



Fluid dynamics of cerebrospinal venous flow in multiple sclerosis

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ABSTRACT

Stenotic immobile valves and other malformations obstruct normal cerebrospinal venous outflow, resulting in reflux flow which combines with the normal outflow to produce standing pressure waves in the internal jugular and other cerebrospinal veins. It is hypothesized that, if the cerebrospinal venous structure between the obstruction and the deep cerebral veins is sufficiently non-compliant, the standing wave will result in bidirectional flow in the fine cerebral veins. Bidirectional flow in the fine veins, over extended periods of time, will cause disorder in the veins' endothelial morphology, and ultimately, result in the disruption of the blood-brain barrier as observed in multiple sclerosis.

This physics-based analysis demonstrates a positive correlation between clinically observed MS attributes with the predicted flow patterns and venous malformations that are based on fluid dynamics principles that include venous compliance influences.

The physics-based approach used in this analysis provides new insights into MS pathologies based on predicted pressure and flow patterns.

Introduction

This paper analyzes, through the application of fluid dynamics principles, the patterns of blood flow in cerebrospinal veins (CSVs), particularly the internal jugular veins (IJVs) and deep cerebral veins (DCVs), of multiple sclerosis (MS) patients. A related paper [1] applied the physics of fluid dynamics to the analysis of blood flow patterns in major veins in the thoracic cavity, specifically, in the superior vena cava (SVC) and brachiocephalic veins (BVs). Physics-based analysis predicts the occurrence of non-laminar, vortex flow in the SVC and BVs at confluences with their tributary veins, particularly the IJVs and the azygos vein (AV). The blood's pulsatility causes such vortices to expand and contract with each cardiac cycle, thereby causing localized stagnant and reversing (bidirectional) flow along the wall proximal to the SVC and BV confluences [1–3] with their tributary veins. Stagnant and reversing venous flow, through biomechanical interactions with the walls' cellular structure, results in venous malformations at those vein junctions [2,3]. Such malformations include stenotic, immobile valves proximally located at the confluences of the thoracic veins with IJVs and other tributary veins, malformations that are widely reported to be associated with MS [4–9]. This paper's analysis focuses on abnormal flow patterns which are a consequence of stenotic, immobile valve malformations in the IJVs. Such IJV stenotic, immobile valves have been predicted to give rise to standing pressure waves in the IJV [10].

The hypotheses

This paper hypothesizes that sufficiently obstructed stenotic IJV valves reflect outflowing pulses back on themselves creating standing pressure waves in the IJV have pressure maxima and minima whose magnitudes depend on the distance from the obstruction and the vein's

compliance. Furthermore, if the veins are sufficiently non-compliant, standing pressure waves will extend through the dural sinuses into the deep fine cerebral veins. Such standing pressure waves in the deep fine veins will have zones of hypertension with bidirectional (reversing) flow. Such bidirectional flow will cause remodelling of the fine veins' endothelium, loosening of the tight junctions between endothelial cells and disruption of the blood-brain barrier (BBB). Such disruption of the BBB has been widely observed and reported in MS clinical trials.

Background

Stenotic, immobile valves in the IJVs and AV, are reported [4–9] to cause the obstruction of venous outflow from those veins. Fluid dynamics principles require that venous obstructions, if sufficiently great, cause the reflection (reflux) of most of the venous outflow back toward the cerebral capillary bed. With venous flow being pulsatile and periodic, the forward (normal) and reflux (abnormal) pulse streams combine to form a standing pressure wave [10]. A standing wave is a non-propagating pressure wave whose amplitude oscillates between a maximum determined by the sum of the systolic pressures and a minimum determined by the sum of the diastolic pressures of the forward and reflux waves. The positions within the vein of the standing pressure waves' maxima and minima are relatively stationary [10], while mean blood flow remains toward the heart as determined by the gradient of the mean pressure.

Disruption in the blood-brain barrier has been widely reported in MS [11–20]. Early studies of BBB disruption focused on biochemical effects on the cellular structure based on analyses of surgical or autopsy samples [11–17]. More recent studies of blood-brain barrier breakdown in MS have included the impact of disturbed blood flow on the morphology of the BBB [18–20].

