The Cerebral Venous System and Hypoxia

Mark H Wilson1,2,3,4
Christopher H E Imray 1,2,5

1 The Centre for Altitude, Space and Extreme Environment Medicine, University College London, Gower Street, London WC1E 6BT
2 The Birmingham Medical Research Expeditionary Society, Nuffield House, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TT
3 Imperial Neurotrauma Centre, Imperial College, St Mary’s Hospital, Praed Street, London W2 1NY
4 Institute of Pre-Hospital Care, London’s Air Ambulance, The Helipad, Royal London Hospital, Whitechapel E1 1BB
5 Dept of Surgery, Warwick Medical School, UHCW NHS Trust, Warwick CV2 2DX

Corresponding Author/ Address:
Mark Wilson
m.wilson@imperial.ac.uk
Imperial Neurotrauma Centre, Imperial College, St Mary’s Hospital, Praed Street, London W2 1NY

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Abstract:

Most hypobaric hypoxia studies have focused on oxygen delivery and therefore cerebral blood inflow. Few have studied venous outflow. However, the volume of blood entering and leaving the skull (approximately 700mls/min) is considerably greater than CSF production (0.35mls/min) or edema formation rates and slight imbalances of in- and out-flow have considerable effects on intracranial pressure (ICP). This dynamic phenomenon is not necessarily appreciated in the currently taught static “Monro-Kellie” doctrine which forms the basis of the “Tight-Fit” hypothesis thought to underlie high altitude headache, acute mountain sickness (AMS) and High Altitude Cerebral Edema (HACE).

Investigating both sides of the cerebral circulation was an integral part of the 2007 Xtreme Everest Expedition. The results of the relevant studies performed as part of and subsequent to this expedition are reviewed here. The evidence from recent studies suggests a relative venous outflow insufficiency is an early step in the pathogenesis of high altitude headache. Translation of knowledge gained from high altitude studies is important. Many patients in a critical care environment develop hypoxemia akin to that of high altitude exposure. An inability to drain the hypoxemic induced increase in cerebral blood flow could be an underappreciated regulatory mechanism of intracranial pressure.

Introduction:

In 1783 Alexander Monro (1733-1817) created a concept of intracranial pressure (ICP) by describing the skull as a rigid structure containing incompressible brain and stating that the volume of blood must remain constant unless: “water or other matter is effused or secreted from the blood-vessels” in which case “a quantity of blood, equal in bulk to the effused matter will be pressed out of the cranium” (38). His student, George Kellie in 1824 (26) stated and then John Abercrombie demonstrated that intracranial blood volume was the same no matter the cause of death (contrast extracranial organs such as the spleen which loose blood during exsanguination) (9). None of these three pioneers were aware of cerebrospinal fluid (CSF), which was not an established concept until its description by François Magendie in 1842(33). George Burrows suggested then Harvey Cushing formally conceptualized the “Monro-Kellie” doctrine as we know it today: with an intact skull, the sum of the volume of brain, blood and CSF is constant: an increase in one causing a decrease in one or both of the remaining two (11).

Singh demonstrated raised lumbar CSF pressure in Indian army recruits suffering with severe AMS on the Indian / Pakistan border(50). The relationship of ICP and headache was suggested by Ross in 1985 to account for the “Random Nature of cerebral mountain sickness” (45), however, in the same year, Brian Cummins(58) was already investigating the possibility of cerebral compliance or “Tight Fit” underpinning the incidence of mountain sickness(58). Although only published recently, he demonstrated that invasively measured ICP remained normal at rest in 3
subjects at all altitudes up to 5000m, however in the one subject who suffered with acute mountain sickness (AMS), slight exertion or head turning caused a dramatic rise in ICP. He also performed CT scans of the 10 expedition team members and demonstrated that those independently classified as lacking compliance (small ventricles) on CT developed greater headache and AMS scores at altitude. These findings (albeit with small numbers) supported a “Tight Fit” hypothesis which then became the generally accepted pathophysiology of high altitude headache with AMS progressing through exacerbation of the same phenomenon to potentially life threatening High Altitude Cerebral Edema (HACE).

