Seung-Hoon Lee *Editor*

Stroke Revisited: Pathophysiology of Stroke

From Bench to Bedside

Springer

Stroke Revisited

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Editor

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Preface

It has been 2 years since the publication of *Diagnosis and Treatment of Ischemic Stroke*, the first volume in the "Stroke Revisited" series. As promised, a new volume has now been published, entitled *Pathophysiology of Stroke: From Bench to Bedside*. This is the fourth publication in the series, preceded by *Hemorrhagic Stroke* and *Vascular Cognitive Impairment*. Originally predicted to be published at the end of 2018, this volume was delayed longer than expected due to editing issues. That said, I would like to apologize to readers who showed great interest in the previous volumes and eagerly awaited this volume. I will make every effort to publish the remaining two volumes at the beginning of 2021.

As its title suggests, the fourth volume is a textbook that covers the pathophysiology of stroke. In volume one, *Diagnosis and Treatment of Ischemic Stroke*, the focus was on the practical diagnosis and treatment of ischemic stroke, with minimal discussion of pathophysiology. With this new addition, along with the second volume, *Hemorrhagic Stroke*, I now cover nearly every aspect of stroke medicine. Improving our understanding of stroke pathophysiology, great strides were made in the 2000s, in which we saw significant progress in radiologic imaging technology. In terms of MRI advancements, we are now able to recognize stroke pathophysiology in near real-time and at high resolution via diffusion- and perfusion-weighted sequences, arterial spin labeling techniques, and 3 tesla high-resolution imaging. In addition, the introduction of 64-channel multi-detector CT technology made it easier to obtain perfusion imaging and cerebral angiography. These developments, discussed in this fourth volume, have helped us better understand the pathophysiology of stroke more than ever before. Furthermore, we discuss new disease concepts in depth, such as cerebral amyloid angiopathy or cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL). Finally, in an effort to help readers understand stroke pathophysiology from a cellular level, we address basic aspects of stroke pathophysiology, including cell death and repair mechanisms. As the editor of this volume, I recommend it be read cover to cover rather than as certain chapters only. This will enable the reader to comprehensively understand every aspect of stroke pathophysiology and learn the most cutting-edge research on stroke diagnosis and treatment.

Not many textbooks explore stroke in depth. I used two to three books during my residency and fellowship, and no book sufficiently discussed the significant improvements in stroke care that occurred between 1990 and 2000.

Owing to advancements in brain MRI and CT imaging, it has become possible to gain an immediate understanding of a patient's pathophysiology as it changes moment by moment. Despite these developments, most textbooks published previously still focused on outdated neurological examinations that are unable to support the advances made in the practice field. Moreover, most textbooks simply lacked explanation of core concepts and listed insignificant details about research findings that often conflicted. Before the development of smartphones and tablets, studying stroke required great perseverance. Nowadays, people around the globe are communicating via social media and are exposed to a previously unexperienced wealth of information. In tandem with recent technological advances, textbooks must change the way they deliver medical knowledge in order to provide information in a concise yet precise way. I decided to write a textbook reflecting such changes and contacted *Springer Nature*, who ultimately agreed to publish the "Stroke Revisited" series. Despite facing communication and language obstacles, I would like to thank the many staff members of *Springer Nature* who have nevertheless helped publish this book.

This latest volume targets residents and fellows, physicians and scholars in their early careers who specialize in stroke, and physicians and researchers in other fields who aim to study stroke. Most textbooks are organized according to the traditional academic format, in which it can be difficult to obtain information required in clinical settings. Instead, I strived to organize concise one-subject chapters in order for readers to be able to finish them quickly and efficiently. I have taken great care to compile the best academic expertise and latest findings, and I hope that that effort communicates to readers.

In order to publish this volume with the most extensive and up-to-date information, each chapter was written by the best medical scientists from around the world. I wholeheartedly thank all authors who have participated in this process. I hope that this textbook will be reviewed well and act as a strong example for future textbooks.

Seoul, Korea Seung-Hoon Lee
2019 . 12

Acknowledgment

Although I had an ideal model for a textbook in my brain, I rarely had an active conversation with publishers about my idea. This textbook was conceived in an e-mail proposal of the textbook after an unplanned meeting with Ms. Lauren Kim, the editor of Springer Nature. The editorial team and I have obtained manuscripts from renowned medical experts in the world and have edited the manuscripts according to the principles we have set for this textbook. Therefore, the contents of this book were completed only after tremendous efforts from the editorial team. I would like to especially thank Dr. Min Kyoung Kang as associate editor and other colleagues for their enormous effort for the completion of this book. In addition, I would like to thank the executive members of edition of the publisher, Springer Nature Inc. who agreed with the philosophy behind this textbook and provided the title for this textbook series "Stroke Revisited." Finally, I greatly appreciate the financial and technical support of the Korean Cerebrovascular Research Institute.

Throughout my research career, I focused on publishing papers as an author and becoming a famous, prosperous scientist. I rarely thought of writing a textbook. I would like to express my love toward my wife and my kids for changing my selfish thoughts and helping me understand my responsibilities, that is, to help others and provide education to future medical doctors.

Seung-Hoon Lee

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Part I

Introduction on Stroke

General Facts of Stroke

1

Chan-Hyuk Lee and Seung-Hoon Lee

Abstract

Stroke is the second leading cause of death, causing substantial physical and socioeconomic burden in the world. The decrease in stroke incidence occurred in developed regions, with the increasing trend in developing countries. This has been attributed to rapidly aging population and poor dietary behaviors in developing countries. The incidence of hemorrhagic stroke is higher in Asian than in Western populations. The incidence of aging-related stroke is higher for males than females. However, the fact that females have a longer life expectancy and strokes are more common in older ages has contributed to the result that the incidence is higher for females than for males. The incidence of stroke in females increases substantially after menopausal transition due to estrogen deficiency.

Ischemic stroke is defined as neurological symptoms resulting from focal brain ischemia or necrosis by abrupt occlusion of the cerebral vessels. A patient is diagnosed with a transient ischemic stroke (TIA) if the symptoms are relieved completely within 24 hours, or ischemic stroke if the symptoms persist for more than 24 hours. In fact, the limitation of 24 hours for TIA is not based on the scientific evidence but chosen arbitrarily. In this chapter, we introduce new proposals for the definition of TIA and ischemic stroke, distinguished according to the duration and lesion.

