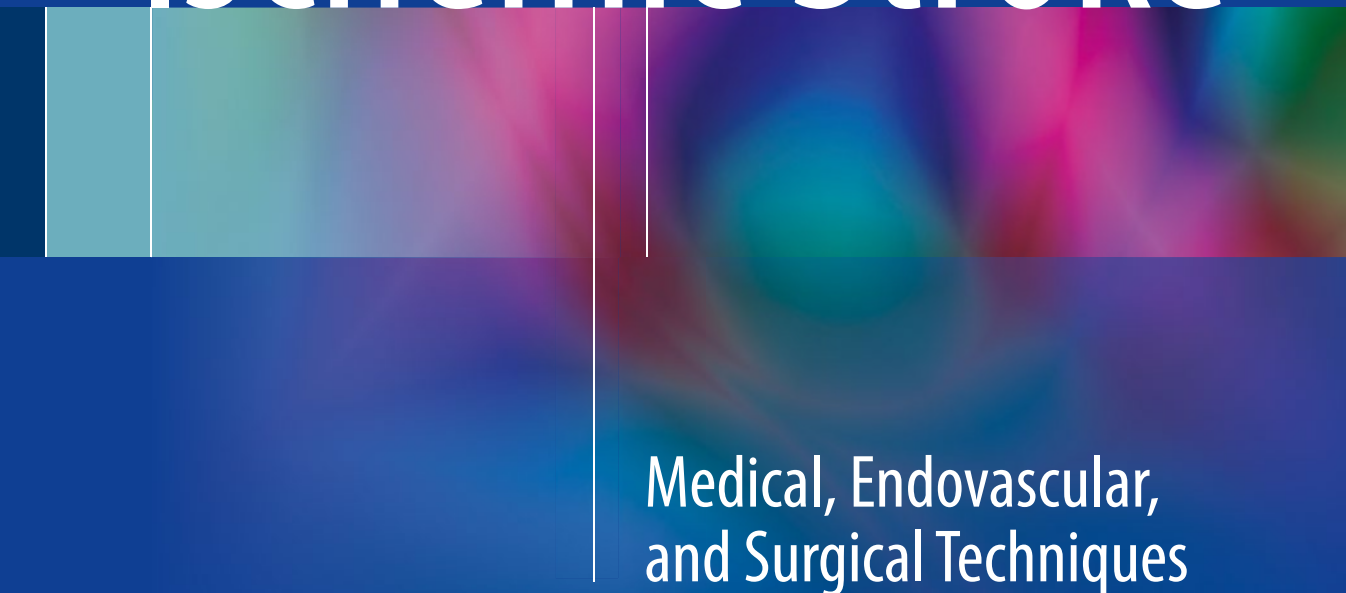
Jaechan Park
Editor

Acute Ischemic Stroke

Medical, Endovascular, and Surgical Techniques



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Preface

Many important advances have occurred in the treatment of acute ischemic stroke for the past two decades. The NINDS clinical trial of thrombolysis using recombinant tissue-type plasminogen activator (rtPA), which was published in 1995, established medical treatment of acute ischemic stroke within 3 h of stroke onset. Ten years later, MERCI clinical trial using a MERCI mechanical thrombectomy retriever opened the endovascular era for acute stroke management within 8 h of stroke onset. Since then, the therapeutic time window for rtPA has been extended to 4.5 h after stroke onset based on the ECASS III clinical trial, and various catheter-based and stent-based endovascular thrombectomy devices were developed. Currently, interdisciplinary management including medical, endovascular, and surgical methods is required to provide the best management for acute ischemic patients.

This book approaches the topic of management of acute ischemic stroke in an interdisciplinary manner, explaining how best to utilize the methods currently available for medical, surgical, and endovascular care. After an opening section on basics including pathophysiology and radiological assessment of ischemic stroke, comprehensive and up-to-date information is provided on each of the available therapies, techniques, and practices. Special attention is paid to recent advances in neurointerventional and neurosurgical procedures, with clear description of important technical details. The book includes plentiful high-quality case illustrations and a wealth of practical information that will prove of value in emergency rooms, angiography suites, operating rooms, and intensive care units. It will aid not only neurologists, neurointerventionists, and neurosurgeons but also all others who are involved in the management of acute ischemic stroke, from radiologists and emergency physicians to healthcare providers.

I would like to express my appreciation and acknowledge the efforts of all contributors to this book. The authors hope that their experience in acute stroke management woven into this book may be of benefit to physicians who care for ischemic stroke patients. We look forward to a future in which more stroke patients are treated with the best possible results due to further advances and innovations in the multidisciplinary management of ischemic stroke.

Daegu, Korea — Jaechan Park, MD, PhD

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Part 1

Basics

Pathophysiology of Ischemic Stroke

1

Seung-Hoon Lee

Here, the classification and pathophysiology of ischemic stroke will be discussed in detail. Ischemic stroke is often classified for academic purposes, but there is actually a very practical reason for its classification. Ischemic stroke is a clinical syndrome, which develops not with a single cause but with multiple causes. Ischemic stroke with a different cause would have a different clinical developmental pattern, and more decisively, the medicine and therapy for treatment and prevention vary. Thus, its proper confirmation would great influence the patient's prognosis. In this chapter, the classification of ischemic stroke and the latest knowledge on the pathophysiology related to it will be presented.

1.1 Classification of Ischemic Stroke

Stroke is classified for various purposes. It is often classified for academic purposes, to describe the characteristics of the patients included in a clinical study or to classify the patient group according to their characteristics, but the clinical purpose of its classification—to determine the appropriate treatment plan for a stroke patient—is also very important. Most of the stroke registry studies that have been conducted so far revealed that 25–40% of all stroke patients could not find the cause of their stroke [1]. The frequency varies depending on the quality, completeness, and examination timing of the diagnostic tests for stroke etiology. The stroke whose cause is not known is called "stroke of unknown cause, or cryptogenic stroke." Moreover, there are many cases where it has more than two possible causes and it is difficult to determine which of the causes is the real one (e.g., a case accompanied by atrial fibrillation and significant stenosis of the internal carotid artery associated with the location of cerebral infarction).

1.1.1 Stroke Data Bank Subtype Classification

A solid classification system for ischemic stroke did not exist previously, but since the advent of computed tomography (CT) opened an era of neuroimaging, classification methods have been suggested. Stroke Data Bank Subtype Classification is a method that was initially derived from the stroke register protocol of Harvard University and that classifies stroke into the following five types indicated in the Stroke Data Bank established by the National Institute of Neurological Disorders and Stroke (NINDS): (1) brain hemorrhage, (2) brain infarction (atherothrombotic and tandem arterial pathological abnormalities), (3) cardioembolic stroke,

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(4) lacunar stroke, and (5) stroke from rare causes or with an undetermined etiology.

The definition of atherothrombotic brain infarction in this classification is more than 90% stenosis in the relevant cerebral artery, which is very limited. For this reason, the proportion of patients diagnosed with atherothrombotic brain infarction was underestimated, and as such, the cases of stroke with an undetermined etiology increased, representing approximately 40% of all the stroke cases. In other words, in this classification method, the etiology of about half of all stroke patients could not be identified. Additionally, the definition of lacunar stroke was too broad, based only on the clinical symptoms and signs, which was inevitable because at the time of establishment of such classification method there were no brain imaging techniques such as CT angiography or MR angiography that could determine the pathology of the intracranial artery.

1.1.2 Oxfordshire Community Stroke Project Subtype Classification

Oxfordshire Community Stroke Project (OCSP) was originally suggested to identify the characteristics of the subjects in epidemiology studies of Oxfordshire community (Table 1.1). At the time, the OCSP researchers were forced to exert efforts to meet the standard of diagnostic tests available in the British public healthcare system because all the stroke patients in the UK are treated by primary care physicians. Besides the clinical findings, CT is the best examination method among others, and there was no way at that time to confirm the problem in the brain vessel itself or the presence of a heart disease. Therefore, the OCSP researchers chose a method of classifying patients depending on the site and size of their ischemic stroke on a clinical basis. As the size and location of ischemic stroke are not determined by the cause of stroke, however, even a patient whose stroke is classified as lacunar stroke has a possibility of having stenosis in the M1 portion of middle cerebral artery or atrial fibrillation, but there is no way to figure this out in most cases. In early stage of ischemic stroke, lesions are not clearly shown on the CT image in many cases, and in such cases, the patients' stroke is classified depending only on the clinical findings. Thus, approximately 20–30% of stroke cases are known to have been misclassified. This classification method, however, depends only on the location and size of the ischemic stroke based simply on the clinical findings and CT; as such, it

Table 1.1 OSCP classification

Type of infarct	Diagnosis
Cerebral infarction	If a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality or an area of irregular high attenuation within a larger area of low attenuation (i.e., an area of hemorrhagic infarction) or if a necropsy examination shows an area of cerebral infarction (pale or hemorrhagic) in a region compatible with the clinical signs and symptoms
Lacunar infarct (LACI)	One of the four classic clinical lacunar syndromes. Patients with faciobrachial or brachiocrural deficits are included, but more restricted deficits are not
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed
Partial anterior circulation infarct (PACI)	Only two of the three components of the TACI syndrome, with higher dysfunction alone or with a motor/sensory deficit more restricted than those classified as LACI (e.g., confined to one limb or to the face and hand but not the whole arm)
Posterior circulation infarcts (POCI)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e., ataxic hemiparesis), or isolated homonymous visual field defect

OCSP Oxfordshire Community Stroke Project

has advantages in that the classification is easy and almost all stroke cases can be classified. The classification is so easy that communication between the physicians and the interobserver reliability is very high. Also, as the prognosis of a patient is determined by the initial severity of the stroke, considerable predictions can be made based on this classification method, even without knowing the cause of the ischemic stroke.

1.1.3 Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Subtype Classification

Since 1993, almost all clinical researchers in the world have used the classification system suggested by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) clinical researchers (Table 1.2). The original purpose of this classification system was to analyze the effect of danaparoid in the subtypes of strokes. The TOAST researchers classified stroke initially into 11 categories, but they later compressed these categories into five groups. This is a classification system whose internal validity can be increased if the researchers follow the pre-planned algorithm, and accuracy in diagnosis may improve if there are more than two evaluators. Lacunar infarction is defined by the clinical symptoms and the size of the ischemic stroke. In this case, if significant stenosis in the M1 portion of middle cerebral artery is not detected because thorough examination of the cerebral artery has not been done, the ischemic stroke caused by large-artery atherothrombosis is likely to be misclassified as lacunar infarction. In addition, the causes of cardioembolism consist of high- and medium-risk factors, and among the medium-risk factors are many factors that are too ambiguous to be considered a cause of cardioembolism, such as patent foramen ovale. Therefore, there is a possibility for a stroke patient with a medium-risk factor, whose intracranial and extracranial arteries had not been thoroughly examined, to be misclassified as cardioembolism. Moreover, the cases of ischemic stroke with an undetermined

Table 1.2 TOAST classification

Type of infarct	Diagnosis
Large-artery atherosclerosis	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with more than 50% lesion or occlusion in an extracranial or intracranial vessel in the distribution of an infarct larger than 1.5 cm by CT or MRI. This diagnosis cannot be made if arterial studies show no evidence of pathology or if there is reasonable suggestion by history or studies that another mechanism is possible
Cardioembolism (high risk/medium risk)	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with a lesion size larger than 1.5 cm on CT or MRI and the presence of at least one high-risk (e.g., atrial fibrillation or mechanical heart valve) or medium-risk cardiac pathology (e.g., lone atrial fibrillation or patent foramen ovale) on diagnostic studies, electrocardiogram, rhythm strip, 24-h cardiac monitoring, and transthoracic or transesophageal echocardiography. Evidence of transient ischemic attacks or strokes in more than one vascular territory or of systemic emboli supports the diagnosis. Finally, other categories (large artery, small artery) must be excluded
Small-vessel occlusion (lacunar)	A lacunar syndrome (pure motor, sensorimotor, pure sensory, ataxia hemiparesis, dysarthria-clumsy hand) with normal CT or MRI or a lesion smaller than 1.5 cm on CT or MRI in the territories supplied by small-vessel penetrators. Large-artery and cardiac sources must be excluded
Stroke of other determined etiologies	Stroke caused by nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders and other rare causes of stroke after diagnostic testing. Other categories must be excluded
Stroke of undetermined etiology (cryptogenic)	This diagnosis is made if two or more etiologies of stroke are possible, a complete evaluation reveals no possible source, or the patient had an incomplete evaluation

TOAST Trial of Org 10172 in Acute Stroke Treatment

cause include both the cases where the stroke has two or more distinct causes or where the cause of the stroke is not found even after sufficient examination. For example, in a case where the patient has more than 50% vascular stenosis and atrial fibrillation, the stroke is in principle classified as ischemic stroke with an undetermined cause. Even all the cases where the physician or researcher can make a diagnosis based on a strong hunch are in principle classified as ischemic stroke with an undetermined cause, and consequently, the proportion of cases of ischemic stroke with an undetermined cause is exaggerated.

1.1.4 The Path of Stroke Classification

Stroke classification does not exist simply for clinical research purposes. It should be well applied to usual patient care, and well used for patients' early diagnosis, for prognosis determination, and for the medication for stroke prevention. The classification made using an expensive equipment or examination method may pose a problem in the country's public health, but if classification is simply made based only on the clinical findings and CT image obtained, there are bound to be too many errors. Each country needs to establish the optimal classification system employing appropriate tests that fit the public health characteristics of the patients in the country.

1.2 Thrombus Formation According to the Stroke Etiology

Occlusion of the blood vessels, a cause of ischemic stroke, is usually caused by a thrombus (or a blood clot). Therefore, the core of stroke pathophysiology is to understand the process of thrombus formation. According to the ischemic stroke classification, a thrombus with a different appearance may develop. Thus, the basic process of thrombus generation must be understood. Thrombi largely consist of two components as an end product of the blood coagulation process: a platelet plug and a fibrin protein cross-linked like a mesh. In general, the condition in which thrombi develop is known as "Virchow's triad," and its description is as follows: (1) damage in the vascular endothelial cell (trauma or arteriosclerosis), (2) abnormal blood flow (loss of laminar flow due to blood stasis in the vein or turbulence in the artery), and (3) hypercoagulability state. The thrombi caused by these reasons are classified into the following depending on the component: white thrombus, whose major components are platelets, or red thrombus, whose major components are red blood cells (Fig. 1.1). Both types of thrombus may develop in ischemic stroke. Depending on the type of thrombus that is the major cause of stroke, the patient's early progression, the effect on the acute-phase treatment, the prognosis, and the secondary prevention vary. Thus, most of all, it is important to identify the

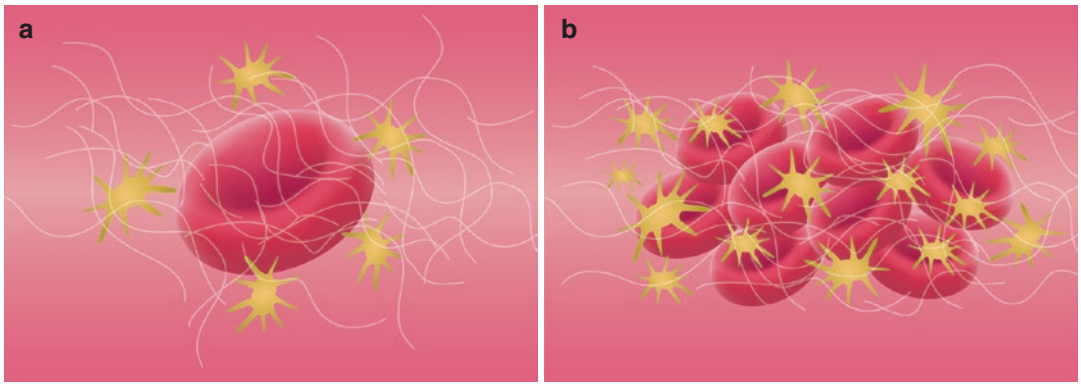

Fig. 1.1 Schematic figures of white thrombi (**a**) and red thrombi (**b**)

onset mechanism, components, and important factors of the thrombus for the appropriate diagnosis and treatment of ischemic stroke patients.

1.2.1 Formation of Platelet Thrombus

In the maintenance of the vascular system and homeostasis, the endothelial cells, the collagen in the subendothelial tissue, and the tissue factor (TF) are important. In particular, the endothelial cells form tunica intima and have three thromboregulators inhibiting thrombus formation: nitric oxide, prostacyclin, and ectonucleotidase CD39 [2].

1.2.1.1 Two Independent Pathways for Platelet Activation

One is the collagen pathway, and the other is the TF pathway (Fig. 1.2). If the vessel wall is disrupted, the collagen and TF are exposed to the blood, and thrombus formation starts. Collagen facilitates platelet coagulation and activation, while TF initiates thrombin formation, activates the platelets, and changes fibrinogen into fibrin. In the two pathways, either of the two can be dominantly activated depending on the situation, but the result is the same in that the platelets are activated.

With regard to the collagen pathway, platelet adhesion occurs through the interaction between the exposed collagen and the glycoprotein VI of the platelet and through the interaction between the von Willebrand factor attached to the collagen and the glycoprotein Ib-V-IX of the platelet. Glycoprotein VI acts as the most important factor in early platelet activation and platelet granule secretion. The platelet activation here is irrelevant to thrombin.

TF causes the formation of the TF pathway, the second most important pathway in early platelet activation. The platelet activation here is irrelevant to the major components of the collagen pathway, the rupture of the vascular endothelial cells, the von Willebrand factor, and glycoprotein VI. Originally, TF has two forms. It is present on the vessel wall in an inactivated or encryptic form, or in an activated form inside the vessel wall. The inactivated TF is

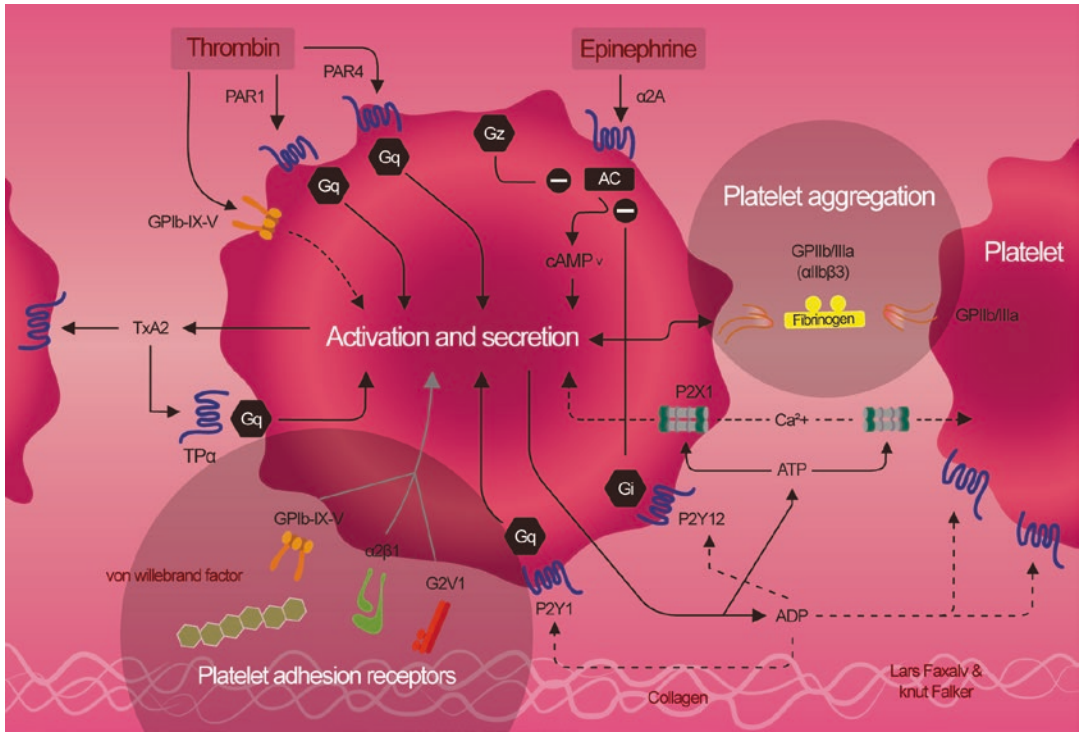

Fig. 1.2 Mechanism of platelet activation

activated by protein disulfide isomerase, and such TF forms a complex with factor VIIa, and the complex produces thrombin along the proteolysis pathway while sequentially activating factor IX. Thrombin activates the platelets while decomposing the protease-activated receptor 4 (Par 4 in mouse; Par 1 in human) on the surfaces of the platelets. As a result, adenosine diphosphate (ADP), serotonin, and thromboxane A2 are secreted from the activated platelets. The secreted substances amplify the signal for thrombin formation while activating different platelets sequentially.

1.2.1.2 Propagation of Thrombi Composed of Platelets

The integrin αIIbβ3 of a platelet plays the role of drawing platelet-platelet and platelet-thrombus interactions while being activated. For αIIbβ3 activation, protein disulfide isomerase is necessary. The activation of a platelet attached to the damaged vessel wall promotes a structural change of αIIbβ3 and consequently makes the ligand of αIIbβ3 increase the affinity with fibrinogen or the von Willebrand factor. At a small shear rate, the affinity with fibrinogen is more important, while at a high shear rate, the affinity with the von Willebrand factor is relatively more important. This does not mean, however, that fibrinogen and the von Willebrand factor are absolutely necessary for thrombus formation in this situation. An activated platelet secretes alpha and dense granules. These secretions play a crucial role in thrombus formation. The alpha granule contains various proteins, and the dense granule contains ADP and calcium ion. The ADP secreted through a dense granule facilitates platelet activation more by attaching to the P2Y1 and P2Y12 receptors of the platelet.

1.2.2 Blood Coagulation

1.2.2.1 Contact Activation Pathway (Intrinsic Pathway)

The contact activation pathway begins with the initial complex composition by high-molecular-weight kininogen (HMWK), prekallikrein, and factor XII (Hageman factor) on collagen (Fig. 1.3). As prekallikrein changes to kallikrein, factor XII is activated into XIIa. XIIa changes factor XI into XIa, while XIa changes factor IX into IXa. IXa makes up a tenase complex with a cofactor, factor VIIIa, and this complex activates factor X to Xa. The contact activation pathway in blood coagulation is very strong for coagulation in in vitro studies, but it is not necessary for starting blood coagulation in in vivo studies. The activation of factor XII is very important because it is the starting point of the formation of the contact pathway, and the absence of this factor has been confirmed to mean a very prolonged partial thromboplastin time. Strangely, however, it is not true that patients who do not have this factor have bleeding disorders. Therefore, the importance of factors XII and XI is slightly vague. As it has been confirmed that both factors are associated with thrombus formation in mice, their roles in different biological species may be different. In humans, the pathway is more likely to be associated with inflammation or a congenital immune system rather than with coagulation.

1.2.2.2 TF Pathway (Extrinsic Pathway)

The TF pathway plays the role of leading an "explosive increase of thrombin," its most important component, through a feedback mechanism in the entire coagulation pathway. As mentioned earlier, TF is a membrane protein with very complex roles. It is mainly expressed in the fibroblast, in the pericyte in the outer membrane of a vessel, and in the smooth muscle cell of the vessel wall and is often expressed in other cells not related to the blood vessels. TF interacts with several less than 1,000-nm microparticles existing in the blood. During thrombus formation, the platelet is attached to the vessel wall and expresses adhesion molecules called P-selectin while being activated. P-selectin is connected with the microparticles, expressing a receptor called P-selectin glycoprotein ligand 1 (PSGL-1), and causes the microparticles expressing the TF derived from monocytes to be captured in the thrombus. Like this, the TF derived from the blood plays an important role in fibrin extension within the thrombus. As TF performs activities related to blood coagulation only in the activated status, for the inactivated TF (in the latent or encrypted form) existing in the vascular endothelial cells to participate in blood

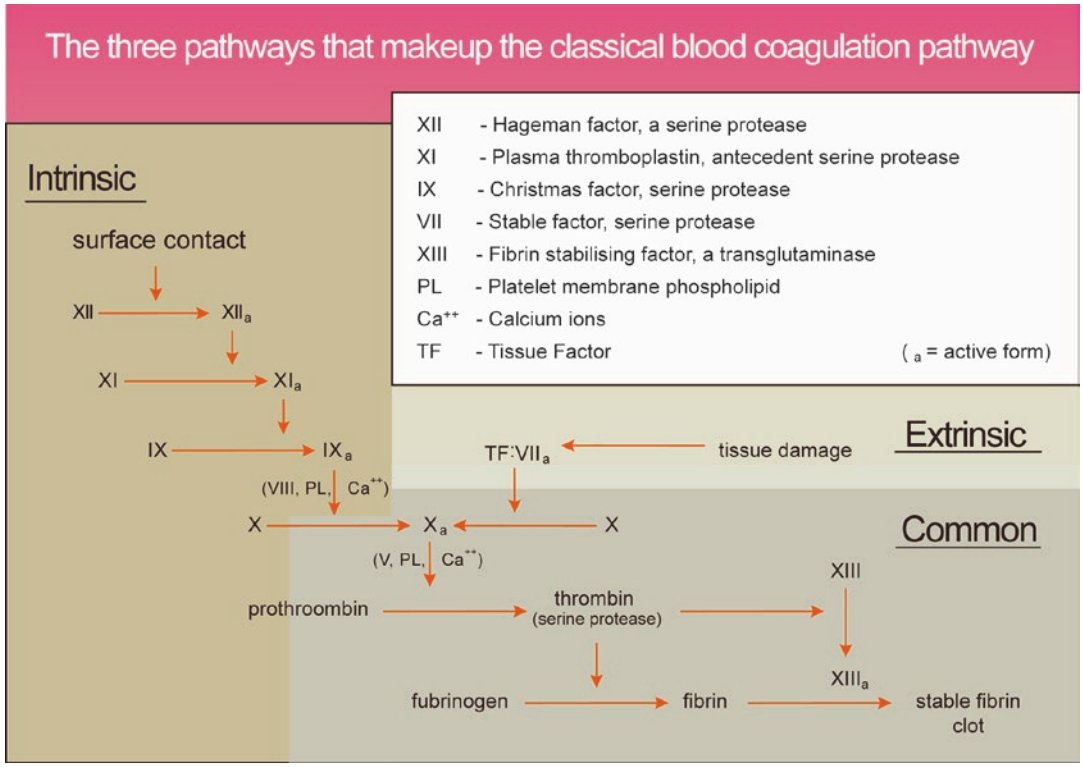

Fig. 1.3 Cascades of clotting factor activation: contact activation pathway (or intrinsic pathway), tissue factor pathway (or extrinsic pathway), and common pathway

coagulation, the activation process is required. The TF activation mechanism is not clear in molecular biology, but it is thought that as the disulfide bonds in the cysteine within the TF protein are separated, it is activated. These bonds are separated by the aforementioned protein disulfide isomerase and are isolated from the activated endothelial cells or platelets. Therefore, protein disulfide isomerase is involved in both fibrin and platelet thrombus formation.

Among the many blood coagulation factors, the amount of factor VIIa in the blood is greater than those of the other coagulation factors. Factor VII is activated by thrombin, XIa, XII, and Xa, and if the blood vessels are damaged, factor VIIa enters the fibroblasts or monocytes containing TF and makes a complex by binding with TF. This complex activates factors IX and X. The activation of X by a complex can be immediately inhibited by the tissue factor pathway inhibitor (TFPI). Factor Xa and its cofactor, factor Va, form a prothrombinase complex, which converts prothrombin into thrombin. Thrombin affects various coagulation factors, and factors V and VIII are applied to this case. As mentioned earlier, the activated factor VIIIa here acts as a cofactor of factor IXa and makes a tenase complex. As this process is repeated, the thrombin formation process is amplified.

1.2.2.3 Common Pathway

The aforementioned pathway is in fact a result from the laboratory, which measures what is activated by the isolated surface (contact activation pathway) or thromboplastin (a complex of tissue factor and phospholipid). Actually, thrombin exists from the time a platelet is initially coagulated and carries out many functions besides the simple conversion of fibrinogen into fibrin. Thus, it is the most important coagulation factor in blood coagulation. With regard to the function of thrombin, simply put, it activates

factors VIII and V, and if thrombomodulin exists, it also activates protein C. Here, the activated protein C inhibits factors VIII and V and compromises the blood coagulation. In addition, by activating factor XIII, it plays the role of cross-linking fibrin monomers into polymers. The common pathway serves to maintain the coagulation trend by continuing to activate factors VIII and IX until they are suppressed by the anticoagulation mechanisms.

1.2.2.4 Cofactor and Modulator

The following components play an important role in maintaining the homeostasis as a whole with the blood coagulation cofactors and modulators. Here, two cofactors and five modulators will be mentioned.

Cofactor

The cofactors include calcium, phospholipid, and vitamin K. Phospholipid, as a component of calcium and the platelet membrane, acts as a cofactor in the function of the tenase and prothrombinase complexes. Besides this, calcium is reported to have a role in the activation of other coagulation factors. Vitamin K is an essential element for an enzyme called hepatic gamma-glutamyl carboxylase attaching a carboxyl group to the glutamic acid residues of factors II, VII, IX, and X and proteins C, S, and Z. In this process, vitamin K itself is oxidized. An enzyme called vitamin K epoxide reductase (VKORC) reverts vitamin K to the activated status. As VKORC is a target substance of warfarin, it is a very important enzyme pharmacologically. By blocking VKORC, warfarin causes vitamin K deficiency and blocks the activation of the coagulation factors.

Modulator

The modulators include protein C, antithrombin, tissue factor pathway inhibitor (TFPI), plasmin, and prostacyclin (PGI2). Protein C is a major anticoagulant in the body and is activated by thrombin, to which the cell surface protein, thrombomodulin, is bonded. Activated protein C decomposes and inactivates factors Va and VIIIa with a cofactor, protein S, and phospholipid. Protein C or S deficiency leads to various forms of thrombosis, including cerebral infarction. Antithrombin is a serine protease inhibitor (serpin) that decomposes thrombin and factors IXa, Xa, XIa, and XIIa, which are serine proteases. It is always in the activated status, and if heparan sulfate exists or if heparin is injected from outside, the effect is enhanced. Also, if there is a deficiency in it, various forms of thrombosis, including cerebral infarction, may occur. As mentioned earlier, the tissue factor pathway inhibitor (TFPI) limits the action of TF. In the liver, plasmin develops through the decomposition of plasminogen. The process is catalyzed by the tissue plasminogen activator (t-PA), which is synthesized and secreted by the vascular endothelial cells. Plasmin decomposes fibrin into the fibrin degradation product (FDP) and inhibits excessive fibrin formation. For the initial treatment of ischemic stroke, the method of injecting recombinant t-PA for thrombolysis is authorized worldwide and is used extensively. Prostacyclin (PGI2) is secreted at the endothelial cells and activates the Gs-protein-linked receptor of the platelet. It sequentially activates adenylyl cyclase and increases the cAMP synthesis. cAMP lowers the calcium level in the cell, suppresses platelet activation, and inhibits the secretion of granules that induce the activation of the secondary platelet/coagulation factor.

1.3 Mechanism of Vascular Occlusion Causing Ischemic Stroke

The classification of ischemic stroke and the mechanisms of thrombus development in the blood have been presented in detail. The reason for the occurrence of acute ischemic stroke, however, is actually that the blood vessel governing the local cerebral region is blocked in an instant. As a lesion that may cause ischemic stroke exists in the blood vessel itself in many cases, it cannot merely be explained with the onset mechanism of thrombus in the blood, and the actual mechanism of occlusion needs to be logically understood. The reason that the blood vessels are occluded is explained differently depending on the TOAST

classification, and here, the mechanism of the occurrence of acute occlusion of the blood vessels will be explained in accordance with the classification. Only the mechanisms in large-artery atherosclerosis, small-vessel occlusion, and cardioembolism, however, which account for approximately 70% of the ischemic stroke cases, will be described herein, and the mechanisms of occlusion in other rare etiologies will not be mentioned here.

1.3.1 Mechanism of Occlusion in Large-Artery Atherosclerosis

Atherosclerosis is a chronic inflammatory disease developed by innate and adaptive immunity with the lipids in the artery wall as major components (Fig. 1.4). At first, it is accompanied by dysfunction in the vascular endothelial cells, and as the blood vessels are exposed to excessive lipids (low-density lipoprotein, LDL), the lipids start to accumulate under the intima. If a person is frequently exposed to different risk factors (hypertension, diabetes, smoking, infection, stress, etc.), the damage in endothelial cells becomes severe, and due to the damaged endothelial cells, more LDL cholesterol particles accumulate in the extracellular matrix (ECM), which becomes the place where the damage caused by the oxidation and decomposition enzymes most frequently occurs. The modified LDL activates various inflammatory responses, and its major mechanism is the infiltration of monocytes, which plays the most important role in innate immunity. Also, it is known that adaptive immunity, including the helper T cells (Th1 and Th2) and the antibodies, plays a significant role in the expansion of arteriosclerosis. If monocytes infiltrate and reach the subendothelial region, they are differentiated into macrophage by the macrophage colony-stimulating factor. Macrophage can be differentiated into subtypes with various types and functions according to the environment around it, and such

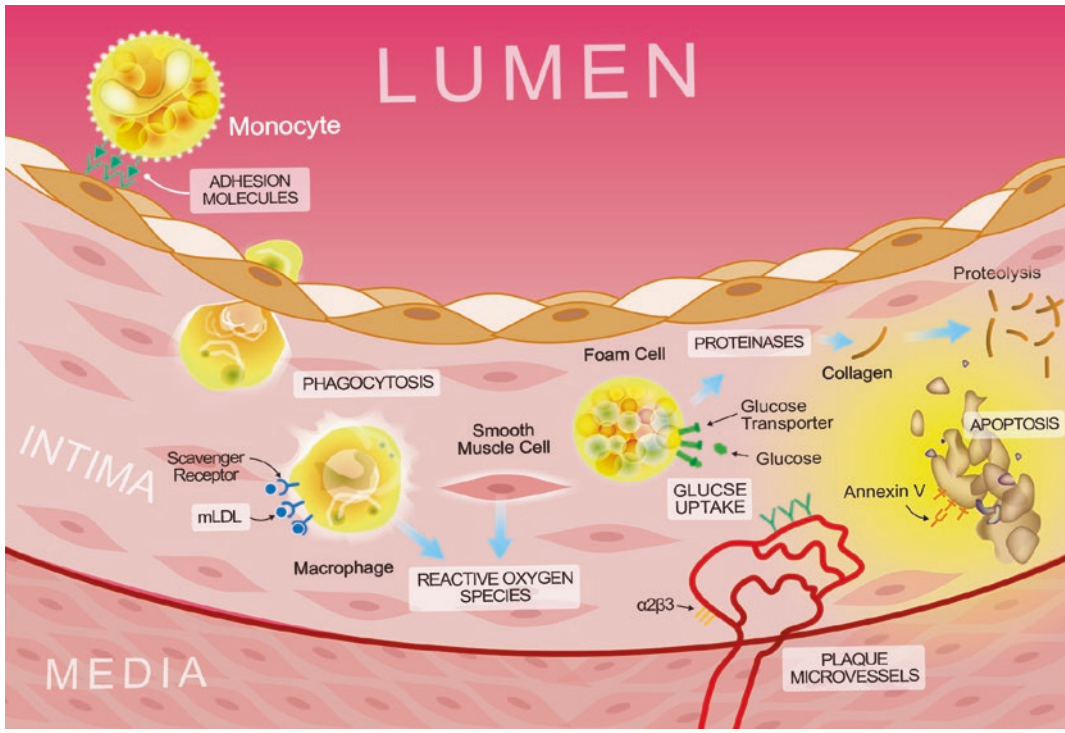

Fig. 1.4 Progression of atherosclerotic lesion (shown as time sequence from left to right)

a process is called "polarization." There are two macrophage subtypes that can be very clearly distinguished from each other depending on the atherosclerosis process, which are known as M1 and M2 (Fig. 1.5). A differentiated macrophage goes through a lipid-containing macrophage while expressing a surface pattern recognition receptor well receiving the modified LDL and changes to a foam cell. As the foam cell secretes cytokines and growth factors, lesions progress, and the vascular smooth muscle cell (VSMC) moves from the media to the intima, where ECM materials, which are important in fibrous cap formation, are produced. In fact, many lipid-containing macrophages are removed by M2 macrophage through the process called "efferocytosis" after initially going through the process of apoptosis. Nevertheless, as macrophage excessively takes apoptosis cells, the endoplasmic reticulum is stressed. Consequently, defects in efferocytosis occur, which isolates the death of the macrophage and lipids, the inflammatory factor, the coagulation factor such as TF, and the matrix metalloproteinases (MMPs). MMP induces the rupture of the atherosclerotic plaque while decomposing the ECM scaffold such as the fibrous cap. The plaque vulnerability is exacerbated as the infiltration of VSMC becomes smaller, and more immature and leaky microvessels occur in the core necrotic plaque.

1.3.1.1 Classification of Atherosclerotic Plaque

WHO classified and reported the atherosclerotic plaque for the first time in 1958, and the four classes are as follows: fatty streak, atheroma, fibrous plaque, and complicated lesion. In the mid-1990s, the American Heart Association (AHA) recommended a new classification standard for the atherosclerotic plaque, and later, several researchers refined the classification system as it was confirmed that plaque erosion could also cause coronary thrombosis [3–5]. Table 1.3 and Fig. 1.6 present the current classification system of coronary atherosclerotic plaque based on this. The classification system of atherosclerotic

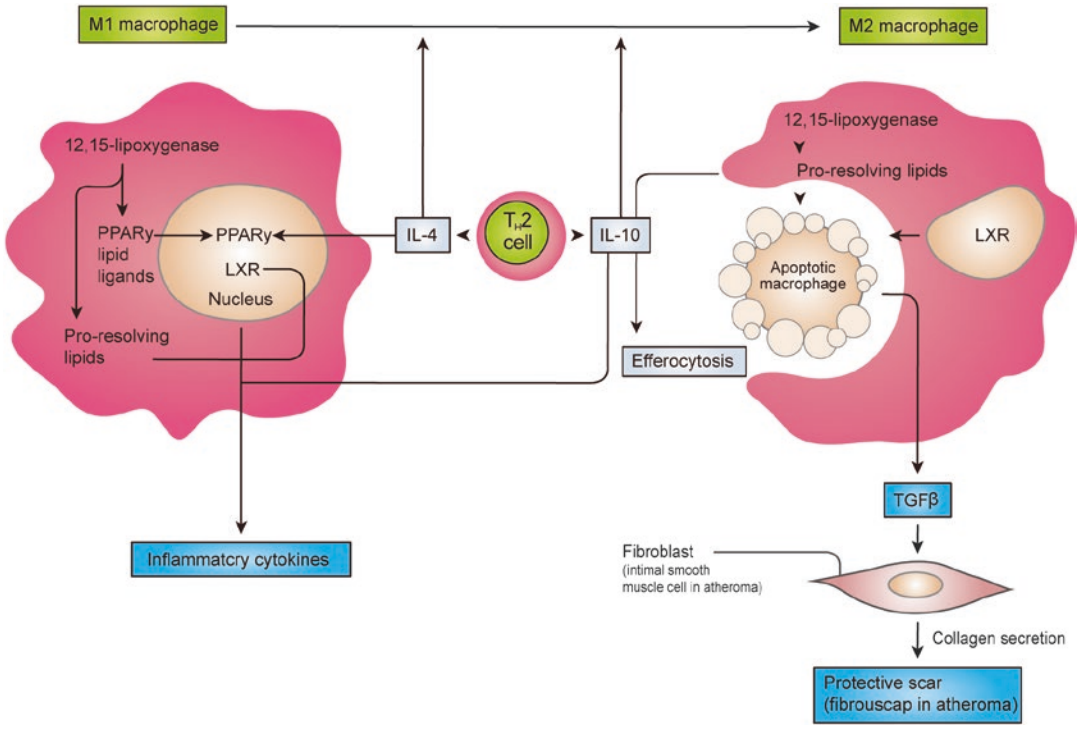

Fig. 1.5 M1 and M2 subtypes of macrophage with differential functions according to atherosclerotic stage

Table 1.3 Classification of atherosclerotic lesion

Type of lesion	Subtype of lesion	Morphological description
Nonatherosclerotic intimal lesions	Intimal thickening	Natural accumulation of smooth muscle cells in the absence of lipid, macrophage foam cells, and thrombosis
	Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core, fibrous cap, or thrombosis
Progressive atherosclerotic lesions	Pathological intimal thickening	Plaque rich in smooth muscle cells, with hyaluronan and proteoglycan matrix and focal accumulation of extracellular lipid. Absence of thrombosis
	Fibroatheroma	During early necrosis: focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap. During late necrosis: loss of matrix and extensive cellular debris with an overlying fibrous cap. With or without calcification. Absence of thrombosis
	Intraplaque hemorrhage or plaque fissure	Large necrotic core (size >10% of plaque area) with hemorrhage, and plaque area shows the presence of angiogenesis. Necrotic core communicates with the lumen through a fissure. Minimal tear without obvious thrombus
	Thin-cap fibroatheroma	A thin, fibrous cap (<65 μm) infiltrated by macrophages and lymphocytes, with rare or no smooth muscle cells and relatively large underlying necrotic core (>10% of plaque area). Intraplaque hemorrhage and/or fibrin might be present. Absence of thrombosis
Lesions with acute thrombi	Plaque rupture	Thin-cap fibroatheroma with cap disruption. Thrombosis is present and might or might not be occlusive. The luminal thrombus communicates with the underlying necrotic core
	Plaque erosion	Can occur on pathological intimal thickening or on a fibroatheroma. Thrombosis is present and might or might not be occlusive. No communication of the thrombus with the necrotic core
	Calcified nodule	Eruptive (shedding) of calcified nodule with an underlying fibrocalcific plaque with minimal or no necrosis. Thrombosis is usually not occlusive
Healed lesions	Healed plaque rupture, erosion, or calcified nodule	Healed lesion composed of smooth muscle cells, proteoglycans, and collagen type III with or without underlying disrupted fibrous cap, necrotic core, or nodular calcification. Lesions can contain large areas of calcification with few inflammatory cells and have a small or no necrotic core. The fibrotic or fibrocalcific collagen-rich plaque is associated with significant luminal stenosis. Absence of thrombosis

An updated version of the modified AHA classification published in 2016, which was based on the original AHA classification published in the mid-1990s

plaque on the cerebral artery has not yet been brought up, but its nature is not thought to be different from the actual nature of atherosclerosis, although the organ and the diameter of the artery are slightly different. Thus, it is appropriate to understand ischemic stroke due to large-artery atherosclerosis based on this [6]. As mentioned in this classification system, atherosclerotic plaque associated with thrombosis can be in the form of plaque rupture, plaque erosion, and calcified nodule. How these three lesions cause thrombosis will be discussed below.

1.3.1.2 Plaque Rupture

Plaque rupture consists of a necrotized core portion and a ruptured fibrous cover on the portion, and the cover is generally infiltrated by macrophage and T cells. The ECM of the fibrous cover consists of type 1 collagen, and VSMC is found extremely rarely. The thrombus

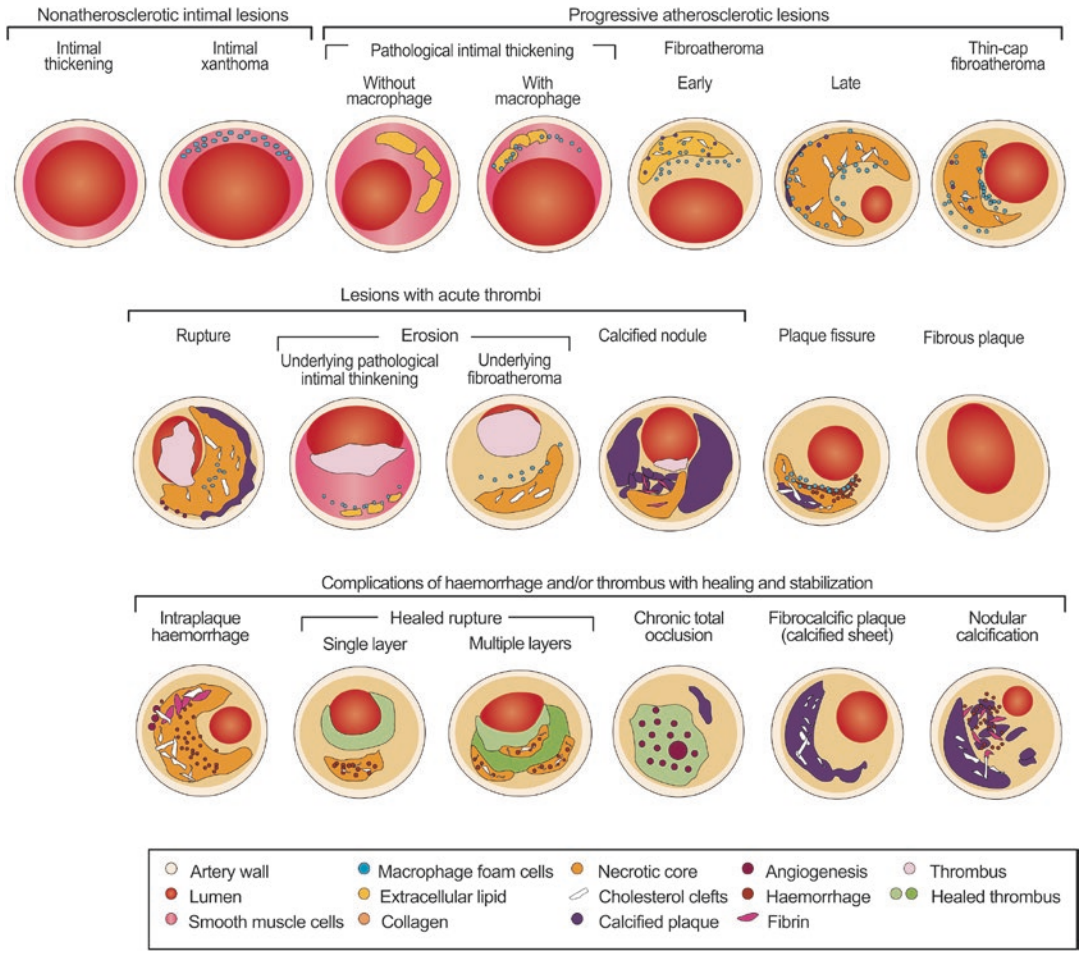

Fig. 1.6 Schematic figures showing composition and morphology of atherosclerotic lesion according to the classification suggested by the American Heart Association

found in the ruptured portion is mostly composed of platelets (white thrombus) and changes into a red thrombus with the image that the red blood cells are embedded in the fibrin layer (lines of Zahn) in the distal or proximal area rather than in the embedded area. If the fibrous cover is ruptured at rest, the rupture occurs in the shoulder area that is considered the weakest in the plaque, and if it occurs when the patient is exercising, rupture is known to occur with the same frequency in the shoulder and center areas. It is applied to the coronary artery, however, and the ruptured site of the plaque in the cerebral artery is not well known. With regard to the underlying mechanisms, there is a possibility that shear stress and tension, which affect the protease secretion from the macrophage and plaque, influence the rupture of plaque. Additionally, for fibrous cover, it is possible for a dying macrophage or a microcalcification derived from VSMC (>5 μm) to induce the separation of the cover due to the pressure and to cause plaque rupture.

1.3.1.3 Plaque Erosion

Plaque erosion is an arteriosclerosis lesion that may cause a thrombus due to the stripped surface of the intima composed of VSMC and proteoglycan matrix without rupture. Most underlying histological findings showing plaque erosion include intimal thickening and early or late fibroatheroma. The inner wall in

most plaque erosion cases is clean compared to the ruptured plaque and shows less inflammation, and the plaque rupture shows a positive remodeling finding but negative remodeling in erosion. Usually, significant calcification is not observed in erosion, but microcalcification is observed at around the 40% region. If a thrombus occurs in erosion, tissues are observed usually as a structure that activated VSMC is embedded into the substrate in which proteoglycan consisting of collagen type III, hyaluronan, and versican is abundant. This is in contrast to the finding that the fibrous cover mainly consists of biglycan, collagen type I, decorin, etc. in ruptured or stable plaque. The lipid level in the patient's blood is irrelevant to the occurrence of plaque erosion, and association with smoking has been reported, but verification of such is required. It has been known that distal microembolism more frequently occurs in a thrombus caused by plaque erosion than in a thrombus caused by plaque rupture. Plaque rupture and plaque erosion were briefly shown in Fig. 1.7.

1.3.1.4 Calcified Nodule

The rarest type of arterial thrombosis is a calcified nodule. The calcified nodule is the rarest cause of thrombosis even in coronary artery disease, accounting for only 5% of the causes, and shows the highest frequency in the coronary artery, in which calcification is considerably advanced. The incidence of calcification of an atherosclerotic lesion is much lower in the cerebral artery than in the coronary artery, and as such, it is difficult to know the frequency of the occurrence of atherosclerotic lesion in ischemic stroke. In this lesion, the mechanism of thrombosis development is unclear. One hypothesis is that the calcified sheet is ruptured by the physical pressure, and if it is decomposed into small nodules, fibrin is accumulated around them, and as a result, the accumulated fibrin can erupt above the plaque. The presence of fibrin within a plaque is common in the non-erupted calcified nodule lesions, but it is in the state of non-linkage with the lumen and is likely to have been derived from the damaged surrounding capillaries. The projectile calcified nodule is common in the asymmetrical-shaped lesion, and due to such eruption, there is a possibility of promoting platelet activation. This lesion is more frequently observed in the elderly. The calcified nodule should not be confused with nodular calcification because nodular calcification may destroy the structure of media but adventitia involvement rarely occurs, and it is also independent from thrombosis.

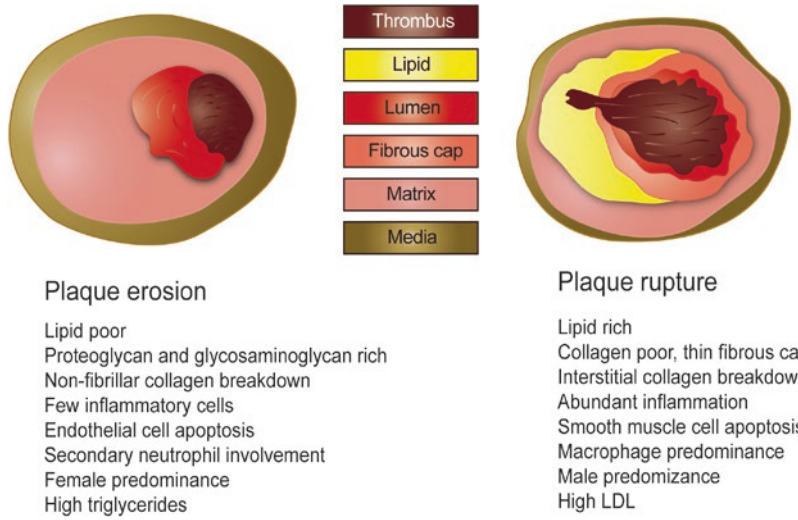

Fig. 1.7 Composition and characteristics of plaque erosion and plaque rupture

1.3.2 Mechanism of Occlusion in Small-Vessel Occlusion

It must be kept in mind that the mechanism of occlusion in small-vessel occlusion is quite different from that in large-artery atherosclerosis. Large-artery atherosclerosis is characterized by the existence of a white thrombus basically caused by platelet activation. The contribution of the platelet in small-vessel occlusion, however, is weak or unclear. In the identification of the occlusion mechanism in small-vessel occlusion, Miller Fisher's study played the greatest role. Dr. Fisher analyzed lacunar infarction in a serial section and confirmed that most lacunar infarction cases are caused by the occlusion of the penetrating artery, and that the diameter of most penetrating arteries is less than 225 μm. In such study, the proportion of lacunar infarction in a blood vessel with a more than 300-μm diameter was very small. It was assumed that the possibility of the occurrence of collateral circulation will be small in the case of occlusion that developed in the smaller vessels. In these vessels, occlusion occurs due to a mechanical blockage on the blood vessels by the degenerated vascular cells that form the wall of the blood vessels mostly denatured into lipohyalinosis. That is, it occurs when the denatured vessel wall itself suddenly blocks the blood flow, and infarction caused by a thrombus, as in large-artery atherosclerosis, very rarely occurs.

About 50% of the cases of occlusion caused by a thrombus in lacunar infarction occur in more than 300-μm-diameter blood vessels. The rest depend on the atherosclerotic plaque itself, or cases of the occurrence of microdetachment and of embolism are reported. Arteriolosclerosis that is a cause of thrombus is located in the proximal penetrating artery in many cases, and this pathological finding is called microatheroma. In particular, microatheroma occurring in the site branching from the great vessel is also called junctional atheroma, and in this case, the penetrating artery from which the thrombus that occurred here branches out is often completely closed.

In fact, the definition of lacunar infarction caused by small-vessel occlusion is ambiguous. Conventionally, it means cerebral infarction caused by the occlusion of the penetrating artery, but it is difficult to distinguish it without pathological findings in actual clinical settings because junctional atheroma that occurred in the large arteries at the previous step is also included in the range of lacunar infarction. Therefore, at the clinical settings in recent years, a less than 1.5- or 2-cm cerebral infarction that occurred deep inside as shown on the diffusion-weighted MRI is defined as lacunar infarction for classification. In this case, however, as even cerebral infarction with a hemodynamic cause or cerebral infarction caused by embolism meets this definition, misclassification is common. Therefore, the discussion of lacunar infarction caused by small-vessel occlusion should be based on a clear definition of it. In most cases, it would be most reasonable if lacunar infarction would be considered to be caused by mechanical occlusion due to the blood vessels denatured into lipohyalinosis.

1.3.3 Mechanism of Occlusion in Cardioembolism

Cardioembolism accounts for approximately 25% of all ischemic stroke cases. It can be generally thought that large-artery atherosclerosis, small-vessel occlusion, and cardioembolism account for 25% of all the cases, with very similar ratios. The remaining 25% of the cases include ischemic stroke with undetermined causes and that with rare causes. Cardioembolism develops when the patient has a heart disease causing blood stasis (e.g., acute myocardial infarction, left ventricular [LV] aneurysm, cardiomyopathy and myocardite, valve disease and/or prosthesis, and atrial fibrillation [AF]) [7]. As the blood directly going to the brain comes from the left side of the heart, the disease causing a thrombus at the left ventricle and left atrium can be seen as a cause of cardioembolism, except for diseases causing right-to-left shunt. The disease causing a thrombus at the left ventricle usually develops at the LV apex, and if the patient has LV aneurysm or acute myocardial infarction, the possibility of thrombus development at the left ventricle is high because myocardial infarction causes dyskinesia (akinesia or hypokinesia) in the heart wall at the left ventricle and consequently results in serious blood stasis. In

acute myocardial infarction, the trend of thrombus production is highest at the time of onset and decreases rapidly over time. If examined based on ischemic stroke, however, the proportion of ischemic stroke caused by old myocardial infarction is much higher than that of ischemic stroke caused by acute myocardial infarction. This is only because the prevalence of old myocardial infarction is much higher, and thus, the number is larger even though the possibility of thrombus formation is lower. Based on the same principle, the possibility of thrombus formation due to atrial fibrillation cannot be seen as very high, but its prevalence is very high in the elderly; thus, it is known as the highest cause of cardioembolism. Therefore, the mechanism of thrombus development by atrial fibrillation will be presented below.

1.3.3.1 Structural Consideration of the Left Atrium

The space attached to each atrium like a pocket is called an "appendage." The left atrial appendage (LAA) has a structure extending to the narrow entrance; thus, it is a probable site of blood stasis (Fig. 1.8). Therefore, LAA is a place where a thrombus most well develops at the atrium not only in a patient with atrial fibrillation but also in a patient with normal rhythm. As atrial fibrillation lasts longer, changes occur in the structure and tissue of the left atrium, and these changes are often associated with the frequency of thromboembolism. The change called "rough endocardium" refers to a finding showing a wrinkled appearance due to swelling, and is a status where fibrin and a thrombus can easily develop, with detached endothelial cells. Besides, findings of myocytic hypertrophy or necrosis, a mononuclear cell infiltrate, etc. are observed. The phenomenon where it is difficult to come back to the normal atrial rhythm even after successful cardioversion in atrial fibrillation patients can be explained by pathological findings like this. Additionally, due to these findings, atrial fibrillation patients are highly likely to require an anticoagulant despite the return to the normal rhythm.

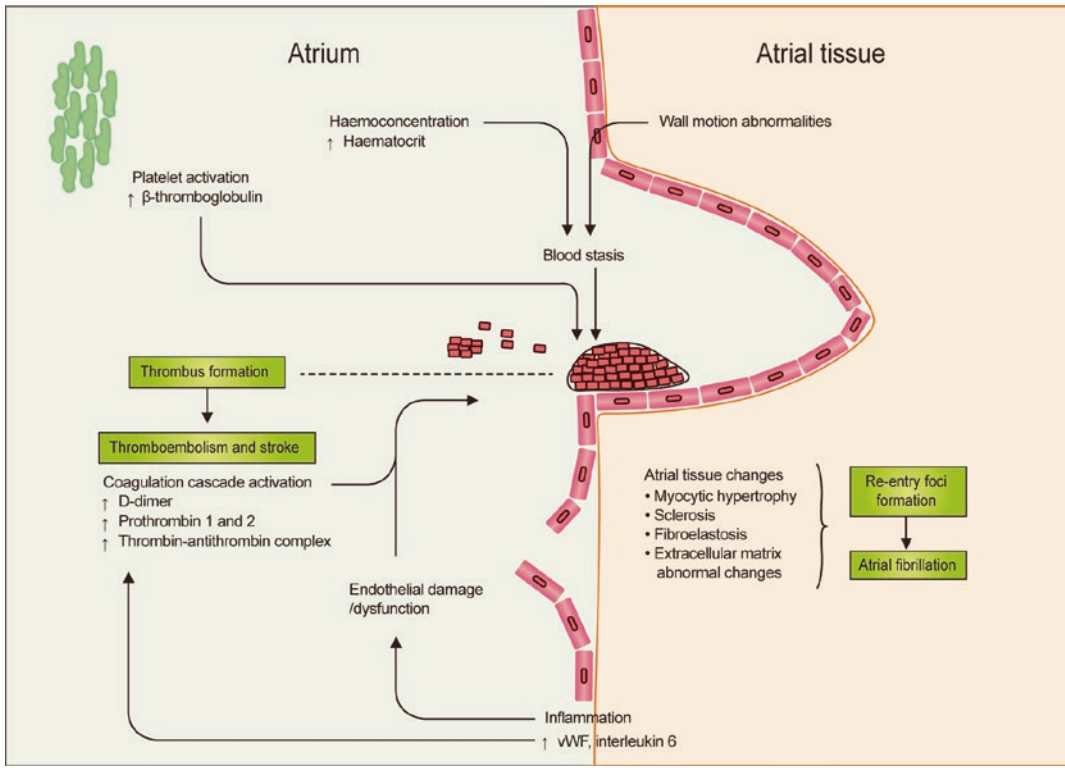

Fig. 1.8 Mechanism of thrombogenesis in left atrial appendage

1.3.3.2 Abnormal Blood Pooling in Atrial Fibrillation

In atrial fibrillation, blood stasis is worsened due to the progressive expansion of the left atrium as well as blood stasis or pooling due to atrial contraction failure [8]. This condition is further exacerbated if mitral stenosis occurs. The expansion of the left atrium increases thrombosis, namely, cerebral infarction, which can be confirmed in many studies in which the size of the left atrium was standardized, adjusting to the size of the body. The blood stasis in the left atrium or left atrial appendage is confirmed with spontaneous echo contrast (SEC) in transesophageal echocardiography (TEE), and SEC is known to be directly associated with the occurrence of stroke. SEC is known to last in about one-third of the cases after atrial fibrillation returns to the normal rhythm, which can explain why persistent anticoagulation therapy is required in this case.

1.3.3.3 Hypercoagulation Status of the Blood

It is known that the fibrin turnover increases in acute/chronic atrial fibrillation, but this actually does not seem to be directly associated with atrial fibrillation and with a structural problem of the heart. Nevertheless, there have been many reports that hypercoagulation biomarkers increased in atrial fibrillation in that ischemic stroke occurred compared to the normal rhythm. Taking into account the previous studies and making a reasonable judgment on the matter, it would be more reasonable to say that the incidence of ischemic stroke is higher in people with atrial fibrillation whose underlying coagulation status was accelerated, than to consider that atrial fibrillation itself accelerates the coagulation status. As a recent study reported that D-dimer was useful in predicting LAA thrombus, there is a possibility for D-dimer to become an important biomarker in atrial fibrillation patients.

1.4 Changes in Brain Tissues According to Cerebral Ischemia

The mechanism of cerebral blood flow (CBF) regulation is very complex and was designed to regulate various mechanisms and important structural components complexly and precisely. Here, the mechanism and its components for regulating the normal CBF will first be discussed, and then the changes that occur in the brain tissues when cerebral infarction occurs will be described.

1.4.1 Mechanism for Regulating the Normal Cerebral Blood Flow

1.4.1.1 Cerebral Blood Flow

The brain of adults is only about 1,350 g and accounts for about 2% of the brain's weight, but an approximately more than 55 mL/100 g/min CBF is normally required, and the amount is about 750 mL/min for the entire brain, which accounts for 20% of the total cardiac output. The brain's oxygen consumption is 3.5 mL/100 g/min even at rest and approximately 50 mL/min for the entire brain, which accounts for about 25% of the body's total oxygen consumption. The ability of the brain to store energy for itself is very small, and much of the glucose that it needs as an energy source must be supplied from outside. The adenosine triphosphate (ATP) obtained in the process of decomposing glucose into carbon dioxide and oxygen is used as an energy source. Therefore, as the brain is very sensitive even to a very short interruption in the blood flow, it is one of the major organs to which blood must be supplied first even when the blood flow to the other organs in the body is insufficient. In general, if the CBF is lowered to a level below 20 mL/100 g/min, electroencephalogram (EEG) and synaptic activity will be reduced, and if it is lowered to a level below 10 mL/100 g/min, irreversible neurological damage will occur.

1.4.1.2 Cerebral Autoregulation

If the brain is stable and if the level of carbon dioxide is properly maintained, the CBF will be very stably maintained [9]. Cerebral autoregulation refers to the operation mechanism for maintaining the CBF even though the atrial pressure from the heart changes. The autoregulation ability is normally maintained if the mean arterial pressure (MAP) is between 70 and 150 mmHg

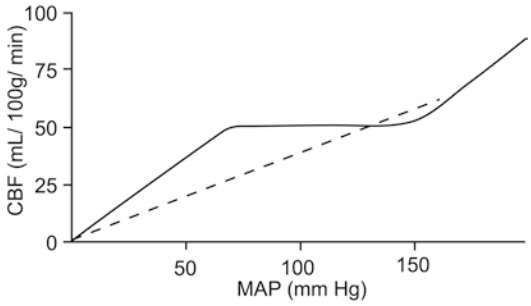

Fig. 1.9 Cerebral autoregulation (*MAP* mean arterial pressure, *CBF* cerebral blood flow)

(Fig. 1.9). The minimum mean arterial pressure in which autoregulation is possible is about 50 mmHg, but it is an available value only in some animals; for humans, a higher pressure is required. The cerebral perfusion pressure (CPP), defined as the value obtained after subtracting the intracranial pressure (ICP) from the mean arterial pressure (MAR) (CPP=MAP-ICP), is the most desirable tool for measuring the CBF, but it is almost impossible to obtain its value by actually measuring it at the clinical setting because there is no easy way to measure the ICP noninvasively. Usually, when the normal ICP at the standing position is considered to be about 10–15 mmHg, the minimum MAP for which autoregulation is possible is about 70 mmHg, and the lower limit of the minimum CPP is about 55–60 mmHg. If the CPP deviates from the range of autoregulation to the extent that it falls below the lower limit, the CBF passively depends on the blood pressure and consequently changes linearly according to the CPP. Even in a case where autoregulation operates within the normal atrial pressure range, a rapid change in the arterial pressure may cause a transient change in the CBF. If a person's CBF is rapidly reduced, the person usually faints (syncope).

The following is a step-by-step description of the change that occurs in the CBF depending on the change in the blood pressure (Fig. 1.10). If the blood pressure decreases, the CPP will also decrease, and as the arteries of the brain expand, the CBF will be relatively constantly maintained (stage 1). If the CPP is continuously reduced, however, it eventually goes beyond the limit of autoregulation ability, and the CBF will gradually decrease. In this stage, the CBF is reduced, but due to the increase in the oxygen extraction fraction, more oxygen will be extracted, and the cerebral metabolic rate will be relatively constantly maintained (stage 2). Here, if the blood pressure drops further, despite the increase in the oxygen extraction fraction, the brain metabolism will be lowered, and cerebral ischemia will occur (stage 3).

Cerebral perfusion pressure (CPP) is defined as the difference between the pressure of the blood flow to the brain and the venous back pressure. The venous back pressure is in the very low level unless the intracranial pressure significantly rises or the flow of the vein is not blocked, and as a result, the CPP can be seen to have a similar change with the mean atrial pressure. As the CBF is determined by the CPP and the cerebrovascular resistance (CVR), it is expressed by the formula CBF=CPP/CVR. If the CPP is constant, the local or partial change in the blood flow will depend on the change in the CVR, and the CVR will be determined complexly by the physical factors, including the blood viscosity and the length and diameter of the blood vessel, and by the biochemical factors, such as the arterial pressure of carbon dioxide ($PaCO_2$).

1.4.2 Structural Factors Involved in the Regulation of the Cerebral Blood Flow

1.4.2.1 Regulation by the Nervous System and the Neurovascular Unit

First, the nerves around the blood vessels play a very important role in the blood flow. Since recently, the theory that the vascular endothelial cells, the nerves around the blood vessels, and the astrocytes play a role in the blood flow as one functional unit rather than as separate units has gradually been admitted as a dogma. The functional unit is called "neurovascular unit" (Fig. 1.11) [10]. The nerve cells acting on the neurovascular unit can be divided into extrinsic and intrinsic innervation. Extrinsic innervation refers to vessel control by the nerves derived from outside. It is divided into the nerves derived from three nerve ganglions (the trigeminal, superior

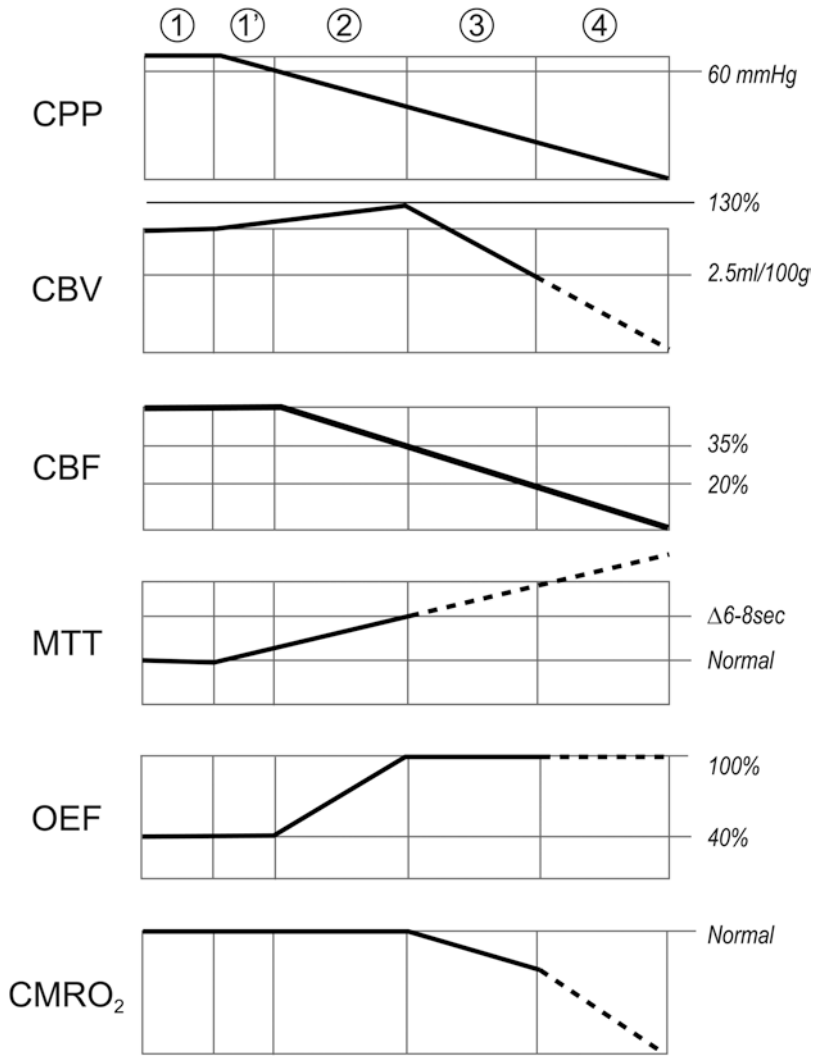

Fig. 1.10 Changes of cerebral blood parameters according to changes of CPP (*CPP* cerebral perfusion pressure, *CBV* cerebral blood volume, *CBF* cerebral blood flow, *MTT* mean transit time, *OEF* oxygen extraction fraction, *CMRO2* cerebral metabolic rate for oxygen)

cervical, and sphenopalatine ganglions), which are the pathways of the sensory, sympathetic, and parasympathetic nerves, respectively. If the blood vessel leaves the Virchow-Robin space and enters the brain parenchyma, the extrinsic innervation is discontinued, and intrinsic innervation begins. Intrinsic innervation is achieved by the subcortical interneuron derived from the distal area or the local interneuron and is achieved through connection to the astrocyte foot process rather than directly being attached to the blood vessel.

1.4.2.2 Vascular Endothelial Cell

The vascular endothelial cells play a central role in the CBF regulation. To date, four substances regulating the function of the endothelial cells have been well known: nitric oxide (NO), endothelium-derived hyperpolarization factor (EDHF), eicosanoids, and endothelins.

NO is a diffusible substance that activates guanylate cyclase and is present in the smooth muscle cell and is considered a substance that has the strongest impact on vascular enlargement. Guanylate cyclase activated by NO relaxes the

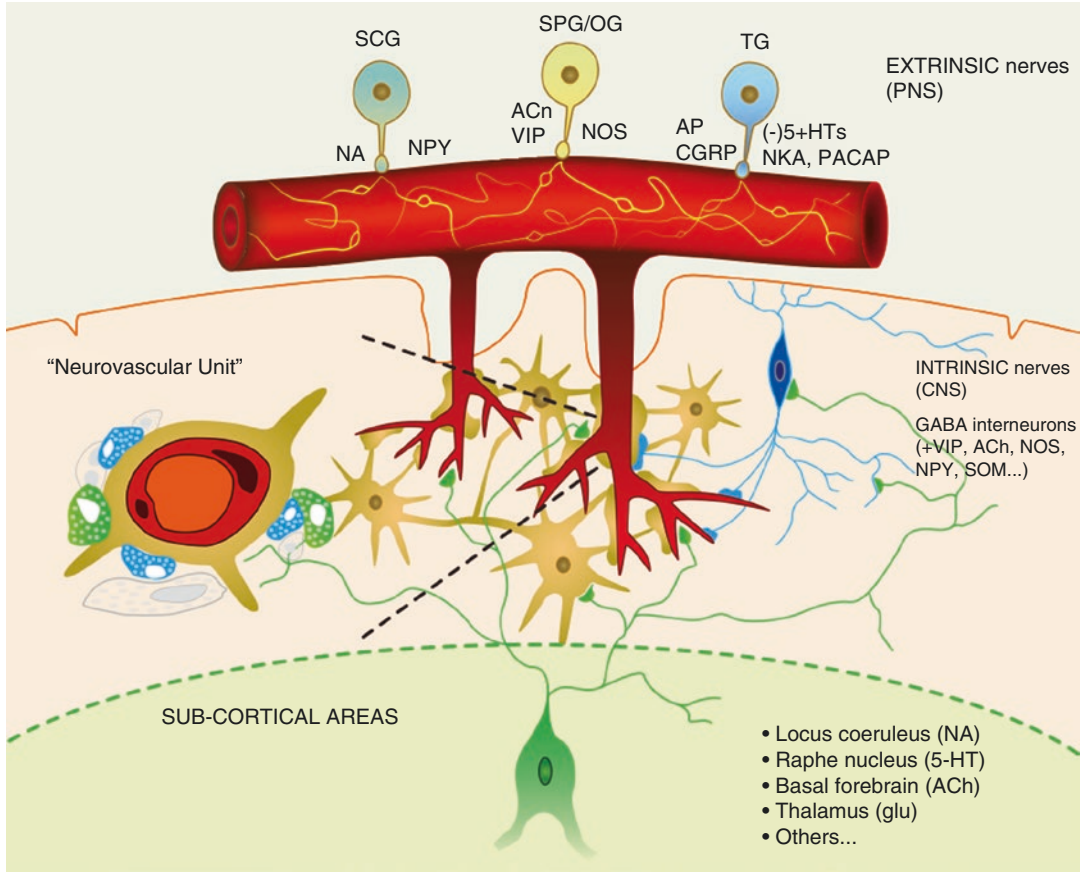

Fig. 1.11 A schematic figure of a neurovascular unit

smooth muscle through the blockage of the voltage-gated calcium channel or the protein kinase G (PKG) activation of the K+ channel while synthesizing cGMP. The enzyme synthesizing NO has several isoforms, and endothelial NOS (eNOS), existing in the cerebral blood vessel, especially in the vascular endothelial cell, plays an important role. EDHF is another diffusible molecule that is activated by the hyperpolarization of the vascular smooth muscle cell and is suppressed by the K+-channel blocker. Eicosanoids are a series of vasoactive substances derived from arachidonic acid, and the following three enzyme systems have been confirmed: cyclooxygenase (COX), lipoxygenase (LOX), and epoxygenase (EPOX). These three enzyme systems are not limited to the endothelial cells but are activated in various cells, including the platelets. Also, as a certain component activated by the enzymes is involved in vascular enlargement, and as another component is involved in vascular contraction, the effect on the overall CBF is determined depending on the activation ratio and locations of these enzymes. Another substance that affects the CBF is endothelin. The system consists of two receptors (ET_A and ET_B) and three ligands (ET-1, ET-2, and ET-3), and its effect on the blood vessels seems to be determined by the receptors rather than the ligands. The ET_A receptor mainly exists in the vascular smooth muscle cells, is stimulated by ET-1 and ET-2, and mediates vascular contraction. On the other hand, the ET_B receptor mainly exists in the vascular endothelial cells, is stimulated by all the three aforementioned ligands, and mediates vascular enlargement. Endothelin is a system associated with a continuous effect rather than with the immediate regulation of the CBF. It is highly

likely to play an important role in pathological conditions such as cerebral ischemia rather than in the regulation of the CBF at rest.

1.4.2.3 Astrocyte

Astrocyte plays a very unique role in CBF regulation. The projection extending from the astrocyte to the outside periphery wraps the capillaries and physically contacts the microvascular structure. Astrocyte has been thought to basically function as the warehouse of extracellular K+, and the possibility of mediating the nerve-blood vessel interaction through communication between the cells through the gap junction was recently raised. As astrocyte has a glutamic acid receptor increasing the level of intracellular calcium, the foot process of astrocyte is assumed to recognize the synaptic signal and to mediate the expansion of the blood vessel associated with it.

1.4.3 Change in the Brain Tissue Caused by Ischemic Stroke

Ever since Astrup first suggested the concept of ischemic penumbra, it has been understood in different ways. The penumbral region is the area typically confirmed around the ischemic core in which the blood flow is reduced to the extent that the ion channel can be maintained even though the electrical activity of the nerve cells cannot be maintained despite the fact that necrosis is not reached. As the electrical activity cannot be maintained, neurological defects occur due to this part, but in this part, if the blood flow is reopened, the previous activity will be regained, and consequently, the patient's symptom will be alleviated. If the decreased blood flow continues, however, various signals (excitotoxicity, spreading depression, oxidative stress, inflammatory response, etc.) exacerbating the brain metabolism function will be generated from the core of the cerebral ischemia to the periphery, and eventually, the patient's symptoms will be exacerbated due to the expansion of the ischemic core [11]. Therefore, properly defining the penumbral region currently confirmed in cerebral ischemia, which is an ultimate goal, is the starting point of ischemic stroke treatment. As it is not easy, however, to clinically visualize the penumbral region for treatment, attempts have been made to approach such region in various ways. Here, several influential concepts will be introduced.

1.4.3.1 Confirmation of the Penumbra Region Through Diagnostic Imaging

In clinical settings, the most appropriate way to define the penumbral region of cerebral infarction is to use neuroimaging. A method of confirming the penumbral region using several protocols has been known while performing MRI for ischemic stroke patients at the early stage. Perfusion-weighted imaging (PWI) can sensitively check the site in which the CBF is reduced, and the site is defined as the cerebral ischemia site, where the blood flow is reduced by vascular occlusion. After diffusion-weighted imaging (DWI) defines the infarction core that has been very severely damaged by vessel occlusion, the rest of the parts, excluding the DWI lesions from the PWI lesions, are collectively defined as the penumbral region (diffusion-perfusion mismatch) (Fig. 1.12) [12]. Here, the DWI high-density part is considered the core of cerebral infarction, but actually, looking at the estimate of

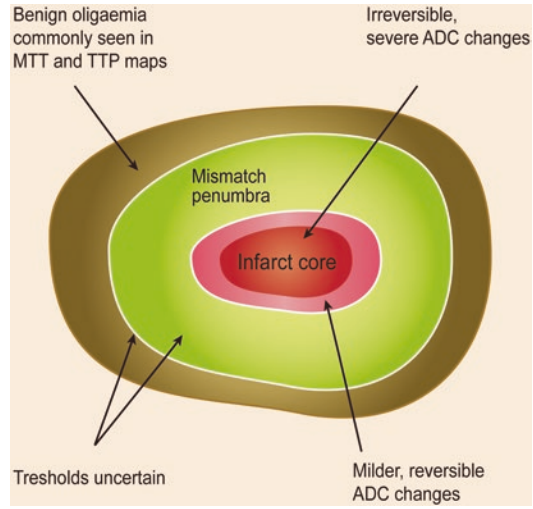

Fig. 1.12 A conceptual figure of diffusion-perfusion mismatch (*MTT* mean transit time, *TTP* time to peak, *ADC* apparent diffusion coefficient)

the apparent diffusion coefficient, a high density is observed before the energy metabolism is completely depleted. Therefore, the DWI high-density part can be said to be seen as larger than the core of the actual cerebral infarction. Also, as PWI is used only when there is a problem with the appropriate oxygen supply, it cannot be thought that PWI shows the ischemic site perfectly. In conclusion, it is reasonable to consider the diffusion-perfusion mismatch site as the sum of the outer portion of the penumbra and the normal tissue part. For this reason, efforts have been exerted to find the penumbra through another method. One of such methods is clinical-diffusion mismatch. In this method, the outline of the ischemic area is estimated by neurological symptoms and signs and compared with the DWI lesion part confirmed at the time. It is a method that is considerably reasonable clinically but has limitations in that standardization is not easy therein, and different opinions can be derived depending on the knowledge or skills of the physician. PET (positron emission tomography) is the golden standard that can confirm the penumbra based on its original definition, but it is impossible to actually utilize it because it is expensive and is impossible to use in emergency situations.

1.4.3.2 Penumbra Region Defined with Biochemical Indicators

To overcome the limitation of the penumbra region confirmed by the imaging indicators described above, the use of biochemical indicators have been suggested. This is an application of the fact that the various molecular biological mechanisms associated with cell death become more active as they move to the core from the penumbra region. If the CBF is reduced, the ATP will decrease, and if the Na+/K+ pump does not work, the extracellular glutamic acid level will increase. These will increase the intracellular calcium level by stimulating the glutamic acid-related receptors (N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). This mechanism is called "excitotoxicity." The intracellular calcium increased through this will increase the generation of free radicals and will ultimately synthesize toxic peroxynitrite radicals by activating neuronal nitric oxide synthase (nNOS). That is, the most important mechanism that cell death due to cerebral ischemia spreads is the diffusion of the extracellular glutamic acid from the cerebral infarction core to the periphery (Fig. 1.13). Glutamic acid is also a key mediator of peri-infarct depolarization and spreading depression. It causes acidosis due to the destruction of the ion homeostasis, increases the energy requirement, and causes the excessive release of neurotransmitters. In animal experiments, brain imaging (e.g., chemical shift imaging) has been attempted to confirm the increase of such glutamic acid. The mechanisms accelerating cell death in the penumbra along with excitotoxicity due to glutamic acid include oxidative stress, nitric oxide overproduction, release of inflammatory cytokines (e.g., tumor necrosis factor-α and interleukin-6), expression of adhesion molecules (e.g., intercellular molecule adhesion-1, vascular cellular adhesion molecule), and production of matrix metalloproteinases.

Contrary to the expectations, active protein production in the penumbra can play the role of an indicator. In general, if cell death starts, protein production and cell metabolism will rapidly decrease, but the stress protein, such as heat shock protein 70 (HSP 70), will be greatly amplified. HSP 70 is a type of intracellular chaperone that handles ordinary intracellular mechanism damage, and when certain cells are extremely stressed, it rapidly increases to suppress cell death. The site where HSP 70 is amplified is sometimes defined as the penumbra (Fig. 1.14). Apoptosis is also a characteristic of the penumbra. If certain cells are rapidly damaged, as mentioned above, they will proceed to the process of necrosis through excitotoxicity, but when moderate damage occurs, as in the penumbra, programmed cell death will be shown, in which the cells will commit suicide according to the planned intracellular mechanism. This is called "apoptosis." Apoptosis is a type of cell death through a planned mechanism; thus, it is characterized by the expression of very distinctive substances. The typical mechanisms include isolation of cytochrome c from the mitochondria and activation of caspase protein. If molecular imaging is

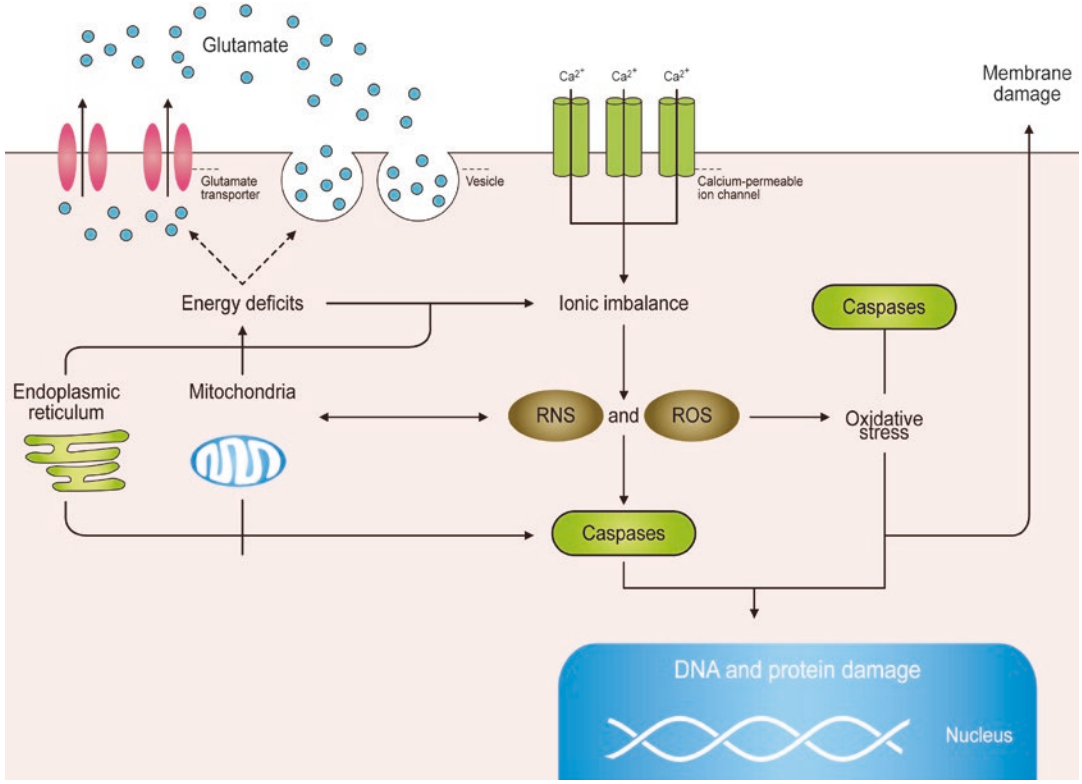

Fig. 1.13 A cell death pathway caused by cerebral ischemia

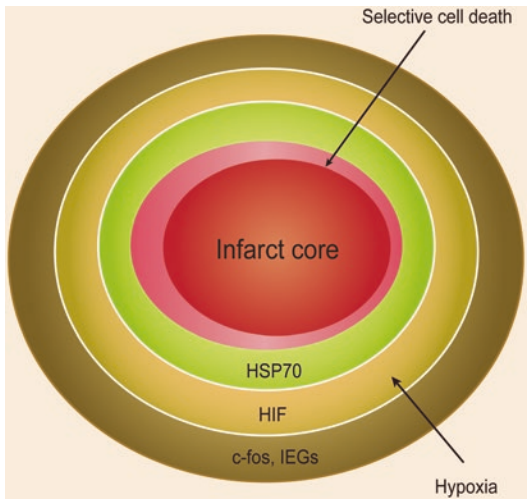

Fig. 1.14 A conceptual figure of penumbra defined by biochemical indicators (HSP70, heat shock protein 70; HIF, hypoxia-inducible factor; IEG, immediate early gene)

possible as a test with high sensitivity and specificity, it can define the molecular biological penumbra. The molecular biological penumbra becomes the target site for examining the effect of neuroprotection drugs on ischemic stroke.

1.4.3.3 Penumbra Region Defined by the Regeneration Mechanism of the Brain

Various molecular biological mechanisms activated by cerebral ischemia often have two sides. These aggravate the secondary brain injury by worsening the inflammation of the brain at the early stage, but after they are stabilized, they repair the brain injury and even play the role of promoting regeneration. In particular, proteins, cytokines, or cells related to inflammation, and typically monocytes, especially macrophages, play such a role. The

macrophage that worsens inflammation at the early stage is called M1 macrophage, and the cell that repairs the damage later is called M2 macrophage as mentioned earlier. The roles of these inflammation cells are not actually significantly different from that in the case of infectious inflammation, but as they are irrelevant to the invasion of microorganisms by foreign substances, the inflammation that they are associated with is called "sterile inflammation." Like this, there is an opinion that the site associated with recovery of brain injury must be newly defined as the penumbra.

Conclusion

In this chapter, the pathophysiology of ischemic stroke was very extensively and deeply discussed. Ischemic stroke developing in the brain is a disease with very diverse subtypes, unlike acute myocardial infarction. In fact, as the onset mechanisms of these subtypes according to the TOAST classification system are too different, it is appropriate to see ischemic stroke as a cerebral infarction syndrome actually caused by a totally different mechanism. The blood vessel occlusion mechanisms are all different in small-vessel occlusion, large-artery atherosclerosis, and cardioembolism. In large-artery atherosclerosis and cardioembolism, the blood vessel is occluded by a thrombus, but its appearance and onset mechanisms are also different. Therefore, the patient's initial treatment and prevention method must be determined taking into account the onset mechanism. The brain usually keeps the CBF constant through autoregulation, but if the local CBF decreases due to ischemic stroke, and the cerebral ischemia condition lasts, cerebral infarction will occur after all. In the areas surrounding the cerebral infarction site, a penumbra region that has not yet reached complete infarction exists, which becomes a treatment target that should be recovered into normal tissues in early acute-phase treatment. It must be kept in mind that the understanding of the pathophysiology of ischemic stroke is the foundation of understanding the various clinical and basic aspects of stroke.

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Pathophysiology of Moyamoya Disease

2

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Moyamoya disease is a chronic progressive steno-occlusive disease of the distal internal carotid artery or proximal anterior cerebral artery and the middle cerebral artery with abnormal moyamoya collateral vessels without associated diseases. The disease has been increasingly reported due to the technological advances of diagnostic radiology and an increase of health check-up. The studies regarding the incidence, prevalence, natural clinical course, disease progression, and surgical treatment outcomes have been increasingly reported. Nevertheless, the precise mechanism of the disease still remains to be investigated further. In addition, heterogeneity of the ethnicity, different age at presentation, different degrees of hemodynamic compromise, surgical techniques such as direct bypass or indirect bypass surgery, and relative small sample size could lead to controversial results. This chapter provides insights into the pathophysiology of the disease including histopathological features, genetics, Ring finger protein 213, microRNAs, molecular biomarkers, vascular progenitor cells, proteomics, metabolomics, and associated autoimmune diseases.

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2.1 Background

Moyamoya disease (MMD) is characterized by the chronic progressive steno-occlusive disease of the distal internal carotid artery (ICA) or proximal anterior cerebral artery (ACA) and the middle cerebral artery (MCA) with abnormal moyamoya vessels [1]. MMD has been highly reported in East Asia, in particular Japan and Korea. In Japan, the estimated prevalence has increased from 3,900 in 1994 to 7,700 cases in 2003 [2]. The crude prevalence rate in Korea also has increased from 6.6 in 2005 to 19.5 in 2013 [3]. MMD shows an approximately 2:1 female predominance and bimodal age pattern [4]. The disease progression of MMD has been reported ranging from 14.6% to 50% [5–7]. Although the patients were asymptomatic, the estimated annual stroke risk rate was 3.2% [8]. As such, MMD has a dynamic nature which requires surgical treatment.

In this chapter, we provide insights into the pathophysiology of the disease including histopathological features, genetics, Ring finger protein 213, MicroRNAs, molecular biomarkers, vascular progenitor cells, proteomics, metabolomics, and associated autoimmune diseases.

2.2 Histopathological Features

The main pathological changes are eccentric fibromuscular thickening of the intima due to abnormal proliferation of smooth muscle cell

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(SMC), thinned media, prominently tortuous internal elastic laminae, and a decreased outer diameter [9–11]. The moyamoya vessels have various histopathological changes such as thinned media, fibrin deposit in the arterial wall, fragmented elastic laminae, attenuated media, and microaneurysm [10–12]. Kaku et al. [13] showed narrowed arterial outer diameter of the ICA and MCA in MMD patients by three-dimensional interference in steady-state MR imaging. They suggested that constrictive remodeling of the affected arteries is a main phenomenon in MMD distinguishing from atherosclerotic stenosis.

2.3 Genetics

Genetic approach to understanding the MMD has been performed using candidate gene association studies including human leukocyte antigen (HLA) genotyping, genome-wide linkage analysis, and genome-wide association study (GWAS). Aoyagi et al. [14] found that HLA-B51-DR4 combination was increasingly noted in Japanese MMD patients. HLA-B35 allele was also significantly noted in Korean MMD patients, in particular female of late-onset MMD [15]. Hong et al. [16] suggested that HLA-DRB1(*)1302 and DQB1(*)0609 haplotype could be related to intimal fibrosis and arterial occlusion. Inoue et al. [17] reported that early-onset MMD showed increased DRB1(*)1501 and DQB1(*)0602. There are conflicting results concerning the association between tissue inhibitor of metalloproteinase (TIMP) genes and MMD. A G/C heterozygous genotype at position −418 of TIMP-2 promoter region was significantly observed in familial MMD [18]. They suggested that G/C heterozygous genotype at position −418 of TIMP-2 promoter region might be a genetic predisposing factor familial MMD through influencing Sp1 binding and subsequent TIMP-2 transcription. On the contrary, Paez et al. [19] did not find significant difference of heterozygous genotype at position −418 in MMD patients. In particular, only one familial MMD (1/7, 14.3%) showed G/C heterozygous genotype. Andreone et al. [20] also did not find the G/C heterozygous genotype in the promoter region of the TIMP-2 genes in monozygotic twins. For genome-wide linkage analysis, several loci such as 3p24–26 [21], 6q25 [22], 8q23, 12p12 [23], and 17q25 [24] were reported to be linked to MMD; however, 17q25 locus was only demonstrated in other series [10, 11].

2.4 Ring Finger Protein 213

A genome-wide linkage and association analyses revealed the Ring finger protein 213 (RNF213) as a susceptible gene for MMD [25, 26]. c.14576G>A (p.R4859K) RNF213 variants was frequently observed in familial MMD (95%) compared to nonfamilial MMD (73%) or control groups (1.4%). Liu et al. [26] also revealed an association between p.R4810K RNF213 variant and Asian MMD patients. Homozygous c.14576G>A RNF213 variant was noted in 95.1% of familial MMD, 79.2% of nonfamilial MMD, and 1.8% of control [27]. Homozygotes were associated with MMD of early onset and poor prognosis than heterozygotes and wild type [25, 27]. Wu et al. [28] reported p.R4810K RNF213 variant rate: familial MMD (n = 4, 80%), nonfamilial MMD (n = 18, 10.9%), and control group (n = 2, 0.39%) in Chinese population. When it comes to clinical presentations, ischemic presenting MMD was associated with p.R4810K variant and hemorrhage presenting MMD was non-p.R4810K variant, more specifically A4399T in Chinese MMD patients [11, 28]. Regarding Korean MMD patients, early-onset MMD (<5 years) and cerebral infarction were related to the homozygous c.14429G>A (p.R4810K) variant [29]. Nevertheless, p.R4810K variant could be more susceptible to East Asian MMD patients. Cecchi et al. [30] found that p.R4810K variant was observed in 56% in 16 MMD patients of Asian descent and 0% in 94 MMD of non-Asian descent in the United States.

Wang et al. [31] evaluated interaction effect on MMD development among PDGFRB (platelet-derived growth factor receptor beta) (rs3828610), MMP-3 (matrix metalloproteinase) (rs3025058), TIMP-2 (tissue inhibitors of metalloproteinase) (rs8179090), and RNF213 (rs112735431 and rs148731719) in Chinese population. They reported that RNF213 may have a

remarkable effect on MMD development; however, three remaining loci were not related to MMD significantly. Accordingly, such five gene polymorphisms could not have distinctive interaction effect on MMD in Chinese population. Nevertheless, the exact mechanism of RNF213 polymorphism remains unknown in MMD occurrence. RNF213 knockdown zebrafish showed irregular arterial wall and abnormal sprouting vessel, although mutant alleles did not affect transcription or ubiquitin ligase activity [26]. However, mice lacking the RNF213 gene [32] or mice with the R4859K mutation of RNF213 gene [33] did not show typical vasculature of MMD. Accordingly, further studies on the role of RNF213 in MMD pathogenesis and its association with MMD phenotypes are required.

2.5 MicroRNAs

MicroRNAs (miRNAs), small noncoding RNAs which regulate gene expression at the posttranscription level by binding to the 3′-untranslated regions of specific miRNAs [34], have been reported to be related to ischemic stroke [35]. Liu et al. [35] reported that miRNA-424 had a protective effect to the cerebral ischemia-reperfusion injury by inhibiting oxidative stress. A genome-wide miRNA analysis [34] showed that miRNA-106b, miRNA-130a, miRNA-126, and miRNA125a-3p were associated with MMD development by inhibiting RNF213 and BRCC3 protein expression which led to defective angiogenesis. Park et al. [36] reported that GT+CC genotype of the SNP rs11614913 in miR-196a2C>T was increasingly observed in MMD patients. Consequently, the role of serum miRNAs in MMD pathogenesis requires further study focusing on therapeutic target.

2.6 Molecular Biomarkers

Arteriogenesis and vasculogenesis are main topics for MMD research. Various enzymes, growth factors, adhesion molecules, and inflammation in the arterial remodeling pathway have been investigated (Table 2.1) [49]. MMD patients showed higher level of matrix metalloproteinases (MMP)-9,

Table 2.1 Relevant studies for Moyamoya disease (MMD) biomarker

Reference	Country	No*	Samples	Main findings
Takahashi et al. [37]	JPN	15	CSF	bFGF ↑
Houkin et al. [38]	JPN	48	CSF	bFGF ↑ in bilateral MMD
Yoshimoto et al. [39]	JPN	38	CSF	bFGF ↑
Malek et al. [40]	USA	37	CSF	bFGF ↑
Hojo et al. [41]	JPN	20	Serum and STA culture	TGF ß-1↑
Soriano et al. [42]	USA	20	CSF and serum	VCAM-1, ICAM-1, E-selectin ↑ in CSF, not serum level
Kim et al. [43]	KOR	20	CSF	CRABP-1↑
Amano et al. [44]	JPN	29	Serum	α1-antitrypsin ↑
Nanba et al. [45]	JPN	39	CSF	HGF↑
Kang et al. [46]	KOR	20	Plasma	VEGF, PDGF BB, MMP-9, MCP-1, IL-1ß↑/ MMP-3, TIMP-1,2↓
Bernard et al. [47]	USA	7	Serum	D-dimer ↑in MMD and cardioembolic ischemic stroke
Jeon et al. [48]	KOR	77	CSF	CRABP-1↑in bilateral MMD in relation to decrease in basal collateral vessels

No*: number of enrolled MMD patients

bFGF basic fibroblast growth factor, *CRABP-I* cellular retinoid acid-binding protein-I, *CSF* cerebrospinal fluid, *E-selectin* endothelial selectin, *HGF* hepatocyte growth factor, *ICAM-1* intercellular adhesion molecule 1, *IL-1ß* interleukins-1ß, *MCP-1* monocyte chemoattractant protein-1, *MMP* matrix metalloproteinases, *PDGF-BB* platelet-derived growth factor BB, *STA* superficial temporal artery, *TGF ß-1* transforming growth factors ß-1, *TIMP* tissue inhibitor of metalloproteinase, *VCAM-1* vascular cell adhesion molecule 1, *VEGF* vascular endothelial growth factor

monocyte chemoattractant protein-1 (MCP-1), interleukins (IL)-1ß, vascular endothelial growth factor (VEGF) and platelet-derived growth factor BB (PDGF-BB), and lower level of TIMP-1 and TIMP-2 compared to controls [46]. Johnson et al. [50] reported that MMP-9 genetic deficiency resulted in decreased formation of intimal hyperplasia and SMC attachment to gelatin. Accordingly, disruption of balance between MMP and TIMP which is an inhibitor for MMP could lead to intimal hyperplasia through excessive SMC migration and proliferation [46]. MCP1 is related to initiation of arteriogenesis [51]. And VEGF to endothelial progenitor cells (EPCs) mobilize under ischemic condition [52]. Consequently, both MCP1 and VEGF could be related to the recruitment of vascular progenitor cells and subsequent MMD vessel formation [46]. Hepatocyte growth factor (HGF) [45] and transforming growth factors ß-1 [41] were also increased in MMD patients. Nevertheless, it remains unclear if inflammatory proteins are specific to MMD itself, not reflecting cerebral ischemic condition (Fig. 2.1).