This anatomically based model implied that generalized brain swelling (edema secondary to hypoxia) was the principal volume shift. A physiological predisposition component was added to this anatomical model by Roach and Hackett (43): those more prone to exercise induced hypoxaemia develop greater brain swelling (largely due to increased CBF and cerebral blood volume) and hence acute mountain sickness (AMS) more readily.

The Monro-Kellie doctrine (as summarized by Harvey Cushing and embraced in critical care) is a very static model of ICP, giving equal weighting to brain, blood and CSF ("an increase in one causes a decrease in one or both of the remaining two"). However, this misses the dynamic reality. At rest the brain receives approximately 14% of the cardiac output (=700mls/min) (36) which is half the average male intracranial volume (1473mls) (1). Clearly the venous outflow has to match the arterial inflow. This cerebral blood flow, dwarfs CSF production (0.35mls/min), hence when considered dynamically, cerebral blood inflow and outflow have a considerably greater and more rapid effect on ICP than either CSF or edema production.

We hypothesized that venous hypertension is an initial pathophysiological process that progresses through AMS and HACE and those with relative insufficient venous outflow capacity may have a theoretical physiological predisposition to high altitude headache (57, 59).

A note on Headache Burden assessment:
Headache severity is a very subjective measure. The assessment of headache in hypoxia and high altitude research improved dramatically with the development of the Lake Louise(42) and Environmental Symptoms Questionnaire AMS-C scoring systems(29).

However, assessing headache burden over time is more complex. Someone with a mild headache all day (grade 1) is recorded as having less of a headache than someone who has a grade 4 headache for 10 minutes. Quantifying headache burden may account for differences between studies that find and fail to find correlations between pathology (e.g. edema) and headache. The lack of animal model and the difficulty quantifying headache and its recovery make ranking of subjects inaccurate at best.
Evidence for Edema:

The diagnosis “High Altitude Cerebral Edema” is a clinical one based on altered neurology following ascent to altitude(16), however its name (by including the word “edema”) implies a definitive pathogenesis, which may well be an end result. Neurological changes (such as altered levels of consciousness) can have many non-edematous causes, acute hypoxia being an example. The underlying mechanisms that occur to cause headache in AMS and the processes that lead to cerebral edema are not clear. A number of imaging studies have investigated the roles of cytotoxic and vasogenic edema in hypoxia(24, 35). The underlying roles of factors such as HIF and VEG-F and their contribution to edema has also been a focus(4).

Figure 1 demonstrates examples implying edema is not the sole pathophysiological process following hypoxia. Cerebral microhaemorrhages have been found in climbers suffering from HACE at post-mortum (figure 1a)(10). T2 star MRI scans of climbers who have suffered “HACE” also demonstrate cerebral microhaemorrhages (figure 1b)(25). Retinal vessel distension and retinal haemorrhages (figure 1c) occur in a third of climbers to Everest Base Camp. Figure 1d demonstrates edema in the corpus callosum of a climber with HACE(17); however, this patient has a very atrophic brain (visualized by the large sulci between gyri) and hence edema would need to be considerably greater than that shown to cause a rise in intracranial pressure.

Figure 1: Examples suggesting additional processes other than simply edema occur with hypoxia. a) Microhaemorrhages seen at post mortem in a climber who died following HACE(10). b) microhaemorrhages in a climber who had previously suffered with HACE(25). c) Retinal venous distension and retinal haemorrhages that are common at altitude. d) MRI demonstrating cerebral edema in the corpus callosum in a patient with HACE(17). The marked cortical sulci imply very low compliance which would argue against any rise in ICP with this level of edema.

Currently, Optic Nerve Sheath Diameter (ONSD) as measured using ultrasound is one of the best non-invasive ICP assessment techniques. Despite this, there are studies demonstrating and failing to demonstrate a correlation between ONSD and AMS headache (28, 31). Similarly, optic disc edema has not been show to correlate with AMS (54). This may relate to headache assessment (see above) or there may be a process prior to edema formation / a rise in ICP that confers headache.