Several stroke classification systems with different criteria tailored to each purpose were introduced. Oxfordshire Community Stroke Project (OCSP) Classification System is fairly easy to identify the subtype of stroke just based on pre-contrast brain CT, whereas OCSP has the disadvantage of not being able to treat based on the cause of the stroke. In contrast, other classification systems based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system divided stroke cases by the cause of the stroke. TOAST classification system can help develop effective treatment plan, but there is a risk of the overestimation of undetermined category.

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1.1 Introduction

Stroke has various symptoms, progression, and prognosis depending on severity and location of insulted lesions. Different treatment methods are

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applied depending on the stroke mechanism. Therefore, in order to understand the stroke properly, it is necessary to grasp the general overview before looking into the details. We have placed contents corresponding to the general overview of the stroke in the first chapter of the textbook, so that readers can understand the following topics more effectively. First, epidemiologic differences according to the region and sex were discussed. Next, we describe the definition of stroke, and then introduce some representative stroke classifications. The stroke classification is described in more detail in the Stroke Revisited series, Chap. 11, so readers are encouraged to refer to the textbook. The authors hope this chapter will help readers understand the general characteristics of stroke.

1.2 Burden of Stroke

According to the World Health Organization (WHO), stroke is the second leading cause of death in the world and is the third leading cause of disability [1]. Globally, 30,000 women and 25,000 men die each year with stroke, and 1 in every 19 people in the United States dies of stroke [2]. Stroke is a disease with high incidence and prevalence. According to the World Stroke Organization, around 15 million new strokes are diagnosed every year worldwide. As of 2013, 25.7 million people worldwide suffer from stroke, of which 10.3 million are the first diagnosis [3]. The incidence of stroke varies from country to country. The trend shows that developed countries are declining in incidence, while the rates of stroke in developing countries are increasing [4]. This is due to the rapid growth of the elderly population as a result of economic development in developing countries and the increased risk factors such as diabetes and hyperlipidemia due to dietary habits which are different from the past.

It can be seen more clearly in the stroke trend of Republic of Korea [5]. Republic of Korea has experienced rapid economic growth since the 1970s, and developed from a developing to an advanced country in only 30 years. Such rapid economic growth and accompanying dietary and lifestyle changes have also affected stroke trends. Stroke mortality is decreasing compared with the past, while the incidence of stroke is increasing, especially in ischemic stroke (Fig. 1.1). This is a good example of a change in the stroke pattern as the economy develops from developing to advanced country.

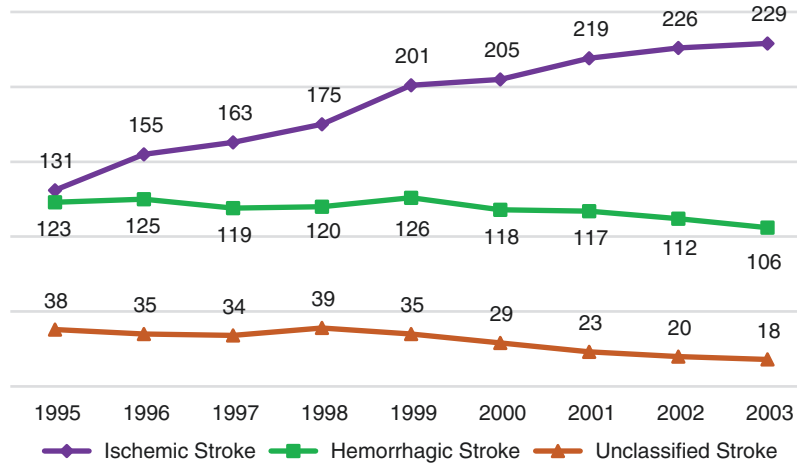

Fig. 1.1 The incidence per 100,000 of stroke according to the stroke classification in the Republic of Korea (1995–2003). Adapted with permission from Journal of Stroke, Copyright Korean Stroke Society

1.3 Epidemiologic Differences According to the Region and Sex

Stroke distribution varies by region and country. According to the neurology in 2013, the Chinese have a relatively high rate of hemorrhagic stroke compared to Caucasians [6]. PISCIS (Proyecto Investigacion de Stroke en Chile: Iquique Stroke Study), which was community-based prospective project in Latin America population, also showed a high rate of hemorrhagic stroke in Hispanic-Mestizo race [7]. As mentioned above, the stroke distribution varies by region and country. Moreover, stroke mortality and morbidity are still higher than other diseases, which results in a great burden on socioeconomic aspects. Considering the cost of treatment, rehabilitation, and secondary prevention of recurrent strokes, the importance of primary prevention is increasing more than ever. Stroke can be prevented adequately if you manage the risk factors of the stroke in advance and guide patients to take appropriate exercise and a balanced diet together.

Stroke has a different distribution depending on sex. The incidence of age-related stroke is higher for males than females. However, females have a longer life expectancy and strokes are more common in older ages, so the incidence is higher for females than for males. In the United States, between 1993 and 2003, the stroke mortality rate for people under 45 years of age was similar for males and females [8]. However, males are at higher stroke mortality rates between the ages of 45 and 74. After 75, the stroke mortality rate of females is higher than males (Fig. 1.2). In addition, the prevalence of stroke was higher in females than in males. Several hypotheses have been proposed regarding the tendency for females to increase in prevalence and mortality as age increases. The role of estrogen is the most widely accepted hypothesis. The rapid reduce of estrogen after menopause is thought to be a cause of stroke [9, 10]. Considering that the elderly themselves are independent risk factors for stroke, postmenopausal estrogen reduction in females is equivalent to the disappearance of another barrier for stroke. Therefore, females who are postmenopausal are more exposed to stroke risk than males, and more active efforts are needed to prevent stroke. It is also a part of this effort to promote females in the global stroke campaign organized by the World Stroke Agency with the slogan "I am Woman."

