The Cerebral Circulation

Second Edition

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The Cerebral Circulation

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COLLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY: FROM MOLECULE TO FUNCTION TO DISEASE #66

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ABSTRACT

This e-book will review special features of the cerebral circulation and how they contribute to the physiology of the brain. It describes structural and functional properties of the cerebral circulation that are unique to the brain, an organ with high metabolic demands and the need for tight water and ion homeostasis. Autoregulation is pronounced in the brain, with myogenic, metabolic and neurogenic mechanisms contributing to maintain relatively constant blood flow during both increases and decreases in pressure. In addition, unlike peripheral organs where the majority of vascular resistance resides in small arteries and arterioles, large extracranial and intracranial arteries contribute significantly to vascular resistance in the brain. The prominent role of large arteries in cerebrovascular resistance helps maintain blood flow and protect downstream vessels during changes in perfusion pressure. The cerebral endothelium is also unique in that its barrier properties are in some way more like epithelium than endothelium in the periphery. The cerebral endothelium, known as the blood-brain barrier, has specialized tight junctions that do not allow ions to pass freely and has very low hydraulic conductivity and transcellular transport. This special configuration modifies Starling's forces in the brain microcirculation such that ions retained in the vascular lumen oppose water movement due to hydrostatic pressure. Tight water regulation is necessary in the brain because it has limited capacity for expansion within the skull. Increased intracranial pressure due to vasogenic edema can cause severe neurologic complications and death.

KEY WORDS

cerebral circulation, neurovascular unit, blood-brain barrier, myogenic, autoregulation, cerebral blood flow, cerebral hemodynamics, perivascular innervation, endothelium-dependent vasodilation, collaterals, pericytes

Preface

The second edition of *The Cerebral Circulation* includes updated information on the function of parenchymal arterioles and how they differ from upstream pial arteries, including new information on tone regulation, ion channel function and the role of these vessels in disease processes; an expanded section on pericytes, including development of specific histologic markers for pericyte identification and their potential role in regulation of cerebral blood flow; updated section on collaterals, including new information on the function of lemptomeningeal anastomoses, their vasoactive properties under normal and hypertensive conditions, and the importance to preserving penumbral flow during ischemia; expanded section on segmental vascular resistance in the brain, including the prominent role of large arteries in determining microvascular pressure and perfusion; and updated references and new figures.

Contents

CHAPTER 1

Introduction

As an organ, the brain comprises only about 2% of body weight yet it receives 15–20% of total cardiac output, making it one of the most highly perfused organs in the body. The high metabolic needs of the brain, relying heavily on oxidative metabolism, necessitates not only a high fraction of cardiac output but also relatively constant blood flow. The brain is also unique in that it is enclosed by the skull, a boney rigid structure that does not allow for expansion either of tissue or extracellular fluid without significant deleterious effects. Swelling of the brain due to vasogenic edema can increase intracranial pressure (ICP) and cause severe neurologic complications and even death. Because of the importance of maintaining ICP within normal ranges, and also to provide an appropriate ionic milieu for neuronal function, water and solute transport from the blood into the brain parenchyma is controlled in very special ways. The cerebral circulation is distinctive in that the large arteries account for a greater proportion of vascular resistance in the brain than in many other vascular beds. This unusually prominent role of large arteries in vascular resistance likely helps to provide constant blood flow to neuronal tissue locally and protect the cerebral microcirculation during fluctuations in arterial pressure. In this e-book, structural and functional aspects of the cerebral circulation will be reviewed, including many of its special properties. Given the large amount of subject matter, however, not all aspects of this circulation will be covered in detail.

