Humans at altitude: physiology and pathophysiology

Revalidation FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 1A01

James PR Brown MBChB (Hons) MRCP FRCA
Michael PW Grocott BSc MBBS MD FRCA FRCP FFICM

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.

James PR Brown MBChB (Hons) MRCP FRCA
Anaesthetic Registrar
Derriford Hospital
Plymouth
UK

Michael PW Grocott BSc MBBS MD FRCA FRCP FFICM
Professor of Anaesthesia and Critical Care Medicine
University of Southampton
UCL Centre for Altitude Space and Extreme Environment Medicine
Southampton
UK

GICU
Level D
Centre Block
Southampton General Hospital
Tremona Road
Southampton SO16 6YD
UK
Tel: +44 2 380 794 159
E-mail: mike.grocott@soton.ac.uk
(for correspondence)

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 ($P_{a_{O_2}}$) 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 ($P_{A_{O_2}}$) and $P_{a_{O_2}}$. 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 $P_{a_{O_2}}$ of 3.3 kPa and arterial partial pressure of carbon dioxide ($P_{a_{CO_2}}$) of 1.8 kPa.

The atmosphere

The fraction of inspired O_2 ($F_{I_{O_2}}$) 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 ($P_{SVP\ Water}$) 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.

$$\text{Partial pressure of inspired oxygen } (P_{i_{O_2}}) = F_{I_{O_2}} \times (P_B - P_{SVP\ Water})$$
$$= 20.9\% \times (36.3 - 6.3)$$
$$= 6.3 \text{ kPa}$$

doi:10.1093/bjaceaccp/mks047 Advance Access publication 5 September, 2012
Continuing Education in Anaesthesia, Critical Care & Pain | Volume 13 Number 1 2013

The alveolar gas equation

The $P_{A_{O_2}}$ differs from Pi_{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

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

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 Pa_{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 Pa_{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 Pa_{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 Pa_{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 Pa_{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 Pa_{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 Pi_{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 subclinical 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 (CaO_2) is measured in ml O_2 100 ml^{-1} blood

It can be calculated

$$CaO_2 = (Sa_{O_2} \times 1.34 \times Hb \times 0.01) + (0.023 \times Pa_{O_2} \text{ in kPa})$$

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

$CaO_2 = (54 \times 1.34 \times 19.3 \times 0.01) + (0.023 \times 3.3) = 14.0$ ml O_2 100 ml^{-1} blood

= 140 ml O_2 litre^{-1}

Sa_{O_2} = Arterial oxygen saturation (%)

1.34 = Huffner's constant (millilitres of oxygen carried by 1 g of Hb *in vivo*)

0.023 = solubility coefficient of oxygen

Hb increases during acclimatization, increasing CaO_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 colleagues[7] 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 Pa_{O_2} and Sa_{O_2}. Individuals at altitude are frequently on the steep segment of the ODC where a small increase in Pa_{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.

$Q = HR \times$ stroke volume (SV)

DO_2 (ml O_2 min^{-1}) = Q (litre min^{-1}) $\times$ CaO_2 (ml O_2 $litre^{-1}$)

e.g. an estimated SV of 60 ml and HR of 80 would give

$Q = 60 \times 80 = 4.8$ litre min^{-1}

$DO_2 = 4.8 \times 140 = 672$ ml O_2 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:
	• 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)]:
	  • 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. Orthopneoa 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 Sa_{O_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

J.P.R.B. has no potential conflicts of interest (financial or otherwise). M.P.W.G. is director of Xtreme Everest/Caudwell Xtreme Everest, which was supported by Mr John Caudwell, BOC Medical (now part of Linde Gas Therapeutics), Eli Lilly, the London Clinic, Smiths Medical, Deltex Medical, and the Rolex Foundation (unrestricted grants), the Association of Anaesthetists of Great Britain and Ireland, the United Kingdom Intensive Care Foundation, and the Sir Halley Stewart Trust.