1.4 Definition of Stroke

The concept of Stroke goes back to BC. In 400 BC, Hippocrates defined nontraumatic brain injury as "apoplexy". After about 2000 years, it was maintained without conceptual change. In 1689 William Cole first introduced the term "stroke". Since the World Health Organization (WHO) referred to the "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death" in 1976, stroke has begun to be established systematically [11]. Since then, the definition of stroke has been redefined several

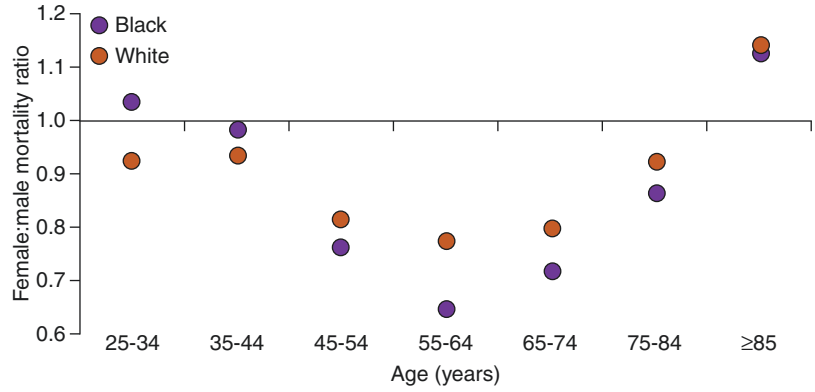

Fig. 1.2 Female-to-male mortality ratio according to age-related stroke in the United State (1999~2003). Adapted with permission from Lancet Neurology, Copyright Elsevier

times since the rapid development of neuroscience and imaging techniques.

The ischemic stroke, a subclass of stroke, has had much more controversy among researchers than the rest of the classification, such as hemorrhagic stroke. This is because the ischemic stroke conceptually overlaps with transient ischemic attack (TIA), which is a transient cerebral ischemic condition. The ischemic stroke presented in the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is as follows: "An ischemic condition of the brain, producing a persistent focal neurological deficit in the area of distribution of the cerebral arteries. The formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow. Infarcts of the cerebrum are generally classified by hemisphere, lobe, arterial distribution, and etiology" [12].

The newly revised ICD-11 defines ischemic stroke as "acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain. Evidence of acute infarction may come either from (a) symptom duration lasting more than 24 hours, or (b) neuroimaging or other technique in the clinically relevant area of the brain". The term does not include infarction of the retina [13]. TIA is defined as "a brief episode (generally within 24 hours) of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction" [14].

However, the authors suggest that it is unreasonable to distinguish between ischemic stroke and TIA on a 24-hour basis. In other words, the guideline is "arbitrary" that patients with ischemic stroke should show neurologic deficits lasting longer than 24 hours. Ischemic lesions based on the imaging can be identified even at a much shorter duration of neurological deficits than 24 hours. Conversely, researchers often encounter that neurological symptoms are permanent, but the ischemic lesions are not detected in the imaging study. In other words, TIA is a concept designed to warn the possibility of permanent neurological deficits by ischemic stroke and to awaken both the physicians and the patients.

In view of the etiologic and pathophysiological aspects, fundamentally, both of them are diseases on the same continuous spectrum. Therefore, it is practically impossible to divide the two by a specific time. Nevertheless, ICD-10 and 11 continue to differentiate between the two and cause conceptual confusion among researchers. We would like to suggest a different concept of ischemic stroke and TIA from the above critical point. Considering the persistence of neurological symptoms and the presence of ischemic lesions in the imaging, it can be classified into three different concepts as shown in Fig. 1.3.

In Fig. 1.3, area A, is an ischemic stroke with persistent neurological deficits and lesions on imaging studies such as Brain CT or MRI. Neurological deficits might persist but not be confirmed by imaging. If the clinical diagnosis is a meaningful, it is appropriate to classify it as an ischemic stroke. Area B is a lesion-positive TIA (LPTIA), which is rapidly disappearing neurological deficit, but lesions are confirmed by imaging. Area C is a lesion-nega-

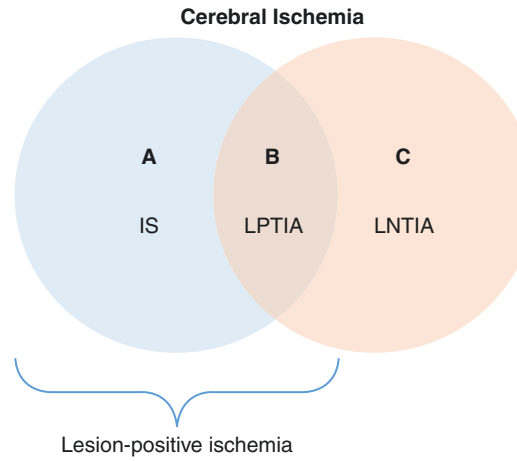

Fig. 1.3 New concept of TIA and stroke. Cerebral ischemia can be classified into three types (A, B, C) according to persistence of neurological symptoms and imaging findings, and A and B can be bound to lesion-positive ischemia. *IS* ischemic stroke, *LPTIA* Lesion-positive transient ischemic attack, *LNTIA* lesion-negative transient ischemic attack

tive TIA (LNTIA), a neurological deficit rapidly disappears and no lesion is detected on imaging. A and B, where lesions are identified, can be grouped into one concept called lesion-positive ischemia. In summary, ischemic stroke refers to "a condition in which sudden and focal neurological deficits caused by cerebral hemodynamic failure are sustained without rapid improvement." Imaging findings might suggest an ischemic stroke, but it is problematic to regard it as absolute evidence. TIA can be described as "a neurological deficit that is completely recovered in a short time, regardless of whether the ischemic lesion is confirmed on imaging," and it is not reasonable that specific time is one of the criteria that distinguishes the two concepts. This should be diagnosed in consideration of each clinical situation. We listed the existing definition of ischemic stroke and TIA, and the definition suggested by the authors (Table 1.1).

