

Neurofluids: A holistic approach to their physiology, interactive dynamics and clinical implications for neurological diseases

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Abstract

There is increasing interest in understanding the physiology of the extracellular fluid compartments in the central nervous system and their dynamic interaction. Such interest has been in part prompted by a vigorous resurgence of the role of the venous system, the recent discoveries of the meningeal lymphatics, the brain waste removal mechanisms and their potential link to neurological diseases, such as idiopathic intracranial hypertension, Ménière's disease, migraine, small vessel disease, and most neurodegenerative diseases.

The rigid cranial cavity houses several space-competing material compartments: the brain parenchyma (BP) and four extracellular fluids, namely arterial, venous, cerebrospinal fluid (CSF) and interstitial fluid (ISF). During cardiac pulsations, the harmonious, temporal and spatial dynamic interaction of all these fluid compartments and the BP assures a constant intracranial volume at all times, consistent with the Monro-Kellie hypothesis. The dynamic interaction involves high-pressure input of arterial blood during systole and efflux of CSF into the spinal subarachnoid space (SSAS) followed by venous blood exiting directly into the vertebral and internal jugular veins towards the heart and intraventricular CSF displacing caudally towards the SSAS. Arterial pulsatile energy is transmitted to the BP that contributes to the smooth movement of fluids in and out of the brain. Perturbing any of these fluid compartments will alter the entire brain dynamics, potentially increase intracranial pressure, affect perfusion and hamper clearance capacity of metabolic waste.

This review of all major extracellular fluid compartments within the brain, advocates a holistic approach to our understand-

ing of the fluid dynamics, rather than focusing on a single compartment when analyzing neurological diseases. This approach may contribute to advance our comprehension of some common neurological disorders, paving the way to newer treatment options.

Introduction

Neurological disorders constitute a major public health challenge and are associated with life-long disability.¹ Much progress has been made in understanding the etiopathogenesis of many of these, however, there are still several gaps in our knowledge of many others, some of which are still considered *idiopathic* (a disease of unknown etiology).

The Monro-Kellie hypothesis formulated by the Scottish anatomist Alexander Monro (secundus) and his former student George Kellie in 1783 remains a cardinal principle in understanding the physiology of the central nervous system (CNS).² This hypothesis, as originally stated, maintains that: i) brain contents are enclosed in a non-expandable bony skull; ii) the volume of skull contents is constant at all times; iii) the brain parenchyma (BP) is largely incompressible; and iv) venous outflow must match the arterial blood inflow within the cardiac cycle.³ However, over the years, parts of the Monro-Kellie doctrine have been challenged largely because it ignored the presence of cerebrospinal fluid (CSF). We now know that in addition to venous outflow, caudal displacement of CSF contributes to counterbalance arterial blood input within the rigid bony skull during each cardiac cycle and these movements occur in a precise temporal order.⁴ These newer concepts help us better understand the dynamic interconnection between the various compartments and how anomalies in one can affect the dynamics of others.⁵ The cranium houses several space-competing material compartments: BP and four extracellular fluids, namely arterial, venous, interstitial fluid (ISF) and CSF. In light of recent renewed interest in fluids such as ISF, the discovery of the meningeal lymphatics⁶ and proposed mechanisms for brain waste clearance mechanisms,⁷⁻⁹ it has become necessary not only to revisit the original Monro-Kellie doctrine but also to comprehend the intricate interplay of the different CNS compartments.

We will do this by reviewing the relevant anatomy and physiology of the BP and single CNS extracellular fluid compartments (we will call them *neurofluids*). Key elements of such interactions and major possible neuro-

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logical diseases that may derive from specific alterations have been schematically illustrated in Figure 1. This will form the basis of our understanding of the proposed brain waste clearance mechanisms and how a holistic approach could help provide answers to still unsolved questions.

Cerebral arterial system

Paired internal carotid and vertebral arteries assure a steady blood supply to the cerebral hemispheres that anastomose at the level of the circle of Willis (Figure 2A). The cardiac input to the brain is approximately 15-20% of the total cardiac output. For a healthy adult weighing 70 kgs, the cardiac output is estimated at approximately 5 L/min and brain arterial input is about 750 mL/min to 1000 mL/min. Each of these arteries will divide progressively into smaller branches (pial or leptomenigeal arteries) as they reach the cortical surface in the cerebral subarachnoid space (CSAS).¹⁰

The cortical surface is lined by glia limitans, a structure that is made up of astrocyt-

ic end-feet and tight junctions. The pia mater overlies the glia limitans and fuses with the basement membrane (BM) of the pial arteries forming the outer wall of a funnel-shaped CSF-filled space.¹¹ Cortical pia mater is also reflected over these leptomeningeal arteries.^{12,13} The adventitial layer of leptomeningeal arteries is surrounded by perivascular spaces (PVS), or compartments which are fluid-filled but also contain connective tissue and cells (Figure 1).^{12,14} PVS are an important exchange route for CSF and ISF for substances including CSF-infused tracers to reach brain parenchyma alongside vessels.¹⁵

