

Anesthesia and the Swollen Brain
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The swollen brain is a challenge to the anesthesiologist in two major respects. For the closed skull (i.e. in the intensive care unit or in the operating room for non-intracranial surgery) the swollen brain can cause elevated ICP (intracranial pressure) that can compromise the perfusion of the brain by lowering the net Cerebral Perfusion Pressure (CPP as defined as the mean arterial pressure minus the ICP [CPP=MAP-ICP]). Secondly, if the brain is swollen during intracranial surgery, the swelling will make the surgery more difficult and reduce the probability of an optimal outcome. Hence, means to manage the swollen brain become key to successful patient care in these circumstances. This lecture will review the considerations for

1. utilizing the normal brain to reduce total brain bulk and compensate for areas of swelling,
2. optimal fluid management to minimize its contributions to brain bulk and swelling, and
3. specific management considerations in selected pathologic circumstances.

Management of the Normal Brain to Reduce Brain Bulk

In many circumstances the deranged physiology and abnormal blood-brain barrier in the pathologic areas of the brain will not allow manipulation of the abnormal tissue to reduce brain swelling. Hence, the normal brain becomes key to the overall management of the swollen brain to reduce total brain bulk and improve ICP or intracranial operating conditions. Both physiologic and anesthetic considerations apply in this circumstance.

One method to examine these effects is to consider the intracranial contents and the methods which apply to these areas. In the normal brain the largest intracranial volume is the brain tissue (about 80% of the intracranial contents). As such, the most effective methods to reduce brain bulk will be focused on reducing brain tissue volume to reduce overall brain bulk. With the exception of surgical removal of tissue, the most effective reduction in brain volume will be aimed at reducing the amount of water in the brain tissue (i.e. dehydrating the normal brain tissue). This water comprises about 80% of the brain tissue making it about 2/3's of the normal intracranial volume. The methods used here include osmotic agents such as mannitol which withdraw water across a normal blood brain barrier and diuretics and corticosteroids which alter tissue water regulation via its effect on the Aquaporins that regulate water transfer (e.g. furesomide, dexamethasone).

The second largest intracranial volume is the cerebral spinal fluid (CSF) which is 10-15% of the normal volume. Methods to reduce CSF production and improve absorption could reduce this volume. Since production and absorption include both passive and active (enzymatic) components, a variety of physiological issues control overall volume. About 40-70% of CSF is formed passively in the choroid plexus by hydrostatic and osmotic pressures (production = $MAP - P_{CSF} + Osm_{CSF} - Osm_{blood}$). Increasing the osmotic pressure in the blood (such as with mannitol) will reduce production and production will fall with CPP below 70 mmHg. The remainder of production occurs as a consequence of metabolism (e.g. water liberated by glucose metabolism) and specific processes of ultrafiltration and secretion across various endothelial and tissue barriers (e.g. furesomide decreases production).

CSF absorption is primarily active transport with drainage into the venous system. Hence methods that will lower the venous pressure will improve CSF absorption (see below). In addition, absorption is increased with CSF pressures above 30 mmHg. Few non-anesthetic agents are available to lower CSF volume although furesomide is effective. Since aquaporins

appear important in water transfer with CSF production and absorption this may explain the beneficial effects of furesomide through a reduction in CSF production.

