British Journal of Anaesthesia **118** (3): 283–6 (2017)
doi:10.1093/bja/aew407

Facing acute hypoxia: from the mountains to critical care medicine

M. M. Berger[1,2] and M. P. W. Grocott[3–6,*]

[1]Department of Anesthesiology, Perioperative and General Critical Care Medicine, Salzburg General Hospital, Paracelsus Medical University, Salzburg, Austria, [2]Department of Anesthesiology, University Hospital Heidelberg, Germany, [3]Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK, [4]Critical Care Research Area, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK, [5]Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK and [6]UCL Centre for Altitude, Space and Extreme Environment Medicine, UCLH NIHR Biomedical Research Centre, Institute of Sport and Exercise Health, First Floor, 170 Tottenham Court Road, London W1T 7HA, UK

*Corresponding author. E-mail: mike.grocott@soton.ac.uk

It was not until 1978 that, after many unsuccessful attempts, the summit of Mount Everest (8850 m) was reached by climbers breathing only ambient air. This challenge was first accomplished by Peter Habeler and Reinhold Messner. Their intriguing success renewed interest in high-altitude physiology and medicine, especially because in the preceding 60 yr a number of physiologists and high-altitude climbers had predicted that it would never be possible to conquer this peak without the aid of supplemental oxygen. This view was based on the assumption that the inspired oxygen partial pressure (P_{O_2}) of ~43 mm Hg[1] at the summit of Mount Everest was at, or even below, the limit of human tolerance to hypoxia at rest, leaving no oxygen available for physical work.

A fascinating opportunity to obtain deeper insights into the physiological challenge of climbing Mount Everest without supplemental oxygen came 29 yr later with the Caudwell Xtreme Everest Expedition. During this expedition, samples of arterial blood were obtained from climbers during their ascent to and descent from the summit of Mount Everest. These data showed that at the Balcony of Mount Everest, at a height of 8400 m, the mean arterial P_{O_2} in subjects breathing ambient air was 3.28 kPa (24.6 mm Hg), with a range of 2.55–3.93 kPa (19.1–29.5 mm Hg).[2] Although these values are among the lowest values for arterial P_{O_2} ever documented in humans, and certainly in normally functioning humans, they were high enough to allow a successful climb of the highest peak on earth. In order to explain the physiological changes that are needed to achieve this, numerous studies have investigated the body's responses to acute hypoxia and how oxygen delivery and consumption are affected in these extreme conditions. Not only have these studies improved our understanding of high-altitude physiology and pathology, but they may also help us to understand how hypoxia affects critically ill patients and other patients in whom hypoxaemia and cellular hypoxia are prevalent.

Tissue hypoxia is a fundamental consequence not only of high-altitude exposure but also of critical illness, where it may occur either as a cause for or as a result of a variety of pathologies. It is conceivable that the mechanisms of adaption to high-altitude-induced hypoxia also play a role in responses to hypoxia in critically ill patients. Therefore, it might be possible to transfer knowledge gained in the mountains to critical care medicine. The approach of investigating mountaineers exposed to hypoxia at high altitude offers the advantage that a relatively homogeneous and healthy population can be studied, in contrast to the heterogeneous and generally less healthy patient population typically observed on critical care units. However, this approach encompasses the possibility that the pathologies of critical illness may modify the responses to hypoxia that occur in a healthy individual and that the full range of adaption may not be available to critically ill patients.

In the past, numerous studies on healthy volunteers ascending to high altitude have shed new light on our understanding of various hypoxia-related diseases. For example, such studies demonstrated, for the first time, the importance of sodium-transport-driven alveolar fluid clearance in the pathogenesis of pulmonary oedema. In individuals prone to the development of high-altitude pulmonary oedema (HAPE), the transepithelial respiratory sodium transport is defective, and this dysfunction is further aggravated during hypoxia.[3] Pharmacological stimulation of this transport by inhalation of the *β*-adrenergic agonist salmeterol decreased the incidence of HAPE in susceptible individuals by ~50%.[3] Later, and on the basis of these data, i.v. salbutamol has been used to accelerate the resolution of alveolar oedema in hypoxic patients with acute lung injury and acute respiratory distress syndrome (ARDS), because in the majority of these patients the capacity of alveolar fluid clearance is impaired.[4] In the very first of these studies, salbutamol reduced the amount of extravascular lung water and improved mechanical ventilation settings.[5] Disappointingly, a subsequent multicentre study of 324 ARDS patients was stopped after an interim analysis, because treatment with i.v. salbutamol was poorly tolerated and increased 28 day mortality.[6] However, despite this setback, interest in measures that stimulate transepithelial sodium transport continues, and it remains to be elucidated whether such stimulation by alternative interventions (e.g. pharmacological agents other than salbutamol, gene therapy) may improve resolution of pulmonary oedema and outcome in ARDS and other conditions where pulmonary oedema is a feature.

