Mini-Review Article

Title: Cerebral spinal fluid dynamics: Effect of hypoxia and implications for high-altitude illness

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Running head: CSF dynamics and hypoxia

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ABSTRACT

The pathophysiology of acute mountain sickness and high-altitude cerebral edema, the cerebral forms of high-altitude illness, remain uncertain and controversial. Persistently elevated or pathological fluctuations in intracranial pressure are thought to cause symptoms similar to those reported by individuals suffering cerebral forms of high-altitude illness. This review first focuses on the basic physiology of the craniospinal system including a detailed discussion of the long-term and dynamic regulation of intracranial pressure. Thereafter, we critically examine the available literature, based primarily on invasive pressure monitoring that suggests intracranial pressure is acutely elevated at altitude due to brain swelling and/or elevated sagittal sinus pressure, but normalizes over time. We hypothesize that fluctuations in intracranial pressure occur around a slightly elevated or normal mean intracranial pressure in conjunction with oscillations in PaO2 and arterial blood pressure. Then these modest fluctuations in intracranial pressure, in concert with direct vascular stretch due to dilatation and/or increased blood pressure transmission, activate the trigeminal vascular system and cause symptoms of acute mountain sickness. Elevated brain water (vasogenic edema) maybe due to breakdown of the blood brain barrier. However, new information suggests cerebral spinal fluid flux into the brain maybe an important factor. Regardless of the source (or mechanisms responsible) for the excess brain water, brain swelling occurs and a “tight fit” brain would be a major risk factor to produce symptoms; activities that produce large changes in brain volume and cause fluctuations in blood pressure are likely contributing factors.

Key words: Acute mountain sickness, high-altitude cerebral edema, headache and intracranial pressure.
Introduction. Acute Mountain Sickness (AMS) is characterized by headache, fatigue, dizziness, and nausea and vomiting, whereas hallmarks of High-Altitude Cerebral Edema (HACE) are ataxic gait, severe lassitude, and altered consciousness, including confusion and impaired mentation. Acute mountain sickness typically occurs when the onset of hypoxemia is rapid and severe i.e. ~4500 m or oxygen saturation ~80%. Under these circumstances, mild symptoms such as headache occur in most individuals (15), with 40-65% of headache suffers being diagnosed with AMS, but astonishingly some remain completely symptom free. In contrast, HACE is rare (0.5 - 1.8%) even with rapid ascent to altitudes greater than 4000 m (11, 31). In spite of decades of investigation, the pathophysiology of AMS and HACE remain uncertain and controversial.

An enticing hypothesis of the cause of AMS and HACE is that persons with smaller intracranial and intraspinal cerebral spinal fluid (CSF) capacity, a "tight fit" brain, would be disposed to develop high-altitude illness because they would not tolerate brain swelling as well as those with more "room" in the craniospinal axis (74). In our opinion, this hypothesis has not received adequate investigation. To reinvigorate scientific enthusiasm for this hypothesis and suggest future research directions, this review will (A) summarize the basic physiology of the craniospinal system focusing on the regulatory mechanisms that control intracranial volume and pressure homeostasis over short and long periods of time; (B) evaluate the effect of hypoxia on brain swelling and CSF dynamics including intracranial pressure (ICP) and (C) link these observations to AMS and HACE.

PHYSIOLOGY OF THE CRANIOSPINAL SYSTEM

Cerebral spinal fluid secretion and reabsorption. Cerebral spinal fluid is secreted predominantly by the choroid plexus at a rate of ~0.4 ml·min⁻¹ (24), which accounts for a total daily production of ~600 ml in the adult. Given that the total volume of CSF, located cranially
(~80%) and spinally (~20%), equals only ~300 ml (39), a constant and equivalent rate of CSF reabsorption is required to maintain volume equilibrium and thus ICP.

Regulation of CSF secretion is highly complex and modulated indirectly by factors such as choroid plexus blood flow (Δsubstrate delivery), ventilation (ΔPCO₂), atrial natriuretic peptide release and carbonic anhydrase activity (19). Cerebral spinal fluid outflow (CSFoutflow or CSF_reabsorption) is predominantly determined by the difference between ICP and sagittal sinus pressure (P_sag), relative to the resistance of CSF movement from its site of production to its site of absorption (R_out, Davson equation, Eq. 1). Put simply, ICP must exceed P_sag for CSF outflow to occur. R_out, is the sum of total resistance of CSF outflow of the system, most importantly at the site of the arachnoid granulations. Nonetheless, the intracranial-venous pressure gradient dominates CSF volume homeostasis over prolonged periods of time, as R_out has been shown to remain stable within the same individual, despite modest elevations in ICP from baseline (3).

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\text{Eq 1. } \text{CSF}_{\text{outflow (ml/min)}} = \frac{(\text{ICP (mmHg)} - \text{P}_{\text{sag}} (\text{mmHg}))}{\text{R}_{\text{out}} (\text{mmHg}\cdot\text{ml}\cdot\text{min}^{-1})}
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The primary route of CSF reabsorption under steady state supine conditions is through the arachnoid granulations into the sagittal sinus (see fig 1H) (20). Simple provocations that obstruct venous outflow such as jugular venous compression and head turning provide empirical support for this proposition; elevated cerebral venous blood volume and P_sag causes a reduction in the transmural pressure gradient (ICP - P_sag) and increased ICP (41, 70). Other routes of CSF reabsorption exist, including: arachnoid villi coursing along spinal nerve roots (draining into the spinal venous plexus (22, 50)) and extracranial lymphatic vessels (47, 89) into the perivascular space (29). These alternate CSF outflow pathways may become important under pathological conditions and even during normal daily activities. Indeed, data suggest that as much as ~60% of spinal CSF_{outflow} is through spinal roots when standing upright, as compared to only ~20% when supine ((22), see fig 1). Furthermore, animal studies suggest that
CSF-interstitial flux (gliolymphatic drainage, see fig 1I) may be predominantly dormant during waking hours, but substantial while asleep (96).

