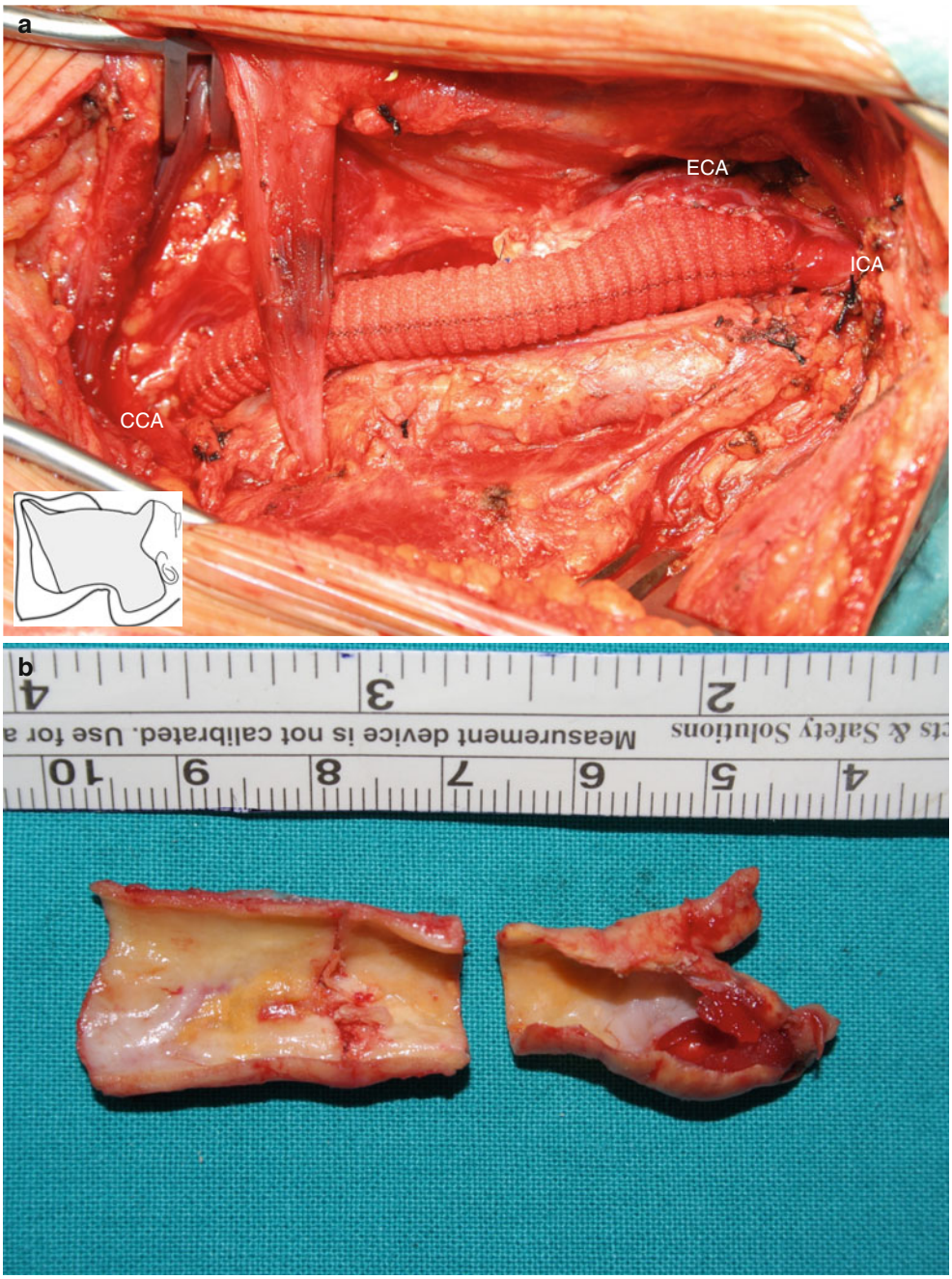

Fig. 11.8 Carotid endarterectomy, resection of the CCA, and bypass. In particular cases, the CCA appears severely diseased, either with stenotic or with ulcerated plaques. A longer endarterectomy can also be performed over the CCA, but the remaining arterial wall might appear to be rough and potentially thrombogenic. In such cases, we recommend the resection of the segment of the CCA and replacement with a vascular graft. Whenever the origin of the ICA is not too slender and the arterial wall not too thin, the direct anastomosis of the prosthesis to the carotid bifurcation (Panel **a**) can be safely performed (the distal anastomosis in performed first). The interior aspect of the plaque in the CCA is presented in Panel (**b**). Alternatively, CEA can be followed by the insertion of a patch ant the vascular graft is anastomosed to the already-enlarged carotid bifurcation (Fig. 11.9)

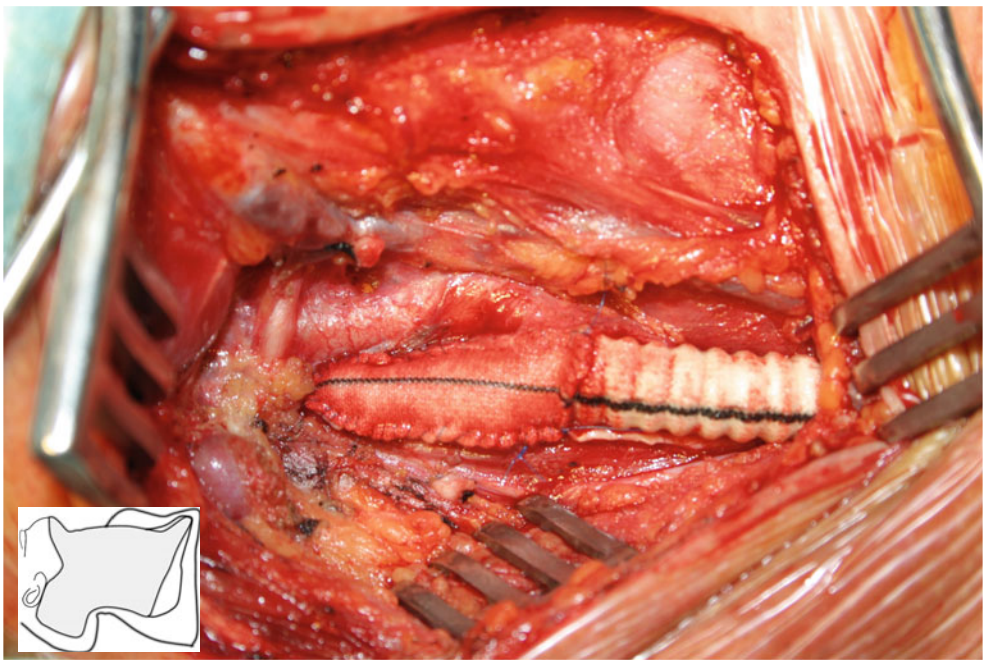

Fig. 11.9 Combined technique: patch plus bypass. This is applied whenever the ICA is of a thinner texture or the diameter is reduced. The patch allows for a safer anastomosis of the graft. The communication between the ICA and the ECA can be declamped before completing the anastomosis with the distal part of the graft and before performing the proximal anastomosis on the more proximal CCA

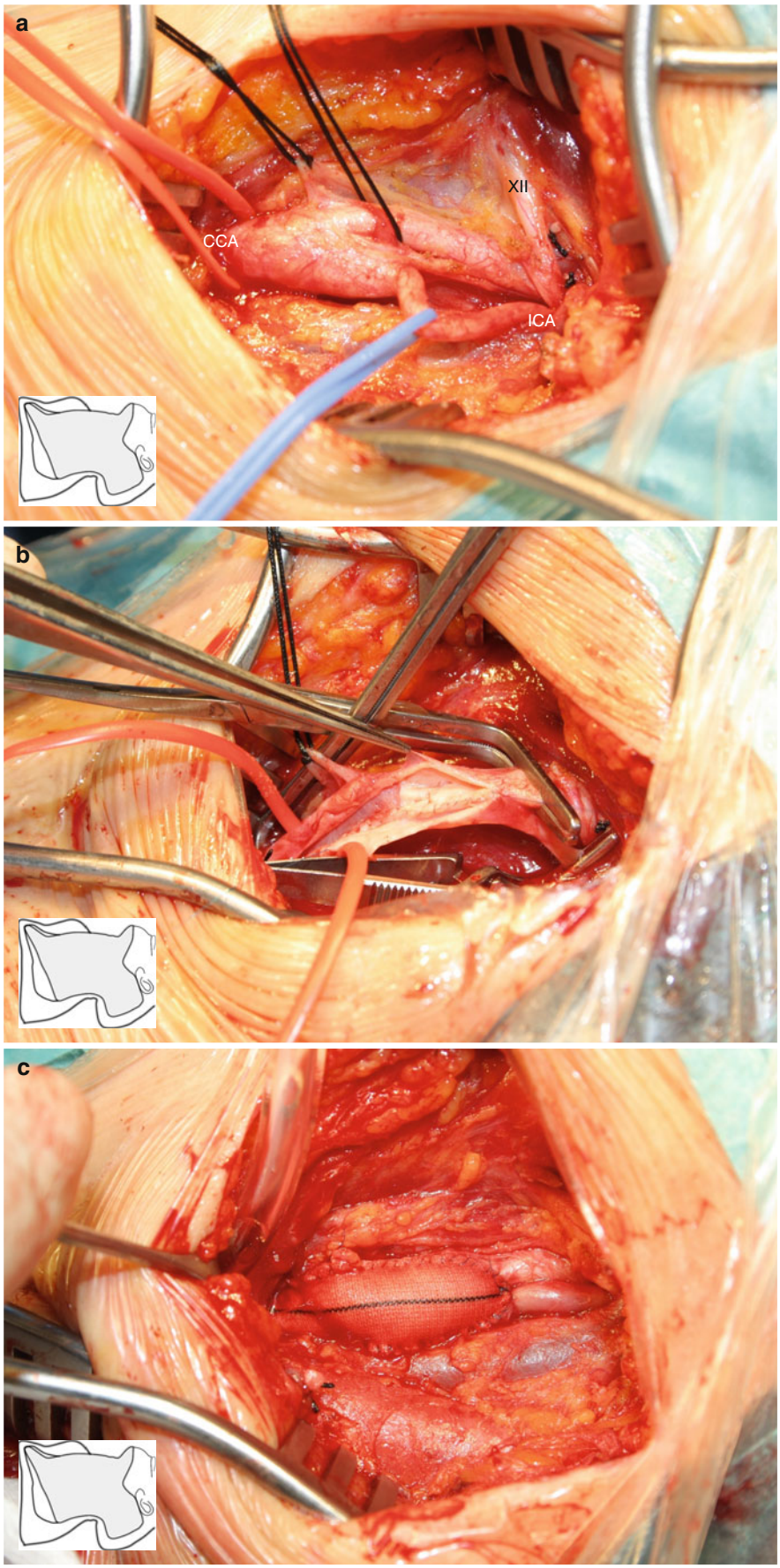

Fig. 11.10 Endarterectomy and "ascent" of the carotid bifurcation. Panel (**a**): intraoperative aspect of a carotid bifurcation with kinking and moderate hypoplasia of the ICA. Note the excess length of the cervical ICA. Panel (**b**): after performing the CEA, the excess of the ICA is trimmed, and the ICA is reanastomosed to the ECA and CCA (as in the regular eversion technique). Part of the ECA is used to enlarge the entrance into the ICA; in this way, the new carotid bifurcation will appear as "ascending." Panel (**c**): the remaining anterior portion of the carotid bifurcation is completed by inserting a synthetic patch

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Vertebral Artery Revascularization

12

Horia Muresian

The vertebrobasilar arterial system represents an important inflow to the brain regarding not only the vascularization of vital regions and centers but also the extent of the territory of vascularization. It is worthwhile noticing that about 20 % of the ischemic events in the brain occur in the vertebrobasilar system. The clinical picture is multifaceted and protean and many times overlooked in the context of concomitant carotid artery stenosis. Not least, less attention is given to the vertebrobasilar system as many physicians still consider that the symptoms in the posterior circulation will amend after correction of the carotid lesion(s). Ischemia in the vertebrobasilar system is caused mainly by occlusive disease or dissection of the vertebral artery (VA), basilar artery (BA), and posterior cerebral artery (PCA) and by cardioembolism or artery-to-artery embolism (from aorta or VA). Particular conditions are represented by dolichoectasia (dilatative arteriopathy) and the subclavian steal syndrome (vertebral steal). Dolichoectasia comprises arterial elongation, widening, and tortuosity [1, 2] eventually leading to brain ischemia, compression of the cranial nerves, and arterial rupture and hemorrhage. The subclavian/vertebral steal syndrome is a cause of intermittent brain ischemia accompanied by signs of superior limb ischemia in case of severe stenosis or occlusion of the subclavian artery or of the brachiocephalic trunk (BCT). It is interesting to note the fact that vertebral steal can occur even if the V0 and V1 segments are occluded, through developed collaterals between the V3 and SCA or ECA.

The anatomy of the vertebrobasilar system is presented in Chap. 1. The clinical manifestations of vertebrobasilar ischemia (including TIAs in the posterior circulation) were presented before in Chap. 2.

In this chapter, the revascularization of the extracranial arteries pertaining to the vertebrobasilar system is presented, comprising mainly the VA and, additionally, the SCA and BCT.

H. Muresian
Cardiovascular Surgery Department,
The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

The greater part of atherosclerotic lesions of the VA involve its origin (V0) and extraosseous segment (V1). Not infrequently, plaques originate from the SCA and extend into the origin of the VA. Besides limited lesions, some VAs may depict more extensive lesions of almost the entire V1 segment, making thus difficult or precluding reimplantation of the VA into the CCA. In our experience, we do not routinely reimplant the VA into the SCA, due to numerous facts: the SCA usually present extensive atherosclerotic lesions; the wall of the SCA is thinner than that of the CCA and more prone to rupture; and the length of available VA must be more extensive for reimplantation into the SCA than for reimplantation into the CCA (the VA needs to be repositioned more distally on the SCA).

Reimplantation of the VA into the CCA (Fig. 12.1) This is the easiest and more frequently applied technique if the anatomy and the localization of the atherosclerotic plaque allow. The surgical approach is through a supraclavicular incision as described in Chap. 4. The anterior scalene muscle is divided. The CCA is dissected and mobilized posterior to the IJV. The quality of the wall of the CCA must be readily assessed. It is important to evaluate the extent of the plaque into the VA after completely dissecting the VA from origin to the transverse process of C_6. The distance between the CCA and the VA must be also estimated, and the future site of reimplantation on the CCA must be marked with a delicate stitch. The position of the VA must be also marked, in order to avoid torsion upon reimplantation. The same neuromonitoring applies as with carotid surgery. After giving heparin (low dose of UFH, 2500 UI i.v. bolus), the VA is clamped first for about 3 min. If no neurological signs (in the awake patient) or alteration of cerebral perfusion is noticed, the VA can be safely disconnected from the SCA (in few cases, we had to insert a temporary shunt from the distal SCA into the VA). The VA is ligated a few millimeters from its origin, and an additional suture is inserted to secure the proximal stump. The VA is temporarily declamped in order to appreciate the retro-

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grade flow and for purging any atheromatous debris. An oblique anastomotic embouchement is created to facilitate reimplantation into the CCA. Preparation of the VA usually takes place while clamping the CCA; thus, tolerance to clamping is evaluated. Clamping of the CCA is generally well tolerated. Adventitia is peeled off at the site of anastomosis (previously marked), and an anastomotic orifice is created with the aid of a vascular punch of 4–4.5 mm. The VA is anastomosed in such a way as to resemble a natural branch of the CCA (the resultant angle of about 60° is facing upward). Note that the anastomotic site lies on the posterior and lateral side of the CCA. The vascular clamps will facilitate the temporary rotation of the CCA, until completion of the anastomosis. Just before closing the anastomosis, the VA is declamped first and reclamped after a few seconds. The CCA is temporarily declamped distal and proximal. The anastomosis is closed. The CCA is declamped proximally, while distally it still remains clamped. A fine needle is inserted into the CCA just under the distal clamp for additional de-airing. The distal CCA clamp is removed while still keeping the needle for 1–2 min in site. The last to be declamped is the VA. It is important to check thoroughly the anastomosis and the VA stump.

With more lengthy plaques on the VA, the opening of the bony canal is indicated to obtain an additional segment of the VA (Fig. 12.2). The transverse process of C_6 can be easily torn with the aid of a rongeur but with the precaution of not leaving in place any bony spicule. Particular attention is needed to protect the nervous trunk of C_6. Numerous venous tributaries will easily bleed and require a good hemostasis. If more extensive lesions involve the V2 segment of the VA, we advocate performing a revascularization of the V3 segment and not to open more cranially the bony canal: this latter procedure is more time consuming, while the anastomosis will be more difficult to perform above the level of C_6.

Reimplantation of the VA into the SCA As stated before, this technique is seldom used in our center, due to the quality of the SCA wall (as compared with that of the CCA). In cases with more suitable SCA wall and when the distance between the CCA and the VA appears greater than usual, the reimplantation of the VA into the SCA can be performed (Fig. 12.3).

CCA-to-VA Bypass In cases when the VA cannot be mobilized enough or there is no sufficient length for a safe reimplantation into the CCA, a bypass can be performed between the two arteries, using autologous vein or a vascular prosthesis (generally, a PTFE graft). The distal anastomosis on the VA is performed first with the same precautions to avoid rotation of the vessels. In complex procedures with aorta-to-carotid bifurcation bypass, the VA can be safely reimplanted into the graft (the neo-CCA). The V1 segment can be also endarterectomized and prepared for bypass or reimplantation (Fig. 12.4).

Indirect VA revascularization is achievable with SCA or BCT revascularization (see Chap. 14).

Revascularization of the V3 segment of the VA (Fig. 12.5) must be considered in many more instances as revealed by the elegant studies of Berguer and Kieffer [3, 4]. Various techniques are available [5]: bypass to the V3 (usually from the carotid bifurcation), transposition of the ECA, transposition of the occipital artery, and transposition of the V3 into the ICA. In our experience, patients required concomitant carotid surgery, and the VA was bypassed from the carotid bifurcation using autologous vein. We describe below the technique we apply. The carotid bifurcation and the V3 segment of the VA are approached through a single cervical incision starting anterolateral at the level of the thyroid cartilage and extending posterior over the SCM and under the mastoid process at about 1 cm (as described in Chap. 4). After partially dividing the SCM and the prevertebral musculature, the distance between the carotid bifurcation and the V3 appears reduced. The loop between C_1 and C_2 will allow exposure of about 2 cm of the VA. When the entire V2 segment is diseased, only a distal bulldog clamp on the VA will suffice. The distal anastomosis on V3 is performed first. The proximal end of the graft is anastomosed on the carotid bifurcation. If lesions are present at this level, the CEA is also indicated, and the proximal end of the graft will serve as patch for the carotid bifurcation too.

Image Gallery

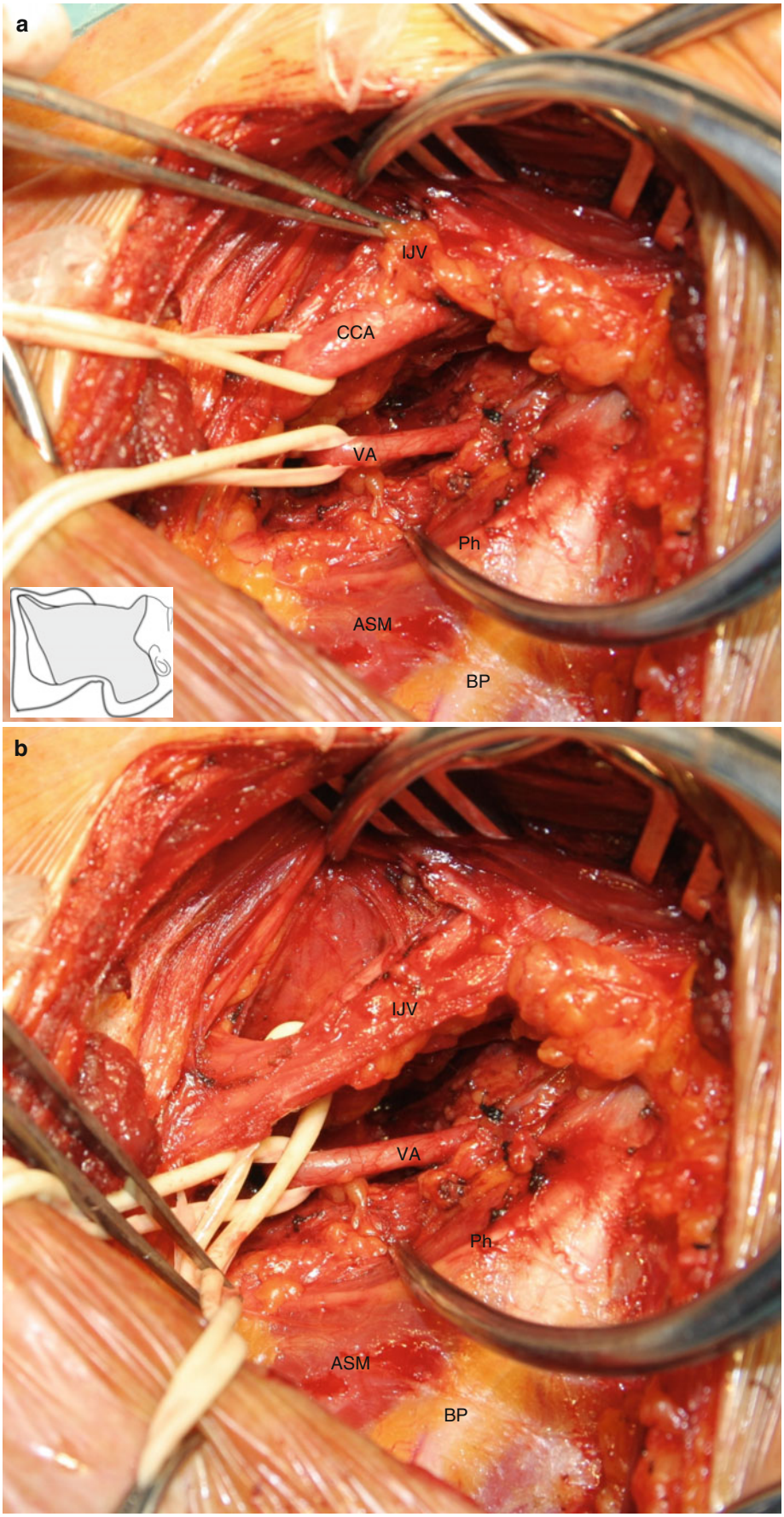


Fig. 12.1 Reimplantation of the VA into the CCA. Panel (**a**) supraclavicular approach to the CCA and VA at origin (V0–V1). The VA is exposed between the CCA and the IJV (the latter is retracted anteriorly). The CCA is mobilized. Note the close relationship between the VA and the CCA. *ASM* anterior scalene muscle, *Ph* phrenic nerve, *BP* brachial plexus. Panel (**b**) the CCA is positioned underneath the IJV, and the VA is also gently mobilized in order to choose the proper point of reimplantation into the CCA. The arteries are additionally inspected and palpated for any lesions or parietal modifications that would otherwise contraindicate reimplantation. Panel (**c**) reimplantation completed. Note the smooth angle of the reimplanted VA, resembling a natural collateral of the CCA. At right: angiographic aspect of the reimplanted VA

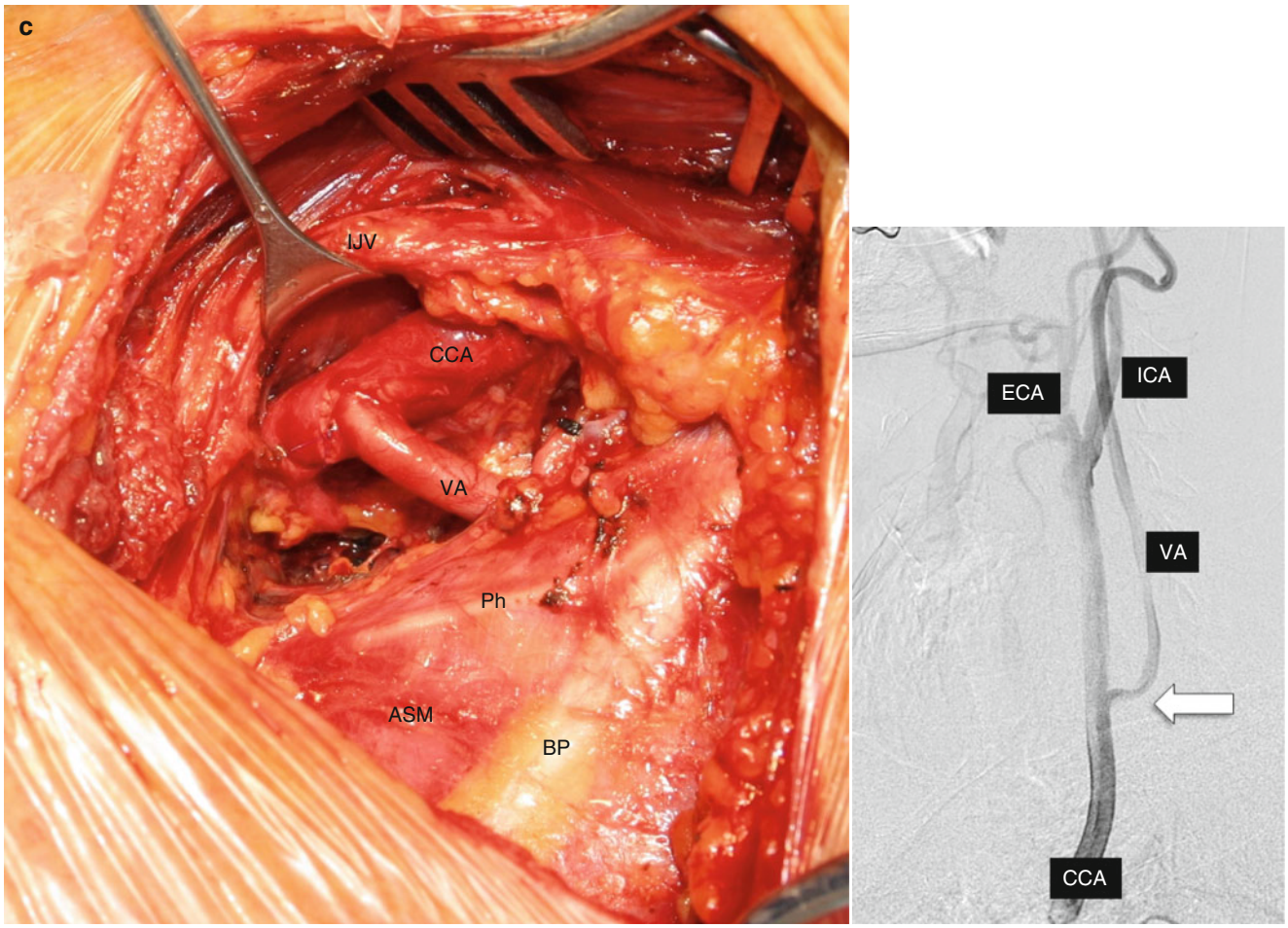


Fig. 12.1 (continued)

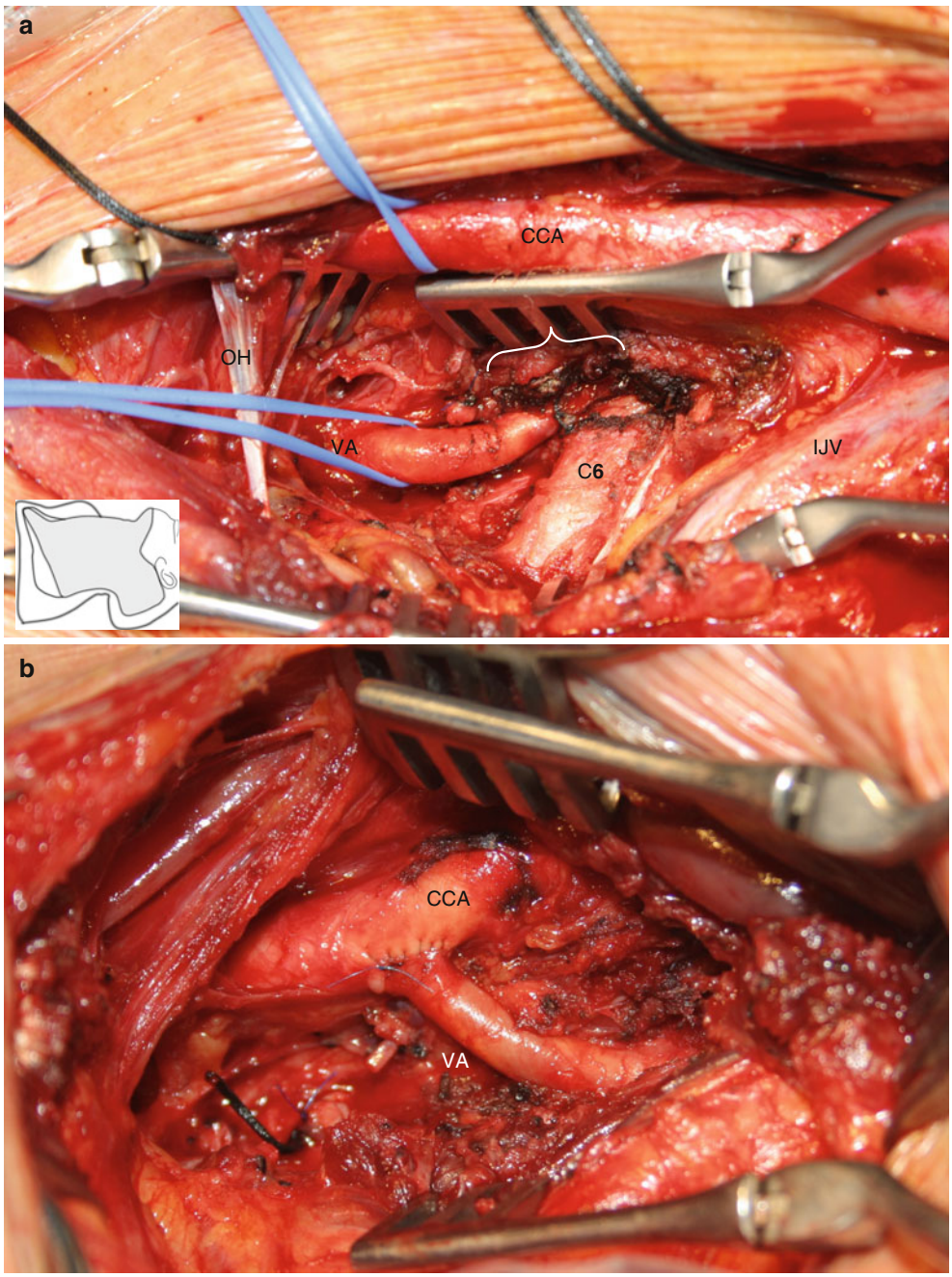
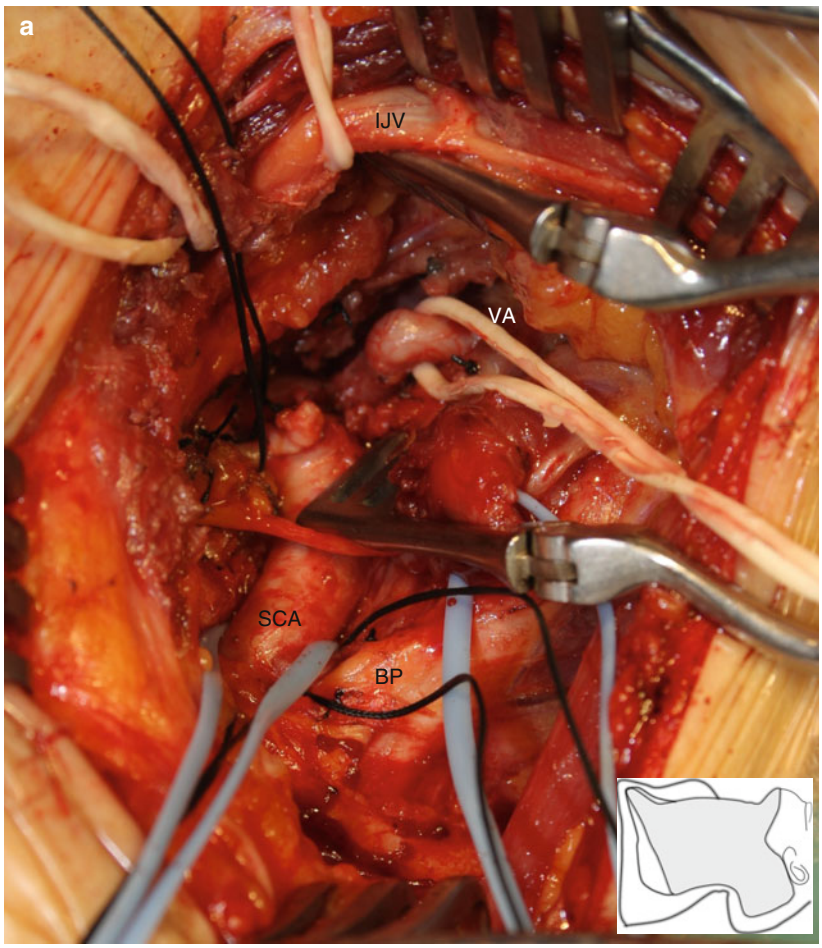


Fig. 12.2 Opening of the bony canal at C6. Panel (**a**) whenever the length of the VA is insufficient or when the V1 segment presents extensive atherosclerotic lesions, a partial exposure in the bony canal of the VA is mandatory. Note the extralength obtained within the bony canal. The trunk of C6 cervical nerve must be protected. Panel (**b**) intraoperative aspect of the reimplanted VA. Note that even in this case, a smooth curve of the VA is obtained



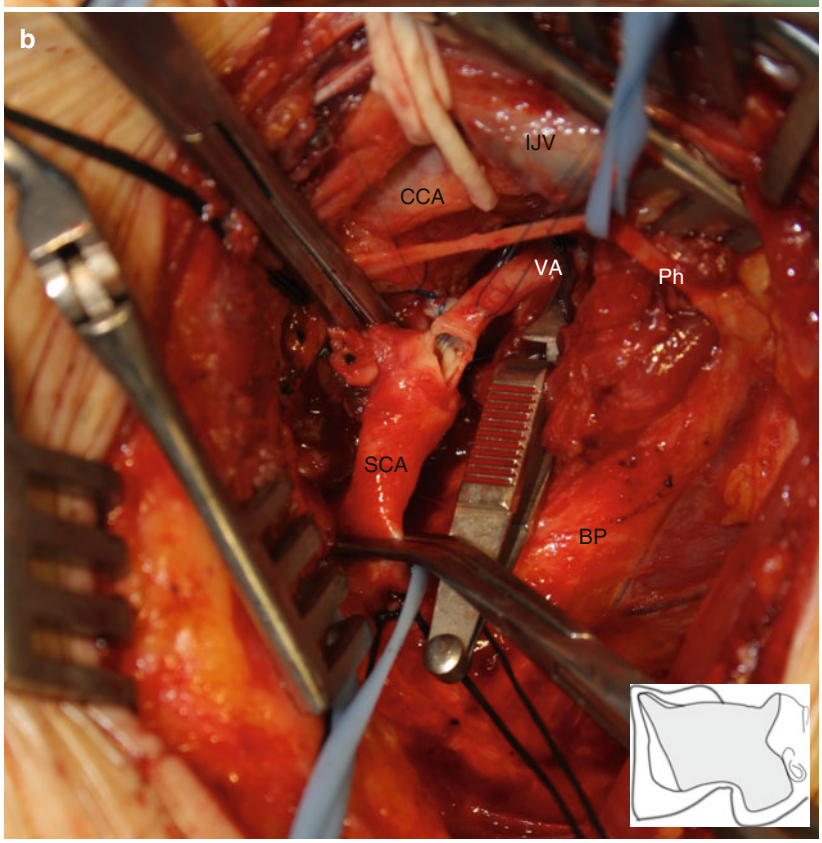
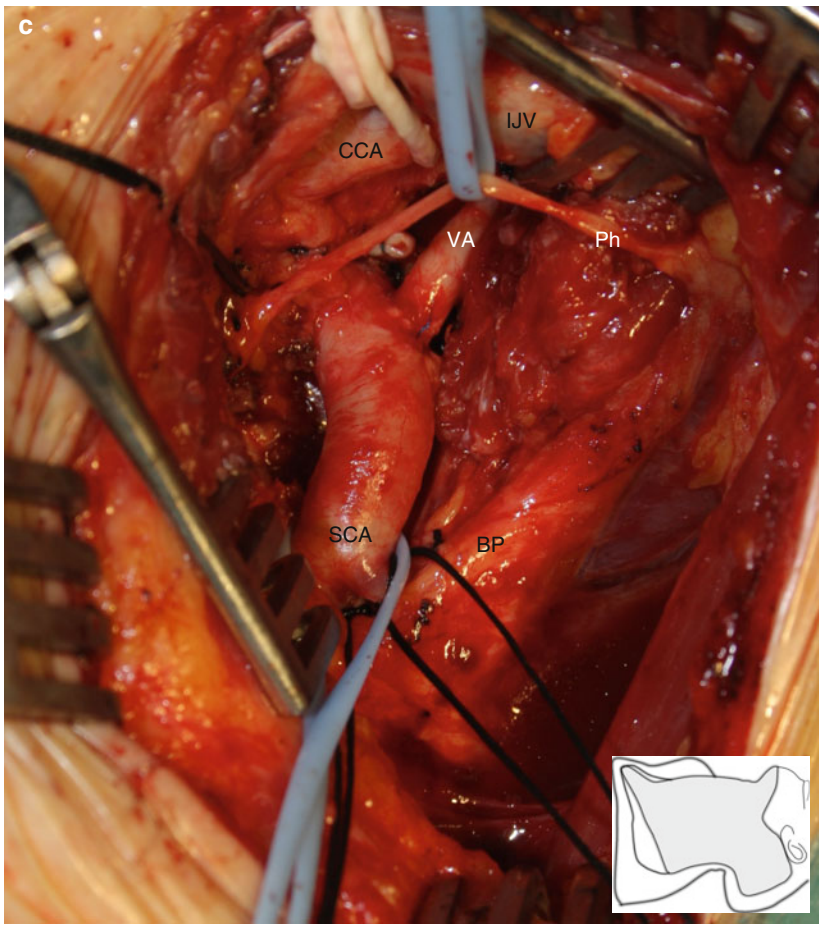


Fig. 12.3 VA reimplantation into the SCA. Rarely performed, the reimplantation into the SCA depends more on the quality of the SCA wall. Panel (**a**) surgical approach through a supraclavicular incision. If necessary, some of the collaterals of the SCA must be divided in order to mobilize the artery. *BP* brachial plexus, *Ph* phrenic nerve, *IJV* internal jugular vein. Panel (**b**) the anastomosis in an L-T fashion, usually performed with a continuous 8-0 Prolene suture. Panel (**c**) reimplantation into the SCA, completed. Note that in these cases, the anterior scalene muscle is divided, for a better exposure. The phrenic nerve is identified and protected

Fig. 12.3 (continued)



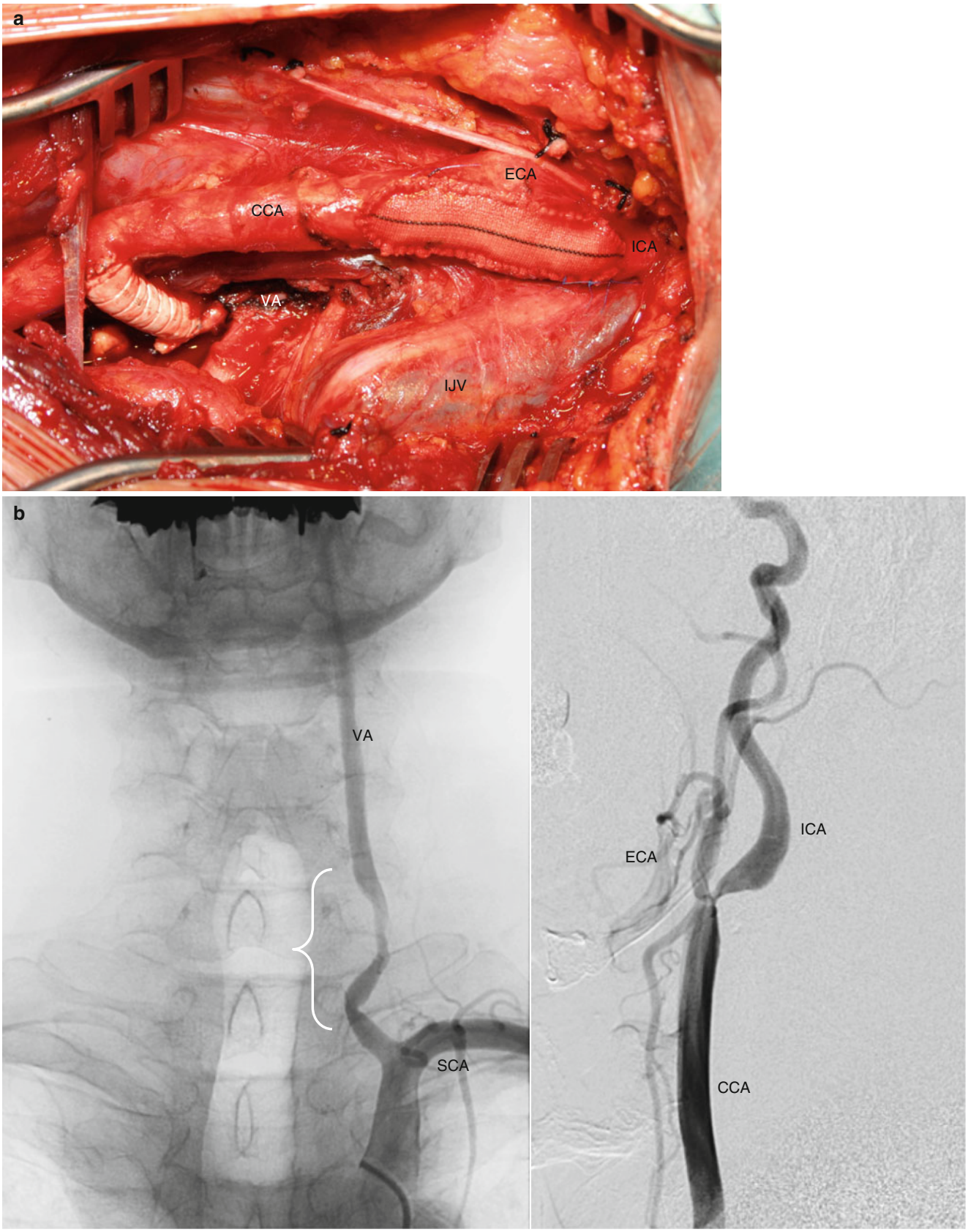


Fig. 12.4 CCA-to-VA bypass. Whenever the direct reimplantation is not possible, a bypass between the CCA and the VA is possible, using prosthetic or autologous venous grafts. Panel (**a**) CCA-to-VA bypass with a 6 mm PTFE graft. A CEA and patching was concomitantly performed. Panel (**b**) angiographic aspect of the same case, showing the severe stenosis at the level of the left carotid bifurcation and the extended lesion at the origin of the VA, the latter requiring endarterectomy of the VA almost to the level of C6. Consequently, the bony canal was opened and extralength was thus obtained. Panel (**c**) the excised plaques, from the VA and from the carotid bifurcation, as seen from the outside and after being sliced. Note the composition of the plaques and the degree of stenosis in both arteries

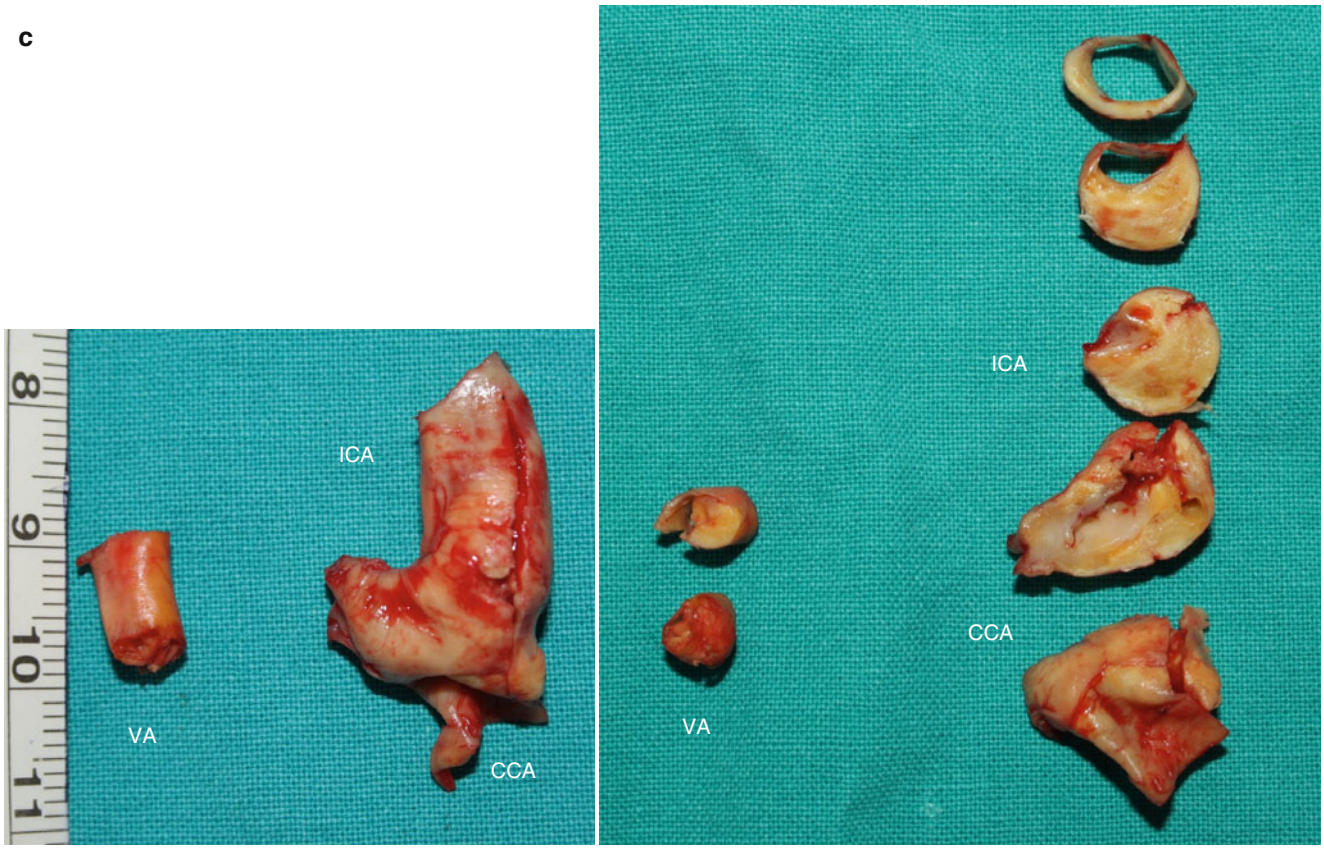


Fig. 12.4 (continued)

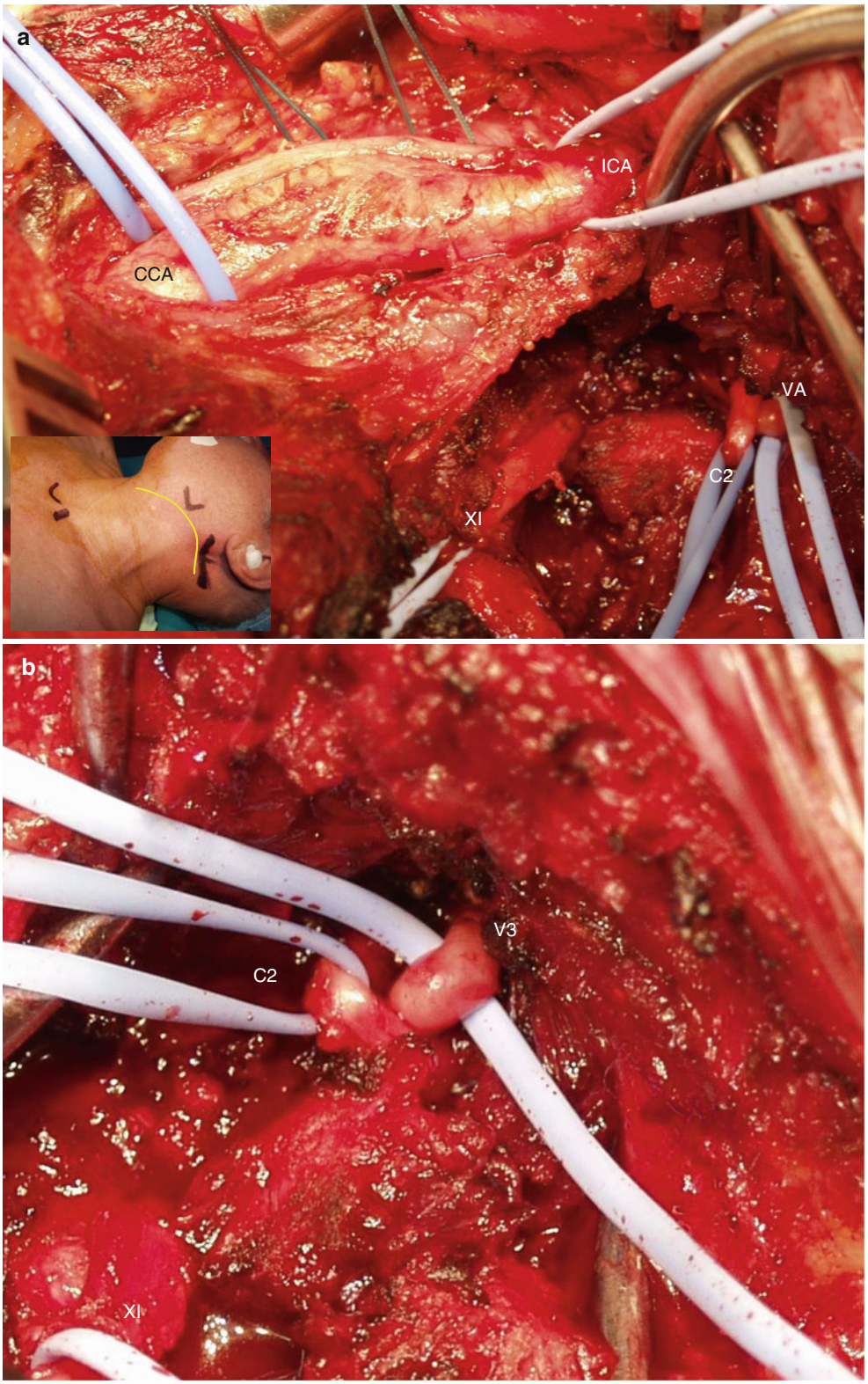


Fig. 12.5 Revascularization of the V3 segment of the VA. Panel (**a**) concomitant surgical exposure of the carotid bifurcation and of the V3 segment of the VA. Note the good landmark offered by the C2 nervous trunk. Panel (**b**) a close-up of the reciprocal relationship between the C2 nerve and the V3 segment. Panel (**c**) bypass completed, with a saphenous graft (*G*). The graft can be tunneled in either pre-jugular or retro-jugular position. A CEA and patching of the carotid bifurcation was also performed in this patient. The angiographic control shows the result obtained

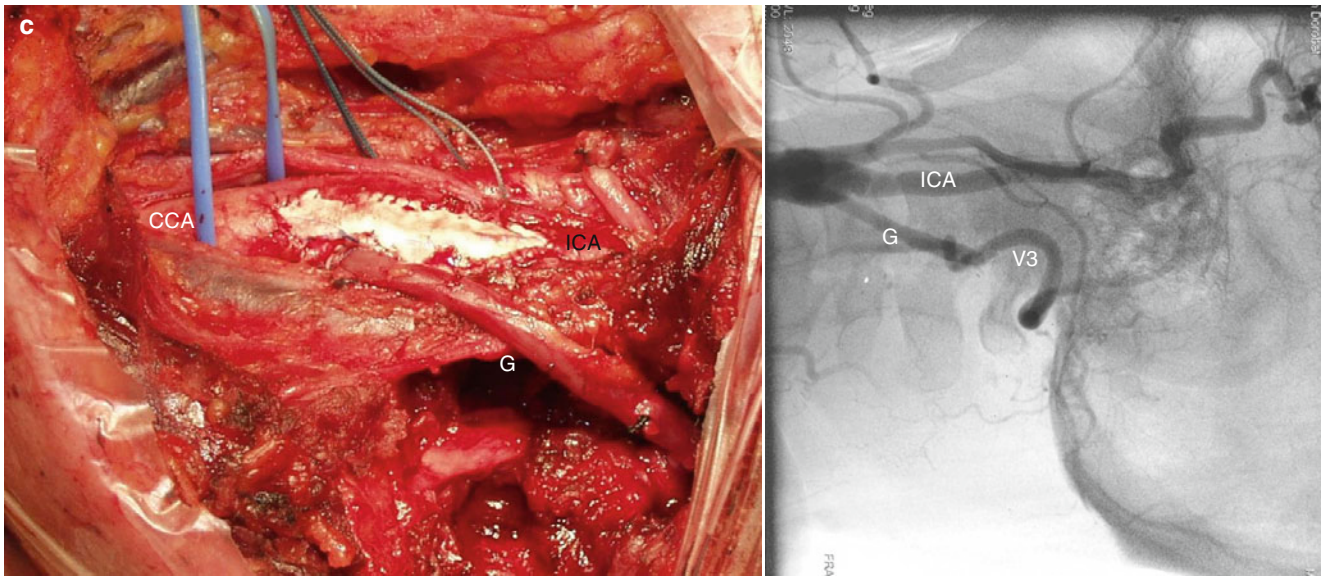


Fig. 12.5 (continued)

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Extensive Cerebrovascular Arterial Revascularization

13

Horia Muresian

Patients with extensive and severe stenotic/occlusive lesions in the superior aortic system represent an important category both regarding the challenging therapeutical strategy and planning and their increasing prevalence. Other important arterial beds are additionally affected in these patients: renal, inferior limbs, and coronary. Signs and symptoms pertaining to cerebral ischemia are frequently intricate, asking for a thorough clinical and diagnostic workup. Operative and anesthetic risk is globally increased, and no solution appears as ideal when weighing the hazard against the benefit while choosing between many more smaller-scale operations under more anesthetic acts (and leaving untreated lesions in place for variable periods of time) on one hand and a single more ample reconstruction, on the other. Not least, extensive revascularization in the cerebral territory may complicate with the cerebral hyperperfusion syndrome (CHS) [1], a severe condition with a grim prognosis. We present in this chapter our experience with cerebrovascular revascularization comprising more than one territory, in the same patient and in a single operative session.