Retinoid signaling pathway was reported to be related to MMD pathogenesis. Higher level of cellular retinoid acid-binding protein-I (CRABP-I) was noted in both pediatric [43] and adult MMD patients [48]. They hypothesized that CRABP-I inhibited the retinoid activity which resulted in neointimal thickening by enhancing

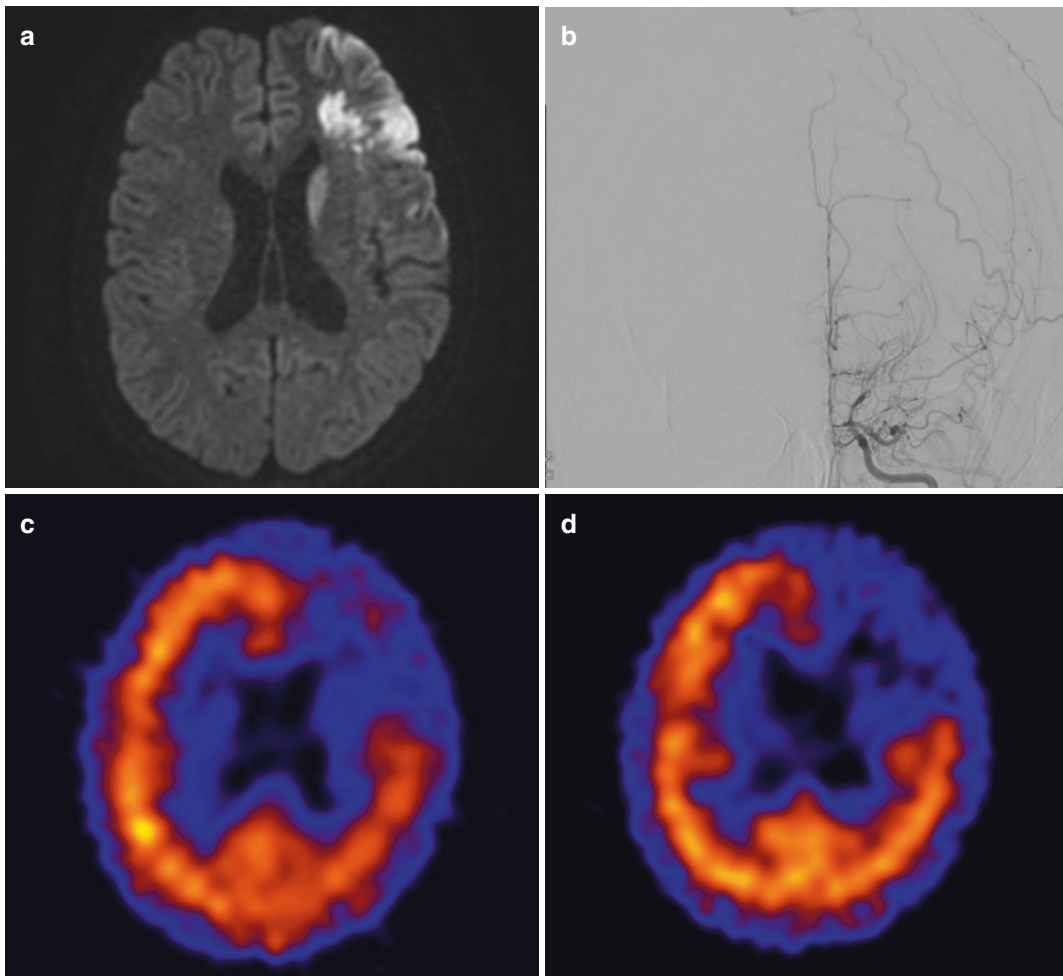

Fig. 2.1 A 30-year-old female presented with sudden onset right side weakness and dysarthria. Diffusion MR revealed acute infarction at Lt. Frontal anterior border zone (**a**). Angiography disclosed nearly total occlusion of the distal ICA occlusion on the left side (**b**). Single-photon emission computed tomography (SPECT) showed perfusion defect in the left frontal area with decreased basal perfusion in the resting state and decreased vascular reserve capacity in the acetazolamide challenge test (**c** and **d**).

growth factors. In particular, for adults, increased CRABP-I was related to typical bilateral MMD [48]. In addition, higher CRABP-I was related to a decrease in basal collateral vessel after bypass surgery. Accordingly, studies of retinoids as a therapeutic target for MMD are needed further.

2.7 Vascular Progenitor Cells

Circulating EPCs have been suggested as a pathogenic marker for MMD. Sugiyama et al. [53] directly stain the specimens of the distal ICA using antibodies of CD34, CD133, and vascular endothelial growth factor receptor-2 (VEGFR2) to localize the circulating EPCs in two adult MMD patients. Histopathological analyses showed that CD34− and VEGFR2+ cells were widely found in the thickened intima of the specimen. Nevertheless, the role of EPCS in MMD pathogenesis remains controversial. Jung et al. [54] reported that MMD patients revealed markedly decreased colony-forming unit (CFU) numbers on 7-day culture and elevated outgrowth cells during 2-month culture than control group. Similarly, decreased level of CD34+, CD133+, and KDR+ cells were noted in pediatric MMD, which were related to less tube formation and increased senescent-like phenotype [55]. Deregulation of retinaldehyde dehydrogenase 2 (RALDH2) of endothelial colony-forming cell was related to defective angiogenesis in pediatric MMD patients [56]. On the contrary, higher level of circulating EPCS was demonstrated in MMD patients [52]. Yoshihara et al. [57] found increased CD34+ cells which could attribute to neovascularization at sites of ischemic injury in MMD patients [57]. Ni et al. [58] also suggested that increased level of circulating CD34+, CXCR4+, and SDF-1α were related to MMD vasculogenesis. Heterogeneity of the ethnics, patients' age, and experimental methods could lead to controversial results among the studies; therefore, further researches are required to yield the EPCs' role in MMD pathogenesis [10].

MMD is characterized by the proliferation of SMC in the affected arteries. Accordingly, isolation of specific smooth muscle progenitor cells (SPCs) and its differentially expressed genes (DEG) analyses can be a dynamic model for MMD research [49]. Kang et al. [59] purified SPCs from peripheral blood in MMD patients (n = 25) and investigated DEGs. The SPC outgrowth cells in MMD patients revealed higher expression of alpha-smooth muscle actin, myosin heavy chain and calponin, and lower expression of CD 31 with more irregular and thickened tubules of SPCs than healthy control group. DEG analyses also showed increased expressed gene related to cell adhesion, cell migration, immune response, and vascular development in MMD SPCs. Further studies to identify relationship to specific change of SPCs in MMD pathogenesis are needed [60].

2.8 Recent Proteomic and Metabolomic Analyses

Two studies for identifying CSF biomarkers have been published using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) and metabolomics [61, 62]. Maruwaka et al. [61] reported increased three peptides of 4,473 Da, 4,475 Da, and 6,253 Da in 20 MMD patients (11 pediatric and 9 adult cases) by SELDI-TOF-MS. In particular, 4,473 Da peptide showed high correlation to postoperative angiogenesis and higher peak in younger MMD patients. Although precise role of 4,473 Da peptide remains unclear, they thought that 4,473 Da peptide could be related to anti-hypoxic effect or inflammation degree in MMD pathogenesis [61]. Jeon et al. [62] compared the CSF metabolites of adult bilateral MMD than those of unilateral MMD and atherosclerosis using a hydrogen-1 nuclear magnetic resonance spectroscopy. Bilateral MMD revealed higher level of glutamine than atherosclerotic stenosis. Considering the association between increased glutamine and intima-media thickness of the carotid and coronary artery disease [63], they postulated that increased glutamine in MMD could be related to more an abnormal SMC proliferation and intima thickness than atherosclerotic stenotic disease, although precise mechanisms is not well understood [62].

2.9 MMD in Association with Thyroid Disease

Several studies have illustrated MMD and concurrent autoimmune diseases, in particular thyroid diseases [64–66]. T-cell dysregulation [64] or increased sensitivity to the sympathetic nervous system of the vessel [65] has been suggested as pathomechanisms of the abnormal SMC proliferation and collateral vessel formation in MMD. Kim et al. [66] found that thyroid autoantibodies were significantly increased in MMD patients. They postulated that immune aberrancies related to thyroid autoimmunity may have a role in MMD pathogenesis. Recently, Chen et al. [67] reported that overall autoimmune diseases were significantly highly observed in unilateral MMD than bilateral MMD. Nevertheless, the actual pathogenic mechanisms of the autoimmune diseases in the development of MMD are still poorly understood. Accordingly, studies about autoimmune mechanism in MMD development, in particular the role of elevated thyroid autoantibodies in MMD development and progression, and its therapeutic target, are needed further [66, 68].

Conclusion

Although a better understanding of MMD has been achieved, the pathophysiology of MMD still remains fully understood. Heterogeneity of the ethnicity, patient age at presentation, and small sample size could lead to controversial results. Accordingly, high-throughput technologies in the effective biomarker for MMD, in particular disease severity or treatment outcomes in more homogeneous condition, are necessary.

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Radiological Assessment of Ischemic Stroke

3

Chul-Ho Sohn

3.1 Introduction

Acute ischemic stroke (AIS) can be treatable if therapy is given early. In general, intravenous thrombolytic therapy should be initiated within 4.5 h of symptom onset, and expeditious revascularization is associated with better clinical outcome [1]. In the assessment of acute ischemic stroke, neuroimaging plays a critical role in determining patient care. Recent clinical trials [2–5] regarding patient selection mostly include radiological imaging criteria. The main goals of imaging in patients with symptoms of AIS are (1) to rule out hemorrhagic stroke, (2) to define the extent of the ischemic damage and to differentiate between the infarct core and the salvageable ischemic penumbra, and (3) to visualize the vessel status (arterial occlusion and collateral circulation). At present there is no consensus on a preferred imaging modality in patients presenting with AIS. The AHA guidelines recommend brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) in all suspected stroke [6]. Current radiological diagnostic strategies for this patient group are discussed in this chapter. Although positron emission tomography (PET) has been considered the gold standard for defining the ischemic core, penumbra, and benign oligemia, it is not a practical imaging modality in the routine, clinical, acute stroke setting. As such, attention has focused on the role of multimodal magnetic resonance imaging (MRI) and multimodal computed tomography (CT) for defining the infarct core and the penumbra.

3.2 Computed Tomography

3.2.1 Noncontrast Computed Tomography

One of the most important roles of noncontrast CT (NCCT) in acute stroke imaging is to exclude the presence of intracranial hemorrhage because there is an increased risk of additional bleeding if a patient with intracranial hemorrhage receives IV-tPA or endovascular therapy.

3.2.1.1 Assessing for Ischemic Infarction

CT findings obtained within the first 3–6 h of cerebral ischemia, when present, are often subtle. Nonetheless, CT remains the initial imaging study for evaluation of acute stroke because it is widely accessible, convenient, has a short imaging time, and is sensitive for detection of hemorrhage. The important CT findings during the early cerebral ischemia can be classified as hypoattenuating appearance of gray matter

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structures and presence of one or more hyperattenuating arteries. Any combination of these findings may be present, or all may be absent.

Early CT ischemic signs include:

1. Hypoattenuation of gray matter: (a) insular ribbon sign – the insular cortex is particularly vulnerable to a proximal middle cerebral artery (MCA) occlusion because it is the region most distal from the potential anterior and posterior collateral circulation, and therefore it is a watershed arterial zone. When ischemic, the insular region shows loss of definition of the gray-white interface, or loss of the "insular ribbon" (Fig. 3.1) [7]. (b) Obscuration of the lentiform nucleus: Due to

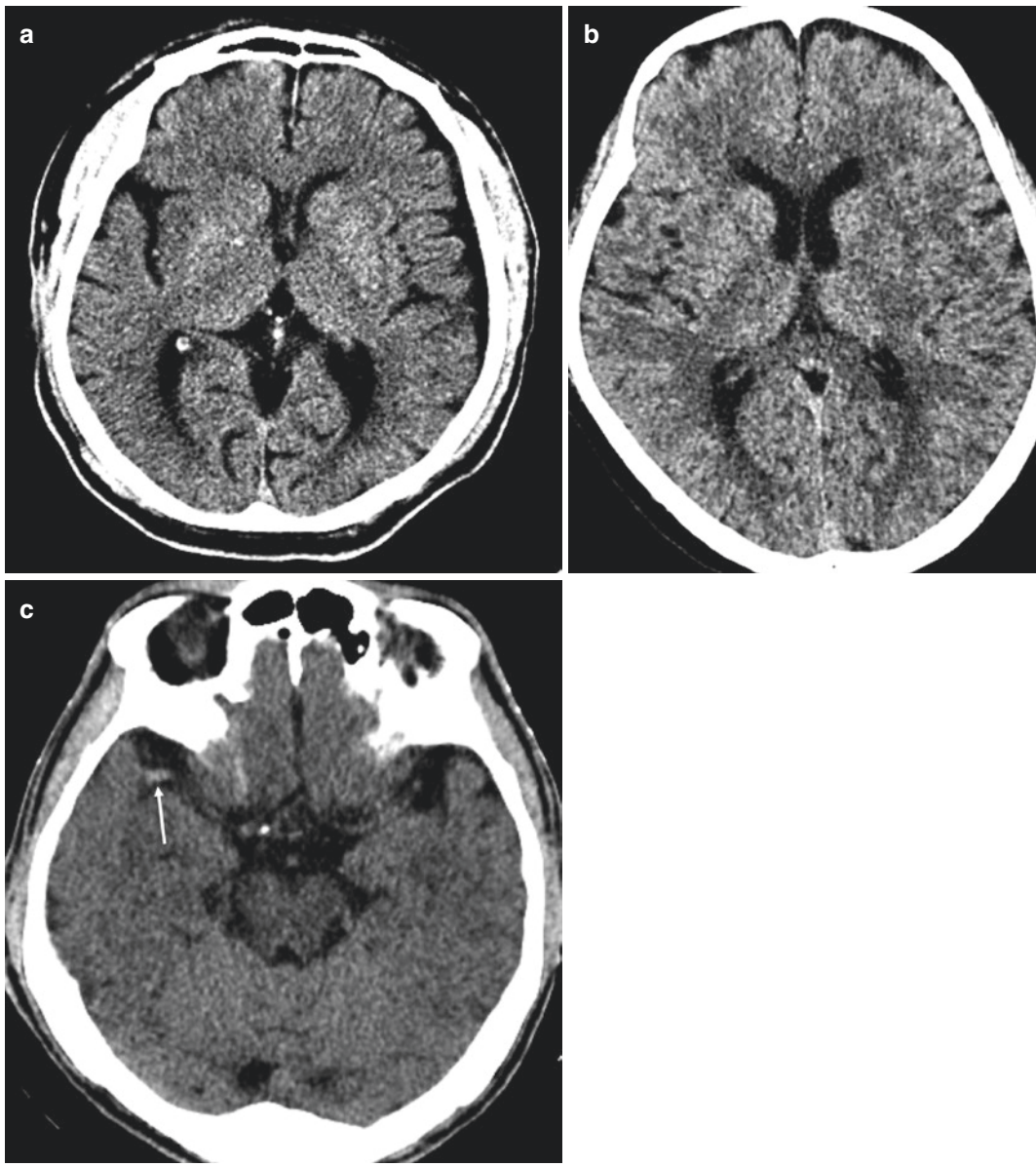


Fig. 3.1 Early ischemic CT signs. Noncontrast CT images show early ischemic changes, loss of insular ribbon at the right side (**a**), loss of lentiform nucleus at the left side (**b**), and hyperdense artery sign (*arrow*) at the right MCA M1 distal segment (**c**)

its blood supply via end arteries, the basal ganglia are also particularly vulnerable to early infarction [8]. When ischemic, an obscured outline or partial disappearance of the lentiform nucleus can be seen on NCCT (Fig. 3.1). (c) Loss of gray-white matter differentiation in cerebral hemisphere

2. Hyperdense artery sign: The presence of an acute thrombus in the MCA creates a linear hyperattenuation on NCCT, the so-called hyperdense artery sign (Fig. 3.1). Contrary to the other early CT signs, this one represents not an infarction but a thrombotic event [9]. Although it is highly specific for ischemia, its sensitivity is poor [10], and false positives such as high hematocrit level or atherosclerotic calcification should be excluded. In those cases, however, the hyperattenuation is usually bilateral [11].

Early signs of ischemia are often subtle on NCCT, also having a high intra- and interobserver variability. Additionally, it can be challenging to identify early ischemic changes within chronic white matter hypodensities. The NCCT signs of ischemia during the first 3 h of symptom onset have a sensitivity of 26–60% and a specificity of 85%; the positive and negative predictive values are 96% and 27%, respectively [12, 13]. In the setting of lacunar infarcts and hypodense changes in the posterior circulation, NECT has a lower sensitivity [14].

Alberta Stroke Program Early CT Score (ASPECTS) The extent of early ischemic change may be differently determined among reviewers because early ischemic change is often difficult to determine. The ASPECTS is a simple and systematic approach to quantifying the extent of irreversibly damaged parenchymal hypoattenuation on pretreatment CT scans in patients with acute ischemic stroke of the MCA (Fig. 3.2) [15]. Although the presence of early ischemic changes on CT, regardless of their extent, is not a contraindication to IV-tPA treatment, it has been shown that detecting early ischemic changes within the

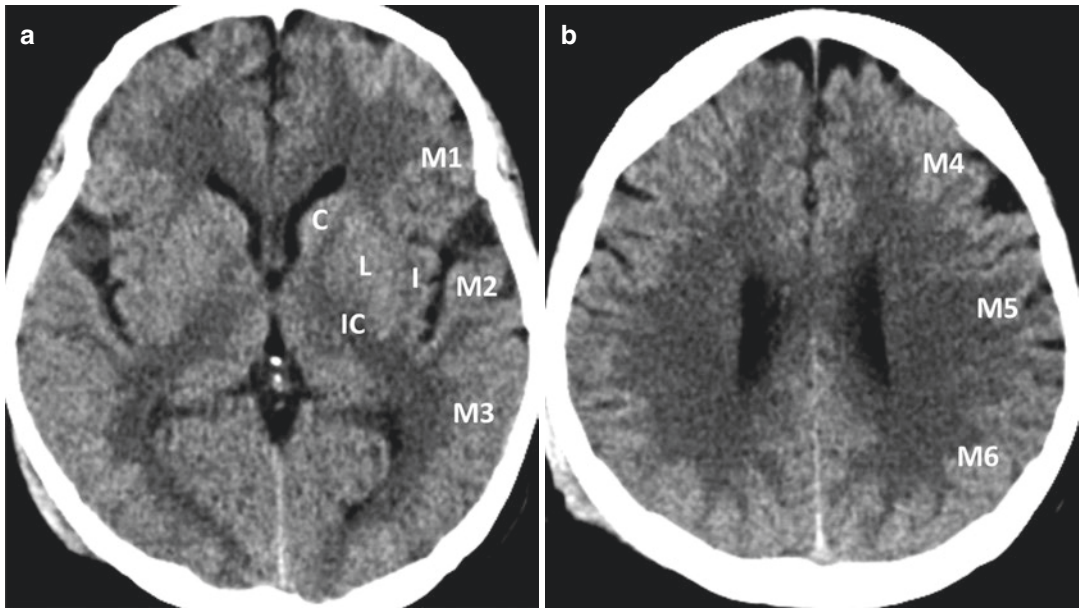


Fig. 3.2 Alberta Stroke Program Early CT score (ASPECTS). The levels of thalamus and basal ganglia and most superior margin of the ganglionic structures ASPECTS slices show normal 10-point areas. Left hemisphere, ASPECTS study form: *C* caudate head, *L* lentiform nucleus, *IC* internal capsule, *I* insular ribbon, *MCA* middle cerebral artery, *M1* anterior MCA cortex, *M2* MCA cortex lateral to insular ribbon, *M3* posterior MCA cortex; *M4*, *M5*, and *M6* are anterior, lateral, and posterior MCA territories, respectively, approximately 2 cm superior to M1, M2, and M3, respectively, rostral to basal ganglia

early period of AIS is important for determining a patient's prognosis and complications [16–18]. ASPECTszz 0–5 indicates exclusion of patients from endovascular treatment because of its futility [18]. However, some patients with ASPECT <5 can benefit from endovascular treatment [16]. Thus, it is still unknown whether such patients should be excluded or not. However, the current AHA/ASA guidelines for acute stroke management list a frank hypointensity (infarct) of greater than one-third of the MCA territory on NCCT as an imaging exclusion criterion for IV t-PA [6]. Additional advantage of ASPECTS is that it combines a semiquantitative estimate of volume along with localization. It weighs smaller volumes in the basal ganglia and internal capsule equally with larger volumes of brain designated M1 through M6. This approach is useful because lesion volume alone on NCCT is only weakly correlated with neurological outcome [19]. The ASPECT score is used more and more and has even been applied to DWI. The ASPECTS, however, has some issues that remain to be resolved: One is no anatomic landmarks for distinction of each M region and another is that the interobserver reliability of each region on CT is relatively low (mean intraclass correlation coefficients were 0.640 in M1–M3; 0.530 in M4–M6; 0.762 in the insula, lentiform nucleus, and caudate; and 0.367 in the internal capsule) [20].

3.2.2 Computed Tomography Angiography

Stroke mimickers such as seizures, metabolic abnormalities, and neuropsychiatric conditions may be difficult to distinguish from acute cerebral ischemia on purely clinical grounds. Thus, an objective method for confirming intracranial vessel occlusions prior to treatment is highly required. This method should be rapid, easily interpretable, be relatively independent of operator skills, and have the potential for widespread availability. CT angiography (CTA) may play an important role in answering these questions. CTA offers the possibility to visualize the location, extent, and aspect of an arterial occlusion, may reveal important information about the collateral circulation, and depicts the extracranial vessels from the aortic arch [21–23]. The addition of CTA over NCCT significantly increased diagnostic sensitivity and likelihood of treatment with tPA in patients with acute stroke [24].

3.2.2.1 Assessment of Vascular Occlusion

In CT angiography (CTA) iodinated contrast is administered intravenously. The scanning typically starts from the aortic arch up to a level above the circle of Willis when the contrast medium is in the arterial phase. The new generation of CT scanners can reconstruct a CT digital subtraction angiography where bone and soft tissue are subtracted, visualizing only the vasculature (Fig. 3.3). Stenoses and occlusions can be detected with high diagnostic accuracy in both extracranial and intracranial arteries thus revealing the origin of the AIS (the mean sensitivity, specificity, PPV, NPV, and accuracy were 83.2% (95%, CI 57.9–100%), 95.0% (95%, CI 74.4–100%), 84.1% (95%, CI 50.0–100%), 97.1% (95%, CI 94.0–100%), and 94.0% (95%, CI 83.0–99.0%), respectively [25]. CTA is a rapid, easily available imaging tool for detecting intracranial occlusions in patients with acute ischemic stroke, thereby guiding therapy (Fig. 3.4) [26].

3.2.2.2 Assessment of Collateral Vascular Status

An acute intracranial occlusion produces an area of ischemic penumbra, the extent being dependent on residual and the collateral blood flow [27–29]. In contrast to digital subtraction angiography, CTA lacks information about the flow of contrast from the arteries via capillaries to the veins. Despite this, CTA can provide a relevant overview of collateral flow, including leptomeningeal collaterals around the ischemic area. This information may be valuable in predicting the probability of salvaging brain tissue. Now we have used leptomeningeal collateral grading system using CTA in anterior circulation stroke (Table 3.1). The poor grade CT collateral which was measured by variable collateral grading system was an independent predictor of extremely poor outcomes [30].

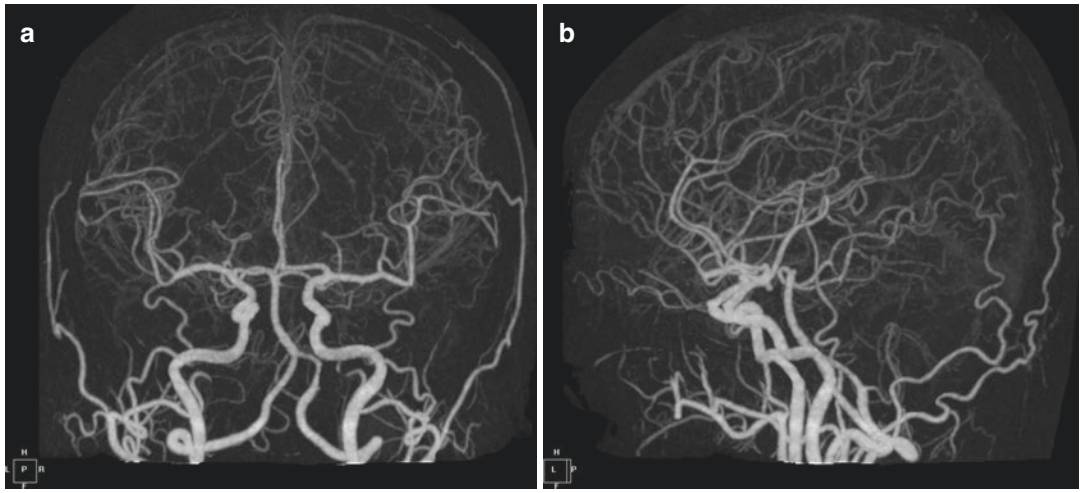


Fig. 3.3 CT angiography – bone subtraction angiography. AP view (**a**) and lateral view (**b**) CTA MIP (maximum intensity projection) images well visualized intracranial arteries

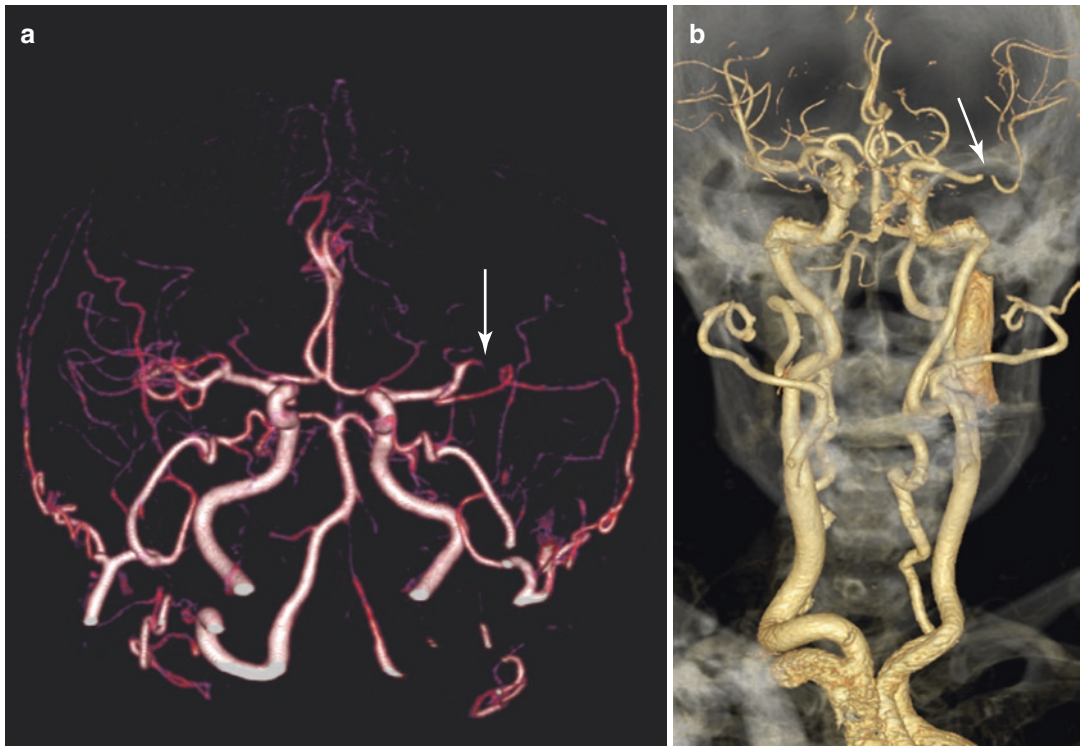


Fig. 3.4 Intracranial CT angiography (**a**) demonstrates occlusion (*arrow*) of left superior division of MCA M1. Intracranial and extracranial CT angiography (**b**) shows occlusion (*arrow*) of left MCA M1 distal segment with visualization of distal MCA branches beyond occlusion site

Single-phase CT angiography does not have temporal resolution; therefore, collateral status may be mislabeled in many patients [31]. A multiphase or dynamic CTA has been shown to be better in predicting clinical outcome in acute ischemic stroke patients compared to single-phase CTA by more accurately depicting the state of collateral vessels [32]. Dynamic CT angiogra-

Table 3.1 Leptomeningeal collateral grading system using CT angiography

rLMC[a]	0–20 point	0 = no visible collateral flow	0–10 poor	SCTA
			11–16 medium	
		20 = collateral flow equal to or stronger than in unaffected hemisphere in all regions	17–20 good	
Miteff[b]	3-point	1 = when contrast opacification is merely seen in distal superficial branches	Poor	SCTA
		2 = vessels can be seen at Sylvian fissure	Medium	
		3 = if vessels are reconstituted distal to occlusion	Good	
PAFS[c]	6-point	0 = when compared with the asymptomatic contralateral hemisphere, there are no vessels visible in any phase within the ischemic vascular territory	Poor	MCTA
		1 = there are just a few vessels visible in any phase within the occluded vascular territory	Poor	
		2 = there is a delay of two phases in filling in of peripheral vessels and decreased prominence and extent or a one-phase delay and some ischemic regions with no vessels	Poor	
		3 = there is a delay of two phases in filling in of peripheral vessels or there is a one-phase delay and significantly reduced number of vessels in the ischemic territory	Poor	
		4 = there is a delay of one phase in filling in of peripheral vessels, but prominence and extent is the same	Intermediate	
		5 = there is no delay and normal or increased prominence of pial vessels/normal extent within the ischemic territory in the symptomatic hemisphere	Good	

[a]*rLMC* regional leptomeningeal collateral [31]
[b]Reference [35],
[c]*PAFS* pial arterial filling score [32], *SCTA* single phase CTA, *MCTA* multiphase CTA

phy is a technique that derives time-resolved images of pial arterial filling from perfusion CT images; however, it needs postprocessing and whole-brain perfusion CT (Fig. 3.5) [33, 34].

3.2.2.3 Detection of Ischemic Change

Hypoattenuation on CTA source image (CTA-SI) is an indicator of reduced cerebral blood volume in the area of ischemia. Numerous studies have also shown that CTA-SI improves the prediction of final infarct size and clinical outcome when compared to NCCT [36–39].

However, this is the case only when CT angiography (CTA) is obtained with relatively slower scanners. Recent scanners with multi-detector rows can obtain arterial phase images much faster than old generation scanners, resulting in larger poor contrast-filling areas in cases of major artery occlusion, which may overestimate infarct core [40–42]. CTA-SI, thus, is not a reliable tool to identify infarct core when it is obtained with faster scanners.

3.2.3 Computed Tomography Perfusion

The practical advantages of CTP are that it is widely available and does not delay treatment decisions because it is fast and most patients already undergo CT scanning [43].

3.2.3.1 Assessment of Ischemic Penumbra

The goal of CT perfusion imaging (CTP) is to assess the ratio of infarct core (irreversibly damaged brain tissue) to penumbra, thus identifying the "tissue at risk." In hypoperfused areas of brain parenchyma, there are typically high MTT values due to supply via collateral circulation. Autoregulation attempts to preserve CBF values by inducing vasodilatation, which results in an increased CBV. When ischemic injury is more severe and prolonged, autoregulation is unable to maintain the CBV above the threshold for neuronal death, and the tissue experiences irreversible

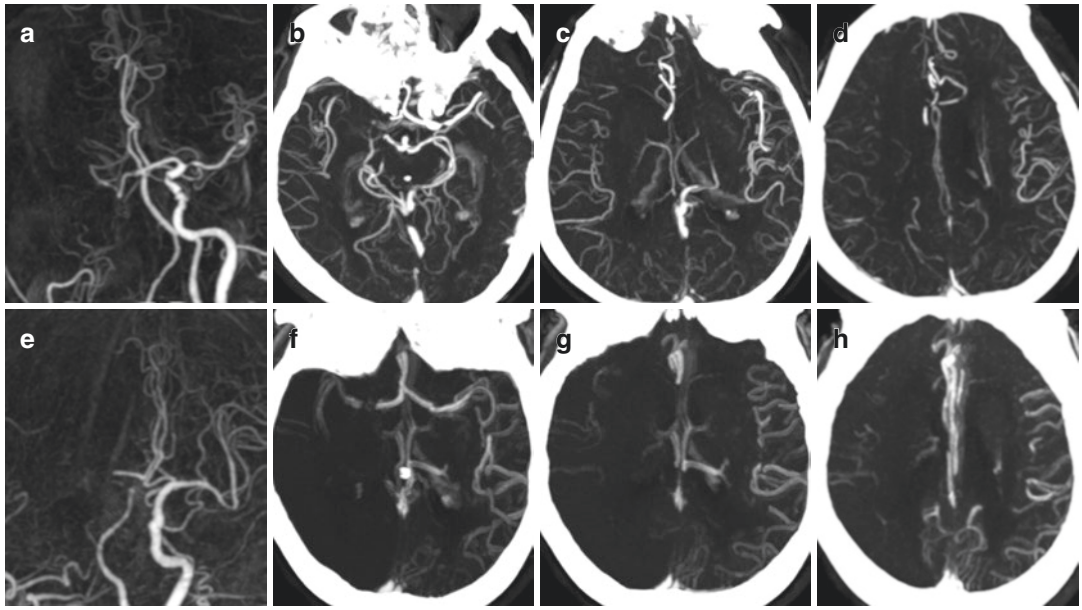


Fig. 3.5 Leptomeningeal collateral grading using dynamic CTA. (**a**–**d**) Good collateral grade. (**a**) A proximal right ICA occlusion on maximum intensity projection (MIP) CTA. Temporal maximum intensity projection (tMIP) images (**b**–**d**) using perfusion CT show well backfilling arteries at the right MCA arteries. (**e**–**h**) Poor collateral grade. (**e**) A proximal right ICA occlusion on MIP CTA. tMIP images (**f**–**h**) using perfusion CT show minimal backfilling of right MCA arteries

hypoxic damage with a subsequent decrease in CBV; this area represents the infarct core, where tissue no longer viable will not benefit from reperfusion and is at risk for hemorrhage (Fig. 3.6). CTP has *caused* confusion with regard to the definition of infarct core. At first, an absolute cerebral blood volume (CBV) value of 2.0 mL/100 g was adopted to determine the infarct core [44–46]. Subsequently, it was suggested that a relative cerebral blood flow (rCBF) <31% threshold best determines infarct core [47]. However, other studies indicate that the most reliable predictor of infarct core is the reduction of the CBF to 30–50% relative to the mean CBF in the contralateral hemisphere [44, 45, 48].

Operational Infarct Core Threshold in CTP

1. Absolute CBF of <12 mL/100 mg/min with CBF ratio of <32% and absolute CBV of <2 mL/100 g with CBV ratio of <68%

The penumbra is the critically hypoperfused tissue, which is still viable if reperfusion is achieved. It is of great interest to differentiate the penumbra from benign oligemia. Outside the penumbra, there is an area of benign oligemia which is hypoperfused to a lesser degree; it remains viable even if reperfusion fails. In that sense, "ischemic penumbra" and "tissue at risk" are interchangeable terms. The penumbral region the levels were 12–25 mL/100 g/min in PET study (oligemic or not at-risk tissue, was also identified by PET and is defined as a region with reduced CBF, increased OEF, and normal CMRO2) [49]. There are several approaches for estimating the penumbra on CTP. The most common one is to presume that areas with solely reduced CBF and/or TTP/Tmax are considered to show the penumbra [44, 45, 50]. Other penumbra threshold has been reported to exist on MTT or Tmax maps [46, 47, 51, 52].

Operational Penumbra Threshold in CTP

1. *CBF <20 mL/100 g/min with Tmax of 5.5 s*
2. *CBV >2 mL/100 g with MTT >145% to contralateral side*

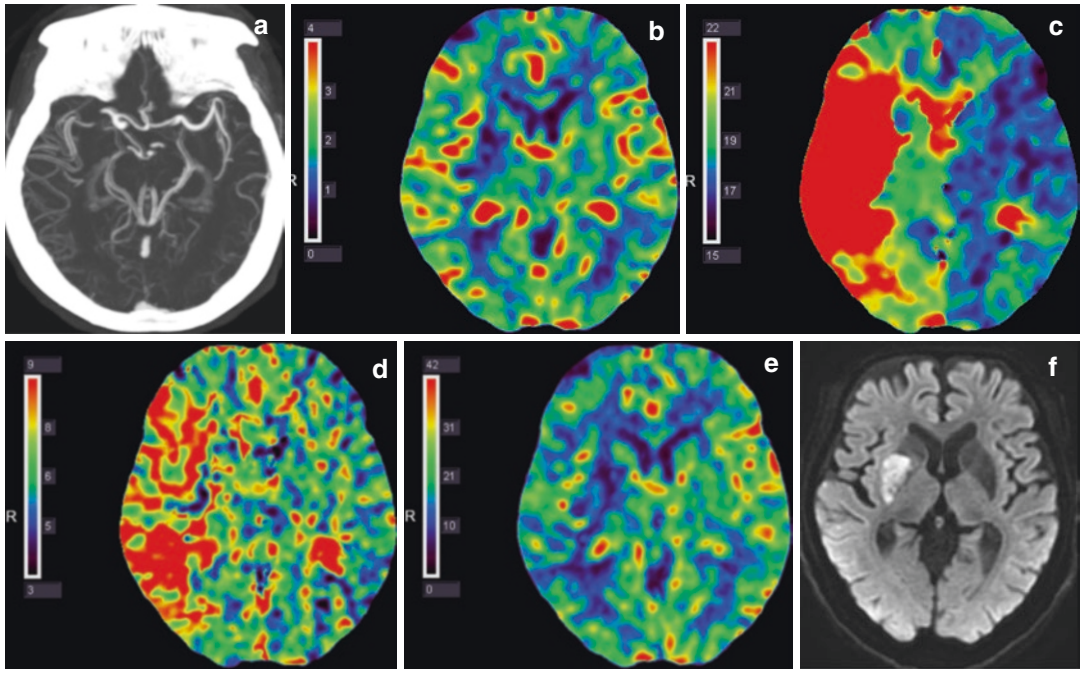


Fig. 3.6 (**a**) MIP CTA shows occlusion of the right MCA M1 segment. (**b**) Decreased CBV at the right lentiform nucleus, (**c**) large area of delayed TTP lesion is visualized at the right MCA territory, (**d**) delayed MTT lesion area is similar to TTP lesion, and (**e**) right MCA territory has decreased CBF. (**f**) Follow-up 1 day DWI shows acute infarcted lesion at the right lentiform area. This lesion is similar to CBV lesion in terms of size and location

3. *CBF 18–37 mL/100 g/min; MTT 1.8–8.3 s relative to the contralateral side* [111]
4. *TTP >5 s to contralateral side*

The visible mismatch between the volume of tissue with decreased blood flow (i.e., delayed TTP, MTT, Tmax and/or low CBF) and that with significantly low CBV can be used as a CTP-based operational definition of the ischemic penumbra [53–55]. CTP provides equivalent results to diffusion/perfusion MRI in terms of characterizing the infarct and penumbra (Fig. 3.7) [40, 46, 47].

3.2.3.2 Techniques of CT Perfusion

CT perfusion (CTP) or MR perfusion (MRP) is a technique where the same area of the brain is repeatedly scanned during the passage of the contrast medium from the arteries through the capillaries to the veins and then into the venous sinuses [13, 56]. Although there are important technical differences between modalities, both CT and MR perfusion imaging are based on the same mathematical models as positron emission tomography (PET). Therefore, the overall clinical applicability of perfusion imaging by using either of these techniques is similar. The most important advantage of CTP is the linear relationship between contrast concentration and attenuation in CT, which facilitates quantitative (versus relative) measurement of CBF and CBV. MR perfusion imaging (MRP) relies on the indirect T2* effect induced in the tissue by gadolinium; the T2* effect itself is not linearly related to the gadolinium concentration, making absolute measurement of CBF and CBV difficult [56].

CTP involves dynamic acquisition of sequential CT slices during rapid IV administration of iodinated contrast material. CTP allows rapid, noninvasive, quantitative evaluation of cerebral perfusion. Based on the multi-compartmental tracer kinetic model, dynamic CTP imaging is performed by monitoring the first pass of an iodinated contrast agent bolus through the cere-

bral circulation. Because the change in CT density (in Hounsfield units) is proportional to the concentration of contrast, perfusion parameters are calculated by deconvolution from the changes in the density-time curve for each pixel using mathematical algorithms based on the central volume principle [57, 58]. Deconvolution-based algorithms allow much lower injection rates, 5 mL/s as reported earlier, compared with algorithms that use other approaches, such as the nondeconvolution-based maximal slope model [56]. These lower injection rates are more practical and tolerable for patients. For the quantification of perfusion parameters, arterial input

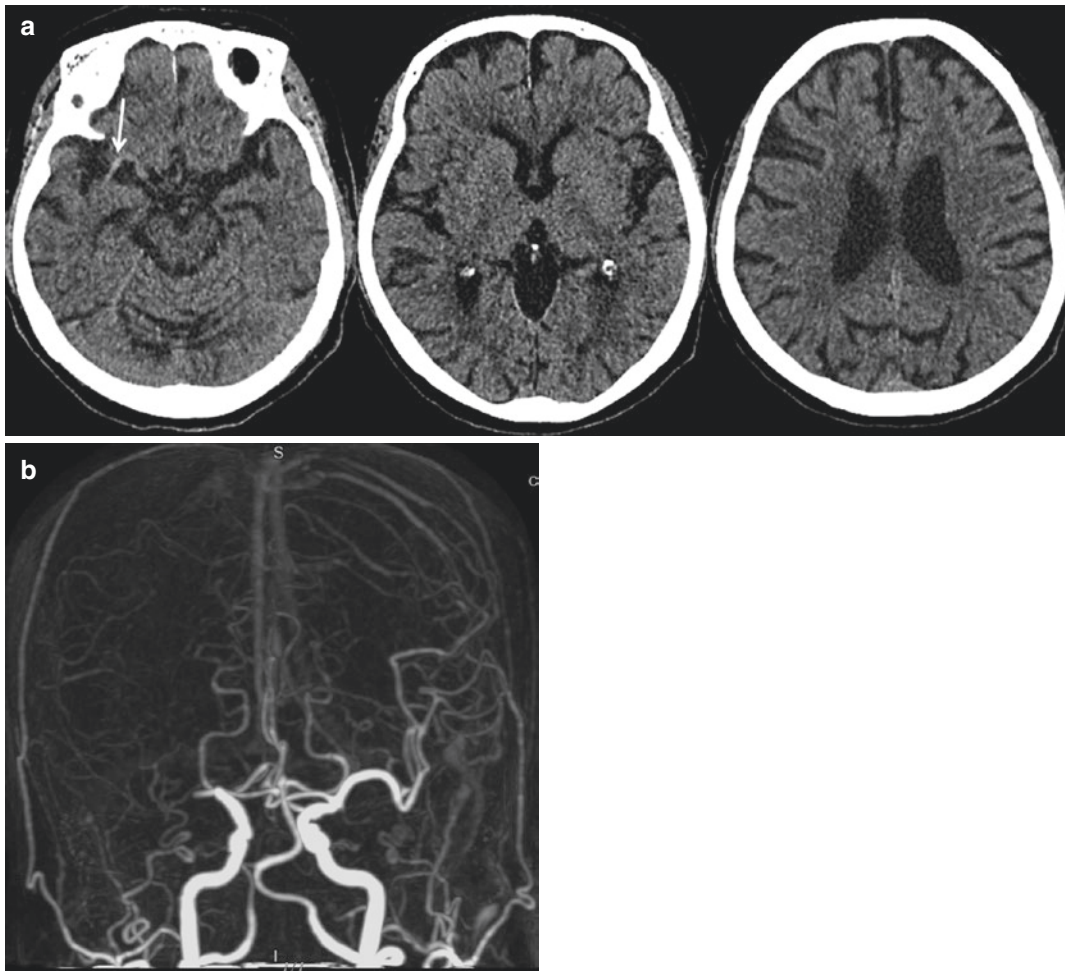
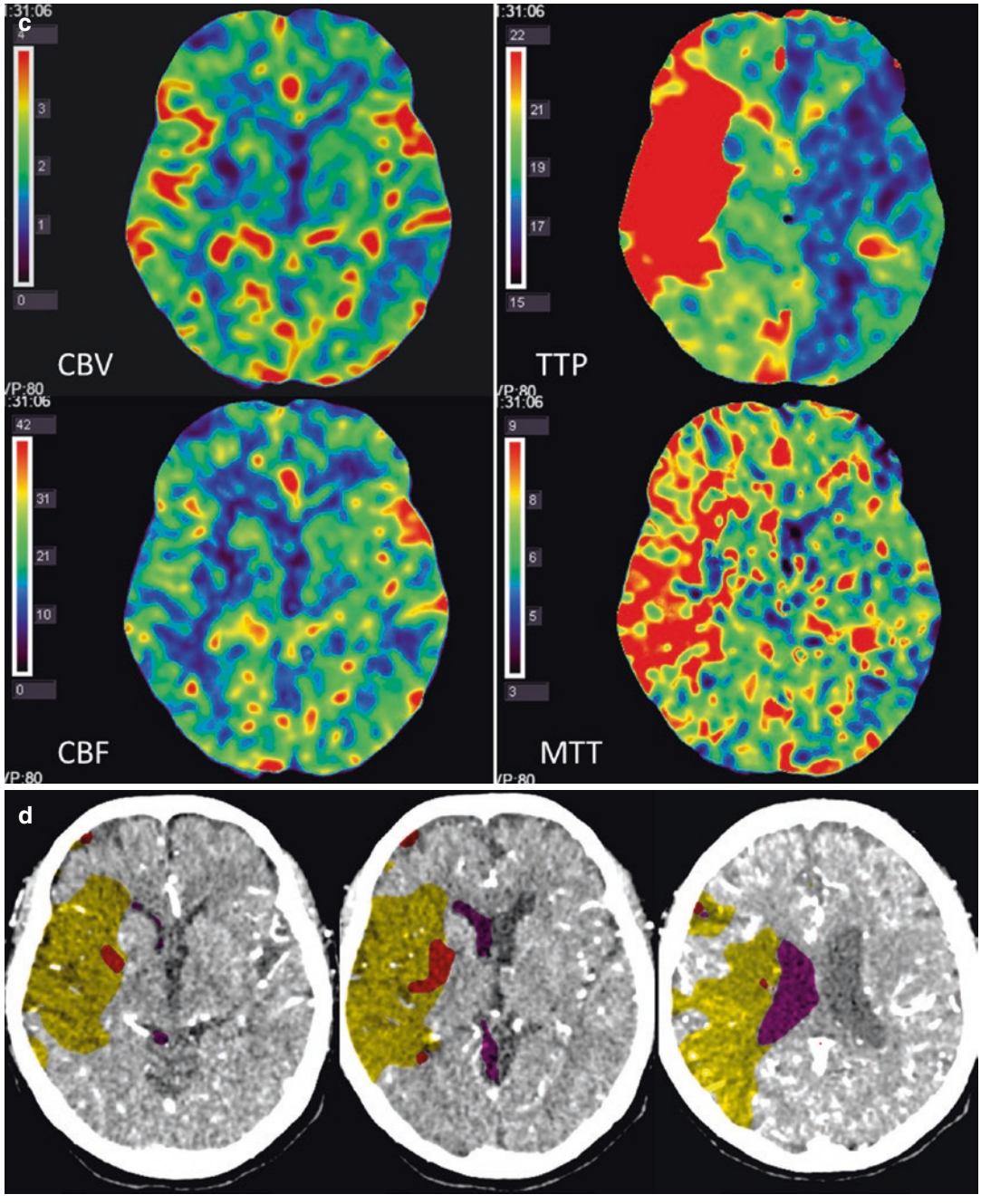


Fig. 3.7 A 91-year-old woman with right-sided weakness and facial palsy (NIHSS 12). She visited ER 60 min after symptom onset. Before IV-tPA therapy, noncontrast CT (NCCT) images (**a**) and CT perfusion (4D CTA) (**b**, **c**) were done. NCCT images (**a**) show hyperdense artery sign (*arrow*) at the right MCA M1 distal segment (*right*) and subtle early ischemic sign (loss of lentiform nucleus) (*middle*). (**b**) MIP CTA shows occlusion of right proximal MCA M1. (**c**) CT perfusion maps show small-sized CBV lesion and large time perfusion parameters (TTP/MTT). (**d**) Probability model map of using TTP + 6.8 s (penumbra, *yellow zone*) and rCBV −41% (infarct core, *red zone*) (ventricle, *purple zone*). (**e**) Dynamic CTA shows retrograde filling of MCA M3, M2 branches (*arrows*) by leptomeningeal collateral flow. (**f**) After stroke imaging, the patient received IV-tPA with no improvement in symptoms. The patient has a large penumbra area and small infarct core; it means it is a good candidate of endovascular therapy. After endovascular therapy, MRA shows complete recanalization (*right*), and diffusion-weighted image shows the infarcted area where the probability map showed. Immediately following endovascular therapy, the patient demonstrated clinical improvement (NIHSS 4)



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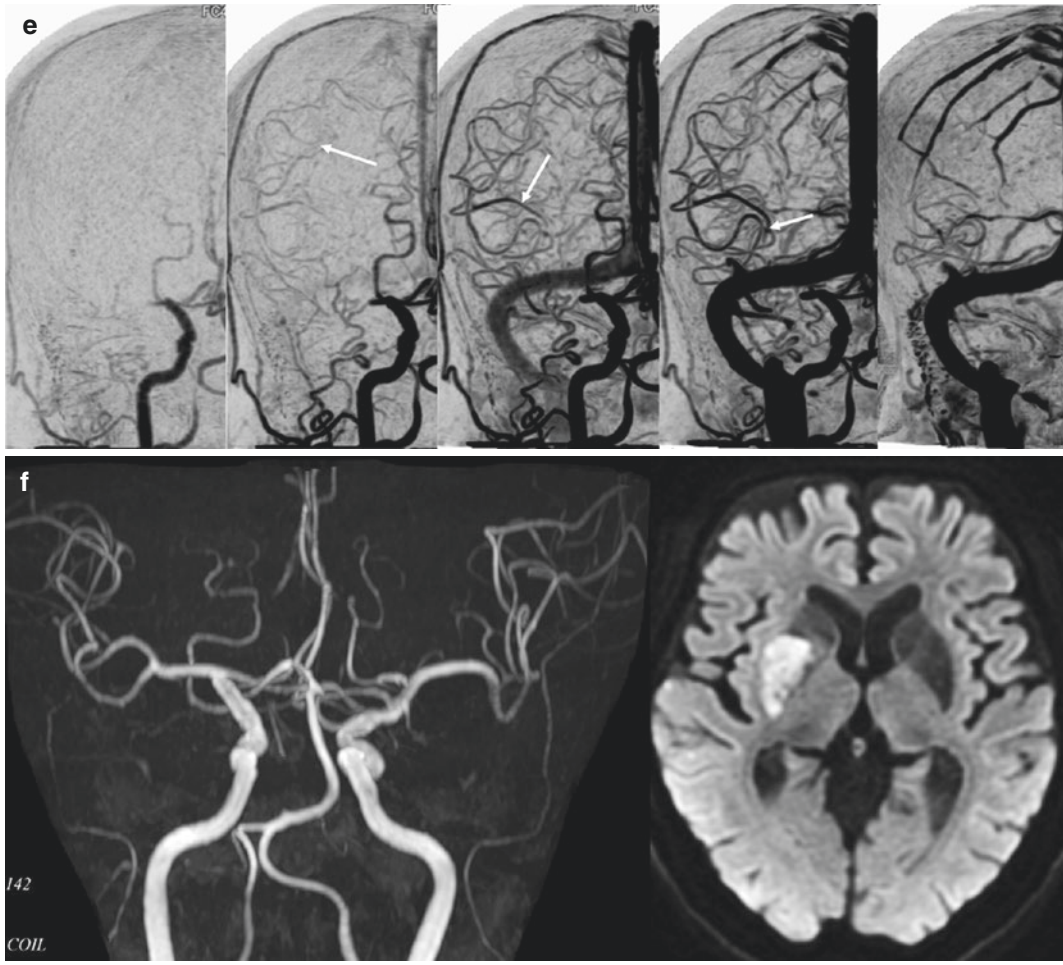

Fig. 3.7 (continued)

function (AIF) should be measured. The ACA or middle cerebral artery (MCA) can be selected as the AIF. A large venous structure such as the torcular herophili is chosen as the output vein. Examination of the venous contrast concentration versus time curve assists in the normalization of the resulting perfusion parameters by helping to correct for partial volume averaging effects. For this reason, analysis of perfusion CT data using the deconvolution method requires the selection of two small regions of interest (ROIs) reflecting representative time–attenuation curves for the arterial input function and venous outflow function [56, 59].

Calculated CT perfusion maps include the following:

1. Mean transit time (MTT) indicates the average time between arrival of the bolus in a given tissue and the outflow of the bolus from the tissue into the venous system also measured in seconds.
2. Cerebral blood volume (CBV) indicates the total volume of blood in the intravascular space of each tissue, including capillaries and large vessels, measured in milliliters of blood/100 g of brain tissue (normal range in gray matter, 4–6 mL/100 g).
3. Cerebral blood flow (CBF) is the volume of blood flowing through a brain tissue per unit time, measured in milliliters of blood/100 g of brain tissue/minute (normal range in gray matter, 50–60 mL/100 g/min).

4. The relationship between CBF and CBV is expressed by the equation CBF = CBV/MTT.
5. Tmax indicates time-to-maximum of the flow-scaled residue function.
6. Additional perfusion parameters:

Time-to-peak (TTP) is an estimate of the time between arrival of the tracer bolus at the pre-capillary arteriole and peak concentration of tracer in the capillary bed, measured in seconds.

First moment (FM) is the centroid of the area under the curve (AUC) of the time-concentration curve onto the time axis.

Bolus arrival time (BAT) of the time-concentration curve (the curve *c* voi (*t*) does not start to rise at the same time point as *c* art (*t*) starts to rise). The difference between these two time points can be defined as the bolus arrival time (BAT) (Fig. 3.8).

3.3 Magnetic Resonance Imaging

A multimodal magnetic resonance imaging (MRI) protocol for AIS patients should be short and effective aiming to show acute ischemic areas, exclude hemorrhage, and also provides identifying the location and extent of intravascular clot as swell as the presence and extent of penumbra. Also, multimodal magnetic resonance imaging (MRI) is useful for determining treatment strategies in the acute stage. In the acute stage, early diagnosis of ischemic stroke and its differentiation from stroke-mimics are important [60, 61]. Although CT is the most commonly used modality for stroke imaging, because of its wide availability and faster acquisition time, some comprehensive stroke centers choose stroke MRI rather than CT for two major reasons. First is higher sensitivity and specificity of MR imaging for detection of hyperacute ischemia. Diffusion-weighted imaging (DWI) provides the most specific way to image acute infarction. The advent of MRI has redefined stroke syndromes such as acute ischemic infarction and TIA. Second is the absence of radiation.

Comprehensive MR stroke protocols have four "p" components: (1) parenchymal imaging, which identifies the presence and size of an irreversible infarcted core, determines presence of hemorrhage, and helps to age the ischemic event; (2) pipes, MRA/CE-MRA to determine the location of arterial occlusion and susceptibility-weighted imaging (SWI/T2*-weighed imaging) to detect presence of an intravascular thrombus that can be treated with thrombolysis or thrombectomy; (3)

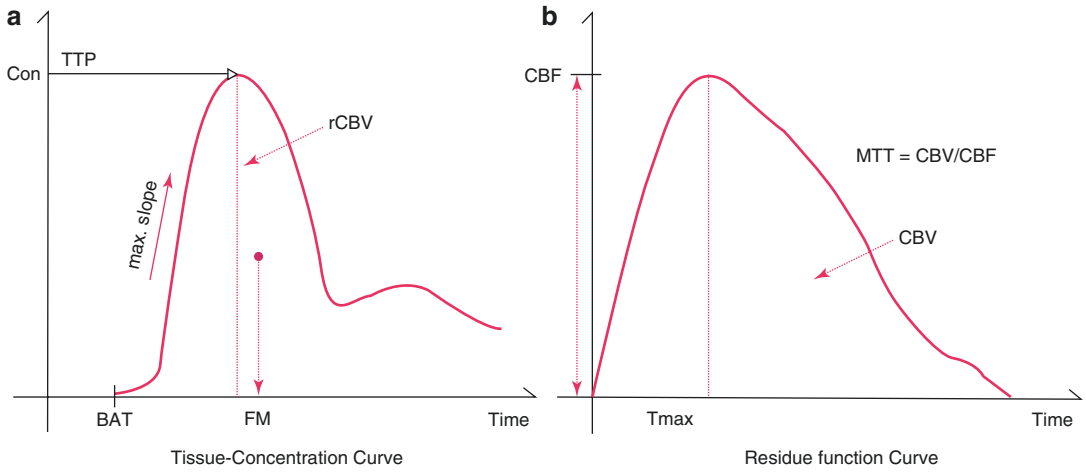

Fig. 3.8 Perfusion parameters that are measured using the time-concentration curve (**a**) and flow-scaled residual function curve (**b**). *BAT* bolus arrival time, *TTP* time to peak, *FM* first moment, *Tmax* time-to-maximum of the flow-scaled residue function, *rCBV* relative cerebral blood volume

penumbral imaging to determine the presence of hypoperfused tissue at risk for subsequent infarction if adequate perfusion is not restored; (4) perfusion imaging to determine sum total CBF arriving at a particular brain region both via normal route and recruited collaterals [62].

3.3.1 Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) detects cytotoxic edema due to restricted water diffusion in brain tissue [63]. DWI has an excellent sensitivity in the detection of acute ischemia compared to CT [64, 65] and shows areas of cytotoxic edema as soon as 3–11 min after onset of AIS [66].

DWI is significantly more sensitive and specific in the identification of early ischemic brain injury (sensitivity 91–100%, specificity 86–100%), far beyond NCCT [67–69]. As such, most lesions with diffusion restriction are generally considered irreversible in clinical practice. There are reports of DWI lesions being reversible especially after mechanical thrombectomy [70]. These initially reversible lesions on an early MR (performed 24–48 h after therapy) may reappear if imaging is repeated 1–2 weeks later [71]. The higher the apparent diffusion coefficient value is, the higher the chance is that the lesion is reversible [72]. Complete reversal of DWI lesions after reperfusion is limited to tiny lesions in embolic stroke patients [73].

Diffusion lesion volume (infarct volume) has become a more important factor to predict clinical outcome. In the anterior circulation, a large infarct with cytotoxic edema on DWI involving more than one-third of the MCA territory, an infarct volume >100 mL is associated with poor clinical outcome [12, 71, 72]. Also some studies suggest that patients with DWI lesion >70 mL [74] or >100 mL [75] do not benefit from endovascular treatment due to futility. In this patient group, reperfusion therapy is not recommended. DWI lesion size may help guide therapeutic decision-making between surgical decompression and recanalization therapy. However, the exact threshold of DWI lesion volume to exclude patients from endovascular treatment has yet to be determined because some patients with larger DWI lesion volumes had favorable outcomes [76, 77].

3.3.2 Susceptibility-Weighted Imaging

Acute stroke imaging requires the differentiation between ischemic stroke and hemorrhagic stroke. A T2*-weighted gradient-echo image or susceptibility-weighted imaging (SWI) is reported to be as accurate as CT in the detection of hyperacute hemorrhage and superior to CT for chronic hemorrhages [78, 79]. SWI can detect acute subarachnoid hemorrhage [80] and is extremely sensitive for subacute and chronic hemorrhage that is not demonstrated with FLAIR or CT [81].

SWI or T2*-weighted image can be used to identify acute thrombus in a similar way to that of unenhanced CT [82] in acute ischemic stroke. The information regarding the presence of intra-arterial thrombus and its location may be useful in planning various treatment options. Intra-arterial thrombus makes the "susceptibility vessel sign" and is defined as the presence of hypointensity within the arteries in which the diameter of the hypointense vessel exceeded the contralateral vessel diameter (Fig. 3.9) [83]. Susceptibility vessel sign was an independent predictor of cardioembolic stroke and subsequent recanalization [84]. However, it is often limited because of the following reasons: First, it may overestimate thrombus extent by dark signal intensity from stagnating blood distal to occlusion. Second, it is prone to artifact, which is problematic at the skull base. Last, it may not be helpful to characterize thrombus [85]. SWI can also demonstrate prominent asymmetrical cortical and transmedullary veins in the region of ischemia, which possibly represent the region of increased oxygen extraction fraction (Fig. 3.9).

Hemorrhagic transformation of ischemic stroke can be a devastating complication especially if the patient is considered for revascularization therapies. It is observed in approximately 20–40% of all stroke patients within the first

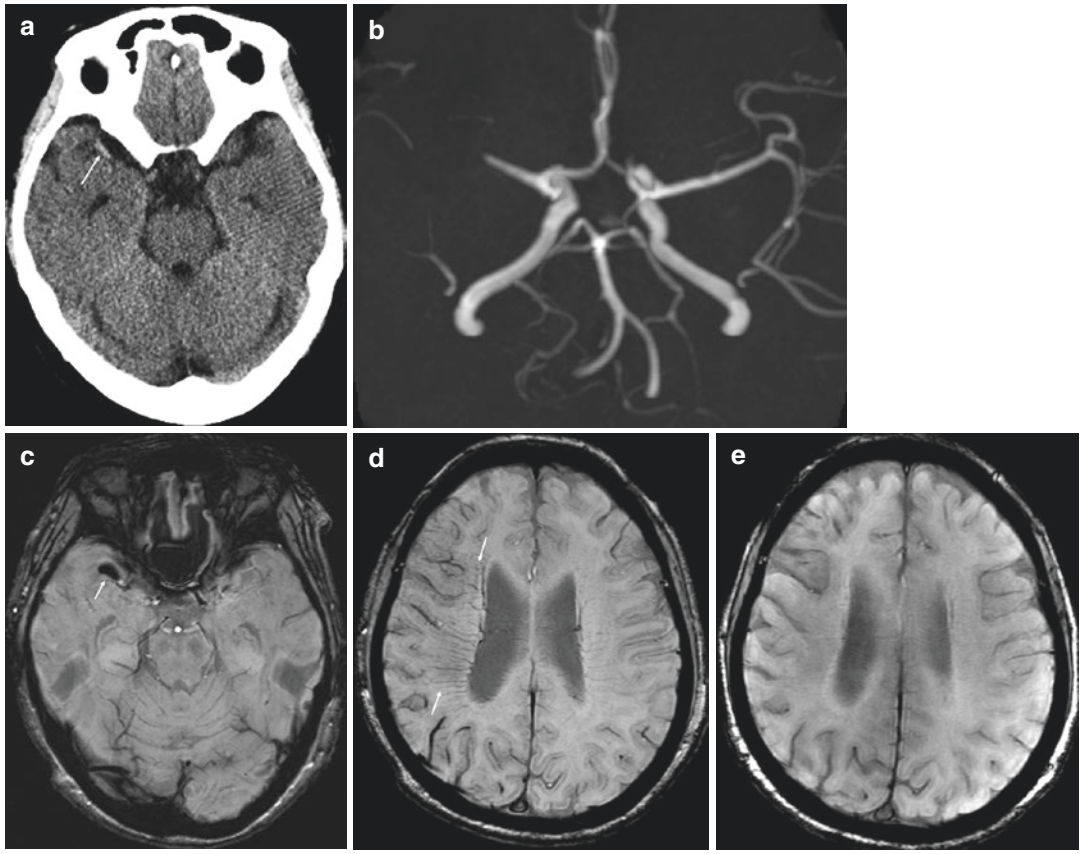

Fig. 3.9 Susceptibility vessel and transverse medullary vein signs. (**a**) Noncontrast CT shows hyperdense artery sign (*arrow*) at the right MCA M1 segment. (**b**) MRA shows occlusion of right MCA M1. Susceptibility-weighted image (SWI) shows dark susceptibility vessel sign (*arrow*) corresponding to CT clot (**c**) and transmedullary vein sign (*arrows*) on ventricular level (**d**). After complete recanalization of occlusion, transmedullary vein sign is disappeared on SWI (**e**)

week of onset [86]. Conventional MRI or NCCT often does not detect these hemorrhagic transformations, especially hemorrhagic infarction type 1 or 2. SWI which is exquisitely sensitive to hemorrhage is able to detect small hemorrhages within the infarct and makes it more conspicuous than T2*-weighted image.

SWI is significantly more sensitive for detection of chronic intracerebral microbleeds, which may be the sequelae of amyloid angiopathy or chronic hypertension. It may be difficult, however, to differentiate smaller acute hemorrhages from older hemosiderin deposits, and their presence is a much disputed contraindication for thrombolysis [48]. But, the risk of hemorrhage in patients with more than five chronic microhemorrhages is unknown [87].

SWI can provide complementary information in stroke patients in the form of:

1. Identification of hemorrhagic transformation of an ischemic infarct occurring due to arterial or venous thrombus.
2. Demonstrating hypoperfused areas of the brain (penumbral brain tissue) in the form of prominent cortical draining veins visible in hypoperfused areas, in which case perfusion-weighted imaging is necessary. Areas with more prominent veins are shown to match with the areas of prolonged MTT on perfusion imaging.

3. Demonstrate acute thrombus occluding the major vessels appearing as hypointensity on phase image and dark on SWI image in a right-handed MR system, similar to the dense thrombus sign seen on CT.

Susceptibility-weighted imaging is a fully velocity-compensated high-resolution 3D gradient-echo sequence that uses magnitude and filtered-phase information, both separately and in combination with each other, to create a new source of contrast. It offers information about any tissue that has a different susceptibility than its surrounding structures, such as deoxygenated blood, hemosiderin, ferritin, and calcium [88]. SWI is three to six times more sensitive than conventional T2*-weighted gradient-echo sequences in detecting the size, number, volume, and distribution of hemorrhagic lesions [89].

3.3.3 MR Angiography

An important aspect of the work-up of patients with AIS or TIA is the imaging of both the intracranial and extracranial vasculature. The most commonly used noncontrast MRA technique is time-of-flight (TOF) imaging. Time of flight (TOF) MR angiography (MRA) gives information about flow in intra- and extracranial arteries. Limitations of TOF-MRA include long acquisition times and overestimation of arterial stenosis caused by spin saturation and phase dispersion secondary to slow, in-plane, turbulent, or complex flow [28, 29]. TOF MRA can be useful in diagnosing proximal vessel occlusions but is not suitable for identification of more distal or smaller branch occlusions [90].

Contrast-enhanced MRA (CE-MRA) is the technique of choice for extracranial artery imaging [91]. It relies on injection of a gadolinium to reduce the T1 relaxation time of tissue and to generate contrast between the intravascular lumen and surrounding tissues [92]. Unlike TOF-MRA, vascular contrast is therefore relatively independent of flow dynamics, and artifacts associated with saturation effects are substantially reduced.

3D TOF MRA is the preferred technique for the examination of intracranial vessels. The advantage of contrast enhanced MRA over TOF MRA is that collaterals distal to an occlusion are visualized [93].

3.3.4 Fluid-Attenuated Inversion Recovery (FLAIR) Imaging

Fluid-attenuated inversion recovery (FLAIR) imaging has recently attracted in acute stroke imaging as a potential surrogate marker for time passage since stroke onset. On T2-weighted FLAIR images, ischemic infarction appears as a hyperintense lesion usually seen within the first 3–8 h after stroke onset [94, 95]. If lesions present on DWI are not visible on FLAIR series, it is anticipated that the ischemic event occurred within the last 4.5 h (Fig. 3.10). Thus, a mismatch between positive DWI and negative FLAIR images appears to be useful in the identification of patients who are likely to benefit from thrombolysis [95, 96].

In the setting of hyperacute stroke, FLAIR images can be useful to detect the loss of the arterial signal flow void in occluded vessels within 3 h of the stroke onset [97]. Hyperintense vessels on FLAIR imaging have been associated with slow flow in collateral arterial vessels [98]. Hyperintense vessels predicted arterial occlusion with high accuracy and are more commonly seen with proximal arterial occlusions and more severe strokes. Their presence has also been associated with larger lesions on perfusion imaging and larger DWI–PWI mismatch volumes [99, 100].

FLAIR images are also highly sensitive to subarachnoid hemorrhage (SAH) [101] as well as acute cerebral venous sinus thrombosis [102, 103]. In 3T high tesla MRI scanner, SWI is a more sensitive and specific tool to detect acute SAH and intraventricular hemorrhage [80]. Fresh thrombus in a cortical vein or a cerebral sinus as found in cerebral venous sinus thrombosis results

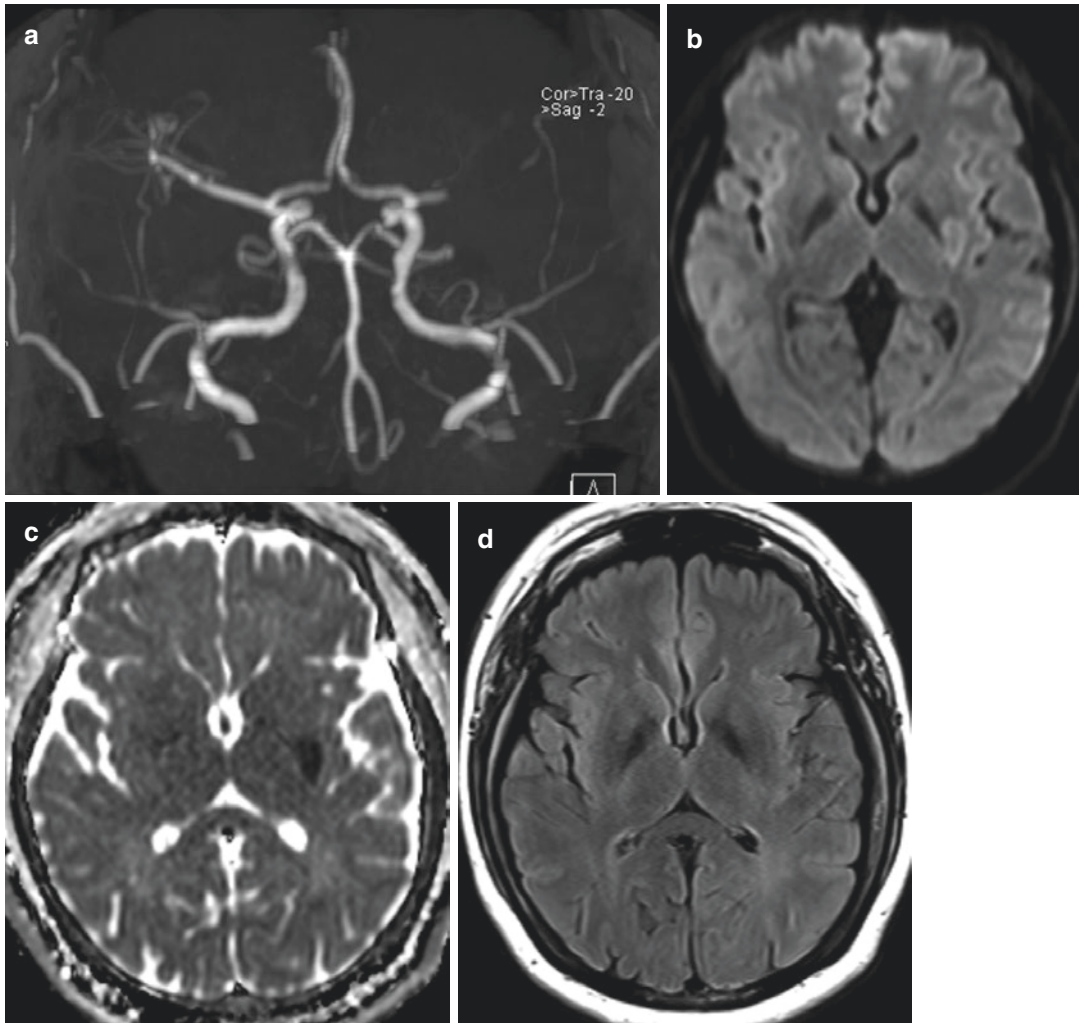

Fig. 3.10 A 46-year-old woman with mild right-sided weakness (NIHSS 3). She visited ER 5 h 15 min after last normal time (wake-up stroke patient). DWI-FLAIR mismatch. (**a**) MRA shows occlusion of left proximal MCA M1. (**b**, **c**) DWI and ADC map show acute ischemic change (decreased ADC value) at the posterior lentiform nucleus. There is no abnormal signal intensity on FLAIR image (**d**)

in increased signal on FLAIR images and obviated flow void signal.

3.3.5 Magnetic Resonance Perfusion Imaging

The goal of stroke perfusion imaging is to estimate the relative volumes of tissue in the penumbra (tissue at risk of infarction but salvageable with early restoration of blood flow) that can be saved from infarction by early recanalization [55], regions of benign oligemia (tissue with reduced blood flow but not at risk of infarction), and infarcted core tissue that cannot be salvaged, but instead conveys a higher risk of hemorrhage and/or reperfusion edema [104].

3.3.5.1 Dynamic-Susceptibility Contrast MR Perfusion

MR perfusion (MRP) is performed by rapid repeated echo planar imaging (EPI) covering the whole brain every 1–2 s during passage of a bolus of intravenous gadolinium-based contrast agents

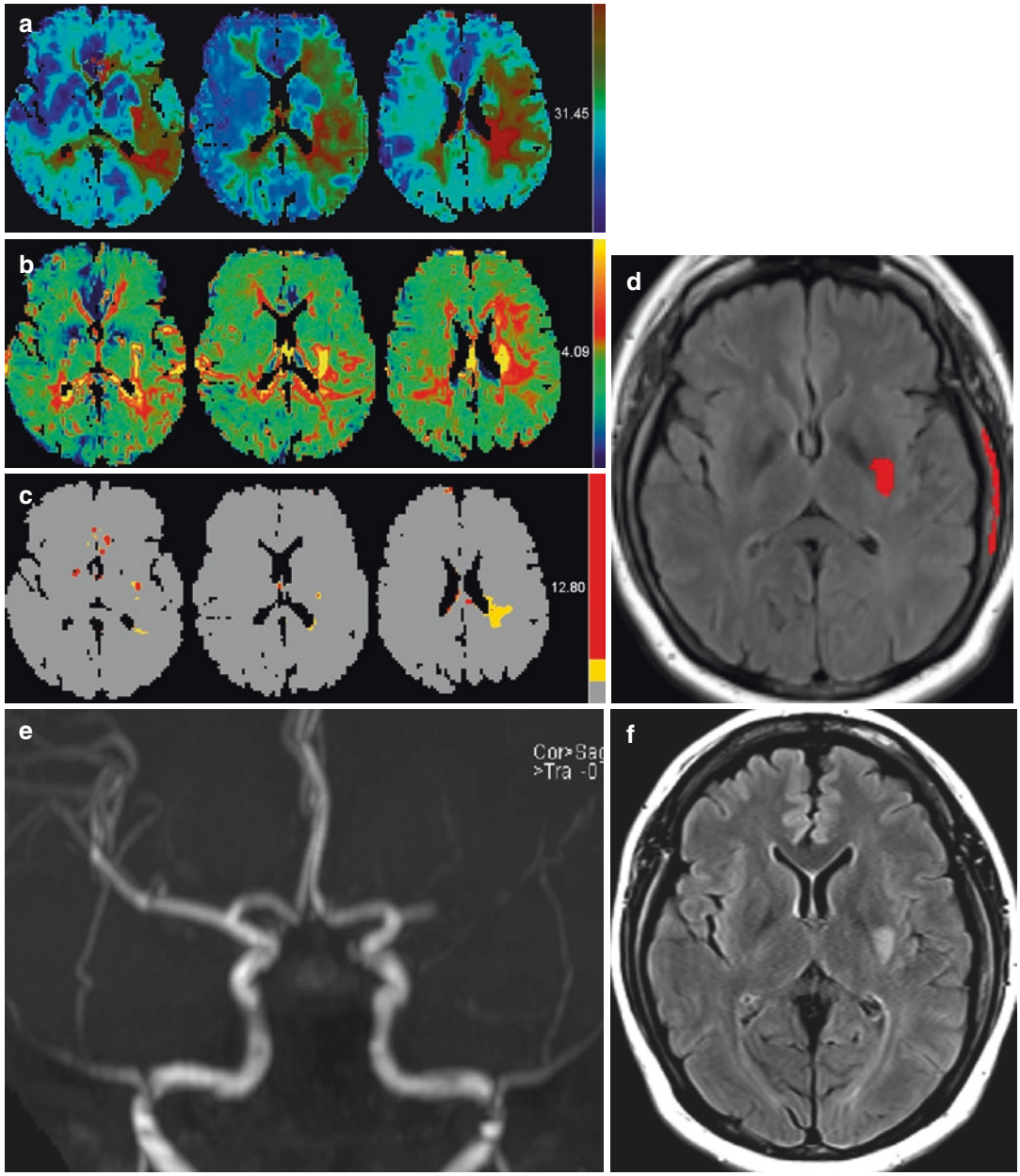

Fig. 3.11 A 46-year-old woman with mild right-sided weakness (NIHSS 3). She visited ER 5 h 15 min after last normal time (wake-up stroke patient, Fig. 3.11 same patient). Dynamic-susceptibility contrast MR perfusion images show different sizes of perfusion lesion, TTP (time-to-peak) (**a**), and MTT (mean transit time); (**b**) map shows large perfusion delayed area and relatively large diffusion/perfusion mismatch. But Tmax >6 s, threshold map (**c**) demonstrates just a tiny penumbra area (*red color zone*). (**d**) *Red* zone on initial FLAIR image means infarct core lesion that is measured by ADC value. There is no IV-tPA and endovascular therapy because of mild neurologic deficit and no penumbra zone. Follow-up 5 days MRA (**e**) demonstrates no recanalization of occlusion site. Also a 5-day-FLAIR image (**f**) shows-infarcted lesion which is the same located DWI lesion

through the brain capillaries. MR perfusion relies on the T2* shortening ("magnetic susceptibility") effects of concentrated intravascular gadolinium contrast; hence, it is referred to as dynamic-susceptibility contrast (DSC) MRP. MR signal intensity is not linearly scaled to concentration, the postprocessing of MR perfusion starts with derivation of a contrast concentration versus time curve and results in perfusion maps that cannot be absolutely quantitated without use of an internal or external reference [104–106]. For this reason, MR perfusion maps are often described as "relative" using the prefix "r" (i.e., rCBV, rCBF), and interpretation is based on values (nCBF, nCBF, nMTT) normalized by the corresponding parameters in the contralateral normal-appearing white matter.

Assessment of Penumbra

To simplify the MR definition of the penumbra, which has been previously defined as the mismatch between the diffusion and perfusion abnormalities, this concept suggests that enlargement of the area of infarction was likely to occur if the area of perfusion deficit was larger than the area of the initial diffusion abnormality, and this mismatch may represent the ischemic penumbra. It has been noted that patients with small initial DWI lesions and larger PWI lesions who do not reperfuse tend to have growth of the DWI lesion into the PWI region. This has led to the DWI/PWI mismatch area as a penumbra area. A significant mismatch has been operationally defined as "at least a 20% discrepancy between the smaller DWI lesion and the larger PWI lesion in their volume" in early study [75]. Identifying irreversibly infarcted lesion is usually straightforward using the high signal intensity DWI lesion. The problem is defining the borders of the penumbra, where the perfusion abnormality is still severe enough to result in irreversible damage if no subsequent reperfusion occurs. Multiple potential perfusion parameters for penumbra can be obtained; they are CBF, CBV, MTT, Tmax, and TTP. What is the best way of defining the penumbra? Time-based perfusion parameters, such as Tmax, TTP, and MTT are generally accepted. More recent studies have used Tmax and TTP. Several studies demonstrated that Tmax >4 s or >6 s was a good threshold to detect CBF values below 20 ml/100 min/min [50, 107]. In DEFUSE II study, mismatch was defined as a ratio between the volumes of Tmax >6 s lesion volume and 80% difference in size between DWI and PWI with an absolute difference ≥15 ml (Fig. 3.11) [108].

DSC-MRP may be helpful in identifying those patients most likely not to profit from reperfusion therapy: In the cohort from the DEFUSE and EPITHET trials, the patients with a Tmax >8 s did not benefit from reperfusion therapy. In the same study, patients without DWI-MRPI mismatch did not profit from reperfusion therapy [109]. In the literature, evidence for the determination of penumbra using CTP is better corroborated compared to MR perfusion [13].

Issues of Mismatch Mild definition of Tmax >2 s as criterion for the penumbra, and a 20% difference in size between DWI and PWI as a definition of DWI/PWI mismatch resulted in mismatch pattern in the most of stroke patients (86% in DEFUSE study). The patients who have small DWI lesions coupled with a proximal artery occlusion will have mismatch pattern, and for this reason perfusion imaging is not needed (PWI does not provide additional information), and only wastes time before implementing treatment. The mismatch volume usually is calculated by the PWI/DWI volume ratio or by the difference between the total PWI and total DWI lesion volumes.

Operational Peumbra Threshold in MRP

1. Tmax > 6 s
2. TTP > 5.0 or 6.0 s

3.3.5.2 Arterial Spin Labeling MR Perfusion

Arterial spin labeling (ASL) is an emerging technique for measuring cerebral blood flow (CBF) at the tissue level. The main advantages of ASL include its noninvasive nature and its ability to provide absolute CBF information within a brief period. These characteristics suggest that this

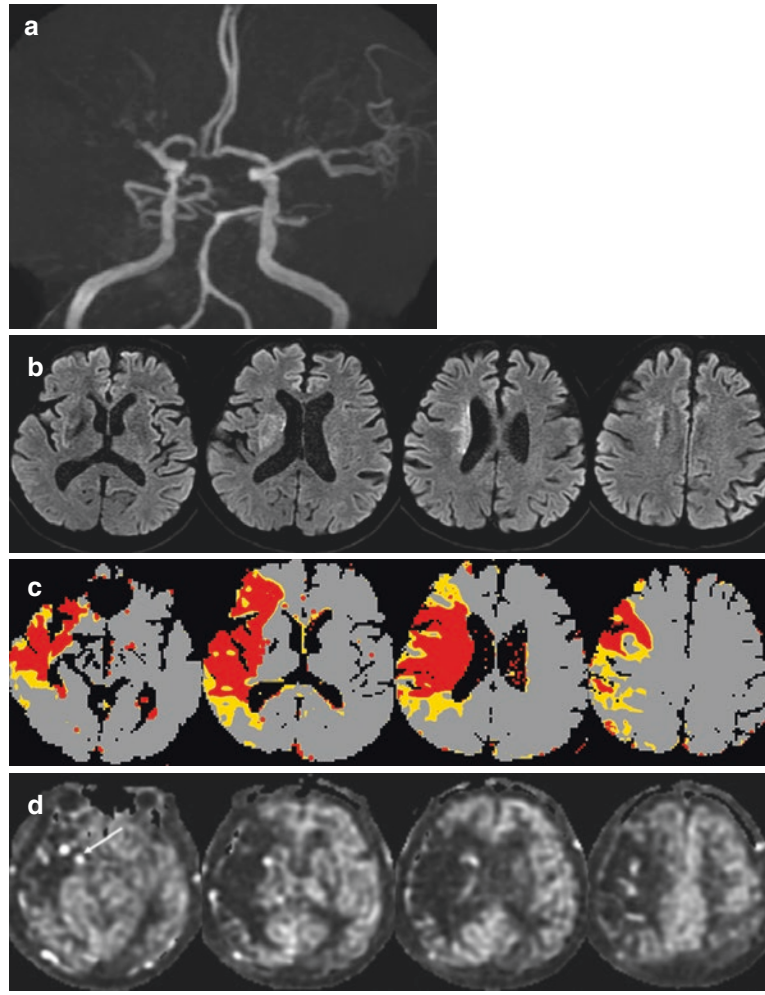

Fig. 3.12 A 72-year-old man with left-sided weakness (NIHSS 13). He visited ER 40 min after symptom onset. (**a**) MRA demonstrates occlusion of the right proximal MCA M1 segment. (**b**) DWI images show the acute infarcted lesion at the right basal ganglia. (**c**) Tmax perfusion maps demonstrate large penumbra zone (*red color*). (**d**) Pseudocontinuous arterial spin labeling MR perfusion images show prominent decreased CBF lesion. Bright vessel sign (*arrow*) is visualized at the right distal MCA M1 area. It means occlusion site of involved artery

technique could be used to detect bilateral disease, which is often present in patients with acute or chronic cerebrovascular disease, and it has been increasingly applied [110–113].

The primary advantage of using ASL for perfusion measurement is that this technique is completely noninvasive and does not expose the patient to radiation or contrast agents and allows repetitive acquisitions. As an alternative method to DSC-MRP, ASL may be used to repetitively and quantitatively monitor changes in cerebral blood flow in regions of ischemic core and penumbra, it can be used to gain new insights into cerebral ischemic change and the response to therapy.

ASL is largely consistent with DSC MRP for depicting hypoperfused areas, although ASL may miss small lesions and may overestimate perfusion/diffusion mismatch region due to delayed arterial transit time (ATT). Among the multiple perfusion parameters generated by DSC-MRP, ASL estimate of CBF was found to best match time parameters of a contrast bolus such as MTT, TTP and Tmax (Fig. 3.12) [113, 114]. Presence of superficial (cortical) delayed arterial transit time in ischemic regions may represent existing collateral flow in that area through leptomeningeal vessels. But still has not been established grading of collateral flow using ASL. Multi-delay ASL approach has several potential advantages over existing single delay ASL scans, including improved accuracy of CBF quantification, imaging of multiple hemodynamic parameters (ATT, CBF and CBV), and

better visualization of collateral flow through dynamic image series [115].

The additional interesting finding of ASL in acute stroke is that the bright vessel appearance is significantly more common in arterial occlusion stroke patients than in the group without occlusion (Fig. 3.12). The bright vessel appearance, when present, was seen proximal or distal to occlusion sites. The bright vessel sign on ASL may provide a clue for the detection and localization of arterial occlusion sites in patient with acute ischemic stroke.

3.3.5.3 Basic Principle of ASL Perfusion Imaging

ASL relies on the detection of magnetically labeled water protons [116, 117]. The magnetization of inflowing arterial blood is inverted and when the inverted spin of the labeled blood reaches the capillaries of the brain tissues, the magnetization of the labeled blood exchanges with that in the capillaries, which prolongs longitudinal magnetization (T1-elongation). Thus, the signal intensity of the tissues reduces in relation to tissue perfusion. The decrease in signal induced by labeled blood is very subtle, as low as 1%, and extraction of such subtle signal change requires acquisition of two sets of images–a set of labeling images in which arterial spins are inverted proximally to imaging slices and a set of control images acquired without labeling pulse. ASL perfusion images are obtained by subtracting labeling images from control images [116, 117]. The signal of subtracted images is related in proportion to the cerebral perfusion (cerebral blood flow).

3.4 Summary

Imaging in acute ischemic stroke has always traditionally focused on the 4Ps – parenchyma, pipes, perfusion, and penumbra. Existing guidelines recommend only noncontrast CT as emergency imaging before intravenous thrombolysis. Vascular imaging (CT/MRA) is recommended only if endovascular therapy is indicated [6]. The benefits of additional imaging beyond CT and CTA or MR and MRA, such as CT perfusion or diffusion- and perfusion-weighted imaging, for selecting patients for endovascular therapy are unknown *(Class IIb; Level of Evidence C)*. However, advanced imaging techniques such as CTA/MRA and perfusion imaging are being widely used in acute ischemic stroke, to identify infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are within 6 h of symptom onset and have unknown onset stroke. Nevertheless MR or CT perfusion imaging is to be used to guide stroke treatment, then clinical decisions should not be based on threshold values at present clinical field. There are other way in which perfusion imaging can be used in stroke without determining thresholds, just positive abnormal perfusion finding is helpful for clinical decision making.

Comprehensive advanced imaging, such as CTA and CTP (simultaneously CTA/CTP, multiphase CTA) and 6 min stroke MRI (DWI, SWI, FLAIR, perfusion imaging) become an essential component of acute stroke imaging in the present and future. “Time is brain” is a common sense and “Perfusion time is brain” is a sophisticated sense.

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4 Histologic Characteristics of Intracranial Clots Retrieved Using Mechanical Thrombectomy

Woong Yoon

A mechanical thrombectomy is currently the standard treatment for patients with acute ischemic stroke due to intracranial large-vessel occlusions [1–3]. The inclusion of a mechanical thrombectomy in stroke management allows the histologic examinations of retrieved clots occluding the intracranial arteries. A histologic analysis of a clot retrieved from an intracranial artery can provide important information on the stroke etiology, impacting secondary stroke prevention strategies. Intracranial clots are traditionally classified as red blood cell (RBC)-rich clots (red clots) or fibrin-rich clots (white clots). Therefore, this chapter covers the basic concepts of clots occluding human intracranial arteries in patients with acute ischemic stroke and presents recent evidence from histopathologic analyses of retrieved clots indicating an association between the clot composition and stroke etiology and imaging characteristics.

4.1 Red Versus White Clot

Blood clots are traditionally classified as red (RBC predominant) or white (fibrin-platelet predominant) clots [4]. Composed of mainly RBCs and fibrin, red clots tend to form in areas of decreased blood flow, and their development does not require an abnormal vessel wall or tissue thromboplastin. Red clots are created by the activation of circulating coagulation factors, where the final step in the coagulation cascade is the conversion of the soluble protein fibrinogen into insoluble polymers called fibrin. The fibrin strands then form a network of fibers that entangle the blood elements (RBCs, platelets, leukocytes) into a clot (Fig. 4.1). As they mainly develop in areas with a reduced blood flow, red clots are commonly harbored in dilated cardiac atria, especially in patients with inefficient contractility as found with atrial fibrillation, regions of hypokinesia of the cardiac ventricles, and frank ventricular aneurysms. Red clots can also be formed in heart chambers when the ejection fractions are low and on the surface of myocardial infarcts. In addition, thrombi in the leg and pelvic veins that pass through defects in the cardiac atrial and ventricular septa or pass through arteriovenous fistula in the lungs are nearly always red thrombi. Both red and white thrombi are often formed along damaged heart valves, especially those made of prosthetic materials [4].

White clots are mainly composed of fibrin and platelets with only a sparse amount of RBCs (Fig. 4.2). White clots are characteristically formed in fast flow circumstances, along with irregular valvular and endothelial surfaces. White clots can also be formed as a result of injury to the endothelium overlying the complicated atheromatous plaque. Clots formed at the site of

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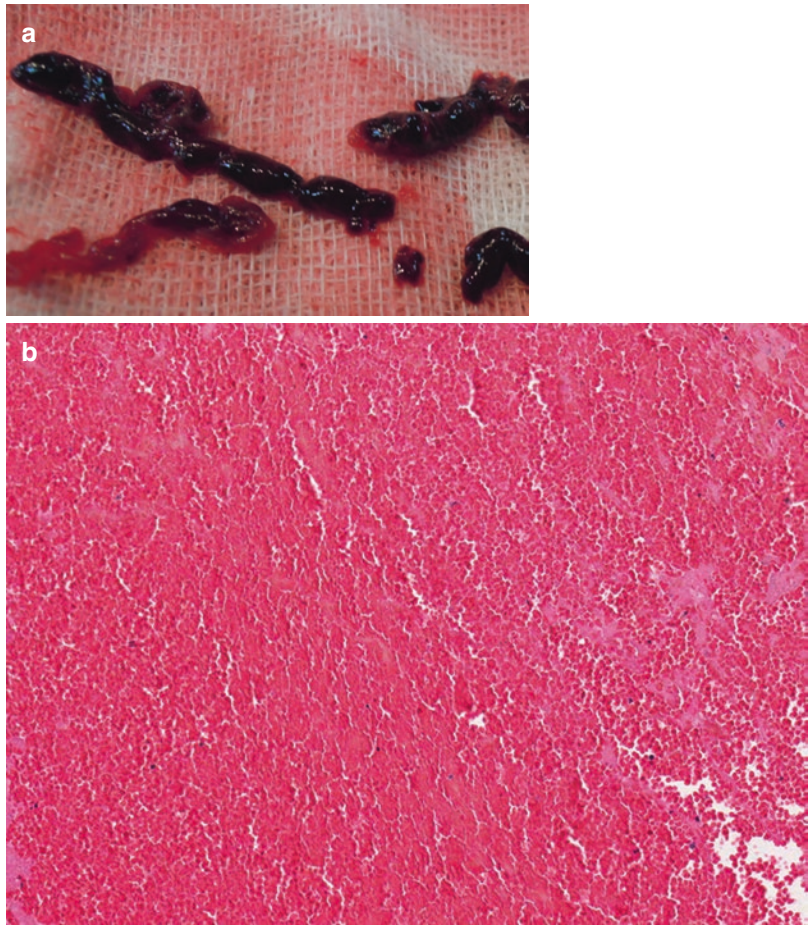


Fig. 4.1 (**a**) Photograph shows multiple fragmented clots having a typical appearance of *red clots* retrieved from a patient with acute ischemic stroke. (**b**) Microscopic view of a retrieved clot shows that most parts of clot consist of red blood cells in a hematoxylin-eosin stained section (×400 magnification)

underlying intracranial atherosclerotic stenosis usually consist of a fibrin network superimposed on the underlying platelet aggregates.

In vitro experimental studies support the traditional classification of clot types. For example, Duffy et al. showed that clots formed under static condition (e.g., cardiogenic thrombi) are replete with RBCs with a low fibrin composition, whereas clots formed under flow conditions are fibrin-rich [5]. Under static conditions (stationary coagulation of whole blood), the mean % areas in the resulting clots were 91% RBCs, 8% fibrin, and 0.98% white blood cells (WBCs). In contrast, under flow conditions mimicking the carotid blood flow rates (approximately 240 mL/min), the mean % areas in the resulting clots were 18% RBCs, 79% fibrin, and 2.7% WBCs [5].

4.2 Histologic Analysis of Retrieved Clots

A mechanical thrombectomy is currently the first-line endovascular therapy for patients with acute large-vessel occlusions [1]. Recent studies have shown that a mechanical thrombectomy using a retrievable stent or flexible aspiration catheter is associated with a high recanalization

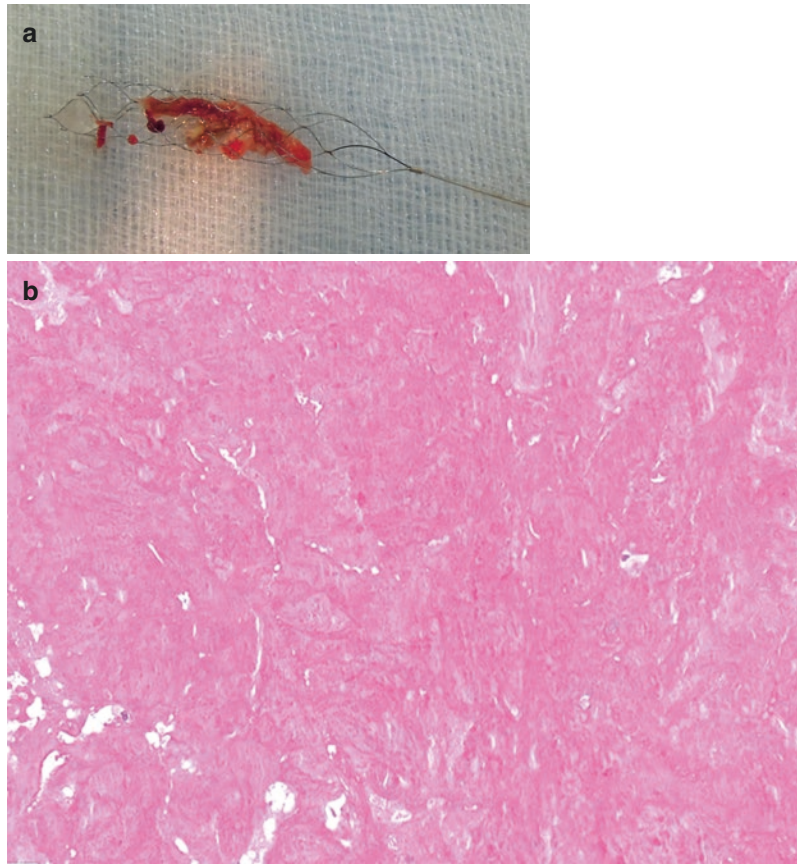
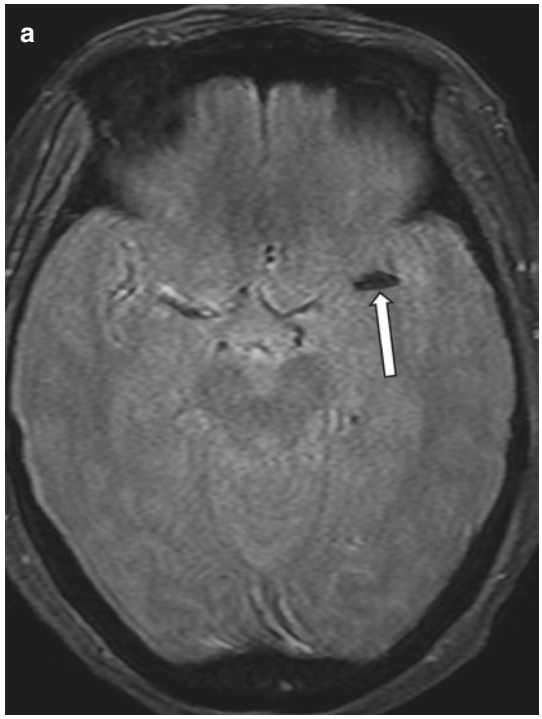


Fig. 4.2 (**a**) Photograph shows *white clots* retrieved with a stent retriever from a patient with acute ischemic stroke and underlying intracranial atherosclerotic stenosis. (**b**) Microscopic view of a retrieved clot shows that most parts of clot consist of fibrin seen as distinctly *pink* in a hematoxylin-eosin stained section (×400 magnification)

rate and low complication rate [2, 3]. Furthermore, the use of a mechanical thrombectomy for acute stroke treatment facilitates the histopathologic examination of clots retrieved from intracranial arteries, providing new insights into the pathogenesis of acute stroke due to an intracranial large-vessel occlusion, along with an understanding of the pathologic basis of early vessel signs on imaging studies in patients with acute ischemic stroke.

Previous studies have demonstrated that the histologic composition of clots retrieved from patients with acute ischemic stroke is typically RBC-dominant (Fig. 4.3), fibrin-dominant (Fig. 4.4), or mixed [6–9]. Liebeskind et al. conducted a histopathologic analysis of clots retrieved from 50 patients with acute anterior circulation stroke and reported that 44% of the clots were fibrin-dominant, 26% were RBC-dominant, and 30% were mixed [8]. Meanwhile, Boeckh-Behrens et al. analyzed clots retrieved from 34 patients with acute anterior circulation stroke and reported that 50% of the clots were fibrin-dominant (>60% of fibrin), 12% were RBC-dominant (>60% of RBC), and 38% were mixed [9]. To date, the histopathologic studies of retrieved clots have mainly focused on the following: (1) the relationship between the histologic composition of clots and the stroke etiology and (2) the relationship between the histologic composition of clots and the imaging characteristics.