The arteriolar walls are lined with layers of smooth muscle cells (SMCs) that form the tunica media and have contractile properties that ensure a constant cerebrovascular tone.¹⁶ These are innervated by the autonomous nervous system or *extrinsic* innervation. Sympathetic innervation will cause vasoconstriction in response to an increase in arterial pressure, and reduce blood flow, whereas parasympathetic innervation will cause vasodilation of arterioles in a situation of low arterial pressure and increase blood flow.¹⁷ Capillaries are innervated by nerves arising within the brain. These are subcortical nuclei in the brainstem such as nucleus coeruleus, raphe nuclei and other nuclei in the basal forebrain.¹⁸ This *intrinsic* innervation is more pronounced at the astrocyte-neuronal junction.¹⁷ The contractile activities of SMCs and pericytes in the arterioles and capillaries are major actors that modulate lumen diameter thereby determining the entity of cerebrovascular resistance (CVR) to flow and assures constant cerebral perfusion pressure (CPP) through a unique process known as cerebral autoregulation (CA).^{19,20}

According to Poiseuille's law, flow Q through a vascular segment of length L is directly determined by the pressure drop ΔP and inversely to the resistance to flow R :

$$Q = \frac{\Delta P}{R} \quad (1)$$

where R is

$$R = \frac{8\eta L}{\pi r^4} \quad (2)$$

η is the blood viscosity and r is the vessel radius. Thus, Q becomes:

$$Q = \frac{\Delta P \pi r^4}{8\eta L} \quad (3)$$

Equation 3, shows how a change in vessel radius will determine a flow change exponentially to the power of four making it a powerful mechanism to instantly regulate Q , or cerebral blood flow (CBF).

CPP is defined as:

$$CPP = MAP - \max\{ICP, JVP\} \quad (4)$$

where ICP is intracranial pressure, JVP is jugular venous pressure and MAP is mean arterial pressure. The normal range of MAP is 70-100 mmHg. Brain capillaries are lined with a single layer of continuous non-fenestrated endothelial cells that are held together with tight junctions and constitute the blood-brain barrier (BBB).²¹ Several specif-

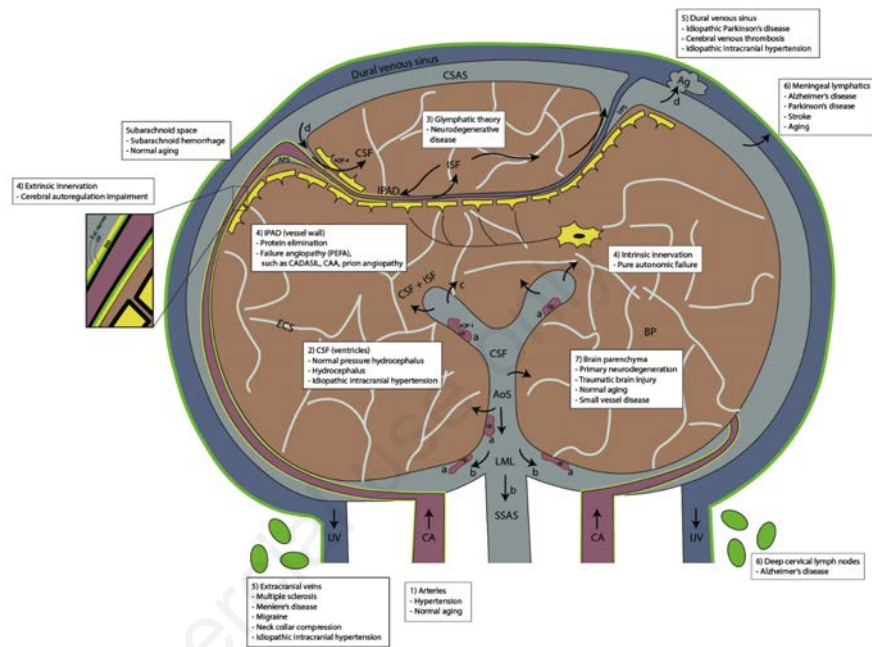


Figure 1. Schematic drawing on a coronal section of the brain illustrating the interaction between neurofluid compartments and brain parenchyma and possible neurological diseases due to their derangement: 1) **Arterial system:** branches of carotid arteries (CA) and vertebral arteries (not shown) reach the CSAS, the walls of which contain sympathetic innervation for smooth muscle cells (ext.nerves) 2) **CSF pathway:** a) CSF is produced via choroid plexi (CP) in the ventricles and flows caudally through the foramina of Lushka and Magendie towards the cerebral subarachnoid space (CSAS), b) CSF flows caudally and reaches the CSAS via foramen of Lushka and Magendie (LML) and towards the spinal (SSAS), c) CSF also moves through the ventricular ependymal wall towards the brain parenchyma (BP), d) CSF drains into the dural venous sinus through arachnoid granulations (Ag); e) CSF from the CSAS enters arterial perivascular space (APS) and into the BP through aquaporin 4 (AQP-4) water channels; d) CSF flows through the ventricular ependymal wall toward the brain parenchyma (BP) and extracellular space (ECS) where it intermingles with interstitial fluid (ISF); 3) **Glymphatic theory:** CSF from arterial perivascular space (APS) enters the BP via AQP-4 and mixes with ISF. Bulk flow and/or diffusion processes move ISF/CSF from the BP towards the venous perivascular space (VPS), transporting metabolic waste out towards the CSAS and into the dural venous sinus. 4) **Intramural periarterial drainage (IPAD):** ISF flows in the opposite direction to arterial flow along the basement membranes (BM) of arteries (zoomed box) and leaves the intracranial cavity along the walls of the CA into the deep cervical lymph nodes. Extrinsic and intrinsic innervations line the arterial and capillary wall respectively and determine cerebrovascular tone and contribute to cerebral autoregulation. 5) **Venous system:** bridging veins (BV) lie on the cortical surface in the CSAS and drain into the superior sagittal sinus (here shown as dural venous sinus). Venous blood flows out the intracranial cavity via internal jugular veins (IJV) and vertebral veins (not shown). 6) **Meningeal lymphatics:** lymphatic channels line dural venous sinus and provide an important pathway for CSF drainage towards the deep cervical lymph nodes. These can also be drained via perineural sheaths around cranial nerves and through the cribriform plate to reach deep cervical lymph nodes. 7) **Brain parenchyma (BP)** is made up of 80-85% of cells and intracellular fluid, the rest is made up of extracellular space (ECS) and contains ISF. A potential list of diseases, already published in the literature, that might affect one or more compartments are listed in the various boxes. CADASIL=cerebral autosomal dominant arterial with subcortical infarcts and leucoencephalopathy, CAA=cerebral amyloid angiopathy, PEFA=protein elimination failure angiopathy.

