*Section A-Research paper*

# An Overview about Physiology and Dynamics of Cerebrospinal Fluid

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**Abstract**

**Background:** For children more than 2 – 3 years, the cranial fontanelles and sutures are closed, and the skull can be considered a rigid container with a fixed volume. Its content includes the brain bulk (80%), the blood volume (10%), and the cerebrospinal fluid (CSF) (10%). According to the Monro-Kellie doctrine, intracranial volume is equal to the sum of the volume of the brain, blood, CSF and other mass lesions. Therefore, an increase in volume of any of these components, such as CSF, can raise intracranial pressure (ICP) and reduce cerebral perfusion pressure and cerebral blood flow. Acute ICP elevation can reduce cerebral perfusion pressure (CPP), which is determined by subtracting ICP from the mean arterial pressure (MAP). A significant change in ICP can lead to changes in brain perfusion which can alter CPP when autoregulation of cerebral blood vessels is impaired (e.g. during stroke), and chronic conditions of elevated ICP can produce papillary oedema, loss of vision and death. Hydrocephalus may also be non-obstructive, in which CSF flow within the ventricular system is not impaired but there is decreased absorption. Additionally, tumours of the choroid plexus may also produce increased CSF secretion in rare cases and if this increased secretion is not compensated for by increased outflow, then hydrocephalus can occur.

**Keywords:** Cerebrospinal Fluid, physiology, dynamics

## Introduction

For children more than 2 – 3 years, the cranial fontanelles and sutures are closed, and the skull can be considered a rigid container with a fixed volume. Its content includes the brain bulk (80%), the blood volume (10%), and the cerebrospinal fluid (CSF) (10%). According to the *Monro-Kellie doctrine*, intracranial volume is equal to the sum of the volume of the brain, blood, CSF and other mass lesions ***(Mokri BA ., 2001).*** Therefore, an increase in volume of any of these components, such as CSF, can raise intracranial pressure (ICP) and reduce cerebral perfusion pressure and cerebral blood flow ***(Wang PP et al ., 2005)***.

The major compensatory mechanism within the intracranial vault appears to be the CSF volume, 90% of which is in the subarachnoid spaces and 10% of which is within the ventricular system. This mechanism can be quantified as the volume-pressure intracranial compliance ($\Delta V/\Delta P$ = compliance) or pressure volume index (PVI). The PVI is the volume of fluid injected or withdrawn that would result in a tenfold change in ICP and can be calculated as: $PVI = \Delta V/\log (P_f/P_0)$, where $\Delta V$ is volume change, $P_f$ is final ICP, and $P_0$ is initial ICP. The PVI varies with age; for example, the PVI is 8 mL in an infant but 25 mL in a 14 years old. Thus a 10-mL addition in volume to the intracranial contents of a 14-year-old may produce a modest and tolerable increase in ICP, but the same addition can be lethal in an infant. However, with infants and very young children who have open fontanelles and sutures, the Monro-Kellie doctrine does not apply because the cranial vault can expand with increased volume (***Avellino AM et al ., 2002).***

Acute ICP elevation can reduce cerebral perfusion pressure (CPP), which is determined by subtracting ICP from the mean arterial pressure (MAP). A significant change in ICP can lead to changes in brain perfusion

which can alter CPP when autoregulation of cerebral blood vessels is impaired (e.g. during stroke), and chronic conditions of elevated ICP can produce papillary oedema, loss of vision and death **(Hiploylee CA et al .,2014)**

The normal range of ICP in healthy adults is around 5–15 mmHg with increases to 30 mmHg considered pathological, and 40 mmHg life threatening **(Dunn LT .,2002)**

Hydrocephalus is caused by disruptions to CSF secretion, flow, or drainage, which lead to increased ICP **(Leinonen V .,2018).** Around 95% of hydrocephalus is thought to be caused by disruptions to CSF flow, commonly caused by tumours throughout the ventricular system, and there is some evidence of transient obstructive hydrocephalus as a complication of intraventricular haemorrhage **(Jergović IE et al.,2016)**