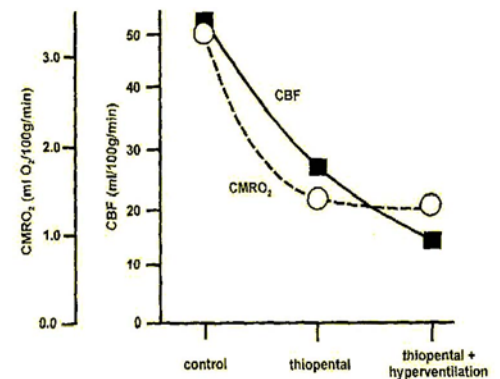
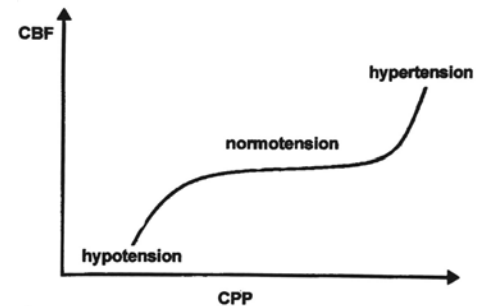
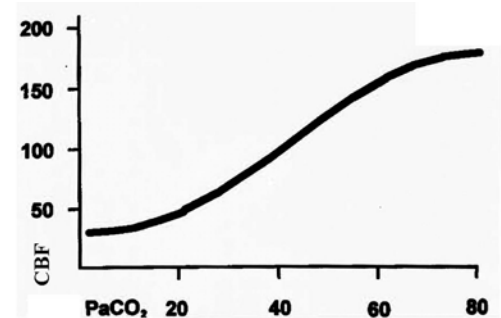
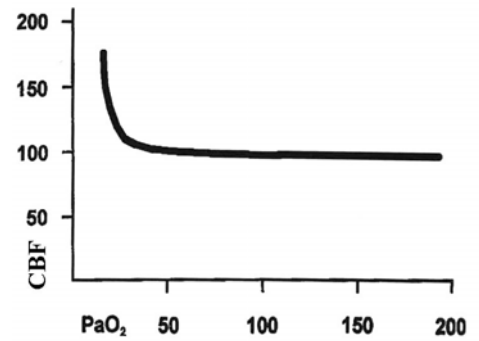
The third largest volume is the blood volume in the brain. The venous system comprises about 2/3 rd's of the 6-8% of the normal intracranial volume. Methods to reduce the venous volume revolve around improving the drainage to the chest cavity by elevating the head, maintaining a neutral neck position (so as to keep draining venous channels open), and minimizing mean intrathoracic pressure. Clearly there are limits to these effects such as reducing the MAP (notable the blood pressure at head level) by the head up position), or reducing positive end expiratory pressure (PEEP) that may be needed to maintain oxygenation (especially with neurogenic pulmonary edema).

The arterial volume is the smallest volume of the normal brain (about 2% total intracranial volume) but potentially the most important to the anesthesiologist as physiological maneuvers can have very prompt beneficial effects and this is the location of the primary anesthetic effects. Physiological control of Oxygenation, ventilation and blood pressure become key with the swollen brain.

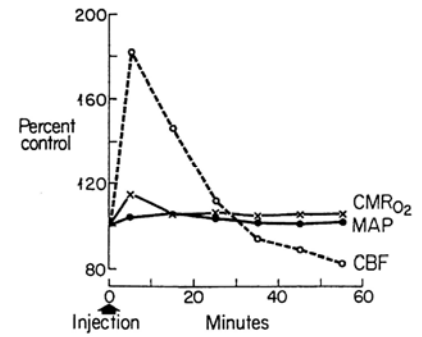
Inadequate oxygenation (PaO₂ values below 50 mmHg) is associated with massive cerebral vasodilation which cannot be overcome with other maneuvers. (Fig 1).

Hyperventilation has long been recognized as a beneficial effect in reducing brain bulk by reducing arterial volume. Here a shift in pH causes cerebral arterial constriction or dilation such that acute hyperventilation will reduce ICP. However excessive hyperventilation can potentially contribute to arterial ischemia by excessive constriction. Prolonged hyperventilation will loose its effectiveness as the renal correction of the pH will restore normal arterial tone. Hence, current recommendations are for limited hyperventilation (PaCO 25-30 mmHg) for short durations when needed to control ICP or brain bulk with restoration of normal ventilation when possible so that hyperventilation can be used later if needed. Unfortunately, hypoventilation results in vasodilation that, like ischemia, is not overcome by other methods.

