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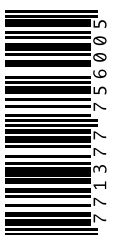
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# High Altitude Research and its Relevance to Critical Illness

Critical illness can be considered as the body's failure to compensate for severe pathophysiological 'stress'. The result is a vicious circle of damage that ultimately ends in organ failure, permanent harm and, unfortunately for many, death. Fortunately, the human body is remarkably resilient. It has the ability to tolerate changes to its internal milieu and defend the cells that make up its vital organs. In the presence of a stressor, such as infection or inflammation, such tolerance occurs via the maintenance of 'normality' through multiple homeostatic mechanisms. However, the ability to preserve a cellular status quo is not unlimited, and if the stressor is sustained over time, or excessive in magnitude, other strategies are required to ensure survival. Adaptation is the process through which biological systems undergo change to tolerate a specific stressor, such as heat or cold.

Critical illness is a complex pathology, but one stressor commonly associated with it is hypoxia: a lack of oxygen for cellular metabolism. Understanding adaptation to hypoxia is vital to advancing the treatment of critically ill patients and all avenues should be explored to achieve this. One experimental model that has gained momentum during the last decade is the study of healthy volunteers ascending to high altitude, where they are subjected to a controllable 'dose' of hypoxia due to the reduced partial pressure of oxygen in the air there. Physiological and cellular responses can be measured and their relationship with performance at altitude studied. The ability to observe integrated human responses over time, through a systems biology approach, makes a high altitude laboratory a potentially fruitful model for mapping the

complex phenomenon of human adaptation to hypoxia, and for testing interventions that have direct clinical applications for hypoxic critically ill patients. In essence, an external environmental stress (the atmospheric hypoxia experienced at high altitude) is used as a translational tool, comparable to that of an animal model, but allowing exploration of species-specific mechanisms. This novel paradigm for hypoxia in critical illness may provide clinically relevant biomarkers and identify novel therapeutic targets.

## High Altitude and Acclimatisation

The key factor limiting ascent to high altitude is the exponential decline in the inspired partial pressure of oxygen that mirrors the change in atmospheric pressure. At the highest point on the surface of the Earth, the summit of Mount Everest (8848m), atmospheric pressure and oxygen partial pressure are approximately one third of that at sea level (West et al. 1983). It is unclear whether this pressure change itself has an independent and compounding effect (to that of the hypoxia) on human physiology (Coppel et al. 2015). By an interesting coincidence, the summit of Mount Everest appears to be the limit of human tolerance to hypoxia, and it is unlikely that humans could ascend much further (West 2009). The effectiveness of adaptation to altitude is in part determined by speed of ascent and the magnitude of altitude gained. Rapid ascent to very high altitude leaves inadequate time for effective adaptation, and can lead to unconsciousness and death (Ernsting 1963). Slow ascent, such as is achieved during a trek, allows sufficient time (days to weeks) for the process of acclimatisation to restore convective oxygen delivery through increases in heart

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rate (and therefore cardiac output), minute ventilation and haemoglobin concentration. This classic description of acclimatisation to altitude was formulated decades ago and has stood the test of time. However, it fails to explain inter-individual performance at altitude, as those with the greatest values for convective oxygen delivery do not necessarily cope best with altitude (Martin and Windsor 2008). Perhaps the reason for this is that beneath these overt and easily measurable systems lies a covert network of complex cellular adaptations to hypoxia, adjusting cells to their oxygen-scarce environment. These two distinct strategies (system level changes in organ function versus cellular alterations) help us to think clearly about the pathophysiology and management of clinical illness. On the one hand the body can restore oxygen delivery at altitude, but its long-term value is questionable, and requires additional energy consumption in an environment when it is in short supply. We emulate this on the intensive care unit (ICU) by augmenting cardiac output, blood pressure, oxygen saturation and haemoglobin concentration; again, often without demonstrable improvements in clinical outcomes

(Hayes et al. 1994). Cellular changes in response to hypoxia, however, tend to alter metabolism in a way that improves the efficiency with which oxygen is used and thus saves valuable energy. If these processes could be mimicked via a therapeutic intervention, new treatments targeting metabolism have the potential to benefit critically ill patients.

