Short-term responses of the kidney to high altitude in mountain climbers

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ABSTRACT

In high-altitude climbers, the kidneys play a crucial role in acclimatization and in mountain sickness syndromes [acute mountain sickness (AMS), high-altitude cerebral edema, high-altitude pulmonary edema] through their roles in regulating body fluids, electrolyte and acid–base homeostasis. Here, we discuss renal responses to several high-altitude-related stresses, including changes in systemic volume status, renal plasma flow and clearance, and altered acid–base and electrolyte status. Volume regulation is considered central both to high-altitude adaptation and to maladaptive development of mountain sickness. The rapid and powerful diuretic response to the hypobaric hypoxic stimulus of altitude integrates decreased circulating concentrations of antidiuretic hormone, renin and aldosterone, increased levels of natriuretic hormones, plasma and urinary epinephrine, norepinephrine, endothelin and urinary adrenomedullin, with increased insensible fluid losses and reduced fluid intake. The ventilatory and hormonal responses to hypoxia may predict susceptibility to AMS, also likely influenced by multiple genetic factors. The timing of altitude increases and adaptation also modifies the body’s physiologic responses to altitude. While hypovolemia develops as part of the diuretic response to altitude, coincident vascular leak and extravascular fluid accumulation lead to syndromes of high-altitude sickness. Pharmacological interventions, such as diuretics, calcium blockers, steroids, phosphodiesterase inhibitors and β-agonists, may potentially be helpful in preventing or attenuating these syndromes.

Keywords: acclimatization, altitude, kidney, mountain sickness, physiology

INTRODUCTION

It is not the mountain we conquer but ourselves.
—Sir Edmund Hillary.

The question, ‘Why do you want to climb Mt. Everest’, posed to British mountaineer George Mallory in a 1923 interview after the failure of two earlier summit attempts, elicited the famously curt response, ‘Because it’s there’ [1]. Mallory continued, ‘Sometimes science is the excuse for exploration. I think it is rarely the reason’. In subsequent interviews, he elaborated on this interpretation of science as a ‘challenge’, an ‘adventure’ and ultimately, as ‘just sheer joy’. Mallory’s next attempt on Everest in 1924 led to his death, his body not to be found until 60 years later. Nonetheless, the joy and the challenge of climbing high mountains have continued to draw prospective mountaineers in ever-growing numbers to the slopes of the Himalayas, the Andes and other high peaks. Many of these climbers are experienced, but the remarkable evolution of climbing equipment and clothing through the decades has facilitated high mountain access for the inexperienced, as well. However, the high mountains remain, in 2013 [2, 3] as in 1924 [4, 5] or 1996 [6], a hostile, unpredictable and potentially deadly environment.

The increased accessibility of high mountains to the sea-level population demands a better understanding of the acute physiological adaptation to high-altitude conditions, including cold, unpredictable weather and low barometric pressure [3]. Sea level barometric pressure of ~760 mmHg decreases by 50% at 5800 m altitude, dropping further to 253 mmHg on the 8848 m summit of Mt. Everest [7]. The absence of
permanent human habitation above 5500 m reflects the limits of the body’s ability to adjust to high altitude. These empirical physiological limits underlie the medical categorization of altitude as high (1500–3500 m), very high (3500–5500 m) and extreme (above 5500 m) [8].

The effects of high altitude on humans were first noted long ago [9], and empiric experience has accumulated for many years. The physiology of human adaptation to high altitude has been examined in controlled studies both on high mountain slopes and in hypobaric chambers in the laboratory. The former include the 1960–61 Silver Hut Expedition (Himalayan Scientific and Mountaineering Expedition led by Sir Edmund Hillary) [10], the 1981 American Medical Research Expedition to Everest (AMREE) [11], the 1993 British 40th Anniversary Everest Expedition, the 2002 Silver Pyramid expedition to Nepal [12] and the 2004 Italian expedition to Mt Everest’s North Face, “K2—2004 50 years later” [13]. The best known hypobaric chamber studies are Operation Everest II [14] and Operation Everest III (low-pressure chamber) [15, 16]. West [7] has distilled the results of these and other studies in his description of three different physiologic responses to altitude: acute acclimatization to high altitude (up to 5000 m), evolutionary adaptation in high-altitude dwellers (up to 5000 m) and physiologic response to extreme altitude (above 7000 m).