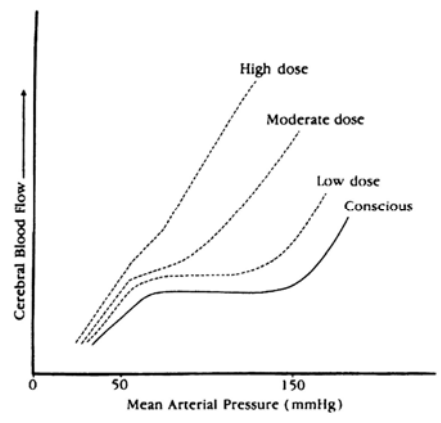
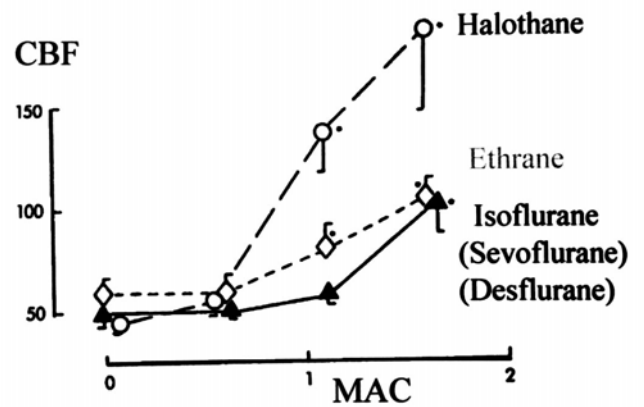
The effect of blood pressure and autoregulation of the brain results from the normal brains ability to regulate cerebral blood flow (CBF) to a "set point" that matches metabolism. Hence, for a given cerebral metabolic rate the brain regulates cerebral arterial tone to adjust flow as CPP changes. This results in vasodilation as CPP falls and vasoconstriction as CPP rises. Since maximal limits of vasodilation (generally CPP 50-60) and constriction exist, the typical autoregulatory curve exists. It is important to recognize that a lowering of CPP will cause arterial dilation that will result in increased brain bulk and/or increased ICP such that maintenance of adequate MAP is very important when ICP is elevated or the brain is swollen.



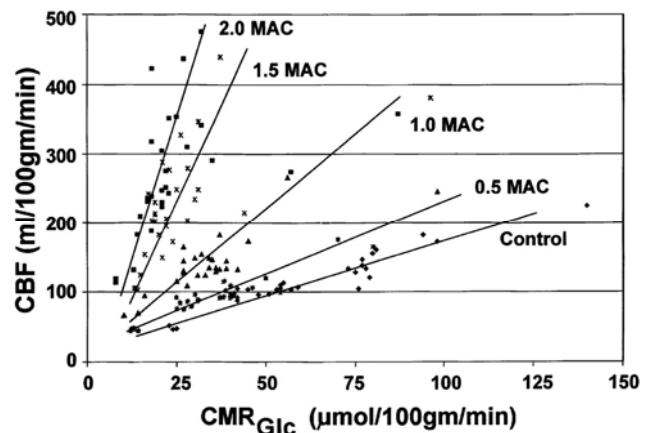
The arterial volume is where the majority of anesthetic effects occur. Much of the effects can be understood by the effect on metabolism and autoregulation. For example most intravenous sedatives (e.g. thiopental, propofol, and etomidate) decrease metabolism through depression of synaptic activity. This reduction results in a lowered CBF by a reduction in arterial diameter and therefore lowered brain bulk. Other drugs, such as opioids, have a more benign effect on metabolism causing little effect. Hence, to the extent that these medications do not compromise the MAP they are desirable agents when ICP is high or the brain is swollen. Hypothermia has been shown to decrease ICP and CBF, however, acute use of mild temperature reductions in the operating room has not been shown to be of benefit. Ketamine is undesirable in that it increases CBF by several mechanisms (e.g. changes in transmembrane Calcium flux, a cholinergic effect) and stimulation of metabolism). Opposite to this is indomethacin which is a cerebral vasoconstrictor, probably acting through astrocytes. The mechanism is unknown and it is unclear if it relates to inhibition of cyclo-oxygenase activity since other inhibitors do not lower ICP. These effects suggest that intravenous anesthetic agents (with the exception of ketamine) are excellent choices for the swollen brain; recommendations for indomethacin are not clear.