Table 1.1 The existing and new definition of ischemic stroke and TIA

Existing definition	
Ischemic stroke	Acute focal neurological dysfunction caused by focal infarction at single or multiple sites of the brain. Evidence of acute infarction may come either from (a) symptom duration lasting more than 24 hours, or (b) neuroimaging or other technique in the clinically relevant area of the brain. The term does not include infarction of the retina.
TIA	A brief episode (generally within 24 hours) of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.
New definition	
Ischemic stroke	A condition in which sudden and focal neurological deficits caused by cerebral hemodynamic failure are sustained without rapid improvement. Most of the lesions are confirmed by imaging, and rarely, lesions are not identified.
TIA	A neurological deficit that is completely recovered in a short time, regardless of whether the ischemic lesion is confirmed on imaging.

TIA transient ischemic stroke

1.5 Classification of Stroke

Stroke is caused by cerebral blood flow obstruction of various causes. Depending on the etiology of the stroke, it has different pathophysiology, which means that different treatment is needed. In other words, the prognosis of the patient depends on the proper treatment, and the treatment depends on the cause of the stroke. Therefore, classification of stroke has been one of the challenges facing researchers.

After classifying stroke using the Harvard Stroke Registry at Harvard University in 1978, various classifications have been introduced [15]. We introduce some key stroke classifications. The first classification to be described is the ASCO Stroke Classification (*A* atherosclerosis, *S* small vessel disease, *C* cardiac disease, *O* other) [16, 17]. The ASCO Stroke Classification classifies only ischemic stroke, taking into consideration the potential likelihood of each stroke and the tests that support it. The next classification is the Oxfordshire Community Stroke Project (OCSP) classification developed by epidemiological study in Oxfordshire, England [18]. In the United Kingdom, primary care physicians are responsible for all stroke patients and only precontrast brain CT is used for image evaluation. This classification was developed to be optimized for the public healthcare system in the United Kingdom. Primary care physicians can be easily accessed to the classification because each case can be categorized solely based on basic physical examination and location and size of the lesions on brain CT (Table 1.2). Unlike stroke of undetermined etiology (SUE) of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which is presented in the next section, there is no ambiguity in classification, so patients can be treated by clear guidelines. On the other hand, it is a disadvantage of this classification that it is difficult to treat based on the mechanism, because it is not classified on the basis of the etiology.

Last, we introduce the TOAST classification. This is currently the most widely used classification

Table 1.2 OCSP classification

Subtype	Details
Lacunar infarct (LACI)	Typical lacunar syndromes (4 types). Faciobrachial or brachiocrural deficits.
Total anterior circulation infarct (TACI)	If the following three symptoms are combined: 1. Higher cortical dysfunction (e.g., dysphasia, dyscalculia). 2. Homonymous visual field defect. 3. Ipsilateral motor and/or sensory deficit (2 or more body parts among face, arms, or legs). ∗ If there is a conscious impairment and the test cannot be carried out, it is assumed that there is a deficit.
Partial anterior circulation infarct (PACI)	1. Two of the three symptoms of TACI are relevant. 2. Higher dysfunction only. 3. Focal motor/sensory deficit.
Posterior circulation infarcts (POCIs)	Two of the three symptoms of TACI are relevant. 1. Ipsilateral cranial nerve palsy + contralateral motor and/or sensory deficit 2. Bilateral motor and/or sensory deficit. 3. Impaired conjugate eye movement. 4. Cerebellar dysfunction without ipsilateral long tract sign. 5. Isolated homonymous visual field defect.

OCSP Oxfordshire Community Stroke Project

in the world and classified into five categories. Each of these are large artery atherosclerosis, small vessel occlusion, cardioembolism, stroke of other etiology, and stroke of undetermined etiology. Three subtypes were further classified in the undetermined cause (Table 1.3). Compared to other classifications, TOAST is capable of causal assessment and criteria of the classification is quite clear. However, there are some problems in that classification. First, the criteria proposed by TOAST are arbitrary. For example, the criteria of large artery atherosclerosis for stenosis of more than 50% in the proximal vessel of the lesion has no specific basis for reference and are not scientific. Depending on the nature of the thrombus, it could be a stable thrombus even if the size is large. Even small thrombosis, if the contents are unstable (ulcerated plaque, intra-plaque

Table 1.3 TOAST classification

Subtype	Details
Large artery atherosclerosis (LAA)	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.
Small vessel occlusion (SVO)	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.
Cardioembolism (CE)	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 (e.g., lone atrial fibrillation or patent foramen ovale) cardiac pathology on diagnostic studies (electrocardiogram, rhythm strip, 24-hour cardiac monitoring, 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.
Stroke of other etiology (SOE)	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 (SUE)	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, *CT* computed tomography, *MRI* magnetic resonance imaging

hemorrhage, etc.), the fragments of the thrombus might migrate to the distal area. The criteria that the size of the lesion should be within 1.5 cm in diameter proposed by the small vessel occlusion is also arbitrary, and there is a possibility that researchers might make errors in determining the treatment options. Another subtype to point out is 2 or more etiologies, one of the subcategories of stroke of undetermined etiology. TOAST classification assesses whether the ischemic stroke mechanism meets arbitrary criteria, and classifies it into "2 or more etiologies" if two or more criteria are met at the same time. It completely excludes clinicians from detecting the cause of stroke by combining various factors (neurological symptoms, medical history, history of drug use, changes in clinical symptoms, imaging findings, etc.). It also reduces the chance of treatment by focusing on clinically suspected causes. These simple and clear criteria are easy to use, but should be kept in mind that they might interfere with the proper care of patients. Rather than suggesting specific figures that divide each stroke subtype, somewhat vague criteria that allow physicians to actively judge could be more helpful. Stroke classifications are described in detail in the Stroke Revisited series, Chap. 11. Also, we have covered the details of stroke classification in the remainder of this textbook.

1.6 Conclusion

We have covered in this chapter what we need to know in order to define the basic concept of stroke, such as definition, classification, mechanism, and diversity of stroke. As you have already seen in this chapter, stroke is not a stereotypical disease that can be defined as one. Rather, it shows the most complex and diverse characteristics among all diseases that humans can suffer. Researchers around the world are struggling to conquer a stroke with this complexity, but it is still far from reality. The shortcut for overcoming stroke begins with an understanding of its nature. The authors hope that this chapter will be a valuable first step for readers to understand the nature of stroke.