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Disturbed blood flow is measured clinically, not in the region of the white matter scleroses (where flow measurement technology is currently inadequate because of the veins' fineness and inaccessible), but measured distal to the region of the CNS scleroses. Often flow is measured extracranially, where it is relatively easily measured [4–9,21–25]. The absence of flow measurements directly in the fine veins that center the CNS scleroses is thought to be a contributing factor to the debate regarding an association of abnormal cerebrospinal (CS) flow with MS and other neurological disorders [26–31].

There is a continuous fluid-flow channel of connecting veins and dural sinuses between obstructed IJV valves (or other CS venous obstructions) and the deep cerebral veins. Fluid dynamics requires the existence of physics-based relationships between the pressure and flow patterns everywhere in the fluid channel, including the IJV (or other CS veins), DSs and the DCVs. Such physics relationships between pressure in the IJV and in the deep cerebral veins rationalize the applicability and validity of measuring flow in the neck veins as an indirect indicator of pressure and flow in the deep cerebral veins.

Any physics relationships between pressure and flow patterns in an obstructed IJV and in the deep veins require the inclusion of the vein and dural sinus boundary conditions. Such boundary conditions include the diameter, compliance (or distensibility) and wall frictional forces of each of the vein and dural sinus channel segments. In particular, the pulse storage capabilities of IJVs and sinuses contribute to the smoothing of pulsatility, pressure and flow through the influence of the Windkessel effect. Since the walls of the DSs are composed of bone and dura mater, the sinuses' compliances are taken to be similar to those of rigid vessels. Hence, pulsatile pressure and bidirectional flow smoothing is dominated by the substantially more compliant veins. The pressure pulsatility and bidirectional flow which is transmitted from the sinuses into the DCVs (and the associated blood-brain barriers in the fine DCVs) is, hence, substantially determined by the pressure at the IJV venous obstruction and the compliance of the internal jugular vein.

While disturbed blood flow, particularly bidirectional, stagnant and reversing flow, has been associated with disruption of the blood-brain barrier [18–20], hypertension in the deep cerebral veins has also been related to blood-brain barrier compromise [10,20,32,33]. A proposed mechanism for BBB compromise is that an increase in transmural venous pressure causes radial distention of the fine veins which, in turn, causes a separation by mechanical forces of the BBB's endothelial cells' tight junctions [33].

Biochemical mechanisms have also been related to disruption of the blood-brain barrier in MS [11–17]. The cascade of specific biomechanical and biochemical interactions accompanying the disruption of the BBB has been described and reviewed elsewhere [14–21,34–40] and are addressed only briefly here. Also, the description of the biochemical interactions which occur within the cerebral parenchyma after BBB disruption is beyond the intended scope of this paper.

Blood flow in straight segments of a healthy (non-obstructed) internal jugular vein is widely accepted to be laminar and unidirectional, as indicated by values of Reynolds number for IJV flow, and as discussed in a related paper [1]. The value of the Reynolds number characterizes flow stability. The value of Reynolds number is determined primarily by the vein's diameter, the mean blood flow velocity and the viscosity of the blood. Above a critical value of Reynolds number, flow transitions from laminar to non-laminar [1]. However, the critical transition value of Reynolds number is also affected by the compliance of the vein [1,41–44]. (The Womersley number, which is also used to characterize the stability of pulsatile arterial flow, is not used here since two of the Womersley assumptions are not applicable to the cerebrospinal veins, specifically the peak to peak pressure excursion is not large compared to the mean pressure, and the incremental distension in diameter of the vessel wall under systolic pressure is not small compared to the diastolic diameter).

The primary CS veins for flow in the supine position are the IJVs and AV. As was the case in the related paper [1] this paper also focuses on

blood flow in the supine position. Laminar flow is predicted in the IJVs and other finer veins as a consequence of a small vein diameter and sufficiently large blood viscosity that the friction forces from the close proximity of the vein walls suppresses the onset of turbulence. Unidirectional laminar flow in healthy IJVs applies unidirectional shear stress to the veins' endothelial cells, causing elongation of cells in the direction of flow [39,45].