The effect of the inhalational anesthetic agents is the net effect of the metabolic depression of the synaptic effects and the changing of the CBF set point for a given metabolic rate (as the partial pressure increases there is a corresponding increase in the CBF set point so that CBF increases with increasing concentrations). This gives rise to a change in the autoregulatory curve that appears to suggest that autoregulation is “disrupted.” Isoflurane, desflurane and sevoflurane have the most favorable profile as the metabolic depression at lower partial pressures offsets the increase in CBF that would otherwise occur. Hence CBF, brain bulk from arterial vasodilation, and ICP will not rise in the normal brain until inhaled concentrations exceed 1 MAC. On the other end of the spectrum is halothane (which has less metabolic suppression) where CBF increases occur above ½ MAC and Nitrous Oxide which little metabolic suppression (and may actually increase metabolism in man). These effects suggest that inhalational agents should be utilized in limited concentrations or replace with intravenous agents when ICP or brain swelling issues are paramount.



Although the major anesthetic issues appear to revolve around the effect on CBF described above, anesthetic agents also have effects on CSF



production and absorption. Best summarized by Artru (see suggested reading), the net effect on ICP through CSF mechanisms appears to parallel the effect on CBF.

Fluid Management in Intracranial Surgery

Fluid management is extremely important in the management of the swollen brain to reduce brain bulk and/or lower ICP because of the large volume represented by the tissue water in the skull. As above, the normal brain becomes key for management as pathologic mechanisms may prevent normal water regulation in abnormal tissue. Before discussing fluid choices it is important to note that glucose management is key in fluid choices as unneeded glucose can enter the brain tissue passively and contribute to worsened cellular injury (hence glucose is normally withheld from fluids unless hypoglycemia exists).

Water regulation in the brain tissue differs from the remainder of the tissues in three key respects. First, the 0.7-0.9 nm pore sizes for water and solute transfer at the endothelial blood brain barrier allow water passage but do not allow electrolyte transfer. As a consequence sodium concentrations in the blood create an osmotic effect that regulates net water transfer since it is the major electrolyte. In the other tissues, the 4-5 nm pore size allows electrolyte passage such that electrolytes do not play such a role. This coupled with the second major difference, no lymphatics to drain excess fluid from the brain (all fluids must drain to the CSF), means that the brain functions as an osmometer and that normonatremic fluids are exceptionally important to preventing unnecessary fluid transfer to the brain tissue. Hypernatremic fluids have been used to dehydrate the brain, however, the potential adverse consequences appear to outweigh any potential benefits.

The third major difference is the compliance of the brain and peripheral tissues to colloids which are impermeable in both the brain and periphery. In the brain a tight network of glial cells results in a very low compliance to colloids. In the periphery the compliance is much greater so that tissue swelling can become rather marked due to changes in colloid oncotic pressure. As such, increases in oncotic pressure have minimal effects in the brain; osmotically the normal 20 mmHg osmotic pressure created by colloids is minimal compared to the 5,560 mmHg of sodium and compliance is such that little brain swelling will occur as colloid pressure falls. As such manipulation of colloid pressure by dehydration or administration of colloids will not markedly change brain swelling. To the contrary, the maintenance of adequate blood volume and blood pressure may make adequate hydration and the use of colloids advisable to maintain brain perfusion. In this regard the brain appears to regulate its water content differently from the body such that rats dehydrated to near death still have normal water content demonstrating that dehydration is not beneficial. However, with pathology excessive fluid administration can contribute to edema.

It is important to reiterate that the preceding discussion relates to the regulation of brain volume in the normal brain whose change will generally be used to compensate for an inability to decrease swelling in abnormal tissue. In the next section we will explore the derangements in the most common pathologies that lead to the clinical problem of brain swelling.

Management of Selected Pathology

The most common pathologies lead to one of two types of pathologic circumstances that contribute to brain swelling by edema formation. These are best understood by considering brain tissue to be divided into two basic compartments. First is the intracellular compartment which is regulated by the cellular membrane. Second is the extracellular compartment which is regulated by the blood brain barrier. As such most pathology can be divided into derangements in these

compartments. Vasogenic edema is the result of permeability of the blood brain barrier (BBB) leading to welling in the extracellular compartment and cytotoxic edema is a derangement in the cellular regulation of water leading to intracellular water accumulation and swelling.

