

Medicine in extreme environments: danger and opportunity

JK Baillie

Clinical Lecturer, University of Edinburgh, Edinburgh, UK

ABSTRACT The problems encountered by expedition doctors are diverse and can be immensely challenging. They range from decompression sickness to high-altitude cerebral oedema, and from immersion hypothermia to the management of multiple trauma patients without any medical kit. Advice was presented on how to deal with these problems and many more. Our understanding of the pathophysiology of high-altitude cerebral oedema is still incomplete, but there is hope that work currently under way may identify genes that predispose individuals to altitude illness. There is active debate among experts about what factors limit exercise performance at high altitude. The accepted explanation has been that a failure of bulk oxygen delivery to the tissues is the limiting factor, but it has been proposed that alternatives such as inefficient microvascular flow or alterations in mitochondrial function may be more important.

KEYWORDS Acute mountain sickness, altitude, diving expedition, high-altitude cerebral oedema, high-altitude pulmonary oedema

DECLARATION OF INTERESTS No conflict of interests declared.

Exposing humans to extreme physiological stresses can teach us a great deal about physiology, and may advance our understanding of diverse aspects of medicine. Medical practice in remote environments presents particular problems, but while these may be very difficult to cope with, past experience suggests that careful preparation can prevent disaster.

SESSIONS 1 AND 2 PRACTICAL ASPECTS OF EXPEDITION MEDICINE

It is common for doctors of all specialties to be asked to take on the role of expedition doctor. Although there are a variety of short training courses available, there is no widely accepted route to becoming competent as an expedition medic. Doctors should be aware that accepting even a small discount on a commercial trip alters a doctor's legal responsibility, creating a duty of care for the other members of the team. For mountain expedition work the diploma in mountain medicine (DiMM), run by the charity Medex (www.medex.org) and the University of Leicester, is becoming the gold standard.

One of the directors of that course, Dr Paul Richards (Honorary Lecturer in Travel Medicine, UCL, and Director, Medex) gave a comprehensive overview of the problems encountered by expedition doctors. In addition to the problems of remote medical care and the environmental hazards of altitude, cold and dehydration, Dr Richards identified many risks that may be less immediately apparent. These include river crossings, road traffic accidents and sunburn, as well as out-of-character risk-taking behaviour, including sexual risks. It is of crucial importance not to forget about basic hygiene measures

such as hand-washing to prevent the spread of infections through the group. Readers are referred to the section by Dr Richards in the *Oxford Handbook of Expedition and Wilderness Medicine* for more information.¹

Dr Stephen Hearn (Consultant in Emergency and Retrieval Medicine, Royal Alexandra Hospital, Paisley) concentrated on the specific problems of medical emergencies in remote environments. It is important to consider that an event that causes serious injury may also destroy medical equipment, as happened to one catastrophic military expedition at the end of which a patient with an unstable cervical spine fracture had to walk to safety with no immobilisation at all.² Evacuation is a particular challenge in the absence of safe air transport. A stretcher has not yet been invented that is portable, comfortable and easy to carry. Dr Hearn's mountain rescue experience shows that a team of 24 people are required to carry a stretcher over a long distance.

Repatriation of seriously ill patients is covered by expedition insurance policies, but a liberal application of hard currency is essential to ensure safe passage out of many countries. It is easy to forget the patient's or the doctor's passport, and this could lead to a fatal delay.

ENDOWED LECTURE – NEUROLOGICAL PROBLEMS OF HIGH ALTITUDE

Drawing on his own considerable clinical experience at high altitude, Dr Charles Clarke (President, British Mountaineering Council, and Consultant Neurologist) reported many interesting observations relating to high-altitude cerebral oedema (HACE). A striking improvement

Published online March 2009

Correspondence to JK Baillie, Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Little France, Edinburgh EH16 5SA, UK

tel. +44 (0)131 242 1000

e-mail j.k.baillie@doctors.org.uk

in clinical condition occurs with only a slight descent in patients with HACE or high-altitude pulmonary oedema (HAPE), and this phenomenon has yet to be fully explained by any model of the pathophysiology of either condition. Furthermore, patients with severe HACE respond incredibly rapidly to dexamethasone: ataxia sometimes resolves within minutes of administration.

The molecular basis of HACE is unknown. Dr Clarke proposed that vascular endothelial growth factor may be implicated, since it is elevated in humans at high altitude³ and leads to increased permeability of the blood-brain barrier. The first magnetic resonance imaging (MRI) studies of HACE demonstrated a pattern consistent with vasogenic oedema in the corpus callosum.⁴ A sea-level condition, posterior leucoencephalopathy, which occurs in malignant hypertension, renal failure and pre-eclampsia, has much in common with HACE. High-altitude cerebral oedema seems to have a predilection for brain tissue supplied by the vertebrobasilar circulation, which is phylogenetically older brain. Dr Clarke speculated that this ancient portion of the brain may have escaped from the evolution of more sophisticated autoregulation systems.