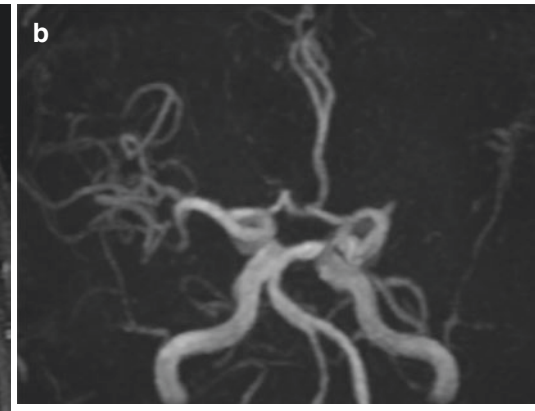


Fig. 4.3 Brain images from an 86-year-old woman with acute MCA occlusion and atrial fibrillation. (**a**) Axial gradient-echo MR image reveals a positive susceptibility vessel sign (*arrow*) in the M1 segment of the left MCA. (**b**) 3D TOF MR angiography shows the occlusion in the proximal M1 segment of the left MCA. (**c**) Microscopic view of a retrieved clot shows that most of the thrombi consist of red blood cells in a hematoxylin-eosin stained section (×100 magnification). (**d**) CD 61 immunostained section shows small areas of platelet infiltration (*brown*) in the periphery of the clot (×100 magnification)

4.3 Clot Compositions and Stroke Etiology

A clot composition analysis can potentially reveal important information regarding the stroke etiology, helping physicians to make a strategy for secondary stroke prevention. However, it remains unclear whether clot composition analysis can be used to predict a stroke mechanism in the case of an acute large-vessel occlusion. As yet, only a few studies have focused on this topic and yielded vague and contradictory results due to differences in the histologic staining methods, quantification methods, and component assignment [6–9].

Kim et al. suggested that the histologic composition of clots retrieved from cerebral arteries in the case of acute anterior circulation stroke differed between patients with a cardioembolism and patients with large-artery atherosclerosis [6]. In a semiquantitative proportion analysis to quantify the RBC, fibrin, platelets, and WBC by area after staining, the clot tissue with hematoxylin-eosin and antibodies for platelet glycoprotein IIIa, CD 61, the RBC, and fibrin percentages differed significantly between the patients with a cardioembolism and the patients with large-artery atherosclerosis, where the former had a significantly higher proportion of RBCs and lower proportion of fibrin than the latter (Figs. 4.3 and 4.4). No significant differences were found in the proportions of platelets and WBCs between the patients with a cardioembolism and the patients

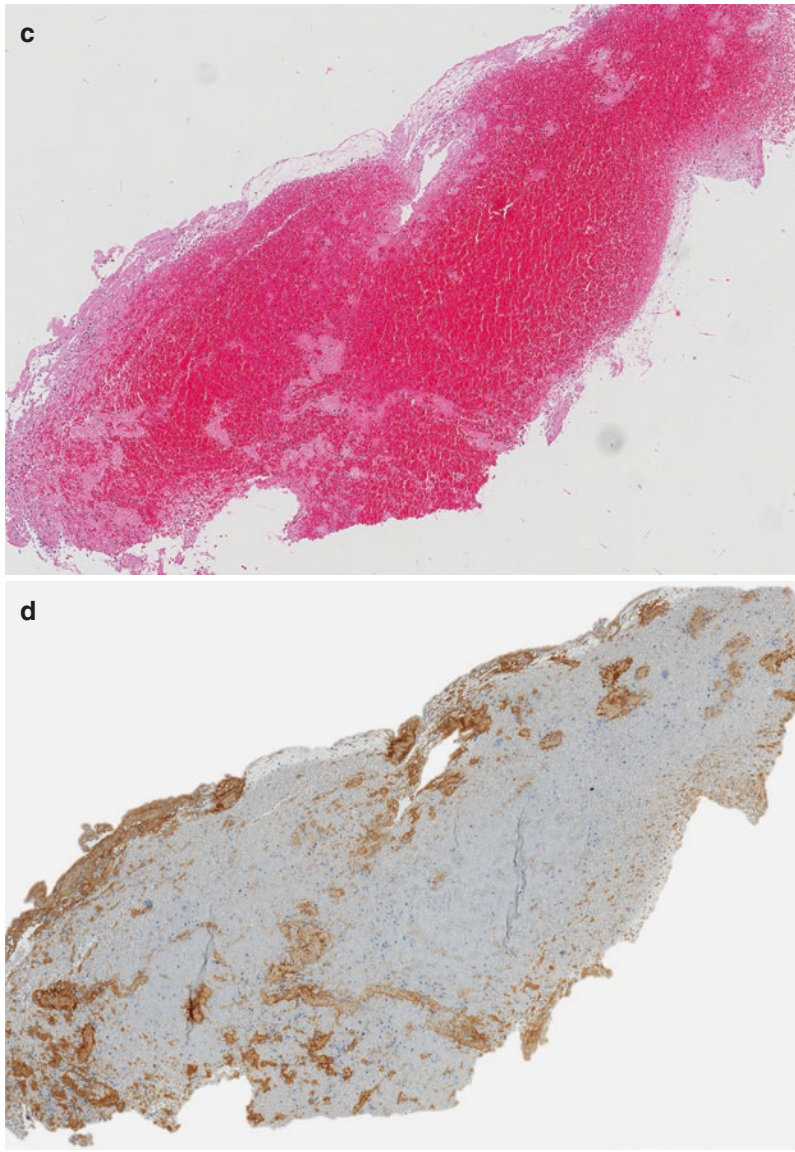
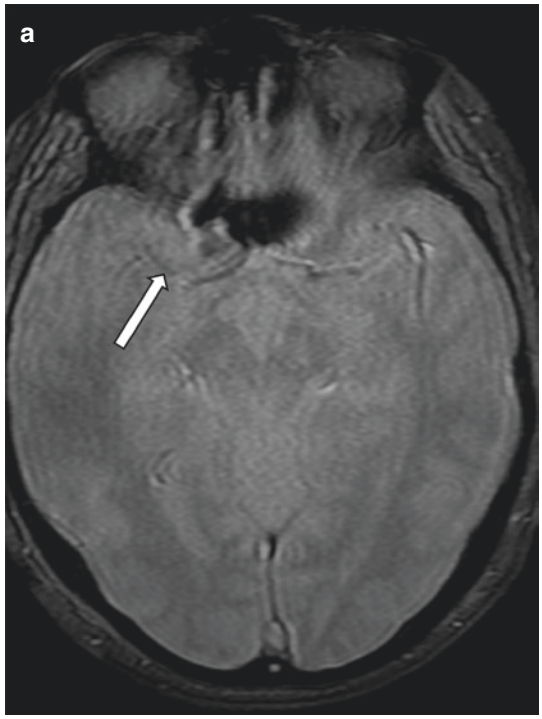


Fig. 4.3 (continued)

with large-artery atherosclerosis. Thus, Kim's study supports the concept that, in an acute ischemic stroke setting, cardioembolic thrombi forming in regions of blood stasis or slow flow are mainly composed of entrapped RBCs while thrombi occurring in the context of atherosclerotic large arteries are mainly composed of fibrin and platelets. Kim's findings also match the results of a postmortem study by Sato et al., which examined the cerebral arteries and thrombi of 17 patients who died of cardioembolic (n = 11) and large-artery atherosclerotic (n = 6) strokes within 30 days of stroke onset [10]. Similarly, Sato el al. found that the ratio and total area of RBCs were significantly larger in the cardioembolic thrombi than in the large-artery atherosclerotic thrombi, while the ratio of fibrin was threefold higher in the large-artery



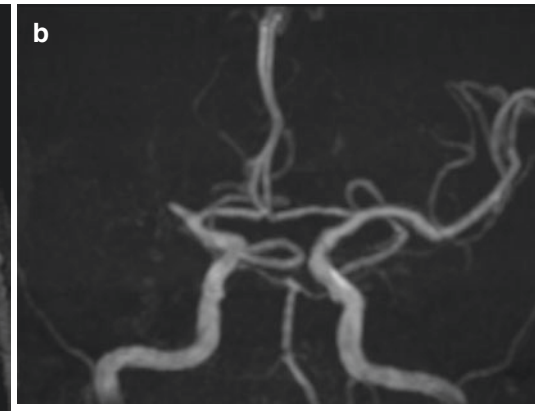
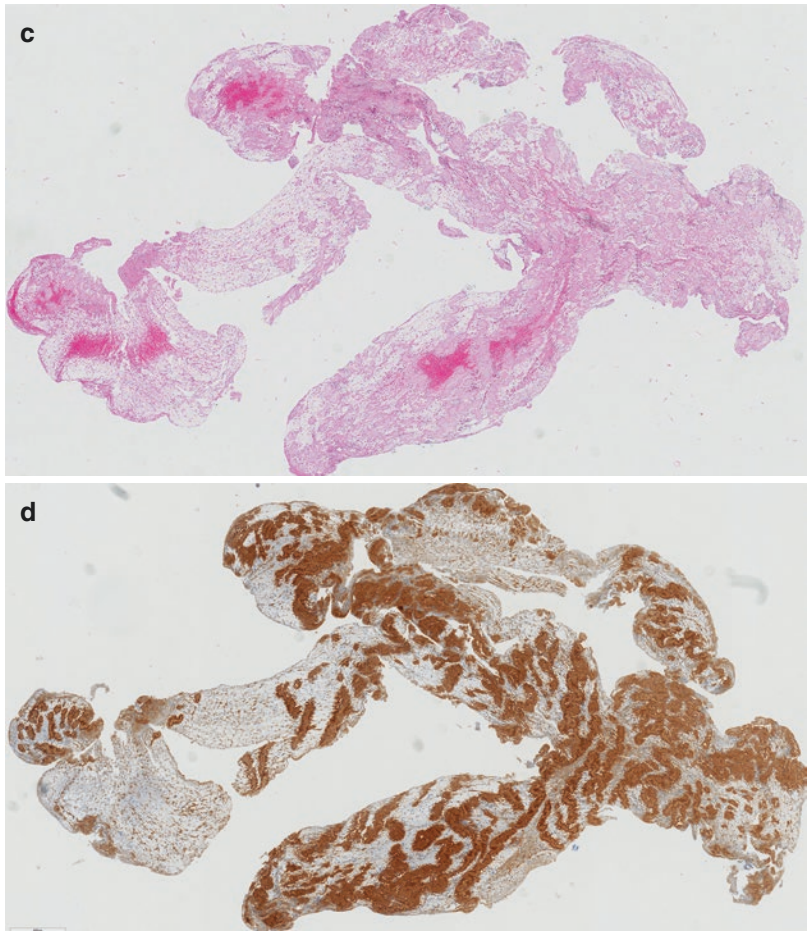


Fig. 4.4 Brain images from a 74-year-old man with acute MCA occlusion and underlying intracranial atherosclerotic stenosis. (**a**) Axial gradient-echo MR image reveals a negative susceptibility vessel sign (*arrow*) in the M1 segment of the right MCA. (**b**) 3D TOF MR angiography shows the occlusion in the proximal M1 segment of the right MCA. (**c**) Microscopic view of a retrieved clot shows that most of the thrombi consist of organized fibrin aggregates with sparse cellular elements in a hematoxylin-eosin stained section (×100 magnification). (**d**) CD 61 immunostained section shows abundant infiltrations of platelets (*brown*) in the central and peripheral portion of the clot (×100 magnification)

atherosclerotic thrombi than in the cardioembolic thrombi [10].

Liebeskind et al. performed a histopathologic analysis of clots retrieved from 50 patients with acute ischemic stroke who had undergone an endovascular thrombectomy and reported that the clot composition was unrelated to the stroke etiology; however, no detailed data was provided [8]. When Niesten et al. investigated 22 thrombi retrieved using a mechanical thrombectomy from patients with acute ischemic stroke, in contrast to Kim's study, they reported that clots originating from large-artery atherosclerosis had the highest percentage of RBCs compared with other stroke subtypes and no significant differences in the proportion of fibrin and platelets between the different stroke subtypes [7]. The major limitation of their study was a small patient population: large-artery atherosclerosis (n = 8) and cardioembolism (n = 6). Boeckh-Behrens et al. investigated the histopathology of clots retrieved from 34 patients with acute anterior circulation stroke and reported a significantly higher proportion of WBCs in the cardioembolic thrombi when compared with the other stroke subtypes [9]. No detailed data was provided regarding the proportions of RBCs and fibrin between the different stroke subtypes [9].

Brinjikji et al. recently conducted a systematic review and meta-analysis of research on the histologic characteristics of clots in the case of acute ischemic stroke [11]. Based on four studies with extractable data, they found no significant difference in the proportion of RBC-rich thrombi between the cardioembolic and large-



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artery atherosclerotic etiologies (OR 1.62, 95% confidence interval 0.1–28.0, $P = 0.63$). The mean RBC composition was 39.3% for cardioembolic strokes and 29.5% for large-artery atherosclerosis (mean squared deviation [MSD] 9.8, 95% CI −15.9 to 35.5, $P = 0.45$). The mean fibrin composition was 28.4% for cardioembolic strokes and 40.0% for large-artery atherosclerosis (MSD −11.6, 95% CI −41.8 to 18.7, $P = 0.46$). The I^2 values were >50% for all outcomes, indicating substantial heterogeneity. Accordingly, they concluded that the current characteristics of clots, as determined by conventional histologic staining techniques (i.e., H&E), do not reveal any meaningful information on stroke etiology, and further research examining cell subtypes using immunohistochemical staining methods is needed to explore the association between stroke etiology and clot compositions [11].

4.4 Clot Compositions and Imaging Characteristics

A histopathologic analysis of retrieved clots has been found to facilitate an understanding of the pathologic basis of early vessel signs in imaging studies of patients with acute ischemic stroke. Several studies have shown that a hyperattenuated vessel sign on a CT and susceptibility vessel sign on gradient-echo (GRE) MR

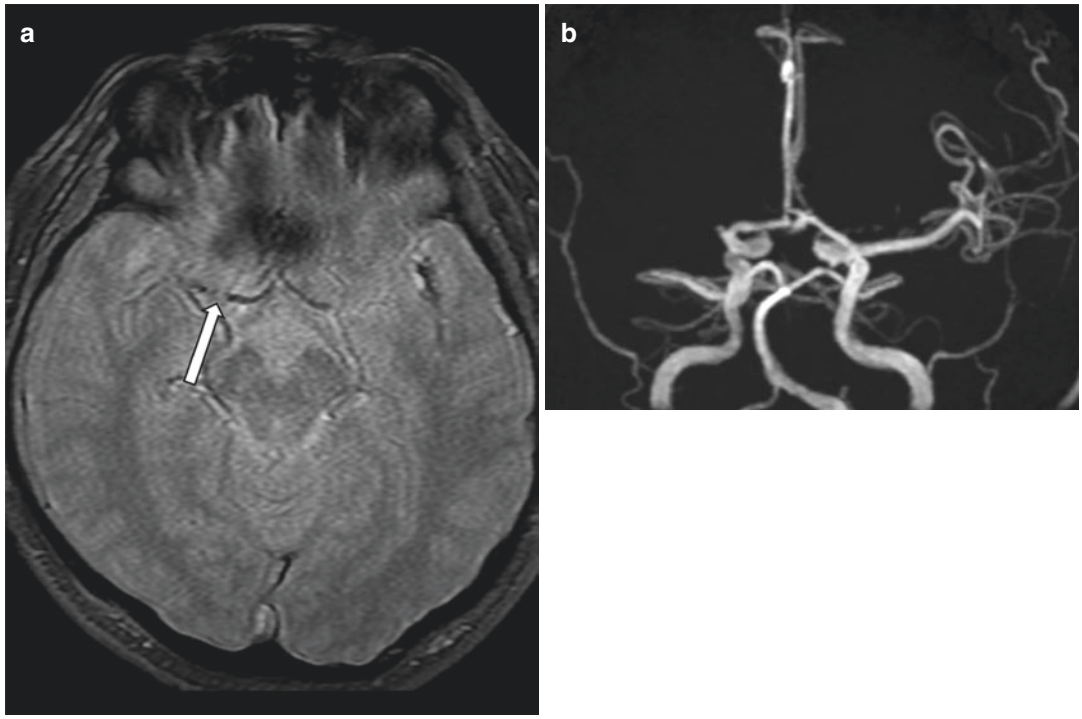
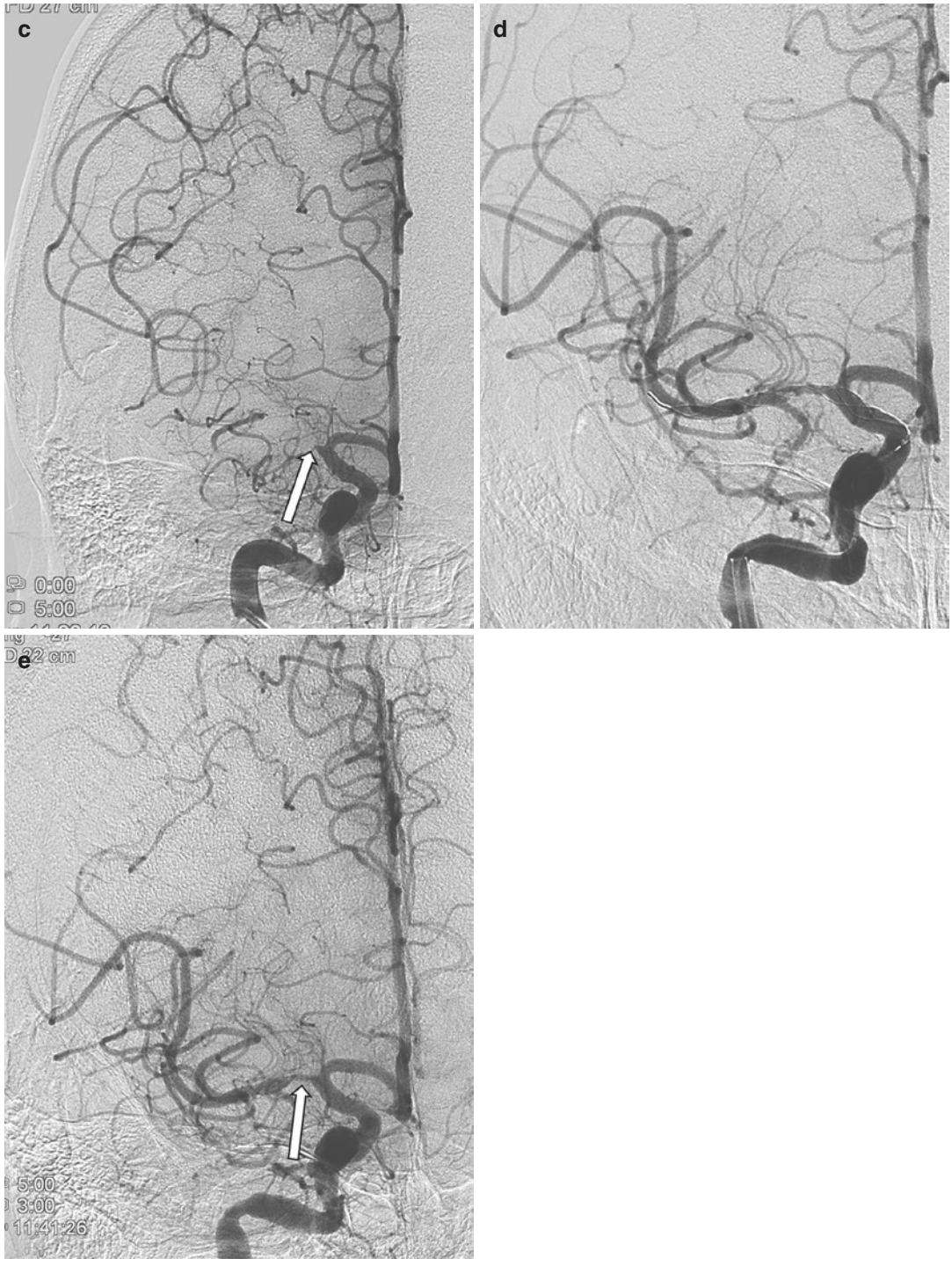


Fig. 4.5 Brain images from a 30-year-old man with acute MCA occlusion and underlying intracranial atherosclerotic stenosis. (**a**) Axial gradient-echo MR image reveals a negative susceptibility vessel sign (*arrow*) in the M1 segment of the right MCA. (**c**) Conventional angiography shows the occlusion (*arrow*) in the M1 segment of the right MCA. (**d**) Conventional angiography obtained after placement of a stent retriever across the occluded segment shows restoration of blood flow in the right MCA territory. (**e**) Angiography after passage of a stent retriever reveals severe underlying intracranial stenosis (*arrow*) in the proximal M1 segment of the right MCA. No visible thrombi were retrieved with a stent retriever

imaging are invariably associated with RBC-rich red clots rather than fibrin-rich white clots (Fig. 4.3) [6–9, 12]. Paramagnetic intracellular deoxyhemoglobin in acute clots leads to a non-uniform magnetic field and resultant rapid dephasing of spins, which causes a marked signal loss on GRE MR imaging, that is, a susceptibility vessel sign [6]. A meta-analysis of three articles showed an association between a hyperattenuated vessel sign on a CT and RBC-rich clots, meaning that patients with a hyperattenuated vessel sign are more likely to have an RBC-rich clot than patients without a hyperattenuated vessel sign (OR 9.0, 95% CI 2.6–31.2, $P < 0.01$) [11].

Meanwhile, Kim et al. showed a clear relationship between the clot composition and early vessel signs on MR imaging. Based on 37 patients with an acute MCA occlusion, the percentages of RBCs, fibrin, platelets, and WBCs were compared between patients with a positive and negative susceptibility vessel sign on GRE imaging [6]. The mean percentage of RBCs was significantly higher in the clots with a positive susceptibility vessel sign than the clots with a negative susceptibility vessel sign, whereas the percentage of fibrin was significantly higher in the clots with a negative susceptibility vessel sign than in the clots with a positive susceptibility vessel sign. Moreover, the proportion of platelets was significantly higher in the clots with a negative susceptibility vessel sign than in the clots with a positive susceptibility vessel sign.

Similarly, Liebeskind et al. correlated a susceptibility vessel sign on GRE MR imaging and the composition of clots retrieved from 32 patients



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with acute MCA stroke [8]. They found that a susceptibility vessel sign was more common in the case of RBC-dominant and mixed clots when compared with fibrin-dominant clots, plus the mean percentage of RBCs was greater in clots with a susceptibility vessel sign than in clots without a susceptibility vessel sign. Niesten et al. also performed CD 31 immunostaining to investigate the platelet composition in retrieved clots and correlated the clot composition with attenuation on a noncontrast CT [7]. In this case, a nonsignificant, weak negative correlation was found between CT attenuation and the proportion of platelets.

More recently, Kim et al. proposed that a negative susceptibility vessel sign, defined as an absence of a hypointense signal change within the occluded artery on GRE MR imaging, is a sensitive marker with a high negative predictive value for the presence of underlying intracranial atherosclerotic stenosis in patients with acute ischemic stroke due to MCA occlusion (Fig. 4.5) [13]. Essentially, fibrin-dominant clots formed at the site of underlying intracranial stenosis should not appear as a hypointense vessel on GRE MRI due to the lack of deoxyhemoglobin. Thus, all the cases with underlying intracranial stenosis in the occluded MCA exhibited a negative susceptibility vessel sign on the gradient-echo MRI.

4.5 Summary and Recommendations

A mechanical thrombectomy facilitates a histopathologic examination of clots retrieved from intracranial arteries, which may provide new insights on the mechanisms involved in the thromboembolic occlusion of intracranial arteries. Several studies have already established a clear relationship between clot compositions and early vessel signs on CT or MR imaging, where a hyperattenuated vessel sign on a CT and susceptibility vessel sign on GRE MR imaging are more often associated with RBC-rich red clots than fibrin-rich white clots. However, the currently known characteristics of clots as determined by conventional H&E staining techniques have not yet provided solid evidence of an association between clot compositions and stroke etiology [11]. Thus, further research including histologic examination using immunohistochemical staining methods is needed to explore the association between stroke etiology and clot compositions [14].

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Part 2

Medical Practices

5 General Management and Intensive Care in Acute Ischemic Stroke

Yang-Ha Hwang and Yong-Won Kim

Reperfusion of the occluded artery by administration of thrombolytics and/or endovascular therapy and stroke unit care is widely considered the only effective approach for improving the outcome of stroke. However, successful reperfusion can only be established in a few cases of acute ischemic stroke; therefore, developing efficient strategies for the management of patients not eligible for reperfusion is important to decrease complications and improve the clinical outcome. In this chapter, we focus on the practical measures for preventing medical and neurological complications in cases of acute management of ischemic stroke and improving the neurological outcome.

5.1 General Supportive Care

General management of acute ischemic stroke pertains to the maintenance of the following parameters: (1) airway patency, (2) patient position, (3) body temperature, (4) cardiac activity, (5) intravenous fluid distribution, (6) blood pressure level, and (7) blood glucose level.

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5.1.1 Airway Management and Oxygen Supply

Ischemic stroke is a neurovascular event that results in localized primary failure of tissue oxygenation and energy supply. Constantly monitoring of stroke patients is necessary to detect oxygen desaturation or respiratory compromise. Further, patients with decreased consciousness or brainstem dysfunction are at increased risk of airway compromise because of impaired oropharyngeal mobility and loss of protective reflexes [1]. Therefore, airway support and ventilatory assistance are recommended for the treatment of acute stroke patients with decreased consciousness or airway compromise with bulbar dysfunction [2]. Generally, 2–4 L/min administered via the nasal tube is sufficient, but mask ventilation may be necessary to provide oxygen supply required to maintain oxygen saturation at >94 % [2].

If intubation is indicated, it should be planned beforehand and performed by an experienced physician because the risk of cerebral blood flow reduction during the procedure is high. Such a reduction, in turn, can trigger unwanted autonomic reflexes and blood pressure changes, thereby precipitating intracranial shifts or bleeding.

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5.1.2 Patient Position

The lying position of the stroke patient can influence oxygen saturation, cerebral perfusion pressure, and intracranial pressure (ICP). However, the ideal position of a stroke patient to optimize these parameters is unknown. In patients who can maintain oxygen saturation when supine, the position may promote cerebral perfusion [3]. Patients at risk for airway obstruction or aspiration and those with suspected elevated ICP should lie with the head of the bed elevated at 15–30° [2].

5.1.3 Body Temperature

Approximately one-third of patients admitted with stroke may be hyperthermic (body temperature >37.6 °C) within the first few hours of stroke onset [4]. Hyperthermia may be a marker of stroke severity, may reflect infectious complications, or may be an independent prognostic factor adversely affecting morbidity and mortality. A landmark study by Reith et al. showed that body temperature at admission is highly correlated with initial stroke severity and infarct size as well as with poor outcome and mortality [5]. In addition, they found that the relative risk of poor outcome increased by a factor of 2.2 for each 1 °C increase in body temperature and that this relationship was independent of stroke severity. They also reported that the presence of infection was not an independent predictor of poor outcome.

Because of the negative effects of hyperthermia, maintenance of normothermia or lowering of an acutely elevated body temperature is believed to improve the prognosis of stroke patients. A large-scale, randomized, double-blind, placebo-controlled trial comprising 2500 subjects was conducted to determine whether early treatment with acetaminophen improved functional outcome by reducing body temperature. The study showed that fever prevention did not result in any statistically difference between the groups with and without fever pretreatment; however, the trial was terminated prematurely (after 1400 patients) because of lack of funding [6]. Post hoc analysis revealed a beneficial effect in patients with a baseline body temperature of 37–39 °C. Therefore, it is imperative that the sources of hyperthermia (body temperature >38 °C) are identified and treated and antipyretic medications administered to lower the body temperature in hyperthermic stroke patients [2].

In cases of acute ischemic stroke, hyperthermia is associated with poor neurological outcome, possibly secondary to increased metabolic demands, enhanced neurotransmitter release, and increased free radical production.

5.1.4 Cardiac Monitoring

Cardiac arrhythmias and myocardial ischemic secondary to stroke are common. Electrocardiography (ECG) should be performed in every stroke patient, followed by continuous ECG monitoring. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias likely to necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 h of admission [2].

5.1.5 Intravenous Fluid Management

On admission, patients presenting with acute ischemic stroke may have hypovolemia to some extent, which has been associated with a less favorable outcome [7]. Hypovolemia may predispose patients to hypoperfusion, exacerbate the ischemic brain injury, cause renal impairment, and potentiate thrombosis. For stroke patients who are hypovolemic at presentation, it is reasonable to initiate rapid replacement of the depleted intravascular volume followed by maintenance intravenous fluids. Without unusual losses, daily fluid maintenance for adults is estimated to be 30 mL per kilogram of body weight [2]. A substantial proportion of hypotonic solutions, such as 5 % dextrose or 0.45 % saline, is distributed into the intracellular spaces, which may exacerbate ischemic brain edema. On the other hand,

isotonic solutions such as 0.9 % saline are more evenly distributed into the extracellular spaces (interstitial and intravascular) and may be better for patients with acute ischemic stroke than hypotonic solutions.

5.1.6 Blood Pressure and Arterial Hypertension

Blood pressure is a dynamic and simple physiologic parameter that can fluctuate significantly in the acute period of ischemic stroke and may affect the clinical outcome. The blood pressure is typically maximal at admission but decreases spontaneously thereafter, during the natural course of stroke [8, 9]. Extreme arterial hypertension is clearly detrimental because it can lead to encephalopathy, cardiac complications, and renal insufficiency. Theoretically, moderate arterial hypertension during acute ischemic stroke might actually help improve cerebral perfusion of the ischemic tissue. Thus, it may be possible to define an arterial blood pressure range as optimal during acute ischemic stroke in any given case, depending on the stroke subtype and other patient-specific comorbidities. Unfortunately, such an ideal blood pressure range has not yet been clearly determined.

A U-shaped relationship has been reported between outcomes and the admission blood pressure in the acute setting, with the optimal systolic blood pressure ranging from 121 to 200 mmHg and diastolic blood pressure ranging from 81 to 110 mmHg [10, 11]. However, a more recent study found no J- or U-shaped relationship; instead, the study revealed that a high blood pressure was associated with a low probability of good neurologic recovery during hospitalization, a high risk of neurologic deterioration during hospitalization, and poor functional outcome at 3 months [12].

According to the current guidelines, blood pressure greater than 220 mmHg systolic and 120 mmHg diastolic should be treated actively even on admission [2]. The decision to treat blood pressure also depends on factors such as previous blood pressure level as well as on the use of anticoagulants or thrombolytic therapy, during and after which blood pressure should not exceed 180/105 mmHg. Currently, there is a dearth of specific set of recommendations on managing blood pressure in the setting of expansive infarct edema with or without increased intracranial pressure.

5.1.7 Blood Glucose and Hyperglycemia

Hyperglycemia is common during the acute phase of ischemic stroke. Some studies have shown that hyperglycemia on admission is noted in a substantial proportion (up to 40 %) of patients with acute ischemic stroke and that it entails a poorer clinical outcome than normoglycemia [13]. Hyperglycemia may sometimes reflect preexisting but unrecognized diabetes, but mostly, it occurs as part of acute stress response or "stress hyperglycemia." Thus, high levels of glucose on admission do not allow for the distinction between stress hyperglycemia and diabetes. Under these conditions, elevated levels of HbA1c (≥6.5 %) are indicative of the presence of previously undiagnosed diabetes [14, 15].

Hyperglycemia has some deleterious effects that can increase the infarct size and cause hemorrhagic transformation (Fig. 5.1). The unadjusted relative risk of in-hospital or 30-day mortality among patients admitted after an ischemic stroke is 3.3 (95 % CI, 2.3–4.7) for those with hyperglycemia at admission but no history of diabetes and 2.0 (95 % CI, 0.04–90.1) for those with a known history of diabetes, as compared to those normoglycemic at admission [16]. This strong and consistent association between admission hyperglycemia and poor prognosis after ischemic stroke in nondiabetic patients suggests that blood glucose level is an important risk factor for morbidity and mortality after stroke.

The observed relation between hyperglycemia and poor outcome in patients with ischemic stroke raises the question of whether the outcome can be improved by glucose-lowering treatment. However, improvement in the clinical

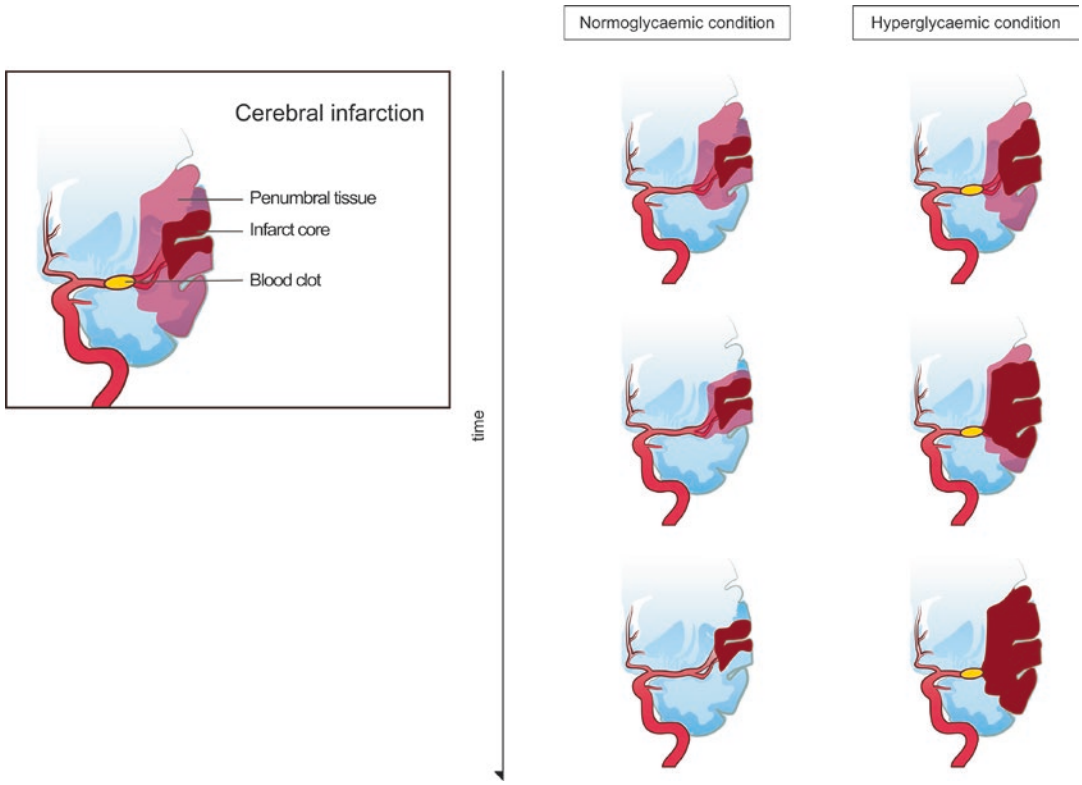

Fig. 5.1 Potential effects of hyperglycemia over time on pathophysiological processes involved in development of cerebral ischemia

outcome by administration of glucose-lowering treatment in patients with acute ischemic stroke has not yet been clinically demonstrated. Findings of randomized controlled trials specifically targeting individuals with stroke have failed to show beneficial effects of anti-hyperglycemic treatment. In a meta-analysis of 1,583 patients with acute ischemic stroke from 11 trials, intensively monitored intravenous insulin treatment (aimed at maintenance of glucose concentrations between 72 and 136 mg/dL) was compared with usual care [17]. No intergroup difference was noted in the outcome (odds ratio 1.0, 95 % CI 0.8–1.2), but the risk of symptomatic hypoglycemia was significantly higher in the group treated with insulin (odds ratio 14.6, 95 % CI 6.6–32.2). Currently, there is no clinical evidence that restricting blood glucose level at a particular level during the acute phase of ischemic stroke improves the clinical outcome. The main risk from aggressive hyperglycemia correction in acute stroke appears to be hypoglycemia. Considering this, it may be reasonable to maintain blood glucose in the range of 140–180 mg/dL in all hospitalized patients [2].

5.2 Antithrombotic Therapy in Acute Ischemic Stroke

Aspirin is the most extensively tested antiplatelet agent. The combined results of two large, randomized, unblended intervention studies indicate that aspirin administered within 48 h of stroke onset reduces the risk of recurrence (7 per 1000 patients treated) and death without further stroke (4 per 1000 patients treated) [18–20]. However, it remains to be determined whether aspirin limits the adverse neurological consequences of stroke itself.

Evidences on the use of clopidogrel or dipyridamole in acute stroke are limited. Recently, Wang and colleagues reported the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial [21]. Among 5170 Chinese patients with acute minor ischemic stroke or transient ischemic attack (onset within the previous 24 h) at high risk of recurrence, the addition of clopidogrel to aspirin reduced the relative risk of recurrent stroke at 90 days by 32 %. However, it is unclear whether clopidogrel facilitates early neurological recovery.

Current literature indicates a small but statistically significant decline in mortality and unfavorable outcomes with the administration of aspirin within 48 h of stroke. The primary effects of aspirin may be attributable to a reduction in early recurrent stroke. Data regarding the utility of other antiplatelet agents, including clopidogrel, with or without aspirin, in acute ischemic stroke are limited.

5.3 Intensive Care

Considerable advances have been made in the management of acute ischemic stroke, including extended time window for intravenous recombinant tissue-type plasminogen activator (rt-PA), development of endovascular devices, and aggressive therapies such as hypothermia induction and craniectomy.

These advances have been paralleled by an increase in the number of ischemic stroke patients requiring intensive care management. Intensive management is generally required for patients receiving intravenous rtPA therapy or endovascular reperfusion therapy and those with large hemispheric or cerebellar infarction, hemorrhagic complications, loss of consciousness, or respiratory compromise. Intensive care is mainly important for neurological monitoring as well as early recognition and management of complications for minimization of secondary neurological injury. Neurointensive care is reported to reduce the duration of hospitalization and improve the outcome at discharge [22].

5.3.1 ICP Monitoring

The main complications of acute ischemic stroke are ischemic brain edema and intracranial hemorrhage (ICH). Symptomatic ICH occurs in 3.6–7.7 % of the patients receiving intravenous or intra-arterial thrombolytic therapy and anticoagulation therapy [2, 23–27]. Massive cerebral infarction is associated with cytotoxic or vasogenic brain edema and ICH, which can in turn increase ICP. Increased ICP can reduce cerebral perfusion, cause tissue hypoxia, and finally lead to brain herniation [28].

Increased ICP can be recognized by serial changes in neurological symptoms, including pupillary dilatation, loss of brainstem reflex, and change in breathing patterns. However, the appearance of these symptoms may indicate that it may be too late for the effective management of ICP. Therefore, AHA/ASA guidelines recommend early monitoring of patients with high risk of brain edema [2]. Establishment of a ventricular drain with an external pressure gauge is the current gold standard for ICP monitoring [29]. This drainage system provides information about ICP as well as intracranial compliance and can be used to control ICP through cerebrospinal fluid drainage. This measurement represents the global ICP. In cases of acute ischemic stroke, focal measurement of ICP may accurately reflect the pressure changes caused by compartmentalization [30]. Intraparenchymal monitoring devices are effective for focal ICP measurement and easier to apply than intraventricular devices. However, these monitoring techniques are invasive and entail a risk of complications, including infection, hemorrhage, and technical problems.

Since most patients are not in a sedated state, it is necessary to develop noninvasive methods of ICP monitoring. One such method is fundoscopy to detect papilledema. However, papilledema develops only several hours after increase in ICP, and absence of papilledema cannot rule out elevated ICP. Ocular ultrasonography has been studied for the assessment of ICP. The diameter of the optic nerve sheath can be determined by measurement of the width measured at a distance behind the optic disc via ocular sonography

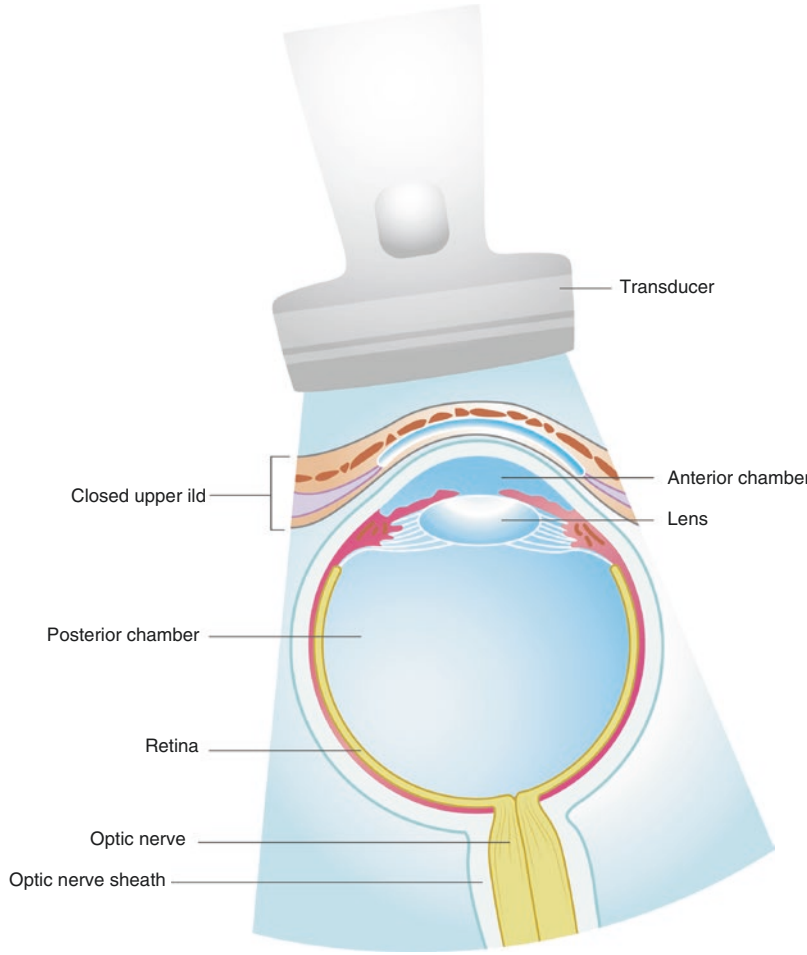

Fig. 5.2 Ocular sonography for measurement of optic nerve sheath diameter

(Fig. 5.2) [31]. The optic nerve sheath is enlarged when ICP is greater than 15 mmHg and is an easily measured sign of raised ICP [31–33].

Transcranial Doppler (TCD) is also used for ICP monitoring. TCD can provide continuous hemodynamic information about blood flow velocity, pulsatility index (PI), and waveforms of major intracranial arteries. ICP and PI are reported to show a positive correlation in patients with brain injury [34, 35]. However, ICP prediction based on PI should be done with caution because of many possible confounding factors such as arterial stenosis, spasm, arterial pulse, and heart rate [35].

The normal ICP ranges from 5 to 15 mmHg. In general, ICP above 20 mmHg should be actively treated. Cerebral perfusion pressure is measured as the difference between meal arterial pressure and ICP. Because many patients with acute ischemic stroke require blood pressure management, it is necessary to account for both ICP and CPP during ICP monitoring. Before reducing ICP, maintaining the CPP is also important. Maintaining CPP over 60 mmHg is reported to prevent secondary brain injury [36].

5.3.2 Therapeutic Hypothermia

Therapeutic hypothermia is reported to exert a neuroprotective effect and facilitate ICP con-

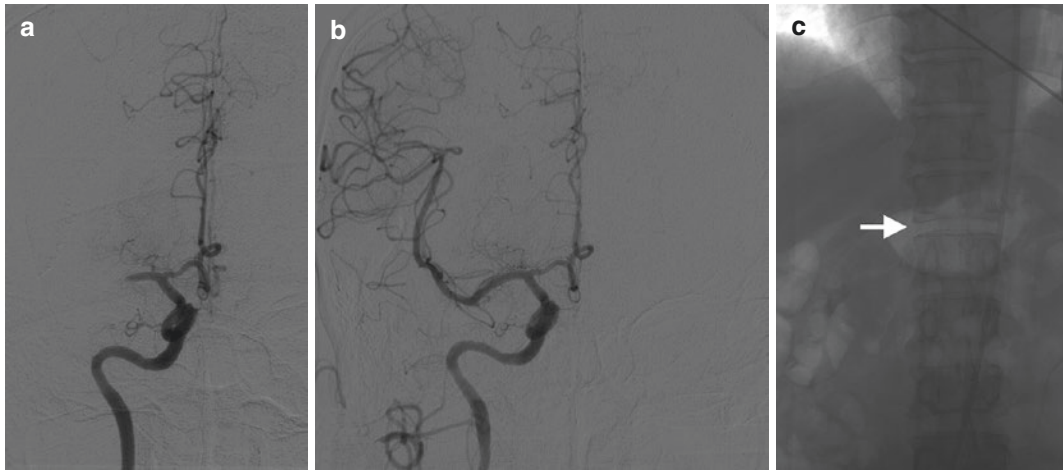

Fig. 5.3 Immediate post-reperfusion cooling. (**a**) Baseline angiography shows right MCA occlusion. (**b**) Final angiography reveals complete recanalization. (**c**) Endovascular cooling catheter (*white arrow*) is inserted in the inferior vena cava

trol in various conditions such as hypoxia, stroke, and traumatic brain injury. The underlying neuroprotective mechanism is believed to involve a reduction in cerebral metabolism, oxygen consumption, glucose metabolism, neuroinflammation, free radical production, and cell death [37]. Various neuroprotective measures have been proposed in cerebral ischemia [38]. In addition, reduction of cerebral blood volume, vasogenic edema, and blood–brain barrier disruption have been identified to be effective in ICP control [37]. Studies have demonstrated improvement of neurological outcome and decrease of mortality achieved by indication of therapeutic hypothermia after cardiac arrest [39, 40]. In experimental studies of stroke, initiation of therapeutic hypothermia early after from stroke onset revealed decrease in infarction volume and improvement in the functional outcome. Small pilot studies have been undertaken in stroke patients, which suggest the potential benefits of therapeutic hypothermia in terms of neurological outcome and mortality.

The optimal time for the initiation of hypothermia induction has not yet been clearly established. However, early initiation of hypothermia has been shown to produce a neuroprotective effect in animal models. Recent human studies on the induction of hypothermia immediately after reperfusion therapy have also shown an improvement in the clinical outcome [41] (Fig. 5.3). Most clinical studies on hypothermia for acute ischemic stroke have mainly focused on mild hypothermia (core temperature of 32–35 °C) and cooling duration of 5–72 h [41–45]. The cooling duration differs with the purpose of hypothermia induction. Studies based on edema control pertain to the maintenance of hypothermia for a longer duration (34–72 h) [42, 46].

The rewarming process should also be executed with caution due to the risk of rebound cerebral edema, increased ICP, and rebound hyperthermia. Gradual rewarming, generally at the rate of 0.1–0.25 °C/h, is important to prevent such complications. Recent studies pertaining to the effectiveness of therapeutic hypothermia for ischemic stroke are summarized in Table 5.1.

The commonly used cooling methods are surface cooling and endovascular cooling. Surface cooling systems consist of cooling blankets or surface pads and offer the advantages of easy application, rapid initiation, and relatively low rate of complications. However, the disadvantages of this method are frequent shivering, skin irritation, and difficulty in maintaining

Table 5.1 Recent studies of therapeutic hypothermia for ischemic stroke

Studies	Cases	Patients	Target temperature	Cooling method	Cooling duration	Clinical outcomes	Notable feature
Martin-Schild et al. [49]	20	Cortical ischemic stroke	33–34.5 °C	Surface or endovascular	24 h	50 % of discharge mRS 0–2	Hypothermia with caffeinol
Hemmen et al. [50]	28	Acute ischemic stroke	33 °C	Endovascular	24 h	17.9 % of mRS 0–1 at 3 months	No differences between hypothermia and normothermia
Ovesen et al. [51]	17	Acute ischemic stroke	33 °C	Surface or Endovascular	24 h	Median mRS 3 at 3 months	Feasibility of hypothermia
Hong et al. [45]	39	Anterior circulation	34.5 °C	Surface or Endovascular	48 h	48.7 % of mRS 0–2 at 3 months	Cooling after recanalization
Piironen et al. [52]	18	Acute ischemic stroke	34.5 °C	Surface	23 h (median)	38.9 % of mRS 0–2 at 3 months	Cooling after iv-rtPA
Hwang et al. [41]	18	Anterior circulation	34 °C	Endovascular	51 h (median)	55.6 % of mRS 0–2 at 3 months	Immediate post-reperfusion cooling

a steady temperature. In the endovascular cooling method, a cooling catheter is introduced through the femoral or subclavian vein. Cooling is achieved by circulating cooled saline within the cooling catheter. This system offers the advantage of accurate temperature control during maintenance and rewarming period. However, no differences have been reported in the outcomes achieved with both cooling methods [47]. Potential risks associated with induction of hypothermia are infection and venous thrombosis.

The most frequent complication is shivering, which can interfere with the cooling process and increase the rate of systemic metabolism [48]. In conscious patients, endovascular cooling devices are more effective in reducing shivering than surface cooling devices. Assessment of the severity of shivering using the Bedside Shivering Assessment Scale is useful for early intervention [48]. According to literature, oral buspirone and intravenous meperidine exert an anti-shivering effect. Skin warming is also reported to be effective in controlling shivering. The cardiopulmonary complications associated with hypothermia include bradycardia, arrhythmia, hypotension, pneumonia, and pulmonary edema. Electrolyte imbalance such as hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia has also been reported as accompanying complications. Once therapeutic hypothermia is induced, it is difficult to recognize complications by clinical symptoms. Therefore, continuous monitoring via serial chest radiography and laboratory tests is important for the detection of complications.

Conclusions

Understanding the underlying stroke pathophysiology in each acute stroke patient is important for planning acute management strategies, including intensive care. Adhering to the latest guidelines for general and intensive managements in stroke can help physicians effectively manage cases of acute stroke and achieve improved patient outcome.

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6 Cardiac Evaluation and Management After Ischemic Cerebral Stroke

Se Yong Jang and Dong Heon Yang

Large proportion of ischemic stroke is attributable to cardioembolic source. Cardiovascular diseases such as atherosclerotic coronary artery disease, atrial fibrillation, valvular heart disease, or heart failure are closely related to increased risk of ischemic strokes. Furthermore, recent investigations are revealing that substantial portion of cryptogenic strokes arises from cardioembolic source. These cardioembolic strokes often recur early and repeatedly in a long lifetime, even after all the efforts preventing recurrent stroke. Thus, prevention and management after cardioembolic stroke are particularly important issues in practical fields. Evidence-based strategies have been established in prevention and management of some spectrum of cardioembolism, such as atrial fibrillation. Meanwhile, there is little, we know, in some other cardioembolic sources in terms of pathophysiology and prevention of strokes. We focus on currently available methods and practical evaluations to identify cardioembolic stroke and stroke preventions related to diverse cardiac conditions such as atrial fibrillations, valvular heart disease, myocardial infarctions, heart failure, and intracardiac and extracardiac shunt in this chapter.

6.1 Background

Embolism of cardiac origin accounts for 15–30 % of ischemic strokes [1–3]. Cardioembolic stroke has higher in-hospital morality and more frequent fatal recurrence than other causes of stroke [4–6]. Identification of embolic source is often challenging in some patients. However, discovering cardioembolic source is an important issue in stroke patients when deciding treatment and prevention strategy. Patients with atrial fibrillation, heart failure, valvular heart disease, prosthetic heart valve, and symptom and sign of endocarditis are obviously candidates for the cardiac evaluation. In patients with multiple ischemic lesion or concomitant systemic emboli, cardioembolism should be strongly considered, either. Table 6.1 is demonstrating potential cardioembolic sources of ischemic stroke. This chapter will discuss about cardiac evaluation and management after acute ischemic stroke.

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Table 6.1 Common cardioembolic sources in ischemic stroke

Major source	Minor source
Atrial fibrillation	Patent foramen ovale
Rheumatic valve disease (mitral stenosis)	Atrial septal defect
Prosthetic valve	Ventricular septal defect
Infective endocarditis	Calcified aortic stenosis
Marantic endocarditis	Mitral annular calcification
Atrial myxoma	Fibroelastoma
Acute myocardial infarction	Lambl's excrescence
Heart failure	Mitral valve prolapse

6.2 Cardiac Evaluation

6.2.1 Electrocardiogram (ECG)

Standard 12-lead ECG is mandatory in all patients with acute stroke. ECG abnormalities are observed in 60–90 % of the patients with acute stroke [7, 8]. Not only heart rhythm disorder like atrial fibrillation (AF) but also diverse ECG changes following acute stroke can be detected on ECG. Myocardial ischemia-like ECG changes, such as ST-segment deviation, T wave abnormalities, and QTc prolongations are most frequent secondary ECG changes after acute stroke, which can mimic acute myocardial ischemia.

AF detection rate in acute stroke patients varies from 7 to 25 % [9–11]. Absence of AF in standard ECG test cannot exclude AF as a cause of the stroke event. Dedicated effort to detect paroxysmal AF possibly affect the AF detection rate. One study demonstrated that serial ECG follow-up during 72 h from stroke event can increase the chance of AF detection by 2.6-fold [12]. Continuous cardiac monitoring for at least 24 h is reasonable to detect AF and other serious arrhythmias [13, 14].

Arrhythmias other than AF also can be associated with acute phase of stroke. Serious arrhythmias, such as ventricular tachycardia, supraventricular tachycardia, various degrees of atrioventricular block, as well as AF, can be seen in approximately 25 % of the patients with acute stroke in first 3 days [15]. Arrhythmic events are especially frequent in the first 24 h and decline with time.

6.2.2 Holter Monitor

There is no strong recommendation of patient selection, time, and duration of Holter monitoring in patients with acute stroke. Detection rate of paroxysmal AF on 24-h Holter monitoring after ischemic stroke is between 2 and 7 % [16–18]. Some limited studies expressed a doubt about the efficacy of routine Holter monitoring to detect AF and other serious arrhythmias after acute stroke, because of the low detect rate and poor cost-effectiveness [16, 17, 19]. However, such findings might result from unselected patients, varying time and duration of monitoring. The Holter monitor can be especially effective in detecting cardiac rhythm disorder in patients with embolic infarction pattern, old age, and concomitant coronary artery disease [20]. Stroke patients with large deficits or right hemispheric stoke are at risk of various cardiac pathologic conditions, such as AF, myocardial ischemia, congestive heart failure, and other serious cardiac arrhythmias, and may need close cardiac monitoring and Holter monitoring [21]. One study suggested that routine Holter monitoring for over 24 h can identify new AF/atrial flutter in 1 out of 20 patients [18].

6.2.3 Event Recorder

The longer duration of ECG monitor definitely increases the detection rate of AF and other cardiac arrhythmia. Table 6.2 demonstrated monitoring type and detection of paroxysmal AF [22]. Seven days of ECG monitoring using external event recorder revealed 16–25 % patients with paroxysmal AF among the patients who did not show AF in 24-h Holter monitoring [23, 24]. More prolonged monitoring may be considered up to a year or more using implantable loop recorder in patients with cryptogenic stroke or highly suspected heart rhythm disorder like AF. One study including patients with cryptogenic stroke revealed that

Table 6.2 Type of monitoring and detection of paroxysmal atrial fibrillation (AF)

Type of monitoring	Invasiveness	Duration	Rate of AF detection (%)
Admission ECG	Noninvasive	N/A	2.7
Inpatient continuous telemetry	Noninvasive	3–5 days	5.5–7.6
Holter monitoring	Noninvasive	24 h	3.2–4.8
		48 h	6.4
		7 days	12.5
Mobile continuous outpatient telemetry	Noninvasive	21–30 days	16–25
Implantable loop recorders	Invasive	6 months	9
		36 months	30

Adapted from Yaghi et al. [22]

16 % of the patients had an event of paroxysmal AF using an implantable loop recorder during over a year of follow-up [25].

6.2.4 Transthoracic Echocardiography (TTE)

Echocardiography can provide information about functional and structural abnormalities inside and even outside of the heart. We should focus on the size and functions of left atrium (LA) and left atrial appendage (LAA), right ventricular and left ventricular (LV) function and regional wall motion abnormality, valvular disease, prosthetic valve, intracardiac shunt, and atheromatous embolic sources of aorta. All ischemic stroke patients with embolic character or without other clear etiology may need to undergo TTE. Although, some data suggested that transesophageal echocardiography (TEE) presented higher diagnostic yields in detecting embolic source compared to TTE [26, 27], TTE still has strong clinical advantages, which is noninvasive test, relatively lower price, and easier to perform and repeat. Furthermore, TTE is often better to evaluate native or prosthetic valve function and usually better for the detection of LV thrombus compared to TEE.

TTE is presenting very high sensitivity and specificity for detecting LV thrombus (Fig. 6.1) [28]. It is also an essential part to identify the presence of regional or global wall motion abnormality of left ventricle related to LV thrombus. However, in some patients who have poor echocardiographic window or spontaneous echocontrast around the suspected area, it is quite challenging to define thrombus. Contrast echocardiography technique can help to visualize thrombus in such cases. Computed tomography and cardiac magnetic resonance imaging can be options otherwise.

In patients with AF, most common site of the thrombus formation is LAA. TTE has limitations on visualizing LAA thrombus in patients with AF compared with TEE. LAA emptying velocity, which can be measured by LAA contraction using TEE by pulsed Doppler, is a parameter of the LAA dysfunction, and low velocity (≤20 cm/s) is related to risk of thrombus formation [29]. Some data showed that new technique of second harmonic imaging allows TTE to evaluate LAA function with better sensitivity [30, 31].

One of the most serious conditions causing embolic event is infective endocarditis (IE). Clinically, diagnosis of IE is made on basis of clinical, echocardiographic, and biological findings. Modified Duke criteria have been widely used in diagnosis of IE (Table 6.3) [32]. Vegetation, abscess, valvular regurgitations, and prosthetic valve dehiscence are frequently observed in IE (Fig. 6.2). Echocardiographic findings play a key role in diagnosis of IE. In patients with IE, embolic risk can be estimated by echocardiographic findings, such as size and mobility of the vegetation. Vegetation size in response to antibiotic therapy is also associated with risk of embolic event [33–36]. Vegetation size >10 mm tends to be highly embolic [37].

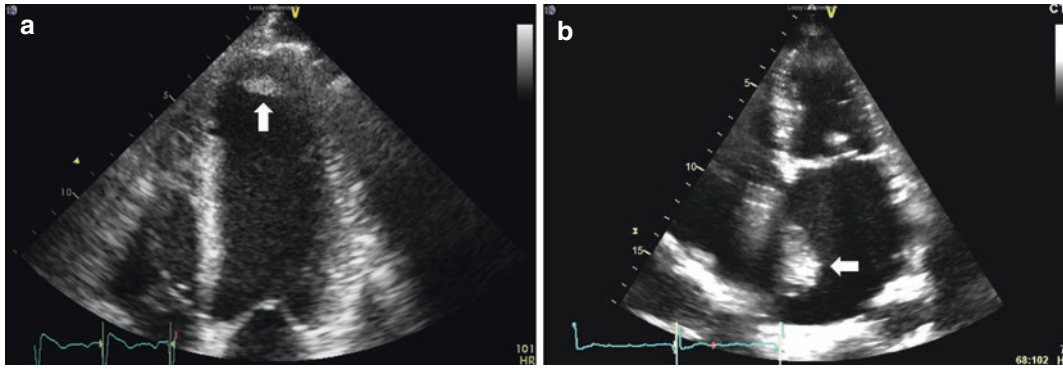

Fig. 6.1 (**a**) Patients with acute myocardial infarction and mural thrombus at left ventricular apex, (**b**) left atrial thrombus attached to interatrial septum in patients with rheumatic mitral valve disease and severe left atrial dilatation

Table 6.3 Modified Duke criteria of infective endocarditis (IE)

Major criteria	
Blood cultures positive for IE:	
Typical microorganisms consistent with IE from two separate blood cultures:	
Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococci, in the absence of primary focus	
or	
Microorganisms consistent with IE from persistently positive blood cultures:	
At least two positive blood cultures if blood sample drawn > 12 h apart or all of three or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)	
or	
Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer > 1:800	
Evidence of endocardial involvement	
Echocardiography positive for IE	
Vegetation – abscess – new partial dehiscence of prosthetic valve	
New valvular regurgitation	
Minor criteria	
Predisposition: predisposing heart condition, infection drug use	
Fever: temperature > 38 °C	
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhages, conjunctival hemorrhage, Janeway lesions	
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor	
Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE	
Definite IE	**Possible IE**
2 major criteria	1 major and 1 minor criteria
1 major and 3 minor criteria	3 minor criteria
5 minor criteria	

Adapted from Li et al. [32]
※HACEK: *Haemophilus*, *Aggregatibacter* (previously *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella*

Paradoxical embolism is originated from venous side and cross to the systemic circulation through a shunt. Intracardiac shunt could be detected by echocardiography. TTE usually detect secundum- or primum-type atrial septal defect (ASD). Chamber size and pulmonary artery pressure also should be evaluated for further management. TEE is often needed in case of

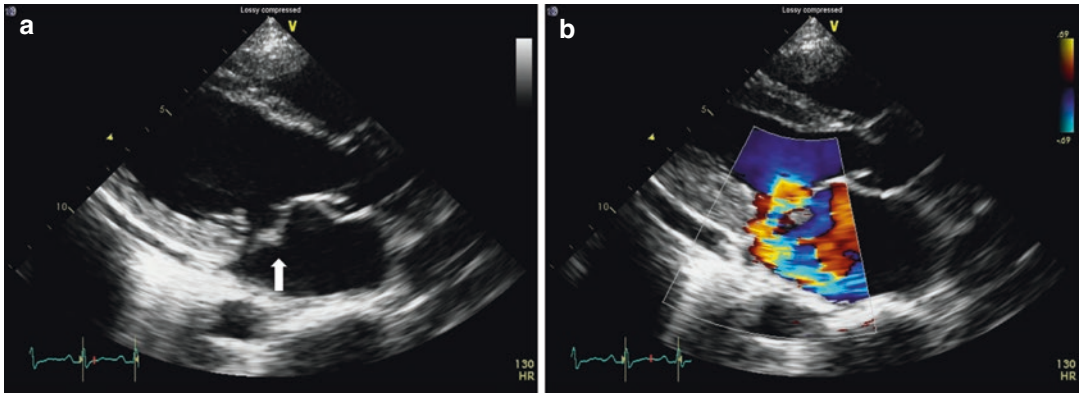

Fig. 6.2 Apical two-chamber view revealing mitral leaflet prolapse (**a**, *white arrow*) and severe mitral regurgitation (**b**) in patient with infective endocarditis

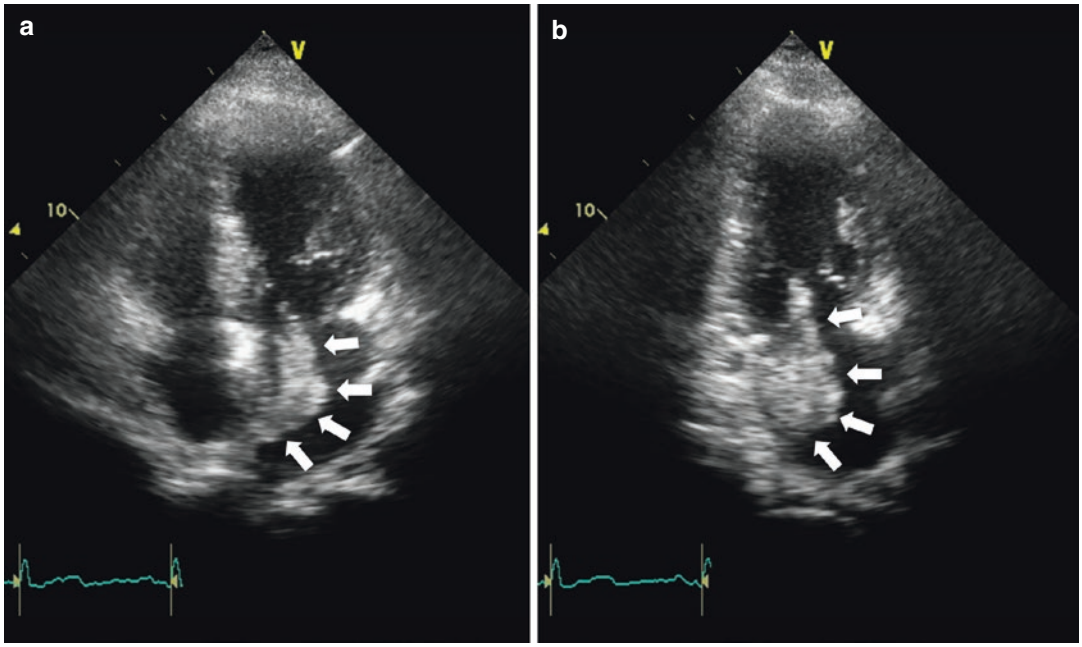

Fig. 6.3 Apical two chamber (**a**) and two-chamber view (**b**) of cardiac myxoma (*white arrows*) in the left atrium, which caused ischemic stroke and systemic embolism in a 40-year-old male

sinus venosus defect. Patent foramen ovale (PFO) also can cause paradoxical embolisms. Traditionally, TEE with Valsalva maneuver after agitated saline injection is the gold standard test for detecting PFO. However, with recent advance in techniques, TTE may be sufficient for the agitated saline test by using second harmonic imaging [38, 39].

Cardiac tumor frequently causes embolic event [40]. TTE provides not only anatomical information but also functional significance in those cardiac tumors. Cardiac myxoma is the most common primary tumor in the heart. Approximately 90% of cardiac myxoma occurred in LA [41], which can be highly associated with cardioembolic stroke (Fig. 6.3). Most common valve-associated tumor, fibroelastoma, is also related to embolic risk [42, 43]. Differential diagnosis between fibroelastoma and Lambl's excrescences or infective endocarditis is often challenging.

6.2.5 Transesophageal Echocardiography (TEE)

Although TEE is an invasive, more expensive procedure which needs experienced physician, complication rate is less than 0.02 % [44], and diagnostic sensitivity can be superior than that of TTE especially for detection of thromboembolic source [26]. TEE can provide better spatial resolution of intracardiac structure even in patients with poor transthoracic window. Because TTE and TEE have their own pros and cons, respectively, the physician should make proper decision based on clinical circumstances as well as the cost-effectiveness.

TEE can sensitively detect LAA thrombus directly and highly thrombogenic conditions like spontaneous echocontrast in patients with AF. Doppler measurement in LAA is also a useful tool for evaluating thrombogenic risk in atrial fibrillation. LAA is not an immobile structure but is believed to have contraction and dynamic flow changes inside of it. LAA contraction forced blood out, and LAA emptying velocity is considered as a parameter of LAA function. The velocity below 20 cm/s is associated with risk of thrombus formation in LAA [45]. LAA emptying velocity also can be a parameter for successful cardioversion in patients with AF.

Regarding paradoxical embolism, sinus venosus-type or coronary sinus-type ASDs are often difficult to be found in TTE. TEE provides higher resolution around the inferior and superior vena cava area and even in the coronary sinus area. TEE also is a gold standard for PFO diagnosis. In differential diagnosis between PFO and pulmonary arteriovenous malformation as a source of paradoxical emboli, TEE test can be more accurate.

Presence of prosthetic valve is a highly thrombogenic condition. Although TTE has an important role in evaluating prosthetic valve function, TEE is required in many cases. In circumstances when prosthetic valve malfunction is present, differential diagnosis between pannus formation and thrombus formation is a crucial part in therapeutic strategy. High-resolution TEE image can provide important additional information in differential diagnosis [46].

Approximately 60 % of the patients 60 years or older who had stroke have aortic arch atherosclerosis (Fig. 6.4) [47]. Complex atheroma with ulceration and high mobility is closely related to the embolic stroke. TTE can approach aortic arch in suprasternal window, but imaging quality and information are often limited. TEE provides high-resolution images of ascending, descending aorta, and aortic arch. Thickness of atheroma and ulceration and presence of highly mobile portions can be assessed to estimate the embolic risk [45].

6.3 Management and Prevention of Cardioembolic Stroke

6.3.1 Atrial Fibrillation (AF)

Dilatation and contractile dysfunction of the left atrium (LA) and left atrial appendage (LAA) in AF are significantly associated with blood stasis and thrombus formation. Ischemic stroke patient with AF can present worse short-term and long-term survival than those without, as well as higher recurrence rate of stroke [9]. There is a large body of evidence that anticoagulation is recommended in patients with AF according to their risk factors. Risk stratification using CHA2DS2-VASc score has been widely used to determine anticoagulation (Tables 6.4 and 6.5) [48]. Many studies showed that benefit of anticoagulation overweighs the risk in patients with AF and elevated risk of embolization. Thus, all patients with stroke/TIA who have AF got at least 2 points and should be anticoagulated unless there is contraindication for anticoagulation.

Traditionally, anticoagulation using vitamin K antagonist, warfarin, had been widely used in stroke prevention of AF patients. Recently, new anticoagulation agent blocking a specific target of coagulation cascade became popular, as an alternative to warfarin. Dabigatran, rivaroxaban, apixaban, and edoxaban are non-vitamin K antagonist oral anticoagulant, abbreviated as NOAC. NOACs demonstrated non-inferior efficacy in prevention of ischemic stroke compared to warfarin and secured their safety profiles in patient with non-valvular AF

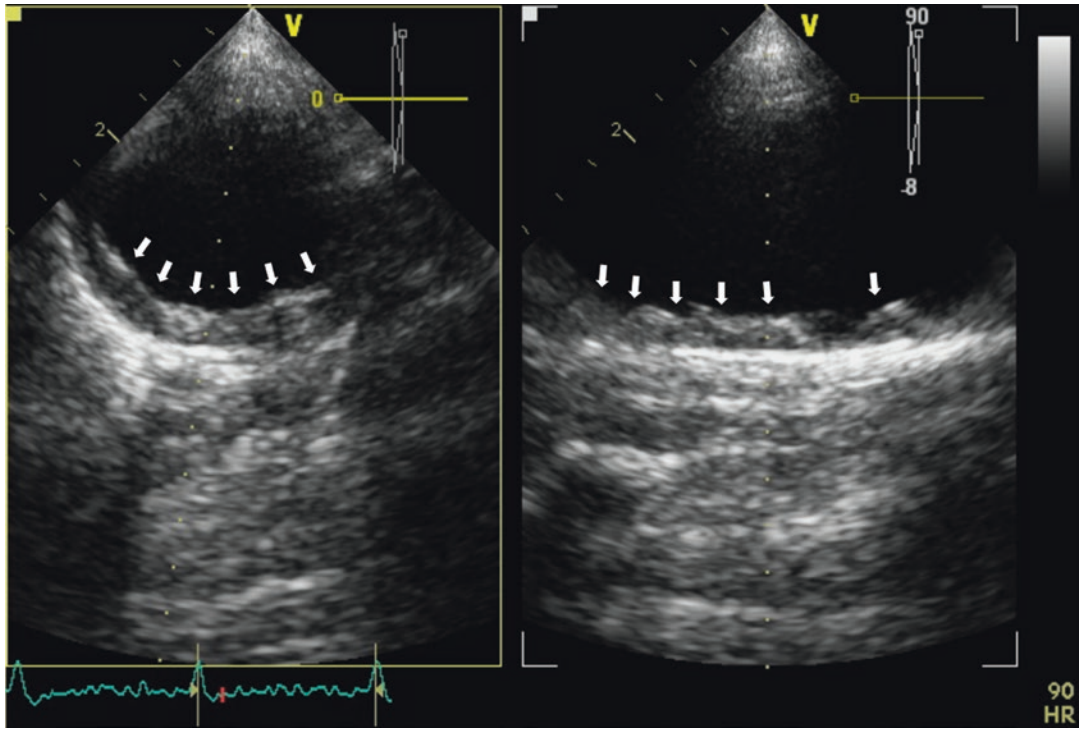

Fig. 6.4 Diffuse atherosclerotic plaque of approximately 10 mm thickness (white arrows) in aortic arch of 60-year-old male who presented with acute ischemic stroke

Table 6.4 CHA2DS2-VASc score

CHA2DS2-VASc acronym	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, pad, or aortic plaque)	1
Age 65–74 years	1
Sex category (female sex)	1
Maximum score	9

Adapted from Friberg et al. [48]
TIA transient ischemic attack, *TE* thromboembolic event, *MI* myocardial infarction, *PAD* peripheral artery disease

Table 6.5 Stroke risk with CHA2DS2-VASc score

Score	Unadjusted ischemic stroke rate (%)
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7
7	11.2
8	10.8
9	12.2

Adapted from Friberg et al. [48]

[49–52]. Because NOACs have their own pharmacokinetics, different renal excretion, side effect, and drug interaction, selection of the agent should be based on patients' condition, risk factors, economic status, tolerability, and preference.

For patients who are not indicated for or cannot tolerate anticoagulation, antiplatelet treatment may be considered. Options can be aspirin monotherapy or dual antiplatelet therapy in combination with clopidogrel. However, evidences are not supporting the efficacy of aspirin preventing stroke in patients with AF [53]. Dual antiplatelet therapy in combination of aspirin and clopidogrel may be superior to aspirin monotherapy

in preventing stroke but at the cost of increased bleeding [49].

6.3.2 Left Ventricular Thrombus

Incidence of LV thrombus within 3 months after acute myocardial infarction (MI) vary from 3 to 16 % [54–57]. Recently, more aggressive antiplatelet therapy in acute stage may reduce the incidence of thrombus formation after MI. More than 10 % of the patients with LV thrombus are at risk of embolic event unless they are treated with anticoagulation [58, 59]. Available data is supporting the use of warfarin to reduce embolic risk at the presence of LV thrombus after MI. One meta-analysis data demonstrated 86 % reduction of embolic risk with warfarin in patients with LV thrombus after anterior MI [59]. It is reasonable to start unfractionated heparin or a low molecular weight heparin as soon as possible before warfarin effect gets to the therapeutic rage of international normalized ratio (INR) 2–3. There is limited data on the duration of anticoagulation therapy. Decision may need physician's discretion based on the degrees of LV dysfunction, LV reverse remodeling during follow-up, and recurrence of thrombi. There is also limited data available about NOAC reducing the embolic risk of patients with LV thrombus.

6.3.3 Mitral Stenosis (MS)

Patients with mitral stenosis (MS) who suffered from ischemic stroke are recommended to receive warfarin therapy regardless of accompanying AF. In mitral stenosis patients with sinus rhythm who had ischemic stroke, paroxysmal AF or complicated infective endocarditis should be considered as an aggravating factor for stroke. Limited data suggested that adding aspirin to warfarin can reduce major adverse event compared to warfarin alone [60]. Regarding NOAC in patients with mitral stenosis, most of the NOAC studies excluded patients with highly thrombogenic conditions such as mitral stenosis and presence of prosthetic valve. Thus, there is little evidence of using NOAC in patients with MS to date.

6.3.4 Prosthetic Heart Valve

Presence of mechanical prosthesis is also one of the highly thrombogenic conditions. Warfarin is routinely recommended for all patients with mechanical prosthesis to prevent thromboembolic event [61, 62]. Intensity of the treatment is different according to the site of the prosthesis. Therapeutic rage or INR 2.5–3.5 and 2.0–3.0 is recommended for mitral and aortic mechanical prosthesis, respectively [63–66]. Low-dose aspirin (75–100 mg) may have additional benefit on top of warfarin monotherapy in patients with mechanical prosthesis [67, 68].

Bioprosthesis is usually less thrombogenic than mechanical prosthesis with exception of the first 3 months after surgery. Anticoagulation may be reasonable for the first 3 months after bioprosthetic valve replacement, but supporting data is lacking [61, 62]. After 3 months from bioprosthetic valve replacement, antiplatelet therapy with aspirin is generally recommended for stroke prevention unless there is other indication for anticoagulation. One study investigating the effect of dabigatran in patients with mechanical prosthesis demonstrated unfavorable results of increased thromboembolic event and higher bleeding risk compared to warfarin [69]. There is no evidence of NOAC in patients with prosthetic valve to prevent thromboembolic events.

When ischemic stroke occurs in spite of adequate anticoagulation in patients with mechanical prosthesis, low-dose aspirin should be added in patients not taking aspirin. If the patient is taking aspirin already, target INR can be increased with care, taking into account the individual bleeding risk [62]. In patients with bioprosthetic valve thrombus who are taking aspirin monotherapy, anticoagulation should be considered when ischemic stroke occurs.

6.3.5 Atrial Septal Abnormality

Paradoxical embolism is a phenomenon that thromboembolism originated from venous vasculature cross to arterial circulation resulting in arterial embolism in the presence of intracardiac shunt or pulmonary shunt. Patients with atrial

septal defect (ASD) have increased risk of paradoxical embolism. Some data reported the risk of paradoxical embolism in patients with ASD is up to 14 % [70, 71]. ASD closure is usually decided on the basis of pathologic changes in the right heart. However, in the presence of paradoxical embolism, ASD closure is reasonable, whether surgically or percutaneously [72].

PFO is seen in 15–25 % of adults and recently considered as one possible cause of cryptogenic stroke. Some data is supporting evidence that younger patients have a higher PFO-attributable stroke fraction than the older patients in cryptogenic stroke [73]. For patients with isolated PFO, who experienced ischemic stroke, there is insufficient evidence for the superiority of anticoagulation over antiplatelet therapy [74, 75]. Thus, aspirin monotherapy is recommended for patients with PFO, who had ischemic stroke. Exceptions are stroke patients with PFO and concomitant deep vein thrombosis (DVT), pulmonary thromboembolism, or venous thrombosis. Anticoagulation is indicated in those patients. There is a controversy whether PFO and concomitant atrial septal aneurysm (ASA) increase the risk of ischemic stroke or not. One study suggested the increased risk of PFO plus ASA [76], whereas other data did not [77, 78]. Prevalence of ASA is very low (≤2 %) in general population. Scarce data is available for isolated ASA in terms of the risk of stroke and optimal treatment. There are three random trials which tested efficacy of PFO closure preventing recurrent stroke in patients who experienced stroke [79–81]. None of them presented significant benefit of PFO closure in intention-to-treat analysis, whereas procedure-related complications, like new-onset AF, were higher with PFO closure. Thus, PFO closure is not recommend in patients with PFO, who had ischemic stroke. One exception is in patients with PFO and concomitant DVT. PFO closure may be considered in those patients depending on the recurrence risk of DVT [82].

6.3.6 Infective Endocarditis (IE)

IE is a fatal infectious condition of high mortality and morbidity [83]. Approximately 15–35 % of the patients suffer from clinically evident systemic embolism, and silent ischemic events are supposedly much more frequent [62]. Prompt antibiotics can reduce the risk of embolization significantly [84]. Embolic events are most frequent during the first day following the initiation of antibiotics, and incidence decreases gradually until 2 weeks [37, 85, 86]. Early surgery may reduce the incidence of embolic event in patients with large vegetation size and severe valve disease [87]. Timing of surgery should be decided based on multidisciplinary approach taking into account the embolic risk, heart failure, severity of valvulopathy, duration of antibiotics therapy, and comorbidities. Because of the risk of hemorrhagic transformation of embolic infarction, temporary discontinuation of anticoagulation may be considered at the time of diagnosis [85].

6.3.7 Aortic Atheroma

Aortic atherosclerotic plaque can cause systemic embolization [47, 88, 89]. Complex aortic plaques, which defined thickness >4 mm, or ulceration, or mobile component, are at high risk of embolization. Optimal treatment for aortic atheroma in preventing ischemic stroke is not clear. Although limited data suggested the superiority of warfarin therapy over antiplatelet therapy [90, 91], they are observational study and included patients are limited in number. The benefit of warfarin therapy over antiplatelet therapy is still not clear. One random trial that compared efficacy of dual antiplatelet therapy (aspirin plus clopidogrel) to anticoagulation revealed that dual antiplatelet therapy significantly reduced major vascular events versus warfarin [92]. Available data demonstrated that there is no additional benefit of dual antiplatelet therapy over aspirin monotherapy. Single antiplatelet therapy seems a reasonable treatment in patients with aortic atheroma at present. Although available data is limited [93], statin therapy in patients with aortic atheroma may be reasonable to stabilize atherosclerotic plaque and prevent embolic event. There is no data available for NOAC preventing embolic event in patients with aortic atheroma to date.

There is also limited data on surgical atherectomy. One study demonstrated event higher stroke incidence in patients underwent atherectomy than patients without atherectomy [94].

6.4 Summary and Recommendations

Stroke from cardioembolic source is generally associated with high recurrence and poor prognosis. Diverse spectrum of cardiac disease can contribute to the ischemic stroke. Identification of underlying cardiac condition can be mandatory for proper management and prevention in those patients. There is considerable disagreement in proper methodology for cardiac evaluation, management, and prevention of stroke in different cardiac conditions. In spite of all the efforts to reveal the cause of ischemic stroke, approximately 30 % of the stroke patients remain cryptogenic stroke. Based on understanding of cardiac evaluation techniques, systemic approach will be needed to improve prognosis in patients with ischemic stroke.

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Intravenous Thrombolytic Therapy

7

Man-Seok Park

In this chapter, we review the history and current status of intravenous thrombolysis in the treatment of acute ischemic stroke. Since the recombinant tissue plasminogen activator (rtPA, alteplase) was approved by the Food and Drug Administration (FDA) in 1995, intravenous thrombolytic therapy has been increasingly used. Through successful large clinical trials, the therapeutic window of tPA was extended to 4.5 h from stroke onset. Recently, several randomized controlled trials demonstrated the efficacy of endovascular mechanical recanalization in large-vessel occlusive ischemic stroke. Therefore, intravenous tPA followed by endovascular therapy is expected to be frequently used in comprehensive stroke centers in the future. This chapter provides information about intravenous thrombolysis, including the introduction of intravenous thrombolytic agents, the action mechanism and clinical trials of each drug, the protocol and inclusion criteria for tPA use, and management guidelines during and after tPA administration. In addition, approaches combining intravenous thrombolysis with other treatment options will be discussed.

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7.1 Introduction

During ischemic stroke due to acute obstruction of cerebral blood flow, timely revascularization can rescue the hypoperfused tissues in the penumbra area. Compared with no revascularization, restoration of blood flow to the ischemic brain tissue leads to improved functional outcomes and reduced mortality rate at 3 months [1]. Therefore, urgent reperfusion of the ischemic brain tissue is the major target of acute ischemic stroke treatment. Currently, intravenous tPA is only approved by the FDA for use within the 4.5-h time window, beyond which the risk of intracranial bleeding may increase. However, many patients are still not eligible for thrombolysis owing to delay in presentation; only 3.4–5.2% of all patients with acute ischemic stroke in the United States receive intravenous tPA [2].

Since its FDA approval, intravenous tPA has been generally used as a first-line drug for the acute treatment of ischemic stroke. However, the risk of intracerebral hemorrhage, a narrow therapeutic window, and a low recanalization rate of large-vessel occlusion were drawbacks of intravenous tPA. Efforts have been made to extend the therapeutic window and to enhance the thrombolytic action of intravenous thrombolytic treatment. New thrombolytic agents that have higher fibrin specificity and provide better safety were developed. Combinations of intravenous thrombolysis and other treatment options are also being attempted.

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7.2 Mechanism of Thrombus Formation and Thrombolysis

Physiologic thrombosis is a crucial part of the normal hemostatic process that prevents hemorrhage caused by any vascular injury. It is counterbalanced by endogenous antithrombotic responses and fibrinolysis; therefore, thrombosis does not induce obstruction of blood flow under normal conditions. However, under pathologic conditions, thrombosis causes the formation of blood clot at the lumen of vessels, obstructing the blood flow to a tissue [3]. Endothelial cell injury, platelet activation, and thrombin generation are typically involved in the process of thrombosis. Of these factors, thrombin has a major role in clot formation: it cleaves fibrinogen into fibrin, resulting in the formation of a clot matrix. Thrombin also activates factor XIII, which results in interfibrin cross-linking [3, 4]. Figure 7.1 illustrates the coagulation pathway [5]. Extrinsic and intrinsic pathways induce a fundamental reaction that generates thrombin formation and produces fibrin.

In addition to circulating anticoagulants (activated protein C and protein S), the endogenous thrombolytic system including plasmin also regulates thrombus growth. Endogenous tPA is the naturally circulating plasminogen activator that mediates plasmin formation from plasminogen. On the surface of a thrombus, fibrin binds endogenous tPA neighboring its substrate plasminogen, which accelerates plasmin formation and contin-

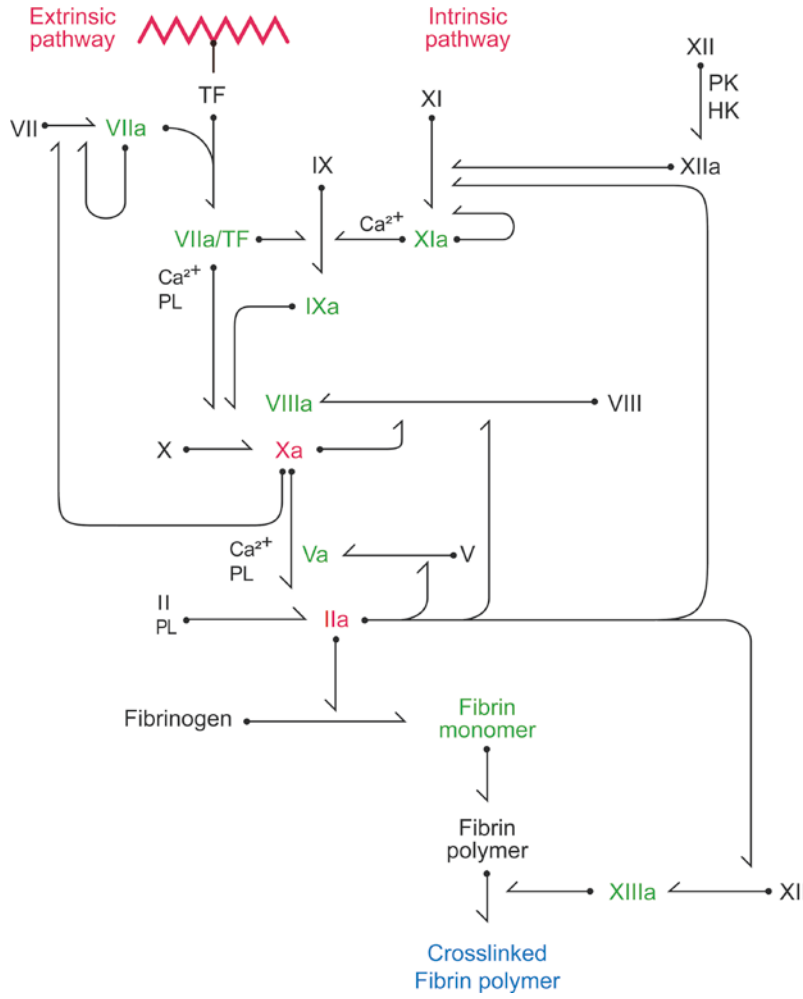

Fig. 7.1 Coagulation cascade. The coagulation cascade has two initial pathways that result in fibrin formation: the contact activation pathway (intrinsic pathway) and the tissue factor pathway (extrinsic pathway). Both pathways cause the same fundamental reactions that produce fibrin. *HK* high-molecular-weight kininogen, *PK* prekallikrein, *PL* phospholipid (Adapted from: Ferguson et al. [5])

ues thrombus remodeling. Plasmin has a very short half-life of approximately 0.1 s, and endogenous fibrinolysis is controlled by several inhibitors of plasmin, such as α_2-antiplasmin, thrombospondin, and plasminogen activator inhibitor-1 (PAI-1). The potential risk for thrombosis is determined according to the relative concentration of these inhibitors and the endogenous tPA. The complex formed by endogenous tPA, fibrin, and plasminogen accelerates the activation of plasminogen and increases the clot-selective fibrinolysis. Therefore, fibrinolysis takes place predominantly within the thrombus, and clot lysis can be achieved with comparatively low bleeding risk when thrombolytic agents (exogenous tPA) are used. All currently used thrombolytic agents are endogenous or exogenous plasminogen activators that act on fibrin and thrombin.

7.3 Drugs for Intravenous Thrombolysis

7.3.1 Tissue Plasminogen Activator (tPA)

Streptokinase and urokinase are first-generation thrombolytic agents. Streptokinase is derived from purified streptococci bacteria. It has no fibrin specificity; therefore, its action is not limited at the location of thrombus formation. Trials of streptokinase in acute ischemic stroke were terminated early owing to high mortality and high hemorrhage rates compared to placebo [6]. Urokinase is formed by the kidney and found in urine. Its clinical use is limited due to fibrinogenesis. In the Prolyse in Acute Cerebral Thromboembolism II trial (PROACT II, 1999), intra-arterial infusion of recombinant prourokinase in 180 patients showed better outcomes at 90 days despite an increased rate of symptomatic intracranial hemorrhage (ICH) [7]. Thus far, the PROACT II study is the only favorable intra-arterial urokinase trial. However, the specificity of streptokinase and urokinase for plasminogen-bound fibrin is much lower than that of second- and third-generation thrombolytic drugs (alteplase, desmoteplase, or tenecteplase).

The tPA is a second-generation thrombolytic agent and a 70-kDa serine proteinase found in endothelial cells of blood vessels. Its plasma half-life is 4–8 min. Figure 7.2 illustrates the amino acid sequence of tPA. It has four domains, and the active site for plasminogen cleavage is in the COOH-terminal serine proteinase domain. tPA for commercial use could be produced through recombinant DNA techniques. Because tPA has fibrin-selective properties, it is classified as a fibrin-specific agent. There are also other fibrin-specific thrombolytic agents, the characteristics of which are compared in Table 7.1. tPA (alteplase) is the only thrombolytic drug currently approved by the US FDA for acute myocardial infarction, acute ischemic stroke, and acute pulmonary embolism.

7.3.2 Large Clinical Trials on tPA

The National Institute of Neurological Disorders and Stroke (NINDS) tPA trial in 1995 caused a paradigm shift in the management of acute ischemic stroke [10]. It emphasized the importance of rapid assessment and initiation of tPA administration. Six subsequent randomized trials have been conducted to compare tPA and placebo at various time windows of 0–6 h from stroke onset. The benefit of tPA within the 4.5-h time window became evident regardless of stroke severity or patient age; however, the efficacy and safety beyond 4.5 h remained unconfirmed [11]. The tPA studies are summarized in Table 7.2.

7.3.2.1 ECASS I

The result of the European Cooperative Acute Stroke Study (ECASS) was reported in 1995. ECASS is the first large, randomized, blinded, placebo-controlled clinical trial on high-dose intravenous tPA, which was designed to investigate if this thrombolytic therapy is beneficial and safe in patients with acute stroke [12]. A total of 620 patients with acute ischemic stroke were enrolled and randomized to treatment with 1.1 mg/kg body weight tPA or placebo within 6 h from the onset of symptoms. However, there was no significant difference in clinical efficacy in the

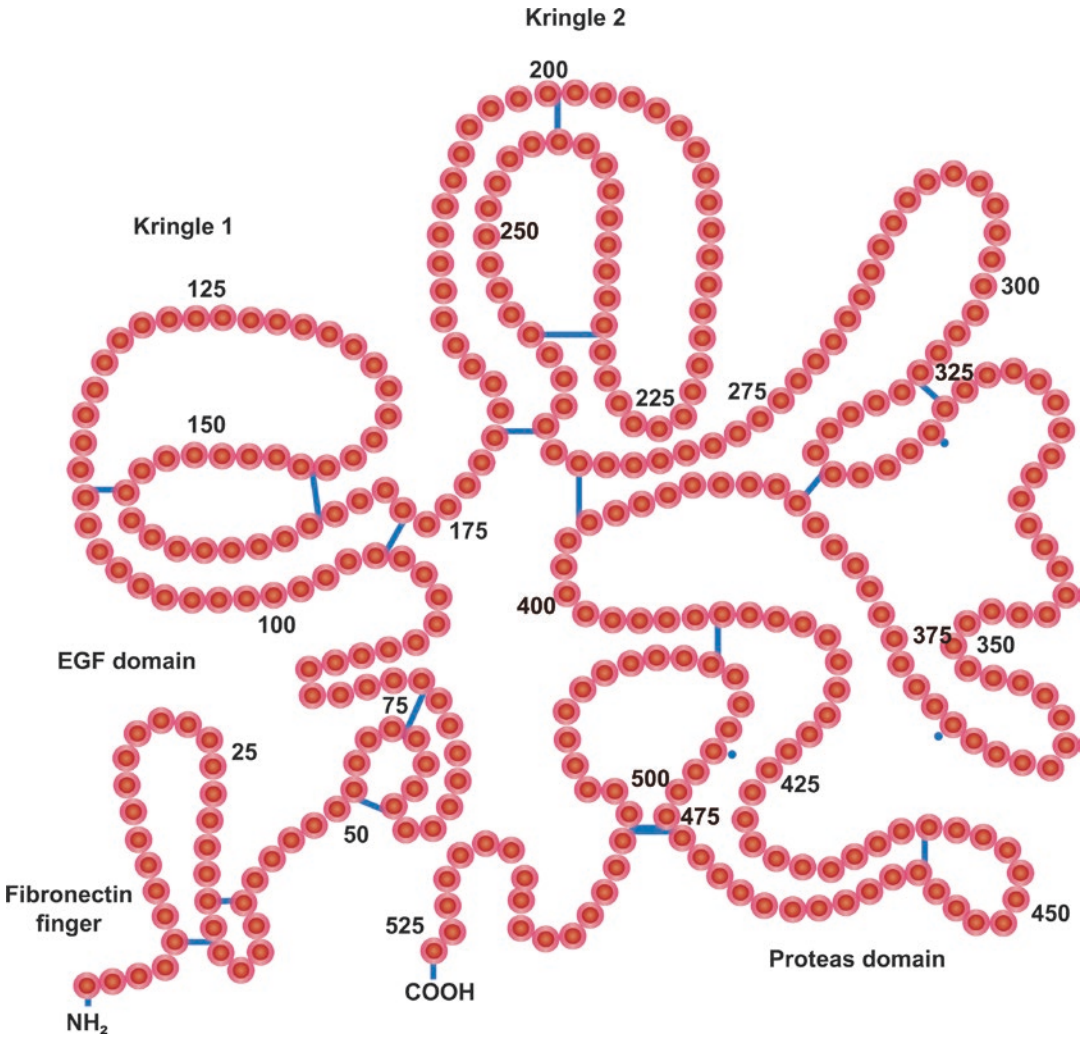

Fig. 7.2 The molecular structure of tissue plasminogen activator (alteplase) [8, 9]

Table 7.1 A comparison of thrombolytic agents

Agent	Half-life (min)	Fibrin selectivity	PAI-1 inhibition
Urokinase	15	–	+++
tPA (alteplase)	4–8	++	+++
Tenecteplase	11–20	+++	–
Desmoteplase	138	++++++	?

intention-to-treat population analysis, whereas the per-protocol population analysis revealed a significant difference in the modified Rankin Scale (mRS) score in favor of tPA-treated patients. Thus, intravenous thrombolysis was found unacceptable for general use in ischemic stroke within 6 h from symptom onset.

7.3.2.2 NINDS

In 1995, the National Institute of Neurological Disorder and Stroke (NINDS) study was published [10]. This study included ischemic stroke patients within 3 h from the onset of stroke symptoms and used 0.9 mg/kg body weight tPA, which were different from ECASS I. The trial had two parts; 291 patients were enrolled in part 1 and 333 patients were enrolled in part 2. Part 1 investigated whether tPA has a clinical benefit, as defined by an improvement of 4 points from the

Table 7.2 Summary of the tPA studies

Year	Study name	n	Time from onset (h)	No. of patients aged >80 years	tPA (mg/kg)	Outcome (tPA vs. placebo)	Symptomatic ICH (tPA vs. placebo)
1995	NINDS	624	0–3	54	0.9	43% vs. 27%[a†]	6.4% vs. 0.6%
1995	ECASS	620	0–6	0	1.1	45% vs. 40%[b]	19.8% vs. 6.5%
1997	ECASS II	800	0–6	0	0.9	54% vs. 46%[b†]	8.8% vs. 3.4%
1999	ATLANTIS-A	142	0–6	0	0.9	35% vs. 25%[c]	11.3% vs. 0%[†]
1999	ATLANTIS-B	547	3–5	0	0.9	34% vs. 32%[c]	7% vs. 1.1%[†]
2008	EPITHET	100	3–6	25	0.9	47% vs. 41%[b]	7.7% vs. 0%[†]
2009	ECASS III	821	3–4.5	0	0.9	52% vs. 45%[a†]	2.4% vs. 0.2%[†]
2012	IST-3	3,035	0–6	1696	0.9	37% vs. 35%[d]	7% vs. 1%[†]

tPA tissue plasminogen activator, *ICH* intracerebral hemorrhage, *NINDS* National Institute of Neurological Disorders and Stroke, *ECASS* European Cooperative Acute Stroke Study, *ATLANTIS* Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, *EPITHET* Echoplanar Imaging Thrombolytic Evaluation, *IST* International Stroke Trial, *mRS* modified Rankin Scale, *NIHSS* National Institute of Health Stroke Scale score, *OHS* Oxford Handicap Score

[†] $p < 0.05$

[a] mRS 0–1 at day 90

[b] mRS 0–2 at day 90

[c] NIHSS 0–1 at day 90

[d] OHS 0–2 at day 180

baseline NIHSS score or the recovery from the neurologic deficits within 24 h after the stroke onset. Part 2 assessed functional outcomes at 3 months, according to the Barthel index, mRS, Glasgow Outcome Scale, and NIHSS scores. In part 1, there was no difference between the tPA and placebo groups in the proportion of patients with neurologic improvement at 24 h. In part 2, the long-term clinical advantage of tPA was observed for the tPA group at 3 months for all four outcome measures. As compared with placebo-treated patients, patients treated with tPA were at least 30% more likely to show minimal or no disability at 3 months on the evaluation of neurological status. The rate of symptomatic ICH occurrence within 36 h after treatment was higher in the tPA group than in the placebo group (6.4% vs. 0.6%); however, the mortality rate was similar between the two groups. Conclusively, the NINDS study showed that treatment with intravenous tPA within 3 h of the onset of symptoms improved clinical outcomes at 3 months despite an increased incidence of symptomatic ICH (Fig. 7.3).