Some studies have demonstrated the development of vasogenic, cytotoxic and extracellular edema with hypoxia, but no correlation with AMS severity(34, 46). Others have demonstrated mild cytotoxic edema in subjects with AMS(24, 48). We previously reviewed this literature (60). However, while edema may well be a common final result of hypoxia, it would appear that at least in the early stages an additional pathophysiological process occurs. It is not as simple as the “Tight-Fit” model would suggest.

Evidence for Venous System involvement in Headache:
In 1940 Ray and Wolff specifically reported on the sensations perceived by stimulation of intracranial structures in 30 patient subjects (41). They demonstrated that stimulation of the venous sinuses (particularly tension at the margins) caused significant headache pain as indicated in figure 2. Structures such as the cavernous sinus are surrounded by sympathetic and trigeminal fibers which convey fullness/discomfort and pain. The role the sympathetic system has in cerebral venous tone is unknown but not considered to be great.

Figure 2: Tension in the areas indicated cause headache as shown (from Rey and Wolff)(41)

Arterial Delivery

Increased cerebral blood flow early on in hypoxia is well established (3, 23, 27, 49). Using both transcranial Doppler and confirming results with a separate MRI study, we demonstrated that (at rest) cerebral artery dilatation contributed significantly to the increase in CBF(56). Despite hyperventilatory hypocapnia, exercise maintains this increased CBF(2). Although over days of acclimatization, CBF returns to baseline, this initial increase in cerebral blood inflow has to be matched by an equally sustained increase in outflow or a cycle of venous hypertension and venous outflow obstruction may occur.

Brain Oxygenation

Assessing regional brain oxygenation (rSO₂) non-invasively can be achieved using Near Infrared Spectroscopy (NIRS). Unlike peripheral saturation monitors (which report arterial oxygen saturation), NIRS devices report the oxygenation of the tissue bed they interrogate. Hypoxic exercise causes a reduction in rSO₂(51, 52). Heine et al demonstrated in 2009 that a relative increase in the venous contribution to NIRS explained a larger amount of cerebral desaturation than a reduction in CBF (due to hypocapnic vasoconstriction)(18).

Venous Outflow

Retinal Vessel distension:
The retinal vasculature, because of its direct connection, is often considered to reflect changes in cerebral vasculature. A number of studies have demonstrated retinal artery dilatation/increased tortuosity and vein distension with hypobaric hypoxia. In 24 subjects ascending to 5300m, we demonstrated retinal venous distension correlated with the sum of an individual’s headache scores during the ascent (Spearman rho = 0.553, p = 0.005)(55). Although arterial distension was also noted, this did not correlate. It should be noted that although venous distension is almost universal, some studies have not demonstrated a correlation with
headache\(^{(53)}\). This may relate to difficulties in assessing headache burden (as described above), or may be correct, hence further studies are needed.

**MRI studies:**

Initial interest in venous changes with hypoxia resulted from a pilot study using susceptibility weighted MRI after 3 hours of hypoxia (\(\text{FiO}_2 = 12\%\); \(n=7\)). The dramatic increase in venous caliber (figure 3) however could have itself been artifact and influenced by the altered susceptibility (MRI signal characteristics) of de-oxygenated blood\(^{(57)}\). The study was therefore repeated with one hour of hypoxia (\(\text{FiO}_2 = 11\%\); \(n=11\)) using Gadolinium (which does not alter susceptibility in hypoxia) enhanced T1 imaging and again, venous prominence increased with hypoxia\(^{(55)}\).

Figure 3: Increased prominence of cerebral venous vessels at the end of 3 hours continuous hypoxia (\(\text{FiO}_2 = 11\%\))\(^{(57)}\).