Dr Clarke also described some of the less well-known neurological problems that occur at high altitude. One interesting phenomenon that climbers often report⁵ is the feeling that an imaginary person is beside them – the 'third man'. This may be a consequence of the combination of cerebral hypoxia, loneliness and the tremendous feeling of isolation during high-altitude climbs. This common psychological response may well be important in other types of exploration.⁶

There are many unanswered questions in this field, but two that are particularly pressing are the identification of genetic determinants of altitude illness and the potential of calcium channel blockers as therapy for HACE. No genes have yet been identified, but work under way by Dr H Montgomery and his team at UCL is very promising.⁷ Calcium channel blockers are effective in preventing HAPE⁸ and may also be effective in HACE, but good trial evidence is lacking.

Finally, altitude physicians are frequently asked what to recommend for prophylaxis of altitude illness. For Dr Clarke, the answer is careful acclimatisation, acetazolamide if desired,⁹ but in view of the side effect profile it is better to reserve dexamethasone for the treatment of acute illness.^{10,11} Readers are referred to a recent review for a detailed appraisal of this topic.¹²

HIGH-ALTITUDE RESEARCH PRESENTATIONS

Dr Jeremy Windsor (SpR in Anaesthesia, University College London) and colleagues used the hyperventilation response to high altitude to evaluate the performance of oxygen delivery devices at extremes of ventilation

during the recent Caudwell Xtreme Everest expedition. The team compared continuous-flow and demand-flow oxygen delivery systems with a partially closed-loop circle system during exercise in five climbers at 6,100 m. The circle system, which would be theoretically capable of delivering 100% oxygen with a minimal fresh gas flow, considerably outperformed the other devices. This result is consistent with the prediction of simple mathematical modeling that, even on the summit of Everest where barometric pressure is about one third of that at sea level, a fractional inspired oxygen concentration (FiO₂) of 75% would be sufficient to normalise oxygenation to sea-level values.¹³

Dr Roger Thompson (Clinical Fellow in Respiratory Medicine, Sheffield) presented results of a preliminary study of osteoprotegerin (OPG), a novel marker of vascular remodelling.¹⁴ He investigated the kinetics of the change in OPG following acute onset of hypoxic pulmonary hypertension at high altitude in 18 subjects. OPG increased significantly by 18% but did not correlate with pulmonary hypertension or the development of pericardial effusions.¹⁵

Both of these studies are good examples of how research conducted at high altitude has the potential to inform and advance sea-level medicine.

Mr David Hall (Medical Student, University of Edinburgh) presented the preliminary results of a cognitive research study from a recent expedition to the Himalayas. His team made serial measurements of choice reaction time. Subjects became faster over time, presumably due to a practice effect, but were slower at high altitudes. A novel analysis of reaction time variability is currently under way. It is encouraging to see this continuing participation in high-altitude research by Edinburgh medical students. Another medical student research expedition from Edinburgh is planned for the summer of 2009 (www.altitude-sickness.org).

SESSION 3 PHYSIOLOGY OF EXERCISE AT HIGH ALTITUDE

Exercise physiology at high altitude has received a great deal of attention in the last few decades, in part because of the discovery that exposure to altitude may improve athletic performance at sea level.¹⁶ Prof. Jean-Paul Richalet (Université Paris 13, Bobigny, France) presented an authoritative overview of the limiting factors of exercise performance at high altitude and provided evidence that the limitation of exercise performance at high altitude is explained by the reduction in arterial oxygen content (CaO₂) and maximal cardiac output, and the consequent reduction in bulk oxygen delivery.¹⁷ Above 4,000 m, the reduction in maximum exercise capacity (VO_{2max}) is greater than expected from the reduction in CaO₂.