In-vitro trials [2,3] have been carried out, using bovine aortic endothelia, in which flow over a step in the endothelial surface produced vortex and reversing flow [1]. These trials found that, while unidirectional laminar flow aligned the cells in the direction of flow and strengthened intercellular junctions [2,3]; reversing flow disordered the endothelial cellular structure and weakened intercellular junctions. At flow stagnation points [1], the growth of additional cells was observed [2,3]. The compliance of the section of aorta was reported to be substantially reduced with reversing flow (i.e. flow-induced arteriosclerosis).

Assuming unidirectional and bidirectional blood flow affects arterial and venous endothelia similarly then venous unidirectional laminar flow is predicted to sustain or increase vein compliance (i.e. resistance to the effects of aging and other factors which tend to reduce venous compliance). In contrast, regions of stagnant or reversing venous flow are predicted to cause disordered and malformed intraluminal walls and valves [4–9] and disordered BBB [17–20].

Reversing flow in internal jugular and fine cerebral veins

The hypothesis of this paper is addressed through consideration of flow in an internal jugular vein which possesses an immobile stenotic valve at its confluence with the brachiocephalic vein. A previous analysis [10] concluded that an immobile stenotic valve in an IJV could, with sufficient obstruction, cause a reflection of an outflowing periodic pulsatile waveform back on itself. The combination of the outflow and reflux waveforms results in a standing pressure wave [10]. Such a standing wave possesses nodes of relatively low and steady (non-fluctuating, constant) pressure every half wavelength along the IJV. It also possesses localized segments of periodic hypertension at midway points between the constant pressure nodes, with one hypertensive segment located at the immobile valve. The pressure at the immobile valve would fluctuate each cardiac cycle between the sum of the waves' systolic pressures and the sum of their diastolic pressures. Such hypertensive segments would occur at each half wavelength point (between steady nodes) proceeding from the immobile valve toward the venules.

The previous analysis [10], while accommodating some flow leakage through collateral veins or incomplete blockage at the immobile valve, was based on the simplifying assumption of negligible vein compliance (i.e. the rigid tube assumption). There is substantial evidence, however, that vein compliance needs to be included in the analysis of flow in the IJV and deeper veins [1,41,44–47] in order to represent a more realistic physics model of the phenomena. In addition to vein compliance, relatively steady (i.e. non-pulsatile) flow through the capillaries and into the venules (a widely accepted view of capillary flow) needs to be an included boundary condition in the IJV flow analysis. Flow emerging from the capillaries and venules will change from relatively steady (non-pulsatile) to pulsatile as it travels through the DCVs and dural sinuses toward the IJV confluence with the brachiocephalic vein.

The veins and sinuses in the IJV/DS/DCV channel include deep cerebral veins, inferior sagittal sinus, straight sinus, confluence of sinuses, transverse sinus, sigmoid sinus and internal jugular vein. In a healthy venous system (free of obstructions), pressure pulsatility (peak to peak variation) grows as the pulse flows from the venules toward the heart. Fig. 1 provides a diagrammatic representation of the left IJV/DS/DCV structure with unidirectional IJV outflow into the brachiocephalic vein (BV).