**Intracranial pressure.** Contents of the craniospinal compartment include brain, spinal cord, arterial and venous blood, and CSF. Under steady state resting conditions, brain, spinal cord, and blood volumes are essentially constant. Therefore, solving Eq 1. for ICP highlights that the mean static ICP operating point is governed by the rate of CSF production, $R_{out}$ and $P_{sag}$. As CSF production equals CSF$_{outflow}$ in the steady state condition, ICP typically reflects changes in $P_{sag}$ over prolonged periods.

A typical supine resting ICP in healthy young individuals is ~11 mmHg. However there is considerable inter-individual variability in the “normal” ICP, ranging from 7 to 15 mmHg (24, 60). Moreover, hydrostatic pressure gradients affect ICP, whereby ICP with reference to the head is progressively lowered with increasing upright tilt angles (72) and typically -5 to +10 mmHg (4, 5, 25) while in the upright posture. To obtain accurate measurements, clinical and/or experimental control is essential, as simple maneuvers that effect $P_{sag}$ in the supine posture, such as simply elevating the head or legs on a pillow can either reduce (~5 mmHg; (26)) or increase (~3 mmHg) ICP (personal observations).

Around the static operating point, ICP varies with changes in peripheral and central vasomotor tone, respiration and intra-thoracic pressure and with the cardiac cycle (36, 71, 86), (see fig 1G). Each contraction of the left cardiac ventricle produces a small (1.5 to 2.0 ml (85),) increase in arterial cerebral blood volume (see fig 1F), expansion of the brain parenchyma, and a rise in ICP and translocation of CSF though the foramen magnum into the spinal thecal sac (87). During diastole the reverse is observed, including declining ICP and a reversal of CSF flow into the cranium (see fig 1F).
Intracranial compartment volumes. In the context of the current review, two intracranial compartments are of interest for alterations in CSF dynamics: cerebral blood volume, and water content. Two likely causes of elevated cerebral arterial and venous blood volume are active dilation or passive distension. Venous volume may also increase due to restricted venous outflow. Importantly, this is not due to a mismatch between blood inflow and outflow; if inflow exceeds outflow by even 0.1\% (0.7 ml min^{-1}, assuming a total inflow of 700 ml min^{-1}), ICP would increase uncontrollably and death would follow. Instead, focal narrowing of the intracranial transverse sinus causes elevated venous pressure proximal to the stenosis; P_{sag} and thus ICP are proposed to rise in proportion to the degree of stenosis and increased resistance, if the sinus were the only outflow pathway. This mechanism has been advocated in patients with idiopathic intracranial hypertension, but a number of questions remain including: a) identifying causation between elevated ICP and venous stenosis and b) explaining the lack of collateral venous drainage that is effective in the upright posture. Finally, increased brain water in the form of vasogenic brain edema causes increased intracranial volume, but fluid shifts between compartments do not.

Craniospinal axis compensation and compliance. The brain parenchyma, spinal cord, arterial and venous blood and CSF are encased within a rigid container (skull and vertebral column). Intracranially the meninges (dura mater, arachnoid space and pia mater), separate the brain from the inner surface of the skull. The meninges also separate the spinal cord from the vertebral column, although the lumbar dura and thecal sac are less restrained as the dura mater is separated from the vertebral lining by fatty tissue and a venous plexus (63). Cerebral spinal fluid forms a freely communicating fluid column between the cranium and spinal thecal sac. Thus, craniospinal axis compensation (see below) and compliance includes the interaction between the physical (anatomical) and physiological (hemo- & hydrodynamic) properties of the cranial vault and vertebral column (58, 62, 82). The ability of the craniospinal system to
accommodate changes in volume can be divided into spatial compensation and craniospinal compliance (\(\Delta V/\Delta P\)) (7).

Spatial compensation represents the degree to which volume increments can be accommodated by compensatory reductions in the volume of other intracranial compartments. First, internal spatial compensation represents the translocation of CSF from the intracranial to the spinal thecal sac. Internal spatial compensation is determined by the magnitude of the internal pressure gradient between the cranium and spinal thecal sac and the compliance of the spinal dura or more likely the spinal epidural venous plexus. As such, the spinal dura sac acts as a reservoir for changing cerebral volume with a finite ability to maintain normal ICP ((63), see fig 2B). The second component is spatial compensation via quasi-static reductions in craniospinal CSF volume through increased CSF reabsorption (CSF_{outflow}). As long as \(P_{sag}\) remains normal, this compensation will occur over time whereby ICP will gradually return to the steady state condition as predicted by CSF formation rate, \(R_{out}\) (see fig 2A). The spinal subarachnoid CSF volume, and thus the potential spinal compensatory capacity, varies considerably between individuals (figure 2C). Once spatial compensation is exhausted, further increases in volume result in sustained intracranial hypertension. The capacity of craniospinal spatial compensation is dominated by CSF volume, whereas the time constant (delay) is determined by the increase in brain volume, the shape of the compliance curve, the ICP - \(P_{sag}\) gradient and \(R_{out}\). The variability of spatial compensation can be appreciated by examination of figure 2. Figure 2D shows the mean response of ICP to slow inflation of an extradural balloon in a group of non-human primates, whereby 5 ml of volume increases ICP to 45 mmHg. In contrast, in a single non-human primate, 5 ml of volume only increased ICP to 10 mmHg (figure 2E) (57).

