Introduction

Spontaneous subarachnoid hemorrhage is a bleeding into the subarachnoid space without trauma. Aneurysms are the underlying cause in 80% of the cases. Among other causes are arteriovenous malformations, anticoagulation, vasculitis and brain tumor. Spontaneous subarachnoid hemorrhage is a serious disease where up to half of the patients die. Of those who survive, only half return to work and many have a reduced quality of life **.**

Aneurysmal subarachnoid hemorrhage (SAH) accounts for only 1–7% of all strokes but is responsible for 27% of all stroke-related years of life lost before the age of 65 years. Delayed cerebral ischemia (DCI) is a common complication of aneurysmal SAH and is associated with poor clinical outcome and death. Cerebral vasospasm (arterial narrowing occurring 3 to 14 days after aneurysmal SAH) is considered the main culprit of DCI .

Spontaneous subarachnoid hemorrhage is presented by severe headache with rapid onset, vomiting, confusion or disturbed consciousness, neck stiffness and sometimes seizures and complicated by cerebral vasospasm and obstructive hydrocephalus **.**

Vasospasm is defined by using terms including symptomatic vasospasm, delayed cerebral ischemia (DCI), transcranial doppler vasospasm, and angiographic vasospasm**.**

Despite effective treatment of the aneurysm, delayed cerebral ischemia (DCI) is observed in 30% of patients with a peak on the tenth day resulting in significant infirmity and mortality. Cerebral vasospasm occurs in

more than half of all patients and is recognized as the main cause of delayed cerebral ischemia after subarachnoid hemorrhage.

Anatomical and Physiological Considerations of Cerebral Circulation

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Anatomical Considerations of Cerebral Circulation:

Vascular Anatomy of The Cortex:

The most comprehensive and influential work is the one by Duvernoy et al., (1981), who described the vascular system of the human cortex in detail. Most of the general aspects are valid not only for the human cortex but also for many of the most widely used experimental animals, such as non-human primates ***(Weber et al., 2008).***

Cortical vessels can be divided into short, inter-mediate and long vessels, depending on their cortical penetration depth. Duvernoy et al., (1981), have extended this classification to six groups. Group 1 vessels feed/drain cortical layers I and II, whereas group 2 vessels reach layer III. The most numerous vessels are the group 3 vessels that feed/drain cortical layer IV, as well as the lower layer III and layer V. Group 4 vessels reach layer VI and white matter. Group 5 arteries and veins vascularize the cortex as well as the adjacent white matter. Group 6 vessels are restricted to arteries that run through the cortex without branching to vascularize exclusively the white matter ***(Hirsch et al., 2012)***.

An interesting aspect is the ratio between descending cortical arteries and ascending cortical veins. Many authors have previously estimated this (AV) ratio to be 1.6 in favor of arteries ***(Weber et al., 2008)***.

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*. 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 Sir Thomas Willis who 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***(Cipolla et al., 2009)***.

Cerebral Vascular Architecture:

The pial vessels are intracranial vessels on the surface of the brain within the pia–arachnoid (also known as the leptomeninges) or glia limitans (the outmost layer of the cortex comprised of astrocytic end-feet). Pial vessels are surrounded by cerebrospinal fluid (CSF) and give rise to smaller arteries that eventually penetrate into the brain tissue (Fig. 1) ***(Cipolla et al., 2009)***.

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. The penetrating arteries become parenchymal arterioles once they penetrate into the brain tissue and become almost completely surrounded by astrocytic end-feet ***(Hirsch et al., 2012)***.

There are several important structural and functional differences between pial arteries on the surface of the brain and smaller parenchymal arterioles. First, pial arteries receive perivascular innervation from the peripheral nervous system also known as “extrinsic” innervation, whereas parenchymal arterioles are “intrinsically” innervated from within the brain neuropil. While parenchymal arterioles have only one layer of circumferentially oriented smooth muscle, they possess greater basal tone and are

unresponsive to at least some neurotransmitters that can have large effects on upstream vessels (e.g., serotonin, norepinephrine) ***(Cipolla et al., 2009)***.

Lastly, pial vessel architecture forms an effective collateral network such that occlusion of one vessel does not appreciably decrease cerebral blood flow. 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 ***(Hirsch et al., 2012)***.