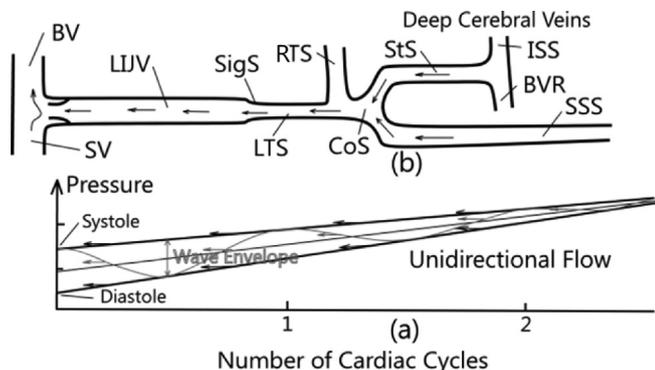


Fig. 1. (a) Pulsatile venous outflow in healthy (unobstructed) vein/sinus structure, (b) Representation of IJV, DV, DCV structure: BV – Brachiocephalic, SV - Subclavian Vein, LJJV - Left Internal Jugular Vein, SigS – Sigmoid Sinus, LTS – Left Transverse Sinus, RTS – Right Transverse Sinus, CoS – Confluence of Sinuses, StS – Straight Sinus, SSS – Superior Sagittal Sinus, BVR - Basal Vein of Rosenthal, ISS - Inferior Sagittal Sinus.

Fig. 1 shows a pressure wave for almost three cardiac cycles and assumes that one wavelength is approximately equal to the length of the internal jugular vein. The figure shows that the mean pressure is greater at the venule end of the vein/sinus structure than at the brachiocephalic outflow end. At any point along the IJV/DS/DCV channel the instantaneous flow direction is down the pressure gradient as determined by the pressure envelope at that point and time. Irrespective of the wave being at systole or diastole, flow is unidirectional, but pulsatile, everywhere in the channel and is from right to left in Fig. 1. The incremental pressure, peak to peak, is small in the deep cerebral veins, consistent with the widely held view of relatively steady (non-pulsatile) flow in the capillaries, and grows as it flows toward the BV.

With immobile valves, however, the sum of the pressures of the outflow and reflected waves forms standing pressure waves as shown in Fig. 2(b) and (c) for two different conditions of vein compliance. Fig. 2(a) shows the standing wave envelope (maxima and minima corresponding to systole and diastole respectively) for a compliant IJV;

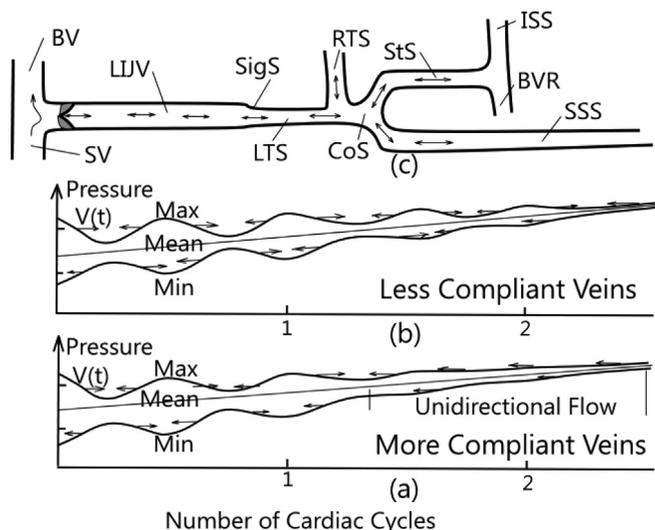


Fig. 2. Top: Cerebrospinal vein map. Bottom: Sums of forward and reflux pressure waves. Arrows indicate direction of flow in response to maximum and minimum sum pressures (assumes flow velocity lags pressure wave by about 90 degrees): BV – Brachiocephalic, SV - Subclavian Vein, LJJV - Left Internal Jugular Vein, SigS – Sigmoid Sinus, LTS – Left Transverse Sinus, RTS – Right Transverse Sinus, CoS – Confluence of Sinuses, StS – Straight Sinus, SSS – Superior Sagittal Sinus, BVR - Basal Vein of Rosenthal, ISS - Inferior Sagittal Sinus.

a vein in which the dilation is sufficient that the volume of the reflux pulse during systole is stored by dilation in the IJV, thereby reducing the pulse pressure that is transmitted further into the DSs and DCVs. This results in reversing pulsatile flow in the compliant IJV segment of the IJV/DS/DCV channel, but unidirectional pulsatile flow in the deep cerebral veins as shown in Fig. 2(a).