Craniospinal compliance typically reflects the elastic properties of the craniospinal system and reflects the acute volume-pressure (\(\Delta V/\Delta P\)) relationship at any specific point in time. It is worth noting that the pressure volume index (volume required to increase ICP by a factor of
10) exemplifies the finite craniospinal compliance; 25 ml would increase ICP from 10 to 100 mmHg if not for spatial compensatory mechanisms. As noted above, small volume increments occur during each heartbeat and give rise to the CSF pulse pressure waveform. This phenomenon is synonymous with continuous, small volume-pressure tests, whereby the ICP pulse amplitude increases linearly with increasing ICP (reduced compliance, see fig 2A) above an individual’s specific ICP threshold point (71), therein reflecting the compliance of the craniospinal system. Craniospinal axis compliance and thus “buffering capacity” dictates the slope of the volume-pressure curve and thus the rate of rise in ICP. This capacity depends on the overall biomechanical properties of the cranium and spinal canal (61, 62) including: the rigidity of the brain, spinal cord, meninges, spinal dura and the tone and collapsibility of the vascular bed, specifically the low capacitance venous segments.

**Impact of reduced spatial compensation and craniospinal compliance.** As volume is added to the intracranial space, four stages can be identified. Stage 1: Initial spatial compensation, whereby ICP rises very modestly, or not at all, despite added volume. As spatial compensation becomes exhausted and the spinal intra-dural volume reaches its capacity, free movement of CSF is hindered and its pulse dampening (windkessel) effect reduced, and as a result intracranial pulse transmission is enhanced. Stage 2: Spatial compensation is exhausted and patients suffer headache and drowsiness. Spontaneous pathological oscillations in arterial blood pressure and ICP Lundberg pressure waves (59) are observed, especially with the addition of hypercapnia or hypoxia. At this stage, further increments in volume lead to exponential elevations in ICP. Stage 3: Autoregulatory capacity is absent and cerebral vasomotor paralysis occurs with a flattening of the volume-pressure curve and stabilization of high ICP. At this stage, patients experience fleeting episodes of altered consciousness and fluctuations in arterial blood pressure cause reciprocal changes in ICP. Stage 4: The patient is unconscious, intracranial hypertension is irreversible, arterial and cerebral perfusion pressure fall and death follows (54).
What constitutes altered CSF dynamics? A central question is exactly when do altered CSF dynamics cause pathological symptoms? Clinical guidelines regard steady state supine ICP to be elevated when it rises above ~20 to 25 mmHg (27). Given the wide inter-individual variation in resting steady state supine ICP (~7 to 15 mmHg), it seems unlikely that a single absolute mean pressure adequately describes pathologically elevated ICP in all individuals. In contrast to mean pressure, increases in the ICP pulse amplitude may be important. In the supine position, intracranial pulsatility increases linearly beyond an individual’s ICP operating point (71), usually close to the patient’s normal ICP at rest. Therefore, an increase in mean ICP from 10 to 20 mmHg in one individual would result in twice the amplitude gain, and theoretically increased pathology, compared to another individual whose ICP rose from 15 to 20 mmHg. Interestingly, patients diagnosed with idiopathic intracranial hypertension, visual disturbances and headache often present with elevated intracranial pulsatility despite over 50% having normal mean ICP during waking hours (23).

Intracranial instability and the occurrence of pressure waves are also of pathological concern. Perhaps the best illustration of such a phenomena occurs in patients with idiopathic intracranial hypertension without papilledema (83). Continuous ICP monitoring demonstrates that mean ICP remains “normal” for prolonged periods of time (particularly during wakefulness), but instability in the form of large spontaneous intracranial pressure waves (Lundberg A- and B-waves, (59)) are observed during sleep. Headache is a common complaint in these patients. These observations in patients with intracranial hypertension highlight that dynamic changes in ICP, revealed by long-term recordings, are important and a ‘snap shot’ of mean pressure may not be sufficient to recognize altered CSF dynamics.

HYPOXEMIA AND CEREBRAL SPINAL FLUID DYNAMICS
Since non-invasive methods for measuring ICP are not very accurate, the remainder of this review will focus on animal and human experiments that used direct or indirect invasive recordings of ICP, supported by data from neuroimaging. For a comprehensive review of changes in ICP at high altitude, using predominantly non-invasive methods, see the recent review by Wilson and colleagues (94).

The cerebral arterial vascular response to hypoxia encompasses a threshold (PaO$_2$ ~60 mmHg) dependent increase in cerebral blood flow and pial artery and arteriolar dilatation (i.e. a reduction in cerebrovascular resistance and increased arterial blood volume, (6, 17, 48, 77, 90). Venous capacitance vessels will also dilate (55, 88, 91), thus also increasing the cerebral venous blood volume pool.

