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Cerebral venous outflow and cerebrospinal fluid dynamics

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Abstract

In this review, the impact of restricted cerebral venous outflow on the biomechanics of the intracranial fluid system is investigated. The cerebral venous drainage system is often viewed simply as a series of collecting vessels channeling blood back to the heart. However there is growing evidence that it plays an important role in regulating the intracranial fluid system. In particular, there appears to be a link between increased cerebrospinal fluid (CSF) pulsatility in the Aqueduct of Sylvius and constricted venous outflow. Constricted venous outflow also appears to inhibit absorption of CSF into the superior sagittal sinus. The compliance of the cortical bridging veins appears to be critical to the behaviour of the intracranial fluid system, with abnormalities at this location implicated in normal pressure hydrocephalus. The compliance associated with these vessels appears to be functional in nature and dependent on the free egress of blood out of the cranium via the extracranial venous drainage pathways. Because constricted venous outflow appears to be linked with increased aqueductal CSF pulsatility, it suggests that inhibited venous blood outflow may be altering the compliance of the cortical bridging veins.

Introduction

Traditionally, the cerebral venous drainage system has been viewed simply as a network of collecting vessels channeling blood from the brain to the heart; with the result its regulatory role has tended to be over-looked. However, in recent years there has been renewed interest in the cerebral venous drainage system, because of the discovery of the vascular syndrome chronic cerebrospinal venous insufficiency (CCSVI),1 which is characterized by restricted cerebral venous outflow and increased hydraulic resistance to blood flow back to the heart.2 Although the subject of CCSVI has been mired with controversy,2 with many disputing the validity of the syndrome,3 there is increasing evidence that venous drainage anomalies may be associated with physiological changes in the intracranial space.2,4 This has precipitated renewed interest in the role that venous anomalies might play in neurological disease,5 something which has highlighted the close link between the venous drainage system and the dynamics of the cerebrospinal fluid (CSF) system.6 In this review we investigate the link between restricted cerebral venous outflow and the biomechanics of the CSF system.

Intracranial fluid volume regulatory mechanism

Being encased in a rigid enclosure, the brain employs a complex intracranial fluid regulatory mechanism to control the pulsatility of blood flow through the cerebral vascular bed.7,8 This system utilizes a sophisticated windkessel mechanism to compensate for the transient increases in arterial blood volume that occur during systole, by displacing an approximately equal volume of CSF out of the cranium into the spinal column14 (Figure 1). As such, the system maintains Monro-Kellie homeostasis and ensures that the flow of blood through the cerebral capillary bed is smooth and non-pulsatile in healthy young adults.19,20 The whole system is driven by volumetric changes in the arterial pulse, which are transferred to the CSF, causing it to pulse backwards and forwards across the foramen magnum (FM). Although in healthy young adults blood flow through the cerebral capillary bed is normally free of any pulse, by the time it reaches the dural sinuses it once again exhibits pulsatile characteristics.11,16 This suggests that the CSF pulse interacts with the venous flow somewhere in the cranium to regulate blood outflow. While this mechanism has generally been thought to be a passive interaction,19 recent evidence has emerged to suggest that active venoconstriction of the large extracranial veins may also play a part in the regulatory process.17 Deeper insights into the dynamics of the intracranial fluid system can be gained by considering how the fluid flows in and out of the cranium vary over the cardiac cycle. Transient arterial, venous, and CSF flows in and out of the cranium are illustrated in Figure 2, which shows the cervical pulses for a typical healthy individual.19 From this it can be seen that the system is driven by the arterial pulse, which as it enters the cranium during systole greatly increases the volume of blood in the pial arteries.19 This peaks at about 0.23 of the cardiac cycle and is closely followed by the peak in CSF flow through the FM, which occurs at 0.28 of the cardiac cycle. Finally, in late systole at about 0.35 of the cardiac cycle, there is a peak in the venous blood flow leaving the cranium. Figure 2 also shows the CSF pulse in the Aqueduct of Sylvius (AoS), which in comparison to the cervical CSF pulse, exhibits a much smaller amplitude and is out of phase.