Cardiac acclimatisation occurs quickly and is likely to be an effective protective response to mitigate myocardial hypoxia. Maximal heart rate falls such that at 8,000 m maximal heart rate is around 120 bpm. This prevents excessive oxygen consumption and excessively short diastolic flow time. There is evidence for downregulation of β -adrenoreceptors and increased parasympathetic tone. Maximal cardiac output is limited by acclimatisation to high altitude, meaning that, with acclimatisation to high altitude, one of the advantages that trained athletes have over untrained individuals is lost. This is one reason why sprint athletes would be expected to perform better at high altitude without acclimatisation. This was the approach taken by the Edinburgh cyclist Chris Hoy for his 2007 world record attempt in La Paz, Bolivia.¹⁸

Athletes also experience greater arterial hypoxaemia during exercise and a greater fall in $\text{VO}_{2\text{max}}$ at altitude than untrained individuals. One reason for this is that training, particularly endurance training, increases muscle capillary density and mitochondrial volume, and so trained subjects have less capacity to improve oxygen extraction with acclimatisation. The oxygen extraction ratio can rise to above 90% during exercise at high altitude, leading to profound end-capillary hypoxia.¹⁹

With adaptation to altitude over generations, remarkable physical performance is possible. Prof. Richalet reported that the record for the Cerro de Pasco marathon in Peru, run at an altitude of 4,300 m, is 2 hours 30 minutes. Needless to say, this record was set by an Andean runner.

Despite many efforts, no gene has been identified that confers risk of mountain sickness. An ongoing study of the *SDHC/SDHD* mutations in the succinate dehydrogenase gene, which are known to be important in causing paragangliomas,²⁰ has yielded promising early results. However, there is at present no method to predict susceptibility to altitude illness and so the only advice that can be given to prospective travellers is to ascend carefully.

The physiological determinants of reduced exercise capacity at high altitude were discussed further by Dr Daniel Martin, Deputy Research Leader of the recent Caudwell Xtreme Everest expedition. A core hypothesis of this expedition is that changes in exercise capacity at high altitude may be explained by factors other than bulk oxygen delivery. Two potential limiting factors suggested by the team are microcirculatory delivery and failure of oxygen utilisation. This expedition is a landmark in the history of high-altitude medicine and will accumulate a vast database of experimental results, including genetic data, detailed exercise tests, thousands of blood samples and the first muscle biopsies from humans at high altitude. The overwhelming task of analysis continues, and Dr Martin reported that some results will be published in the near future.

Dr Martin was able to tell us his own arterial oxygen tension (PaO_2) from near the summit of Everest – a startlingly low 2.55 kPa. This is substantially lower than the results obtained in hypobaric chamber studies.¹⁹ The average PaO_2 of four climbers at 8,400 m was 3.3 kPa.²¹ One possibility is that this may have been due to sub-clinical pulmonary oedema. Interestingly, two of the four subjects had substantially lower arterial oxygen content and larger alveolar-arterial oxygen differences, similar to those recorded during exercise at a simulated altitude of 8,848 m.¹⁹ If this additional hypoxia was caused by pulmonary oedema, considerable ventilation-perfusion mismatch, equivalent to a shunt fraction of greater than 50%, would be necessary²² and clinical signs would be expected.

An alternative explanation could be that some of the subjects were cold and shivering, or moving to keep warm. Precipitous oxygen desaturation occurs during light exercise at altitude because blood exits the lungs without equilibrating with alveolar gas.²³ During exercise, shorter pulmonary capillary transit times and lower venous oxygen content combine with critical diffusion-limited oxygen uptake to cause profound hypoxaemia.^{19, 23, 24}

SESSION 4 MEDICINE AT PHYSIOLOGICAL EXTREMES

Dr Stephen Glen (Consultant Cardiologist, Stirling Royal Infirmary) provided a fascinating exploration of the physiological challenges associated with diving. Without pressurisation of inspired gas, the extrinsic pressure at a depth of 50 m leads to substantial collapse of the lungs, causing the heart to twist and almost completely preventing venous return. Vascular resistance is increased so much that systolic blood pressure in free divers rises above 300 mmHg. The challenge of dealing with decompression illness in remote environments was discussed at length. In-water recompression is a controversial and very dangerous alternative, but portable compression chambers will soon be available similar to the Gamow bags that are used to treat altitude illness.²⁵ 100% oxygen should be given if available, in order to provide the greatest possible concentration gradient for the removal of nitrogen from the blood. If a helicopter is available, it must fly low and fast to the nearest decompression unit. One problem with portable compression chambers is that, in contrast to high altitude where even a very slight increase in barometric pressure causes substantial improvement in symptoms, a much higher pressure difference is required for adequate treatment.

Dr Peter Davis (Consultant in Emergency Medicine, Southern General Hospital, Glasgow) gave a comprehensive description of the problems of hypothermia and drew attention to the important phenomenon of rescue collapse. During the Second World War, an estimated 25–30,000 sailors died shortly after being rescued from cold water. After the sinking of the *Titanic* there were numerous reports that described

the almost immediate death of people who seemed otherwise well after being pulled onto lifeboats several hours after being immersed in the sea. Rescue collapse is believed to be a consequence of redistribution of blood with gravity after sudden removal of hydrostatic compression of the lower body.²⁶ It is particularly common in cold immersion injury, but also occurs in dry hypothermia, perhaps in part because of fluid loss due to cold diuresis. Hence hypothermic patients should be rescued in a horizontal position if at all possible.