**Acute effect of hypoxia – animal models.** Using a severe hypoxia model (8% O$_2$) in anesthetized dogs, Small et al., (80) noted a uniform increase in central venous pressure and ICP, averaging a peak pressure change of 7 and 4 mmHg respectively, within ~4 – 5 minutes. Hamer et al. (36) observed that reducing PaO$_2$ to 60 and then to 35 mmHg in anesthetized artificially ventilated dogs caused a dose-dependent increase in ICP and in the ICP pulse amplitude (See fig 3A). Subsequent experiments in the same experimental model reproduced the mild elevation in ICP alongside a small increase in P$_{sag}$ (35). In a series of experiments conducted in dogs, cats and rabbits, transient (2 - 3 min) and brief (2 - 3 breaths) periods of hypoxia caused elevated ICP in almost all instances (46).

To examine the effect of cerebrovascular dilatation (i.e. reduced vascular tone) on the CSF pulse waveform morphology, Portnoy and Chopp (69) exposed 19 anesthetized mongrel cats to 10% oxygen (PaO$_2$, 29.4±8.5 mmHg) or 10% carbon dioxide (PaCO$_2$, 71.8±4.1 mmHg) for ten minutes. Acute hypoxia and hypercapnia caused mild elevations in mean ICP (hypoxia, ∆6.3 mmHg; hypercapnia, ∆9.3 mmHg) and ICP pulse amplitude (hypoxia, ∆1.5 mmHg; hypercapnia, ∆3.0 mmHg, See fig 3B). Hypoxia and hypercapnia cause arteriolar dilatation,
which causes a greater transmission of the arterial pulse pressure into the cerebral capillaries and veins, which is ultimately reflected into the ICP pulse amplitude (See fig 3B). The profile of acute increases in ICP during hypoxia seem to follow a similar threshold-dependent (PaO₂ ~50 mmHg) increase as cerebral blood flow (See fig 3C) (67).

Prolonged effect of hypoxia – animal models. Krasney and colleagues completed an elegant series of experiments in unanesthetized hypoxemic sheep. The main findings of interest for this review are 1) a consistent increase in ICP over the first 6 hours of hypoxia, which can be explained by vasodilatation and the observed rise in P_{sag} (44, 97, 98). 2) By 24 hours, ICP is only slightly elevated, but substantial variability exists and the sheep showed signs of exhausted spatial compensation (i.e. the investigators were unable to remove CSF from the lateral ventricle), and reduced vascular or intracranial compliance (large increase in CSF pulse amplitude ((18), See fig 3D)). 3) Sagittal sinus pressure declined to near baseline values by 24 hours; thus brain edema or increased cerebral blood volume (or both), explain the elevated ICP in sheep with signs of severe high-altitude illness.

Acute and prolonged effects of hypoxia – Humans. Direct measurements of ICP in humans during high-altitude illness or after recovery are rare. In persons with moderate to severe AMS and HACE, mean ICP is elevated (40, 53, 64, 79, 95). For example, lumbar puncture showed that mean ICP was elevated by 4 to 15 mmHg in Indian soldiers during severe high-altitude sickness compared to recovery values (79). Moreover, case studies document mean ICP by lumbar puncture is often greater than 25 mmHg in individuals with severe AMS or high-altitude cerebral edema despite descent to lower altitude (40). In such individuals, magnetic resonance imaging reveals brain edema (33). Thus, convincing evidence indicates that hypoxia can, increase ICP either because cerebral volume exceeds craniospinal compensatory capacity, or
sagittal sinus pressure becomes elevated, or both. Thus, a limited compensatory capacity ‘tight fit’ (74) is a rational explanation for a predisposition to severe AMS and HACE.

In a well-designed series of experiments, Schaltenbrand (75) performed continuous measurements of ICP by lumbar puncture during acute reductions in atmospheric pressure. Although the threshold altitude varied between patients, CSF pressure rose consistently, especially above 3000 m. In one subject exposed to 4500 m for ~10 min, ICP rose from 11 to 20 mmHg, gradually decreasing to settle at 18 mmHg. Administration of oxygen aborted the rise in ICP or restored ICP to normal in most cases. Hartig and Hackett (37) conducted a pilot study with three subjects whereby ICP was measured via lumbar catheter. Subjects breathed hypoxic gas acutely (11% O₂, 10 min) and were exposed to a hypobaric altitude of 5000 m for around 6 hours. ICP increased in two of the three subjects during acute hypoxic gas breathing (See fig 3E) and remained elevated after 6 hours (See fig 3E). Over this time period, two of the three subjects reported moderate headache, but only one had slightly elevated mean ICP. Similar to the data obtained in unanesthetized sheep (18, 97), lumbar punctures obtained in healthy volunteers before and after 16 hours exposure to simulated altitude of 4500 m documented no change in mean ICP (10) (See fig 3E). Perhaps the greatest endeavor to measure ICP during gradual exposure to hypoxia (similar to trekking with partial acclimatization) was undertaken by Dr Brian Cummings, a British neurosurgeon (93). Trans-dural pressure was measured by implanting invasive telemetric monitoring devices into three individuals, including himself. At 5029 m in the resting supine position, ICP was normal in one individual and rose by ~7 mmHg and ~5 mmHg in two others. The same investigation also noted that individuals with the smallest intracranial ventricles at sea level, and thus intraventricular CSF volume, suffered the worst headache (93).