13.1 Simultaneous Bilateral Carotid Endarterectomy

There is still much debate regarding the indications for the simultaneous treatment of bilateral carotid lesions, either by performing the simultaneous bilateral carotid endarterectomy (SBCE), the simultaneous carotid angioplasty and stenting (CAS), or the combined procedure carotid endarterectomy plus stenting (CEA + CAS). The main points to be taken into account are the real necessity of a concomitant treatment/the risk of leaving untreated one of the lesions (however severe and symptomatic) (Fig. 13.1) the risk of cerebral hyperperfusion syndrome and the risk of bilateral cranial nerve paralysis (especially the recurrent laryngeal nerves or the hypoglossal nerves), and these must be compared with the theoretical risk of a cerebral infarction while waiting for the second operation.

The pros for SBCE include the increased hazard from a double anesthetic and surgical procedure in generally higher-risk patients (however with a theoretical life expectancy of more than 5 years), the risk of acute intraplaque bleeding during and after the first CEA, the difficulty in obtaining the patient's acceptance for a second procedure, and the alleged lower incidence of cerebral complications after SBCE [2].

Against SBCE stand mainly the following: the higher possibility of developing cervical hematoma with more severe prognosis if bilateral/extended cervical hypesthesia after carrying out two (especially longitudinal) incisions, the risk of tongue ischemia (bilateral lingual artery interruption), the risk of bilateral cranial nerve lesion especially the recurrent laryngeal (bilateral vocal cord paralysis and suffocation), superior laryngeal (lower voice intensity and laryngeal fatigue), and hypoglossal (tongue paralysis and atrophy), and, not least, the cerebral hyperperfusion syndrome.

The main indications for performing SBCE are:

- Bilateral carotid stenosis >70 % and intraplaque hemorrhage
- Ipsilateral symptomatic stenosis >70 % plus contralateral asymptomatic stenosis >80 % and complicated plaque (ulcerated or hemorrhage)
- Bilateral asymptomatic stenosis >80 % plus bilateral plaque hemorrhage

H. Muresian
Cardiovascular Surgery Department,
The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

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- Bilateral asymptomatic stenosis plus the necessity of performing other major surgical procedures, such as coronary revascularization [3, 4]

Some precautions must however be borne in mind. The morphology of the CoW (and direction of flow) should be thoroughly assessed for the surgical planning (which side to treat first, how to better estimate the effect of clamping, and so forth). The presence of concomitant disease in the vertebrobasilar system (Fig. 13.2) raises other important particular questions, among which the necessity or benefit of performing the vertebral revascularization in the same operative session (in our experience, we had six patients in whom SBCE and VA reimplantation were performed during the same operation. The six patients had critical bilateral carotid stenosis and stenosis of the VA with occluded contralateral VA). The same applies to concomitant intracranial arterial disease, especially at the level of larger trunks where heterogeneity in blood distribution is expected after performing SBCE. The hemodynamic shifts during bilateral carotid revascularization are important factors to be taken into account. The patient is initially in a state of chronic cerebral hypoperfusion. In spite of the preventive measures instituted by the anesthesia team, the patient will experience a further diminution of cerebral perfusion during carotid clamping. Clamping of the ICA is usually well tolerated in patients with unilateral high-degree stenosis but evidently less in patients with bilateral high-degree stenosis (a situation similar to unilateral carotid stenosis but with contralateral occlusion. However, in these cases, collateral compensatory circulation develops over a longer period of time) [5]. Brisk blood flow on the treated side ensues accompanied by an abrupt perfusion discrepancy between the two sides of the brain. This discrepancy is further augmented during the clamping of the still untreated carotid bifurcation. Final declamping brings the restored blood flow to the entire brain.

SBCE represents a challenge for both the anesthesia/surgical team and the patient. Numerous hazards and complications may ensue and some in spite of the preventive measures. The most severe is the cerebral hyperperfusion syndrome (CHS). The reported incidence of the CHS is between 2 and 15 % of the cases. The favoring conditions are the disturbances of the cerebral microcirculation and the presence of multiple lacunar infarcts. The mortality rate is high, between 30 and 60 %. The patient at risk may be detected by transcranial Doppler examination, the acetazolamide test, and SPECT. As general precautions the morphology and function of the CoW must be assessed preoperatively. Intraoperative and postoperative treatment of hypertension and avoidance of hypertensive crises are strongly recommended. The CHS may manifest with acute focal edema (stroke-like presentation) as acute hemorrhage or delayed presentation (after 24 h) with seizures, focal motor weakness, and late intracerebral hemorrhage. It is worthwhile noticing the fact that CHS develops even after CAS, after stenting of the intracerebral arteries in the carotid or vertebrobasilar system [6].

The benefit of SBCE appears to be significant after a longer period of time (5 years) and not in the case of patients older than 75 years of age and not for very sick patients (with more and severe comorbidities). The procedure is recommended in patients with a life expectancy above 5 years in whom a perioperative risk for stroke, myocardial infarction, and death is less than 3 %. Longer follow-ups are needed and comparisons between larger statistics. SBCE represents however a procedure with indications beyond the current guidelines, asking consequently for a thorough clinical judgment, an assiduous team work, and a good selection of patients. Major advantages regarding the intraoperative course and monitoring are offered by the use of locoregional anesthesia.

In our experience, we performed the neat, *pure* SBCE and SBCE associated with other arterial reconstructions in a total number of 138 patients, as follows (Table 13.1):

The surgical technique merits some clarifications. The approach can be either through two separate cervical incisions (longitudinal or oblique) or by single transverse incision, depending on the shape of the neck, cosmetic reasons, the presence of thyroid disease, the degree of extension of carotid lesions (e.g., comprising the CCA), the height of the carotid bifurcations, and so forth (Fig. 13.3). The technique (endarterectomy and patching or eversion) asks for the same indications as in the case of single CEA. Either technique can be applied on one side or both, in the same patient. Both bifurcations are approached and ECA, ICA, and CCA are separately isolated with vessel loops. The first side to be treated is usually either the most severely stenosed or the symptomatic one. Some authors would indicate treating the side feeding the dominant hemisphere first. With both carotid bifurcations exposed, we usually try to detect which side is less vulnerable to clamping and treat that side first. In patients

Table 13.1 Simultaneous bilateral carotid endarterectomy (SBCE)

SBCE not associated to other cerebrovascular arterial reconstructive procedures	
Total number of patients	*125 cases*
Bilateral cervical block	106
General anesthesia	19
Death	1
Stroke	2
Major complication rate (death + stroke)	1 + 2 = 3 cases (2.4 %)
SBCE in complex arterial reconstructions[a] *= 19 cases*	

[a]VA reimplantation/SCA-to-bilateral ICA bypass/ascending aorta-to-bilateral ICA bypass

with insufficient collateral circulation through the CoW, we had to shunt both sides: even after treating the first side, the patient did not tolerate clamping of the opposite carotid artery. Both sides are drained, even with single cervical incision as the risk of cervical hematoma is higher in these patients. Collaboration with the anesthesia team is essential during these complex procedures. In cases with unstable plaques, we recommend clamping first the ICA distal to the bifurcation and complete the exposure of the entire bifurcation afterward. Plaque morphology and volume, in our surgical experience of SBCE, are among those of highest risk (Fig. 13.4).

13.2 Synchronous Carotid and Vertebral Artery Revascularization

13.2.1 CEA + VA Reimplantation

This technique is offered to patients presenting with severe lesions at the level of carotid bifurcation (with classical indication for CEA) associating critical stenosis of the dominant or singular VA (contralateral VA marked hypoplasia or occlusion). The access to the target arteries is dictated by the height of the carotid bifurcation, extent of the VA lesion, and length and shape of the neck. Consequently two approaches are used: single longitudinal cervical incision along the anterior margin of the SCM and two parallel horizontal incisions (one supraclavicular and one submandibular). The two horizontal incisions can be made shorter and with more cosmetic results (*for the surgical approaches*, *see* Chap. 4). The reimplantation of the VA is performed first, followed by the CEA. Exposure of the CCA and VA and of the carotid bifurcation was presented in Chap. 5. The reimplantation of the VA into the CCA progresses as presented in Chap. 12 and the CEA as presented in Chap. 11 (see also Figs. 2.14, 5.8a and b, 13.3a).

The associated procedures included in our series are: the extensive exposure of the VA in the bony canal and endarterectomy of the V1 segment of the VA (see Fig. 12.4c).

13.2.2 SBCE + VA Reimplantation: The Operation *3 in 1* (Fig. 13.5)

This technique was applied in six patients with severe lesions in both carotid arteries and at the origin of the dominant VA. The operations were performed under bilateral cervical block (regional anesthesia). On the side with the VA to be reimplanted, the surgical approach comprised a longer longitudinal incision. The order of treating the lesions was as follows: first, the carotid bifurcation opposite the diseased VA; second, the VA reimplantation; and third, the carotid bifurcation on the side with the reimplanted VA. A case with SBCE by eversion technique and reimplantation of the right VA into the CCA is presented in Fig. 13.5. No intraoperative events were noted. No phrenic nerve paralysis was encountered. Patients had a normal postoperative course.

13.3 Occlusive Disease of the BCT

Occlusive disease of the BCT can be treated surgically in various modes. The anatomic reconstruction comprises endarterectomy and patch insertion and ascending aorta-to-subclavian and carotid bypass. We do not recommend the former, for more reasons. First, a well-performed endarterectomy of the BCT requires clamping of the origin of the BCT or the adjacent aorta. This is best done and safely through a proper access, i.e., partial superior sternotomy. Second, lesions of the BCT are not limited to the BCT but extend for various lengths into the SCA and CCA. Third, in case of concomitant lesions at the level of the carotid bifurcation, this will require surgical treatment (CEA and patching). Consequently, it is more convenient, safer and with more favorable long-term results to perform the ascending aorta-to-subclavian and carotid artery bypass (when concomitant disease in the carotid bifurcation is present, we associate CEA and the bypass is anastomozed on the endarterectomized carotid bifurcation) (Fig. 13.6).

The extraanatomic reconstruction comprises bypass on the SCA and CCA from alternative cervical sources: contralateral SCA or CCA. This procedure can be performed under locoregional anesthesia.

Each of the techniques mentioned above has advantages and certain limits. The anatomic reconstruction has theoretically a longer patency rate but comprises more extensive surgery. In case of extraanatomic bypass, the limited quality of the donor artery and the particular hemodynamics limit its effects and patency in time. It may be however performed under locoregional anesthesia.

13.4 CEA + Revascularization of the Subclavian Artery

Revascularization of the SCA by surgical bypass between the CCA and the SCA is indicated in occlusion of the origin of the SCA, high-degree stenosis and unsuccessful angioplasty (due to local factors), lengthier stenosis of the origin of the SCA, or multiple lesions involving the areas of greater mobility of the shoulder joint (partial covering of the origin of the VA does not represent a contraindication for SCA stenting). Vertebral steal is present in patients with SCA occlusion or tight stenosis, although not always symptomatic. As mentioned before, vertebral steal may ensue even in

cases with proximal occlusion of the VA (V0 and V1 segments), through enlarged collaterals between the V3 segment of the VA and SCA or ECA. In most of the cases, where no lesions of the carotid artery bifurcation are present, a simple bypass between the CCA and the SCA is performed. However, in cases with moderate-to-severe lesions of the carotid bifurcations, two types of concomitant revascularization are performed:

- CEA and CCA-to-SCA bypass. Dacron or PTFE grafts are used for the bypass, with diameters of 6–8 mm, depending on the quality of the vessels (Fig. 13.7a). As stated before, the anterior scalene muscle is divided, and the SCA is exposed distally down to the third (extrascalenic) segment. Alternatively, a venous graft may be used for the bypass (Fig. 13.7b). Rarely, a more distal bypass on the axillary artery is needed.
- Bypass between the carotid bifurcation and the SCA with Dacron of PTFE graft (Fig. 13.8). The bifurcation is endarterectomized, and the graft is used as enlargement patch for the carotid bifurcation. The graft is tunneled underneath the SCM.

The reverse is applied for occlusion of the CCA: a bypass is accomplished between the SCA and the carotid bifurcation (associating whenever necessary the CEA).

13.5 Aortic Arch Syndrome

Extensive lesions of the origin and proximal portions of the arch vessels are included under the generic denomination of *aortic arch syndrome* in spite of the fact that the initial name applied to Takayasu's arteritis. Atherosclerotic lesions have a tendency to be more extensive with concomitant involvement of more distal arterial segment too. Consequently, this type of lesions may affect the entire superior aortic system. Clinical symptomatology appears protean due to the many categories of lesions and types of compensatory flow.

Whenever a single supraaortic trunk is not diseased (or of a fair quality), this may be used as donor artery for one or more extraanatomic bypasses (see above: Sect. "Occlusive disease of the BCT"). Carotid-to-carotid bypass is a valid technique, especially in patients requiring bilateral endarterectomy (Fig. 13.9: SBCE + Carotid-to-carotid bypass).

When a complete revascularization is contemplated, the donor artery is the ascending aorta (Fig. 13.10). The operation begins with dissection of the target vessels through two or more cervical incisions. The aorta is approached through median sternotomy. The pericardial cavity is opened and the aorta is circled with a tape. A vascular graft is chosen after the donor and target arteries are accurately examined. The graft is tailored and prepared for the vessels chosen to be approached. A bifurcated graft is usually employed; if required, supplementary branches are added (either to the common body of the graft or to its arms). A quadrifurcated graft may need extra room underneath the sternum and behind the sternoclavicular joints. The supplementary branches can be anastomosed L-T in the neck to the arms of the bifurcated graft. The branches are tunneled under the strap muscles and the SCM and posterior the venous plane (behind the left brachiocephalic vein and the IJV). The common body of the graft is anastomosed in a right lateral position on the ascending aorta (resembling the position of the BCT albeit in a lower position). This will render the graft less prominent underneath the sternum and less compressive on adjacent mediastinal structures. The lateral clamping of the ascending aorta is well tolerated. The order of performing the distal anastomoses is chosen depending on the clinical symptomatology and on the degree of stenotic lesions of the recipient arteries. We usually revascularize first the SCAs to increase the flow through the VAs. Afterward, the carotid artery with higher degree of stenosis or the symptomatic one is revascularized first. Even in this type of operation, we administer lower doses of unfractionated heparin (2500 UI i.v. bolus) requiring no neutralization at the end of operation. The neck and sternum are drained and closed in the usual fashion.

Alternatively, the BCT may be chosen as the donor artery, in cases with calcification of the ascending aorta or dilatation of the same (Fig. 13.11).

The presentation of particular procedures follows.

13.6 Revascularization of the ECA

In very selected patients with bilateral ICA occlusion and no efficient compensatory flow from the posterior (vertebrobasilar system), one or both stenotic ECAs can be revascularized either by endovascular (see Chap. 6) or surgical procedures, thus contributing to the filling of the intracranial ICAs by means of preexisting natural collaterals. Clinical improvement and increased flow detected and documented at transcranial Doppler examination favor this type of procedure that might be considered analogous to an extracranial-to-intracranial bypass. The carotid bifurcation is approached in the usual manner. More extensive lesions on the ECA require lengthier exposure of the ECA. Endarterectomy of the distal CCA and ECA must be performed under direct vision (not by eversion) followed by insertion of a patch (Fig. 13.12). Alternatively, an autologous patch may be created from the occluded ICA. The surgeon must pay attention and make sure that the plaque was completely removed and that the branches of the ECA maintain their patency. A synthetic patch may distort more

easily the shape of the main trunk of the ECA, as compared with patching of the ICA.

Another situation consists in revascularizing both the ICA and the ECA. More severe lesions may occlude the origin of the ECA; it appears wiser treating the entire lesion which extends into the origin of the ICA and ECA equally.

13.7 ICA Thrombectomy

ICA can be *recuperated* and revascularized in cases of recent or limited thrombosis of the artery at its origin (Fig. 13.13). The benefit of revascularizing a hypoplastic or a recently thrombosed ICA remains however controversial, but the subject must be looked upon in two ways:

- The indication depends on the clinical condition of the patient and of the status of the contralateral ICA. A precise assessment of intracranial circulation (angio, angio-CT, TCD) is mandatory.
- The thrombosed ICA may appear as an intraoperative surprise (Fig. 13.14) in patients with tight carotid stenosis. The ICA may occlude during the time interval from diagnosis to surgery (in some patients, even over a period of 1–2 weeks). If convenient backflow from the distal ICA is obtained after thrombectomy, a regular patching of the bifurcation and ICA is performed. Otherwise, the ECA alone will be patched (see above). Alternatively, a bifurcated patch ("swallow tail") (Fig. 13.15) may be tailored and inserted, enlarging both the ICA and ECA. In case of unsuccessful thrombectomy of the ICA, subsequent patching of the ECA is performed.

13.8 Endarterectomy Extended over the CCA

In many circumstances, the CCA appears significantly diseased in order to warrant surgical therapy. It is also not infrequent that the lesions on the CCA, which did not appear as severe and as extended during diagnostic interrogation, reveal intraoperatively as critical as to ask for an extended endarterectomy and, in some cases, impose resection and graft replacement. In this paragraph, we will present the former condition, as the latter was already presented (Fig. 13.16).

13.8.1 CEA + *CCA-to-SCA Bypass* + Bypass on V3

This type of operation was selected in a case with occlusion of the left SCA, occlusion of the left VA (V1–V2), and vertebral steal syndrome + stenosis of the left carotid bifurcation. The surgical result is presented in Fig. 13.17.

13.9 Particular Situations

This comprises patients with severe comorbidities and/or in severe conditions (Table 13.2). The preferred technique is CEA (either with patching or eversion) under regional anesthesia.

13.10 Conclusive Remarks

Complex reconstructive procedures are by no means rare events, counting in our experience a significant number of patients (Table 13.3). Indeed, in such cases, the indications go well beyond the guidelines but are by no means the result of a thorough diagnostic investigation and choice of therapy. Results are encouraging, especially when comparing the major complications rate between "simple CEA" and SBCE, for example, (and not forgetting the fact that the SBCE patients have a heavier atherosclerotic load and possible complications in many systems and organs). Such versatile techniques can be also applied in patients with aneurysms of the aortic arch with selective perfusion of the neck vessels or in debranching procedures.

Table 13.2 Particular/critical situations

Condition	No. of patients (% of the total CEA performed)
Chronic renal failure in hemodialysis	2 (0.4 %)
Ischemic dilated cardiomyopathy	3 (0.6 %)
Mechanical valvar prosthesis	2 (0.4 %)
Laryngectomy and tracheostomy	3 (0.6 %)
COLD – severe form	4 (0.8 %)
Neurologically unstable	6 (1.2 %)
Total	*20 (4.2 %)*

Table 13.3 Complex reconstructive procedures

Type of operation	Number of patients
SBCE (as single procedure)	125
CEA + VA reimplantation	28
Aortic arch syndrome (various bypasses from the ascending aorta to the neck vessels)	22
SBCE + VA reimplantation	6
Total[a]	*181*

[a]Other types of operations, e.g., extraanatomic bypass CCA-to-SCA, carotid-to-carotid, VA reimplantation (without CEA), etc., were not counted here as these are considered as *simple*. Also, compare this number of patients with the total number of CEAs performed, i.e., 478

Image Gallery

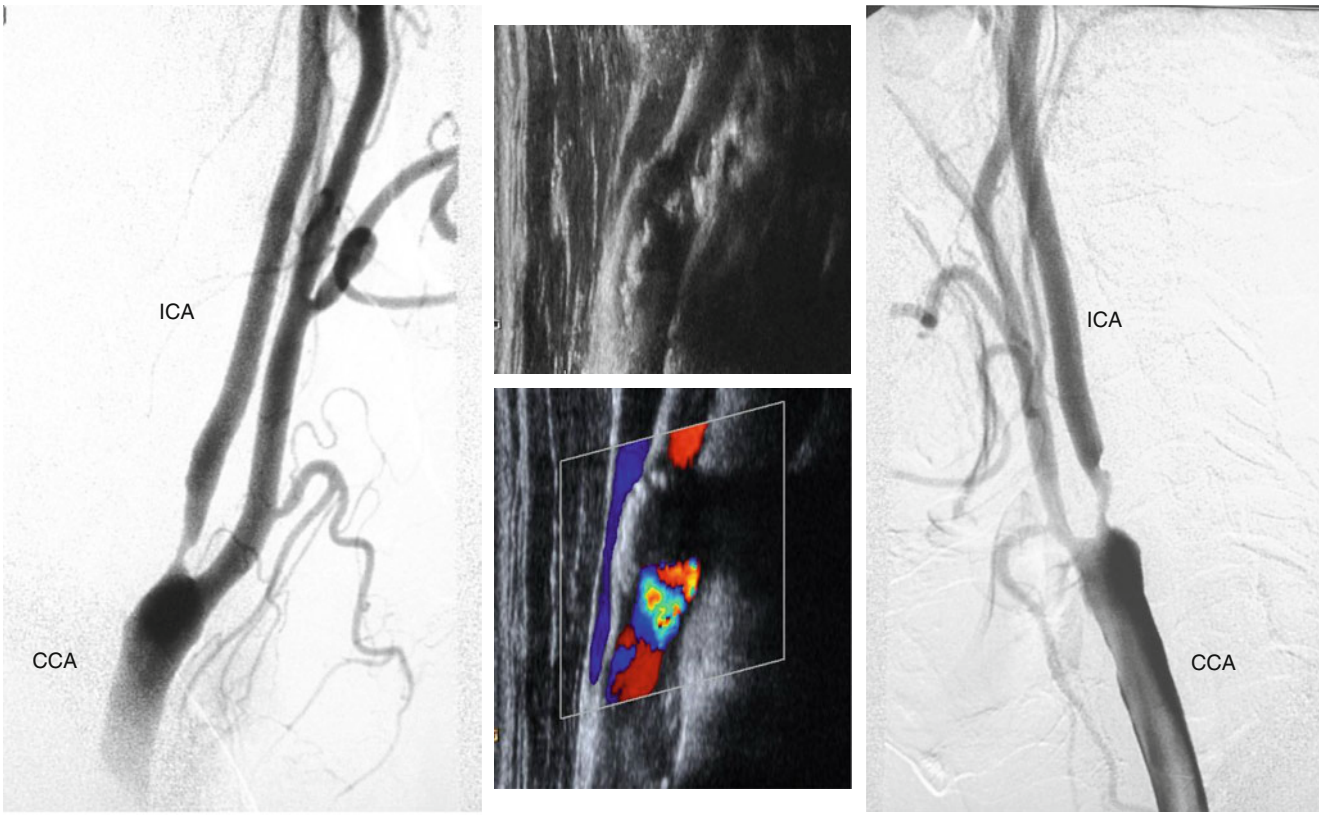


Fig. 13.1 *SBCE.* The general aspect of a patient referred for the SBCE procedure, with drop attacks and severe, pre-occlusive stenoses at both carotid bifurcations. Angiographic and Doppler aspects

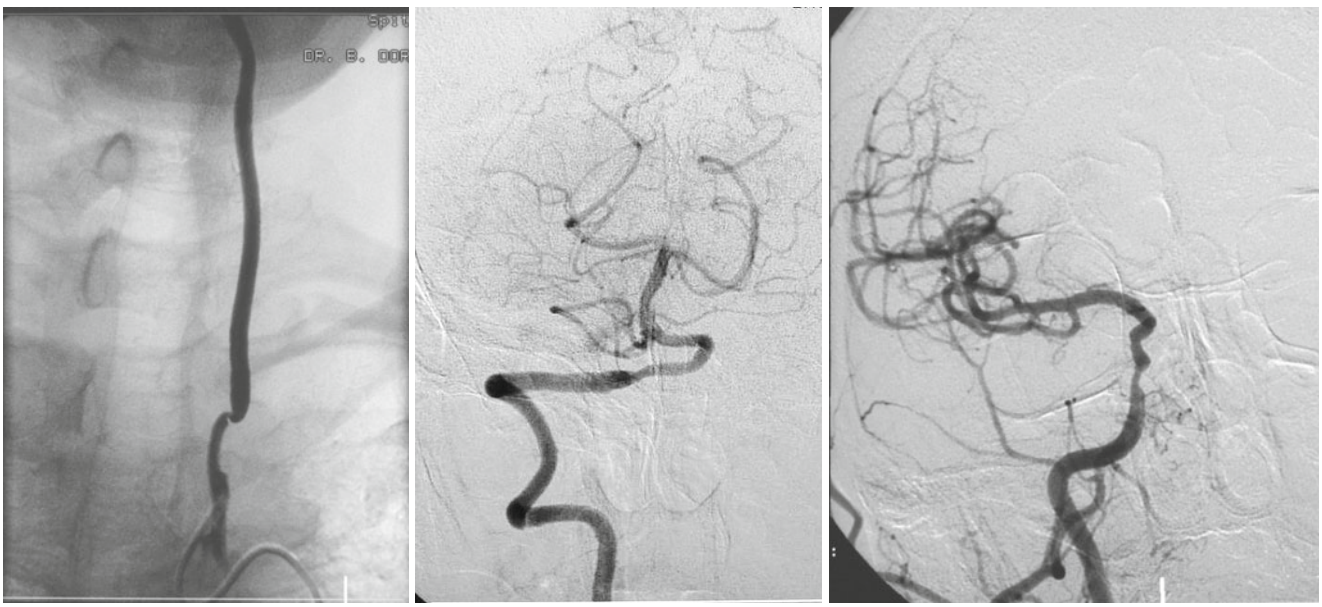


Fig. 13.2 Associated lesions. Associated lesions in the vertebrobasilar system (either extra-, intracranial, or both) as well as in the intracranial segments of the ICA warrant particular consideration and attention, as these may change, complicate, or even contraindicate the performance of selected reconstructive arterial procedures. The compensatory capacity of the CoW is however best appreciated intraoperatively in the awake patient under regional anesthesia

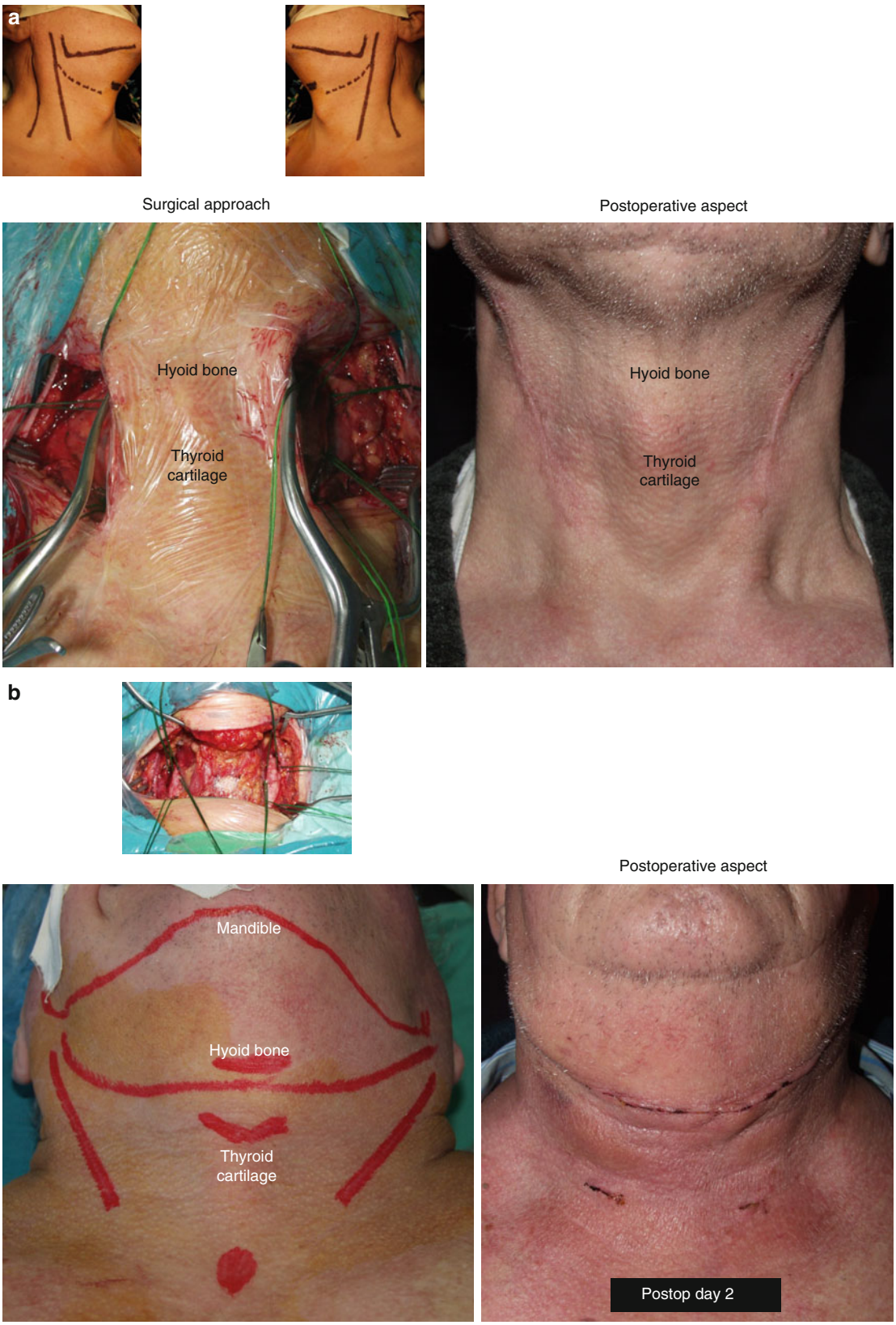


Fig. 13.3 Surgical approach for SBCE. Panel (**a**) classical approach by two separate longitudinal cervical incisions. Alternatively, oblique incisions can be used. Panel (**b**) single transversal cervical incision for concomitant exposure of the carotid bifurcations. Note the best cosmetic result. The risk of cervical hematoma is however higher with this approach

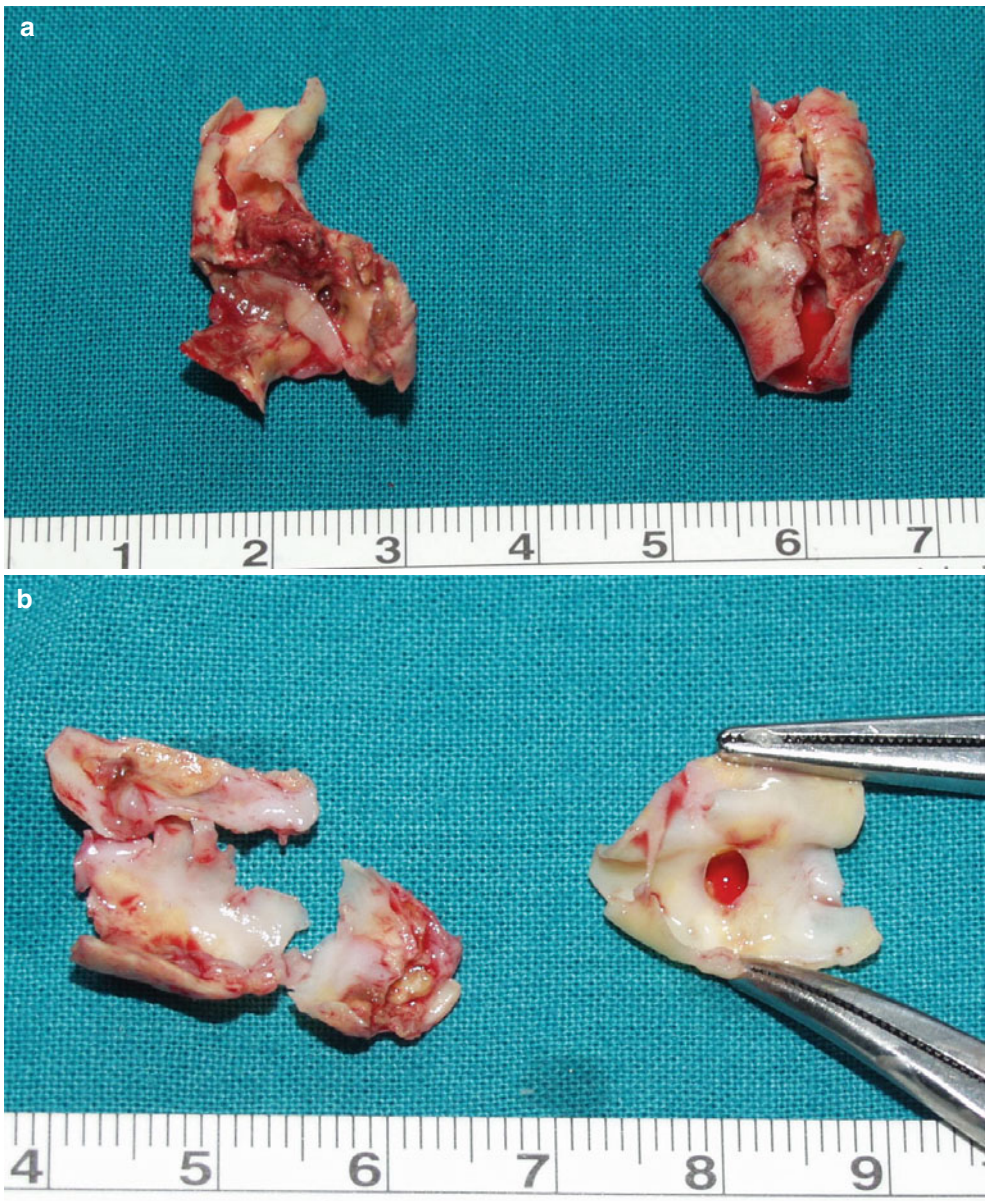


Fig. 13.4 Plaque morphology in SBCE. Panel (**a**) association of severe bilateral stenosis and unstable plaques with conspicuous lipid core. Panel (**b**) severe stenosis and opposite ulcerated and symptomatic plaque. These examples illustrate the polymorphous types of lesion in the carotid bifurcations and, not least, the unfavorable associations between high-degree stenosis and complicated plaque

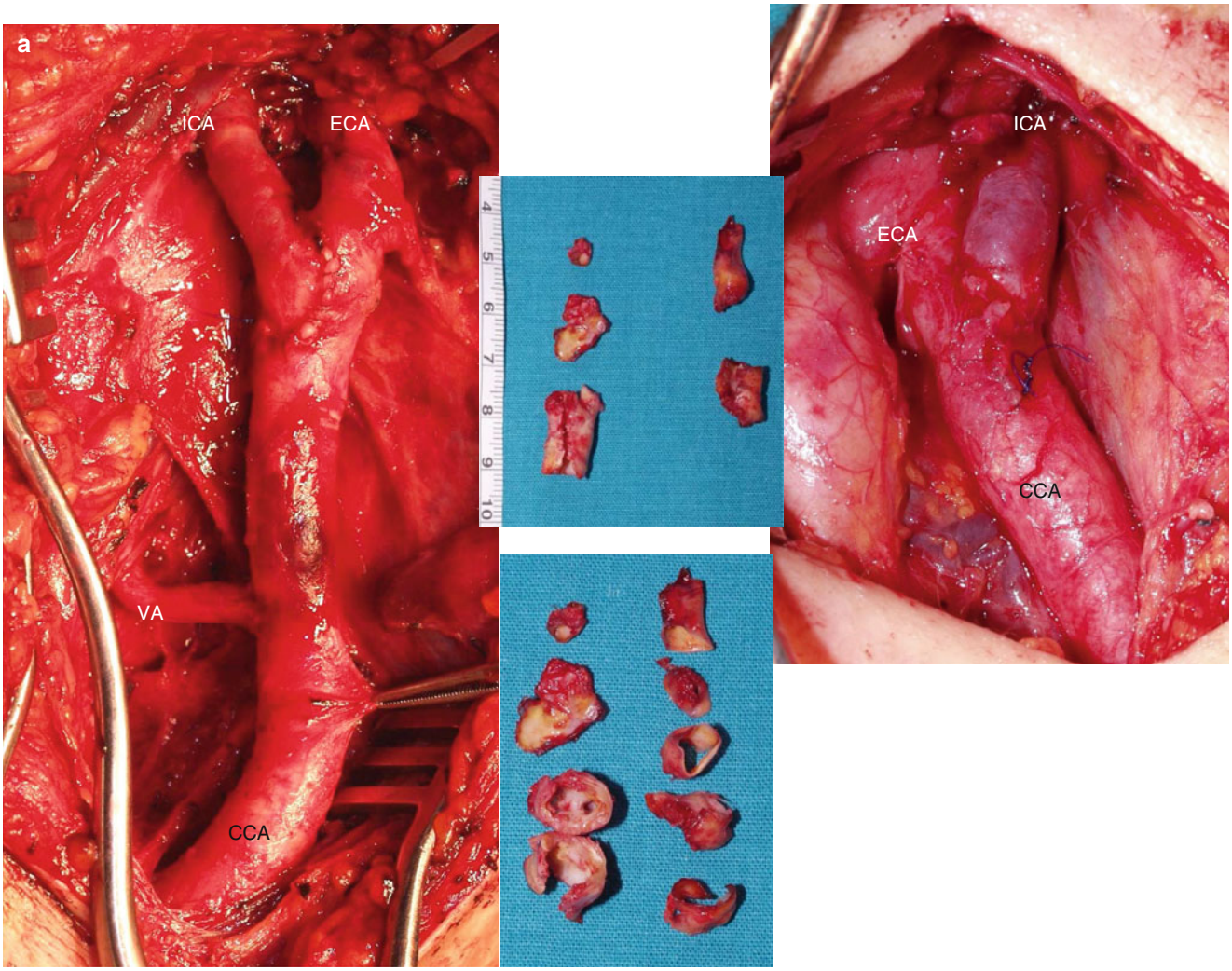
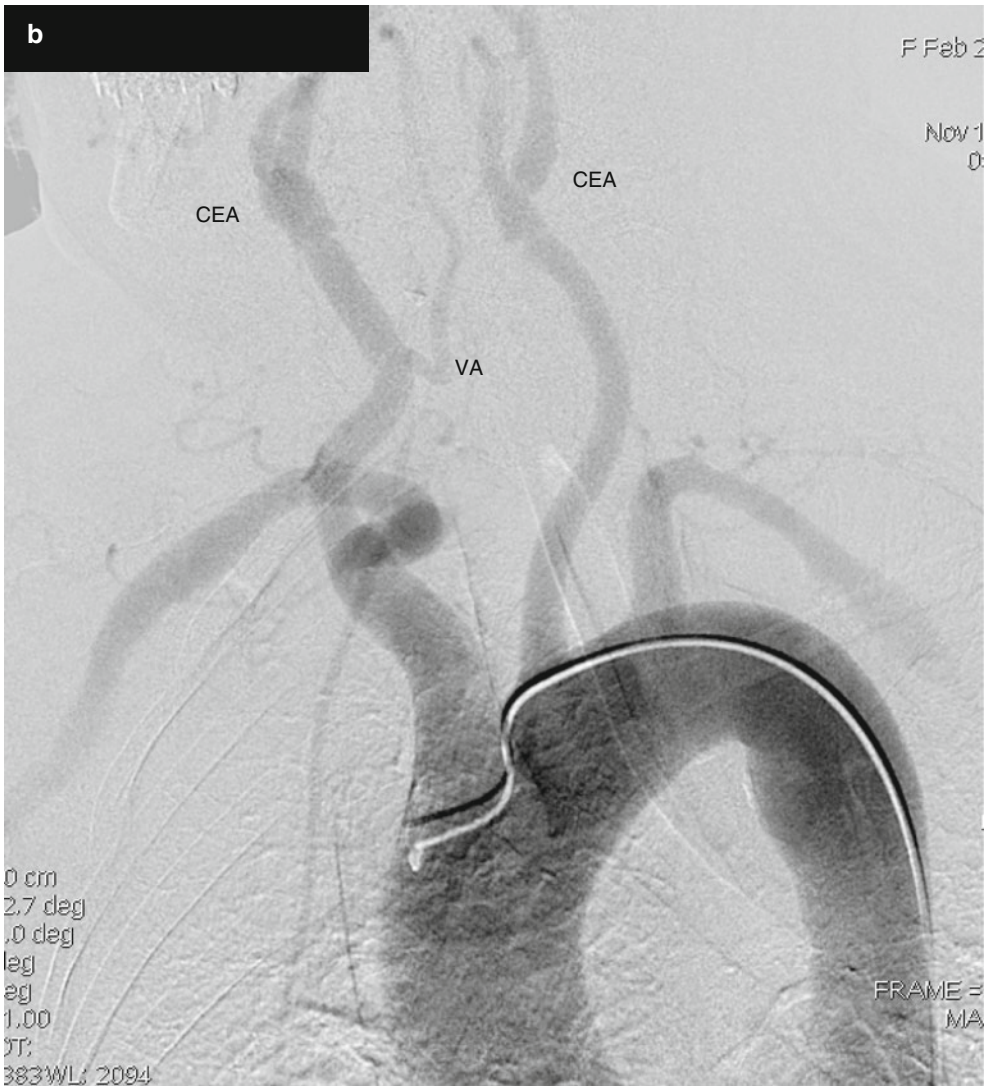