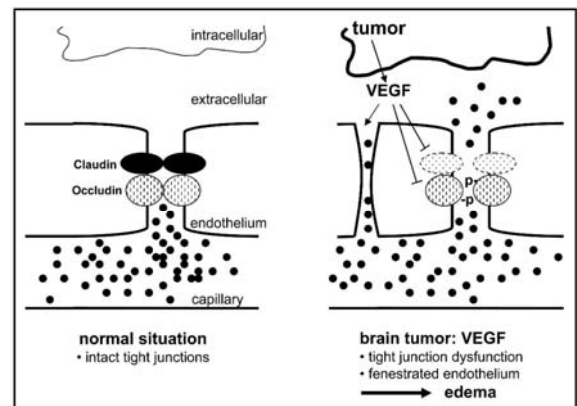
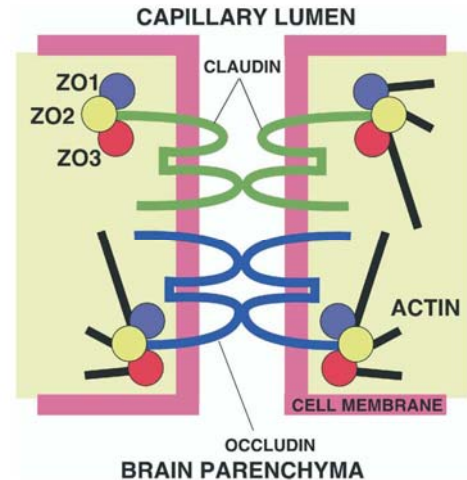
Brain Tumor Edema

The typical example of vasogenic edema is the brain swelling that occurs within and surrounding brain tumors. In this case the BBB becomes permeable to electrolytes and proteins as the tight junctions open as a consequence of vasoactive mediators (e.g. leukotriene C4, other inflammatory mediators, and VEGF: vascular endothelial growth factor) secreted by all tumors to produce angiogenesis. This results in protein rich exudates in the interstitial space with no cellular swelling. This is generally predominant in the white matter because of lower resistance to water flow (tissue compliance). This also occurs surrounding inflammatory masses such as abscesses and with head trauma where various mediators are released leading to vasogenic edema (e.g. glutamate, lactate, nitric oxide, arachadonic acid and its metabolites, free oxygen radicals, histamine and kinins).

The opening of the BBB relates to the down regulating of the proteins occludins, claudins, and the junctional adhesion molecules in the tight junctions whose presence is largely regulated by astrocytes whose end feet surround the microvessels. These transmembrane proteins bind intracellular proteins such as ZO-1 and ZO-2 which bind the tight junctions to the cytoskeleton of the endothelial cells. The reduced expression of these proteins as a consequence of VEGF is suggested to open the BBB. Further, there appear to be a reduced number of astrocytes within the region of an aggressive tumor bed. Other factors in opening the BBB have been suggested to be aquaporin-4 which is highly upregulated in high-grade gliomas. It is unclear if this change contributes to edema or the clearance of edema fluid to the CSF, however it should be noted that it is normally the major method for eliminating water from the brain.

In this form of edema, this area of the brain is unable to sustain any osmotic gradient and water and electrolytes passes freely into the interstitial region. The net transfer of fluid relates to the tissue compliance and the cerebral blood flow and the hydrostatic pressure. Hence agents (ketamine, inhalational agents) and physiologic changes which increase CBF will increase this form of edema. Further, overhydration can increase the interstitial fluid accumulation, especially if the osmotic gradient is disturbed. Hypertension can lead to increased hydrostatic pressure leading to increased water transfer and edema.

Glucocorticoids, likely through their effect on stabilizing the BBB possibly by mimicking the normal control mechanisms of the astrocytes, have a rapid (less than 1 hour) beneficial effect on this swelling and can markedly improve function in the non-anesthetized patient since the edema may contribute more to the clinical dysfunction than the tumor. These agents may also reduce VEGF and the production of the inflammatory mediators that produce the vascular derangements leading to the edema. Of note, the effect on the BBB may reduce the probability of



chemotherapeutic agents to enter into the tumor and the hyperglycemic effect may contribute to ischemic injury.