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Cerebral Vascular Anatomy

2

Hyoung Soo Byoun and Gyojun Hwang

Abstract

The brain is about 2% of the body's weight, weighing between 1250 and 1450 g. The heart sends 15% of all blood to the brain, and 20% of total oxygen is consumed by the brain. Strokes occur due to problems with blood supply to the brain, and these can include hemorrhage, infarction, and transient ischemic attack. The emergent and proper management for strokes should be performed immediately and can prevent or minimize the otherwise devastating consequences. A fundamental concept of territories of the brain supplied by cerebral vessels and the functions of these territories is essential for effective therapeutic approach to stroke. At this point, defining and understanding cerebrovascular anatomy is the cornerstone to safe and successful treatment of stroke.

This chapter addresses the basic anatomical structures, courses, relationships, and functions of the cerebral vessels.

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2.1 Introduction

The cerebral blood flow is supplied by the internal carotid arteries (ICAs) and vertebral arteries (VAs) [1]. The ICAs take charge of the anterior circulation and the VAs take charge of the posterior circulation, sending 80 and 20% of the cerebral blood flow. The circle of Willis is an anastomotic system of arteries located at the base of the brain connecting anteroposterior and bilateral flows. The right innominate artery, left common carotid artery (CCA), and subclavian artery originate from the aortic arch. The right innominate artery is then divided into right CCA and right subclavian artery. The right VA originates from right subclavian artery and the left VA from the left subclavian artery. The CCA bifurcates to the ICA and the external carotid artery (ECA) at the level of the C4 vertebral body. Then, the anterior cerebral artery (ACA) and middle cerebral artery (MCA) are separated from the ICA. After branching of the posterior inferior cerebellar artery (PICA) from both VAs, the basilar artery (BA) is formed by the union of two VAs. As it ascends superiorly, the BA ramifies the anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA), and is divided into two posterior cerebral arteries (PCAs).

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2.2 Internal Carotid Artery

The ICA separates from the CCA at the level of fourth cervical vertebrae, and passes through the carotid canal into the cranium [2]. The diameters of the CCA, carotid bulb, and proximal ICA are approximately 7.0 mm, 7.5 mm, and 4.5 mm, respectively [3]. The ICA penetrates the petrous bones, the cavernous sinus, and the dura, and finally separates into the ACA and MCA.

The ICA segment is divided into seven segments: cervical, petrous, lacerum, cavernous, clinoid, ophthalmic, and communicating segments from the bottom (Fig. 2.1).

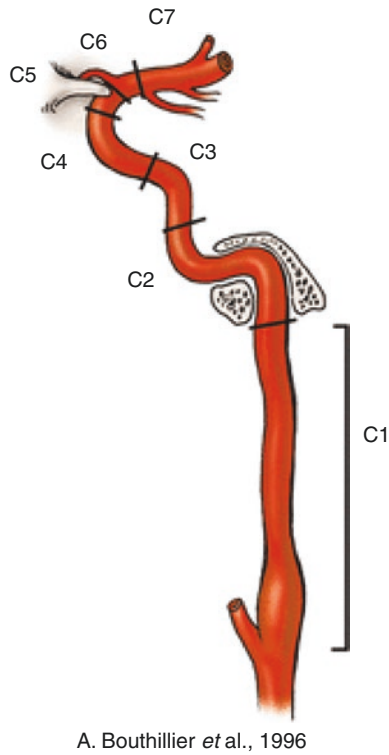

Fig. 2.1 The classification scheme of the internal carotid artery. C1, cervical; C2, petrous; C3, lacerum; C4, cavernous; C5, clinoid; C6, ophthalmic; and C7, communicating segment. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

2.2.1 Segments of the ICA

2.2.1.1 Cervical Segment

The cervical segment of the ICA is the section from the CCA bifurcation to the carotid canal of the temporal bone. The ICA is initially located at the posterolateral portion of the ECA and then courses medially to the ECA as it ascends toward the carotid canal. The ICA lies anteromedial to the internal jugular vein. The glossopharyngeal nerve, vagus nerve, accessory nerve, and hypoglossal nerve course between the ICA and the internal jugular vein [5]. There is no important branch arising from this segment.

2.2.1.2 Petrous Segment

The petrous segment of the ICA enters the skull base through the carotid canal and courses in the petrous temporal bone. This segment subdivides into the short vertical segment, genu, and long horizontal segment. The sympathetic chain and venous plexus surround the petrous segment [6]. The caroticotympanic artery and vidian artery arise from this segment.

2.2.1.3 Lacerum Segment

The lacerum segment of the ICA is a section from the end of the petrous segment to the petrolingual ligament (Fig. 2.1).

2.2.1.4 Cavernous Segment

The cavernous segment of the ICA begins from the petrolingual ligament and enters the cavernous sinus. It consists of the posterior genu, horizontal segment, and anterior genu. The meningohypophyseal trunk, inferolateral trunk, and capsular arteries of McConnell arise from the cavernous segment of the ICA (Figs. 2.1 and 2.2).

The meningohypophyseal trunk arises from the posterior genu of the cavernous segment of the ICA. It ramifies three branches including the tentorial arteries, inferior hypophyseal artery, and lateral clival artery. The tentorial arteries course medially and superiorly along the margin of the tentorial incisura or run laterally and inferiorly