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 nutrients, solutes and water between the brain and the blood, the cerebral endothelium is known as the blood–brain barrier (BBB) ***(Cipolla et al., 2009)***.

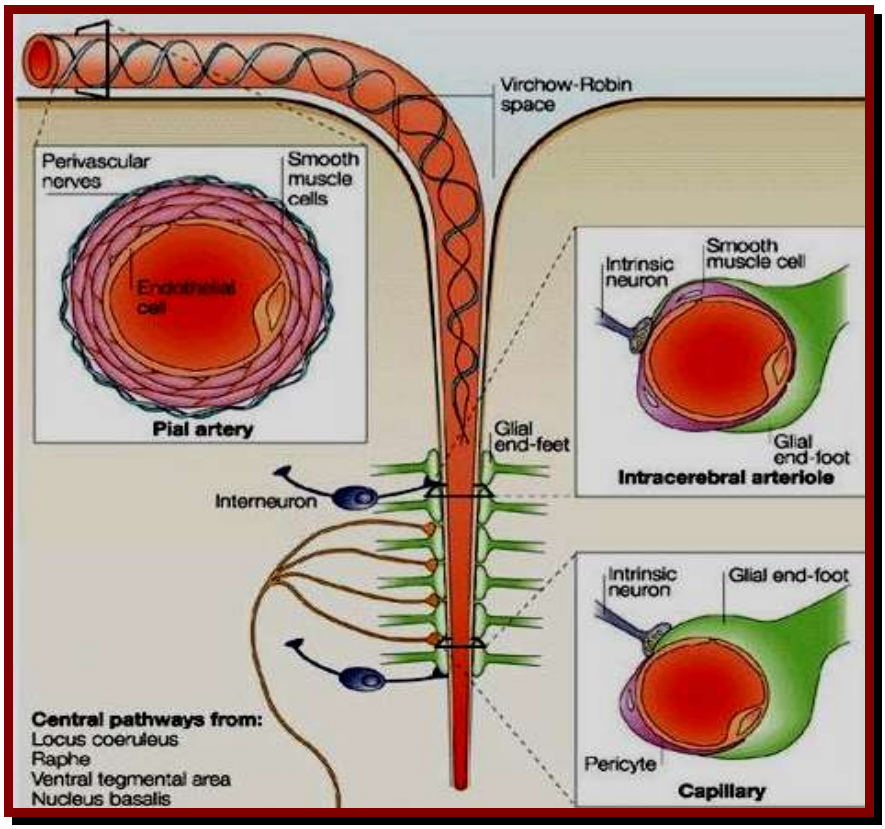

Fig. 1: Pial arteries on the brain surface have perivascular nerves that give rise to penetrating arteries within the Virchow–Robin space. As penetrating arterioles become parenchymal arterioles within the brain neuropil, they become associated with neurons and astrocytes. Parenchymal arterioles supply the cerebral microcirculation, known as the neurovascular unit *(Cipolla et al., 2009)*.

The Veins:

The cerebral venous system is a freely communicating and interconnected system comprised of dural sinuses and cerebral veins. Venous outflow from the cerebral hemispheres consists of two groups of valveless veins which allow for drainage: the *superficial cortical*

veins and the *deep or central veins* ***(Kilic and Akakin, 2008)***.

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, basal vein and the great vein of Galen (Fig. 2) ***(Cipolla et al., 2009)***.