ic molecules form the unique tight junction, such as occludins, claudins and junctional adhesion molecules.²² BBB selectively restricts paracellular transport of solutes and cells across brain capillaries and limits dangerous fluctuations in local concentrations of ions, proteins, glucose, neuromodulators, and neurotransmitters and to prevent entry of pathogens and toxins inside the brain.²³

Cerebrospinal fluid

There are multiple controversies and lack of conclusive data in the literature regarding CSF dynamics.²⁴ The historical understanding is that CSF is produced within the choroid plexi in the lateral, third and the fourth ventricles and flows through the foramen of Magendie and Luschka into CSAS and caudally towards the SSAS (Figure 1,2F). It is produced at a rate of 0.3-0.4 mL/min²⁵. Total CSF volume is approximately 189±29 mL in adults and varies with age and gender.²⁶ CSF subserves nutritional, immunologic, metabolic and clearance functions in addition to protecting the brain and spine from external injury.²⁷

Choroidal capillaries are characterized by multiple fenestrations and are bounded by a single layer of choroidal epithelium. The CSF facing surface, or the apical surface of the epithelial cells, is lined with tight junctions and contain microvilli forming the blood-CSF barrier.²⁸ Multiple ion channels and water ion channel aquaporin 1 (AQP-1) on the apical and the basolateral surfaces operate to create a favorable osmotic gradient through secretion of Na⁺, facilitating water movement through AQP-1 channels across the CP epithelium into the ventricles.²⁹ CSF is absorbed into the dural venous sinuses through subarachnoid granulations or villi that contain fine water channels in their core¹² (Figure 2E). Thus, CSF also enters PVS and flows in a centripetal direction towards the BP via aquaporin 4 water channels (AQP-4) (glymphatic theory)^{7,30,31} (Figure 1). CSF also exits through the cribriform plate towards nasal lymphatics and the cranial cavity *via* major foramina of the skull base alongside cranial nerves, arteries, and veins towards the deep cervical lymph nodes^{8,31-33} (Figure 1). In addition, true meningeal lymphatics along the meninges surrounding the dural venous sinuses also drain CSF towards the deep cervical lymph nodes as observed in both animal^{6,33} and human studies³⁴ (Figure 1).

An alternative view of CSF dynamics, also known as the Bulat-Klarica-Oresković hypothesis, strongly advocates that CSF

production and absorption occurs within the entire BP and that its formation in the choroid plexi and absorption in the dural venous sinuses may be of less importance.³⁵ According to these authors, CSF is produced and absorbed at the capillary level through Starling forces acting between plasma and the extracellular fluid in the extracellular space (ECS).^{35,36} There is also evidence for transepndymal CSF flow into the brain parenchymal ECS where it may intermingle with ISF.^{27,37,38}

Intraventricular CSF flow is bidirectional, primarily driven by cardiac activity (expansion of choroidal arteries in the plexi), although it is also affected by breathing.³⁹ During systole, CSF from the ventricular system flows caudally towards the SSAS (also known as, net negative flow) and flows cranially during diastole (also known as, net positive flow) with minimum net displacement in the cranial direction. CSF dynamics can be quantified using validated and more reliable cine phase-contrast flow magnetic resonance imaging (PC-MRI) techniques.^{40,41}

Cerebral venous system

Three different venous drainage networks exist in the brain. An outer, superficial segment of veins that drain the scalp, muscle and tendons and an intermediate segment that serves the skull tables and the dura mater (diploic veins).⁴² The third set of veins are intra-parenchymal veins that may be further subdivided into superficial and deep veins (Figure 2B,C). Several anatomical variations are possible and veins can vary in number, size, symmetry and their drainage patterns.⁴³ The different venous networks can communicate with each other according to physiological needs or pathological conditions (Figure 3C). Intracranial veins and sinuses are valveless allowing flow to reverse in the case of downstream venous obstruction.⁴⁴ Bridging veins (BV) however, drain into dural sinuses at the level of arachnoid granulation through a cuff-like segment lined with circularly arranged SMC⁴⁵ (Figure 2E). This segment remains closed until transmural pressure