Up to this point we have discussed either spot measurements of ICP or continuous data reported as mean values. Given the reduction in vascular tone and in CSF volume, and a slight increase in mean resting ICP, craniospinal dynamics are likely altered in many individuals at
Indeed, in the only study to continuously measure ICP, Hartig and Hackett (37), noted that ICP became markedly elevated during exertion and spontaneous periodic breathing while awake. One of their subjects with periodic breathing demonstrated a remarkable threefold increase in CSF pressure from 10 to 30 mmHg in phase with the nadir of the oscillating oxygen saturation (See fig 3F). Furthermore, in these subjects, hypoxic gas breathing produced a greater increase in ICP at high altitude than sea level. No other investigations have performed prolonged continuous ICP monitoring in hypoxic subjects.

These invasive data are generally consistent with most neuroimaging studies. Using high-resolution magnetic resonance imagining, Dubowitz et al., (21) noted a mean increase in brain volume of 3 and 8 ml after 20 and 40 minutes at a simulated altitude of 3800 m (12.5% oxygen). Spatial compensation was apparent, as CSF volume decreased by a similar amount. Employing a similar magnetic resonance imaging technique, brain volume increased by 7 and 59 ml after 2 and 10 hours at a simulated altitude of 4500 m (12% oxygen) (55). Again, evidence for spatial compensation was noted by reductions in ventricular and subarachnoid CSF volume. Finally, in the same subjects who underwent lumbar punctures (10), average brain volume was only slightly increased (7±4.8 ml) after 16 hours at 4500 m, although substantial variability existed; subjects suffering the worst symptoms had the largest increase in brain volume (10), but cerebral spinal fluid volume was not reported. Interestingly, under these acute hypoxic conditions, increased brain water has rarely been noteworthy, but fluid shifts within white matter are observed consistently (42, 49, 56, 66, 76).

**Summary.** The available animal and human literature suggests that acute moderate to severe hypoxia causes profound cerebral vasodilatation and an increase in cerebral arterial and venous blood volume. Intracranial pressure is acutely elevated in animal models; in the few humans that have been studied, ICP seems to be mildly elevated acutely and remains elevated at least over the first six hours. The initial rise in ICP may be explained by elevated cerebral blood volume,
whereas the maintenance of elevated ICP can be explained by elevated $P_{\text{sag}}$ as seen in animal models. What causes an acute increase in $P_{\text{sag}}$ is unknown, but heterogeneous intracranial venous anatomy or collapse of the non-dominant transverse sinus (12, 55, 91, 92) are possible explanations. In some animals ICP remains elevated for 24 hours associated with brain edema; spatial compensation is evident. In others, ICP returns towards normal values, which is consistent with data obtained in humans. However, in the only experiment to continuously measure ICP, large dynamic fluctuations were observed after 6 hours in hypobaric hypoxia.

**PERSPECTIVES**

**High-altitude headache and acute mountain sickness.** Investigations on the mechanisms of high-altitude headache are to some extent studies of AMS. One could even argue that it is the headache itself that causes other symptoms such as anorexia, nausea, lassitude, and insomnia, as is commonly seen in migraine or tension headaches, and that mild AMS is essentially due to headache.

Headache is generally caused by activation of the trigeminal vascular system (28). High-altitude headache occurs in most individuals after rapid ascent to high altitude (15), is often dull, confined to the front of the head (78) and takes a number of hours to develop (15). Although speculative, these anatomical and physiological features suggest a possible role for prolonged low-grade activation of trigeminal afferents innervating dura or pial arteries or tributary veins that pass into the venous sinus (73). Theoretically, chronic or transient elevations in ICP could activate trigeminal afferents. Alternatively, as arterial and venous vessel tone is reduced, greater transmission of the arterial pressure into the arteries and veins would be sensed during every heartbeat in multiple receptive fields and could produce summation of afferent recruitment, which exceed the threshold for pain sensation. Note that the latter situation does not necessitate constantly elevated ICP. With either scenario, subsequent central or peripheral sensitization (14, 68) in combination with feed forward parasympathetic activation and/or diffuse...
inflammatory mediator release could be responsible for further vasodilatation, sensitization and expansion of trigeminal nociceptive fields and enhanced mechanosensitivity to previously non-painful stimuli as is observed clinically i.e. coughing, bending and exercising, see fig 4 (78).

Nausea and vomiting may also be due to vagal activation or transient reductions in blood flow to vomiting centers within the lateral reticular formation and/or the chemoreceptor trigger zone around the 4th ventricle (13), although at present this is speculative. If, similar to animal models, human $P_{\text{sag}}$ normalizes over time, facilitated $\text{CSF}_{\text{out}}$ should also normalize ICP. However, ICP may titrate the “knee” of the spatial compensation-compliance curve (See figure 4B) and large fluctuations around a normal mean pressure will be observed in conjunction with fluctuation in $\text{PaO}_2$ and arterial blood pressure. Reductions in symptom intensity will result from the interaction between numerous factors including: decreased cerebral blood flow and cerebral blood volume with ventilatory acclimatization (77), the time constant for spatial compensation, and central/peripheral trigeminal sensitization.

Acute hypoxia causes increased accumulation of intracellular water within astrocytic cells (49, 56, 76) that seems more severe in individuals with established AMS (49, 56, 76). Fluid shifts within white and grey matter are also related to illness severity with prolonged hypoxia (2 – 7 days, (42)). A common explanation for these observations is disruption of cellular membrane $\text{Na}^+/\text{K}^+$ ATPase. At present, no evidence of global or localized ischemia or hypo-metabolism exists, but elevations in ICP have been shown to disturb energy metabolism in the periventricular white matter independent of $\text{PaO}_2$ (1). Alternatively, hypoxia has been shown to upregulate the expression of neuropeptide corticotrophin releasing factor, which activates the water channel aquaporin-4 and facilitates water (from CSF) influx into glial cells (16). Indeed, aquaporin-4 located at the terminal end-feet of astrocytes are the most abundant water channels in the brain, giving glia ~four times greater water permeability (34). In addition, Iliff and colleagues (43) have shown that CSF–interstitial fluid flux (the glymphatic system) is driven by cerebral arterial pulsations. We propose that hypoxia increases arterial pressure transmission...
within the intracranial space, which are more severe in those with poor craniospinal compensatory capacity and AMS (see fig 4). Therefore, enhanced CSF-interstitial fluid flux may partly explain altered white matter water mobility in hypoxic individuals with AMS.

