HIGHLIGHTED TOPIC | Hypoxia 2015

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

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Lawley JS, Levine BD, Williams MA, Malm J, Eklund A, Polaner DM, Subudhi AW, Hackett PH, Roach RC. Cerebral spinal fluid dynamics: effect of hypoxia and implications for high-altitude illness. J Appl Physiol 120: 251–262, 2016. First published October 22, 2015; doi:10.1152/japplphysiol.00370.2015.—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 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) may be due to breakdown of the blood-brain barrier. However, new information suggests cerebral spinal fluid flux into the brain may be 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.

acute mountain sickness; high-altitude cerebral edema; headache and intracranial pressure

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. AMS typically occurs when the onset of hypoxemia is rapid and severe i.e., ~4,500 m or oxygen saturation ~80%. Under these circumstances, mild symptoms such as headache occur in most individuals (15), with 40-65% of headache sufferers 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 >4,000 m (11, 31). Despite decades of investigation, the pathophysiology of AMS and HACE remains 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 1) 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; 2) evaluate the effect of hypoxia on brain swelling and CSF dynamics, including intracranial pressure (ICP); and 3) link these observations to AMS and HACE.

**PHYSIOLOGY OF THE CRANIOSPINAL SYSTEM**

CSF is secreted predominantly by the choroid plexus at a rate of ~0.4 ml/min (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 spinal (~20%), equals only ~300 ml (39), a constant and equivalent rate of CSF reabsorption (CSF\textsubscript{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 [change (\(\Delta\)) in substrate delivery], ventilation (\(\Delta\)P\textsubscript{CO\textsubscript{2}}), atrial natriuretic peptide release, and carbonic anhydrase activity (19). CSF outflow (CSF\textsubscript{outflow} or CSF\textsubscript{reabsorption}) is predominantly determined by the difference between ICP and sagittal sinus pressure (P\textsubscript{sag}) relative to the resistance of CSF movement from its site of production to its site of absorption (R\textsubscript{out}, Davson equation, Eq. 1). Put simply, ICP must exceed P\textsubscript{sag} for CSF\textsubscript{outflow} to occur. R\textsubscript{out} is the sum of total resistance of the arachnoid granulations. Nonetheless, the intracranial-venous pressure gradient dominates CSF volume homeostasis over prolonged periods of time, as R\textsubscript{out} has been shown to remain stable within the same individual, despite modest elevations in ICP from baseline (3).

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\text{CSF}_{\text{outflow}} (\text{ml/min}) = \left[\frac{\text{ICP} (\text{mmHg})}{\text{P}_{\text{sag}} (\text{mmHg})}\right] / \text{R}_{\text{out}} (\text{mmHg ml.min}^{-1}) \tag{1}
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The primary route of CSF\textsubscript{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\textsubscript{sag} cause a reduction in the transmural pressure gradient (ICP - P\textsubscript{sag}) and increased ICP (41, 70). Other routes of CSF\textsubscript{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\textsubscript{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\textsubscript{outflow} is through spinal roots when standing upright, compared with only ~20% when supine (22) (see Fig. 1). Furthermore, animal studies suggest that CSF-interstitial flux (gliothelial drainage; see Fig. 1J) may be predominantly dormant during waking hours, but substantial while asleep (96).

ICP. 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\textsubscript{out} and P\textsubscript{sag}. As CSF production equals CSF\textsubscript{outflow} in the steady-state condition, ICP typically reflects changes in P\textsubscript{sag} over prolonged periods.

A typical supine resting ICP in healthy young individuals is ~11 mmHg. However, there is considerable interindividual 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 affect P\textsubscript{sag} in the supine posture, such as simply elevating the head or legs on a pillow, can either reduce (~5 mmHg; Ref. 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 intrathoracic 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; Ref. 85) increase in arterial cerebral blood volume (see Fig. 1F), expansion of the brain parenchyma, 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 present 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, assuming a total inflow of 700 ml/min), ICP would increase uncontrollably, and death would follow. Instead, focal narrowing of the intracranial transverse sinus causes elevated venous pressure proximal to the stenosis; \( P_{\text{sag}} \) 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 1) identifying causation between elevated ICP and venous stenosis; and 2) 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 venousplexus (63). CSF forms a freely communicating fluid system between the cranium and spinal thecal sac. Thus craniospinal axis compensation (see below) and compliance include the interaction between the physical (anatomical) and physiological (hemodynamics) 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 (Δvolume/Δpressure) (7).