Other unique insights into the pathophysiology of pulmonary oedema formation that were gained in mountaineers with HAPE

susceptibility and that are of relevance for every patient at risk for developing lung oedema came from haemodynamic measurements performed with a pulmonary artery catheter at 4559 m. These measurements show that the critical pathophysiology in HAPE is an excessive hypoxic pulmonary vasoconstriction, leading to increased microvascular pressure despite normal left atrial pressure and left ventricular function.[7] The resultant hydrostatic stress causes both dynamic changes in the permeability of the alveolar capillary barrier and mechanical injuries, leading to leakage of proteins and erythrocytes into the alveolar space in the absence of inflammation.[8] The normal capillary hydrostatic pressure is ~1.7 kPa (13 mm Hg) at the arteriolar end and 0.8 kPa (6 mm Hg) at the venous end.[9] Right heart catheterization studies by Maggiorini and colleagues[7] indicate that the critical pulmonary capillary pressure threshold value for oedema formation is ~2.7 kPa (20 mm Hg). This finding is in line with experimental observations in dogs, showing a critical microvascular pressure of 1.1–1.6 kPa (17–24 mm Hg), at which the lungs continuously leak fluid and gain weight.[10] Furthermore, Maggiorini and colleagues[7] observed that some HAPE-susceptible subjects with equivalent high pulmonary artery pressures but lower pulmonary capillary pressure values did not develop clinical or radiological evidence of pulmonary oedema formation, suggesting that increased microvascular pressures associated with pulmonary arterial hypertension rather than upstream arterial pressure elevation alone is crucial in the pathophysiology of oedema formation. This is supported by a recent study showing that an exaggerated high-altitude-induced increase in pulmonary artery pressure alone does not trigger oedema formation in a HAPE-susceptible population.[11] When inflammation is present, such as in ARDS, increased permeability of the alveolar–capillary barrier decreases the threshold for oedema formation, and pulmonary fluid extravasation occurs in the face of physiologically normal capillary pressure values. Taken together, these results suggest that an acute increase in pulmonary capillary pressure values to >20 mm Hg is the central haemodynamic factor in the pathophysiology of pulmonary oedema formation even when no co-morbidities are present, and that pulmonary artery pressure is not an adequate variable for estimating the hydrostatic pressure in the pulmonary capillary bed. The basis for the exaggerated hypoxic pulmonary vasoconstriction in HAPE-susceptible subjects is complex and multifactorial. Recent studies suggest that a hypoxia-induced endothelial dysfunction in both the systemic and the pulmonary circulation, with an imbalance between vasoconstrictors (e.g. endothelin-1) and vasodilators (e.g. nitric oxide) and an increased production of reactive oxygen species, is of major importance.[12–14] These substances are also implicated in other forms of pulmonary arterial hypertension, suggesting that the study of the underlying molecular pathways of diseases occurring in healthy individuals in a hypoxic environment has the potential to improve the understanding of these interactions in the critically ill.

The physiological response to acute hypoxia and high-altitude exposure is characterized by an increase in cardiac output (i.e. heart rate and stroke volume), ventilation and haemoglobin concentration. These changes serve to ensure that oxygen carriage is not the limiting factor for maximal oxygen consumption at altitude. In recent years, the focus of numerous studies has shifted away from the adaptive processes of the cardiorespiratory and haematological system towards the peripheral microcirculation and the process of ATP production that occurs within the mitochondria. These studies suggest that adaption to a hypoxic environment might occur not only by increasing the oxygen flux, but also by decreasing its utilization. Indeed, hypoxia-tolerant species rarely activate anaerobic metabolism, but rather tend to reduce oxygen demand by decreasing total energy turnover and cellular activities, such as ion pumping and protein turnover.[15] These mechanisms may also pertain in septic and other critically ill patients, where the onset of disease is often characterized by a hyperdynamic circulation with an elevated cardiac output, whereas as the course of the disease progresses mitochondrial activity in general, and oxidative phosphorylation in particular, are reduced.[16] In these conditions, increasing oxygen delivery is of no benefit and may be harmful.[17] Thus, in both critical illness and high-altitude exposure the acute response to hypoxia is characterized by an increased oxygen delivery, whereas the longer-term responses seem to be focused on reducing utilization. Such observations highlight the potential value of exploring these mechanisms further by exploiting the opportunity to study humans exposed to decreased P_{O_2} at high altitude in order to elucidate mechanisms important in established critical illness. This change in focus from oxygen delivery to oxygen utilization may also serve to alter our therapeutic focus towards measures increasing the efficiency of oxygen utilization rather than improving delivery.