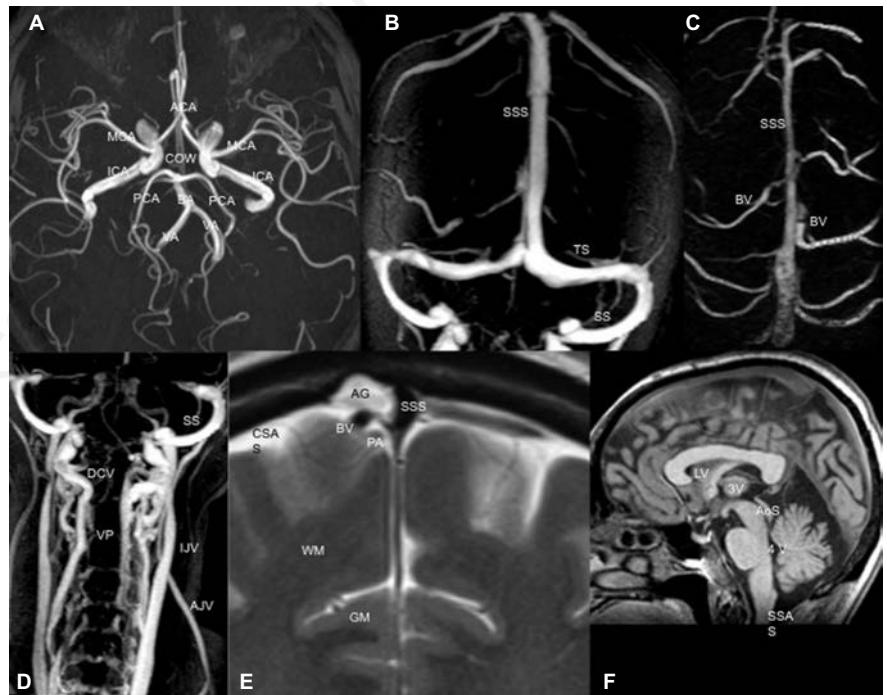


Figure 2. Normal anatomy. A) 3D time-of-flight (TOF) magnetic resonance angiography image illustrating the main intracranial arteries and the circle of Willis (COW). ICA=internal carotid artery, MCA=middle cerebral artery, ACA=anterior cerebral artery, PCA=posterior cerebral artery, VA=vertebral artery; B) contrast enhanced magnetic resonance venography (CE-MRV) illustrating the main superficial dural venous sinuses. SSS=superior sagittal sinus, TS=transverse sinus, SS=sigmoid sinus; C) CE-MRV showing bridging veins (BV) or cortical veins; D) CE-MRV of the intracranial veins of the neck. DCV=deep cervical veins, VP=vertebral plexi, IJV=internal jugular vein, AJV=anterior jugular vein; E) T2 weighted coronal MRI illustrates the subarachnoid space and its principle contents. AG=arachnoid granulation, CSAS=cerebral subarachnoid space, WM=white matter, GM=gray matter, PA=pial artery; F) T1 weighted sagittal image. LV=lateral ventricle, 3V=third ventricle, AoS=aqueduct of Sylvius, 4V=fourth ventricle, SSAS=spinal subarachnoid space.

builds up such that BVs expand and venous blood flows into the dural sinuses.⁴⁶ BVs are sensitive to transmural pressure. Increase in ICP can cause a collapse of such veins, whereas an increase in venous sinus pressure will cause engorgement of BV. In both cases venous outflow will be severely impacted (Figure 3).

Intracranial venous vessels are in direct continuity with extracranial neck vessels and the intra- and extra-spinal venous systems, also termed as the craniocervical venous system (CCVS).⁴⁷ The CCVS is an extensive network of intricately communicating veins connected to the azygos, hemiazygos veins and both superior and the inferior vena cava.⁴⁷ Internal jugular veins (IJV) are considered the major recipients of intracranial venous blood from the sigmoid sinuses in around 72% of healthy individuals (*jugular drainers*) (Figure 2D).⁴⁸

Veins carry oxygen-depleted blood towards the heart. They also represent the primary route for the removal of metabolic waste products from tissues. The role of venous vessels in maintaining ICP is underscored by the fact that these high capacitance vessels contain 70% of the entire intracranial blood volume such that both passive and active control of venous SMCs can cause important intracranial blood volume shifts, significantly affecting ICP.⁴⁹ Veins are easily collapsible and the cross-sectional area (CSA) of veins can be influenced by multiple internal and external factors. Internal factors include upstream and downstream pressure, flow rates and gravitational forces whereas the predominant external factor is the surrounding ICP. There is also an active neurogenic control of venous vessels via monoaminergic innervation.⁵⁰

Recalling Equation (1), venous flow:

$$Q = \frac{P_v - CVP}{R} \quad (6)$$

where P_v is venous pressure, CVP is pressure within the right atrium (central venous pressure) and R represents resistance to flow (largely determined by venous CSA). In the veins, R is relatively low as they readily expand to allow venous blood to flow unhindered towards the heart. Both extracranial (*e.g.* IJV) and intracranial strictures (*e.g.* dural venous sinus) will increase the denominator R in equation 6, severely affecting Q unless compensatory mechanisms, such as recruitment of additional collateral venous outflow pathways become active (Figure 3A-C).⁵¹ Impaired venous outflow will result in engorgement of upstream cortical veins, reduce CPP, direct-

ly affect Starling forces at the capillary bed and perturb reabsorption of fluids and solutes^{5,35,52,53} (Figure 3D-F).