References

1. Clarke C. Acute mountain sickness: medical problems associated with acute and subacute exposure to hypobaric hypoxia. *Postgrad Med J* 2006; **82**: 748–53
2. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery H. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; **360**: 140–9
3. Wolff C. The physiological control of respiration. *Mol Aspects Med* 1992; **13**: 445–567
4. Milledge JS, West JB, Schoene B. *High Altitude Medicine and Physiology.* London: Hodder Arnold, 2007
5. Wagner PD, Sutton JR, Reeves JT, Cymerman A, Groves BM, Malconian M. Operation Everest II: pulmonary gas exchange during a simulated ascent of Mt. Everest. *J Appl Physiol* 1987; **63**: 2348–59
6. Martin D, Windsor J. From mountain to bedside: understanding the clinical relevance of human acclimatisation to high-altitude hypoxia. *Postgrad Med J* 2008; **84**: 622–7
7. Martin DS, Ince C, Goedhart P, Levett D, Grocott M. Abnormal blood flow in the sublingual microcirculation at altitude. *Eur J Appl Physiol* 2009; **106**: 473–8
8. Hackett PH, Roach R. High-altitude illness. *N Engl J Med* 2001; **345**: 107–14
9. Scherrer U, Rexhaj E, Jayet PY, Allemann Y, Sartori C. New insights in the pathogenesis of high-altitude pulmonary edema. *Prog Cardiovasc Dis* 2010; **52**: 485–92
10. Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. *Prog Cardiovasc Dis* 2010; **52**: 467–84

Please see multiple choice questions 13–16.

Humans at altitude: research and critical care

Revalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 3C00 2C04

James PR Brown MBChB (Hons) MRCP FRCA
Michael PW Grocott BSc MBBS MD FRCA FRCP FFICM

Key points

Acclimatization restores oxygen delivery, but exercise tolerance and oxygen utilization are reduced at altitude.

Reduced overall oxygen utilization may be a consequence of oxygen flux limitation (most likely in the microcirculation), increased cellular efficiency, or reduced cellular oxygen utilization.

Understanding processes involved in effective adaptation to hypoxia could lead to novel therapies that may improve outcome in critically ill patients.

Understanding why some individuals function more successfully at altitude may identify factors associated with better outcomes after critical illness.

Altitude provides a laboratory to test theories and potential therapies for critically ill patients.

James PR Brown MBChB (Hons) MRCP FRCA
Anaesthetic Registrar
Derriford Hospital, Plymouth
UK

Michael PW Grocott BSc MBBS MD FRCA FRCP FFICM
Professor of Anaesthesia and Critical Care Medicine
University of Southampton
UCL Centre for Altitude Space and Extreme Environment Medicine
Southampton
UK
GICU, Level D, Centre Block
Southampton General Hospital
Tremona Road
Southampton SO16 6YD
UK
Tel: +44 2380 79 4159
E-mail: mike.grocott@soton.ac.uk
(for correspondence)

Hypoxia

Tissue hypoxia, defined as reduced oxygen availability at a cellular or mitochondrial level, is the final common pathway of many critical illnesses. Decreased oxygen delivery (DO_2) [more correctly, this should be referred to as '*oxygen flux*'. '*Oxygen delivery*' is commonly used to describe the total amount of oxygen dispatched from the left ventricle into the systemic circulation and is assumed to be equivalent to the oxygen delivered to the tissues. This assumption may be incorrect (e.g. microcirculatory blood disturbance) and therefore the term is potentially misleading] to tissues may result from a variety of mechanisms:

- hypoxaemia [reduced partial pressure of arterial oxygen (Pa_{O_2})], for example, pulmonary pathology;
- anaemia, for example, haemorrhage;
- decreased cardiac output, for example, cardiogenic shock;
- maldistribution of blood flow due to microvascular dysfunction, for example, sepsis.

