

Humans at altitude: physiology and pathophysiology



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Key points

High-altitude illness occurs in unacclimatized individuals who ascend too rapidly.

Acclimatization results in restoration of oxygen delivery towards sea-level values.

Acute mountain sickness is common.

Mild symptoms, if ignored, can progress to more serious illness.

High-altitude pulmonary oedema and high-altitude cerebral oedema are uncommon but may be fatal if not managed appropriately.

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This article describes the physiological challenge associated with exposure to environmental hypoxia at high altitude along with adaptive (acclimatization) and pathological (acute high-altitude illness) responses to this challenge.

The challenge: the environment

Barometric pressure (P_B) decreases in a non-linear fashion with altitude, vertical height gain above the Earth's surface. The percentage of oxygen in the atmosphere remains constant (20.9%), but atmospheric partial pressure of oxygen (P_{O_2}) reduces proportionally with P_B . At the summit of Mount Everest (8848 m), the P_B and atmospheric P_{O_2} are about one-third of sea-level values.

An individual acutely exposed to extreme altitude (>5500 m) may lose consciousness. Over 8000 m, this occurs reliably within <3 min.¹ However, if the body is gradually exposed to increasing altitude, it can adapt and survive. This process is called acclimatization. One of the lowest documented arterial partial pressures of oxygen (P_{aO_2}) in a healthy individual is 2.55 kPa, which was taken at 8400 m on Everest.² This measurement demonstrates that with adequate acclimatization, in selected individuals, it is possible to function normally with profound hypoxaemia.

Definitions vary, but high altitude generally refers to altitudes over 2500 m. To put this in context, La Paz (Bolivia) is the highest capital in the world at 3500–4000 m. The increasing number of individuals travelling to high altitude for work or adventure tourism is a public health issue. The World Health Organization estimates ~35 m people a year travel to over 3000 m.¹

The response: acclimatization

Reduced atmospheric P_{O_2} leads to a decrease in alveolar partial pressures of oxygen (P_{AO_2})

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and P_{aO_2} . This leads to an initial reduction in oxygen delivery DO_2 . Acclimatization is the process by which the body responds to this challenge. Traditional belief is this adaptation is achieved by increasing DO_2 through respiratory, haematological, and cardiac changes.

Respiratory changes

The oxygen cascade is a physiological description of the step-wise decrease in the partial pressure of oxygen from the atmosphere to mitochondria. Altitude and acclimatization affect various levels of the cascade.

The following illustrates changes to the oxygen cascade at extreme altitude using four arterial blood samples obtained from climbers on The Balcony of Mount Everest (altitude = 8400 m) as an example.² These samples demonstrated a mean P_{aO_2} of 3.3 kPa and arterial partial pressure of carbon dioxide (P_{aCO_2}) of 1.8 kPa.

The atmosphere

The fraction of inspired O_2 (FI_{O_2}) is constant (20.9%) and atmospheric P_{O_2} decreases proportionally with P_B . At 8400 m, $P_B = 36.3$ kPa and atmospheric $P_{O_2} = 20.9\% \times 36.3 = 7.6$ kPa.

Humidification of airway gases in the upper airways

Saturated vapour pressure of water ($P_{SVP \text{ Water}}$) is 6.3 kPa at body temperature. It is unaltered by altitude. Consequently, respiratory humidification has a proportionally greater effect; this reduces the partial pressure of oxygen in the airways at altitude more than at sea-level.

$$\begin{aligned} \text{Partial pressure of inspired oxygen} \\ (P_{iO_2}) &= FI_{O_2} \times (P_B - P_{SVP \text{ Water}}) \\ &= 20.9\% \times (36.3 - 6.3) \\ &= 6.3 \text{ kPa} \end{aligned}$$

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The alveolar gas equation

The $P_{A_{O_2}}$ differs from $P_{i_{O_2}}$ as it is reduced by carbon dioxide (CO_2) in the alveolar space.