While pulmonary and circulatory physiology have been the focus of previous studies of acute adaptation to high altitude, less attention has been directed to short-term changes in kidney physiology in response to the stresses of high altitude over periods of hours to days. In this article, we focus on acute acclimatization of sea-level dwellers to high and extreme altitude.

**HIGH-ALTITUDE SICKNESS AND ACCLIMATIZATION**

**High-altitude syndromes**

High-altitude-related health problems include acute mountain sickness (AMS), and the two life-threatening conditions of high-altitude, cerebral edema (HACE) and high-altitude pulmonary edema (HAPE). AMS is relatively frequent, affecting ∼25% of those traveling above 2500 m [17], and is self-limiting if recognized early. Both HACE and HAPE need to be treated aggressively [8]. High-altitude renal syndrome is an asymptomatic chronic condition of high-altitude dwellers defined as high-altitude polycythemia, systemic hypertension, microalbuminuria and hyperuricemia with relatively preserved glomerular filtration rate (GFR) [18, 19].

AMS is typically characterized by headache, gastrointestinal symptoms (anorexia, nausea, vomiting), sleep disturbances, dizziness and fatigue, with clinical severity graded by the Lake Louise AMS scoring system [20]. The symptoms of AMS have been attributed to hypoventilation, impaired gas exchange, fluid retention and redistribution, and increased sympathetic drive.

The pathophysiology of AMS and HACE is not well understood, but seems to be associated with vasodilatation, blood-brain barrier permeability [21] and capillary leakage from microvascular beds resulting in edema. These changes may be influenced by individual responses to inflammation, since resistance to AMS is associated with marked anti-inflammatory and/or anti-permeability responses. However, the opposite is not true, such that exaggerated inflammatory responses are not necessarily associated with predisposition to AMS [22]. The involvement of growth factors in AMS and HACE has been proposed. Increased free plasma VEGF on ascent to altitude is associated with AMS; while soluble VEGF receptor (sFlt-1) is lower in subjects with AMS compared with those without AMS symptoms [23]. However, in a prospective study of climbers on Mount McKinley in Alaska at 14 200 feet, no correlation between plasma VEGF and symptoms of AMS was observed [24]. Thus, while VEGF levels change during acclimatization [25] and ascent to high altitude [26], reports of their involvement in AMS pathogenesis have been inconsistent [27].

HAPE has been attributed to elevated pulmonary artery pressure caused by pulmonary vasoconstriction and leading to non-cardiogenic pulmonary edema [28]. Vasoconstriction and pulmonary edema might be caused by hypoxia, decreased bioavailability of nitric oxide in the lungs, inflammatory processes and by impaired reabsorption of alveolar fluid [29, 30]. The characteristically uneven pattern of pulmonary vasoconstriction suggests uneven perfusion potentially contributing to pulmonary edema [31].

**Hypoxic ventilatory response and acclimatization**

In parallel with the fall in barometric pressure, the partial pressure of oxygen (pO2) in inspired air drops from 149 mmHg at sea level to 43 mmHg at the summit of Everest [7]. The pO2 is ∼39% less at 5800 m than at the sea level. However, during acclimatization to altitude, the symptoms of AMS can subside as the body adapts to hypoxia. Acclimatization is a well-coordinated set of physiological responses to improve tissue oxygenation through specific changes in the respiratory system (increases in pulmonary ventilation and diffusing capacity; Figure 1), cardiovascular system (initial increase in cardiac output; Figure 2), hematologic system (increased erythropoiesis drive by increased renal erythropoietin secretion; Figure 3) and tissue adaptations that enhance tissue oxygen delivery [8] and extraction.