From Figure 2 it can be seen that during diastole there is a decrease in the venous blood flow rate leaving the cranium. Given that blood flow through the cerebral capillary bed remains relatively constant throughout the cardiac cycle, this implies that during diastole, venous blood is being stored somewhere in the cranium, only to be rapidly ejected during systole. While the physiological mechanisms associated with this strange phenomenon are poorly understood, it is known that approximately 70% of intracranial blood volume is located within the venous compartments,19 many of which are thin-walled veins that can readily expand and collapse with small changes in transmural pressure.20,21 It is therefore likely that blood is stored in these vessels during diastole. A number of researchers have reported the presence of regulatory sphincters,22,23 which control the discharge from these veins into the superior sagittal sinus (SSS), and it has been postulated that constriction of these sphincters causes the cortical veins to engorge and puff out, before periodically discharging into the SSS.22 Evidence supporting this hypothesis comes from Greitz24 and Nakagawa et al.,25 who both observed the pulsatile compression of cortical bridging veins by the sub-arachnoid CSF.

Key words: cerebral venous drainage, cerebrospinal fluid, chronic cerebrovascular venous insufficiency, intracranial pressure, normal pressure hydrocephalus, multiple sclerosis.

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Cerebrospinal fluid bulk flow

In addition to the CSF pulse, there is a slow bulk flow of CSF from the choroid plexus (CP) to the SSS, via the arachnoid villi (AV), driven by the pressure gradient between the two. While it used to be assumed that all the CSF was absorbed through the AV into the SSS, it is now thought that some CSF drains to the lymph nodes via nasal lymphatics. In animals, as much as 50% of CSF drains to the lymph nodes, whereas in adult humans a greater proportion appears to drain directly into the venous blood via the AV, with lymphatic drainage playing only a minor role. The SSS acts as a collecting vessel for CSF from the sub-arachnoid space (SAS). CSF absorption into the SSS via the AV, which has been measured in the range 4.5-9.4 mm^3/s in healthy individuals, is very susceptible to changes in the pressure difference between the SAS and SSS. In a study involving 100 healthy adults, Ekstedt demonstrated that there is a linear relationship between this pressure difference and CSF absorption through the AV, with the average rate of absorption being 2.397 mm^3/s/mmHg. They measured the mean CSF pressure in the SAS (i.e. the intracranial pressure (ICP)) as being 10.55 mmHg when supine, and calculated that the mean pressure in the SSS was 7.57 mmHg, which equates to a mean pressure drop of 2.78 mmHg across the AV.

CSF is produced in the CP, which are located in the walls of the third, fourth and lateral ventricles. The endothelium of the CP is leaky, with no tight junctions, allowing the transfer of fluid (water) between the blood vessels and the CSF. A number of researchers have attempted to quantify CSF production rates in humans. Cutler et al. found the mean CSF production rate in healthy children to be 6.00 mm^3/s, whereas Cutler et al. in a study involving children with sclerosing panencephalitis and Pontine glioma, measured the mean rate of formation of CSF to be 5.83 mm^3/s. In a similar study, Lorenzo et al. found the mean CSF production rate in healthy children to be 6.00 mm^3/s. It is possible to obtain a rough estimate of the CSF production rate by monitoring the flow of CSF through the AoS and calculating the difference between the net negative CSF flow (NNF) in the caudal direction and the net positive flow (NPF) per heartbeat. Using this methodology, Magnano et al. found the bulk aqueductal CSF flow in healthy adults to be 7.1 mm^3/beat (approximately 8.28 mm^3/s), whereas Beggs et al. and Gorucu et al. in similar studies found mean flow to be 4.0 mm^3/beat (approximately 4.65 mm^3/s) and 2.17 mm^3/s, respectively. Given that measured CSF production rates appear to be of similar magnitude to absorption rates through the AV, it suggests that lymphatic drainage of CSF plays only a relatively minor role in humans.

