3 Concept of Large Artery and Small Vessel

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Abstract

In the TOAST classification of ischemic strokes, large-artery atherosclerosis and small-vessel occlusion are major subtypes. However, the meaning of "large artery" and "small vessel" is unclear. Histologically, the arterial system of the human body comprises of elastic and muscular arteries, arterioles, and capillaries. Among them, muscular arteries are distributed to each organ in the body and are present in the subarachnoid space of the brain. Arterioles usually have a diameter of 10–100 μm and are mostly located in the brain. "Large arteries" and "small vessels" under the TOAST classification system are not found in the histological classification of arteries. This discrepancy causes a major hurdle in the understanding of stroke pathophysiology. In this chapter, we will thoroughly explore the different concepts of large arteries and small vessels and provide a basis to understand the stroke pathophysiology.

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The TOAST classification system of ischemic strokes is based on its pathophysiology and includes some unique subtypes, such as large-artery atherosclerosis and small-vessel occlusion, that are uncommon in other classifications [1]. It is important to understand the meaning of "large artery" and "small vessel." Histologically, the arterial system of the human body comprises of elastic and muscular arteries, arterioles, and capillaries, determined by their size and proximity from the heart and does not include large arteries or small vessels, the strokes of which are the main subtypes in the TOAST system. Therefore, early career physicians and physicians-in-training of neurology intuitively assume that "large arteries" mean aorta and muscular arteries, while "small vessels" mean arterioles and capillaries. Such intuitive assumptions may not be correct, and because these words are key to the proper understanding of stroke pathophysiology, they must be clearly defined. Nevertheless, most textbooks and articles on stroke pathophysiology have not provided any obvious explanation of the terms.

The paper by Adams Jr. et al., Stroke 1993 on TOAST classification described large-artery atherosclerosis as "clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery" [1]. In their description, large arteries referred to the major brain arteries and branches to the brain cortex, and their histolog-

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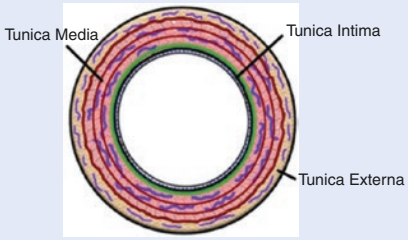
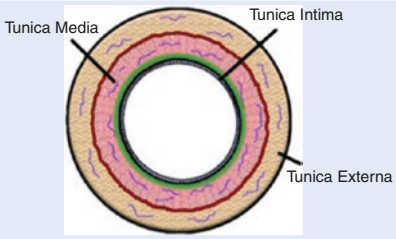
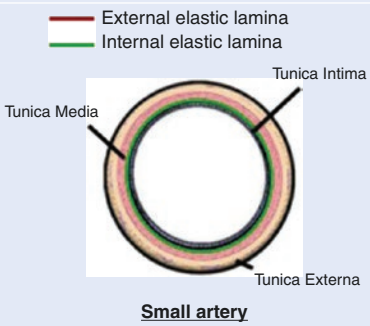
ical categories were not mentioned. Moreover, they described the strokes caused by small-vessel occlusion as "strokes are often labeled as lacunar infarcts in other classifications," without explaining the concept of small vessels. The global confusion on large arteries and small vessels must have begun here. To understand the pathophysiology of ischemic strokes, we must know the vessels involved and the pathological conditions they are involved in. In this chapter, we will thoroughly explore the different concepts of large arteries and small vessels and provide a basis to understand the stroke pathophysiology.

3.1 Histological Classification of Arteries

Table 3.1 describes the histological classification of the arterial system. The arteries from the heart to the individual organs are generally categorized as elastic and muscular arteries and arterioles [3, 4].