The clinically most prominent physiologic change at high altitude is the hypoxic ventilatory response: hypopnea and tachypnea leading to hypocapnia [32]. Hypoxia may trigger several receptors, including airway chemoreceptors [33]. Tissue hypoxia also induces the production of hypoxia-inducible factor (HIF) transcription factors [34, 35] likely involved in long-term adaptation. Further adaptive processes include an increased mean number of capillaries per unit area of the muscle fiber [36] due either to net increase in capillary density and/or to muscle wasting, leading to an increased ratio of capillary density/muscle fiber [37]. Other adaptive mechanisms to tissue hypoxia involve changes in metabolic pathways including oxidative metabolism, cell cycle and diminished myogenesis [38] and changes in hemoglobin oxygen affinity that would affect arterial oxygen saturation and release to tissues [39, 40]. Changes in mitochondrial number and in cytochrome oxidase have been described during chronic or relatively long-term exposure [41, 42], but mitochondrial function is largely unaltered during short-term (7–9 days)
exposure to high altitude [43]. This review considers altitude-induced adaptation mechanisms associated with volume regulation and diuretic response, central to short-term adaptation to altitude, but not long-term adaptation mechanisms (e.g. increased blood flow, vasodilation and increased concentration of NO products described in Tibetians living at high altitude [44]).

FIGURE 1: The process of respiratory system acclimatization to high altitude: responses to hypoxia that should improve tissue oxygenation through increased pulmonary ventilation and diffusing capacity.

FIGURE 2: Cardiovascular adaptations to altitude.

RENAL PLASMA FLOW AND CLEARANCE AT ALTITUDE

Residence at high altitude leads to several renal changes in high-altitude dwellers, including reduced renal plasma flow with preserved GFR due to increased filtration fraction [45, 46] and glomerular hypertrophy [47]. However, during relatively short-term exposure to altitude in mountain climbers, the effect of altitude on renal plasma flow and glomerular filtration rate remains controversial. In some reports, high altitude did not change effective renal plasma flow and GFR [48], whereas other studies demonstrate a significant change. Swenson [49] postulated that hypocapnic hypoxia may elevate renal blood flow by 5–10%, however decreased GFR [50, 51] and renal plasma flow have been demonstrated by others. Effective renal plasma flow decreased 38% upon moving from sea level to 5800 m, as blood viscosity increased to the same degree [52]. A more recent study in 34 healthy mountaineers on expedition to China to climb Muztagh Ata Mountain (7549 m) also demonstrated decreased renal function after ascent from low to high altitude [51]. Blood was sampled at five altitudes: Zurich pre-expedition (450 m), base camp (4497 m), Camp 1 (5533 m), Camp 2 (6265 m) and Camp 3 (6865 m). GFR was estimated from cystatin C and creatinine measurements (Mayo Clinic quadratic equation). Estimated GFR decreased significantly from pre-expedition to just before Camp 3 with a linear decrease of ~3.1 mL/min/1.73 m² per 1000 m increase in altitude, and varied inversely with Lake Louise AMS scores [51].
Changes in electrolytes concentration (e.g., calcium, phosphate, sodium) as well as acid-base status have been observed in high altitude climbers. Acclimatization at high altitude was accompanied by decreased plasma calcium and phosphate concentrations in the setting of increased PTH levels [53]. Climbing or trekking to high altitudes was also associated with decreased plasma concentrations of sodium and bicarbonate, without change in plasma potassium and chloride concentrations. Hypoxic and exertional hyperventilation is associated with hypocapnic respiratory alkalosis, reflected in increased mixed venous blood pH from a value of 7.34 at sea level to 7.43 at 3500 m and sustained alkalosis at 5800 m [52]. Arterial pH at the summit of Mt Everest has been estimated at 7.7–7.8 [54]. Indeed, in a study of Everest climbers, the mean PaCO2 levels gradually decreased from 36.6 mmHg at sea level to 20.4 mmHg at 5300 m, 18.2 mmHg at 6400 m and 16.7 mmHg at 7100 m, with respective arterial pH values of 7.40, 7.46, 7.51 and 7.53 [55].