The wide and poorly explained interindividual variation in performance at high altitude and susceptibility to high-altitude illness is mirrored in the large differences in outcome observed in critically patients with apparently similar initial pathophysiology. This phenotypic variation is, in turn, underpinned by genetic variation that may explain fundamental differences between individuals in their physiological responses to acute hypoxia. Thus, it is plausible that genes conferring benefit for high-altitude performance might be related to an increased likelihood of survival in critical illness. In keeping with this hypothesis, the *ACE* gene insertion allele is associated with improved high-altitude performance,[18] and with both a lower incidence of ARDS in patients with severe sepsis and a lower mortality in established ARDS.[19] Furthermore, upregulation of heat shock protein-70 has been reported to improve hypoxic tolerance and to protect against acute lung injury.[20]

The management of hypoxaemia in the critically ill patient is challenging, and for decades the avoidance of hypoxaemia was considered to be much more important than taking into account the possible side-effects associated with hyperoxaemia. Thus, many acute treatment algorithms recommended liberal use of oxygen, often without first confirming the presence of hypoxaemia. However, hyperoxia has long been recognized to cause vasoconstriction, and more recently, identified to reduce microvascular perfusion.[21] Therefore, it is questionable whether an increase in the fraction of inspired oxygen reliably increases oxygen tensions in the peripheral tissue. Indeed, accumulating evidence suggest that hyperoxaemia might increase morbidity and mortality in numerous disease states, including myocardial infarction, stroke, and cardiac arrest.[22] In many situations, moderate hypoxaemia may not be harmful, whereas hyperoxaemia-induced local vasoconstriction and oxidative stress may be associated with harm. Consequently, conservative oxygen therapy approaches that avoid excess hyperoxaemia (e.g. targeting an arterial oxygen saturation of 88–95% during and after successful resuscitation) are now recommended,[23] and there is increasing focus on achieving more precise control of arterial oxygen concentrations and consideration of the notion of 'permissive hypoxaemia'.[24]

The change towards this more restrictive administration of oxygen is not surprising when considered in the context of the relationship between atmospheric oxygen concentrations and the development of life on earth over geological time frames.

The earth formed ~4.5 billion yr ago in an atmosphere that did not contain any oxygen. The first oxygen appeared in the atmosphere ~3 billion yr ago as a byproduct of the biochemical transformation of carbon dioxide and water into carbohydrates by photosynthetic organisms. Saturation of terrestrial oxygen sinks (e.g. sea water, exposed terrestrial iron deposits), leading to an elevation in atmospheric oxygen concentration, is believed to have caused the subsequent mass extinction event through oxygen toxicity. The endosymbiotic relationship between primitive unicellular organisms and the *Rickettsia*-like bacteria that eventually became mitochondria is believed to have been the key step that facilitated the development of eukaryotic organisms and multicellular life. This narrative highlights the complex relationship between oxygen and eukaryotic metabolism, in particular the potential harmful effects of uncontrolled hyperoxia.

During the next 2.5 billion yr, the oxygen concentration in the earth's atmosphere gradually increased to the current value of ~21%. On this background, the evolution of *Homo sapiens* and our ancestors started only 7 million yr ago and created the world we live in today: throughout the entire evolution of *Homo sapiens*, human physiology has never been exposed to oxygen concentrations exceeding 21%, equivalent to an inspired P_{O_2} of ~20.9 kPa (156 mm Hg) at sea level. In contrast, populations living at high altitude, such as Tibetans or Andean natives, have been exposed and adapted to lower inspired P_{O_2} values. At an altitude of 5000 m, the highest at which humans reside, the inspired P_{O_2} is only about half of the sea-level value. This value emphasizes the degree of hypoxia to which the physiology of high-altitude populations can adapt. However, nowhere in the earth's atmosphere does the atmospheric P_{O_2} exceed ~20.9 kPa (156 mm Hg) experienced at sea level, so that there has been no recent evolutionary stimulus to drive human adaptive mechanisms to hyperoxia. We should not be surprised that the high oxygen concentrations administered in numerous medical conditions where oxygen therapy is liberaly administered are commonly ineffective, and in some circumstances, harmful.[22]