The elastic arteries are the aorta and pulmonary arteries, which begin directly from the heart. They are the largest in diameter among all arteries in the body. However, the vessel walls are relatively thin. They are abundant in elastin, and the elasticity is necessary to take blood from the

Table 3.1 The histological classification of the arterial system

Subtype	Details		
	Intima	Media	Adventitia
Elastic artery (conducting artery)			
 **Elastic artery**	A single layer of endothelial cells is supported by elastin-rich collagen IEL is not distinct	It consists of abundant concentrating layers of elastic laminae EEL is not distinct	It contains elastic and collagen fiber, vasa vasorum, and nervi vascularis
Muscular artery (distributing artery)			
 **Muscular artery**	It is relatively thin with well demarcated IEL It is made up of an endothelium	It is consisted mainly by smooth muscle fibers It is separated from tunica adventitia by prominent EEL	It consists of elastic and collagen fibers There is few fibroblasts, vasa vasorum and nervi vascularis
Arteriole (local regulating artery)			
 **Small artery**	It is very thin and consists of only a single layer of endothelium	It consists of one to six layers of smooth muscle cell There is no EEL	It is about the same size as tunica media

IEL internal elastic laminar, *EEL* external elastic laminar. Adapted from EC cardiology [2]

heart and deliver it. The tunica intima is composed of a single layer of endothelial cells and is supported by elastin-rich collagen. The tunica media is thick and has concentric sheets of elastin, but the smooth muscle cells are few. The tunica adventitia has a vasa vasorum for its own blood supply. The internal and external elastic lamina (IEL and EEL) are not found in elastic arteries.

The muscular arteries are the blood vessels distributed in the individual organs of our body, which course through the subarachnoid space in the brain. The tunica media contains many smooth muscle cells that can shrink and relax while supplying blood to the organs, and the elastin component is less. The tunica intima is composed of a single layer of endothelial cells, while the tunica adventitia is thick and composed mainly of collagen and elastin. Muscular arteries characteristically have distinct IEL and EEL.

Arterioles usually have a diameter of 10–100 μm and almost always course through the brain tissue. The three layers of tunica intima, media, and adventitia are intact but are much thinner compared to muscular arteries. The tunica media consists of 1–6 layers of smooth muscle cells, and the tunica adventitia has almost the same thickness as tunica media. The IEL is intact, but there is no EEL.

In the histological classification of the arterial system, large arteries and small vessels are not present. In addition, it is unclear why one of the terms has "arteries" and the other "vessels." It might have been an attempt to include venous diseases, but that is unlikely. It can be concluded that the concept of large arteries and small vessels in the arterial classification are clinical, and not histological.

3.2 Differentiation of Large Arteries and Small Vessels

Dr. Leonardo Pantoni et al. published an interesting research in 2006 [5]. Considering that small vessels have been defined poorly for clinical neurologists, they conducted a survey on the definition of a small vessel among principal investigators responsible for the top neuropathological centers around the world. The answers for the definition of small vessels had the agreement of less than 50%. This result is surprising because the respondents to this survey were prominent experts in the field of neuropathology. Their answers diversely ranged from the diameter of less than 50 μm to less than 500 μm and to only arterioles, etc. In view of the situation of no material agreement on the definition of large arteries and small vessels, we have clinically dealt with the diseases of those vessels.

Small vessels do not generally course through the subarachnoid space. As mentioned above, vessels present in the subarachnoid space are muscular arteries histologically [6]. Hence, it is reasonable to regard muscular arteries coursing through the subarachnoid space as large arteries. Moreover, these large arteries penetrate the brain parenchyma in a perpendicular fashion [7, 8]. They are also called as deep perforating arteries, which are the previously defined large arteries. Deep perforating arteries representatively include (1) posterior circulation: perforators to thalamus and brain stem arising from the posterior cerebral artery and the basilar artery, and (2) anterior circulation: lenticulostriate arteries to basal ganglia arising from the middle cerebral artery [9]. The lenticulostriate arteries have a diameter of 300–700 μm at the branching site on the middle cerebral artery, but the other perforators have a smaller diameter [9, 10]. After branching into the deep perforating arteries, the large arteries course through the subarachnoid space in the brain, and finally, penetrate the cerebral cortex [8]. These vessels are called superficial perforating arteries, which are the previously defined small vessels.