Although the exertion of climbing in hypoxic conditions might theoretically increase plasma lactate from increased anaerobic metabolism, little if any elevation of plasma lactate was observed [7]. The respiratory alkalosis produced by hypoxia at altitude promotes compensatory increases in renal bicarbonate excretion. This renal adaptation is completed within 24 h at low-to-moderate altitude. However, the time to achieve a new steady state for bicarbonate excretion is thought to be longer at higher altitudes, an effect attributed to the inhibition of renal tubular H+ secretion [56]. Blood gas analyses of 1865 residents living at 3510 m revealed normal pH [57] in contrast to the alkalemia and hypocapnea observed after short-term exposure [58].

In addition, a dramatic physiologic perturbation in response to altitude is an altitude-induced diuresis, which seems to be an obligatory early phase of adaptation to altitude. Hypoxia and respiratory alkalosis (secondary to hypoxic tachypnea) may promote increased natriuresis, water diuresis and fluid shift away from intravascular space. The attendant increases in renal excretion of sodium and water associated with 25–50% reduction in inspired O2 [61] have been described as the 'hypoxic diuretic response'. The hypoxic diuretic response is triggered within hours of exposure to hypoxia [62–65], but prolonged hypoxia leads to restoration of renal sodium and fluid excretion rates at or below the sea level baseline [48, 66, 67]. The initial part of the hypoxic diuretic response in humans occurs without natriuresis [63], and its mechanism is unknown. Possibilities include reduced urinary concentrating ability due to increased medullary hypoxia reducing active chloride reabsorption by the medullary thick limb [68, 69], an acute decrease in circulating antidiuretic hormone (ADH) [70] with potentially decreased ADH sensitivity of the collecting duct.

This initial phase is followed by a coordinated humoral response involving norepinephrine, renin and ADH [71] (Figure 4), triggered by hypoxia-induced chemoreceptor stimulation. The response is mediated by increased atrial natriuretic peptide (ANP) and suppressed ADH [48, 63, 64], leading to inhibition of renal sodium reabsorption despite low water and sodium intake [72], and to a natriuretic diuresis [48, 63, 64]. However, Swenson et al. [65] argued against roles for aldosterone, renin, ANP and ADH in the hypoxic diuretic response, based on the correlation between the hypoxic ventilatory response (invoked as a measure of chemoreceptors sensitivity) and hypoxic diuresis [65, 73]. They postulated chemoreceptor activation as the trigger for the hypoxic diuretic response, but the mechanism for activation of diuresis was not described [65]. Complicating these considerations is the apparent non-linearity of the hypoxia–diuresis relationship. Thus, Swenson [49] reported the absence of diuresis for FiO2 >0.16, dramatically increased diuresis by FiO2 between 0.12 and 0.16, but further decreases in FiO2 below 0.12 are antidiuretic and anti-natriuretic.

Finally, hypoxia acts directly in the kidneys to increase local production of endothelin and adrenomedullin [12, 74],
leading to suppression of circulating ADH, renin and aldosterone. These processes together can decrease total body water by 1–3 L [61], a loss reflected in the previously described 38% increase in blood viscosity at 5800 m, followed by 38% decreased viscosity upon return to sea level [52].

However, the phenomenon of hypoxia-induced diuresis is still debated, since the diuresis has been attributed entirely to respiratory alkalosis. Respiratory alkalosis enhances both renal sodium excretion and extravascular fluid shift, by mechanisms independent of hypoxia. A plasma volume reduction of 13% [75, 76] is caused at least in part by compensatory renal excretion of bicarbonate, accompanied by a significant urinary sodium loss [77]. Additionally, contributing to the hypovolemia is a shift of protein-poor fluid into the extracellular compartment that has been attributed to enhanced capillary permeability and/or increased capillary hydrostatic pressure [75, 76]. This is clinically expressed as peripheral edema or, in severe cases, pulmonary and cerebral edema. Thus, high-altitude-induced hypovolemia can be harmful, but might it also be adaptive? Or should intravascular volume be expanded at the high altitude?