Spatial compensation represents the degree to which volume increments can be accommodated by compensatory reductions in the volume of other intracranial compartments. First, intracranial 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 (Ref. 63; see Fig. 2B). The second component is spatial compensation via quasi-static reductions in craniospinal CSF volume through increased CSF reabsorption (CSFoutflow). As long as Psag remains normal, this compensation will occur over time, whereby ICP will gradually return to the steady-state condition, as predicted by CSF formation rate, Rout (see Fig. 2A). The spinal subarachnoid CSF volume, and thus the potential spinal compensatory capacity, varies considerably between individuals (Fig. 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-Psag gradient, and Rout. The variability of spatial compensation can be appreciated by examination of Fig. 2. Figure 2D shows the mean response of ICP to slow inflation of an extradural balloon in a group of nonhuman primates, whereby 5 ml of volume increases ICP to 45 mmHg. In contrast, in a single nonhuman primate, 5 ml of volume only increased ICP to 10 mmHg (Fig. 2E) (57).

Craniospinal compliance typically reflects the elastic properties of the craniospinal system and reflects the acute volume-pressure (Δvolume/Δpressure) 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” dictate 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 cranial 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 is initial spatial compensation, whereby ICP rises very modestly, or not at all, despite added volume. As spatial compensation becomes exhausted and the spinal intradural 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. In 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. In 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. In 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 ~20–25 mmHg (27). Given the wide interindividual variation in resting steady-state supine ICP (~7–15 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 with 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 ICP waves (Lundberg A- and B-waves; Ref. 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 CSF DYNAMICS**

Since noninvasive 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 noninvasive methods, see the recent review by Wilson and colleagues (94).

The cerebral arterial vascular response to hypoxia encompasses a threshold- [arterial PO$_2$ (Pa$_{O_2}$) ~60 Torr] dependent
increase in cerebral blood flow and pial artery and arteriolar dilatation (i.e., a reduction in cerebrovascular resistance and increased arterial blood volume; Refs. 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% O2) 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 min. Hamer et al. (36) observed that reducing PaO2 to 60 Torr and then to 35 Torr in anesthetically 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 (PaO2, 29.4 ± 8.5 Torr) or 10% carbon dioxide [arterial PCO2 (PaCO2), 71.8 ± 4.1 Torr] for 10 min. Acute hypoxia and hypercapnia caused mild elevations in mean ICP (Δhypoxia, 6.3 mmHg; Δhypercapnia, 9.3 mmHg) and ICP pulse amplitude (Δhypoxia, 1.5 mmHg; Δhypercapnia, 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 Torr) 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 hypoxic sheep. The main findings of interest for this review are 1) a consistent increase in ICP over the first 6 h of hypoxia, which can be explained by vasodilatation and the observed rise in P_sag (44, 97, 98). 2) By 24 h, 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 (Ref. 18; see Fig. 3D)]. 3) P_sag declined to near baseline values by 24 h; 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 4–15 mmHg in Indian soldiers during severe high-altitude sickness compared with recovery values (79). Moreover, case studies document mean ICP by lumbar puncture is often >25 mmHg in individuals with severe AMS or HACE, 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 P_sag becomes elevated, or both. Thus a