Functional cellular hypoxia may also result from metabolic changes within the cells including dysfunction due to sepsis or other causes of a systemic inflammatory response.

Physiological and pathophysiological responses to tissue hypoxia are poorly understood. Understanding these responses is valuable in developing new interventions that might beneficially modify disease processes. Research into these issues in critically ill patients is challenging for several reasons:

- An inability to make pre-morbid control measurements, to compare against observations taken when patients are critically ill.
- Heterogeneity of individual phenotypes, presenting conditions, established co-morbidities, and treatment.
- Ethical considerations of obtaining informed consent, assent, or both.

The challenge of studying tissue hypoxia has led to the development of research at altitude to investigate responses of healthy individuals to hypobaric hypoxia (i.e. hypoxia related to reduced atmospheric pressure). This research makes the assumption that the adaptive processes to tissue hypoxia are similar regardless of aetiology. The results seen in healthy subjects at altitude may not be directly transferable to critically ill patients as it is possible that their underlying disease processes may prevent 'acclimatization' or that the disease pathology may modify adaptive mechanisms. However, alternative models of investigating hypoxic adaptation also have significant limitations. Translation of results derived from laboratory and animal studies into clinical practice is frequently unsuccessful. Furthermore, research undertaken at altitude has already led to the development of therapies for evaluation in a clinical context [e.g. β-agonists and acute lung injury (ALI)].[1] Altitude research has provided novel insights into a variety of physiological (e.g. cerebral artery dilatation in response to hypoxia) and pathophysiological mechanisms [e.g. nitric oxide (NO) metabolism, microcirculatory changes, and mitochondria regulation].[2] Results from altitude experiments have shifted the focus of research on hypoxia in the critically ill from DO_2 to oxygen utilization.

Supply and demand

Traditional explanations of acclimatization focus on adaptive mechanisms that ensure effective oxygen transfer from ambient air into pulmonary blood (e.g. hypoxic ventilatory response) and mechanisms that increase DO_2 (i.e. maintaining oxygen saturation, and also increasing cardiac output and haemoglobin). These physiological responses normalize arterial oxygen transport towards sea-level values.

doi:10.1093/bjaceaccp/mks048 Advance Access publication 30 August, 2012
Continuing Education in Anaesthesia, Critical Care & Pain | Volume 13 Number 1 2013

On acute exposure to altitude, exercise capacity is limited by DO_2, and peak oxygen utilization [(VO_2 peak), demonstrated with an incremental exercise test] changes proportional to DO_2. With acclimatization, this relationship is lost. Data from adequately acclimatized individuals have shown that VO_2 peak is reduced by 30–35%, while DO_2 is maintained at comparable values to sea-level.[3] Decreased DO_2 is therefore unlikely to be the factor limiting performance.[4] In other words, an equivalent amount of oxygen is available (global DO_2) at altitude as at sea-level, but less oxygen is utilized. There are several possible explanations for this observation:

- alterations in microcirculatory flow limiting oxygen diffusion at a tissue level; resulting in inadequate cellular DO_2 in the face of adequate global DO_2;
- reduced cellular oxygen consumption;
- improved efficiency of adenosine triphosphate (ATP) production (e.g. more ATP produced per molecule of oxygen).

Alterations in the microcirculation

Rheology of blood is altered due to increased haematocrit and microcirculatory flow at altitude is significantly reduced. Derangement of blood flow potentially limits tissue DO_2 and could explain the limitation in VO_2, despite preserved global DO_2. Even in the absence of microcirculatory disturbance, diffusion of oxygen from capillary to cell may be limited due to the low capillary P_{O_2}. However, empirical support for this theoretical limitation is currently lacking.