Hydrocephalus may also be non-obstructive, in which CSF flow within the ventricular system is not impaired but there is decreased absorption. Additionally, tumours of the choroid plexus may also produce increased CSF secretion in rare cases and if this increased secretion is not compensated for by increased outflow, then hydrocephalus can occur **(Leinonen VA .,2018).** To understand the pathophysiology of hydrocephalus, one must first understand the normal physiology and dynamics of CSF compartment ***(Rekate HL, 2004).***

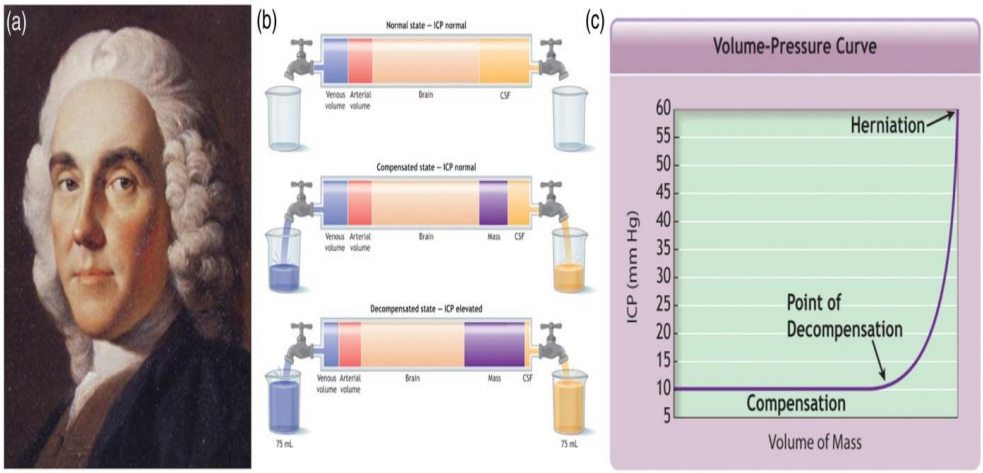


**Fig.(1):**a) Alexander Monro secundus (1733–1817). Eminent Scottish physician. (b) Adaptation of current explanation of Monro-Kellie doctrine (c) Demonstrates that once the period of compliance that this displacement affords runs out, there is an exponential rise in pressure. This description fails to explain the importance of volume flow. **(Aschoff AA et al .,2000)**

***Physiology of Cerebrospinal Fluid:***

The first citations regarding cerebral fluid content are from the writings of ancient Egypt, particularly the medical text known as the papyrus of Edwin Smith, from 1700 BC **(Breadsted JA 1930)** Throughout ancient times, and during the Middle Ages, it was believed that the ventricular content was not a liquid, but air. The understanding of the production and circulation of the CSF has undergone a major evolution over time . **(Liddelow SA et al .,2011) .**

Cerebrospinal fluid (CSF) is normally a clear colorless fluid with a specific gravity of 1.007 and a pH of about 7.33-7.35. 80% is produced by the choroids plexuses, located in both lateral ventricles (accounts for approximately 95% of CSF produced in the choroid plexuses) and in the 4th ventricle. Most of the rest of intracranial production occurs in the interstitial space. A small amount may also be produced by the ependymal lining of the ventricles. In the spine, it is produced primarily in the dura of the nerve root sleeves **(Nielsen NA et al ., 2013)**.

It is assumed that most CSF that circulates within the ventricles comes from the choroid plexus, but this is controversial **(Miyajima MA et al .,2015)** . Other CSF production sites, such as the brain parenchyma, are currently described as contributing to the total amount of circulating CSF **(Oi SA et al .,2000)**.