**High-altitude cerebral edema.** Clinically diagnosed HACE occurs in only a few individuals despite rapid ascent to very high altitudes (11, 31, 32). Therefore, anatomical and pathological interactions that result in overt symptomology (ataxic gait, altered consciousness etc.) are apparently rare. Since the main pathologic process is brain swelling, an anatomically poor spatial compensatory capacity (“tight fit”) would be a major risk factor. Poor compensatory capacity, cranio-spinal axis compliance, and high $R_{out}$ likely govern a general neural intolerance to high altitude, but a specific predisposition to HACE. However, it must be emphasized that anatomical differences are only risk factors; although HACE is rare with current ascent profiles, brain edema may develop in many individuals if they ascend too high too fast. Moreover, despite an anatomical predisposition, extreme altitudes can be achieved by most individuals with slow ascent.

Potential mechanisms for vasogenic edema have been reviewed previously and mainly encompass mechanical breakdown and increased leakiness of the blood brain barrier (8, 30, 32, 52). At high altitude, arterial blood pressure is elevated together with pronounced low frequency (0.05Hz) sympathetic vasomotor oscillations, which are transmitted into the intracranial space due, in part, to reduced vasomotor tone and impaired autoregulation (9, 45, 81). Brain regions with poor sympathetically mediated vasoconstriction would be particularly susceptible (38). In line with this rationale, the tendency for vasogenic edema to occur within the splenium of the corpus callosum could be explained by its vascular pattern (65) and adrenergic innervation (51) that favors arterial pressure transmission, increased capillary pressure and fluid filtration (28). An alternative or contributing factor may be paravascular CSF flux into the brain via the low-resistance glymphatic pathway noted above. During acute mountain sickness,
fluid redistribution seems benign; however, over time Na+ influx into the brain may set up an oncotic potential to further potentiate brain edema. In fact, the interaction between transient rises in capillary pressure relative to brain tissue pressure (ICP) and an elevated oncotic potential (Starling forces) will substantially dictate fluid filtration across the blood brain barrier. Factors that likely accelerate vasogenic brain edema include classic risk factors that increase cerebral blood volume too quickly (fast and high ascent) and activities that produce large fluctuations in blood pressure, such as prolonged strenuous mountaineering and sleep at high altitude (2). Sleep at high altitude likely presents a “perfect storm” and the cumulating event to the development of intracranial pressure waves and vasogenic brain edema in most but not all individuals i.e., fluctuating PaO₂, PaCO₂, thoracic (i.e. central and sagittal venous pressure) and arterial blood pressure (84) and enhanced para-arterial (lymphatic) fluid transport (43), see fig 4). HACE is most common after a night or two sleeping at high altitude.

FUTURE RESEARCH DIRECTIONS

The major challenge to test the hypotheses put forward in this review will be to obtain continuous direct measurements of intracranial pressure in humans during prolonged periods of hypoxemia, with and without pharmacological treatment for high altitude illness. Careful documentation of pathological pressure waves and the impact of changes in posture, sleep and exercise will be critical. In this regard, the combination of advanced neuroimaging and high-resolution hemodynamic monitoring will lead to a greater understanding of the pressure-flow dynamics both globally and regionally within the hypoxic brain. Extended physiological monitoring during sleep at high altitude will also substantially advance this field. Clearly, some individuals seem more susceptible to high-altitude illness than others. Identifying which anatomical factors, if any, predispose individuals to high-altitude illness, especially the life threatening condition HACE, will be valuable. Future research focusing on inter-individual variations in spatial compensatory capacity, cranial and spinal compliance, R_out and intracranial
venous anatomy is warranted. Finally, new experimental models that reproducibly cause brain edema (increased multi-echo T2 relaxation on MRI) in human subjects are required; at present, frank evidence of brain edema in any short-term human investigation is marginal at best. Once developed, experimental models aimed at modulating water flux through both endothelial and glial blood-brain interfaces will be important.

Conclusions. As hypothesized by Ross, (74), inter-individual variability in craniospinal compensatory capacity is a rational explanation for the individual susceptibility to cerebral manifestations of high-altitude illness. We hypothesize that 1) individuals who are asymptomatic despite rapid ascent to high altitude possess a compensatory capacity (large spinal compliance and/or low R_{out}) that outweighs changes in brain volume, whereby arteriolar tone is not exhausted and pressure transmission is not facilitated. Importantly, the compensatory capacity of the spinal thecal sac, which is a central tenant of the tight-fit hypothesis, has never been assessed in individuals with and without high-altitude illness. 2) Acute increases in ICP will be observed in individuals with poor spinal compliance (acute spatial compensatory capacity) relative to large increases in brain volume; ICP will return towards the normal operating point slower in individuals with a concomitant high R_{out}. Conversely, ICP will remain elevated if P_{sag} is elevated. 3) If mean ICP returns to near-normal, it will titrate the “knee” of the spatial compensation-compliance curve and large fluctuations will be observed in conjunction with fluctuations in PaO2 and arterial blood pressure, which contribute to symptoms of high-altitude headache and AMS. Direct arterial or venous dilatation or increased arterial pressure transmission, independent of ICP, could also cause AMS symptoms. 4) Continual acute elevations in ICP will be observed with gains in altitude, but if gradual, will return to normal on every occasion due to increased CSF_{outflow} and normalization of P_{sag}. However, at some point, each individual will reach their compensatory capacity for a given altitude gain and ascent rate.
At this point, despite the appearance of acclimatization, further ascent, exercise and sleep will be disastrous, brain edema will develop, A- and B-waves will be observed, and HACE will occur.
Figure legends