CHAPTER 2

Anatomy and Ultrastructure

2.1 THE ARTERIES

The brain is one of the most highly perfused organs in the body. It is therefore not surprising that the arterial blood supply to the human brain consists of two pairs of large arteries, the right and left *internal carotid* and the right and left *vertebral* arteries (Figure 1). The internal carotid arteries principally supply the cerebrum whereas the two vertebral arteries join distally to form the *basilar* artery. Branches of the vertebral and basilar arteries supply blood for the cerebellum and brain stem. Proximally, the basilar artery joins the two internal carotid arteries and other communicating arteries to form a complete anastomotic ring at the base of the brain known as the *circle of Willis*, named after

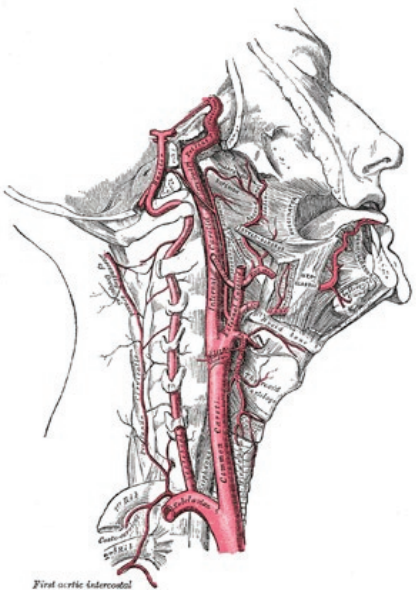

FIGURE 1: The internal carotid and vertebral arteries. Right side. Reproduction of a lithograph plate from *Gray's Anatomy* from the 20th U.S. edition of *Gray's Anatomy of the Human Body*, originally published in 1918. It is not copyrightable in the U.S. as per Bridgeman Art Library v. Corel Corp.

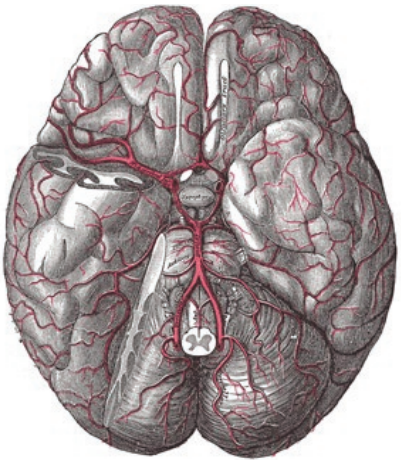

FIGURE 2: The arteries of the base of the brain. The tempora pole of the cerebrum and a portion of the cerebellar hemisphere have been removed on the right side. Reproduction of a lithograph plate from *Gray's Anatomy* from the 20th U.S. edition of *Gray's Anatomy of the Human Body*, originally published in 1918.

Sir Thomas Willis first described the arterial circle (*circulus arteriosus cerebri*). The circle of Willis gives rise to three pairs of main arteries, the *anterior*, *middle* and *posterior* cerebral arteries, which divide into progressively smaller arteries and arterioles that run along the surface until they penetrate the brain tissue to supply blood to the corresponding regions of the cerebral cortex (Figure 2).

2.2 CEREBRAL VASCULAR ARCHITECTURE

The pial vessels are intracranial vessels on the surface of the brain within the pia-archnoid (also known as the leptomeninges) or glialimitans (the outmost layer of the cortex comprised of astrocytic endfeet) [1]. Pial vessels are surrounded by cerebrospinal fluid (CSF) and give rise to smaller arteries that eventually penetrate into the brain tissue (Figure 3). Penetrating arterioles lie within the Virchow-Robin space and are structurally between pial and parenchymal arterioles. The Virchow-Robin space is a continuation of the subarachnoid space and varies considerably in depth by species [1]. The penetrating arteries become parenchymal arterioles once they penetrate into the brain tissue and become almost completely surrounded by astrocytic end feet in some brain regions [2, 3].

There are several important structural and functional differences between pial arteries on the surface of the brain and smaller parenchymal arterioles that are in the brain neuropil. First,