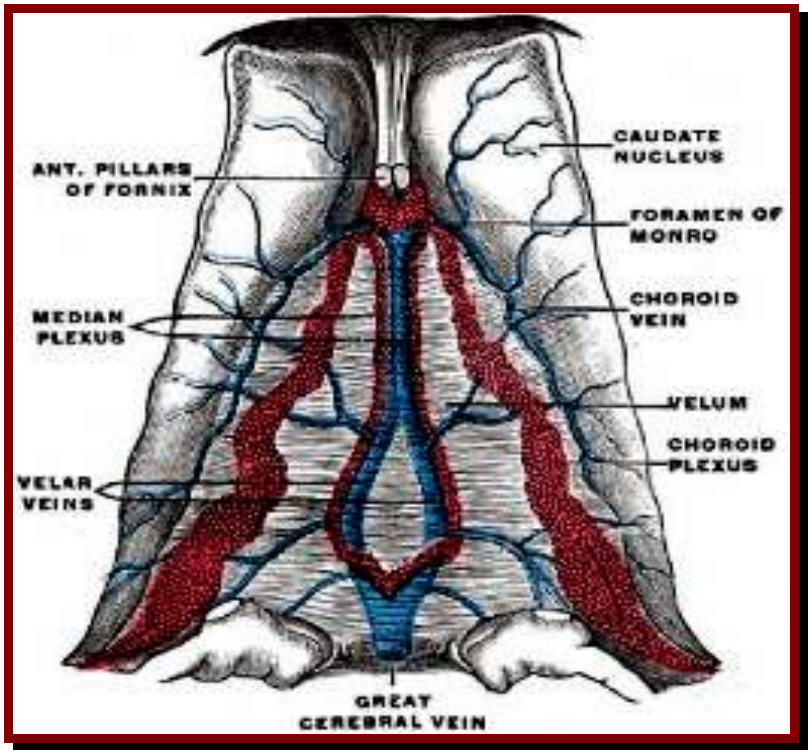

Fig. 2: Deep or central veins *(Cipolla et al., 2009)*.

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 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 ***(Cipolla et al., 2009)***.

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. The total length of capillaries in the human brain is ~400 miles. 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 ***(Zlokovic, 2008)***.

In the brain, all capillaries are perfused with blood at all times and it has been estimated that nearly every neuron in the brain has its own capillary, demonstrating the critical relationship between the neuronal and vascular compartments ***(Zlokovic, 2008)***.

Pericytes:

Pericytes were discovered in 1890 by Rouget as cells adjacent to capillaries that share a common basement membrane with endothelial cells. 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. Pericytes can be oriented along a blood vessel or circumvent the vessel with long processes that cover a large part of the luminal surface. Pericytes have a number of potential roles in the brain, although it has been difficult to define these roles in vivo. They contribute to the stability of the vessel and release growth factors and matrix important for microvascular permeability, remodeling and angiogenesis ***(Duffy, 2008)***.

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 (Fig. 3). 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 ***(Cipolla et al., 2009)***.

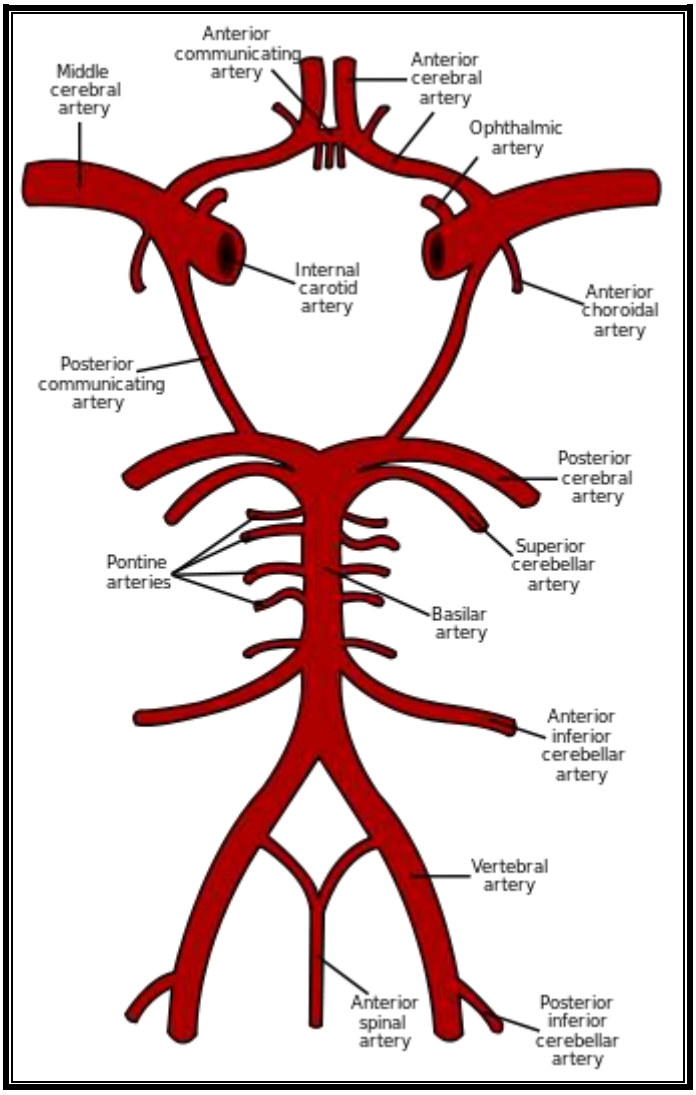

Fig. 3: Diagram of the arterial circulation at the base of the brain (*Cipolla et al., 2009*).