![Fig. 3. Effect of hypoxia on ICP. A and B: acute increase in mean ICP and in the ICP_amp with moderate and severe hypoxia. C: threshold-dependent [arterial P_O2 (PaO2) ~ 50 Torr] increase in ICP, which is similar to that observed for cerebral blood flow (CBF). D: prolonged increase in mean ICP and in the ICP_amp in one sheep after 24-h hypoxia. E: Increased ICP after 10 min of 11% O2, which is sustained for ~5.5 h at 5,000 m in humans. Single-point lumbar punctures at sea level and after 16 h breathing 12% O2 reveal ICP is unchanged with prolonged sustained hypoxia in humans. F: Large fluctuations in ICP are evident in the only study to continuously measure ICP in hypobaric hypoxia. SaO2, oxygen saturation. [A, B, and D are redrawn from Refs. 69, 36, and 18, respectively, with permission.]](http://jap.physiology.org/cgi/content/full/doi:10.1152/japplphysiol.00370.2015)
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 3,000 m. In one subject exposed to 4,500 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 5,000 m for around 6 h. ICP increased in two of the three subjects during acute hypoxic gas breathing (see Fig. 3E) and remained elevated after 6 h (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-h exposure to simulated altitude of 4,500 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 Cummins, a British neurosurgeon (93). Transdural pressure was measured by implanting invasive telemetric monitoring devices into three individuals, including himself. At 5,029 m in the resting supine position, ICP was normal in one individual and rose by ~7 mmHg and ~5 mmHg in the other two. 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 high altitude. 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 imaging, Dubowitz et al. (21) noted a mean increase in brain volume of 3 and 8 ml after 20 and 40 min at a simulated altitude of 3,800 m (12.5% oxygen). Spatial compensation was apparent, as CSF volume decreased by a similar amount. With employment of a similar magnetic resonance imaging technique, brain volume increased by 7 and 59 ml after 2 and 10 h at a simulated altitude of 4,500 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 h at 4,500 m, although substantial variability existed; subjects suffering the worst symptoms had the largest increase in brain volume (10), but CSF 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. ICP is acutely elevated in animal models; in the few humans who have been studied, ICP seems to be mildly elevated acutely and remains elevated at least over the first 6 h. 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-sag, as seen in animal models. What causes an acute increase in P-sag is unknown, but heterogeneous intracranial venous anatomy or collapsibility of the nondominant transverse sinus (12, 55, 91, 92) are possible explanations. In some animals, ICP remains elevated for 24 h, associated with brain edema; spatial compensation is evident. In others, ICP returns toward 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 h in hypobaric hypoxia.

PERSPECTIVES

High-altitude headache and AMS. 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 ofafferent 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 nonpainful 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 fourth ventricle (13), although at present this is
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A. Hypoxia

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

B. Intracranial pressure

- Volume (ml)
- Knee
- Intracranial pressure (mmHg)
- BP (mmHg)
- ICP (mmHg)
- Time (hours)

C. Spatial compensation

- Normalized steady state ICP
- Transient increases in ICP (exercise, vasa vasorum, sleep apnea, hyper- & hypotension)

D. Trigeminal vascular sensitization

- Pressure on vessel (kPa)
- Baseline
- Headache + symptoms of acute mountain sickness

E. Compliance

- CPP, CBV, CVR, CBF
- Autoregulation
- Escape way (negative feedback)

F. Para-arterial and tight junction fluid flux into tissue

- AQP-4
- CSF
- Intravascular water

Brain edema with or without diagnosis of High altitude cerebral edema
speculative. If, similar to animal models, human P_{sag} normalizes over time, facilitated CSF_{outflow} should also normalize ICP. However, ICP may titrate the “knee” of the spatial compensation-compliance curve (see Fig. 4B), and large fluctuations around a normal mean pressure will be observed in conjunction with fluctuation in P_{O2}, 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 gray matter are also related to illness severity with prolonged hypoxia (2–7 days; Ref. 42). A common explanation for these observations is disruption of cellular membrane Na+/K+-ATPase. At present, no evidence of global or localized ischemia or hypometabolism exists, but elevations in ICP have been shown to disturb energy metabolism in the periventricular white matter, independent of P_{O2} (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 approximately four times greater water permeability (34). In addition, Iliff and colleagues (43) have shown that CSF-interstitial fluid flux (the lymphatic system) is driven by cerebral arterial pulsations. We propose that hypoxia increases arterial pressure transmission within the intracranial space, which is 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.

HACE. 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 pathological process is brain swelling, an anatomically poor spatial compensatory capacity (“tight fit”) would be a major risk factor. Poor compensatory capacity, craniospinal 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 (0.05 Hz) 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 lymphatic pathway noted above. During AMS, 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

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Footnotes and references are not included in this snippet.
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 ICP 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 (glymphatic) 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 ICP 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 interindividual 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 multiecho T2 relaxation on magnetic resonance imaging) 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), interindividual 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 arterial 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 toward 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.

REFERENCES


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