Although mannitol may be used to reduce the normal brain bulk so that the overall brain swelling is reduced, mannitol will not work in the edema area because the loss of an intact BBB will not allow the development of an osmotic gradient. In fact, mannitol may contribute to opening of the BBB and by diffusing into the interstitium a rebound swelling may occur. Obviously these effects are less important if surgery is being conducted to remove the tumor.

Hence, when brain swelling is predominantly vasogenic, as with brain tumor edema, important considerations include avoiding increases in CBF through physiologic and anesthetic choices, avoiding overhydration and hypertension, and maintaining the beneficial effects of glucocorticoids. Since reducing the edema is difficult, reducing the whole brain bulk will require management of the normal brain.

Ischemic Injury

The typical circumstance leading to cytotoxic edema is cellular injury from ischemia. Certainly processes such as head injury can also lead to ischemic injury. The primary event appears to be a loss of intracellular energy homeostasis. This could occur from intracellular injury or from a lack of adequate CBF (energy failure usually occurs when CBF falls below 10 cc/min/100gm) as may occur during brain injury or cardiac arrest.

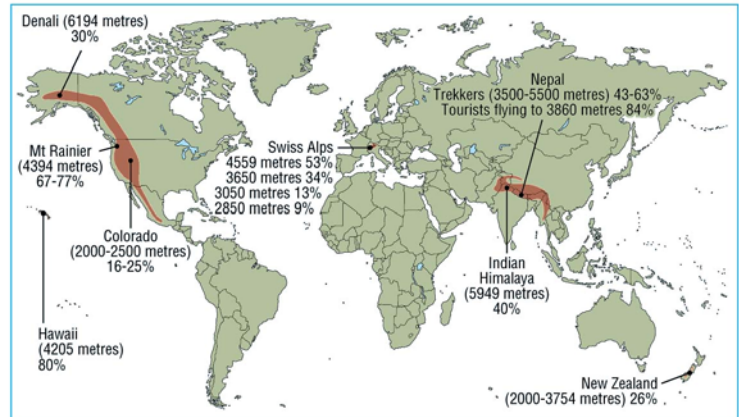
With ischemia from low CBF (such as trauma), edema can occur within a matter of minutes following energy failure. Initially the edema involves a shift of extracellular water into the cells with no net brain water change in the first hour. Eventually (at least 3-6 hours in some studies the extracellular water is restored and some vasogenic edema may eventually occur as the CBF is restored. With traumatic injury the predominant edema is thought to be cytotoxic.

In this case the cell loses its ability to regulate intracellular water content and the cell swells (predominantly astrocytes). This is likely a consequence of dysfunction of ATP-dependant sodium pumps with increased Na⁺ and K⁺ permeability, uptake of osmotically active solutes leading to the passive accumulation of these substances (and associated water) that would normally be actively excluded from the cell. A second mechanism likely involves the aquaporin4 (AQP4). This bidirectional water pore moving water along osmotic gradients is linked to the Kir4-1 potassium pore and water is actively excreted with K⁺ influx ("siphoning"). With dissociation between these transport pores and energy failure water can enter the cell passively, a function which may explain the lack of benefit of glucocorticoids or furesomide on cellular water content. As a consequence astrocytes and neurons accumulate water without increases in protein content. Since astrocytes cells outnumber neurons (20:1), and can swell to 5 times their normal size, the astrocytes are the predominant contribution to the edema. Because the cytotoxic injury is predominantly cellular phenomena, it is seen more prominent in the grey matter where the concentration of cells is higher.