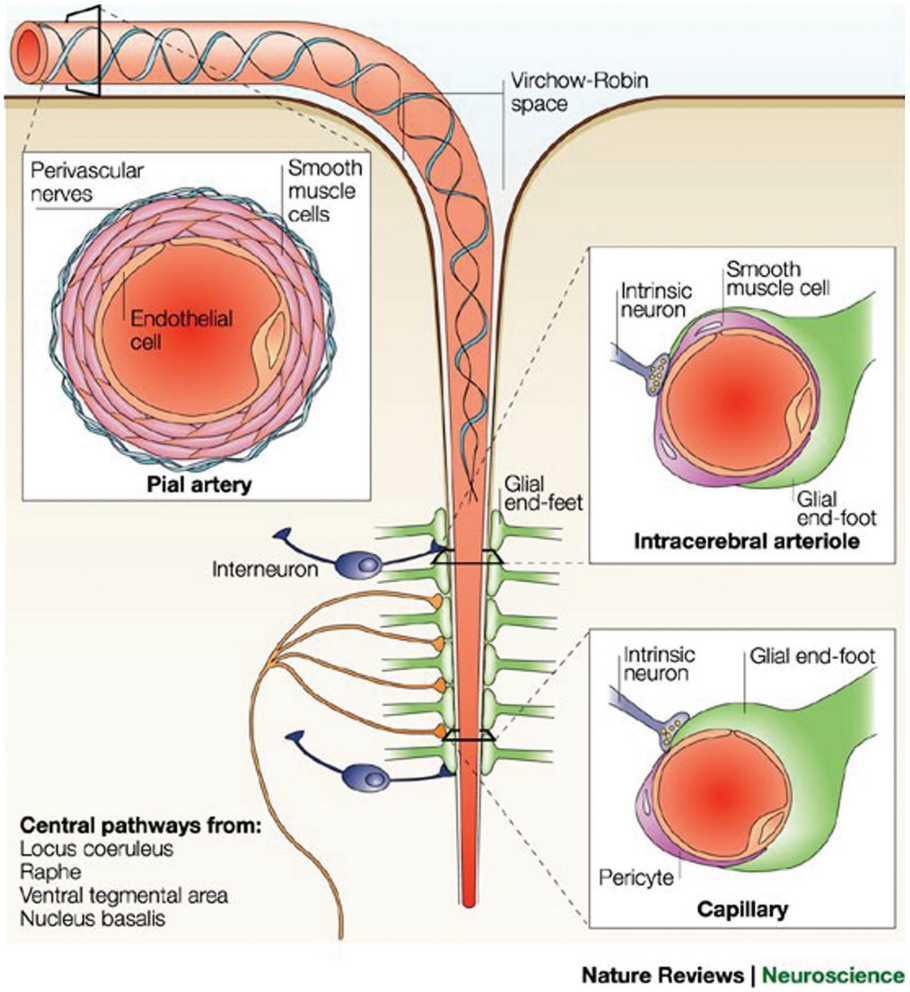

FIGURE 3: Pial arteries on brain surface have perivascular nerves that give rise to penetrating arteries within the Vichow-Robbin space. As penetrating arterioles become parenchymal arterioles within the brain neurolpil, they become associated with neurons and astrocytes. Parenchymal arterioles supply the cerebral microcirculation, known as the neurovascular unit. Used with permission from *Nat Rev Neurosci* 2004;5:347–360.

pial arteries receive perivascular innervation from the peripheral nervous system also known as "extrinsic" innervation, whereas parenchymal arterioles are "intrinsically" innvervated from within the brain neuropil (see *Perivascular innervation*) [4]. Second, while parenchymal arterioles have only one layer of circumferentially oriented smooth muscle, they possess greater basal tone due to smooth muscle that is more depolarized [5]. Third, parenchymal arterioles are unresponsive to at least some neurotransmitters that can have a significant effect on upstream vessels (e.g., serotonin, norepinephrine) [4]. Fourth, the influence of the endothelium on basal tone appears to involve endothelium-derived hyperpolarization (EDH) in addition to nitric oxide (NO) (see *Endothelial regulation of tone*) [6]. Fifth, smooth muscle from parenchymal arterioles have large-conductance calcium-activated potassium channels (BK_{Ca}) that are uncoupled from calcium sparks (see *Regulation of Cerebrovascular Tone*), which likely contributes to its more depolarized state at lower pressures [7]. Lastly, pial vessel architecture forms an effective collateral network such that occlusion of one vessel does not appreciably decrease cerebral blood flow [8]. However, penetrating and parenchymal arterioles are long and largely unbranched such that occlusion of an individual arteriole results in significant reductions in flow and damage (infarction) to the surrounding local tissue [8].