Interstitial fluid

The brain ECS accounts for about 15-20% of the total brain volume.⁵⁴ In an average 1400 mL of brain weight, 210-280 mL is made up of ECS. The geometry of ECS is characterized by tortuous spaces surrounding neural and glial cells. ECS contains ISF and is made up of ECM, which is attached to cell membranes. The most important constituents of ECM are glycosaminoglycans, proteoglycans (*e.g.* hyaluronic acid), and glycoproteins (*e.g.* laminins, collagen, fibronectin) creating a negatively charged environment to maintain a well-hydrated ambient for cellular communication and transport of substances.⁵⁵ The cellular composition of the brain differs from region to region creating important changes to diffusion properties which would either facilitate or further impede ISF movement.⁵⁴ A damaged ECS will hinder flow of ISF thereby disrupting the electrochemical environment

necessary for optimal neuronal signaling, favor synaptic plasticity, sustain local and remote transmission of neurotransmitters (volume transmission), promote enzymatic degradation of plaques and to support brain repair mechanisms including clearance of metabolic waste.^{54,56}

The water component of ISF is likely derived through several different pathways. First, it is a by-product of glucose oxidation whereby glucose is converted to CO_2 and H_2O at a rate of approximately $28 \text{ nl g}^{-1} \text{ min}^{-1}$.⁵⁷ Second, Starling forces at the capillary level cause water to filtrate from the blood plasma into the ECS.⁵⁷ Third, part of CSF that enters the BP *via* AQP-4 lined astrocytic end-feet, intermingles with ISF in the BP.³⁰

The drainage of ISF has been the topic of intense research during the last few decades starting from seminal works by Helen Cserr.⁵⁸ Two alternative pathways (one may not exclude the other) have recently been proposed. The glymphatic theory proposes the movement of CSF from the CSAS towards the arterial perivascular space (APS), which enters BP *via* AQP-4

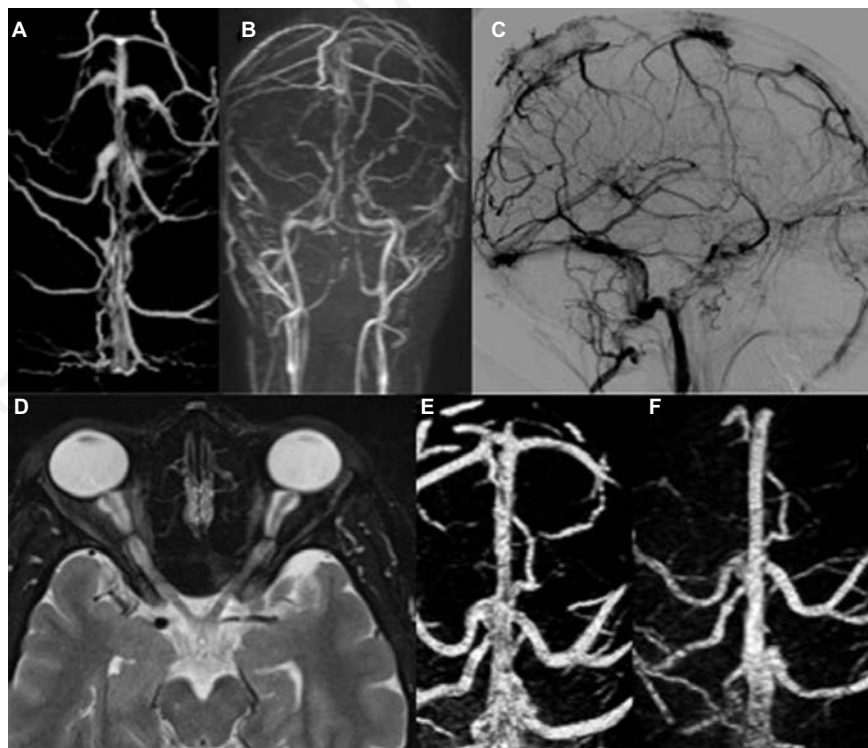


Figure 3. Venous pathology. Top row: 26yr old M with headaches and visual acuity loss with chronic venous thrombosis A) CE-MRV shows multiple stenosis of the SSS, irregular lumen of the BV which are puffed at the junction with the SSS; B) phase contrast coronal MRV shows multiple anastomosis of the intra and extracranial veins; C) digital subtraction angiography in the venous phase confirms massive anastomosis between the intra and extracranial veins due to thrombosed dural venous sinuses. Middle row: a 34yr old F with a diagnosis of IIH D) bilateral papilledema in IIH, E) increased lumen of SSS and all BV due to transverse sinus (TS) stenosis before stent placement in the TS, and F) reduction in the lumen (and thus volume) of the SSS and BV after stenting of the TS. Bottom row: 25yr old F with a diagnosis of intracranial hypotension.