Figure 1. Cerebral spinal fluid dynamics. Blood flow over a cardiac cycle within the internal carotid and vertebral arteries (Panel A), sagittal sinus (Panel B) and jugular veins (Panel C). To and fro flushing of cerebral spinal fluid through the Sylvius aqueduct (Panel D) and spinal canal at C2-C3 (Panel E). Pulsatile arterial flow (internal and vertebral arteries) over the cardiac cycle leads to a small (1.5 to 2.0 ml) increase in CBV (Panel F). ICP pulsatility (cardiac pulsations) represents the contribution of change in CBV and craniospinal compliance, whereas respiratory oscillations are due to changes in CVP and $P_{sag}$ (Panel G). Cerebral spinal fluid absorption.

Primary site of cerebral spinal fluid absorption through arachnoid granulations into the sagittal sinus (Panel H), which is driven by the ICP-$P_{sag}$ pressure gradient. Glymphatic system.

Interstitial solute and fluid clearance from the brain is facilitated by para-arterial influx of cerebral spinal fluid and paravenous clearance. Convective bulk interstitial fluid flow is facilitated via aquaporin-4 studded on astrocyte end-feet (Panel I). Greater spinal fluid absorption in the active (1 min walking) upright compared to resting supine posture (left, Panel J); measured by the radionuclide clearance from sacral/lumbar to thoracic/cervical level immediately (0) and 20, 40 and 60 minutes after injection (right, Panel J). Small letters identify the location of blood or CSF flow in panels A-E. CBV, cerebral blood volume; ICP, intracranial pressure; ECG, Electrocardiogram; $P_{sag}$, sagittal sinus pressure; BP, arterial blood pressure; CVP, central venous pressure. Panel E, F and H are redrawn from (7, 22, 36)

Figure 2. Craniospinal compensation and compliance. Intracranial pressure response to a sudden (20 ml) increase in cerebral blood volume. In the simulation, 10 ml of CSF is abruptly translocated into the spinal thecal sac, reducing ICP to ~11 mmHg. With $R_{out}$ and $P_{sag}$ (green line) remaining stable, CSF absorption is increased due to the elevated pressure gradient across the arachnoid granulations ($ICP - P_{sag}$). ICP gradually declines to the steady state condition as predicted by the Davson equation. Solid line represents the mean pressure level around which pulsatility occurs. Note $ICP_{AMP}$ increases as mean pressure rises due to a concomitant reduction in intracranial compliance (Panel A). Serial radiographs of a Pantopaque-filled lumbosacral spinal dural sac from a single subject during maneuvers aimed at altering cerebral volume. Note narrowing and cranial movement of spinal dural sac with decreased cerebral blood volume (hyperventilation), the reverse is observed with $CO_2$ breathing and bilateral jugular compression (Panel B). Subarachnoid space (upper lines) and sagittal diameter of spinal cord (lower lines) throughout the vertebral column in two age groups. Shaded area around the upper lines represents the wide between subject variations in subarachnoid space within the 18-69 year group (Panel C). Average ICP during steady state (1ml/15 min) inflation of extradural balloons in eight adult baboons. Solid line represents hypothetical (pressure volume index) compliance curve. (Panel D). These two curves illustrate the difference between the brains limited capacity to deal with rapid changes in volume (compliance) and modest ability to compensate for volume changes over longer time frames (spatial compensation). ICP during steady state (1 ml/15 min) inflation of extradural balloon in a single baboon (Panel E). Note the greater spatial compensatory capacity as ~5 ml of volume only increased ICP to 10 mmHg,
which is in contrast to 45 mmHg when all baboons are combined (panel D). In this baboon, 5 ml approximates the ‘knee’ of the spatial compensation-compliance curve, where the relationship between volume and pressure increases exponentially (Panel E). ICP, intracranial pressure; ICPAMP, intracranial pressure pulse amplitude, CSF, cerebral spinal fluid; Psag, sagittal sinus pressure; Rout, outflow resistance. Panels A, B, E and D are redrawn from (57, 63, 74).

Figure 3. Effect of hypoxia on intracranial pressure. Acute increase in mean ICP and in the ICP pulse amplitude with moderate and severe hypoxia (Panel A & B). Threshold dependent (PaO2 ~50 mmHg) increase in ICP, which is similar to that observed for cerebral blood flow (Panel C). Prolonged increase in mean ICP and in the ICP pulse amplitude in one sheep after 24 hours hypoxia (Panel D). Increased ICP after 10 minutes of 11% O2, which is sustained for ~5.5 hours at 5,000 m in humans (Panel E). Single point lumbar punctures at sea level and after 16 hours breathing 12% O2 reveal ICP is unchanged with prolonged sustained hypoxia in humans (Panel E.). Large fluctuations in ICP are evident in the only study to continuously measure ICP hypobaric hypoxia (Panel F). ICP; intracranial pressure; SaO2; oxygen saturation. Panels A - F are redrawn from (10, 18, 36, 37, 67, 69).