Fig. 13.5 SBCE + VA reimplantation: The operation *3 in 1*. Panel (**a**) intraoperative aspect of the complex reconstruction consisting in SBCE and reimplantation of the right VA into the CCA. In the *middle*, the excised plaques. Both carotid bifurcations were treated in this case by using the eversion technique. Panel (**b**) completion angiogram in the same patient. *CEA* carotid endaterectomy, *VA* vertebral artery

Fig. 13.5 (continued)



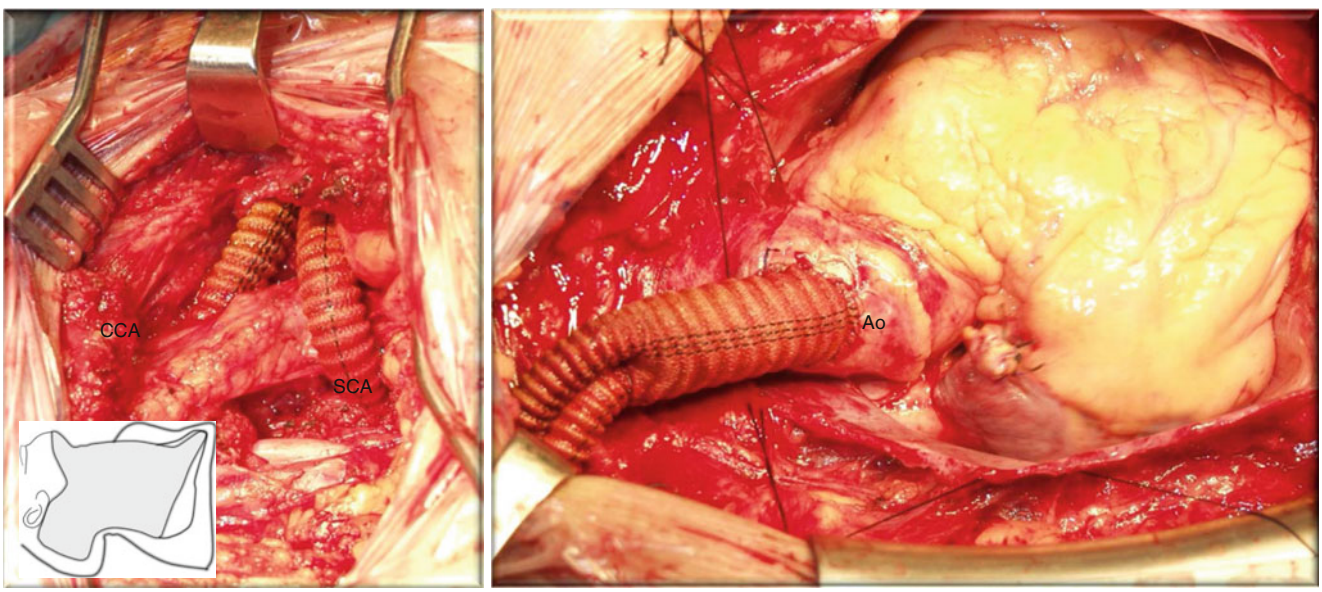


Fig. 13.6 Bypass for occluded BCT. Anatomic reconstruction for the occlusion of the BCT: bypass from the ascending aorta to the right SCA and right CCA. Whenever the bifurcation appears diseased, the carotid limb is anastomosed to the right carotid bifurcation after CEA

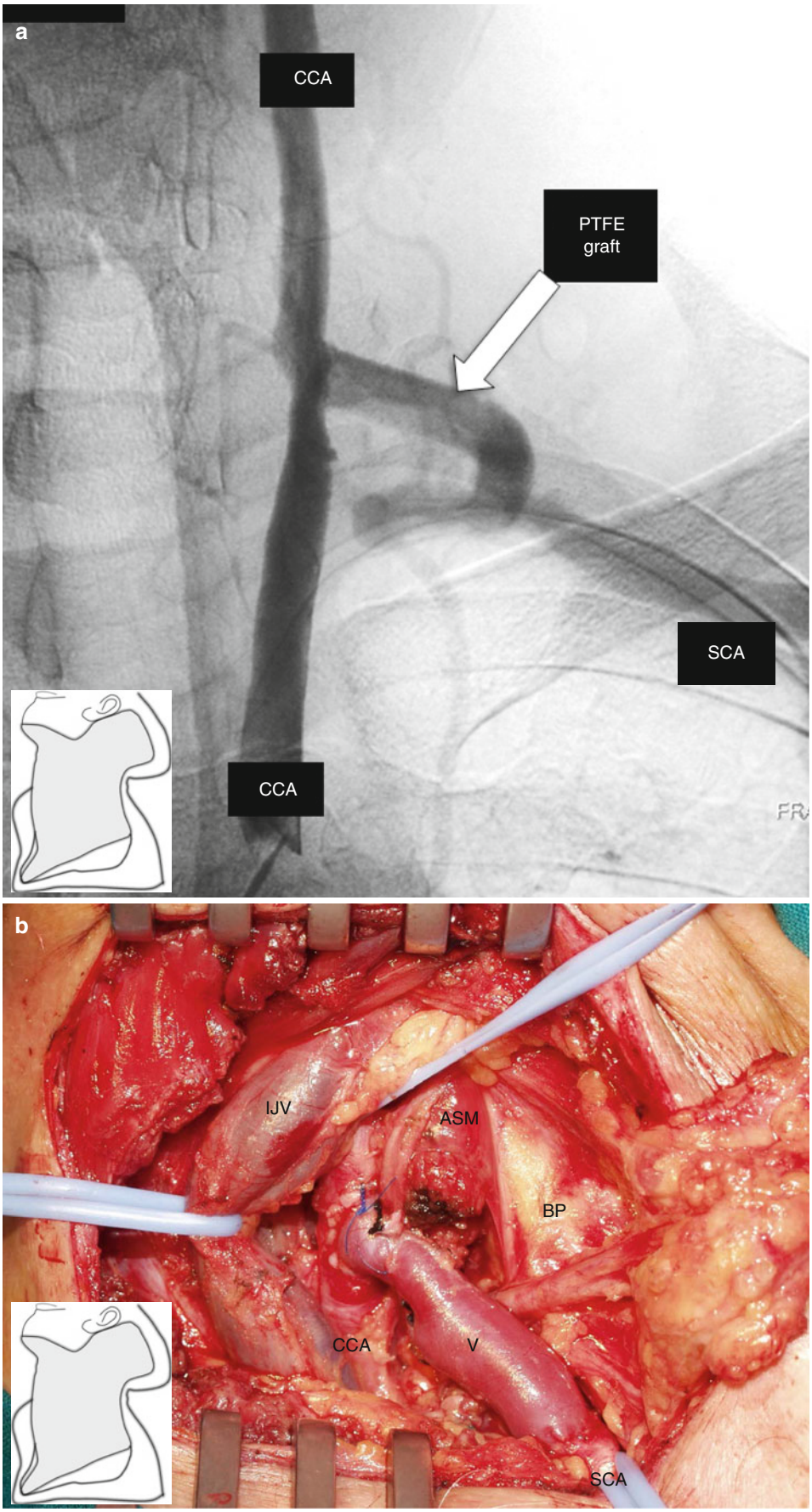


Fig. 13.7 CEA + revascularization of the SCA. Panel (**a**) completion angiogram illustrating the bypass from the CCA to the occluded SCA with PTFE graft. Note also the retrograde filling of SCA branches. Particular attention is focused on the purging (air, thrombi) as embolic material may pass either into the distal CCA and ICA or into the VA. Panel (**b**) alternative surgical solution by using an autologous venous graft (*G*). Note the position of the bypass posterior to the IJV. The ASM was cut

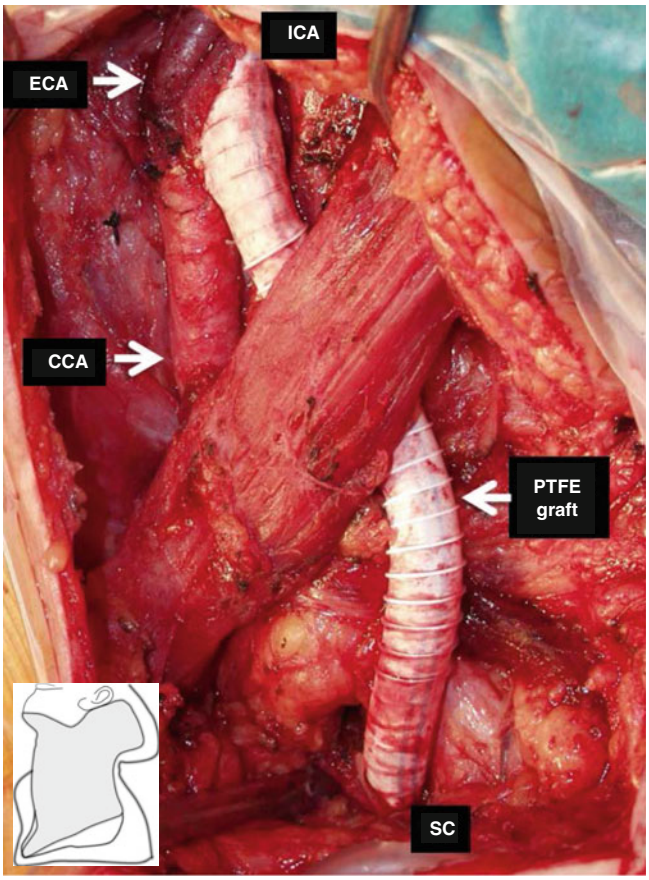


Fig. 13.8 Carotid bifurcation-to-SCA bypass. The technique includes CEA and bypass from the endarterectomized carotid to the occluded SCA. The superior part of the PTFE graft serves as an enlargement patch for the carotid bifurcation. The graft is tunneled underneath the SCM

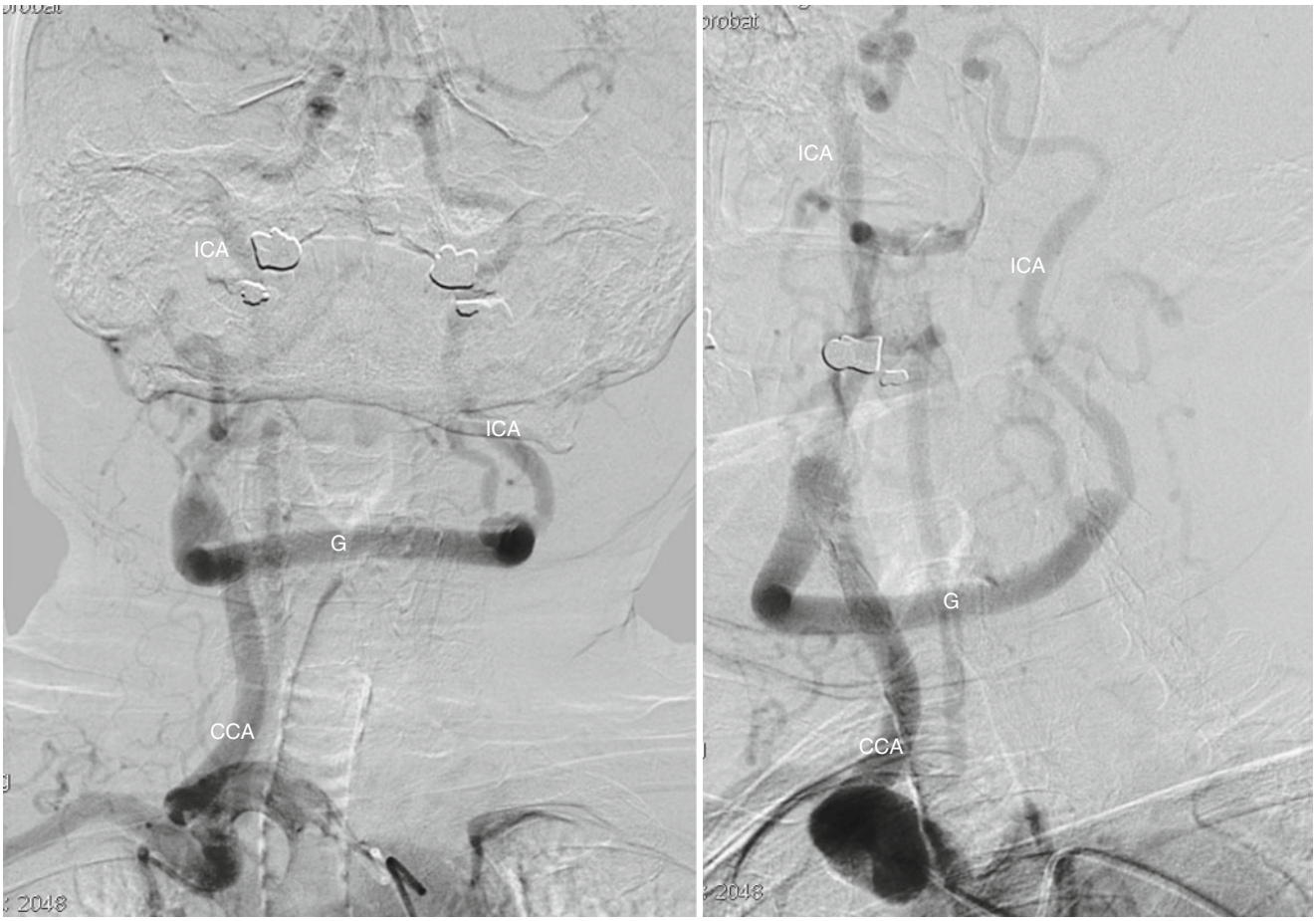


Fig. 13.9 Extraanatomic carotid-to-carotid bypass. The figure illustrates the case of an old female patient, with severe atherosclerotic lesions in all neck vessels, and having the only fair donor vessel, the right CCA. The left CCA was occluded but the bifurcation remained patent. Both carotid bifurcations had atherosclerotic lesions, requiring the SBCE. A prelaryngeal PTFE graft (*G*) was used to revascularize the left carotid system

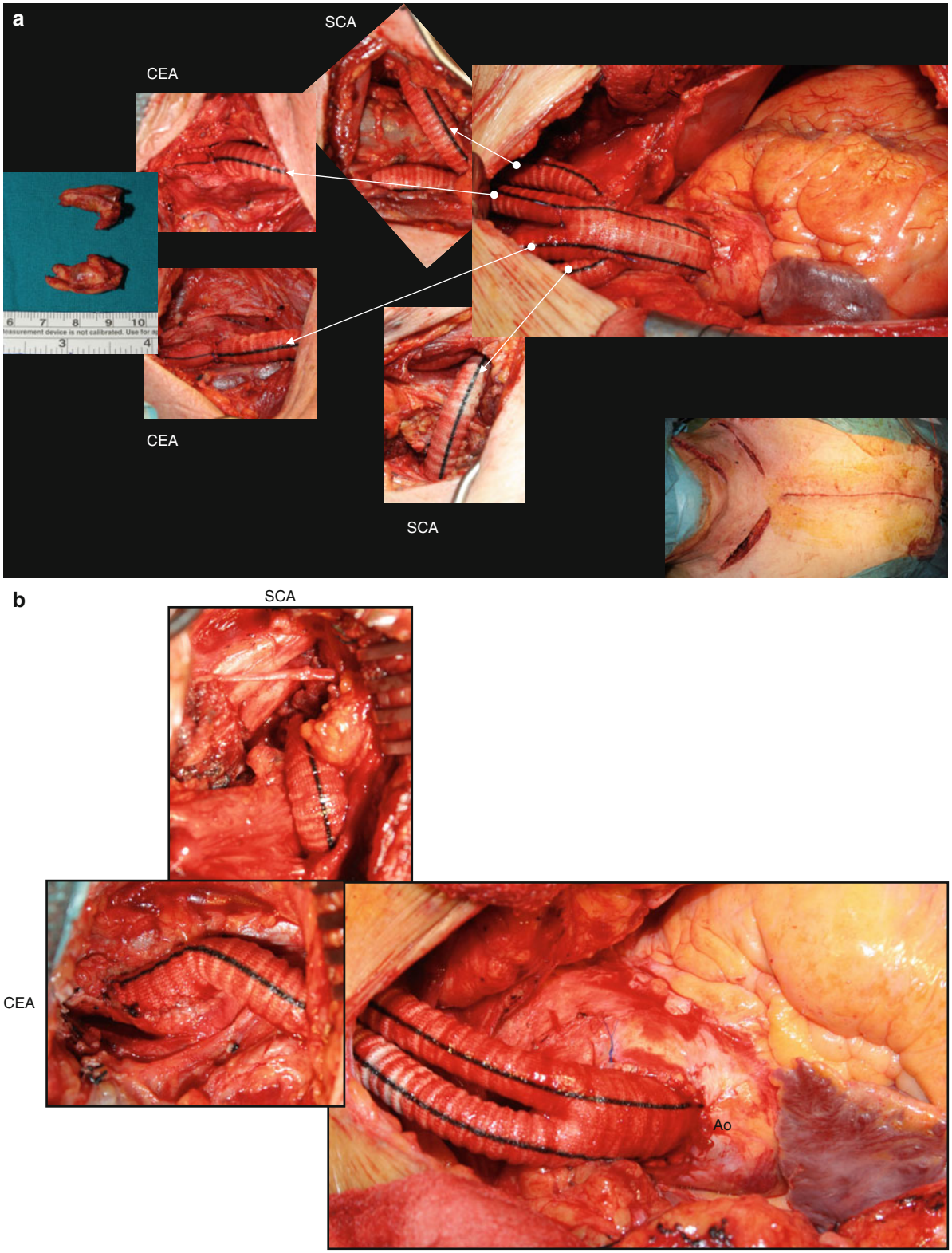
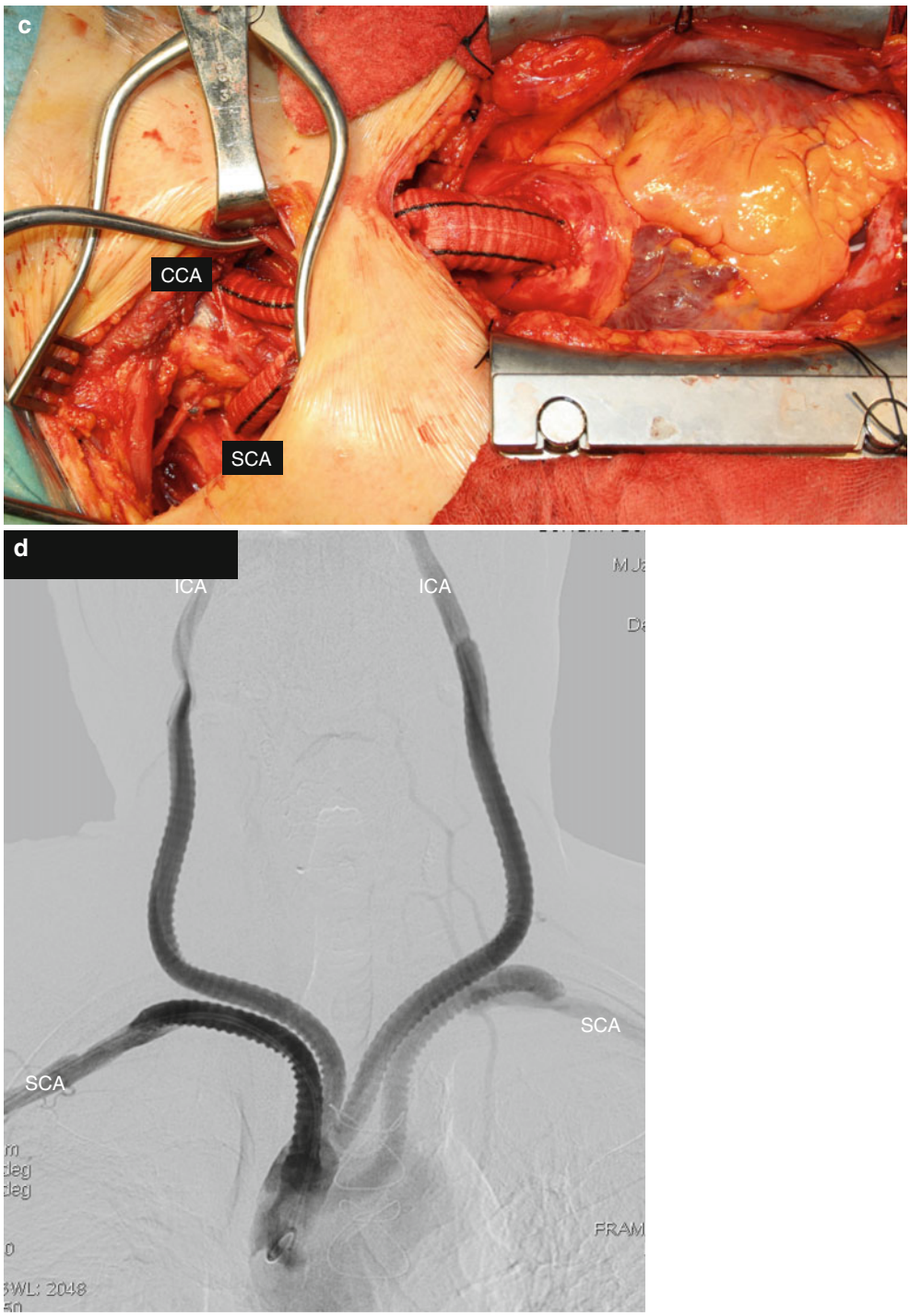


Fig. 13.10 Bypasses from the ascending aorta. Numerous variations and types of bypasses are performed, for the vascularization of the neck vessels. All these variants can be easily applied in cases with aneurysms of the aortic arch or as debranching procedures. Panel (**a**) a quadrifurcated graft (with the additional two branches anastomosed ad hoc) was inserted on the ascending aorta. The branches reach the SCA on both sides and the carotid arteries on both sides too. Note that the bifurcations were endarterectomized (excised plaques shown in the left extremity), and synthetic patches were inserted. *Right lower* Panel (**d**) demonstrates the incisions for the combined approach: sternotomy and bilateral double parallel incisions. We prefer cervical parallel incisions instead of a single longitudinal incision. Panel (**b**) bypass from the ascending aorta to the left neck vessels: ICA and SCA. Note that even in this case, the carotid limb is used as an enlargement patch. Panel (**c**) a similar reconstruction on the right side, in case of obstruction of the BCT. Panel (**d**) completion angiogram in a patient with a quadrifurcated graft



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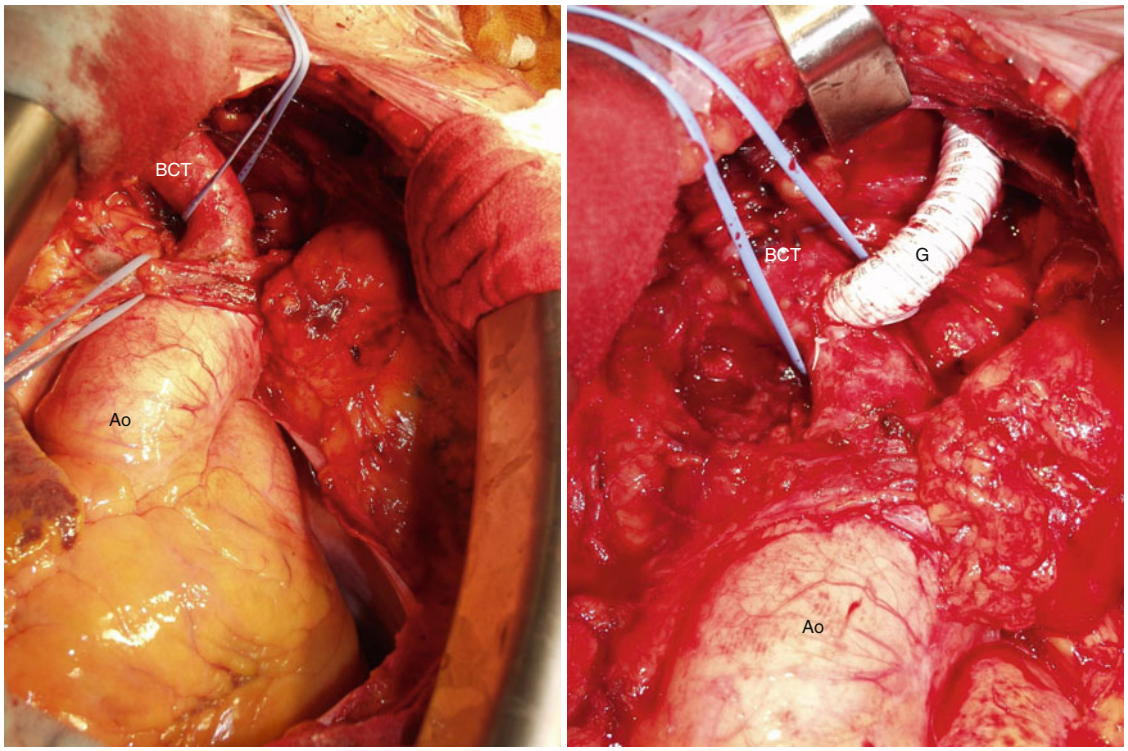


Fig. 13.11 The BCT as a donor vessel. Whenever the quality of the ascending aorta limits the use of this vessel for bypass, or when the patient cannot tolerate the lateral clamping of the ascending aorta, the BCT may offer a good alternative. Preoperative diagnostic interrogation must rule out dilatations of the ascending aorta or the presence of heavy and extensive calcifications, but in some cases, this may come as an intraoperative surprise, in spite of all the precautions previously taken. This is also valid for coronary bypass grafting when the proximal graft anastomosis may be performed on the BCT instead of the ascending aorta

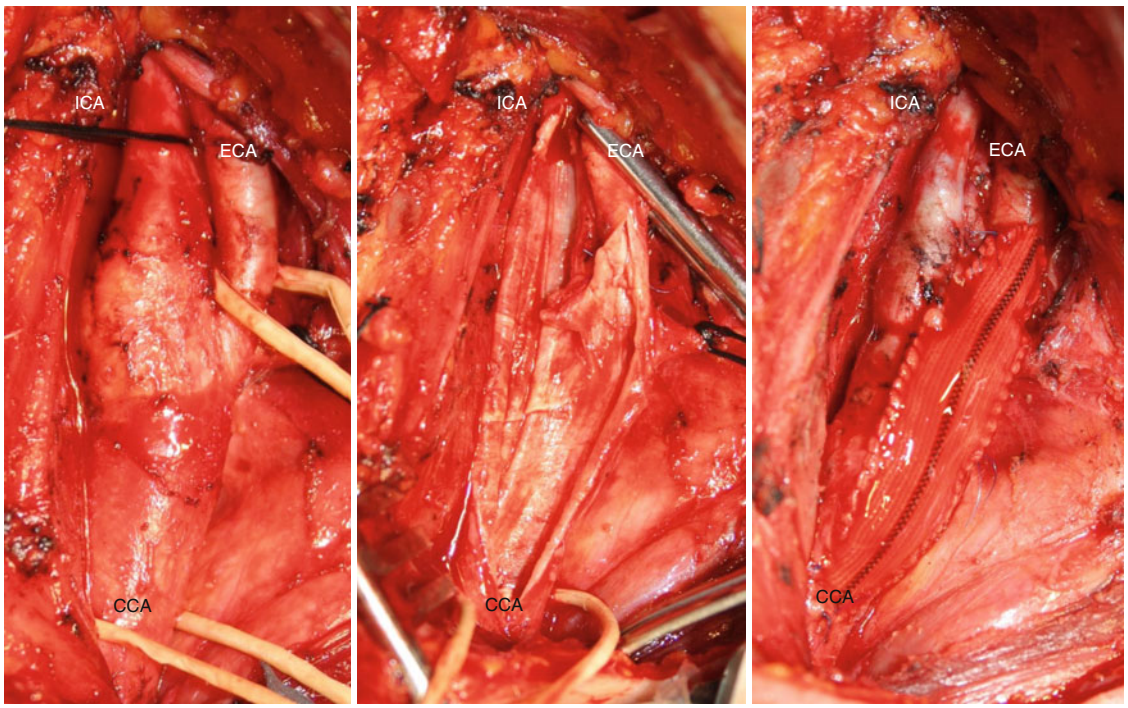


Fig. 13.12 Revascularization of the ECA. Severe stenotic lesions at the origin of the ECA in patients with bilateral occlusion of the ICA are treated either by endovascular procedures (see Chap. 7) or by surgery. Intraoperative aspect of the right carotid bifurcation. The ICA is occluded (note that the ICA is declamped and no back bleeding is present). After performing the endarterectomy of the origin of the ECA, the patch is inserted and oriented toward the ECA

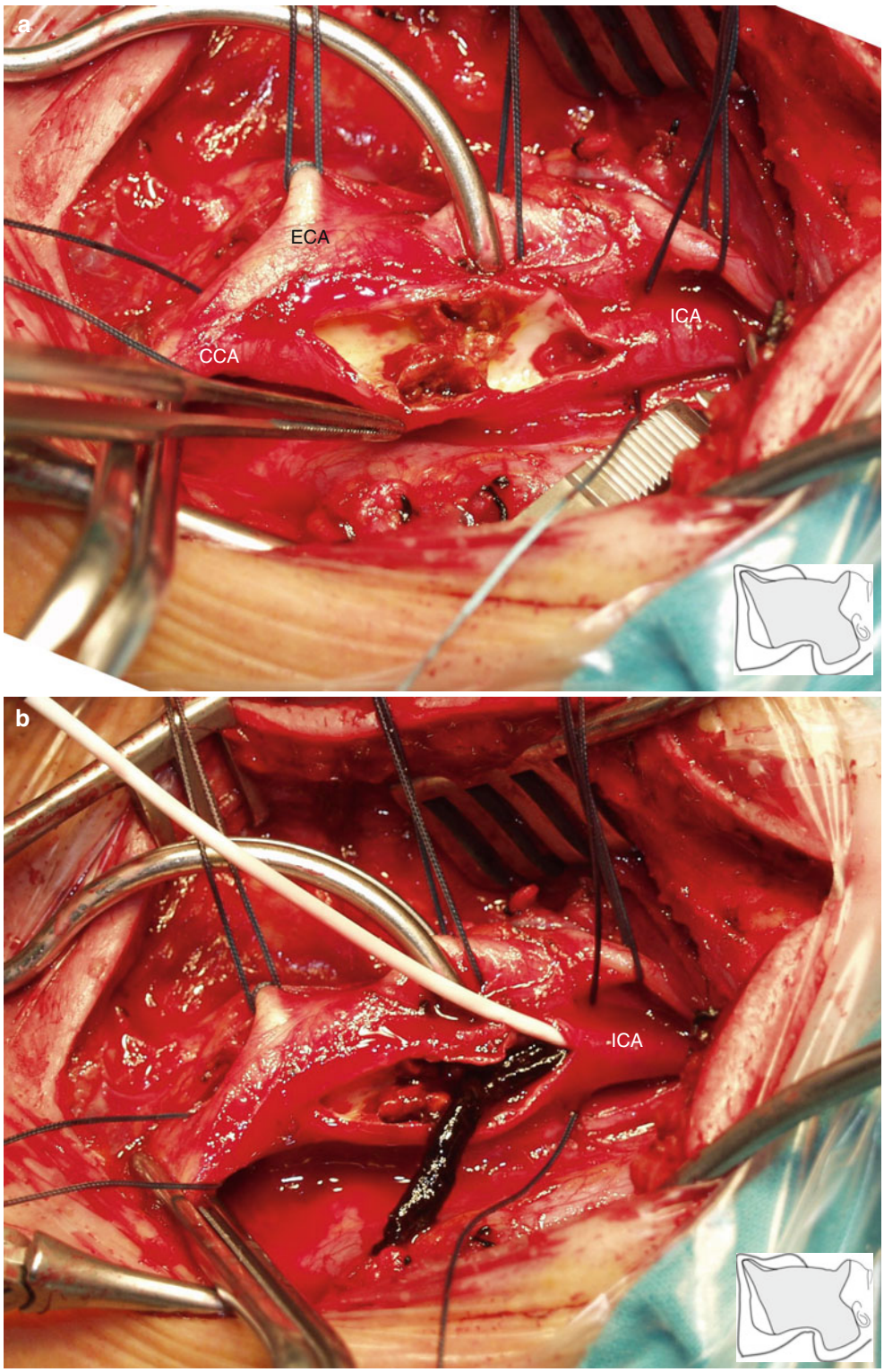
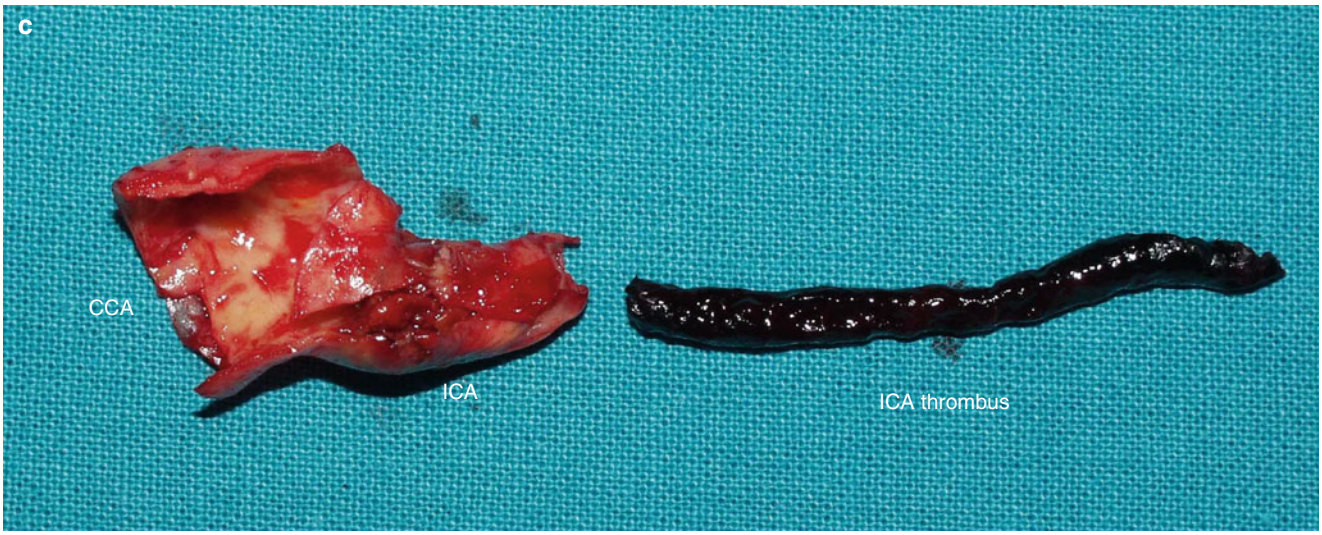


Fig. 13.13 Thrombectomy of the ICA (1). Recently thrombosed ICAs can be restored by thrombectomy and subsequent patching. Panel (**a**) occlusive stenosis at the origin of the left ICA (note also the intraplaque hemorrhage). The end of the thrombus appears at the origin of the ICA. Panel (**b**) the ICA is dethrombosed with a Fogarty catheter. The plaque is removed and the bifurcation is closed with a patch. Panel (**c**) macroscopic aspect of the excised carotid plaque and thrombus from the ICA. Retrograde flow from the intracranial segments of the ICA prevents distal embolization of the thrombotic material



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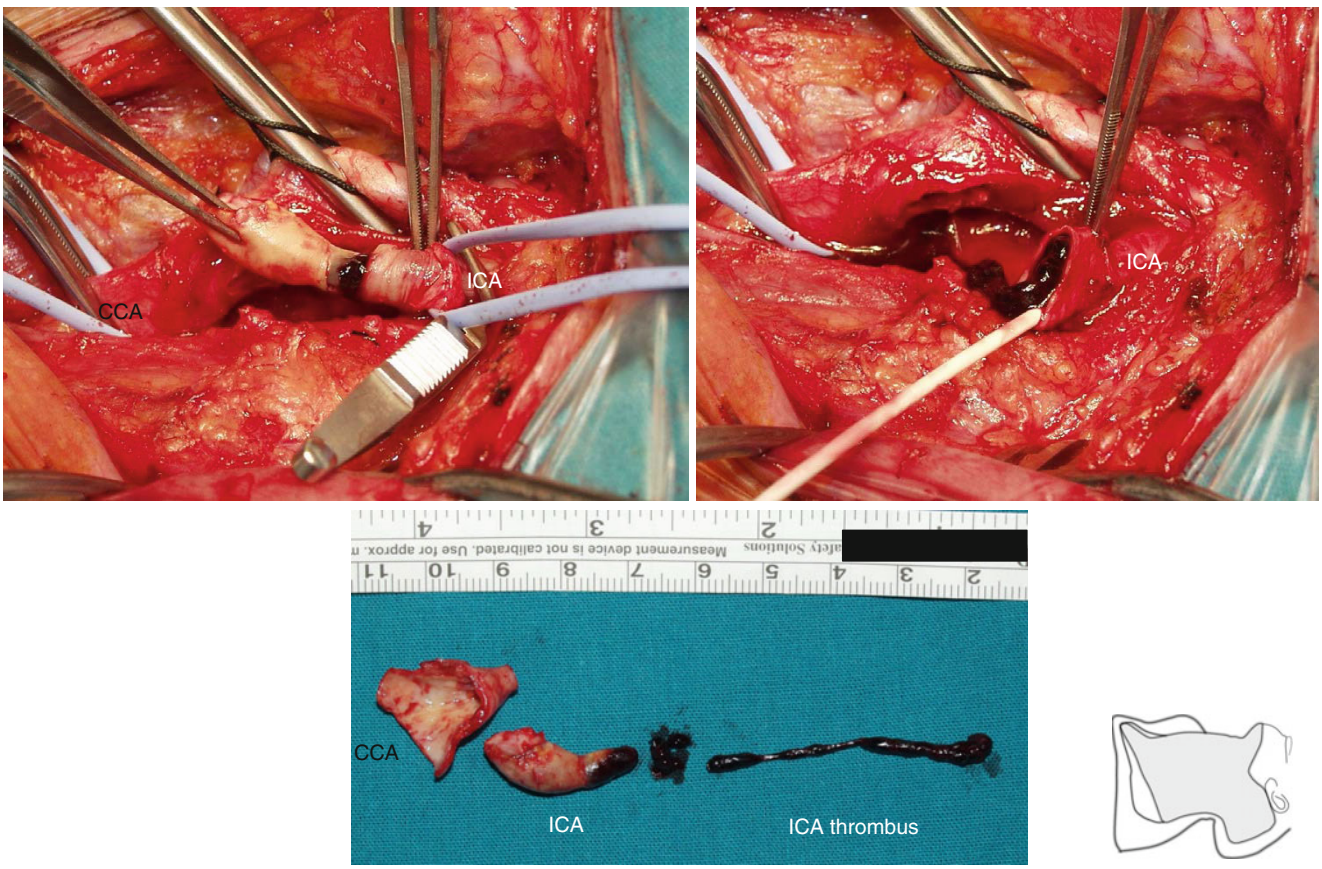


Fig. 13.14 Thrombectomy of the ICA (2). Thrombosis of the ICA appears as an intraoperative surprise, in a patient referred for CEA, and known to have a pre-occlusive stenosis. In the time interval from diagnosis to surgery, the ICA is occluded. The ICA was treated as above. The plaque was removed by using the eversion technique

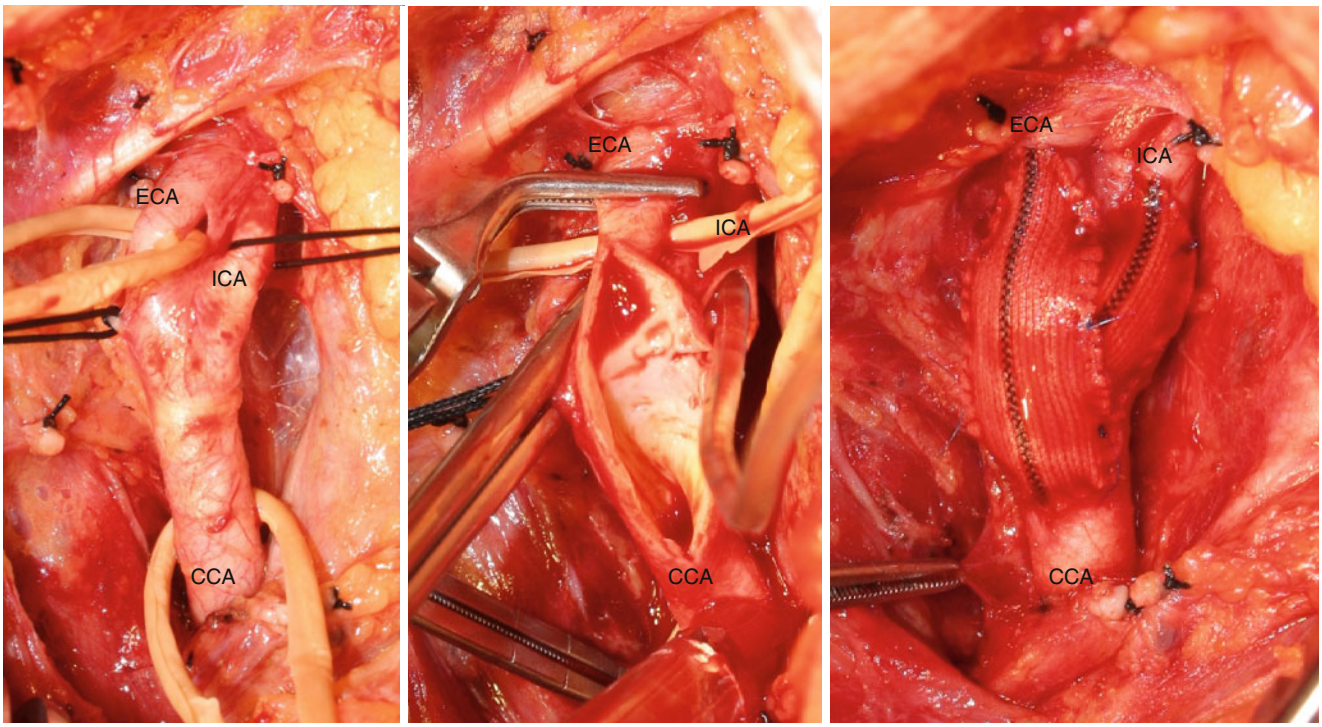


Fig. 13.15 Bifurcated patch. Intraoperative aspect of the right carotid bifurcation. The ICA appears hypoplastic (compare the diameter with that of the ECA). Patency of the ICA was probed with a malleable catheter. With the bifurcation opened, it appears evident that the origin of the ECA is larger, and the normal patch was inserted toward the origin of the ECA. An additional *tail* of the patch is used to enlarge the origin of the ICA. Should the ICA occlude with time, the ECA will remain patent

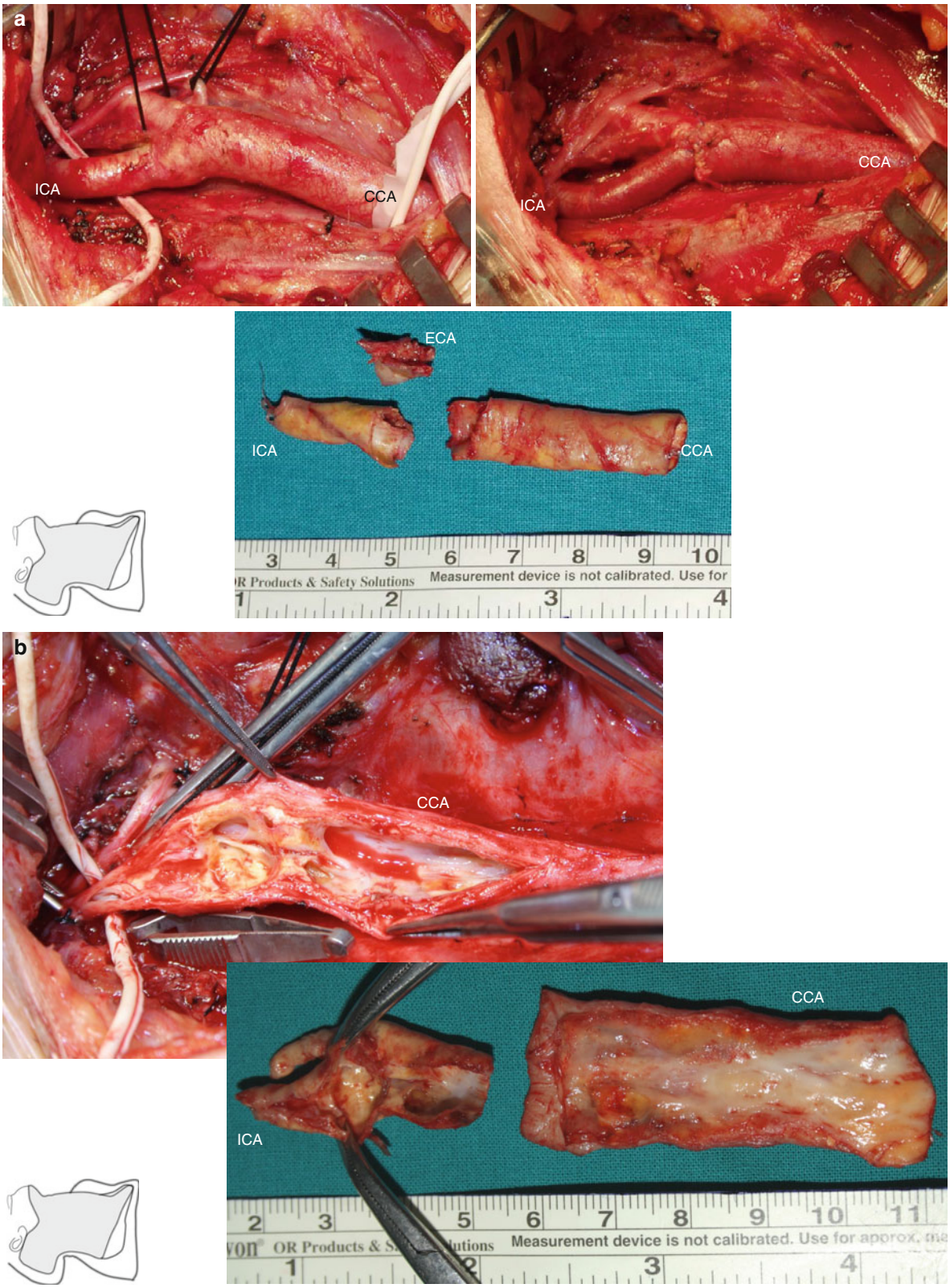
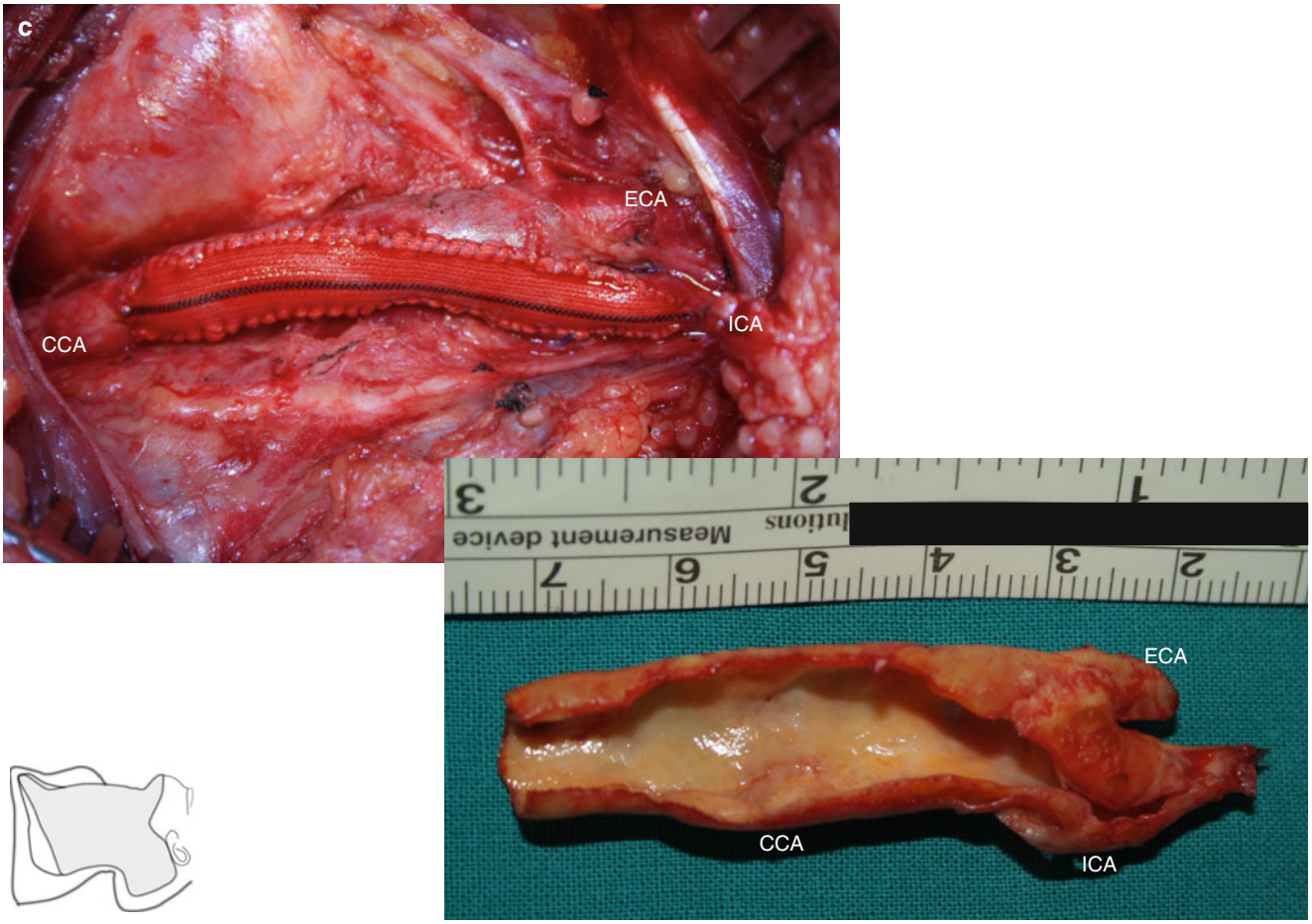