Despite differences in vessel architecture, all vessels in the brain have endothelium that is highly specialized and has barrier properties that are in some ways more similar to epithelium than endothelium in the periphery. Because of these unique barrier properties that tightly regulate exchange of solutes and water between the brain and the blood, the cerebral endothelium is known as the blood-brain barrier (BBB) [9, 10] (see *Blood–brain barrier*).

2.3 THE VEINS

The cerebral venous system is a freely communicating and interconnected system comprised of dural sinuses and cerebral veins [11, 12]. Venous outflow from the cerebral hemispheres consists of two groups of valveless veins that allow for drainage: the *superficial cortical veins* and the *deep* or *central veins* (Figure 4). The superficial cortical veins are located in the pia matter on the surface of the cortex and drain the cerebral cortex and subcortical white matter. The deep or central veins consist of subependymal veins, internal cerebral veins, the basal vein and the great vein of Galen (Figure 5). These veins drain the brain's interior, including the deep white and gray matter surrounding the lateral and third ventricles or the basal cistern and anastomose with the cortical veins, emptying into the *superior sagittal sinus (SSS)*. Venous outflow from the SSS and deep veins is directed via a confluence of sinuses toward the sigmoid sinuses and jugular veins. The cerebellum is drained primarily

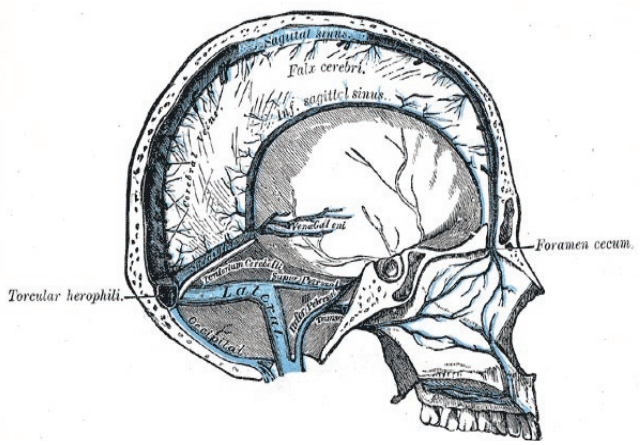

FIGURE 4: Superficial cortical veins and dural sinuses. Reproduction of a lithograph plate from *Gray's Anatomy* from the 20th U.S. edition of *Gray's Anatomy of the Human Body*, originally published in 1918.

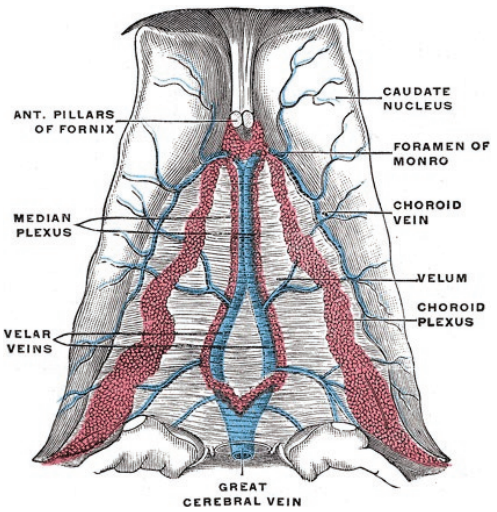

FIGURE 5: Deep or central veins**.** Reproduction of a lithograph plate from *Gray's Anatomy* from the 20th U.S. edition of *Gray's Anatomy of the Human Body*, originally published in 1918.

by two sets of veins, the *inferior cerebellar veins* and the *occipital sinuses*. The brain stem is drained by the veins terminating in the inferior and transverse petrosal sinuses.