Figure 4. Pathophysiology of AMS and HACE. Hypoxia causes elevated CBF, CBV and a reduction in vascular tone, which causes a rise in ICP (Panel A). However, if transverse sinus stenosis and elevated Psag are present, ICP remains elevated (ICP must be higher than Psag to maintain CSF absorption). Two curves highlight extremes in spatial compensation capacity and craniospinal elasticity (left panel). In a person with anatomical/physiological characteristics typical of curve (a), an additional 3 ml would increase ICP to ~20 mmHg, no change in ICP would occur for the same volume change in curve (b). Once entering the steep part of the compliance curve, a 1 ml change in volume (during each heartbeat), causes a much larger increase in ICP pulsatility in curve a than curve b. Red circles identify the ICP operating points, note the close proximity to the “knee” of the compensatory-compliance curve in a but not b (Panel B). Hypothetical model of dynamic pressure fluctuations over the first few hours at high altitude (right panel). Due to reduced vessel tone and altered intracranial compartment volumes, intracranial pressure waves are observed during every heart beat and low frequency BP oscillations. Furthermore, evidence from animal models suggests Psag is increased, thus ICP is persistently elevated. Over time, mean Psag decreases and ICP normalizes due to both translocation of CSF into the spinal canal and increased CSF absorption (spatial compensation), but pathological ICP waves are persistently observed (Panel B). Vascular stretch due to vasodilatation and/or increased pressure transmission causes activation of trigeminal afferents (green lines) innervating dura or pial arteries or tributary veins that pass into the venous sinus causing headache. Thereafter feedforward parasympathetic activation (orange lines) causes the release of potent vasodilators and further vasodilatation. (Panel C) Central or peripheral sensitization causes a reduced threshold and greater firing rate of meningeal nociceptors, which causes expansion of trigeminal nociceptive fields and enhanced mechanosensetivity to previously non-painful stimuli, as is observed clinically i.e. coughing, bending and exercising (Panel D). Although dependent on ascent rate and altitude gain,
persons resistant to acute mountain sickness may exhibit an advantageous anatomical/physiological response at any stage in this schema (i.e. greater ventilatory drive and PaO$_2$ at any given altitude, lower cerebral vascular reactivity to hypoxia, greater spatial compensatory capacity, intracranial compliance or a high nociceptive threshold for trigeminal activation or pain processing). At high altitude, apnea and arousals during sleep cause large fluctuations in SaO$_2$, PaCO$_2$ and BP. ICP passively rises with BP. With the fall in BP, autoregulation increases CBV leading to a vasodilatory cascade and the appearance of large pressure waves. Several negative feedback loops are included that stabilize ICP. (Panel E) Elevated brain water occurs due to para-arterial influx of CSF, which is facilitated by greater arterial pulsations and expression of corticotropin releasing factor. Increased leakiness of endothelial tight junctions due to circulating inflammatory mediators, in concert with blood pressure dependent opening of the blood brain barrier, may lead to fluid flux into the cerebral parenchyma from the vascular space (Panel F). ICP, intracranial pressure; BP, arterial blood pressure; P$_{sag}$, sagittal sinus pressure; OP, operating point; SaO$_2$, oxygen saturation; CSFV, cerebrospinal fluid volume; CPP, cerebral perfusion pressure; CBV, cerebral blood volume; CBF, cerebral blood flow, CVR, cerebrovascular resistance. Panels D and E are redrawn from (68, 84).
References


Intracranial compliance (Spatial compensation)

Acute spatial compensation

Secondary compensation (phase II)

ICP set point

ICP = CSFoutflow * Rout + Psag

B

C

D

E
PaO$_2$ = 120 mmHg  
PaO$_2$ = 60 mmHg  
PaO$_2$ = 35 mmHg

ICP (mmHg)

Animal experiments

- PaO$_2$ = 50.4 mmHg
- PaO$_2$ = 18 mmHg

Normoxia  
Hypoxia (24 hours)

Human experiments

- PaO$_2$ = 5,000 m  
- SaO%  
- ICP peak (mmHg)
**HYPOXIA**

- Arterial and venous dilatation (reduced vessel tone)
- Cerebral blood volume
- Sagittal sinus pressure
- Transverse sinus stenosis
- Over expression of corticotropin releasing factor

**Spinal compensation**

- Normalized steady state ICP

**Transient increases in ICP**

(exercise (valsalva), sleep apnea, hyper- & hypotension)

**Parasympathetic and sympathetic activity**

- Autoregulation

**ICP**

- Pressure on vessel (kPa)

**Baseline**

- Pressure on vessel (kPa)

**Headache +

symptoms of acute mountain sickness**

**Brain edema with or without diagnosis of High altitude cerebral edema**

**Arterial and venous dilatation**

- (reduced vessel tone)

**Sagittal sinus pressure**

- Transverse sinus stenosis

**Spinal compensation**

- Normalized steady state ICP

**Transient increases in ICP**

(exercise (valsalva), sleep apnea, hyper- & hypotension)

**Parasympathetic and sympathetic activity**

- Autoregulation

**ICP**

- Pressure on vessel (kPa)

**Baseline**

- Pressure on vessel (kPa)