In contrast, for a relatively non-compliant IJV in which the volume of the reflux pulse cannot be fully stored by dilation of the IJV, the standing pressure wave redistributes to take a form as shown in Fig. 2(b). For a non-compliant IJV, the standing pressure wave extends through the dural sinuses into the DCVs where it gives rise to reversing pressure gradients and reversing flow direction (flow direction oscillating within each cardiac cycle). Such reversing flow inherently possess moments of stagnant flow (i.e. zero velocity).

Depending on the degree of obstruction in the IJV (and the amount of collateral and other venous leakage around the obstruction), the pressure near the valves at systole may be nearly double the systolic pressure in a non-obstructed vein. The percentage of obstruction required to create reversing flow in the DCVs will be dependent on the value of the IJV’s compliance. In order for reflux to affect the pulsatility index in the DCVs, the obstruction must be substantial, perhaps in the range of 80% or more reduction in the vein’s cross-sectional area. As the pressure at the stenosed, immobile valve reaches its maximum and forces flow back toward the venules, it will also force flow out any collateral veins or valve leakage paths. Hence, any flow into the BV, would be forced through collateral and leakage paths by the pressurized vein. Such pressurized flow is predicted to exceed the normal flow velocity and occur for a portion of each cardiac cycle. Since in-vivo measured values of vein and sinus compliances are limited in the current literature [48], quantitative calculations of pressure and flow distributions are not carried out here.

As shown in Fig. 2, flow in the deep fine veins and venules has a low pulsatility index [49], based on the generally accepted concept of relatively steady (non-pulsatile) flow in the capillaries. As shown in Fig. 2, there is an increase in the pulsatility index moving toward the immobile valves. The wavelength of the standing wave will be determined by the pulse rate and the velocity of the pulse pressure wave which is a function of the venous compliance. If the vein’s compliance is sufficiently large (and it may be 30 times more compliant than arteries [50]) then the velocity of the pressure wave may be comparable to the velocity of the fluid’s flow. (In arteries the pulse pressure velocity may be 5 to 10 times that of the fluid flow and is measured clinically as a test for arterial compliance and potential cardiovascular disease [51,52].) Irrespective of the value of the wavelength, at every half wavelength moving back from the stenosed valves toward the venules, there would exist stationary, large peak to peak excursions in the combined pressure waveform, as the waves cycle through their respective systolic and diastolic pressures. Between these large pressure excursions, one quarter wavelength distance, relatively constant lower pressure nodes would exist. At these steady pressure nodes, if the transmural pressure is sufficiently low, the vein may collapse at the node, creating a stenosis. Clinical observations of such venous stenotic nodes or flattening of the vein, without apparent obstruction, have been reported [40,53,54]. Such stenotic nodes would be consistent with the proposed standing wave model if such venous stenotic nodes could be shown to be one quarter-wavelength removed from an immobile valve or other obstruction. However, the reports of such nodes are not sufficiently detailed that the cardiac period or pulse velocity, which determine the wavelength, are known. Based on estimates of dimensions from referenced pictorials and typical pulse velocities and cardiac cycle periods, such pressure nodes appear at points on the vein that are consistent with a standing pressure wave in the vein.

Fig. 3 compares the pressure and flow patterns in obstructed and unobstructed IJV/DS/DCV channels. This comparison demonstrates the substantial difference in flow and pressure patterns that is introduced by an obstruction in the IJV.

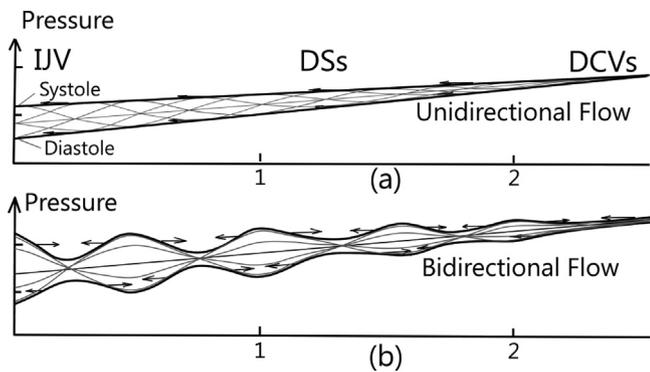


Fig. 3. A comparison of pressure and flow patterns in the internal jugular vein, dural sinuses, deep cerebral vein structure (a) for an unobstructed IJV; and, (b) an obstructed IJV.