The $P_{A_{O_2}}$ is predicted by the alveolar gas equation

$$P_{A_{O_2}} = P_{i_{O_2}} - (P_{A_{CO_2}}/R)$$

 R , respiratory quotient
 = CO_2 produced/ O_2 consumed in unit time (at a cellular level)
 R is dependent on diet. The mean R in the climbers was measured at 0.74.²
 Alveolar partial pressure of CO_2 ($P_{A_{CO_2}}$) is assumed equal to $P_{a_{CO_2}}$

$$P_{A_{O_2}} = 6.3 - (1.8/0.74) = 3.9 \text{ kPa}$$

Oxygen is taken up from the alveolus by deoxygenated blood.

Minute ventilation

Changes in $P_{a_{CO_2}}$ (and $P_{A_{CO_2}}$) are inversely proportional to alveolar ventilation (V_A). V_A is increased with ascent to altitude. Underlying mechanisms are complex. At sea-level, mild hypoxia does not increase V_A . This is proposed to be a result of hypoxic peripheral chemoreceptor stimulation and central chemoreceptor inhibition from decreased cerebral extra-cellular partial pressure of CO_2 cancelling each other out. It is thought that increased cerebral blood flow (CBF) maintaining cerebral oxygen delivery in the face of arterial hypoxaemia ‘washes out’ CO_2 , producing a central alkaline environment and preventing increased V_A .³ Acclimatization inhibits this central response, increasing V_A for any given $P_{a_{O_2}}$. The mechanisms underlying this inhibition are unclear, but are associated with a decrease in cerebrospinal fluid (CSF) bicarbonate (HCO_3^-).

Increased V_A produces a respiratory alkalosis, which is metabolically compensated for by renal loss of HCO_3^- . The mean serum HCO_3^- in the climbers was 10.8 mmol litre⁻¹.

Increased V_A and decreased $P_{a_{CO_2}}$ and $P_{A_{CO_2}}$ result in an increase in $P_{A_{O_2}}$, as described by the alveolar gas equation.

If hyperventilation did not occur and $P_{a_{CO_2}}$ remained at sea-level values (~4.5 kPa), $P_{A_{O_2}}$ would be greatly reduced and incompatible with life, for example,

$$P_{A_{O_2}} = 6.3 - \left(\frac{4.5}{0.74} \right) = 0.2 \text{ kPa}$$

Alveolar–arterial (A–a) gradient

Ventilation–perfusion (V–Q) mismatch, shunting, or reduced diffusion capacity may explain the difference between $P_{A_{O_2}}$ and $P_{a_{O_2}}$, known as the A–a gradient or difference. At sea-level, a normal A–a gradient in a young healthy individual would be <1.3 kPa.⁴ In simulated ascent with direct measurement, the A–a gradient has been shown to decrease with decreasing $P_{i_{O_2}}$ such that in

the climbers, it would be predicted to be around 0.3 kPa.⁵ The climbers’ mean measured A–a gradient was 0.7 kPa.² It is postulated that the measured increased gradient was due to either sub-clinical high-altitude pulmonary oedema (HAPE), functional diffusion limitation, or posture-related increase in V–Q mismatch (subjects were supine when samples were drawn).²

Haematological changes

Oxygen carriage in the microcirculation

Oxygen is primarily transported reversibly bound to haemoglobin (Hb). A small amount is dissolved in plasma.

Arterial oxygen content (Ca_{O_2}) is measured in ml O_2 100 ml⁻¹ blood
 It can be calculated

$$Ca_{O_2} = (Sa_{O_2} \times 1.34 \times Hb \times 0.01) + (0.023 \times Pa_{O_2} \text{ in kPa})$$