7.3.2.3 ECASS II

The ECASS II study assessed the safety and efficacy of intravenous thrombolysis with tPA (0.9 mg/kg body weight) within 6 h of stroke symptom onset, including 800 patients with ischemic stroke and by using computerized tomography (CT) to exclude patients with signs of major infarction [13]. Patients with early ischemic changes on CT in more than one-third of the middle cerebral artery (MCA) territory, stupor and comatose, and hemiplegia with eyeball deviation were excluded. Anticoagulants and antiplatelet agents were not used for the first 24 h after randomization of patient treatment. The results did not confirm a statistical benefit for tPA. One hundred sixty-five (40.3%) tPA-treated patients and 143 (36.6%) placebo-treated patients had

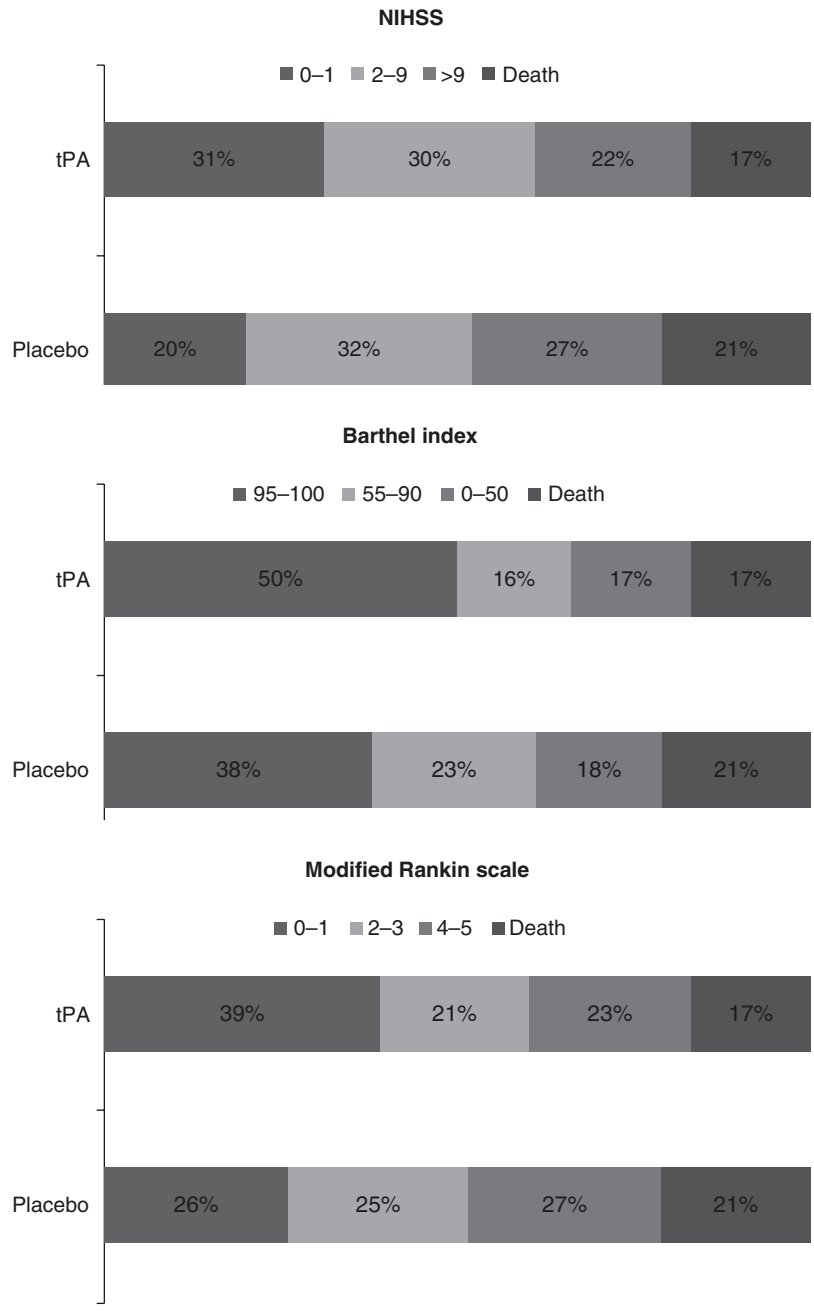

Fig. 7.3 Statistically significant differences between IV tissue plasminogen activator (tPA) and placebo-treated patients on three assessment scales in the National Institute of Neurological and Communicable Diseases and Stroke (NINDS) study, part 2. Values do not total 100% because of rounding. The National Institutes of Health Stroke Scale (NIHSS) score, Barthel index, and modified Rankin Scale (mRS) score at 3 months are shown, and there is a statistically significant improvement in the tPA-treated patients as compared with placebo in each of these categories

favorable mRS (0–1) outcomes (p = 0.277). However, despite the increased risk of intracranial hemorrhage, thrombolysis with tPA (0.9 mg/kg body weight) in selected patients may lead to a clinically relevant improvement in outcome (although statistically not significant).

7.3.2.4 ATLANTIS

In 1999, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study was published. It was a double-blind, randomized trial assessing the efficacy and safety of 0.9 mg/kg intravenous tPA in

patients with acute ischemic stroke within 6 h of symptom onset (part A) [14]. After an interim safety analysis, the time window was changed to 0–5 h, and it was decided to restart enrollment as a separate study (part B) [15]. This trial was terminated prematurely because of the absence of a beneficial effect. In the analysis of part B, the median time to treatment was 4.5 h. The efficacy was not different between the two groups. However, the symptomatic ICH rate was significantly increased in the tPA group. In 2002, a subgroup analysis of ATLANTIS data was released on the clinical outcomes of the 61 patients enrolled in the ATLANTIS study, who were randomized to receive intravenous tPA or placebo within 3 h of stroke symptom onset. The primary end point was the percentage of patients who had complete recovery, as determined by an NIHSS score of ≤1 at 90 days after treatment. Despite a significant increase in the rate of symptomatic ICH, tPA-treated patients had a favorable outcome (NIHSS score ≤1) at 3 months ($p = 0.01$). These data supported the NINDS-based recommendation to administer intravenous tPA to ischemic stroke patients within 3 h of symptom onset.

7.3.2.5 Pooled Analysis of NINDS, ECASS, and ATLANTIS Data

In 2004, the investigators of the ATLANTIS, ECASS II, and NINDS trials conducted a pooled analysis of six randomized controlled trials on tPA (up to 6 h) to evaluate the effect of time to treatment on functional outcome [16]. This analysis demonstrated a strong association between time to treatment and functional outcome. As the time interval to treatment increased, the odds ratio (OR) of a favorable outcome (mRS <2) decreased ($p < 0.005$). The ORs were 2.8 for 0–90 min, 1.6 for 91–180 min, 1.4 for 180–270 min, and 1.2 for 271–360 min. Symptomatic ICH occurred in 5.9% of patients treated with tPA compared with 1.1% of placebo-treated patients ($p < 0.0001$). The results of this study showed a clear association between the time interval to tPA and the treatment efficacy; however, it also suggested a potential benefit beyond 3 h. The most important finding from this pooled analysis was that the odds of favorable outcome decreased with every minute of delay from the stroke symptom onset.

7.3.2.6 ECASS III

In 2008, the ECASS III study assessed the safety and efficacy of tPA administered between 3 and 4.5 h after stroke onset [17]. A total of 821 patients were enrolled in this study and randomly assigned to the tPA ($n = 418$) and placebo ($n = 403$) groups. The trial excluded patients older than 80 years old, those with baseline NIHSS >25, and those taking anticoagulants or who had a history of stroke. The median time for the administration of tPA was 3 h 59 min. More patients showed clinical benefits with tPA than with placebo (52.4% vs. 45.2%; $p = 0.04$). The incidence of ICH was higher with tPA than with placebo (for any type of ICH, 27.0% vs. 17.6%, $p = 0.001$; for symptomatic ICH, 2.4% vs. 0.2%, $p = 0.008$). Despite a tenfold increase in symptomatic ICH, there was no significant difference between the tPA and placebo groups in terms of mortality (7.7% vs. 8.4%). ECASS III demonstrated a benefit of intravenous tPA beyond the conventional 3-h time window established in the NINDS trial, effectively extending the window for tPA to 4.5 h (Fig. 7.4).

7.3.2.7 IST-3

The third International Stroke Trial (IST-3) was designed to determine whether more patients might benefit up to 6 h from stroke onset [18]. In this international, multicenter, randomized, open-treatment trial, patients were assigned to either the 0.9 mg/kg intravenous tPA group or the control group. The inclusion criteria were broad, and there was no upper age limit for inclusion; more than half of the 3,035 patients were aged >80 years. The primary outcome was the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS) of 0–2, at 6 months. The 3,035 patients were enrolled by 156 hospitals in 12 countries. At 6 months, 554 (37%) patients in the tPA group versus 534 (35%) in the control group were alive and independent (OHS 0–2; adjusted OR, 1.13;

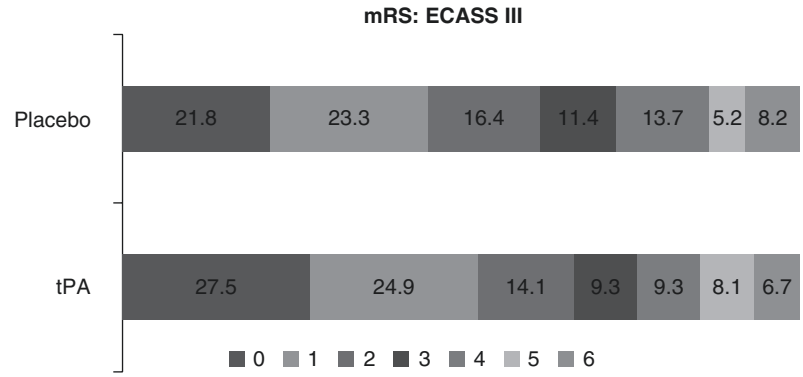

Fig. 7.4 European Cooperative Acute Stroke Study (ECASS) III trial 3-month outcome intention-to-treat group (modified Rankin Scale [mRS] scores). More patients had a favorable outcome (mRS score ≤1) with tissue plasminogen activator (tPA) than with placebo (52.4% vs. 45.2%; OR, 1.34; 95% confidence interval [CI], 1.02–1.76; $p = 0.04$)

95% CI, 0.95–1.35; $p = 0.181$). Despite early fatal ICH, tPA within 6 h did not affect the longer-term survival and improved the functional outcome. The benefit was greatest among patients treated within 3 h and did not decrease among elderly patients or those with severe stroke. For every 1,000 patients with tPA within 3 h of stroke, 80 more will live independently than if they had not been given tPA. There was an increased risk of early death due to symptomatic ICH in the first week. These results encourage physicians to consider thrombolytic treatment for a wider range of patients (particularly those aged >80 years), and treat those with more severe neurologic deficits from stroke. It also contributes to the increase in the proportion of ischemic stroke cases treated within 3 h.

7.3.2.8 SITS-MOST and SITS-NEW

In September 2002, the European Agency for the Evaluation of Medicinal Products (EMEA) conditionally approved tPA for the treatment of ischemic stroke within 3 h of onset of symptoms. One of the conditions for this approval was that treatment safety should be monitored in accordance with a study protocol (Safe Implementation of Thrombolysis in Stroke—Monitoring Study [SITS-MOST]) [19]. Under European Union regulations, SITS-MOST was required to evaluate the safety profile of tPA in clinical practice by comparison with results from previous randomized controlled trials. A total of 6,483 patients were enrolled from 285 centers in 14 countries between 2002 and 2006 for this prospective observational study. The baseline clinical characteristics of patients in SITS-MOST were largely similar to those in the pooled randomized controlled trials. At 24 h, the proportion of patients with symptomatic ICH was 1.7%; at 7 days, the proportion with the same condition as per the Cochrane definition was 7.3% compared with 8.6% in the pooled randomized controlled trials. The mortality rate at 3 months in SITS-MOST was 11.3% compared with 17.3% in the pooled randomized controlled trials. This study confirmed that intravenous tPA is beneficial and safe when used within 3 h of stroke onset, even in hospitals with little previous experience with thrombolytic therapy for acute ischemic stroke. In 2014, Safe Implementation of Thrombolysis in Stroke—Non-European Union World (SITS-NEW) was carried out to assess the safety of intravenous tPA in an Asian population by comparison with results from SITS-MOST and pooled analysis of previous randomized controlled trials [20]. The standard dose of intravenous tPA (0.9 mg/kg) was safe and efficacious in the Asian population, as observed in the previous studies, when used in routine clinical practice within 3 h after stroke onset.

7.3.2.9 Trials for Enhancing the Thrombolytic Activity of tPA

Recanalization with tPA treatment cannot be easily achieved in occlusions of more proximal cerebral arteries. The rate of early successful recanalization with tPA was about 25% in cases of proximal MCA occlusion and 10% in cases of internal carotid artery (ICA) occlusion [21]. The

rate of reocclusion of a distal artery due to thrombus breakdown and migration was as high as 30% with tPA [22]. Therefore, methods enhancing thrombolytic activity are required to increase the recanalization rate and reduce the reocclusion of distal blood vessels.

Ultrasound-enhanced thrombolysis has been attempted in vitro and in vivo to promote the activity of thrombolytic drugs [23]. The microbubbles in blood vessels generated by ultrasound induce microstreaming of blood to the occlusion as a delivery route for tPA. Ultrasound also enlarges the fibrin mesh, facilitating the binding and penetration of tPA into a thrombus [24]. A continuous transcranial ultrasound at 2 MHz greatly increased the rate of early recanalization in patients treated with tPA [25]. However, these studies did not guarantee the validation in terms of assessing the degree of recanalization, because they used only transcranial Doppler change instead of angiography. A phase III sonolysis trial (CLOTBUST-ER) that combines lysis of thrombus with ultrasound and systemic tPA for emergent revascularization has completed patient enrolment and will commence soon [26]. Intravenous administration of microbubbles as a contrast agent, with the intention of increasing the available volume of microbubbles for ultrasound, is expected to enhance the thrombolytic activity of tPA.

7.3.3 Other Thrombolytic Agents

7.3.3.1 Tenecteplase

Tenecteplase, a noble and genetically engineered mutant tPA, was developed to improve thrombolytic efficacy and safety. Three specific alterations in the original amino acid sequence of the tPA molecule resulted in a longer half-life of 17 ± 7 min, greater specificity for fibrin, and more resistance to endogenous PAI-1. With these properties, tenecteplase appears to be a more effective and safer thrombolytic agent than tPA (alteplase). Two randomized prospective clinical trials have either been conducted or are under way to compare tenecteplase with alteplase for acute ischemic stroke. The first was a small phase 2B open-label blinded outcome trial completed in 2011, randomly assigning 75 patients to receive alteplase (0.9 mg/kg body weight) or tenecteplase (0.1 or 0.25 mg/kg body weight) at <6 h after the onset of ischemic stroke in a 6-h window [27]. The co-primary end points were the proportion of the CT perfusion deficit that was reperfused at 24 h on perfusion-weighted magnetic resonance imaging (MRI) and the extent of clinical improvement at 24 h as assessed on the NIHSS scale. The results were positive for co-primary end points. The two tenecteplase groups with different dosages showed significantly improved reperfusion ($p = 0.004$) and better clinical outcomes ($p < 0.001$) at 24 h than the alteplase group. There were no significant between-group differences in intracranial bleeding or other serious adverse events. The higher dose of tenecteplase (0.25 mg/kg) was superior to the lower dose and to alteplase for all efficacy outcomes. The following secondary end points were also positive: infarct growth at 24 h and 90 days, complete or partial recanalization at 24 h, major neurological improvement (NIHSS reduction of 8) at 24 h, and excellent or good recovery at 90 days [27]. A phase 3 trial, the Norwegian Tenecteplase Stroke Trial (NORTEST), is also ongoing, randomizing 954 patients to identify a 9% or more difference in excellent outcome for intravenous tenecteplase at a dose of 0.4 mg/kg compared with a standard dose of intravenous alteplase [28]. The primary outcome measure for this study is mRS score at 90 days, with secondary end points of NIHSS score and recanalization at 24 h.

7.3.3.2 Desmoteplase

Desmoteplase is a plasminogen activator derived from the saliva of the vampire bat *Desmodus rotundus*. The DNA sequences of plasminogen activators in vampire bat saliva were completely analyzed in 1991. Of them, alpha 1 (rDSPAα1, desmoteplase) is the most active and shows a 72% homology to human tPA [29]. Desmoteplase has very high fibrin specificity, longer half-life (138 min), and no effect on the blood-brain barrier, making it a promising thrombolytic agent. The first clinical trials on desmoteplase (Desmoteplase in Acute Ischemic Stroke [DIAS])

demonstrated a higher rate of reperfusion and better functional outcome of lower weight-adjusted desmoteplase dose compared with the placebo [30, 31]. The Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) study also demonstrated the efficacy and safety of 125 μg/kg intravenous desmoteplase in acute ischemic stroke [31, 32]. However, the phase 3 trial, DIAS 2, did not show a beneficial effect of desmoteplase at 3–9 h after stroke onset [31, 33]. The limitations of the study were the small sample size and lack of standardized criteria for image selection. The subsequent analysis of pooled data from DIAS and DIAS 2 revealed that patients with a proximal cerebral artery occlusion or high-grade stenosis showed much greater mismatch tissue volumes and a positive response to desmoteplase in comparison to placebo. In 2009, the DIAS 3 and DIAS 4 phase 3 trials were started, enrolling 400 patients with acute ischemic stroke. The participants were treated with desmoteplase as an intravenous bolus dose of 90 μg/kg within 3–9 h after stroke symptom onset. Only patients with occlusion or high-grade stenosis in proximal large cerebral arteries as assessed by magnetic resonance or CT angiography were selected. Additional perfusion-weighted and/or diffusion-weighted imaging could be performed. However, those two additional phase 3 trials with advanced imaging selection criteria failed to show the benefits of desmoteplase in acute ischemic stroke. DIAS 3 showed no beneficial effect overall when given at 3–9 h after symptom onset to patients with major cerebral artery occlusion, and DIAS 4 was terminated early owing to the result of DIAS 3 [34].

7.3.3.3 Ancrod

Intravenously administered ancrod reduces serum fibrinogen levels, leading to an anticoagulation effect. It decreases blood viscosity and increases blood flow to the ischemic area of the brain. Ancrod, a serine protease, is extracted from the venom of the Malayan viper [35]. It showed beneficial effects in acute ischemic stroke when initiated within 3 h of stroke onset [31, 36, 37]. The Stroke Treatment with Ancrod Trial (STAT), a randomized, double-blind, placebo-controlled trial, was conducted between August 1993 and January 1998. A total of 500 ischemic stroke patients were randomized to receive ancrod (n = 248) or placebo (n = 252) as a continuous 72-h intravenous infusion initiated within 3 h of symptom onset. Favorable functional outcome was achieved by more patients in the ancrod group (42.2%) than in the placebo group (34.4%, p = 0.04), and mortality was not different between the groups. There was a trend toward more symptomatic ICH cases in the ancrod group than in the placebo group (5.2% vs. 2.0%; p = 0.06) [36]. Subsequent studies with an extended treatment window to 6 h from stroke onset have not revealed any significant improvement in clinical outcome [31, 37, 38].

7.3.3.4 Glycoprotein IIb/IIIa Antagonist

Glycoprotein (GP) IIb/IIIa antagonists inhibit activation of platelets, preventing reocclusion and promoting thrombus breakdown [39]. Platelet activation by ADP causes a conformational change in platelet GPIIb/IIIa receptors that induces its binding to fibrinogen. In large clinical trials, GPIIb/IIIa antagonists were effective for the treatment of acute coronary syndromes. However, their safety and efficacy in acute ischemic stroke were uncertain until the Safety of Tirofiban in acute Ischemic Stroke (SaTIS) trial was completed [40]. Tirofiban is a highly selective, fast-acting GPIIb/IIIa platelet receptor inhibitor. A total of 260 patients with acute ischemic stroke (NIHSS score 4–18) were randomized in the SaTIS trial and intravenously received either tirofiban or placebo within 3–22 h after stroke onset for 48 h. The rate of intracerebral hemorrhagic transformation did not differ between the two groups. The mortality rate after 5 months was significantly lower in patients treated with tirofiban. The study confirmed the safety of tirofiban; however, there was no difference in neurological/functional outcome after 5 months between the groups. Another GBIIb/IIIa antagonist, abciximab, was tested for the treatment of acute ischemic stroke within 5 h in the Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). This trial did not show either the efficacy or safety of intravenous administration of abciximab for the treatment of patients with acute ischemic stroke irrespective

of the end point or population studied. Instead, there was a significant increase in fatal or symptomatic ICH in the abciximab groups [41]. Eptifibatide is the third inhibitor of GPIIb/IIIa. The efficacy and safety of combined intravenous tPA and eptifibatide compared with intravenous tPA alone were evaluated in the Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke—Enhanced Regimen stroke trial (CLEAR-ER). The combination therapy cohort showed a lower occurrence of symptomatic ICH and a trend for good functional outcome (mRS 0–1, 49.5% vs. 36%) [42].

7.3.3.5 Argatroban

Argatroban is a direct thrombin inhibitor with a relatively short half-life of 45 min. The Argatroban Anticoagulation in Patients with Acute Ischemic Stroke (ARGIS-I) trial has demonstrated its safety, but not its efficacy, in 2003 [43]. Patients within 12 h of stroke onset were enrolled. The rate of symptomatic ICH was not significantly higher in the argatroban groups; however, argatroban did not demonstrate better clinical outcomes than did placebo. The Argatroban with tPA for Acute Stroke (ARTSS) study reported complete recanalization rate of 63% at 24 h with combination treatment with argatroban and tPA [31, 44]. Phase II ARTSS-2 was conducted. It was designed to randomly assign patients to a high or low dose of argatroban infusion for 48 h and intravenous tPA versus tPA alone, and recruitment was completed in 2015 [45]. In patients treated with intravenous tPA, adjunctive argatroban appears safe; however, the observed clinical benefit warrants further study in a future clinical trial.

7.4 Practical Use of Intravenous tPA in Acute Ischemic Stroke

7.4.1 Protocols for Intravenous tPA Therapy

Intravenous tPA (0.9 mg/kg, maximum 90 mg) is recommended for selected patients with acute ischemic stroke who could be treated within 3 h of symptom onset. The exclusion and inclusion criteria for tPA use are listed in Tables 7.3 and 7.4. A recommended treatment plan for patients receiving intravenous tPA is explained in Table 7.5. The beneficial effect of tPA is time dependent; therefore, initiation of tPA should begin as quickly as possible. The door-to-needle time needs to be within 60 min from hospital arrival. For patients who cannot be treated within 3 h, intravenous tPA (0.9 mg/kg, maximum dose 90 mg) should also be considered for eligible patients in the time period of 3–4.5 h after a clearly defined stroke onset (Table 7.4). These are in line with recent guidelines from the American Heart Association (AHA)/American Stroke Association [46]. The eligibility criteria for treatment in this extended time window are the same as those for patients treated within 3 h, except for the following exclusion criteria: (i) patients >80 years old, (ii) those taking oral anticoagulants regardless of the international normalized ratio (INR), (iii) those with a baseline NIHSS score of >25, (iv) those with imaging evidence of ischemic injury involving more than one-third of the MCA territory, or (v) those with a history of both stroke and diabetes mellitus (Table 7.4). In general, blood pressure should be controlled below 185/110 mm Hg with antihypertensive agents before and during intravenous tPA infusion. In patients receiving intravenous tPA, clinicians should pay attention to the potential adverse effects of tPA, such as bleeding problems and angioedema that may lead to airway obstruction. Intravenous tPA could be used in patients with a seizure at the time of stroke onset, if there is supporting evidence that the residual neurologic impairments are due to a stroke and not a postictal state. Intravenous tPA in acute ischemic stroke patients with mild deficits, rapidly improving symptoms, major surgery history within 3 months, and recent myocardial infarction could be considered cautiously, and the risk of tPA use against its benefits should be assessed. Patients with rapidly improving stroke symptoms (RISS) were excluded for tPA use in clinical trials to avoid tPA treatment of transient ischemic attack. However, there is recent consensus that tPA use in RISS should be excluded only for patients who improve to a degree that any

Table 7.3 Inclusion and exclusion criteria of IV tissue plasminogen activator within 3 h from symptom onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Age ≥18 years
Exclusion criteria
Significant head trauma or stroke in the previous 3 months
Symptoms suggestive of subarachnoid hemorrhage
Arterial puncture at a noncompressible site in the previous 7 days
History of ICH
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
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
Recent experience suggests that under some circumstances—with careful consideration of risk over benefit—patients may receive fibrinolytic therapy despite one or more relative contraindications. Consider the risk-to-benefit ratio of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within the previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within the previous 21 days)
Recent acute myocardial infarction (within the previous 3 months)

aPTT activated partial thromboplastin time, *CT* computed tomography, *ECT* ecarin clotting time, *INR* international normalized ratio *PT* partial thromboplastin time, *rTPA* recombinant tissue plasminogen activator, *TT* thrombin time (From Jauch et al. [46])

remaining deficits seem nondisabling [47]. The therapeutic decision should be made on the basis of close monitoring of neurologic deficits by the physician. Despite limited evidence, patients who regain consciousness with ischemic stroke (unclear onset stroke) and have no early ischemic changes on initial brain CT can also benefit from intravenous thrombolysis [48, 49].

Assessing coagulation abnormalities is critical in administering thrombolytic agents. However, coagulation studies and platelet count are not mandatory before tPA treatment according to current guidelines, unless there is clinical suspicion for coagulation abnormality. This increases

Table 7.4 Additional inclusion and exclusion criteria of IV tissue plasminogen activator within 3–4.5 h from symptom onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3–4.5 h before beginning treatment
Relative exclusion criteria
Age >80 years
Severe stroke (NIHSS >25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and ischemic stroke

INR international normalized ratio, *IV* intravenous, *NIHSS* National Institutes of Health Stroke Scale, *rtPA* recombinant tissue plasminogen activator (From Jauch et al. [46])

Table 7.5 Treatment of acute ischemic stroke: intravenous administration of tPA

Infuse 0.9 mg/kg (maximum dose 90 mg) during 60 min, with 10% of the dose given as a bolus for 1 min
Admit the patient to an intensive care unit or stroke unit for monitoring
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has worsening neurological findings, discontinue the infusion (if IV rtPA is being administered) and obtain an emergent CT scan
Measure blood pressure and perform neurological assessments every 15 min during and after IV rtPA infusion for 2 h, then every 30 min for 6 h, and then hourly until 24 h after IV rtPA treatment
Increase the frequency of blood pressure measurements if the systolic blood pressure is >180 mm Hg or if the diastolic blood pressure is >105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels (Table 7.6)
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them
Obtain a follow-up CT or MRI scan at 24 h after IV rtPA before starting anticoagulants or antiplatelet agents

CT computed tomography, *IV* intravenous, *MRI* magnetic resonance imaging, *rtPA* recombinant tissue plasminogen activator (From Jauch et al. [46])

tPA use, which seems safe. Past warfarin use is not a contraindication provided that the INR is <1.7 according to observational studies. The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban are widely used in practice. The challenge for physicians who decide the use of thrombolytic agents is in estimating the potential increased risk of bleeding complication after thrombolytic treatment. However, these new classes of anticoagulants do not have appropriate tools for monitoring anticoagulation effects. According to the 2013 AHA guidelines for the management for acute ischemic stroke, the use of intravenous tPA in patients taking direct thrombin inhibitors or factor Xa inhibitors may be harmful and is not recommended unless sensitive coagulation parameters (such as activated partial thromboplastin time [aPTT], INR, platelet count, and ecarin clotting time [ECT]), thrombin time (TT), or appropriate direct factor Xa activity assays are normal or the patient has not taken these agents for at least 2 days. Recently, positive experiences with intravenous tPA in patients receiving direct thrombin inhibitors or factor Xa inhibitors have been reported [50–53]. However, recommendations should be conservative in the absence of accumulated experience with those non-vitamin K oral anticoagulants. Similar considerations should be given to patients who need intra-arterial tPA [15].

7.4.2 Management During and After Thrombolytic Treatment

Patients treated with tPA should be managed in a special unit such as a stroke unit or intensive care unit where close observation is available 24 h a day. Continuous cardiovascular monitoring, blood pressure control, and frequent neurologic examination should also be performed during and 24 h after thrombolysis. According to the AHA guidelines, blood pressure should be monitored every 15 min for 2 h from the initiation of tPA treatment, then every 30 min for 6 h, and then every 60 min during the rest of the 24 h after starting of tPA infusion [54]. The protocol for blood pressure control after thrombolysis is listed in Table 7.6. The recommended drugs listed in the table have a rapid onset of action and predictable effects with a low potential for overshooting.

Placement of a central catheter and arterial puncture should be avoided in the first 24 h after tPA infusion. However, considering the short serum half-life of tPA, if clinical circumstances require a central catheter for cardiovascular monitoring, such catheterization could be conducted safely an hour or more after the end of thrombolysis therapy. Placement of an indwelling bladder catheter (Foley catheter) should be restricted during and at least 30 min after tPA. Placement of

Table 7.6 Potential approaches to arterial hypertension in acute ischemic stroke patients who are candidates for acute reperfusion therapy

If the patient is otherwise eligible for acute reperfusion therapy except that the BP is >185/110 mm Hg:
Labetalol 10–20 mg IV during 1–2 min may repeat one time; or nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h. When the desired BP is reached, adjust to maintain proper BP limits. Other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate
If BP is not maintained at or below 185/110 mm Hg:
Do not administer rtPA
Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:
Monitor BP every 15 min for 2 h from the start of rtPA therapy, then every 30 min for 6 h, and then every hour for 16 h
If systolic BP is >180–230 mm Hg or diastolic BP is >105–120 mm Hg:
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or nicardipine 5 mg/h IV, titrate until the desired effect is achieved by 2.5 mg/h every 5–15 min, maximum 15 mg/h
If BP not controlled or diastolic BP is >140 mm Hg:
Consider IV sodium nitroprusside

BP blood pressure, *IV* intravenous, *rtPA* recombinant tissue plasminogen activator (From Jauch et al. [46])

a nasogastric tube should also be avoided during the first 24 h after the initiation of tPA treatment; however, as with central lines and arterial puncture, this tube can be routinely placed earlier, if necessary [55].

ICH is a major concern during and after thrombolytic therapy. If the patient develops severe headache, nausea, or vomiting or has acute hypertension or neurological deterioration, the infusion of tPA should be discontinued, and an emergent CT scan should be performed. The best ways to prevent bleeding complications are careful selection of eligible patients, meticulous care and close observation, and monitoring of patients with high blood pressure (Fig. 7.5).

7.5 Factors Affecting the Outcome of Thrombolysis

The aim of thrombolytic therapy in acute ischemic stroke is prompt restoration of blood flow to ischemic tissue with clot lysis. The results of thrombolysis are affected by multiple factors, such as the type, location, and extent of thrombus; degree of collateral circulation; underlying comorbid diseases; patient age; time to starting tPA infusion; and time to recanalization.

7.5.1 Thrombus Location, Composition, and Burden

Studies have demonstrated that proximal arteries with a large diameter are resistant to intravenous thrombolysis alone [21, 31, 56]. According to transcranial ultrasound studies, the recanalization rates with intravenous thrombolysis were 44.2% for distal MCA (M2) occlusion and 30% and 6% for proximal MCA (M1) and distal ICA, respectively [31, 56]. The successful recanalization rate negatively correlates with the thrombus burden. A thrombus <8 mm in length is more likely to be responsive to thrombolytic drugs [57, 58]. Another recent study also demonstrated that the length of occlusion with an optimal cutoff value of 12 mm in the M1 segment in patients with proximal MCA occlusion, measured on the basis of the temporal maximum intensity projection derived from CT perfusion data, was an independent predictor of intravenous tPA recanalization after 24 h and favorable clinical outcome after 3 months [59]. The age and composition of clot are also correlated with the efficacy of thrombo-

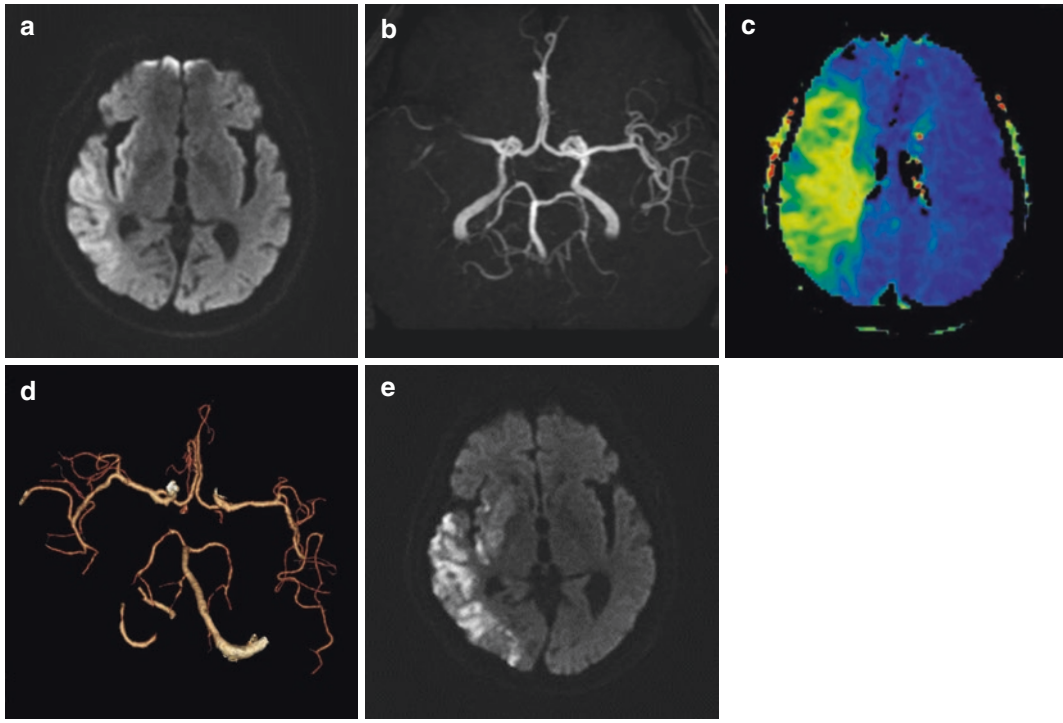

Fig. 7.5 A case of successful intravenous thrombolysis with tissue plasminogen activator (tPA). A 61-year-old woman presented with left hemiplegia, anosognosia, and eyeball deviation to the right side. The National Institute of Health Stroke Scale (NIHSS) score was 13, and tPA (0.9 mg/kg) was intravenously administrated at 4 h after stroke symptom onset. On the initial magnetic resonance image, diffusion restriction lesion was noted in the right middle cerebral artery (MCA) territory mainly involving the cortex. (**a**) Magnetic resonance angiography showing occlusion at the distal M1 segment of right MCA. (**b**) Perfusion-weighted image demonstrating delayed mean transit time in the right MCA territory. (**c**) Computed tomography angiography after 3 days of intravenous thrombolysis showing recanalization of the right MCA. (**d**) Follow-up diffusion-weighted image showing slight extension of the previous diffusion-restricted lesions (**e**). The patient's NIHSS score was 6 at discharge

lytic drugs. Intravenous tPA is likely to disrupt embolic clots with red blood cells; however, other types of thromboembolic material, such as calcification, are resistant to thrombolytic therapy. A study demonstrated that fibrin-rich cardioembolic clots achieved faster and more frequent recanalization with intravenous tPA than did large-artery atherosclerotic occlusions [60]. Recent thromboembolic clots may be more suitable targets for intravenous thrombolytic drugs than old clots, because, over time, the fibrin and plasminogen component of thrombi, which have a high affinity to tPA, become degraded and less responsive to lytic drugs. According to a case series with intravenous tPA, 20% of patients with complete or partial recanalization had early reocclusion, and the risk factors for this were a high NIHSS score (>16) at baseline and severe ipsilateral carotid artery stenosis (>70%) [61].

7.5.2 Hyperglycemia

Hyperglycemia has a detrimental effect on ischemic tissue and is significantly correlated with increased infarct size and poor outcome after intravenous tPA treatment. Additionally, hyperglycemia is a strong independent factor for failure of recanalization with thrombolytic drugs [22]. While these findings suggest that the control of hyperglycemia before reperfusion is important for achieving the beneficial effect of

intravenous tPA, there is no clinical trial data to establish this hypothesis.

7.5.3 Blood Pressure and Blood Pressure Variability

High blood pressure before and during thrombolytic treatment can increase the risk of ICH. Blood pressure variability is often reported to negatively affect the outcome of thrombolytic therapy [62]. However, there have been no large clinical trial data for this suggestion. IST-3 was a large randomized controlled trial of thrombolytic treatment within 6 h of onset of ischemic stroke. This study recorded blood pressures, blood pressure variability, and the use of blood pressure-lowering agents during the first 24 h. In this trial, high baseline blood pressure and high pressure variability during the first 24 h appeared to be associated with a poor prognosis, whereas a large reduction in blood pressure and the use of blood pressure-lowering treatment during the first 24 h was associated with a favorable clinical outcome [63].

7.5.4 Age

Despite a high mortality rate, intravenous thrombolysis seems to be beneficial for patients age 80 years or older. The occurrence of symptomatic ICH may also be increased in old patients when treated with intravenous tPA; however, there is no firm evidence yet. A total of 1,711 patients who were >80 years of age and 5,174 patients who were ≤80 years of age were analyzed in a meta-analysis of trials with intravenous thrombolysis in 2012 [64]. Patients age 80 years or older showed a similar response to those younger than 80 years, particularly when treated early. For thrombolysis with a 0–3 h time window, the ORs for a favorable clinical outcome were similar for both age groups (>80 years, OR 1.68, 95% CI 1.20–2.34; ≤80 years, OR 1.51, 95% CI 1.18–1.93). In the analysis of patients treated with intravenous thrombolysis from the SITS-ISTR registry ($n = 23{,}062$) and control patients from the VISTA registry ($n = 6166$), the ORs for favorable clinical outcome at 3 months after intravenous tPA were similar for patients >80 years old (1.4, 95% CI 1.3–1.6) compared with those ≤80 years old (1.6, 95% CI 1.5–1.7) [65]. According to those studies, excluding older patients from intravenous thrombolysis for acute ischemic stroke should be reconsidered.

7.5.5 Time to Thrombolytic Treatment

Thrombolytic treatment should be initiated within 3 h from the time of symptom onset; however, numerous previous studies demonstrated that the benefit of therapy was greater when tPA was given earlier in this time window. Patients treated within 90 min of symptom onset showed a higher improvement rate at 24 h and a higher favorable outcome at 90 days than patients treated between 91 and 180 min after symptom onset. Times of treatment within 3 h were not associated with the occurrence of ICH. A combined analysis of all studies on intravenous tPA for acute ischemic stroke revealed that the OR for a favorable clinical outcome with thrombolytic therapy compared to placebo decreased with increasing time from symptom onset to treatment (Fig. 7.6) [16]. The benefit of tPA is greater than that of placebo if the OR is >1.

7.5.6 Dosage of tPA

The dose of tPA has long been a safety concern. A lower (0.6 mg/kg) than standard (0.9 mg/kg) dose of intravenous tPA for acute ischemic stroke may be safe because of the reduced risk of ICH. Intravenous tPA at a dose of 0.6 mg/kg produces comparable clinical outcomes to the standard dose (0.9 mg/kg) in Korean patients with acute ischemic stroke [20]. Use of low-dose tPA is not infrequent in the East Asia, owing to concerns over the risk of ICH. The Enhanced Control of Hypertension and Thrombolysis Stroke Study

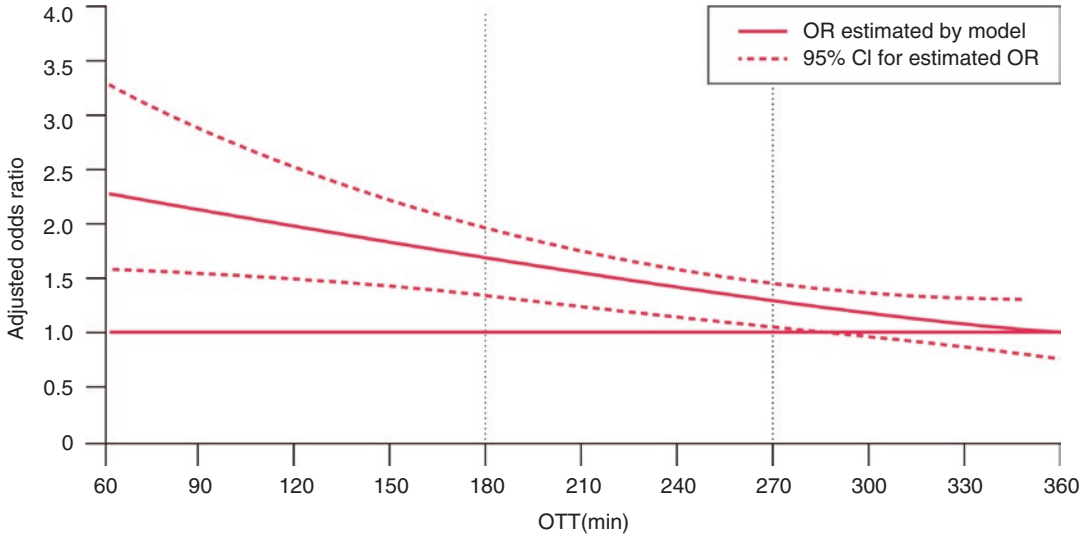

Fig. 7.6 ORs for favorable outcome at 3 months from the pooled analysis of NINDS 1 and 2 (0–3 h), ECASS I and II (0–6 h), ATLANTIS A (0–6 h), and ATLANTIS (3–5 h). *OTT* onset to treatment time, *NINDS* National Institute of Neurological Disorders and Stroke, *ECASS* European Cooperative Acute Stroke Study, *ATLANTIS* Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, *OR* odds ratio (From Hacke et al. [16])

(ENCHANTED) trial compared standard-dose tPA (0.9 mg/kg) with low-dose (0.6 mg/kg) tPA in 3,310 acute ischemic stroke patients who were within the 4.5-h time window [66]. The median age of patients was 67 years, and 63% were Asian. The primary objective was to prove the noninferiority of low-dose tPA compared with standard-dose tPA, with the primary outcome of death or disability (mRS 2–6) at 90 days. The primary outcome occurred in 53.2% of the low-dose group and in 51.1% of the standard-dose group (OR, 1.09; 95% CI, 0.95–1.25). However, the results showed a greatly reduced risk of major symptomatic ICH with the low dose (1.0% vs. 2.1%, $p = 0.01$). Death at 7 days was also reduced with the low dose (0.5% vs. 1.5%, $p = 0.01$). Mortality at 90 days did not differ significantly between the two groups (8.5% vs. 10.3%, respectively; $p = 0.07$). The ENCHANTED trial, which included predominantly Asian patients with acute ischemic stroke, did not prove the noninferiority of low-dose (0.6 mg/kg) to standard-dose (0.9 mg/kg) tPA with respect to mortality and disability at 90 days. However, there was a significantly reduced risk of symptomatic ICH with low-dose tPA.

7.6 Complications of Thrombolytic Therapy

7.6.1 Thrombolysis-Related Intracranial Bleeding

The risk of ICH increases after tPA treatment. Intravenous tPA can change the permeability and integrity of the vascular basal lamina at the site of injury, which leads to dissolution of the blood-brain barrier and the development of brain edema and ICH. The clinical and neuroradiologic factors related to an increased risk of ICH after tPA are listed in Table 7.7. These predicting factors include increasing age, stroke severity, elevated blood pressure and serum glucose, large diffusion-weighted imaging lesion size, cerebral microbleeds, and leukoaraiosis [67, 68]. However, no individual factor can precisely identify patients with ischemic stroke at a high risk of ICH.

ICH after systemic thrombolysis typically occurs within the first 24–36 h after the initiation of treatment. The rates of symptomatic ICH were about 5–7%, and most of tPA studies have shown similar rates [10]. ICH in acute ischemic stroke after thrombolysis therapy is called hem-

Table 7.7 Predictors for post-thrombolysis symptomatic intracranial hemorrhage in ischemic stroke

Clinical
Increasing age
Higher National Institutes of Health Stroke Scale (NIHSS) score at admission
Elevated blood pressure and serum glucose concentration
Pretreatment use of aspirin and clopidogrel combined or alone
A history of hypertension and/or statin prescription
Congestive heart failure
Ischemic heart disease
Atrial fibrillation
Renal impairment
Neuroimaging
Visible ischemic lesion in brain imaging/ASPECTS ≤7
Leukoaraiosis
Large lesion size on diffusion-weighted imaging
Cerebral microbleeds (T2*-weighted gradient-recalled echo [T2* GRE] magnetic resonance [MR] imaging)
Hyperintense acute reperfusion marker on MR fluid-attenuated inversion recovery scans
Abnormal visibility of transcerebral veins (AVV) on MRI T2* GRE scans
Very low cerebral blood volume

From Karaszewski et al. [68]

orrhagic transformation and classified clinically as symptomatic or asymptomatic. It was also radiologically classified by the ECASS group into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) [69]. Each class is divided into two types: HI-1 is defined as small petechial hemorrhage along the margins of the infarct, HI-2 as confluent petechial hemorrhage within the infarcted area but no space-occupying effect, PH-1 as blood clot <30% of the infarcted area with a space-occupying effect, and PH-2 as blood clots in >30% of the infarcted area with a space-occupying effect. The risk of symptomatic hemorrhagic transformation after thrombolysis in a pooled analysis of six trials was 5.9% in the tPA groups compared to 1.1% in the control groups [16].

Risk scoring systems predicting tPA-related ICH have been developed. However, recent meta-analysis of those risk instruments, including GRASPS (Glucose, Race, Age, Sex, Pressure, Stroke Severity), DRAGON (Dense Artery, Rankin Score, Age, Glucose, Onset to Treatment Time, NIHSS), SEDAN (Sugar, Early Infarct Signs, Dense Artery, Age, NIHSS), HAT (Hemorrhage after Thrombolysis), and THRIVE (Totaled Health Risks in Vascular Events), found that there was only modest predictive value for identifying patients at a high risk of ICH [70–75]. The low predictive value of a risk prediction scoring system including clinical and CT-based imaging variables indicates our lack of understanding of the fundamental mechanisms of tPA-related symptomatic ICH, which are probably complex and associated with individual patient characteristics. Developing new methods to identify patients at a high risk of tPA-related ICH, or new measures to decrease hemorrhagic risk, are real challenges in acute stroke treatment research.

Symptomatic ICH should be considered when abrupt neurological deterioration, a loss of consciousness, severe headache, nausea and vomiting, or a sudden elevation of blood pressure developed within the first 24 h of treatment. In this setting, tPA infusion should be discontinued and brain CT should be performed. Blood samples should be collected by cross matching, and prothrombin time, aPTT, platelet count, and fibrinogen should be measured. If symptomatic ICH is detected on CT, the administration of cryoprecipitate and platelet concentration should be considered [76]. Prothrombin complex concentrates, recombinant factor VIIa, aminocaproic acid, and tranexamic acid are also available treatment options [77, 78]. Neurosurgical evacuation can be considered; however, this technique is still controversial (Fig. 7.7).

7.6.2 Systemic Bleeding

Oozing from intravenous infusion sites, petechiae, and gum bleeding are typical mild systemic bleeding complications that do not need discontinuation of tPA. Serious systemic bleeding complications are gastrointestinal or genitourinary system bleeding. In this setting, tPA should be discontinued. Because pericardial

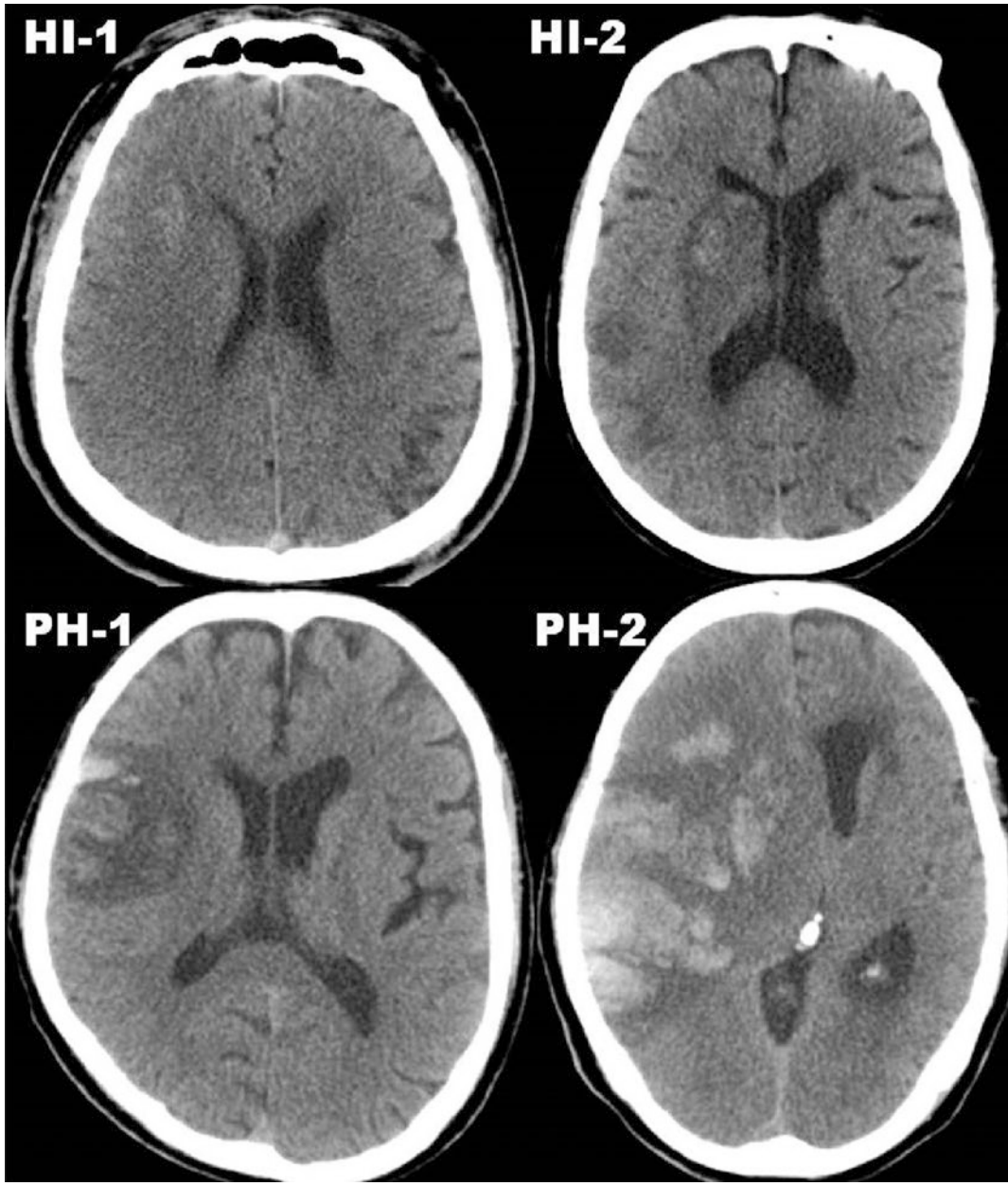

Fig. 7.7 Noncontrast computed tomography scans showing examples of the radiographic types of thrombolysis-related intracranial hemorrhage, according to the European Cooperative Acute Stroke Study classification. HI-1, hemorrhagic infarction type 1; HI-2, hemorrhagic infarction type 2; PH-1, parenchymal hematoma type 1; PH-2, parenchymal hematoma type 2

bleeding in patients with recent myocardial infarction is a rare complication of tPA, patients who become hypotensive after tPA treatment should be urgently assessed with echocardiography.

7.6.3 Angioedema

In 1–8% of patients treated with tPA, orolingual angioedema often occurs in the orolingual area [79, 80]. However, it is usually mild and transient.

7.6.4 Reperfusion Injury

Reperfusion injury is also a serious complication after recanalization of an occluded vessel that potentiates stroke damage. It attenuates the benefit of restoration of cerebral blood flow after thrombolytic treatment for acute ischemic stroke. To understand this paradoxical injury, we emphasize the phenomenon in which reperfusion of blood to the ischemic area may lead to increased excitatory neurotransmitters like glutamate, which results in rapid influx of calcium and excitotoxicity [81]. Restored blood flow may allow the formation of free radicals [82]. Another main contributor to reperfusion injury is the no-reflow phenomenon in which blood flow to the ischemic tissue is still not improved after restoration of spontaneous circulation [83]. It results from microvessel lumen collapse, which is caused by the local activation of platelets, leukocytes, and coagulation signaling cascades, and microvessel compression by tissue edema and endothelial cell swelling. In addition, broken clot due to tPA may cause distal embolization. Owing to the lack of understanding of the complex mechanism and the absence of an effective treatment, postischemic reperfusion injury presents a big challenge to physicians and researchers. Further understanding of the molecular and cellular response to reperfusion injury and development of advanced neuroimaging techniques could produce significant improvements in the treatment of stroke.

7.7 Combination of Intravenous Thrombolysis and Other Treatment Options

The combination of intravenous thrombolysis and other treatment options has not demonstrated a beneficial effect thus far in clinical studies. Combining thrombolysis with anticoagulation was assessed in the MAST-E study, which combined streptokinase and heparin [84]. There was no significant beneficial effect, and the study was prematurely terminated because of increased ICH in the combination group. Streptokinase with antiplatelet treatment is also associated with a higher risk of ICH in the MASE-I study [85]. Therefore, no antithrombotics are allowed within 24 h of tPA treatment.

Combining neuroprotective agents with thrombolysis have been studied in animal models of stroke and in clinical trials. MK-801, a glutamate antagonist, with tPA showed more beneficial effects than did tPA alone in a stroke model, reducing neurologic damage after brain ischemia [86]. In 1999, Zhang et al. also demonstrated that anti-CD18 antibodies with thrombolysis extended the therapeutic time window of thrombolysis from 2 to 4 h [87]. Neuroprotective agents are believed to stabilize vascular endothelium and attenuate reperfusion injury, reducing the adverse effects of thrombolysis. However, these results were not proved by clinical studies. There were another two clinical studies of combination treatment in which lubeluzole and clomethiazole were tested. Lubeluzole inhibits the glutamate-activated nitrous oxide pathway, and clomethiazole enhances the action of the GABA neurotransmitter. These drugs were administered with tPA in acute stroke patients [88, 89]. There was no difference between the combination group and the tPA alone group in the primary outcome measures of BI, mortality, ICH, and serious adverse events. This study showed that such a combination treatment is safe and feasible.

7.8 Intravenous Thrombolysis Followed by Endovascular Mechanical Thrombectomy

Intra-arterial endovascular mechanical thrombectomy has a higher probability of successful recanalization than intravenous thrombolysis alone. However, it is available only in comprehensive stroke centers, and it requires time to activate an endovascular therapy team. Thus, the combined use of intravenous thrombolysis and intra-arterial endovascular recanalization therapy for acute large-artery occlusion could be useful because intravenous tPA should be done during the preparation for endovascular

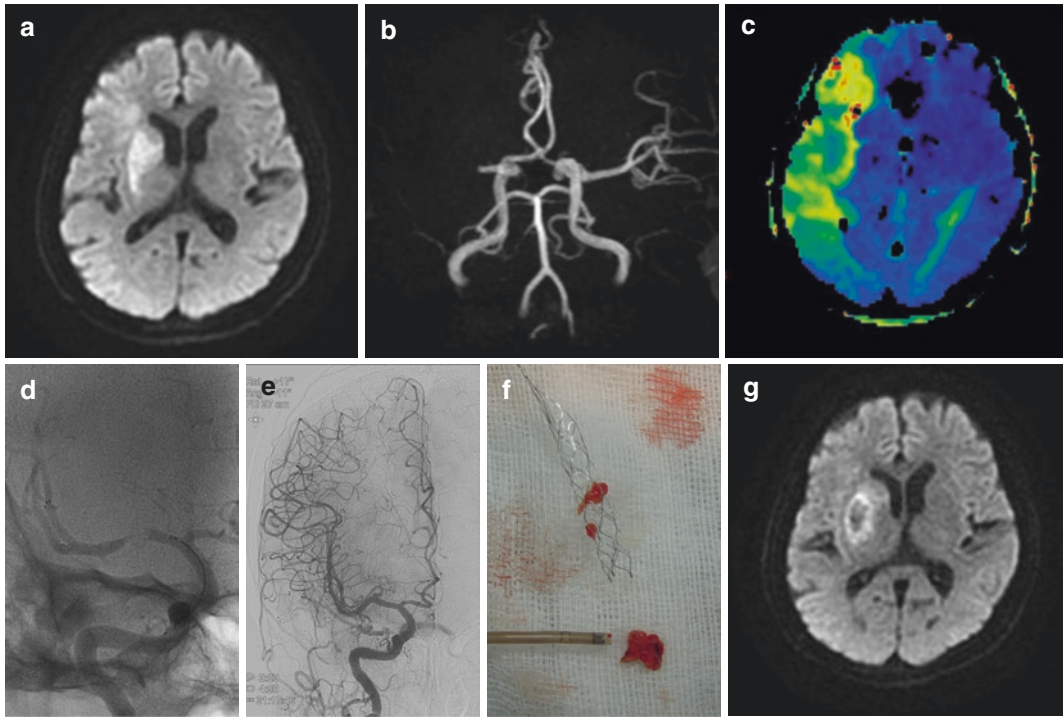

Fig. 7.8 A case of combined treatment with intravenous tissue plasminogen activator (tPA) and endovascular mechanical thrombectomy. A 67-year-old male patient presented with right hemiplegia and right-sided eyeball deviation. His National Institutes of Health Stroke Scale (NIHSS) score was 12 and stroke symptoms developed 3 h previously. Intravenous tPA was started at 220 min after stroke onset. The initial diffusion-weighted image showed diffusion restriction in the right basal ganglia and frontal cortex. (**a**) Magnetic resonance angiography image showing the occluded right middle cerebral artery at the M1 segment. (**b**) The mean transit time is delayed in the right middle cerebral artery territory on the perfusion-weighted image. (**c**) Neurologic deficits did not improve after tPA administration. Thus, subsequent endovascular mechanical thrombectomy was performed (**d**), and full recanalization was achieved with successful removal of the thrombi (**e**, **f**). (**g**) Follow-up diffusion-weighted image showing no significant extension of the previous lesion; however, hemorrhagic transformation occurred in the right basal ganglia. The patient's NIHSS score was 3 at discharge

treatment. If neurologic deficits remain after tPA infusion, intra-arterial endovascular therapy could be considered for the completion of vessel recanalization. Recent randomized controlled trials (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA, and REVASCAT) support the superiority of endovascular mechanical recanalization therapy incorporating the use of second-generation mechanical thrombectomy devices (stent retrievers) as the best medical treatment with or without IV-tPA for an acute large-artery occlusion. Intravenous tPA followed by endovascular therapy is now increasingly used in clinical practice [90–94] (Fig. 7.8).

Conclusions

Within 3 h of a clear onset of stroke symptoms, intravenous tPA should be initiated for eligible patients with acute ischemic stroke. Although there are additional relative exclusion criteria, intravenous tPA could also be used in acute ischemic stroke patients if treatment is initiated within 3–4.5 h of a clearly defined stroke symptom onset. The most critical factor in thrombolytic therapy of acute ischemic stroke is rapid initiation of treatment. The advantages of thrombolysis continuously decrease over time from stroke onset. The sooner tPA is intravenously administered after acute ischemic

stroke, the more likely it is to be beneficial. The contraindications of tPA need to be discussed in terms of the benefit-risk ratio of thrombolytic therapy. Recanalization is closely related to improved functional outcomes and decreased mortality in acute ischemic stroke. Some of the factors affecting successful thrombolytic therapy are the location of the occlusion; degree of collateral flow development; and clot characteristics such as size, composition, and source. Stroke with large-vessel occlusion shows poor response to intravenous thrombolytic therapy. For patients with this type of stroke, integrating endovascular mechanical thrombectomy and intravenous thrombolysis will enhance the prospects of greatly improving functional outcomes.

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Acute Ischemic Stroke in Children

8

Soonhak Kwon

Stroke can occur at any time during the life, but causes, clinical features, and other clinical perspectives differ depending on the patient's age. In this chapter, I try to focus on risk factors, clinical manifestations, diagnosis, management, and other important issues in childhood arterial ischemic stroke.

8.1 Background

Arterial ischemic stroke (AIS) in children is a rare but serious condition which may result in neurologically significant sequelae such as permanent cognitive, motor deficits, and epilepsy. While tremendous efforts have been made to build up the knowledge about adult stroke, it still remains under-recognized even among pediatricians. Previous reports suggest that etiologies, clinical features, and outcomes are different from those of adult stroke. Whereas adult risk factors are primarily related to cardiac arrhythmia, hypertension, and atherosclerosis, a wide range of multiple underlying systemic factors were reported in childhood AIS, of which prothrombotic conditions, infection, arteriopathy, sickle cell disease, congenital heart diseases, and hereditary/metabolic conditions seem to play a major role in the pathogenesis of childhood AIS [1–4].

Based on the data from recent population-based studies of pediatric stroke, the overall annual incidence is estimated at 1–3 per 100,000 children [5–7]. Based on estimates from population-based studies of neonates younger than 1 month of age, the incidence of perinatal stroke is even higher and occurs in approximately 1 in 4000 term births [8].

Onset of age in childhood AIS ranged from 1 month to 13 years [9].

Childhood AIS usually presents with sudden onset of focal neurologic signs and middle cerebral artery (MCA) is the most frequently affected. Perinatal stroke is quite different from pediatric and adult stroke in many aspects, mainly overlapping with hypoxic ischemic encephalopathy. In addition, it presents with nonspecific or vague signs such as apnea, sleepiness, irritability, poor feeding, hypotonia, and seizures. Many of these children are left with permanent neurologic deficits, epilepsy, and behavioral and cognitive impairments.

The diagnosis of childhood AIS is often delayed because the initial presentation can be nonspecific. As a result, neuroimaging is crucial in defining diagnosis. MRI with diffusion-weighted image is considered as the most sensitive tool to identify early and small lesions.

Since little evidence still exists regarding optimal treatment strategies to improve outcomes, standard treatment practices are mainly

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extrapolated from research in adults. The outcome is mainly dependent on stroke size and site, comorbid conditions, and age of onset [10].

8.2 Risk Factors of Childhood AIS

The risk factors of childhood AIS are still poorly understood, mainly due to its low incidence in the pediatric population and the lack of sufficient data, even though recent studies have identified lots of presumptive risk factors and have identified novel associations with childhood AIS. As per previous studies, the traditional risk factors in adults, such as hypertension, atherosclerosis, and diabetes mellitus, are uncommon among children with AIS. More than one risk factor is often identified, but the etiology remains unclear in the majority of cases and about one fourth of cases are still considered as idiopathic or unknown [11]. Known major risk factors include cardiac disorders, preceding infections, vasculopathies such as moyamoya disease, prothrombotic conditions such as sickle cell disease or leukemia, and genetic conditions (Table 8.1).

With regard to cardiac risk factors, 8–31% of children with AIS had cardiac diseases such as congenital heart disease (CHD), especially complex CHD, valvular heart disease, cardiac arrhythmias, and cardiomyopathy at initial presentation [12–15]. Structural or functional alterations of the cardiac walls, valves, and major vessels may result in aberrant blood flow and formation of thrombi that can spread to the cerebral vessels, especially in the case of right-to-left shunting. The role of patent foramen ovale (PFO) for childhood AIS has been debated because a PFO can act a potential right-to-left shunt and might allow emboli to reach the cerebral arteries. However, an isolated PFO was reported in only about 5% of children, far less than the prevalence of the general population. Furthermore the role and benefit of its closure in otherwise cryptogenic childhood AIS remain unclear [14–17].

Central nervous system (CNS) infections such as meningitis and encephalitis have been implicated as causes of childhood AIS. The common pathogens associated with stroke include human immunodeficiency virus (HIV), varicella zoster virus (VZV), Japanese B encephalitis virus, *Mycobacterium tuberculosis*, *Taenia solium*, cryptococcus, aspergillosis, histoplasmosis, and mucormycoses in adults [18]. Likewise preceding minor infections can highly be associated with childhood AIS [14, 19]. This association was more significant in children with unilateral stenosis called a focal cerebral arteriopathy (FCA) compared to those with other arteriopathies such as moyamoya disease [1]. Minor infections might be responsible for the pathogenesis of stroke, either by causing a prothrombotic condition or direct vascular injury. Varicella zoster virus-related arteriopathy is known to be the case of a direct vascular infection leading to AIS [20, 21]. Other pathogens such as adenoviruses

Table 8.1 Risk factors of ischemic stroke in children

Cardiac disorders	Congenital heart diseases, especially cyanotic or complex
	Endocarditis, aortic/mitral stenosis, cardiac arrhythmia
Infections	Meningitis, encephalitis, sinusitis, otitis media
Vascular disorders/	Moyamoya disease, Takayasu disease, Kawasaki disease
Vasculitis	Fibromuscular dysplasia, SLE, JRA, polyarteritis nodosa
	Dermatomyositis, hemolytic uremic syndrome
	Inflammatory bowel diseases, TCA/FCA, migraine
Prothrombotic conditions	Polycythemia, thrombocytosis, antiphospholipid antibodies
	DIC, antithrombin III/protein C/protein S deficiency
	Factor V Leiden deficiency
Sickle cell disease	
Genetic/metabolic disorders	Homocystinuria, MELAS, glutaric acidemia type I, Fabry disease, Menkes syndrome, urea cycle disorders
	CADASIL
Trauma	Arterial dissection, A-V fistula, pseudoaneurysm
Drugs	Cocaine, amphetamine
Others	Radiation, ECMO

TCA transient cerebral arteriopathy, *FCA* focal cerebral arteriopathy, *DIC* disseminated intravascular coagulation, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *ECMO* Extracorporeal membrane oxygenation

and *Mycoplasma pneumoniae* have also been implicated in pediatric case reports [22, 23].

Arteriopathy is one of the most common diagnostic findings in childhood AIS [12]. A recent study also showed the evidence of arteriopathy in majority of patients who underwent arterial imaging [1]. The subtypes include arterial dissection, moyamoya disease, and FCA. Many cases of arterial dissections may be associated with significant or even minor trauma [24] and some with connective tissue disorders such as Ehlers-Danlos or Marfan syndrome, but are often unclear [25]. The diagnosis of arterial dissection can be made by pertinent clinical features as well as magnetic resonance imaging (MRI)/magnetic resonance angiogram (MRA) or conventional angiography. Moyamoya disease or syndrome is a non-inflammatory progressive arteriopathy characterized by bilateral stenosis of major cerebral arteries with collateralization which results in the pathognomonic "puff-of-smoke" appearance on conventional cerebral angiogram. Moyamoya disease commonly occurs in previously healthy children in Japan, Korea, and other East Asian countries and may be associated with RNF213, a susceptibility gene for MMD [26, 27]. Moyamoya syndrome can be associated with neurofibromatosis, sickle cell disease, Down syndrome, radiation, and other conditions [28]. FCA is considered as focal cerebral arterial stenosis of unknown etiology. Inflammatory or parainfectious process might contribute to the development of FCA because a preceding mild upper respiratory infection is highly associated with FCA. It has also been suggested that varicella or other viral illnesses can be the causal factor in focal unilateral stenosis of a large cerebral artery [1, 21, 29].

Hypercoagulable state may contribute to childhood AIS risk by arterial thrombosis or embolism from the venous thrombus through a right-to-left cardiac shunt. The risk factors include thrombocytosis; antiphospholipid antibodies; polycythemia; iron deficiency anemia; anticoagulant deficiencies of protein C, protein S, or antithrombin; increased lipoprotein; factor V Leiden mutation (G1691A); prothrombin polymorphism (G20210A); and methylenetetrahydrofolate reductase mutation (MTHFR C677T and A1298C) [10, 30, 31]. Anticoagulant deficiencies tend to occur after viral infection such as varicella [10]. Hypercoagulable state is relatively common in children and often interacts with other risk factors in a multifactorial manner, rather than being an independent cause in childhood AIS. In addition, further trustworthy studies are required to evaluate the association of genetic polymorphisms and childhood AIS.

Sickle cell anemia (SCA) is one of the major risk factors in childhood AIS, which might develop cerebral arteriopathy, moyamoya syndrome, and intracardiac shunting. Abnormal transcranial Doppler (TCD) of the middle cerebral artery or internal cerebral artery (average mean maximum velocity ≥200 cm/sec) was able to predict stroke [32]. The prevention is partly possible through chronic blood transfusion in children with SCA and abnormal TCD velocities [33, 34].

Many inborn metabolic disorders are likely to be associated with childhood AIS, even though they are rare. They include homocystinuria from cystathionine-β-synthase deficiency, Fabry disease, Menkes syndrome, urea cycle disorders, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [31].

Trauma has been reported as a common risk factor in childhood AIS. Common types of injury include motor-vehicle accidents, non-accidental trauma, and sports-related injuries [19]. The putative mechanisms are thought to be stretching or tearing of major arteries from sudden, forceful hyperextension or rotation of the neck. This leads to arterial dissection, arteriovenous fistula, or pseudoaneurysm which ultimately interrupts blood flow or causes thromboembolism [35].

Cocaine or amphetamine is another possible etiologic factor in childhood AIS, especially among adolescents. This may result from hypertension or vasospasm [36]. Other sympathomimetic agents such as methylphenidate remain unclear.

Regardless of underlying malignancy, cranial radiation and chemotherapy may increase risk of childhood AIS [37–39].

8.3 Clinical Presentation

The clinical presentation of childhood AIS is quite different from adults' in many aspects. It depends on the age and the involved artery.

Infant and younger children commonly present with nonspecific symptoms such as lethargy, decreased activities, seizures, or mild fever at the onset, while older children and adolescents often present with more specific symptoms such as hemiplegia. Typical features of AIS depending on the involved arterial territory are summarized in Table 8.2. Generally speaking, the presence of hemiparesis, hemisensory deficit, aphasia, or hemianopsia suggests the involvement of one or more of major cerebral arteries, while ataxia and multiple cranial nerve signs suggest the involvement of branch vessels of vertebrobasilar arteries. Small- to medium-sized events tend to present with acute onset focal deficit with preserved consciousness, while larger events tend to have more severe focal deficits and alteration of consciousness. Pure motor or sensory deficits from deep penetrating artery occlusion are rare in children. Furthermore, acute hemiparesis is more likely due to other conditions such as postictal Todd's paralysis, migraine, and neuro-infectious or inflammatory diseases in children. Seizures have been noted in about one third to half of cases, which means that they can be part of major clinical presentations regardless of ages and independently from the subtype in childhood AIS [40]. Furthermore, the patients who had seizures within first 24 h will be at a higher risk for epilepsy over the next 6 months [41]. Strokes from metabolic causes such as MELAS frequently present with a progressive course of stroke-like episodes.

Table 8.2 Clinical features of ischemic stroke depending on the involved location

Large vessel occlusion	
Internal carotid A	Hemiparesis, hemisensory loss, hemianopsia, aphasia
Anterior cerebral A	Hemiparesis, hemisensory loss (legs)
Middle cerebral A	Hemiparesis, hemisensory loss (face/arms), hemianopsia, aphasia
Vertebrobasilar A	Coma, bilateral motor/sensory deficits, cerebellar signs, cranial nerve signs, dizziness
Posterior cerebral A	Hemianopsia (macular sparing), visual agnosia oculomotor nerve palsy, anomic aphasia
Branch vessel occlusion	
ACA branches	
MCA branches	
PCA branches	Midbrain syndrome, Weber syndrome, thalamic syndrome
BA branches	SCA syndrome, AICA syndrome, PICA syndrome, Benedikt syndrome, Millard-Gubler syndrome, locked-in syndrome
Deep penetrating artery occlusion	
Lenticulostriate A	Pure motor hemiparesis
Thalamogeniculate A	Pure sensory loss
Perforating branches of BA	Dysarthria/clumsy hand, ataxic hemiparesis

A artery, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *BA* basilar artery, *SCA* superior cerebellar artery, *AICA* anterior inferior cerebellar artery, *PICA* posterior inferior cerebellar artery

8.4 Diagnostic Approach of Childhood AIS

The diagnosis of childhood AIS is not easy and often delayed due to subtle and nonspecific clinical presentations as well as a complicated differential diagnosis listed in Table 8.3. Considering the complexity, the sudden onset of a focal neurological deficit can be stroke until proven otherwise. Besides hemiparesis, hemisensory, aphasia, and visual or balance impairment also occur. With respect to obtaining clinical history, a vari-

Table 8.3 Differential diagnosis of ischemic stroke in children

Space-occupying lesions: brain tumors, brain abscess, etc.
Hemiplegic migraine
Cerebral sino-venous thrombosis
Seizure related: Todd's paralysis, hemiplegic seizures, etc.
Infection: meningitis, encephalitis, cerebellitis, etc.
Inflammatory diseases: ADEM, multiple sclerosis, NMO, etc.
RPLS
Pseudotumor cerebri
Drug intoxication
Metabolic disorders
Mitochondrial disorders: MELAS
Psychogenic disorders

ADEM acute disseminated encephalomyelitis, *NMO* neuromyelitis optica, *RPLS* reversible posterior leukoencephalopathy syndrome, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

ety of risk factors for childhood AIS should be considered and particular attention should be paid to the presence of recent infections, trauma, congenital heart diseases, family history, etc. A complete physical and neurological examination should be performed considering the brain territories potentially involved.

In general, diagnostic investigation in childhood AIS is more complex and extensive than in adult strokes due to a variety of different causes and a complicated differential diagnosis.

Neuroimaging is essential to make a confirmative diagnosis. In the acute setting, laboratory evaluation involves a complete blood counts (CBC), routine chemistry, electrolytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), coagulation studies, lipid profiles, toxicology screen, and β-hCG in adolescents. Further evaluation into specific conditions such as genetic, metabolic, vasculitic, and infectious diseases should be considered under different circumstances (Table 8.4). Electrocardiogram and echocardiogram with venous saline injection are mandatory for any children with suspicion of congenital heart disease or unknown etiology. In some cases, hemoglobin electrophoresis may be indicated to identify SCA or other hemoglobinopathies.

Table 8.4 Laboratory evaluation of children with ischemic stroke

CBC, electrolytes, glucose, LFT profiles, BUN/Cr, ESR, CRP, etc.
Coagulation studies: PT/PTT, fibrinogen, D-dimer, protein C, protein S, antithrombin III, factor VIII, factor V Leiden, etc.
ANA, anti-DNA, antiphospholipid antibodies
Hemoglobin electrophoresis if necessary
Lipid profiles: cholesterol, TG, LDL, HDL, etc.
Screening for IEM: ABGA, ammonia, urine organic acids, plasma amino acids, carnitine, if necessary
Urine toxicology screen
Urine β-hCG (adolescent)
Mitochondrial work-up: lactate/pyruvate, mitochondrial DNA mutation, if suspected
Lumbar puncture if necessary
Viral work-up: VZV, HSV, EBV, enterovirus, if suspected

CBC complete blood count, *LFT* liver function test, *BUN/Cr* blood urea nitrogen/creatinine, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT/PTT* prothrombin time/partial thromboplastin time, *ANA* antinuclear antibody, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *IEM* inborn errors of metabolism, *ABGA* arterial blood gas analysis, *hCG* Human chorionic gonadotropin, *VZV* Varicella zoster virus, *HSV* herpes simplex virus, *EBV* Epstein–Barr virus

To determine whether the focal neurological deficit is vascular origin or not, it requires a high-grade neuroimaging. Although brain computer tomography (CT) can exclude hemorrhagic stroke and be a first-line tool for the diagnosis of childhood AIS, especially in mature AIS, brain MRI with diffusion-weighted imaging became the gold standard modality for the evaluation of early and small infarcts due to its greater sensitivity and specificity [42]. Diffusion-weighted MRI can demonstrate the lesions within half an hour of onset and up to a week after onset (Figs. 8.1 and 8.2). Magnetic resonance angiography (MRA) or CT angiography (CTA) is considered as the first-line imaging modality unless the case is suggestive of small-vessel occlusion in which case conventional angiography is indicated. MRA may be sufficient to make a diagnosis of moyamoya disease if it shows the typical "puff-of-smoke" pattern of stenosis or occlusion of major cerebral arteries and the abnormal arterial vascular network near the steno-occlusive lesions (Fig. 8.3). However, conventional angiography is warranted because MRA may underestimate or overestimate the degree of condition. By recommendation, the vascular imaging should be done within the first 24 h after onset of symptoms [43]. Single photon emission computed tomography (SPECT) may be helpful to detect areas of hypoperfusion present prior to infarction. Doppler studies including transcranial Doppler imaging can provide valuable dynamic information regarding flow patterns but are still limited in pediatric practice.

8.5 Treatment of Childhood AIS

The main objective of treatment of childhood AIS is to protect the developing brain by minimizing acute injury from various causes. Since clinical data are quite limited regarding both acute management and secondary prevention of childhood AIS, treatment guidelines are mainly extrapolated from studies in adults. Initial man-

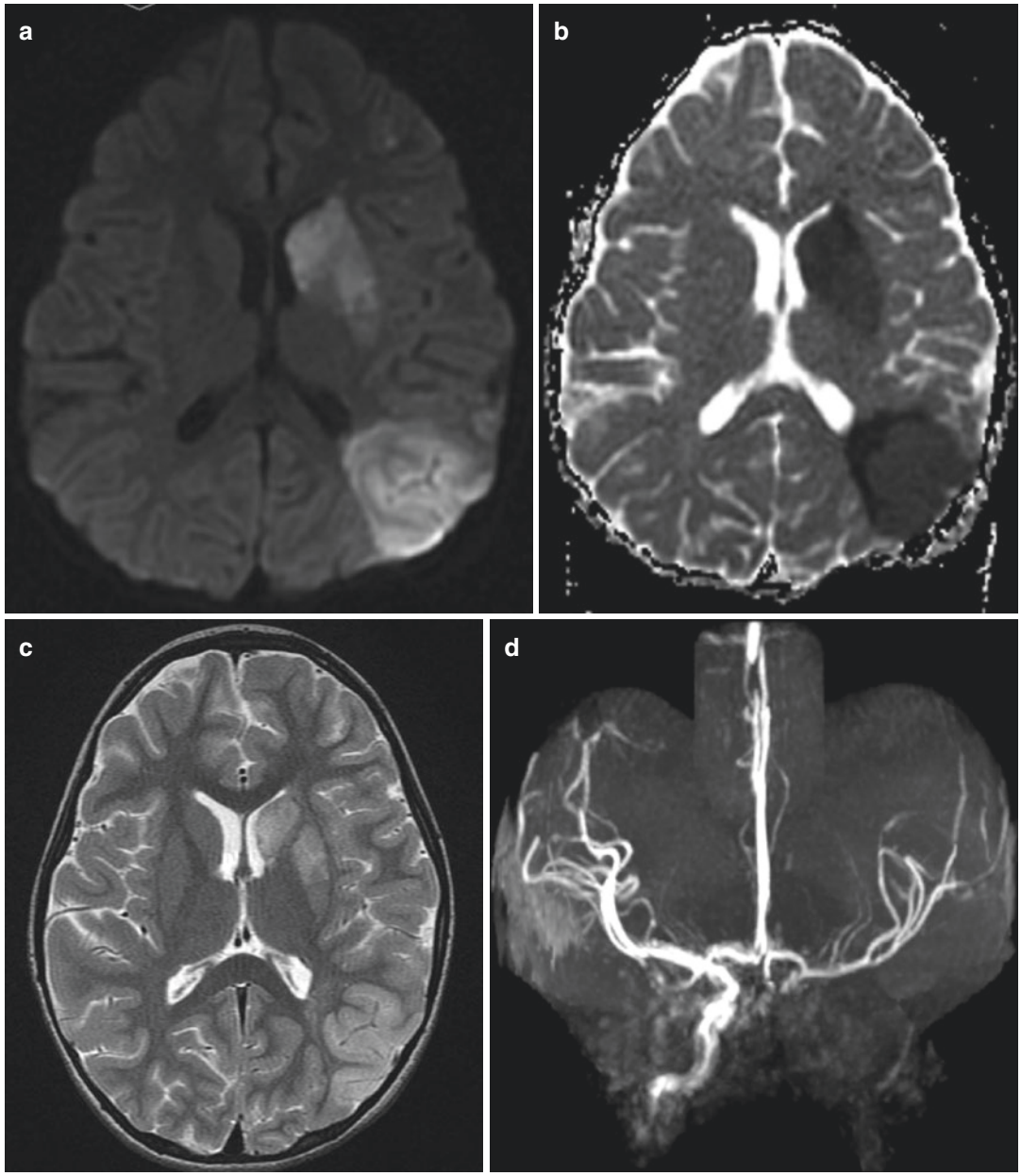

Fig. 8.1 Brain infarction involving the L. MCA territory from the complete occlusion of Lt. ICA in a 5-year-old girl with mycoplasma pneumonia. Diffusion-weighted MRI (**a**), ADC map (**b**), and T2-weighted axial images (**c**) show an infarct involving the Lt. temporal lobe and the Lt. basal ganglia. MRA (**d**) shows no demonstrable contrast filling of Lt. ICA suggestive of complete occlusion

agement of childhood AIS should emphasize supportive cares to minimize the acute brain injury. This includes airway stabilization, administration of oxygen, maintenance of normal blood glucose, normalization of blood pressure to age appropriate ranges, and control of fever or seizures if present.

Several hyperacute interventional options such as intravenous or intra-arterial administration of tissue plasminogen activator (tPA) and endovascular clot retrieval devices are available in adults, but guidelines do not recommend the use of them in children outside specific research protocol yet. However, these techniques have

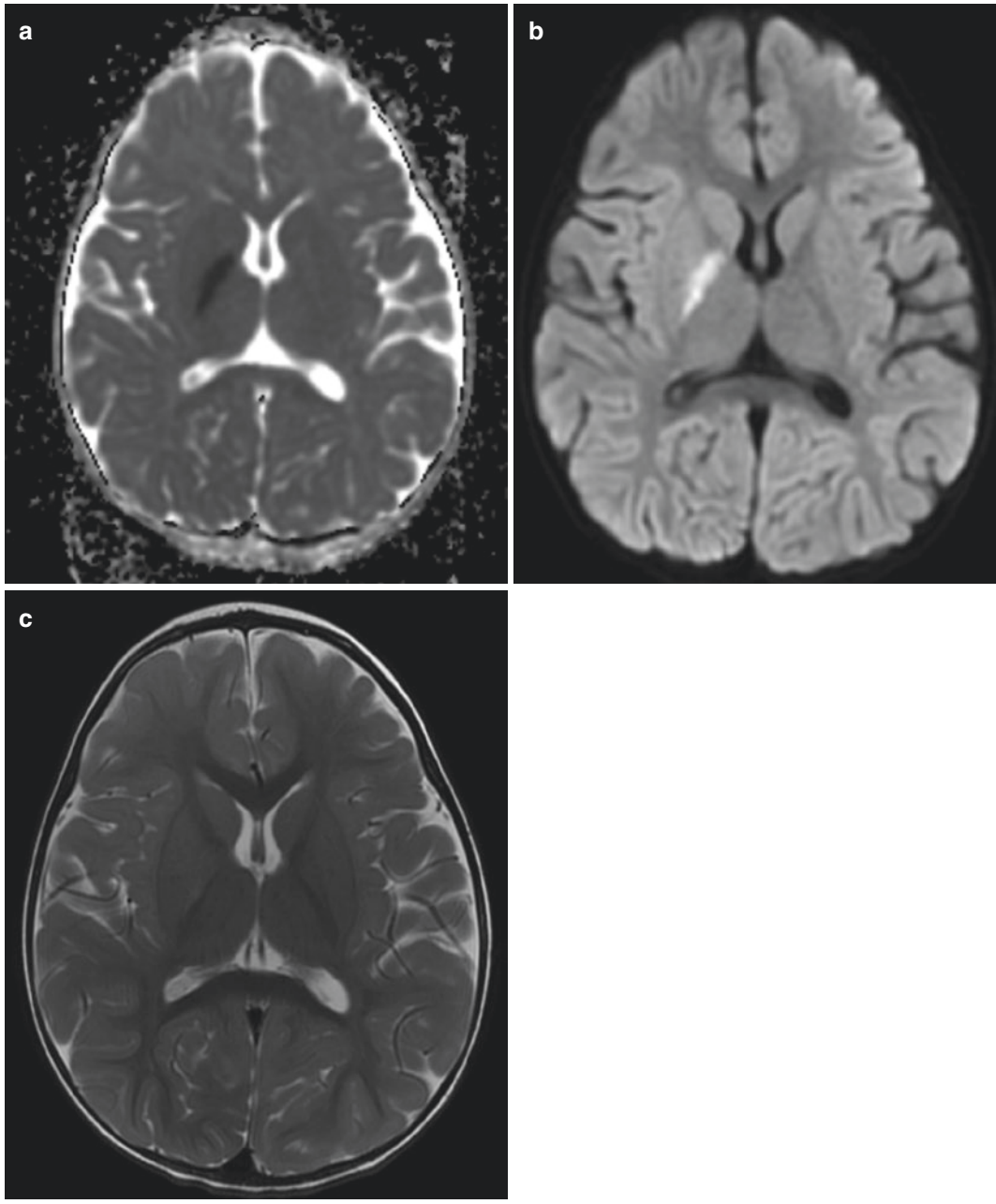

Fig. 8.2 A lacunar infarct of unknown etiology in the right basal ganglia in a 17-month-old girl. Diffusion-weighted MRI (**a**), ADC map (**b**), and T2-weighted axial images (**c**) show an infarct of hyperacute or acute stage involving right basal ganglia of lenticulostriate artery territory. There is only a small area of subtle hyperintensity in T2-weighted image

been applied to children with fair results despite the lack of evidence of safety and efficacy in children [4, 44–47].

There are no randomized controlled trials on antithrombotic therapy in childhood AIS with the exception of AIS from SCA, but guidelines recommend its use in several specific conditions such as arterial dissection, cardioembolism, prothrombotic conditions, and recurrent AIS while on antiplatelet therapy based on expert consensus, cohort studies, and extrapolation from adult studies. It is important that hemorrhagic stroke

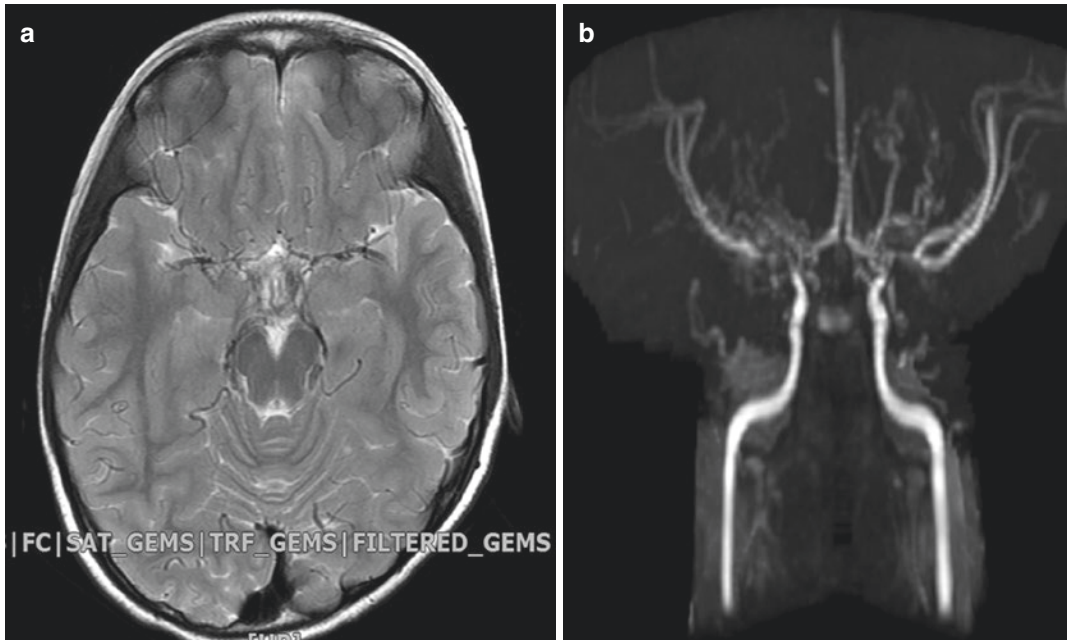

Fig. 8.3 Moyamoya disease depicting the characteristic "puff-of-smoke-like" arterial structures in an 11-year-old girl. MRI T2-weighted image (**a**) shows reduced luminal caliber of fluid void signals in region of circle of Willis. MRA (**b**) shows reduced luminal caliber of terminal portions of both carotid arteries and M1 segments of middle cerebral arteries along with collaterals at the base of the brain

should be excluded before starting the treatment. Childhood AIS is commonly treated with antithrombotic agents, such as heparins (UFH, unfractionated heparin, or LMWJ, low molecular weight heparin) or even aspirin except for a case of SCA. The American College of Chest Physicians (ACCP) recommends all non-sickle cell childhood AIS should be treated with UFH or LMWH for 5–7 days and until cardioembolic stroke and arterial dissection are excluded. For cases of cardioembolic stroke or arterial dissection, they should be on anticoagulation for 3–6 months. Heparin-based anticoagulation should be monitored with anti-factor Xa activity. It is considered as a therapeutic range 0.30–0.7 anti-factor Xa activity U/mL (activated partial thromboplastin time 60–85 s) for unfractionated heparin in samples obtained 4 h after initial administration or every change in the dose and 0.5–1.0 anti-factor Xa activity U/mL for LMWH in samples 4 h after subcutaneous injections.

After discontinuation of anticoagulation with antithrombotic agents, long-term aspirin therapy is recommended in all children with AIS (Table 8.5) [48]. The recommendation dose is that 3–5 mg/kg per day is reasonable considering a reduction to 1–3 mg/kg in the case of dose-related adverse events [49]. The optimum duration of aspirin therapy is poorly defined, but a

Table 8.5 Acute treatment of children with ischemic stroke

Supportive management for neuroprotection: airway stabilization, control of blood glucose, temperature, seizures, maintenance of cerebral perfusion pressure
Antithrombotic therapy (UFH/LMWH) in specific conditions: arterial dissection, cardioembolism, prothrombotic conditions, recurrent AIS while antiplatelet therapy
Guidelines from ACCP
1. Non-SCD: LMWH for 5–7 days (1 mg/kg/dose twice a day) and until cardioembolism or arterial dissection is excluded
2. SCD: exchange transfusion
3. Arterial dissection or cardioembolism: LMWH for 3–6 months
After discontinuation of anticoagulation therapy, long-term aspirin therapy is recommended at a dosage of 3–5 mg/kg/day[a]

UFH unfractionated heparin, *LMWH* low molecular weight heparin, *ACCP* American College of Chest Physicians, *SCD* sickle cell disease

[a]1–3 mg/kg/day in case of dose-related adverse events

minimum of 2 years of treatment is suggested. When children with AIS are not suitable for aspirin for any reason, clopidogrel can be considered as an alternative at dose of about 1 mg/kg per day.

As far as stroke from SCA is concerned, ACCP recommends exchange transfusion to reduce hemoglobin S to levels less than 30% for acute stroke and long-term regular transfusions.

Based on findings from the Stroke Prevention Trial in Sickle Cell Anemia (STOP), regular transfusions can prevent primary stroke in children with SCA at high risk due to transcranial Doppler time-averaged maximum velocities exceeding 200 cm per second [50]. ACCP also recommends transcranial Doppler screening for checking arteriopathy every year in children with SCA who are older than 2 years.

Childhood AIS from moyamoya disease or syndrome is commonly treated with surgical interventions. Given much higher risks for recurrent AIS and bleeding, neurosurgical revascularization such as encephaloduroarteriomyosyangiosis (EDAMS) or direct means and superficial temporal artery branch to MCA branch bypass generally are preferred as first-line treatment.

8.6 Rehabilitation of Childhood AIS

The developing brain is known to be more pliable to external stimuli as compared to the adult one. Rehabilitation for children following AIS usually can lead to favorable impact in the recovery of the child and enormous improvements in long-term outcomes. Multidisciplinary team care is fundamental and can effectively improve rehabilitation intervention with psychosocial model and supports the emotional well-being of the family following AIS. Rehabilitation should begin as early as possible after a stroke. Task-oriented training targeted at child's daily activities can contribute to functional recovery, especially where it takes place in the patient's own environment. Furthermore, add-on therapies such as constraint-induced movement therapy, bimanual training, and transcranial magnetic stimulation have shown encouraging results when given in the critical period [51–54].

8.7 Outcomes

According to the previous study, 3.4% of children with AIS were dead at hospital discharge [55]. It has been known that long-term outcome in children is better than in adults because of better neuronal plasticity in children. However, the study showed more than half of survivors of childhood AIS face long-term neurological disabilities as well as cognitive impairment [56]. The risk for recurrence of childhood AIS varies between about 20 and 40% at a follow-up duration of 5 years [57, 58]. Previous studies showed that certain risk factors such as elevated serum levels of lipoprotein (a), congenital protein C deficiency, and vasculopathy are associated with a higher recurrence risk [59]. Furthermore, locations such as cortical involvement, the right middle cerebral artery territory, younger age, and presence of fever at initial presentation were associated with poor outcomes [60].

8.8 Summary

Arterial ischemic stroke (AIS) in children is a rare condition but may result in neurologically significant sequelae later on. Etiologies, clinical features, and outcomes are quite different from those of adult stroke. Whereas cardiac arrhythmia, hypertension, and atherosclerosis are generally associated with adult AIS, prothrombotic conditions, infection, arteriopathy, congenital heart diseases, and hereditary/metabolic conditions are related to the pathogenesis of childhood AIS. AIS should be taken into account when any child presents with new-onset focal deficits, altered speech, seizures, altered mental state, or other neurological symptoms. MRI with diffusion-weighted imaging is still considered the gold standard modality for initial evaluation even though other diagnostic techniques are required in the specific conditions. Clinical data are still limited regarding both acute management and secondary prevention, so the guidelines are mainly extrapolated from studies in adults. Initial management should emphasize supportive cares to minimize the acute brain injury. All non-sickle

cell childhood AIS should be treated with UFH or LMWH for 5–7 days or until cardioembolic stroke and arterial dissection are excluded. After discontinuation of anticoagulation with antithrombotic agents, long-term aspirin therapy should be undertaken. Rehabilitation for children following AIS can lead to favorable effect in the recovery of the child and significant improvements in long-term outcomes. Some children have less residual dysfunction from a stroke than adults with a comparable lesion.

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Part 3

Endovascular Practices

History and Overview of Endovascular Stroke Therapy

9

Dong-Hun Kang

9.1 Introduction and Recent Evolution of Acute Stroke Management

Stroke occurs in an estimated 33 million people worldwide each year, and it is the second leading global cause of death behind ischemic heart disease. Ischemic stroke itself accounts for approximately 2.8 million deaths worldwide on an annual basis, despite a 37% reduction in ischemic stroke mortality in high-income countries and a 14% reduction in low- and middle-income countries over a 20-year period from 1990 to 2010 [1]. Prior to the recent era of endovascular recanalization using mechanical devices, the main line of treatment for acute ischemic stroke had been the intravenous application of recombinant tissue plasminogen activator (rt-PA). The NINDS (National Institute of Neurological Disorders and Stroke) rt-PA stroke trial in 1995 was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rt-PA for acute ischemic cerebral infarction [2]. The trial demonstrated that rt-PA given within 3 h of stroke onset improved clinical outcome at 3 months despite a slight increase in the incidence of symptomatic intracerebral hemorrhage (ICH). Additionally, a meta-analysis of 12 well-designed, randomized trials based on a total of 7,012 patients showed that rt-PA given within a 6-h time window of stroke onset significantly increased the odds of survival and good outcome defined as modified Rankin Scale (mRS) 0–2 at final follow-up [3]. An alternative option has been intra-arterial recombinant prourokinase, with trials such as PROACT II (Prolyse in Acute Cerebral Thromboembolism) showing significant improvement in recanalization rate and outcome compared to the control group in 1999 [4].

Regarding the mechanical thrombectomy technique, there have been several attempts for recanalization of occluded cerebral artery, which majorly based on mechanical clot disruption. However, most of such earlier attempts were small case series and limited to use as an adjuvant or rescue strategy for the cases refractory to the thrombolytic therapy. The first mechanical thrombectomy trial published in 2005 to demonstrate its effectiveness for large intracranial arterial occlusions was the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial. In that trial, the rate of recanalization in the patients treated with Merci retriever (Concentric Medical, CA, USA) was significantly higher than in the historical control (46% vs. 18%, $P < 0.0001$) [5]. And a trial of the second-generation Merci retriever, the multi-MERCI trial, showed

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recanalization rates that improved to 57.3% on the prior generation of devices [6]. The next mechanical thrombectomy device to achieve success was the Penumbra system (Penumbra, CA, USA). The Penumbra pivotal stroke trial in 2009 demonstrated a successful revascularization, defined as Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3, rate of 81.6% for 125 eligible patients within an 8-h time window from symptom onset [7]. Thus, successive generations of thrombectomy devices were demonstrating higher recanalization rates in general.

The first stent retriever was Solitaire (Medtronic Neurovascular, CA, USA), which was approved by the US Food and Drug Administration (FDA) in 2012 and quickly became the first choice for most neurointerventional doctors on the back of the SWIFT (Solitaire With the Intention For Thrombectomy) trial, where the study was halted due to the overwhelming success of the Solitaire device. Successful recanalization defined as TIMI grade 2 or 3 was achieved in 60.7% of patients where the Solitaire stent was used compared to 24.1% of patients where the Merci device was used. Good clinical outcome as mRS 0–2 at 90 days (58.2% vs. 33.6%) and mortality (17.2% vs. 38.2%) were favorable for the Solitaire stent as well, giving further evidence of the positive advancement in mechanical thrombectomy devices [8]. Likewise, the Trevo device (Stryker Neurovascular, CA, USA) compared favorably to the Merci device, with a recanalization rate, defined as Thrombolysis in Cerebral Ischemia (TICI) of two more, of 86% with the Trevo retriever versus 60% with the Merci device [9]. Enthusiasm for the prospects of mechanical thrombectomy was high; however, that enthusiasm was dampened in 2013 when three separate randomized clinical trials showed mechanical thrombectomy was no better than medical treatment alone.

First was the IMS III (Interventional Management of Stroke) trial in 2013, which compared endovascular treatment plus intravenous rt-PA versus intravenous rt-PA alone, and found no significant differences in the outcome parameters. As a result, the study was halted early due to its futility (mRS 0–2 at 90 days: 40.8% vs. 38.7%, respectively) [10]. Second in 2013, the MR RESCUE (Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy) trial sought to determine if imaging techniques could identify patients most likely to benefit from endovascular treatment and whether such treatment was superior to standard care. The results here were also negative (mean mRS: 3.9 in endovascular vs. 3.9 in standard treatment, $P = 0.99$). Likewise, imaging revealed no situational advantages for endovascular treatment (mean mRS with a favorable penumbral pattern: 3.9 vs. 3.4, $P = 0.23$, without a favorable penumbral pattern: 4.0 vs. 4.4, $P = 0.32$, respectively) [11]. Third, the SYNTHESIS Expansion trial in 2013 randomly assigned 362 patients with acute ischemic stroke to endovascular therapy or intravenous rt-PA. At 3 months, 30.4% of the patients in the endovascular group were alive without disability, whereas 34.8% of the patients in the intravenous rt-PA group were alive without disability [12]. Here again, the conclusion was that clinical outcomes were no better than medical treatment alone despite great advancement in endovascular therapies with better recanalization profile.