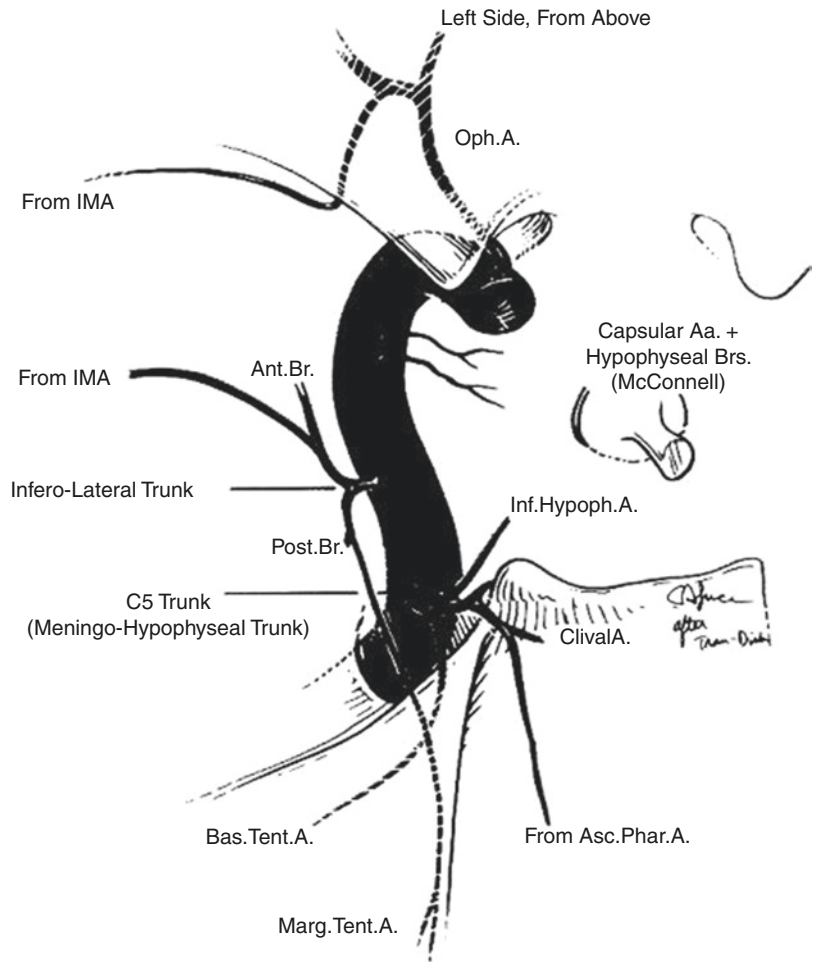

Fig. 2.2 The branches of cavernous internal carotid artery segments. Adapted with permission from Neurology, Copyright Wolters Kluwer Health [7]

into the tentorium. Near the petrous ridge and sigmoid sinus, they connect with the middle meningeal artery and dural arteries of the posterior fossa. The inferior hypophyseal artery which anastomoses with the superior hypophyseal artery and its contralateral flow supplies the pituitary gland. The clival artery supplies dura covering the clivus and has a connection with the ascending pharyngeal artery of the ECA.

The inferolateral trunk that arises from the lateral aspect of the horizontal ICA segment supplies the oculomotor nerve, trochlear nerve, gasserian ganglion of the trigeminal nerve, abducens nerve, dura mater of the cavernous sinus, and tentorium. It connects with several branches from the ECA including branches of the internal maxillary artery and the ascending pharyngeal artery.

The capsular arteries of McConnell arise from the medial aspect of the cavernous segment of the ICA and supplies the pituitary gland irregularly. They are too small to be seen during angiography in the normal state. Medially directed aneurysms of cavernous segments of the ICA can present in these arteries. They can penetrate the diaphragm sellae and occupy the sellae to cause subarachnoid hemorrhage (if ruptured) and hypopituitarism. These branches of the cavernous segment serve as important collaterals in the ICA occlusion.

2.2.1.5 Clinoidal Segment

The clinoidal segment of the ICA is the section from proximal dural ring to distal dural ring. It is the shortest section of the ICA. There is no branch arising from the clinoidal segment of the ICA.

2.2.1.6 Ophthalmic Segment

The ophthalmic segment of the ICA is the section from the distal dural ring to the origin of the posterior communicating artery. The ophthalmic artery and superior hypophyseal artery arise from this section (Fig. 2.1). The ophthalmic artery has important branches including the central retinal artery, the anterior and posterior ethmoidal arteries, lacrimal branch, recurrent meningeal branch, and branches supplying muscles and orbital content. They may receive collateral flows from the ECA when the ICA is occluded [8]. A connection between the facial or superficial temporal artery and the lacrimal branch can serve as an important collateral route. The recurrent meningeal branch can collateralize with the middle meningeal artery or the inferior lateral trunk of the cavernous segment of ICA.

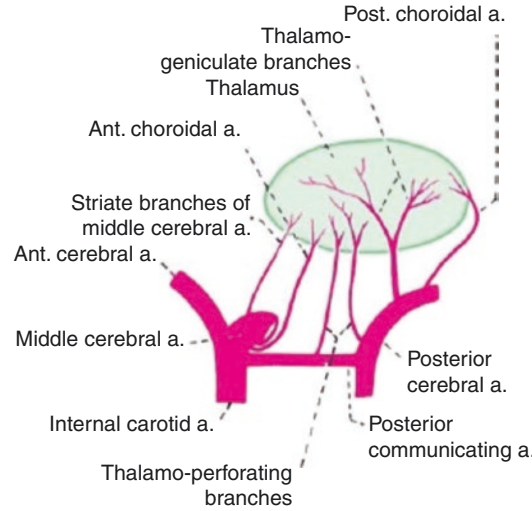

Fig. 2.3 Perforating branches of the thalamus. Adapted with permission from brainkart@com

2.2.1.7 Communicating Segment

The communicating segment of the ICA is a section from the origin of the posterior communicating artery (PCom) to the bifurcation of the ICA. The PCom and anterior choroidal arteries (AChA) arise from this section (Fig. 2.1).

The anterior thalamoperforator arteries (the most prominent branch of the anterior thalamoperforators is called premamillary artery or tuberothalamic artery), seven to ten in number, come from the superolateral aspect of the middle third of the PCom (Fig. 2.3). They supply the anterior portion of the thalamus, mammillothalamic tract, ventral amygdalofugal pathway, internal medullary lamina, posterior aspect of the optic chiasm, the proximal portion of the optic radiations, the posterior hypothalamus, and cerebral peduncle [9]. Twenty percent of people have fetal-type PCom which is a common variant. In individuals with fetal type PCom, the P1 segment of the PCA is absent or hypoplastic [10, 11]. The AChA arises from the posterior wall of the ICA between the origin of the PCom and the ICA bifurcation (Fig. 2.4). It is divided into two main segments: cisternal segment and intraventricular segment. The cisternal segment courses posterior medially below the optic tract and superomedially below the temporal lobe uncus then it turns laterally. After it curves around the cerebral peduncle in the crural cistern, it continues toward the lateral geniculate body. It turns sharply toward the choroidal fissure near the lateral geniculate body, and then, it enters the temporal horn through the choroidal fissure and the intraventricular segment begins. The sharp angle of the AChA at the choroidal fissure is known as the "plexal point." The intraventricular segment continues along the choroidal plexus and curves around the pulvinar of the thalamus anteriorly. The AChA supplies the