**FIGURE 4**: Mechanisms of the hypoxic–diuretic response leading to decreased plasma volume.

**HUMORAL MECHANISMS OF PLASMA VOLUME REGULATION**

**Atrial natriuretic peptide, brain natriuretic peptide and antidiuretic hormone**

Exposure to high altitude has been shown to promote release of ANP and suppression of ADH secretion, both leading to diuresis [64]. In contrast, in the hypobaric chamber, during Operation Everest 3 (6000 m), plasma atrial natriuretic factor was lower at high altitude than at sea level [16], and in eight climbers at 4559 m, ANP levels were unchanged [50]. A possible explanation for the variable results came from the demonstration of acute but transient elevation of ANP [78], consistent with the early and transient nature of the high-altitude diuretic response.

Brain natriuretic peptide (BNP) levels have also been reported to increase after exposure to altitude. In 32 healthy subjects at 5150 m, plasma BNP was on average significantly higher than at lower altitudes. However, not all subjects demonstrated increased BNP levels, and those with increased BNP also exhibited significantly higher Lake Louise AMS scores, suggesting BNP as a marker for pathological fluid retention, predicting and possibly promoting development of AMS [79].

The association of acclimatization with decreased circulating volume might predict that ADH levels should fall at high altitude. Indeed, within 90 min of hypobaric exposure, ADH levels decreased in those who eventually acclimatized successfully. In contrast, ADH levels increased in those who later developed AMS, with the extent of rise correlating with AMS severity [80]. A reduction in renal sensitivity to ADH after 2 days of exposure to high altitude has also been reported [81]. In another study, baseline ADH levels at sea level and at 4300 m were similar in seven healthy males, despite altitude-related increases in plasma osmolality. However, during 24 h water deprivation, the maximal ADH elevation was increased compared with that at sea level. The authors concluded that hypoxia appeared to alter ADH regulation by raising the osmotic threshold and increasing ADH responsiveness above that threshold [81].
**Renin–aldosterone–angiotensin system**

High altitude was associated with decreased plasma concentrations of renin and aldosterone [48, 50], suggesting that hypoxia-induced chemoreceptor stimulation may promote natriuresis through direct suppression of the renin–aldosterone–angiotensin system [78]. While this effect was largely unresponsive to exercise [78], high-altitude exercise-induced increases in plasma aldosterone and ADH were greater in those subjects who subsequently developed AMS during a 3 day sojourn at 4559 m than in those who remained well [82].

However, when subjects in the Operation Everest 3 study exercised to exhaustion after 10 days of simulated high altitude, plasma renin and aldosterone were unchanged compared with initial baseline sea level values, perhaps reflecting normalization of the hypoxic diuretic response. Renin and aldosterone levels in this group after return to sea level were higher than at initial baseline, in parallel with the normal re-expansion of plasma volume [16].

However, other studies reported no significant correlations between plasma levels of ADH, aldosterone, urodilatin, or ANP and diuresis or natriuresis [63, 83]. The variable hormonal responses might reflect variable proportions of subjects prone to AMS, in whom the humoral response seems more vigorous than in those less likely to be ill [82, 83]. The magnitude of hormonal responses may also reflect high-altitude exposure duration.

**Epinephrine and endothelin-1**

Hypoxia of high altitude is associated with slight increases in plasma and urinary epinephrine, which also could play a role in the hypoxic diuretic response [63, 48]. Exercise also gradually increased plasma norepinephrine [48], suggesting that these changes at high altitude might reflect increased adrenosympathetic activity [48].