The pial network of leptomeningeal vessels comprises secondary collaterals and are responsible for redistribution of flow when there is constriction or occlusion of an artery

distal to the circle of Willis. These vessels comprise distal anastomoses from branches of the anterior, middle and posterior cerebral pial arteries (Fig. 4) ***(Hossmann, 2006)***.

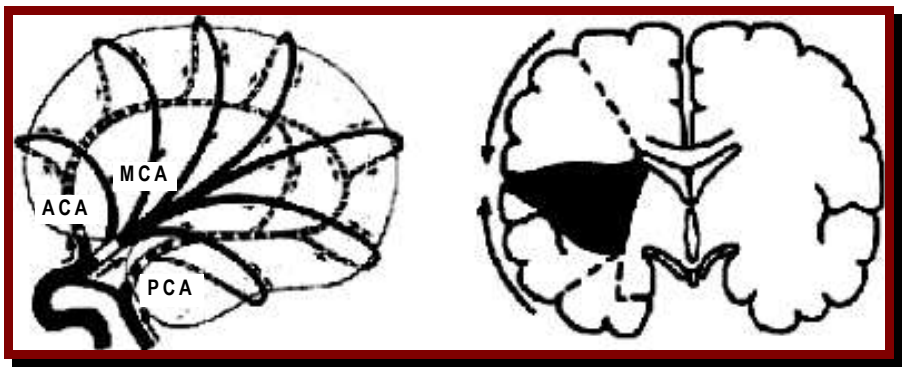

Fig. 4: Collateral circulation of the brain. Heubner's leptomeningeal anastomoses connect the peripheral branches of the brain arteries and provide collateral blood flow to the peripheral parts of the adjacent vascular territories, ACA: Anterior cerebral artery, MCA: Middle cerebral artery, PCA: posterior cerebral artery *(Hossmann, 2006)*.

The functional capacity for collateral supply is dependent on the number and luminal caliber of the vessel that can be quite variable in the leptomeningeal anastomoses. Venous collaterals exist as well to augment drainage when primary routes are occluded or during venous hypertension. The superficial cerebral veins are highly anastomosed with each other to provide a network of collaterals. The deep veins are anastomosed with other venous systems and also provide collateral support for drainage ***(Cipolla et al., 2009)***.

Pial Network:

The pial network consists of large arteries and veins. Arteries usually run on top of the veins. However, this does not always apply and therefore cannot be used for reliable differentiation. It is well established that the pial vessels form numerous loops within the arterial and also within the venous network ***(Hirsch et al., 2012)***.

Intra-cortical Vascular Network:

The neocortex has been intensively studied with respect to the architecture of the neuronal circuits. Although normal information processing of neurons greatly depends on a sustained delivery of nutrients and oxygen, the cortical vasculature has been studied much less vigorously although it is far less complex than the neuronal network ***(Hirsch et al., 2012)***.

The differences in the cortical layers with respect to the neuronal architecture are paralleled by changes in the vascular organization. A closer look at the vascular density reveals that there is a distinct laminar profile. Some authors however, found that the metabolic profile as measured by cytochrome oxidase (COX) activity perfectly matches the vascular density ***(Weber et al., 2008)***.

This observation can be interpreted to indicate that the number of neurons and synapses determines an upper

bound of the activity. The spatial correspondence of mean metabolic activity and vascularization, however, reflects the neural activity that represents a ‘default’ mode of brain steady state. Staining for COX activity can be used to map functional units of the neocortex. As an example, the primary visual cortex shows patches of increased COX activity in layers II and III, the so-called blobs ***(Hirsch et al., 2012)***.