Fig. 13.16 CEA extended over the CCA. Panel (**a**) intraoperative aspect of the right carotid bifurcation. Endarterectomy was extended over the CCA, with a long plaque (almost 4 cm) excised by everting the CCA. Panel (**b**) aspect of the carotid plaque, both in situ and after excision. Note the multilevel sites of obstruction to flow and the complicated character of the plaque. The plaque on the CCA depicts also a conspicuous lipid core and is also ulcerated. Panel (**c**) another example of a longer endarterectomy plaque and the aspect of the patch which surpasses the regular dimensions (almost 7 cm in this patient). Note also the medium-degree stenosis on the CCA but with ulcerated plaque



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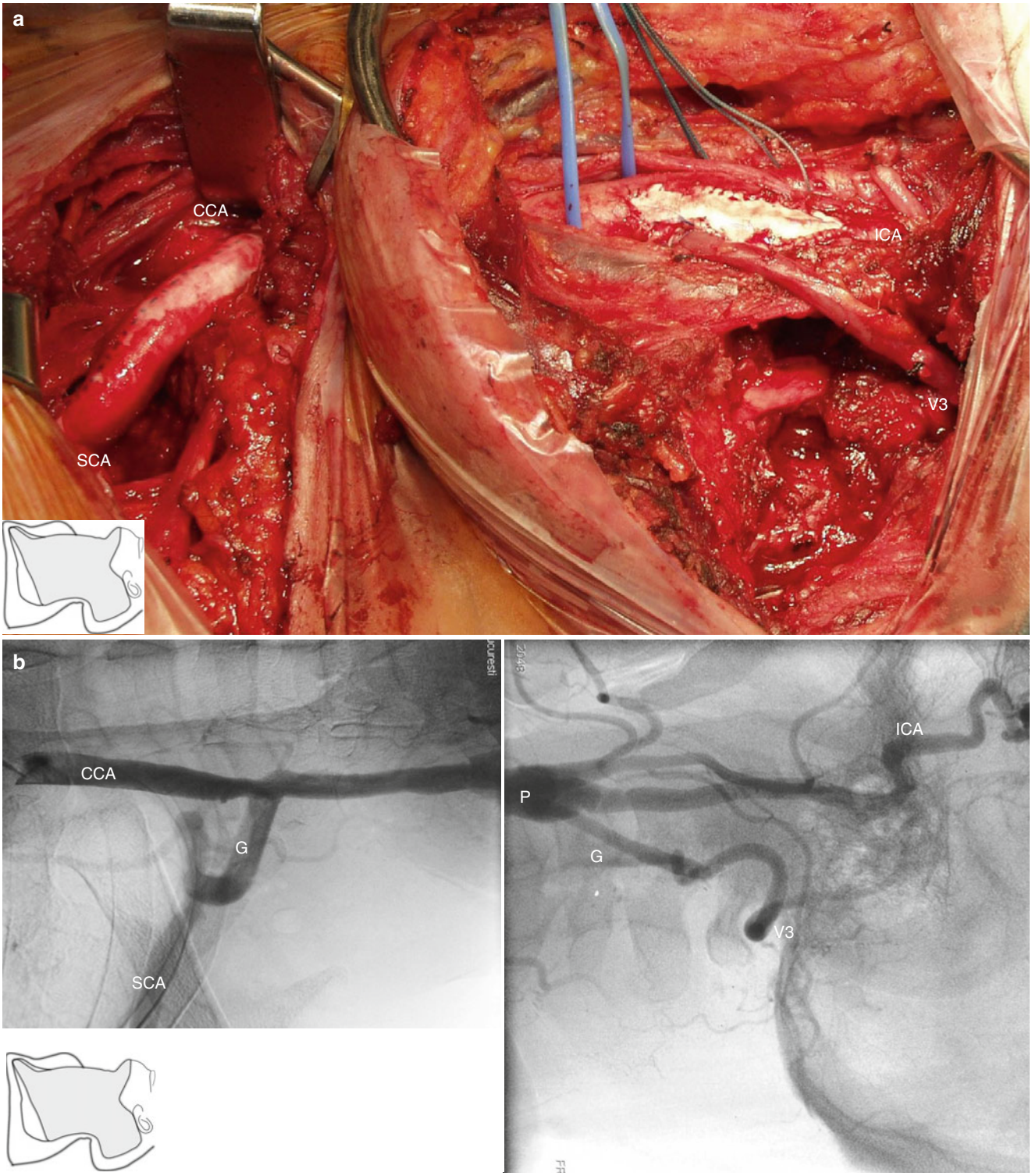

Fig. 13.17 CEA + *CCA-to-SCA bypass* + bypass on V3. The complex of revascularizing the SCA, the VA, and the CEA is presented here. Panel (**a**) intraoperative aspect. Two parallel horizontal incisions are performed to expose the vessels: the supraclavicular incision for the CCA and SCA. The superior incision for exposure of the carotid bifurcation and the V3. The CCA-to-SCA bypass was performed first with a PTFE graft. The distal end of the saphenous graft (*G*) was anastomosed to the V3. The CEA and patching of the carotid bifurcation were subsequently performed. Upon completing the insertion of the patch, the proximal end of the saphenous graft was anastomosed to the carotid bifurcation. No shunt was used. Panel (**b**) angiographic aspect of the arterial reconstruction. Both grafts are indicated (*G*): on the left, the PTFE graft and on the right side, the saphenous graft. The carotid bifurcation has become a *trifurcation*

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Cervico-cerebral Arteries Dissection

14

Florina Antochi and Athena Mergeani

14.1 Cervical Artery Dissection

14.1.1 Epidemiology, Pathophysiology, and Risk Factors for Cervical Artery Dissection

Cervical artery dissection (CAD) is defined as a splitting at some point in the artery's lining and the formation of an intimal flap, which allows blood to penetrate into the vessel wall [1]. It represents a major cause of cerebral ischemic events in young adults, manifested either as stroke or as transient ischemic attack, but it also can lead to various clinical symptoms, some of which are benign such as headache, neck pain, Horner's syndrome, and cranial nerve palsy [2].

The incidence for CAD is low in general population; the incidence rates for internal carotid artery dissection have been reported to be 2.6–2.9 per 100,000 [3]. The internal carotid artery is more affected than the vertebral artery. According to Redekop, the annual incidence of spontaneous carotid artery dissection is 2.5–3 per 100,000, while the annual incidence of spontaneous vertebral artery dissection is 1–1.5 per 100,000. Overall, dissections are estimated to account for only 2 % of all ischemic strokes [4], and they are common in young adults with a mean age of 44 years and may account for as many as 20 % of strokes in patients younger than 30 years [5]. CAD is rare in patients older than 65 years. A slight predominance in males was reported in the European series (53–57 %), the age of occurrence being higher in men [2]. The cervical arteries are made up of three layers: intima, media, and adventitia. The tunica intima is the innermost layer, composed of endothelial cells supported by a thin layer of connective tissue, being thinner and more fragile than the others, and more susceptible to tearing [6]. It is the typical site of an initial defect that forms in a developing dissection. The tunica media is the middle muscular layer and the thickest layer. The tunica adventitia is the outermost layer that mainly consists of longitudinally arranged collagen fibers. This layer merges with bone surfaces at various points along the course of the arteries, which anchors their position [7]. The extracranial parts of the cervico-cerebral arteries are more vulnerable to dissection than their intracranial parts due to the fact that they are more exposed to injury and more susceptible to strain in the case of carotid arteries and in the case of vertebral arteries due to high mobility and change of direction from vertical to horizontal after they become fixed [8].

When a tear appears in the arterial wall, blood enters between the layers of the arterial wall and forms an intramural hematoma that may determine either stenosis when it is situated between intima and media or aneurysmal dilatation when it is situated between media and adventitia [9].

Dissections are usually classified as either traumatic or spontaneous [10].

Patients with CAD may have a predisposing arterial wall weakness. Also there are described concomitant structural and functional arterial abnormalities like the presence of larger aortic root diameter [11], increased stiffness of carotid wall material and circumferential wall stress [12], endothelial dysfunction [13], and arterial redundancies (kinks, coils, or loops) [14, 15].

There are also few diseases associated with spontaneous CAD. Hereditary connective tissue disorders, in particular the vascular Ehlers–Danlos syndrome type IV, are known to be a risk factor for spontaneous dissections [16]. Spontaneous CAD has been associated with fibromuscular dysplasia, a rare, non-atherosclerotic, noninflammatory disease of the intermediate-sized arteries, which mainly affects the carotid and renal arteries [17], and with reversible cerebral vasoconstriction syndrome, a very rare condition that corresponds to vasoconstriction of intracranial arteries that manifest clinically by thunderclap headache and can lead either to cerebral ischemia or to intracerebral hemorrhage [18]. Other conditions associated with CAD are Marfan's syndrome, autosomal dominant polycystic kidney disease, osteogenesis imperfecta type I [19, 20], or Loeys–Dietz syndrome [21].

F. Antochi (✉) • A. Mergeani
Department of Neurology, University Hospital Bucharest, Milan, Italy
e-mail: flrant@yahoo.com

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CAD may also be precipitated by trauma, most often a minor trauma. Hyperextension or rotation of the neck, coughing, vomiting, sneezing, or chiropractic manipulation of the neck are reported to determine CAD [22]. It may also occur during intubations for general anesthesia or cardiopulmonary resuscitation [23, 24].

Other potential risk factors for CAD are recent infections such as purulent tonsillitis, purulent and non-purulent pharyngitis, otitis media, sinusitis [25], and respiratory infection [26]. The infections may lead to CAD via endothelial damage or pro-thrombotic mechanisms, with acute CAD being associated with high white blood cell counts and high CRP levels [15, 27].

Several studies indicated a link between CAD and migraine. Migraine, especially without aura, is more common among CAD than in non-CAD ischemic stroke (35.7 vs. 27.4 %, $P < 0001$) [28].

Recent studies suggest that vascular risk factors as hypertension, although less prevalent than in patients with a non-CAD ischemic stroke, could be a risk factor for CAD, whereas hypercholesterolemia, obesity, and overweight are inversely associated with CAD [29]. CAD is associated with hyperhomocysteinemia [30] and low levels of alpha-1 antitrypsin [31].

Genetic factors are also important for the pathophysiology of CAD, most frequently as a multifactorial predisposition and rarely as part of a single gene disorder. There was a meta-analysis which found a significant association between MTHFR 677TT genotype and CAD (OR, 1.67; 95 % CI, 1.21–2.31). Few association studies found also a link between CAD and other genes as ICAM-1 and COL3A1, but these studies had small sample size and could not be replicated [32].

14.1.2 Clinical Symptoms in Cervical Artery Dissection

Patients with CAD may present with a wide variety of clinical symptoms. They may have local manifestations, neurologic signs corresponding to the localization of ischemia, or both. For example, patients with internal carotid artery dissection may present focal signs determined by cerebral ischemic stroke or transient ischemic attack and retinal ischemia but also with local signs like headache or neck pain, Horner's syndrome, and cranial nerve palsies [33, 34]. Symptoms in patients with vertebral artery dissections may consist of signs determined by ischemia in the posterior circulation or occipital headache, posterior neck pain, or both. A rare complication of CAD is subarachnoid hemorrhage as we will present in one of our cases further on. Sometimes symptoms related to CAD may be determined by a combination of ischemic lesions and subarachnoid hemorrhage [35–37].

14.1.3 Acute Treatment and Secondary Prevention in Patients with CAD

First randomized clinical trial, in which there were 250 enrolled patients, that compared antiplatelet and anticoagulant treatment for CAD found no significant difference between the two treatments and showed that recurrent stroke at 3 months has been rare. In the group treated with anticoagulants, there were less ischemic events than in the antiplatelet group, but this was counterbalanced by one major subarachnoid hemorrhage in the anticoagulant group [38].

The observation that the ischemic stroke in CAD is caused in the majority of cases by thromboembolism rather than by hemodynamic factors favors the use of anticoagulant therapy [39], while other arguments such as aspirin being superior to heparin in acute phase of ischemic stroke favor the treatment with antiplatelets [40].

Regarding the secondary prevention for patients with ischemic stroke or TIA and CAD, treatment with either antiplatelet or anticoagulant therapy for at least 3–6 months is reasonable (Class IIa; level of evidence B) [41].

A meta-analysis that comprised two treatment groups intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT) – IAT being defined as treatment with IAT only, IVT followed by IAT, or IAT in combination with any endovascular procedure, such as mechanical thrombectomy or stent placement – showed that in patients with CAD and ischemic stroke, thrombolysis should be performed according to the inclusion and exclusion criteria, because it seems to be safe taking into account that the rates of mortality and intracerebral hemorrhage, as well as outcome, after thrombolysis in these patients appear to be similar to the rates in stroke patients from all causes treated with thrombolysis [42].

Endovascular treatment proved to be efficient in a small series of cases [43, 44]. Stents are useful in maintaining the patency of the affected vessel by obliteration of the false lumen and preventing the apposition of the dissected part and the vessel wall [45].

According to the ASA/AHA guidelines for the prevention of stroke published in 2014, the endovascular treatment should be considered in patients with extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite medical therapy (Class IIb; level of evidence C) [41].

In our opinion and experience, the endovascular treatment should be performed only in selected cases after an accurate evaluation of the patient regarding the clinical status and evolution of symptoms, the laboratory, ultrasonography, and imaging findings.

The surgical treatment may be considered in patients with CAD and recurrent ischemic event, although they received optimal medical therapy and also failed or are not candidates for endovascular treatment (Class IIb; level of evidence C) [41].

14.2 Intracranial Artery Dissection

14.2.1 Epidemiology, Pathophysiology, and Risk Factors for Intracranial Artery Dissection

Intracranial artery dissection (IAD) is characterized by the presence of a hematoma in the wall of an intracranial artery. IAD has an unknown incidence, probably lower than CAD in the European population with a mean age of onset of 50.4 years. Patients with IAD and subarachnoid hemorrhage tend to be older than those without subarachnoid hemorrhage. The risk factors and the predisposing conditions are also unknown. There are small case series reporting IAD in association with trauma, Loeys–Dietz syndrome, Marfan's syndrome, and fibromuscular dysplasia [46].

Probably due to the fact that intracranial arteries have a thicker internal elastic lamina, fewer elastic fibers in the media, and a thinner adventitia and lack an external elastic membrane compared with extracranial arteries, the dissection is frequently situated between the intima or internal elastic lamina and the media, whereas in case of CAD, it occurs in the outer layers of the media or between the media and the adventitia. When the hematoma is localized between the internal elastic membrane and the media, it causes a mass effect on the lumen but without disrupting the outer media or adventitia determining stenosis of the vessel, with or without a post-stenotic dilatation. IAD may rupture into the subarachnoid space by involving the subadventitia [47, 48]; this condition with subarachnoid hemorrhage represents about 50–60 % of all reported series of IAD [46].

IAD of the anterior circulation typically manifests as ischemic events, especially when it is associated with aneurysms, while dissections of the posterior circulation are usually associated with subarachnoid hemorrhage [49–51], this observation being supported by the cases of intracranial dissections described later in this chapter.

The mechanism of the ischemic event in case of IAD could be either hemodynamic, thromboembolic, or due to occlusion of a perforating artery by the mural hematoma [46].

14.2.2 Clinical Symptoms

Clinical symptoms in patients with IAD may be determined by mass effect secondary to pseudoaneurysm formation, which causes compression on the brainstem or cranial nerves [52],cerebral ischemia, subarachnoid hemorrhage, or rarely by a combination of those [53]. It is to be mentioned that prodromal headache is present in about 80 % of patients with IAD [46].

14.2.3 Treatment of IAD

Due to the fact that there are no large sample-sized randomized controlled trials regarding the treatment of IAD, the optimum therapy is not very well established. Most of the patients with IAD without subarachnoid hemorrhage received medical treatment for acute stroke and for long-term prevention of ischemic event. Surgical or endovascular treatment is performed in most of the patients with subarachnoid hemorrhage and in some of the patients without subarachnoid hemorrhage due to the risk of rupture of the dissecting aneurysm [46, 54].

In all of the next sections of this chapter, we will present instructive cases with different types of dissections with their particularities and treatment (whether medical or endovascular), after we have discussed about the general aspects of every type of dissection.

14.3 Carotid Artery Dissection

14.3.1 Common Carotid Artery Dissection

CAD affects most frequently the internal carotid artery and vertebral artery and rarely the common carotid artery, most of the time associated with aortic dissection. It was estimated that the prevalence of common carotid artery dissection (CCAD) is about 1 % from all CAD [55].

In a review published in 2012 regarding the common carotid artery dissection (CCAD), there were 43 patients with this type of dissection. 20 patients had spontaneous CCAD, 11 had traumatic CCAD, 4 cases had iatrogenic CCAD, and 12 patients presented with CCAD associated with aortic arch dissection [56]. In the experience of our daily practice, most of the patients with CCAD had also aortic dissection. These patients presented to our emergency room with signs of ischemic stroke and electrocardiography changes.

The ultrasonography of the cervical arteries is an accessible and useful exam for the detection of CAD [57, 58].

There are few pathognomonic findings like the presence of a mural hematoma and the depiction of a true and false lumen. The blood flow velocities at the site of the false lumen are decreased [59] leading to complete occlusion or peripheral embolization secondary to thrombosis [60]. Besides the presence of the double lumen, mural hematoma, carotid occlusion, or changes in flow/velocity suggesting a stenosis, an intimal flap and hyperechoic/isoechoic lesion within the vessel or a pseudoaneurysm [56] may be observed.

The imaging findings observed on CT angiography and MR angiography as well as on digital subtraction angiography are similar to those seen on internal carotid artery dissection, and these will be discussed further on in the next sections.

In this section we will present an instructive case of a young patient with CCAD and multiple embolic and

hemodynamic strokes following the dissection. It is to be remarked the association of hyperhomocysteinemia.

14.3.2 Extracranial Internal Carotid Artery Dissection

As discussed in the previous section, cervico-cerebral dissections tend to affect extracranial segments of the arteries much more frequently than intracranial segments. This increased incidence may be explained, as already stated, by the fact that this segment of the artery is more mobile and is also prone to damage by bony structures such as the vertebrae and styloid processes. The most common site of dissection involving the cervical arteries is the internal carotid artery, the extracranial internal carotid artery dissection (ICD) accounting for nearly 2.5 % of all first strokes [61, 62]. The ICDs are three to five times more common than vertebral artery dissections (VAD) [7].

The site of dissection for cervical arteries differs quite much from that of the atherosclerosis process. In case of ICD, the dissection involves the pharyngeal and distal parts of the internal carotid artery, while atherosclerosis usually affects the origin and the carotid bulb. The extracranial ICD occurs most commonly between the ages of 35 and 50, affecting both sexes equally [62].

ICDs are diagnosed on the basis of specific clinical presentation; imaging studies like conventional angiography, CT/CT angiography, MR imaging/MR angiography, and ultrasonography; and the exclusion of other diseases that affect the internal carotid artery, particularly atherosclerosis [63].

The cervical arteries ultrasonographic examination is the primary method frequently used in the evaluation of ICA dissection because of its large availability. It may give details regarding abnormalities present in ICD that may be further confirmed by magnetic resonance imaging (MRI), computed tomography (CT), and more invasive methods like digital subtraction angiography. Ultrasonography of the cervico-cerebral vessels represents a useful diagnostic tool in patients with suspicion of ICD and is also necessary in the follow-up of these patients by demonstrating spontaneous recanalization with normalization of carotid circulation or, in case of persistent occlusion, improvement of collateral blood supply [64, 65].

ICD may be identified using duplex Doppler examination by the presence of an intimal flap, a double lumen, an anechoic thrombus, bidirectional high resistance or absent flow, and high velocity [66–68].

In the color mode of the cervical arteries Doppler ultrasonography, different flow directions may be identified besides the features listed above [65]. The ultrasonographic exam may reveal the absence of atherosclerotic wall changes, an important finding that suggests non-atherosclerotic stenosis, with accelerated flow in the high cervical segment, or occlusion without a recordable signal from the internal carotid artery at any level. Transcranial Doppler is used to assess the hemodynamic consequences of the internal carotid artery occlusion or stenosis secondary to dissection with collateral flow across the circle of Willis and also the dampened pulse wave of the middle cerebral artery ipsilateral to the ICD [64].

Although MRI/MR angiography (MRA) and CT/CT angiography (CTA) have different strengths and weaknesses, these noninvasive imaging techniques are used for the confirmation of the diagnosis and also for the follow-up of the patients with ICD. The MRI axial T1-weighted fat-suppressed sequences can determine the presence of crescent-shaped hyperintense area, representing deposits of methemoglobin of the intramural hematoma within the false lumen, around an eccentric flow void corresponding to the vessel lumen [63].

The subacute intramural hematoma may also be identified by time-of-flight (TOF) MRA, because it does not suppress completely stationary tissues with short T1 values, whereas phase-contrast MRA and contrast-enhanced MRA may evaluate only the vessel lumen [69].

On T1-weighted images, the mural hematoma is frequently isointense to surrounding structures during the first week and the chronic period, making it difficult to be observed, and almost invariably bright between the second week and 2 months. It becomes isointense within 6 months or disappears [70].

MRA may also reveal the presence of a dissecting aneurysm by an increase of the external diameter of the artery [71]. Diffusion-weighted MR imaging is very good in identifying acute stroke [72].

While unenhanced brain CT is useful in the diagnosis of ischemic and hemorrhagic events associated with ICD, CTA may provide high-resolution and high-contrast images of the arterial lumen and wall [69]. Narrow eccentric lumen and increased external diameter of the internal carotid artery are characteristic findings on CTA, these findings associated with thin annular enhancement being very specific but less sensitive for ICD [73–75].

The intramural hematoma may also be detected by CTA as a wall thickening but is considered less specific than a methemoglobin crescent sign [71].

The unenhanced cerebral CT scan may reveal the presence of a spontaneous crescent-shaped hyperattenuating area corresponding to a wall hematoma in cases of acute cervical ICD in the upper portion of ICA, but in CTA sequences, the intramural hematoma cannot be distinguished from a thickening secondary to atherosclerosis or thrombus, because it appears isoattenuating to the surrounding muscles [76]. The CT/CTA may also show the presence of the intimal flap or dissecting aneurysm [69].

The diagnosis of ICD can also be made by cervico-cerebral angiography, considered the method of choice, the gold standard for the ICD diagnosis, but it should be kept in mind that this is an invasive method that is indicated to be performed only if necessary because recently developed techniques of MRI/MRA and CT/CTA have been shown to be effective for visualization of dissected arteries. There are few common signs for ICDs found at the angiography examination like the string sign, a long, narrow column of contrast material that begins beyond the ICA origin and might extend to the base of the skull and the flame-shaped tapering of the lumen. The internal carotid artery is often occluded, beginning more than 2 cm distal to the arterial origin. Sometimes aneurysmal dilatation may be present, both proximal and distal and also intimal flaps [77]. In this section we present three cases of ICD, one of the cases having posttraumatic bilateral extracranial ICD (Case 14.3), and the other two unilateral spontaneous dissection (Cases 14.2 and 14.4). The endovascular treatment was performed in only one of the cases with subocclusive stenosis after 6 months from the initial event (Case 14.2). The association of ICD with migraine and respiratory tract infection in one case is to be noticed. Regarding the medical treatment, all of the patients received double antiplatelet therapy except one of the cases that initially received anticoagulation and after 3 months switched to antiplatelets.

14.3.3 Intracranial Internal Carotid Artery Dissection

Intracranial ICD are less frequent than extracranial ones [78], though it is possible for intracranial ICD to be underestimated due to the lack of specific imaging features. Intracranial ICD generally affects more younger patients than extracranial ones, most commonly in their second or third decades of life, being usually associated with large strokes and having high mortality rates of about 75 % [62].

Intracranial ICD usually involves the supraclinoid portion of the artery and often extends to the internal carotid bifurcation and sometimes into the anterior and middle cerebral artery [77].

Imaging diagnosis of intracranial ICD may be challenging due to the small size of intracranial arteries and to the subtle and nonspecific signs, which tend to develop with time. As described in extracranial ICD, the pathognomonic imaging findings are the mural hematoma, intimal flap, and double lumen, but the difference is made by the necessity of high-resolution imaging (i.e., 3 T MRI) to increase the sensitivity and specificity of images. While the mural hematoma is best evaluated by high-resolution MRI, the intimal flap is probably best seen using cerebral digital subtraction angiography [46].

The MRA sequences may show normal flow in all major cervical arteries including the extracranial part of the affected internal carotid artery but with poor flow or absence of flow of respective internal carotid artery in the intracranial part from the entrance in the skull until the dissected segment ends. The MRI/MRA may detect the presence of an intramural hematoma with different thickness from one case to another as described previously and poor flow of the ipsilateral sylvian or anterior cerebral artery.

Angiographic findings presented in extracranial ICD, like flame-shaped occlusion or irregular stenosis, are not as specific for intracranial ICD. Although cervico-cerebral digital subtraction angiography is the gold standard method for the evaluation of vessels lumen and for detection of the occlusions, stenosis and aneurysms secondary to intracranial ICD, it is recommended to be used only when other noninvasive methods of investigation like MRA and CTA are inconclusive, both imaging techniques having a high capacity of detecting these abnormalities and also in offering information regarding the vessel wall [46]. In this section dedicated to intracranial ICD, we choose to present a case of intracranial and extracranial ICD complicated with an aneurysmal dilatation which determined cranial nerves involvement causing Villaret syndrome (Case 14.5), another one case with intracranial spontaneous ICD without significant hemodynamic stenosis (Case 14.7) and one (Case 14.6) of posttraumatic bilateral intracranial ICD with important stenoses in whom angioplasty with stent was performed on both internal carotid artery (see Case 14.6). All the patients received double antiplatelet therapy but with the comment that the patient with Villaret syndrome initially received 6 months of anticoagulant treatment.

14.4 Vertebral Artery Dissection

14.4.1 Extracranial Vertebral Artery Dissections VAD

As stated earlier, VAD is less common then ICD. The most vulnerable part of the vertebral arteries is corresponding to C1 and C2 vertebrae, where the arteries leave the transverse foramen of the axis vertebra and suddenly turn to enter the cranium, this part being more predisposed to dissection [62]. VAD can also involve the proximal (V1) portion of the vertebral artery; frequently the process starts at some distance above the origin from the subclavian artery and affects the artery before it enters the intervertebral foramina at C5 or C6. Distal VADs may extend intracranially or proximally to the V2 segment [77]. Extracranial VAD affects women 2.5 times more frequently than men [79].

Similarly to ICD, dissections affect distal parts of the extracranial vertebral artery, whereas atherosclerosis tends to involve the proximal segments [62]. Besides the clinical manifestations described in the general part of this chapter, a

specific feature of this type of dissection is the occasional association with spinal cord infarctions determined by the involvement of branches of the vertebral artery that supply the cervical spinal cord [80].

Ultrasonography of the cervico-cerebral arteries may be a useful diagnostic tool also in patients with extracranial VAD. Color-flow Doppler examination may detect the intramural hematoma, vessel wall irregularities, dissecting membranes, tapering stenosis, true and false lumens, and intravascular echoes. Narrowed or dilated vascular segments are seen on Duplex ultrasound findings. The Doppler exam might provide indirect signs of dissection by revealing absent flow or high-resistance flow patterns at the atlas loop of the extracranial vertebral artery, and decreased velocities within proximal arterial segments that seemed normal on B-mode images and sometimes compensatory high-flow velocities in the unaffected vertebral artery [77].

The diagnosis may be confirmed by follow-up ultrasonographic exam revealing the vessel recanalization because atherosclerotic lesions rarely disappear even with optimal treatment [81].

MRI/MRA and CT/CTA are noninvasive techniques that are increasingly used in the diagnosis of VAD, allowing the visualization of the vessel wall, the presence of an occlusion, and the quantification of the grade of stenosis. Combined modern CT and MRI techniques allow the accurate assessment of the entire vertebral artery considering that the artery has a small size, and a lot of bony artifacts may be present.

CTA is widely available and is easily performed after an initial axial CT scan. The association between an increased diameter of the vessel wall thickening and luminal stenosis or occlusion is highly suggestive of VAD. Sometimes, the increase in total vessel wall diameter may lack probably due to subintimal rather than intramural or subadventitial dissection [82].

When using digital subtraction angiography, the diagnosis is commonly established by the presence of imaging findings like pseudoaneurysms, intimal flaps, or a double-lumen appearance, but sometimes these features are lacking. More often, nonspecific findings such as irregular stenoses or occlusions are observed when digital subtraction angiography is performed, but these may also be detected in arteries with atherosclerosis or partially recanalized embolic occlusion. Therefore, in these cases, the diagnosis is made by the association of angiographic findings, clinical presentation, and follow-up studies. Advances made in the latest years regarding CT and MR techniques permit CT and MR angiography to replace digital subtraction angiography in the diagnosis of VAD in selected cases because they can show the intramural hematoma itself, which is especially important in the diagnosis of dissection with subtle luminal abnormalities or nonspecific occlusion. In one study, it was found that CTA is also excellent in detecting VAD, with a sensitivity of 100 % and a specificity of 98 % when compared with extracranial IAD that has been reported to have a sensitivity and specificity of 100 % [74, 76].

MR imaging has proven to be less sensitive for diagnosing VAD than ICD [71] probably due to the fact that vertebral arteries have a smaller size than carotid arteries and because it is difficult to distinguish the methemoglobin crescent sign from normal epidural venous plexus [63]. Further on, we present a case of extracranial VAD with occlusion of the vertebral artery (Case 14.8) and a second case (Case 14.9) that illustrates the complications that may appear during angiography confirming the observations from the literature that this invasive investigation should be performed only in selected cases taking into account its inherent risks. In this case during angiography the subclavian artery dissected and it was necessary angioplasty with stenting of both the subclavian artery that had a dissection acquired during the procedure but also of vertebral artery.

14.4.2 Intracranial Vertebral Artery Dissections

Opposite extracranial VAD, intracranial VAD is more common in men, more than 50 % of intracranial VADs being associated with subarachnoid hemorrhage [83]. Basilar artery dissections are very rare, being associated with significant morbidity and mortality [84].

When dissecting aneurysms of the vertebrobasilar circulation are suspected, MRA may replace cerebral angiography if there are necessary repeated evaluations, because in the latest years, multiple studies were performed that show that the findings on MRA in case of dissecting aneurysms are concordant to those seen on cerebral angiography [85].

Intracranial VADs cannot be directly evaluated by ultrasonography; the diagnosis in such circumstances is made by the presence of indirect signs like high-resistance flow pattern that indicates distally obstructed flow with a normal caliber of the artery. When the distal intracranial segment of the vertebral artery is occluded and cannot be visualized, transcranial duplex imaging, with the use of contrast agents if necessary, may be useful for the confirmation or support of the diagnosis [81].

Even in this case, additional imaging investigations like CT/CTA and MRI/MRA discussed earlier are needed for an accurate diagnosis, and in selected cases, digital subtraction angiography may be the only method that confirms the diagnosis. To point out all the issues discussed above for this section, we present an interesting case of intracranial VAD associated with subarachnoid hemorrhage in which the imaging findings were very helpful, but the lumbar puncture was essential for an accurate diagnosis.

Figure 14.10

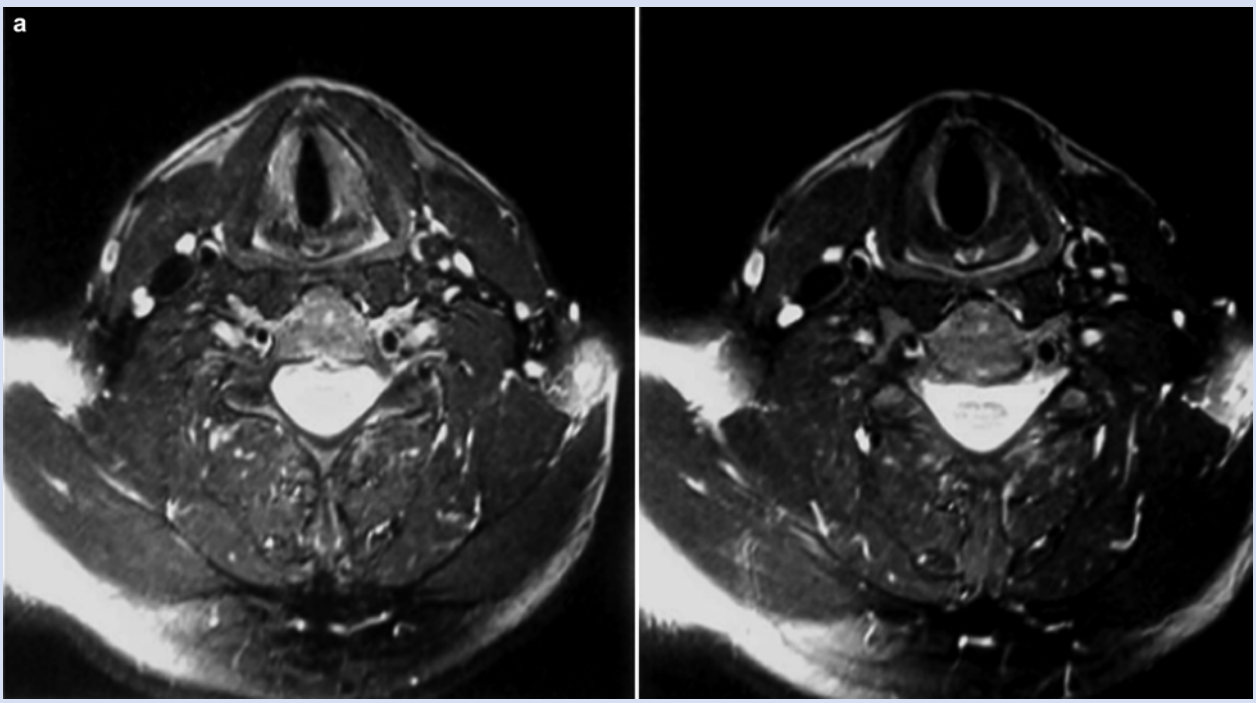
Image Gallery

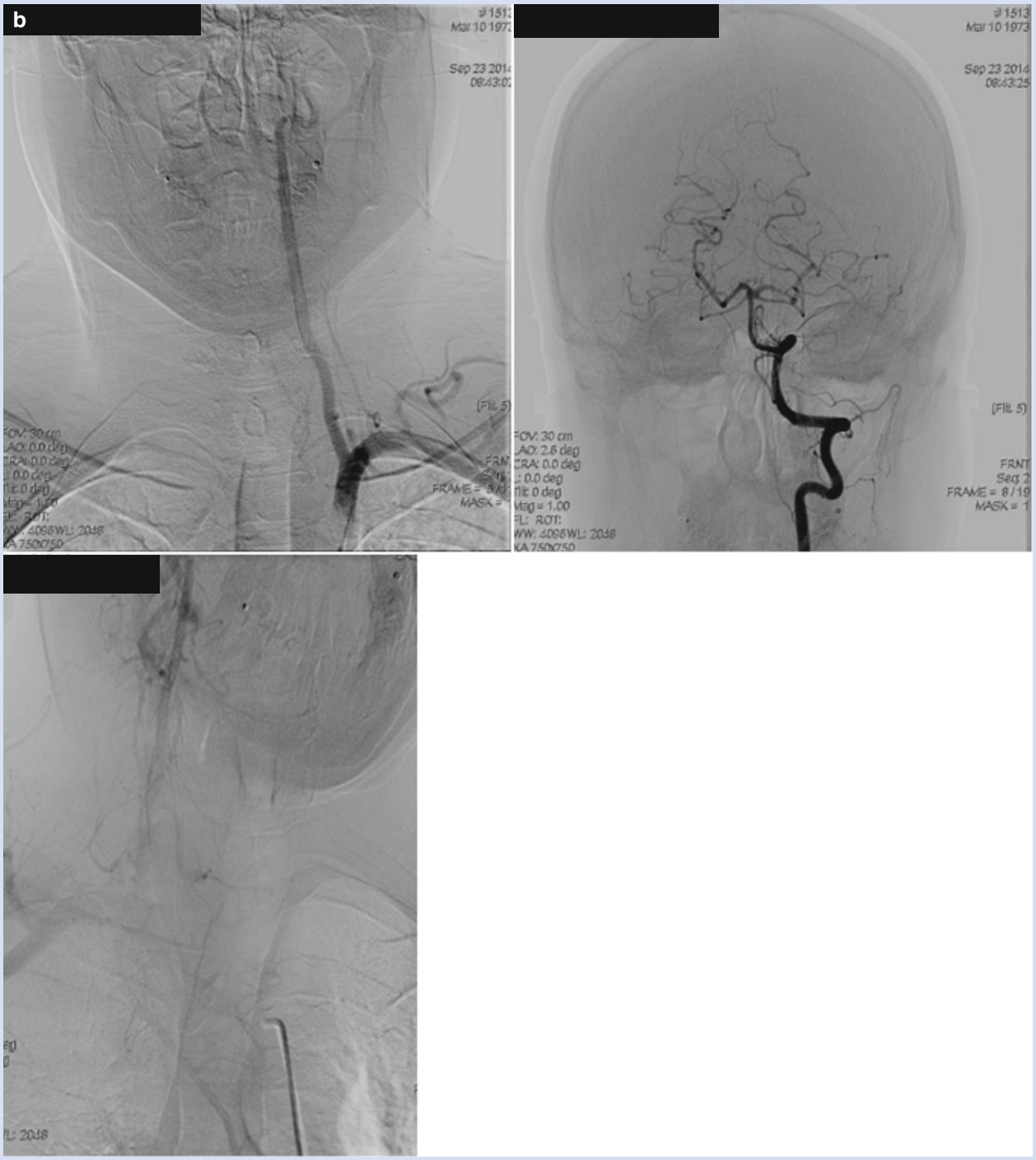
Case 14.1: A case of spontaneous CCAD associated with hyperhomocysteinemia

- 42-year-old male
- Medical history of ischemic stroke 3 weeks before admittance, hyperhomocysteinemia and hyperuricemia

Ultrasonography of the cervico-cerebral vessels revealed the presence of a hypo-/isoechogenic image in the medium 1/3 of the left common carotid artery with uniform narrowing of the arterial lumen up to the bifurcation. The right carotid artery and vertebral arteries were normal without atheroma plaques. *Cerebral MRI* revealed the presence of multiple areas of ischemia in the superficial and deep territories of left middle cerebral artery and watershed ischemic area between anterior and middle cerebral artery.

MRA and *MRI of the neck with i.v. contrast* (*panel A*) showed medial and anterior thickness of the wall of the left common carotid artery on a length of 32.1 mm compatible with CCAD. *Cervico-cerebral digital subtraction* (*panel B*) depicted the narrowing of the left common carotid artery but without significant hemodynamic stenosis. The patient received treatment with double antiplatelet therapy with aspirin and clopidogrel.

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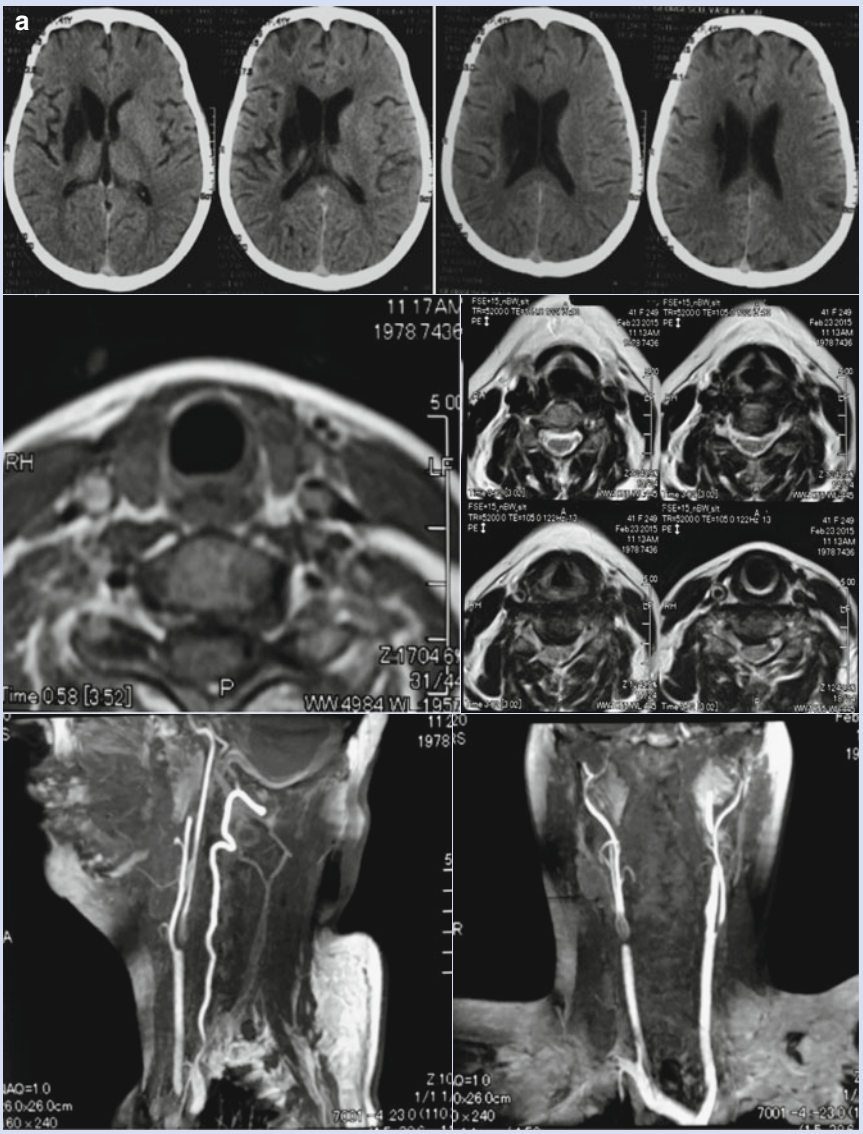
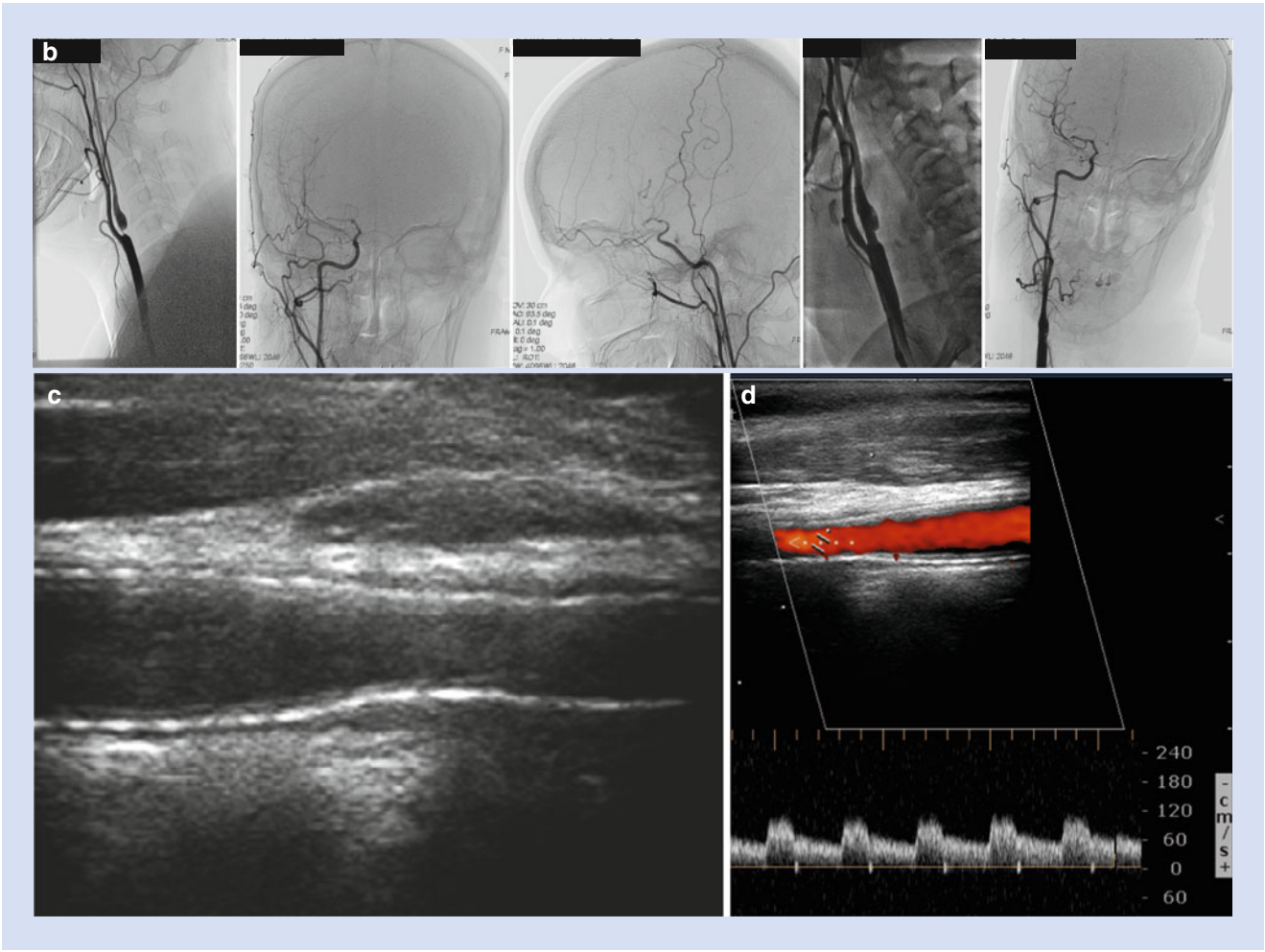
Case 14.2: A case of spontaneous right extracranial ICD with severe stenosis

- 41-year-old female
- Medical history of hypertension but without treatment
- Suffered an ischemic stroke 6 months before admittance

Ultrasonography of the cervico-cerebral vessels revealed the presence of a subocclusive stenosis of the right internal carotid artery. *Cerebral CT scan* (*panel A*) showed the presence of an ischemic hypodensity in the territory of the deep branches of the middle cerebral artery. *MRA* and *MRI of the neck with i.v. contrast* (*Panel B*) showed circumferential thickness of the wall of the right common carotid artery with a high-grade stenosis at the origin of the right internal carotid artery having a diameter of approximately 4.5 mm on a length of 6 mm. *Cervico-cerebral digital subtraction angiography* (*Panel C*) confirmed the presence of the subocclusive stenosis at the origin of the right internal carotid artery with reduced intracerebral filling of the right middle cerebral artery and right anterior cerebral artery from the left internal carotid artery. *Angioplasty with stent* was performed without any peri- or post-procedural complications. *Ultrasonography of the cervico-cerebral vessels* (*panel D*) performed 7 days later revealed the patency of the right internal carotid artery without signs of thrombosis. We started the treatment with double antiplatelet therapy with aspirin and clopidogrel.