Link between venous outflow and cerebrospinal fluid dynamics

A number of studies have linked constricted venous outflow with changes in the dynamics of the cerebrospinal fluid system. Under normal circumstances, in healthy individuals the CSF NPF per heartbeat is slightly less than the CSF NNF, with the mathematical difference between NNF and NPF representing the bulk flow percolating through the ventricles. In a magnetic resonance imaging (MRI) study involving 67 multiple sclerosis (MS) patients and 35 healthy controls, Magnano et al. observed a significant 48% mean decrease in bulk CSF flow in the patients with MS and a 45% increase in mean NPF. Mean NNF was also increased in the MS patients, although this was not significant. Similar results were obtained by Gorucu et al., who also investigated MS patients. However, although these studies associated altered CSF dynamics with MS, they did not observe the venous characteristics of the subjects. By contrast, Zamboni et al. investigated MS patients who were diagnosed with CCSVI. As with the other studies, they observed a large reduction in bulk CSF flow and a tendency towards increased aque ductal pulsatility in MS patients compared with healthy controls. This suggested that in MS patients venous hypertension in the dural sinuses may be inhibiting absorption of CSF into the SSS, reducing bulk flow and altering aqueductal pulsatility. This opinion is reinforced by the findings of an interventional study in which venous angioplasty was performed on MS patients with CCSVI. Prior to the intervention, these patients exhibited increased CSF pulsatility in the AoS, which was lessened when the restricted venous outflow pathways were opened up.

If altered CSF dynamics in patients with MS is due to constricted venous outflow, then one might expect the same phenomenon to be observed in healthy individuals diagnosed with CCSVI. In order to test this hypothesis, Beggs et al. performed a study on healthy individuals not related to MS patients. The findings of this study were similar to those of Magnano et al. [page 82] [Veins and Lymphatics 2014; 3:1867]
and revealed a statistically significant 32% increase in CSF NPF in the CCSVI positive sub-
jects, compared with the CCSVI negative indi-
viduals, with a tendency towards reduced CSF bulk flow. As such, they suggested that CCSVI is
associated with altered CSF dynamics, irres-
pective of whether on not MS is present, rein-
forcing the opinion that increased aqueductal
CSF pulsatility is primarily a biomechanical
phenomenon associated with restricted
venous outflow from the cranium.

Increased cerebral blood flow pulsatility has
been linked with microstructural white matter
(WM) damage.38-40 Increased pulsatility in the
cerebral vascular bed is indicative of decreased
arterial compliance, and is associated with
arteriosclerosis41 and hypertension.42 Hyper-
tension, a known risk factor for small vessel
disease43 and leukaemia (LA),44 is thought to
be associated with changes in vascular
mechanics.39,42 It has been suggested45 that
increased vascular pulsatility might cause WM
damage indicative of early stage LA.45

Bateman45 found blood flow through the WM to
be highly pulsatile in individuals with LA and
concluded that this would increase endothelial
shear stress, which in turn would cause WM
damage.45

Jolly et al.46 found both increased blood flow
pulsatility and increased aqueductal CSF pulse
volume to be associated with microstructural
WM changes in elderly subjects. Daouk et al.47
found apparent diffusion changes, an early
indicator of microstructural changes, to be
strongly correlated with aqueductal stroke vol-
ume in Alzheimer’s disease (AD) patients.
Furthermore, Magnano et al.48 found increased
aqueductal pulse to be associated with more
severe T1 and T2 lesion volumes in MS
patients. This raises intriguing questions
about the relationship between vascular pul-
satility and aqueductal CSF pulsatility. Greitz46
postulated a link between increased pulsation
in the cerebral vascular bed and CSF pulsatility
in the AoS, arguing that pulsations in the cere-
bral capillaries were transmitted through the
parenchyma to the lateral ventricles. However,
Beggs et al.49 demonstrated that increased
aqueductal pulsatility is associated with con-
stricted cerebral venous outflow in healthy
adults, suggesting that other mechanisms may
be at work. Contrary to Greitz, Beggs argued
that impairment of cerebral venous outflow
would induce retrograde hypertension in the
dural sinuses, reducing intracranial compli-
ance and resulting in altered CSF dynamics.10