An appealing notion to consider is whether all humans have the potential to (re)activate effective mechanisms of oxygen tolerance, given that each and every one of us has been exposed to severe and sustained hypoxia during fetal life.[25] The degree of hypoxia *in utero* is very rarely experienced in adult life except in the profoundly unwell or in individuals exposed to severe environmental hypoxia at extreme altitude. The thriving fetus *in utero* suggests a universal capacity to tolerate severe hypoxaemic stress in certain circumstances and offers the hope that clinically useful interventions may be developed to (re)activate the relevant cellular mechanisms. It is notable that many of these fetal physiological mechanisms serve to maintain adequate oxidative tissue metabolism through modifying oxygen consumption rather than modulating oxygen delivery.[26] Thus, strategies used to endure the relative hypoxia *in utero* may provide insights for the management of severe hypoxaemia in adult life.

Conclusion

Exposure of healthy individuals to hypoxaemia caused by environmental hypobaric hypoxia at high altitude provides an opportunity to explore physiological mechanisms of adaptation to acute hypoxia at a whole-body 'integrative physiology' level that may be of value in improving understanding of the causes and consequences of hypoxia in critical illness. The mechanisms that distinguish survivors from non-survivors during critical illness may lie, at least in part, in the cellular control of oxygen consumption via the signalling pathways discussed above. Investigating these processes in healthy individuals ascending to high altitude may provide new insights into the body's response to hypoxia in those with critical illness. This approach is appealing because it offers the advantage that a relatively homogeneous study population can be studied, in contrast to the heterogeneous population typically observed on our intensive care units.

Authors' contributions

Writing and revising the manuscript; approval of the manuscript in its current version: M.M.B., M.P.W.G.

Declaration of interest

M.M.B.: none declared. M.P.W.G. is executive chair of the Xtreme Everest (XE) Oxygen Research Consortium and chairs the XE Scientific Advisory Board. M.P.W.G. is joint editor-in-chief of the BioMedCentral journal *Extreme Physiology and Medicine*. M.P.W.G. serves on the medical advisory board of Sphere Medical Ltd.

Funding

Some of this work was undertaken at University College London Hospital, University College London Biomedical Research Centre, which received a proportion of funding from the United Kingdom Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. Some of this work was undertaken at University Hospital Southampton, University of Southampton Respiratory Biomedical Research Unit, which received a proportion of funding from the United Kingdom Department of Health's National Institute for Health Research Biomedical Research Units funding scheme. The Xtreme Everest Oxygen Research Consortium have received unrestricted financial support from John Caudwell, BOC Medical (Linde GmBH) Royal Free Hospital NHS Trust Charity, the Special Trustees of University College London Hospital NHS Foundation Trust, the Southampton University Hospital Charity, the UCL Institute of Sports Exercise and Health, The London Clinic, University College London, University of Southampton, Duke University Medical School, the United Kingdom Intensive Care Society, the National Institute of Academic Anaesthesia, the Rhinology and Laryngology Research Fund, The Physiological Society, Smiths Medical, Deltex Medical, Atlantic Customer Solutions, and the Caudwell Xtreme Everest and Xtreme Everest 2 volunteer participants who trekked to Everest Base Camp.

References

1. West JB. Barometric pressures on Mt. Everest: new data and physiological significance. *J Appl Physiol* 1999; **86**: 1062–6
2. Grocott MP, Martin DS, Levett DZ, 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
3. Sartori C, Allemann Y, Duplain H, *et al.* Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 2002; **346**: 1631–6
4. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001; **163**: 1376–83
5. Perkins GD, McAuley DF, Thickett DR, Gao F. The β-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006; **173**: 281–7