Endothelin-1 also contributes to the hypoxic diuretic response [63]. Endothelin levels doubled during an 8-day exposure to 4559 m [50] and appeared to contribute to high-altitude acclimatization [74]. Healthy volunteers were randomly assigned in a double-blind fashion to receive the endothelin receptor antagonist bosentan or placebo at sea level, and after rapid ascent to high altitude (4559 m). Exposure to high altitude was followed by increased urinary excretion of endothelin-1 (likely nephrogenic), in parallel with increased diuresis and increased clearance of water and sodium. However, these diuretic effects were blunted by bosentan [74], suggesting possible inhibition by endothelin-1 of ADH-stimulated water reabsorption by the collecting duct (Figure 4). Bosentan may be helpful when used early in reducing pulmonary hypertension at high altitude [84] but potentially detrimental for volume adaptation. Endothelin-1 has been shown to inhibit vasopressin-stimulated cAMP accumulation in and water transport by isolated cortical collecting ducts [85]. The activated endothelin B receptor may also promote diuresis by inhibition of Na⁺–K⁺–ATPase activity in the inner medullary collecting duct [86].

**Adrenomedullin**

The role of adrenomedullin was studied in climbers of the 2002 Silver Pyramid project [12]. The authors demonstrated increased diuresis and natriuresis on transition from low-to-moderate altitude (~3500 m) and further diuresis and natriuresis with subsequent progression to high altitude (~5000 m), in parallel with increased urinary adrenomedullin concentration. Urinary (but not plasma) adrenomedullin concentration correlated directly with diuresis, urine sodium and urine osmolality [12], consistent with substantial adrenomedullin production by the kidney [87, 88]. Adrenomedullin release was increased by hypoxia [89] both in hypoxia-sensitive renal parenchyma and in vascular cell cultures [90]. Adrenomedullin decreased ADH and aldosterone levels [91]; in addition, it directly affects the kidneys raising renal blood flow, diuresis and natriuresis. Adrenomedullin also inhibited renal sympathetic nerve activity but increased renin release in a paracrine fashion [92] (Figure 4). The related, hypoxia-inducible and ischemia-protective peptide intermedin (adrenomedullin-2) [93] has not been studied in relation to altitude adaptation.

**ASSOCIATION BETWEEN VOLUME STATUS AND AMS: ADAPTIVE OR MALADAPTIVE?**

**Risks and benefits of hypovolemia at high altitude**

As described above, one of the most remarkable changes in response to brief exposure to high altitude is diminished plasma volume. While hypovolemia makes sense from the perspective of an increased oxygen-carrying capacity of concentrated blood [94], this is popularly described as ‘dehydration’. Climbers are encouraged to drink more and consume more salt to counter dehydration, potentially promoting interstitial fluid accumulation, edema and, less frequently, AMS. Furthermore, the usual recommendations of aggressive fluid intake and use of the diuretic acetazolamide have not been well justified (although acetazolamide likely acts through additional mechanisms beyond its diuretic effect [95]). It remains unknown whether the altitude-induced decrease in plasma volume is adaptive or potentially harmful. If adaptive, then less effort should be made to correct ‘dehydration’, and fluid intake should be limited to simply following the thirst mechanism and to offsetting insensible losses (admittedly difficult to estimate, much less measure, on the mountain). Indeed, as discussed above, fluid retention rather than dehydration is associated with AMS [83]. Perhaps diminished plasma volume is part of the body’s effort to supply oxygen to the most vital organs, overriding the not insubstantial risks of hyperviscosity and thrombosis associated with hemoconcentration [96].

Swenson [49] has proposed two beneficial effects of high-altitude diuresis: (i) early hemoconcentration elevates the blood concentration of hemoglobin prior to the slower onset of EPO-stimulated erythropoiesis; (ii) volume depletion reduces intravascular pressure and volume load on the lungs and brain, and may decrease renal oxygen consumption (90% of which reflects renal sodium reabsorption) due to diminished filtration. Under normal circumstances, the latter statement might be debatable, as volume depletion may in fact increase oxygen consumption to minimize fractional excretion of sodium by maximizing sodium reabsorption.
Who develops AMS

Individuals differ in their responses to altitude and hypoxia, but 50–90% of the general population are believed to be susceptible to AMS [97]. Individuals who acclimatize better tend to exhibit a less profound ventilatory response to hypoxia (i.e., a measure of chemoreceptors sensitivity), whereas those with a strong hypoxic ventilatory response also exhibited high diuretic and natriuretic responses [65, 73]. These observations are consistent with fluid retention being important to AMS pathogenesis [83]. Those who remained well exhibited diuresis unaccompanied by changes in plasma renin activity, aldosterone, or ANP, and fluid intake that symptomatically did not exceed fluid output [83]. In contrast, those who developed AMS and retained fluid showed an inadequate diuretic response, as judged by failure to decrease ADH levels [80], with greater increases in exercise-induced plasma aldosterone and ADH [82]. The higher magnitude of BNP increase has also been associated with greater likelihood of developing AMS [79]. Thus, a pronounced hormonal response to hypoxia might predict predisposition to AMS [65, 98].