However, this situation served as a learning opportunity with respect to the limitations of the 2013 trials, which included lower recanalization rates with first-generation mechanical thrombectomy devices, delayed workflow toward achieving fast recanalization, and a lack of effective and fast imaging with respect to following exclusion criteria [13]. In more detail, the newer and more effective devices at the time, stent retrievers or the Penumbra System, were only used for 22% in IMS III, 39% in MR RESCUE, and 19% in SYNTHESIS Expansion. Thus, the reported rates of TICI 2b or 3 recanalization were 40% in IMS III and only 27% in MR RESCUE. And that was not clearly reported in SYNTHESIS Expansion. Additionally, there was a lack of routine screening of large arterial occlusion cases, for example, only MR RESCUE routinely checked CT angiography or MR angiography to detect large arterial occlusions, which could result in the selection of the patients without large arterial occlusion into endovascular treatment arm (approximately

20% in IMS III and 10% in SYNTHESIS Expansion). In 2015, a series of trials, which are designed to overcome the aforementioned limitations, finally validated the efficacy of mechanical thrombectomy, which has ushered in what some now call "the era of endovascular stroke therapy using mechanical thrombectomy" (Table 9.1).

MR CLEAN (Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) was the first trial in 2015 to demonstrate the efficacy and safety of mechanical thrombectomy within a 6-h time window from stroke onset. With a cohort of 500 patients, favorable outcome defined as mRS 0–2 occurred in 32.6% of patients receiving intra-arterial treatment compared to 19.1% of patients receiving standard care alone. In addition, there were no significant differences in mortality or the occurrence of symptomatic ICH [14]. The second clear victory for mechanical thrombectomy in 2015 was the EXTEND-IA (EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy) trial, specifically for the Solitaire FR stent retriever. The trial was stopped early for ethical reasons given its efficacy. Patients in the endovascular therapy group, where the Solitaire FR was the device used, had a much higher incidence of good favorable outcome as compared to patients receiving intravenous rt-PA alone (mRS 0–2 at 90 days: 71% vs. 40%, $P = 0.01$) [15]. The third positive result for mechanical thrombectomy came in 2015 with the ESCAPE (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times) trial. Endovascular intervention with available mechanical thrombectomy devices resulted in 53% of patients with a 90-day mRS score of 0–2 versus 29.3% for patients receiving standard care in the control group ($P < 0.001$). In addition, there was no significant difference between groups with respect to the incidence of symptomatic ICH (3.6% vs. 2.7%, $P = 0.75$) [16]. The fourth large trial in 2015 was SWIFT PRIME (Solitaire With the Intention For Thrombectomy as PRIMary treatment for acute ischemic stroke). The study showed that for patients receiving intravenous rt-PA for acute ischemic stroke in the proximal anterior circulation, thrombectomy with a stent retriever within a 6-h time window from onset resulted in improved functional outcomes (mRS 0–2 at 90 days: 60% vs. 35%, $P = 0.001$). Like the previous 2015 trials, there was no significant difference in the incidence of symptomatic ICH (0% vs. 3%, $P = 0.12$) [17]. The fifth in a string of positive trials, all published in the New England Journal of Medicine in the same year, was REVASCAT (Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 h). Here, the time window was within 8 h. The safety and efficacy of mechanical thrombectomy were demonstrated as with the other trials (mRS 0–2 at 90 days: 43.7% vs. 28.2% and symptomatic ICH: 1.9% for both groups) [18]. All of these five trials provided strong evidence of benefit from mechanical thrombectomy for management of acute ischemic stroke secondary to large arterial occlusion. And, this is prompting worldwide changes in the guidelines for acute stroke care. Moreover, two more trials, THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) and THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke), presented their preliminary data with similar results to the aforementioned five trials at the 2015 European Stroke Conference and will be published soon.

9.2 Indications and Considerations for Mechanical Thrombectomy

Following the lessons learned from the failure of three 2013 trials, finding good candidates for endovascular stroke therapy is very important relative to patients' outcome. However, even in the five recent randomized controlled trials which showed the overwhelming efficacy of mechanical thrombectomy, there still existed some variation regarding the indication for recanalization procedures. They can be largely divided as clinical,

Table 9.1 Summary of baseline characteristics and results of recent major trials regarding endovascular stroke therapy

Study	Treatment modality: Endovascular vs control	Age criteria (years)	Time window	Territory	NIHSS criteria	Vascular imaging	Other imaging	Number of cases	Mean age (years)	NIHSS median, (range) or [IQR]	Time onset to groin (min): Mean ± SD or median, [IQR]
IMS III (2013)	IV rt-PA + IA drug or any approved device vs IV rt-PA	18–82	5 h to IAT	Any	≥10 or 8–9 with occlusion	Non-contrast CT only	NR	434/222	69	17 (7–40)/16 (8–30)	208 ± 47
SYNTHESIS Expansion (2013)	IA drug or any approved device vs IV rt-PA	18–80	6 h to IAT	Any	No thresholds	Non-contrast CT only	NR	181/181	67	13 (2–26)/13 (9–18)	225 [194–260]
MR RESCUE (2013)	IV rt-PA + IA mechanical (Merci or Penumbra system) vs IV rt-PA	18–85	8 h to IAT (stop by 9 h)	Anterior circulation	6–29	CT CTA MRI	Multimodal CT/MR for stratification	64/54	66	18 (12–22)/18 (11–23)	381 ± 72
MR CLEAN (2015)	IV rt-PA + IA any approved device (82% stent retriever) vs IV rt-PA	>18	6 h to IAT	Anterior circulation	>2	CT CTA MRA	NR	233/267	66	17 [14–21]/18 [14–22]	260 [210–313]
ESCAPE (2015)	IV rt-PA + IA any approved device (79% stent retriever) vs IV rt-PA	>18	12 h to randomization	Anterior circulation	>5	CT CTA	Multiphase CTA to identify core size and collaterals	165/150	71	16 [13–20]/17 [12–20)	Onset to CT 134 [77–247] CT to groin 51 [39–68]
SWIFT PRIME (2015)	IV rt-PA + IA stent retriever vs IV rt-PA	18–80	6 h to IAT	Anterior circulation	8–29	CT CTA ± CTP or MRI	CT/CTP or MRI to identify ischemic penumbra (the first 71 pts) and ASPECTS ≥6 (the remaining 125 pts)	98/98	65	17 [13–20]/17 [13–19]	224 [165–275]
EXTEND-IA (2015)	IV rt-PA + IA stent retriever vs IV rt-PA	≥ 18	6 h to IAT	Anterior circulation	No thresholds	CT CTA CTP	NR	35/35	69	17 [13–20]/13 [9–19]	224 [165–275]
REVASCAT (2015)	IV rt-PA + IA stent retriever vs IV rt-PA	18–80	8 h to IAT	Anterior circulation	≥ 6	CT CTA ± CTP or MRI	NR	103/103	66	17 [14–20]/17 [12–19]	269 [201–340]

Study	TICI 2b-3 recanalization	Time to reperfusion (min) mean ± SD or median, [IQR]	Favorable functional recovery at 3 months (mRS 0–2; endovascular vs control)	Symptomatic ICH (endovascular vs control)	Mortality at 3 months (endovascular vs control)
IMS III (2013)	41%	325 ± 52	41% vs 39% (RR 1.0, 0.8–1.2)	6.2% vs 5.9% ($p = 0.83$)	19% vs 22% ($p = 0.52$)
SYNTHESIS Expansion (2013)	NR	NR	42% vs 46% (p = not reported)	6% vs 6% ($p = 0.99$)	8% vs 6% ($p = 0.53$)
MR RESCUE (2013)	27%	NR	Used mean mRS comparison 3.9 vs 3.9 ($p = 0.99$)	5% vs 4% ($p = 0.24$)	19% vs 24% ($p = 0.75$)
MR CLEAN (2015)	58.7%	332 [279–394]	33% vs 19% (RR 1.7, 1.2–2.3)	7.7% vs 6.4% (p = NA)	21% vs 22% (RR 1.0, 0.7–1.3)
ESCAPE (2015)	72.4%	241 [176–359]	53% vs 29% (RR 1.8, 1.4–2.4)	3.6% vs 2.7% ($p = 0.75$)	10% vs 19% (RR 0.5, 0.3–0.8)
SWIFT PRIME (2015)	88%	252 [190–300]	60% vs 35% (RR 1.7, 1.2–2.3)	0% vs 3.1% ($p = 0.12$)	9% vs 12% (RR 0.7, 0.3–1.7)
EXTEND-IA (2015)	86%	248 [204–277]	71 vs 40% (RR 1.8, 1.1–2.8)	0% vs 5.7% ($p = 0.49$)	9% vs 20% (RR 0.4, 0.1–1.5)
REVASCAT (2015)	66%	355 [269–430]	44% vs 28% (RR 1.6, 1.1–2.3)	1.9% vs 1.9% ($p = 1.00$)	18% vs 16% (RR 1.2, 0.6–2.2)

CTA CT angiography, *CTP* CT perfusion, *IA* intra-arterial, *IV* intravenous, *MRI* MR imaging, *MRA* MR angiography, *NR* not reported, *rt-PA* recombinant tissue plasminogen activator

radiologic, and anatomical indications. In this section, the five recent trials are revisited to find consistency and also to provide an acceptable standard of indication for mechanical thrombectomy that can be applied in real clinical practice for contemporary neurointerventional doctors.

9.2.1 Clinical Indications

9.2.1.1 Time Window

Regarding the time window from stroke onset to the initiation of endovascular recanalization therapy, there were some differences between the five major trials of 2015. MR CLEAN, EXTEND-IA, and SWIFT PRIME set the time window at 6 h from onset; on the other hand, ESCAPE had a 12-h and REVASCAT had an 8-h time window. However, those differences are less meaningful when it is considered that 84% of the patients in the ESCAPE trial had stroke onset within 6 h, and 90% of the patients in the REVASCAT trial had onset within 6 h, representing that the vast majority of patients had onset within this time window. Meanwhile, there are a few ongoing trials to extend this time window to 12 h (POSITIVE trial: PerfusiOn Imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy) and to 24 h (DAWN trial: DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) through the use of more selective perfusion MR imaging protocols. Therefore, some degree of time window expansion is expected in the near future because of recent developments in stroke imaging and mechanical thrombectomy devices.

9.2.1.2 Age

Regarding age as an exclusion criterion for endovascular treatment, there has been some controversy of the upper limit, specifically for patients over the age of 80. Three of the trials had no upper age limit, though all trials had a lower age limit at 18. However, both the SWIFT PRIME trial and REVASCAT set the upper age limit at 80. It is difficult to assess the effect of setting the upper age limit on outcome. With respect to functional outcome defined as mRS 0–2 at 90 days, the differences are comparable [with age limit of 80: SWIFT PRIME (60%), REVASCAT (44%) vs. without age limit: MR CLEAN (33%), EXTEND-IA (71%), ESCAPE (53%)]. And with respect to mortality, the differences are not pronounced [with age limit of 80 SWIFT PRIME (9%), REVASCAT (18) vs. without age limit: MR CLEAN (21%), EXTEND-IA (9%), ESCAPE (10%)]. Further studies seem necessary to address the issue of upper age limits for endovascular treatment.

Other important practical issues related to elderly patients are long-term quality of life after endovascular recanalization therapy and procedural difficulties related with the patient's tortuous anatomy. Patients over 80 have been shown to have a higher incidence of poor clinical outcome, even with a positive recanalization score [19]. It is also reported that patients over 80 have a higher mortality during hospitalization or immediately after release following endovascular treatment. These possibly are associated with a higher incidence of comorbid medical conditions of the elderly patients. In addition, during the mechanical thrombectomy procedure, gentle and safe advancement of the devices are strongly required for rapid and successful recanalization. Tortuous vascular anatomy and underlying atherosclerosis can potentially elevate the risk of the procedure, which can make difficulties involving advancement and stable positioning of the devices. Such vascular tortuosity and atherosclerosis are mainly caused by age and chronic hypertension. Therefore, in real practice for elderly patients, these considerations should be explained to the patient's family during the process of consent and pre-procedural discussion.

9.2.1.3 National Institute of Health Stroke Scale (NIHSS) Score

The five trials of 2015 also showed some variation with respect to NIHSS cutoff. EXTEND-IA had no literal neurological cutoff, while SWIFT PRIME had the strictest cutoff (NIHSS≥8). MR CLEAN (NIHSS≥2), ESCAPE (NIHSS≥6), and REVASCAT (NIHSS≥6) had cutoffs between 0 and 8. On the basis of these studies, at least at the

present, it may be acceptably determined that the majority of centers are using NIHSS≥6 or 8 as a cutoff value for enrolling mechanical thrombectomy for anterior circulation stroke.

9.2.2 Radiologic Considerations

Primary imaging modality used to assess stroke patients still varies from institution to institution. Each imaging modality has its strengths and weakness. The two major techniques used are MR and CT scan. Transcranial Doppler (TCD) ultrasound is offered at some institutions, usually as an adjunctive modality. MR with diffusion-weighted imaging (DWI) sequences is often regarded as the gold standard for acute stroke diagnosis and patient selection [20]. Perfusion-weighted imaging (PWI) represents brain regions with tissue at risk for neuronal death. Together, DWI and PWI are used to determine the penumbra, the area that endovascular treatment intends to preserve. Additional MR modalities include fluid-attenuated inversion recovery (FLAIR), MR angiography, and gradient recall echo (GRE). FLAIR can help demonstrate abnormal or retrograde flow, predict post-reperfusion hemorrhage, or determine the age of DWI positive infarcts [21]. Intracranial MR angiography can help demonstrate abnormal or retrograde flow surrounding a proximal occlusion. And GRE can help determine the location of a thrombus, along with preexisting hemorrhages that might serve as a contraindication of intravenous or intra-arterial thrombolytic infusion. Alternatively, CT angiography and perfusion data are sometime used in virtue of its fast imaging process. Disadvantages include that CT angiography and perfusion require a large amount of contrast, which carries additional risks. However, CT scan is useful in many contexts. For example, although it is not as precise as MR DWI and PWI penumbra mismatch identification, comparing mean transit time, cerebral blood flow, and cerebral blood volume can provide an estimate of the penumbra area [22]. CT scan may also provide information regarding the location of thrombus as well as the existing of preexisting hemorrhage. Nevertheless, MR is still considered as the gold standard in many contexts. TCD is rarely used as the primary imaging technique in an acute stroke setting, but it is sometimes useful as an adjunct. One positive benefit of TCD is that it offers real-time evaluation of recanalization, and due to the benefit, it becomes widely used for patient monitoring.

9.2.3 Anatomical Considerations

All trials included the intracranial carotid artery (ICA) and M1 segment of the middle cerebral artery (MCA). It is somewhat controversial whether or not to include the MCA M2 segment. While MR CLEAN, EXTEND-IA, and ESCAPE included MCA M2 segment in their study, SWIFT PRIME and REVASCAT did not. SWIFT PRIME had the strictest inclusion criteria across many categories among the five trials of 2015. In practice up to now, whether to recanalize an occlusion at the M2 segment strongly depends on the practitioner's discretion on the basis of the patient's neurologic and anatomic condition. In addition, although mechanical thrombectomy is an emerging therapeutic option for posterior circulation stroke, such as acute basilar artery (BA) occlusion, there have not been rigorously evaluated, randomized, and controlled trials regarding the efficacy of mechanical thrombectomy for stroke presented at that location. So far, most previous studies are limited as small case series or safety reports. Further studies seem necessary to address the issue of endovascular treatment for these variant of stroke.

9.3 Evolution of Endovascular Stroke Therapy

Although intravenous rt-PA has been demonstrated to improve patients' outcome [2, 18], the time window was short, and the rate of successful recanalization was also limited. And, there was another concern for this drug regarding increasing the risk of symptomatic ICH. Eventually, attempts to overcome the

aforementioned limitations were tried. The earlier attempts included using the intra-arterial route for local administration of a thrombolytic agent with a smaller dose and using some mechanical methods to disrupt or remove the thrombus. Here, it describes the evolution of different endovascular approaches and techniques and the concept of each recanalization method, including brief review of the data.

9.3.1 Various Old Techniques

9.3.1.1 Mechanical Clot Disruption

One of the earliest techniques was mechanical clot disruption (MCD), which commonly involved probing the thrombus with a microguidewire and/or a microcatheter, often resulting in a greater degree of success than standardized treatment alone at the time (Fig. 9.1). The major concept of MCD was recanalization of a large artery by disrupting the main clot, but it is inevitably involved with distal clot migration or embolization to smaller artery. However, early results were promising. As a typical example involving mechanical clot disruption, in one study, favorable outcome was achieved in 59% of patients with a final recanalization rate of 75% [23]. Safety profile was also acceptable as there were no immediate procedure-related complications, 9.4% of symptomatic ICH and 12.5% of overall mortality.

9.3.1.2 Intra-arterial Local Urokinase Infusion

Another earlier attempt was intra-arterial administration of a thrombolytic agent [4]. In the PROACT II trial, patients were randomized to receive 9 mg of recombinant prourokinase via the intra-arterial route plus heparin (n = 121) versus heparin only (n = 59) within 6 h from onset of MCA occlusion. This showed a significantly better recanalization rate (66% vs. 18%, $P < 0.001$) and favorable outcome (mRS 0–2: 40% vs. 25%, P = 0.04). However, the remaining concern of this treatment was the rate of symptomatic ICH, which also was significantly increased (10% vs. 2%, P = 0.06).

9.3.1.3 Mixed Mechanical Clot Disruption and Intra-arterial Local Urokinase Infusion

Attempts were then made to combine MCD with local intra-arterial thrombolysis, as intra-arterial thrombolysis can be applied with or without MCD [24]. In the groundbreaking PROACT II trial, MCD was not allowed according to the protocol of the study. However, a later attempt at performing MCD during intra-arterial thrombolysis was indeed shown to improve recanalization rates (79% intra-arterial thrombolysis with MCD vs. 66% intra-arterial thrombolysis without MCD) [25, 26].

9.3.1.4 Percutaneous Balloon Angioplasty

Percutaneous balloon angioplasty can be considered as a type of clot disruption, as it involves advancement of a balloon-mounted catheter to the occlusion site and inflation to achieve recanalization (Fig. 9.2a). As the earliest trials did not involve placing a stent, this method can be considered a pure form of clot disruption, instead of a hybrid solution where a stent is placed. Recanalization rates were further improved by application of this technique. For example, in one period-to-period analysis compared percutaneous balloon angioplasty and intra-arterial thrombolysis alone as a control, TIMI 2 or 3 recanalization was achieved in 91.2% of balloon angioplasty group and in 63.9% of thrombolysis-alone group ($P < 0.01$) [27]. Good functional recovery as mRS 0–2 was also significantly better in the angioplasty group than in the thrombolysis-alone group (73.5% vs. 50.0%, P = 0.04). Additionally, the incidence of symptomatic ICH was significantly less in the angioplasty group (2.9% vs. 19.4%, P = 0.03).

9.3.1.5 Intraluminal Clot Disruption Using Ultrasound

One advanced form of clot disruption involved local application of ultrasound in conjunction with intra-arterial thrombolysis to disrupt a thrombus (Fig. 9.2b). The technique named EKOS MicroLys US infusion catheter (EKOS Corporation, WA, US) was attempted in a

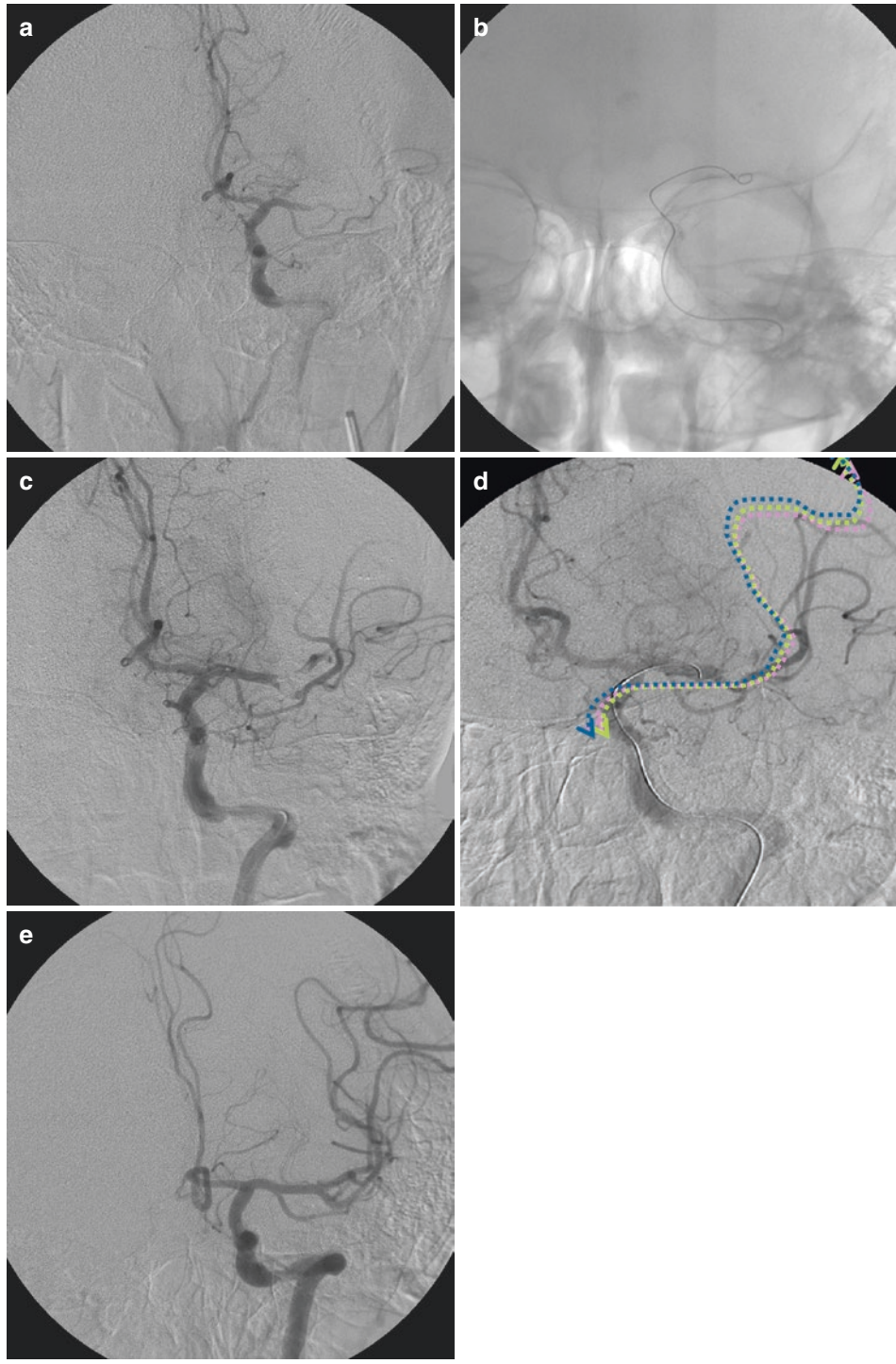

Fig. 9.1 A case example of MCD. Baseline angiography (**a**) shows total occlusion of the M1 segment of the left middle cerebral artery. A microcatheter and a loop-shaped microguidewire are advanced to the thrombus (**b**). Angiography after first attempt of MCD (**c**) shows partial reperfusion. Second MCD is attempted using back and forth movement of the microcatheter and the microguidewire (**d**). Final angiography (**e**) shows complete recanalization

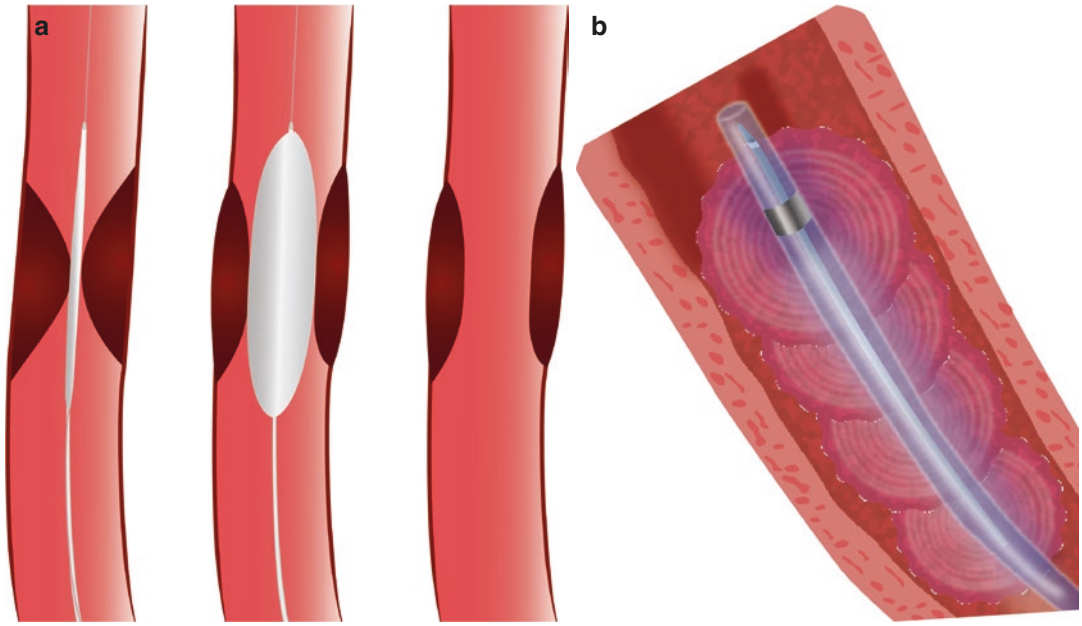

Fig. 9.2 Illustrations (**a**) demonstrate balloon angioplasty for recanalization of the occluded artery. EKOS system (**b**)

small trial of 14 patients, 10 patients presented with anterior circulation stroke and 4 patients with posterior circulation [28]. TIMI 2 or 3 recanalization was achieved in eight patients (57.1%) in the first hour, and average time to recanalization was 46 min. No catheter-related adverse events were reported but three deaths occurred at 24 h: two from hemorrhage and one from cerebral swelling. And notably, this technique was included in the IMS II trial and demonstrated a recanalization rate of 73% [29].

9.3.1.6 Intraluminal Clot Disruption Using Laser Technology

Another advanced form of clot disruption involved was called endovascular photoacoustic recanalization (EPAR; Endovasix Inc., CA, US), which consisted in mechanical clot fragmentation by converting photonic energy from a laser into acoustic energy [30]. The effect of generating acoustic energy subsequently was emulsification of the clot. In a representative trial studying this technique involving six centers in Europe and North America, 34 patients were enrolled: 22 patients with anterior circulation stroke (10 of ICA and 12 of MCA occlusion) and 12 patients with posterior circulation stroke (11 of vertebrobasilar and 1 of posterior cerebral artery occlusion). The overall recanalization rate was 41.1% (14/34). Specifically, complete EPAR treatment was possible in 18 patients, with vessel recanalization in 11 patients (61.1%) after EPAR. The average EPAR lasing time was 9.65 min and device-related adverse event occurred in only one patient.

9.3.2 Merci Retriever

Following various attempts of chemical thrombolysis or mechanical clot disruption, a series of new mechanical thrombectomy devices were introduced. The Merci device (Concentric Medical), named after the MERCI trial, was the first thrombectomy retrieval device in this series to receive FDA approval [5, 6]. Regarding the specifics, the Merci clot retrieval system is comprised of the Merci retriever, the Merci balloon guide catheter (BGC), and the Merci microcatheter. The Merci retriever is a tapered wire with five helical loops at its distal end which can trap

Fig. 9.3 Merci retriever L5 type is a flexible, tapered nitinol wire that is advanced through a microcatheter. The microcatheter is passed through the clot, then Merci retriever is deployed across the clot. The retriever is then slowly moved back to fully ensnare the clot. The balloon on the guide catheter is inflated to arrest flow to prevent distal clot embolization; the retriever and the microcatheter are then withdrawn into the guide catheter

a thrombus, and the BGC is a 9 French catheter with a 2.1 mm lumen and a balloon located at its distal tip. The procedure involves advancement of the Merci retriever through the microcatheter in its straight configuration and is deployed into the occluded intracranial artery to ensnare the thrombus (Fig. 9.3). As noted previously, successful recanalization was achieved in 46% of patients, which was significantly higher than the recanalization rate of 18% in the PROACT II trial, and favorable clinical outcome was achieved in 27.7% of patients [31].

9.3.3 Penumbra System

The next device to be approved by the FDA was the Penumbra aspiration system in 2007 (Penumbra). The Penumbra system includes a thrombectomy device designed to remove a thrombus through a combination of aspiration using a reperfusion catheter and clot fragmentation or disruption using a clot separator. Regarding the specifics, an aspiration catheter is advanced up to the site of occlusion, and then a separator device is introduced through the aspiration catheter. Subsequently, an electric pump provides negative pressure while the separator device is moved in and out of the aspiration catheter. The clot fragments are dislodged and are subsequently aspirated into the catheter (Fig. 9.4).

There have been numerous trials involving the Penumbra system [7, 32, 33]. For example, the Penumbra pivotal stroke trial prospectively enrolled 125 stroke patients within an 8-h time window of symptom onset, and recanalization was achieved in 81.6% of patients. However, favorable clinical outcome was achieved in only 29% of patients with successful recanalization [7]. Other trials with the Penumbra system during this period reported better results, and for one example, Kulcsar et al. reported a successful recanalization rate of 93% and favorable clinical outcome of 48% [34].

9.3.4 Clot Aspiration Thrombectomy

Some early reports on mechanical thrombectomy involved the use of direct aspiration with catheters in one context or another [35, 36]. Standardly in clot aspiration, a large catheter (4 or 5 French for vertebrobasilar artery and 7 or 8 French guide catheter for ICA) is attempted to advance to the proximal surface of the clot and then a negative pressure is applied by manual aspiration using a syringe. Thrombus entrapment is indicated when there is an absence of backflow. Once the thrombus is trapped, the catheter is slowly retrieved with constant negative pressure to avoid losing the thrombus. After retrieval of clot fragments, the procedure is repeated until recanalization is achieved.

New techniques involving mechanical clot aspiration began to emerge after introducing new-generation devices specially designed for cerebral vasculature. The first of such techniques, forced arterial suction thrombectomy (FAST), involved 22 consecutive patients (mean NIHSS, 18) treated with an advanced form of aspiration thrombectomy alone. They used the origi-

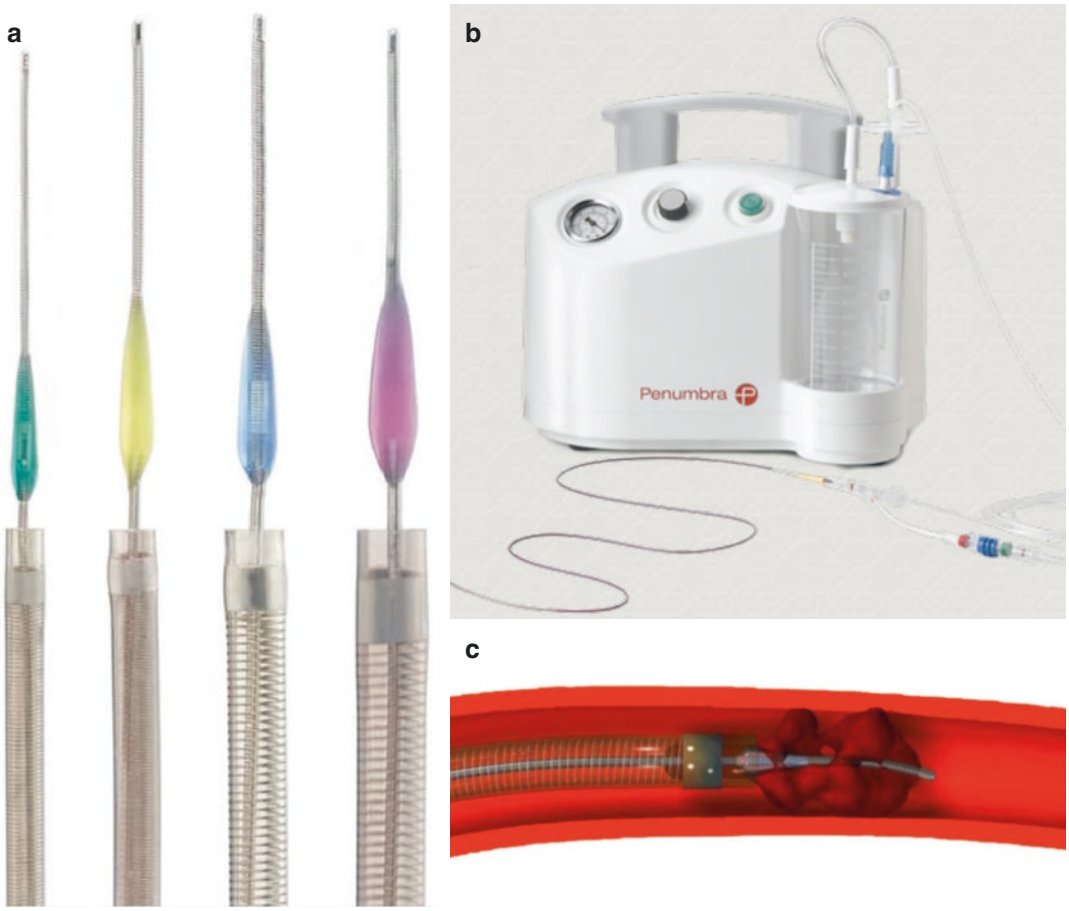

Fig. 9.4 Penumbra system is composed of reperfusion catheters, separators, aspiration tubing, and pump (**a**, **b**). The clot pieced by a separator is ingested into the reperfusion catheter by negative pressure of the aspiration pump; flushing the clot fragments into the reperfusion catheter follows (**c**)

nal version of Penumbra reperfusion catheter for aspiration of the thrombus, and the negative pressure was made by 20 or 50 mL syringes. In that study, recanalization was achieved in 81.9% of the patients, and a favorable clinical outcome was observed in 45.5% of patients [37]. A later, similar technique for clot aspiration came about known as the ADAPT, a direct aspiration first pass technique, which also is a direct aspiration technique where a large-bore aspiration catheter is used as the primary method for vessel recanalization. Results of an initial trial involving 37 patients were also favorable, with a TICI 3 recanalization rate of 65% and an average improvement in NIHSS of 4.2 points [38]. The commonalities and the differences between FAST and ADAPT will be described more in the following chapter.

9.3.5 Stent Retriever Thrombectomy

The final technique reviewed in this section involves the use of a stent retriever. Stent retrievers or stentrievers are self-expandable stent for thrombectomy that are deployed past the occlusion site with the use of an appropriate microcatheter, usually between 0.021- and 0.027-inch as inner diameter. The stent retriever is then expanded to capture the thrombus, which immediately may restore blood flow. And, theoreti-

cally, such flow restoration can enhance the efficacy of systemic thrombolytic drugs if already in the circulation. After a period of up to 10 min, usually 3–5 min depending of the location and clot size, the stent can be retrieved by pulling back the deployed stent into the guide catheter under proximal aspiration through the guide catheter. The addition of a proximal balloon guide catheter can aid aspiration and help thrombus retrieval when the stent retriever is being dragged back into the guide catheter.

The first dedicated stent retriever thrombectomy device for acute ischemic stroke was the Solitaire FR (Medtronic Neurovascular) [39–41]. The Solitaire FR can be fully deployed, fully resheathed, and recovered. The Solitaire is an FDA-approved stent retrieval device for use in ischemic stroke. The SWIFT trial, as mentioned previously compared the Merci device with Solitaire, was halted early due to the demonstrated superiority of the Solitaire device [8]. As previously mentioned, successful recanalization of TIMI grade 2 or 3 was achieved in 60.7% of patients with the Solitaire stent retriever versus 24.1% with the Merci device used, and good clinical outcome (mRS 0–2 at 90 days: 58.2% vs. 33.6%) and mortality (17.2% vs. 38.2%) were favorable for the Solitaire stent as well.

The Trevo embolectomy device (Stryker Neurovascular) is an alternative stent retriever device that can be advanced through a microcatheter past the occlusion site and deployed to cover the entire thrombus. Similar to the technique of Solitaire, the Trevo retriever is deployed for at least 5–10 min to ensure the clot is ensnared and flow is restored. After that, a BGC is inflated proximal to the clot to prevent anterograde flow, and the microcatheter and the embolectomy device are gently withdrawn through the guide catheter under continuous proximal aspiration [42–44]. The Trevo retriever has various lineups, and one distinguishing feature of this retriever from the generation of Trevo Provue is the fully visible stent-strut under fluoroscopy. The TREVO 2 trial demonstrated the success of the Trevo device in comparison to the Merci device in a similar fashion to the SWIFT trial. Recanalization rates with TICI 2 or 3 were 86% in the Trevo group versus 60% in the Merci group, though there was no statistically significant difference regarding procedure-related adverse events between the two groups (15% in the Trevo group vs. 23% in the Merci group, $P = 0.18$) [9].

9.4 Summary

Endovascular therapy with mechanical thrombectomy is a landmark change in stroke management. Now it stands as a frontline therapy, and it certainly has huge potential benefits for stroke patients everywhere. In that regard, guidelines should recommend mechanical thrombectomy as a level 1 evidence-based treatment worldwide. Under those circumstances, enrolling more patients for endovascular stroke therapy within the therapeutic window will be a significant area for future investigation. And, the role of prehospital care will be very important for that, such as building a faster emergency medical service delivery system and making a direct alarm system from the ambulance to the adjacent stroke center. Moreover, improving ambulance capabilities with a mobile CT scanner and a thrombolysis unit will possibly reduce treatment times for stroke [45]. Likewise, extending the time window is another effective way to enroll more stroke patients for mechanical thrombectomy. So far, the best evidence for endovascular stroke treatment has been established for stent retrievers where treatment is started within 6 h of stroke symptom onset. There are a few ongoing trials which focus on extending the time window to 12 h (POSITIVE trial: PerfusiOn Imaging Selection of Ischemic STroke PatIents for EndoVascular ThErapy), or even to 24 h (DAWN trial: DWI/PWI and CTP Assessment in the triage of Wake-up and late presenting strokes undergoing Neurointervention), both with the use of perfusion imaging selection. More importantly and basically, the availability of stroke-related resources, personnel (including vascular neurologists, neurointerventionalists, neuroradiologists, vascular neurosurgeons, radiology technologists, and nurses), and equipment (including carotid ultrasound, catheter angiography, computed

tomographic angiography, MRI, and transcranial Doppler) are strongly required for highlighting the benefit of the recent advent of mechanical thrombectomy techniques.

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Clot Aspiration Thrombectomy in Acute Ischemic Stroke

10

Dong-Hun Kang

10.1 Earlier Attempts Using Clot Aspiration Thrombectomy

Clot aspiration thrombectomy has its origins in large vessel manual aspiration techniques [1]. With respect to the technique, a large-bore catheter from 4 to 8 French is advanced to the proximal surface of a clot and manual suction is applied using a syringe (50 mL or 60 mL). The virtues of this method are that it is not expensive, fast to apply, and technically simple. However, it was used primarily for proximal occlusions, such as proximal intracranial carotid artery (ICA) occlusions below the cavernous segment, which were accessible to the large and stiff catheters available at the time. One of the earliest case series on ICA mechanical aspiration thrombectomy involved three patients contraindicated for chemical thrombolytic agents. In these patients, catheterization involved a 7-French guide catheter to the proximal ICA, where the thrombus was aspirated using a 60 mL syringe. All three patients had successfully restored flow with Thrombolysis in Myocardial Infarction (TIMI) grade 3 [2]. Another early case series involved thromboaspiration in the basilar artery. Two cases of acute basilar artery (BA) occlusion were reported; one was spontaneous occlusion 20 h from the first symptoms, and the other was hyperacute thrombus formation during the coiling of the BA top aneurysm. Although both cases in this series showed successful recanalization, thromboaspiration at this time strongly required favorable anatomic conditions, non-tortuous vessels without severe atherosclerosis, and fresh nonadhesive clots. Thus, while mechanical aspiration thrombectomy was available in some cases of acute BA occlusion, it was not widely available for most intracranial occlusions [3].

After 2002, many additional attempts at direct clot aspiration thrombectomy were conducted. In one case series of 14 ICA occlusion patients, 10 involved the use of a balloon guide catheter (BGC), and 4 involved the use of a general guide catheter. The four patients treated with the general guiding catheter had no recanalization. However, of the ten patients treated with the BGC, seven obtained complete or partial recanalization. Moreover, of the seven patients with successful recanalization, six had a favorable functional outcome at 3 months [4]. Another case series demonstrated the efficacy of clot aspiration technique in two patients. The angiographic results were excellent in both cases as TIMI 3, and good clinical recovery was seen at the time of

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discharge (National Institute of Health Stroke Scale [NHISS] score 2 and 4) and at 3 months (modified Rankin Scale [mRS] score 1 and 2). However, the application of the technique was also limited to non-tortuous vessels due to the large and stiff catheters available at the time [5]. Many studies pointed out the need for a stroke-dedicated device that allowed for intracranial thrombus removal, as forced insertion of a large and stiff catheter into smaller or tortuous intracranial vessels might induce luminal injury such as dissection or perforation. As such, previous catheters were limited to use for large and proximal arterial occlusions in favorable anatomic conditions. But, after the launching of the Penumbra system (Penumbra, CA, USA) in this field, things began to change as a result of the Penumbra reperfusion catheter, which had large internal diameter but not too stiff, and therefore it was very effective at advancement into intracranial vessels. This prompted practitioners to begin to apply the Penumbra reperfusion catheter for direct clot aspiration of smaller intracranial artery occlusions. Two examples of this new clot aspiration technique were forced arterial suction thrombectomy (FAST) and a direct aspiration first pass technique (ADAPT). The first version was FAST, and a couple of years later ADAPT followed. In the following chapter, we will describe in detail the two techniques [6, 7].

10.2 New-Generation Clot Aspiration Techniques: FAST and ADAPT

With the introduction of the Penumbra system, with its larger but more flexible large-bore aspiration catheter, it became possible to apply aspiration techniques to smaller intracranial vessels. However, even though the Penumbra phase 1 trial reported a 100% revascularization rate with respect to TIMI 2 or 3, recanalization may not be achieved in all occlusion cases, particularly where there is a firm thrombus or occlusion of a severely tortuous segment. This leads to the modification of the technique at some centers while adopting as many advantages of the Penumbra system as possible, which included an easily navigable reperfusion catheter and suction for revascularization. The modifications were simple and intuitive, which originated from the substitution of Penumbra reperfusion catheters for outdated stiff catheters during clot aspiration thrombectomy. Specifically, (1) the tip of Penumbra reperfusion catheter was used as a vacuum pad for the thrombus, and (2) forceful pulling of a syringe plunger allowed for intensified suction (Fig. 10.1). This modified technique provided several benefits. First, as it was a simplification of the standard Penumbra system, no additional equipment was required. Second, revascularization could be achieved in an expedited manner,

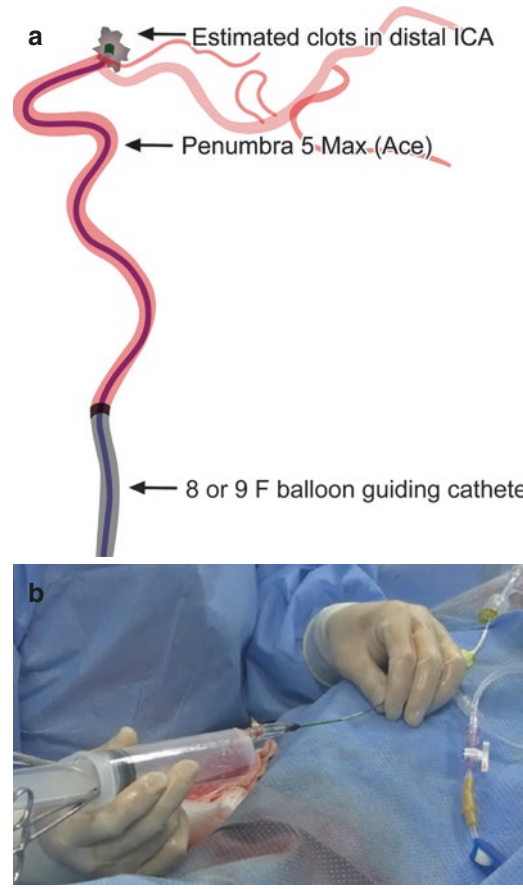

Fig. 10.1 Illustration (**a**) of FAST, forced arterial suction thrombectomy, in a patient with internal carotid artery terminus occlusion. Photograph (**b**) shows that the 20 or 50 mL syringe is connected to the proximal hub of the reperfusion catheter with forceful suction

because the technique itself was brief. Third, if failure occurred, conversion to the standard Penumbra system technique or stent retriever thrombectomy was easy.

10.2.1 FAST: Forced Arterial Suction Thrombectomy

The first cases series on FAST was published in 2011 under the title, "Direct thrombus retrieval using the reperfusion catheter of the Penumbra system: Forced-suction thrombectomy in acute ischemic stroke" [6]. In that case series, 22 consecutive patients with large artery occlusion acute ischemic stroke within the 8 h time window of stroke onset underwent FAST. Any patients that were at high risk of bleeding, or had brain edema, or uncontrolled hypertension, were excluded. The safety of the technique was evaluated according to the incidence of procedural complications, and the efficacy was assessed by the incidence of successful revascularization of the target vessel following the technique, defined as Thrombolysis in Cerebral Ischemia (TICI) grade 2 or 3. The mean interval from the onset of symptoms to arterial puncture was 5.3 h, and the mean baseline NIHSS score was 18.1. The target-vessel locations were 14 middle cerebral artery (MCA) (63.6%), 4 ICA (18.2%), and 4 BA occlusions (18.2%). All the treated target vessels were TICI 0 before the procedure; and all 81.9% of the patients were successfully recanalized as TICI 2b (10/22, 45.5%) or 3 (8/22, 36.4%) after the FAST procedures. The mean procedure time from groin puncture to revascularization was 40.2 min, including diagnostic angiographies. A Penumbra reperfusion catheter 041, the original version of the catheter, was primarily used in every patient and a Penumbra reperfusion catheter 032 was additionally used in two cases of distal embolization to the M2 segment of the MCA. Adjuvant procedures were performed in four patients; balloon angioplasty was undertaken in one patient due to the underlying stenosis of the BA following revascularization of acute BA occlusion, and rescue carotid stenting at proximal ICA was performed in three patients. And there was only one procedural complication, cervical segment ICA dissection occurred while placing the guide catheter in the tortuous vessel, although recovery was confirmed on follow-up MR angiography 5 days after the procedure. Overall intracerebral hemorrhage (ICH) occurred in seven patients (31.8%) and among them, two (9.1%) were symptomatic. The favorable functional outcome (mRS score 0–2) at 3 months was 45.5% (10 of 22 cases).

One year later, the authors of the first FAST paper reported the efficacy of FAST in acute distal ICA occlusions by comparing FAST and MCD and showed greater improvement in functional outcome in the FAST group [8]. In that period-to-period analysis, the rate of successful recanalization, defined as TICI grade 2 or 3, was significantly higher in the FAST group compared to the mechanical clot disruption (MCD) group (85% vs. 32%, $P < 0.001$). Additionally, favorable outcomes at 3 months, defined as mRS score 0–2, were 45% in the FAST group and 16% in the MCD group. Though this was a comparison between a new technique FAST and an outdated MCD at the time, the authors concluded FAST could be a viable option for acute distal ICA occlusion based on the high rate of successful recanalization and functional recovery.

10.2.2 ADAPT: A Direct Aspiration First Pass Technique

In 2013, another investigation of manual aspiration thrombectomy, with the modification of the standard Penumbra system, took place called ADAPT [7]. In that study, 37 consecutive cases of acute ischemic stroke were treated with the ADAPT technique, 30 of which involved the anterior circulation, seven involving the posterior. The ADAPT, as discussed in that publication, was very similar to the FAST technique (Fig. 10.2). Regarding the specific findings of ADAPT study in 2013, the average time from groin puncture to recanalization was 28 min, and revascularization was successful

in all cases. TICI grade 3 recanalization was achieved in 65% of the cases. Patients presented with an admitting NIHSS score of 16.3, and improved to 4.2 by the time of discharge. In that study, there was one procedural complication. And two patients died from parenchymal hematomas.

The authors of the ADAPT study pointed out some differences between the early FAST technique and ADAPT. For example, they indicated that the FAST series reported more modest results than their ADAPT results likely due to smaller caliber and older technology aspiration catheters. In detail, they indicated that the FAST series involved an older generation aspiration catheter, such as 041 and 032 family of Penumbra reperfusion catheters, as opposed to their more modern devices (Penumbra 5 Max) used 2 years after the FAST study. They mentioned two major advantages of using the new aspiration catheter for ADAPT: (1) the increased internal diameter of the Penumbra 5 Max aspiration catheter allowed for an increased surface area, which provided better contact at the catheter tip-thrombus interface, and (2), additionally, the Penumbra 5 Max was more spacious in its proximal segment, which increased its luminal volume and provided an increased aspiration capacity.

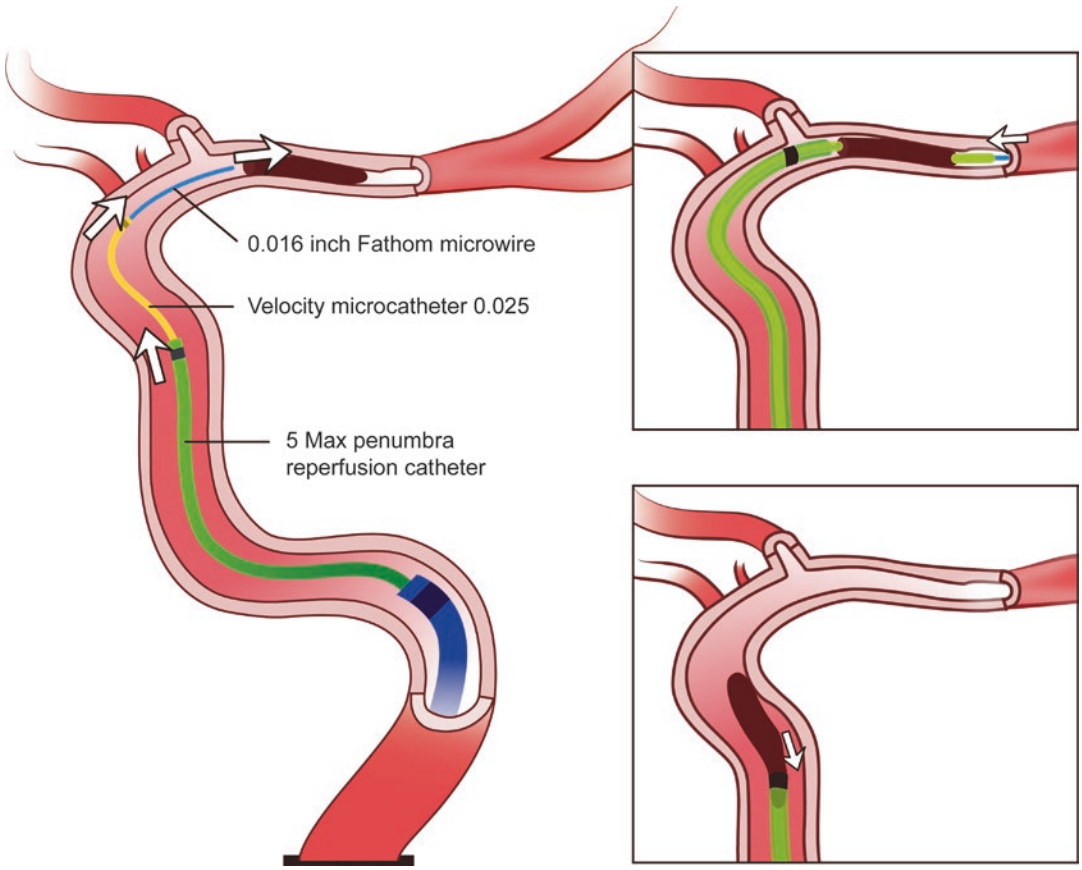

Fig. 10.2 Illustration of ADAPT, a direct aspiration first pass technique, in a patient of middle cerebral artery occlusion. Neuron Max guide catheter is positioned as distally as possible in the parent artery. Penumbra 5 Max reperfusion catheter is advanced over a 0025 in. microcatheter with a 0.016 in. microguidewire through the guide catheter. The microguidewire and the microcatheter are then passed distal to the thrombus to provide support for the Penumbra 5 Max to be advanced to the thrombus. Aspiration is applied until wedging is accomplished between the catheter tip and the thrombus, then the Penumbra 5 Max is removed while maintaining aspiration

10.2.3 Difference Between FAST and ADAPT Focusing on the Usage of a Balloon Guide Catheter

The techniques of early FAST and ADAPT were very similar in many ways; both techniques were mainly composed of advancement of large-bore catheter to the occlusion site and a forceful aspiration thereafter. From the FAST author's viewpoint, it was with the additional use of a BGC in subsequent years that set FAST slightly apart from ADAPT. The only possible disadvantage of using a BGC is the time for preparation of a balloon in BGC. But there are several potential advantages here.

The first advantage is that using BGC in the FAST procedure may minimize distal clot migration or embolization. For example, in an in vitro study published in 2013, the incidence of distal embolization was investigated [9]. In that study, the Merci retriever, Solitaire FR (Medtronic Neurovascular, CA, USA), and Trevo devices (Stryker Neurovascular, CA, USA) were compared with and without the use of a BGC to ascertain the number of distal emboli generated during thrombus retrieval. They found that the use of the BGC during thrombus retrieval significantly reduced the formation of large distal emboli with a diameter >1 mm, regardless of the device used ($P < 0.01$). Additionally, they found that applying aspiration using the BGC in place of a conventional guide catheter resulted in a significant increase of flow reversal ($P < 0.0001$). The findings related to be reduced embolic events with use of a BGC have also been demonstrated in animal models [10]. In an experimental ischemic stroke model, the number of embolic events was significantly higher with distal thrombectomy device, such as Catch retriever (Balt Extrusion, Montmorency, France), without proximal balloon occlusion compared with use of distal devices with proximal balloon occlusion (42% vs. 9%, OR, 7.1; 95% CI). That brings up the second potential advantage. It may be the case that using a BGC might enhance aspiration efficacy during the FAST or ADAPT procedure by blocking proximal flow. Note that this is a theoretical point; there is no apparently reported evidence to confirm this conjecture yet. However, because the distal part is already blocked by the clot, proximal occlusion with a BGC can make a vacuum there, which then may make the negative pressure more effective. Clearly, this is an area where in vitro confirmation is needed. The third advantage is that it can allow for easy and prompt switching to stent retriever technique in case of failure using the FAST. This may be an important point, especially in light of modern trials, because all the large volume stent retriever trials recommend using the BGC, for example, Solitaire with the intention for thrombectomy (SWIFT) and Solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke (SWIFT PRIME) [11, 12]. Regarding the use of the BGC in stent retriever technique, there was a swine model testing the Solitaire device [13], which noted that the clot would be engaged within the struts and would shear off the device during retrieval into the tip of the BGC in many cases. It was possible to aspirate the clot into the guide catheter and prevent distal emboli. Another study published in 2014, which examined the safety and efficacy of the BGC, demonstrated that the use of a BGC with the Solitaire FR device resulted in better revascularization results, faster procedure times, and improved clinical outcomes [14]. In that study, 149 patients (44%) had placement of a BGC. What they found was that procedure time was shorter in patients where the BGC was used (120 vs. 161 min, $P = 0.02$), and TICI 3 reperfusion scores were higher in patients with the BGC (53.7% vs. 32.5%, $P < 0.001$). Although rates of distal embolization and emboli in new territory were similar between the two groups, mean discharge NIHSS score (12 vs. 17.5, $P = 0.002$) and good clinical outcome at 3 months were significantly better in patients where the BGC was used compared with patients without (51.6% vs. 35.8%, $P = 0.02$). Additionally, it was shown in multivariate analysis that the use of the BGC was an independent predictor of good clinical outcome (OR, 2.5; 95% CI).

10.2.4 Step-by-Step Description of the FAST Technique

10.2.4.1 Step 1: Femoral Arterial Puncture and Sheath Insertion

Same as the beginning of other endovascular procedures, the target for safe femoral puncture is the midportion of the common femoral artery, which is defined as the arterial segment between the inferior epigastric artery and the bifurcation of the superficial and profunda femoral arteries. This is usually located around the central part of the femoral head, so in any difficult cases of puncture, perhaps due to diminished pulse or patients' obesity, using fluoroscopy to find such bony landmarks can be helpful to confirm a safe puncture site. Then, the puncture needle should enter the artery slightly higher than the skin entry site with an angle about 30° from the horizontal. Incidentally, for large-diameter sheaths or in anticipation of vascular closure devices, a subcutaneous tunnel is helpful for easier device insertion, which permits blood to exit to the surface instead of accumulating in the leg. A single, front wall arterial puncture is the recommended technique, as it reduces the chance of bleeding from an inadvertent puncture leak. Advancement of the needle slowly up the artery is followed by the gentle introduction of a straight or a J-tipped guidewire into the artery. After the guidewire is positioned in the iliac artery, the needle is removed with firm hand pressure applied over the puncture site while the sheath is placed over the wire. Then, the sheath-dilator assembly is advanced, and followed by aspiration and flush of the sheath through the side arm with heparinized saline.

10.2.4.2 Step 2: Balloon Guiding Catheter Placement

The next step begins by advancing the guiding catheter to the proximity of the occluded target vessel. Conventional angiographic techniques are used to achieve a stable guiding catheter position for the thrombectomy procedure. Common selections for a guiding catheter during the FAST technique include either an 8-French or a 9-French BGC. Specifically, the author mostly used a 9-French BGC either an Optimo (Tokai Medical Products, Aichi, Japan) or a Merci (Stryker Neurovascular, CA, USA). A 120 cm diagnostic catheter, one of either a 4-French Headhunter or a Simmons-2 (Cook, IN, USA), is inserted coaxially and is used to select the common carotid artery in the anterior circulation occlusion or the subclavian artery in the posterior circulation occlusion, after which the BGC is advanced coaxially over the diagnostic catheter. Angiographies are then performed to confirm the location of the occlusion and to evaluate for preexisting stenosis at the proximity of the internal carotid or vertebral artery (Fig. 10.3a). If it is safe and available, the BGC is positioned into the internal carotid or vertebral artery using a similar coaxial advancement technique. For the cases of vertebral artery which is not allowed for an 8-French or a 9-French BGC due to small caliber, any general 6-French guide catheter can be used as a substitute. An alternative technique begins with selection of the proximal common carotid or subclavian artery with a diagnostic catheter. Then, the diagnostic catheter is exchanged for a BGC over an exchange wire. With either of these techniques, which can depend on the patient's vascular anatomy and the practitioner's preference, the distal tip of a BGC can be advanced to distal cervical segment of ICA or to proximal vertebral artery.

10.2.4.3 Step 3: Advancement of Large-Bore Aspiration Catheter

Once the BGC is optimally positioned, it is attached to a rotating hemostatic valve, through which a set of microsystems can be introduced coaxially while simultaneously allowing for continuous saline flushing and preventing air entry into the system. Then, the microcatheter and microguidewire can be advanced through the system up to the occlusion (Fig. 10.3b). For the FAST technique, it is recommended that a 2.0-French (Excelsior 1018; Stryker Neurovascular, CA, USA) or a 2.3-French microcatheter (Prowler Select Plus; Cordis Neurovascular, FL, USA) with a 0.014 in. (Synchro, Stryker Neurovascular) or a 0.016 in. microguidewire (GT; Terumo, Tokyo, Japan) inside it is introduced into a large-bore aspiration catheter (Penumbra 4/5 Max

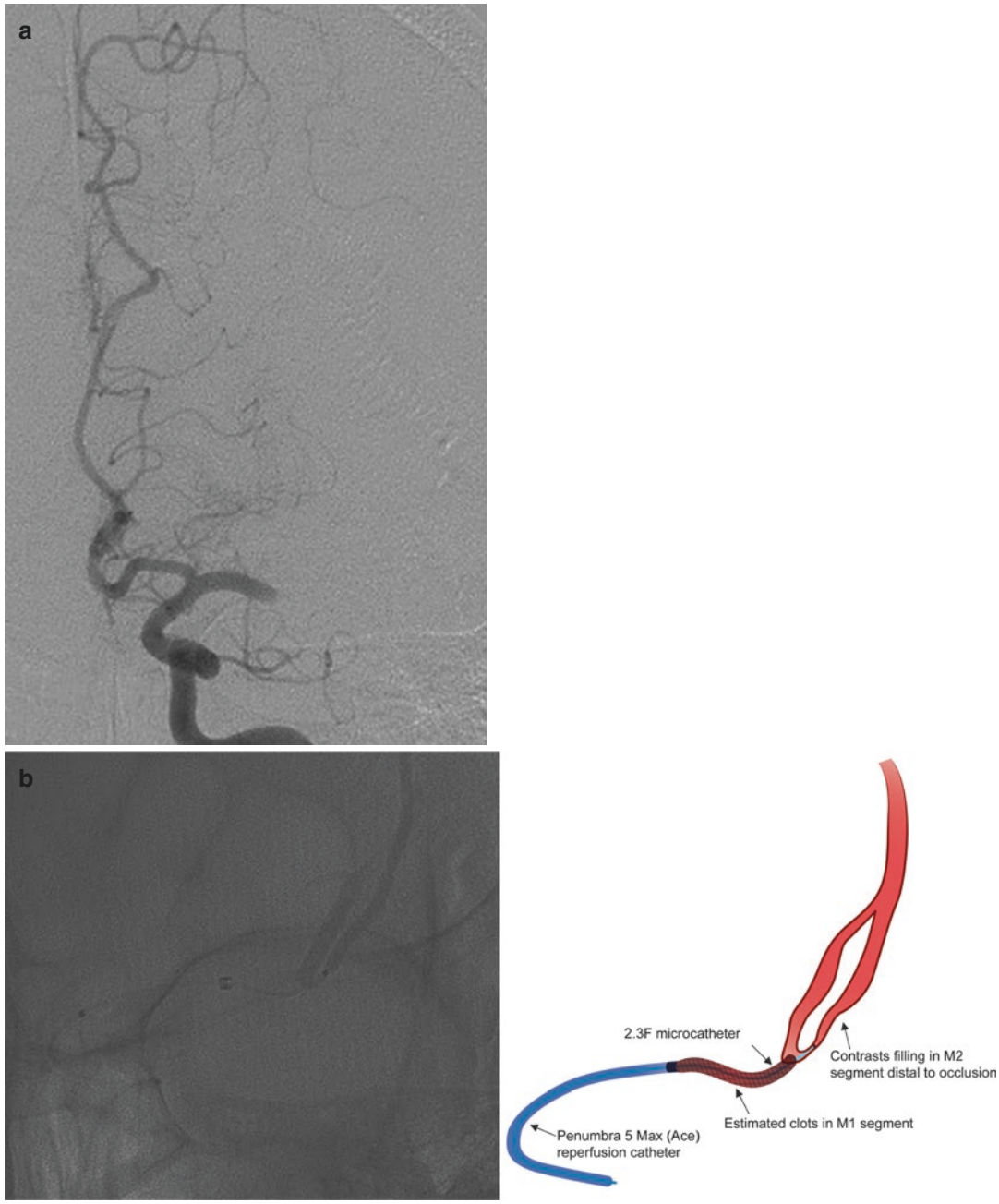

Fig. 10.3 Baseline angiography (**a**) shows total occlusion of the M1 segment of the left middle cerebral artery. Angiogram and illustration (**b**) of the FAST procedure show the occlusion site and surrounding angioarchitecture. The balloon of the guiding catheter is inflated during forceful aspiration (**c**). Examples of retrieved clot are shown: fragmented type (**d**) and whole type (**e**). Final angiography (**f**) shows complete revascularization

or 5 Max Ace; Penumbra). This set of construct is introduced into the BGC as a unit and is advanced to the occlusion site.

In this stage, it is recommended to avoid distal passage of the thrombus by a microcatheter or a microguidewire, because distal passage itself can

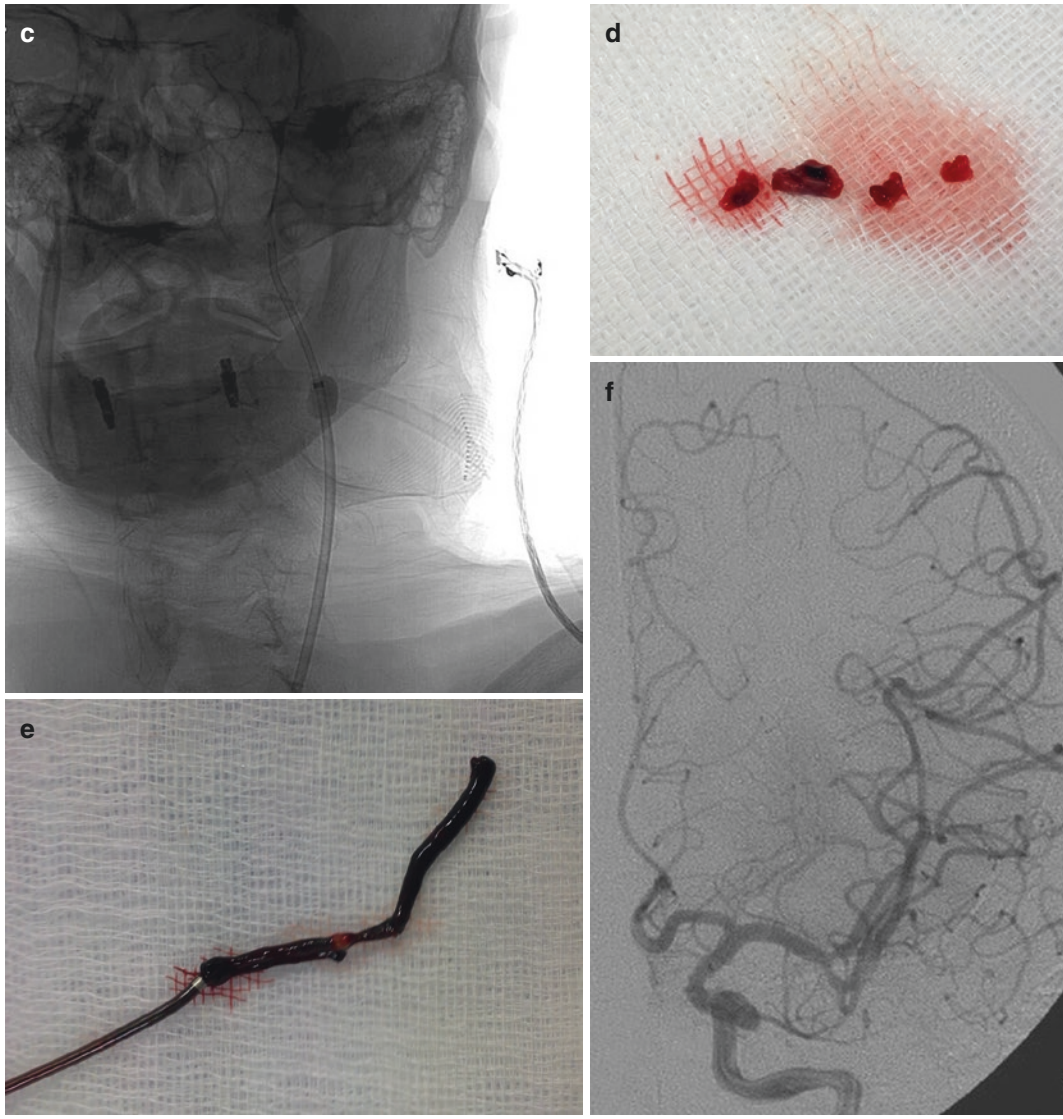

Fig. 10.3 (continued)

theoretically elevate the chance of clot disruption and distal migration. Therefore, in cases where the patient's vascular anatomy allows easy passage, the Penumbra catheter is directly advanced to the thrombus without any distal passage of the clot by an inner microcatheter or a microguidewire. However, in the cases where a patient's arterial anatomy is tortuous, an inner microcatheter is necessarily advanced past the thrombus over a microguidewire. Then, the large-bore aspiration catheter is advanced over it up to the thrombus to make a wedge between the tip of the catheter and the thrombus. If required, local angiography can be performed before aspiration is done to predict the original path of the occluded segment and to outline the occlusion, including the extent of thrombus. Once the large-bore aspiration catheter is located optimally, the inner microcatheter and microguidewire are then removed. Thereafter, the proximal hub of the Penumbra catheter directly is connected to a 20 mL or 50 mL syringe.

10.2.4.4 Step 4: Balloon Inflation and Manual Aspiration with a Syringe, Then Catheter Retrieval Maintaining Aspiration Force

After connecting the proximal hub of Penumbra catheter directly to a 20 mL or 50 mL syringe, slight negative pressure is attempted by partial pulling of the plunger to confirm direct wedging and a vacuum state between the tip of Penumbra catheter and the clot. At this point, absence of backflow mostly indicates the thrombus is trapped in the catheter. There are a few notable points to make. First, try to use the largest possible reperfusion catheter to maximize suction power. Second, try to keep the direction of the tip of Penumbra reperfusion catheter parallel to the presumptive path of the occluded vessel for prevention of direct contact between the tip and the endothelium. Just before applying the negative pressure, the balloon of the BGC is inflated to block proximal flow (Fig. 10.3c). Then negative pressure applied by forceful pulling of the plunger of the syringe for a period of 60–90 s. After that, the large-bore aspiration catheter is slightly advanced further into the thrombus and then slowly withdrawn under continuous aspiration. The procedure can result in one of either type of the following conditions. First, the vacuum state is unexpectedly lifted, followed by entry of free blood flow into the catheter, suggesting that the wedged clot is disrupted and sucked into the catheter (Fig. 10.3d). Then, the catheter is manually aspirated with a syringe to remove any residual thrombus fragments within the Penumbra catheter. Second, if the wedging or vacuum state persists, so no free blood flow in the syringe tubing is restored upon withdrawing the large-bore aspiration catheter into the BGC, the aspiration catheter is slowly and carefully removed from the patient under continuous aspiration from the Penumbra catheter and syringe (Fig. 10.3e). And the BGC is manually aspirated with a syringe to remove any residual thrombus fragments. Finally, the balloon of the BGC is slowly deflated to restore proximal blood flow. This process can be repeated until successful reperfusion is achieved (Fig. 10.3f). However, if three FAST passes fail to achieve incremental reperfusion, then stent retriever thrombectomy may be employed as a rescue procedure.

There are two available methods to make negative pressure; manual syringe aspiration and the Penumbra aspiration pump. FAST is performed under manual aspiration only. A 50 mL syringe is usually used for ICA occlusions and the M1 segment of MCA occlusions. And, a 20 mL syringe is usually used for the M2 segment of MCA occlusions and BA occlusions. However, if the 20 mL syringe fails, it can be switched to the 50 mL syringe to intensify suction power. Based upon the experiences, one certain benefit of manual syringe aspiration is its technical simplicity and cheap price. However, each method can have its own benefit. And there has been no proven evidence yet for which is better regarding clot retrieval efficacy and safety. Therefore, the practitioners can choose their preferential aspiration method using either a syringe or the aspiration tubing and Penumbra aspiration pump.

10.2.5 Technical Tips to Overcome Tortuous Segment During the FAST

Despite recent huge advances in the large-bore aspiration catheter's tracking facility, crossing the curved segment of cerebral arteries, such as the carotid siphon, is still not always easy. Tortuosity itself is one big barrier for passage, and the anatomic condition where a small artery is arising from the tortuous segment, such as an ophthalmic artery origin from the carotid siphon, can be another challenging situation during advancement (Fig. 10.4a). Moreover, underlying atherosclerotic stenosis is another potential barrier for catheter passage by making the endothelial surface uneven and rough. In this section, a few technical tips to overcome such obstacles will be introduced.

10.2.5.1 Use the Softest Aspiration Catheter on the Practitioner's Hand and Maximize Guiding Catheter Support

This tip is intuitive and simple to convey. First, the softer the aspiration catheter is (relative to similarly

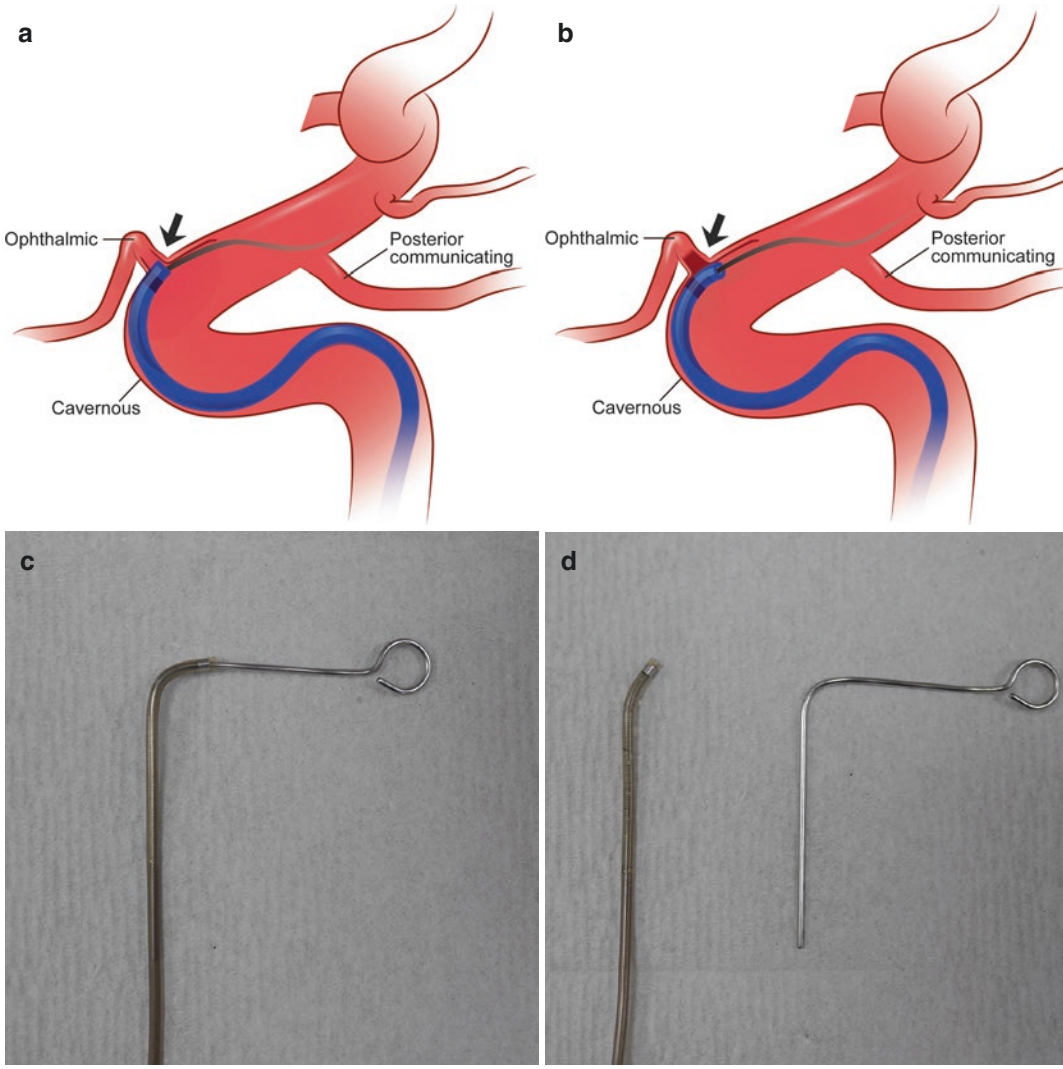

Fig. 10.4 Illustration (**a**) shows how the navigation difficulty originates from the large-caliber of the aspiration catheter and vascular anatomy, such as high curvature or origin of ophthalmic artery. Steam shaping of the tip of Penumbra catheter (**b**) can be a solution. The examples of steam shaping are shown as the following: 45° curved (**c**, **d**), 90° curved (**e**, **f**), and J shape (**g**, **h**)

sized large-bore catheters), the better the tracking ability will be. All of the FAST cases are based on the experiences using the Penumbra reperfusion catheter from the first generation of the 041 and 032 family to the 5 Max Ace. However recently, several new large-bore catheters for clot aspiration have been continuously launched in this field, such as ACE 64 (Penumbra), Sofia (MicroVention, CA, USA), Arc (Medtronic Neurovascular), and Catalyst (Stryker Neurovascular), so the practitioner can use any of these catheters for the FAST technique. Again, the most important point in selecting an aspiration catheter is to choose the largest and simultaneously softest aspiration catheter available to the practitioner's hand. Second, likewise, maximizing the guiding catheter support intuitively allows for more stable behavior of the aspiration catheter. This naturally means better control of aspiration catheter by practitioner. These intuitive points are easy to state and understand and are left to the

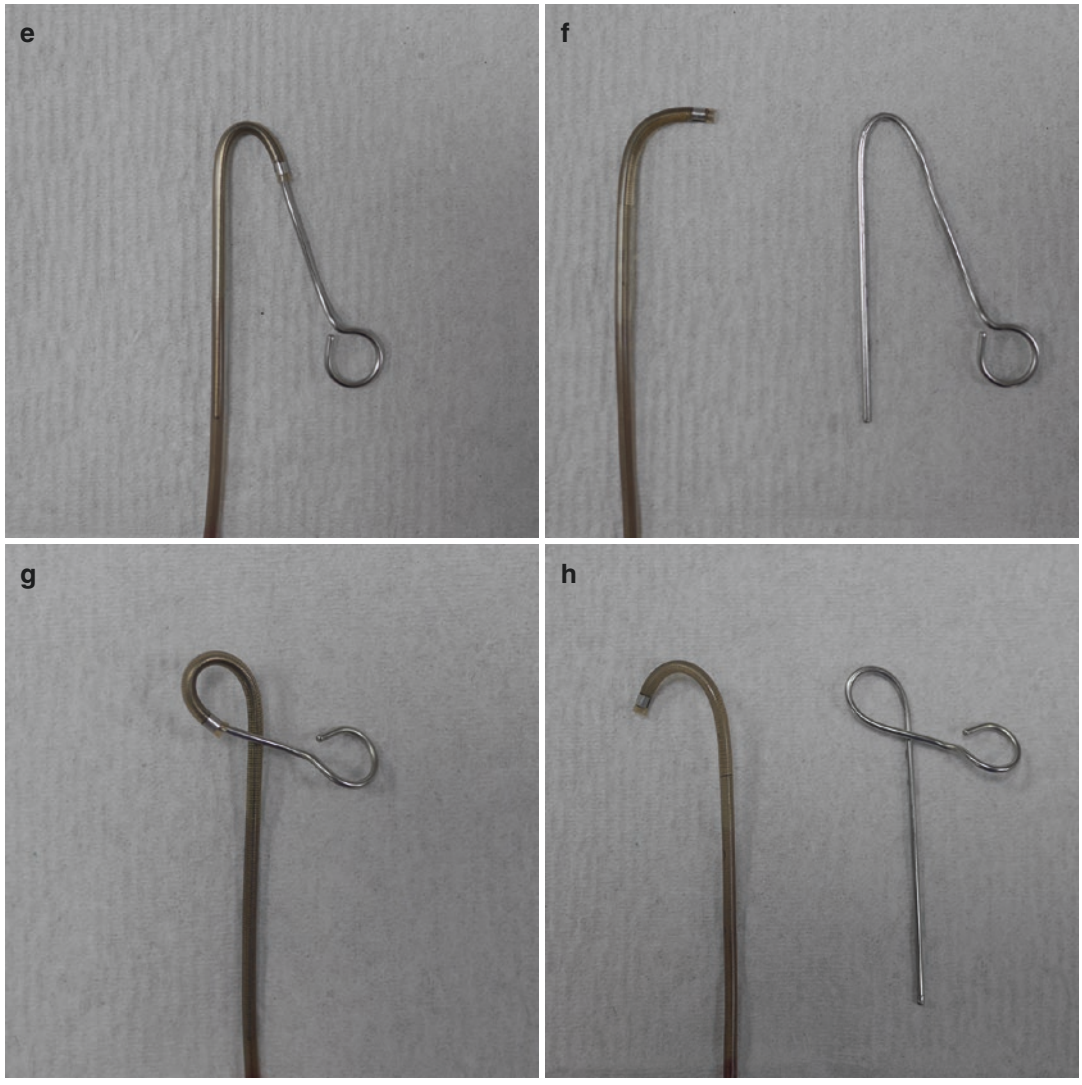

Fig. 10.4 (continued)

discretion of the practitioner. However, they should be emphasized as noteworthy, nevertheless. The next two technical tips will require more explanation.

10.2.5.2 Steam Shaping of the Tip of Penumbra Aspiration Catheter: 45°, 90°, and J-Shape

As an aspiration catheter becomes larger in diameter, passing the curved segment can be technically more unlikely in some tortuous cases with its original straight shape of the tip of the aspiration catheter. This can be achieved through steam shaping (Fig. 10.4b). There are various shapes available for the tip of microcatheter, such as straight, simple-curved (45°, 90°, and J), preshaped-C, pigtail, and preshaped-S [15, 16]. Among the various shapes, there are three grades of "simple-curved" steam shaping that are recommended for navigating tortuous segments with the Penumbra aspiration catheter. This steaming usually takes 30–60 s, and steamed microcatheters are then soaked in normal saline for 30 s or more. In most of the cases, a 45° curved shape is the recommended choice. By

steam shaping the tip of Penumbra aspiration catheter with a 45° curved shape prior to its application, advancement through tortuous segments is more easily achieved. However, in some proportion of the cases with extreme tortuosity or severe stenosis due to underlying atherosclerosis, which is determined by the practitioner (but accounts for less than 20% of cases in the author's experience), a 90° curved or J-shape can be used (Fig. 10.4).

10.2.5.3 Coaxial Advancement Technique of the Penumbra Catheter

If a microguidewire is just used for advancing the large-bore aspiration catheter, the gap between the two devices will be large. This can result in difficulty steering and controlling the catheter, because the angle vectors of the two devices may be at different directions during the passage of curved segment. Specifically, this means that the Penumbra aspiration catheter will have too much freedom of motion during advancement when only guided by the microguidewire. And, advancement through a highly curved segment is technically unlikely due to all this freedom of movement for the Penumbra catheter. To overcome such problem, the coaxial advancement technique is recommended here, which means introducing another microcatheter of intermediate size between the Penumbra catheter and microguidewire to reduce the gap between them (Fig. 10.5a). This serves to restrict the freedom of movement of the Penumbra reperfusion catheter to a necessary extent, which will allow greater ability to steer and control the large-bore catheter during advancement through the curved segment.

The author's technical "recipe for coaxial assembly" is as follows (Fig. 10.5). In each case, an appropriate size for the inner microcatheter is necessary. For the ICA and the proximal M1 segment of MCA, it is recommended to use the Penumbra 5 Max or 5 Max Ace with a 2.3-French inner microcatheter, with which the author preferred a Prowler Select Plus preshaped 45 or 90 (Cordis Neurovascular) and a 0.016 in. microguidewire (GT; Terumo). For the distal M1 segment or the M2 segment of MCA, it is recommended to use the Penumbra 4 Max with a 2.0-French inner microcatheter, with which the author preferred an Excelsior 1018 preshaped 45 or 90 (Stryker Neurovascular) and a 0.014 in. microguidewire (Synchro; Stryker Neurovascular).

10.2.6 Additional Case Examples of the FAST

10.2.6.1 Acute ICA Terminus Occlusion

Here a case is presented where FAST was used for an ICA terminus occlusion. In this case, a 72-year-old man presented with sudden onset left hemiparesis. CT findings were normal, and carotid angiography demonstrated near-complete occlusion of the terminal segment of the right ICA. Cardioembolic stroke was diagnosed, and immediate recanalization was performed using the FAST technique 3 h after symptom onset (Fig. 10.6). A 9-French Optimo BGC (Tokai Medical Product) was placed on the cervical segment of the ICA and was followed by advancing the Penumbra 5 Max Ace to the proximal part of the clot coaxially with a 2.3-French Prowler Select Plus microcatheter (Cordis Neurovascular) and a 0.016 inch GT microguidewire (Terumo). The first forceful aspiration with a 50 mL syringe was attempted at MCA M1 segment, some clot fragments were then retrieved, but the following angiography showed still occluded anterior cerebral artery. Thereafter, the second forceful suction at proximal anterior cerebral artery enabled retrieval of the larger sized clot, which resulted in TICI 3 recanalization. The interval from arterial puncture to revascularization was 20 min. No procedure-related complications or ICH occurred, and the patient improved in NIHSS score from 14 at baseline to 5 at 24 h after the procedure. Functional recovery was mRS 1 at 3 months after the procedure.

10.2.6.2 Acute MCA Occlusion at M2 Segment

Another case example is presented where FAST was used for an M2 segment occlusion. In this

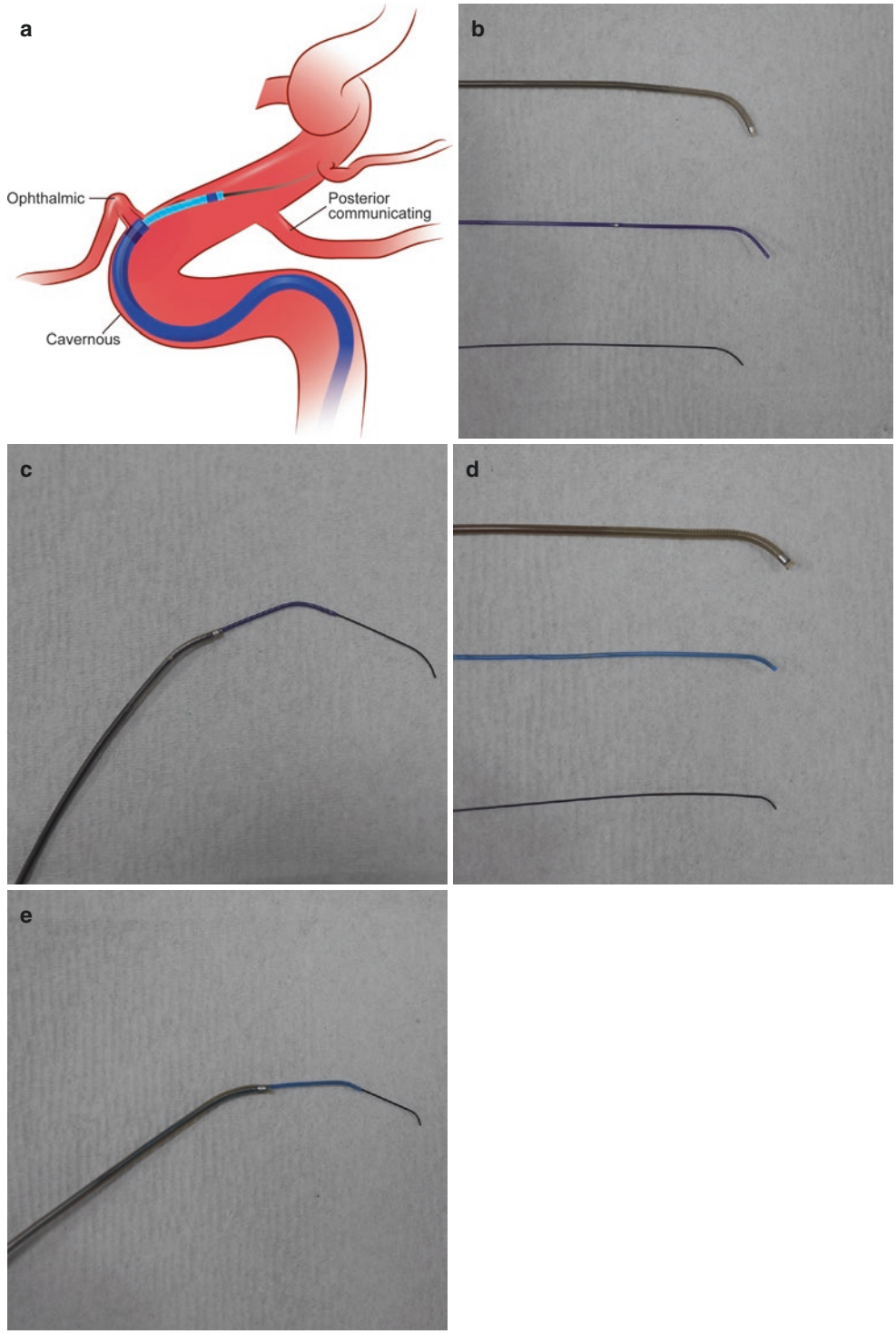

Fig. 10.5 Coaxial advancement technique with an inner, intermediate-sized microcatheter (**a**) can be another solution to overcome navigation difficulty. The examples of coaxial assembly are shown, Penumbra 5 Max or 5 Max Ace is nicely assembled with a 2.3-French inner microcatheter and a 0.016 in. microguidewire (**b**, **c**), and Penumbra 4 Max is assembled with a 2.0-French inner microcatheter and a 0.014 inch microguidewire (**d**, **e**)

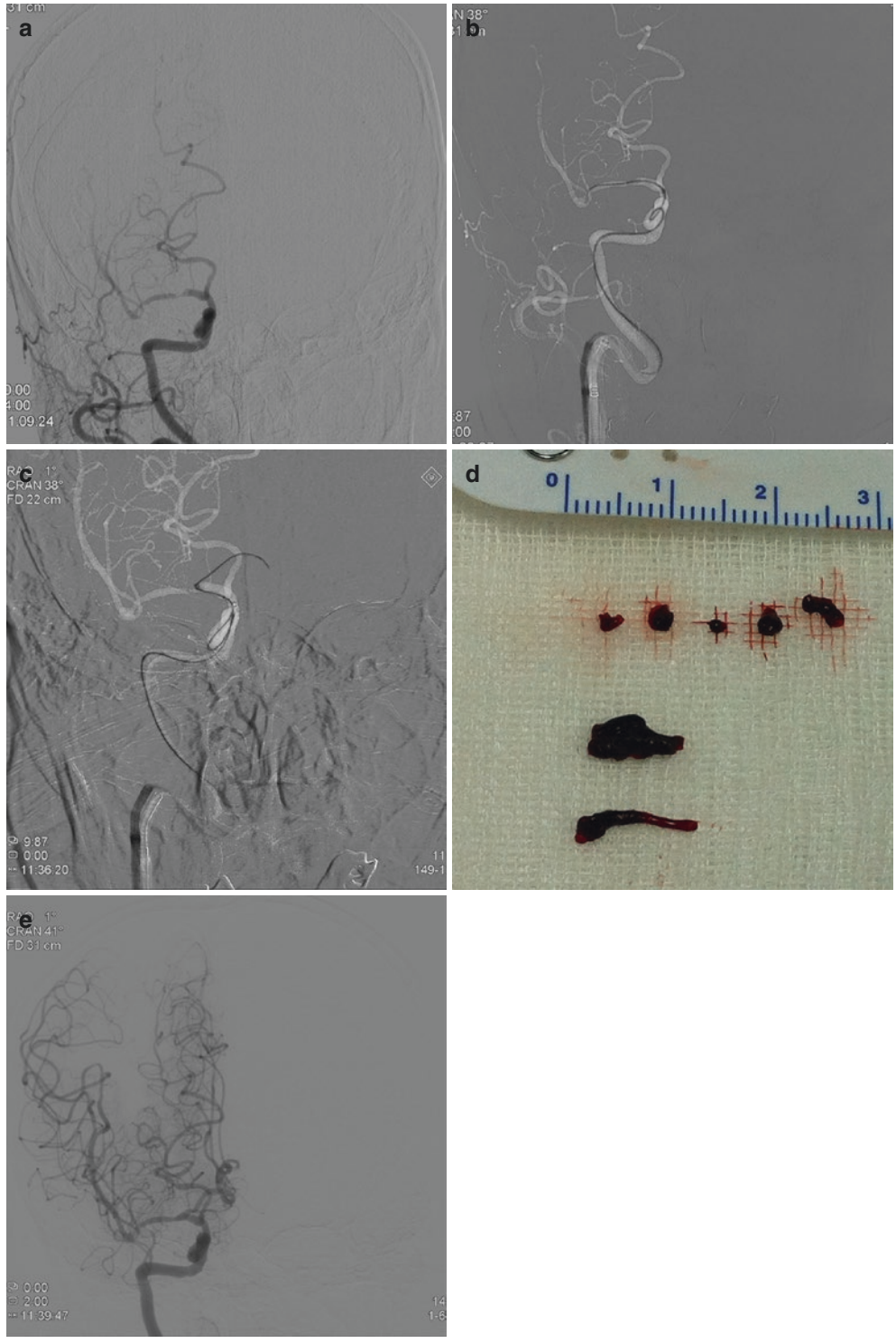

Fig. 10.6 Baseline angiography (**a**) shows an ICA terminus occlusion on the *right*. Penumbra 5 Max Ace is advanced to the clot coaxially with a 2.3-French microcatheter and a 0.016 in. microguidewire (**b**, **c**). Clot fragments (**d**) are retrieved via FAST technique; final angiography (**e**) shows complete revascularization

case, a 60-year-old woman presented with acute onset right hemiparesis and global aphasia within a 2.5 h time window. Left carotid angiography demonstrated complete occlusion of the M2 segment of the MCA. FAST was attempted to recanalize the vessel (Fig. 10.7). A 9-French Optimo BGC (Tokai Medical Product) was placed on the cervical segment of the ICA and was followed by advancing the Penumbra 4 Max to the proximal part of the clot coaxially with a 2.0-French Excelsior 1018 microcatheter (Stryker Neurovascular) and a 0.014 inch Synchro microguidewire (Stryker Neurovascular). After wedging the reperfusion catheter to the proximal part of the clot, a single forceful suction with a 20 mL syringe enabled retrieval of the whole clot and resulted in TICI 3 recanalization. The interval from arterial puncture to revascularization was 15 min. No procedure-related complications or ICH occurred, and the patient improved in NIHSS score from 18 at baseline to 10 at 24 h after the procedure. Good functional recovery was achieved as mRS 1 at 3 months after the procedure.

10.3 Combined Usage of Direct Clot Aspiration and Stent Retriever Thrombectomy: Switching Strategy and Solumbra Technique

There are two major mechanical thrombectomy techniques that have emerged as the dominant strategies in the present era of endovascular stroke therapy. The primary involves the use of a stent retriever, such as the Solitaire FR (Medtronic Neurovascular) or the Trevo device (Stryker Neurovascular). The second type of technique is the use of direct clot aspiration, using either the FAST or the ADAPT techniques with a large-bore aspiration catheter, such as the Penumbra 5 Max or 5 Max Ace (Penumbra). In addition, there have been a few attempts to enhance the rate of successful recanalization through a combination of the two major techniques, stent retriever and direct clot aspiration. The background of such attempts is straightforward. Despite advancement of the devices and techniques, 100% successful recanalization cannot be guaranteed solely using a primary mechanical thrombectomy, whether the stent retriever or clot aspiration is adopted as the primary technique. In the cases of a stent retriever being used as the primary device, the rate of successful recanalization was 83% in the SWIFT trial (TIMI 2–3: 45/54) and 85% in the TREVO 2 trial (TICI 2–3: 73/86) [11, 17]. Even in the more recent randomized controlled trials of 2015, which were mostly based on stent retriever thrombectomy, the rate of successful recanalization defined as TICI 2b or 3 was 59% in Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN; 82% of the device used was stent retriever), 86% in EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA; only Solitaire FR is used), 72% in Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE; 79% of the device used was stent retriever and 61% was Solitaire FR), 88% in SWIFT PRIME (only Solitaire FR used), and 66% in Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 h (REVASCAT; only Solitaire FR used) [12, 18–21]. Although the detail of the interventional strategy was slightly different in each trial, these findings apparently demonstrate that practitioners were required to prepare adjuvant rescue procedures for the patients without successful recanalization through the primary devices. Similar findings were reported regarding the use of clot aspiration as the primary technique. The rate of successful recanalization defined as TICI 2b or 3 was 82% in the first FAST trial, 65% in the next FAST trial for acute ICA occlusions, and 75% in the ADAPT trial [6–8]. Likewise with stent retriever thrombectomy methodology, if clot aspiration with a large-bore catheter is adopted as the first-line technique, the practitioner may need to employ potential salvage with a stent retriever or another treatment, if several passes fail to achieve successful recanalization or

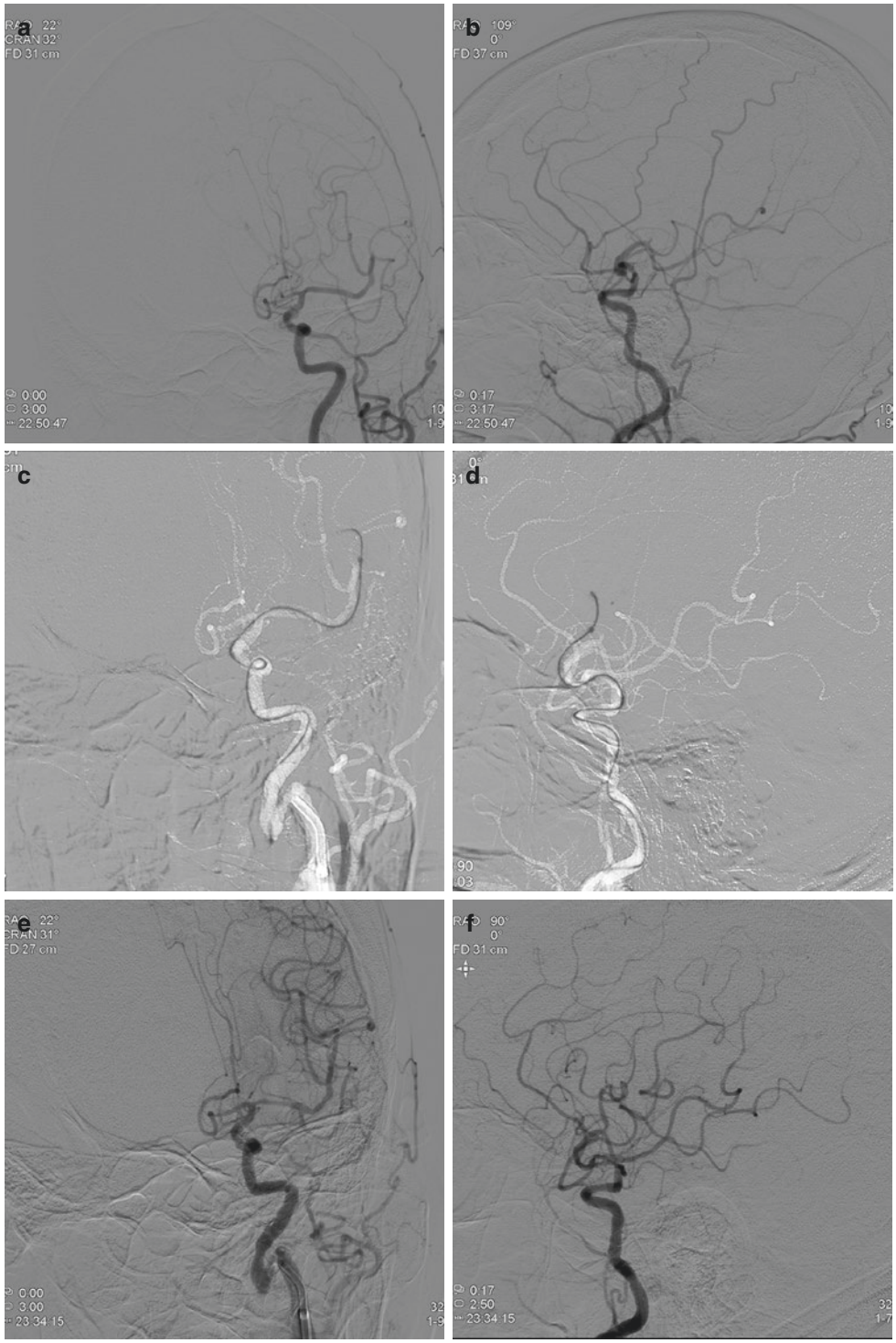

Fig. 10.7 Baseline angiographies (**a**, **b**) show an M2 segment occlusion on the *left* MCA. Penumbra 4 Max is advanced to the proximity of the clot coaxially with a 2.0-French microcatheter and a 0.014 inch microguidewire (**c**, **d**). Whole clot is retrieved via FAST technique, and final angiographies (**e**, **f**) show complete revascularization

if advancement of the large-bore aspiration catheter to the occlusion site fails by the vascular tortuosity.