 The climbers mean Sa_{O_2} was calculated as 54% and the measured Hb was 19.3 g dl⁻¹

$$Ca_{O_2} = (54 \times 1.34 \times 19.3 \times 0.01) + (0.023 \times 3.3) = 14.0 \text{ ml } O_2 \text{ 100 ml}^{-1} \text{ blood}$$

$$= 140 \text{ ml } O_2 \text{ litre}^{-1}$$

 Sa_{O_2} = Arterial oxygen saturation (%)
 1.34 = Huffer’s constant (millilitres of oxygen carried by 1 g of Hb *in vivo*)
 0.023 = solubility coefficient of oxygen

Hb increases during acclimatization, increasing Ca_{O_2} . This occurs through several mechanisms:

- Acutely: plasma volume is reduced by ~20%, producing haemoconcentration.⁶
- Over time: within hours, erythropoietin is released in response to hypoxia. Red cell production increases occur within days and continue for weeks.⁴

Martin and colleagues⁷ demonstrated an *in vivo* disruption of microcirculatory flow at altitude (4900 m). Although difficult to directly investigate, this may be a viscosity effect secondary to increased haematocrit, so although advantageous for oxygen carriage, the increase in Hb concentration may paradoxically impair tissue DO_2 .

Oxygen release from Hb and intracellular diffusion to mitochondria

The affinity of Hb for oxygen molecules is determined by the oxygen dissociation curve (ODC). This describes the sigmoid relationship between $P_{a_{O_2}}$ and Sa_{O_2} . Individuals at altitude are frequently on the steep segment of the ODC where a small increase in $P_{a_{O_2}}$ leads to a significant increase in Sa_{O_2} . Acutely, hyperventilation and respiratory alkalosis shifts the ODC to the left. Over a period of days to a week, this is moderated by an increase in 2,3-diphosphoglycerate and rightward correction, returning the ODC to its sea-level position in fully acclimatized individuals.

Cardiovascular changes

Increased sympathetic activity leads to an initial increase in cardiac output (Q). This is primarily achieved by an increase in heart rate (HR).

DO_2 can be calculated by the product of Q and CaO_2 .
 $Q = HR \times \text{stroke volume (SV)}$
 $DO_2 \text{ (ml O}_2 \text{ min}^{-1}\text{)} = Q \text{ (litre min}^{-1}\text{)} \times CaO_2 \text{ (ml O}_2 \text{ litre}^{-1}\text{)}$
 e.g. an estimated SV of 60 ml and HR of 80 would give
 $Q = 60 \times 80 = 4.8 \text{ litre min}^{-1}$
 $DO_2 = 4.8 \times 140 = 672 \text{ ml O}_2 \text{ min}^{-1}$

Initial reduction in plasma volume with altitude reduces preload and SV. After several weeks, Q returns to sea-level values, but SV remains reduced with a consequential chronic elevation in HR. The underlying mechanisms are unclear.

Other changes

Capillary and mitochondrial densities were previously considered to increase with acclimatization. Subsequent research has not supported this finding. Microscopy demonstrates decreased muscle mass, producing apparent increased relative capillary densities, rather than neovascularization. Muscle biopsies have shown a 30% reduction in mitochondrial density.⁶

Discussion

The above physiological adaptations represent the traditional explanation: acclimatization restores DO_2 to sea-level values by increasing oxygen saturation, cardiac output, and Hb. However, this may not be the whole story.

Acclimatization shows wide inter-individual variability; some individuals acclimatize quicker, more effectively, or both than others and are, therefore, relatively less susceptible to acute high-altitude illness. For example, after Habeler and Messner became the first to summit Everest without supplemental oxygen, they were extensively physiologically evaluated and compared with controls. Investigators concluded, 'elite high-altitude climbers do not have physiological adaptation to high altitude that justify their unique performance'.⁶ In particular, they did not show any characteristics suggesting outstanding ability to maximize DO_2 . Furthermore, changes in physical performance at altitude, at least up to 7100 m, are unrelated to changes in oxygen content or delivery.²

Taken together, these findings suggest that changes in systemic oxygen delivery (oxygen flux) may not be the key determinant of successful or unsuccessful adaptation to high altitude. Alternative explanatory mechanisms might include changes in cellular oxygen consumption and disturbances of oxygen flux at the microcirculation level. Determining the physiological basis of these changes may improve understanding of the wide inter-individual variation

in ability to adapt to hypoxia at high altitude. Further investigation of acclimatization might additionally lead to clinically important insights into survival in critically ill patients challenged by hypoxia from other aetiologies. These ideas are discussed in a follow-up article.