Susceptibility to AMS might be dependent on multiple genetic factors. Genetic adaptation to altitude has been postulated [18] based on polymorphisms in several genes that may play adaptive roles in high-altitude dwellers [99]. Polymorphisms in numerous genes, including the hypoxia-responsive transcription factor subunit EPAS1/HIF2α [100, 101] and additional genes in the HIF pathway linked to hemoglobin level, have been associated with differences in susceptibility to or severity of AMS or associated conditions [99, 102], and with adaptation to high altitude among the highland residents of Tibet [100, 103], Dagestan [104] and Ethiopia [105]. A recent, preliminary study of four climbers has identified hundreds of genes with altered transcription after 2 weeks at or above 5600 m (including summiting at 8000 m) [97]. In addition to induction by altitude of known genes related to hypoxic erythropoiesis, this study highlights induction of the stem cell master gene OCT4 as a novel, potential regulator of early erythropoiesis at extreme altitude.

Role of ‘therapeutic’ intravascular volume expansion

The practical question for mountain climbers is whether one should make an effort to expand volume rather than assuming that hypovolemia is physiologic and adaptive. This question was addressed in the Operation Everest 3 study, which subjected eight male subjects to 31 days of the barometric equivalent of Mt Everest (8848 m). Their plasma volume fell 26% at high altitude, and after return to sea level atmospheric pressure, plasma volume exceeded the pre-study baseline by 10%. While in the decompression chamber, the subjects performed maximal exercise without and with plasma volume expansion by 6% Hesteril (hydroxyethylstarch) infused at 4 mL/kg during exercise (219–292 ml) at sea level, at high altitude (equivalent to 6000 m) after 10–12 and 1–3 days after return to sea level. At high altitude, exercise to exhaustion was associated with reduced maximal oxygen uptake by 58% when compared with that at sea level, and maximal oxygen uptake after return to sea level remained 11% below the pre-ascent value. However, plasma volume expansion produced a 19% increase in maximal oxygen uptake. The greater the individual reduction in plasma volume at high altitude, the larger was the increase in maximal O2 uptake by plasma volume expansion [16].

The beneficial results of plasma volume expansion in the Operation Everest 3 study may be specific for the timing of the experiment (7 days at 4350 m followed by 10–12 days into the simulated ascent to peak altitude. By that time, the hypoxic diuretic response had likely subsided, and long-term regulatory mechanisms were likely already activated, including up-regulation of EPO-dependent erythropoiesis with increased red cell mass. Volume contraction might have been beneficial at the start of the simulated trip, but not as important at a later portion of the ‘trip’. In addition, the effect of the oncotic agent Hesteril was intravascular, whereas the standard mountaineer’s oral intake of water and salt distributes throughout intra- and extravascular space. Interestingly, in a similar experiment, autologous erythrocyte infusion did not affect diminished maximal O2 uptake at 4300-m altitude [106].

PRACTICAL CONSIDERATIONS ON HOW TO HANDLE VOLUME

Recommendations should be generated taking into account the altitude anticipated, timing of the trip and the individual climber’s characteristics. The timing and progressive increase in the altitude experienced by those traveling in the mountains may change their physiologic responses and diuretic reactions (Figure 5), such that the therapeutic impact of hydration or diuretics might differ at different times and at different elevations.