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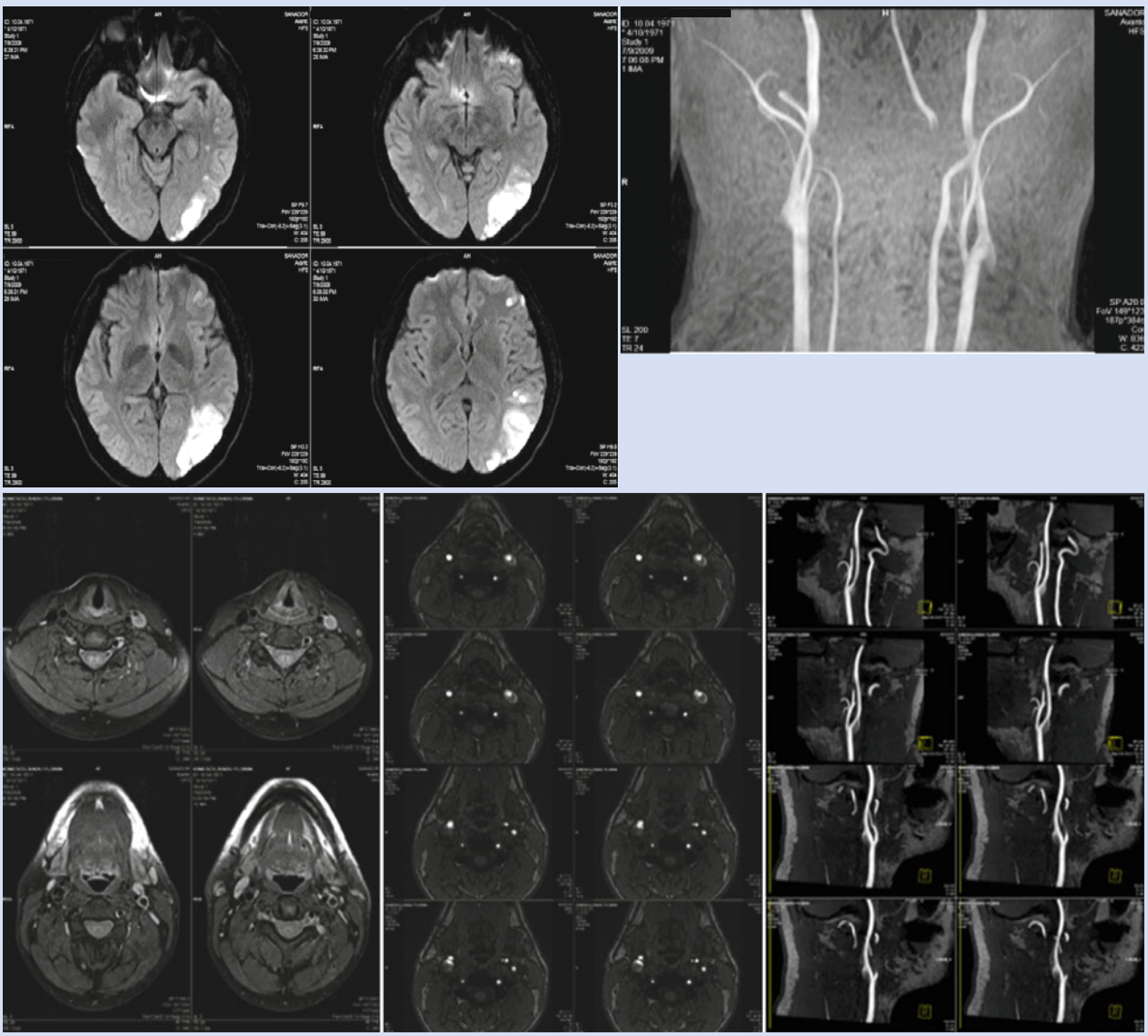
Case 14.3: A case of posttraumatic bilateral cervical ICD

- 38-year-old male, former smoker, occasional alcohol consumer; no drug abuse with multiple chronic dental inflammatory foci
- Sudden movement of the head and neck 4 days before admittance
- 2 days before admittance: right upper limb paresthesias for a few hours
- Short episodes of impaired speech in the last 12 h prior to admittance

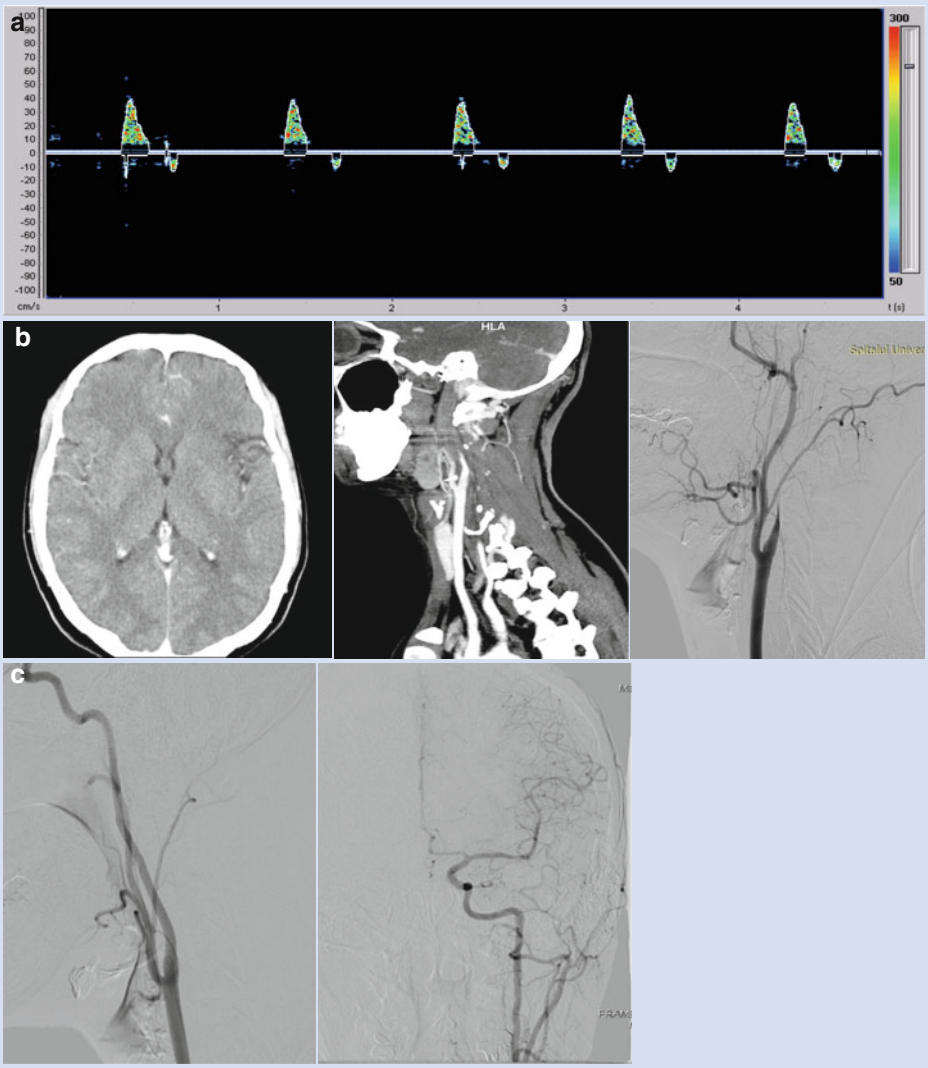
Cerebral and cervical region MRI and MRA with i.v. contrast showing the presence of bilateral cervical ICD and multiple zones suggestive of subacute ischemic infarcts in the left cerebral hemisphere. Anticoagulant therapy was initiated. The patient remained free of symptoms. *The 3 months follow-up using ultrasonography and cervical MRI* showed recanalization of the arteries and the patient was switched to antiplatelet therapy due to the presence of an ischemic stroke for the secondary prevention.



Case 14.4: A case of spontaneous extracranial ICD with recanalization

- 39-year-old female
- Medical history of migraines without aura, in the last several years, and an upper respiratory tract infection with fever and cough 3 weeks before admittance
- Admitted for abrupt onset of slurred speech accompanied by left laterocervical pain which developed a week before presentation.

Cerebral CT scan demonstrated early signs of cerebral ischemia in the left middle cerebral artery territory. *Doppler ultrasonography examination of the cervico-cerebral arteries* (A) exhibited the presence of a thin flapping fold of the vessel wall, distal to which a thrombus occluded the origin of the left internal carotid artery. *CT angiography* (B) illustrated gradually narrowing of the left internal carotid artery, with the absence of blood flow at the level of the second cervical vertebrae and a circumferential parietal hematoma. *Cerebral angiography* (C) confirmed the occlusion of the left internal carotid artery at the origin and the presence of collateral flow through the circle of Willis. The patient underwent a favorable course on receiving dual antiplatelet therapy with aspirin and clopidogrel. At the 3 months follow-up visit, the ultrasonography of the cervico-cerebral arteries revealed almost complete spontaneous recanalization of the left internal carotid artery, also confirmed by cerebral angiography, which demonstrated recanalization, with irregularity of the artery wall and a good intracerebral perfusion.



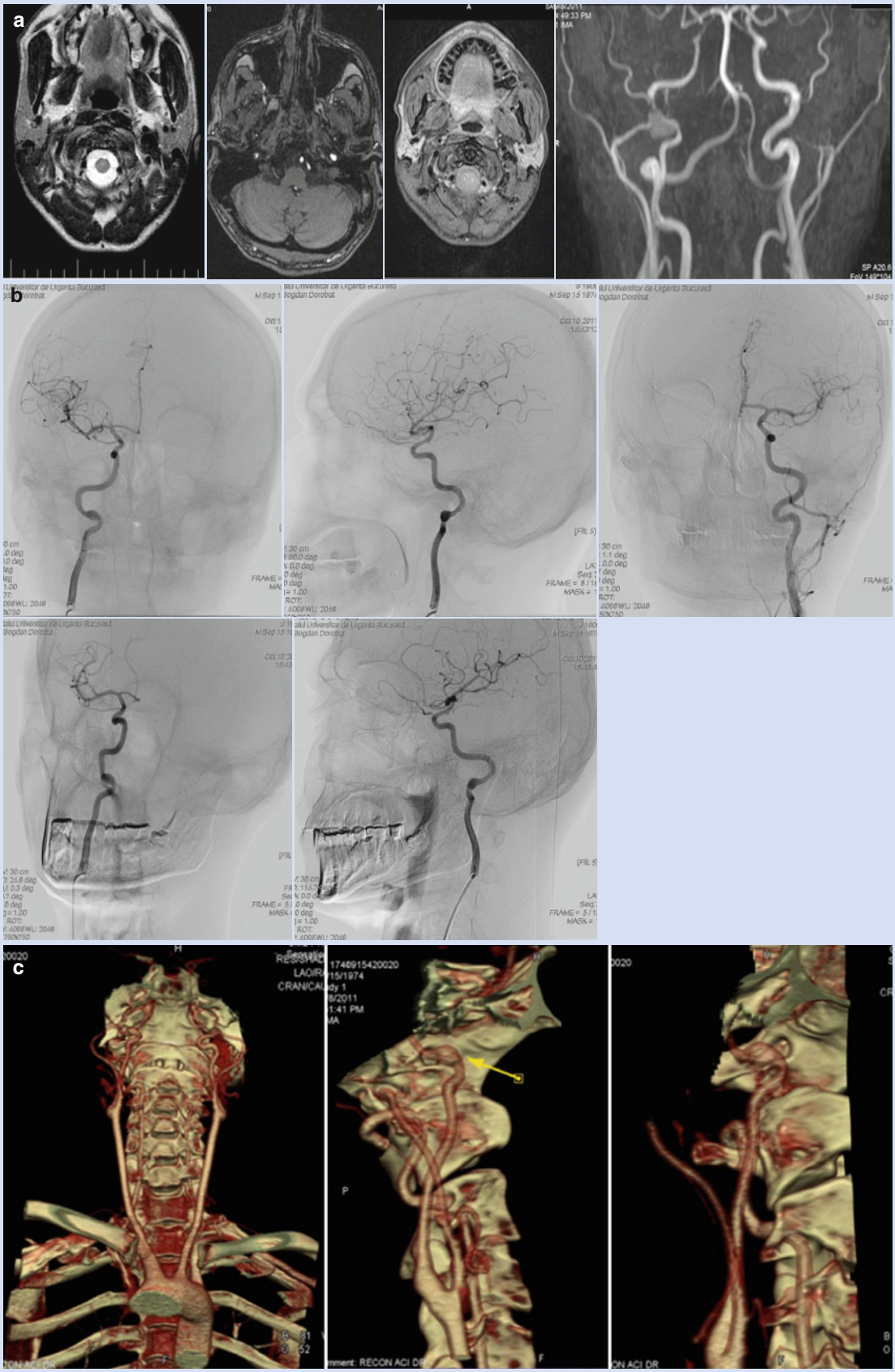
Case 14.5: A case of spontaneous ICD with fusiform aneurysm and Villaret syndrome

- 37-year-old male
- No known history of any disease, also no family history suggestive of any disease
- Presented to the hospital 2 weeks after sudden onset of left laterocervical pain associated with difficulty in swallowing and pupillary abnormalities after lifting heavy weights; the symptoms attenuated over time and upon arrival they were minimal.
- Clinical examination revealed a right Horner syndrome, involvement of the cranial nerves IX, X, XI, and XII on the right side.

Cerebral MRI of the brain was normal. *MRA* revealed a dilatation of the internal carotid artery in the cervical segment, while *the native MRI of the neck* showed a small hematoma in the wall of the right internal carotid artery. *Cervico-cerebral digital subtraction angiography* (*B*) depicted a small fusiform dilatation of the right internal carotid artery. *CTA with 3D reconstruction* (*C*) revealed the shape, caliber, and orientation of the fusiform aneurism. *Ultrasonography of the cervico-cerebral vessels* revealed no thrombus or atheroma plaques on carotid and vertebral arteries.

- We started the treatment with oral anticoagulants with warfarin for 6 months and then switch on antiplatelet therapy with clopidogrel.
- The outcome was good; the patient did not have any new symptoms.
- The control MRI 6 months later showed the same aspect.

This is a rare case of Villaret syndrome caused by a fusiform aneurism of the right internal carotid artery secondary to a dissection of the right internal carotid artery.


a
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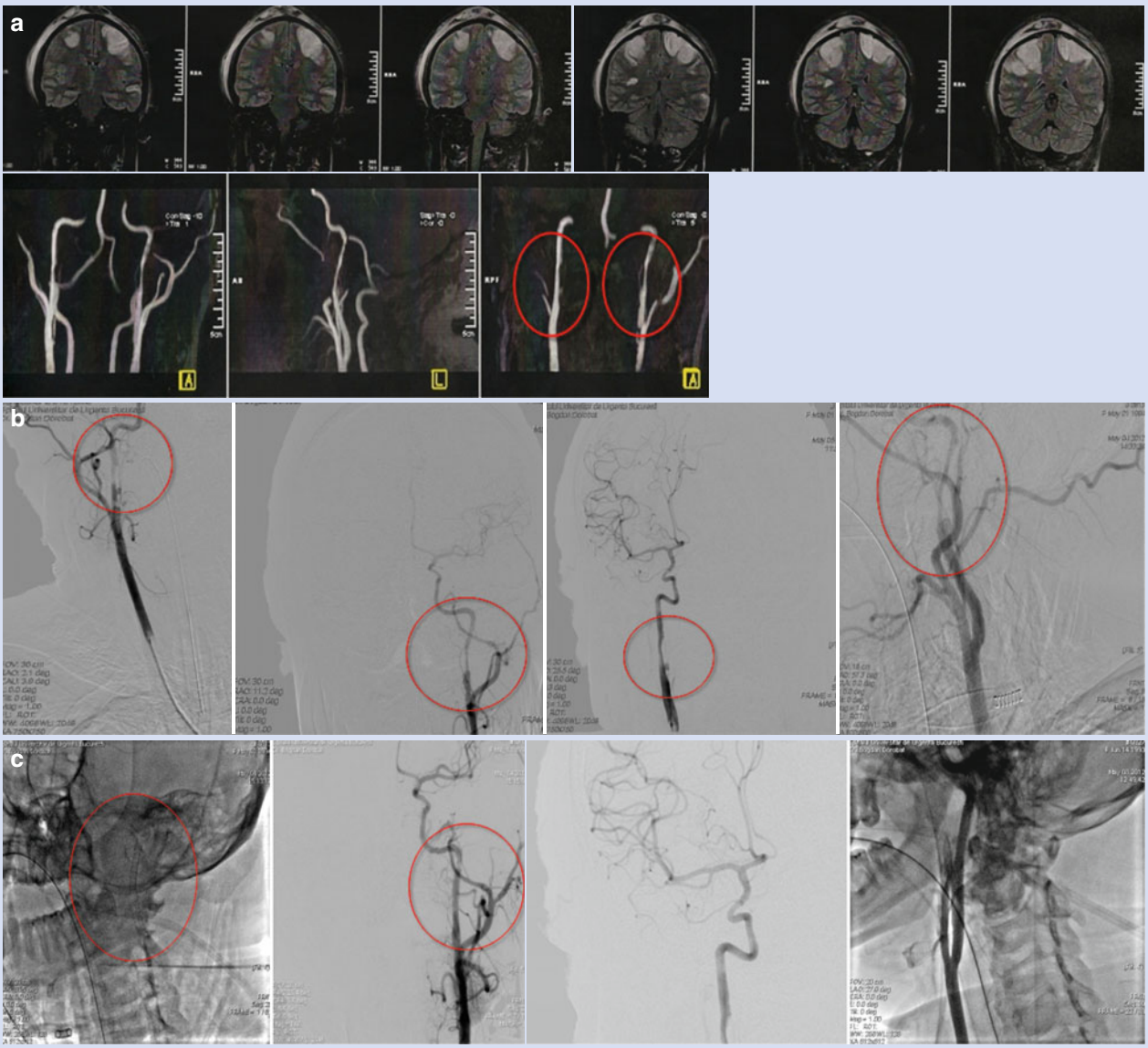
Case 14.6: A case of posttraumatic bilateral ICD in intracranial part

- 18-year-old female without any medical history
- Cervical and cerebral traumatism due to a car accident
- Tetraparesis predominantly affecting the upper limbs, areflexia, and urinary disturbances

Cerebral and cervical region MRI and MRA with i.v. contrast (A) showing the presence of bilateral intracranial ICD with multiple areas of ischemia in ICA territory. *DSA confirmed the presence of bilateral intracranial ICD* (*B*). *Percutaneous angioplasty with carotid stenting was performed* (*C*) for the intracranial part of left ICA in the distal segment from carotid canal with good intracerebral filling (left images) and for the intracranial right ICA (right images). Both ICDs determined hemodynamic significant stenoses. The patient received double antiplatelet treatment with aspirin and clopidogrel with improvement of the neurologic deficits. Control DSA performed 7 days later confirmed the patency of both ICA in the intracranial part with good intracerebral filling.

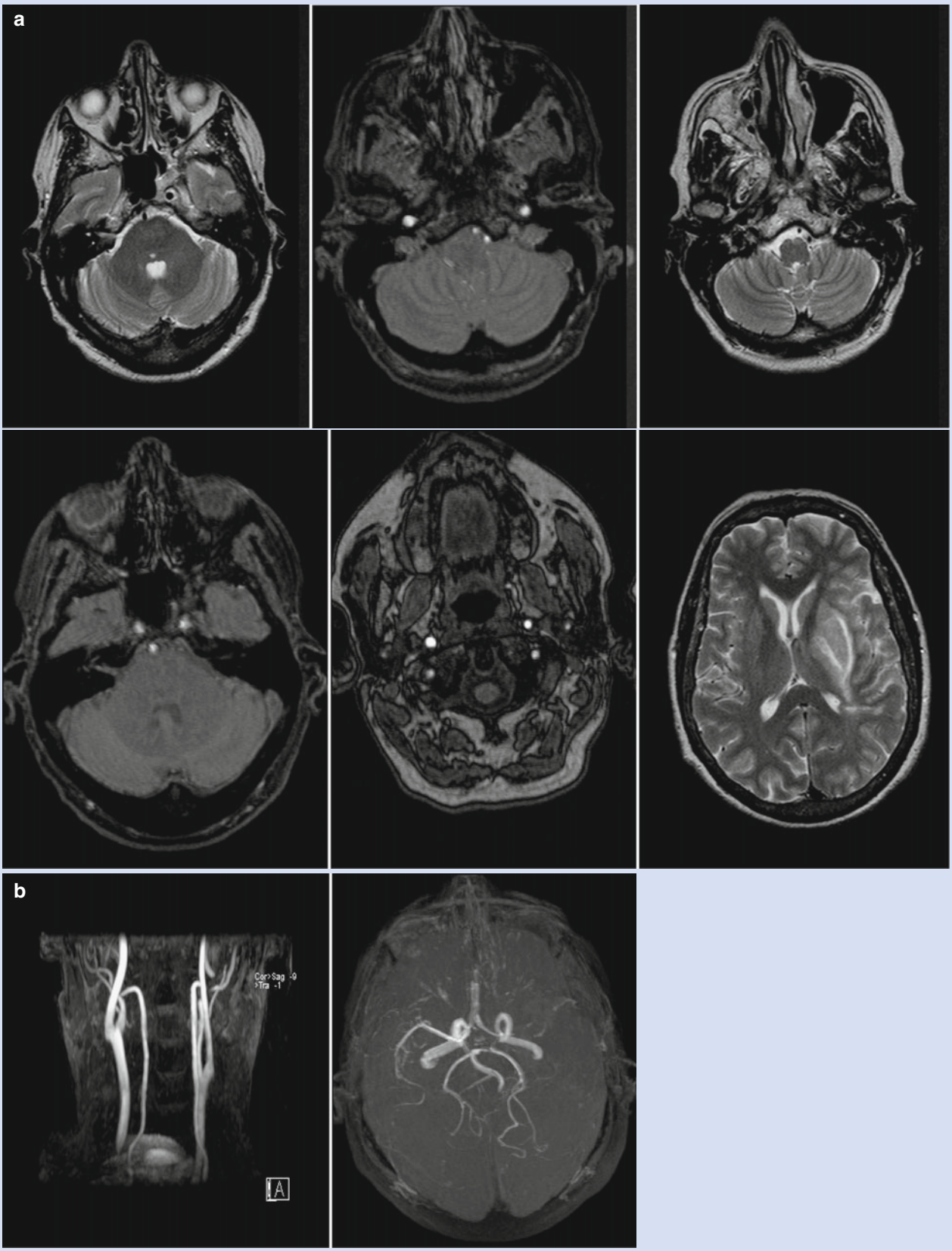


Case 14.7: A case of spontaneous intracranial ICD

- 64-year-old Caucasian female
- No medical history
- Admitted for abrupt onset of language disorder and muscle weakness on her right side

Cerebral and cervical region MRI and MRA with i.v. contrast (A) showing the presence left intracranial IAD.

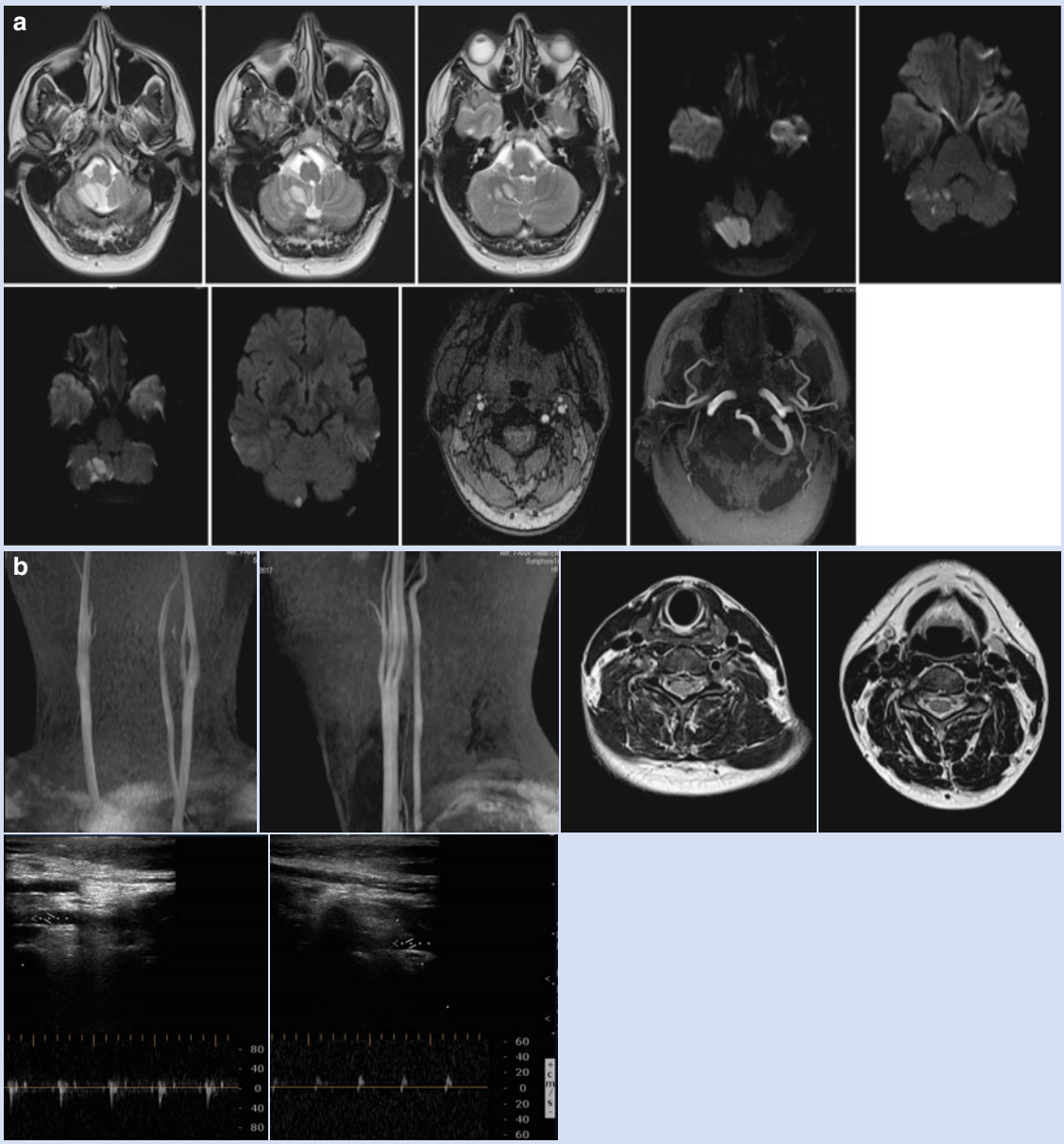
- Intramural hematoma with thickness of 2–3 mm in the intracranial part of internal carotid artery.
- Capsular–lenticular hyperintensity on T2-weighted MRI in the territory of deep branches of the left middle cerebral artery.
- Normal flow in all major cervical arteries including left internal carotid artery but with poor flow of the left internal carotid artery in the intracranial part (reduced with approximately 50 %) from the entrance in the skull till the supra-clinoidian segment.
- Poor flow of the left sylvian artery visible only in the first part of the M1 segment (B). The patient received double antiplatelet therapy with aspirin and clopidogrel with a good outcome. Digital subtraction angiography was not performed due to the fact that the diagnosis was confirmed by MRI/MRA, and there were no recurrent ischemic events that would lead to the indication of endovascular treatment.


a
b

Case 14.8: A case of extracranial right VAD

- 36-year-old male
- No medical history
- Admitted for dizziness, balance disorder, and vomiting

Cerebral MRI/MRA (A) detected multiple areas of T1-weighted hyposignal and T2 and FLAIR hypersignal with diffusion restriction on DWI in the inferior part of the right cerebellar hemisphere and the absence of arterial flow in the right vertebral artery. MRI of the neck with MRA performed 4 days later (B) showed low flow in V3 and V4 and no flow in the V2 segment of the right vertebral artery, with asymmetric wall thickness at C4–C5 level and hypointensity in T1-weighted images and hyperintensity in T2-weighted images representing the intramural hematoma and tendency to thrombosis of the right posterior inferior cerebellar artery. *The ultrasound examination of cervico-cerebral arteries* (C) showed a typical aspect of dissection, as we discussed earlier, in V1 and V2 segment of the right vertebral artery with a high-resistance flow velocities on duplex examination. The patient received treatment with double antiplatelet therapy with improvement of the symptomatology.



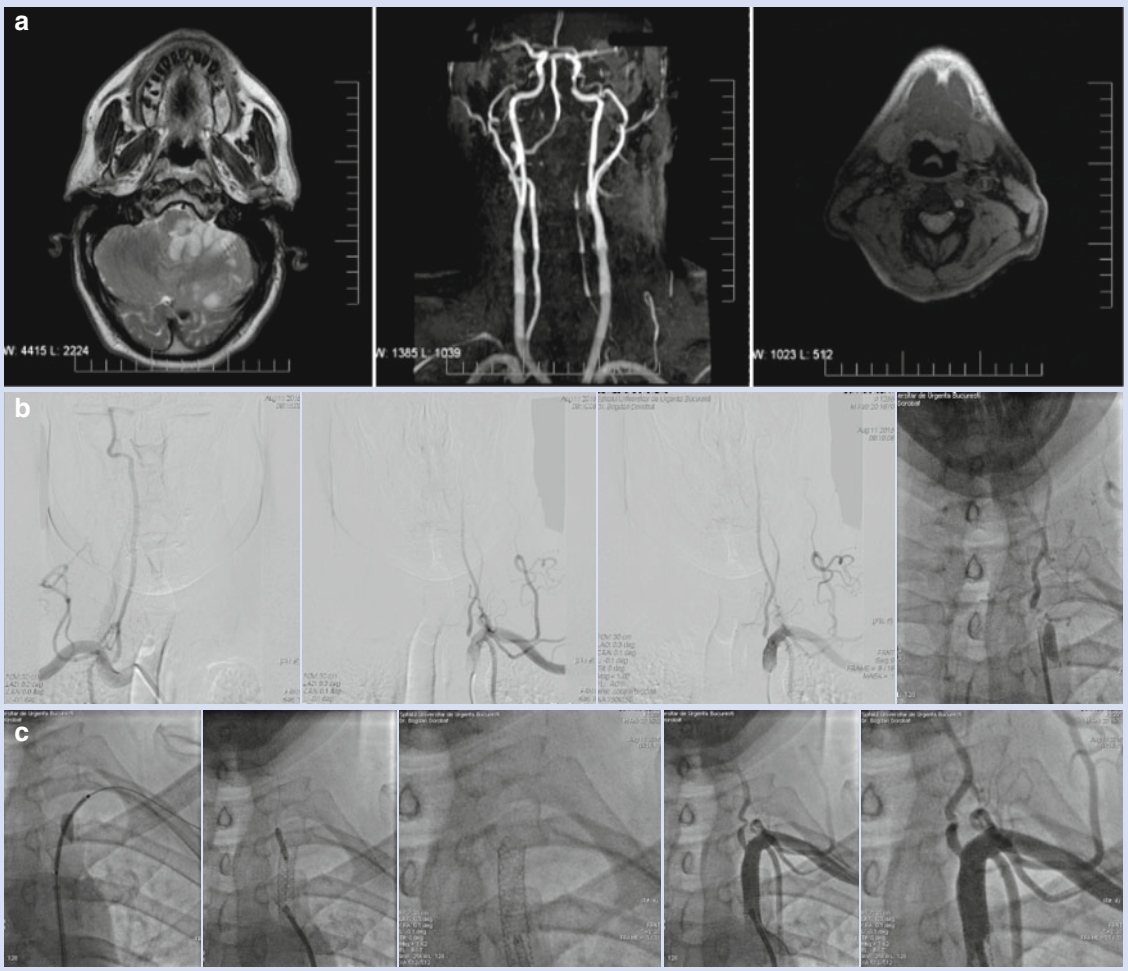
Case 14.9: A case of extracranial spontaneous left VAD

- 45-year-old male
- No medical history
- Admitted for dizziness, balance and deglutition disorder, dysphonia, coordination disorder, and motor deficit of the left limbs

Cerebral MRI/MRA detected multiple areas of T1-weighted hyposignal and T2 and FLAIR hypersignal with diffusion restriction on DWI in the inferior part of the left cerebellar hemisphere and the left medulla. *MRI of the neck with MRA* (A) depicted the presence of an intramural hematoma in the acute phase (hyperintensity in T1-weighted images and hypointensity in T2-weighted image) situated in V1 segment extending to V2 of the left vertebral artery. The patient received treatment with double antiplatelet therapy with improvement of the symptomatology.

Repeated ultrasound examination of cervico-cerebral arteries showed a typical aspect of dissection of the left vertebral artery with significant hemodynamic stenosis.

The digital subtraction angiography (*B*) performed 2 months later showed normal aspect of both carotid arteries, no stenosis of the right vertebral artery, and critical stenosis of the left vertebral artery. During the procedure, the left subclavian artery was catheterized, and when attempting to pass the guidewire in the left vertebral artery, the contrast agent injection showed a new area of dissection of the left subclavian artery. Angioplasty with stenting of the artery was decided. Afterward, the guidewire is placed in the left vertebral artery, and we proceeded to successive predilatations with the balloon of the ostium of this artery and to subsequent stenting. We achieved an optimal result at the end of the procedure without any residual stenosis or areas of dissection.



Case 14.10: Intracranial left VAD with subsequent subarachnoid hemorrhage

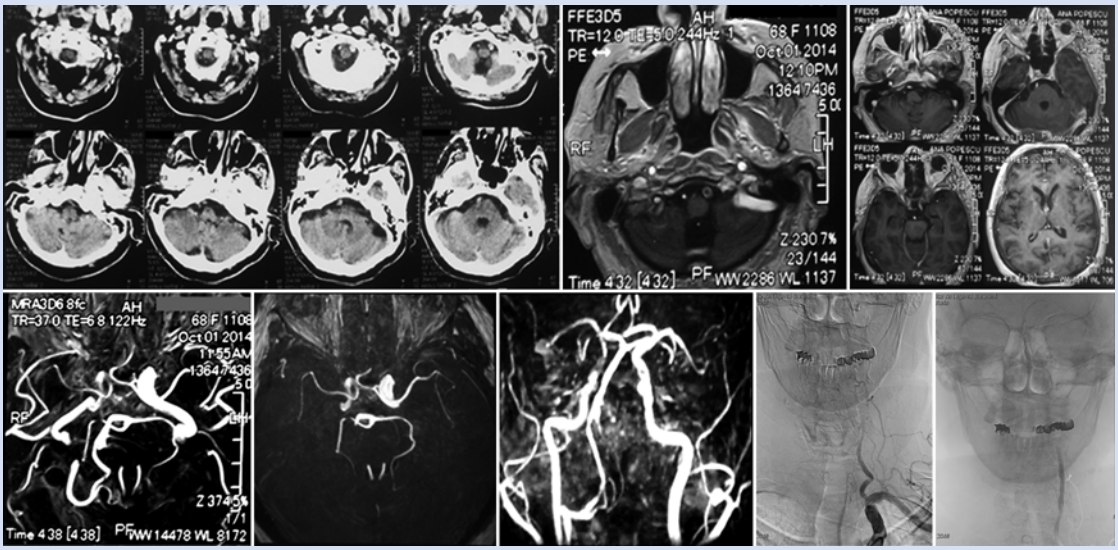
- 69 year-old, female, diabetic, hypertensive patient
- Admitted in our clinic for: dizziness, balance disorder, vomiting, transient neck pain
- Neurological examination: tendency to retropulsion, no other neurological signs
- Few days after her admittance in the clinic, the patient developed intense headache, photophobia, phonophobia, neck stiffness
- Serial lumbar punctures were performed, all detected a hemorrhagic cerebrospinal fluid, the traumatic spinal tap being excluded

Cerebral CT scan showed large caliber of left vertebral artery, no signs of ischemia or hemorrhage.

Cerebral MRI/MRA detected left vertebral artery occlusion (with a thrombus in the distal V2, V3 and proximal V4 segments), suggesting a vertebral artery dissection with subsequent occlusion.

Cervico-cerebral angiography confirmed the left vertebral artery occlusion and 75% stenosis at the origin of right vertebral artery was also present.

Although the initial symptoms suggested a vertebrobasilar stroke, the evolution of the patient, the lumbar punctures and the imaging results guided to the diagnosis of VAD with subsequent subarachnoid hemorrhage. The patient received treatment with oral nimodipine and antiplatelet therapy with clopidogrel for secondary prevention of ischemic events with improvement of symptomatology.



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Extracranial Carotid and Vertebral Artery Aneurysm

15

Horia Muresian

Extracranial aneurysms of the carotid and vertebral arteries are uncommon conditions [1]. The most frequent cause is represented by atherosclerosis, generally in the context of high blood pressure. Besides, fibromuscular dysplasia, inflammatory disorders, and connective tissue disease are alternative causes for the development of aneurysms of the extracranial arteries. A distinction must be made between true aneurysms on the one hand and pseudoaneurysms/false aneurysms or anastomotic aneurysms on the other. In true aneurysms, all components of the arterial wall are present albeit modified by the disease process; the wall of pseudoaneurysms is only partially constituted by the normal arterial parietal components. Blunt trauma may lead to formation of true aneurysms, while penetrating trauma causes more frequently pseudoaneurysms. The V2 segment of the vertebral artery (VA) is particularly prone to various types of traumatic lesions, both through elongation, angulation, and contusion, direct laceration by penetrating agents or bone fragments. Mycotic aneurysms of the extracranial arteries need particular attention, as the local evolution may be complicated by failure of the vascular reconstruction and, not least, by distal embolization into the cerebral circulation.

Various types of extracranial carotid artery aneurysms are described with respect to the level and extension of the lesion: type I = isolated segment of ICA; type 2 = entire ICA including the bifurcation; type 3 = bifurcation only; type 4 = CCA and ICA; and type 5 = CCA [2]. The more proximal aneurysms are fusiform, while the distal cervical ICA aneurysms are saccular, the latter developing also toward the neck viscera and compressing the pharynx, larynx, or adjacent nerves (laryngeal recurrent, vagus, sympathetic trunk, hypoglossal). Whiplash mechanism of injury is mostly hazardous for the upper cervical ICA and V2 segments of the VA especially when the neck is also rotated.

As any other type of aneurysms, the extracranial carotid and vertebral artery aneurysms may herald their presence by the mass effect (compression of adjacent structures), thrombosis (with consequent distal hypoperfusion especially during certain postures or rotation of the head), distal embolization (again, sometimes posture dependent), rupture (and development of compressive neck hematoma or frank rupture into the pharynx), and infection. A cervical mass with systolic pulsation and expansion (in all diameters) plus local bruit may draw attention toward the presence of an aneurysm at this level. Clinical evaluation without supplementary imaging may be misleading: cervical tumors may appear as a pulsatile mass; the real extent of the aneurysm cannot be appreciated by clinical examination only; enlarged glomus tumors which are hypervascularized may appear as pulsatile masses with bruit. Extracranial VA aneurysms may manifest with phenomena of cervical nerve roots or sympathetic compression/irritation. Compression with or without thrombosis of the IJV may accompany the presence of a cervical aneurysm. Swallowing may also become difficult due to compression of the glossopharyngeal (IX), and vagus (X) nerves, or of the pharynx. In other circumstances, swallowing may induce transient ischemic attacks by embolization from the carotid aneurysm (Fig. 15.1).

Diagnostic workup must include an accurate clinical evaluation for detecting the presence of aneurysms located contralaterally, intracranially, or at other various levels (renal, splanchnic, abdominal aorta, etc.) – depending of course on the etiology of the aneurysmal disease. Imaging must certify the clinical supposition, and it must also offer important data on the nature of the aneurysm, extension, and anatomical relationships, suggesting the most indicated type of therapy or repair. Additional tests must also rule out the presence of infection. Ultrasound examination offers most valuable data (at local level) and is usually followed by angiography, CT angiography, or MRA (for further particulars at local level

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Milan, Italy
e-mail: cvsurg@hotmail.com

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and for screening for aneurysms with other locations in the same patient).

The cervical area includes numerous types of viscera and tissues; consequently, the differential diagnosis should take into account the possible presence of conditions mimicking aneurysms, such as adenopathy, tumors (especially of the thyroid, parathyroid glands, or of ectopic thyroid tissue), branchial cysts, and abscesses (peritonsilar, parapharyngeal, etc.). This holds true especially for aneurysms with conspicuous intraluminal thrombosis, which may appear less pulsatile at clinical evaluation. We also routinely recommend ENT clearance for two reasons: the general checkup of the oral, pharyngeal, and laryngeal areas on the one hand and the precise evaluation of the function of the cranial nerves IX, X, and XII in the preoperative assessment on the other. Borderline lesions or preexistent lesions or these nerves may be overlooked by the patient but may become evident after surgery, suggesting sometimes a postoperative complication.

Kinking of the CCA, ICA, or VA (V1 segment) may manifest as pulsatile masses in the neck and should be differentiated from true aneurysms. Hemangiomas and posttraumatic arteriovenous fistulas may also mimic a cervical aneurysm if deeply located and with no accompanying skin modifications. With the advent and development of numerous imaging techniques, the diagnosis is usually straightforward and inadvertent; fatal incision and drainage of "cervical collections" remain anecdotic nowadays. A particular type of lesion consists of alternating segments of stenosis and aneurysmal dilatation on a carotid artery with excessive kinking (Fig. 15.2).

The principal discussion at present is regarding the modalities of treatment. As cervical aneurysms are rare findings, there are no large or randomized studies regarding the advantage of one technique over the other. Endovascular repair appears more attractive than surgery, but the choice depends on many factors (see Table 15.1).

The accurate assessment of the entire cerebral circulation must be performed, for more reasons:

1. Coexistent aneurysms must be detected in the extra- and intracerebral territory.
2. The presence of anatomical variations of the cerebral arteries must be ruled out.
3. The diameter of the contralateral carotid and VA must be taken into account as a reference, including the definition of the aneurysm (we do not recommend following absolute diameters for the carotid artery but to take into account the largest dimension at aneurysm site over the non-diseased portion; if the first is more than twice the normal diameter, there is a clear indication for repair either endovascular or surgical).

The possibility of performing a safe ligature of the VA, e.g., in aneurysms of the V2 segment of the VA, must be considered.

The indication for repair stands also in further particulars:

- The diameter of the aneurysm (not only absolute but also relative to the remainder adjacent normal arterial segments)
- The rate of development/expansion in time
- The thickness of the arterial wall (if prone to rupture, repair is indicated no matter the diameter)
- The presence of intraluminal thrombosis
- The internal lining of the dilated artery (ulcerations, incipient dissections, etc.)
- The presence of neurological symptoms (TIAs, cranial nerve compression)
- The general condition of the patient, age, life expectancy

Carotid artery pseudoaneurysm after CEA is extremely low and has two major causes: first, dehiscence of the patch-to-carotid artery anastomosis due to very thin arterial wall after CEA or infection, and second, aneurysmatic degenerescence of the venous patch (used less nowadays).

In our surgical experience, we treated three patients with aneurysms of the carotid artery: one at the very origin of the left CCA (and adjacent aortic arch; type V), one of the distal ICA (type I), and one a mycotic aneurysm of the carotid bifurcation and ICA (type II). The cases are illustrated and explained in detail in Figs. 15.3 and 15.4.

An excellent recent review of the management of the extracranial carotid artery aneurysms is presented in the reference [3].

Aneurysms of the extracranial VA are extremely rare and recognized as major causes of trauma both penetrating and blunt. The clinical presentation can be as a cervical mass or, more frequently, as cervical radiculopathy. In other cases, VA aneurysms present as dissecting aneurysms [9]. Endovascular repair is preferred for two major reasons. First, the direct approach of the V2 segment of the VA is cumbersome, and the possibility of cervical nerve lesion is high. Second, surgical exclusion of the VA by proximal and distal ligation does not prevent the future development of the aneurysm which will continue to be fed by the numerous collaterals. As with popliteal artery aneurysms, collateral circulation results in the development of the aneurysm and rupture. Infection remains another important complication. Endovascular repair may be difficult or even impossible due to the particular development of such aneurysms (tortuous, angulated, with alternating zones of dilatation and stenosis) [4].

Table 15.1 Choice of type of repair for extracranial arterial aneurysm

Element	Surgery	Endovascular repair
Volume of aneurysm	Large and compressive aneurysm need complete excision and vascular reconstruction	Stent graft may migrate Endoleak more probable Large thrombosed cervical mass may impede physiological acts (swallowing, phonation)
Location of aneurysm: high in the neck	A distal segment of at least 4–5 mm of the ICA must be available for distal clamping and anastomosis	Higher location of aneurysm. Difficult or impossible clamping during surgery
Location of aneurysm: origin of the left common carotid artery	Unusual location but surgery is indicated	Difficult or impossible
Infection	Resection and autologous venous graft (alternatively arterial homograft)	Stent graft may maintain local infection Local infection not cured. Stent graft may be displaced or thrombose
Hostile neck anatomy/previous radiation therapy	Relative contraindication	Mostly indicated
Conspicuous intra-aneurysmal thrombosis	Surgery more indicated	Placement of stent graft with distal protection device
Inherited connective tissue disorders	Resection of the entire diseased artery beyond the aneurysm	Possibility of late dehiscence or migration of stent graft
Cranial nerve compression	Aneurysm excision and reconstruction	Not indicated
General condition of the patient and comorbidities	Aneurysm surgery requires general anesthesia	Most cases under locoregional anesthesia ± sedation

Primary aneurysms of the extracranial VA occur in individuals with hereditary connective tissue disorders. Aneurysm exclusion and reconstruction may be performed with open or combined techniques with optimal results [5].

In cases with difficult exposure or with associated occlusion/absence of contralateral VA, open repair under deep circulatory arrest was also indicated [6]; however, progressive VA occlusion for favoring the development of collateral circulation must be also taken into account.

Stroke after open surgical repair appears to occur more frequently as compared with the endovascular therapy, but such differences may be also due to the different types of aneurysms treated with each technique [7, 8].