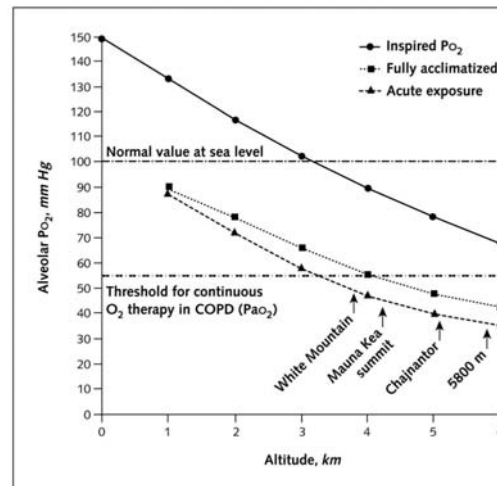
Management objectives with cytotoxic injury should focus on methods to maintain the viability of the neural tissue which is at risk (especially the penumbra). If the edema is solely cytotoxic, the net brain swelling may not be excessive as the extracellular volume may be contracted. However, as the pathology unfolds (such as with trauma), vasogenic edema will contribute to brain swelling and the issues above will also be of concern.

Cerebral Edema with High Altitude Sickness

Brain swelling with high altitude sickness is common in people ascending to more than 2500 meters (16-25% climbers at Vail the altitude, approximately 2500 meters), especially if the ascent is rapid and above 3500 meters. Usually occurring with 6-12 hours and benign, most illness (“mountain sickness”) is mild and short lived consisting of headache, nausea or vomiting, anorexia, fatigue or weakness, dizziness or lightheadedness, and difficulty sleeping. These symptoms are largely due to cerebral edema (with more severe forms being related to pulmonary edema) and resolve within 1-3 days (the insomnia may persist). This has been termed high-altitude cerebral edema (HACE).



The common pathophysiologic process of hypobaric hypoxia, (at Vail the barometric pressure is about 572 mmHg with an inspired PO₂ 110 mmHg, and an estimated alveolar PO₂ of 68-70 mmHg). This produces a neurohumoral response (possible induced through hypoxia inducible factor-1 complex) and a hemodynamic response that results in an overperfusion of cerebral microvascular beds, elevated hydrostatic pressure, capillary leakage and edema (vasogenic edema). Possible mediators opening the BBB may include VEGF, nitric oxide synthetase and bradykinin. Some studies suggest that all persons have some degree of cerebral edema and that high altitude illness may depend on an individuals ability to compensate for the edema (perhaps those with a higher % of CSF are better able to compensate for the edema).



Headache appears to be related to the vasodilatation or its effectors (e.g. nitric oxide) perhaps through the trigeminovascular system. The headache may lead to the nausea and malaise that is often seen. Ibuprofen (400-600 mg) or aspirin (325 mg every 4 hours for three doses) has often resolved the headache..

The normal accommodation process helps reduce the edema. Hyperventilation causes a respiratory alkalosis that increases the CSF pH to reduce CBF for 2-3 days until renal compensation. An increased Hct (dehydration from hyperventilation in dry cold air) increases oxygen delivery and reduces CBF by viscosity changes, and polycythemia (starts in several days, takes several weeks to stabilize). The acclimatization increases the PO₂ by about 10 mmHg within several days. Symptoms can usually be successfully treated using acetazolamide (250 mg three times daily) or dexamethasone (8 mg initially, then 4 mg q 6 hr). Acetazolamide inhibits carbonic anhydrase reducing CSF formation and stimulating the respiratory drive via bicarbonate diuresis thus raising PaO₂. It also promotes ion transfer across the BBB. The glucocorticoid dexamethasone appears to block VEGF, inducible nitric oxide and lipid peroxidation which helps restore normal BBB function.

When severe, the cerebral edema can progress with signs of mental impairment or a change in behavior. Headache, nausea and vomiting can progress to ataxia, hallucination and disorientation; seizures are uncommon. It can lead to papilledema and retinal hemorrhages, coma and death (1:10,000 climbers at 2500 meters). Generally coma usually takes several days and may be the result of cytotoxic edema produced by hypoxic injury. Severe cases also may have pulmonary edema which appears to be formed by similar breakdown in microvascular wall integrity and pulmonary hypertension. The treatment of choice for severe illness is supplementary oxygen and descent to lower altitudes (interestingly as little as 500 to 1000 meters will help but more may be required for resolution of cerebral and pulmonary edema).

Suggested additional reading

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