Large arteries coursing through the brain undergo progressive narrowing of the internal diameter with decreasing blood pressure, so the superficial perforating arteries have lower blood pressures and smaller diameters than the deep perforating arteries [11]. Small vessels do not have a vascular network with the adjacent small vessels without a collateral circulation [12]. Thus, regardless of the cause, if one small vessel is obstructed, lacunar infarction can occur because of no alternative blood supply.

The histological category of the clinical small vessels must also be determined. As the vascular microangiopathy of small vessels damaged by long-standing hypertension is called "arteriolosclerosis," there have been prejudices that the small vessels are arterioles [13]. However, as mentioned above, because the internal diameters of arterioles are 10–100 μm and of deep perforating and leptomeningeal arteries are approximately 50–800 μm, the small vessels are larger than arterioles. We can conclude that small vessels are histologically (1) "small" muscular arteries and (2) "large-sized" arterioles. As shown in Fig. 3.1, small vessels do not histologically belong to a single category and range from small-size arteries to large-size arterioles [14, 15]. Therefore, they are called "small vessels" rather than "small arteries," and it should be noted that the venous system is not included in the category of small vessels. From large arteries to small vessels, the lumen diameter dramatically reduces, but the blood pressure is almost constant as shown in Table 3.2 and Fig. 3.2 [11]. Hence, small vessels are the most vulnerable to long-standing hypertension. Chronic or long-standing hypertension leads to hypertensive microangiopathy (arteriolosclerosis), which ultimately causes lacunar infarction or intracerebral hemorrhage [14, 15]. Moreover, small vessels do not include capillaries. Disorders of the capillary circulation in the brain are generally not associated with strokes because the proportion of blood flow through the capillaries is too small to cause ischemia or hemorrhage. Chapter 6 describes cerebral microangiopathy in detail.