AMS and dehydration may represent two poles of the spectrum of body fluid handling in the high mountains. Dehydration at high altitude can be caused by elevated insensible losses, the altitude-related diuresis response, decreased oral intake and the common, prophylactic use of acetazolamide. AMS is characterized by fluid retention and interstitial redistribution. The pattern of this redistribution of body fluid remains unclear (i.e. uniform increase in total body volume versus hypervolemia of interstitium with intravascular volume depletion). In this context, across-the-board recommendations should be generated taking into account the altitude anticipated, timing of the trip and the individual climber’s characteristics.

**FIGURE 5**: These two ‘before and after’ pictures illustrate time-dependent changes in systemic volume status at high altitude. At left, A.S.G.-R. at $\sim$5000 m on trip day 6, when the hypoxic diuretic response was supposedly the predominant adaptation mechanism. At right, A.S.G.-R. at 6094 m on trip day 10, when the climber is more prone to fluid retention.
to drink and expand volume with a high sodium diet are probably inadequate, with the potential to increase the risk of volume overload, edema and AMS.

Thus, increased fluid intake in the initial period of the ascent associated with dehydration might be advisable. Dehydration, which is loss of free water (due to water diuresis and insensible losses), might increase plasma osmolality, with consequent intra- and extracellular volume contraction. Drinking water with minimal added salt (as opposed to products with high salt content) should predominantly distribute into the intracellular compartment with minimal extracellular space expansion.

During the second week at altitude, when the hypoxic diuretic response has run its course and fluid accumulation becomes an issue (Figure 5), water intake should be monitored carefully, and food intake needs to be maintained in the face of likely anorexia. At this point, the use of diuretics might be better justified, although careful monitoring is required in the context of intravascular volume depletion. There is still no good enteral path to acutely increase plasma oncotic activity so as to mimic the oncotic effects of IV Hesteril [16].

Several observational reports of AMS have suggested the effectiveness of pharmacologic intervention, including acetazolamide, ibuprofen, dexamethasone, salmeterol and phosphodiesterase inhibitors [28, 29, 95, 107–111]. The Denali Medical Research Project conducted at the high-altitude research station (4200 m) on Alaska’s Mt McKinley demonstrated that acetazolamide improved pulmonary gas exchange and relieved symptoms in AMS [112]. Proposed mechanisms included: (i) increased diuresis; (ii) increased chemoreceptor sensitivity to hypoxia secondary to bicarbonaturia-induced metabolic acidosis offsetting the respiratory alkalosis of hyperventilation; (iii) enhanced ventilation driven by increased (respiratory) tissue acidosis; and (iv) improved quality of sleep due to carbonic anhydrase inhibition in the carotid body [95]. Acetazolamide administration at 250 mg twice per day was consistently effective for AMS [113], but reports of benefit varied for one per day dosing [112, 114]. Acetazolamide might not be effective in HAPE, as it fails to decrease pulmonary arterial pressure [115].

CONCLUSION

Systemic fluid balance and its renal regulation are at the core of adaptation to high altitude and high-altitude sickness. The initial decrease in plasma volume is a quick and powerful reaction to hypoxia that is based on several mechanisms. The magnitude and characteristics of this response may be helpful in predicting the symptoms of AMS. While hypovolemia develops as part of the hypoxic diuretic response, it is extracellular fluid accumulation, and in more serious cases, vascular leak, rather than systemic water loss, that leads to AMS and other syndromes of high-altitude sickness. Recommendations to avoid mountain sickness should be based on the individual climber characteristics, trip timing and altitude. While the individual response is still largely unpredictable, pharmacological intervention may be beneficial in some cases.

ACKNOWLEDGEMENTS

A.S.G.-R. expresses his appreciation to the esteemed mountain climbers Greg Vernovage (International Mountain Guides, Inc., USA) and the late Dasha Yashina (Asia Mountains, Inc., Russia), for their help and advice during A.S.G.-R.’s climbing trips to the mountains of Bolivia and Pamir. S.L.A. was supported by NIH DK34854 (The Harvard Digestive Diseases Center) and by the Doris Duke Charitable Foundation.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 20.12.2012; Accepted in revised form: 24.1.2013