In the same publication, multiple cerebral volumes were studied in 12 MRI scans of climbers to investigate other potential anatomical predisposing factors. We hypothesized that relative restriction in venous outflow (be that anatomical through venous sinus narrowing/compression or physiological through raised cervical/central venous pressures) would result in greater intracranial hypertension and headache. This was demonstrated to be the case with an inverse correlation between the smallest transverse sinus volume and ascent headache score (the sum of headache scores during ascent to 5300m; \(n=12\); \(r=-0.56, p=0.03\))\(^{(55)}\). Lawley et al failed to demonstrate a relationship between venous outflow caliber and AMS, however they did confirm that hypoxia induced cerebral swelling over a 10 hour period compressed transverse sinus volume \((30)\). Using a novel MRI based technique to assess ICP they performed a further study \((n=13, \text{FiO}_2 = 12\%)\) that demonstrated that although there was no change in intracranial pressure or cerebral perfusion pressure despite an increase in brain volume, there was a statistically significant relationship between change in intracranial pressure and acute mountain sickness severity \((R^2 = 0.71, B = 2.3, p < 0.01\) after 10 hours\(^{(32, 60)}\).

Recently further studies performed by our group \((n=12\) with 22 hours of hypoxia) have demonstrated edema occurring in the corpus callosum, increased parenchymal whole brain volume, a reduction in CSF volumes and an element of venocclusion at the level of small and deep cerebral veins \((47)\). Venocclusion compounds intracranial hypertension by restricting venous outflow. Poiseuille’s law requires an increased driving pressure to maintain flow across a narrower vessel. Such increased pressures increase the hydrostatic (Starling) pressures across vessel walls and hence contribute to edema formation.

A similar phenomenon of venocclusion has been described in idiopathic intracranial hypertension where a cycle of venous hypertension causes parenchymal swelling which results in further venous compression \((39)\) (see below).

**Proposed Model:**
A simple analogy of intracranial venous hypertension underlying the initial pathogenesis of hypoxia induced headache can be a running bath analogy. If you turn on a tap with the plug unplugged, the water will reach a steady-state level. If you turn on the tap more, the water level rises to a new steady state (rather than overflowing), the increase in depth in turn increasing venous outflow pressure.

Figure 4 demonstrates how in the context of hypoxia driven increased CBF, venous outflow is potentially restricted by the caliber of anatomical structures such as transverse sinus / jugular foramen and also back pressure from jugular venous pressures (which also contains transmitted cervical, thoracic and abdominal pressures). Once parenchymal swelling occurs, this will result in compression of venous structures themselves, further restricting venous drainage, compounding any rise in intracranial pressure.

Increased pulmonary artery pressures (as may occur in high altitude pulmonary edema) could theoretically increase right atrial and central venous pressures, further compounding venous drainage insufficiency. This could account for HACE and HAPE often occurring concurrently.

Figure 4: Diagram of intra-and extra-cranial influences on venous drainage. Anatomical (e.g. jugular foramen) and physiological (central venous pressures, which transmit cervical, thoracic and abdominal pressures) can act to limit venous outflow. This may compromise initial ability to drain hypoxia induced increases in CBF. Parenchymal swelling can compress venuoles and venous sinuses which can act like Starling resisters further restricting venous outflow and increasing transmural hydrostatic pressures and hence edema formation. Compression of the distal part of the intracranial venous tree (transverse sinuses) would create the greatest venous back pressures.

Figure 5 demonstrates a model of high altitude headache developed from our current understanding of the pathophysiological changes that occur with hypoxia.

Acute hypoxia causes an increased CBF. Some people, for either anatomical (e.g. venous sinus capacitance) or physiological (e.g. raised central venous pressure) reasons, are unable to drain this increased volume adequately resulting in intracranial venous hypertension. This causes proximal venous distension. The increase in hydrostatic pressure across the microvascular bed results in vasogenic edema formation. This parenchymal swelling then compresses the venous outflow structures, and acting like a Starling resister, further restricts venous outflow.

Figure 5: Proposed model of pathophysiological processes indicating how inadequate venous drainage can form a cycle of intracranial hypertension and edema formation.