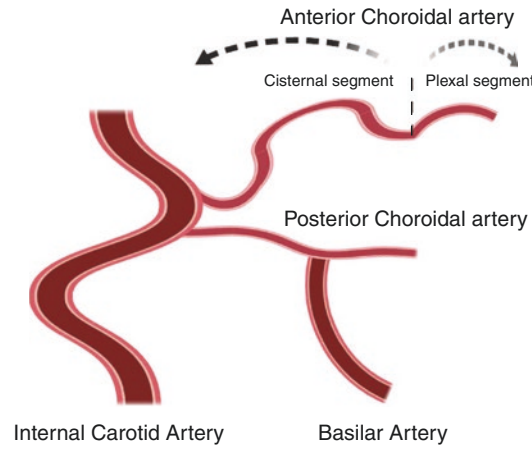

Fig. 2.4 The schematic illustration of angiographic feature of the anterior choroidal artery. *ICA* internal carotid artery, *BA* basilar artery, and *PCoA* posterior communicating artery

uncus, piriform cortex, tail of the caudate nucleus, hippocampus, amygdala, thalamus, lateral geniculate body, optic tract, genu and posterior limb of internal capsule, cerebral peduncle, choroid plexus, and subthalamic nucleus. Occlusion of the AChA causes clinical symptoms which include variable degrees of hemianesthesia, contralateral hemiplegia, and hemianopsia with memory loss and somnolence [12].

2.2.2 Anatomic Variants of the ICA

Agenesis of the ICA has been reported rarely. Unilateral agenesis of the ICA is more common than bilateral agenesis. Due to the development of the collateral circulations or alternative routes, clinical symptoms may not occur. This agenesis can be confirmed by absence of the carotid canal.

The aberrant ICA is thought to be associated with atresia or regression of the cervical portion of the ICA. It usually occurs bilaterally and may be misdiagnosed as a middle ear mass on axial images. Pseudoaneurysm and severe bleeding may occur due to biopsy of the misdiagnosed lesion.

2.2.3 Carotid-Basilar Anastomoses

Transient segmental connections between the primitive carotid and hindbrain circulations including the trigeminal, otic, hypoglossal, and proatlantal intersegmental arteries, present during development of fatal craniocerebral circulation (Fig. 2.5). These vessels course parallel with the cranial nerves and are named according to these nerves except for the extracranial proatlantal intersegmental arteries. Normally, these vessels disappear as the PComs develop. However, if these vessels are not obliterated and persist into adulthood, they are termed carotid-basilar anastomoses.

The persistent trigeminal artery is the most common of four carotid-basilar anastomoses. It arises from the posterior genu of the cavernous ICA. It curves laterally and posteriorly around the dorsum sella, following the trigeminal nerve

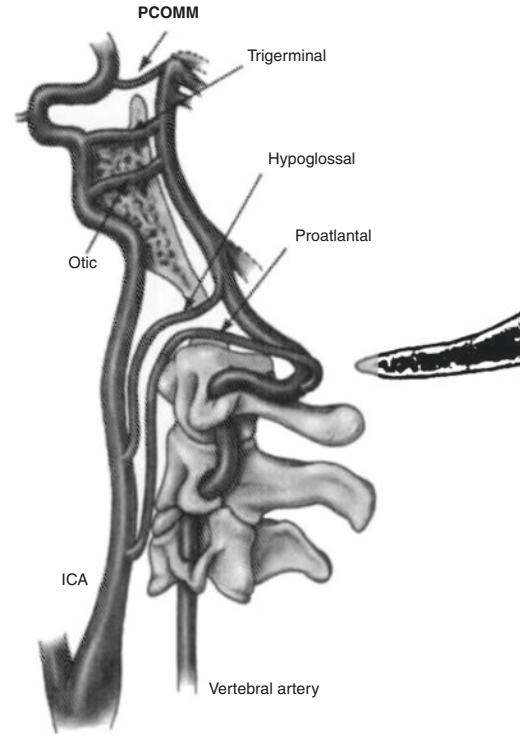

Fig. 2.5 Carotico-basilar anastomoses. Adapted with permission from American Journal of Roentgenology, Copyright American Roentgen Ray Society [13]

(parasellar course) or directly posteriorly to pierce the dorsum sellae to anastomose with the basilar artery (intrasellar course). The persistent trigeminal artery is frequently associated with other vascular abnormalities including aneurysm. The primitive otic artery arises from the petrous segment of the ICA. It emerges from the internal auditory meatus and joins the BA. The persistent otic artery is extremely rare. The persistent hypoglossal artery, the second most common anastomosis, arises from the cervical segment of the ICA at the level of C1 or C2. After that it curves posteromedially to the hypoglossal canal and passes through the hypoglossal canal to join the BA without passing the foramen magnum. In cases of persistent hypoglossal artery, the PCom is absent and the ipsilateral VA is hypoplastic. The proatlantal intersegmental artery arises from ICA (type 1) or ECA (type 2) at the level of C2 or C3, and runs posterolaterally and superiorly outside of the intervertebral foramen. Then, it passes through the foramen magnum and joins the VA.

2.3 Anterior Cerebral Artery

The ACA supplies the medial aspects of cerebral hemisphere, lentiform nucleus, and base of the frontal lobe (Fig. 2.6). The ACA is divided into three segments [14, 15]:

- A1: precommunicating segment (horizontal)
- A2: postcommunicating segment (vertical)
- A3: distal segment

The A1 segment extends horizontally from the ICA bifurcation to the origin of the anterior communicating artery (ACom). Divided from the ICA, it courses medially toward the interhemispheric fissure over the optic nerve or optic chiasm and below the anterior perforated substance.