The remainder of this article describes what happens to individuals who do not allow sufficient time for acclimatization and develop one of the clinical syndromes of acute high-altitude illness.

Acute high-altitude illness

Acute high-altitude illness describes the neurological or pulmonary syndromes experienced when unacclimatized individuals ascend too rapidly. Acute mountain sickness (AMS) has been reported at altitudes as low as 2000 m. Incidence increases with increasing altitude and has been reported in up to 40% of people at 3000 m.⁸ Potentially fatal HAPE and high-altitude cerebral oedema (HACE) are less common; they are diagnosed in <2% of individuals ascending over 4000 m.¹ The faster the ascent and the higher the maximum altitude reached, the more likely individuals will suffer from high-altitude illness. The symptoms and signs of AMS, HACE, and HAPE are presented in Table 1. Prevention of these conditions, through controlled ascent, is the simplest means of reducing the burden of illness, and prophylaxis, treatment, and management are discussed in Table 2.

Pathophysiology of acute high-altitude illness

AMS and HACE may share the same underlying pathophysiology and represent a spectrum of severity; the mechanism is not fully understood. It is hypothesized that hypoxia induces neurohumeral and haemodynamic responses causing vasodilatation, hyperaemia, and microcirculatory changes, increasing capillary hydrostatic pressures, resulting in capillary leak and cerebral oedema.⁹ Hypoxia-inducible factor and inducible nitric oxide synthase appear to have important roles in the activation of vascular endothelial growth factor fuelling the process.¹

Sufferers of AMS differ in their response to altitude when compared with successful acclimatizers in the following ways:¹⁰

- reduced hyperventilatory response;
- impaired gas exchange;
- fluid retention;
- increased sympathetic drive.

The cardinal symptom of AMS and HACE is headache. In AMS, headache is presumed to be due to increased volume of the intracerebral contents with limited buffering by CSF and a consequent risk of elevated intra-cranial pressure. Susceptible individuals may exhibit any of the following:

- Increased cerebral venous volume. CBF increases in response to hypoxia and is balanced by hypocapnic cerebral vasoconstriction. Nitric oxide has been suggested as a mediator.

Table 1 Acute high-altitude illnesses

| Symptoms | Diagnosis | Miscellaneous | |
|----------|--|---|--|
| AMS | Symptoms are non-specific. There is no gold standard for diagnosis. The Lake Louise AMS scoring system is used to quantify symptoms and assess severity for research. A diagnosis of AMS requires the following: <ul style="list-style-type: none"> Recent ascent within last 4 days (>2500 m) Headache Presence of ≥ one other symptom (listed below) A total symptom score of ≥ 3 on a self-reported questionnaire. Each of the following categories are scored for severity from 0 to 3 [none (0), mild (1), moderate (2), or severe (3)]: <ul style="list-style-type: none"> Headache Gastrointestinal disturbance (i.e. anorexia, nausea, or vomiting) Insomnia Fatigue or weakness Dizziness or lightheadedness Mild AMS: Score of 3–5 Severe AMS: Score of ≥6 | | |
| HACE | Those of AMS plus ataxia or cognitive impairment (i.e. irrational behaviour, confusion, drowsiness, or coma) | Clinical diagnosis. AMS plus evidence of impaired cognition or ataxia (e.g. difficulty heel-toe walking) | Rarely occurs without preceding symptoms of AMS May not recur on re-ascent if given further time for acclimatization |
| HAPE | Early symptoms may be limited to a dry cough and reduced functional capacity from dyspnoea. Orthopnoea and haemoptysis are late occurrences Signs and symptoms of AMS are often present HACE and HAPE can occur in combination, this is associated with an increased mortality | A high index of clinical suspicion and early diagnosis are essential. Clinical signs are tachycardia, tachypnoea, pyrexia and inspiratory crackles Hypoxia from HAPE can produce confusion, but HACE should be considered as a cause | Responsible for the majority of the mortality from high-altitude illness; it can be fatal in hours. Risk is increased by rapid ascents, vigorous exercise, and concurrent respiratory viral illnesses In some susceptible individuals, HAPE occurs consistently at return to the same altitude that symptoms first occurred |