At the heart of cellular acclimatisation is the genetic transcription factor hypoxia-inducible factor (HIF), the master regulator of hypoxic responses (Semenza 2000). The HIF complex exists in every cell of the body; it proliferates in hypoxic conditions, and up-regulates many different genes involved with oxygen delivery and consumption, cell proliferation, and a vast array of metabolic processes. The importance of this oxygen sense-and-response system is highlighted by the fact that it is preserved throughout most living organisms on Earth (Iyer et al. 1998). We should, therefore, rest assured that HIF is constantly ready to protect us from hypoxia, through the initiation of a complex network of cellular changes. Of note, no such rescue system exists to protect us from hyperoxia-induced reactive oxygen species damage, beyond a limited supply of endogenous antioxidants.

The study of native high altitude populations, such as Andeans, Ethiopians and Tibetans, can provide fascinating insights into long-term hypoxic adaptation. Tibetans in particular display phenomenal adaptation to hypoxia, perhaps unsurprising given that their altitude ancestry stretches back over 20,000 years. Whilst genetic alterations that have occurred during this time have been reported (Simonson et al. 2010; 2012), the successful phenotype of this population remains elusive (Gilbert-Kawai et al. 2014). One thing that we can be certain of is that, contrary to popular belief, Tibetans do not have a raised haemoglobin concentration at altitude (Beall et al. 1984). Understanding more about the biology of Tibetans may also benefit critically ill patients, through interventions that reproduce their hypoxia survival strategies. Thus far, almost every genetic locus identified to be positively selected for in these ancestral high altitude populations appears to be involved in the HIF complex or its downstream target genes.

## Examples of Translational Findings from High Altitude

### Permissive Hypoxaemia

On 23 May 2007, four climbers descending from the summit of Mount Everest stopped at an altitude of 8400m to take femoral arterial blood gases from one another for rapid analysis in a standard benchtop analyser at 6400m (Grocott et al. 2009). The results revealed some of the lowest levels of blood oxygenation ever reported in humans, one of which was an incredible 19.1 mmHg. With the caveats that these were healthy, physically fit individuals known to perform well at altitude, these data allow us to speculate on whether normoxaemia is truly a necessary target for the critically ill (Martin and Grocott 2013). An intriguing coincidence is that similar levels of hypoxaemia are observed in every normally-developing human foetus, suggesting that all humans possess the innate ability to withstand significant hypoxaemia

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(Martin et al. 2010). Since these data were presented, a number of studies have been undertaken to explore the benefits of 'permissive hypoxaemia' (generally considered to be an SpO<sub>2</sub> of between 88-92%) in the critically ill (Suzuki et al. 2014; Panwar et al. 2016; Helmerhorst et al. 2016). Whilst the safety and efficacy of permissive hypoxaemia has yet to be fully elucidated this could lead to a substantial shift in practice with the potential to benefit critically ill patients.

### The Microcirculation

There has been a great deal of interest in measuring microcirculatory blood flow for many years; reduced and heterogeneous flow in capillary beds has been associated with worse clinical outcomes in the critically ill (Bezemer et al. 2012). Microcirculatory flow index (MFI) in the sublingual microcirculation decreases on ascent to high altitude whilst

capillary density increases (Martin et al. 2009; 2010). The reduction in blood flow may be due to the polycythaemia that accompanies acclimatisation, and may actually represent maladaptation. This hypothesis is supported by the fact that a reduction of flow is not observed in Sherpas (of Tibetan descent) when they ascend to altitude (Gilbert-Kawai et al. 1985). Tibetans have been shown to have more than double the forearm blood flow of low-altitude residents, resulting in greater than sea level oxygen delivery to tissues (Erzurum et al. 2007). From this it can be deduced that local capillary blood flow is a crucial component of convective oxygen delivery that may have a significant influence on performance.