The rate of CSF formation in humans is 0.3–0.4 ml/min, with the total volume of CSF being approximately 90–150 ml in adults **(Brinker TA et al .,2014)** Also, it was traditionally assumed that CSF flows from the lateral and third ventricles, areas with higher concentrations of choroid plexus, reaching the fourth ventricle

via the cerebral aqueduct and finally the subarachnoid space through the apertures of Magendie and Luschka, by being absorbed into the venous blood at the arachnoid granulation level **(Miyajima MA et al .,2015)**

The CSF is termed as the "third circulation" comparable to that of blood and lymph. From the principal site of CSF formation in the lateral ventricles, it flows downward through the interventricular foramen "foramen of Monro" into the third ventricle and mixes with the CSF produced there. Cerebrospinal fluid from the third ventricle flows through the cerebral aqueduct into the fourth ventricle. All CSF exits the ventricular system through three openings, two lateral openings termed the foramina of Luschka and one in the midline roof of the fourth ventricle termed the foramen of Magendie. The midline and lateral foramina empty into a large CSF subarachnoid cistern, the cerebello-medullary cistern "cisterna magna". From this cistern, CSF flows into the subarachnoid space, over the surface of spinal cord and brain to leave the subarachnoid space and enter the dural venous sinuses, through the arachnoid granulation **(Lalou AD et al., 2018)**.

**Production:**

The brain produces roughly 500 mL of cerebrospinal fluid per day, at a rate of about 25 mL an hour. This transcellular fluid is constantly reabsorbed, so that only 125–150 mL is present at any one time. CSF volume is higher on a mL per kg body weight basis in children compared to adults. Infants have a CSF volume of 4 mL/kg, children have a CSF volume of 3 mL/kg, and adults have a CSF volume of 1.5–2 mL/kg. **(Kimelberg HK ., 2004)**

Additionally, the larger CSF volume may be one reason as to why children have lower rates of postdural puncture headache. Most (about two-thirds to 80%) of CSF is produced by the choroid plexus. The choroid plexus is a network of blood vessels present within sections of the four ventricles of the brain. It is present throughout the ventricular system except for the cerebral aqueduct, and the frontal and occipital horns of the lateral ventricles. **(Sakka LA et al .,2011)**

CSF is also produced by the single layer of column-shaped ependymal cells which line the ventricles; by the lining surrounding the subarachnoid space; and a small amount directly from the tiny spaces surrounding blood vessels around the brain. CSF is produced by the choroid plexus in two steps. Firstly, a filtered form of plasma moves from fenestrated capillaries in the choroid plexus into an interstitial space, with movement guided by a difference in pressure between the blood in the capillaries and the interstitial fluid**(Kimelberg HK ., 2004)**

This fluid then needs to pass through the epithelium cells lining the choroid plexus into the ventricles, an active process requiring the transport of sodium, potassium and chloride that draws water into CSF by creating osmotic pressure. Unlike blood passing from the capillaries into the choroid plexus, the epithelial cells lining the choroid plexus contain tight junctions between cells, which act to prevent most substances flowing freely into CSF. Cilia on the apical surfaces of the ependymal cells beat to help transport the CSF. ***(Sakka LA et al ., 2011)***

Water and carbon dioxide from the interstitial fluid diffuse into the epithelial cells. Within these cells, carbonic anhydrase converts the substances into bicarbonate and hydrogen ions. These are exchanged for sodium and chloride on the cell surface facing the interstitium. Sodium, chloride, bicarbonate and potassium are then actively secreted into the ventricular lumen. This creates osmotic pressure and draws water into CSF, facilitated by aquaporins. Chloride, with a negative charge, moves with the positively charged sodium, to maintain electroneutrality. ***(Brinker TA et al., 2014)***

There are circadian variations in CSF secretion, with the mechanisms not fully understood, but potentially relating to differences in the activation of the autonomic nervous system over the course of the day. Choroid plexus of the lateral ventricle produces CSF from the arterial blood provided by the anterior choroidal artery. ***(Brinker TA et al., 2014)***