There is evidence that occlusion of the
venous drainage pathways can cause blood to
accumulate within the cranium, something
that theoretically could alter intracranial com-
pliance. In an experiment involving healthy
subjects, Kitano et al.47 showed that compres-
sion of the internal jugular veins (IJVs) result-
ed in a 5-20% increase intracranial blood vol-
ume. Frydrychowski et al.48 also performed bi-
lateral compression of the IJVs on healthy indi-
viduals and found that it caused a reduction in
the width of the SAS - a finding consistent with
the storage of blood in the cortical veins. Fur-
thermore, in a recent study involving AD
patients, Beggs et al.49 found jugular venous
reflux to be strongly associated with increased
brain parenchyma volume, something that
they postulated was possibly due to blood
retention within the brain. Because CSF is
incompressible, any reduction in the compli-
ance of the cortical bridging veins due to blood
retention should, in theory, impact on the
windkessel mechanism smoothing blood flow
to the cerebral vascular bed. Evidence to sup-
port this, comes from the study by
Frydrychowski et al.48 who observed that dur-
ing compression of the IJVs, pulsatility in the
pial arteries traversing the SAS increased by
107%. Collectively, this suggests that venous
drainage anomalies are associated with blood
retention in the cerebral veins, and that this in
turn is associated with altered biomechanical
characteristics within the intracranial space.

Intracranial compliance
and venous drainage

Intracranial compliance is generally charac-
terized by the arteriovenous delay (AVD)
between the arterial pulse entering the crani-
um and the venous pulse leaving it.43 One of
the major paradoxes of the intracranial fluid
system is associated with the AVD. How is this
possible, in a system where all the fluids
involved are incompressible and the cranium
is apparently a rigid container, to have a time
lag between the blood flow signals entering
and leaving the cranium? The brain parench-
yma tissue contains no gaseous material and is
generally thought to be incompressible,49 due
to its very high water content.50 One possible
explanation to this apparent paradox lies in
the cortical bridging veins, which are coupled
via the dural sinuses to the extracranial
venous drainage system. These collapsible
thin walled vessels are thought to play an influ-
ential role in regulating intracranial compli-
ance.50,51 The ability of the cortical veins to
store venous blood and delay outflow is
dependent on their compliance, with more
compliant veins storing greater volumes of
blood than incompressible ones.51 As a result,
compliant veins exhibit greater pulsatility in
blood flow. Indeed, Bateman50 eloquently
showed that in patients with normal pressure
hydrocephalus (NPH), cortical vein pulsatility
was 60% less than in the SSS, suggesting that
the disease is characterized by a reduction in
the compliance of the veins that bridge the
SAS. Bateman found that cortical vein compli-
ance was significantly increased following
shunt surgery, indicating that the compliance
attributed to these vessels is primarily func-
tional, not structural, and dependent on the
transmural pressure difference between the
venous blood and the sub-arachnoid CSF. This

Figure 2. Transient intracranial blood and cerebrospinal fluid (CSF) flow rates over the
cardiac cycle in a healthy individual (the figure is based on data published in Ambarki et
al., 200746).
implies that the compliance of cortical bridging veins is dependent both on the craniospinal compliance 28 and the ability of any venous blood stored in them to freely exit the cranium via the extracranial veins. Therefore, any constriction of the extracranial venous drainage pathways could, in theory, influence the compliant behaviour of the cortical veins.

A strong correlation has been demonstrated between intracranial pressure (ICP) and venous pressure in the dural sinuses,29 and it has been shown that venous sinuses stenting in patients with idiopathic intracranial hypertension (IIH) can rapidly normalize ICP.24 While this relationship is poorly understood, there is evidence that the cortical bridging veins play an influential role.26 Some have likened the action of the cortical bridging veins to a Starling resistor, which collapses, occluding the blood flow, when the transmural pressure reaches a certain threshold.27 The fluid flow through the bridging veins appears not to be regulated by the pressure difference between the two ends of the vessels, but rather by the pressure difference between the blood in the veins and the sub-arachnoid CSF. The cortical bridging veins are very sensitive to small changes in transmural pressure. As such, they are required to open and close to regulate blood flow from the cortex, the cortical venous pressure is only about 2 to 5 mmHg higher than the ICP.53 This means that small changes in ICP or venous pressure can greatly influence the behavior of blood flow from the cortex. Indeed, it has been estimated that a change of as little as 1.5 mmHg in the difference between ICP and the pressure in the bridging veins could be responsible for the difference between severe hyperemia (CBF=1000 mL/min) to serve ischemia (CBF=300 mL/min).55