If the A1 segment is hypoplastic or absent, the opposite A1 supplies both ACA territories through the ACom. The ACom complex has variations according to the relative size of the A1 segment and the ACom. If the diameter of the A1 segments is 1.5 mm or less, it is defined as hypoplastic. The ACom varies in diameter up to 3.4 mm, in length up to 7 mm. The greater the diameter of the ACom, the more asymmetry of the A1 segments occurs. Asymmetry of the A1 segments may affect aneurysm formation in the ACom [16, 17].

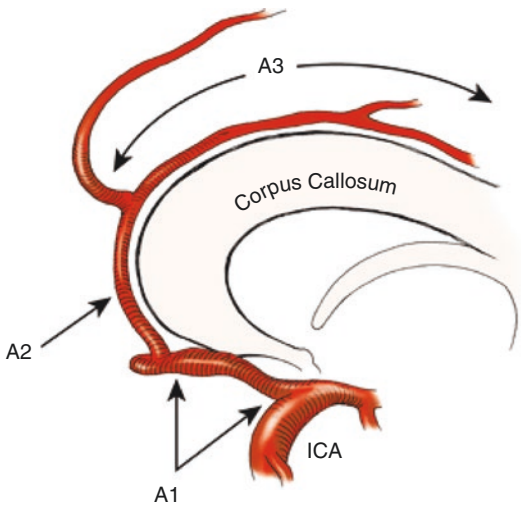

Fig. 2.6 The segments of anterior cerebral artery. Adapted with permission from Essential Neurovascular Anatomy, Copyright Springer Nature [4]

The A2 segment is the section from the origin of the ACom to the junction where the rostrum of corpus callosum and genu of corpus callosum meet. It courses upward within the interhemispheric fissure, anterior to the lamina terminalis and rostrum of corpus callosum.

The A3 segment begins at a point where the ACA is divided into the pericallosal artery and callosomarginal artery around the genu of corpus callosum. The callosomarginal artery courses over the cingulate gyrus and within the cingulate sulcus posteriorly. The pericallosal artery runs posteriorly above the corpus callosum with various lengths.

2.3.1 Perforating Branches

The medial lenticulostriate artery arises from the A1 segment, runs posterosuperiorly through the anterior perforated substance (Fig. 2.7). It supplies anterior hypothalamus, septum pellucidum, the medial part of the anterior commissure, the pillars of the fornix, and the anterior aspect of the striatum [14, 19].

The recurrent artery of Heubners arises from the proximal portion of the A2 segment (34–50%), A1 segment (17–45%), or ACom (5–20%) (Fig. 2.7). It runs back on the course of its parent vessel. It courses laterally above the A1 and M1 segments and supplies the head of the caudate nucleus, anterior limb of the internal capsule, anterior portion of the hypothalamus, and globus pallidus. Then, it terminates in the lateral aspect of the anterior perforated substance [20].

Inferiorly directed small perforating branches from A1, proximal A2, and ACom supply the optic chiasm and nerve. Also, perforating branches from the ACom are directed toward the anterior cingulum, corpus callosum, fornix, and septal region. The anterior basal perforating branches of the ACom complex supply the hypothalamic region. If these vessels are injured, neurologic and psychiatric syndromes will be generated [14, 21, 22].

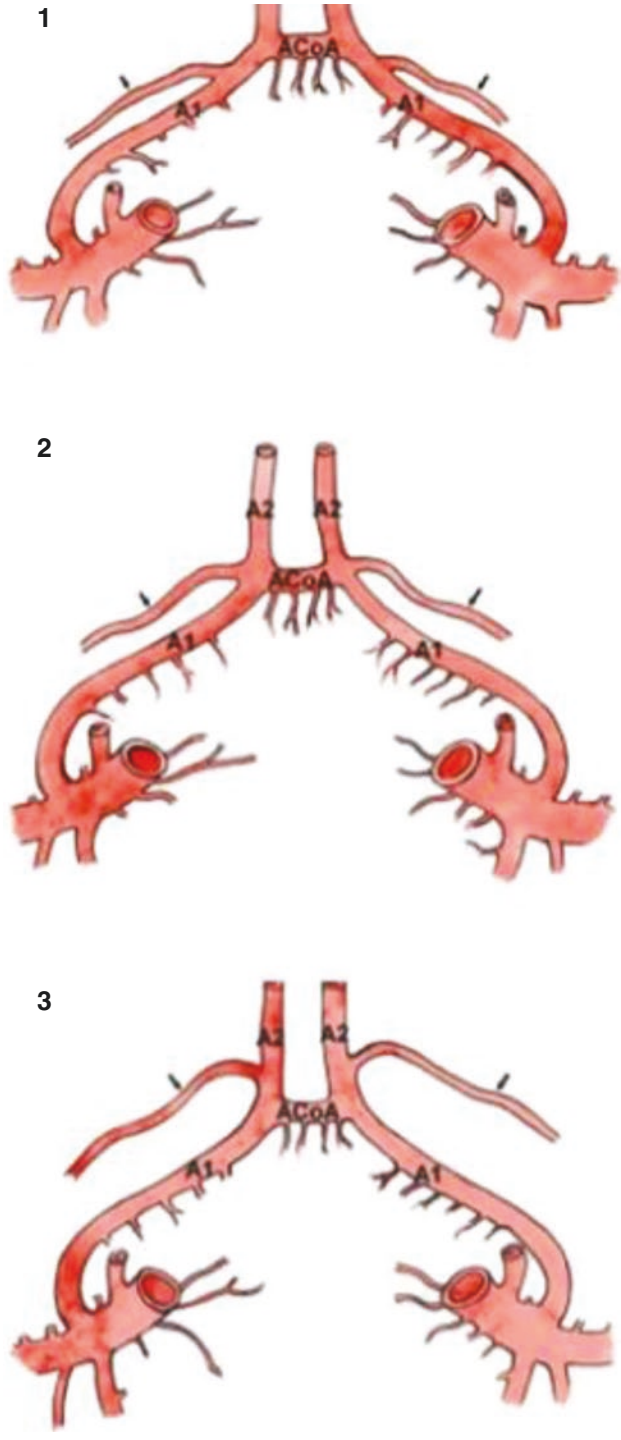

Fig. 2.7 The areas of origin of the recurrent artery of Heubner. Adapted with permission from BioMed Research International [18]