In the fourth ventricle, CSF is produced from the arterial blood from the anterior inferior cerebellar artery (cerebellopontine angle and the adjacent part of the lateral recess), the posterior inferior cerebellar artery (roof and median opening), and the superior cerebellar artery. ***(Sakka LA et al , 2011)***

| |
|---|
| Production sites |
| Choroid plexus |
| Extra-choroidal sites |
| 1. Ventricular ependyma |
| 2. Subarachnoid space |
| 3. Pia-arachnoid capillary |
| 4. Brain parenchyma |
| Absorption routes |
| Arachnoid villi →superior sagittal sinus |
| Extra-arachnoid villus sites |
| 1. Ventricular ependyma→subependymal vein |
| 2. Leptomeninges→cortical vein |
| 3. Pia-arachnoid capillary→venous system |
| 4. Choroid plexus→deep venous system |
| 5. Perineural space→lymphatic channel |

Table 1. Production sites and absorption routes of CSF **(Oi SA et al .,2006)**.

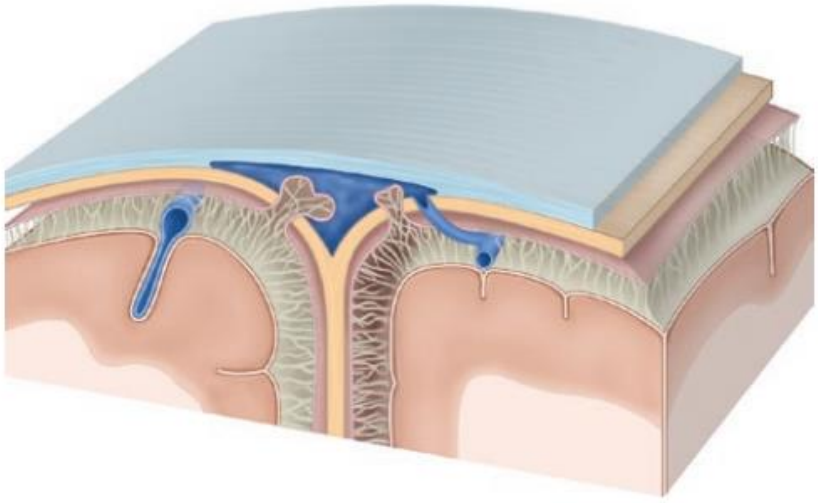

**Fig.(2):**Traditional third circulation model of CSF pathway ending in the arachnoid granulation, and later flowing toward the superior sagittal sinus **(Tascioglu AO et al .,2005)**

**Fig.(3):**Arachnoid granulation in detail. In fact, arachnoid granulation is an expansion, through the dura, of the subarachnoid space to the venous system **(Tascioglu AO et al .,2005)**

The generation of CSF is driven by the hydrostatic pressure gradient between the blood, choroid plexus epithelial cells, and the ventricles—according to Starling's law of filtration. This means that increased ICP, observed in hydrocephalus, may attenuate CSF secretion and, conversely, decreased pressure will increase CSF secretion. The role of pressure gradients in CSF secretion is unclear (**Johanson CE et al .,2008)**

**Contents:**

CSF is derived from blood plasma and is largely similar to it, except that CSF is nearly protein-free compared with plasma and has some different electrolyte levels. Due to the way it is produced, CSF has a higher chloride level than plasma, and an equivalent sodium level. CSF contains approximately 0.3% plasma proteins, or approximately 15 to 40 mg/dL, depending on sampling site. **(Kimelberg HK ., 2004)**

The composition of the CSF and its pressure is maintained relatively constant by various mechanisms. However in disease conditions the composition and pressure of CSF can be altered. Hence analysis of CSF by various methods will help in diagnosis as well as prognostication and response to therapy. CSF analysis is particularly useful in various acute neurological conditions and helps in rapid diagnosis of the conditions and initiate therapeutic measures. CSF analysis usually consists of opening pressure measurement, biochemical analysis, cytology, biomarkers assay, and microbiological evaluation. **(Hepnar DA et al .,2019)**

| Normal composition of CSF | |
|---|---|
| | *Normal range* |
| Color | Clear |
| Specific gravity/pH | 1.006–1.007/7.4 |
| Opening pressure | 50–200 mm $H_2O$ |
| RBCs count | Nil |
| WBC count | 0–5 (upto 30 in neonates) |
| WBC types | Lymphocytes |
| CSF Proteins | 15–40 mg/dL |
| CSF lactate | 1–3 mmol/ L |
| CSF glucose | 50–80 mg/dL (two thirds of blood glucose |
| Microbial examination | No microorganism |