Reduced oxygen consumption

Attaining a hypometabolic state with reduced oxygen consumption has theoretical survival advantages as tissues await correction of hypoxia, delaying cellular apoptosis, and enabling the opportunity for functional recovery.[5] Such a state is achieved by humans *in utero* and other mammals in response to hypoxia (e.g. diving turtles).[4] Reducing oxygen consumption is a therapeutic strategy commonly utilized in critically ill patients (i.e. sedation, mechanical ventilation, and/or removal of skeletal muscle oxygen consumption by neuromuscular paralysis). The unexpected survival advantage associated with neuromuscular paralysis demonstrated in a recent large randomized controlled trial (RCT) might in part be explained by this mechanism.[6]

Persistent uncompensated cellular hypoxia results in multi-organ failure (MOF), which may represent the clinical manifestation of a whole-organism hypometabolic state. There is evidence to support MOF being a functional change with limited structural damage. Pathophysiological changes associated with MOF are frequently reversible, for example, the majority of individuals requiring renal replacement therapy, as a result of a tissue hypoxia related to critical illness, will not require long-term dialysis.[5] Histological examination of organs in patients who die with MOF are normal in the majority of cases.

Improved efficiency of ATP production

Much of our understanding and traditional description of the biochemistry of respiration, in particular aerobic metabolism, oxidative phosphorylation, and mitochondrial function, come from *in vitro* investigations performed in non-physiological, relatively hyperoxic conditions, for example, room air at sea-level. *In vivo* mitochondria are required to perform at much lower oxygen tensions. In health, a proportion of the proton gradient across the inner mitochondrial membrane is dissipated without ATP production through the action of uncoupling proteins. Up- or down-regulation of these proteins, and also dynamic alteration in mitochondrial membrane proton pump activity, can alter the relationship between oxygen consumption and ATP production and thereby modulate the efficiency of aerobic metabolism.[4] There is *in vitro* evidence demonstrating more efficient ATP production in isolated mitochondria in the setting of hypoxia.[4]

Altitude research

Understanding and influencing the response to hypoxia

Both critical illness and exposure to altitude demonstrate acute and chronic phases in response to hypoxia. At altitude, the physiological response of acute exposure to hypoxia is increased catecholamine levels, 'fight or flight'. A similar response is observed in early phases of critical illness; intervention and correction of DO_2 at this point reduces mortality.

Once acclimatization has occurred, DO_2 tends to decrease. In established critical illness, increasing DO_2 provides no outcome benefit, which has implications for critical care. We routinely measure and aim to restore DO_2, such as by using cardiac output monitoring in conjunction with fluid challenges, inotropes, transfusion of red blood cells, and ventilation. However, if our patients have 'acclimatized' to hypoxia, DO_2 may not be the factor limiting their 'performance' and subsequent survival. Such interventions may not be beneficial, or may even be harmful. Clinical evidence in this area is limited. Direct measures of cellular oxygen consumption at a local tissue level are not available. Instead, global estimates of the balance between DO_2 and oxygen consumption are inferred from measurements such as mixed venous oxygen saturation.

Therapies to improve cellular efficiency, reduce oxygen consumption, or improve microvascular flow may be of benefit in critical illness. Further research into the control of cellular metabolism and tissue blood flow in response to hypoxia, along with better understanding of what constitutes a successful phenotype or genotype in the context of hypoxia is directly relevant to critical care. These areas are discussed in more detail below.

Control of cellular metabolism

Cellular metabolism is proportional to mitochondrial activity. Mitochondria are the site of oxidative phosphorylation and ATP production; they are responsible for 90% of oxygen consumption.[5] VO_2 can, therefore, be used as a surrogate for mitochondrial activity.[7] Inhibition of mitochondrial function leads to a reduction in VO_2.

Support for the reduced cellular oxygen consumption theory includes a demonstrated 30% reduction in mitochondrial density and a 20% reduction in activity of mitochondrial enzymes in individuals acclimatized to altitude.[4]

Control of mitochondrial activity

Control of mitochondrial function is multi-factorial. Reactive oxygen species, NO, and inflammatory mediators all have a direct inhibitory effect. Endocrine changes (altered levels of thyroid and sex hormones, insulin, and glucocorticoids) have an indirect effect.