water channels lined astrocytes. The CSF mixes with ISF and this fluid exits the space around veins, or venular perivascular space (VPS) (Figure 1).⁷ This paravascular movement of fluids and solutes is probably facilitated by arterial pulsations and respiration and represent the principal drivers of bulk flow, although recent evidence demonstrates diffusion within the ECS to be more likely.⁵⁹⁻⁶¹ An alternative model suggests that CSF enters BP through BM within the walls of penetrating arteries whereas neurotoxic waste such as amyloid β and τ is removed *via* ISF drainage along the BM, assisted by contractile activity of the SMC (aka vasomotion) in an opposite direction to arterial flow towards the deep cervical lymph nodes, also known as the intramural periarial drainage (IPAD)^{9,62,63} (Figure 1). Computational modeling of IPAD suggests that such movement of ISF is faster than diffusion through BP.⁶⁴

Brain parenchyma

With over 100 billion neurons, the brain is one of the most metabolically active, high-energy demanding organ in the human body.⁶⁵ Oxygen and glucose are primary substrates for the production of high energy adenosine triphosphate molecules (ATP) that assure the functioning of $\text{Na}^+\text{-K}^+$ ATPase pumps, necessary to maintain the integrity of cell membranes and also to generate action potentials that form the basis of all neuronal activity. This activity continues relentlessly at all times including sleep.⁶⁶ Since glucose is not stored in the brain, a steady supply of primary substrates is necessary for normal brain function and warrants an adequate CPP and CBF at all times. Interruption of CBF for just 10 seconds can cause neuronal dysfunction and if not restored promptly, irreversible damage can occur in a matter of a few minutes.⁶⁷

BP consists of gray matter (GM) and white matter (WM) (Figure 2E). There is an outer layer of cortical GM and an inner mass of WM. Within the depths of WM, there are additional nuclei of cells, also known as subcortical gray matter nuclei and are largely represented by basal ganglia, thalami, and hippocampi. GM is a more hydrophilic environment that contains a larger quantity of fluid, is less tightly packed with cells and has a higher capillary density reflective of its elevated energy needs.⁶⁸ MRI based measurements have quantified a total CBV (arterial and venous) in the GM to be about 5.5 mL and in the WM to be approximately 1.5 mL of every 100 mL of brain weight.⁶⁹ WM, on the other

hand, is made up of heavily myelinated tracts creating a highly anisotropic environment that restricts the movement of water molecules in the direction of least resistance. The mechanical and visco-elastic properties (brain compliance) of the BP vary and depend on cellular morphology, capillary distribution, the compactness of white matter axons, their orientation and ECM composition.⁷⁰ These properties are different both at a macroscale (WM is stiffer than GM) and at a microscale (cortical GM is stiffer than hippocampal GM; WM in the corpus callosum is stiffer than WM in the corona radiata).⁷⁰ Brain compliance is a measure that expresses the brain pressure-volume relationship. In a well-compliant BP, changes in volume will not affect pressure until it reaches a certain threshold, whereby even small volume changes would result in very large ICP changes.⁷¹ Such characteristics are constantly changing with water content in the brain, during both neurodevelopment in early stages of life and neurodegeneration in later stages of life and will affect brain compliance.⁷² In an early MRI-based study, Greitz *et al.* observed brain tissue pulsatile movement caused by systolic arterial expansion, noting that re-modelling of the brain enables its piston-like action that aids CSF venting to SSAS and compression of ventricles, thus promoting intra-ventricular flow. They identify cranio-spinal dynamics, as the interplay resulting from the spatial requirements of BP and neurofluids. Brain compliance can be influenced by age-related changes, pathological processes and also by simple manual external compression of IJVs, no doubt BP dynamics must be part of any study concerned with cranio-spinal dynamics in a holistic setting, as advocated here.⁷³

Craniospinal inter-compartment fluid dynamics and waste clearance

Main tasks of the brain fluid-mediated transport systems are: i) to supply oxygen and nutrients to sustain high-energy demands of the brain; and ii) to collect and remove metabolic waste efficiently, avoiding an accumulation of neurotoxic materials in the brain's delicate structures. The first task involves the arterial system providing fast advective transport of solutes in the blood, which is then partly delivered at the level of the microvasculature involving various forms of transport across the vessel wall. As indicated by the Einstein space-time relation for diffusion, time is propor-

tional to the square of the distance ($t \propto x^2$) which means that diffusion is hopelessly slow for long distances but fast for very short distances. The thickness of brain capillary walls is of the order of 1 μm and therefore in this situation, diffusion is sufficiently fast.

Transport across the vessel wall is a two-way process; in addition to the delivery of oxygen and nutrients from lumen to tissue, there is absorption into the bloodstream across the capillary/venule wall. Many diseases are likely in part due to disturbance of the two types of transport: i) fast, long-range advective transport dominated by pressure gradients; and ii) slow, short-range, diffusion dominated transport. The integrity of the intricate morpho-functional aspects of neurofluids and BP are major determinants for the smooth delivery of vital substances for neuronal functioning and for effective transport of metabolic waste. Altered fluid dynamics will result in altered pressure, altered flow, altered wall shear stresses, altered perfusion, altered absorption, altered clearance of metabolic waste, edema, accumulation and deposition of materials in the vessel wall and the BP. Neurofluid dynamics are thus closely coupled to waste clearance mechanisms (Figure 1). A major clinical implication of such combined transport systems is their role in clearance of metabolic waste and neurotoxic substances such as amyloid β and τ and their potential biophysical link of neurofluid dynamics to neurological diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), idiopathic intracranial hypertension (IIH), Ménière's disease (MD), multiple sclerosis (MS), migraine and other neurodegenerative diseases.⁷⁴ There are however many questions to be answered with regards to brain waste clearance systems. For example, the forces responsible for the transport of CSF into the BP, exit route through the VPS and the character of such transport, advective or diffusive remain controversial and yet to be identified.