2.4 STRUCTURE OF CEREBRAL VESSELS

The wall of cerebral arteries and arterioles consist of 3 concentric layers: the innermost layer is the *tunica intima* that consists of a single layer of endothelial cells and the internal elastic lamina (IEL); the next layer out is the *tunica media* that contains mostly smooth muscle cells with some elastin and collagen fibers; and the outermost layer is the *tunica adventitia*, composed mostly of collagen fibers, fibroblasts and associated cells such as perivascular nerves (in large and small pial arteries) and pericytes and astrocytic endfeet (in parenchymal arterioles and capillaries). Unlike systemic arteries, cerebral arteries have no external elastic lamina, but instead have a well-developed IEL [13]. Other differences from systemic arteries include a paucity of elastic fibers in the medial layer, and a very thin adventitia. The number of smooth muscle cell layers varies depending on the size of the vessels and species with large arteries such as the internal carotid artery having as many as 20 layers. Smaller pial arteries contain ~2–3 layers of smooth muscle, whereas the penetrating and parenechymal arterioles contain just one layer of smooth muscle. In addition, smooth muscle in the medial layer of cerebral arteries and arterioles are circularly arranged and oriented perpendicular to blood flow with essentially a zero-degree pitch. Cerebral veins are very thin-walled compared to arteries. The larger pial veins have circumferentially oriented smooth muscle that is not present in veins in the brain parenchyma. Unlike veins in the periphery, cerebral veins do not contain valves [12].

2.5 THE MICROCIRCULATION AND THE "NEUROVASCULAR UNIT"

The capillary bed of the brain is comprised of a dense network of intercommunicating vessels that consist of specialized endothelial cells and no smooth muscle [2]. The total length of capillaries in the human brain is ~400 miles [14]. It is the primary site of oxygen and nutrient exchange, which in turn is dependent on the path length and transit time of red blood cells. In the brain, all capillaries are perfused with blood at all times [15] and it has been estimated that nearly every neuron in the brain has its own capillary [16], demonstrating the critical relationship between the neuronal and vascular compartments. The intravascular pressure gradient between the precapillary arteriole and

postcapillary venule is the primary regulator of capillary flow. Dilatation of resistance arteries and arterioles increases the microvascular pressure gradient and increases capillary flow. Thus, regulation of flow in the microcirculation is dependent on the regulation of flow and microvascular pressure in the brain arterioles. Red cell velocity in the cerebral capillary microcirculation is remarkably high (~1 mm/sec) and heterogeneous (range: 0.3 to 3.2 mm/sec) [17]. The heterogeneous flow velocity is important for effective oxygen transport to neuronal tissue that has considerable metabolic needs that fluctuate regularly.

Under normal conditions, the density of brain capillaries varies significantly within the brain depending on location and energy needs with higher capillary density in gray vs. white matter [18]. Pathological, physiological and environmental states can influence or promote changes in capillary density. For example, chronic hypoxia increases capillary density through activation of angiogenic pathways (e.g., hypoxia inducible factor-1 and vascular endothelial growth factor) driven by a decrease in the driving force of PaO_2 [19, 20]. Brain capillary density nearly doubles between 1 and 3 weeks of chronic hypoxic exposure [19]. This adaptive increase in capillary density during chronic hypoxia increases cerebral blood volume [21] and restores tissue oxygen tension [22]. Hypertension also affects brain capillary density. Similar to the peripheral microcirculation, hypertension causes rarefaction (decrease in number) of capillaries and impaired microvessel formation that can increase vascular resistance [23]. In contrast, pregnancy has been shown to increase capillary density in animal models [5].

Brain capillary structure is also unique compared to other organs. Endothelial cells and pericytes are encased by basal lamina (~30–40 nm thick) containing collagen type IV, heparin sulfate proteoglycans, laminin, fibronectin and other extracellular matrix proteins [15, 24]. The basal lamina of the brain endothelium is continuous with astrocytic endfeet that ensheath the cerebral capillaries (Figure 6). Astrocytes have a significant influence on capillary function, including regulating cerebral blood flow locally, upregulating tight junction proteins, contributing to ion and water homeostasis and interfacing directly with neurons [2, 3, 15, 25, 26]. Although the barrier properties of the BBB are at the level of the tight junction in endothelial cells (see *Blood-brain barrier*), there is an important role for other components of the BBB, including the basement membrane, pericytes, astrocytes and neurons. There is complex cross-talk between all entities and cell types, collectively known as the "neurovascular unit." Consideration of the neurovascular unit is important for disease processes that induce hemorrhage, vasogenic edema, infection and inflammation [15, 24, 25, 26]. The neurovascular unit may be the primary site of dysfunction for some disease states, however, for others such as atherosclerosis, large arteries are predominantly affected. For others, such as chronic hypertension, all segments of the circulation are affected.