Nitric oxide

The role of NO in the control of mitochondrial function is complex. In the acute phase when produced in high concentrations by the action of inducible nitric oxide synthetase (NOS), NO is inhibitory. Conversely, in the recovery phase when produced at lower concentrations by endothelial NOS, NO promotes mitochondrial function.

Endocrine changes

Tissue hypoxia of all aetiologies results in an acute phase response, increasing levels of glucocorticoids, catecholamines, vasopressin, glucagon, growth hormone, and inflammatory mediators [e.g. tumour necrosis factor α, interleukin (IL)-8 and IL-6]. These endocrine changes augment DO_2, mobilize energy substrates, and initially increase VO_2 by up to 200%.[7] If tissue hypoxia persists, the endocrine profile changes markedly with a reduction in vasopressin, thyroid hormones, and glucocorticoid levels,[7] and critical illness enters the chronic phase.

Hypoxia-inducible factor

Hypoxia-inducible factor (HIF-1) is a transcriptional regulator of the cellular response to hypoxia. The activity of HIF-1 is dependent on the expression of the HIF-1α subunit, which signals hypoxia to the transcriptional machinery in the nucleus of all cells.[8] Multiple target genes for HIF-1α have been identified (e.g. NOS, lactate dehydrogenase, erythropoietin, adrenergic receptors, glucose transporters, and insulin-like growth factor).[8] HIF-1α is a key player in the response to hypoxia and an important target for research.

There are wider implications in understanding and controlling HIF than for critical care patients. HIF is involved in the pathophysiology of cancer, cardiovascular disease, chronic respiratory diseases, and the regulation of cell death.[8]

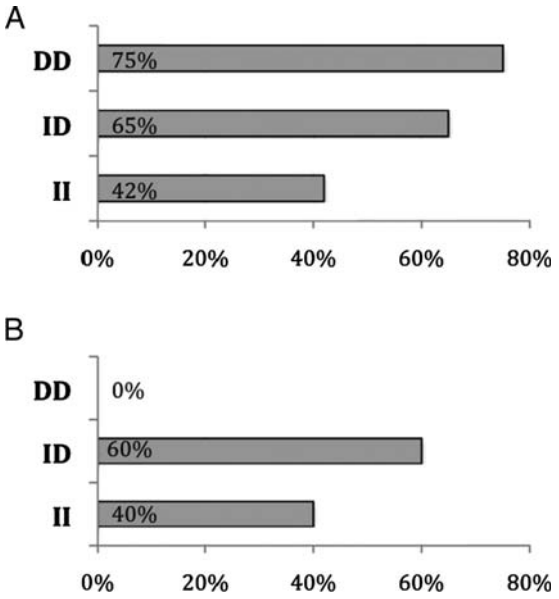

Fig 1 Graphs demonstrating ACE genotype frequency in two study populations. (A) Twenty-eight day mortality from ARDS (n=101, P=0.036).[9] (B) Climbers successful over 8000 m without supplementary oxygen (n=15).[10] D represents the deletion allele of the ACE gene and I is the insertion. In the general population, the genotype frequency as expected is 25% DD and II and 50% ID.

Genotypes behind successful phenotypes

Variation in the human genotype determines success in response to environmental challenges such as hypoxia. Multiple gene loci are likely involved, which reflects the range of phenotypic responses to altitude and survival of critical illness. The majority of relevant gene loci have not yet been identified. One genotype has been identified and supports the model that hypobaric hypoxia is a surrogate for critical illness hypoxia. Improved performance at altitude is associated with the insertion variant of the angiotensin-converting enzyme (ACE). This is implicated in cellular efficiency of oxygen utilization. The presence of this same allele has been shown to convey survival benefit in acute respiratory distress syndrome (ARDS) and other critical illnesses[9] (Fig. 1).