Image Gallery

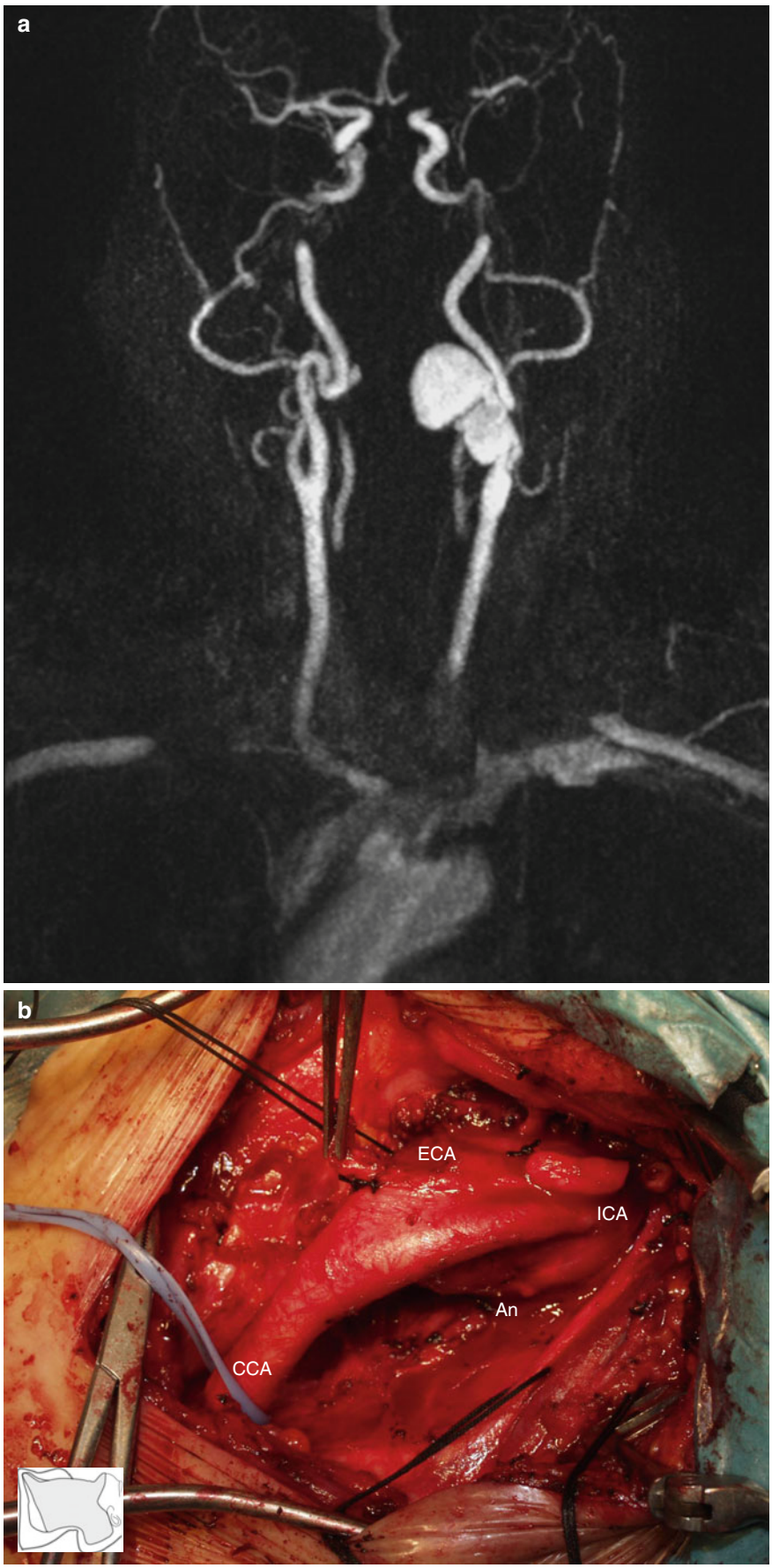
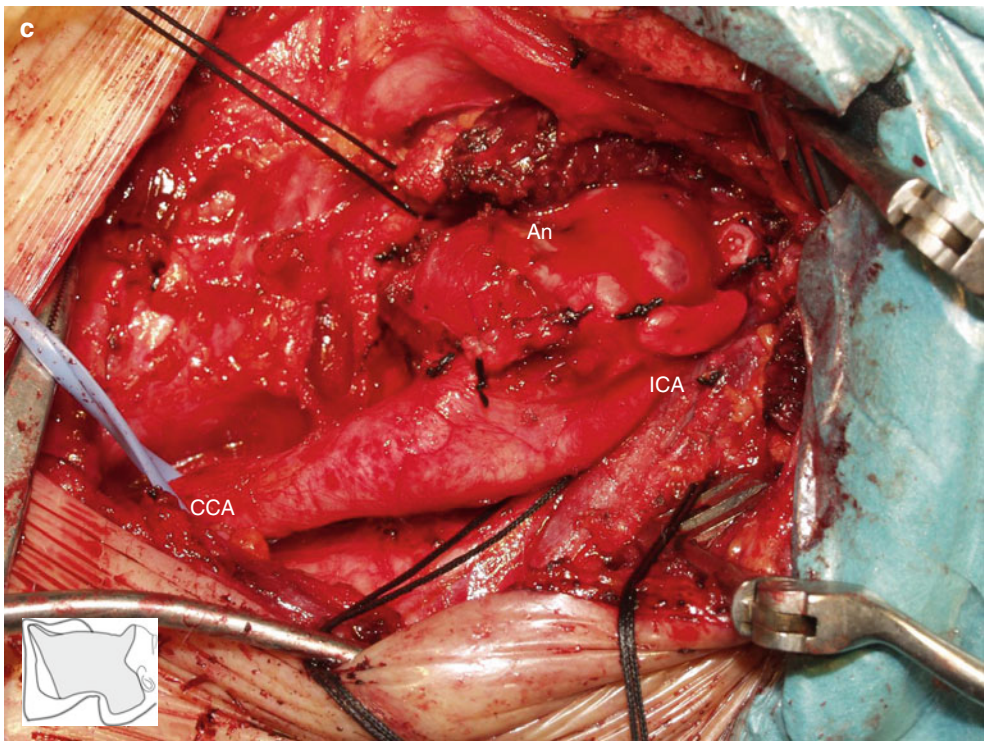


Fig. 15.1 Atypical presentation of carotid aneurysm. The patient presented TIAs with swallowing. Ultrasound interrogation subsequently completed with MRA Panel (**a**) demonstrated aneurysm of the proximal segment of the cervical internal carotid artery (ICA) on the left side. Note that the aneurysm appears as bilocular and is developed against the lateral wall of the pharynx. ENT examination confirmed the compressive effect of the aneurysm. Panel (**b**) intraoperative aspect of the left carotid bifurcation. The aneurysm is barely visible, deep to the bifurcation. Panel (**c**) mobilization of the carotid bifurcation reveals the entire aneurysm and its relationships with the lateral wall of the pharynx. Panel (**d**) the aneurysm is excised. Panel (**e**) the continuity of the carotid axis is reestablished. As the aneurysm developed on the proximal segment of the ICA, this very portion was excised *en bloc* with the aneurysm. The remaining portion of the ICA was pulled down (note on the MRA – Panel (**a**) that both ICAs depict important kinking and excess of length) and reanastomozed with the remainder part of the ICA (the anastomosis is visible just above the XII nerve). *ECA* external carotid artery, *XII* hypoglossal nerve

Fig. 15.1 (continued)



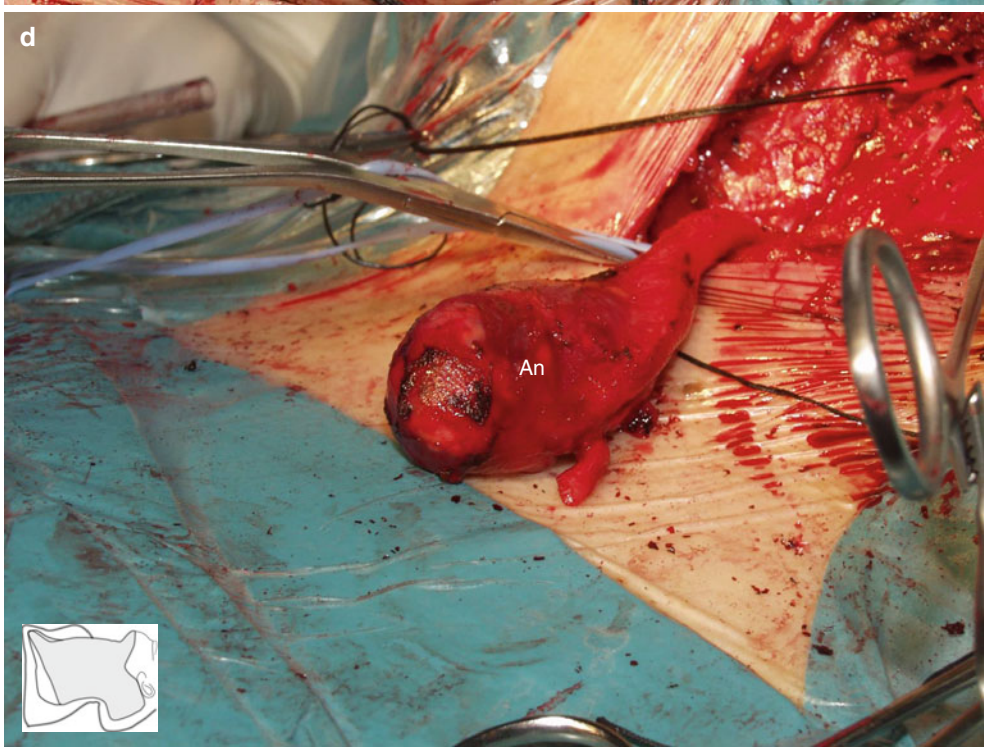
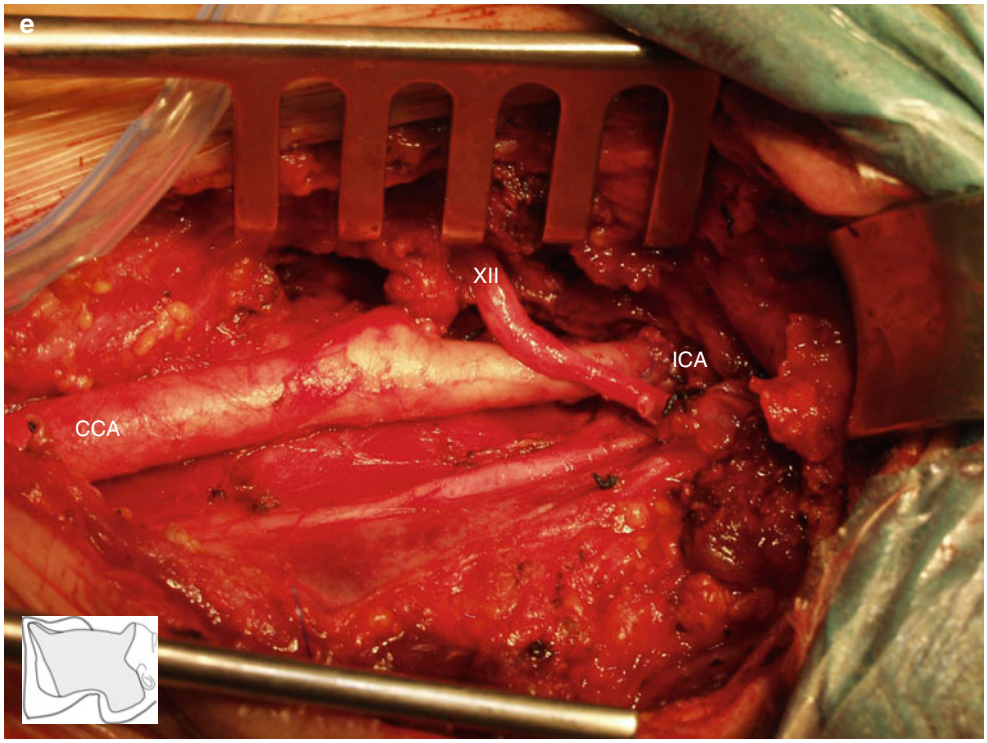


Fig. 15.1 (continued)



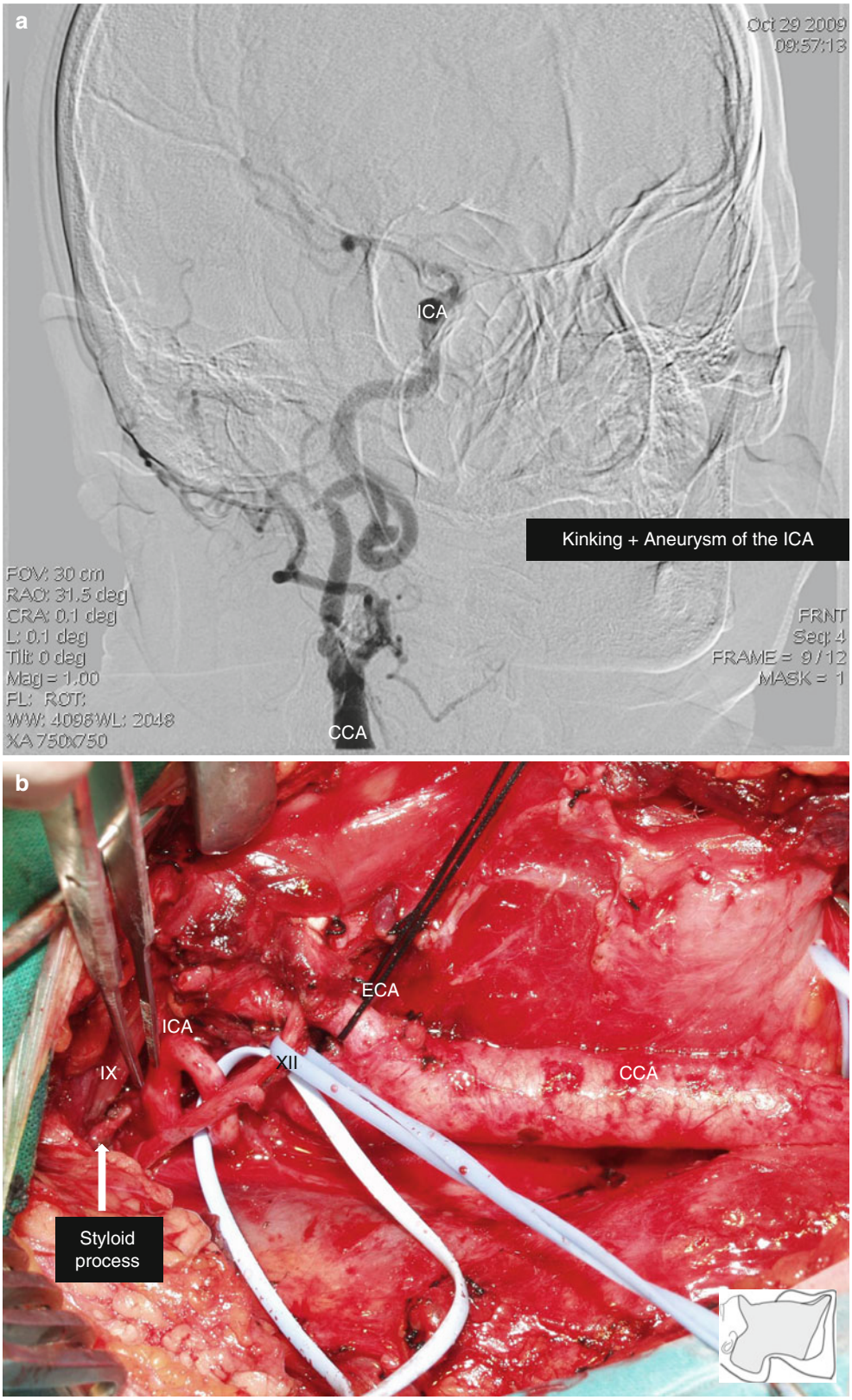
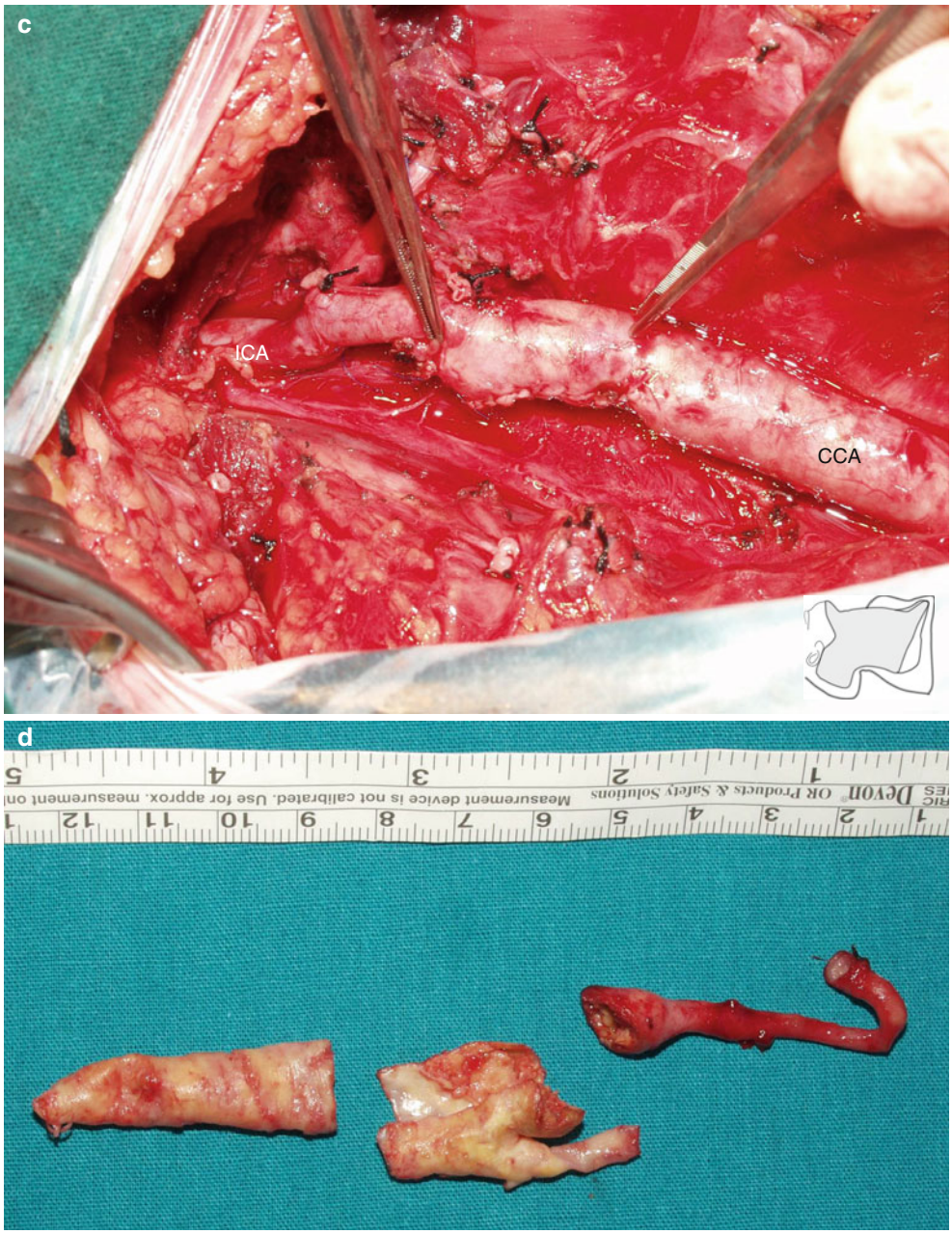


Fig. 15.2 Particular type of lesion: kinking, stenosis, and aneurysm of the ICA. All marks of atherosclerosis are present in this case: excessive kinking of the cervical ICA, stenosis, and aneurysmal dilatation. The aneurysm could have been treated by endovascular route except that the very narrow lumen just distal to the aneurysm impeded the maneuver. Panel (**a**) angiographic aspect in an oblique projection. Note that the ICA appears with a double kink; the origin of the ICA depicts a severe stenosis, and there is an additional stenosis in the first curve of the kink. The second curve shows an aneurysmal dilatation. Panel (**b**) intraoperative aspect with high exposure of the distal ICA, by dividing the posterior belly of the digastric muscle, the stylohyoid, and the styloid muscles (note the "bare" styloid process). The cranial nerves IX, X, and XII were isolated and protected. The entire diseased segment of the ICA is well exposed, up to the carotid canal of the petrous temporal bone. Panel (**c**) the diseased portion was removed, and the continuity of the right carotid axis was reestablished as in the eversion technique, by reanastomozing the ICA to the CCA (note that the XII nerve was left deep to the reimplanted ICA). Panel (**d**) the diseased portions removed. On the left, the plaque occupying the lumen of the distal CCA. In the middle, the plaque at the level of the carotid bifurcation (including the portion occupying the origin of the ECA). On the right, the distal cervical segment of the ICA, comprising the aneurysmal dilatation

Fig. 15.2 (continued)



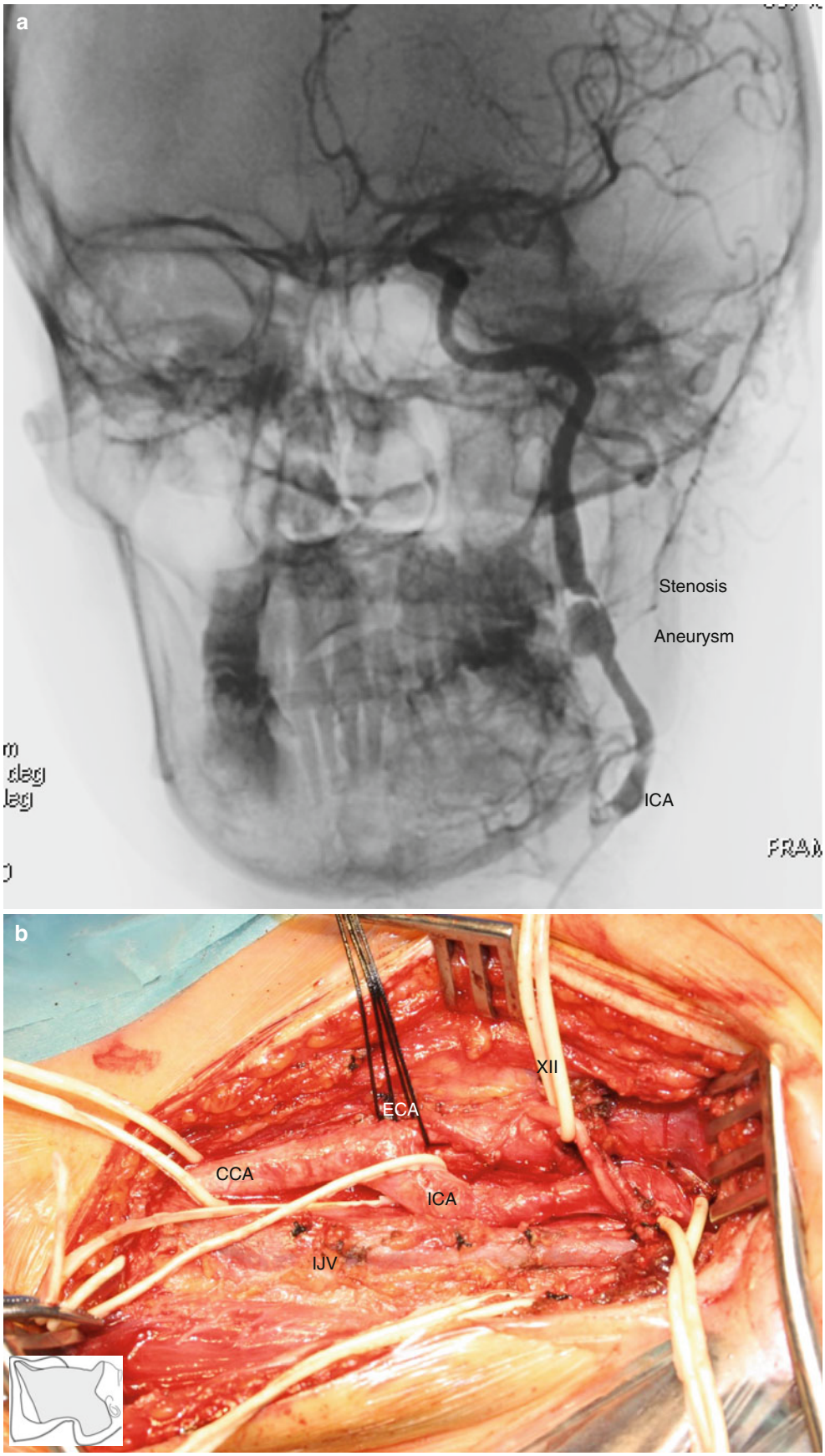
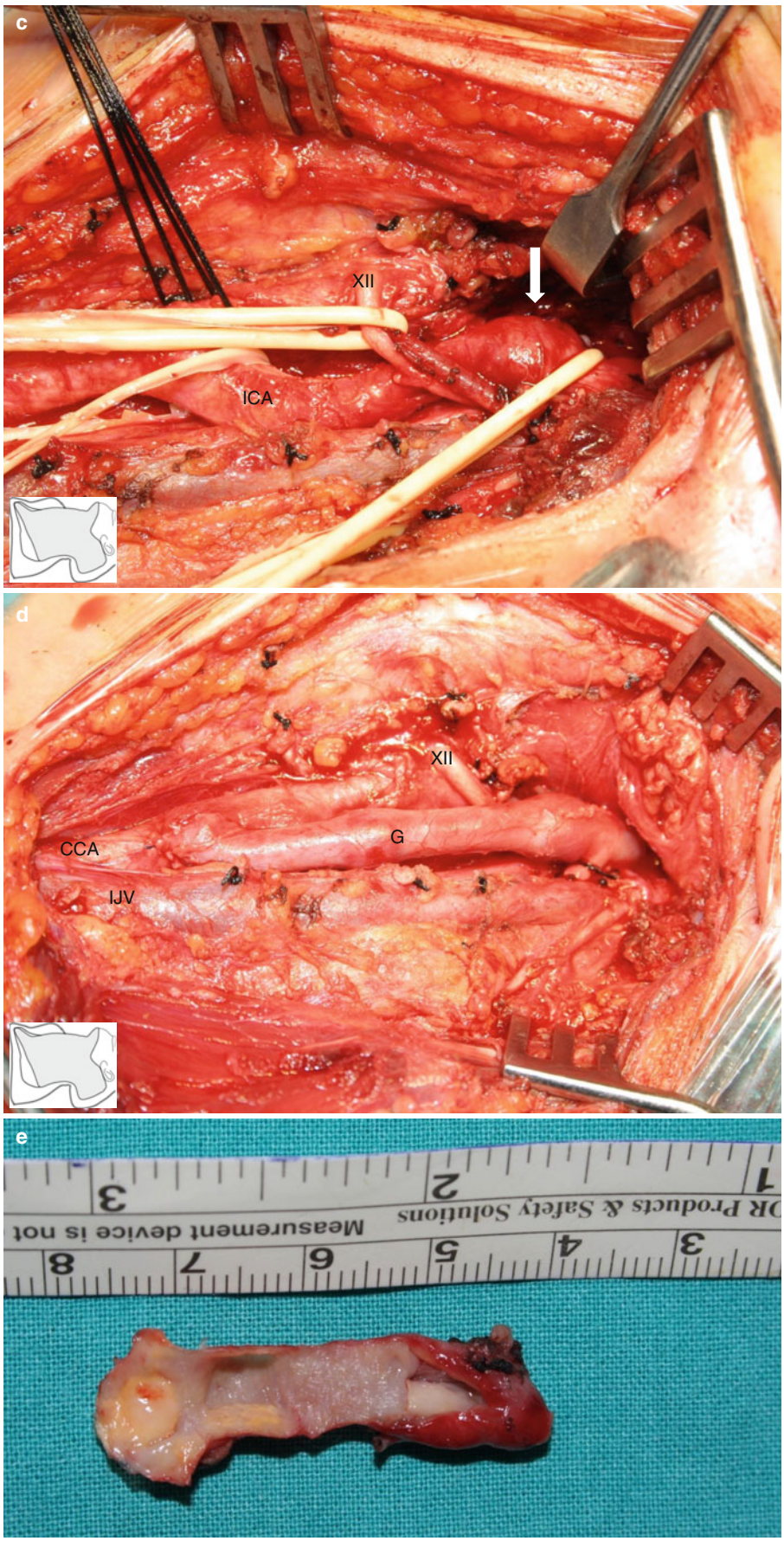


Fig. 15.3 Aneurysm of the distal cervical ICA. Aneurysm developing in a young female patient, with no additional atherosclerotic lesions. Panel (**a**) note that the patient associates aneurysm and severe stenosis of the cervical segment of the ICA. Panel (**b**) surgical approach to the aneurysm and to the carotid bifurcation. A higher exposure in the neck was necessary, however, without dividing the posterior belly of the digastric or the stylohyoid muscles. Panel (**c**) the aneurysm is freed from any adherences. The XII nerve and the occipital artery are gently mobilized. The ICA is dissected well beyond the aneurysm, up to the carotid foramen (*white arrow*). Panel (**d**) the diseased portion of the ICA is removed, and an autologous venous graft (*G*) is interposed between the carotid bifurcation and the distal ICA (the distal CCA 5 mm). Panel (**e**) the aneurysmal portion of the ICA is open; note the significant parietal modifications

Fig. 15.3 (continued)



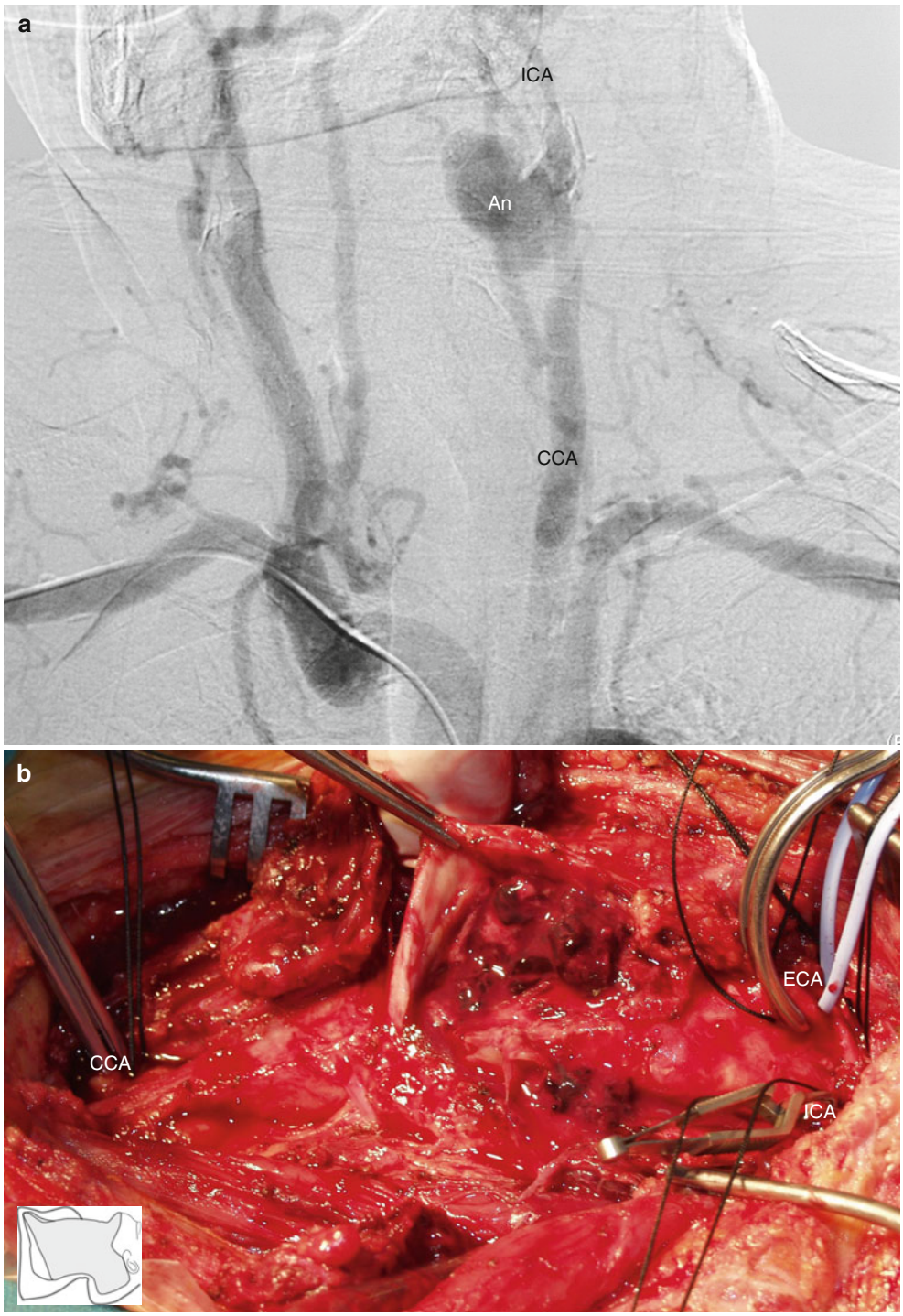
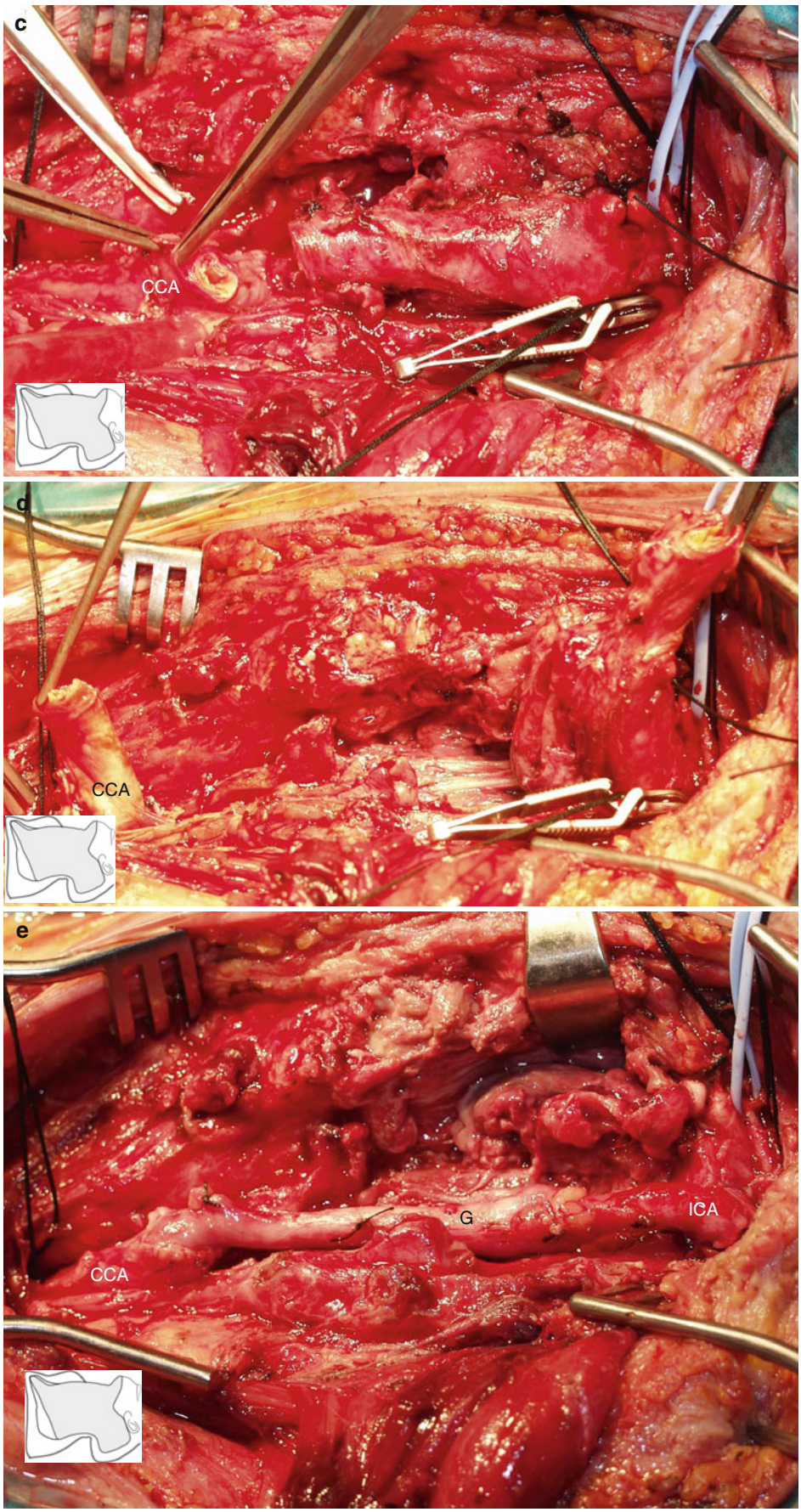


Fig. 15.4 Mycotic aneurysm of the cervical ICA. Panel (**a**) angiographic aspect of the aneurysm developing at the level of the left carotid bifurcation. Panel (**b**) the cavity of the aneurysm is opened after proximal and distal control of the vessels (CCA, ECA, and ICA). Panel (**c**) the entire diseased and infected carotid bifurcation is removed. In cases with suspected infection, we usually send samples for direct examination (smear, Gram coloration); this maneuver helps in identifying the type of germ and to start a more directed antibiotic therapy until the final bacteriological result. Panel (**d**) the carotid bifurcation is elevated just before excision, revealing the diseased and infected adjacent tissues, in direct contact with the pharyngeal wall and with the prevertebral musculature. Panel (**e**) an autologous saphenous graft (**g**) was interposed, between the CCA and the ICA. The ECA was ligated. Panel (**f**) the excised tissues. In the upper part: the carotid bifurcation. In the lower part: the adjacent tissues which completed the wall of the pseudoaneurysm. Panel (**g**) the carotid bifurcation seen from the inside, and revealing the parietal defect (from where the pseudoaneurysm has developed)

Fig. 15.4 (continiued)



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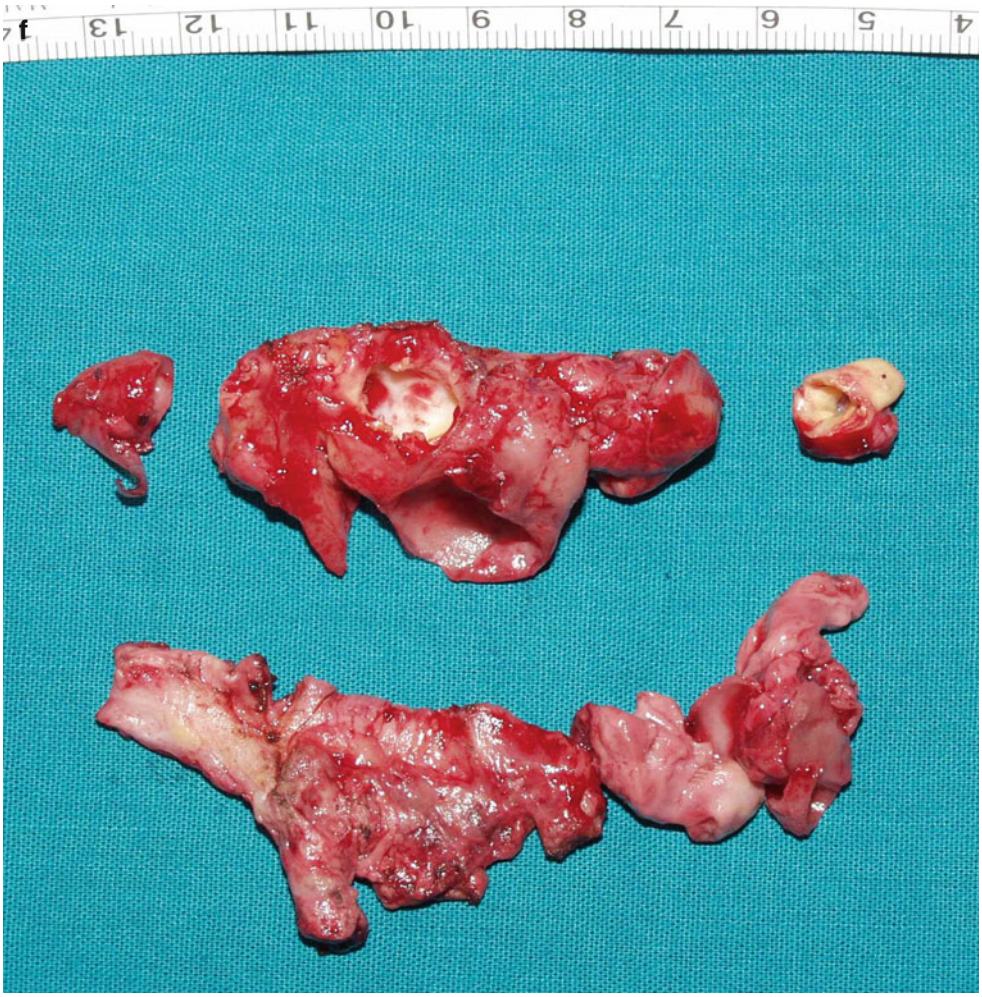

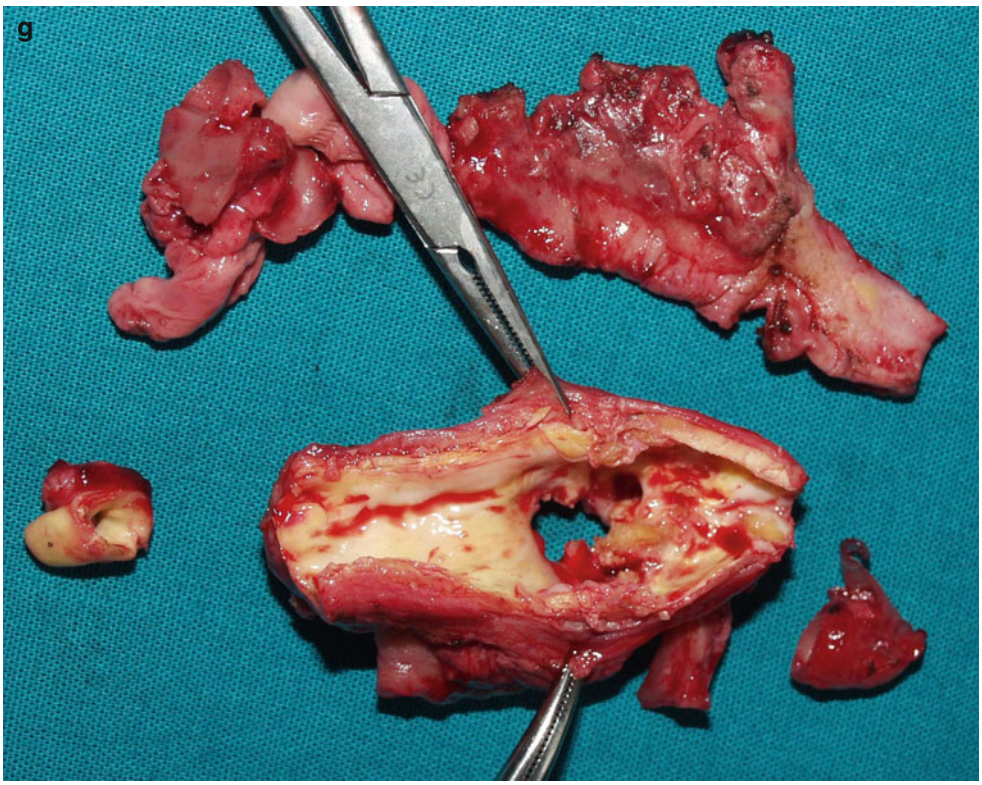

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Asymptomatic Carotid and Vertebral Artery Stenosis

16

Horia Muresian

The subject of asymptomatic carotid and vertebral artery stenosis comprises more aspects and asks for a detailed discussion. Generally speaking, the most frequent lesions responsible for cerebral ischemia are located at the level of the distal common carotid artery (CCA), origin of the internal carotid artery (ICA) and, respectively, the origin of the vertebral artery (VA, V0 and V1 segments). Such lesions may compromise cerebral blood flow and metabolism through embolization, thrombosis (as a consequence of stenosis and/or plaque ulceration), or hemodynamic deficiency (flow reduction). Focusing solely on these levels will select a category of patients in whom revascularization will be of a certain benefit or not, depending on the degree of stenosis, age, sex, comorbidities, and life expectancy. The current clinical practice, however, asks for a broader evaluation of the individual patient and consideration of associated factors that may change, expand, or contraindicate the indication for revascularization in asymptomatic patients with carotid and vertebral artery stenosis.

Revascularization by means of carotid endarterectomy (CEA) is beneficial for male patients with stenosis above 60 %, having a life expectancy of more than 5 years and when performed in dedicated centers with a combined perioperative risk of death and stroke <3 % [1]. Short- and mid-term results of revascularization through carotid angioplasty and stenting (CAS) seem to be less effective than through CEA, although long-term results appear to match. Nonetheless, modern medical therapy will continuously improve the evolution of patients by combining antiplatelet therapy, statins, a better control of diabetes and of high blood pressure, and through and a more appropriate control of risk factors (smoking, weight reduction) [2]. Screening low-risk populations for asymptomatic carotid artery stenosis in not recommended.

The patients considered to be at high risk include the following categories: unfavorable plaque morphology (ulceration, ulceration + thrombus, conspicuous lipid core with thin intimal cap, plaque volume, intraplaque hemorrhage) [3, 4], reduced cerebral blood flow reserve, progression in the severity of carotid stenosis and plaque characteristics (at serial ultrasound examinations), asymptomatic carotid embolism, and ipsilateral silent embolic infarcts (diagnosed by CT or MRI), although it seems quite unnatural considering the latter two conditions as pure "asymptomatic." In our opinion, silent embolic infarcts denote the presence of "*active carotid plaques*" requiring particular attention and indicate that these patients are not totally asymptomatic.

Additional important factors to be taken into account in the clinical judgment and therapeutical strategy include the following:

- The status of the contralateral carotid arterial axis (extra- and intracranial segments)
- The presence of additional lesions on the ipsilateral carotid axis (including the CCA and intracranial ICA)
- Severe stenotic lesions in the vertebrobasilar system: the condition in which the posterior circulation is deficient and depends on collateral flow from the anterior circulation
- Variations in the arterial circle of Willis (CoW) and branches
- The possibility of developing an unheralded carotid stroke (i.e., stroke not preceded by TIA) especially in patients with high-degree asymptomatic carotid stenosis [5]
- The presence of comorbidities and the medical and surgical perspective of the patient, including the need for major surgery such as aortic aneurysm, CABG (coronary artery bypass graft), etc.

The issue of asymptomatic VA disease is less studied, and no precise indications for the revascularization of the VA do exist at the present moment. The general opinion is that lesions in only one of the VAs will compensate from the contralateral VA (if not severely hypoplastic) or even from the

H. Muresian
Cardiovascular Surgery Department, The University Hospital of Bucharest, Milan, Italy
e-mail: cvsurg@hotmail.com

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anterior circulation, in spite of the fact that distal embolization from a thrombosed or occluded VA may also occur. It is still difficult to envisage and to predict the amount of hemodynamic compromise in this complex circulatory system, vascularizing vital cerebral structures, in the individual patient. Generally, lesions suggesting being the cause of patient's symptoms are treated by endovascular route or surgically. Asymptomatic but severe stenoses, especially if on the dominant VA, are usually treated associated to carotid revascularization (and less, as singular, targeted procedure).