The fall in temperature that occurs after rescue, known as afterdrop, is often overlooked and may be fatal. Shivering is usually absent below 32°C, so the patient lacks the endogenous capacity to generate heat. It is therefore essential that, in addition to insulation, exogenous heat is provided from whatever sources are available. If transport is available, hypothermic patients in cardiac arrest should be taken to a hospital that has intensive care, and can provide cardiopulmonary bypass or extracorporeal oxygenation.

REFERENCES

- Johnson C, Anderson S, Dallimore J et al. *Oxford handbook of expedition and wilderness medicine*. Oxford: Oxford University Press; 2008.
- Villar RN. Casualties on Everest – an evacuation problem. *Injury* 1986; 17:138–42.
- Dorward DA, Thompson AA, Baillie JK et al. Change in plasma vascular endothelial growth factor during onset and recovery from acute mountain sickness. *Respir Med* 2007; 101:587–94.
- Hackett PH, Yarnell PR, Hill R et al. High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology. *JAMA* 1998; 280:1920–5.
- Windsor JS. Voices in the air. *BMJ* 2008; 337:a2667.
- Baisden DL, Beven GE, Campbell MR et al. Human health and performance for long-duration spaceflight. *Aviat Space Environ Med* 2008; 79:629–35.
- Grocott M, Richardson A, Montgomery H et al. Caudwell Xtreme Everest: a field study of human adaptation to hypoxia. *Crit Care* 2007; 11:151.
- Bartsch P, Maggiorini M, Ritter M et al. Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med* 1991; 325:1284–9.
- Grissom CK, Roach RC, Sarnquist FH et al. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med* 1992; 116:461–5.
- Maggiorini M, Brunner-La Rocca HP, Peth S et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med* 2006; 145:497–506.
- Hackett PH, Roach RC, Wood RA et al. Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med* 1988; 59:950–4.
- Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. *Lancet Neurol* 2009; 8:175–91.
- Baillie JK, Simpson A. *Interactive altitude physiology & medicine calculators*. 2006. Available from: <http://www.altitude.org/calculators/oxygencalculator/oxygencalculator.htm>
- Lawrie A, Waterman E, Southwood M et al. Evidence of a role for osteoprotegerin in the pathogenesis of pulmonary arterial hypertension. *Am J Pathol* 2008; 172:256–64.
- Thompson AA, Baillie JK, Toshner M et al. Pericardial effusions in healthy lowlanders after acute ascent to high altitude. *Heart* 2006; 92:539–40.
- Stray-Gundersen J, Chapman RF, Levine BD. 'Living high-training low' altitude training improves sea level performance in male and female elite runners. *J Appl Physiol* 2001; 91:1113–20.
- Favret F, Richalet JP. Exercise and hypoxia: the role of the autonomic nervous system. *Respir Physiol Neurobiol* 2007; 158:280–6.
- Moore R. *Heroes, villains and velodromes: Chris Hoy and Britain's track cycling revolution*. London: HarperSport; 2008.
- Sutton JR, Reeves JT, Wagner PD et al. Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol* 1988; 64:1309–21.
- Niemann S, Müller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nat Genet* 2000; 26:268–70.
- Grocott MPW, Martin DS, Levett DZH et al. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; 360:140–9.
- Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J Appl Physiol* 1949; 1:825–47.
- Wagner PD, Gale GE, Moon RE et al. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol* 1986; 61:260–70.
- Wagner PD, West JB. Effects of diffusion impairment on O₂ and CO₂ time courses in pulmonary capillaries. *J Appl Physiol* 1972; 33:62–71.
- Austin D. Gammow bag for acute mountain sickness. *Lancet* 1998; 351:1815.
- Golden FS, Hervey GR, Tipton MJ. Circum-rescue collapse: collapse, sometimes fatal, associated with rescue of immersion victims. *J R Nav Med Serv* 1991; 77:139–49.
- Firth PG, Zheng H, Windsor JS, Sutherland AI et al. Mortality on Mount Everest, 1921–2006: descriptive study. *BMJ* 2008; 337:a2654.
- Sutherland AI. Why are so many people dying on Everest? *BMJ* 2006; 333:452.

CONCLUSION

Expedition medicine presents unique and sometimes insurmountable challenges, but most of these have been encountered before and so should not be unexpected. Taking humans to their physiological extremes, particularly the hypoxia of high altitude, has great potential to advance not only our understanding of physiology but also some aspects of clinical practice back at sea level.