**Postural changes**

Body position is known to have a profound effect on the fluids in the cranium. When upright the pressure in the IJVs becomes sub-atmospheric, with the result that they collapse. This causes the cerebral venous drainage pathways to be diverted through the vertebral and epidural veins.28 Also, when upright the venous pressure at the confluens sinuum in the dural sinuses becomes sub-atmospheric, in adults dropping from a mean of 8.5 mmHg when supine, to –8.6 mmHg when upright.52 The ICP, which is normally in the range 7-15 mmHg when supine,28 also falls when upright. Alperin et al.,29 in an MRI study involving healthy young adults, found that in the upright position there was a reduction in ICP, which fell from a mean of 10.6 mmHg when supine, to 4.5 mmHg when upright. However, others disagree with this finding and instead believe that ICP becomes sub-atmospheric when in the upright position. For example, based on the work of Chapman et al.,49 Czosnyka and Pickard51 concluded that ICP in adults in the vertical position is negative, with a mean of around –10 mmHg.

Given the magnitude of the pressure changes involved in moving from the supine to upright positions, there is reason to believe that this might alter the functional behaviour of the cortical bridging veins and also overall intracranial compliance. Alperin et al.,29 found that in adults in the upright position, venous outflow became considerably less pulsatile (a 43% reduction in the venous pulsatility index), with flow occurring predominately through the vertebral plexus, rather than the IJVs, which were the principle drainage pathway when supine. As such, their findings appear to corroborate those of Valdueza et al.,30 Importantly, Alperin et al also observed a 2.8-fold increase in intracranial compliance when in the upright position compared with supine position, which was associated with 2.4-fold decrease in oscillatory volume of the cerebral CSF flow. They also found changing posture to the upright position resulted in a 12% reduction in CBF. Alperin et al.’s findings are supported by those of Ragauskas et al.,62 who also observed increased intracranial compliance when in the upright position. While the precise physiological mechanisms involved in the posture-related regulatory process are not understood, these findings appear to be consistent with greatly reduced pressure in the dural sinuses when in the upright position.52

**Normal pressure hydrocephalus**

Because increased aqueductal CSF pulsatility appears to be associated with constricted venous outflow, it is perhaps worth considering NPH in more detail, a disease that is thought by some 31,48,54 to be associated with venous anomalies and which is characterized by increased aqueductal pulsatility.62,79 Normal pressure hydrocephalus occurs when there is an abnormal accumulation of CSF in the ventricles, causing them to become enlarged,9 but with little or no increase in ICP.23 NPH is associated with significantly reduced CSF absorption through the AV into the SSS.47,48 Given that ICP does not substantially increase in individuals with NPH, this suggests that CSF is being resorbed elsewhere.59 Bateman49 postulated that CSF resorption is likely to occur in the subependymal brain parenchyma and some have identified ventricular reflux in NPH patients,7,23 leading to oedema and neuronal degeneration.70 Tracer studies have shown that CSF can pass through the ependymal wall of the ventricles and enter the brain parenchyma.29 Tight junctions are absent from most of the ependyma lining the ventricles, making it relatively permeable to the retrograde transport of water, particularly when the CSF pressure is raised.55 Trypan blue injected into the CSF in the ventricles readily spreads into the brain,7 and tracers injected into the ventricles are taken up by perivascular macrophages,69 suggesting that CSF can permeate the perivascular spaces. In hydrocephalus patients, due to impaired drainage of CSF from the ventricles, CSF can pass into the periventricular WM as ventricular reflux causing interstitial edema.81,84

Bateman41 found the AVD to be 53% shorter in NPH patients compared with healthy controls. A similar reduction in AVD in NPH patients was observed in a subsequent study,52 and Mase et al.,53 independently confirmed this finding, showing a 64% reduction in intracranial compliance in NPH patients compared with healthy controls. This suggests that NHP is characterized by reduced intracranial compliance. Bateman59 showed that in NPH patients cortical vein pulsatility was 60% less than in the SSS, indicating a reduction in the compliance of the bridging veins. However, following shunt insertion this situation was reversed and there was a 186% increase in cortical vein compliance within 3-5 days of the intervention.