Based on the aforementioned background, there have been a few attempts to improve recanalization by using the stent retriever and clot aspiration together. The first was called the "switching strategy," which involved switching from FAST to Solitaire stent thrombectomy and the second is the "Solumbra technique," which uses the two devices simultaneously [22–26]. Although both attempts bear similarities in terms of the concept of combined usage of two major techniques, the detail is very different. Some of the difference lies in the regulatory rules and laws prevailing in the originating countries. For example, the switching strategy of mechanical thrombectomy actually originated as a result of a limitation in the health insurance system in South Korea. Specifically, the public health insurance system supported by government in South Korea pays for about 90% of the price of the first device, either a stent retriever or a large-bore aspiration catheter during the mechanical thrombectomy for a major stroke patient. This means that if the practitioner used a second device for rescue, the patient's family pays fully for the second device. Therefore, the practitioners under such health insurance system naturally try their best to achieve successful recanalization by using only one device and then "switch" to a second device as a rescue procedure. On the other hand, in some other countries such as the USA, practitioners are allowed to simultaneously use both the stent retriever and the large-bore aspiration catheter at once under the practitioner's discretion during the procedure, so some practitioners routinely use both devices to enhance the rate of successful recanalization. The most common combination is to use the Solitaire FR stent (Medtronic Neurovascular) and the Penumbra reperfusion catheter (Penumbra), so this has come to be known as the "Solumbra technique." The details of both the switching strategy and the Solumbra technique will be discussed in the following.

10.3.1 What Is the Switching Strategy for Mechanical Thrombectomy?

The origins of the switching strategy came from a desire to improve recanalization rates following thrombectomy procedures. A period-to-period comparison analysis for introducing the switching strategy was published in the year of 2013 [22]. In the former period (period 1, from April 2009 to October 2010), the investigators used FAST only for a mechanical thrombectomy procedure. Then they applied switching strategy from FAST to stent retriever thrombectomy in difficult cases in a subsequent one and half year period (period 2, from October 2010 to January 2012). In the paper, "difficult case" was defined as three or more failed attempts by the FAST for recanalization. During period 1, they inevitably kept using only FAST in the difficult cases because that was the only approved thrombectomy technique in South Korea at the time. From the time when Solitaire stent was available, at the beginning of period 2, they began to apply switching strategy of mechanical thrombectomy in the difficult cases with FAST, under the hypothesis that additional attempts with a different mechanism (Solitaire stent) could improve recanalization (Fig. 10.8). One hundred and 35 consecutive patients who presented with acute large vessel occlusion in the anterior circulation and treated with mechanical thrombectomy, enrolled to this analysis; 61 in period 1 and 74 in period 2. Although puncture-to-recanalization time was not significantly different between the two periods, the patients in period 2 showed a trend for better angiographic outcome (TICI 2b-3: 73.8% in period 1 vs. 85.1% in period 2, $P = 0.10$). And notably, period 2 showed a significantly better 3-month functional outcome (mRS 0–2: 49.2% vs. 67.6%, $P = 0.030$). The subgroup analysis of the "difficult cases" showed that the difference of successful recanalization was more pronounced in between non-switching and switching cases (TICI 2b-3: 52.7% vs. 82.9%, $P = 0.030$), which suggested the switching of mechanical thrombectomy techniques in difficult

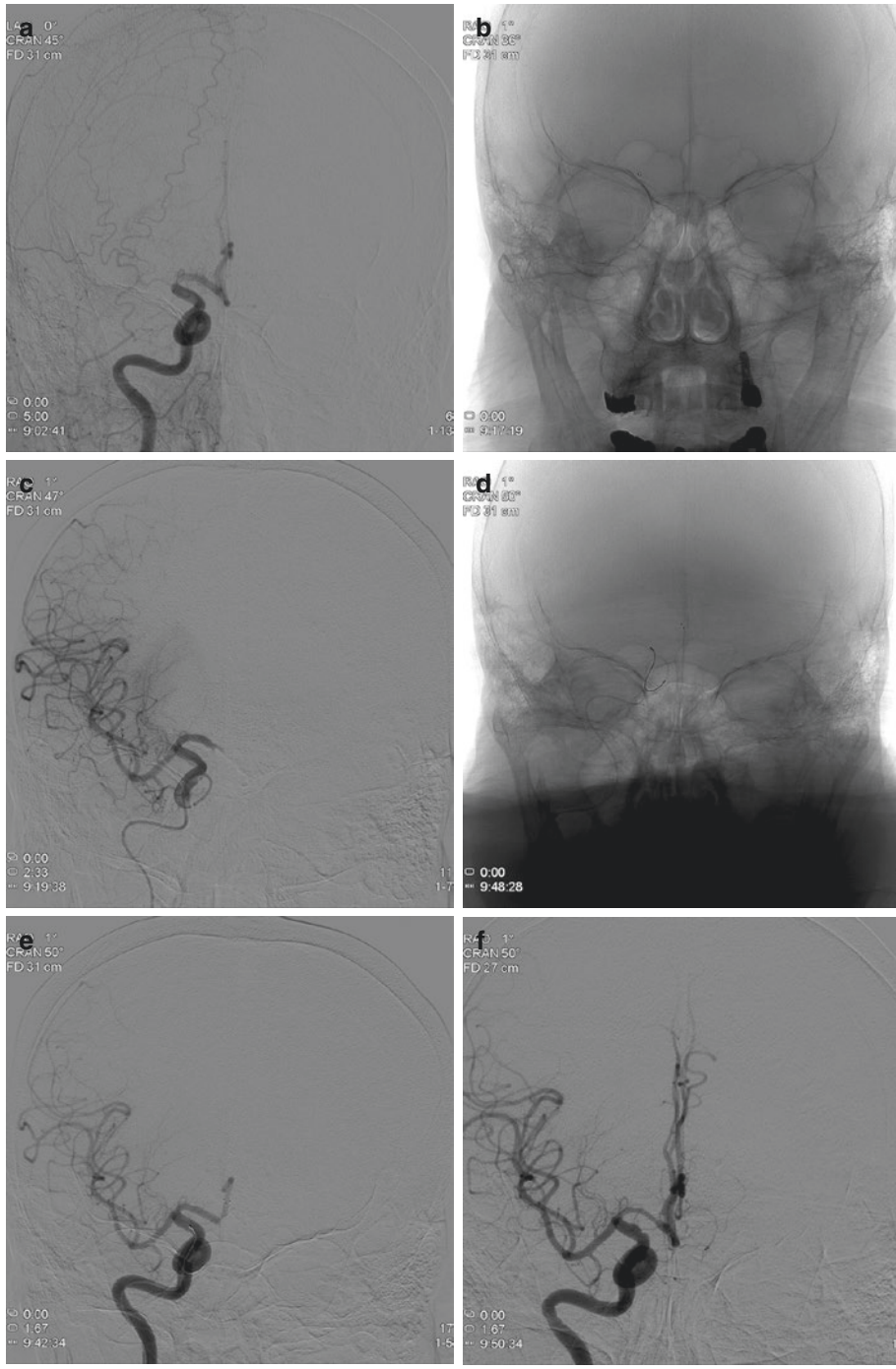

Fig. 10.8 A case example of switching strategy, from FAST to Solitaire, applied for an ICA terminus occlusion on the *right*. Baseline angiography (**a**) shows ICA terminus occlusion, Penumbra 5 Max is then advanced to the clot (**b**). After single forceful aspiration using FAST, ICA and middle cerebral artery is fully recanalized, but ACA is still occluded (**c**). Another FAST is attempted for ACA occlusion, but advancement is not available due to small caliber and acute angle. Method of thrombectomy is switched to stent retriever, then Solitaire FR deployed across the clot on proximal ACA (**d**, **e**). Three minutes later, the Solitaire FR stent is carefully retrieved, and complete revascularization (**f**) is then confirmed

cases played a major role to improve the recanalization and outcome. But the differences in symptomatic ICH and procedure-related complications were not statistically significant between the two subgroups.

10.3.2 What Is the Solumbra Technique?

The essential difference between the switching strategy and the Solumbra technique is the following. Switching is more a strategy itself, which involves using one device and then switching to another device in certain situations; however, the Solumbra is more a technique, which involves using the two devices simultaneously, Solitaire and Penumbra, thus "Solumbra" (Fig. 10.9). The detail of the Solumbra technique is described here. First, a guide catheter is introduced into the proximal segment of the target artery. Then, a 2.3-French or a 2.5-French microcatheter with a 0.014 or a 0.016 inch microguidewire inside it is inserted into a Penumbra reperfusion catheter. The entire unit is advanced into the guide catheter. Importantly, as a featured technical part of Solumbra begins from this step, the inner microcatheter is introduced past the thrombus. Then, the Penumbra 5 Max or 5 Max Ace (Penumbra) is advanced as close to the proximity of the thrombus as possible. The Solitaire FR (Medtronic Neurovascular) is then deployed across the thrombus via the inner microcatheter. Next, the inner microcatheter is removed completely from the patient. After a standard waiting period of 3–5 min, the Penumbra aspiration catheter is connected to a 50 mL syringe for manual aspiration or the Penumbra aspiration pump. Negative pressure is thus applied to pull the stent retriever into the aspiration catheter while simultaneously advancing the aspiration catheter up into the thrombus. If the thrombus becomes lodged between the stent retriever and the tip of the aspiration catheter, then the system is carefully removed as a unit under continuous aspiration while also manually aspirating through the guiding catheter.

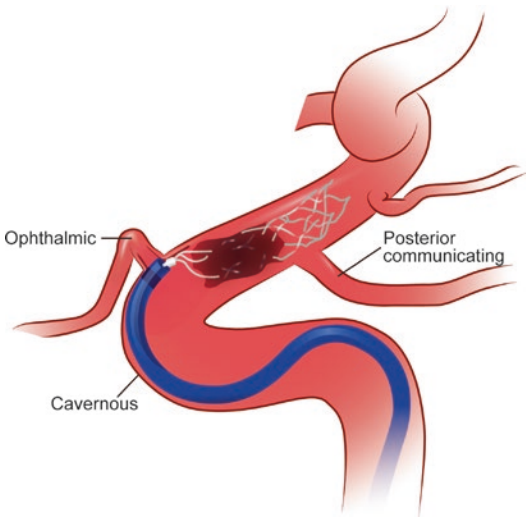

Fig. 10.9 Illustration of Solumbra technique is shown. After advancement of the Penumbra 5 Max or 5 Max Ace to the proximity of the thrombus, the Solitaire FR stent is then deployed across the thrombus via the inner microcatheter

The Solumbra technique combines the use of the stent retriever and aspiration device, and this can provide several potential synergistic effects. Localized aspiration at the site of the thrombus may promote entrapment of the thrombus within the stent. Flow control in the affected vascular territory may also reduce the incidence of thrombus fragmentation and distal embolization. The use of local aspiration may reduce or altogether eliminate emboli to new territories, which observed in 7–9% of cases in the SWIFT and TREVO trials, and in up to 11% in subsequent registries [11, 17]. Removal of the delivery microcatheter from the Penumbra 5 Max or 5 Max Ace leaves a larger cross-sectional surface area for the aspiration of the thrombus, thereby substantially increasing the amount of suction which can be applied during the removal of the stent retriever device.

There have been a number of case series and clinical studies associated with the Solumbra technique. The first report is a technical note that dates back to 2013 [23]. In that report, the author described a technique where a 6-French triaxial system was used to deliver the Solitaire FR stent through a Penumbra aspiration catheter in order to provide intracranial aspiration in close proximity

to the stent. According to this, a BGC must be used to apply negative suction and reverse flow to minimize the chance of antegrade blood flow dislodging the thrombus from the stent. The technique arose from the need to provide adequate aspiration in the vertebrobasilar system, where only one vertebral artery was accessed and aspirated. Another report showed that Solumbra was effective in an ICA terminus occlusion [24]. The authors investigated the feasibility of combined stent retriever and clot aspiration thrombectomy for more effective recanalization of acute ICA terminus occlusion. Ten consecutive patients with acute ICA terminus occlusion treated using the Solumbra technique were analyzed. Recanalization as TICI 2 or 3 was achieved in 80% of the patients. However, ICH occurred in four patients, though parenchymal hematoma type 2 was not observed. Four of the ten patients died within 3 months. In 2015, a multicenter, retrospective review of the Solumbra technique was undertaken in the USA [25]. Of the 105 patients who met the inclusion criteria for that retrospective study, successful recanalization as TICI 2b or 3 was achieved in 88% of these patients. Additionally, 44% of the patients had favorable outcomes at 90 days. Five cases of symptomatic ICH were reported, and there were three procedure-related deaths. They concluded that the Solumbra technique might be an effective and safe strategy for mechanical thrombectomy of acute large vessel occlusions. Although there have been some reports showing the benefits of Solumbra technique, this is still an area of controversy. For example, in a 2015 paper entitled "Comparison of clinical outcomes in patients with acute ischemic strokes treated with mechanical thrombectomy using either Solumbra or ADAPT techniques," the ADAPT technique was associated with significantly better clinical outcomes at 90 days in patients with acute ischemic stroke compared to patients where Solumbra was used [26]. Specifically, 100 patients were included in that study, 55 in the Solumbra group and 45 in the ADAPT group. There was no difference in the rates of successful recanalization (TICI 2b-3: 84% in the Solumbra group vs. 89% in the ADAPT group, $P = 0.6$) and the procedure time (51 min vs. 50 min, $P = 0.8$). They found that patients in the ADAPT group had a trend toward a lower rate of symptomatic ICH than patients in the Solumbra group (2.2% vs. 12.7%, $P = 0.07$). And patients in the ADAPT group had a significantly higher rate of good clinical outcome at 90 days (55.6% vs 30.9%, $P = 0.015$). Accordingly, this is an important area of research of which further investigation is required.

10.4 Role of Clot Aspiration Thrombectomy and FAST in Special Conditions of Acute Ischemic Stroke

10.4.1 Proximal Aspiration Thrombectomy for Clot Burden Reduction for ICA Occlusions

Patients with extensive clot burden, as can be frequently found in terminal ICA occlusions, still encounter difficult recanalization and poor functional outcomes in spite of recent huge advances in mechanical thrombectomy devices and techniques. During the thrombectomy procedure in such conditions, a larger thrombus burden may engender a slower response to thrombolytic agent, or more passages with the thrombectomy device, or a prolonged time to recanalization. Such delays in recanalization can result in larger territory infarctions and a worse functional recovery. Additionally, more extensive thrombi may cause the occlusion of important collateral channels, as the original thrombus itself or migration of the thrombus may pervade noninvolved vascular territories. Furthermore, this may contribute to more rapid and extensive infarction and worse patient outcomes. Alternative methods have been recently attempted to reduce clot burden by using a variant of clot aspiration thrombectomy. One such method involved the use of manual suction through a BGC in an ICA L- or T-type occlusion. In that method described in a technical note [27], manual suction using a 60 mL syringe was applied through an 8-French BGC that was positioned in the cervical carotid vasculature to

create proximal flow arrest. The result was a significant reduction of the clot burden, which facilitated further intervention leading to full recanalization.

An investigation with a similar concept into proximal aspiration thrombectomy (PAT) was undertaken as a modification of the direct clot aspiration methodology. PAT for clot burden reduction in ICA occlusions features manual clot aspiration at the cervical segment ICA, which is usually far proximal to the occlusion site, with a 6-French coaxial guide catheter through a 9-French BGC (Fig. 10.10). After a couple of attempts of PAT, standard mechanical thrombectomy is following in cases of remaining occlusions [28]. In that study, "responders" were defined as patients where some amount of clot was retrieved by PAT and where angiography showed partial or full recanalization. Fifteen of 53 patients (28.3%) were responders to PAT. The results showed a significantly shorter puncture-to-reperfusion time (94.5 min versus 56.0 min, $P = 0.002$) in the PAT group, along with a significantly higher rate of TICI 2b or 3 reperfusion (45.5% vs. 73.6%, $P = 0.009$), but only a trend for better 3-month favorable outcome (mRS 0–2: 36.4% vs. 54.7%, $P = 0.097$). Additionally, there was no increase in the incidence of procedure-related complications or intracranial hemorrhage in the PAT group. They concluded such modifications of the standard manual aspiration technique might provide better outcomes in difficult cases of ICA occlusions through reducing clot burden.

10.4.2 FAST for Vertebrobasilar Artery Occlusions

It is well known that the prognosis for acute BA occlusions is more dismal than occlusions involved in the anterior circulation artery. Traditionally, acute BA occlusion have presented with rates of mortality of 40–86% and good outcomes of only 13–21% [29, 30]. Despite advances in recanalization techniques from intravenous thrombolytic agent to intra-arterial mechanical thrombectomy, the effect of therapeutic intervention on patient outcome generally has been limited in acute BA occlusion cases. Intravenous infusion of recombinant tissue plasminogen activator (rt-PA) was the first method attempted; however, it was not very effective in the recanalization of acute BA occlusions [31, 32]. Next, endovascular treatment for acute BA occlusion was attempted using local infusion of fibrinolytic agent. Although intra-arterial fibrinolysis achieved a higher recanalization rate when compared to intravenous rt-PA administration, clinical outcomes did not differ between the treatments [33, 34]. Recently, several mechanical thrombectomy techniques have been applied, which has led to a further improvement in recanalization rate, but no method to date has been clearly proven to improve clinical outcomes.

As an example, a study on mechanical thrombectomy was undertaken to determine outcomes of patients with vertebrobasilar occlusion using Merci retriever [35]. In that study, recanalization was achieved in 78% of the patients. Mortality was 44% and good outcomes were seen in 41%. Outcomes for patients with vertebrobasilar occlusions treated with the Merci retriever in that study thus compared favorably with historical reports. However, acute BA occlusions still presented a therapeutic challenge. Another study was undertaken to evaluate the technical feasibility and efficacy of stent retriever thrombectomy in acute BA occlusions [36]. In that study, 14 consecutive patients with BA occlusion underwent endovascular therapy using the Solitaire FR stent. Additionally, the multimodal treatment approaches were included such as clot aspiration, intravenous or intra-arterial thrombolysis, and permanent stent placement. Successful recanalization defined as TICI 2b or 3 was achieved in all patients, and the average number of device passes was 1.3. The median procedure time to recanalization was 47 min and no device-related complications occurred. However, good functional outcome of mRS 0–2 at 3 months was observed only in 28.6% of cases, and the overall mortality was 35.7%. In 2014, a study was undertaken to investigate the use of FAST for the treatment of acute BA occlusion [37]. The study compared revascularization rates and outcomes between intra-arterial fibrinolytic treatment and FAST for patients with acute BA

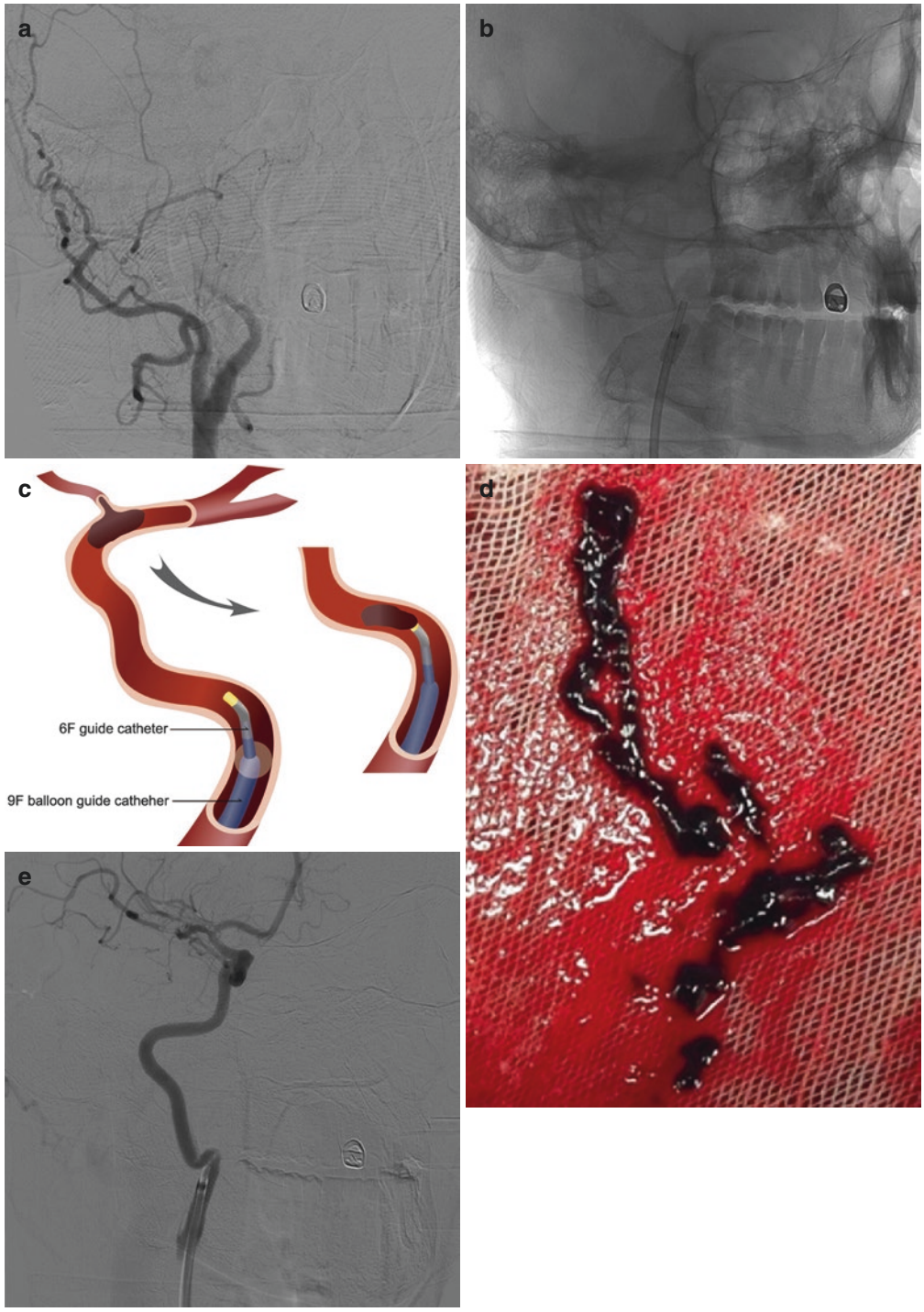

Fig. 10.10 Baseline angiography (**a**) shows ICA terminus occlusion; proximal aspiration thrombectomy (**b**) is then performed through a 100 cm, 6-French guide catheter (Envoy, Cordis Neurovascular), while the balloon of an outer 85 cm, 9-French balloon guide catheter (Optimo, Tokai Medical) is inflated. Illustration (**c**) of the proximal aspiration thrombectomy is demonstrated. Clots (**d**) are retrieved and final angiography (**e**) shows near-complete reperfusion

occlusions (Fig. 10.11). In that study of 57 patients with acute BA occlusion, 25 were treated with intra-arterial fibrinolysis and 32 were treated with FAST. The results were that the FAST group had a shorter procedure time (75.5 min vs. 113.3 min, $P = 0.016$) and a higher successful

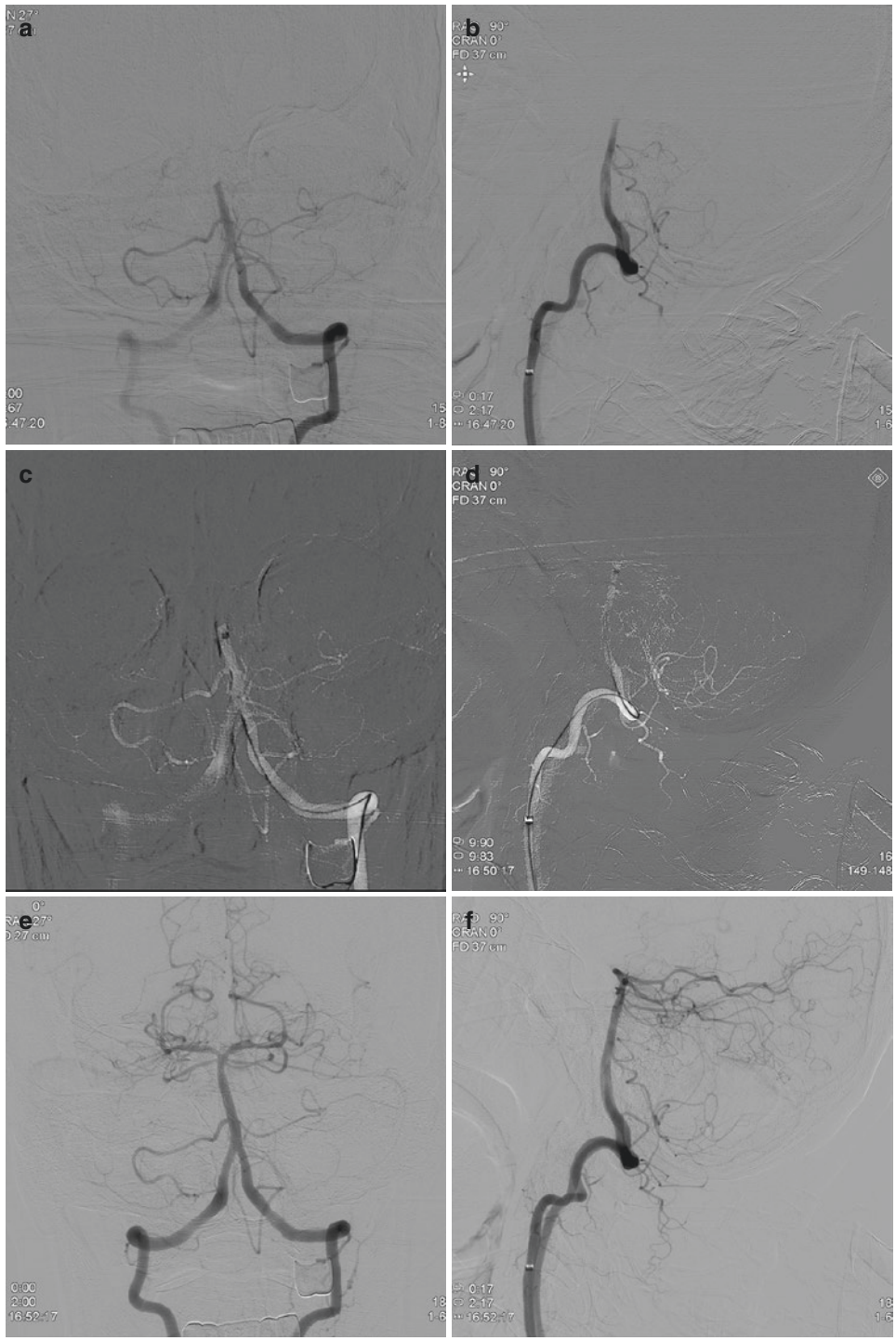

Fig. 10.11 Baseline angiographies (**a**, **b**) show an acute BA occlusion. Penumbra 4 Max is advanced to the thrombus, FAST is then performed (**c**, **d**). Final angiographies (**e**, **f**) show complete recanalization

revascularization rate (88% vs. 60%, $P = 0.017$) than the fibrinolysis group. Fair outcome, defined as a mRS of 0–3 at 3 months, was achieved in 34% of patients undergoing FAST and 8% of patients undergoing fibrinolysis ($P = 0.019$). Additionally, the mortality rate was significantly lower in the FAST group (25% vs. 68%, $P = 0.001$). Multiple logistic regression analysis identified the FAST method as an independent predictor of fair outcome, after adjustment for age, sex, initial NIHSS score, and the use of intravenous rt-PA (OR, 7.8; 95% CI). They concluded that FAST might result in higher revascularization rates and improved clinical outcomes in cases of acute BA occlusion, when compared with traditional intra-arterial fibrinolysis. Accordingly, multimodal endovascular approaches for acute BA occlusion could result in high recanalization rates with very low complication rates. However, good functional outcome still remained elusive.

The optimal strategy for acute BA occlusion treatment has not yet been established. However, one certain knowledge is that earlier and better recanalization itself is one of the most important prognostic factors for improving outcome of the patients. Until the present era, if earlier and better recanalization could not sufficiently achieve good outcomes in acute BA occlusion patients, more attempts to find additional beneficial factors for achieving better outcomes seems requiring further investigation, such as improved clinical or imaging criteria or reformatted time windows.

10.4.3 FAST and Acute Stroke Involving Underlying Intracranial Atherosclerotic Stenosis

The intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of ischemic stroke worldwide [38, 39]. It is particularly prevalent in Asian, Black, Hispanic, and Indian populations. Thus it frequently can be encountered during mechanical thrombectomy of acute large vessel occlusions. Nevertheless, an important effect related to this patient group, the so-called in situ thromboocclusion (IST) which is defined as an infarct extensively involving a stenosed arterial territory, has not been sufficiently investigated. Reports of overall reocclusion rate after endovascular therapy range from 18 to 22% in patients with stroke, and, theoretically, endothelial damage may occur more easily during mechanical thrombectomy for ISTs [40, 41]. Therefore, underlying ICAS can be a hidden cause of reocclusion after modern thrombectomy procedures involving either stent retriever or direct clot aspiration. Here is a briefing of the initial results of two different strategies for ISTs. One primarily involves the stent retriever thrombectomy and the other primarily involves the FAST technique [42, 43].

The first study investigated the outcomes of multimodal endovascular therapy in patients with hyperacute stroke with and without underlying ICAS, though the primary device was the stent retriever [42]. A total of 172 consecutive patients with acute stroke were treated with multimodal endovascular therapy, which heavily weighted toward stent retriever thrombectomy in general and intracranial angioplasty with or without stenting in the cases involved underlying ICAS. It was found that ICAS was responsible for acute ischemic symptoms in 40 patients (22.9%). Additionally, successful revascularization and 3-month favorable outcome occurred more frequently in the ICAS group than in the control group (TICI 2b-3: 95% vs. 81.8%, $P = 0.04$ and mRS 0–2: 65% vs. 40.2%, $P = 0.01$). Moreover, the median baseline NIHSS score was significantly lower in the ICAS group compared with the control group (10 vs. 12, $P = 0.002$). And finally, there were no significant differences between the two groups in the rates of symptomatic hemorrhage or mortality. The authors concluded that intracranial angioplasty with or without stenting was safe and feasible, yielding a high rate of revascularization and favorable outcome in patients with underlying ICAS.

A second study involving FAST focused on ISTs occurring in major cerebral arteries, where

the rate of instant reocclusion during mechanical thrombectomy was compared with non-ISTs [43]. A treatment strategy of intra-arterial tirofiban administration was additionally introduced to prevent reocclusion following recanalization. In that study, 168 consecutive patients were treated with the FAST-based mechanical thrombectomy. If angiography revealed reocclusion after initial thrombectomy procedure, repeat recanalization was performed using the same technique, but it was followed by low-dose intra-arterial tirofiban infusion after checking angiographic CT scan to rule out ICH already developed. The incidence of IST was 30.3%. And, there were significant differences in baseline NIHSS score between the two groups (14.5 in the IST cohort vs. 17.9 in the non-IST cohort, $P < 0.001$). This might have been related to the higher proportion of cases with atrial fibrillation and cardioembolic stroke in the non-IST cohort or the higher chance of preformed collaterals in the IST cohort due to underlying ICAS. The rate of instant reocclusion during the mechanical thrombectomy procedure was very often as 65% in the IST cohort, compared with 3.3% in the non-IST cohort ($P < 0.001$). Intra-arterial low-dose tirofiban infusion, the strategy for preventing reocclusion after achieving successful repeat recanalization, resulted in 85.7% of TICI 2 or 3 and 74.3% of TICI 2b or 3 recanalization. And, there were no cases of symptomatic ICH following this strategy. The conclusion of the study was that ISTs have a significantly higher chance of instant reocclusion during mechanical thrombectomy, and in such cases, low-dose intra-arterial tirofiban administration may be effective and safe.

Although different strategies were applied in cases of acute stroke in relation to underlying ICAS, little difference was shown in the results regarding successful recanalization as TICI 2b or 3 and 3-month functional outcome as mRS 0–2. However, both are regarded as the key papers pointing the way for future investigation, and the common findings of two studies are important. The common findings are as follows: (1) the incidence of this type of stroke is high as 22 and 30% in Asian population, and (2) baseline NIHSS is better in ISTs, which may be due to previously formed collateral support, owing to the underlying ICAS, and (3) reocclusion is frequent during mechanical thrombectomy of this variant of stroke.

10.5 Applications of FAST Technique in Other Neurointerventional Procedures

10.5.1 FAST for Thromboembolism During Coil Embolization of Ruptured Cerebral Aneurysm

Historically, no definite management has been established for the treatment of thromboembolism that occurs during coil embolization of cerebral aneurysms. Intravenous heparin, intra-arterial fibrinolytic agents, and intravenous or intra-arterial glycoprotein IIb–IIIa inhibitors have been the primary form of the management up to now [44]. However, two major concerns may arise related to the pharmacologic treatments. First, recanalization may not always be possible if the thrombus is not sufficiently responded to any agents. Second, risk of rebleeding can be increased if the event occurs during coiling of acutely ruptured cerebral aneurysms. Theoretically, FAST may overcome the aforementioned concerns. In a study of four refractory cases involving conventional chemical treatment of thromboembolism during coiling, rescue treatment using FAST was attempted (Fig. 10.12). In all four cases, the occluded vessels achieved successful recanalization with TICI 2b or 3 [45]. Furthermore, no complications associated with this technique occurred. The conclusion of the study was that FAST could play a role as an adjuvant management or as a last resort, combined with local injection of fibrinolytic agents or glycoprotein IIb–IIIa inhibitors, in thromboembolic events that occurred during coil embolization of an acutely ruptured cerebral aneurysm.

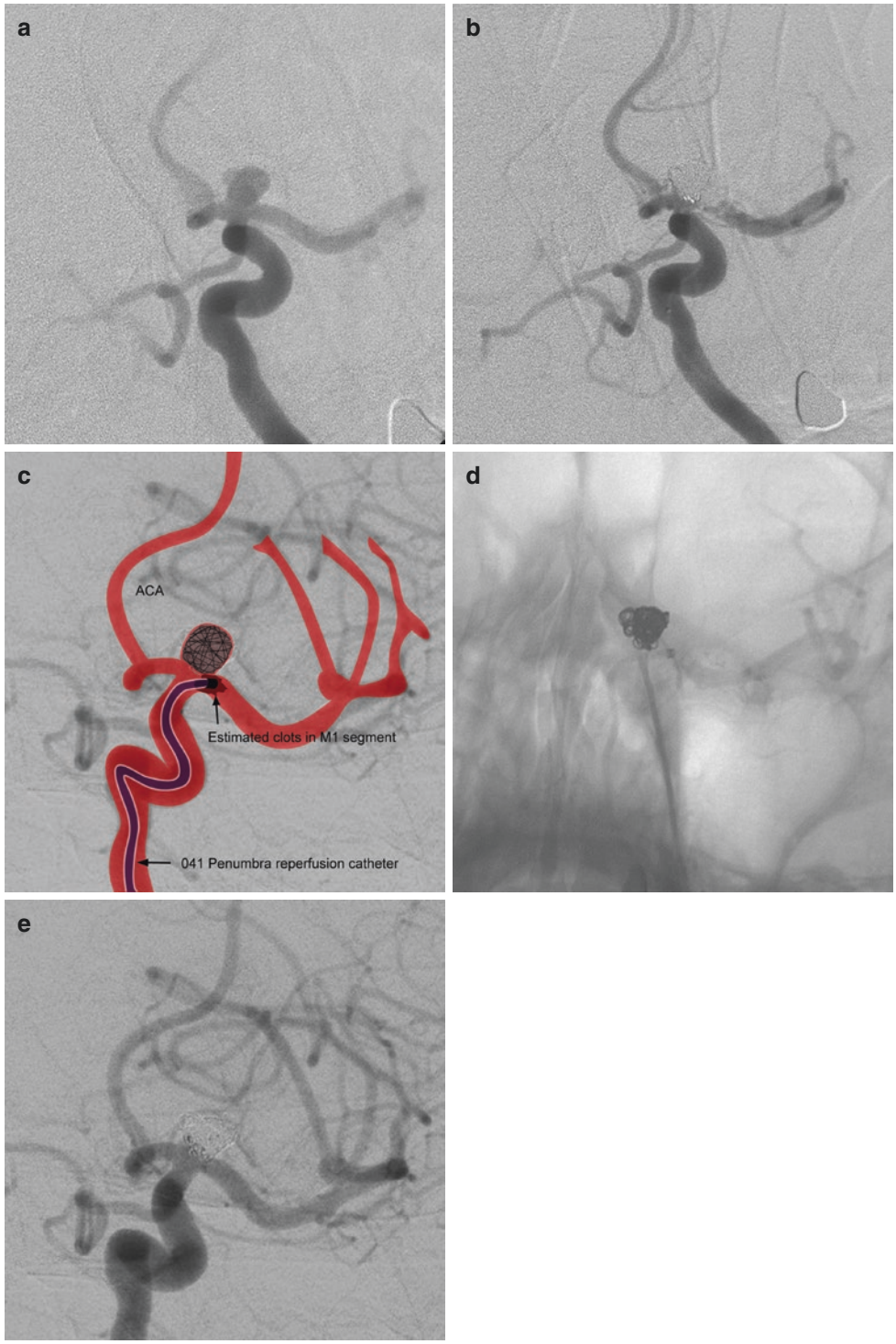

Fig. 10.12 Angiography (**a**) shows a ruptured ICA bifurcation aneurysm on the *left*. At the end of the coiling, local thrombosis and near-complete occlusion (**b**) of the parent artery is encountered. Penumbra reperfusion catheter 041 is advanced to the occlusion and FAST is undertaken (**c**, **d**). Visible thrombus is retrieved and final angiography (**e**) shows full recanalization

10.5.2 FAST for Acute Carotid Stent Thrombosis During Carotid Artery Stenting

It is well known that ICA flow arrest can be one of the most devastating complications related to carotid artery stenting procedure. Acute carotid stent thrombosis (ACST), a rare etiology of ICA flow arrest during carotid artery stenting with distal filter protection, perhaps is the most devastating. Additionally, no definitive management strategy has been established for treating ACST. In 2013, a strategy using FAST was introduced for such conditions [46]. In that study, three cases of ICA flow arrest caused by ACST underwent recanalization using the FAST technique. Successful recanalization with a TICI score of 3 was achieved for all three patients. Additionally, no complications associated with the FAST technique occurred. Two major findings were in the paper: (1) a selective microangiography within the segment of stenting was effective for differential diagnosis of ICA flow arrest, and (2) the FAST technique was also very effective and safe as a rescue method for recanalization of ACST.

10.6 Complications of the FAST Technique

10.6.1 Groin Complication

The combination of intravenous rt.-PA and mechanical thrombectomy with an 8- or 9-French guiding catheter, and correspondingly large femoral sheaths, can certainly increase the risk of significant groin complications. Therefore, such patients need to be appropriately monitored and managed. As the use of the BGC is recommended with the FAST technique, and the first generation BGC was 9 French in diameter, arteriotomy closure is an important step to prevent significant groin complications, such as hematoma, arteriovenous fistula, and dissection. For safe arteriotomy closure, a suture-type closing device, such as Perclose Proglide (Abbott Vascular, CA, USA) is recommended at the finish of the FAST procedure. However, groin hemostasis recently has not been a serious issue, given the newer 8-French BGC or smaller size and advances in arteriotomy closure devices.

10.6.2 Dissection and Perforation

Complications related to dissection and perforation arising from a Penumbra catheter or a microguidewire advancement may result during FAST procedure (Fig. 10.13). The competing considerations of stiffness, which improves stability and responsiveness, and pliability, which can minimize trauma, are always involved in the technical innovations associated with catheter development. Regardless of the advancements in technology, endothelial damage can occur anywhere along the course of catheter insertion, from the groin to the target artery. Therefore, consideration related to dissection and perforation is always warranted.

10.6.3 Procedure-Related Subarachnoid Hemorrhage

Procedure-related subarachnoid hemorrhage is another potential complication arising from FAST, although there are conflicting reports concerning the relative incidence rates between direct clot aspiration and stent retriever thrombectomy techniques (Fig. 10.14a). Extravasation into the subarachnoid space can occur as often as 20% for the older Merci retriever; however, there have not been systematic attempts to study the incidence rate to date. The rate of subarachnoid hemorrhage was reported as between 0.9 and 4.9% in the recent randomized stent retriever trials in 2015: MR CLEAN (2/233, 0.9%), ESCAPE (5/165, 3.0%), REVASCAT (5/103, 4.9%), and SWIFT PRIME (4/98, 4%) [12, 18–21]. Comparatively, the rate of SAH was 0–2.7% in various clot aspiration trials: FAST (0) and ADAPT (1/37, 2.7%) [6, 7]. The clinical significance of subarachnoid hemorrhage after mechanical thrombectomy has not been clearly determined yet, but early evidence suggests it is more or less benign [47].

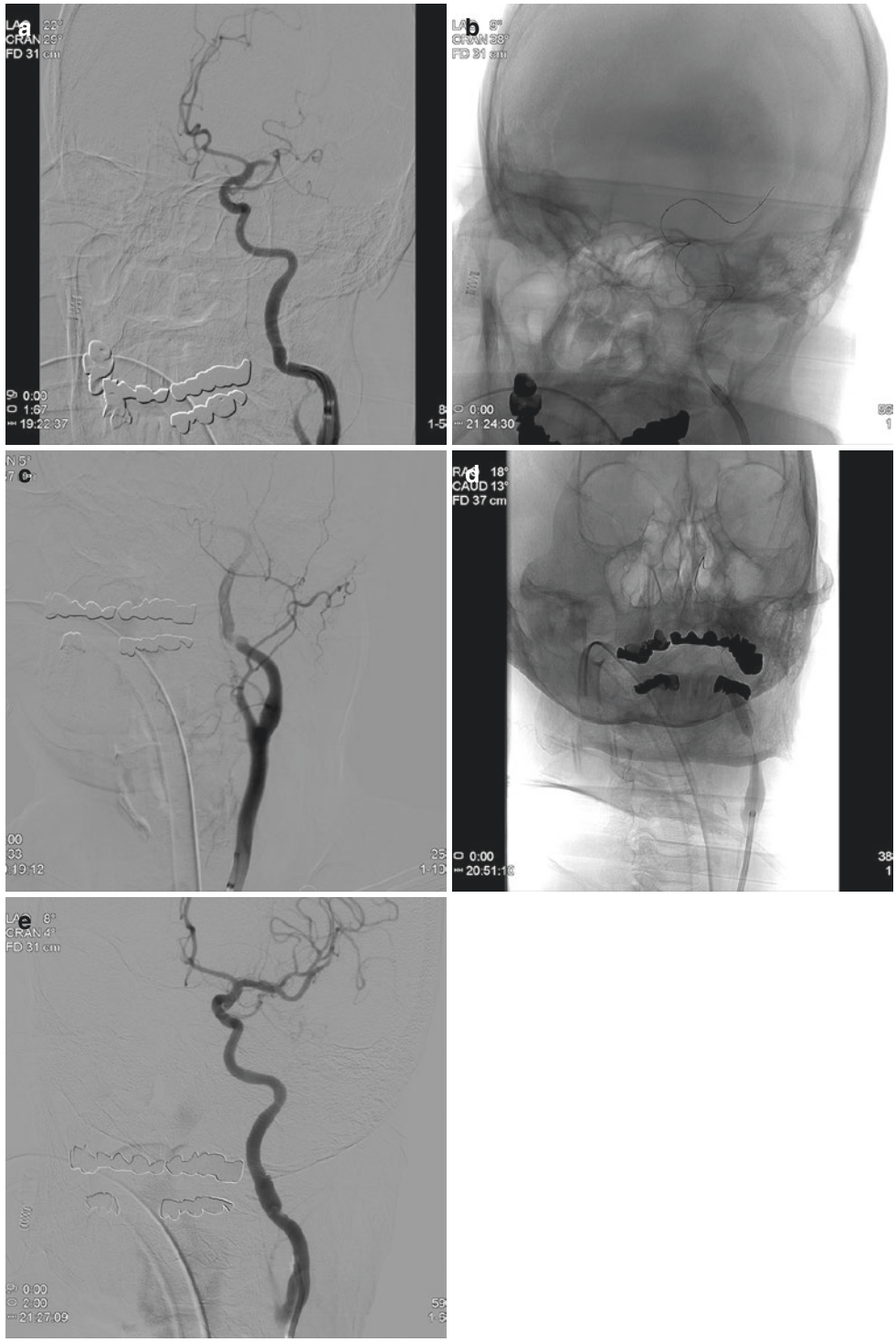

Fig. 10.13 Baseline angiography (**a**) shows an occlusion at MCA on the *left*. FAST is attempted using Penumbra 5 Max Ace under balloon inflation of the guiding catheter (**b**). After the FAST, dissection and subsequent flow stagnation (**c**) are noted at proximal ICA. Balloon angioplasty (**d**) is then performed at dissection segment, and final angiography (**e**) shows the full recanalization

During the stent retriever thrombectomy, restricting the number of attempted passes or limiting the retraction force may be helpful to reduce the likelihood of subarachnoid hemorrhage. Likewise, choosing an appropriately-sized catheter and gentle advancement using the aforementioned steam shaping or coaxial assembly may reduce the chance of subarachnoid hemorrhage during the FAST procedure.

10.6.4 Reperfusion Injury Related to Symptomatic Intracranial Hemorrhage

Symptomatic ICH occurs more often following the use of thrombolytics than with mechanical thrombectomy; however, the risk associated with mechanical thrombectomy is still not negligible (Fig. 10.14b). Following thrombectomy for large intracranial vessel occlusion, many patients are hypertensive. Likewise, autoregulatory mechanisms may be in effect to increase or maintain cerebral perfusion pressure from the collaterals. Successful recanalization in the face of excessive hypertension can create a mechanism for ICH to occur. Blood pressure in excess of 185 mmHg in systole or 110 mmHg in diastole may serve as a contraindication of mechanical thrombectomy procedure. The rate of symptomatic ICH was reported as between 0 and 7.7% in the recent randomized stent retriever trials in 2015: MR CLEAN (18/233, 7.7%), EXTEND-IA (0), ESCAPE (6/165, 3.6%), REVASCAT (5/103, 4.9%), and SWIFT PRIME (0) [12, 18–21]. Likewise, the rate of symptomatic ICH was between 5 and 9% in clot aspiration trials; FAST (2/22, 9.1%) and ADAPT (2/37, 5.4%) [6, 7].

10.6.5 Thrombus Fragmentation and Distal Embolization to New Territories

A controversial issue involves the relative probability of distal embolization between stent retriever and clot aspiration thrombectomy. Theoretically, thrombus fragmentation and distal embolization can occur while using either technique, although there are considerations involved in both cases

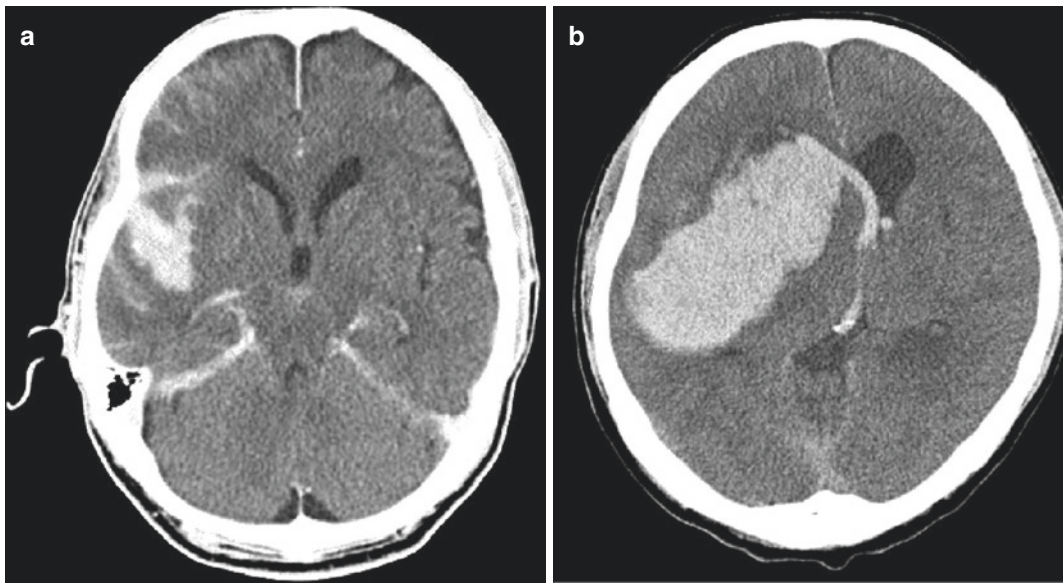

Fig. 10.14 Subarachnoid hemorrhage (**a**) and reperfusion parenchymal hemorrhage (**b**) after the FAST procedure are shown

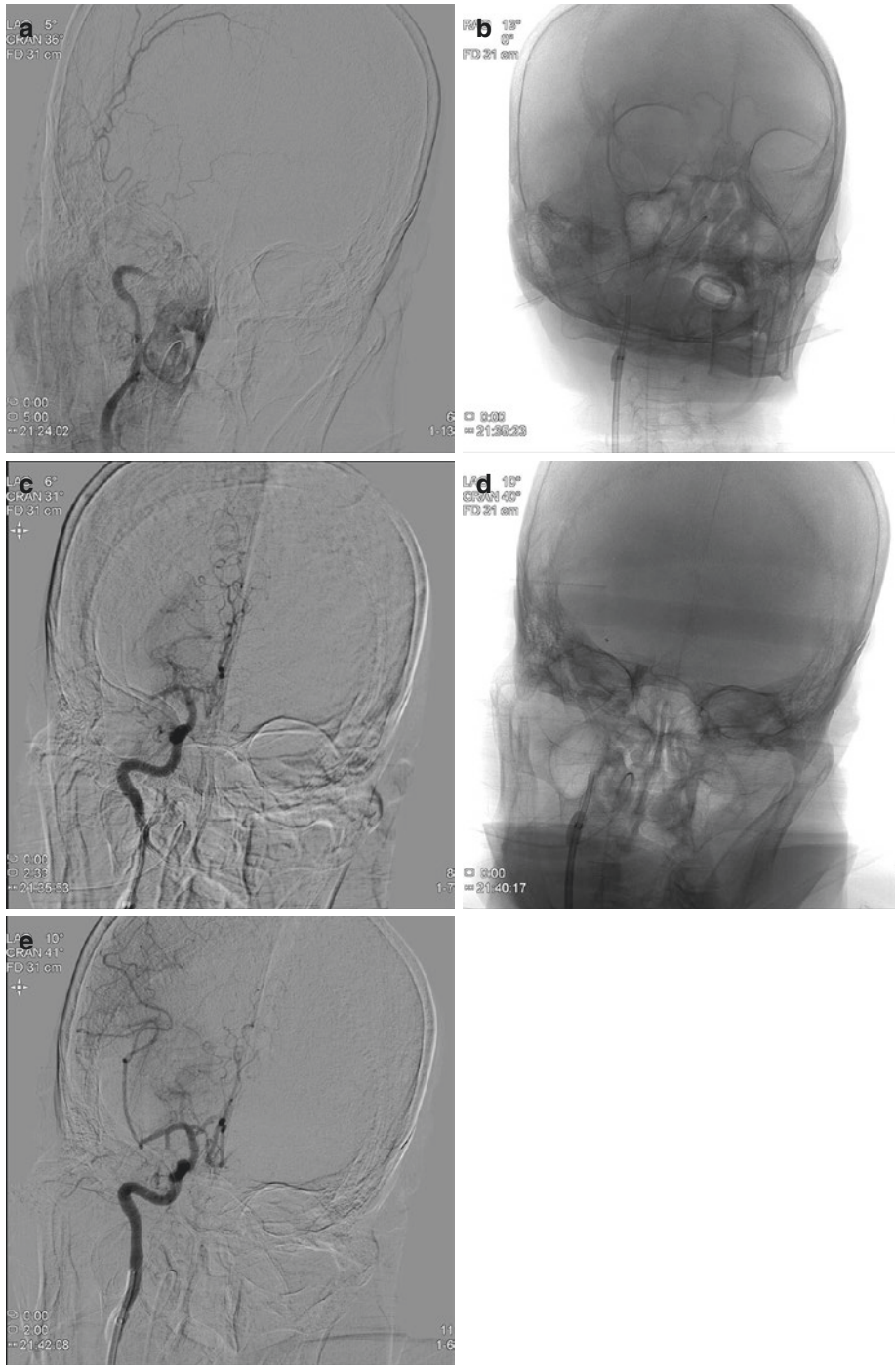

Fig. 10.15 Baseline angiography (**a**) shows ICA terminus occlusion on the *right*. Proximal aspiration thrombectomy (**b**) is performed through a 6-French guide catheter, while the balloon of an outer 9-French balloon guide catheter is inflated. Angiography (**c**) immediately after proximal aspiration thrombectomy shows full recanalization of ICA but demonstrates an occlusion by distal clot embolization at M1 segment of MCA. FAST is then performed using Penumbra 5 Max Ace (**d**). Angiography (**e**) after the FAST shows full recanalization of M1 segment but demonstrates an M2 segment occlusion by repeated distal embolization

(Fig. 10.15). In either case, the addition of a BGC would reduce the likelihood of distal embolization, although there is not enough sufficient evidence to determine the issue. The rate of uninvolved territory embolization has been reported to be between 4.9 and 6% in the recent randomized stent retriever trials: MR CLEAN (13/233, 5.6%), EXTEND-IA (2/35, 6%), and REVASCAT (5/103, 4.9%) [18, 19, 21]. Additionally, the rate of distal embolization was reported to be up to 16% in clot aspiration trials: FAST (not applicable) and ADAPT (6/37, 16.2%) [6, 7]. The two main issues related with distal embolization are as follows.

10.6.5.1 Are There Any Differences in the Incidence of Distal Embolization According to the Technique Used?

One study examined laboratory data related to distal embolization. In that study, mechanical thrombectomy with either a stent retriever, or clot aspiration, or Solumbra was simulated in a vascular phantom with collateral circulation [48]. Two types of clots were generated, hard fragment-prone clots and soft elastic clots. The study reported that Solumbra had the best results for reducing hard-clot fragmentation ($P < 0.05$), while the use of a BGC was the best for preventing soft-clot fragmentation ($P < 0.05$). Also, direct aspiration significantly increased the risk of soft-clot fragmentation by at least twofold compared with the stent retriever thrombectomy. However, they emphasized that this was based on lab results, so there are inevitably limitations involved, and that the results can be different with real clinical practice. However notably, they found that clot fragmentation and distal embolization can be different according to the thrombectomy methods involved, the type of guiding catheter used (BGC or a general guiding catheter), and the characteristics of the clot. Further confirmation in real clinical practice seems to be highly required in this endovascular era for the treatment of stroke.

10.6.5.2 Can Using a BGC Reduce the Incidence of Distal Embolization?

As it was discussed in the earlier section, there have been several previous reports regarding the issue of whether a BGC can reduce the incidence of distal embolization. Specifically, in an in vitro study published in 2013 [9], the Merci retriever, Solitaire FR, and Trevo devices were assessed to determine the occurrence rate of distal emboli with and without the use of a BGC. In that study, they found that the use of the BGC during thrombectomy, regardless of the device used, significantly reduced the formation of large distal emboli with a diameter >1 mm ($P < 0.01$). Furthermore, regarding the use of a BGC with the stent retriever technique, swine model testing was done with the Solitaire device, which demonstrated that in many cases the clot would engage within the struts and shear off during retrieval into the tip of the BGC. It was found to be possible to aspirate the clot into the guide catheter and prevent distal emboli [13]. Additionally, in another study published in 2014, which examined the safety and efficacy of the BGC, it was demonstrated that the use of a BGC with the Solitaire FR resulted in better revascularization results (TICI 3: 53.7% vs. 32.5%, $P < 0.001$) and faster procedure times (120 min vs. 161 min, $P = 0.02$) [14]. However, they found no significant difference regarding the rates of distal embolization (18.2% vs. 16%, $P = 0.7$) and emboli in new territory (5% vs. 5.2%, $P = 0.9$) between the two groups. Nevertheless, good clinical outcome at 3 months was significantly better in patients where the BGC was used (mRS 0–2: 51.6% vs. 35.8%, $P = 0.02$). One possible explanation, by referencing a recent laboratory study, is that this may be due to an inability by current imaging modalities to observe microemboli <20 μm, which may account for more than 90% of clot fragments generated during procedures [48]. Moreover, microemboli <20 μm may occlude possible collateral routes and cerebral microcirculation with a diameter <10 μm, which

can worsen clinical outcomes [49]. The topic of thrombus fragmentation and distal embolization into new territories is of urgent interest, and further research on this topic appears highly warranted.

10.7 Penumbra Reperfusion Catheter and Other Aspiration Catheters

There are two major versions of direct clot aspiration techniques in the present era, which are FAST and ADAPT, both focus on engaging and removing clots without the use of a separator by relying on the aspiration force generated through the catheter. Relatedly, the efficacy of this technique is strongly associated with the force of aspiration at the tip of the large-bore aspiration catheter. Therefore, differences in the properties of each catheter may inevitably determine different aspiration forces and thus result in different efficacy related to the clot aspiration procedure itself.

In 2014, one in vitro study compared various parameters of four large-bore catheters that were commercially available at the time [50]. Two devices were designed for aspiration, the Penumbra 5 Max and 5 Max Ace (Penumbra), and the other two devices were designed as intermediate guide catheters, the DAC 057 (Stryker Neurovascular) and the Navien 058 (Medtronic Neurovascular), which although were not aspiration catheters designed for use had end-hole sizes similar to the 5 Max. In that study, they analyzed catheter tip force, aspiration flow rate, and effective flow lumen to determine the optimal catheter for clot aspiration thrombectomy based on the hemodynamic background. They found that a variety of variables may play contributing factors regarding the force of aspiration at the catheter tip. At one end is catheter tip corking. Regarding this, the major parameters are aspiration flow rate and catheter tip force. Aspiration flow rate serves to dynamically pull the clot into the catheter, which ensures the catheter is sufficiently corked. Secondly, tip force is the static force imparted by the catheter tip to the thrombus when the thrombus is corked at the catheter tip. Regarding specifics, the governing law is $P = F/A$, where the area (A) is $(\pi/4)\times d2$, and the diameter is the internal diameter of the catheter. For a certain input pressure (P), the catheter having the largest tip internal diameter has the greatest tip force (F). At the other end is clot ingestion, which is found more often through the use of the newer 5 Max Ace catheter. With clot ingestion, the system flow rate draws the clot into the catheter lumen and into the syringe or aspiration tubing and pump. Regarding the results of that study, the tip force was the largest with the Penumbra 5 Max Ace, which had the largest internal diameter, and thus is consistent with theoretical considerations. Moreover, flow rate analysis showed the 5 Max Ace produced the highest flow rate, followed by the 5 Max, Navien 058, and DAC 057 catheter. The aspiration efficiency of the 5 Max Ace may have been increased by enlarging the distal and proximal lumen compared to the 5 Max. Even though the Navien 058 has the slightly larger distal internal diameter, the increased flow rate of the 5 Max in comparison with the Navien 058 catheter may be due to the larger 0.064 inch proximal internal diameter of the 5 Max. This would result in a lower overall resistance compared with the unidimensional lumen of the Navien 058. The tapered lumen technology found in the 5 Max may allow for increased aspiration efficiency compared with conventional neurovascular catheters that have large distal end-holes but unidimensional lumens. The study demonstrated that the Penumbra 5 Max Ace catheter outperformed the three other catheters regarding the aforementioned hemodynamic properties, perhaps due to its larger lumen and tapered design. Thus, they concluded the 5 Max Ace was considered the optimal catheter for direct clot aspiration at the time.

However, there recently have been several new large-bore catheters that have just started to be commercially available in this field (Table 10.1). These include the ACE 64 (Penumbra), Arc (Medtronic), Catalyst (Stryker), Revive IC (Codman), and Sofia (MicroVention). Therefore, additional in vitro study to compare the hemodynamic parameters of the new catheters is required. And more importantly, the accumulation of

Table 10.1 Specification of the recently launched large-bore catheters for both clot aspiration and providing support

Product name (Company)	Length (cm)	Proximal OD (inches)	Proximal ID (inches)	Distal OD (inches)	Distal ID (inches)
ACE 64 (Penumbra)	132	0.080	0.068	0.075	0.064
Arc (Medtronic Neurovascular)	132	0.080	0.069	0.069	0.061
Catalyst (Stryker Neurovascular)	132	0.079	0.060	0.071	0.060
Sofia (MicroVention)	125	0.068	0.055	0.068	0.055
Sofia Plus (MicroVention)	125/131	0.083	0.070	0.082	0.070
Revive IC 044 (Codman Neurovascular)	136	0.053	0.044	0.053	0.044
Revive IC 056 (Codman Neurovascular)	121	0.065	0.056	0.065	0.056

ID inner diameter, *OD* outer diameter

experience and clinical data from real practice is strongly required with regard to the evaluation of new devices.

10.8 Summary

Improving successful recanalization rates and patient outcomes will be continuously key areas for future investigation. For that, the manufacturers have to keep developing new devices with the aim of offering better safety profiles and minimizing distal clot embolization. And the practitioners have to keep developing new and better techniques and strategies [51]. Based on the level of evidence reported so far, mechanical thrombectomy using the stent retrievers (Solitaire FR, Medtronic Neurovascular or Trevo device, Stryker Neurovascular) as the primary method and clot aspiration thrombectomy (FAST or ADAPT) as a solid secondary rescue method will be the trend at least for some time. Moreover, the efficacy of combined usage of both stent retriever and clot aspiration thrombectomy is continuously improving due to recent development in device technology. Therefore, it seems necessary for the practitioner to learn how to perform stent retriever thrombectomy, clot aspiration thrombectomy, as well as a combined usage of both, whether choosing the switching strategy or the Solumbra technique.

Regarding the location of the stroke, patients with acute ICA and proximal MCA occlusions are clearly beneficial from mechanical thrombectomy, but there is residual uncertainty in the case of more distal MCA occlusions and in patients with vertebrobasilar artery occlusions. This is another important area where the refinement of the criteria for mechanical thrombectomy using the most recent devices and highly selective imaging modalities is required. Additionally, it seems valuable to determine the situations of stroke in which one certain device or technique may be preferable to another. For example, it may be the case that clot aspiration seems better for BA occlusions regarding less chance of procedure-related perforator infarction, while the stent retriever seems better for M2 segment occlusions regarding safer advancement of microcatheter through the small caliber artery.

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11 Stent Retriever (Stentriever) Thrombectomy for Acute Ischemic Stroke

Byung Moon Kim

Following the success of five randomized controlled trials comparing intra-arterial recanalization treatment plus standard medical therapy with standard medical treatment, a stent retriever (stentriever) thrombectomy is now recommended as the first-line treatment for acute stroke due to an intracranial large artery occlusion (ILAO) of the anterior circulation [1–11]. As a result, the ability to perform a stentriever thrombectomy is an essential skill for neurointerventionalists, where the learning curve is relatively short for normal cases of endovascular acute stroke treatment [12]. However, in complicated situations, recanalizing an occluded large intracranial artery using a stentriever can become difficult. Therefore, this chapter explains the basic procedure of a stentriever thrombectomy and then suggests some problem-solving techniques for various complex situations.

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11.1 Basic Technique

11.1.1 Guiding Catheter Placement

For a stentriever thrombectomy, a large bore (8 or 9 F) balloon tip guiding catheter (BGC, Cello; Covidien/ev3, Irvine, CA) is preferred over a conventional guiding catheter, as a BGC improves the recanalization rate and clinical outcome [13, 14]. The BGC inflation arrests the blood flow and thus prevents distal embolization of captured clots during the retrieval of the clots engaged by the stentriever [15]. Therefore, the intra-arterial recanalization treatment begins with the safe and speedy placement of the BGC in the relevant cervical artery. However, placing the BGC can often be troublesome when the acute stroke patient is elderly and has a tortuous configuration between the aortic arch and the takeoff of the common carotid artery. Thus, a coaxial technique is invariably easier for the BGC placement than an exchange technique. For the coaxial technique, a 5 F 125-cm length angiocatheter is introduced inside an 8 F or 9 F BGC. The relevant artery is catheterized using the 5 F angiocatheter and the external carotid artery navigated using a 0.035-inch wire. The 5 F angiocatheter is then advanced over the 0.035-inch wire, followed by the BGC (Fig. 11.1). In rare instances, a triple coaxial technique, a 5 F long (125-cm length) angiocatheter within a 100–115-cm length 6 F guiding catheter (Envoy, Envoy DA, Navien, or Revive) within a 9 F BGC, is needed to overcome very

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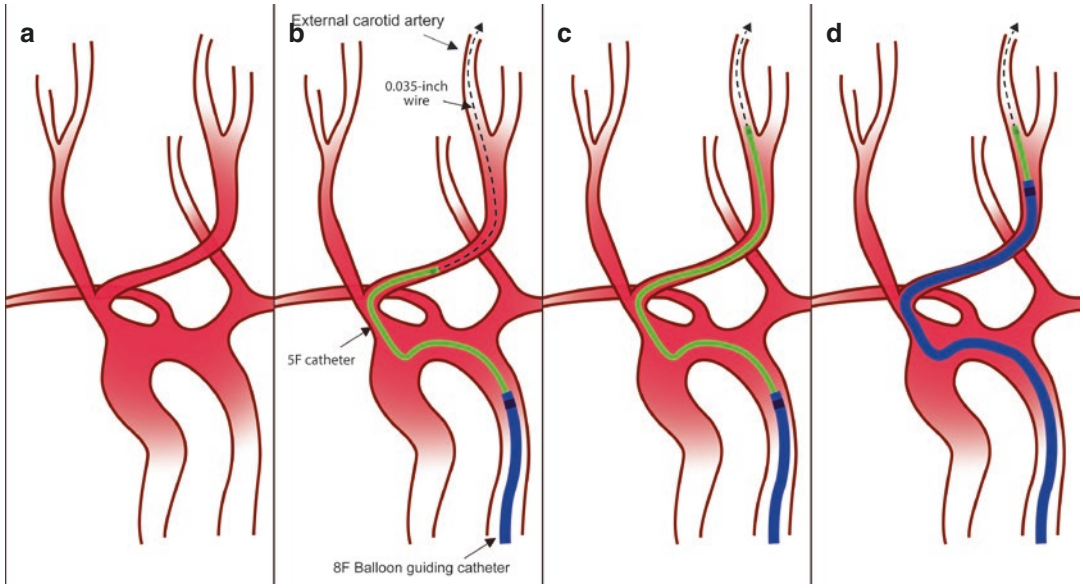


Fig. 11.1 Illustrations of coaxial technique for placing balloon guiding catheter. (**a**) Bovine-type left common carotid artery origin. (**b**) The origin of the left common carotid artery is catheterized using a 5 F angiocatheter, and the left external carotid artery is navigated using a 0.035-inch wire. (**c**) The 5 F angiocatheter is advanced over the 0.035-inch wire to the external carotid artery. (**d**) The balloon guiding catheter is advanced over the 5 F catheter and 0.035-inch wire. If needed, the 0.035-inch wire is replaced with a stiff 0.035-inch wire before advancing the balloon guiding catheter

tortuous anatomy or ledge effect at the origin of the relevant artery.

11.1.2 Microcatheter Navigation and Stentriever Deployment

A 4-mm diameter stentriever is compatible with a microcatheter with a 0.0195-inch inner diameter. Thus, any type of microcatheter (Excelsior 1018, Rebar-18, or Prowler Plus) with a ≥0.0195-inch inner diameter can be used according to personal preference. However, when using a 5-mm or 6-mm diameter stentriever, a microcatheter with a 0.027-inch inner diameter is required. The microcatheter is navigated beyond the occluded point of the relevant intracranial artery using a 0.014-inch microwire. Thereafter, a small amount of contrast material is infused to confirm that the microcatheter has been correctly positioned in the main branch of the occluded parent artery. An appropriate-sized stentriever is then introduced and deployed to span the entire length of the occluded clot. After positioning the distal tip marker of the stentriever, instead of unsheathing the microcatheter, the stentriever is deployed by pushing the stentriever delivery wire, the so-called "push and fluff" technique (Fig. 11.2). This technique leads to a better wall apposition of the stentriever and cell size/configuration, which in turn promotes better engagement of the clot with the stentriever and increases the chance of first-pass recanalization [16]. A control angiogram is generally obtained immediately after deploying the stentriever to confirm the accuracy of the stentriever position and restoration of the blood flow beyond the initial occlusion site.

11.1.3 Retrieval of Stentriever

An additional control angiogram is obtained after waiting 3–5 min and inflating the BGC balloon, which appears as cylindrical. During the simultaneous retrieval of the stentriever and the microcatheter, the BGC needs to be continuously

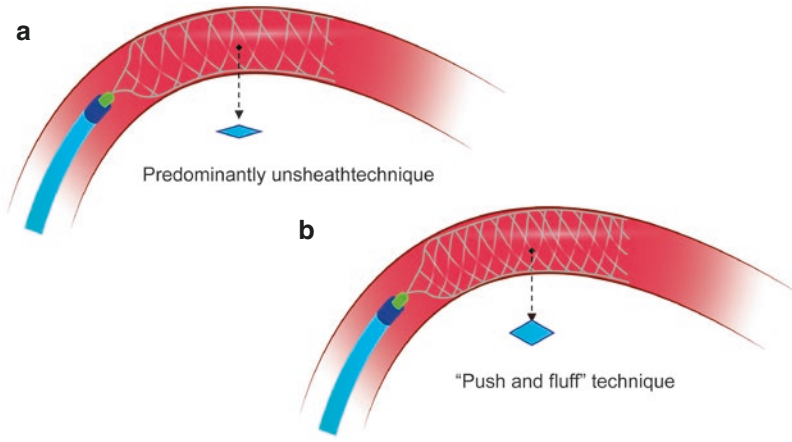


Fig. 11.2 Ideal technique of stentriever deployment. (**a**) Illustration of predominant unsheathing of the microcatheter: this can leave a gap between the stent and the vessel wall at the curvature. Note the cell configuration is elongated. (**b**) "Push and pull" for unsheathing the distal segment of the stentriever, plus "push and fluff" technique for deployment of the remaining segment of the stentriever. This facilitates better apposition of the stentriever to the vessel wall at the curvature. Note more fluffing of the cell configuration, which promotes thrombus engagement with the stentriever

suctioned to prevent any distal embolization. Plus, after retrieving the stentriever, the BGC still needs to be continuously suctioned until clear blood without any clot debris is aspirated. Finally, the BGC is deflated and a control angiogram is obtained. Figure 10.3 shows the steps of a stentriever thrombectomy after placing the BGC (Fig. 11.3a–j).

11.2 Complex Situations

11.2.1 Very Tortuous Cervical and Cavernous Segment

If the relevant parent artery is very tortuous or includes a stenotic segment proximal to the occlusion site, the probability of losing the stentriever-engaged clots increases, plus continuous suction of the BGC may not be effective to prevent distal embolization. In this case, the coaxial use of a 4 or 5 F intermediate (Envoy DA, Navien, Revive, and Neuron, etc.) or aspiration catheter (Penumbra) can help to increase the chance of complete clot retrieval. An aspiration catheter (Penumbra, Alameda, CA) or an intermediate catheter (Navien, Revive, Neuron, etc.) is coaxially introduced through the BGC and advanced as close as possible to the stentriever-engaged clots (Fig. 11.4). This helps to prevent the loss of engaged clots when pulling the stentriever back through the tortuous (Fig. 11.5) or stenotic segment (Fig. 11.6) of the parent artery. It also facilitates the sequential or simultaneous performance of a stentriever thrombectomy and aspiration thrombectomy (Figs. 11.5 and 11.6).

11.2.2 A Large Amount of Clots in the Cervical and/or Cavernous Segment

In the case of a large amount of clots in the cervical artery concomitant with a tandem intracranial artery occlusion, it is actually impossible to remove all the clots using just a stentriever. In this situation, it is more effective to perform a suction thrombectomy first using a BGC and/or large bore shuttle sheath before the stentriever thrombectomy. Plus, since the BGC can be occluded by packed clots during the suction thrombectomy, a coaxial combination of an 8 F BGC within an 8 F shuttle sheath is also needed, which, in the case of occlusion, allows the BGC

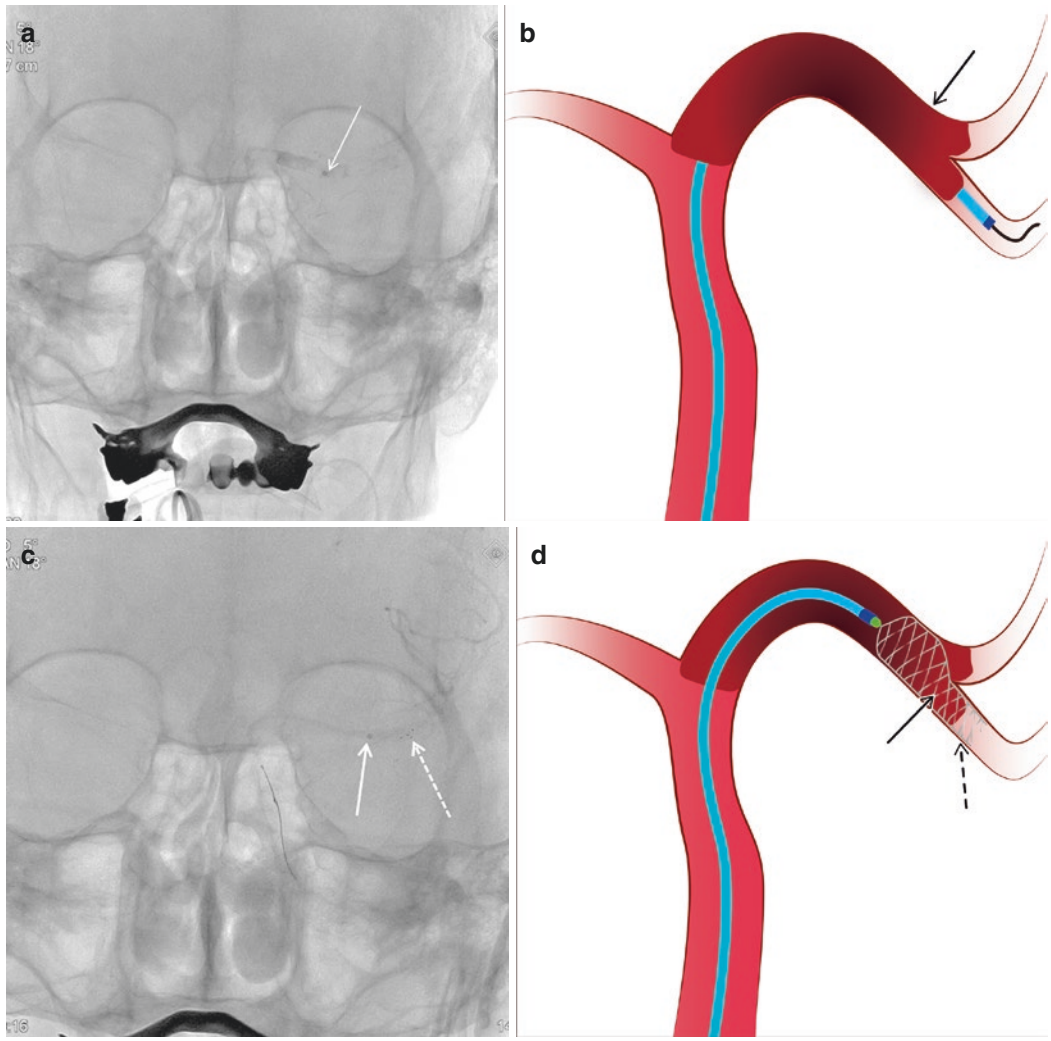
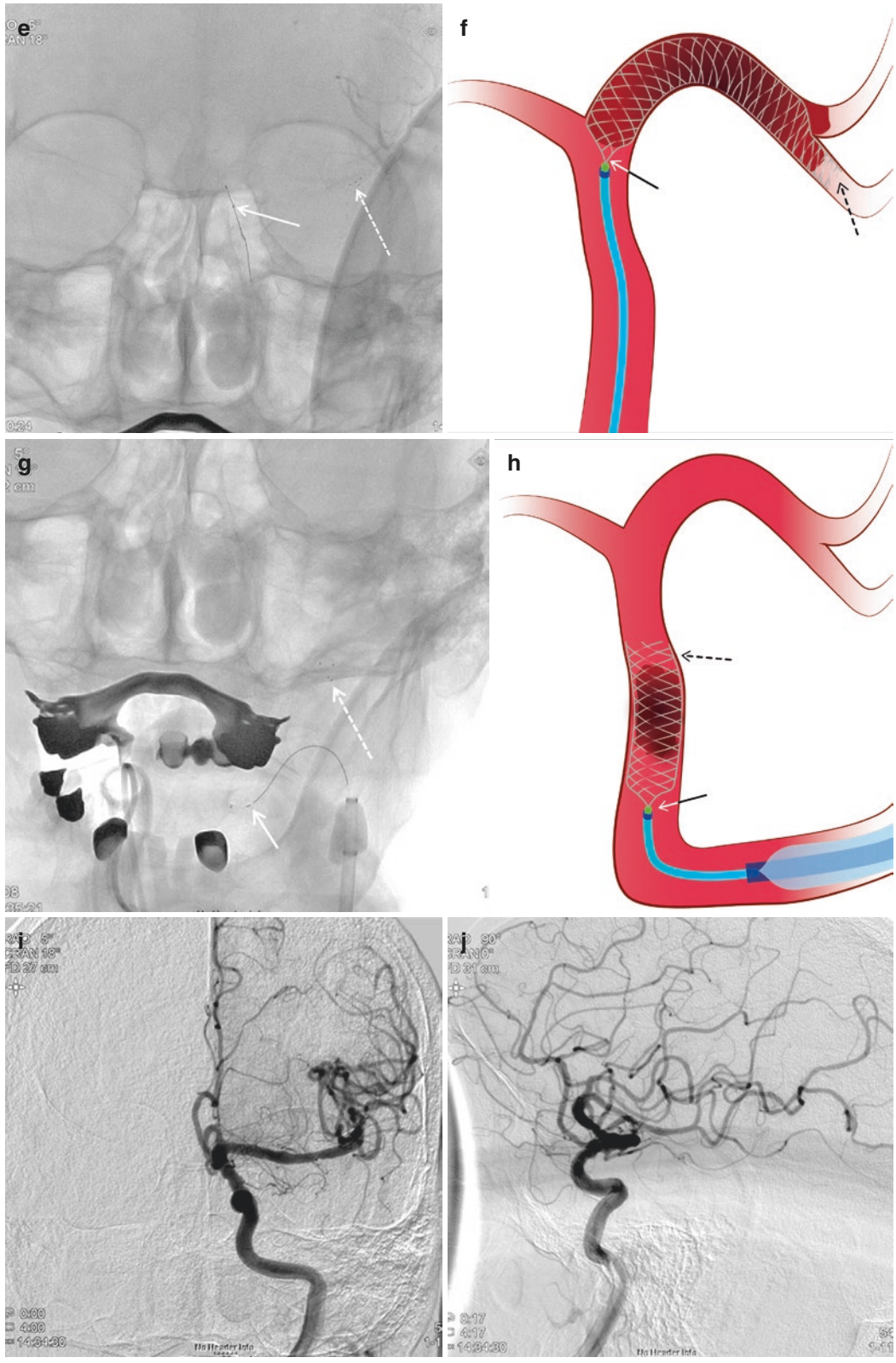


Fig. 11.3 Basic steps of stentriever thrombectomy after balloon guiding catheter placement. (**a**) The left middle cerebral artery occluded with a large amount of clots is navigated blindly using a microcatheter and wire. The *arrow* indicates the microcatheter tip marker. (**b**) Illustration of Fig. 11.3a. (**c**) Deployment of the stentriever. The microcatheter tip is located within the clots. The *distal markers* of the stentriever are placed at the inferior branch of the left middle cerebral artery. (**d**) Illustration of Fig. 11.3c. (**e**) Fully deployed stentriever. (**f**) Illustration of Fig 11.3e. (**g**) After waiting 3–5 min, the balloon guiding catheter is inflated to arrest the blood flow, and the stentriever and microcatheter are then simultaneously retrieved. The balloon guiding catheter needs to be continuously suctioned during and immediately after the retrieval until clear blood without any clot debris is aspirated. (**h**) Illustration of Fig. 11.3g. The *line arrows* and *dotted arrows* indicate the tip marker of the microcatheter and distal markers of the stentriever. (**i**, **j**) After the aspiration of clear blood without any clot debris from the balloon guiding catheter, the balloon is deflated and a control angiogram obtained. Frontal (**i**) and lateral (**j**) angiograms showing complete recanalization



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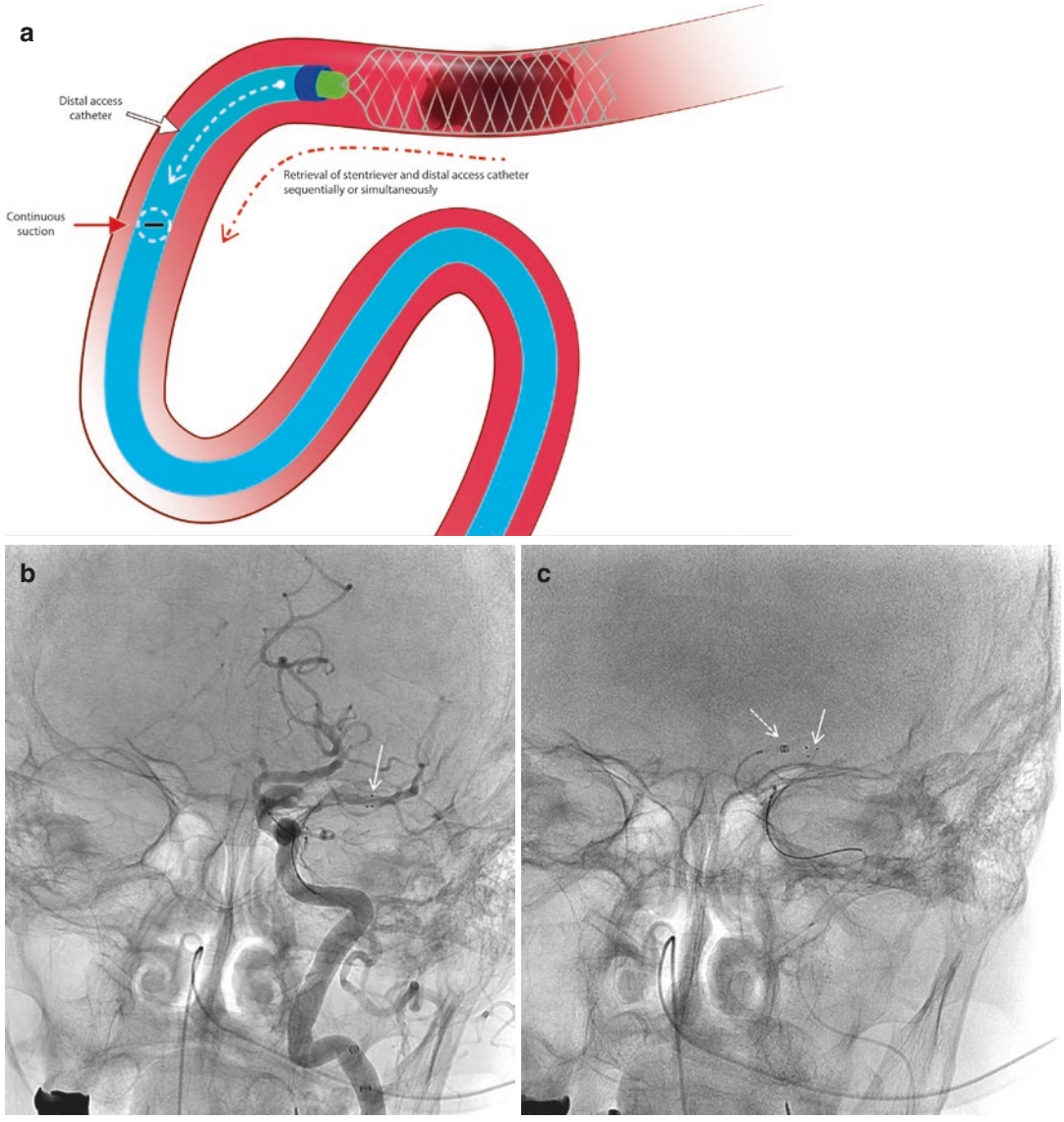


Fig. 11.4 Simultaneous utilization of aspiration and stentriever thrombectomies. (**a**) Illustration of simultaneous utilization of stentriever thrombectomy and suction thrombectomy. (**b**) Angiogram immediately after stentriever deployment (*line arrow*). This patient has a tortuous cervical internal carotid artery and left terminal internal carotid artery occlusion. (**c**) After three failed passes of the stentriever via a balloon guiding catheter, a 5 F intermediate catheter (*dotted arrow*) is advanced over the microcatheter, then a stentriever is deployed for suction, and a stentriever thrombectomy is performed simultaneously

to be deflated and retrieved outside the shuttle sheath, while maintaining the negative suction of the BGC. Thereafter, the shuttle sheath left in the cervical artery needs continuous suctioning until clear blood is aspirated (Fig. 11.7). Following the suction thrombectomy, a stentriever thrombectomy can be performed to remove any remnant distal clots (Figs. 11.5 and 11.7).

