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) (2). None of these three pioneers was 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, which forms the basis of the “Tight-Fit” hypothesis thought to underlie high altitude headache, acute mountain sickness, and high altitude cerebral edema. 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 supports a relative venous outflow insufficiency as 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.

acute mountain sickness; headache; hypoxia; intracranial pressure; venous

Singh demonstrated raised lumbar CSF pressure in Indian army recruits suffering with severe acute mountain sickness (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 (59) was already investigating the possibility of cerebral compliance or “Tight Fit” underpinning the incidence of mountain sickness (59). Although only published recently, he demonstrated that invasively measured ICP remained normal at rest in three subjects at all altitudes up to 5,000 m; 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 computed tomography (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 that 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 hypoxemia develop greater brain swelling [largely due to increased cerebral blood flow (CBF) and cerebral blood volume] and hence 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 ~14% of the cardiac output (~700 ml/min) (36), which is half the average male intracranial volume (1,473 ml) (1). Clearly the venous outflow has to match the arterial inflow. This cerebral blood flow dwarfs CSF production (0.35 ml/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 (58, 60).

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 min. 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 after 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 nonedematous 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 hypoxia-inducible factor and vascular endothelial growth factor, and their contribution to edema has also been a focus (5).

Figure 1 demonstrates examples implying edema is not the sole pathophysiological process after hypoxia. Cerebral microhemorrhages have been found in climbers suffering from HACE at post mortem (Fig. 1A) (10). T2 star MRI scans of climbers who have suffered “HACE” also demonstrate cerebral microhemorrhages (Fig. 1B) (25). Retinal hemorrhages (Fig. 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.

Fig. 1. Examples suggesting additional processes other than simply edema occur with hypoxia. A: microhemorrhages seen at post mortem in a climber who died after high altitude cerebral edema (HACE) (10). B: microhemorrhages in a climber who had previously suffered with HACE (25). C: retinal venous distension and retinal hemorrhages that are common at altitude. D: MRI demonstrating cerebral edema in the corpus callosum of a climber with HACE (17). The marked cortical sulci imply very low compliance that 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 noninvasive 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 shown to correlate with AMS (55). This may relate to headache assessment (see above) or there may be a process before edema formation/a rise in ICP that confers headache.

Some studies have demonstrated the development of vaso-genic, 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 (61). However, although 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 (41) specifically reported on the sensations perceived by stimulation of intracranial structures in 30 patient subjects. They demonstrated that stimulation of the venous sinuses (particularly tension at the margins) caused significant headache pain as indicated in Fig. 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.

**ARTERIAL DELIVERY**

Increased cerebral blood flow early on in hypoxia is well established (4, 23, 27, 49). By 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 (57). Despite hyperventilatory hypocapnia, exercise maintains this increased CBF (3). 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) noninvasively 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 (52, 53). Heine et al. (18) 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 5,300 m, 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) (56). 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 (54). 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 h of hypoxia (FIO₂ = 12%; n = 7). The dramatic increase in venous caliber (Fig. 3), however, could have itself been an artifact and influenced by the altered susceptibility (MRI signal characteristics) of deoxygenated blood (58). The study was therefore repeated with 1 h of hypoxia (FIO₂ = 11%; n = 11) using gadolinium (which does not alter susceptibility in hypoxia) enhanced T1 imaging and again, venous prominence increased with hypoxia (56).

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 5,300 m; \( n = 12; r = -0.56, P = 0.03 \)) (56). Lawley et al. (30) failed to demonstrate a relationship between venous outflow caliber and AMS; however, they did confirm that hypoxia-induced cerebral swelling over a 10-h period compressed transverse sinus volume. 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 h (32, 61).

Recently further studies performed by our group (\( n = 12 \) with 22 h of hypoxia) have demonstrated edema occurring in the corpus callosum, increased parenchymal whole brain volume, a reduction in CSF volumes, and an element of venocompression at the level of small and deep cerebral veins (47). Venocompression 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 venocompression has been described in idiopathic intracranial hypertension where a cycle of venous hypertension causes parenchymal swelling that 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 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 resistor, further restricts venous outflow.

EXAMPLES OF CLINICAL RELEVANCE

Neurocritical Care

Intracranial pressure is routinely monitored in many acute neurological situations. Most traumatic brain injury protocols aim to keep ICP below 25 mmHg. 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 (9, 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 characterized by headache, loss of peripheral vision, and nausea (6, 7)] is associated with focal transverse sinus stenosis (14), whereas bilateral stenosis is found in up to 90% of sufferers (8, 20, 39). Endoluminal stenting of stenotic regions can dramatically improve symptoms (13). Diffuse brain swelling can also cause generalized 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 et al. (39) studied CSF and sagittal sinus pressures in nine patients with IIH. During CSF drainage, CSF pressure decreased below central venous pressure (CVP), whereas 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 (58). 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 craniovertebral 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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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.H.W. and C.H.I. conception and design of research; M.H.W. and C.H.I. performed experiments; M.H.W. analyzed data; M.H.W. interpreted results of experiments; M.H.W. prepared figures; M.H.W. drafted manuscript; M.H.W. and C.H.I. edited and revised manuscript; M.H.W. and C.H.I. approved final version of manuscript.

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