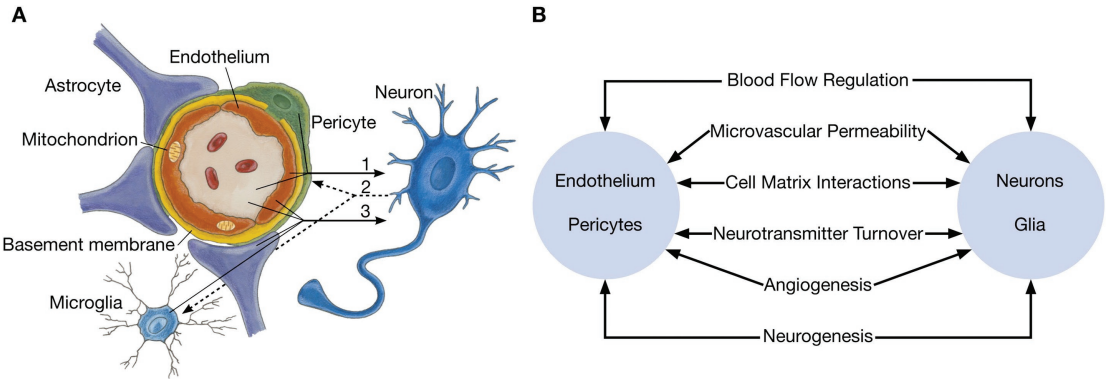

FIGURE 6: Schematic of the Neurovascular Unit. (A) Endothelial cells and pericytes are separated by the basement membrane. Pericyte processes sheathe most of the outer side of the basement membrane. At points of contact, pericytes communicate directly with endothelial cells through the synapse-like peg-socket contacts. Astrocytic endfoot processes unsheathe the microvessel wall, which is made up of endothelial cells and pericytes. In cases of neuronal disorders that have a primary vascular origin, circulating neurotoxins may cross the BBB to reach their neuronal targets, or proinflammatory signals from the vascular cells or reduced capillary blood flow may disrupt normal synaptic transmission and trigger neuronal injury (arrow 1). Microglia recruited from the blood or within the brain and the vessel wall can sense signals from neurons (arrow 2). Activated endothelium, microglia, and astrocytes signal back to neurons, which in most cases aggravates the neuronal injury (arrow 3). In the case of a primary neuronal disorder, signals from neurons are sent to the vascular cells and microglia (arrow 2), which activate the vasculo-glial unit and contributes to the progression of the disease (arrow 3). (B) Coordinated regulation of normal neurovascular functions depends on the vascular cells (endothelium and pericytes), neurons, and astrocytes. Used with permission from Neuron 2008;57:178-201.

2.5.1 Pericytes

The discovery of pericytes has been largely attributed to Rouget in 1879 as cells adjacent to capillaries that share a common basement membrane with endothelial cells [27, 28]. The pericyte:endothelia ratio is high in the brain compared to the vasculature of other organs, e.g., 1:3 in brain vs. 1:100 in skeletal muscle [29]. Pericytes can be oriented along the length of a blood vessel or circumvent the vessel with long processes that cover a large part of the abluminal surface. The cytoplasmic processes can be quite long and span several endothelial cells. The gold standard for identification of pericytes is by ultrastructural analysis. However, several pericyte-specific histologic markers have been proposed [30, 31], including platelet-derived growth factor receptor β (PDGFβ) [32], NG2 [33], desmin [34] and vimentin [35]. Pericytes have a number of potential roles in the brain

and brain vasculature, although it has been difficult to define some of these roles in vivo. Pericytes contribute to the stability of the vessel and release growth factors and matrix important for microvascular permeability, remodeling and angiogenesis [36].