Perhaps even more challenging, is the interaction of these fluid transport systems with the venous system, especially in pathological conditions. This point, to the authors' knowledge, has not yet been addressed. Here we anticipate some points that might be of interest to consider in craniospinal venous pathological conditions. First, recall that venous system: i) is a sink to CSF via arachnoid-villi drainage into the superior sagittal sinus; ii) collects ISF and solutes that is reabsorbed across vessel walls of capillary and venules; and iii) CSF/ISF flows into the deep cervical lymph nodes which empties lymph into the subcla-

vian veins between the internal and the external jugular vein junctions.⁷⁵ This powerful role of the venous system cannot be undermined and must be incorporated in the global picture of waste drain mechanisms. A thorough quantitative investigation of APS and VPS in BP is needed and seems to be lacking at present. From the point of view of the clearance capacity of the lymphatic system, the size of the VPS and its variability under pathological conditions seems most important. Transmural pressure across venular walls is the difference between pressure outside the venular wall (external pressure) and the pressure from inside the venules (internal pressure).⁷⁶ In this regard, it is reasonable to suggest that in conditions of cerebral venous hypertension, venous engorgement from the inside and increased ICP from the outside would contribute to reduce the size of the VPS. Such changes will occur in cases of increased pressure in the intra or extracranial venous vessels.^{76,77} An obvious consequence of this would be the hampering of fluid and solute transport proposed by Iliff *et al.*⁷

Clinical implications

The most complex morphological and functional structure of the brain in which the microvasculature is embedded is the neurovascular unit (NVU), made up of neurons, astrocytes, and the vascular structures. The coupling of astrocytes and neurons in the delivery of glucose and oxygen and their combustion into ATP, the molecular processes underlying the constant and prompt turnover of neurotransmitters, the processes underlying synaptic activity, volume transmission of neurotransmitters, ions and proteins, the maintenance of a healthy ECM, ISF flow, instant dynamic removal of waste products are just some of the functions of the NVU. Damage to the NVU at any level will cause irreversible damage to processes leading to the normal functioning of the neurons.

Arterial pathology

Arterial hypertension and arteriosclerosis will weaken the walls, increase shear stress, alter the cerebral autoregulatory mechanisms, increase arterial pulsatility, affect Windkessel mechanism and consequently reduce CBF and CPP.⁵² Chronic hypoperfusion will damage NVU, cause rarefaction of WM, accelerate demyelination, damage ECM, disintegrate the BBB, SMC, and pericytes, resulting in lacunar infarcts all of which are characteristic of small vessel disease (SVD) and leukoaraio-

sis⁷⁸⁻⁸⁰ SVD is also characterized by dilated PVS, considered a biomarker of reduced drainage of ISF and solutes and correlate directly with increased risk of vascular dementia.⁷⁹ Gliosis increases tortuosity of the ECS and reduces brain compliance.⁵⁴ Failure of elimination of proteins and ISF along arterial walls *via* IPAD can occur in a variety of genetic diseases such as cerebral autosomal dominant arteriopathy and subcortical inflammatory leukoencephalopathy, cerebral amyloid angiopathy and neurodegenerative diseases (*e.g.* AD).⁸¹ Arteriole walls become fragile and prone to hemorrhage, there is increased amyloid-beta deposition within the BP and arterial walls, that lead to a cascade of events and finally neuronal degeneration, a mechanism common to protein elimination failure arteriopathies and dementia.⁸²

Venous pathology

The role of veins in neurological diseases was brought to the forefront by Zamboni, ten years ago where he found a significantly increased number of patients with multiple sclerosis with inefficient extracranial venous drainage, also termed chronic cerebrospinal venous insufficiency (CCSVI).⁸³ Various degree of CCSVI can cause retrograde reflux of venous blood, increased intracranial venous pressure and local venous hypertension, increase CSF pulsatility in the AoS, reduce clearance of ISF, promote iron deposition, inflammation, breakdown of BBB and myelin disintegra-

tion.⁷⁴ Higher number of venous collaterals is present in MS patients with CCSVI as a physiological compensatory response to reduced venous output.⁸⁴

There is a direct interdependency between cerebral venous flow and CSF dynamics such that intra and/or extracranial strictures will directly affect CSF flow parameters within the ventricular system in normal and pathological conditions.⁴ In healthy subjects MR elastography and PC-MRI techniques have demonstrated that compression of IJVs in the neck directly increases CSF pulsatility in the AoS, decreases CBF and, increases brain tissue stiffness.⁸⁵⁻⁸⁷ The most striking evidence of such interdependency was communicated by Hans Queckenstedt more than 100 years ago (1916), modern confirmations of which are contained in the work of Alperin *et al.*, who in the context of IIH discovered the presence of both intracranial and extracranial venous strictures that impeded normal venous drainage thereby increasing intracranial venous volume and overall altered intracranial dynamics, with raised ICP as one consequence.^{88,89} Extracranial IJV compression was recently proposed as a direct cause of dilated ventricles and increased ICP in a patient in a possibly new syndrome which the authors call the JEDI syndrome (jugular entrapment, dilated ventricles, intracranial hypertension).⁹⁰ Intracranial venous strictures can also affect cerebral venous outflow. An example of such strictures is the idiopathic intracranial