Figs. 2(b) and 3(b) show periodic (with the cardiac cycle) bidirectional flows in the deep cerebral veins for sufficiently non-compliant veins. Such cyclical bidirectional flow is predicted to be laminar, but also reversing within each cardiac cycle. Such reversing flow has been clinically shown to cause disordered endothelial layers [2,3], various venous malformations [4–9] and disruption of the blood-brain barrier [18–20].

Blood-brain barrier disruption is predicted at points in the fine deep cerebral vein structure at which there is cyclically reversing flow with near simultaneous local hypertension. Such points will occur only at specific points on the standing wave. The location of those reversing flow points depends on the pulsatility wavelength which in turn depends on the pulse pressure velocity and the periodicity of the cardiac cycle. These factors, pulse pressure velocity and cardiac period, will determine which points in the CNS are affected by reversing venous flow. If these factors are each stable for extended periods, and if the vein is sufficiently non-compliant, then the resulting standing wave and reversing flow would cause disordered fine DCV endothelial structure and disruption in the blood-brain barrier at specific points in the CNS. Such points would vary with changes in either cardiac period or pulse wave velocity and hence would be different from time to time and from person to person.

The venous flow patterns and subsequent vein and valve malformations described above are analogous to flow patterns and arterial malformations as are widely recognized in arteriosclerosis and atherosclerosis [55–58]. As with arteriosclerosis, the course, timing and rate of venosclerosis development in MS are all expected to be most variable. The beginning of venous malformation development is probably weighted somewhat to the growth stages of the teen years and early twenties. However, as with arteriosclerosis, it may start sooner than teen years or later than the early twenties. It is expected that the rate of venous plaque development will be highly variable, as with arteriosclerosis and atherosclerosis.

Discussion

Vein compliance is predicted to be an important factor in deep cerebral vein bidirectional flow and local hypertension as caused by obstructions in the internal jugular (and other CS) veins. With such obstruction, if the IJVs are compliant, then cyclically reversing pulses may be absorbed by vein expansion (i.e. venous Winkessel effect). With compliant veins, the reflux component of flow into the fine veins and venules may be sufficiently small that it does not substantially affect normal outflow from the venules. For compliant veins, deep cerebral vein flow is expected to be unidirectional and the venous walls relatively quiescent. If, however, the veins are relatively non-compliant then reflux pulses in the IJV may give rise, through the creation of standing pressure waves (without dilation absorption) to abnormal,

bidirectional, perhaps vortex, flow in the larger DCVs such as the great vein of Galen and the basal vein of Rosenthal. Such flow in the larger deep veins would give rise to bidirectional flow in their finer tributary cerebral veins.

While this paper focuses on stenosed, immobile valves in the IJV, other forms of obstruction such as muscular or cervical subluxation, as observed in MS [59–65], may cause similar standing pressure waves and associated stagnant and reversing flow patterns. Hence, the analysis is not dependent on stenosed valves, but is dependent on the obstruction being sufficiently large that any standing waves in deep cerebral veins have sufficiently large pulsatility indices, that reversing flow occurs in the DCVs.

For sufficient reverse flow in the IJVs to cause even modest reverse flow in the distal DCVs, the percentage of blockage in the IJV is likely required to significantly exceed 50% and is probably in the 80% of greater range. Computer modeling [66] of reverse flow caused by a 50% vessel stenoses produces a small deviation in distal flow disturbance. Significant distal flow disturbance occurs only if the stenoses are 70% or more. In order that reverse flow occurs also in the DCVs, with vein dilation effects included, it is estimated the required percent obstruction in the lower IJV is significantly in excess of 70%.