11.2.3 Acute Stroke due to Cervical Artery Atherosclerotic Occlusion

Cervical carotid artery atherosclerotic disease is responsible for 15–30% of acute strokes, the majority of which are due to an artery-to-artery embolism with or without a concomitant cervical

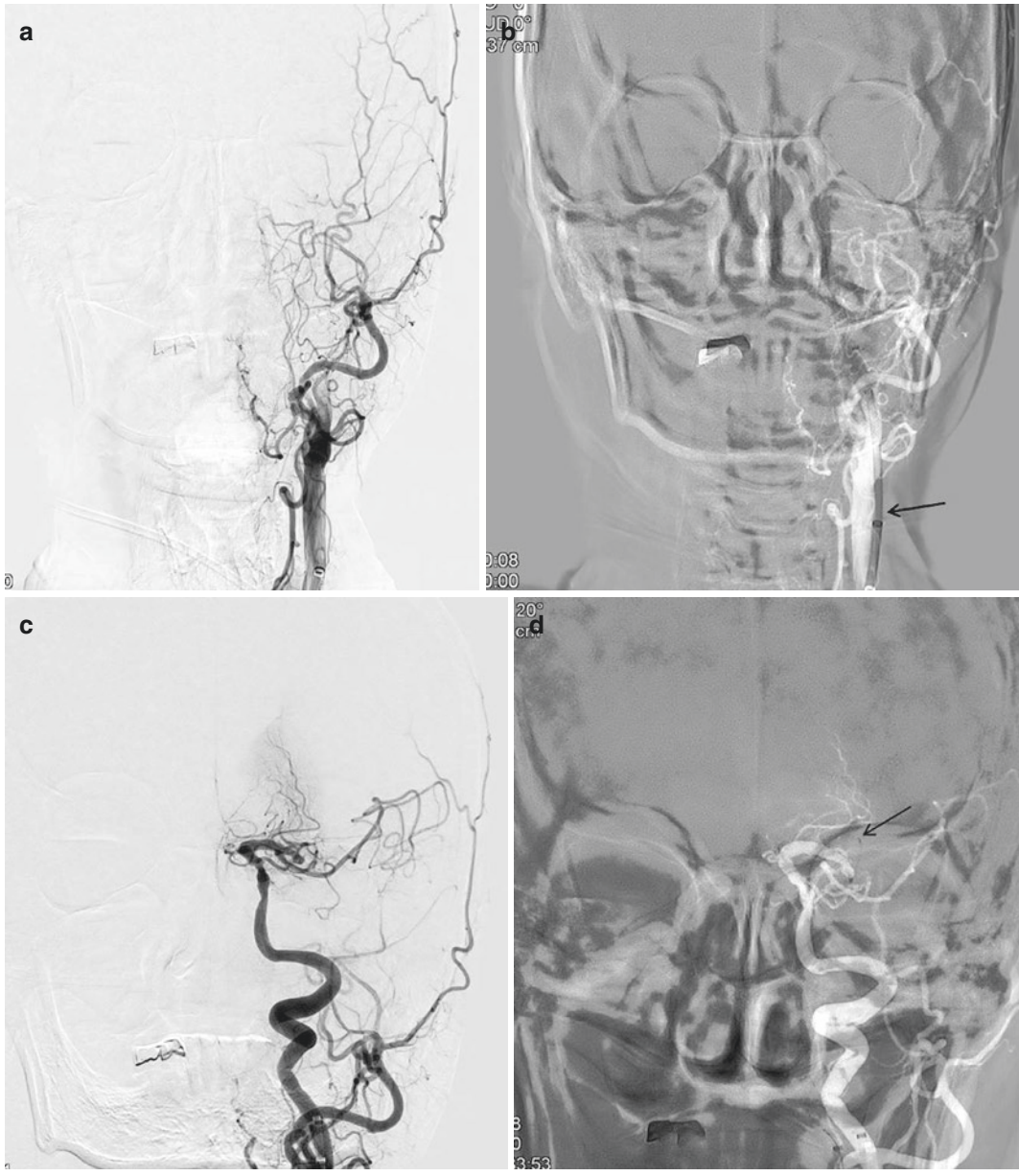


Fig. 11.5 A 77-year-old woman presenting with initial NIHSS score of 18. (**a**) Left carotid angiogram revealing occlusion of the left cervical internal carotid artery. (**b**) A suction thrombectomy is conducted using a balloon guiding catheter (*arrow*). (**c**) Angiogram taken immediately after the suction thrombectomy revealing a tandem occlusion of the left middle cerebral artery. Note that the cervical segment of the internal carotid artery is tortuous. (**d**) A microcatheter (*arrow*) is navigated under roadmap image. (**e**) Angiogram immediately after the stentriever deployment revealing a clot at the left middle cerebral artery bifurcation. (**f**) Repeated failure of a stentriever thrombectomy. (**g**) A Penumbra is advanced to meet the occluding clot via a roadmap. (**h**) Complete recanalization is achieved after an aspiration thrombectomy using the Penumbra

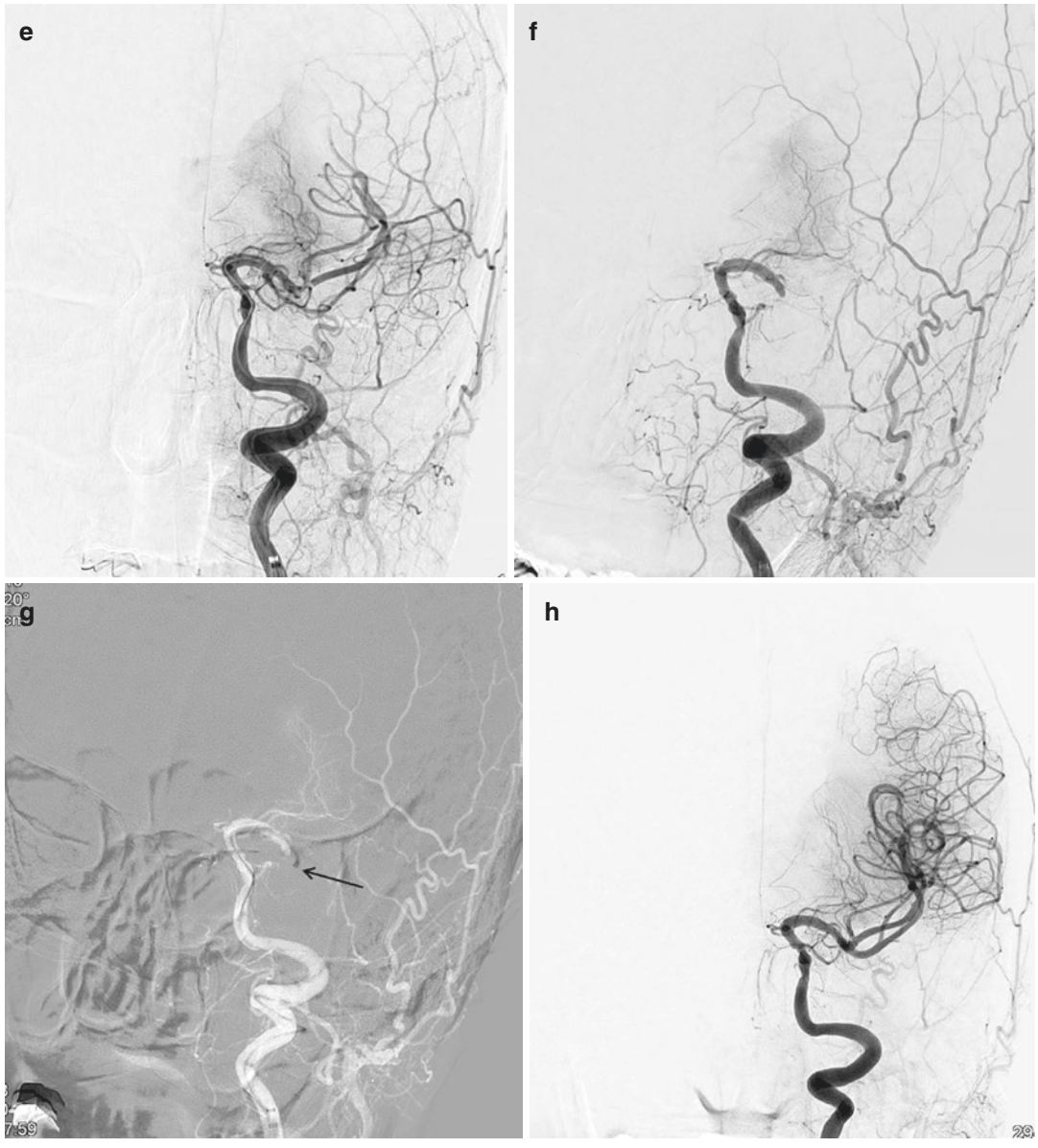


Fig. 11.5 (continued)

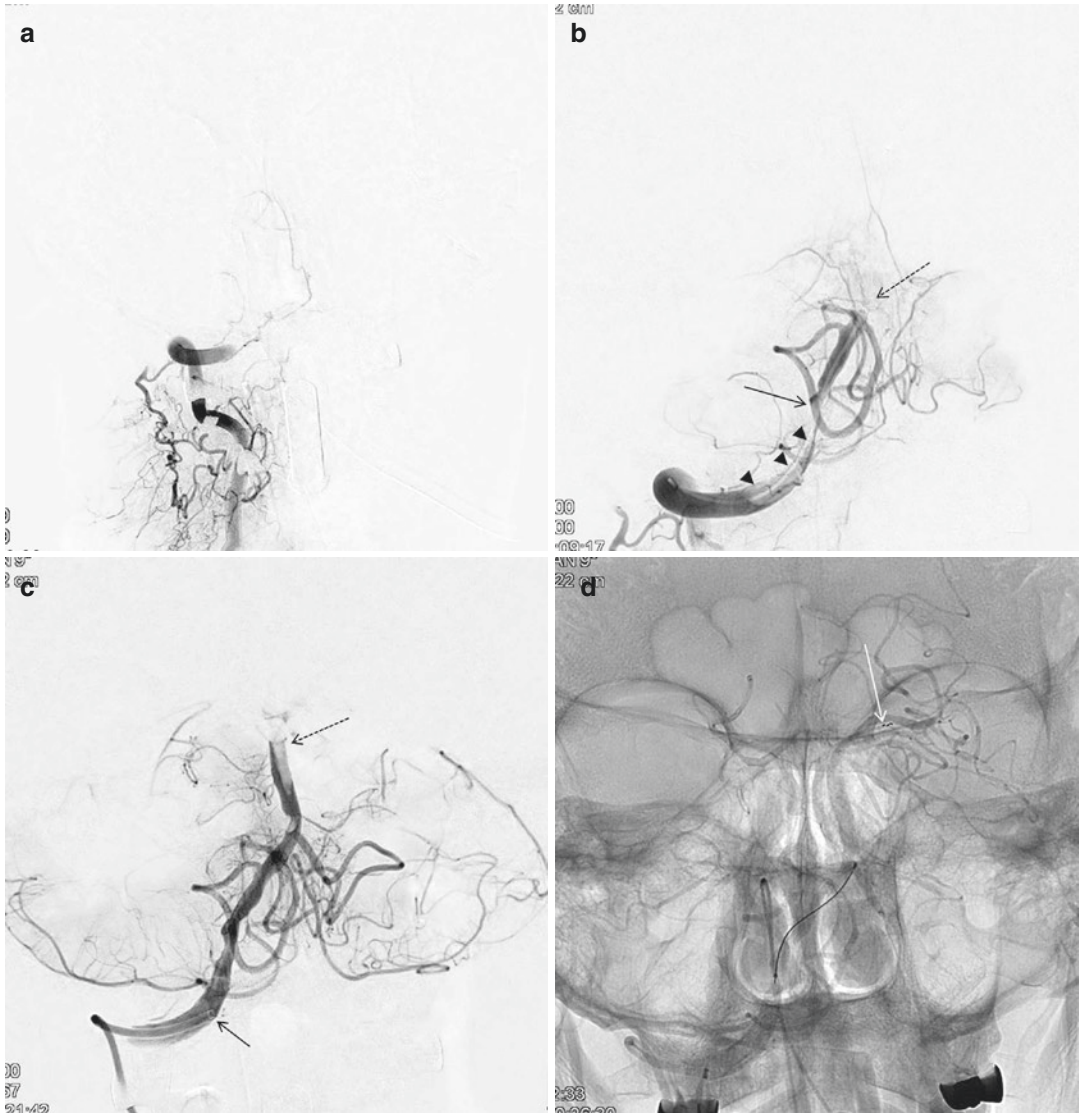
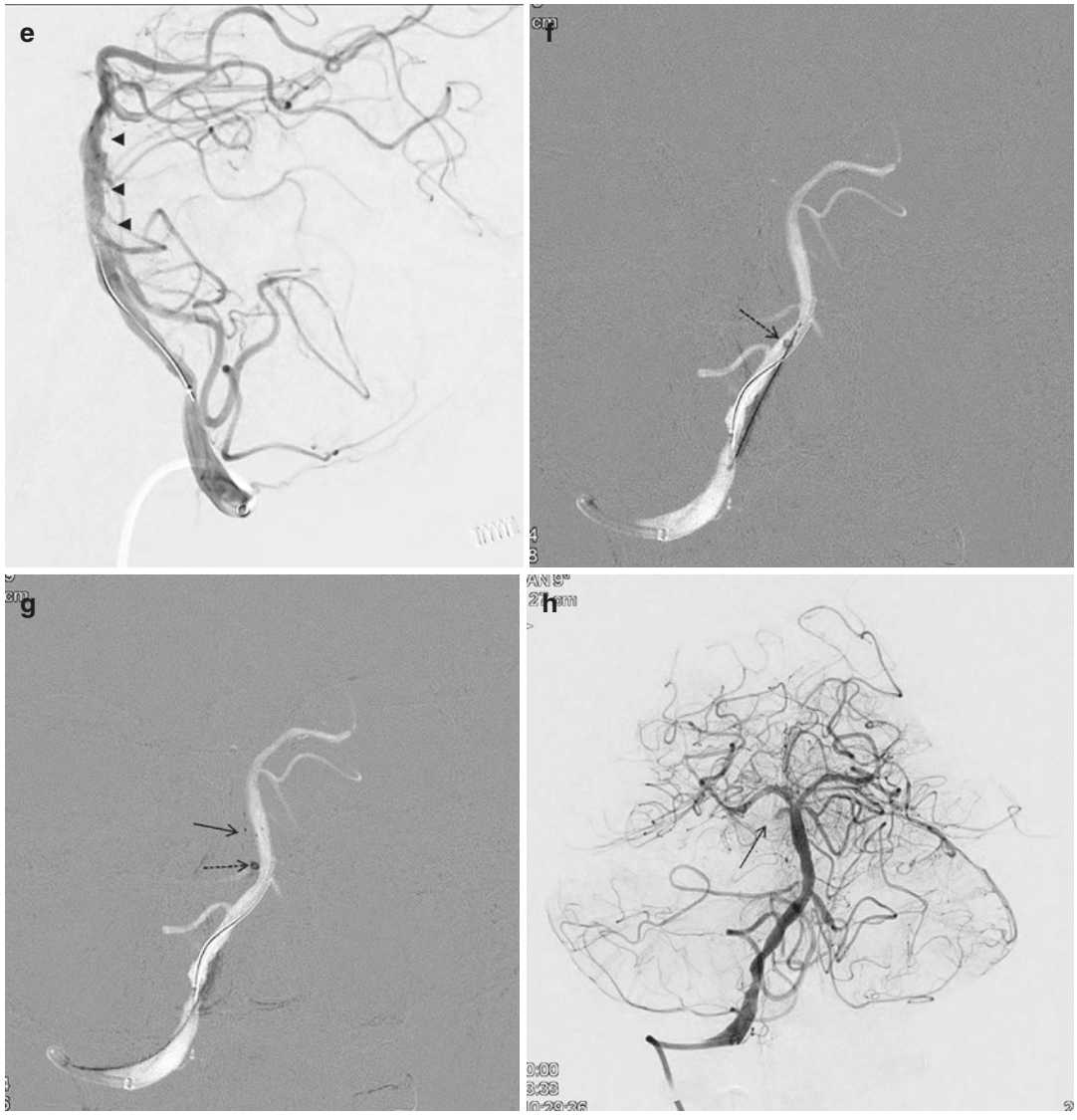


Fig. 11.6 A 69-year-old man presenting with mental change. (**a**) Right vertebral angiogram showing occlusion of the left vertebral artery V4 portion. The left vertebral artery is occluded (not shown). (**b**) Angiogram after navigation of a microcatheter into the basilar artery revealing tandem occlusion of the vertebral artery and basilar artery (*dotted arrow*). Note thrombi (*arrowheads*) proximal to a focal stenosis (*arrow*). (**c**) After simultaneous application of a suction thrombectomy using a 5 F intermediate catheter (*arrow*) and a stentriever thrombectomy, angiogram revealing remnant occlusion of the basilar artery with floating clots (*dotted arrow*). (**d**) Unsubtracted angiogram following stentriever deployment from the basilar artery to the left posterior cerebral artery (*white arrow*). (**e**) Lateral angiogram immediately after stentriever deployment showing clots (*arrowhead*) jailed by the stentriever along the posterior wall of the basilar artery. (**f**, **g**) The intermediate catheter (*dotted arrow*) is advanced to bypass the stenotic segment of the vertebral artery, followed by stentriever retrieval (*arrow*). (**h**) Immediately following simultaneous suction and a stentriever thrombectomy, angiogram revealing recanalization of the basilar artery, yet remnant occlusion of the right superior cerebellar artery (*arrow*). (**i**) The stentriever is deployed in the superior cerebral artery via a roadmap. (**j**) Angiogram after one pass of the stentriever showing complete recanalization. (**k**) 10-min delay angiogram showing recoiling of the stenosis (*arrow*) of the vertebral artery toward reocclusion. (**l**) Following intra-arterial administration of glycoprotein IIb/IIIa inhibitor, the stenosis (*arrow*) is improved. (**m**) MR angiogram on the next day showing a focal severe degree of stenosis of the right vertebral artery and occlusion of the left vertebral artery



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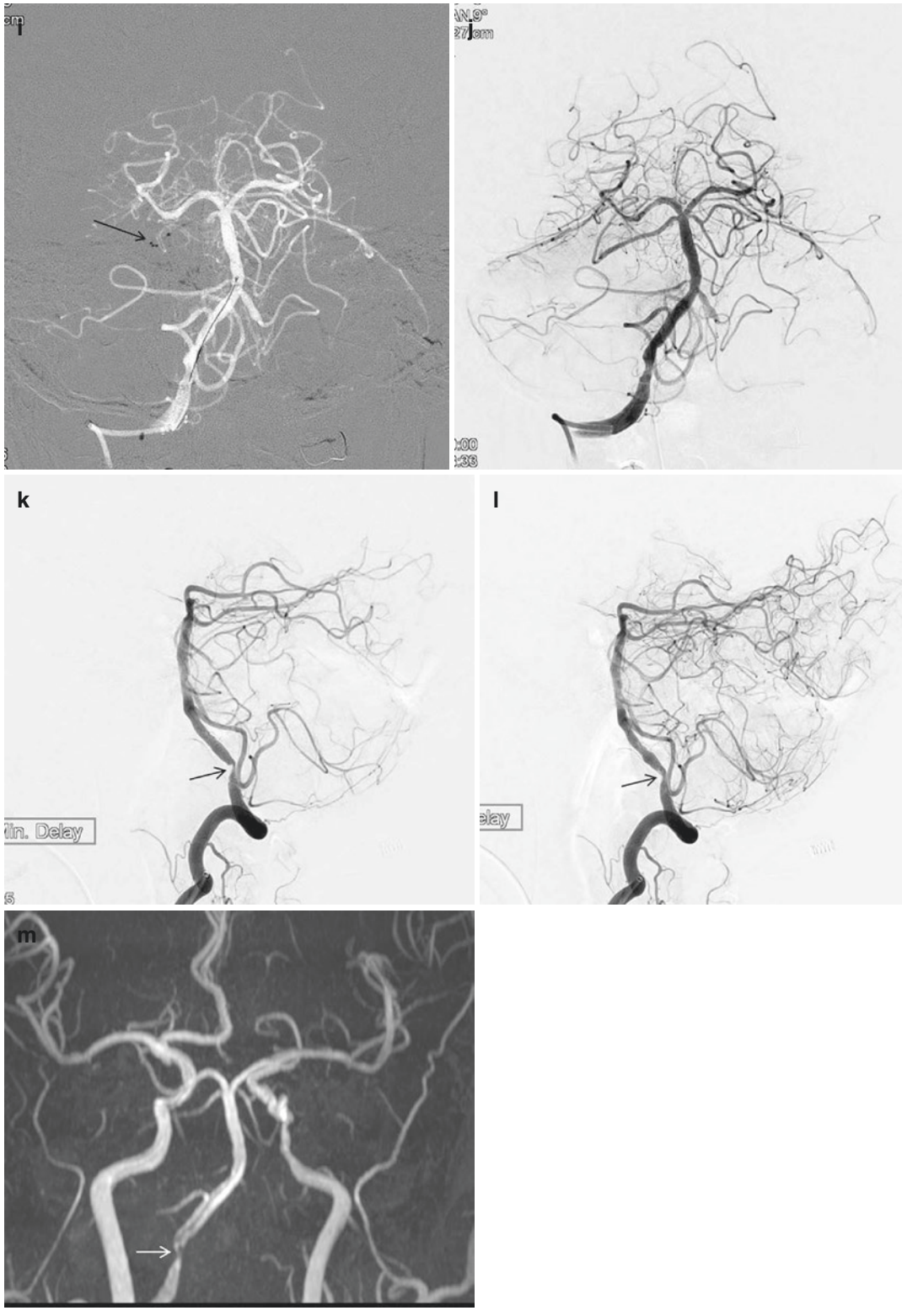

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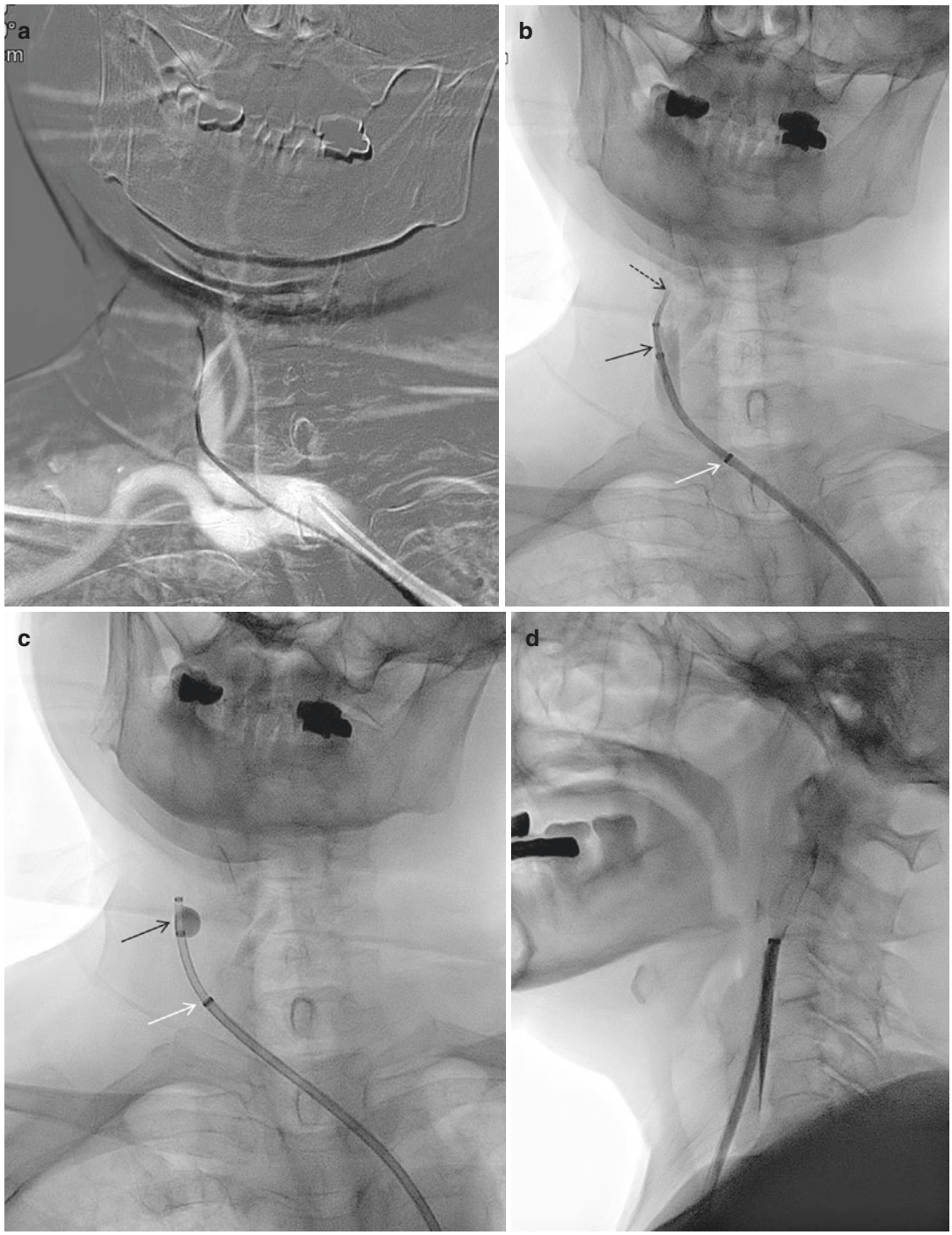


Fig. 11.7 A 62-year-old woman presenting with NIHSS score of 18. (**a**) Roadmap image showing occlusion of the right common carotid artery at the proximal segment. (**b**) The balloon guiding catheter (*black arrow*) is advanced over the 5 F angiocatheter (*dotted arrow*) to face the occluding clots. The *white arrow* indicates the tip of the 8 F shuttle sheath. (**c**) A suction thrombectomy is performed through the balloon guiding catheter after inflating the balloon. (**d**) The 8 F shuttle sheath is advanced to face the huge number of remnant clots in the cervical internal carotid artery bulb following the suction thrombectomy via the balloon guiding catheter,

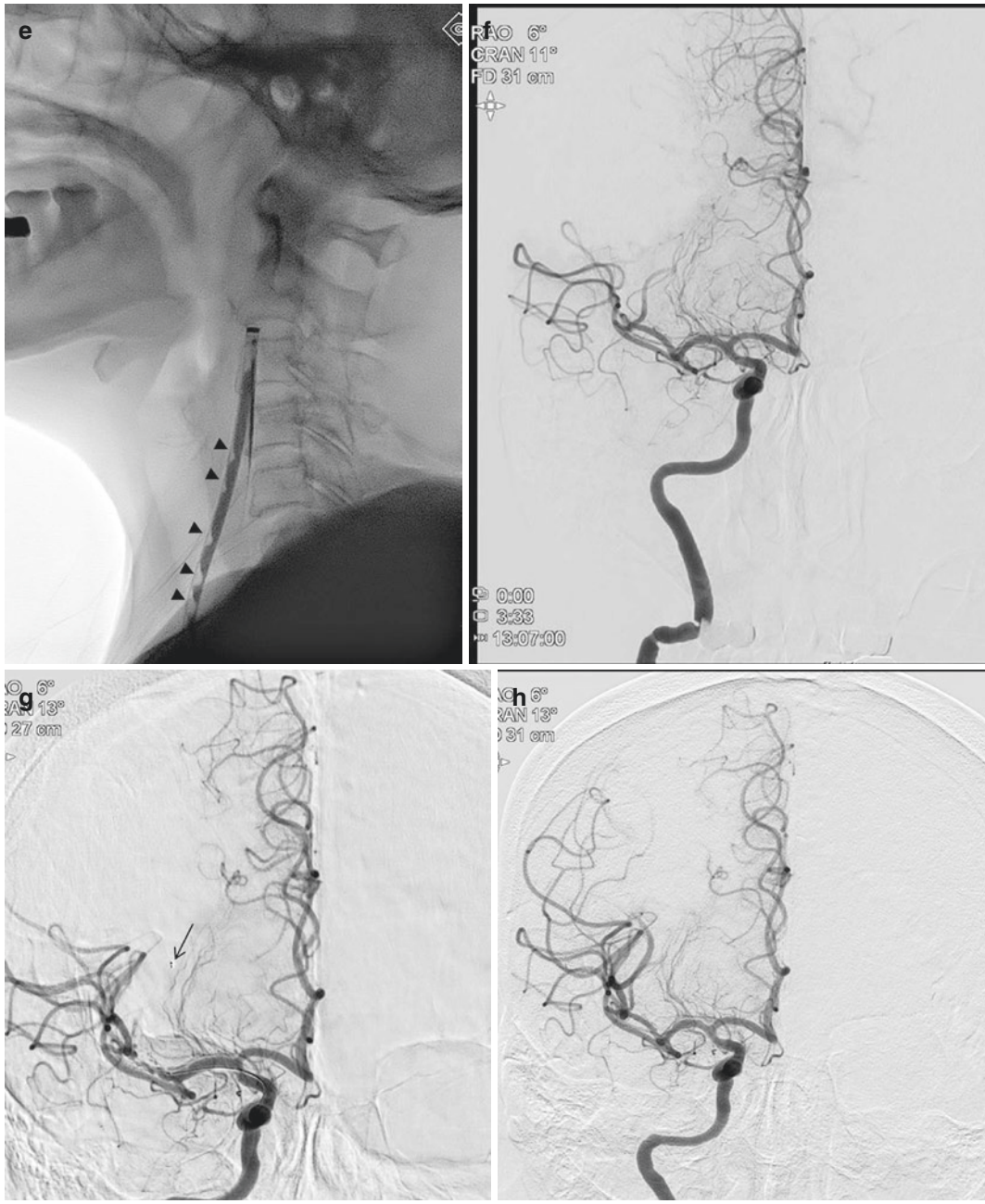


Fig. 11.7 (continued)

which is retrieved due to internal occlusion by packed clots. (**e**) Spot image of the suction thrombectomy through the 8 F shuttle sheath. Note many fragmented clots (*arrowheads*) are aspirated through the shuttle sheath. (**f**) Angiogram immediately after the suction thrombectomy revealing occlusion of the right middle cerebral artery superior division. (**g**) Angiogram after stentriever deployment. The arrows indicate the distal markers of the stentriever. (**h**) After one pass of the stentriever, control angiogram showing near complete recanalization. Only 43 min passed from puncture to near complete recanalization

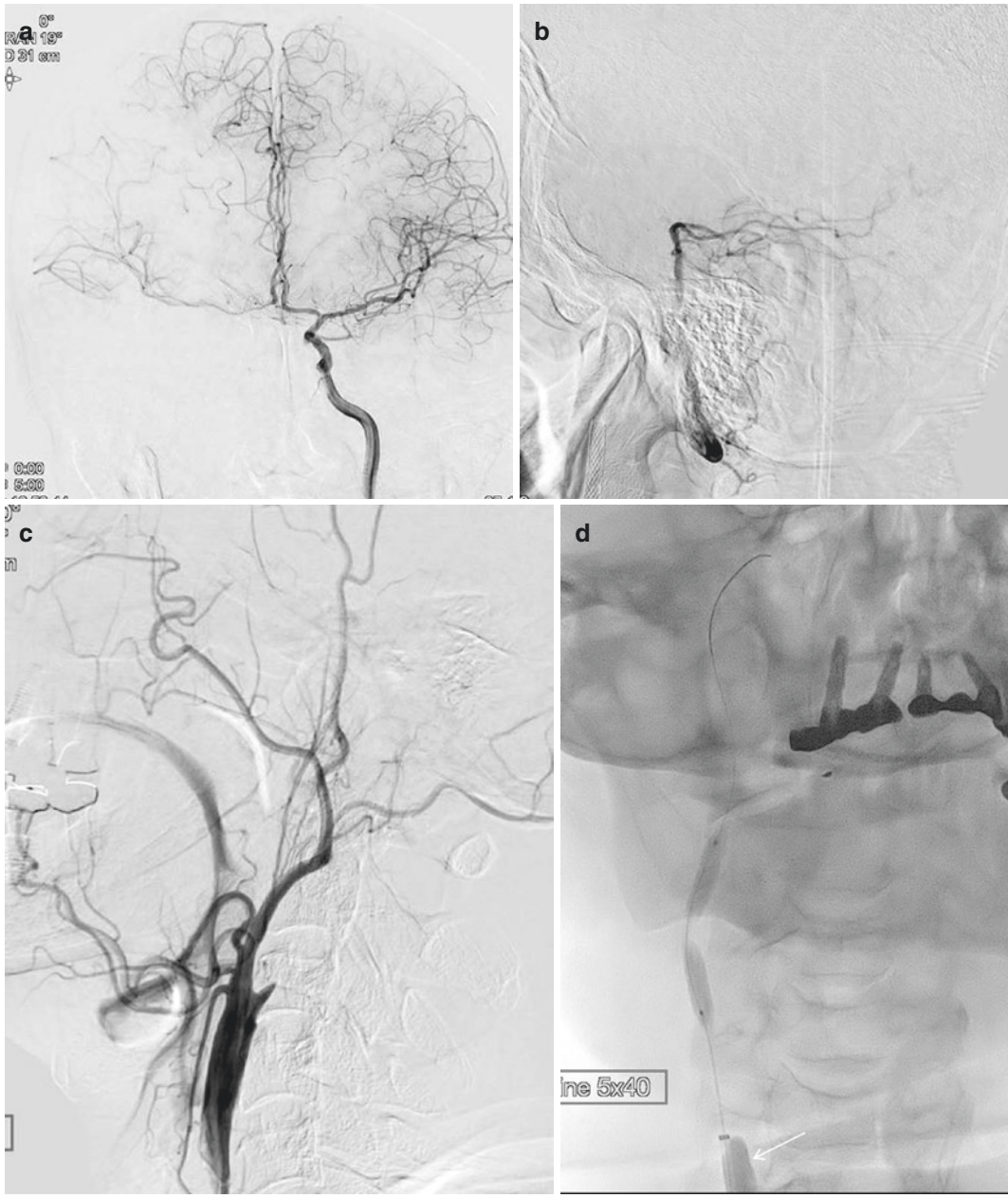


Fig. 11.8. A 68-year-old man presenting with NIHSS score of 14. (**a**) Left carotid angiogram showing insufficient cross collateral from the left to the right middle cerebral artery due to a hypoplastic right anterior cerebral artery A1 segment. (**b**) Lateral view of vertebral angiogram showing a poorly developed posterior communicating artery. (**c**) Right carotid angiogram revealing occlusion of the right internal carotid artery bulb. (**d**) Spot image during balloon angioplasty of the occluded right ICA bulb after inflating the balloon guiding catheter (*white arrow*). (**e**) Spot image after carotid stenting. Note, the balloon guiding catheter remains inflated throughout the balloon angioplasty and stenting. (**f**) Once clear blood is suctioned through the balloon guiding catheter, the balloon guiding catheter is deflated. Control angiogram showing complete perfusion without any distal embolization

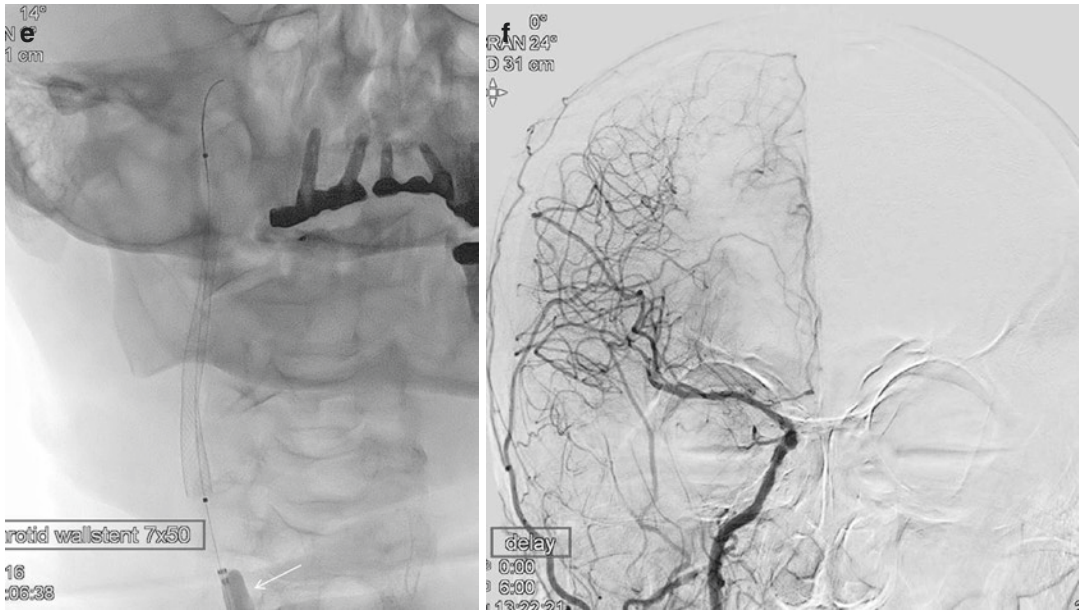


Fig. 11.8 (continued)

carotid artery occlusion. Although infrequent, hemodynamic infarction can occur when the cervical carotid artery is acutely occluded due to very poorly developed cross collaterals via the anterior and posterior communicating arteries. Similarly, vertebral artery orifice stenosis can also cause acute posterior circulation stroke.

As the hemodynamic mechanism is essentially a combination of acute cervical artery occlusion and poorly developed cross collaterals, the treatment is straightforward to reopening the occluded cervical artery (Fig. 11.8).

However, if the cervical carotid artery or vertebral artery disease causes tandem cervical and intracranial artery occlusions, which is the usual case, it remains controversial whether to treat the intracranial artery occlusion first or the cervical artery occlusion. However, in the stentriever thrombectomy era, neurointerventionalists seem to favor treating the cervical artery occlusion first, followed by a stentriever thrombectomy for the tandem intracranial artery occlusion, as the cervical artery must be sufficiently dilated when using a stentriever [17–23]. Another reason for treating the cervical artery disease first is that a tandem intracranial occlusion can spontaneously dissolve after sufficient dilatation of the cervical ICA [18]. Finally, timely recanalization of the cervical ICA not only improves the collateral flow to the ischemic Penumbra, but also augments the regional perfusion pressure and delivers fresh blood to the intracranial occlusion site to facilitate endogenous thrombolysis, thereby possibly leading to recanalization after finishing the procedure even in the case of a failed intracranial thrombectomy [24–26]. The procedural details are described below.

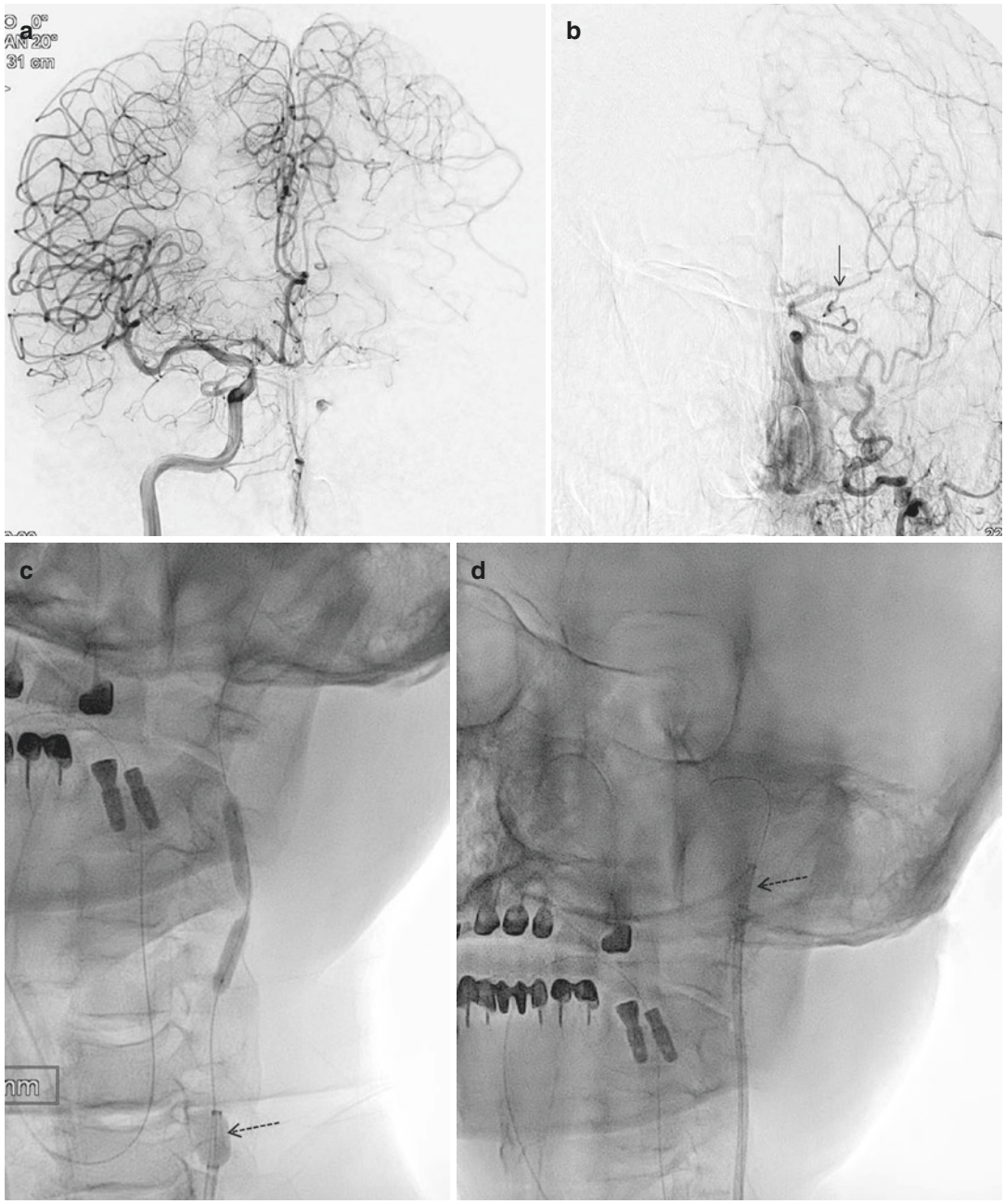
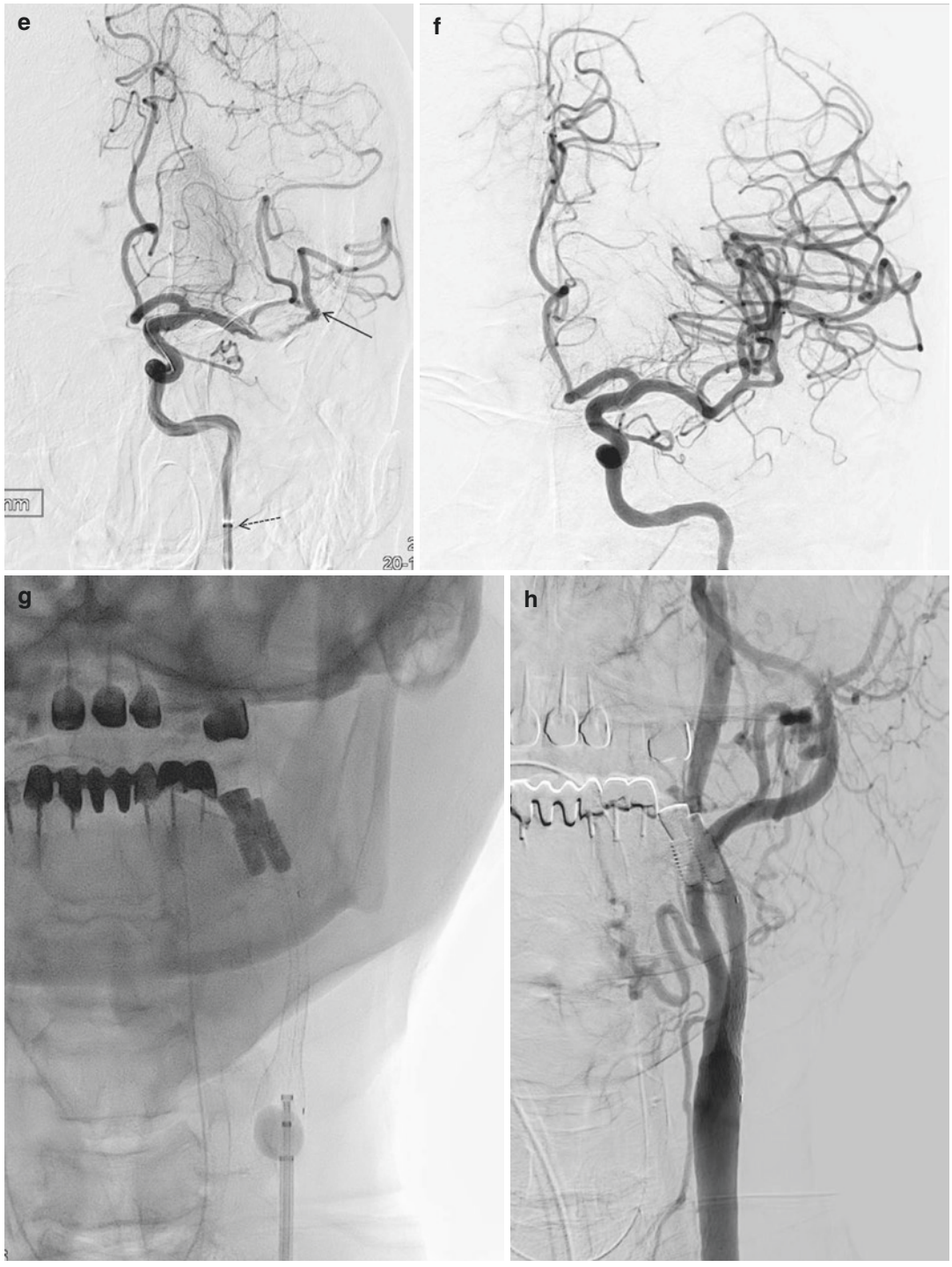


Fig. 11.9 A 60-year-old man presenting with NIHSS score of 20. (**a**) Right carotid angiogram showing contrast material filling the right anterior cerebral artery via the leptomeningeal collateral from the right middle cerebral artery, followed by the left anterior cerebral artery via an anterior communicating artery and then the left middle cerebral artery via the left anterior cerebral artery A1 segment. (**b**) Left carotid angiogram revealing occlusion of the left cervical internal carotid artery and reconstitution of the distal internal carotid artery via anastomosis between the internal and external carotid arteries. Note a tandem occlusion of the left middle cerebral artery (*arrow*). (**c**) Spot image during the balloon angioplasty after inflating the balloon guiding catheter. (**d**) The balloon guiding catheter (*dotted arrow*) is advanced beyond the occlusion site of the internal carotid artery once clear blood is suctioned though the balloon guiding catheter. (**e**) Angiogram immediately following stentriever (*arrow*) deployment. (**f**) After one pass of the stentriever, complete recanalization is achieved. (**g**) The carotid stenting is conducted while the balloon guiding catheter is inflated. (**h**) Angiogram immediately following the carotid stenting



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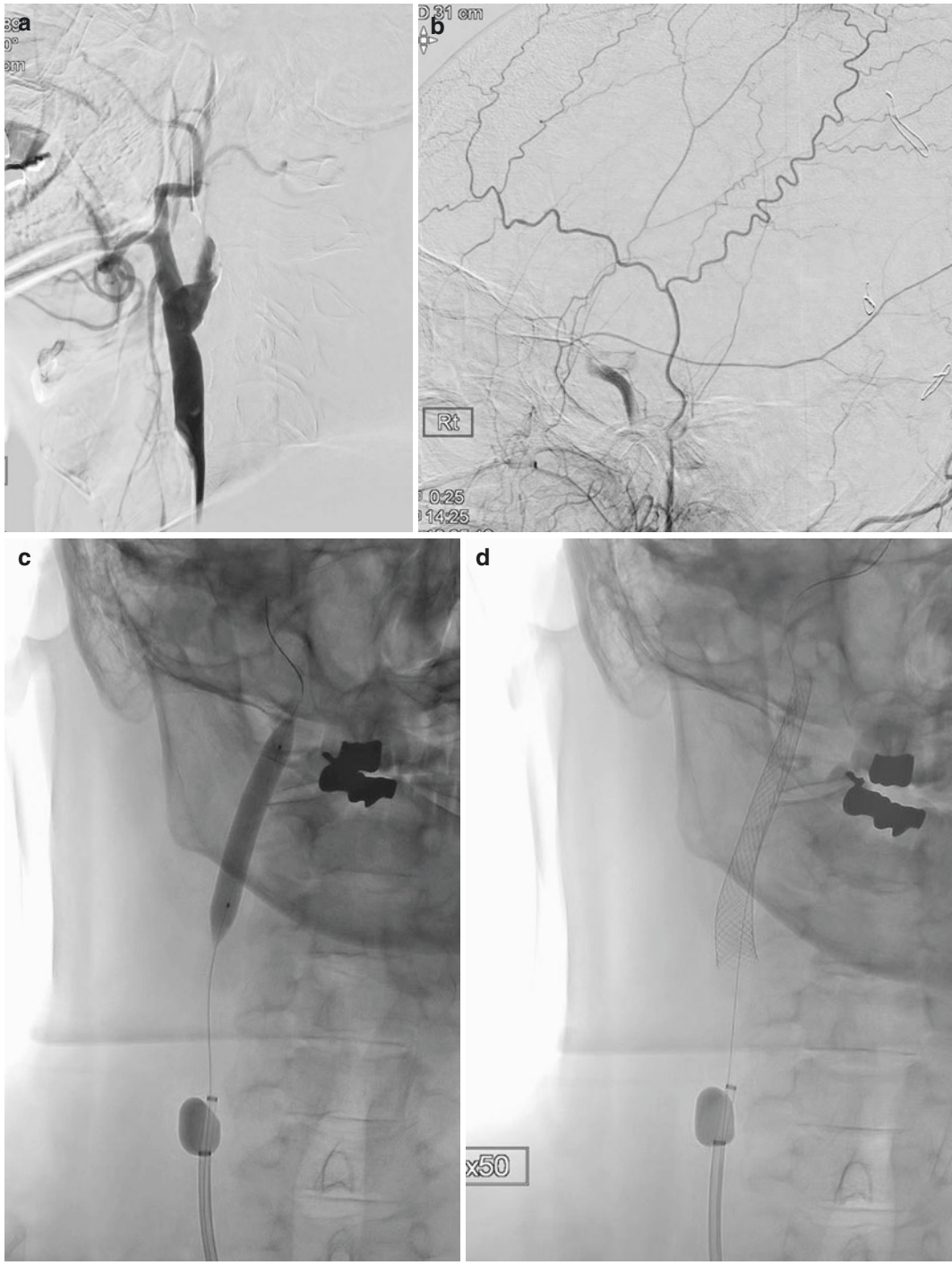

Fig. 11.10 60-year-old man presenting with NIHSS score of 19. (**a**) Lateral view of right carotid angiogram showing carotid bulb occlusion. (**b**) A tandem occlusion of the carotid artery cavernous segment is revealed external to the internal carotid artery anastomosis. (**c**) Spot image during the balloon angioplasty after inflating the balloon guiding catheter. (**d**) Spot image during stenting. The balloon guiding catheter is not deflated until clear blood is aspirated after stenting. (**e**) Angiogram after advancement of the balloon guiding catheter (*arrow*) to the end segment of the stent showing a tandem occlusion of the cavernous carotid artery. (**f**) Spot image during stentriever (*arrow*) deployment. Note the balloon guiding catheter tip (*arrow*) is located at the end of the stent. (**g**) After one pass of the stentriever, control angiogram showing complete recanalization

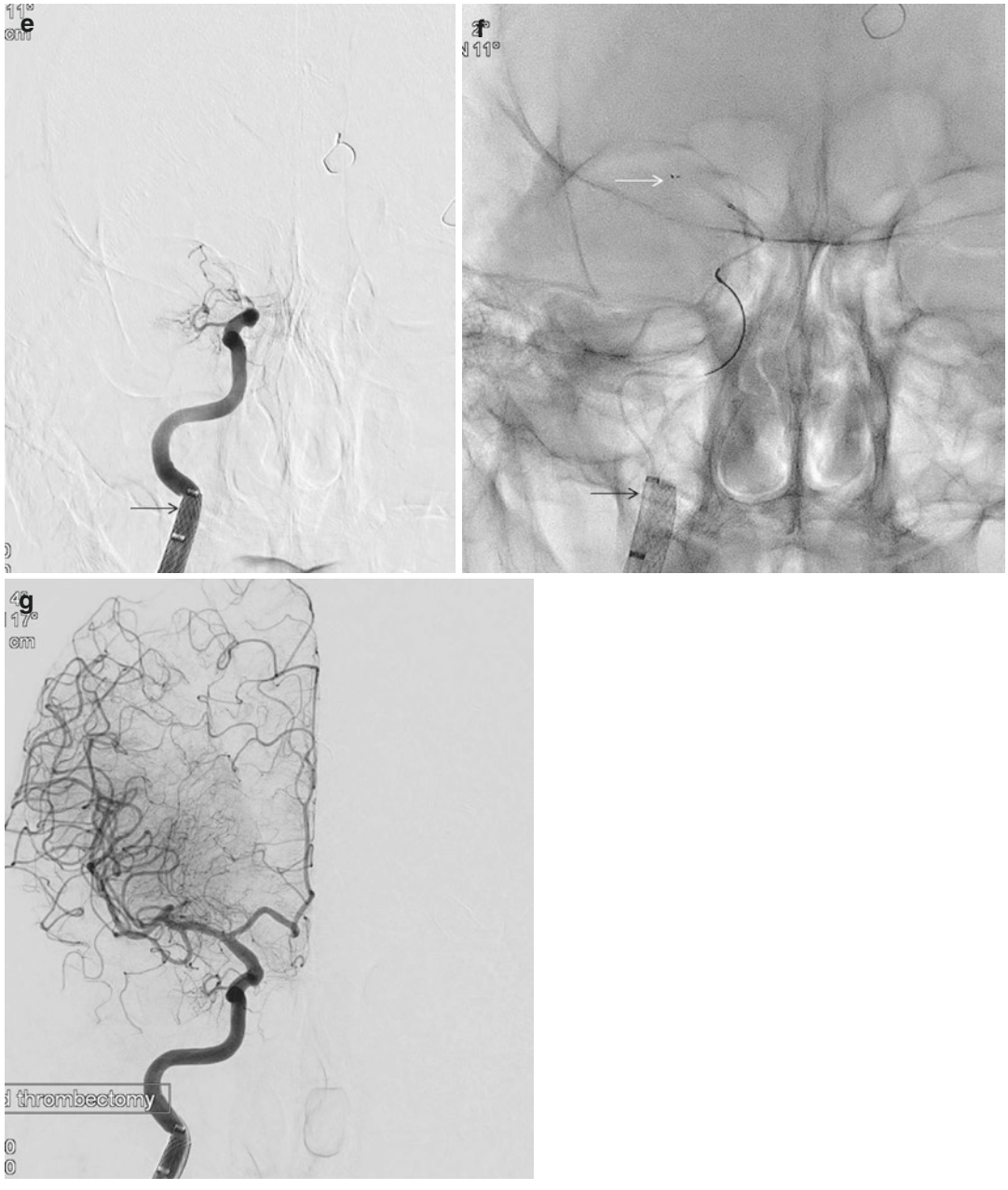

Fig. 11.10 (continued)

1. An 8 or 9 F BGC is placed proximal to the occluded carotid artery using a coaxial technique, as described previously. A 9 F is preferred over an 8 F BGC, as the inner lumen of the BGC should be ≥6 F to facilitate various sizes of carotid stent.
2. The BGC balloon is inflated and the occluded cervical segment is accessed using a 0.014-inch microwire. A 4–5-mm diameter balloon is then advanced over the wire. If access to the occluded segment is difficult with just the microwire, an exchange technique using a microcatheter and 300-cm length exchangeable microwire can be utilized before introducing the angioplasty balloon.
3. Following the angioplasty for an occluded cervical carotid artery, the BGC should be suctioned to aspirate any debris before deflation.
4. Depending on the patient's medical status and surgeon's preference, a stentriever thrombectomy for an ILAO can be performed first, followed by carotid artery stenting (Fig. 11.9) either immediately or later if dual antiplatelet medication is contraindicated for the patient. Another option is to perform the carotid artery stenting first, followed by a stentriever thrombectomy (Fig. 11.10).
5. If the carotid stenting is performed first, the BGC is advanced to the distal end of the stent to avoid the stentriever becoming stuck on the struts of the placed carotid stent. For the same reason, a closed-cell-type carotid stent is preferred over an open-cell-type stent (Fig. 11.10). Meanwhile, if the stentriever thrombectomy is performed first, the BGC is advanced beyond the occluded segment of the cervical carotid artery over the deflated angioplasty balloon immediately following the angioplasty (Fig. 11.9).
6. A control angiogram is obtained to confirm any remnant intracranial artery occlusion.
7. Thereafter, the steps are the same as for a standard stentriever thrombectomy for an intracranial artery occlusion.

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12 Refractory Occlusion to Stentriever Thrombectomy: Etiological Considerations and Suggested Solutions

Byung Moon Kim

While a stentriever thrombectomy is 70–75% successful in achieving recanalization (modified thrombolysis in cerebral ischemia [mTICI] 2b-3) of an anterior circulation intracranial large artery occlusion (ILAO), 25–30% of ILAOs remain refractory to a stentriever thrombectomy [1, 2]. The etiology of an acute ILAO can play a key role in the response to a stentriever; plus certain complications, such as inadvertent detachment, the stentriever getting stuck, and repeated reocclusion, have also been reported in relation to stroke etiology [3–8]. Therefore, this chapter discusses the pathomechanism of refractoriness to a stentriever, along with suggested solutions.

12.1 Etiological Considerations for Refractoriness to Stentriever

It is important to classify the cases that are hard to recanalize using only a stentriever. Chapter 11 already discussed several such situations, including anatomical tortuosity and/or a large amount of clots and tandem cervical and intracranial artery occlusions.

However, other possible causes of refractoriness include a non-embolic ILAO or embolic yet organized (hard) clot. The action mechanism of a stentriever, which retrieves by engaging an occluding clot, is most effective in the case of embolic ILAOs. In contrast, in the case of a non-embolic occlusion, intracranial atherosclerotic stenosis (ICAS) or intracranial artery dissection can render a stentriever ineffective and even dangerous. On the other hand, for an embolic occlusion, a soft (fresh) clot engages better with a stentriever than a hard (organized) clot [9]. Thus, despite being an embolic occlusion, an ILAO from a hard clot can be refractory to a stentriever.

12.2 Angiographic Discrimination of Non-embolic from Embolic ILAO

As the majority of first-ever acute stroke patients present with little information on the embolic source, most etiologic assumptions rely on procedural angiographic findings, unless the initial electrocardiography reveals an evident abnormality, such as atrial fibrillation. However, it is often hard to discriminate a non-embolic occlusion from an embolic ILAO based on the angiographic findings during the procedure. Thus, to help with this discrimination, a recently

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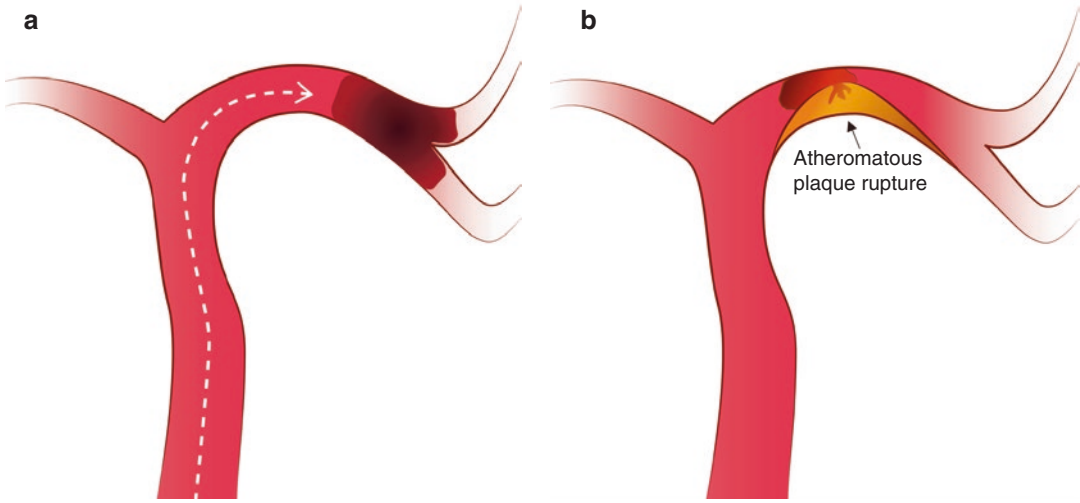


Fig. 12.1 Schematic illustrations of (**a**) embolic occlusion and (**b**) in situ thrombo-occlusion due to intracranial atherosclerotic stenosis

published study suggested an angiographic marker (truncal-type versus branching-site occlusion): essentially, an embolus or floating clot is more likely to lodge at an arterial branching site except for the perforator origin, or where the diameter abruptly decreases due to underlying stenosis. It is very unlikely that a floating clot is stopped in a normal-looking arterial trunk. In contrast, ICAS predominantly involves the arterial trunk before a bifurcation (Fig. 12.1). Therefore, while an embolic occlusion mainly involves a main branching site (branching-site occlusion, BSO), an ICAS thrombo-occlusion affects the arterial trunk with a bifurcation site being saved (truncal-type occlusion, TTO) (Fig. 12.2). In that study, this angiographic marker (TTO) was independently associated with the embolic source (−) of an ILAO (odds ratio [OR] 9.07; 95% confidence interval [CI] 3.74–22.0) [8]. Thus, if a TTO is recognized during intra-arterial recanalization therapy, this is a useful predictor of a non-embolic ILAO, of which the majority is due to ICAS [8].

12.3 Suggested Solutions for Refractory ILAO Based on Pathomechanism

12.3.1 Solution for Refractory Occlusion Due to Underlying ICAS

In Asian populations, ICAS is one of the major causes of acute stroke, with recent studies showing that ICAS is responsible for 15–20% of acute ILAO strokes [7, 8, 10, 11]. The majority of non-embolic occlusions are truncal type, as revealed in angiograms during intra-arterial recanalization treatment, and most are due to ICAS thrombo-occlusion, especially in Asian patients [8]. This type (TTO) of occlusion shows refractoriness to a stentriever due to repeated reocclusion [7, 8, 10, 11]. While there are no reports of intimal damage from the use of a stentriever for acute ischemic stroke treatment of Western patients, in whom ICAS is rare as the cause of an ILAO [12], the application of a stentriever can damage the

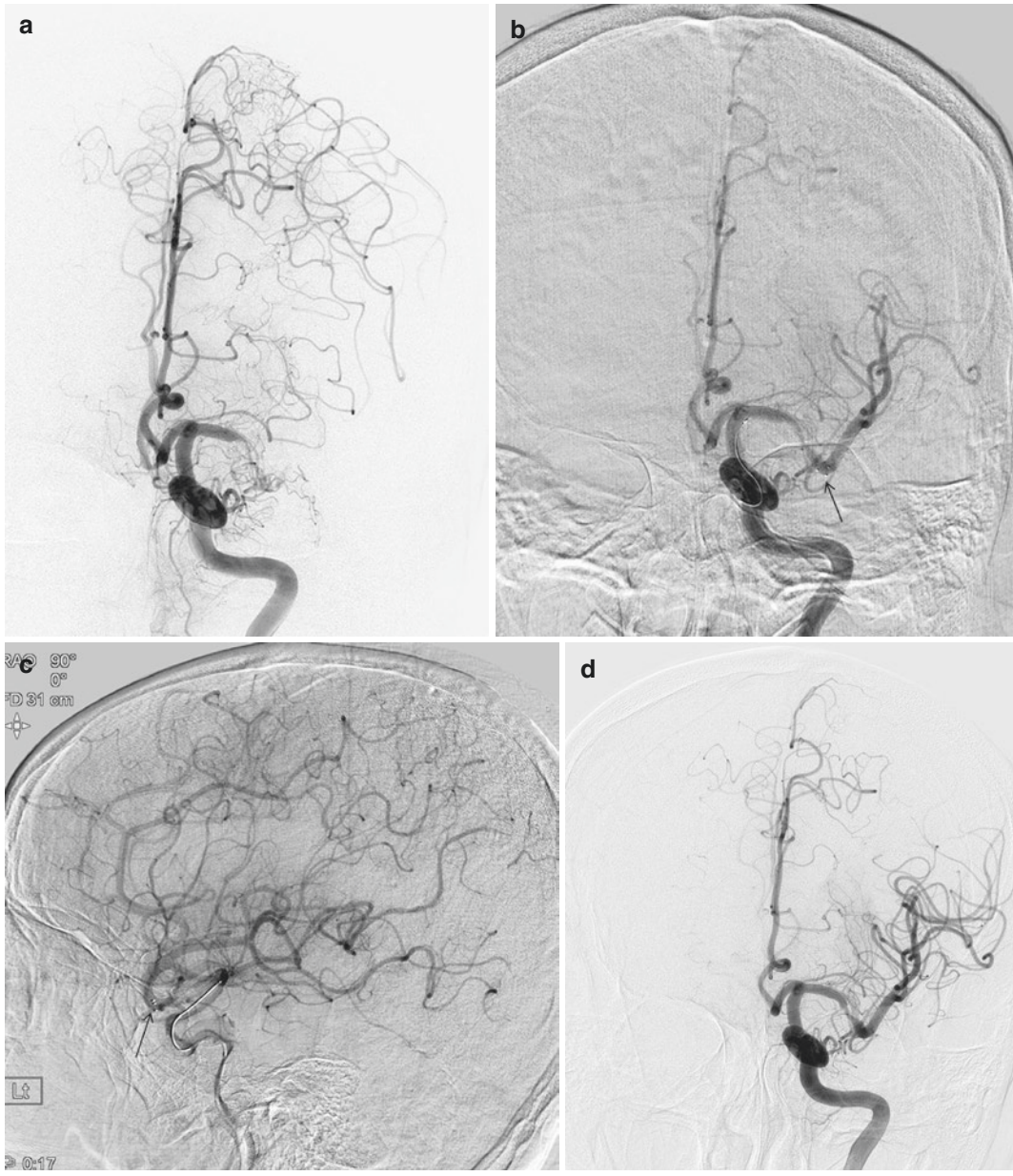


Fig. 12.2 A 56-year-old man presenting with NIHSS score of 15. (**a**) Left carotid angiogram showing occlusion of the left middle cerebral artery M1 segment. (**b**) Frontal and (**c**) lateral angiogram immediately after stentriever deployment showing complete recanalization with a focal stenosis in the M1 trunk. Note that the bifurcation of the middle cerebral artery is preserved without stenosis or clots. (**d**) Immediately after stentriever retrieval, angiogram revealing complete recanalization with a focal stenosis in the M1 trunk. (**e**) Reocclusion is noted in a 5-min delayed angiogram. (**f**) Angiogram immediately after four passes showing complete recanalization. (**g**) Rotational angiogram disclosing a focal stenosis (*arrowheads*) in the M1 trunk without involving the bifurcation site after multiple passes of the stentriever followed by repeated reocclusion. (**h**) A 20-min delayed angiogram after glycoprotein IIb/IIIa inhibitor showing complete recanalization yet a slowed flow due to remnant stenosis in the M1 trunk

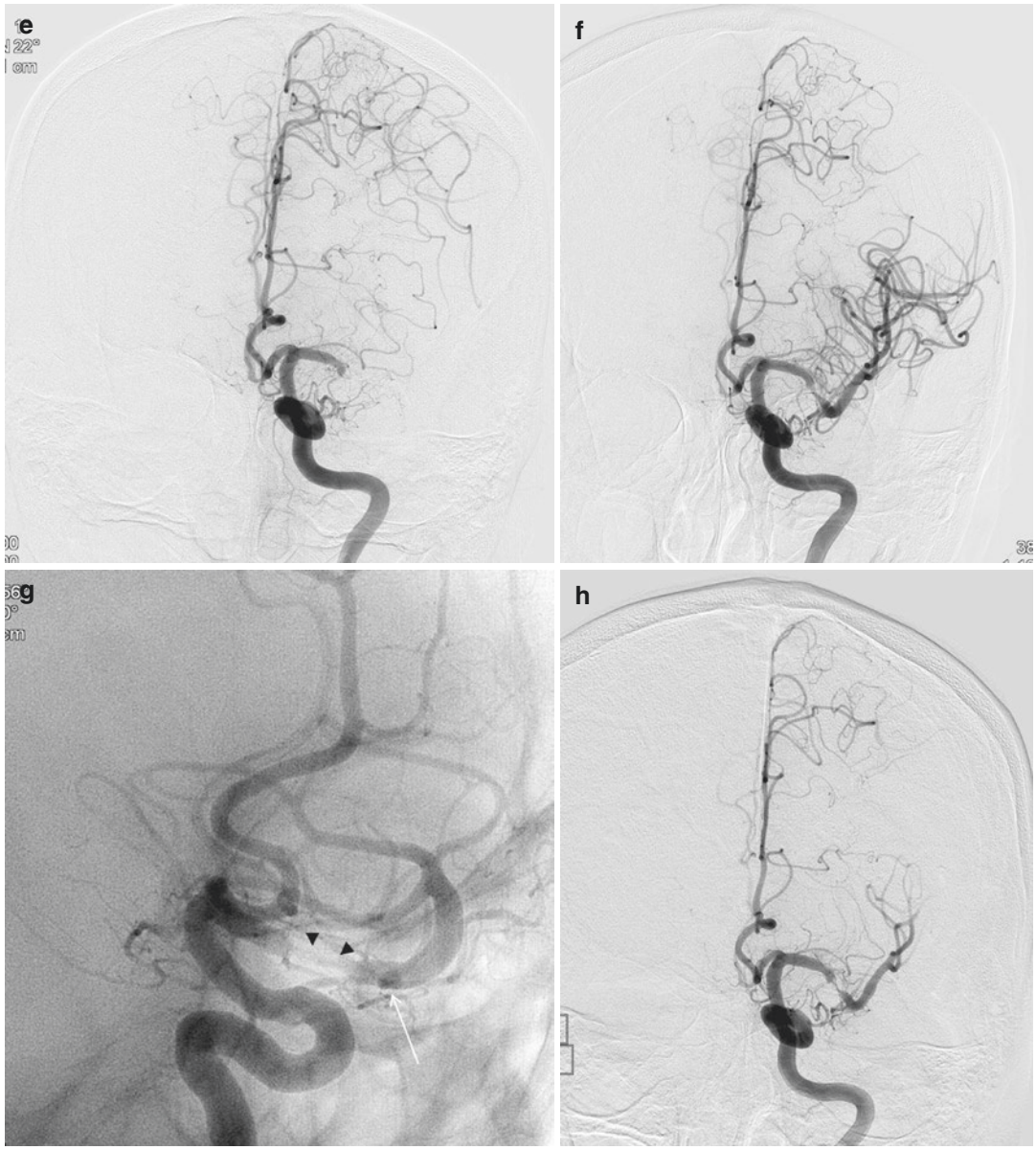


Fig. 12.2 (continued)

atheromatous surface if an acute ILAO is due to an ICAS thrombo-occlusion. In this case, the use of a stentriever can result in increased platelet activation, leading to repeated reocclusion and even dissection [8, 13].

To prevent repeated reocclusion in the case of an ILAO due to ICAS, inhibiting the platelet function can play a key role. Therefore, the first option is to administer a glycoprotein IIb/IIIa inhibitor, which inactivates platelets and thereby prevents repeated reocclusion (Fig. 12.3) [7]. However, ICAS occlusions are occasionally refractory to glycoprotein IIb/IIIa inhibitors. For recanalization in such a case, permanent stenting with or without balloon angioplasty may be effective [8, 10, 14].

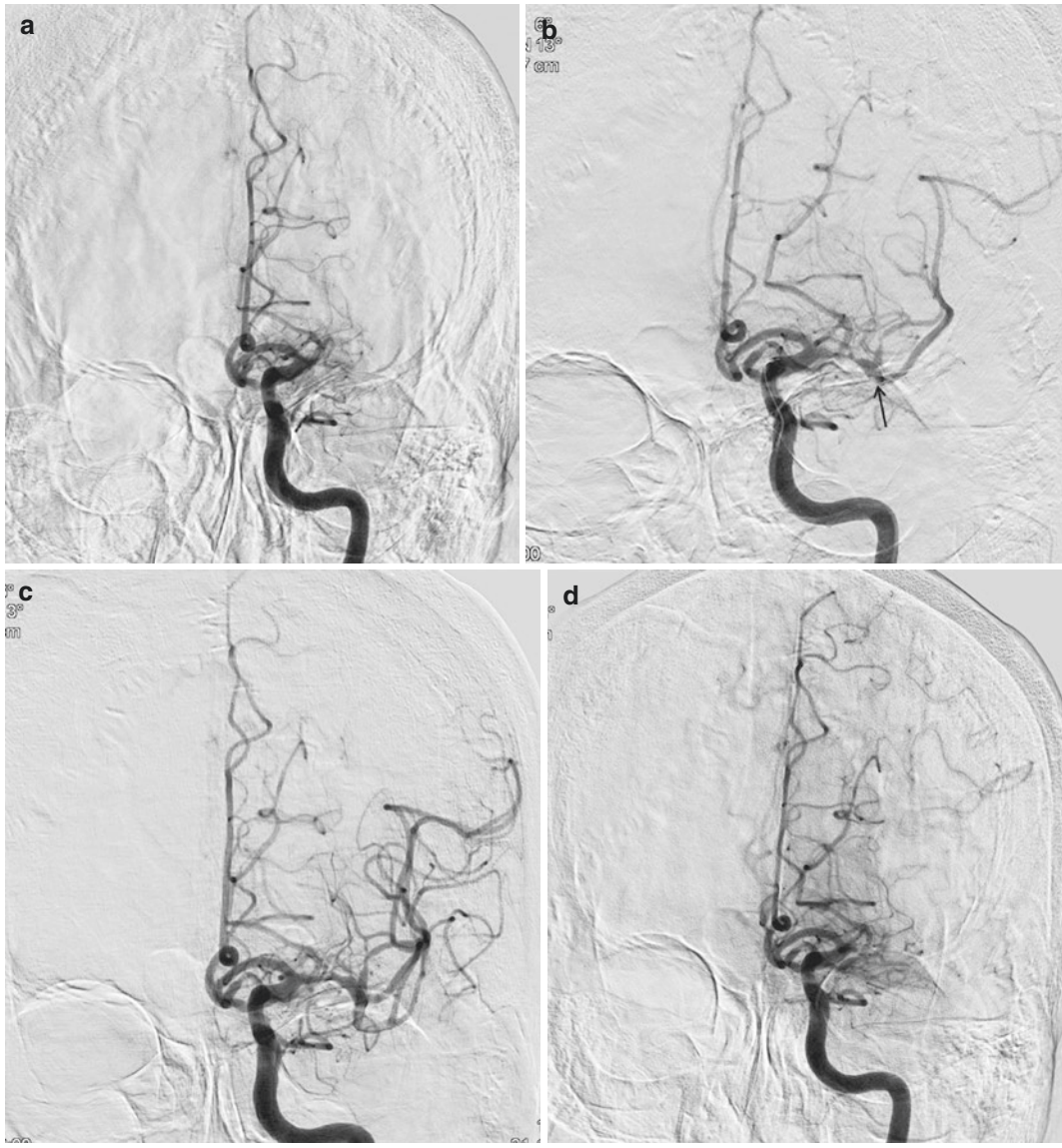


Fig. 12.3 A 60-year-old man presenting with NIHSS score of 17. (**a**) Initial angiogram showing left middle cerebral artery M1 segment occlusion. (**b**) Angiogram immediately after stentriever deployment at the focal stenosis without involving the bifurcation. (**c**) Angiogram after multiple passes of the stentriever followed by repeated reocclusion showing irregular stenosis in the M1 trunk getting toward reocclusion. (**d**) A 5-min delayed angiogram showing reocclusion. (**e**) Angiogram after fifth pass of stentriever showing recanalization. (**f**) A 20-min delayed angiogram after glycoprotein IIb/IIIa inhibitor showing persistent recanalization with irregular stenosis in the M1 trunk. The flow speed is also improved

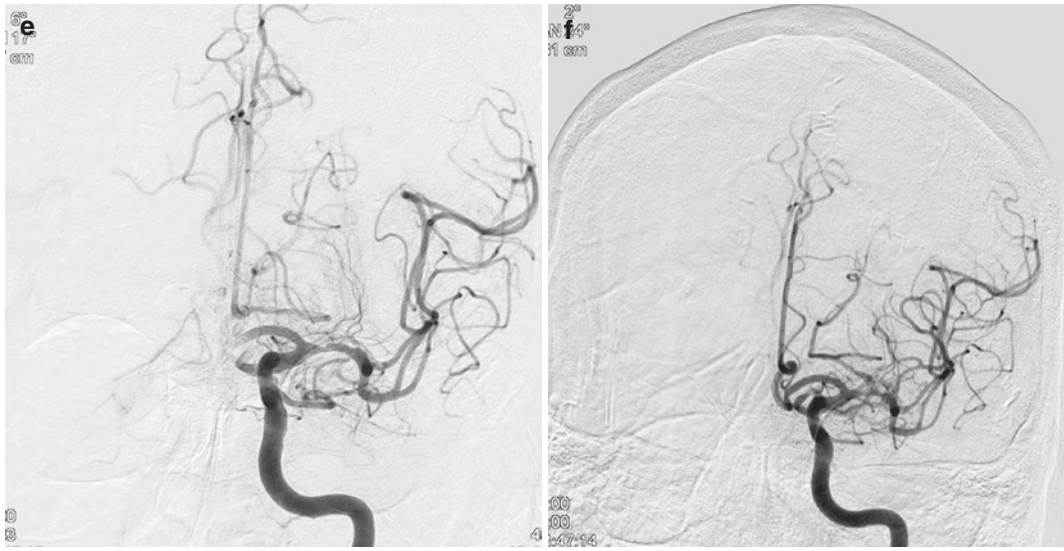


Fig. 12.3 (continued)

12.3.2 Solution for Refractory Occlusion Due to Embolic Organized (Hard) Clot

An organized (hard) clot is resilient and less sticky in character, making it less engaged with a stentriever and leading to clot loss during stentriever retrieval, especially in the case of a tortuous and large proximal artery. Plus, since an organized clot causes more tension in the stentriever-deployed segment of the parent artery, this can also cause an arterial spasm. Such effects then increase the probability of stentriever failure.

For successful recanalization of an ILAO due to an organized clot, the first option is to apply a vasodilator, which releases the tension of the stentriever-deployed arterial segment, thereby increasing the chance of successful clot retrieval. The second option is to switch to an aspiration thrombectomy or the simultaneous utilization of a stentriever and an aspiration thrombectomy. After deploying the stentriever, an aspiration catheter (Penumbra) or intermediate catheter is advanced as close to the clot as possible. A stentriever and suction thrombectomy can be performed simultaneously, as described in Chap. 11 (Figs. 11.4 and 11.5).

If the organized clot is still refractory after switching to aspiration and the simultaneous utilization of a stentriever and aspiration thrombectomy, permanent stenting can be considered as the final resort [14]. The organized clot may be refractory due to less engagement with the stentriever [9]. In contrast, if permanent stenting is conducted, the stented artery becomes more patent as the organized clot is less engaged inside the stent struts (Fig. 12.4) [14].

12.4 Permanent Stenting for Acute ILAO

In a meta-analysis of five recent randomized clinical trials, 25–30% of ILAO cases failed to achieve recanalization with a stentriever thrombectomy [2]. Irrespective of the etiology of the refractoriness of an ILAO, a rescue modality is needed for such refractory cases, as successful recanalization is the most powerful factor for a good outcome. One possible modality is the intra-arterial infusion of thrombolytics (tissue

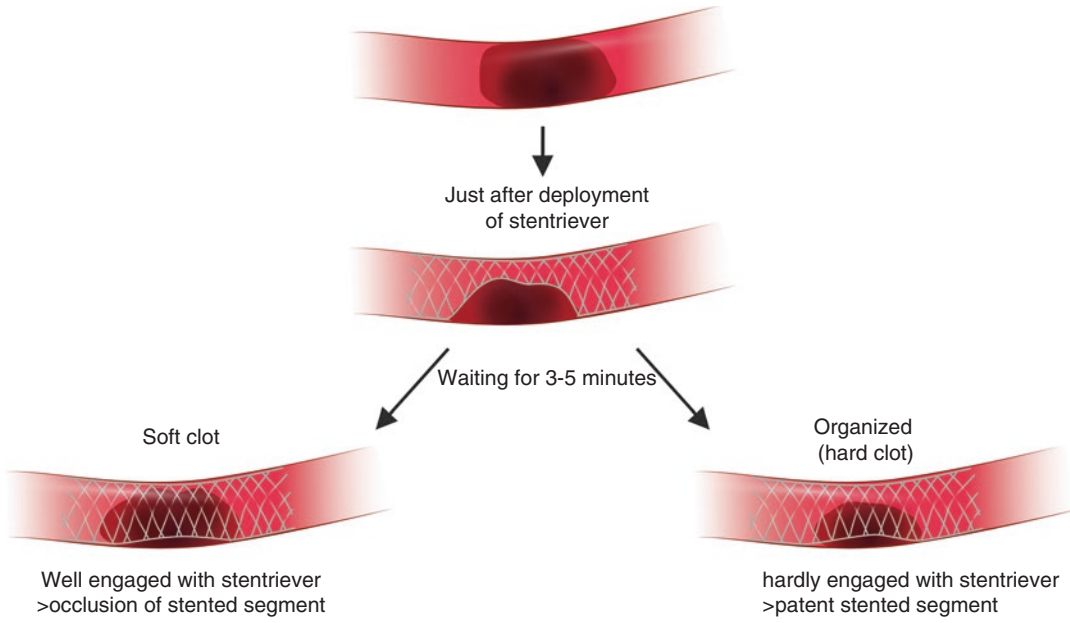


Fig. 12.4 Schematic drawing of the interaction between a stentriever and a clot according to the clot characteristics

plasminogen activator or urokinase) and/or antiplatelets (glycoprotein IIb/IIIa inhibitor), which can promote mTICI 2b-3 recanalization in some refractory ILAOs due to ICAS [7, 8, 14]. However, the final rescue modality is permanent stenting, which has also been suggested as a primary approach or rescue tool for the recanalization of an acute ILAO [8, 10, 14–20]. A stentriever-failed ILAO is likely due to either ICAS, intracranial artery dissection, or an organized (hard) clot, as previously described [8, 9, 14, 22]. In the case of an ICAS occlusion, the refractoriness is mainly due to repeated reocclusion [7, 8, 11]. As mentioned above, a glycoprotein IIb/IIIa inhibitor can help to prevent such reocclusion [7, 8]. Notwithstanding, ICAS occlusions are often refractory to glycoprotein IIb/IIIa inhibitors, probably because of underlying severe stenosis. In such cases, permanent stenting combined with a glycoprotein IIb/IIIa inhibitor can be very effective (Fig. 12.5) [14]. Permanent stenting can also be the last resort after the failure of a stentriever and aspiration thrombectomy due to an organized (hard) clot (Fig. 12.6). In a recently published study on the safety and efficacy of permanent stenting following a failed mechanical thrombectomy, 83.3% of the stented patients showed thrombolysis with a cerebral ischemia 2b-3 recanalization rate. Among 17 stented cases, only 40% underwent balloon angioplasty [14]. A Wingspan stent was used in seven cases, while a Solitaire stent, which is also used for thrombectomies, was used in ten cases. These results suggest that most of the refractory occlusions were due to a soft plaque ICAS or organized embolus, rather than a hard plaque ICAS. In other words, the radial force of the Solitaire stent was enough to open the occlusion, and angioplasty was not always required in the case of a soft plaque or hard embolus occlusion [14]. Meanwhile, platelet inactivation by a glycoprotein IIb/IIIa inhibitor was found to be essential to prevent reocclusion due to acute in-stent thrombosis [14]. The stented patients had significantly more favorable outcomes (modified Rankin Scale score [mRS] of 0–2, 35.5%) and less cerebral herniation (11.8%) than the non-stented patients (mRS, 0–2, 7.1%; cerebral herniation, 42.9%), while there were no differences in the symptomatic intracranial hemorrhage and

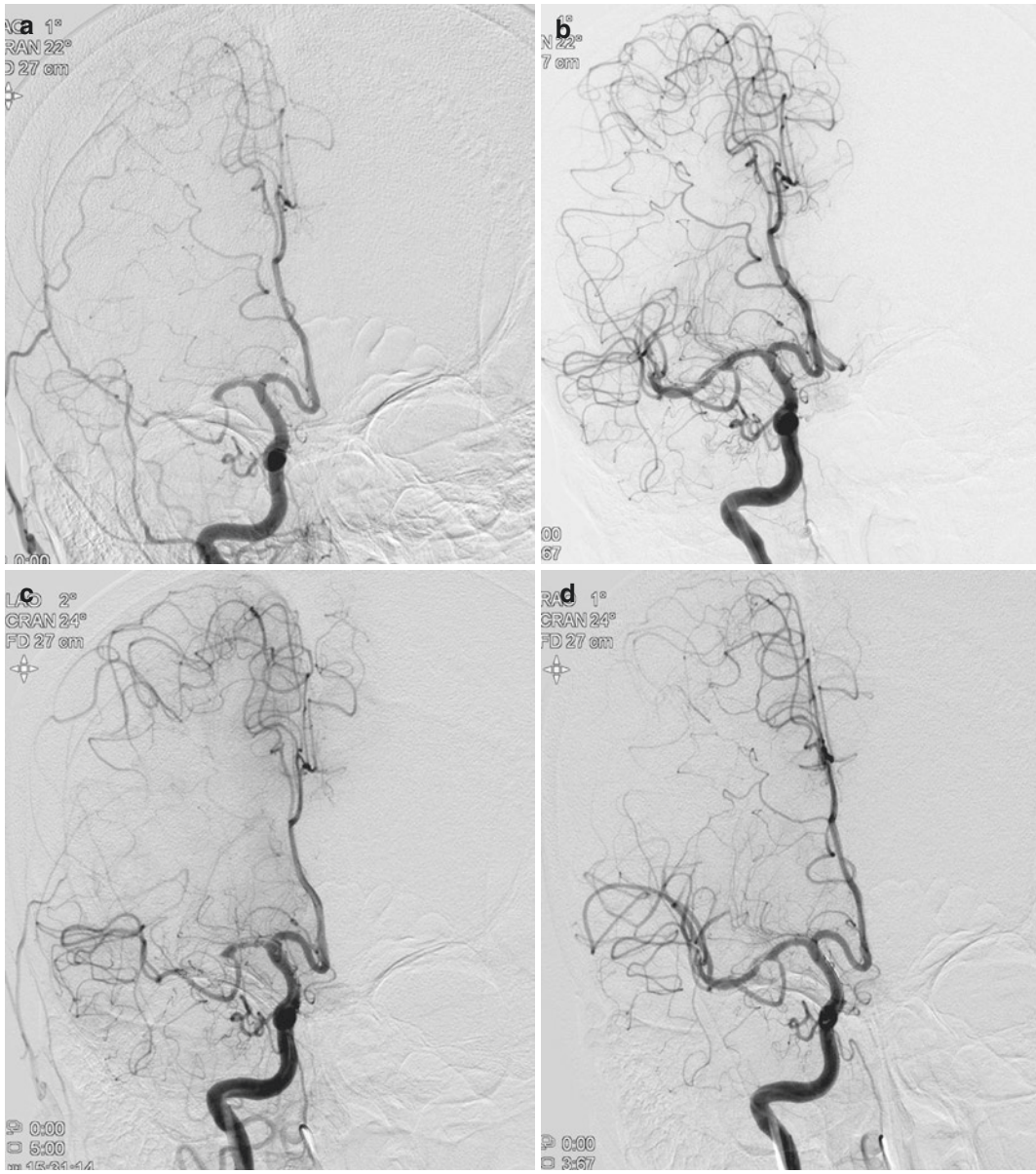


Fig. 12.5 A 45-year-old man presenting with NIHSS score of 14. (**a**) Initial angiogram showing occlusion of the right middle cerebral artery M1 segment just distal to the takeoff of the anterior temporal artery. (**b**) Angiogram immediately after one pass of the stentriever showing recanalization yet a slowed flow. (**c**) A 5-min delayed angiogram after multiple stentriever passes followed by repeated reocclusion showing reocclusion. (**d**) A 20-min delayed angiogram with stentriever in place showing persistent recanalization. The stentriever is detached. (**e**) A 3-month follow-up angiogram showing that the right middle cerebral artery is patent. (**f**) Unsubtracted angiogram revealing improvement of stenosis. *Arrow* indicates the distal markers of the implanted stentriever

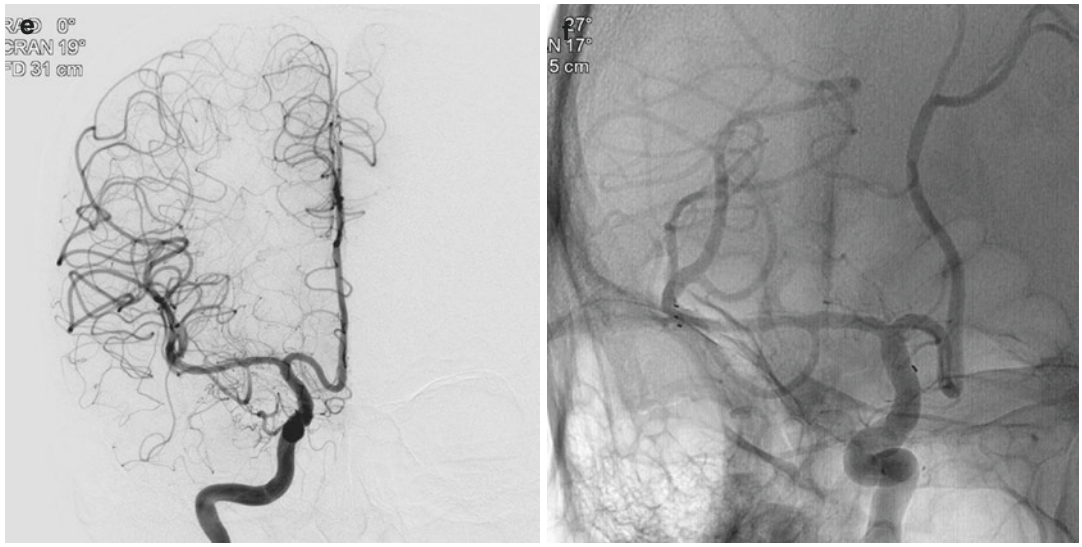


Fig. 12.5 (continued)

mortality rates between the patient groups (symptomatic hemorrhage and mortality, 11.8 and 23.9% in stented group versus 14.3 and 39.4% in non-stented group) [14]. While the major concern with permanent stenting is that it requires antiplatelet medication, thereby increasing the risk of intracranial hemorrhage in an acute stroke setting, the results of previous studies suggest that the benefit of recanalization's success by permanent stenting outweighs this drawback in patients with a stentriever-failed ILAO that is otherwise left non-recanalized [8, 10, 15–21].

Intracranial artery dissection (IAD) can cause an acute ILAO, which typically appears as a truncal-type occlusion or severe degree of stenosis with or without a tandem distal occlusion [22]. A stentriever thrombectomy is not only ineffective but also dangerous in the case of an acute IAD. In an angiogram obtained during intra-arterial treatment, an acute IAD appears as a truncal-type occlusion or severe degree of stenosis, plus intimal flap/pseudolumen with contrast material stagnation, and an intramural hematoma on a flat panel angiographic CT (Fig. 12.7). If an IAD is suspected as the cause of an acute ILAO, permanent stenting would seem to be the safest and most effective course of treatment (Fig. 12.7) [19, 22].

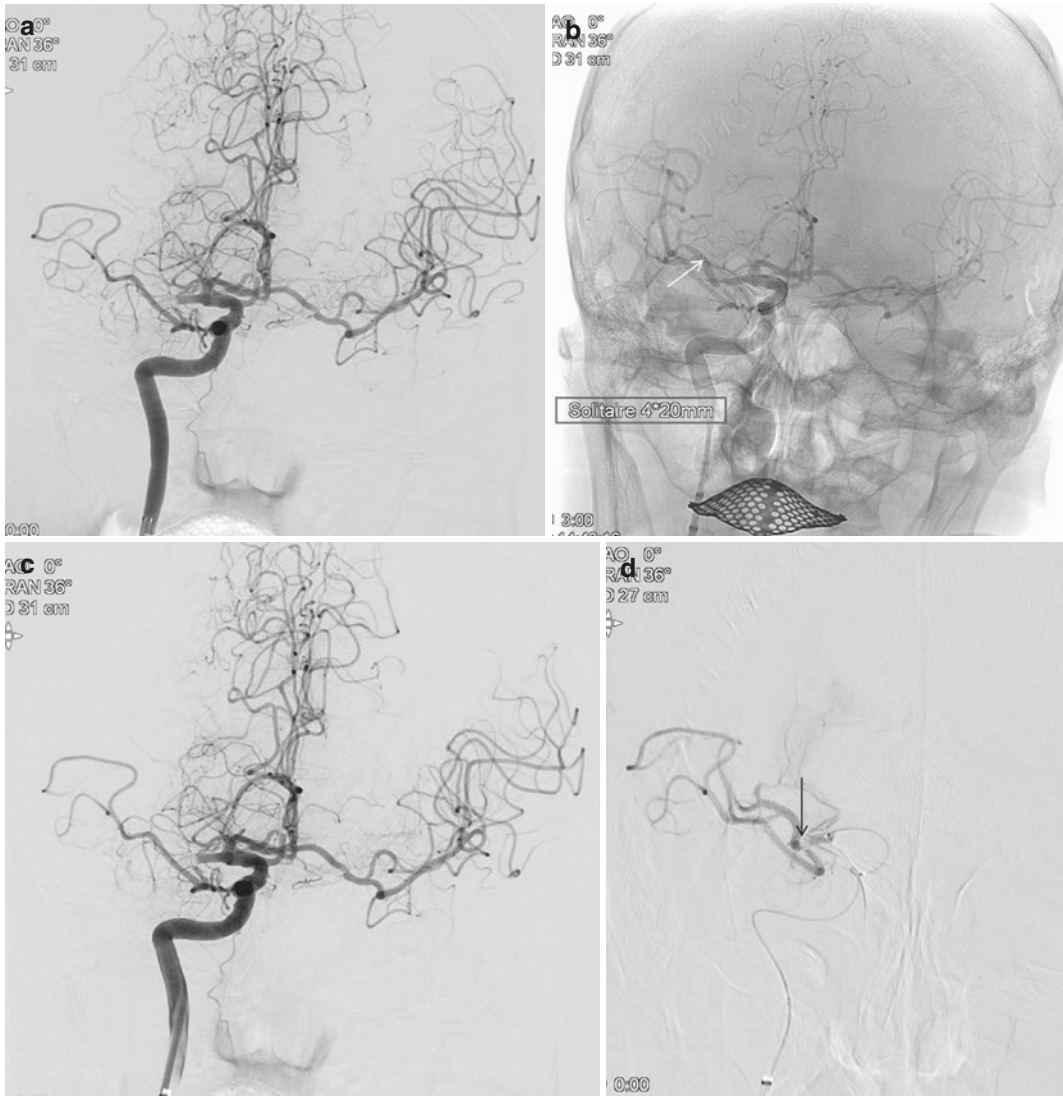
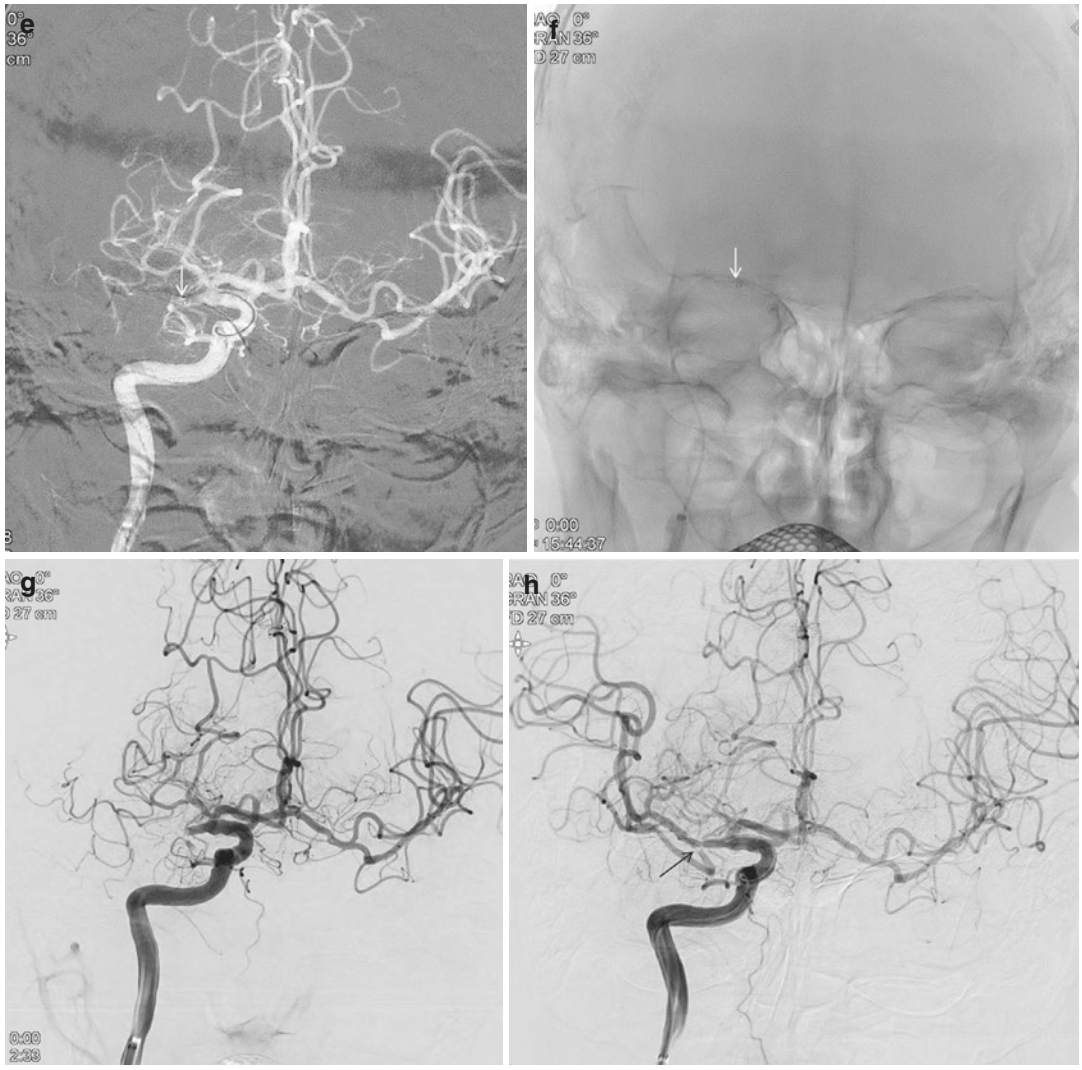


Fig. 12.6 A 76-year-old man presenting with NIHSS score of 19. (**a**) Right carotid angiogram showing right middle cerebral artery M1 occlusion. The left middle cerebral artery is visualized via an anterior communicating artery due to a proximal left carotid artery occlusion. (**b**) Unsubtracted angiogram after stentriever deployment revealing a clot (contrast material filling defect) at the right middle cerebral artery bifurcation. (**c**) In spite of multiple passes of the stentriever, the clot retrieval failed: angiogram showing persistent occlusion at the same location. (**d**) Microcatheter angiogram disclosing a clot lodging at the bifurcation. (**e**) A Penumbra (*arrow*) is advanced to the clot via a road map. (**f**) Spot image during an aspiration thrombectomy using a Penumbra (*arrow*). (**g**) Angiogram after multiple failures of an aspiration thrombectomy showing an occlusion at the same location. (**h**) A 20-min delayed angiogram with stentriever in place showing persistent recanalization; therefore, the stentriever is detached. *Arrow* indicates a small clot jailed by the deployed stentriever



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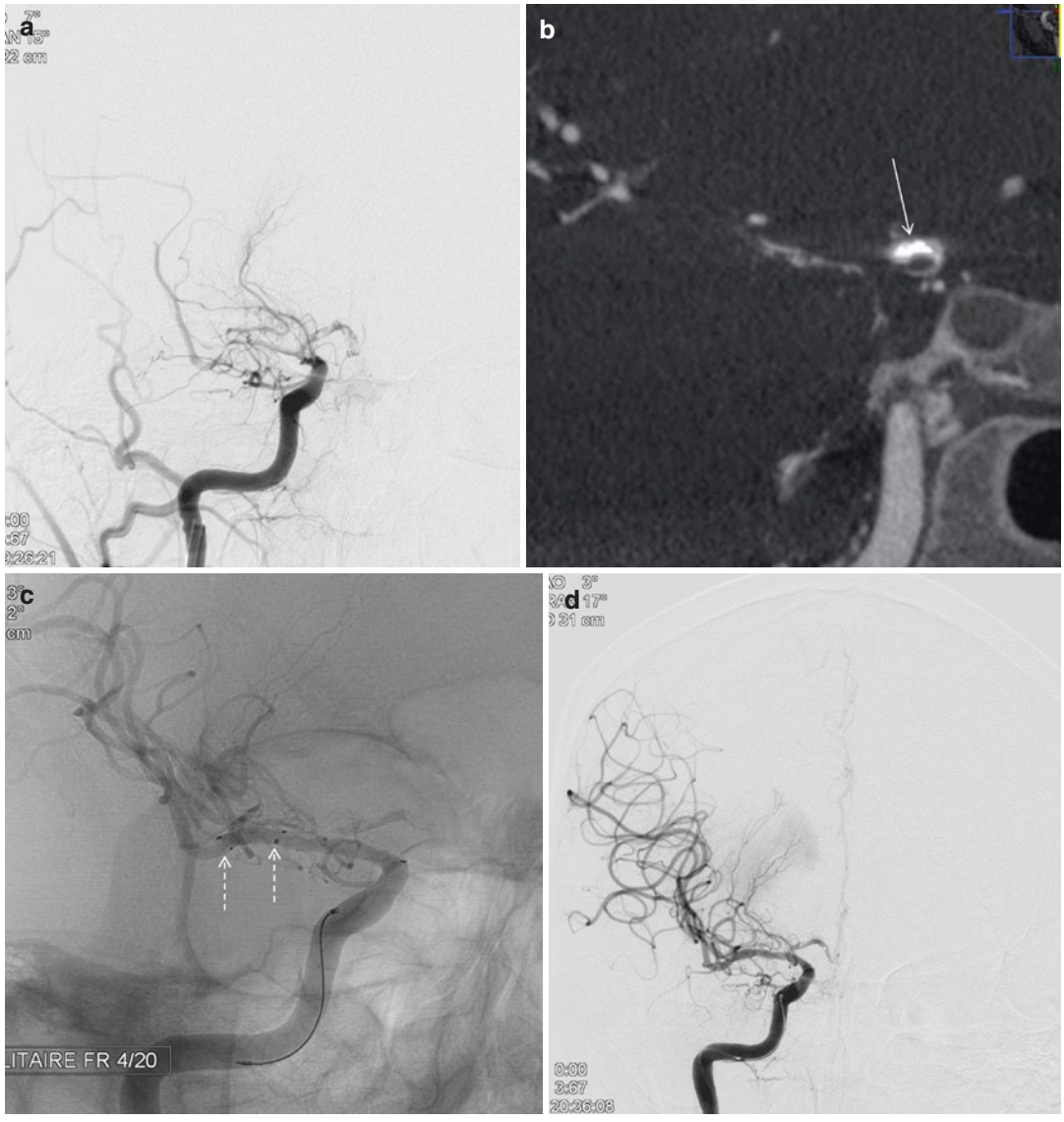

Fig. 12.7 A 20-year-old man presenting with NIHSS score of eight. (**a**) Right carotid angiogram showing occlusion of the right middle cerebral artery. (**b**) Flat panel angiographic CT revealing double lumen sign with contrast material stagnation in the pseudolumen (*arrow*). (**c**) Unsubtracted angiogram after implantation of two Solitaire stentrievers in the telescopic manner showing complete recanalization of the right middle cerebral artery. *Dotted arrows* indicate distal markers of two detached Solitaire stentrievers. (**d**) Control angiogram after two Solitaire stentrievers revealing complete recanalization of the right middle cerebral artery. The right anterior cerebral artery is supplied via the anterior communicating artery from the left side (not shown). (**e**) The 3-month follow-up angiogram showing that the stented right cerebral artery is patent. (**f**) Unsubtracted angiogram revealing the distal markers of the previously detached two Solitaire stentrievers

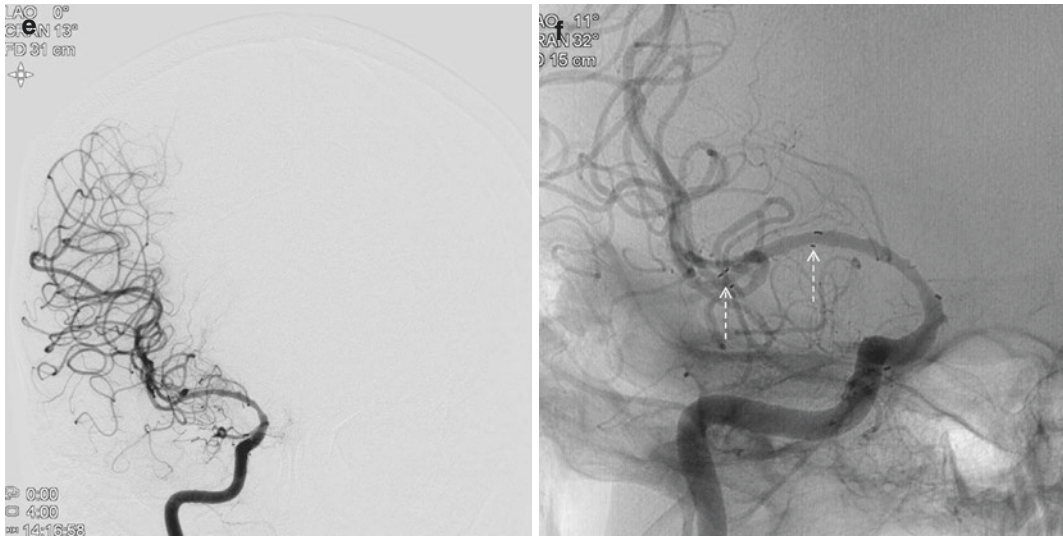

Fig. 12.7 (continued)

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Part 4

Surgical Practices

Surgical Embolectomy for Acute Ischemic Stroke

13

Jaechan Park

This chapter focuses on the role of a surgical embolectomy in the multidisciplinary management of an acute ischemic stroke, especially in cases of occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA). When endovascular recanalization therapy fails, a surgical embolectomy may be an efficient rescue treatment if the patient is still within the therapeutic time window for restoring the cerebral blood flow. This surgical option is based on the author's clinical experience. A minimally invasive and rapid surgical embolectomy (MIRSE) using a superciliary or supraorbital keyhole approach is a direct and straightforward approach that provides rapid access to the circle of Willis and the occluded vascular lesion. Advancements in surgical techniques to reduce the operative time, effective recanalization of the occluded vessels, and positive surgical results are all presented.

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13.1 Background

13.1.1 Surgical Embolectomy Revisited

Since 1956, a variety of case reports and small case series have confirmed the effectiveness of a surgical embolectomy for treating an acute middle cerebral artery (MCA) occlusion [1–5]. Conventionally, a surgical embolectomy involves a pterional craniotomy, dissection of the sylvian fissure, a longitudinal incision of the occluded MCA, removal of the embolus via an arteriotomy, and microsuturing to close the arteriotomy.

However, the extended operative time of a surgical embolectomy precludes its use for acute stroke management that has a relatively short therapeutic time window for restoring the cerebral blood flow. Consequently, intravenous (IV) thrombolysis and endovascular recanalization are currently the standard therapies for acute stroke management [6–22].

Following an acute ischemic stroke, the therapeutic time window for restoring the cerebral blood flow differs according to the treatment modality. In the case of intravenous and intra-arterial (IA) thrombolysis, the time window is restricted to 4.5 h and 6 h, respectively [10, 14, 17]; however, an IA mechanical thrombectomy has lengthened the time window to 8 h, according to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial in 2005 that evaluated the safety and efficacy of an endovascular device

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for restoring the patency of occluded intracranial vessels [21, 22]. Accordingly, the results of endovascular recanalization, along with the extended therapeutic time window and efficacy of recanalization, present a new opportunity for considering the role and efficacy of surgical recanalization. As a result, the present authors utilized the extended 8-h time window from an IA mechanical thrombectomy for performing a surgical embolectomy.

13.1.2 Results of Endovascular Recanalization Therapies

An IA mechanical thrombectomy using recent endovascular devices has achieved high recanalization rates in association with good neurological outcomes and becomes a standard therapy for acute occlusion of proximal intracranial arteries [18–22]. However, despite the application of recent endovascular treatments, including catheter-based devices, stent-based devices, and an IA recombinant tissue plasminogen activator (rt-PA), cases of failed endovascular recanalization still remain.

The Solitaire with the intention for thrombectomy (SWIFT) trial published in 2012 reported a 69% successful recanalization rate with a grade 2 or 3 thrombolysis in myocardial ischemia (TIMI) flow after using Solitaire [20]. This rate increased to 89% after rescue treatment using other endovascular devices and intra-arterial fibrinolysis.

Meanwhile, in the TREVO 2 trial, also published in 2012, that compared the efficacy and safety of a mechanical thrombectomy using a Trevo Retriever or a Merci Retriever, the Merci group achieved a 66% successful recanalization rate, which increased to 77% after rescue endovascular treatment, while the Trevo group achieved an 85% successful recanalization rate, which increased to 92% after rescue endovascular treatment [18]. Importantly, even following rescue treatment with all available neurovascular thrombectomy devices and IA rt-PA, the recanalization failure rate was still 11% and 8% in the SWIFT and TREVO 2 trial, respectively. Thus, surgical treatment can offer an important rescue solution in the case of endovascular failure when the time after stroke symptom onset is still within 8 h.