Identifying other loci that are overrepresented in successful acclimatizers may guide future research and gene-based therapies.

Other potential areas of interest

Cells that respond directly to hypoxia

An alternative area of research is investigating cells that respond directly to Pa_{O_2}, such as in carotid bodies, the ductus arteriosus, and smooth muscle of pulmonary arteries. The common mechanism of action is through altered cellular potassium flux. These cells that respond to Pa_{O_2} are intimately involved in acclimatization.

In pulmonary artery smooth muscle cells, hypoxia inhibits membrane ion channels, leading to membrane depolarization,

calcium influx, and contraction. This response produces hypoxic pulmonary vasoconstriction (HPV), which is partly brought about by voltage-gated and TASK potassium channels.

If hypoxia is localized, this process has physiological advantage, by reducing ventilation/perfusion mismatch, diverting blood to better oxygenated alveoli. In hypobaric hypoxia, the same process occurs throughout the lungs, producing pulmonary hypertension.

When individuals are acutely exposed to hypoxia, such as by rapid ascent to altitude, they increase their pulmonary artery pressure by HPV. Understanding the processes involved may improve treatments of pulmonary hypertension, a significant cause of morbidity and mortality in patients with chronic lung disease.

TASK potassium channels also influence other responses to hypoxia. They are involved in:

- brainstem respiratory-related neurones (they also respond to changes in pH),
- adrenal aldosterone secretion,
- renal acid–base balance and volume regulation,
- pro- and anti-apoptotic effects.

Identifying and manipulating relevant ion channel subtypes may lead to potential therapies.

High-altitude pulmonary oedema

Research groups have successfully used high-altitude pulmonary oedema (HAPE) as a model for investigating mechanisms of impaired vascular function and lung oedema.[1] Investigation of HAPE-prone individuals at altitude demonstrated defects in transepithelial sodium transport. Stimulation by β-adrenergic agonists reduced the incidence of HAPE. Results have translated to clinical trials in the critically ill, showing a reduction in extravascular lung water in patients with ALI.[1]

Potential practical applications

Information obtained from high-altitude research might be applied in several ways.

Plasma biomarkers

The plasma biomarkers associated with successful acclimatization to high altitude can be used as markers of beneficial adaptation or prediction of harm in the setting of critical care. In combination with genetic data, these markers may provide prognostic data, allowing improved risk prediction and stratification in critical illness. Furthermore, markers of poor adaptation or harm might be used to guide therapies (see the 'Permissive hypoxaemia' section).

Examples of potential biomarkers include inflammatory markers (e.g. IL-6), organ injury markers (e.g. S100 protein), and plasma nitrogen oxides (markers of NO production and activity). Although the role of NO in acclimatization is yet to be fully understood, increased NO production and availability appears to be beneficial for successful acclimatization.[2]

Identifying biomarkers might also provide insight into potential mechanisms that could be empirically explored, for example, the association between NO metabolism and tissue blood flow in acclimatizing lowlanders and resident highlanders is provocative and suggests novel therapies for hypoxic critically ill patients.

Permissive hypoxaemia

Could a lower Pa_{O_2} be safely tolerated in patients with ALI? Well-acclimatized humans can tolerate arterial oxygen tension as low as 2.55 kPa, with apparently normal function and subsequent survival.[3] Adoption of a lower target Pa_{O_2} has the potential to reduce iatrogenic pulmonary damage from a high inspired fraction of oxygen (mediated by free radicals) and high pulmonary inspiratory pressure associated with aggressive mechanical ventilation.[4] This intriguing concept is currently not for clinical application, but research is ongoing to evaluate the potential efficacy in selected patients.

Theories for clinical research findings

The theory that VO_2 is the limiting factor in established critical illness, as opposed to DO_2, may explain why therapies demonstrating an increase in Pa_{O_2} in ARDS have not demonstrated a survival benefit (e.g. inhaled NO).