Table 2 : Normal composition of CSF . **(Seehusen DA et al .,2003)**

**Function:**

CSF serves several purposes:

- Buoyancy: The actual mass of the human brain is about 1400–1500 grams; however, the net weight of the brain suspended in CSF is equivalent to a mass of 25-50 grams. The brain therefore exists in neutral buoyancy, which allows the brain to maintain its density without being impaired by its own weight, which would cut off blood supply and kill neurons in the lower sections without CSF. ***(Shahan BA et al ., 2021)***

- Protection: CSF protects the brain tissue from injury when jolted or hit, by providing a fluid buffer that acts as a shock absorber from some forms of mechanical injury. ***(Shahan BA et al ., 2021)***
- Prevention of brain ischemia: The prevention of brain ischemia is aided by decreasing the amount of CSF in the limited space inside the skull. This decreases total intracranial pressure and facilitates blood perfusion. ***(Brinker TA et al., 2014)***
- Homeostasis: CSF allows for regulation of the distribution of substances between cells of the brain, and neuroendocrine factors, to which slight changes can cause problems or damage to the nervous system. For example, high glycine concentration disrupts temperature and blood pressure control, and high CSF pH causes dizziness and syncope. ***(Giovannoni GA ., 2014)***
- Clearing waste: CSF allows for the removal of waste products from the brain, and is critical in the brain's lymphatic system, called the glymphatic system. Metabolic waste products diffuse rapidly into CSF and are removed into the bloodstream as CSF is absorbed. CSF can be toxic, such as in amyotrophic lateral sclerosis, the commonest form of motor neuron disease. ***(Sakka LA et al , 2011)***

A number of functions have been assigned to the CSF over the years, from the mechanical protection function, the path for metabolite flow, and neuroendocrine communication **(Rodriguez EM et al .,2010)** .

Currently, there is much scientific evidence that the CSF also plays an important role in the development and embryonic organization of the central nervous system, acting as a neuronal guide **(Sawamoto KE et al ., 2006)** . The ventricles are lined by ependyma, a single-layer tissue of ciliated cells called ependymocytes that are directly in contact with the CSF **(Del Bigio MR 1995)**. The impetus for the CSF circulation results from macro-scale phenomena, such as the pulsation of the choroid plexus and the movement of the ventricular wall – both induced by cardiac systole – and micro-scale phenomena, such as the ciliary beat of ependymocytes . This ciliary movement occurs periodically, generating a CSF flow in the vicinity of the ventricular wall .**(Siyahhan BA et al .,2014)**

The CSF flow is believed to also serve as a signpost for neuronal migration during embryogenesis, keeping in mind that progenitor cells are born below the ependymal layer in the lateral ventricles, later migrating to distant sites, such as the olfactory bulb, where they differentiate into neurons and astroglia.**(Siyahhan BA et al .,2014)**. Conversely, deficiency in ciliary motility can change the CSF flow and the migration of neuroblasts **(Banizs BA et al .,2005)** , and such results suggest a strong inter relationship between neuronal migration and the CSF circulatory dynamics near the ventricular wall **(Siyahhan BA et al .,2014)**

Currently, the unidirectional nature of the CSF flow is being questioned, and the CSF flow is also considered to be a location for the dilution and diffusion of substances **(Miyajima MA et al .,2015) .** The concept of the third circulation has been accepted since the work of Cushing in the decade of the 1920s, suggesting that CSF flows through the ventricles, cisterns, and subarachnoid space and is reabsorbed into the blood through the arachnoid granulation **(Johanson CE et al .,2008)**