The condition of concomitant treatment of carotid and VA lesions, in which either one or both lesions are asymptomatic, is even less studied. Physician's sagacity and personal experience may play an important role in this respect, although certain important points must be taken into account:

- The indication for endovascular or surgical therapy must be thoroughly established and seen as a long-term investment and especially because such an approach going well beyond the guidelines must have a strong motivation.
- The indication must not be perceived as an experiment. This is again difficult to motivate, and, not least, to assess because personal and general statistics are limited to fewer and/or sparse cases.
- Any endovascular or surgical reconstruction has an inherent risk of complications or failure that should be low enough in order to make it recommendable and attractive.
- Any endovascular or surgical reconstruction has a limited duration in time, even when performed in perfect conditions and even when not followed by any complication. Consequently, the patient must be offered a longer-lasting treatment on one hand, while on the other, an alternative must be available at the time when the former reconstruction has become inoperative. The principle of not doing everything one knows or is capable of, applies perfectly in this case.
- Not least, the patient may request a one-stage complete repair especially when feeling uncomfortable with subsequent intervention(s) or if concerned about the risk of stroke while leaving asymptomatic lesions not treated.

We believe that presentation of relevant cases (either singular or short series) from personal statistics and dialogue between all the specialists who diagnose and treat cerebrovascular diseases will help in illustrating the important points mentioned above. Regarding our experience, the reader is led to Chap. 13 (*Extensive Cerebrovascular Revascularization*) and related figures. We would also stress the fact that personal experience should never replace the larger statistics and the randomized studies, but to complete these, with pertinent and thoroughly elaborated indications, whenever considered necessary.

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Lessons from Experimental-Induced Atherosclerosis: Valuable for the Precision Medicine of Tomorrow

17

Manuela Calin, Elena Butoi, Simona-Adriana Manea, Maya Simionescu, and Adrian Manea

Identifying, preventing, and treating the subjects under the risk of developing an acute ischemic attack remain the most provocative challenges in cardiovascular clinical care. In this chapter, we describe in brief some of the recent lessons learned from basic and preclinical studies on the molecular pathobiochemistry of atherosclerosis highlighting new mechanistic concepts of the implications of inflammation and oxidative stress and the emergent nanotechnologies meant to improve diagnosis and treatment.

17.1 Introduction

Despite the advances in the primary and secondary prevention strategies, cardiovascular diseases (CVD), such as coronary heart disease, cerebrovascular disease, and peripheral vascular disease, remain the leading cause of morbidity and mortality in the world. According to European Heart Network, CVD will cause each year over four million deaths in European population (http://www.ehnheart.org). The major cause of CVD is atherosclerosis, a systemic disease characterized initially by lipid deposition in the artery wall and/or an associated low-grade inflammatory process.

The development of an atherosclerotic plaque is due to either dyslipidemia and/or an inflammatory process mediated by chemokines and cell adhesion molecules expressed on the surface of endothelial cells (EC) that attract circulating leukocytes (e.g., monocytes, lymphocytes) to the growing lesions through a complex process that includes rolling, firm adhesion, and diapedesis through EC. Within the subendothelial space, the recruited monocytes differentiate into activated macrophages, which take up oxidatively modified low-density lipoproteins (mLDL) and turn into foam cells (Fig. 17.1a, b). The latter contribute significantly to the local inflammatory response producing a large number of compounds such as reactive oxygen species (ROS), cytokines/chemokines, components of the complement system, tissue factor, fibrinogen, proteases and inhibitors of proteases, prostaglandins, leukotrienes, and matrix metalloproteinases [1, 2]. In the developing plaque, both in the artery wall and in the heart valves, the number of macrophage-derived foam cells increases and the matrix become disorganized (Fig. 17.2). The growing atherosclerotic plaque induces the formation of new blood vessels (angiogenesis). In the advanced stages, upon plaque destabilization and rupture, the matrix components become exposed to the blood leading to thrombosis and its clinical symptoms, myocardial infarction or stroke.

The complexity of the processes associated with atherosclerotic lesions progression has limited the development of an effective treatment to be applied in routine clinical practice. Yet, apart from the introduction of statins in 1987, little significant breakthrough in treating atherosclerosis emerged. Indeed, the failure of cholesteryl ester transfer protein (CETP) inhibitor torcetrapib, a potent HDL-raising drug, emphasized the need to consider other targets apart from lipid-lowering-focused treatment [3].

In fact, about 50 % of patients develop atherosclerosis in the absence of systemic hypercholesterolemia [4], and this point out to the need to develop new innovative-targeted therapies to directly aim at the inflammatory molecules and the cells of the vascular wall.

17.2 Vascular Inflammation in Atherosclerosis

Accumulation of leukocytes, especially monocytes/macrophages, is a central event of the inflammatory process associated with atherosclerosis and takes place from the early until the advanced stages of plaque evolution. Manifestation of vascular inflammation begins in the arterial endothelium

M. Calin • E. Butoi • S.-A. Manea, PhD • M. Simionescu • A. Manea, PhD (✉)
Institute of Cellular Biology and Pathology "Nicolae Simionescu" of the Romanian Academy,8, B.P. Hasdeu Street, Bucharest 050568, Romania
e-mail: adrian.manea@icbp.ro

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with the impairment of adhesive properties of EC, due to an increased expression of different cell adhesion molecules (CAM) and chemokines. In normal conditions, adhesion molecules such as selectins, immunoglobulin receptors, integrins, cadherins, and connexins expressed on the EC surface interfere in the cell–matrix interactions and regulate vascular permeability. Increased expression of these adhesion molecules during the inflammatory process mediates the interactions between leukocytes and activated endothelial cells that is followed by leukocyte activation and extravasation (reviewed in [5]).

Recruitment of the inflammatory cells and the accumulation of smooth muscle cells (SMCs) in the intima favors the leukocyte-SMC cross talk, exacerbates the inflammatory process [6], and further contributes to atherosclerosis aggravation. Interestingly, soluble forms of several adhesion molecules are released into the circulating blood and their plasma levels are used as diagnostic markers of systemic endothelial injury associated with vascular disorders [7]. Uncovering the specific molecules and the mechanisms of the inflammatory process would provide sources for diagnosis and for the use of CAM and cytokine antagonist approaches in the prevention/treatment of vascular disease (see below).

17.2.1 At the Early Stage of Inflammation Associated with Atherosclerosis in Lesion-Prone Areas, the Endothelial Cells Express More/New Cell Adhesion Molecules that Attract Immune Cells and Start a Robust Inflammatory Reaction

The initial event of the vascular inflammation is the activation of endothelial cells covering the lesion-prone area. This is characterized by modifications and increases of the CAM expression on the EC surface that may take place in the absence of overt dyslipidemia. The process continues with the leukocyte migration, whose main steps are CAM-mediated capture, rolling, adhesion, and transmigration through the EC [8].

In the first steps of the process – *capture and rolling* – the transient interactions between leukocytes and EC are mediated by selectins: endothelial E- and P-selectins, and leukocyte L-selectin and PSGL-1, which slow down the leukocyte's passage on the endothelial cell surface. Interestingly, P-selectin (CD62P) is constitutively stored in the Weibel-Palade bodies and is rapidly released and exposed on the surface upon endothelial cell activation [9]. The E-selectin (CD62E) is rapidly upregulated by different inflammatory stimuli, such as TNF-α and IL1-β, by activation of Rho-GTPases and Rac1 signaling pathway [10]. The major ligands for selectins are the cell surface glycans that possess a specific sialyl-LewisX-type structure. We have reported that exposure of EC to lipopolysaccharide (LPS) upregulates E-selectin, and exposure to hydrogen peroxide increases the expression of P-selectin, whereas high glucose levels induces the expression of both E- and P-selectin [11, 12]. Moreover, we and others have found that the increased expression of these selectins is dependent on MAPK signaling pathways and NF-kB and AP-1 transcription factors. The increased expression of selectins on the EC not only mediates the first step of transendothelial migration of leukocytes but also induces intracellular signals (using Rho-GTPase) that lead to modifications such as remodeling of actin stress fibers and increased calcium concentrations [13]. These processes modify the structure and motility of the endothelium, making it more adhesive for leukocytes. Although leukocyte rolling is a prerequisite event for further firm adhesion to the surface of blood vessels, the selectin-mediated rolling of leukocytes does not lead to firm adhesion and transmigration unless members of the immunoglobulin family are involved. Thus, in the step two – *firm adhesion* – the robust interaction between leukocytes and endothelial cells is initiated upon binding of immunoglobulin members – intercellular adhesion molecule 1 (ICAM-1) and vascular CAM (VCAM-1) – to leukocytes integrins (LFA-1 and VLA-4).

The ICAM-1, which is constitutively expressed on the EC surface, is significantly upregulated by endothelial activation [14]. Upon binding of leukocyte LFA-1/Mac-1 to the extracellular domain of ICAM-1, the latter becomes clustered into membrane rafts and further initiates intracellular signaling resulting in rearrangement of the EC actin cytoskeleton [14, 15].

VCAM-1 is weakly expressed on resting endothelium but is highly upregulated upon stimulation with inflammatory mediators [14]. Since VCAM-1 is not expressed in quiescent conditions and is only present to the sites of inflammation, it is an ideal target for nanotherapy; some of our promising results in this field are detailed in the final section. Similar with ICAM-1, clustering of VCAM-1 induces intracellular signaling, leading to ROS production, p38MAPK phosphorylation, and protein tyrosine phosphatase 1B activation [16, 17].

In summary, both immunoglobulin members, ICAM-1 and VCAM-1, undergo increased expression in immunological inflammatory processes and mediate the leukocyte firm adhesion. Moreover, clustering of these molecules by their leukocyte receptors (LFA-1 and VLA-4) triggers the activation of several signaling pathways within the EC, an increased intracellular Ca^{2+}, and activation of several kinase cascades and of Rho-GTPases, which lead to multiple effects on the endothelium, such as leukocyte *transendothelial migration*.

Regarding endothelial transmigration, some authors admit the existence of two different ways used by leukocytes to transmigrate the endothelium: (i) the paracellular pathway

(through the endothelial cell junctions) or (ii) transcellular pathway (through the endothelial cell body, without perturbing the inter-endothelial junctions) [18]. In the case of paracellular transmigration, the leukocyte and the endothelial membranes maintain a close contact during diapedesis and, afterwards, the endothelial membranes reseal. The process is initiated when the leukocytes reach an appropriate site for transmigration (i.e., a gradient of adhesion molecules, such as PECAM-1, CD99, and JAMs, as well as chemokines present at the luminal EC surface). At these sites, leukocytes expand and the cells move across the space between the two adjacent EC. The process is dependent on different molecules, with LFA-1 integrin having a predominant role. Binding of leukocyte LFA-1 to ICAM-1 or JAM-A (on endothelial cells) mediates the contact between the leukocyte and the endothelium [19]. Other molecules (ICAM-2, JAM-B, JAM-C, PECAM-1, and CD99) insure the homophilic or heterophilic interaction that maintain the inter-endothelial junctions or the leukocyte–endothelial interactions [20].

Transcellular transmigration takes place preferentially in the microvasculature, the blood–brain barrier, or high endothelial venules of the secondary lymphoid organs, and less in the macrovasculature [21]. During transcellular migration, the leukocytes produce invasive podosomes that contact EC and subsequently develop into the transcellular pores. The process is regulated by calcium, SNARE-containing complexes, and a number of molecules such as ICAM-1, caveolin-1, and vimentin [22].

As mentioned above, these initial stages of the inflammatory process associated with cardiovascular diseases (CVD) are accompanied by upregulation of different CAMs. Interestingly, the soluble forms of some of CAMs are also increased and can be detected and quantified in the patient blood, helping to disease prediction. In the last decades, several serum inflammatory markers have been proposed as tools for risk assessment in patients bearing atherosclerotic lesions of the carotid artery, among which the soluble CAMs. Thus, soluble P-selectin was proposed as a biomarker of inflammatory-related pathologies including cardiovascular and peripheral vascular diseases [23]. In a large case-control study investigating markers of inflammation in patients with internal carotid artery (ICA) stenosis, it was reported that the level of soluble VCAM-1 (sVCAM-1) is significantly increased compared with normal controls [24]. In another study, enhanced levels of soluble ICAM-1 (sICAM-1) were associated with carotid atherosclerosis progression [25]. Moreover, Rohde's group found a positive correlation between measures of carotid artery and both sICAM-1 and sVCAM-1 levels [26]. Despite these data, not all the studies that investigated association between soluble CAM and cardiovascular disease had positive results. Thus, sICAM-1 levels were not found increased in patients with ICA stenosis [24]. The contradictions in the results could be due to differences in stages of CVD and/or the effects of medication, such as statin, which are known to reduce the sICAM-1 and sP-selectin.

The advances in our knowledge on the molecules and molecular mechanisms that govern the early processes of inflammation in vascular diseases, i.e., leukocyte transmigration, allowed the identification of suitable molecular targets to be employed for the anti-cell adhesion therapy in inflammation (as detailed in the final section).

17.2.2 Cytokines and Chemokines Intensify Inflammation in Atherosclerosis

17.2.2.1 Cytokines

A diverse group of low-molecular-weight proteins, glycoproteins, peptides, and cytokines (over 100 identified so far) are produced by different immune and vascular cells, bind to specific receptors, and modulate various cell and tissue functions. Generally, cytokines are present in soluble form, although some of them are membrane-bound or associated with extracellular matrix. Interestingly, a single cytokine may act on several cell types (pleiotropy) and, depending on the cell type and conditions, produce different biological activities; alternatively, similar effect can be produced by different cytokines [27]. Due to this "functional overlap," the specific pathophysiological role for a particular cytokine is difficult to evaluate.

Among different classes of cytokines, there are tumor necrosis factors (TNF), interleukins (IL), interferons (IFN), chemokines, colony-stimulating factors, and transforming growth factors [28]. Cytokines are involved in the initiation and progression of atherosclerosis and have a profound influence on the inflammatory process associated with this disease. Vascular and inflammatory cells present in the atherosclerotic plaque are able to both produce cytokines and respond to them [28].

Both the innate and adaptive immune responses in atherosclerosis are orchestrated by different cytokines, which regulate all stages of the disease [29]. Thus, in the early stages of atherosclerosis, cytokines alter endothelial functions by upregulating the CAMs, modifying the permeability, and having a chemoattractant effect on leukocytes [5]. These endothelial changes further promote reorganization of the intercellular junctions, leading to loss of barrier function and facilitating leukocyte transmigration. Once in the intima, transmigrated monocytes are activated by local cytokines becoming activated macrophages that in turn produce new cytokines [30]. The locally or newly produced cytokines mediate the transformation of macrophages into foam cells by stimulating the expression of various scavenger receptors and enhancing the cell-mediated oxidation [31].

In the advanced stages of atherosclerosis, the pro-inflammatory cytokines promote extracellular matrix destruction and SMC apoptosis, thus destabilizing the atherosclerotic plaques [32]. Several pro-inflammatory cytokines (i.e., IL-1, TNF-α, and IFN-γ) are reportedly involved in the progression toward a vulnerable plaque, inducing SMC and macrophage apoptosis, modulating expression of matrix metalloproteinases (MMPs) their inhibitors [33], and inducing extracellular matrix remodeling and destruction [34].

Finally, cytokines and, more specifically, TNF-α and IL-1, have a direct prothrombotic potential decreasing the production of tissue plasminogen activator and increasing the production of type I plasminogen activator inhibitor, thus leading to thrombus formation and the development of acute coronary syndromes [28].

17.2.2.2 Chemokines

Chemokines, a structurally related family of chemotactic cytokines, are classified in subgroups based on the position of the N-terminal cysteine residues (CC, CXC, CX3C, XC). They interact with receptors that activate heterotrimeric G-proteins and associated intracellular signaling pathways. Expressed by activated EC and SMC, as well as by emigrated leukocytes, chemokines were initially identified to direct leukocytes to sites of inflammation. Now, there is evidence that chemokines and their receptors play important roles in both the initial stages of inflammation associated to atherosclerosis and in the later stages of the diseases.

In the initial stages of atherosclerosis, chemokines facilitate the capture of monocytes from the blood and their endothelial transmigration. In these processes, a major role is played by monocyte chemoattractant protein (MCP-1) and fractalkine.

MCP-1 is a potent chemotactic factor for monocytes that is upregulated at sites of inflammation. It has been detected in the atherosclerotic lesions of both human and experimental animals and plays important roles in the pathogenesis of atherosclerosis [35]. Ligation of MCP-1 to the CCR2 receptor sets off a signaling cascade resulting in chemoattraction and integrin activation, a crucial step involved in the firm arrest of monocytes on activated endothelium. Studies on mice deficient of CCR2 reported significantly reduced atherosclerotic lesions in these animals [36].

Evaluation of serum levels of MCP-1 in patients with unstable angina showed an association between the MCP-1 level and the extent of coronary atherosclerosis [37]. In patients with unstable coronary syndromes, MCP-1 levels were associated with an increased risk of death or myocardial infarction (at 10 months), even after adjustment for traditional risk factors [38]. Moreover, Mine's group have reported that circulating levels of MCP-1 that are increased in patients with diabetes mellitus potentially contribute to the augmented recruitment of monocytes to the vessel wall [39]. In a recent study, it was found that both lower and higher MCP-1 levels are associated with an increased risk of all-cause and CVD mortality among CAD patients [40].

Fractalkine (CX3CL1), the sole member of the CX3C chemokine family, is a structurally and functionally unique chemokine having a dual function, as CAM and as chemokine, existing in both transmembrane and soluble form. In its membrane-bound form, fractalkine facilitates firm adhesion to and transmigration of leucocytes through endothelial cells, whereas in its soluble form, it acts as a chemoattractant for CX3CR1-expressing cells and assists in leukocyte capture. As for the other chemokines, fractalkine recognizes a pertussis toxin-sensitive G-protein-coupled receptor (CX3CR1), signaling primarily via the G-protein pathway. Importantly, binding of fractalkine to its cell receptor, CX3CR1, occurs at high affinity under both static and flow conditions and with a higher avidity than the VCAM-1–VLA-4 interaction [41]. Furthermore, the activation of both systems, i.e., the integrin system and fractalkine – CX3CR1 interaction – leads to the generation of a greater response than that of either component individually. This cooperative relationship appears to be mediated by G-protein-associated enhancement of the surface integrin's ligand avidity following CX3CR1 activation [42]. Thus, monocyte recruitment to the vessel wall through the fractalkine/CX3CR1 axis might occur in two different modes: via direct shear-resistant adhesion of the membrane-bound chemokine domain of fractalkine to CX3CR1 or via the classical chemokine functions exerted by the proteolytically released soluble fractalkine domain [43]. Our previous work underscored that fractalkine is directly involved in monocyte adhesion to human endothelial cells [12]. Together, these data revealed fractalkine as a highly versatile molecule regulating both cell–cell interactions (in its membrane-bound form) and the cell migration (in its soluble form). The soluble variants of serum fractalkine are upregulated under various inflammatory conditions such as in patients with arthritis [44]; active systemic lupus erythematosus [45]; coronary artery disease, particularly when unstable [46]; or type 2 diabetes mellitus [47]. As such, the soluble form of the molecule may serve as an inflammatory marker.

Both fractalkine and MCP-1 are induced by TNF-α, IL-1, and LPS [48, 49]. Moreover, we have reported that high glucose concentration and resistin upregulate fractalkine and MCP-1 expression in vascular cells by mechanisms involving activation of MAPK signaling pathway and AP-1 and NF-kB transcription factors [50, 51].

Other chemokines involved in atherosclerosis progression and detected in atheromatous lesions are the CXC chemokines, of which the most studied member – CXCL8 (interleukin-8/IL-8) – binds and activates the receptor CXCR2. High levels of serum IL-8 are positively correlated with carotid intima-media thickness in patients [52].

The IL-8 receptor CXCR2 is also involved in vascular diseases. The LDL−/− mice transplanted with CXCR2$^{-/-}$ bone marrow are protected from atherosclerotic lesion formation [53]. The CXCR2 is involved in macrophage accumulation and initiation of neovascularization in atherosclerotic lesions [54].

An important ligand of CXCR2, mediating arterial monocyte recruitment, is the migration inhibitory factor (MIF) that is released in response to diverse inflammatory stimuli from macrophages and also from vascular cells [55]. MIF has been associated with a clear pro-inflammatory and pro-atherogenic role in multiple studies of patients and animal models [56]. Besides binding the cell surface CD74, MIF directly interacts with both CXCR2 and CXCR4 and induces monocyte recruitment and macrophage and T-cell accumulation in atherosclerotic lesions. Blocking MIF action in mice with advanced atherosclerosis decreases the monocyte and T-cell content within the plaques, resulting in a more stable atheroma phenotype [55].

The best-studied chemokine receptor related to plaque regression is CCR7. Various studies showed that CCR7 is necessary for the egress of macrophages during lesion regression [56], although CCR7-deficient T cells show an impaired entry and exit capacity from atherosclerotic lesions [57].

Overall, accumulating evidence suggest that chemokines are directly involved in inflammation associated with vascular diseases. Consequently, in the manipulation of chemokine, chemokine receptor axis represents a novel and promising approach for the treatment of inflammatory disease.

17.2.3 Cross Talk Between Cells Within the Plaque Orchestrates and Intensifies the Inflammatory Process

In the atheroma, key events take place upon the communication between monocytes and endothelial cells with the consequent cell transmigration (as discussed above) and between monocyte/macrophages and smooth muscle cells, either by direct or indirect cross talk (via various mediators).

Macrophages, the most numerous leukocytes present in the atherosclerotic lesion, and the SMCs are the main cellular contributors to the lesion's physical size. After transendothelial migration, monocytes are exposed to different microenvironmental factors and interact with the cells present in the plaque with consequences on their own phenotype and on the inflammatory process. Recently, we have demonstrated that the direct interactions between monocytes and SMCs induce activation of monocytes characterized by overexpression of TNF-α, IL-6, IL-1β, CX3CR1, MMP-2, and MMP-9 gene and protein [6]. Expression of CD36 and resistin is also increased in monocytes after their coculture with SMC [58, 59], suggesting that monocyte cross talk with SMC partake to the transition of monocyte to activated macrophages. Further, the plaque macrophages communicate directly or indirectly with migrated SMCs, and this has important consequences on macrophage phenotype and plaque evolution. Therefore, we have found that macrophages cocultured with SMC exhibit an additional upregulation inflammatory molecules compared with expression levels obtained when monocytes were cocultured with SMC [6, 58]. Other work reveal that upon macrophage-SMC cross talk, the pro-protein convertase subtilisin/kexin type 9 (PCSK9) secreted by human SMCs becomes functionally active and capable of reducing LDL receptors expression in macrophages [60]. Moreover, lysosomes loaded with acetylated LDL or cholesterol can be transported from macrophages to SMCs modulating the behavior of the latter [61].

Because of cell-to-cell communication, changes in cell phenotype occur in SMC as well. It is known that in atherosclerosis, SMC undergo a shift from the "contractile" phenotype to a "synthetic" phenotype: the genes that define the contractile SMC are suppressed, the inflammatory molecules are upregulated, and the cell proliferation, migration, and increased matrix production are induced [62]. Moreover, it is considered that in human atherosclerotic lesions, SMCs from the vessel's media are contractile cells, expressing proteins such as smooth muscle myosin heavy chain, α-actin, vimentin, calponin, transgelin, and desmin. In contrast, intimal SMCs express lower levels of these proteins and have a higher proliferative index and a higher capacity to synthesize proteases and inflammatory molecules [63]. Moreover, using proteomic analysis of media layers from human atherosclerotic and pre-atherosclerotic coronary arteries isolated by laser microdissection, it was demonstrated that even medial vascular SMC switch toward a synthetic phenotype, in vivo [64]. This result is sustained by cell cross-talk experiments in vitro showing that soluble factors released by macrophages substantially promote human aortic SMC proliferation and migration [65]. Moreover, macrophage-derived factors (IL-6 and/or TNF-α) enhance SMC production of MMP-1 [66] and expression of bradykinin B1 receptor on SMC that is dependent on a macrophage-mediated mechanism [67].

Other evidence showing that macrophages affect the SMC phenotype came from a cell–cell coculture model, were macrophages (and not endothelial cells), promoted vascular SMCs calcification via secreted soluble factors [68]. In a direct model of interaction, the IL-6 and MCP-1 concentrations were significantly enhanced in the supernatant of SMC–monocyte cocultures, compared with the cytokine secreted in the conditioned media of SMCs or monocytes cultured separately [69]. Using the same experimental model of direct interaction between monocytes and SMCs, followed by separation and

individual analysis, we have found that SMCs are profoundly affected upon the cross talk with monocytes. Thus, SMC separated after their interaction with monocytes exhibits increased levels of TNF-α, IL-6, IL-1β, CX3CR1, MMP-2, and MMP-9, indicating a significant phenotype modification [6].

Together, these data provide evidence for the switch of SMCs to the inflammatory phenotype induced upon the cross talk with macrophages. They are consistent with the results obtained in human and experimental models of atherosclerosis which found that SMCs may take on a "pro-inflammatory" phenotype, secreting cytokines and expressing cell adhesion molecules (IL-8, CCL20, IL-6, CXCL6, and VCAM-1) which, in turn, may functionally regulate monocyte and macrophage adhesion and other processes during atherogenesis [70]. A diagrammatic representation of different stages in atheroma formation is depicted in (Fig. 17.3).

Overall, direct or indirect communication between monocytes/macrophages with SMCs affects both cells phenotype and aggravates the inflammatory process, contributing to the progression of atherosclerotic plaque.

17.3 Oxidative Stress Is Closely Linked to Atherosclerosis

17.3.1 Emerging Concepts on the Role of Reactive Oxygen Species and Redox Signaling in Atherosclerosis

All aerobic cells produce constitutively reactive oxygen species (ROS). As the name suggests, ROS are highly reactive molecules generated upon enzymatic or nonenzymatic reduction of molecular oxygen (O_2). The electron reduction of O_2 gives rise to superoxide anion ($O_2\bullet^-$) or hydrogen peroxide (H_2O_2), respectively.

Superoxide anion is a short-lived molecule that, by interaction with nitric oxide (NO), produces highly reactive and toxic-free radicals such as peroxynitrite anion ($ONOO^-$). The latter, a powerful oxidizing agent, induces irreversible structural and functional alterations of proteins, lipid, and nucleic acids and the ensuing severe cell damage and apoptosis.

Chemical decomposition of H_2O_2 in the presence of free transition metal ions such as Fe^{2+} and Cu^{2+} results in the formation of highly reactive hydroxyl anion (HO•) that is a short-lived molecule which instantly reacts with polyunsaturated fatty acids initiating the lipid peroxidation chain reactions. The latter generate (after a sequence of nonenzymatic reactions) a number of biologically active lipid peroxidation products such as 4-hydroxy-2*E*-hexenal (4-HHE), 4-hydroxy-2*E*-nonenal (4-HNE), and 4-hydroxy-2*E*,6*Z*-dodecadienal (4-HDDE) [71].

In addition of being a harmful molecular species, ROS and some of their oxidative derivatives (e.g., lipid peroxidation products) produced at low physiological level control key biological activities such as cell growth, proliferation, migration, differentiation, apoptosis, and protein synthesis [72]. The primary signaling targets of ROS attack are the transcription factors and protein tyrosine phosphatases (PTPs) whose highly reactive sulfhydryl groups (R-SH) are susceptible to reversible oxidation resulting in the formation of intermolecular disulfide bonds [73].

The biological functions and actions of different ROS are dictated by several mechanisms including the rate of ROS formation, intracellular compartmentalization, chemical stability and reactivity, the potential to diffuse across the cellular membranes, and the existence of natural occurring antioxidants [74]. Based on the fact that excess formation of ROS is associated with the development of several diseases such as cancer, cardiovascular and metabolic disorders, and neurodegeneration, the oxidative stress has been extensively incriminated as an important factor that contributes (in part) to various stages of these maladies. Oxidative stress characterizes a redox imbalance defining a disproportion among the rate of ROS formation and neutralization. Emerging evidence suggests that oxidative stress may occur in various intracellular compartments rather than being a condition translated to an entire cell or to a whole tissue or organ. This particular aspect reflects the difficulties to detect and efficiently quantify the transient oxidative stress-related molecular processes.

The implication of oxidative stress in atherosclerosis and plaque vulnerability is well established. NO neutralization by $O_2\bullet^-$which results in the formation of $ONOO^-$ is a major mechanism underling EC dysfunction. In addition, oxidation of LDL is the pathological change that relates severe oxidative stress and atherosclerosis. Moreover, ROS-induced phenotypic switch of SMC represents a maladaptive response to vascular insults that plays a critical role throughout atherosclerotic lesion expansion from early stages to complicated plaque and rupture. Nonetheless, the mechanisms underlying ROS formation and function are not completely known. Understanding the molecular sources and the signaling pathways converging to ROS upregulation and/or their defective neutralization is a prerequisite for the development of more efficient anti-atherosclerotic therapies.

17.3.2 Sources of Reactive Oxygen Species in Atherosclerosis

Multiple mechanisms promoting vascular redox state imbalance and oxidative stress-related insults have been described. They include upregulation and/or malfunction of various

enzymatic sources of ROS, dysregulations of the antioxidant system, and the generation of highly reactive molecular species that are not efficiently decomposed by the non-/enzymatic antioxidants such as $ONOO^-$, HO• [75].

The vascular sources of ROS are broadly distributed into two major categories: (1) enzymes whose primary function is the production of ROS, namely, the NADPH oxidase (Nox) family, and (2) enzymes that generate ROS as secondary reaction products. The latter group comprises, among others, the mitochondrial respiratory chain whose main function is the generation of adenosine triphosphate (ATP), uncoupled NO synthase which produces $O_2^{\bullet-}/H_2O_2$ by one-/two-electron reduction of O_2, cyclo-/lipoxygenases whose function is related to the production of biologically active lipid peroxidation products (e.g., prostaglandins), and xanthine oxidoreductase, an important enzyme of the purine metabolism [76].

17.3.3 Role of NADPH Oxidase Complex

NADPH oxidases, also known as Nox enzymes, have been identified in different cell types, including in those of the cardiovascular and immune systems. The unique function of the Nox enzymes is to produce ROS in a highly regulated manner, in response to hormones, vasoactive agents, growth factors, cytokines, lipid mediators, and physiological shear stress. Nox-derived ROS controls multiple aspects of cell physiology via redox-activated signaling pathways; however, Nox overactivity (i.e., significant upregulation of its expression) has been increasingly reported in numerous pathologies. In addition, studies performed in in vitro and in vivo experimental models of cardiovascular and metabolic disorders indicate that pharmacological inhibition of Nox as well as incapacitating Nox function by genetic ablation reduces the oxidative stress-induced cellular detrimental effects. As a consequence, pharmacological targeting of Nox represents a promising therapeutic strategy in the management of various cardiovascular diseases [77].

The Nox family comprises seven members (Nox1 to 5, Duox1, Duox2), each of them exhibiting specific patterns in cell-type expression, intracellular compartmentalization, regulation, and biological function. Functionally active Nox1, Nox2, Nox4, and Nox5 isoforms have been detected in cardiovascular cells (e.g., EC, SMC, pericytes, cardiac myocytes, and adventitial fibroblasts) and in immune cells interacting with the blood vessels (e.g., monocytes/macrophages, lymphocytes, platelets, dendritic cells, and mast cells) [78]. Expression of Duox1 in human aortic SMCs and in macrophages has been also reported [79, 80], but its potential implication in the development of cardiovascular diseases needs further investigation. Besides the catalytic core protein, various Nox isoforms (i.e., Nox1 and Nox2) require cytosolic regulatory subunits for their activation (e.g., p40phox, p47phox, p67phox, NoxA1, NoxO1). Nox4 is constitutively active and needs polymerase delta-interacting protein 2 (Poldip2) for its function [79, 81]. Nox1, Nox2, and Nox4 subtypes form bound complexes with p22phox, an essential subunit that mediates the electron transfer from NADPH to O_2. Unlike Nox1–Nox4 isoforms, Nox5 is directly activated by calcium ions and phosphorylation [78, 82].

Because Nox is activated in response to a large number of cardiovascular risk factors, the signaling pathways that account for Nox regulation were extensively investigated in an attempt to find ways to correct its aberrant overexpression and/or activation under pathological conditions (atherosclerosis, hypertension, diabetes, and obesity). However, the precise molecular mechanisms of Nox regulation and the biological function of Nox-derived ROS are not fully elucidated.

We and others have demonstrated that several pro-inflammatory transcription factors, such as nuclear factor kB (NF-kB), activator protein-1 (AP-1), signal transducers and activators of transcription (STAT) 1/3, and CCAAT/enhancer binding proteins (C/EBP), regulate Nox expression [75, 76, 83].

Since NF-kB, AP-1, STAT1/3, and C/EBP are highly expressed and activated in atherosclerotic plaques and control key genes linked to inflammation and immunity, pharmacological targeting of these pro-inflammatory transcription factors may represent an attractive strategy to reduce the deleterious effects of Nox-induced ROS overproduction [75, 84].

Interestingly, recent evidence suggests that not all Nox isoforms are implicated in vascular pathology. It has been postulated that ROS generated by upregulated Nox1, Nox2, and Nox5 play a role in various stages of atherosclerosis, such as endothelial dysfunction, fatty streak formation, development of fibrolipid atherosclerotic lesions, and plaque complication/rupture [85, 86]. These enzymes are important sources of $O_2^{\bullet-}$, the major free radical implicated in the neutralization of NO, a condition that results in impaired vasorelaxation and vascular damage due to the accumulation of highly toxic ONOO- in the cells.

Unlike the aforementioned isoforms, Nox4 produces H_2O_2, a more stable and non-radical ROS that is unable to chemically react with NO. The augmented expression and function of Nox4 has been detected in numerous cardiovascular pathologies but its function remains arguable. Evidence exists that the enhanced formation of Nox4-derived H_2O_2 induces vascular SMC phenotypic changes, vascular remodeling, and macrophage death in response to oxidized LDL [87, 88]. A schematic depiction of the mechanism underlying the important role of the oxidative stress in ath-

erosclerosis is shown in (Fig. 17.4). It was also reported that genetic deletion of endothelial Nox4 has anti-atherosclerotic effects and that activation of Nox4 increases NO bioavailability by enhancing the expression of eNOS [89, 90]. In addition, it has been shown that Nox4 is an inducible source of ROS protecting the cardiac myocytes against the pressure overload and hypoxia in failing hearts [91].

On the same line, we recently demonstrated that activation of Nox may lead to the generation of lipid peroxidation products that could function as natural endogenous ligands for peroxisome proliferator-activated receptor (PPAR) α and β/δ [92]. Since some members of the PPAR family have anti-inflammatory effects by interacting with or regulating the expression of NF-kB, AP-1, and STAT, a better understanding of the role of Nox – lipid peroxidation products – PPARs axis in vascular inflammation may well lead to the development of novel or additional and better anti-atherosclerotic therapies.

Inhibition of various protein kinases that regulate the function of a number of pro-inflammatory transcription factors may be also considered as an alternative strategy to counteract the combined effects of inflammation and ROS overproduction in atherosclerosis. We have shown that tyrphostin AG-490, a selective pharmacological inhibitor of Janus-activated kinase (JAK) 2, reduces Nox expression and function, the presence of $CD68^+$ macrophages, and the formation of atherosclerotic lesions in the aorta of apolipoprotein-deficient ($ApoE^{-/-}$) mice fed with a high-fat diet [93]. Of particular importance is the fact that the non-receptor protein tyrosine kinase JAK2 transduces the signals of numerous pro-inflammatory mediators and ROS. Thus, targeting of upstream regulators of Nox may represent an attractive strategy to moderate the ROS production in cardiovascular diseases.

17.3.4 Antioxidant Therapies and Pharmacological NADPH Oxidase Inhibitors in Atherosclerosis: Targeting the Consequence or the Cause of Oxidative Stress

Compelling evidence demonstrates that overproduction of ROS induces cell damage via multiple mechanisms such as structural and functional alterations of macromolecules (i.e., proteins, nucleic acids, lipids, carbohydrates), NO neutralization, and aberrant activation of intracellular signaling pathways. Thus, various strategies were designed to counteract the detrimental effects of oxidative stress, most of which entailed the use of antioxidant vitamins such as vitamin E and vitamin C. Although these strategies gave positive results in various in vitro and in vivo experimental models, the results of several clinical trials such as HOPE and HPS were disappointing, indicating the lack of effectiveness of vitamins E and C in the treatment of cardiovascular diseases [94]. Moreover, several meta-analysis studies indicate that antioxidant supplements could worsened the patient clinical condition and increased the risk of death [95]. Although enhanced formation of ROS- and oxidative-related changes in cardiometabolic diseases is irrefutable, these observations have changed completely the perception of the clinicians and researchers about the actual role of ROS and oxidative stress in the cardiovascular pathology and put into the question the rationale of using antioxidants as drugs or food supplements [96].

The antioxidant vitamin-based therapies have major drawbacks that might explain the absence of any therapeutic benefit. The limitations could be determined by the insufficient concentration of the vitamins at the location of vascular injury at the right time, some ROS intermediates are not efficiently scavenged by vitamins E and C, and in addition vitamins themselves, rather than acting as ROS scavengers, may become the targets of ROS attack and be converted into free radicals that may further amplify the oxidative stress reaction [97, 98]. However, one can safely assume that antioxidant vitamins are designed to treat the consequence and not the cause of ROS overproduction.

All these data changed the modern perception on the oxidative stress theory in cardiovascular diseases. Moreover, accumulating evidence suggests that pharmacological targeting of vascular sources of ROS rather than scavenging ROS has the potential to interfere in the progression of cardiovascular disorders. Thus, it has become evident that Nox enzymes may be the right candidates for drug targeting owing to their unique biological function to produce, in response to insults, diverse and large amounts ROS in the cardiovascular cells. Accumulating data show that Nox expression and function are negatively influenced by several conventional cardiovascular drugs, including statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and calcium channel blockers [99]. Thus, several "positive side effects" of the aforementioned drugs might be due to their potential to reduce oxidative stress apart from their primary therapeutic benefits.

Recently, the first class of the dual Nox1 and Nox4 pharmacological inhibitors, GKT137831, received the approval for phase II clinical trial for the treatment of diabetic nephropathy. According to a recent (September 2015) press release of Genkyotex, the leading pharmaceutical company that develops Nox inhibitors, treatment of patients with diabetic nephropathy with GKT137831 reported a significantly reduced liver enzyme and inflammatory marker levels in these patients. Moreover, the beneficial effects of GKT137831 were reported in several experimental models of disease, including atherosclerosis, hypertension, and diabetes [100, 101, 102]. Yet, further clinical studies are required to demonstrate the effectiveness of Nox inhibitors in cardiovascular diseases.

17.4 Nanotechnology-Based Therapies: A New Prospect for Diagnosis and Treatment of Atherosclerosis

17.4.1 Designing "Smart" Nanocarriers

Nowadays, the "smart" targeted therapies are highly attractive because, in addition to the ability to target drugs to specific areas of the body, they have the advantage to reduce the drug concentrations at nontarget sites resulting in fewer side effects. Recently, the emergence of nanotechnology use in medicine (i.e., nanomedicine) has opened a new prospect for the development of targeted therapies for atherosclerosis based on drug nanocarriers [103].

Nanoparticles (NP) employed for biomedical applications typically have sizes below 100 nm and are similar to those of biological macromolecules such as proteins and DNA. They can be manufactured from a variety of organic materials (carbon, lipids, polymers), metallic or inorganic materials (gold, silver, or metal oxides), or hybrids of these materials [104].

Conceptually, the various molecules and cells involved in atherogenesis could be used as potential targets for diagnosis, therapy, and/or prevention and regression of atherosclerosis using approaches based on nanoparticles. The development of different nanocarrier systems with tunable composition, architecture, and functionalities designed to improve diagnosis and clinical intervention in atherosclerosis has been boosted in the last few years. The strategies envisaged for diagnosis and therapy of atherosclerosis using nanoparticles are summarized in Fig. 17.5.

For diagnosis purpose, nanoparticles can improve molecular imaging of subclinical atherosclerosis (disease without symptoms) due to their ability to incorporate and transport various contrast agents to the atherosclerotic lesions. Thus, nanoparticles can carry paramagnetic metals such as gadolinium or iron oxide for magnetic resonance imaging (MRI), heavily iodinated organic compounds such as iopromide for computed tomography (CT) imaging, and radiotracers like ^{18}F or ^{64}Cu for positron emission tomography (PET), ^{111}In for single-photon emission computed tomography (SPECT) imaging, fluorophores or quantum dots for optical imaging or can encapsulate gas bubbles for ultrasonography [103]. With these new instruments, the detection of different molecules and processes (e.g., inflammation, angiogenesis, enzymatic activity) is achievable, and more importantly, the stage of atherosclerosis development can be determined and the appropriate therapy applied.

The nanotechnology-based therapies in atherosclerosis aim at the design and production of nanoparticles able to normalize the lipids profile (lower LDL and/or increase HDL), to decrease the vascular wall inflammation and the oxidative stress, to manifest pro- or anti-angiogenic effects, or to have thrombolytic or anticoagulant properties. Moreover, nanoparticles can satisfy the principle of theranostics (the use of the same nanosystem for diagnosis and treatment) and be used to follow the localization of delivered drugs or to estimate the therapeutic effect after treatment by measuring the expression of relevant biomarkers. Advanced strategies based on nanotechnology aimed at developing targeted nanoparticles able to homing and delivering imaging agents or/and drugs to sites of atherosclerotic plaque are discussed below.

17.4.2 Nanoparticles Designed to Diagnose Atherosclerosis

Because the atherosclerotic plaques build up slowly (in decades), this pathology is often identified only in advanced stages when its clinical manifestations become apparent.

The major goal of the search for new molecular imaging probes for atherosclerosis is to improve the detection of subclinical atherosclerosis when very early modifications occur in the vascular wall. Nanoparticles have been proposed as useful tools to fulfill this goal by increasing the imaging signal from the area of interest.

Current strategies based on nanotechnology in atherosclerosis imaging are based on the identification of molecules (e.g., MMP, cathepsins, receptors involved in angiogenesis) and cells (e.g., endothelial cells, macrophages) implicated in the plaque progression [105].

Another approach to diagnose atherosclerosis at early stages of its progression is to use biosensors based on nanoparticles, nanotubes, nanowires, and nanocomposites to detect in blood or urine multiple biomarkers of cardiovascular diseases (e.g., high sensitive CRP, cardiac troponin I, myoglobin, IL-6, and TNF-α) by spectrophotometry or electrochemistry (reviewed in [106]).

17.4.3 High-Density Lipoproteins-Like Nanoparticles Have a Natural Affinity for Atheroma

A special interest in designing nanoparticles to target atherosclerotic plaques was given to nanoparticles mimicking lipoproteins, especially HDL (high-density lipoproteins) due to their natural affinity for the plaque [107]. The HDL particle subpopulations vary in size from very small (preβ-1: ~ 6 nm), small (α-3: ~ 8 nm and α-4: ~ 7 nm), large (α-2: ~ 9 nm), to very large (α-1: ~ 12 nm) particles. They are made up of a core, containing predominantly cholesteryl ester and triglycerides that is covered with apolipoproteins (mainly apoA-I) and a monolayer of phospholipids. HDLs are responsible for reverse cholesterol transport from the

artery wall to the liver via bloodstream. Nowadays, HDL subpopulations are significantly better predictors of coronary heart disease than HDL cholesterol values [108]. High levels of the very small preβ-1 and small α-3 and α-4 HDL particles are markers of high risk of clinical or subclinical cardiovascular disease [108]. Reconstituted HDL nanoparticles were obtained by reconstituting human ApoA-I in spherical or discoidal nanoparticles with a core of cholesteryl esters and triglycerides covered by phospholipids and labeled with both a gadolinium (Gd)- chelate (Gd-DTPA-DMPE), making the particle visible for MRI, and a green emitting fluorophore (NBD-DPPE) for confocal microscopy investigation. The administration of reconstituted HDL-like nanoparticles in ApoE-deficient mice revealed the association of the nanosystem with the plaques macrophages, the MRI signal being proportional with macrophage content [107]. Furthermore, fully synthetic HDL mimics nanoparticles composed of phospholipids, and different ApoA-I-derived peptides were tagged with both Gd chelates and a phospholipid derivative of a fluorophore (rhodamine-PE) and successfully used for MRI and fluorescence plaque imaging in atherosclerotic mouse model [109]. Other HDL-mimicking nanoparticles are nanocrystal HDL decorated with iron oxide, Au, and quantum dots rendering them with multimodal imaging properties for detection by MRI, CT, and optical imaging [110].

17.4.4 Iron Oxide Nanoparticles Are Useful but Need More Investigations

The ultra-small superparamagnetic particles of iron oxide (USPIO) have been introduced as magnetic resonance imaging (MRI) contrast agents to visualize carotid atherosclerotic lesions and stroke in animals and patients; based on their progressive uptake by macrophages in these inflammatory areas [111, 112], they proved to be useful to differentiate between low- and high-risk plaques [113]. Moreover, it was demonstrated that USPIO-enhanced MRI is a helpful imaging tool for the assessment of the response to the "anti-inflammatory" therapy in patients with carotid atherosclerotic lesions [114]. A comprehensive review on the synthesis and biofunctionalization of magnetic nanoparticles for MRI can be found in [115].

Iron oxide nanoparticles targeted to vascular cell adhesion molecule (VCAM-1) exposed by activated endothelium [116] were introduced for early detection of atherosclerotic disease. The oxidation-specific epitopes in the atheroma of ApoE-deficient mice were successfully detected by MRI using lipid-coated ultra-small superparamagnetic iron particles and superparamagnetic iron particles conjugated with antibodies targeted to either malondialdehyde-lysine or oxidized phospholipid epitopes [117].

PET-CT imaging was used to detect the accumulation of dextran-coated iron oxide nanoparticles radiolabeled with PET tracer ^{64}Cu in atherosclerotic lesions of ApoE-deficient mice [118]. Of potential clinical concern for introducing iron oxide nanoparticles in routine clinical practice is the release of soluble iron, a potent oxidant, after the metabolization of iron oxide nanoparticles by the macrophages which may further contribute to the oxidative stress in the atherosclerotic plaque [119]. This emphasizes the need to investigate in detail the impact of the metabolism of iron oxide nanoparticles on plaque stability before introducing them in clinical practice and could explain why USPIO are not presently approved by FDA.

17.4.5 Liposomes as Excellent Delivery Carriers

One of the most studied nanosystem in drug delivery, the liposomes, are artificial vesicles consisting of one or multiple phospholipid bilayers surrounding an aqueous compart ment [120]. The encapsulation of a CT contrast agent (e.g., iopromide) into conventional or PEGylated liposomes demonstrated the imaging potential of liposomes in animal models [121]. Liposomes encapsulating 5-[N-acetyl-(2,3-dihydroxypropyl)-amino)]- N, N′- bis(2,3-dihydroxypropyl)-2,4,6- triiodo- benzene- 1,3- dicarboxamide (iohexol) and conjugated with an antibody to intercellular adhesion molecule 1 (ICAM-1) were used to detect inflamed endothelium (a hallmark of atherosclerotic plaque) using CT angiography [122]. Targeted echogenic large liposomes (ELIP) with size of 500–800 nm coupled with various antibodies (anti-ICAM-1, anti-VCAM-1, anti-fibrinogen, anti-fibrin) have been proposed as tools to identify the stage in the development of atherosclerotic lesion by intravascular and transvascular ultrasound imaging [123]. Recently, liposomes having sizes of ~200 nm and composed of phosphatidylserine (PS), a phospholipid exposed on the surface of apoptotic cells and recognized by macrophages, were radiolabeled by encapsulating ^{111}In-nitrilotriacetic acid, and the aortic atherosclerotic plaques were successfully visualized by SPECT at 48 h after i.v. administration in ApoE-/- mice and Watanabe heritable hyperlipidemic rabbits [124].