Research in action

The Caudwell Xtreme Everest group is a project set up specifically to test the theories laid out in this article, investigating a large number of healthy volunteers ascending to altitude. It is organized through the UCL Centre of Altitude Space and Extreme Environment Medicine (CASE). In 2007, a group of 198 trekkers and 24 investigators followed a controlled ascent profile to Everest Base Camp (5300 m). Fifteen investigators ascended to 8000 m and eight progressed to the summit (8848 m). Daily recording of simple physiological variables were undertaken. At set stages of the ascent, more detailed physiological measurements were recorded, including cardiopulmonary exercise testing (Fig. 2), plasma biomarker sampling, near infra-red spectroscopy of the brain and exercising muscle, and neuropsychological assessment. On descent from the summit, four of the investigators took the first arterial blood samples to be obtained over 8000 m. Samples from all subjects have been obtained for genetic characterization. In 2009, 45 more trekkers followed the same ascent profile. New areas of investigation were undertaken, including effects of altitude on renal function, hydration, cardiac function, and sleep studies. This in turn led to an expedition to the European Alps (4598 m) in the summer of 2010 involving RCT testing an intervention suggested by results from 2007. The expeditions have produced large amounts of data, much of which are still being analysed. A further Everest expedition is planned for 2013 with the goal of exploring Sherpa physiology.

Fig 2 Detailed physiological measurement—cardiopulmonary exercise testing at altitude. Caudwell Xtreme Everest (2007).

Many of the original research papers referenced in this article, relevant reviews, further discussion, and future planned projects can be found in the publications section of the Caudwell Xtreme Everest website: www.xtreme-everest.co.uk.

Conclusions

Research with healthy individuals at altitude may become transferable to the management of the critically ill. This research investigating changes in physiology and cellular pathways at altitude is still in its infancy, but it is an important step before developing and testing new therapies. Given the ubiquitous nature of tissue hypoxia as a mechanism of injury in the critically ill, being able to therapeutically manipulate the physiological response to hypoxia has significant potential to impact patient mortality and morbidity.

Declaration of interest

J.P.R.B. has no conflicts of interest (financial or otherwise) to declare. M.P.W.G. is director of Xtreme Everest/Caudwell Xtreme Everest, which was supported by Mr John Caudwell, BOC Medical (now part of Linde Gas Therapeutics), Eli Lilly, the London Clinic, Smiths Medical, Deltex Medical, and the Rolex Foundation (unrestricted grants), the Association of Anaesthetists of Great Britain and Ireland, the United Kingdom Intensive Care Foundation, and the Sir Halley Stewart Trust.

References

1. Scherrer U, Allemann Y, Jayet PY, Rexhaj E, Sartori C. High altitude, a natural research laboratory for the study of cardiovascular physiology and pathophysiology. *Prog Cardiovasc Dis* 2010; **52**: 451–5
2. Levett DZ, Fernandez BO, Riley HL *et al.* The role of nitrogen oxides in human adaptation to hypoxia. *Sci Rep* 2011; **1**: 109
3. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; **360**: 140–9
4. Martin D, Windsor J. From mountain to bedside: understanding the clinical relevance of human acclimatisation to high-altitude hypoxia. *Postgrad Med J* 2008; **84**: 622–7
5. Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfuction in sepsis-induced organ failure. *Crit Care* 2006; **10**: 228
6. Papazian L, Forel JM, Gacouin A *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107–16
7. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; **364**: 545–8
8. Semanza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol* 2000; **88**: 1474–80
9. Jerng JS, Yu CJ, Wang HC, Chen KY, Cheng SL, Yang PC. Polymorphism of the angiotensin-converting enzyme gene affects the outcome of acute respiratory distress syndrome. *Crit Care Med* 2006; **34**: 1001–6
10. Montgomery HE, Marshall R, Hemingway H *et al.* Human gene for physical performance. *Nature* 1998; **393**: 221–2

Please see multiple choice questions 17–20.