**Reabsorption:**

CSF returns to the vascular system by entering the dural venous sinuses via arachnoid granulations. These are outpouchings of the arachnoid mater into the venous sinuses around the brain, with valves to ensure one-way drainage. This occurs because of a pressure difference between the arachnoid mater and venous sinuses. CSF has also been seen to drain into lymphatic vessels, particularly those surrounding the nose via drainage along the olfactory nerve through the cribriform plate. ***(Sakka LA et al , 2011)***

The pathway and extent are currently not known but may involve CSF flow along some cranial nerves and be more prominent in the neonate. CSF turns over at a rate of three to four times a day. CSF has also been seen to be reabsorbed through the sheathes of cranial and spinal nerve sheathes, and through the ependyma. ***(Sakka LA et al , 2011)***

Historically, it was always held that the absorption of CSF into the circulating blood is really more notable in the arachnoid granulation **(Johanson CE et al .,2008)** . This Motion is based on the first experiments performed by Key and Retzius, with the injection of colored gelatin into human cadavers in 1875. In fact, the distribution of the dye was noted throughout the CSF system, as was its passage to the arachnoid granulation in the direction of the venous sinuses **(Key AR et al .,1875)** .

However, their results were questioned because the gelatin was injected at a pressure of 60 mmHg, which could have caused a rupture in the arachnoid granulation. Since then, other means of CSF absorption have been suggested. **(Johanson CE et al .,2008)** . The arachnoid granulation has a developmental mechanism in humans that is comparable to that in other animals lower on the phylogenetic scale **(Oi SA et al .,2006)**.

The primary site of CSF absorption is through specialized organs at the level of the sagittal sinus. These organs are the arachnoid villi (microscopic) or the arachnoid granulation (macroscopic). Arachnoid granulations have the appearance of berry like clumps protruding into the superior sagittal sinus, its associated lacunae, sinuses and large veins. With advancing age, the granulations increase in size and number, sometimes pushing against or through the periosteal dura and causing bone resorption and depressions in the skull cap **(Orešković DA et al., 2017).**

Most of the cerebrospinal fluid is resorbed at the level of the cranial venous sinuses. This resorption, or more exactly the flow of cerebrospinal fluid into the venous blood, is a passive phenomenon that obeys the pressure gradient existing between the subarachnoid space and the sinus. **(Baunbaek GE et al., 2017).**

Other sites of CSF absorption exist. At physiologic pressure, these alternative CSF pathways probably exert minor influence on the rate of CSF absorption, but have significant role at higher pressure, especially when

there is obstruction to flow within the sagittal sinus. These sites are brain capillaries, choroid plexus and lymphatics of the cranial and spinal nerves **(Oi SA et al .,2006)**.

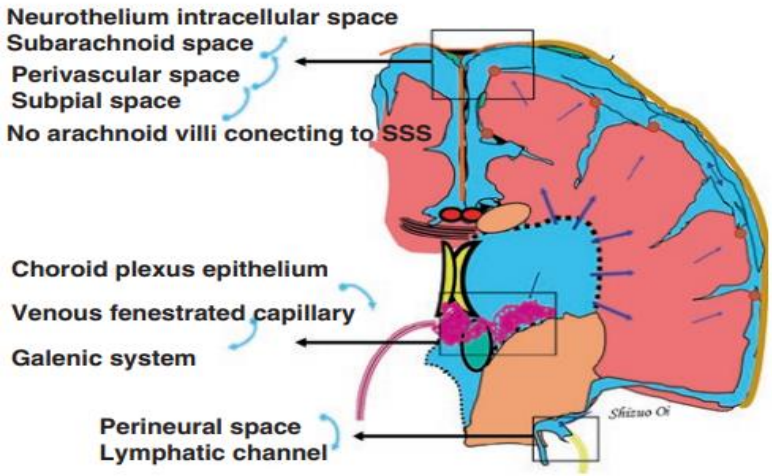


**Fig.(4):**Minor CSF pathway in immature brain **(Oi SA et al .,2006)**.

Currently, although controversial, much importance has been attributed to the CSF circulation around the blood vessels penetrating from the subarachnoid space towards the Virchow-Robin space . This space accompanies vessels deep in the brain parenchyma and is involved in a significant exchange between CSF and the interstitial fluid **(Miyajima MA et al .,2015)**. This circulation not only provides the cleaning of molecules from the brain, but also provides inter action with the immune system. In this important exchange, physiological functions may be activated, such as the regeneration of the brain during sleep **(Brinker TA et al .,2014)**