### Nitric Oxide Biology

Ascent to altitude leads to an elevation in biomarkers of nitric oxide production (nitrate and nitrite) and activity (cGMP) (Levett et al. 2011). Furthermore, MFI correlates inversely with plasma nitrite concentration (Levett et al. 2011). When compared to lowland residents, Tibetans were seen to have more than ten times the circulating concentrations of bioactive nitric oxide products (plasma and red blood cell nitrate and nitroso proteins and plasma nitrite), suggesting this mechanism is advantageous in hypoxic adaptation. It is therefore conceivable that nitric oxide levels determine peripheral and microcirculatory blood flow and are central to the acclimatisation process. Therapies that manipulate nitric oxide biology may therefore be of value to the critically ill.

### Metabolism

The ultimate consumers of oxygen are the mitochondria, whose ability to produce ATP is ultimately limited by the partial pressure of oxygen. Imbalance between mitochondrial oxygen supply and demand will not only reduce the energy available to drive cell functions, but also increase the local production of damaging reactive oxygen species (ROS), exacerbating dysfunction and cell death. Mitochondrial function in critical illness is known to influence mortality, with reduced ATP levels observed in the skeletal muscle of non-survivors of severe sepsis (Brealey et al. 2002), and early mitochondrial biogenesis

associated with recovery (Carre et al. 2010). During prolonged exposure to high altitude, humans demonstrate adaptation at the mitochondrial level, in both cardiac and skeletal muscle (Murray 2016). At altitudes >5500m there is a marked loss of mitochondrial density, and downregulation of specific respiratory complexes in skeletal muscle (Levett et al. 2012). It has been hypothesised that this reduction in mitochondrial numbers may reduce the oxygen demand of non-vital tissues, sparing oxygen for more vital organs, whilst also reducing the burden of oxidative stress by removing the principal source of reactive oxygen species (Howald and Hoppeler 2003). This seems to occur in regulated manner, with decreased density mirroring the reduction in mitochondrial biogenesis factor PGC-1 $\alpha$  during prolonged exposure to high altitude (Levett et al. 2012). Compensatory changes have been observed to promote ATP production in the face of diminished oxygen availability and reduced mitochondrial numbers at high altitude. Remaining mitochondria appear to

become more efficient. There is increased coupling between oxygen consumption and ATP generation; perhaps mediated by uncoupling protein (UCP) 3, which is shown to be downregulated at high altitude (Levett et al. 2012). A stoichiometric increase in the yield of ATP produced per molecule of oxygen consumed can be achieved by a switch away from fatty acid oxidation (Hinkle et al. 1991), and is observed in Sherpas (Hochachka et al. 1992).

Pathways underlying metabolic acclimatisation are potentially important targets for optimising outcomes in critical illness. HIF-target genes, whose levels are controlled in response to cellular oxygen levels, include many different metabolic enzymes and regulators, including the master regulator of fat metabolism, peroxisome proliferator-activated receptor alpha (PPAR- $\alpha$ ) and its target proteins, enzymes of fatty acid oxidation and UCP3 (Narravula and Colgan 2001). Pharmacological manipulation of these metabolic pathways may allow us to boost the metabolic efficiency

and oxidative stress defences of patients under conditions of hypoxic stress.

## Conclusions

Recent studies of volunteers ascending to high altitude have focused attention on adaptation to hypoxia at a cellular level. Similar changes are likely to be occurring in critically ill patients and commonality in these responses may yield new programmes of clinical research and the development of novel biomarkers and treatments. The paradigm of ascent to high altitude has now become accepted as an alternative to the mouse or petri dish and is likely to continue shining light on an otherwise obscure pathophysiology that has yet to be tamed. ■

## Conflict of Interest

Daniel Martin declares that he has no conflict of interest. Helen McKenna declares that she has no conflict of interest.

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