A potential role for pericytes in regulating CBF has been proposed, but their exact involvement has been difficult to discern. Some pericytes express contractile proteins and are located on capillaries where smooth muscle is absent, leading some investigators to propose they are involved in microvascular flow regulation. However, there are conflicting reports that pericytes regulate flow and are involved in neurovascular coupling (see *Neurovascular coupling*). One study demonstrated pericyte regulation of capillary flow in a brain slice preparation and in cortex in vivo [37] and suggested they play a role in neurovascular coupling. In contrast, Hill et al. excluded the role of pericytes in regulating flow but instead reported that precapillary arterioles are the primary site of flow regulation to the microcirculation [38]. Another report showed pericytes dilated capillaries in response to neural stimulation [39]. However, because capillaries do not possess smooth muscle, dilation of capillaries independent of a change in pressure gradient is unlikely. In other words, capillaries do not actively dilate.

A role for pericytes in ischemic brain injury has also been proposed. Some investigators have suggested pericyte contractions in response to ischemia cause distal microvascular occlusions that contribute to "no reflow" [40]. However, Hill et al. [38] demonstrated a major role for arterioles and arteriolar smooth muscle contraction in response to ischemia with no effect on pericytes. Other studies using isolated parenchymal arterioles also demonstrated increased vasoconstriction and smooth muscle calcium sensitization in response to ischemia and reperfusion, further supporting that arterioles in the brain are major regulators of microvascular flow under normal and disease states [41, 42]. However, given the heterogeneity of these cells in number, size, orientation and location, it is likely there are subclasses of pericytes with different structures and functions.

2.6 COLLATERALS

The collateral circulation in the brain consists of vascular networks that allow for maintenance of cerebral blood flow when principal inflow conduits fail due to occlusion or constriction. The circle of Willis at the base of the brain allows for redistribution of blood flow when extracranial or large intracranial vessels are occluded [43, 44] (Figure 7). This anastomotic loop provides low-resistance connections that allow reversal of blood flow to provide primary collateral support to the anterior and posterior circulations. However, the anatomy of the circle of Willis varies substantially with species and individuals and is often asymmetric [44]. The circle of Willis collateral support is important for carotid occlusions and stenosis that are prevalent in the population.

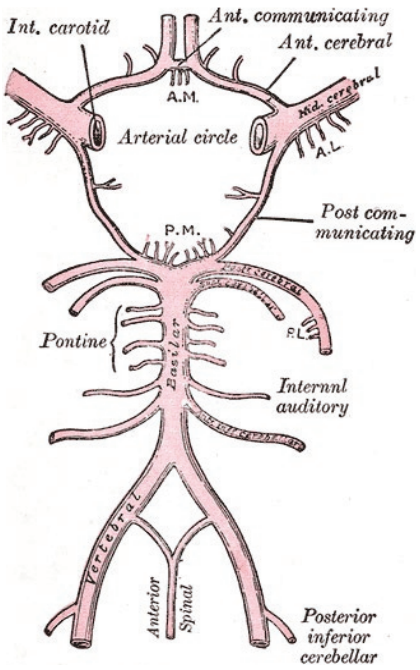

FIGURE 7: Diagram of the arterial circulation at the base of the brain. Reproduction of a lithograph plate from *Gray's Anatomy* from the 20th U.S. edition of *Gray's Anatomy of the Human Body*, originally published in 1918.

The pial network of leptomeningeal anastomoses comprises secondary collaterals that are responsible for redistribution of flow when there is constriction or occlusion of an artery distal to the circle of Willis [43, 45]. These vessels comprise distal anastomoses from branches of the anterior, middle and posterior cerebral arteries (Figure 8). The functional capacity for collateral supply is dependent on the number and luminal caliber of the vessel that can be quite variable. Studies using genetically altered mice showed that brain infarction after middle cerebral artery occlusion varied depending on the extent of leptomeningeal collaterals with more collaterals the smaller the infarction [45]. This is likely due to the ability of the leptomeningeal anastomoses to promote retrograde flow from the anterior cerebral artery territory to the middle cerebral artery territory to create a *penumbra* during focal occlusion of the middle cerebral artery. The penumbra is a region of constrained blood supply during focal ischemia that is potentially salvageable if blood flow is restored to normal quickly or neuroprotective agents are present to prevent cell death [43]. The ability of leptomeningeal anastomoses to sustain penumbral flow during an occlusion has been largely attributed to the ability of these vessels to promote bidirectional flow that is passive in nature [45]. However, little is known