Currently, in regard to CSF absorption, the importance of aquaporin 4 (AQP4) is also cited. AQP4 is a membrane transport protein, present in the central nervous system, particularly in the membrane of the astrocytic feet and the basolateral membranes of ependymal cells. It has also been noted that there are no tight junctions between the cells of the pia mater and the ependyma, so water and other substances pass freely between the cerebral parenchyma and subarachnoid space **(Miyajima MA et al .,2015)**.

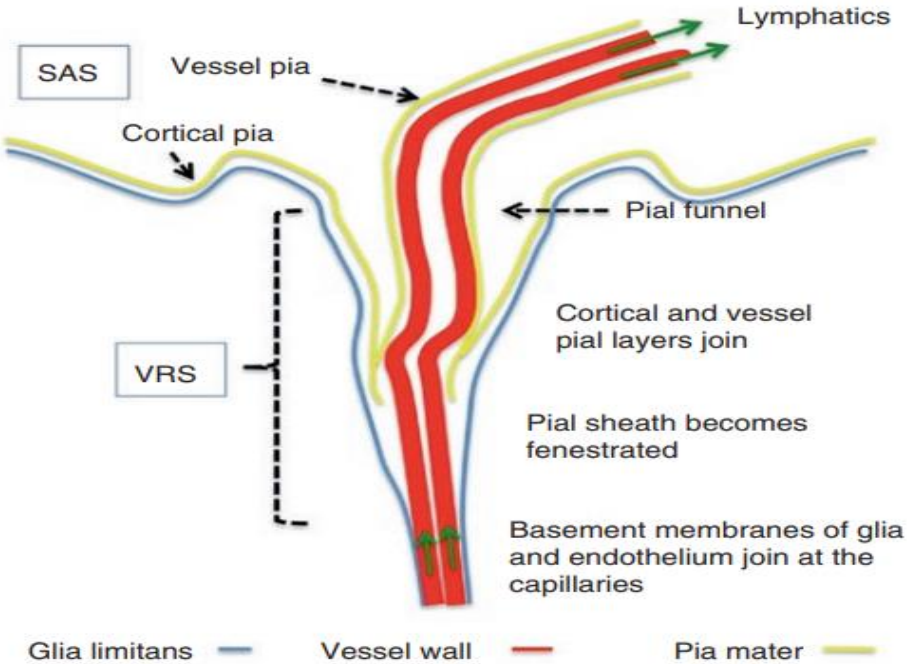


**Fig.(5):**Morphology of the Virchow-Robin space (VRS). Delineated by the basal membranes of the glia, pia, and endothelium, the VRS consists of the space surrounding vessels that penetrate into the parenchyma.

The VRS is obliterated at the capillaries where the basement membranes of the glia and endothelium join. Abbreviations: VRS Virchow-Robin space, SAS subarachnoid space **(Brinker TA et al .,2014)**

**Regulation:**

The composition and rate of CSF generation are influenced by hormones and the content and pressure of blood and CSF. For example, when CSF pressure is higher, there is less of a pressure difference between the capillary blood in choroid plexuses and CSF, decreasing the rate at which fluids move into the choroid plexus and CSF generation. ***(Giovannoni GA , 2014)***

The autonomic nervous system influences choroid plexus CSF secretion, with activation of the sympathetic nervous system decreasing secretion and the parasympathetic nervous system increasing it. ***(Sakka LA et al , 2011)***

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