With a substantial obstruction in the internal jugular vein causing the summation of outflowing and reflux pulse pressures at the obstruction, the resulting overpressure will cause outflow through collateral and valve leakage paths for part of each cardiac cycle. The velocity of such over-pressurized outflow is predicted to be substantially greater than normal outflow. In the supine position, and in unobstructed IJVs, normal flow velocities have been reported [67–69] to be in the 10–60 cm/sec range, but the reported values are dependent on a number of factors, including, if the measurement is in the right or left IJV, if it is a mean or peak velocity and if it is during apnea or aspiration. Reported velocity measurements are also dependent on patient age and exercise state. In comparison, with an obstructed IJV, the peak outflow velocity has been reported [65] to be 200 cm/s or more, substantially higher flow velocities than for unobstructed IJVs. Such high velocity flow ejection is anticipated to be periodic with each cardiac cycle. There is, however, an absence of standardization in the measurement and reporting of such venous flow velocities.

With the premise that periodic bidirectional flow causes disordering of endothelial structure as may exist in the fine deep cerebral veins which center CNS scleroses, it implies that vortex or periodic bidirectional flow occurs also in the larger DCVs, such as the great vein of Galen and the basal vein of Rosenthal. However, the measurement of flow in the DCVs is reported to be difficult [70,71] and measurement technique dependent. The application of time-resolved 3D phase contrast MRI (4D flow MRI) has been shown to successfully measure, in the major cerebral veins and sinuses, not only flow velocity, but also flow direction, flow distribution across veins and flow evolution with time [72,73]. Such 4D flow MRI measured images show substantial flow turbulence, including clearly defined vortex and helix flow patterns, particularly at the confluence of sinuses and at the confluences of the transverse and sigmoid sinuses and also at the confluence of the straight sinus with the basal vein of Rosenthal.

The premise of this paper is that turbulence and vortex flow at curves and confluences in the larger deep cerebral vein/sinus structure could produce venous malformations at those curves and confluences. Such malformations have been clinically measured and reported [74–76] particularly at the confluence of the straight sinus and the great vein of Galen. In numerous cadaveric dissections, three types of malformation have been observed and are replicated below (after [75]).

The position and form of the three types of three types of growths or malformation as shown in Fig. 4, and as reported in [75], are at the location and of forms consistent with cellular malformation associated with vortex flow at the confluence and as predicted in [1]. In particular, the middle configuration in Fig. 4, showing a flap extending upstream, is consistent with cell deposition at the flow joining stagnation point of

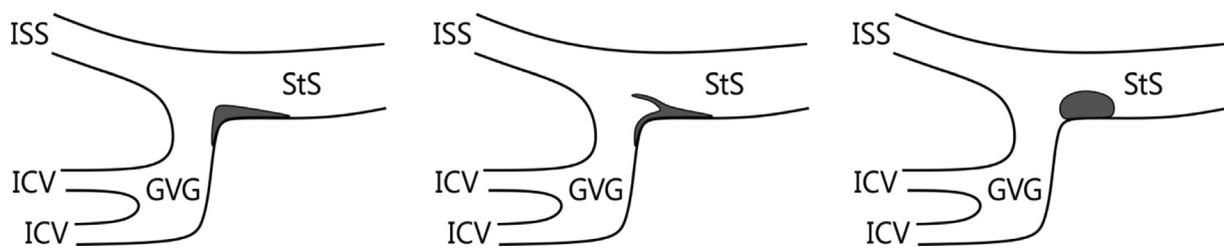


Fig. 4. Configuration of three types of venous formation at the downstream corner of the confluence of the Great Vein of Galen (GVG) with the Internal Sagittal Sinus (ISS), forming the Straight Sinus (StS) as shown in (75). ICV = Internal Cerebral Vein.

vortex flow at the confluence.

Summation of hypothesis

Vortex flow at the confluence of an internal jugular vein and the subclavian/brachiocephalic junction causes venous malformation and stenotic valves proximal to that junction. Such stenotic valves cause reflux pulses which combine to form standing pressure waves in the IJV. Standing pressure waves in the IJV may, if the IJV are not sufficiently compliant, be transmitted through the dural sinuses (DSs), causing bidirectional flow in the fine deep cerebral veins (DCVs), which in turn may cause endothelial disordering and blood-brain barrier compromise in the fine deep veins.