6. Gao Smith F, Perkins GD, Gates S, *et al*. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012; **379**: 229–35
7. Maggiorini M, Mélot C, Pierre S, *et al*. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 2001; **103**: 2078–83
8. Swenson ER, Maggiorini M, Mongovin S, *et al*. Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *JAMA* 2002; **287**: 2228–35
9. MacIver DH, Clark AL. The vital role of the right ventricle in the pathogenesis of acute pulmonary edema. *Am J Cardiol* 2015; **115**: 992–1000
10. Homik LA, Bshouty Z, Light RB, Younes M. Effect of alveolar hypoxia on pulmonary fluid filtration in in situ dog lungs. *J Appl Physiol* 1988; **65**: 46–52
11. Dehnert C, Mereles D, Greiner S, *et al*. Exaggerated hypoxic pulmonary vasoconstriction without susceptibility to high altitude pulmonary edema. *High Alt Med Biol* 2015; **16**: 11–7
12. Berger MM, Hesse C, Dehnert C, *et al*. Hypoxia impairs systemic endothelial function in individuals prone to high-altitude pulmonary edema. *Am J Respir Crit Care Med* 2005; **172**: 763–7
13. Berger MM, Dehnert C, Bailey DM, *et al*. Transpulmonary plasma ET-1 and nitrite differences in high altitude pulmonary hypertension. *High Alt Med Biol* 2009; **10**: 17–24
14. Bailey DM, Dehnert C, Luks AM, *et al*. High-altitude pulmonary hypertension is associated with a free radical-mediated reduction in pulmonary nitric oxide bioavailability. *J Physiol* 2010; **588**: 4837–47
15. Hochachka PW, Buck LT, Doll CJ, Land SC. Unifying theory of hypoxia tolerance: molecular/metabolic defense and rescue mechanisms for surviving oxygen lack. *Proc Natl Acad Sci USA* 1996; **93**: 9493–8
16. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence* 2014; **5**: 66–72
17. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, metaanalysis, and meta-regression of cohort studies. *Crit Care Med* 2015; 43: 1508–19
18. Wang Y, Lu H, Chen Y, Luo Y. The association of angiotensin-converting enzyme gene insertion/deletion polymorphisms with adaptation to high altitude: a meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2016; **17**: 1470320315627410
19. Marshall RP, Webb S, Bellingan GJ, *et al*. Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; **166**: 646–50
20. Aschkenasy G, Bromberg Z, Raj N, Deutschman CS, Weiss YG. Enhanced Hsp70 expression protects against acute lung injury by modulating apoptotic pathways. *PLoS One* 2011; **6**: e26956
21. Orbegozo Cortés D, Puflea F, Donadello K, *et al*. Normobaric hyperoxia alters the microcirculation in healthy volunteers. *Microvasc Res* 2015; **98**: 23–8
22. Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. *Crit Care* 2015; **19**: 284
23. Monsieurs KG, Nolan JP, Bossaert LL, *et al*. European resuscitation council guidelines for resuscitation 2015: Section 1. Executive summary. *Resuscitation* 2015; **95**: 1–80
24. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med* 2013; **41**: 423–32
25. Martin DS, Khosravi M, Grocott MP, Mythen MG. Concepts in hypoxia reborn. *Crit Care* 2010; **14**: 315
26. Itskovitz J, LaGamma EF, Rudolph AM. The effect of reducing umbilical blood flow on fetal oxygenation. *Am J Obstet Gynecol* 1983; **145**: 813–8

British Journal of Anaesthesia **118** (3): 286–8 (2017)
doi:10.1093/bja/aew474

Medical research and the ethics of medical treatments: disability-free survival

P.-A. Lönnqvist[1,2]

[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden and [2]Paediatric Anaesthesia, Karolinska University Hospital, Stockholm, Sweden

Corresponding author. E-mail: per-arne.lonnqvist@ki.se

Interest in relevant patient-centred outcomes, instead of surrogate outcomes, continues to increase, and for good reason. An example in the setting of anaesthesia and intensive care is that therapeutic measures that improve oxygenation in the setting of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) ("blood gas cosmetics"), do not translate into improved survival as might be expected. Other measures (e.g. ICU mortality or even 30-day post-ICU discharge survival) do not really reflect what many medical staff and laypeople believe represents valid outcome parameters. Using surrogate end-points or mortality rates can also lead to spurious results when it comes to clinical research.

Myles and colleagues[1–3] have recently introduced the concept of "disability-free survival" (DFS) as a new and more relevant approach in randomized clinical trials (RCT) of resource intensive medical treatments, including various types of surgical