Using direct cannulation of the cortical veins, venous sinuses and the SAS in dogs with hydrocephalus, Portnoy et al.,66 were able to show that the cortical vein-to-CSF pressure difference in hydrocephalic animals was much greater than that in the normal animals. In the hydrocephalic dogs the cortical vein pressure was 21.54 mmHg when the CSF pressure was 16.37 mmHg and the SSS pressure was 8.43 mmHg, compared with respective values of 11.72, 10.46 and 5.15 mmHg in the normal animals. Interestingly, while the hydrocephalic dogs exhibited an increase of only 3.28 mmHg in SSS pressure, this was accompanied by a 9.82 mmHg increase in cortical vein pressure, indicating that hydrocephalus profoundly altered the functional relationship between these two vessels. This suggests that in hydrocephalic patients, the sub-arachnoid CSF may be interacting with cortical bridging veins at their junction with the SSS, compressing them so that the up-stream venous pressure is greatly increased. Bateman59 hypothesized that this increase in cortical venous pressure would be transmitted up-stream to the capillaries resulting in increased production of interstitial fluid. This, together with reduced CSF absorption through the AV, would result in an overproduction of fluid, which as Bateman demonstrated using nuclear cisternography, might result in retrograde CSF flow in the AoS and ventricular reflux.29
Hypothesis and perspectives

From the discussion above it can be seen that while understanding of the intracranial fluid system has improved over the years, much still remains unknown. There is no unifying model which adequately explains the dynamic behaviour of all the component fluids in the intracranial space, and the role of the intracranial fluid system in either preventing, or promoting, neurological disease is poorly understood. In particular, the regulatory role of the cerebral venous system is not well understood. While the contribution of venous anomalies to various neurological pathologies is becoming clearer, much remains to be discovered. For example, there is a need to understand the extent to which venous drainage influences intracranial compliance. If one considers the timing of the peaks in the respective pulses shown in Figure 2, it can be seen that arterial flow into the cranial peaks first, followed closely by the cerebral CSF peak in the caudal direction, which is then followed by the peak in venous flow out of the cranial. This indicates that volumetric changes are being rapidly transferred from one fluid to another, which is what one would expect from a system containing non-compressible materials. Having said this, the presence of an AVD indicates that compliance must exist somewhere in the system. While the mechanisms involved are poorly understood, the time delay between the arterial and venous peak flows is likely to be due to a combination of spinal column compliance and the ability of the cortical bridging veins to freely expel stored blood from the cranium via the dural sinuses and extracranial venous pathways. However, while this is a plausible explanation, there is paucity of good quality data on the subject and there is need to better characterize the functional behaviour of the cortical bridging veins both in healthy individuals and patients with neurological conditions. A better understanding of the interaction between the CSF, the bridging veins and the SS should enable new insights to be gained into the pathophysiology of conditions such as NPH and IIH.

From Figure 2 it can be seen that when the cerebral CSF flow reverses during diastole and starts to flow back into the cranial, two things happen: firstly, the volume of arterial blood entering the cranium starts to fall, reducing the volume of blood in the pial arteries; and secondly, the volume of venous blood exiting the cranial also starts to fall, indicating that venous blood is being stored in somewhere in the cranial, presumably in the compliant cortical veins. Given that positive aqueductal flow, towards the lateral ventricles, occurs late in diastole, this suggests that the venous pulse is likely to influence the dynamics of the CSF flow in the AoS. Although, the mechanics of this relationship are not understood, there is good reason to believe that the two pulses might be connected. Nakagawa et al.25 and others26-28 all observed the pulsatile compression of cortical bridging veins by the sub-arachnoid CSF, suggesting that the venous signal strongly reflects transist volumetric changes in the cortical bridging veins and thus the overall volume and compliance of the SAS.29,30 Given that the SAS is a relatively large volume, with low resistance to CSF flow,26 it is therefore reasonable to assume that the CSF returning to the cranium during diastole will first tend to fill the SAS, before forcing its way up the relatively high resistance AoS towards the third ventricle. This can be clearly seen in the lag between the cerebral and aqueductal CSF signals in Figure 2. The fact that the aqueductal CSF pulse lags the cerebral CSF pulse by 0.2 to 0.3 of a cardiac cycle suggests that its dynamic influence is by the compliance of the SAS. Evidence supporting this opinion comes Beggs et al.,3 who found that constricted venous outflow was strongly associated with increased aqueductal pulsatility healthy adults. The hydraulic resistance of the extracranial venous drainage system has been shown to be on average 63.5% greater in MS patients diagnosed with CCSVI compared with CCSVI negative healthy controls.3 If constriction of the venous drainage pathways inhibits free egress of blood transiently stored in the cortical bridging veins, then this is likely to reduce the compliance of the whole SAS. This would mean that there would be less room to accommodate the returning CSF in the SAS, with the result that more of the fluid would be forced up the AoS towards the third ventricle, which is exactly what Beggs et al. observed. Similar, results have also been observed in MS patients.34-36 Furthermore, Zivadinov et al.,37 who performed venous angioplasty on MS patients diagnosed with CCSVI, found that the procedure normalized the CSF pulsatility in the AoS, adding weight to the argument that the functional compliance of the cortical bridging veins profoundly influences the dynamics of the aqueductal CSF pulse.