In reverse order the chain of events leading to the disruption of the blood-brain barrier may be summarized as follows:

- a. Disruption of the blood-brain barrier;
- b. Disordering of the endothelium in the fine deep cerebral veins;
- c. Periodic bidirectional flow in the fine deep cerebral veins;
- d. Periodic bidirectional or vortex flow in the larger deep cerebral veins or sinuses;
- e. Periodic bidirectional or vortex flow in the dural sinuses;
- f. Periodic bidirectional flow and standing waves in the internal jugular vein (for which flow rates and vein diameters are not normally sufficient to support vortex or turbulent flow);
- g. Substantial (80% +) occlusion in the internal jugular vein from:
 - a. Extrinsic influences such as external pressure from mis-aligned vertebrae or proximal muscles or arteries
 - b. or,
 - c. Intrinsic influences such as venous malformations or immobile valves from vortex flow at internal jugular vein curvatures and/or confluences with the subclavian/brachiocephalic veins.

Potential clinical implications

Pressure distributions and periodically reversing flow in the larger deep cerebral veins, such as the great vein of Galen and the vein of Rosenthal, most directly affect the flow in the deep fine cerebral veins. Assuming measurement of flow directionality in the fine deep veins is not feasible, then measurement of the flow and pressure patterns in the larger deep cerebral veins is of next primary importance. Existence of periodic bidirectional or vortex flow in the larger deep veins should be taken as a significant indicator of the potential for periodic bidirectional flow in the fine veins and, therefore potential endothelial disordering in those veins. Vortex flow in the larger deep veins is not dependent on the existence of non-laminar or bidirectional flow in the dural sinuses (although such flow in the dural sinuses may be a factor). Vortex flow in the larger deep cerebral veins as a consequence of the curvature and confluence configurations in the larger veins themselves.

Measurement of standing pressure waves or periodic bidirectional flow in the internal jugular veins, may provide an indicator of bidirectional flow in the dural sinuses and DCVs, but flow in these latter sinuses and veins, under the influence of IJV pressure and flow patterns,

will also be dependent on the existence and location of collateral veins. Such collateral veins may substantially influence the pressures and flows transmitted through the sigmoid sinuses and other dural sinuses into the DCVs. However, the relatively tight curvatures in the sigmoid sinuses may, themselves, induce vortex flow in the sinuses.

If standing pressure waves and periodic bidirectional flow are measured in the internal jugular veins, their influences on flow patterns in the deep cerebral veins will be dependent on a number of factors, including the amount of reflux compared to the amount of normal outflow. In the extreme case of complete 100% obstruction in the IJV, and in the absence of other pressure influences such as respiration or Valsalva, the period of time in which reflux dominates normal outflow would be half a cardiac cycle or nominally 0.4 s. With lesser percentage of obstruction, the reflux time would be less than 0.4 s. With substantially less obstruction, the influence of any IJV reflux on the flow distributions in the fine deep cerebral veins, considering the influence of vein and sinus compliance and morphology, may be negligible compared to that of normal unidirectional outflow in those fine veins. Hence, if reflux flow measurement in the IJV is used as a diagnostic, then a reflux time in the range of perhaps 0.2 to 0.4 s would match the standing wave model proposed. Also, if percentage IJV obstruction is used as a diagnostic, then a value in excess of 70%, perhaps 80% to 90% cross sectional area would match the standing wave model proposed [1,10].

The further, detailed validation of the hypothesis that sufficiently obstructed non-compliant veins, especially internal jugular veins, sets in motion a chain of events that ultimately causes disruption of the blood-brain barrier, would include the tailoring of clinical trials specific to measuring the compliance of the IJVs, DSs and DCVs. Such specific measurements are limited in currently available literature [47]. It would also call for the measurement of vortex and bidirectional flow in the larger deep cerebral veins and in their finer tributary veins.

Declaration of Competing Interest

Dr. Tucker has no competing or conflicting interests. No grants or other funding for this research was required or received.

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