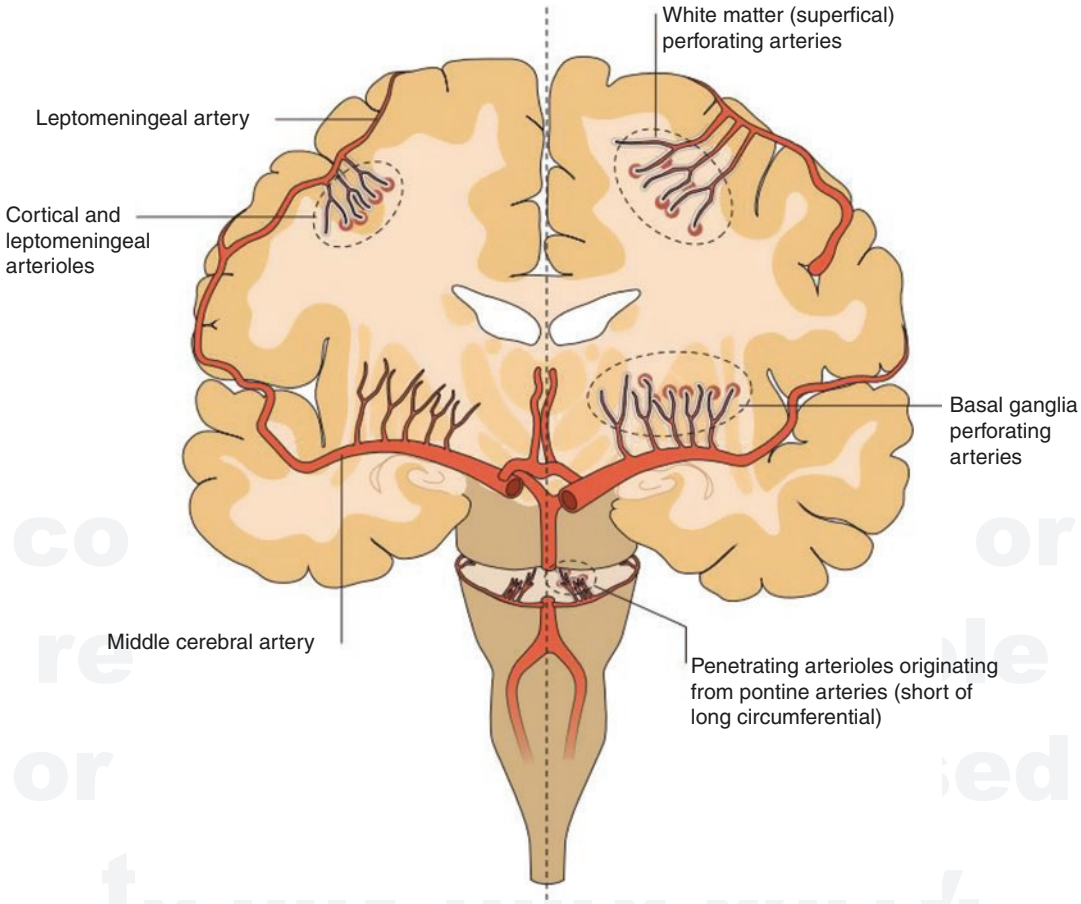


Fig. 3.1 Anatomical location of small vessel diseases. The red spots in the brain parenchyme is frequent regions of small vessel disease. Adapted with permission from Nature Reviews Neurology, Copyright Springer Nature [14]

Table 3.2 Diameter and arterial pressure at several cerebral arterial locations

Subtype	Diameter (mm)	SBP (mmHg)	DBP (mmHg)
Internal carotid	4.84	117	77
Basilar	3.45	113	73
Poserior cerebral	1.63	111	71
Distal medial striate	0.55	110	70
Prefrontal	0.96	95	61
Temporal branch of MCA	0.92	98	62
Lenticulostriate	0.58	113	73
Arterioles of lenticulostriate bed	0.19	102	65
Posterior parietal branch of MCA	1.04	85	54
Arterioles of posterior parietal bed	0.19	66	42

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MCA* middle cerebral artery. Adapted with permission from Stroke & Vascular Neurology, Copyright BMJ Publishing Group Ltd. [11]

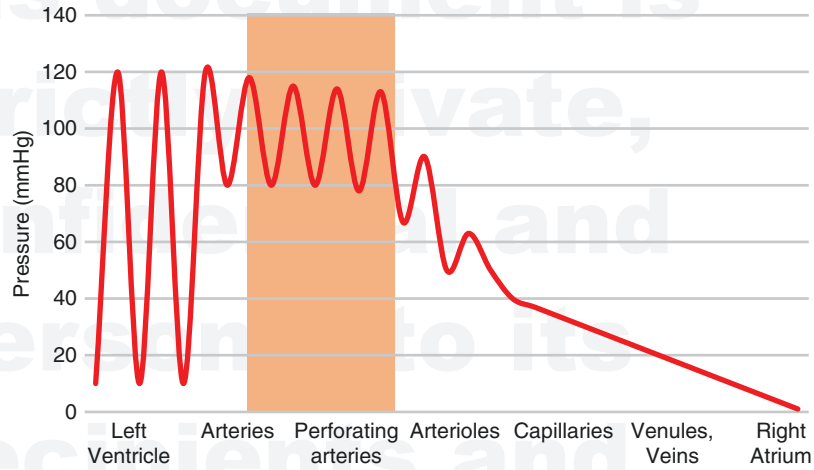


Fig. 3.2 Blood pressure in various blood vessels. The highlighting area shows blood pressure throughout the perforating arteries

3.3 Conclusions

The terms "large arteries" and "small vessels," used in the clinical classification of ischemic strokes, have caused confusion among physicians in neurology. This is because they have not been covered in basic medical contexts, such as anatomy and histology. Large arteries refer to the extracranial cerebral arteries (carotid and vertebral arteries) and intracranial muscular arteries coursing through the subarachnoid space, while small vessels refer to the deep perforating arteries and superficial perforating arteries that penetrate the brain tissue. Histologically, small vessels are the small-size muscular arteries and large-size arterioles and are most vulnerable to high blood pressure. Long-standing hypertension may result in cerebral microangiopathy (arteriolosclerosis), ultimately leading to lacunar infarction or intracerebral hemorrhage. The descriptions of large arteries and small vessels would aid in understanding stroke pathophysiology.

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