Table 2 Therapy for acute high-altitude illnesses. *Doses as recommended by medex.org.uk (http://medex.org.uk/medex_book/english_version.php)

| Therapy | Description of therapy | AMS | HACE | HAPE |
|--|--|----------------|------|------|
| Controlled rate of ascent (prevention) | Prevention is better than cure, e.g. above 3000 m aim to ascend 300 m day ⁻¹ with rest days every 2–3 days ¹⁰ | x | x | x |
| Descent | Descent (>500 m) is considered definitive treatment, although symptoms may improve with more modest descents. This may be aided by a combination of therapies | x | x | x |
| Simple analgesia | Symptomatic control | x | x | |
| Oxygen | Supplementary oxygen (titrated to SaO ₂ >90%) | Only if severe | x | x |
| Acetazolamide* | Acetazolamide, a carbonic anhydrase inhibitor, is used in prevention or treatment of AMS. A preventative dose of 125 mg b.d. may be as effective as higher doses, but the optimum regime is debated. Treatment dose for HACE and HAPE is 250 mg t.d.s. Side-effects include: paresthesia in hands and feet, diuresis, and making carbonated drinks taste flat. Acetazolamide is a sulphonamide and has associated hypersensitivity reactions | x | x | x |
| Dexamethasone* | 8 mg improves symptoms in the short term to facilitate descent. Exact mechanisms are not fully understood but are probably a combination of attenuating cytokine and inflammatory responses and reducing capillary permeability | x | x | x |
| Hyperbaric chamber | For example, Gamow bag. These are used for treatment, simulating descent | x | x | x |
| Nifedipine* | 20 mg modified release initially if descent delayed or supplementary oxygen is not available. Reduces pulmonary artery pressure. Maintenance doses can be given to those suffering recurrent episodes of pulmonary oedema | | | x |

- Increased net CSF production or increased brain tissue (cellular oedema). AMS sufferers retain fluid; diuresis is an element of successful acclimatization.
- Decreased intracranial buffering capacity to accommodate these increases in volume (individuals with generalized brain atrophy may be relatively protected).

These postulated mechanisms for headache in AMS and HACE have not yet been rigorously and systematically investigated.

The occurrence of HAPE in susceptible individuals is a result of an imbalance between forces driving fluid into and out of the alveolar space.⁹ Alveolar capillary leak is related to the level and heterogeneity of the pulmonary hypertension that occurs in all

individuals as a result of global hypoxic pulmonary vasoconstriction. Initially, HAPE appears to be a direct pressure effect as there is no evidence of inflammatory mediators in early bronchoalveolar lavage. Pulmonary capillary stress failure due to high transmitted pressures from some pulmonary arterioles has been demonstrated. An exaggerated pulmonary hypertensive response is demonstrated in susceptible individuals and impaired pulmonary (endothelial and epithelial) nitric oxide synthesis has been implicated as a cause. The increased sympathetic drive seen in AMS/HACE is also present in HAPE. Alveolar fluid reabsorption secondary to epithelial sodium transport is less effective in some HAPE-susceptible individuals.

Other health risks associated with altitude

Remote travel is associated with diarrhoeal illness and other infections. The presentation of many infections may be non-specific (e.g. flu-like illness) and difficult to distinguish from AMS.

The combination of hypoxia and polycythaemia contribute to an increase in thrombotic events at altitude (e.g. myocardial infarction and ischaemic stroke). These events can be misdiagnosed as high-altitude illness.