17.4.6 Other Nanoparticles Are on the Way to Be Developed

Perfluorocarbon nanoemulsions labeled with the contrast agent Gd-DTPA were targeted to fibrin by functionalization with anti-fibrin F(ab)′ fragments to detect thrombi in dogs by MRI [125]. This nanosystem was proposed as a useful tool for early diagnostic of an imminent stroke or myocardial

infarction in patients presenting with prognostic symptoms that require appropriate therapeutic measures immediately.

Similar nanoemulsions were targeted to integrin by conjugation of Arg-Gly-Asp mimic peptide to detect plaque angiogenesis in atherosclerotic rabbits [126].

To monitor proteases, enzymes secreted by inflammatory macrophages in atherosclerotic plaque, Nahrendorf et al. developed polymeric nanoparticles with an iron oxide core conjugated with an inactivated fluorochrome-labeled peptide (epsilon-protected lysine oligopeptides labeled with a near-infrared fluorochrome VivoTag-S680) which became activated after protease cleaving. The function of proteases was examined in ApoE-deficient mice by fluorescence molecular tomography (FMT) in combination with high-resolution CT angiography [127].

Other nanosystem used for target-specific imaging of apoptosis in atherosclerotic plaque, by MRI and fluorescence imaging, are small micellar annexin A5-functionalized bimodal nanoparticle labeled with both Gd-DTPA-di(stearylamide) and rhodamine-PE. The micelles recognize phosphatidylserine exposed by apoptotic cells in the plaques of ApoE-deficient mice and they are quite promising nanoparticles to predict the plaque vulnerability [128]. Nanotechnology-based methods are also focused on the detection of biomarkers of cardiovascular disease in the blood or urine. Citrate-capped gold nanoparticles were developed as sensors for colorimetric detection of CVD biomarker homocysteine thiolactone-induced protein modification (protein homocystamide) in the sera [129]. Recently, an elegant study by Lin K et al. reported the development of iron oxide nanoworms (NWs) conjugated with a thrombin-sensitive substrate in tandem with a ligand-encoded reporter able to circulate in the blood and release the reporter at areas with vascular thrombosis. Subsequently, the reporter is measured in the urine by ELISA. The results demonstrated that the level of the marker detected in urine correlates with the aggregate burden of clots formed in the lungs in a mice model of thromboplastin-induced pulmonary embolism [130].

17.4.7 Nanoparticles Designed for the Therapy of Atherosclerosis

As mentioned above, the strategies envisioned for nanoparticles-based therapies of atherosclerosis were designed to interfere with the pro-atherogenic processes induced by LDL (the so-called bad cholesterol), to potentiate the effect of HDL (the so-called good cholesterol), to decrease the oxidative stress and the vascular wall inflammation, and to exhibit pro-/anti-angiogenic effects or thrombolytic and anticoagulant properties. A brief description of these strategies is described below.

17.4.8 Nanoparticles Designed to Modulate LDL and HDL Levels

The strong correlation between the increased plasma LDL concentrations and the cardiovascular diseases led to several attempts devoted to lower circulating LDL cholesterol. Targeting of apolipoprotein B (ApoB), the main apolipoprotein associated with LDL, was considered to have an important impact in decreasing LDL-induced vascular inflammation. To this purpose, liposomes encapsulating small interfering RNA (siRNA) have been administered in cynomolgus monkeys to silence ApoB gene and as a consequence to reduce LDL level [131]. The results were encouraging, showing a significant reduction of ApoB mRNA (more than 90 %) in the liver and a reduction in plasma levels of ApoB, cholesterol, and LDL.

Other studies reported the silencing of pro-protein convertase subtilisin/kexin type 9 (PCSK9, the endogenous regulator of LDL receptors in the liver) in rodents and nonhuman primates using liposomes carrying PCSK9-targeting siRNA. After one i.v. administration, a reduction of plasma LDL cholesterol concentrations (up to 60 % of the normal value), with no influence on HDL cholesterol or triglyceride levels, was detected for 3 weeks [132]. The nanosystem was tested in a clinical trial and the results of the randomized, single-blind, placebo-controlled phase I trial are promising [133].

Recently, a revolutionary method, namely, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated 9 (Cas9), referred to as CRISPR/Cas9, which is inspired from the immune system used by bacteria to defend from viruses, was introduced to perform gene-editing in mammalian cells [134]. Ding et al. delivered in vitro transcribed RNA encoding Cas9 nuclease and CRISPR-guide RNA targeting mouse PCSK9 gene formulated in lipid nanoparticles and provided the proof of principle of knocking out the PCSK9 gene in the liver using CRISPR/Cas9 system [135].

Apart from lowering blood LDL cholesterol level, other strategies were developed to stimulate the reverse cholesterol transport mediated by HDL. The latter function as cholesterol acceptor promoting the efflux of cholesterol from atherosclerotic plaque and its delivery to the liver. Thus, the development of HDL-mimicking nanoparticles received special interest. One study showed that liposomes containing 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) interact with HDL and the complexes formed exhibit an improved capacity to solubilize cholesterol. In an atherosclerotic mouse model, the infusion of DMPC liposomes, once per week for 5 weeks, lead to a reduction of aortic cholesterol and of the plaque number [136].

Interestingly, it was reported that a mutation in ApoA-I, named ApoA-I Milano, protects from atherosclerosis an Italian

family [137]. The infusion of HDL-like nanoparticles formed by a mixture of recombinant ApoA-I Milano with palmitoyl-2-oleoyl phosphatidylcholine-mimicking HDL in atherosclerotic rabbits led to a higher regression of atherosclerotic plaque than when wild-type HDL was administered [138].

Serum amyloid A 2.1 is a protein associated with HDL that stimulates cholesterol ester hydrolyzation with subsequent cholesterol efflux in vitro and in vivo [139]. It was reported that the treatment of ApoE-deficient mice with serum amyloid A 2.1-derived peptides encapsulated into liposomes prevents and reverses the lipid accumulation into the aorta [140].

HDL-like lipid nanoparticles containing recombinant human ApoA-I, the phospholipids 1-myristoyl-2-hydroxy-sn-glycero-phosphocholine (MHPC) and 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine (DMPC), were used to encapsulate lipophilic simvastatin and to deliver the complex to the atherosclerotic plaque. These nanocarriers reduced plaque inflammation either when administered for long term at low concentration (12 weeks biweekly doses of 15 mg/kg statin, 10 mg/kg ApoA1) or for short time at high doses (1 week four times/week 60 mg/kg statin, 40 mg/kg ApoA1) [141].

17.4.9 Targeted Delivery of Nanoparticles to Reduce the Vascular Wall Inflammation

Since endothelial cells (EC) and monocyte-derived macrophages are crucial participants at the inflammatory process which accompanies the initiation and progression of atherosclerotic lesions [5], they emerged as attractive targets for the treatment of atherosclerosis. We and others work out strategies based on nanoparticles to target either activated EC or monocyte/macrophages having the purpose of delivering anti-inflammatory compounds and reducing the inflammatory status or to target the interaction between monocytes and endothelium and impede the monocyte infiltration into the plaque. By position, surface biochemically differentiated microdomains, and functional characteristics, the EC have a key role from the inception to the last stages of the atherosclerotic process. The activated ECs expose their surface-specific cell adhesion molecules (CAM) such as E-selectin, P-selectin, and VCAM-1 that can be used as targets to deliver drugs and compounds to inflamed endothelium.

Pioneering work on specific targeting of endothelial CAM with immunoliposomes (liposomes coupled with antibodies) started some years ago [142, 143]. Our group also provided evidence that immunoliposomes targeted to VCAM-1 (over-expressed in vivo by activated EC covering the developing atheroma) bind selectively to activated human endothelium and are internalized mainly by clathrin-coated vesicles. The data strengthen the concept that immunoliposomes directed to molecules expressed on activated EC surface may be used efficiently as carriers and therapeutic tool for the selective delivery of drugs in cardiovascular diseases [144]. In another study, anti-VCAM-1-coupled immunoliposomes carrying the anti-inflammatory prostaglandin PGE2 was reported to be taken up at the inflammatory sites and to reverse the atherosclerotic lesions when administered daily for 2 weeks in LDL receptor knockout (ldlr−/−) mice kept on atherogenic diet [145]. Recently, Kheirolomoom et al. showed that cationic lipoparticles decorated with a PEGylated peptide with affinity for VCAM-1 and containing anti-miR-712 were functional in delivering silencing miR-712 to inflamed endothelium and inhibiting atherosclerosis development in a model of ApoE-deficient mice with partial carotid ligation; no significant off-target tissue effects after treatment were detected [146].

For drug delivery to the brain to provide neuroprotection in stroke, transferrin receptors were used as target because they are present on the membrane of EC forming the blood–brain barrier and function in the receptor-mediated endocytosis and transcytosis of transferrin. We showed that liposomes with covalently attached transferrin bind specifically and are internalized by EC via the specific pathway of transferrin receptors [120]. In a mouse model of stroke, the pre-ischemic systemic administration of chitosan nanoparticles (NP) conjugated with antibodies against transferrin receptor and loaded with fibroblast growth factor or a small peptide inhibitor of caspase-3 (z-DEVD-FMK) led to the accumulation of NP in the brain and a significant reduction of the infarct volume after 2 h of cerebral artery occlusion and 22-h reperfusion [147]. These data point out to the feasibility of targeting the brain and usefulness of drug delivery nanoparticles for neuroprotection in stroke.

Besides targeting molecules expressed on the EC surface, targeting of matrix protein exposed after endothelial injury has been foreseen. Hybrid core-shell NP made by a polymer core loaded with slow-eluting poly(lactic acid) conjugates of paclitaxel, a lipid shell interface and an external PEG layer conjugated with peptides recognizing collagen type IV, was administered to rats and reported to attach to injured carotid artery and release the drug over a 2-week period [148]. Other nanoparticles designed to target components of subendothelial matrix, namely, PEG-conjugated liposomes containing the glucocorticoid and prednisolone and having high affinity to chondroitin sulfate proteoglycans (CSPGs), showed a significant suppression of neointimal growth induced by bare stent implantation in atherosclerotic rabbits [149].

Because the plaque stability is directly linked to the number of macrophages present in the plaque, there were several approaches to target drugs or nucleic acids (plasmids, siRNA) to circulating monocytes to modulate their function, with the end purpose of decreasing the monocyte influx into the atherosclerotic lesions. Monocytes are recruited into plaques either from the luminal side of the artery or via the highly permeable neoangiogenic vessels originating from vasa vasorum in the adventitia. An approach to decrease the macrophage content of the plaque was to target circulating monocytes with siRNA that knock down CCR2 chemokine receptor, one of the main receptor used by these cells to infiltrate in the subendothelial space [150]. The systemically administered liposome encapsulating siRNA specific for CCR2 in mice blocked the accumulation of monocytes into the atherosclerotic plaque, thus reducing the lesion size and efficiently improving infarct healing [151].

Because targeting of monocytes has to be made with caution due to their beneficial role in host defense against pathogens, our group introduced a different approach to decrease monocyte influx into the plaque. In a recent study, we developed PEGylated target-sensitive liposomes directed toward VCAM-1 (coupling a peptide with affinity for VCAM-1 at the liposome surface) to deliver a chemokine receptor CCR2 antagonists at the surface of activated endothelium. We reported that these liposomes bind specifically to the aorta of atherosclerotic ApoE-deficient mice and are functional in reducing the monocyte adhesion and infiltration through EC [152]. This was the first evidence that nanocarriers which transport and release chemokine inhibitors at the surface of inflamed endothelium can reduce chemokine-dependent inflammatory processes and holds great promises for the treatment of many inflammation-related diseases, including atherosclerosis.

Having the purpose of determining the role of monocytes/macrophages in lesion formation in hyperlipidemia, in another study, we depleted the circulating monocytes of the hyperlipidemic hamsters using liposomes encapsulating clodronate (dichloromethylene bisphosphonate). We found that long-term administration of clodronate-liposomes (2 months, twice per week) has two consequences: a beneficial role by reducing the expression of pro-inflammatory molecules but also a detrimental effect inducing the expansion of aortic valve atherosclerotic lesions and a significant increase in lipid and collagen accumulation in the lesions [153]. These data were in contrast with previous reports showing that the administration of liposome-encapsulated bisphosphonates in rats and hypercholesterolemic rabbits reduces neointimal proliferation in the carotids after balloon injury [154, 155]. The difference between these results could reflect variation in the vascular bed examined (aortic valve versus carotids) and the special susceptibility of the heart valves for plaque formation. Recently, sugar-based amphiphilic core-shell-layered nanoparticles were used to inhibit the expression of macrophage scavenger receptors and thereby to block the uptake of oxidized lipids. The in vivo administration of these NP in ApoE-deficient mice diminished the lipid accumulation, smooth muscle cells proliferation, and inflammation in atherosclerotic lesions [156].

Conversely, monocytes were employed as a "Trojan horse" to deliver drugs or plasmids into lesions, especially to the brain [157]. Liposomes targeting integrins (RGD-liposomes) or liposomes containing phosphatidylglycerol (PG) were used for monocyte-mediated brain targeting [158]. Cationic liposomes carrying plasmids expressing enhanced green fluorescent protein (EGFP) and fibroblast growth factor-2 (FGF-2) administered via femoral vein mediated the expression of EGFP and FGF-2 in infiltrating macrophages in brain [159].

A different approach envisioned the designing of NP sensitive to changes in shear stress in stenosed arteries. Liposome-like nanocarriers, with a lenticular shape instead of spherical one, due to their composition (1,3-diaminophospholipids) are capable of circulating intact through healthy arteries except for the sites of stenosis where, under shear stress pressure, they release the entrapped nitroglycerin [160].

17.4.10 Nanoparticles Designed to Inhibit or Stimulate Angiogenesis According to the Needs

The inhibition of angiogenesis in atherosclerotic lesions is considered as a potential strategy to promote atherosclerotic plaque stabilization. Neoangiogenic vessels have increased expression of the integrin $\alpha_v\beta3$, which was used to target paramagnetic nanoparticles encapsulating the anti-angiogenic drug fumagillin. A single administration of these nanoparticles in atherosclerotic rabbits is sufficient to inhibit angiogenesis, reported by the same nanocarrier, which function as an MRI imaging system. When administered for 3 weeks, the same nanoparticles reduced the aortic angiogenesis and this effect was augmented when used in combination with atorvastatin given per os [161].

Apart from anti-angiogenic therapy, the induction of angiogenesis is needed to support the formation of new blood vessels in ischemic tissues after infarction and to achieve tissue regeneration. Vascular endothelial growth factor (VEGF) is considered to be a potential therapeutic angiogenic factor and these were attempts to obtain a spe-

cific delivery of this factor to ischemic tissue. In a model of peripheral artery disease (PAD), the murine ischemic hindlimb model, VEGF, was targeted to ischemic tissue by VEGF-conjugated gold nanoparticles via enhanced permeability and retention (EPR) effect. A recovery of blood perfusion over time to a level 93 % of normal tissue and increased capillary densities (two fold) as compared with administration of free VEGF was reported [162]. To obtain a controlled release of VEGF at the ischemic area over time, nanoparticles composed of chitosan, dextran sulfate, and VEGF were embedded into 3D poly(-lactic-co-glycolic acid) PLGA scaffolds. The angiogenesis in 3D implants was significantly improved by VEGF encapsulation into nanoparticles [163]. The dark side of VEGF therapy is that nanoparticles may accumulate into atherosclerotic plaque contributing to neoangiogenesis [164]. Recently, Mroczek-Sosnowska et al. showed that in ovo administration of cupper nanoparticles determines a significant increase in pro-angiogenic and pro-proliferative genes [165].

17.4.11 Nanoparticles as Carriers of Thrombolytic and Anticoagulant Drugs

Thrombolytic and anticoagulant therapy is classically employed to dissolve blood clots, the main cause of myocardial infarction and stroke. To improve the effectiveness of this treatment, target-sensitive liposomes encapsulating the thrombolytic agent, streptokinase, were specifically directed to platelets within the thrombus by conjugation of the RGP peptide on their surface. After binding to the clot, the release of the thrombolytic agent led to a reduction of clot lysis time as compared to nonencapsulated streptokinase [166].

In addition, the delivery of an anticoagulant drug, bivalirudin, by micelles targeted to fibrin deposited on the surface of atherosclerotic lesion resulted in increased antithrombin activity suggesting that the nanocarriers may be used to reduce the risk of thrombus formation after the plaque rupture [167]. Myerson et al. developed perfluorocarbon nanoparticles complexed with a potent thrombin inhibitor (Phe(D)-Pro-Arg-chloromethylketone) as thrombin-inhibiting platforms for localized control of acute thrombosis [168]. Moreover, an ultrasound-responsive PEGylated gelatin NP carrying tissue-type plasminogen activator was introduced for thrombolytic therapy [169].

17.4.12 Clinical Use of Nanoparticles for Diagnosis and Therapy of Atherosclerosis

While nanoparticle-based therapy is available in the clinic for the treatment of cancer (e.g., Doxil, DaunoXome), no specific nanoparticle-based system has yet been approved for the diagnosis or therapy of CVD, even though cancer and atherosclerosis have many common processes (endothelial dysfunction and upregulation of adhesion molecules to recruit the inflammatory cells, increased permeability of the microvasculature, or hypoxia-induced neovascularization). One reason for this could be that in the chronic phase of plaque built-up, the intravenous administration of nanoparticles for prolonged period of time is unrealistic as the disease may remain asymptomatic. In addition, combining a targeted transport and an active therapeutics into one nanosystem has proved challenging and need to be further standardized and clinically validated in atherosclerosis.

Nonetheless, the results of a completed clinical trial, the NANOM-FIM trial that investigated the atheroprotective effect of silica-gold Np administration, were recently published [170]. The trial assessed the safety and the therapeutic effect of administration of two nanosystems: (1) silica-gold nanoparticles in a bioengineered patch and (2) silica-gold iron-bearing nanoparticles with targeted microbubbles and stem cells using a magnetic navigation system combined with plasmonic photothermal therapy versus stenting controls. The treatment determined a significant regression of coronary atherosclerosis in the nano-intervention group.

Another phase II clinical study (BLAST) investigated the safety and efficacy of liposome with alendronate in the treatment of stenotic lesions in coronary arteries in patients undergoing percutaneous coronary intervention with implantation of Presillion™ CoCr bare metal stent. Lately (June 2012), two nanotherapy clinical trials in Europe were registered on www.clinicaltrials.gov by Academisch Medisch Centrum-Universiteit van Amsterdam to be conducted in patients with atherosclerosis: (1) "A Proof of Concept Study to Determine the Local Delivery and Efficacy of Intravenously Injected PEG-liposomal Prednisolone Sodium Phosphate (Nanocort) in Atherosclerotic Tissue in Subjects With Peripheral Artery Disease" and (2) "A Phase I/II, Single-Center, Randomized, Placebo-Controlled Study Evaluating the Therapeutic Efficacy of Intravenously Injected Nanocort® in Subjects With Severe Inflamed Carotid or Aortic Atherosclerosis Plaques." Information about the status of these trials are still pending.

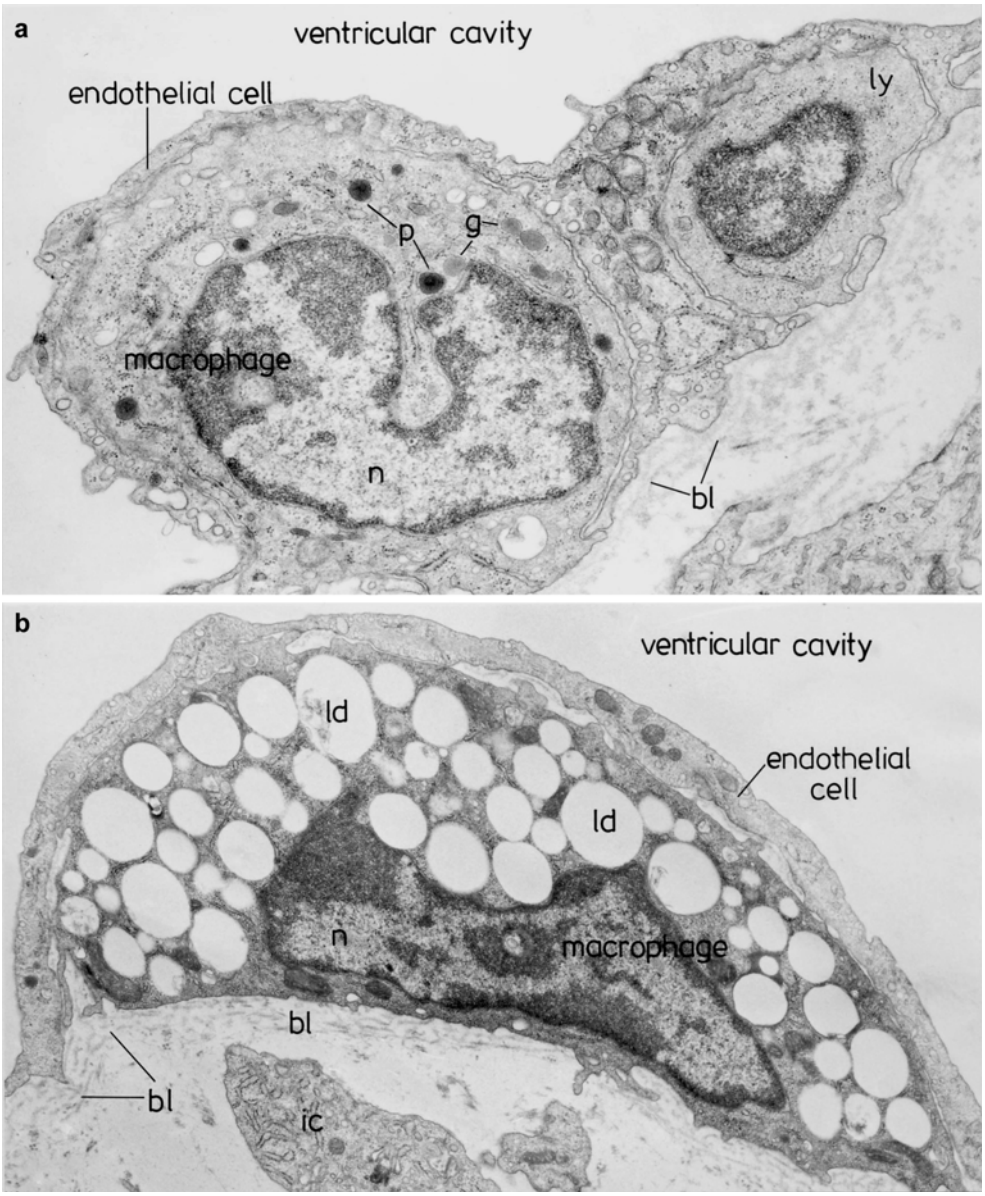

Fig. 17.1 (**a**). The hyperlipidemic diet induces in the heart valve (mouse) diapedesis of monocytes that appear under the valvular endothelial cells and against their basal lamina (*bl*) as monocyte-derived macrophage. They exhibit the characteristic indented nucleus (*n*), peroxisomes (*p*), and small granules (*g*). *Ly* probably an emigrated lymphocyte ×18,000. (**b**). With time, the hyperlipidemic diet triggers the uptake of subendothelial accumulated and modified LDL by macrophages via their scavenger receptors and their turn into macrophage-derived foam cells whose cytoplasm is packed with lipid droplets (*Id*). Note that the macrophage lies within the meshes of the basal lamina (*bl*). *n* nucleus *ic* interstitial cell. ×16,000 (Reproduced with permission from Elsevier after Filip et al., *Atherosclerosis*, 1987)

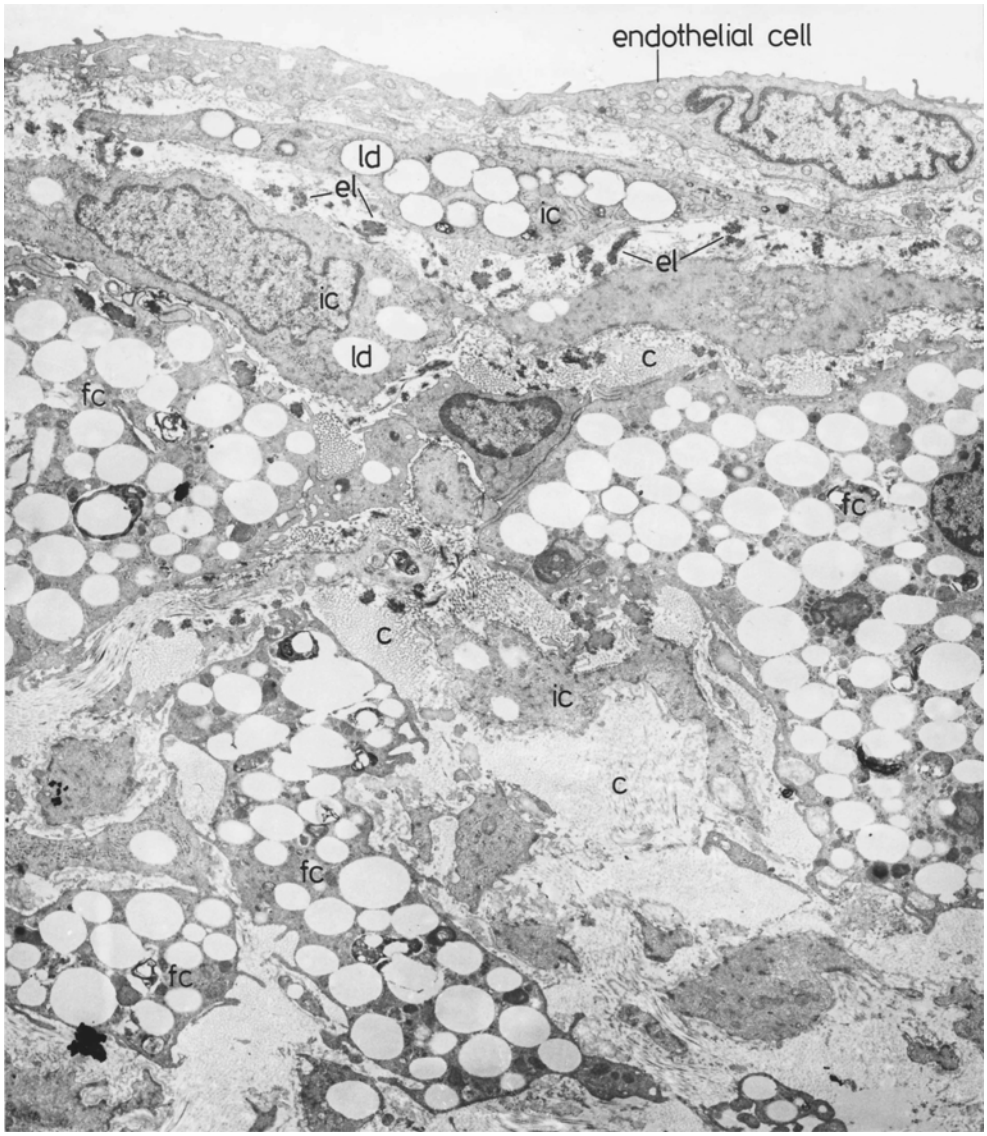

Fig. 17.2 In advanced stages of atherogenesis, the plaque developing in the heart valve (mouse) displays numerous macrophage-derived foam cells (*fc*) and interstitial cells (*ic*) rich in lipid droplet (*Id*) that lie within the heart valvular stroma; the latter displays abundant collagen fibrils (*c*) and numerous elastin fragments (*el*). ×7000 (Reproduced with permission from Elsevier after Filip et al., *Atherosclerosis*, 1987)

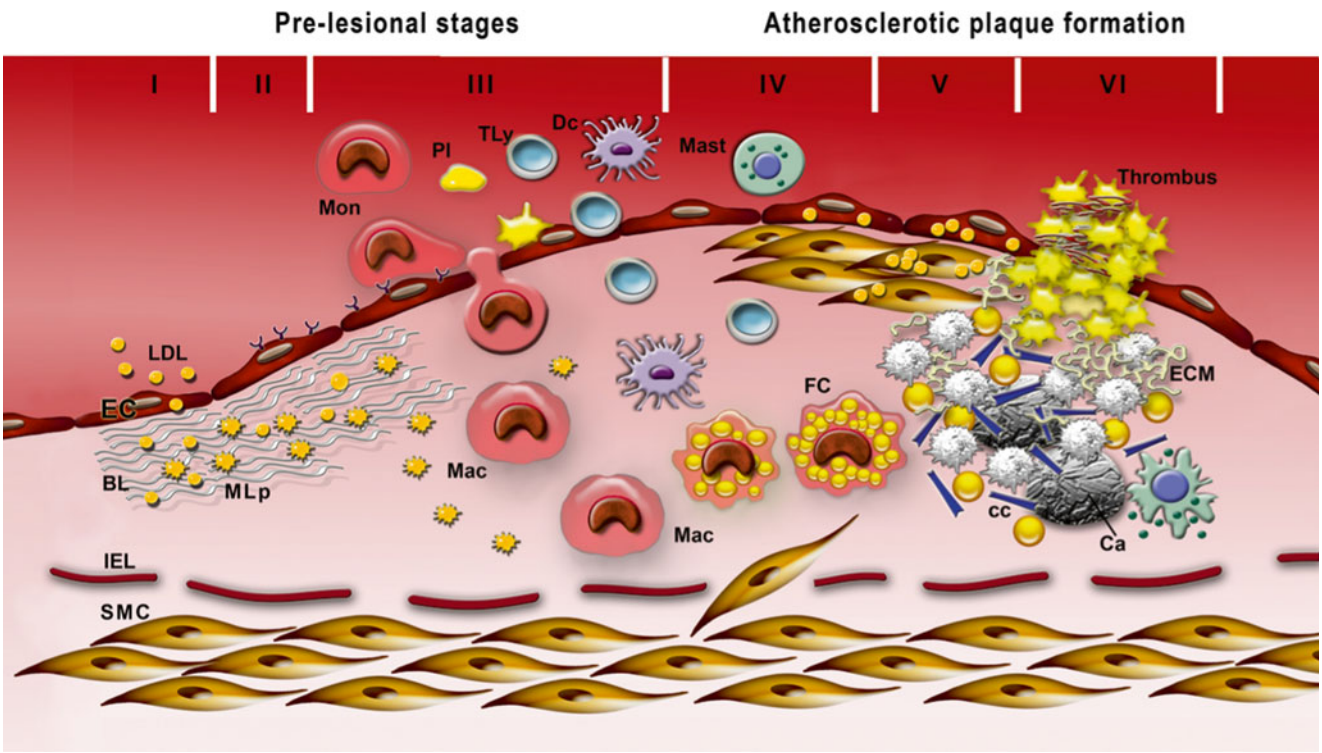

Fig. 17.3 Diagrammatic representation of the arbitrarily delineated consecutive stages in the atheroma formation. *Stage I*, the initiation of the plaque is characterized by modulation of endothelial cell (*EC*) constitutive functions: transcytosis (enhance LDL transport) and synthesis. *Stage I,:* LDL trapped within the intima undergo further alterations (oxidation, glycation), turning into modified lipoproteins (*MLp*) that may cause EC dysfunction, expressed by the appearance of new cell adhesion molecules, chemokines, and cytokines. Stage *III*, a robust inflammatory reaction in which plasma monocytes (*Mon*) assisted by platelets (*Pl*), T lymphocytes (*TLy*), and dendritic cells (*Dc*) adhere and enter the arterial intima. Monocytes become activated macrophages (*Mac*) that express scavenger receptors, take up MLp, and progressively turn into macrophage-derived foam cells (*FC*) characteristic for the fatty streak. In *stage IV*, smooth muscle cells (*SMC*) glide from the media into the intima forming the fibrous cap. *Stage V*, a complicated fibrolipid plaque comprising SMC-, Mac-, and EC-derived foam cells, cholesterol crystals (*cc*), and large calcification cores (*Ca*) embedded in an extracellular matrix (*ECM*). *Stage VI*, the complicated plaque becomes vulnerable, exhibiting fibrous cap thinning and excess inflammatory cytokines that may lead to EC damage and death and the subsequent exposure of the matrix, platelets adherence, and thrombus formation. *BL* basal lamina (Modified with permission from Springer after Simionescu and Sima [171])

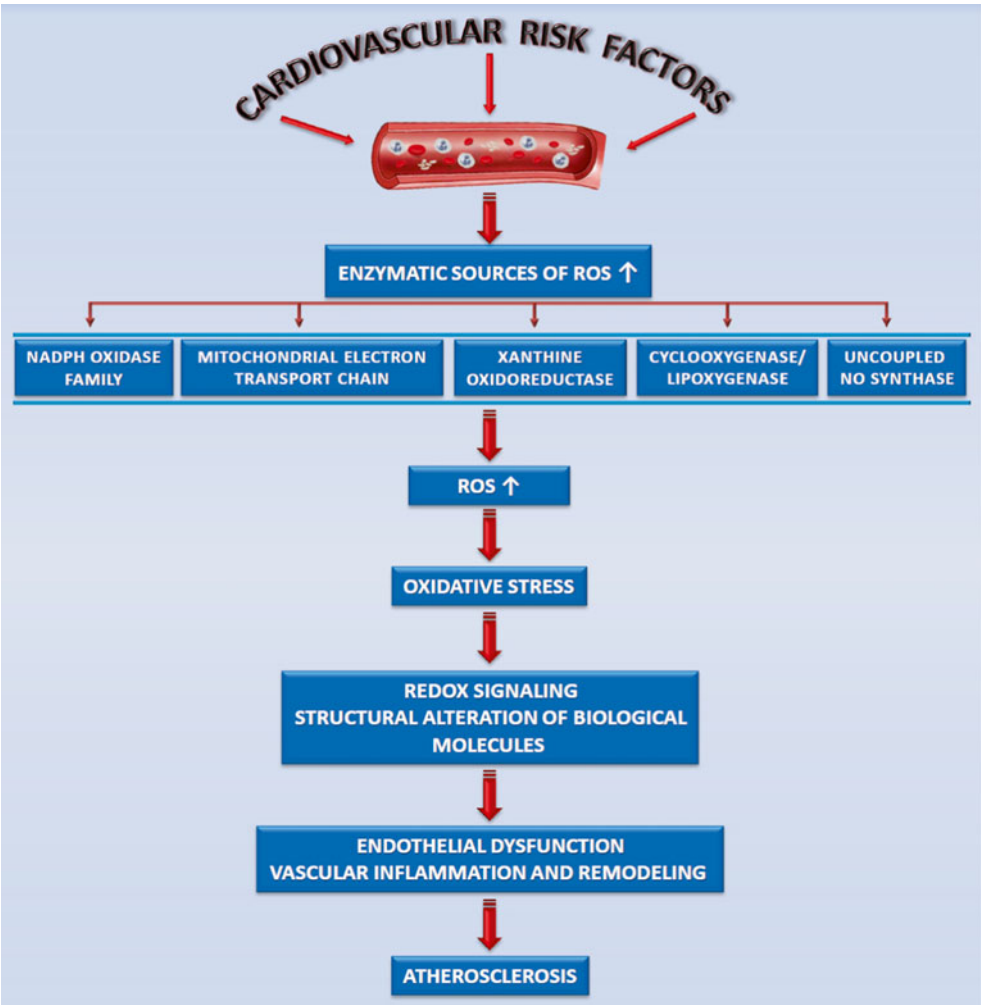

Fig. 17.4 The mechanism underlying the important role of the oxidative stress in atherosclerosis. In response to cardiovascular risk factors (i.e., diabetes, hyperlipidemia, obesity, hypertension, ischemia/reperfusion, life style), vascular cells activate various signaling cascades resulting in the formation of ROS via multiple enzymatic sources such as members of the NADPH oxidase family, mitochondria, xanthine oxidoreductase, cyclooxygenase/lipoxygenase, and uncoupled NO synthase. Excess ROS formation leads to oxidative stress that induces the activation of redox-sensitive pro-inflammatory signaling pathways, NO scavenging, and oxidative alteration of biological macromolecules (nucleic acids, proteins, lipids/lipoproteins, and carbohydrates). These are the major pathological mechanisms whereby oxidative stress generates endothelial dysfunction, the recruitment and activation of immune cells, and phenotypic alteration of vascular smooth muscle cells, leading to atherosclerotic lesion formation

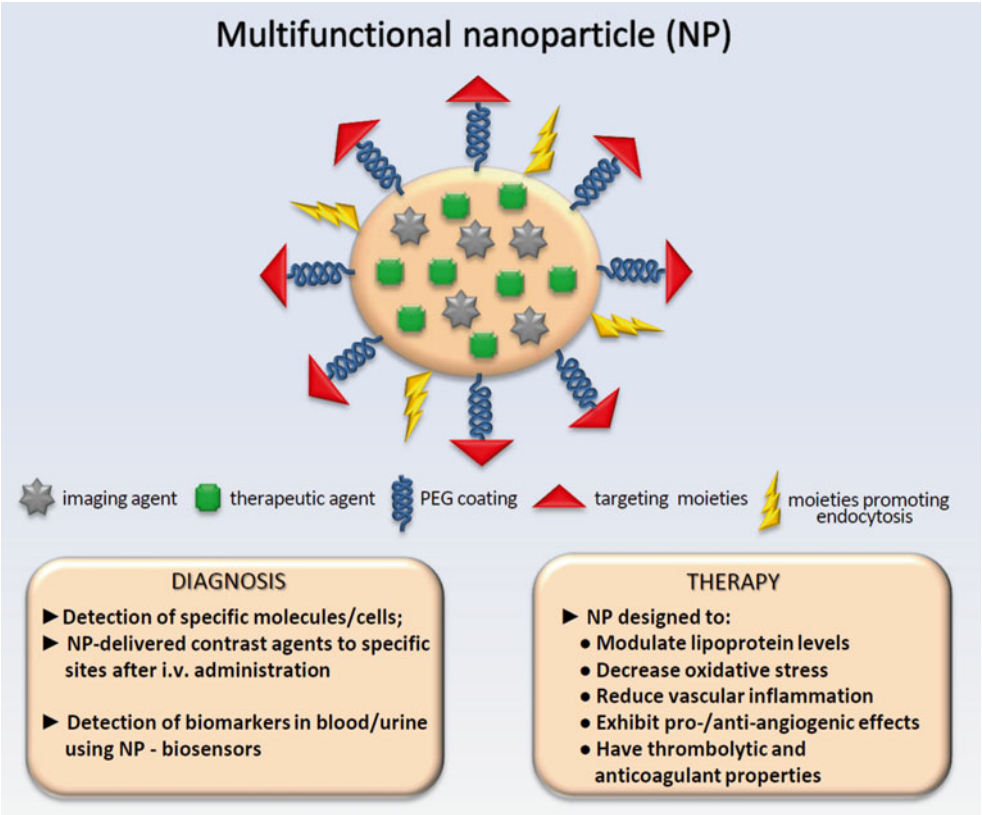

Fig. 17.5 Multifunctional targeted nanoparticles – valuable tools for diagnosis and therapy of atherosclerosis. Hypothetical model of a multifunctional nanoparticle (*NP*) developed so as to exhibit one or more of the following characteristics: (1) ability to avoid the uptake by the mononuclear phagocyte system (*MPS*) by surface modification (e.g., coating with polymers such as PEG or changes in surface charge); (2) entrapping for target delivery of various imaging or therapeutic agents by coupling appropriate targeting moieties (e.g., antibodies or their fragments, peptides, small molecules, aptamers), and (3) if need be, the ability to promote the intracellular uptake (e.g., by nanoparticles functionalization with cell penetrating peptides). For *NP-based diagnosis* of subclinical atherosclerosis, two main approaches are envisaged: (1) detection of molecules (e.g., MMP, cathepsins, receptors) and cells (e.g., endothelial cells, macrophages) implicated in plaque progression using NP (such as HDL-like NP, iron oxide NP, liposomes, nanoemulsions, polymeric NP) and (2) the use of NP-based biosensors to detect in blood or urine multiple biomarkers of cardiovascular diseases (e.g., high sensitive CRP, cardiac troponin I, myoglobin, IL-6, and TNF-α). For *NP-based therapies of atherosclerosis*, the strategies envisaged are designed to modulate the level of lipoproteins, to decrease the oxidative stress and the vascular wall inflammation, and to exhibit pro-/anti-angiogenic effects or thrombolytic and anticoagulant properties

Conclusion

Clinical and experimental data clearly demonstrate the implication of inflammatory mechanisms and oxidative stress in atherosclerosis. Yet, effective anti-inflammatory and anti-oxidative therapeutic strategies to counteract the outcomes of cardiovascular diseases and acute events (e.g., heart attack, stroke) are not yet available.

We and others have shown that inflammation and oxidative stress are interrelated processes in atherosclerosis and that pharmacological or genetic ablation of various Nox subtypes has the potential to reduce the activation of selective pro-inflammatory transcription factors and to blunt the expression of their downstream target genes.

Accumulating preclinical evidence demonstrates the effectiveness of Nox pharmacological inhibitors rather than ROS scavenging by antioxidants in reducing the development of atherosclerotic lesions, vascular oxidative stress, and inflammatory reactions in several models of atherosclerosis and diabetes. Due to their unique biological function to generate excess ROS in response to vascular insults, it has become evident that Nox enzymes may be the right candidates for drug targeting in cardiovascular diseases. Recently, the Nox inhibitor GKT137831 received the approval for phase II clinical trial for the treatment of diabetic nephropathy. Thus, it is expected that selective Nox pharmacological inhibitors are to be translated into clinical practice for the treatment of cardiovascular diseases.

While nanoparticle-based therapy is available in the clinic for the treatment of cancer, no specific nanoparticle-based system has yet been approved for the diagnosis or therapy of atherosclerosis. Combining a targeted transport and an active therapeutics into one nanosystem has proved challenging and has not yet been standardized and clinically validated in the field of atherosclerosis. Nevertheless, it is believed that the developments that emerged in the field of nanotechnology in the last years will force the innovations move from bench to bedside and this will certainly lead soon to new therapies to target molecules or cells with a key role in the initiation and progression of atherosclerosis.

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Choice of the Proper Therapeutic Measure in the Individual Patient and Prevention of Stroke

18

Horia Muresian

Contraria non contradictoria sed complementa sunt
N. Bohr

In the therapy of cardiovascular diseases, contemporary medicine associates *medical therapy*, *endovascular* procedures, and *surgery*. This tripod-like conceptual structure underscores not only the role of each of the methods and approaches but stresses the major clinical relevance of combining these, either in the same time or in sequential order. The limit between these three prongs of the tripod is also not absolutely well demarcated, and some of the methods seem to blend or merge with each other; the best example is offered by the pharmacologically active stents and the combined ("hybrid") endovascular and surgical procedures.

On the other hand, the patient population is continuously changing, with more extreme ages to deal with, and caring for patients with numerous and more severe comorbidities and, not least, with different endpoints, as compared with some decades before. The endpoint "mortality" is surpassed by "quality of life" and "social reintegration." The better understanding of mechanisms of disease has made possible the development of new medical strategies and pharmacological therapies, contributing to the reduction of a number of surgical procedures, or rendering these more targeted and more physiologic.

Specialization, on one hand, has also opened new horizons for numerous categories of doctors who have become "virtuosi" in their corresponding fields by treating their patients with greater efficiency. On the other hand, the better trained specialists need a pertinent dialogue between them and a continuous brain storming-like process when therapeutical strategies are contemplated, in the individual patient. This is the kind of desiderate not always achievable, and not in every medical center. The multidisciplinary team undoubtedly represents the best solution so far, but this may be in many circumstances and locations nothing more than the ideal but unreachable solution. And this represents the first difficult point.

H. Muresian
Cardiovascular Surgery Department,
The University Hospital of Bucharest, Bucharest, Romania
e-mail: cvsurg@hotmail.com

The second difficult point appears when looking beyond the aforementioned "tripod" and considering three more important prongs: *prevention*, *patient follow-up*, and *rehabilitation*. When focusing on stroke, prevention and follow-up appear as significant and as important as the therapeutical modalities. This volume has dealt in substantial degree with therapeutic measures and modalities, illustrating the experience of specialists who diagnose and treat cerebrovascular disease, on a constant basis. Everyday practice has enriched each of us with unparalleled experience, and we find pleasure and interest in discussing and debating on particular cases – patients we take care of. Each of us has already built up a personal database of the patients under our own responsibility, but we still feel the lack of pertinent preventive measures. Some of the measures for stroke prevention were mentioned in Chap. 8 (see *Pharmacological measures for the treatment and prevention of stroke. The choice of initial therapy*). Each of us is facing patients who generally come as emergency cases, with most of the comorbidities either not diagnosed or not treated. At least in our experience, the atherosclerotic burden in most patients is heaviest, making difficult the therapeutic choice. Even more, numerous patients are less compliant to the therapeutic measures and secondary prevention. As illustrated in Chap. 13 (*Extensive cerebrovascular arterial reconstruction*), the complex procedures applied were the result of and dictated by multidistrict arterial disease, comprising not solely more arterial trunks or segments in the superior aortic system, but associating similar disease in the inferior aortic system too. As a consequence, more extensive and ampler reconstructions are indicated, either by the endovascular route, surgery, or both. Many patients would also prefer a single operative session instead of serial/sequential less-extensive (and less-invasive) procedures (during more hospital admissions).

On the other hand, a team has formed, as a result of daily practice and imposed by the complexity of cases, and as each of us was aiming to achieve real medical endeavor. The eventual and major benefit is the patient's. We follow and recommend a thorough clinical examination (including a detailed

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examination of the arterial system), neurologic and cardiologic clearance (including echocardiogram), spirometry, blood tests, and Doppler ultrasound examination of the supraaortic arteries. The Doppler examination is performed by a trained neurologist who is also the most indicated to corroborate clinical particulars with ultrasound data. A second diagnostic modality certifies, completes, or corrects the Doppler examination: angiography, CT angiography, or MRI (MRA). The latter two are indicated in all cases in which evaluation of cerebral parenchyma is also requested. The patient is subsequently referred for one (or more) of the three therapeutical modalities: medical, endovascular, or surgical therapy. There is no absolute landmark dividing the areas of each, and the greatest advantage of our team is that all modalities are equally available, with no logistic limitation. Evidently, the resultant question is: "*should cerebrovascular diseases be treated only in larger centers endowed with all necessary facilities including the stroke unit?*" Ideally, yes, but numerous other factors are to be taken into account including health policy and economic resources.

The confines of CEA and CAS are not sharply demarcated, and the choice of the therapeutic arm (endovascular versus surgery) depends on numerous factors, as presented in this volume, so far. Patient's compliance to therapy and the rate of evolution of atherosclerotic disease in each case add particular difficulties in recommending and choosing the best therapeutic modality.

The risk factors for atherosclerotic disease can be variously classified and considered in patient's management. The non-modifiable risk factors are age, male sex, familial history, and genetic abnormalities. Modifiable factors are dyslipidemia, arterial hypertension, smoking, and diabetes. Additional cardiovascular risk factors comprise obesity, sedentarism, menopause, and infection/inflammation (e.g., chlamydia). All aspects must be taken into account and addressed. Probably, the best approach is considering the entire *circuit* of the patient with cerebrovascular disease as a path consisting of numerous stages and, on which, surgery and endovascular procedures will be indicated once or more during lifetime. Medical therapy will undoubtedly help even more in controlling the atherosclerotic process and in lowering its burden on the various arterial territories. Newer frontiers are open with the development and implementation of therapies targeting the intimate mechanisms of atherosclerosis and inflammation which aim to interrupt the resultant vicious cycles that amplify the vascular injury.

The rehabilitation and social reintegration of the patients warrants particular consideration and attention; at the present time, it probably represents the less advertized and less contemplated modality in patient management.

A pertinent, relevant, and efficient dialogue should ideally be established between all specialists who diagnose and treat cerebrovascular diseases. Sharing experience, knowledge, preferences, and, not least, the negative results will undeniably offer the best approach for the treatment of a complex disease, with versatile manifestations, and affecting a heterogeneous patient population.