13.2 Interdisciplinary Management for Acute Ischemic Stroke

13.2.1 Overall Strategy

Maximizing the successful recanalization rate requires coordinated interdisciplinary management of all available tools, including the medical, endovascular, and surgical methods. At the author's institution, the departments of emergency medicine, cardiology, radiology, neurology, and neurosurgery are all connected with the national cardiocerebrovascular center.

For ischemic stroke patients, intravenous (IV) thrombolysis is initiated within 4.5 h after symptom onset. If the initial CTA or MRA shows a large proximal vessel occlusion, the patient is immediately moved to the angiography suite.

In the case of IV rt-PA failure or contraindication, an IA mechanical thrombectomy is attempted based on the following inclusion criteria: (1) the occlusion of a large proximal vessel, (2) the patient is within 8 h after stroke onset, and (3) a significant MRI diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) mismatch. If all of the available endovascular devices and IA rt-PA are unsuccessful, an immediate surgical rescue treatment is attempted. In the case of endovascular failure, some patients can still undergo a surgical embolectomy, as long as they are still within the therapeutic time window.

13.2.2 Indications of Surgical Embolectomy

A surgical embolectomy can be considered based on the following inclusion criteria. First, the therapeutic time window for surgical recanalization is up to 8 h after symptom onset [23, 24]. This is essentially the therapeutic time window for endovascular mechanical recanalization, as there has been no multicenter, randomized, prospective clinical trial for surgical embolectomies.

Notwithstanding, according to the criteria proposed by Dávalos et al. [25], patients with a clinical/DWI mismatch, defined as a DWI lesion volume less than 25 mL and National Institutes of Health Stroke Scale (NIHSS) score of 8 or greater, can have an extended therapeutic time window. While the DWI lesion may become enlarged, there is good leptomeningeal collateralization to extend the therapeutic time window.

Second, a significant DWI/PWI mismatch in the MRI is critical. Thus, after the failure of endovascular recanalization therapy, if immediate MR imaging is possible, a repeated DWI is recommended to exclude cases of rapid conversion to a matched DWI/PWI pattern.

Third, the occlusion is in the supraclinoid ICA, M1, or proximal M2 segment of the MCA or the A1 or proximal A2 segment of the ACA. Most commonly, the surgical target is an occlusion in the supraclinoid ICA and/or M1 segment including the MCA bifurcation area.

Fourth, an embolic occlusion is more suitable than an in situ thrombosis, where the former can be predicted based on the associated cardiac arrhythmia, angiographic findings, and the response of the clot to the endovascular procedures.

13.3 Presurgical Steps

13.3.1 Presurgical Procedures

The presurgical steps are all performed as rapidly as possible, including a repeated DWI, the acquisition of informed consent, transport to the operating room, and the induction of general anesthesia. Furthermore, since a surgical embolectomy does not require a central venous line, the presurgical steps from the declaration of endovascular failure to the skin incision can take less than 1 h.

The major limitation of this surgical strategy is the time required for patient preparation and transport to the operating room; however, this can be effectively shortened with the use of a hybrid neurovascular facility combining an angiography suite and operating room. [26–28].

13.3.2 Surgical Informed Consent

Obtaining surgical informed consent necessitates appropriate information being given to the patient's family by the physicians involved in the surgical procedure, including the patient's condition, the prognosis without recanalization, and the attendant risks and benefits of a surgical embolectomy as the recommended treatment.

For the purpose of comparison, where the outcomes for recanalized patients who undergo a surgical embolectomy can be considered as similar to the outcomes for revascularized patients who undergo endovascular mechanical recanalization therapy, the results of the Multi MERCI trial published in 2008 reported that 49%, 26%, and 25% of the revascularized patients who underwent endovascular mechanical recanalization therapy achieved mRS ≤2, 3–5, and 6, respectively, while 10%, 38%, and 52% of the non-revascularized patients achieved mRS ≤2, 3–5, and 6, respectively [21].

13.4 Surgical Techniques

13.4.1 Craniotomies

A pterional craniotomy or variant is commonly used for patients with an ICA and/or MCA occlusion, as it provides wide access to occlusion sites in the supraclinoid ICA, M1, M2, M3, and M4 segment of the MCA [1–5]. Notwithstanding, since most occlusions involve the ICA, M1 segment, or MCA division, smaller craniotomies are invariably adequate to access the lesions [23, 24].

The options for a minimally invasive surgical technique include a pterional mini-craniotomy and supraorbital mini-craniotomy, and the surgeon needs to choose the most appropriate to reduce the operative time.

13.4.2 Embolectomy

The dural incision is performed using an operating microscope, and the carotid cistern is then opened to achieve brain relaxation and frontal lobe retraction. Proximal opening of the sylvian fissure per-

mits visualization up to the carotid bifurcation without temporal lobe traction, and further dissection of the distal sylvian fissure exposes the M1 and proximal M2 segments of the MCA.

Normally, the occluded segment of the vessel due to an intravascular blood clot appears bluish, firm, and expanded (Fig. 13.1); however, occasionally, the occluded vessel can appear white with no expansion in a case of a small, white-colored embolus that is mainly composed of platelets.

A proximal temporary clip is applied to the occlusion, and a longitudinal incision is then made in the superior wall of the occluded segment of the vessel that does not exhibit any atherosclerotic change. A 3-mm arteriotomy is usually enough to remove the intravascular blood clot and also easy to repair. According to the location and number of emboli, one to three arteriotomies are normally sufficient.

A solid embolus is extracted via the arteriotomy using forceps, while a viscous clot proximal

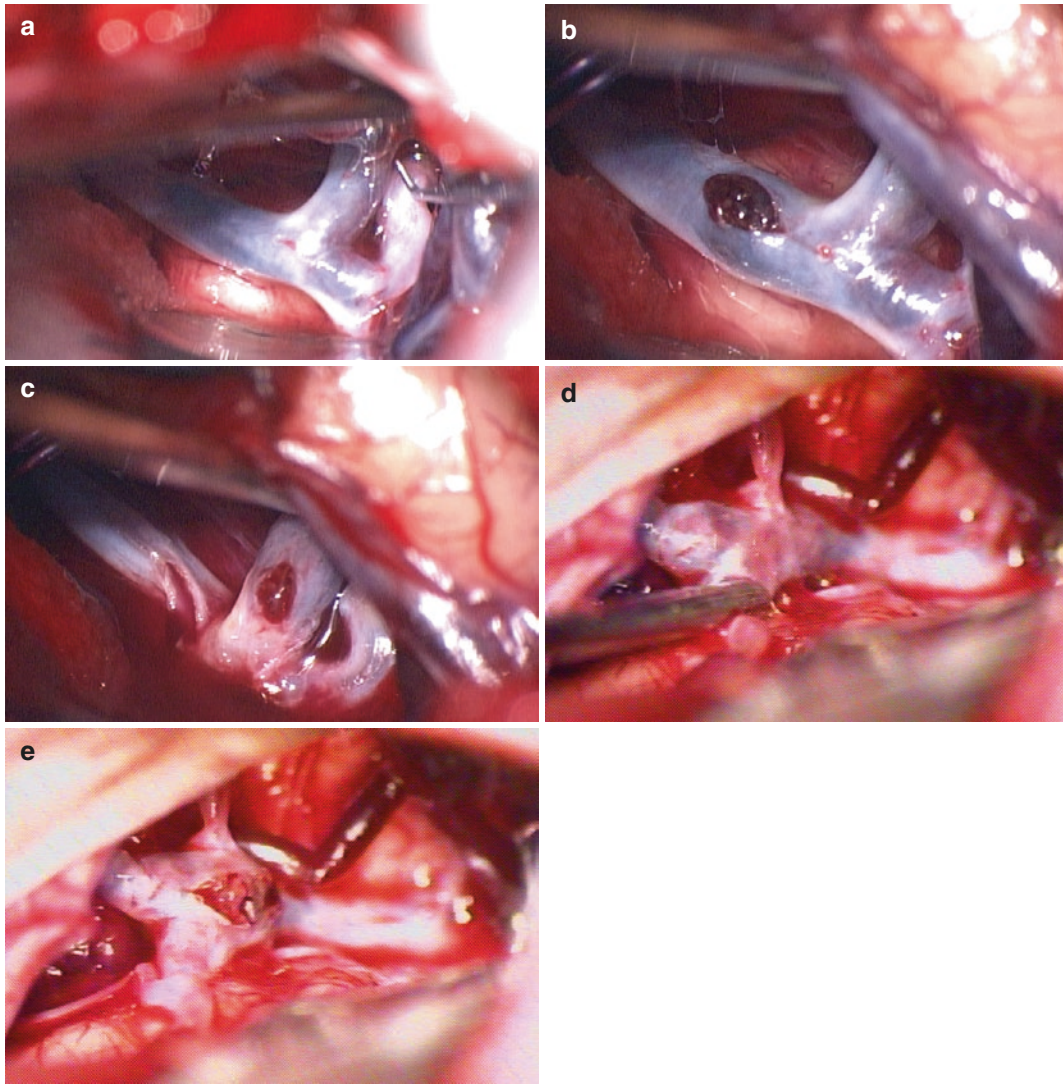


Fig. 13.1 Intraoperative photographs showing embolic occlusion of the intracranial arteries. In Case 1, the occluded segment of the MCA is bluish and firm (**a**–**c**), whereas in Case 2, the occluded segment of the ICA (**d**, **e**) is bluish, firm, and expanded

to a solid embolus can be removed in several ways, including opening the proximal temporary clip to allow an antegrade flow, suction through the arteriotomy, or sequential compression (squeezing) of the artery using forceps. After verifying the antegrade blood flow through a proximal artery, the retrograde blood flow needs to be ascertained. In the case of no retrograde flow, suction through the arteriotomy, sequential compression of the distal artery, and then another arteriotomy may be required.

13.4.3 Repair of Arteriotomy

The last step before reperfusion is repairing the arteriotomy, which can be performed using three surgical techniques. The first option is a conventional microsuture technique [1–5], which involves temporarily trapping the arteriotomy site and 8–0 monofilament sutures to close an arteriotomy in the ICA and 9–0 or 10–0 monofilament sutures to close an arteriotomy in the M1segment or a MCA division. This microsuturing technique requires the most time. For the second option, the arteriotomy is simply repaired using a curved or angled aneurysm clip [23, 24]. This is possible when the arteriotomy is <3 mm (Fig. 13.2a). The clip is applied tangential to the arteriotomy, thereby replacing the microsutures and reducing the operative time. While a standard aneurysm clip can be used to close an arteriotomy in the ICA, a miniclip can be used for an arteriotomy in the MCA. Finally, the third option is applicable when the arteriotomy is >3 mm and cannot be repaired using a tangential clip. This special technique allows immediate cerebral reperfusion as one or two aneurysm clips with curved blades are used as temporary compartmentalizing clips to encircle and separate the arteriotomy site (Fig. 13.2b, c). This creates a transient vascular conduit below the clip blades, allowing a cerebral

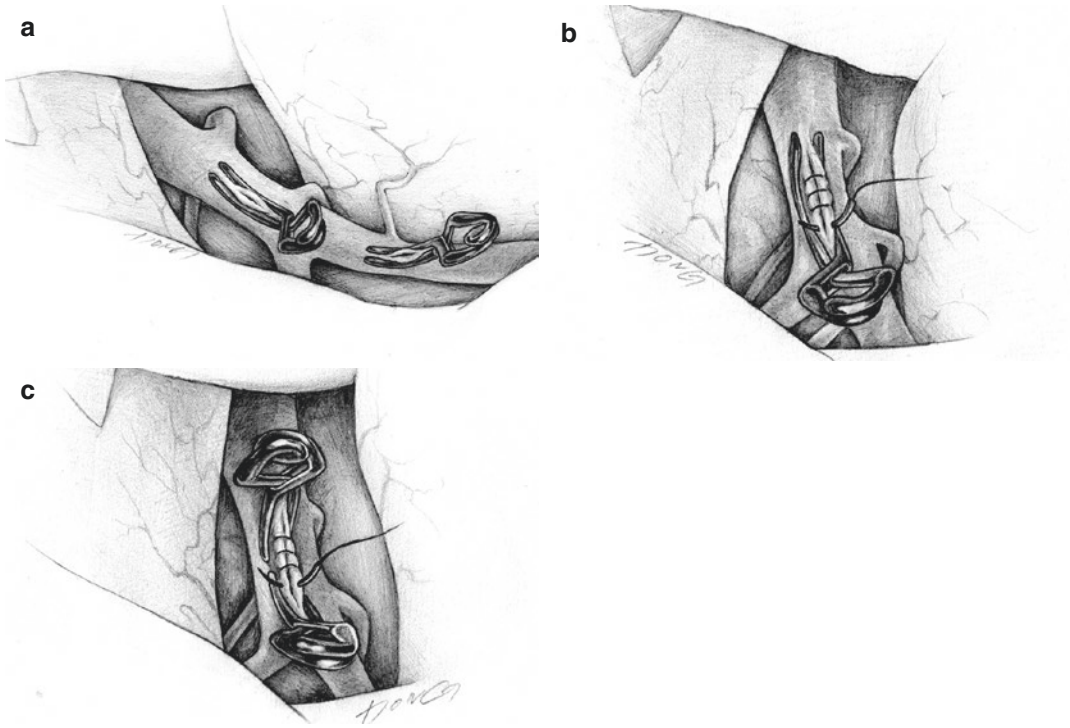


Fig. 13.2 Illustration of arteriotomy repair techniques for rapid reperfusion. (**a**) Tangential application of curved aneurysm clips for direct closure of arteriotomies of the ICA and M1 segment of the MCA. (**b**) Microvascular suture technique using a C-shaped compartmentalizing clip. (**c**) Microvascular suture technique using two curved aneurysm clips to compartmentalize an arteriotomy

blood flow during microsuturing. The clips are then removed after the repair is finished [29].

13.4.4 Minimally Invasive and Rapid Surgical Embolectomy (MIRSE)

The lengthy surgical procedures involved in a conventional surgical embolectomy are unsuitable for endovascular techniques in the case of an acute ischemic stroke [1–5]. In contrast, the recently developed MIRSE technique enables rapid surgical recanalization in a minimally invasive manner within a limited therapeutic time window [23, 24]. Reflecting the acute ischemic stroke management concept of "time is brain," MIRSE minimizes both the surgical invasiveness and the operative time for cerebral reperfusion.

Undoubtedly, the limitations of minimally invasive surgery with a small cranial opening include narrow viewing angles, reduced intraoperative light, reduced maneuverability of the microinstruments, and unidirectional application and coaxial control of the instruments. Yet, these limitations can be overcome using specialized surgical techniques and with surgical experience. Thus, the MIRSE technique consists of a superciliary keyhole approach, an arteriotomy for removing the embolus, and arteriotomy repair techniques for obtaining rapid reperfusion in the case of a small limited craniotomy.

A keyhole approach has several advantages, including rapid access to the lesion with a small operative wound, reduced wound-related pain, no intraoperative blood transfusion, minimal occurrence of postoperative epidural hematomas, an early return to work and normal life, and a decreased patient reluctance for surgery.

13.4.5 Superciliary Keyhole Approach

The MIRSE procedure begins with a superciliary keyhole approach, consisting of a 4-cm eyebrow incision starting from the midpupillary line and a supraorbital mini-craniotomy (Fig. 13.3) [23, 24]. This superciliary keyhole approach has already been used for tumorous and vascular lesions of the anterior cranial fossa and parasellar region [30–37]. While the surgical embolectomy procedures require a 4-cm or 4.5-cm eyebrow incision, unruptured aneurysms can be clipped using just a 3.5-cm eyebrow incision.

Despite the small superciliary skin incision, a relatively large craniotomy is created by cutting and splaying the underlying muscles. A high-speed drill with a footplate attachment is then used to drill a frontobasal lateral burrhole and create a supraorbital bone flap with a diameter of >2 cm. Before drilling, unidirectional skin retraction using a retractor held by an assistant can avoid skin damage and create sufficient space for the craniotomy. Six retraction sutures are positioned at the edge of the skin incision. The inner edge of the craniotomy above the orbital rim is drilled and beveled, while the frontal floor prominences are flattened. Plus, to expose the sylvian fissure area, the sphenoid ridge adjacent to the frontobasal lateral burrhole is slightly drilled.

13.4.6 Intradural Procedures

Following the dural incision, an operating microscope is used to slide a narrow brain spatula over the base of the frontal lobe toward the carotid and optic nerve cisterns, which are then opened to drain the cerebrospinal fluid, achieve brain relaxation, and obtain an intracranial working space. To expose the supraclinoid ICA, dissecting the proximal sylvian fissure provides more frontal lobe retraction and visualization up to the carotid bifurcation. Additional dissection of the sylvian fissure exposes the M1 segment, MCA bifurcation at the MCA genu, and proximal M2 segment. As the sylvian dissection is performed along the frontal side of the sylvian veins, the division of some small fronto-sylvian veins is inevitable.

The identification of the occluded vessel segment, arteriotomy, intravascular blood clot removal, and verification of the antegrade and retrograde blood flow by opening the temporary clips proximal and distal to the arteriotomy are all

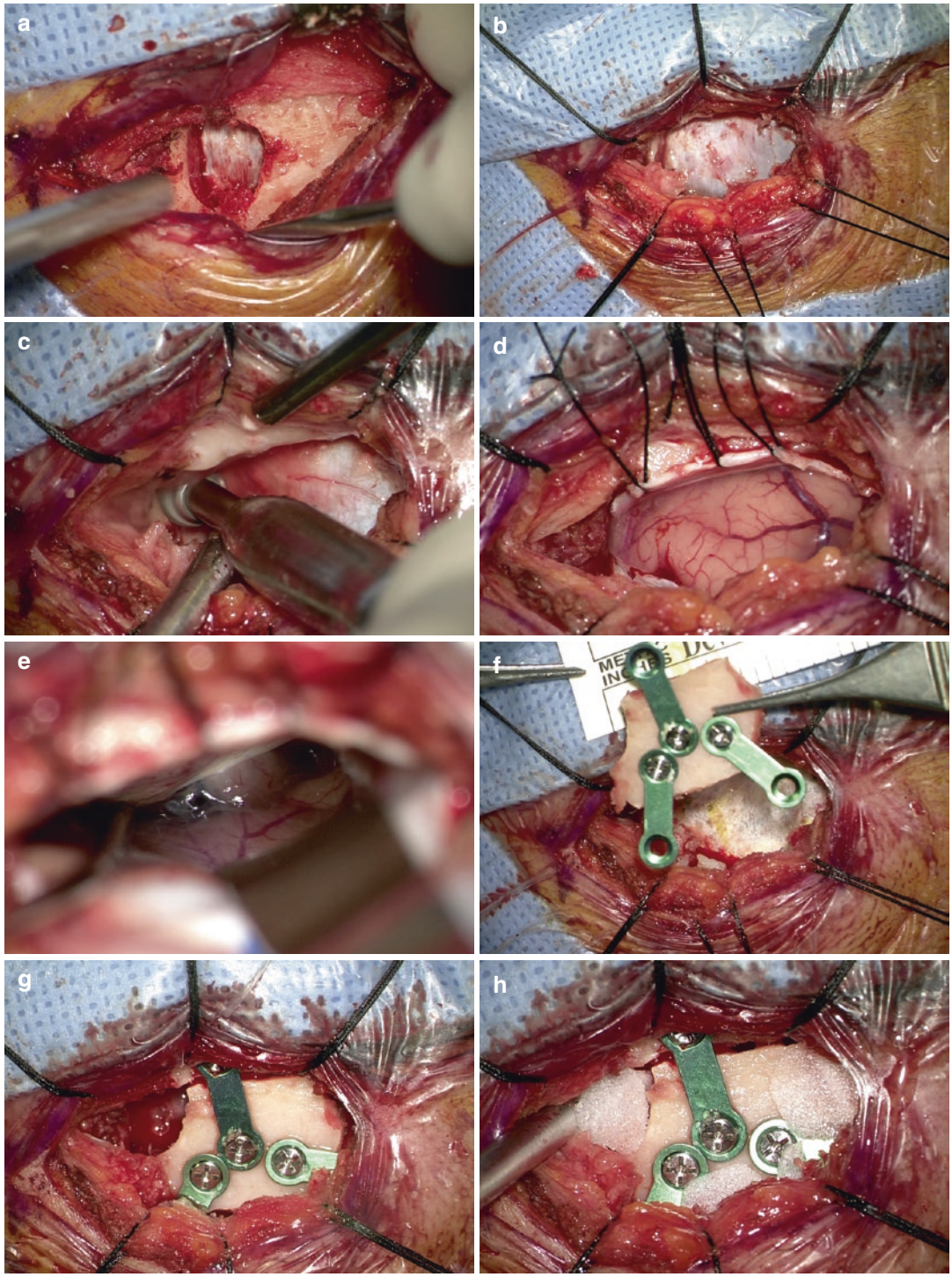
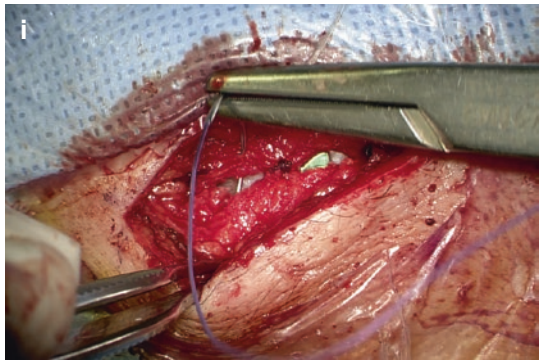


Fig. 13.3 Operative photographs showing the procedures of a superciliary keyhole approach. (**a**) Drilling of key burrhole. (**b**) Six stay sutures with mosquito clamps after creating a bone flap. (**c**) Lateral extension of craniotomy by drilling the sphenoid ridge. (**d**) C-shaped dural incision. (**e**) Opening an optic nerve cistern through a small cranial opening. (**f**) Small bone flap with attached plates. (**g**) Bone flap in place. (**h**) Key burrhole and bone gaps covered with porous high-density polyethylene implants. (**i**) Pericranial sutures. (**j**) Muscular sutures



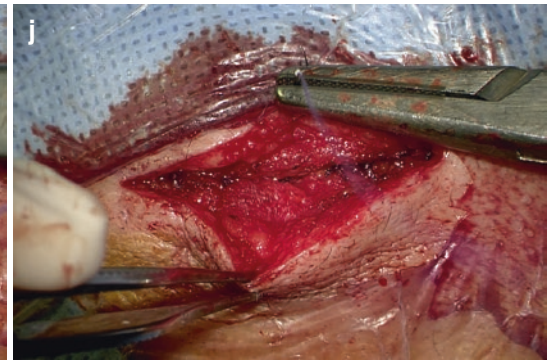


Fig. 13.3 (continued)

performed as described above. All these tasks can be effectively performed via a keyhole approach.

Repairing the arteriotomy is the last step before cerebral reperfusion. Among the three abovementioned techniques for repairing the arteriotomy, microsuturing is the most challenging via a keyhole approach. While passing a needle through the vascular wall in a running manner is feasible using a right-hand needleholder, tying a knot, which involves four separate actions (picking up the thread with the left-hand forceps, making a loop around the tip of the right-hand forceps, picking up the short end of the thread with the right-hand forceps, and pulling the loop off the right-hand forceps), can be difficult when using microinstruments with coaxial movement through a small cranial opening.

Therefore, a new clip-knotting technique is used for tying a knot after microsuturing via a keyhole approach (Fig. 13.4) [38]. With the needleholder in the right hand, the needle and a short (5 cm) thread are passed through the vessel wall several times in a running manner along the arterial incision. After tightening the running stitch to approximate the edges of the lesion, the ends of the thread are both held with forceps using the left hand. To hold both threads in place, an aneurysm clip is then applied using a right-hand clip applier, and any remaining thread beyond the clip is cut appropriately.

If the arterial incision is <3 mm, the simplest way to repair the arteriotomy is the tangential application of a curved or angled aneurysm clip [23, 24].

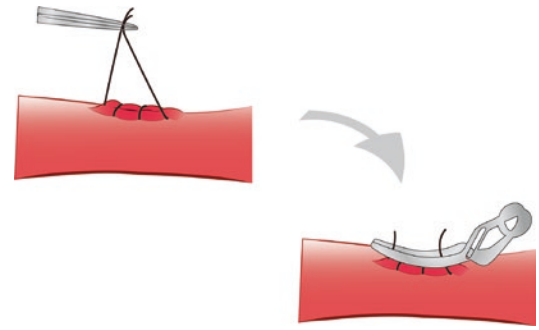


Fig. 13.4 Clip-knotting technique for repairing an artery via a keyhole approach. After pulling the running stitch tight to approximate the edges of the arteriotomy, both threads are held in place using an aneurysm clip

13.5 Postoperative Course

13.5.1 Surgical Results

Our clinical experience has shown that a MIRSE procedure is effective for recanalizing an occluded ICA and MCA in patients with an acute ischemic stroke, as the high recanalization rate and short operative time can provide a final rescue treatment following the failure of endovascular recanalization.

Table 13.1 presents the characteristics of the patients who underwent a MIRSE for an acute occlusion of the MCA and ICA (n = 2), MCA (n = 4), and ICA (n = 4). Reperfusion with the MIRSE was accomplished within 3.0–8.5 h after symptom onset. Complete recanalization was achieved in all ten patients.

At 3 months, nine of the recanalized patients showed mRS grades of 0 (n = 1), 1 (n = 5), 2

Table 13.1 Summary of patients who underwent a MIRSE after the failure of endovascular recanalization for acute ischemic stroke

Case no.	1	2	3	4	5	6	7	8	9	10
Age (year)/sex	50/M	42/F	68/M	28/M	56/M	50/F	69/F	78/F	39/F	71/F
Occluded vessel	Rt MCA	Lt MCA	Lt ICA/ MCA	Rt ICA/ MCA	Lt ICA	Rt MCA	Rt ICA	Rt ICA	Rt ICA	Lt MCA
Cause of stroke	Cardiogenic	Cardiogenic	Cardiogenic	Carotid dissection	Ruptured aneurysm coiling	ICA web	Cardiogenic	Cardiogenic	Cardiogenic	Cardiogenic
Initial NIHSS after stroke	11	15	16	12	15	13	19	18	11	15
Time interval (h)										
Symptom to endovascular failure	4.5	6.0	6.0	5.5	1.2	3.5	3.2	6.0	3.0	4.0
Skin incision to reperfusion	1.0	1.5	1.5	1.0	0.9	0.7	0.7	0.8	0.8	0.8
Symptom onset to reperfusion	7.0	8.5	8.5	7.5	3.0	5.2	4.7	7.6	4.5	6.0
Arteriotomy repair	Aneurysm clip	9–0 sutures, clip	9–0 sutures, clip	Aneurysm clip	8–0 sutures	Aneurysm clip	Aneurysm clip	8–0 sutures	8–0 sutures	9–0 sutures
Postop TICI	3	3	3	2	3	3	3	3	3	3
NIHSS, 7 days	3	6	Dead	8	6	6	8	12	8	4
mRS, 3 months	0	1	Dead	3	1	1	2	3	1	1

ICA internal carotid artery, *MCA* middle cerebral artery, *mRS* modified Rankin scale, *NIHSS* National Institute of Health Stroke Scale, *TICI* thrombolysis in cerebral infarction

($n = 1$), and 3 ($n = 2$). One patient (Patient No. 3) developed a fatal hemorrhage in the basal ganglia several hours after recanalization.

13.5.2 Subdural Fluid Collection

Surgical dissection of the basal cisterns and sylvian fissure, as performed during aneurysm surgery and a surgical embolectomy, is sometimes followed by the postoperative occurrence of a subdural hygroma and resultant chronic subdural hematoma (CSDH).

The sequence behind the occurrence of a subdural hygroma is most probably as follows: after surgical dissection of the arachnoid membrane, a one-way valve is formed due to adhesion of the arachnoid during the healing process, and CSF is then accumulated in the subdural space via this one-way valve [39, 40]. Meanwhile, tearing of the stretched bridging veins and bleeding from the neomembrane of a CSDH may also contribute to development and enlargement of a CSDH.

Although the exact incidence and risk factors of a subdural hygroma and CSDH following a surgical embolectomy are not known, they can be estimated based on previous studies of unruptured intracranial aneurysms, where an advanced age and male gender were identified as risk factors for a CSDH following unruptured aneurysm surgery [41–45].

13.5.3 Intracranial Hemorrhage

In the MERCI and Multi MERCI trials, 7.8% and 9.8% of the patients who underwent endovascular mechanical recanalization therapy developed symptomatic intracranial hemorrhages, subarachnoid or intraparenchymal, respectively [21, 22].

An intracranial hemorrhage can also occur after a surgical embolectomy and recanalization. One of our ten MIRSE patients (Case No. 3) developed a fatal intracerebral hemorrhage in the basal ganglia following successful recanalization [23].

13.5.4 Frontalis Muscle Palsy

The risk of frontalis muscle palsy due to an injury of the frontal branch of the facial nerve can also be a concern with a superciliary keyhole approach. However, none of the MIRSE patients developed permanent palsy of the frontalis muscle, plus our previous case series of unruptured aneurysms had a negligible incidence (<1%) of permanent palsy of the frontalis muscle, although transient severe palsy occurred in approximately 20% of the patients [46].

13.6 Case Illustrations

13.6.1 Case No. 6

A 50-year-old woman presented with left hemiplegia for 1 h. As no intracranial hemorrhage was revealed on a CT scan, intravenous rt-PA was administered immediately. Diffusion-weighted imaging showed faint hyperintensities in the right temporal lobe and paraventricular region, while the perfusion defect on the time-to-peak (TTP) maps involved the entire right MCA territory. Carotid angiograms showed a distal occlusion of the right M_1 segment of the MCA (Fig. 13.5a) and a linear filling defect corresponding to a carotid web at the right internal carotid origin (Fig. 13.5b). While endovascular recanalization therapy was successful in an inferior division of the right MCA, a Penumbra reperfusion catheter and Solitaire AB stent were both unsuccessful in recanalizing the superior division of the MCA (Fig. 13.5c).

Following the endovascular failure, the MIRSE presurgical steps took 1 h, including a repeated DWI, informed consent from the patient's family, transport to the operating room, and the induction of general anesthesia. A supraorbital minicraniotomy revealed an embolic occlusion in the superior division of the MCA, which appeared as a bluish expanded segment (Fig. 13.5d–e). A small 3-mm arteriotomy in the occluded segment allowed the embolus to be removed, and an aneurysm miniclip with a curved blade was used to repair the arteriotomy (Fig. 13.5f–g).

Reperfusion was achieved 40 min after the skin incision and 5.2 h after symptom onset.

Postoperative day 1 showed a significant improvement in the patient's hemiplegia (grade 3.5), and an angiogram confirmed complete restoration of flow in the occluded MCA (Fig. 13.5h). At 3 months, the only sequel was a slight weakness of the left hand, while the cosmetic results of the operative wound were excellent. At 1 year, the patient underwent surgical resection of the carotid web (Fig. 13.5i–l), allowing a change from anticoagulant to antiplatelet medication.

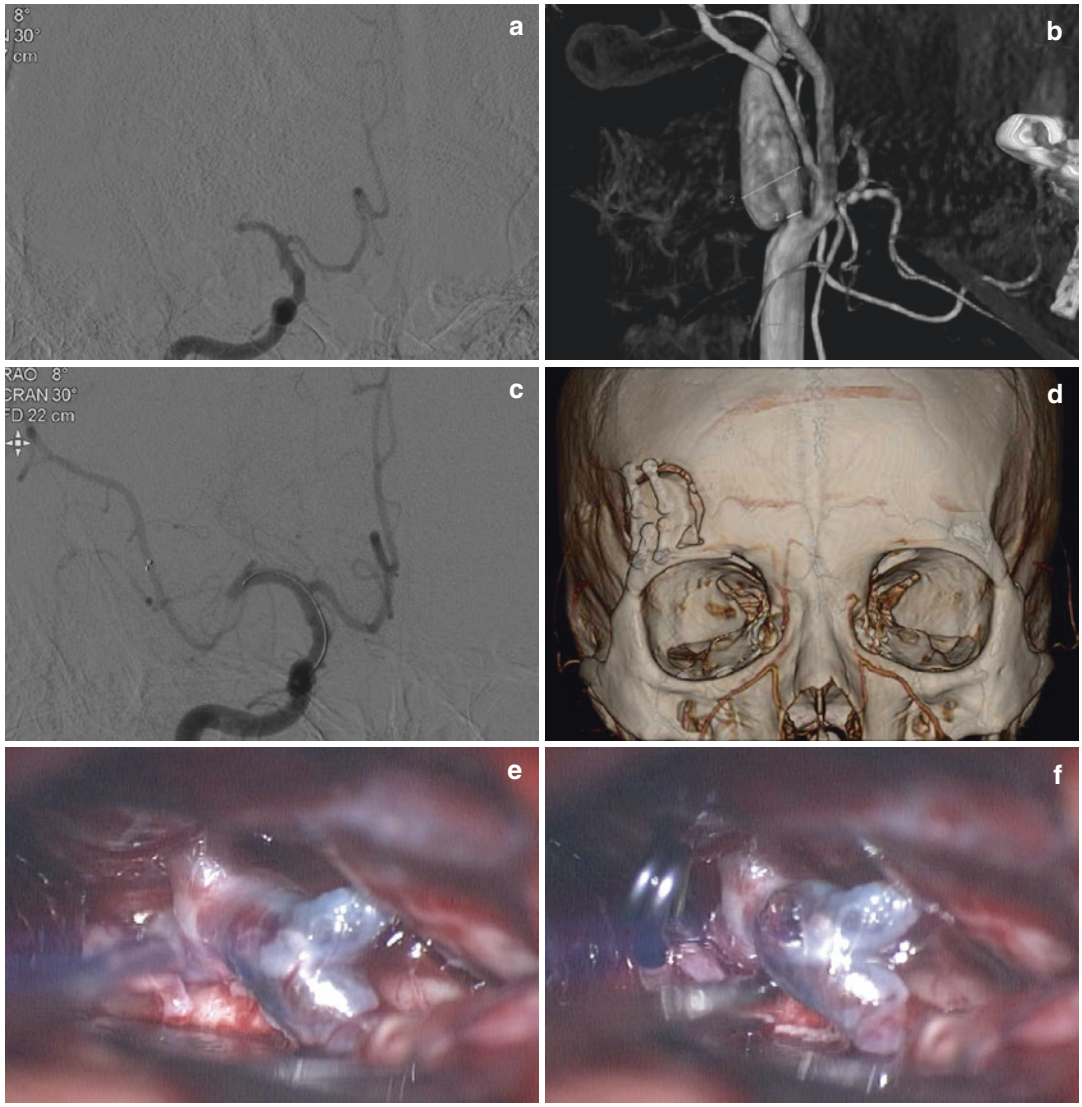


Fig. 13.5 Illustrative Case 6. (**a**) Initial carotid angiogram revealing an occlusion of the distal M1 segment of the right MCA. (**b**) Carotid angiogram demonstrating a carotid web at the right internal carotid origin. (**c**) Carotid angiogram demonstrating an occlusion of the superior division of the MCA following endovascular recanalization procedures. (**d**) Postoperative CT showing supraorbital mini-craniotomy. (**e**) Intraoperative photograph showing an embolic occlusion of the superior division of the MCA, revealed as a bluish and expanded segment. (**f**) Intraoperative photograph showing the occluded vessel with arteriotomy. (**g**) Intraoperative photograph showing the recanalized MCA after repair of the arteriotomy using an aneurysm clip. (**h**) Postoperative carotid angiogram showing complete restoration of flow in the occluded MCA. (**i–l**) Intraoperative photographs showing surgery resecting the carotid web

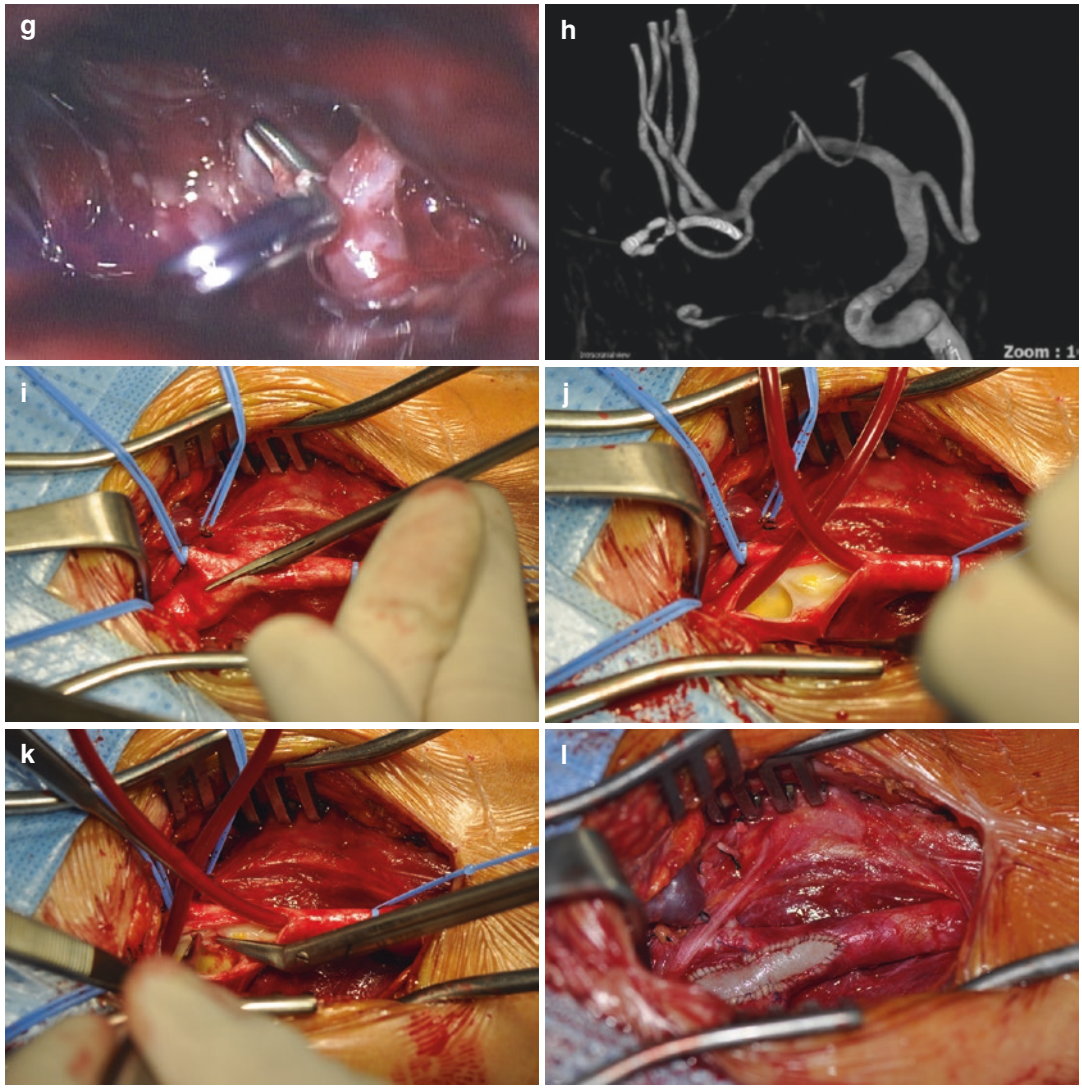


Fig. 13.5 (continued)

13.6.2 Case No. 8

A 78-year-old woman presented to the emergency department 4 h after the onset of left hemiplegia and with a National Institutes of Health Stroke Scale (NIHSS) score of 18. Diffusion-weighted imaging revealed a diffuse hyperintensity in the right paraventricular area (Fig. 13.6a), while the perfusion defect in the time-to-peak maps involved the entire right MCA territory. Carotid angiography revealed an embolic occlusion of the right ICA (Fig. 13.6b). Endovascular recanalization was attempted using a Solitaire AB stent (ev3, Irvine, California, USA), yet during the retrieval, the stent with the embolus became accidentally detached at the level of the supraclinoid ICA and carotid siphon.

After taking 1 h for the angiography and endovascular recanalization procedure, repeated DWI was used to check for any significant increase in the lesion size, and then the patient was immediately rushed to the operating room. Thus, it only took 50 min from the declaration of endovascular failure to the induction of general anesthesia in the operating room.

The supraorbital keyhole approach included a 4-cm eyebrow incision and supraorbital mini-craniotomy. After opening the carotid cistern and proximal sylvian fissure, the intracranial ICA was revealed as severely atherosclerotic and occluded with the Solitaire stent harboring the embolus (Fig. 13.6c). A 5-mm longitudinal incision was made in the superior wall of the ICA containing the distal end of the stent, and then the stent and the associated embolus were extracted using fine forceps (Fig. 13.6d–f). Next, a compartmentalizing clip with C-shaped blades was temporarily applied to the ICA encompassing the arteriotomy, which was then repaired using 8–0 monofilament polypropylene sutures through the small cranial opening

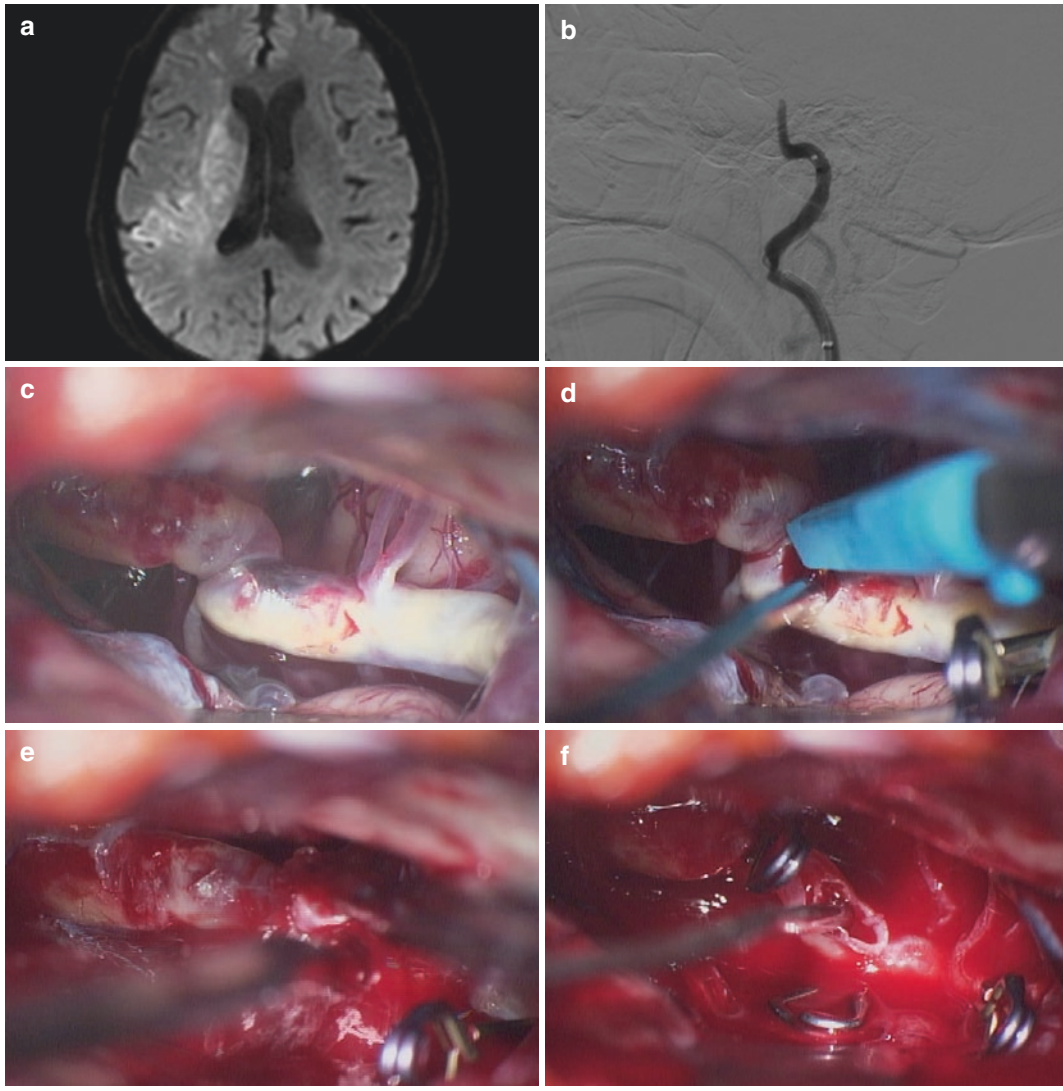


Fig. 13.6 Illustrative Case 8. (**a**) Initial DWI showing hyperintensity in the right paraventricular area. (**b**) Initial carotid angiogram revealing an occlusion of the right ICA. (**c**) Intraoperative photograph showing the supraclinoid ICA that was severely atherosclerotic. (**d–f**) Intraoperative photographs showing the removal of the accidently detached Solitaire stent through an arteriotomy in the ICA. (**g**) Intraoperative photograph showing the repair of the arteriotomy using microsutures after applying a compartmentalizing clip. (**h**) Sutured arteriotomy reinforced with a permanent aneurysm clip. (**i**) Postoperative carotid angiogram showing complete restoration of the blood flow

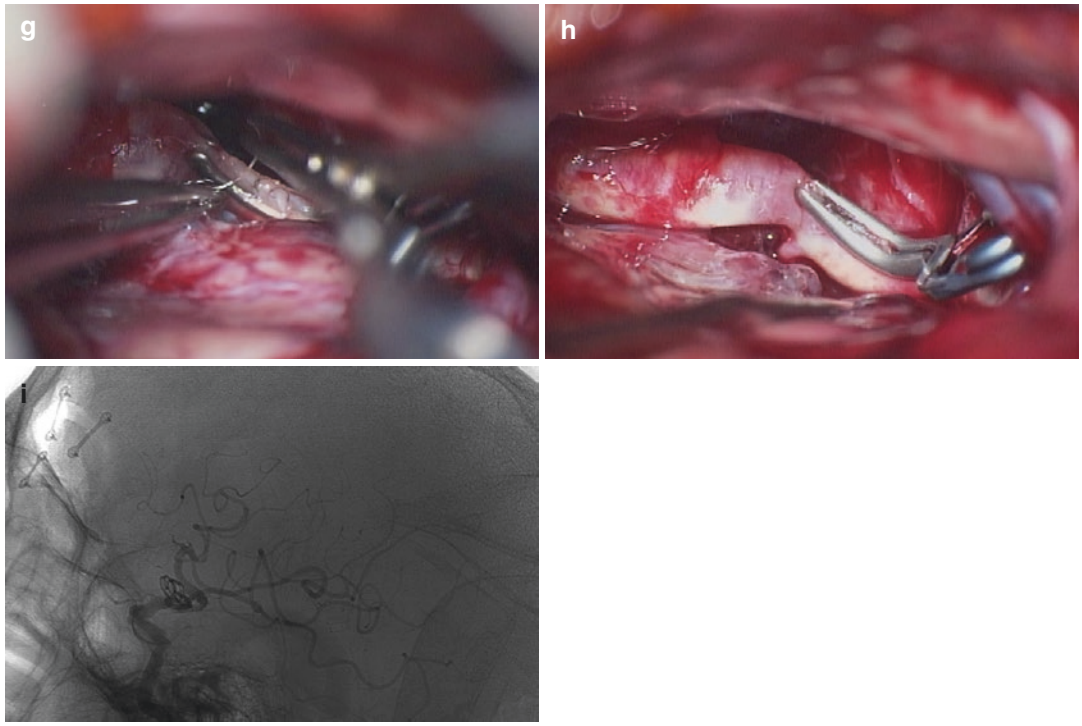


Fig. 13.6 (continued)

(Fig. 13.6g–h). Thus, the compartmentalizing clip allowed immediate blood flow during the final repair of the arteriotomy. Only 35 min elapsed from the skin incision to cerebral reperfusion via the vascular conduit below the clip, thereby valuing the concept of "time is brain."

Complete recanalization of the ICA was revealed by postoperative angiography (Fig. 13.6i), and the perfusion defect in the time-to-peak maps was normalized. At 3 months after surgery, the patient's neurological deficits had improved and her NIHSS score was 8.

13.6.3 Case No. 10

A 71-year-old woman presented with acute onset of right hemiplegia and aphasia. DWI revealed hyperintensities in the left putaminal area and paraventricular region (Fig. 13.7a), while the perfusion defect on the TTP maps involved the entire left MCA territory (Fig. 13.7b). Carotid angiograms showed an occlusion of the left M_1 segment of the MCA (Fig. 13.7c). Endovascular recanalization therapy was attempted using a Penumbra reperfusion catheter and Solitaire stent, yet without success.

A MIRSE was immediately performed and a superciliary keyhole approach revealed the left M1 segment. While there was no bluish and expanded segment suggesting an intravascular blood clot, a whitish segment without expansion was found (Fig. 13.7d). A white and hard embolus was then revealed via an arteriotomy of the whitish segment (Fig. 13.7e). The clip-knotting technique was used to repair the arteriotomy after removing the embolus. Reperfusion was achieved 50 min after the skin incision and 6 h after symptom onset.

Postoperative day 1 showed an improvement in the patient's hemiplegia to grade 3.5, and an angiogram confirmed complete restoration of flow in the occluded MCA (Fig. 13.7f). At 3 months, the only sequel was a slight clumsiness of the right hand.

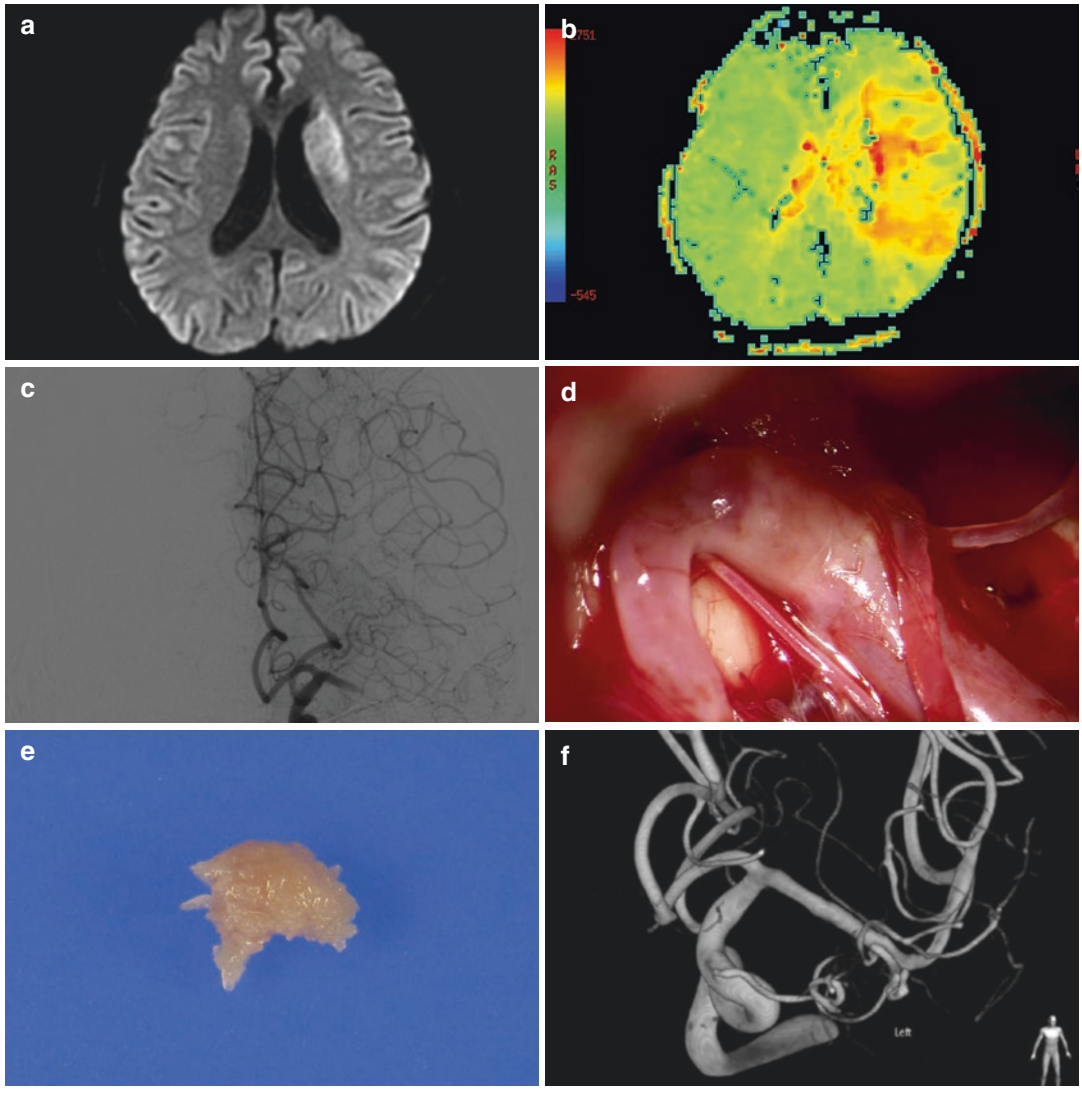


Fig. 13.7 Illustrative Case 10. (**a**) Initial DWI showing hyperintensity in the right putamen and paraventricular area. (**b**) Perfusion defect on the TTP maps involving the entire left MCA territory. (**c**) Carotid angiogram showing complete occlusion of the M1 segment of the left MCA. (**d**) Intraoperative photograph revealing a short white segment of the M1 segment. (**e**) Small, white, and hard embolus removed from the white segment of the MCA. (**f**) Postoperative carotid angiogram showing complete restoration of the blood flow

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Bypass Surgery

14

Jeong Eun Kim, Jin Pyeong Jeon, and Won-Sang Cho

Although the benefit of extracranial–intracranial arterial bypass (EC–IC bypass) surgery compared to medical treatment in preventing recurrent stroke in patients with symptomatic carotid occlusion or high stenosis of internal carotid artery or middle cerebral artery was failed, many studies have been performed to find appropriate candidates for EC–IC bypass surgery. Nevertheless, surgical efficacy has not been well demonstrated, although enrolled patients were at high risk of stroke due to the profound hemodynamic compromise. On the contrary, EC–IC bypass surgery has shown protective effect on preventing future stroke in patients with moyamoya disease (MMD), in particular adult MMD patients with cerebral ischemic symptoms. For MMD patients with hemorrhagic presentation, surgical benefit of bypass surgery is still controversial. In this chapter, we have reviewed the role of EC–IC bypass surgery in patients with atherosclerotic carotid stenosis or MMD. In addition, we have included detailed information about surgical techniques of EC–IC bypass surgery.

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14.1 Background

After the first introduction of superficial temporal artery–middle cerebral artery (STA–MCA) anastomosis for patients with carotid occlusive disease by Yasargil [1], some studies showed surgical efficacy of preventing recurrent stoke with low morbidity and mortality [2, 3]. However, surgical benefit of extracranial–intracranial arterial bypass (EC–IC bypass) surgery has not been documented in randomized controlled studies, although the patients were at high risk of stroke [4–6]. On the contrary, for patients with moyamoya disease (MMD), EC–IC bypass surgery has shown beneficial effect on preventing recurrent stroke [7]. Lee et al. [8] reported that recurrent stroke events were significantly decreased in the surgical group (n = 17, 16.5%) than the conservative treatment group (n = 6, 66.7%) in adult patients with ischemic presentation. Nevertheless, surgical efficacy for MMD patients with hemorrhage presentation remains controversial. In addition, heterogeneity of the enrolled patients (pediatric and adult), the degree of hemodynamic compromise (stable or unstable), and surgical techniques could lead to non-concordant results. In this chapter, we have reviewed the role of EC–IC bypass surgery in patients with atherosclerotic carotid stenosis or MMD, respectively.

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In addition, we have included detailed information about surgical techniques of EC–IC bypass surgery and a case illustration.

14.2 Carotid Occlusive Disease

The North American extracranial–intracranial arterial bypass (EC–IC bypass) study [4] evaluated surgical benefit compared to medical treatment in symptomatic carotid occlusion or high stenosis of internal carotid artery (ICA) or middle cerebral artery (MCA), in preventing future stroke. Indications for entry are as follows: (1) transient ischemic attack (TIA) or transient monocular blindness (TMB) within 3 months before entry, (2) at least 8 weeks after acute ischemic insults, (3) asymptomatic ICA or MCA occlusion, (4) inaccessible atherosclerotic stenoocclusive ICA, and (5) atherosclerotic stenosis or occlusion of the MCA trunk. Mortality and major stroke morbidity were 0.6% and 2.5%, respectively. The bypass patency rate was 96%. Patients underwent bypass surgery experienced more stroke events than those with best medical treatment. Although the study did not demonstrate surgical efficacy in preventing recurrent stroke, some critics existed for the following reasons. First, a substantial number of patients operated outside the trial among patients assigned to surgery [9]. Second, hemodynamic status was not evaluated. Symptomatic lesion with hemodynamic compromise could have a surgical benefit compared to that without hemodynamic compromise [10]. Third, surgical timing, at least 8 weeks after ischemic stroke in the study, could be a confounding factor. That was because most serious recurrence happens within 1 week after ischemic insult and incidence of recurrence lows after 6 weeks. Fourth, the potential of initially embolic stroke in MCA stenosis exists. Fifth, only half of the enrolled patients underwent antiplatelet medication when entering study [11].

Despite discouraging results of the EC–IC bypass surgery in preventing recurrent stroke, some symptomatic carotid artery occlusive (CAO) disease showed good clinical outcomes after operation. Such discrepancy suggested that hemodynamic compromise can be an important determinant for future stroke development. Grubb et al. [12] investigated the role of misery perfusion, increased oxygen extraction fraction (OEF) by positron emission tomography (PET) distal to symptomatic carotid occlusion, in the development of recurrent ischemic stroke in medically treated patients. Patients with misery perfusion revealed increased ipsilateral stroke (11 of 39 cases, 28.2%) than those without misery perfusion (2 of 42 cases, 4.7%) with a mean follow-up period of 31.5 months. Comparison of ipsilateral stroke risk in patients with and without misery perfusion was as follows: 10.6% vs. 2.4% at 1 year and 2.4% vs. 5.3% at 2 years. Accordingly, symptomatic carotid occlusion with misery perfusion was at high risk of recurrent stroke, although medical treatment had been done [12]. EC–IC bypass could reverse misery perfusion with improved cerebral blood flow (CBF) [10], which required additional study of surgical efficacy in preventing recurrent stroke in symptomatic CAO. Two prospective randomized controlled studies [5, 6] were conducted to find specific group which had a benefit from bypass surgery. The carotid occlusion surgery study (*COSS*) [5] evaluated the surgical benefit of EC–IC bypass with the best medical therapy compared to medical therapy only in preventing recurrent ipsilateral ischemic stroke in patients with recently symptomatic atherosclerotic internal carotid artery occlusion (AICAO). Inclusion criteria of the study were as follows: (1) AICAO confirmed by angiography, (2) ischemic stroke within 120 days, and (3) ipsilateral-to-contralateral ratios of mean regional carotid territory OEF measure by PET >1.130. The primary endpoint, 2-year ipsilateral stroke rate, was 23% in medical group and 21% in surgical group ($p = 0.73$). Regarding ipsilateral strokes within 30 days, surgical group revealed 14.4% and medical group did 2.0%, respectively. The trial was terminated early for futility. Although improved cerebral hemodynamics, OEF from 1.258 to 1.109, was noted in the surgical group, there was no overall surgical benefit in preventing recurrent 2-year stroke in surgical group.

The Japanese EC–IC bypass trial (JET) investigated to determine surgical benefit of bypass surgery in preventing recurrent stroke in patients with major cerebral artery occlusive diseases and hemodynamic insufficiency proved by quantitative measurement of cerebral blood flow (CBF) [6]. Surgical indication was as follows: (1) TIA or minor stroke within 3 months and (2) hemodynamic cerebral ischemic condition seen on ^{123}I-IMP (N-isopropyl-p-iodoamphetamine) single-photon emission computed tomography (SPECT), with CBF<80% of normal control and cerebrovascular reserve capacity (CVRC) <10%. Bypass surgery significantly decreased the recurrent ipsilateral stroke compared to medical group ($p = 0.042$). It is still debated, however, whether there was surgical complication or not. The Japanese EC–IC bypass trial (JET) study [13] evaluated the threshold of CBF and CVRC for recurrent ischemic stroke in patients with mild hemodynamic compromise undergoing conservative treatment. Compared to the medical group included in the JET study, all adverse events ($n = 9$, 7.0% in JET-2 vs. $n = 17$, 16.6% in JET; $p = 0.02$) and ipsilateral stroke recurrence ($n = 5$, 3.9% in JET-2 vs. $n = 11$, 10.3% in JET; $p = 0.04$) were significantly decreased in conservative group in JET-2 study. Accordingly, for symptomatic major CAO with mild hemodynamic compromise (CBF>80% or CVRC>10%), EC–IC bypass surgery did not provide better outcomes in preventing ipsilateral stroke recurrence [13]. In our institution, EC–IC bypass has been performed according to the following indications: (1) symptomatic occlusion or severe stenosis of ICA or MCA, (2) no evidence of embolic strokes, (3) failure of best medical treatment, and (4) moderate-to-severe hemodynamic compromise seen on SPECT or PET. Nevertheless, an individual approach to the symptomatic CAO should be done in clinical circumstances, until the data supporting surgical efficacy.

In conclusion, symptomatic CAO with hemodynamic compromise is at higher risk of recurrent stroke, if left untreated or medically treated [14]. However, surgical efficacy of EC–IC bypass has not been demonstrated. Further data or consensus should be developed.

14.3 Moyamoya Disease

Moyamoya disease (MMD) is referred to as chronic progressive steno-occlusive disorder at ICA or proximal MCA and anterior cerebral artery (ACA) with abnormal collateral vessels [15]. Bypass surgery has shown to decrease recurrent stroke and to increase cerebral hemodynamics [16]. The cumulative postoperative or subsequent death or stroke risk at 5 years has been reported to be 5.5% [17] in MMD patients (adults, $n = 233$; pediatric, $n = 96$). During the follow-up period, eight cases of ischemic stroke and seven cases of hemorrhagic stroke associated with neurologic deficits were observed. A recent meta-analysis revealed that bypass surgery significantly decreased recurrent strokes than conservative treatment (OR 0.17; 95% CI: 0.12–0.26, $p < 0.01$) [18]. However, three variables of age at presentation (adult vs. pediatric), clinical presentation (hemorrhagic vs. ischemic), and surgical techniques (direct vs. indirect) take consequence into account in evaluating surgical efficacy of bypass surgery in MMD patients.

MMD shows bimodal age pattern, first peak in the 10- to 19-year age range and second peak in the 50- to 59-year age range [19]. Adult MMD presents more frequently with hemorrhage compared with pediatric MMD which mainly presents with cerebral ischemia [19, 20]. Regarding ischemic presenting MMD, bypass surgery lowered recurrent strokes than conservative treatment group [8, 21]. However, surgical efficacy of bypass surgery in preventing recurrent hemorrhage remains under debate in hemorrhage presenting MMD. Kawaguchi et al. [22] reported that direct bypass (none of 6) significantly decreases recurrent stroke compared to conservative (6 of 11) or indirect bypass (3 of 5). In contrast, Fujii et al. [23] did not demonstrate surgical benefit from direct bypass ($n = 29$, 19.1%) than conservative treatment ($n = 39$, 28.3%) in reducing risk of recurrent hemorrhage. The Japan Adult Moyamoya (JAM) trial [7] evaluated efficacy of bypass surgery in the prevention of recurrent hemorrhage. MMD without bypass surgery ($n = 12$, 31.6%) tended to experience higher hemorrhagic events compared to MMD with

bypass surgery (n = 5, 11.9%). The Kaplan–Meier survival analysis exhibited the importance of bypass surgery with marginal significance (p = 0.042), indicating preventive effects for recurrent hemorrhage in adult MMD.

For pediatric MMD patients, treatment outcomes did not differ according to surgical techniques of direct and indirect bypass [24]. However, surgical efficacy based on surgical techniques remains under debate in adult MMD [25]. Indirect bypass of encephaloduroarteriosynangiosis (EDAS) with multiple burr holes revealed long-term resolution of ischemic and hemorrhagic manifestations [26]. In contrast, combined bypass surgery, mixed direct and indirect bypass, provided better angiographic outcomes compared to indirect bypass in adult MMD [27]. Excellent revascularization area (>two-thirds of the MCA distribution) was more frequently noted in patients with combined bypass surgery (n = 12, 48.0%) than those with indirect bypass surgery (n = 9, 27.3%). It was shown to have clinical improvement and to be stationary 6 months after combined bypass surgery in adult MMD patients [28]. Mean CBF in the MCA territory also increased during the short-term period and became stationary. The annual symptomatic hemorrhage rate was 0.4%/person-year and infarction rate 0.2%/person-year. A meta-analysis [18] revealed that recurrent stroke was more observed in indirect bypass group than direct bypass group (OR, 1.79, p = 0.01). Nevertheless, heterogeneous population (mixed pediatric and adult MMD patients) [18] and potentially confounding factors (mixed symptomatic and asymptomatic patients) [29] were concerns to the interpretation.

Direct bypass is thought to have a high risk of complications than indirect bypass due to technical difficulties and a longer operative time; however, Quian et al. [18] reported that there was no significant difference in surgical complications (OR, 0.8, p = 0.18) according to surgical techniques after analyzing 1,071 MMD patients from 11 studies. Hyperperfusion syndrome (HPS) takes into account after bypass surgery, in particular MMD patients. HPS is a clinical symptom characterized by transient neurologic deterioration without possible causes [16]. Most neurologic deficits relieved within 15 days after procedure. Watershed shift or [30] relative an increase of perfusion to chronic ischemic area [31] can be related to HFS. Although optimal treatment consensus has not been established, strict blood pressure control is recommended [32].

In conclusion, surgical efficacy of bypass surgery in pediatric MMD has been well documented. No definite consensus is made regarding treatment methods for adult MMD; direct or combined bypass surgery can be warranted. Bypass surgery is effective in preventing recurrent strokes in ischemic presenting MMD; however, its efficacy in preventing recurrent bleeding in MMD patients with hemorrhage presentation requires additional data.

14.4 Surgical Steps of Direct Bypass

Direct bypass is defined as the STA–MCA anastomosis. The procedure is performed in the following order (Fig. 14.1a–h): [33]

1. After the patient is positioned with the head toward the opposite side, STA and its branches are marked with a Doppler ultrasound.
2. STA and surrounding galea tissue can be harvested with along the frontal or parietal STA branch (the *white arrow* indicates the parietal STA branch) (Fig. 14.1a). To avoid STA injury, small STA branches can be carefully coagulated and cut 5 mm away from the STA.
3. After burr-hole trephinations, a 4–5 cm craniotomy is made over the midfrontal–temporal bone. Then dura is opened and passed beneath the STA (Fig. 14.1b). During temporal muscle dissection and craniotomy, the STA can be retracted laterally with rubber to avoid STA injury. Diluted papaverine solution can be used to prevent vasospasm of the donor artery.
4. The recipient MCA branch such as angular or posterotemporal branch which shows retrograde flow by a microvascular Doppler sonography is selected (Fig. 14.1c). Small

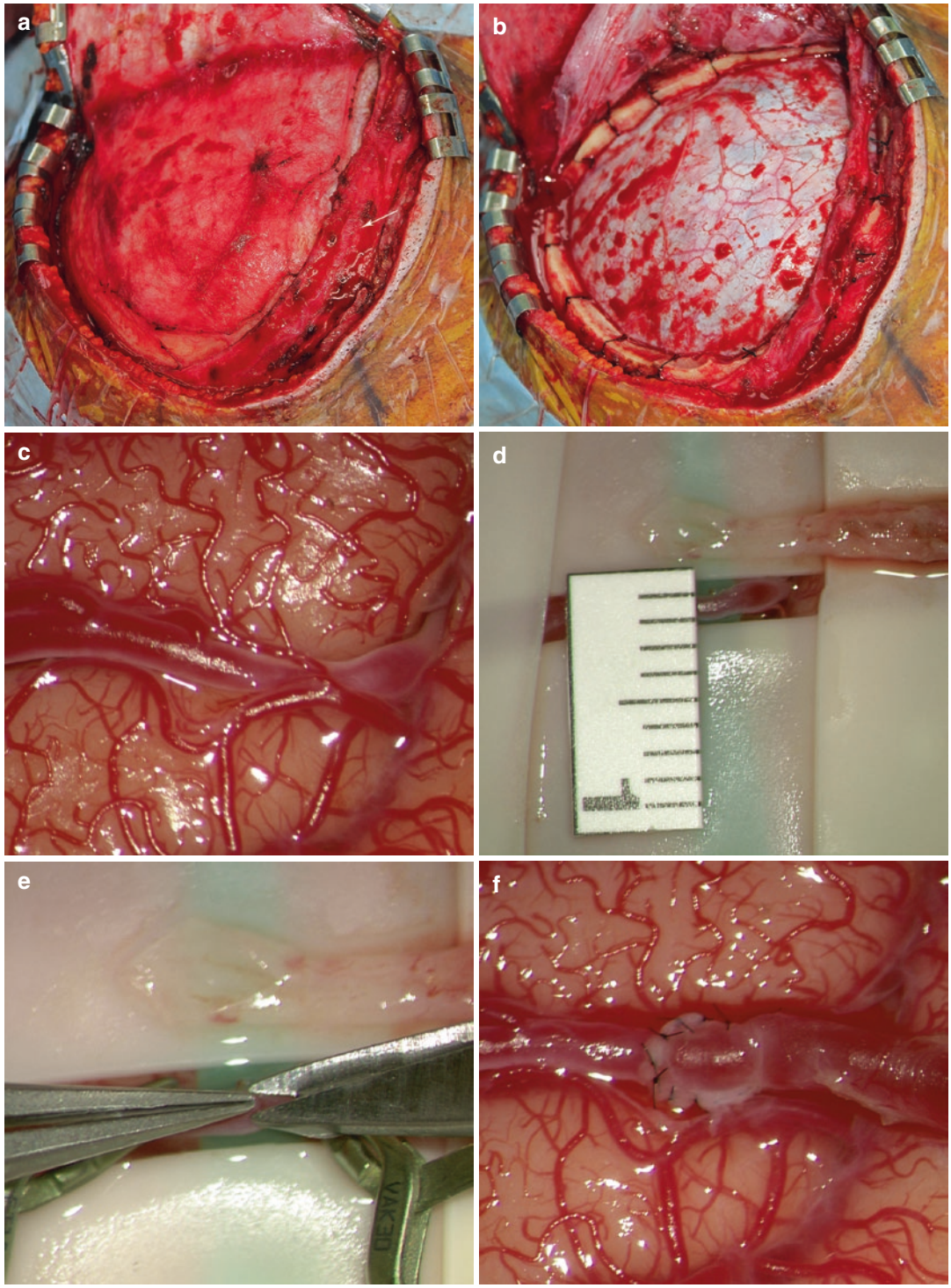
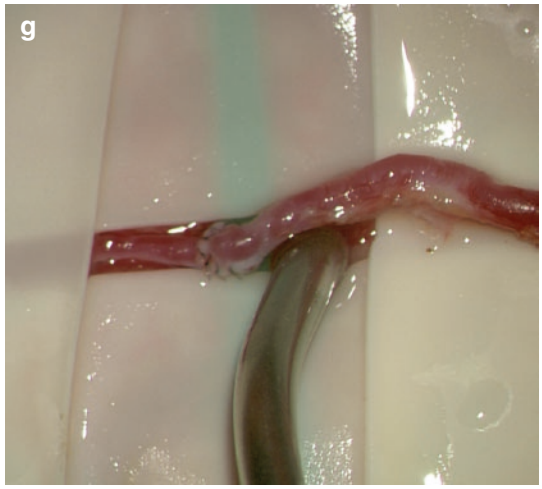


Fig. 14.1 Surgical techniques of superficial temporal artery to middle cerebral artery bypass with encephalo-galeo-duro-synangiosis



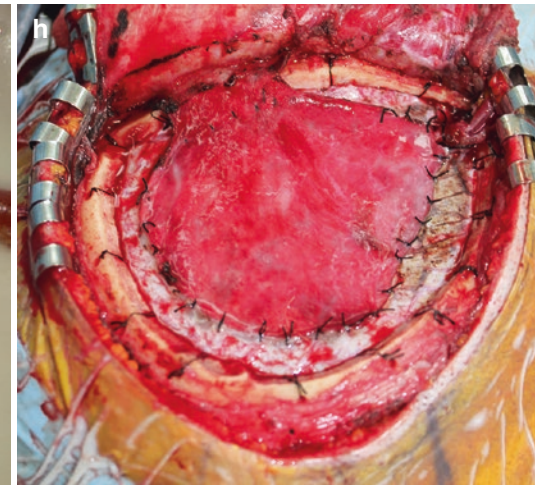


Fig. 14.1 (continued)

cortical branches of the recipient artery can be cauterized with bipolar for mobilization of the recipient artery.

5. After temporary clipping of the proximal STA, distal STA is ligated and cut off in the proper length with slope angle. After heparin–saline irrigation, further dissection of the surrounding tissue of the distal artery is made about 10–20 mm, apart from adventitia layer of the artery (Fig. 14.1d).
6. To reduce cerebral metabolic activity, pentothal sodium can be infused before cross-clamping of the recipient artery. After cross-clamping with Aesculap temporary clips, small arteriotomy is performed on the superior wall of the recipient artery using a microscissors, blade, or needle (Fig. 14.1e). Considering the donor artery size, the arteriotomy size should be twice than the diameter of the recipient artery.
7. Suture is done using a 10-0 nylon from the side of the heel to toe side with regular interval between stitches. In particular for suturing, the whole arterial layer should be included (Fig. 14.1f).
8. After removal of temporary clips, a microvascular Doppler sonography is placed for anastomosis patency (Fig. 14.1g). Then the dural and temporalis muscle (Fig. 14.1h) and bone are closed without tension around the STA graft.

14.5 Case Illustration

A 23-year-old female presented with motor TIA. Angiography disclosed nearly total occlusion of the distal ICA and severe MCA stenosis on the right side (Fig. 14.2a). Single-photon emission computed tomography (SPECT) showed decreased basal perfusion on the right side in the resting state and decreased vascular reserve capacity in the acetazolamide challenge test (Fig. 14.2b, c). The patient underwent STA–MCA bypass with EGDS on the right side. Follow-up angiography revealed anastomotic patency of the STA–MCA (Fig. 14.2d). Postoperative SPECT, 6 months after the procedure, showed improved basal perfusion with vascular reserve capacity (Fig. 14.2e, f). The patient remained asymptomatic during the follow-up of 6 months.

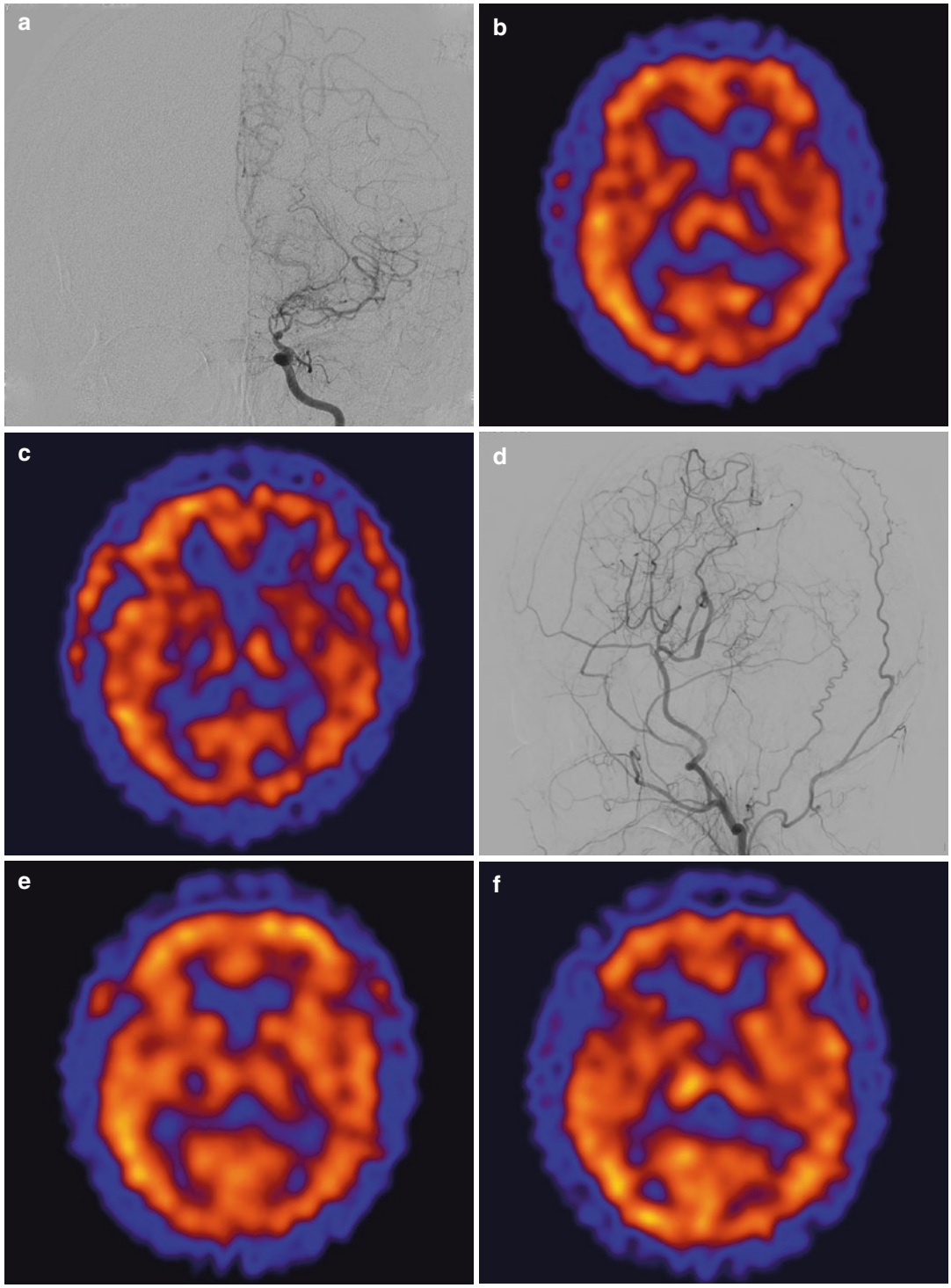


Fig. 14.2 Surgical treatment of moyamoya disease in adult

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15 Decompressive Hemicraniectomy for Malignant Hemispheric Infarction

Jaechan Park

This chapter reviews the use of a decompressive hemicraniectomy for malignant hemispheric infarction following an acute occlusion of the ICA and/or MCA. The results of recent prospective randomized clinical trials are used to explain the expected surgical outcomes according to the patient's age. In addition, radiological predictors of a malignant course, appropriate surgical timing, and surgical techniques for maximum external herniation of an infarcted swollen brain are discussed. This information will help surgeons make the appropriate surgical decision and perform the best surgical treatment.

15.1 Background

When the therapeutic time window for restoring the cerebral blood flow has already passed for an acute occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (MCA), life-threatening brain edema and herniation can occur within 1 week after the onset of stroke symptoms, along with a deterioration of consciousness and pupillary dilation. Thus, high fatality rates, ranging from 59 to 78%, have recently been linked to large hemispheric infarction, and most survivors are left severely disabled [1–5].

In a report by Greenwood from 1968 [6], nine patients with acute infarction involving the MCA or ICA underwent a decompressive hemicraniectomy with resection of the infarcted, necrotic brain tissue, where six patients survived. Subsequently, in 1981, Rengachary et al. [7] reported on three cases of malignant hemispheric infarction, where a decompressive hemicraniectomy was performed without resection of the infarcted brain tissue. While all three patients survived, two patients experienced permanent severe neurological deficits. Originally, decompressive surgery was introduced as a life-saving procedure, leading to external herniation of swollen infarcted brain tissue and relief of brainstem compression. In addition, the procedure can constrain the infarcted area by reducing the intracranial pressure, increasing the cerebral perfusion pressure, and improving the blood flow to the penumbra [8].

15.2 Recent Clinical Trials

While a decompressive hemicraniectomy was originally developed as a life-saving procedure for patients with malignant hemispheric infarction, the severe disability suffered by many survivors remains a serious concern. Notwithstanding,

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Table 15.1 Crucial prospective, multicenter, randomized clinical trials of decompressive hemicraniectomy for malignant hemispheric infarction

Trial	Nation	Patient age (years)	Surgical timing	Patient no. (surgical group, medical group)	Publication
DESTINY	Germany	18–60	<36 h	17, 15	*Stroke*, 2007
DECIMAL	France	18–55	<24 h	20, 18	*Stroke*, 2007
HAMLET	Netherlands	18–60	<4 days	32, 32	*Lancet Neurol*, 2009
DESTINY II	Germany	>60	<48 h	49, 63	*N Engl J Med*, 2014

DECIMAL trial DEcompressive Craniectomy In MALignant middle cerebral artery infarcts trial, *DESTINY trial* DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY trial, *DESTINY II trial* DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY II trial, *HAMLET* Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial

some published case reports and retrospective studies have indicated that surgical decompression lowers mortality without increasing the incidence of severely disabled survivors [4, 9–14].

Thus, to assess the effect of early decompressive surgery on the patient functional outcomes, four European, prospective randomized multicenter clinical trials were conducted (Table 15.1) [2, 3, 5, 15]. The surgical procedure used in all four clinical trials was a decompressive hemicraniectomy without resection of the infarcted brain tissue, and the functional outcomes of the surgical and medical groups were assessed based on a modified Rankin Scale (mRS) 6–12 months after stroke onset.

Three of the trials were conducted between 2001 and 2007; however, the DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarction) trial and DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY) trial were both stopped due to a lack of cases and a significant difference in the mortality between the surgical and medical groups [2, 5, 15].

Notwithstanding, the HAMLET (Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial) study was completed, and the results were published in 2009 [2]. Over a 5-year period, 32 patients were randomly assigned to undergo surgical decompression, while another 32 patients received the medical treatment. As a result, for those patients with large hemispheric infarction who were treated within 48 h of stroke onset, a decompressive hemicraniectomy was found to reduce both the fatality rate and the poor outcomes (mRS 5).

Meanwhile, a pooled analysis of three European randomized controlled trials (DECIMAL, DESTINY, and HAMLET), which included patients aged <60 years who underwent decompressive surgery within 48 h after stroke onset, reported a high (43%) survival rate with functional independence (mRS ≤3) [4].

In a more recent prospective randomized clinical trial, Decompressive Surgery for Treatment of Malignant Infarction of Middle Cerebral Artery-II (DESTINY II trial) published in 2014, the efficacy of a decompressive hemicraniectomy within 48 h after stroke onset was investigated for elderly patients aged >60 years [3]. In this trial, while survival was increased, most survivors experienced severe disability (mRS 4) following surgery with only 6% having functional independence (mRS 3).

15.3 Surgical Timing and Indications

15.3.1 Timely Surgery

Although originally intended as a last resort to prevent a fatal cerebral herniation, recent European clinical trials have proposed the early use of a decompressive hemicraniectomy for better functional outcomes. In particular, patients who underwent decompressive surgery within 48 h after stroke onset were included in both a pooled analysis of three European randomized controlled trials and the DESTINY II trial [2–5, 9].

However, neurological deterioration due to brain swelling varies significantly from <24 h to >6 days, affecting the appropriate timing of early surgery. When Qureshi et al. [16] investigated the timing of neurological deterioration related to cerebral edema after massive MCA infarction, 36 and 32 % of the patients experienced neurological deterioration <24 h and 24–48 h after stroke onset, respectively, while the remaining third (33%) experienced clinical deterioration on day 3 (19%), day 4 (4%), day 5 (4%), and day 6 or after (6%). Thus, instead of a strict timing, the appropriate surgical timing should be before or immediately after the initiation of neurological deterioration related to brain edema, which could be on day 1, day 2, or even day 7 after stroke onset [17–21].

15.3.2 Early Predictors of Malignant Hemispheric Infarction

Various early predictors of malignant hemispheric infarction have already been reported based on clinical and radiological data [17, 22–30]. However, none of these predictors have a sufficient predictive value that allows them to be used to schedule an early decompressive craniectomy before any neurological deterioration. Thus, the decision for decompressive surgery is invariably made on the basis of radiological data and a concomitant clinical course.

While the volume of the infarcted brain tissue can often be used to predict the development of fatal cerebral edema and herniation after acute infarction, infarcts smaller than the cutoff value can also cause fatal cerebral edema due to a variety of other unpredictable factors, including expansion of the initial infarct territory, delayed spontaneous recanalization of the occluded vessel, hemorrhagic transformation of the infarcted brain tissue, and the hydration status of the patient. Thus, monitoring in an intensive care unit (ICU) or stroke unit setting is needed for all patients with acute large hemispheric infarction to expedite timely surgical decompression.

In previous studies, assessing the infarct volume using early CT scans after stroke onset does not provide a satisfactory predictive value: (1) hypodensity covering >50% of the MCA territory within 5 h after symptom onset was predictive of a malignant course with a sensitivity of 61% and specificity of 94% [30]; (2) hypodensity covering >50% of the MCA territory within 12 h was predictive with a sensitivity of 64% and specificity of 66% [31]; and (3) hypodensity covering >50 and 67% of the MCA territory within 18 h was predictive with a sensitivity of 58% and 45%, respectively, and specificity of 94% and 100%, respectively [23].

In contrast, assessing the initial infarct volume using diffusion-weighted imaging (DWI) would seem to be a more promising predictor. In the study by Oppenheim et al. [28], an initial infarct volume >145 cm^3 within 14 h after an acute MCA occlusion was predictive of a malignant course with a sensitivity of 100% and specificity of 94%.

Another useful predictor of malignant hemispheric infarction is a midline brain shift. Gerriets et al. [32] reported that a midline shift of ≥2.5, 3.5, 4.0, and 5.0 mm in transcranial color-coded duplex sonography at 16, 24, 32, and 40 h, respectively, after stroke onset was predictive of a malignant course with a specificity of 100% and positive predictive value of 100%.

An ICU setting can also facilitate the use of predictors with a high cutoff value, providing a high specificity and high positive predictive value for deciding on early surgery before clinical deterioration and thereby avoiding over-inclusive indications of surgical decompression [17]. However, the cutoff values for the lesion volume and associated midline brain shift for predicting a malignant clinical course differ according to the timing of the brain imaging after stroke onset and the severity of brain atrophy [17, 32]. In a retrospective study of radiological predictors for 61 patients with large hemispheric infarction, Park et al. [17] proposed strict cutoff criteria with a high specificity according to the timing of the imaging. For patients without severe brain atrophy (bicaudate ratio <0.16), an initial infarct volume >160 ml in DWI within 14 h of stroke onset was predictive of a malignant course with a 97% specificity and 76% sensitivity, while an infarcted lesion volume >220 ml and midline shift >3.7 mm

in follow-up CT scans 24 h after stroke onset were predictive with a 100% and 98% specificity, respectively.

The final infarct volume can also be assessed using the perfusion CT or perfusion MR images on admission [29, 33]. In the MR perfusion study by Thomalla et al. [29], a perfusion lesion volume >162 mL on a time-to-peak (TTP) map with a TTP delay threshold of >4 s was predictive of a malignant course with a sensitivity of 83% and specificity of 75%.

15.4 Surgical Technique

The surgical decompression of intracranial masses can be performed using external and/or internal decompression. In cases of malignant hemispheric infarction, external decompression can be used with or without internal decompression.

External decompression, including a hemicraniectomy and expansive duraplasty, enables external herniation of the swollen infarcted brain tissue. In the clinical trials DECIMAL, DESTINY, HAMLET, and DESTINY II, the standard surgical technique was external decompression without internal decompression [2, 3, 5, 15]. Internal decompression, including resection of the infarcted brain tissue and/or temporal lobe, is not commonly used for simple MCA infarction due to the difficulty in differentiating between salvageable ischemic and irreversibly infarcted brain tissue. However, when external decompression is unable to reduce the intracranial pressure and relieve brain stem compression (e.g., in the case of whole hemispheric infarction), additional internal decompression should be considered [34].

Figure 15.1 illustrates a decompressive hemicraniectomy using external decompression, where the frontal, temporal, and parietal bones overlying the infarcted hemisphere are removed, allowing for external herniation of the swollen infarcted brain. After administering general anesthesia, a skin incision is initiated just above the zygomatic arch 0.5 cm anterior to the tragus and then continued superiorly and posteriorly over the ear and around the parietal bone to the contralateral frontal midpupillary line. The hemicraniectomy requires the removal of a large fronto-temporo-parietal bone flap, where a minimum diameter of 12 cm is widely accepted [35, 36], although the author recommends a diameter >14 cm for an effective decompressive hemicraniectomy [37].

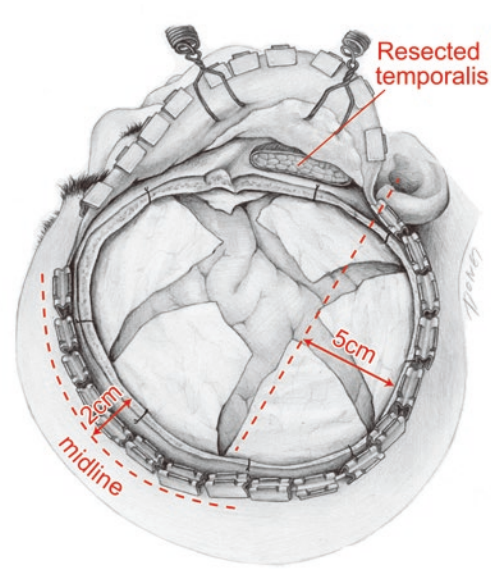

Fig. 15.1 Illustration of decompressive hemicraniectomy. The medial limit of the craniectomy is 2 cm from the midline (*dotted curved line*), while the posterior limit is 5–6 cm posterior to the external auditory canal

The craniectomy is limited by the following boundaries: (1) To avoid violation of the frontal sinus, the bone flap is made anteriorly, except in the case of a large frontal sinus. (2) To minimize venous bleeding on the dura, the medial limit is 2 cm from the midline. (3) The posterior limit of the bone flap is approximately 5–6 cm posterior to the external auditory canal, which covers the MCA territory posteriorly and allows for a neutral head position in bed without compressing the swollen brain. (4) Inferiorly, the temporal squama is removed to the level of the zygomatic arch [38].

Following a stellate-shaped dural incision, the infarcted brain tissue is not normally removed due to the presence of a salvageable penumbra area or viable tissue [2, 5, 15]. Expansive dura-

plasty is then performed using a large flap of pericranial tissue or an artificial dura substitute. The dimensions of the expansive duraplasty should be lengthened to accommodate subsequent aggravation of the brain swelling.

Meticulous hemostasis is critical for preventing a postoperative epidural/subgaleal hematoma, which includes the use of multiple dural tenting sutures, the bipolar coagulation of bleeding points on the dural surface, the application of commercial hemostatic materials, and the placement of one or two closed suction drains in the epidural/subgaleal space. The dural tenting sutures require small holes along the margin of the craniectomy. In addition, self-drilling anchor screws can be used around the sphenoid ridge for easy anchoring of the dural tenting sutures (Fig. 15.2) [39].

Lastly, the temporalis muscle and skin flap are re-approximated and sutured layer by layer. However, the temporalis muscle and fascia can be resected to maximize the external herniation of the swollen brain [38]. Removing the temporalis muscle has a minimal impact on the maximal bite force and does not create problems with chewing, as the grinding phase of the closure stroke only needs one-third of the maximal bite force [40, 41]. On average, resection of the temporalis muscle and fascia creates a twofold volume expansion of the external herniation on postoperative day 3 when compared with the conventional technique (Fig. 15.3) [38]. The technical obstacles to achieving effective external decompression include an insufficient craniectomy size, postoperative epidural/subgaleal hematoma, thick and swollen temporalis muscle compressing the temporal lobe, tough and inelastic temporalis fascia, and tight scalp [36, 38, 42]. Thus, maximizing the external herniation of the infarcted brain requires the hemicraniectomy to

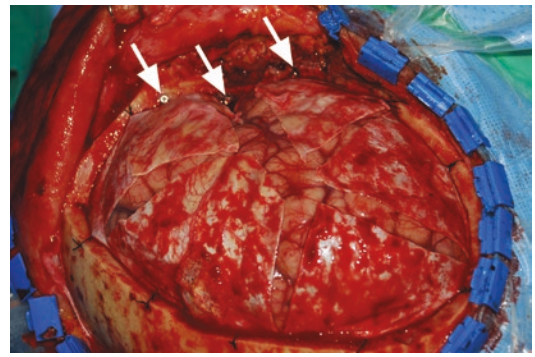

Fig. 15.2 Intraoperative photograph of decompressive hemicraniectomy showing self-drilling anchor screws (*arrows*) for anchoring the dural tenting sutures around the sphenoid ridge

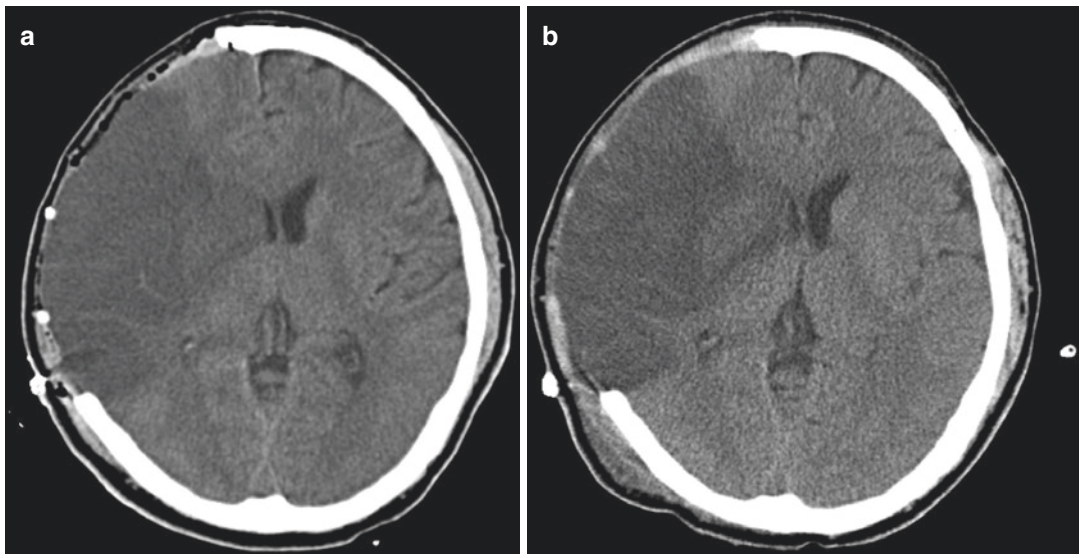

Fig. 15.3 Axial CT scans after decompressive hemicraniectomy and resection of the temporalis muscle on postoperative day 1 (**a**) and day 3 (**b**). Progressive and considerable external herniation of the infarcted brain is noted

be as large as possible, meticulous hemostasis, and resection of the temporalis muscle and fascia. The bone flap is stored in a tissue bank at –70°C, and cranioplasty using the autogenous bone flap is then performed 2–3 months after the craniectomy.

15.5 Surgical Results According to Patient Age

Age has already been established as a critical factor affecting the functional outcome after surgical decompression for malignant hemispheric infarction [5, 43–46], where elderly patients run a higher risk of an unfavorable outcome, including mortality (mRS 6) or survival with functional dependency (mRS 4 or 5) [3, 37, 47–51].

The treatment outcomes following decompressive surgery within 48 h after stroke onset were recently reported according to the patient's age (Fig. 15.4) in several clinical trials, where a pooled analysis of three clinical trials (DECIMAL, DESTINY, and HAMLET) investigated patients aged ≤60 years [4], while the DESTINY II trial included elderly patients aged >60 years [3].

For patients aged ≤60 years (pooled analysis of DECIMAL trial, DESTINY trial, and HAMLET), when compared with the conservative treatment outcomes, surgical treatment reduced the mortality from 71 to 22% [4]. As regards the functional outcomes, the number of patients with functional independence (mRS ≤3) increased from 21 to 43%, and even though the number with moderately severe disability (mRS 4) increased from 2 to 31%, there was no increase (4% vs. 5%) in the number with severe disability (mRS score 5).

Meanwhile, for elderly patients aged >60 years (DESTINY II trial), when compared with the conservative treatment outcomes, surgical treatment reduced the mortality from 76 to 42% [3]. As regards the functional outcomes, there was no change (6% vs. 5%) in the number of patients with functional independence (mRS ≤3); however, the number with moderately severe disability (mRS 4) and severe disability (mRS 5) increased from 11% to 32% and 8–19%, respectively.

In another retrospective study by Park et al. [37] that also investigated the functional outcomes following a decompressive hemicraniectomy for malignant infarction according to the patient's age, 69% of patients aged ≤58 years experienced a favorable outcome (mRS ≤3), while only 25% aged 58–67 years experienced a favorable outcome (mRS ≤3), and 0% >67 years experienced a favorable outcome (mRS ≤3), where 33.3% experienced moderately severe disability (mRS 4).

The increase in the number of survivors with functional dependency (mRS 4 and 5) following a hemicraniectomy is a major dilemma affecting the decision for surgery, and there is no general consensus on the acceptable degree of disability. Neugebauer et al. [52] reported that 79% of physicians consider mRS ≤3 as acceptable, while 38% consider mRS ≤4 as acceptable.

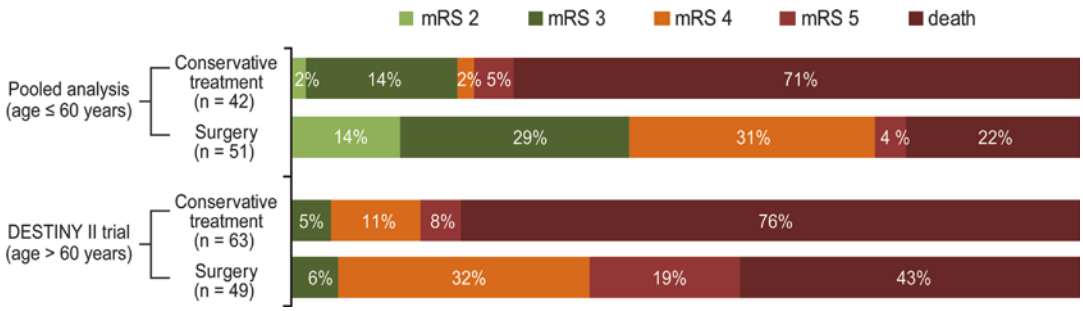

Fig. 15.4 Treatment outcomes following early (within 48 h after stroke onset) decompressive hemicraniectomy according to the patient's age

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