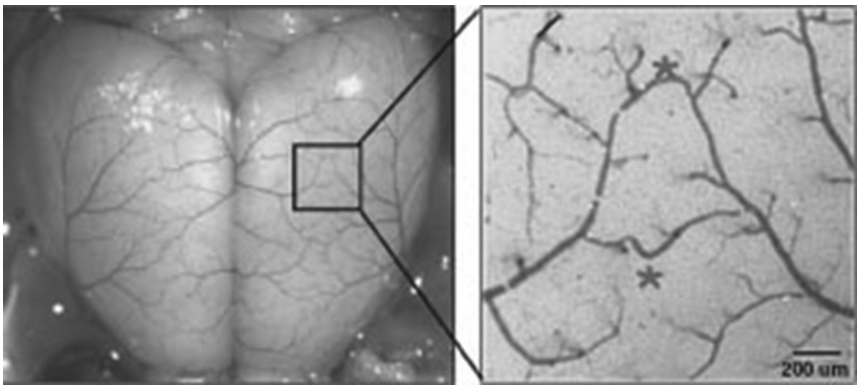

FIGURE 8: Leptomeningeal anastomoses. Inset shows high magnification of pial anastomoses between the anterior and middle cerebral artery territories (*). These small arterioles are functionally unique and provide for bidirectional flow to sustain cerebral blood flow from the unobstructed to the obstructed vascular territory. Used with permission from *J Cerebr Blood Flow Metab.* 2010: 30(5):923–34.

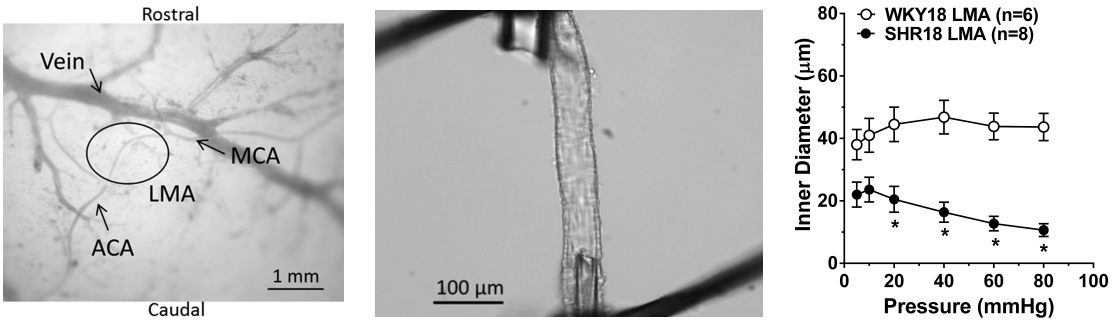

FIGURE 9: Isolation and cannulation of leptomeningeal arterioles (LMAs). Studies of pial arterioles using isolated and pressurized vessel methodology demonstrated that LMAs from normotensive rats had little myogenic tone and reactivity to pressure (graph) whereas LMAs from spontaneously hypertensive rats (SHR) were highly vasoconstricted and responded to pressure with a myogenic response. Used with permission from *Stroke* 2016;47:1618–25.

about their functional capacity. Recently, isolated vessel methodology was used to provide the first evidence of functional changes in leptomeningeal anastomoses in animal models [46]. Compared to pial arterioles that do not anastomose, collaterals are relatively passive under normal conditions and respond to increased pressure with dilation (Figure 9). This passive state would be conducive to retrograde or bidirectional flow. However, collaterals taken from chronically hypertensive animals

were highly vasoconstricted especially in response to increased pressure. The vasoactive nature of pial collaterals during hypertension likely explains why patients and animals with hypertension have large ischemic cores and little salvageable tissue.

Venous collaterals exist as well to augment drainage when primary routes are occluded or during venous hypertension [44]. The superficial cerebral veins are highly anastomosed with each other to provide a network of collaterals [11]. The deep veins are anastomosed with other venous systems and also provide collateral support for drainage [11].