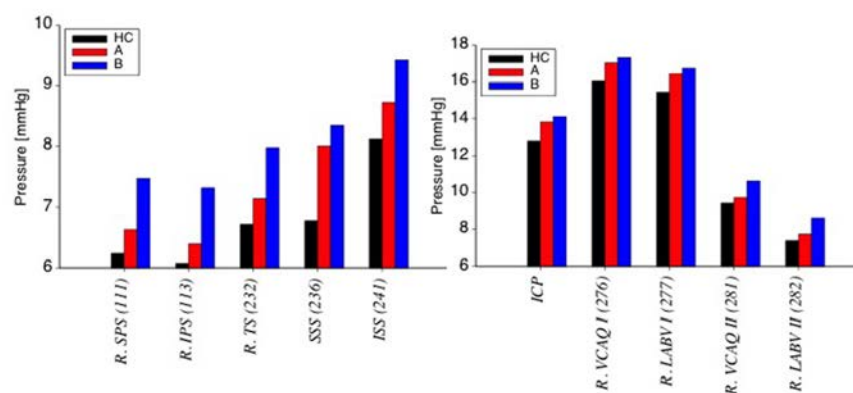


Figure 4. Impact of extracranial venous outflow strictures. Computational results from a validated global, closed-loop mathematical model show that the entire fluid dynamics of the craniospinal system is altered, including raised ICP and increased intracranial venous pressure. The figure shows computed cardiac-cycle averaged pressures for two anomalous cases A and B, compared to the healthy control (HC). The left frame shows pressures for superior petrosal sinus (SPS), inferior petrosal sinus (IPS), transverse sinus (TS), superior sagittal sinus (SSS) and inferior sagittal sinus (ISS). The right frame shows pressures in brain parenchyma (ICP), vein of the cochlear aqueduct (VCAQ) and labyrinthine vein (LABV). *Reproduced from Toro et al., 2018.*¹⁰⁴

hypertension (IH) characterized by a high prevalence of dural venous sinus stenosis (in particular, transverse sinus).^{91,92} Studies consistently report increased CSF pulsatility in the AoS and reduced CBF, both parameters that can be improved after high volume CSF removal during a lumbar puncture or venous stenting but not medical treatment alone.⁵³ This knowledge is leading the path towards newer and efficacious treatments such as venous angioplasty and stenting.⁹³

Alterations of CSF and ISF dynamics

In CSF circulation disorders such as normal pressure hydrocephalus (NPH), PC-MRI have repeatedly shown increased CSF pulsatility in the AoS, reduced vascular compliance and decreased arterial perfusion within the BP.⁹⁴ Increased brain stiffness, gliosis, and demyelination of the periventricular white matter are reflective of a more global alteration that affects transependymal flow, macromolecule transependymal transport and overall neurofluid interactions including CSF and ISF.^{10,95,96} The role of ISF flow has not yet gained sufficient attention in the medical world, mostly because it is hard to visualize and image the ECS and its contents. ECS is a dynamic space greatly affected by the physiologic activity of the astrocytes and neurons but also by physiologic states such as sleep.⁹⁷ Stagnant ISF, impaired drainage of solutes, dilation of PVS are known to cause atrophy of the surrounding axons leading to a vicious cycle of neurodegeneration.^{79,98}

Meningeal lymphatics pathology

The recent discovery of meningeal lymphatics and its drainage pathway within the outer meningeal layers surrounding the dural venous sinus has been revolutionary and since then a number of neurological diseases have been shown to have altered lymphatic drainage.⁶ In essence, solute clearance through the CSF is achieved via drainage into meningeal lymphatics that reach deep cervical lymph nodes. Damage to these pathways, including experimental ligation of deep cervical lymph nodes can cause neurodegeneration in particular AD, aggravate PD and worsen stroke outcome.⁹⁹⁻¹⁰¹

In quantitative science we either measure or we compute. Real-life measurements are difficult and even impossible since they tend to involve invasive methodology. Müller and Toro developed a comprehensive mathematical model for all major full-body fluids, with special attention paid to craniospinal fluids and the venous system in particular.¹⁰² This model has been used to study the effect of

extracranial venous outflow strictures and has demonstrated increased cerebral venous pressure, increased ICP and disturbed overall cranio-spinal dynamics^{77,103} (Figure 4). These theoretical results have confirmed partial previous experimental results and from now on they should be regarded as fact and no longer a matter of opinion or supposition.

Conclusions

Clinicians and researchers tend to focus on single isolated fluid systems, overshadowing the broader picture of neurofluid dynamics within the brain. New observations and developments in neuroscience force us to revise our old dogmas and challenge us to adopt new concepts. By interrogating different physiologic mechanisms that may have been jeopardised in a disease at any one time, understanding the dynamic nature of the entire system and its individual compartments, is likely the only way to find answers to the several neurological diseases that still remain without a specific etiology and treatment (including several *idiopathic* and *atypical* variants of diseases). The venous system in the brain has not yet been carefully studied in a clinical setting and requires urgent attention. Veins are the sink of the entire fluid content in the brain and it would be irrational to not comprehend the extent of their involvement in neurological diseases and to revisit treatment options. Potential consequences still to be established include decreased cerebral perfusion and disturbed CNS clearance system as a result of venous strictures.

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