Examples of Clinical Relevance:
Neuro-Critical Care:
Intracranial Pressure is routinely monitored in many acute neurological situations. Most Traumatic Brain Injury protocols aim to keep ICP below 25mmHg. But ICP is affected, not only by intracranial pathology, but also by factors outside the cranium. Cervical collars (12, 22, 37), chest (40, 61) and abdominal (8, 19) pathology all contribute to raised ICP. By understanding the relative contributions, and the contribution hypoxia plays, we can propose better targeted treatments to lower ICP rather than the generic (e.g. mannitol) type treatments that are often currently used.

Idiopathic Intracranial Hypertension:
Intracranial Hypertension (IIH characterised by headache, loss of peripheral vision and nausea (5, 6)) is associated with focal transverse sinus stenosis (14) while bilateral stenosis is found in up to 90% of sufferers (7, 20, 39). Endoluminal stenting of stenotic regions can dramatically improve symptoms (13). Diffuse brain swelling can also cause generalised venous compression (44) creating an internal Starling type resistor as described above. A cycle of venous hypertension, cerebral swelling, further venous compression and therefore hypertension occurs. This cycle can be broken with CSF drainage although it is likely to recur again, not as CSF accumulates but as venous hypertension recurs. Pickard (39) studied CSF and sagittal sinus pressures in 9 patients with IIH. During CSF drainage CSF pressure decreased below central venous pressure (CVP) while the sagittal sinus pressure fell only to CVP and not lower. This suggests that functional obstruction of venous outflow through the dural sinuses is present in many IIH cases and reflects the interplay between CVP and ICP that probably also occurs in hypoxia.

Visual Impairment-Intracranial Pressure in microgravity:
In recent years a significant number of astronauts have complained of loss of peripheral vision (so-called “Visual Impairment-Intracranial Pressure”) (15), a symptom also occurring in IIH. The lack of gravity results in upper thoracic venous hypertension and hence a similar pathological process may underlie this condition (57). This phenomenon has become a considerable problem, jeopardizing human exploration to Mars until resolved.

Conclusion:
In 1896 Leonard Hill demonstrated that venous and CSF pressures were aligned and suggested that, given the lack of valves in the cranio-vertebral venous system, vena caval pressure reflected CSF pressure, and retinal venous distension could reflect intracranial venous pressure (21). With great insight he suggested that ICP would be more affected by changes in vascular pressure “from the venous side to a far greater degree than from the arterial side, because it is on the arterial side that the resistance lies”.

The traditional Monro-Kellie doctrine is understood as a static phenomenon and does not convey the considerable importance that the balance of cerebral blood in and outflow has on ICP. New tools such as magnetic resonance imaging are
now allowing us to investigate the venous side of the circulation.

Current evidence suggests that a relative venous insufficiency (compared to hypoxia driven increased CBF) is an important initial step in the pathogenesis of Acute Mountain Sickness and High Altitude Cerebral Edema.

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Figure Legends:

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Ring haemorrhages seen at autopsy in HACE sufferers (Clarke 2006)
Normoxia ($\text{FiO}_2=21\%$)

3 hours hypoxia ($\text{FiO}_2=12\%$)
Parenchmal compression of venuoles
Parenchmal compression of sinuses
Specific Transverse sinus compression
Jugular Venous Pressure (= CVP + hydrostatic pressures)
Relative Restriction in Venous Outflow

Increased Cerebral Blood Flow

Compression of Venuoles / Veins / Venous sinuses

Increased Proximal Vessel Volume & Hydrostatic Pressure

Swollen brain Parenchyma

Vasogenic Oedema

Prolonged HYPOXIA

Factors increasing vessel permeability (e.g. VEG-F, HIF 1α)

Early Phase (AMS)

Late Phase (HACE)

ICP

Pain, Microhaemorrhages
Altered neurology

HYPOXIA

Factors increasing vessel permeability (e.g. VEG-F, HIF 1α)

Swollen brain Parenchyma

Vasogenic Oedema

Increased Proximal Vessel Volume & Hydrostatic Pressure

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