High altitude is a hostile environment, remote from emergency services. The risk of trauma is increased (e.g. avalanches or falls whilst climbing) and the consequences (e.g. haemorrhage from fractured femur) will be less tolerated than at sea-level as individuals have reduced physiological reserve.

Reduced atmospheric protection from ultraviolet radiation and extremes in temperature may result in thermal injuries or hypothermia and cold injury (e.g. frostbite).

At extreme altitudes above 5500 m, a phenomenon referred to as high-altitude deterioration occurs.⁴ It is characterized by lethargy, impaired cognitive function, anorexia, and weight loss; this process is distinct from high-altitude illness, for this reason, it is impossible to remain or live above this height for prolonged periods of time.¹⁰ Climbers refer to altitudes above 8000 m as 'the death zone'.

Deeper stages of sleep, rapid eye movement, and sleep quality are all reduced at altitude and periodic or Cheyne–Stokes breathing commonly occur. These changes probably contribute to the symptoms of AMS.

Discussion

There is a wide inter-individual range in the speed and extent to which people ascending to altitude acclimatize. Taking prophylactic therapy may reduce symptoms of AMS, but the main stay should be a controlled ascent to prevent the potentially fatal consequences of HACE and HAPE. Descent to a lower altitude should be the priority with all individuals suffering severe altitude illness (severe AMS, HAPE, HACE) and ascent should be discouraged when mild AMS is diagnosed.

Management of acute high altitude illness

A case study

A trekker walking into Everest Base Camp is following an ascent profile designed to minimize the risk of AMS. He spent several nights at Pheriche (4270 m) before trekking to Lobuje (4940 m). At sea-level, he runs marathons and until reaching Pheriche had been at the front of his trekking group. On arrival, he goes to bed early, foregoing dinner, complaining of a headache and anorexia. If you were leading this group, what would be your approach to managing this individual?

Controlled ascent profiles help reduce the incidence of AMS.¹⁰ A suggested strategy is 300 m a day above 3000 m with a rest day every 1000 m. However, this approach is not always possible because of the geography.

Diagnosis is clinical. Considerations are: Is this AMS, or an alternate diagnosis? Is there evidence to suggest HACE or HAPE? How severe are the symptoms? Is the individual responding to treatment?

Alternate diagnoses should be considered such as dehydration, fatigue, viral illness, hangover, or hypothermia. If there are no obvious features in the patient's history to support an alternate diagnosis then it should be managed as AMS. High-altitude headache is common, but if symptoms persist or worsen despite simple analgesia, a diagnosis of AMS must be considered. It is important to define severity of symptoms to inform treatment and monitor for deterioration (i.e. development of HACE).

- Signs and symptoms of HACE should be actively excluded:
 - Neurological examination—assessment of cognitive function, heel-toe walk test
- Evidence of HAPE should be excluded:
 - History—reduced functional capacity, dry cough
 - Examination—pyrexia (unusual with AMS/HACE), tachypnoea, inspiratory crackles

Treatment for severe AMS or HACE is descent (300–500 m). Mild AMS may be managed by resting at the same altitude. There is level 1 evidence for the following adjunctive therapies:¹⁰

- Acetazolamide: prophylaxis or treatment.
 - mechanisms of action:
 - produces metabolic acidosis, increasing ventilatory drive
 - reduces CSF production
- Dexamethasone: prophylaxis or treatment
- Hyperbaric chamber
- Oxygen: prophylaxis or treatment (level 2 evidence)

This individual had no clinical evidence of HACE or HAPE. He was given simple analgesia (paracetamol and ibuprofen) and acetazolamide 250 mg. He was monitored several times overnight and symptoms were improved by the morning. He remained an extra night to allow further acclimatization and continued taking 125 mg acetazolamide b.d. He successfully reached Base Camp (5380 m) 2 days later.

Declaration of interest

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Please see multiple choice questions 13–16.