The degree to which constriction of the extracranial venous pathways produces retrograde venous hypertension in the dural sinuses is also not well understood. Given that the pressure drop through the extracranial venous system is normally of the order 3-5 mmHg,38 an increase of 63% in the resistance of these vessels (as calculated by Beggs et al.3) would equate to a pressure increase in the region 1.89-3.15 mmHg, assuming that the blood flow rate remains constant. Although only a rough estimation, this calculation is consistent with the 2.21 mmHg mean increase in venous pressure measured in CCSVI positive MS patients by Zamboni et al.39 As such, it suggests that CCSVI is associated with mild venous hypertension (<5 mmHg) in the dural sinuses; something that would tend to reduce absorption of CSF by the AV36-37 and inhibit the bulk flow of CSF.33-34

Body position is known to be an important factor affecting ICP. Macrccordatos et al.30 showed that in anaesthetized neurosurgical patients lying on a flat surface, the ICP could be raised (mean increase) by 2.8-3.1 mmHg through simply flexion of the head to left or right, while rotating the head resulted in an mean increase of 4.1-4.8 mmHg. While the reasons for these changes are not fully understood, there is evidence that rotation of the head can compress both the jugular veins and the vertebral veins,31 inhibiting the cerebral venous drainage. Iwabuchi et al.32 investigated changes in venous pressure in the confluens sinuum associated with neck rotation and found that in the supine position, a mean increase of 30.3% was observed on a rightward rotation, whereas a mean elevation of 1.1% was observed for a leftward rotation. However rather surprisingly, in the sitting position, right and left rotations of the neck resulted in increases in pressure of 85.5% and 18.2% respectively. Collectively, these findings suggest that the cerebral venous drainage system plays an influential role in regulating ICP. Furthermore, they indicate that the functional behaviour of the cerebral venous drainage system is greatly influenced by postural changes. It is therefore surprising that relatively little is known about how changes in posture (e.g. supine to upright) affect the intracranial fluid system, particularly in healthy individuals, who for ethical reasons are rarely studied. The MRI work by Aperin et al.33 revealed marked changes in the behaviour of the intracranial fluid system when healthy subjects move from the supine to upright position. These changes were particularly obvious in the behaviour of the venous system, which became much less pulsatile when upright, something that appears to be associated with greater intracranial compliance in this position.

Clinical relevance

The issue of cerebral venous drainage has for many years been overlooked and it is only recently that the subject has received much attention. The mystery surrounding its apparent connection with the CSF system, only serves to highlight that relatively little is known about the physiological mechanisms that regulate the intracranial fluid system. In particular, the way in which the intracranial fluid system adapts when changing from supine to the upright position is poorly understood. However, there is evidence that
impaired cerebral venous outflow can markedly alter the dynamics of the intracranial fluid system. A better understanding of the physiology associated with cerebral venous outflow may therefore be of great benefit in understanding the progression of neurological conditions such as NPH and IIH.

Conclusions

There is growing evidence that the cerebral venous drainage plays an influential role in regulating the dynamics of the intracranial fluid system. In particular, the compliance of the cortical bridging veins appears to be critical to the behaviour of the system, with abnormalities at this location implicated in NPH. The compliance associated with these vessels appears to be functional in nature and dependent on the free egress of blood out of the cranium via the extracranial venous drainage pathways. Constricted venous outflow appears to be linked to increased CSF pulsatility in the AoS, suggesting that inhibited venous blood flow may be altering the compliance of the cortical bridging veins.

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